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Proteomic studies of human embryonic stem cells in hypoxia

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by

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Abstract

Hypoxia has been shown to promote pluripotency in human embryonic stem cells (hESCs), but the mechanism by which this occurs in poorly understood. To gain insight into this mechanism, we used mass spectrometry to investigate changes in protein expression in hESCs cultured in hypoxia. hESCs in feeder free culture were incubated in 1% oxygen or 20% oxygen for 48 and 72 hours. The medium was not changed during this time to accelerate differentiation. Immunofluroescence localization of Oct-4 revealed that cultures incubated in hypoxia were less differentiated than cultures incubated in normoxia. Electrospray tandem mass spectrometry was performed to compare global protein expression of hESCs from each oxygen condition. Changes were observed in the expression of proteins involved in metabolism, chromatin modification, post-transcriptional modification, and regulation of the transcription factor, c-Myc. The results of this study will improve our understanding of the mechanism by which hypoxia maintains pluripotency of hESCs *in vitro*.

Keywords

Proteomics, human embryonic stem cells, hypoxia, pluripotency

Co-authorship

Chapter 1, Section 1.5

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Section 1.6 of this thesis was adapted from the above literature review. Chris Hughes and Amelia Nuhn wrote the initial draft of the manuscript and Lynne Postovit and Gilles Lajoie revised it.

Declaration

The hESC maintenance, sample preparation, and real-time RT-PCR, Western blotting, immunofluorescence, and mass spectrometry experiments described in Chapter 2 and Chapter 3 of this thesis were performed by Amelia Nuhn.

This work is dedicated to

my family and to my roommates, Rainie, Steph and Tash.

Thank you for always believing in me and being there for me

when I need you. The past two years have been amazing,

largely because of you. I love you all!

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List of Abbreviations, Symbols, Nomenclature

ACN – acetonitrile

ARNT – aryl hydrocarbon receptor nuclear translocator

bFGF – basic fibroblast growth factor

BMP – bone morphogenic protein

BSA – bovine serum albumin

CAK – cdk activating kinase

cAMP – cyclic adenosine monophosphate

CDK – cyclin dependent kinase

CID – collision induced dissociation

CM – conditioned medium

coA – coenzyme A

CT – cycle threshold

DDA – data dependent acquisition

DTT – dithiothreitol

EB – embryoid body

ECM – extracellular matrix

EDTA – ethylenediaminetetraacetic acid

EndRB – endothelin receptor type B

ERK – extracellular signal-related kinase

ESI – electrospray

ETC – electron transport chain

ETD – electron transfer dissociation

FA – formic acid

FT ICR – Fourier transform ion-cyclotron-resonance

hCG – human chorionic gonadotrophin

hDF – human dermal fibroblast

hESC – human embryonic stem cell

HIF – hypoxia inducible factor

HPRT1 – hypoxanthine phosphoribosyltransferase 1

HRE – hypoxia response element

HRP – horseradish peroxidase

HSC – hematopoietic stem cells

ICM – inner cell mass

IDA – iodoacetamide

IE – iterative exclusion

IGF – insulin-like growth factor

iPSC – induced pluripotent stem cell

IT – ion trap

iTRAQ – isobaric tags for relative and absolute quantitation

LC – liquid chromatography

LIF – leukemia inhibitory factor

MALDI – matrix assisted laser desorption ionization

MAPK – mitogen activated protein kinase

MEF – mouse embryonic fibroblast

MEF-CM – mouse embryonic fibroblast conditioned medium

mESC – mouse embryonic stem cell

MM – MEF medium

mPER – mammalian protein extraction reagent

MS – mass spectrometry

MS/MS – tandem mass spectrometry

MSC – mesenchymal stem cell

m/z – mass-to-charge ratio

NO – nitric oxide

NSC – neural stem cell

OCT – octamer binding protein

OMSSA – open mass spectrometry search algorithm

PAGE – polyacrylamide gel electrophoresis

PBS – phosphate buffered saline

PEDF – pigment epithelium-derived factor

PHD – prolyl-hydroxylase domain

PKM – pyruvate kinase muscle

PP2A – protein phosphatase 2A

PTM – post-translational modification

PVDF – polyvinlyidene difluoride

Q-ToF – quadrupole time-of-flight

ROS – reactive oxygen species

RP – reversed phase

RT-PCR – reverse transcription polymerase chain reaction

SAX – strong anion exchange

SCID – severe combined immunodeficient

SCX – strong cation exchange

SDS – sodium dodecyl sulfate

SILAC – stable isotope labelling with amino acids in cell culture

SM – stem cell medium

SRM – selected reaction monitoring

SSEA – stage-specific embryonic antigen

TBS-T – tris-buffered saline with tween

TGF-β – transforming growth factor β

VEGF – vascular endothelial growth factor

XaXa – two active X chromosomes

XCI – X chromosome inactivation

*see Tables 1-4 for a list of abbreviations of the proteins identified in this study

Chapter 1: Introduction

1.1 Human embryonic stem cells

The successful derivation of human embryonic stem cells (hESCs) was a tremendous advancement in medical science, as these cells have exciting potential in a remarkable variety of research and clinical applications [1]. hESCs offer promise in regenerative medicine for the treatment of many diseases including cancer, Alzheimer's and Parkinson's disease [2-5]. They have invaluable potential for use in tissue replacement therapies and provide unique insight into early human development [6-8]. Controlled differentiation of hESCs that possess the genotypic abnormalities of a particular genetic disease could create a powerful system to study that disease [9]. In addition, hESCs can be used in drug efficacy and toxicity testing to facilitate the selection of candidate molecules and to reduce the risk of side-effects in later stages of drug development [10]. hESCs are promising for medical use because they have two special properties. The first is that they are pluripotent, which means they have the ability to differentiate into an impressive diversity of cells from the three primary germ layers: endoderm, mesoderm, and ectoderm [11]. The second is that they have the ability to self-renew continuously in culture while remaining undifferentiated [12].

Thomson *et al.* derived the first hESC lines in 1998 from the inner cell mass of donated blastocysts that were produced by *in vitro* fertilization clinics [13]. A blastocyst is a pre-implantation embryo that consists of an outer layer of cells called the trophoblast, which could become a placenta if the blastocyst implants, and the inner cell mass (ICM), which has the potential to develop into an embryo (Figure 1). In order to derive a hESC line, the inner cell mass (ICM) of the blastocyst was removed, placed on inactivated mouse embryonic fibroblasts (MEFs), and passaged serially. The pluripotency of these cell lines was demonstrated *in vitro* by their ability to form embryoid bodies (EB). It was also demonstrated *in vivo* after injection of the cells into

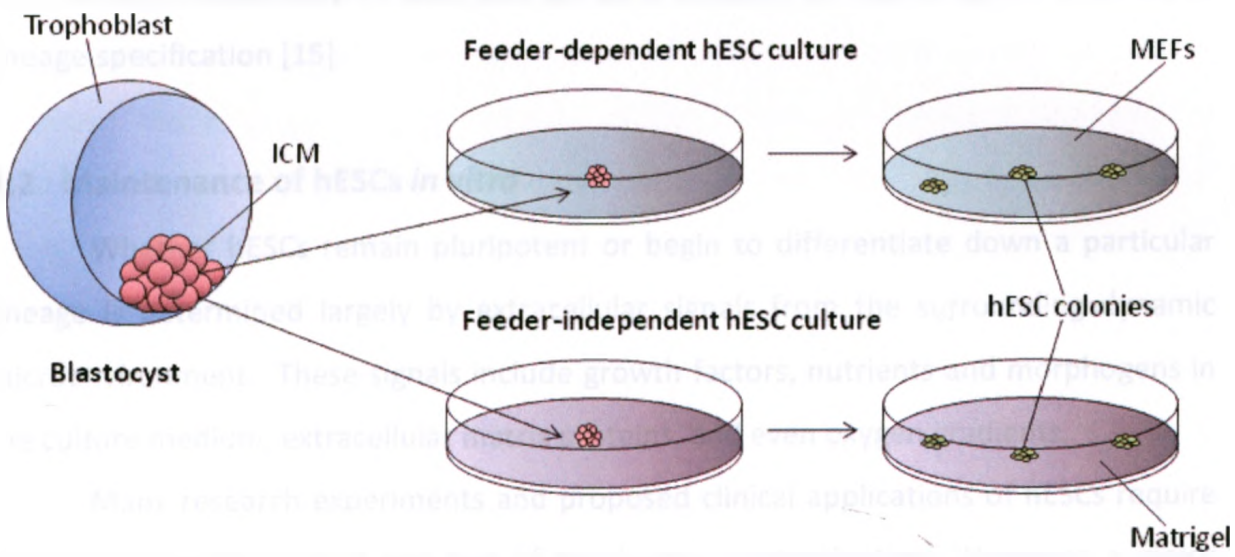

Figure 1. Derivation of hESCs. The inner cell mass of a blastocyst is removed and cultured on a layer of feeder cells, such as MEFs, or on a layer of extracellular matrix, such as Matrigel®. After serial passaging, ICM cells become hESCs.

severe combined immunodeficient (SCID) beige mice produced teratomas, which are tumors with tissue components resembling normal derivatives of all three germ layers [13]. ICM cells differ from hESCs in that they are transient, while hESCs are stable *in vitro* artifacts of the derivation process. However, hESCs are believed to posses the same developmental potential as ICM cells.

Further studies of hESCs revealed that these cells express high levels of the pluripotency associated transcription factor, Oct4 and the telomere extending polymerase, telomerase [14]. Oct4, Nanog, and Sox2 function as core transcription factors in maintaining pluripotency of ESCs and act as a complex to repress genes involved in lineage specification [15].

1.2 Maintenance of hESCs *in vitro*

Whether hESCs remain pluripotent or begin to differentiate down a particular lineage is determined largely by extracellular signals from the surrounding dynamic microenvironment. These signals include growth factors, nutrients and morphogens in the culture medium, extracellular matrix proteins, and even oxygen gradients.

Many research experiments and proposed clinical applications of hESCs require the cells to be pluripotent and free of non-human contamination. However, a major limitation to the use of hESCs in medical research is that they can undergo spontaneous differentiation in culture if proper conditions for pluripotency are not maintained. Either passage must always be performed early, before differentiated cells are observable, or pluripotent cells must be separated from differentiated cells during passage.

Currently, the *in vitro* microenvironment that sustains hESC pluripotency is not well understood. One reason for this is that many breakthrough discoveries in culture conditions for mouse embryonic stem cells (mESCs) are not applicable to hESCs [16]. For example, LIF is sufficient to maintain mESC pluripotency on gelatin as an attachment layer, but LIF does not maintain hESC pluripotency in the absence of feeders [17]. More surprisingly, BMP-4 increases the proliferative capacity of mESCs, but promotes differentiation of hESCs [18].

Since the optimal mixture of factors that maintain hESC pluripotency is unknown, hESCs are often derived on a feeder layer of mitotically inactivated mouse or human fibroblast cells. This layer provides a growth substrate and secretes various growth factors, cytokines, and adhesion related proteins that promote pluripotency [19, 20]. A significant leap forward in hESC culture methods was the discovery by Xu *et al.* that hESCs can be maintained on a layer of basement membrane matrix, called Matrigel®, in media that has been conditioned by γ-irradiated MEFs (MEF-CM) [21]. Matrigel®, which is extracted from Englebreth-Holm-Swarm tumors in mice, is a complex mixture of extracellular matrix (ECM) proteins that is composed primarily of laminin, collagen-IV, and enactin [22-24]. This type of culture is called feeder-free, and it increases the efficiency and consistency of the culture environment compared to feeder-dependant culture. However, both MEFs and Matrigel® provide a source of experimental variability and a risk of xeno-transmission from non-human sources [25, 26]. Moreover, different stem cell lines are cultured on different strains of MEFs, adding an additional layer of complexity. Therefore, it is necessary to determine which of the fibroblast-secreted proteins promote pluripotency so that these alone can be used to maintain hESC cultures.

If the replacement of necessary culture components with defined human factors is incomplete, hESCs may be forced to alter their gene expression in order to adapt. This was demonstrated when Ludwig *et al.*, derived the first hESC lines in defined feeder-free conditions with all proteins derived from human material [27]. High concentrations of bFGF were used instead of MEF conditioning of the media to support hESC self-renewal. Disappointingly, the cultures became unstable in these defined conditions and could not maintain a normal karyotype for more than six months [27].

Future studies that aim to increase our understanding of the regulatory mechanisms involved in hESC pluripotency and differentiation may allow for the development of effective, xeno-free, defined culture conditions. Furthermore, this knowledge will increase our ability to produce homogeneous populations of cells that could be used safely in clinical applications. For this reason, hESC research has focused

as much on revealing mechanisms to maintain hESCs in the pluripotent state as on methods to direct differentiation along specific cell lineages.

1.3 Hypoxia and human embryonic stem cells

Oxygen is not only an essential substrate for metabolism in aerobic organisms, it is also a signaling molecule that influences cellular activity. It is therefore an important component of the cellular microenvironment [28]. In the early days of hESC culture, little attention was paid to the importance of oxygen tensions in the microenvironment, and the cells were thus maintained in atmospheric oxygen [29]. However, atmospheric oxygen tensions are significantly higher than oxygen tensions in the reproductive tract, which is the natural environment of hESCs [30]. During implantation, the embryo has not yet accessed maternal circulation and as a result, it resides in a hypoxic environment of about 2% oxygen at the uterine surface [31]. Not only does the early embryo develop in a hypoxic environment, but studies have shown that oxygen gradients actually have a large influence on embryogenesis [32]. In most mammalian species that have been studied, low oxygen has been shown to improve *in vitro* embryo development and increase cell number of the inner cell mass [33, 34]. This provided the first clue that oxygen concentration may play an important role in hESC fate.

The second clue was from studies of adult human stem cells, which revealed that hypoxia has an important regulatory role in these cells. After air enters the lungs, the partial pressure of oxygen progressively decreases as it travels to organs and tissues [35]. Adult stem cells reside in anatomical compartments that are relatively hypoxic compared to other tissues of the body. For example, hematopoietic stem cells (HSCs), which reside in bone marrow and replenish blood and immune cells, are physically separated from blood vessels by several stromal cells and progenitor cells. Studies have consistently shown that bone marrow aspirates are hypoxic, with some levels as low as 1-2% [36]. It has been demonstrated that HSCs that reside in the hypoxic regions of the bone marrow express higher levels of Notch-1, telomerase, and p21 than cells that reside in regions that are closer to blood vessels [37].

Mesenchymal stem cells (MSCs) are multipotent cells that are capable of differentiating into bone, cartilage, fat, tendon, and other progenitor cells. These cells are located in close proximity to blood vessels, but their niche is still relatively hypoxic because it is within tissues that have low oxygen tensions [38]. Hypoxic culture of MSCs *in vitro* has been shown to increase their proliferative lifespan, to diminish their differentiation capacity [39], and to increase Oct4 expression and telomerase activity [40, 41].

Neural stem cells (NSCs), which are multipotent, self-renewing cells that differentiate into cells of the nervous system, reside in the subventricular zone and the hippocampus. Oxygen tensions in the brain range from 3-4%, and NSCs are believed to reside in especially hypoxic regions because of the distance between their niche and blood vessels [29]. *In vitro* studies have shown that hypoxia increases proliferation and promotes multipotency in NSCs, while atmospheric oxygen tensions lead to mitotic arrest and promote glial differentiation [42].

Since oxygen concentration plays such an important role in the biological niche of adult stem cells, the importance of controlling oxygen concentrations in *in vitro* cell culturing is becoming increasingly appreciated. It is hypothesized that stem cells reside in hypoxic niches because it is important for them to avoid DNA damage since their biological role is to replenish cells [43]. Aerobic metabolism causes some degree of DNA damage through the generation of reactive oxygen species and stem cells may escape this damage by residing in hypoxic niches [37].

1.3.1 Hypoxia Inducible Factors

Hypoxia-inducible factors (HIFs) play a fundamental role in the cellular response to oxygen concentration [44]. Active HIF complexes consist of an oxygen-labile α subunit, which exists in three isoforms, and a stable β subunit [45]. HIF1α is expressed in almost all mammalian cell types, whereas HIF2α and HIF3α are only expressed in specific tissues [45]. In hypoxia, HIFα subunits are stabilized and form heterodimers with the constitutively expressed protein, HIF1β (ARNT). HIF heterodimers regulate

transcriptional responses by binding to hypoxia-response elements (HREs) on their target genes (Figure 2; [46]). In the presence of increased oxygen tensions, HIFα subunits are hydroxylated by prolyl-hydroxylase domain enzymes (PHD), which require oxygen for their activation [47]. Hydroxylated HIFα is subsequently marked for proteosomal degradation by the E3 ubiquitin ligase, von Hippel-Lindau factor (VHL).

Numerous studies have revealed that HIF1α and HIF2α have a role in the maintenance of hESC pluripotency. For example, HIF2α has been shown to regulate Oct-4 expression, which suggests one mechanism by which hypoxia could affect hESC pluripotency [48]. In another study, HIF1α was shown to interact with the Notch intracellular domain to induce expression of Notch target genes, which are important for the maintenance of undifferentiated stem cells [49].

While HIFs are known to play a significant role in the cellular response to hypoxia, it is believed that there are multiple oxygen sensing pathways involved in the response. For example, PHDs hydroxylate proteins other than HIFα in the presence of oxygen, and these other substrates may play an important role in the cell's response to oxygen [50]. In addition, PHDs belong to a family of 2-oxogluterate-dependant dioxygenases, all of which require oxygen for their enzymatic activity [51].

1.3.2 Hypoxia promotes pluripotency of stem cells

A striking study by Ezashi *et al.* in 2005 showed that hESCs not only grow as well in hypoxic conditions as they do in normoxic conditions, but that hypoxic culture actually reduces the amount of spontaneous differentiation that occurs in hESC colonies [52]. In this study, hESCs were cultured on MEFs or Matrigel® in hypoxic (1, 3, 5% oxygen) and normoxic (21% oxygen) conditions for twelve days. After nine days, areas of enlarged, flattened cells that did not express Oct-4 or SSEA-4 appeared in normoxic cultures. In hypoxic conditions, patches of differentiating cells were smaller in size and less numerous, and expression of Oct-4 and SSEA-4 was maintained throughout the colony. Production of human chorionic gonadotropin (hCG), which reflects spontaneous

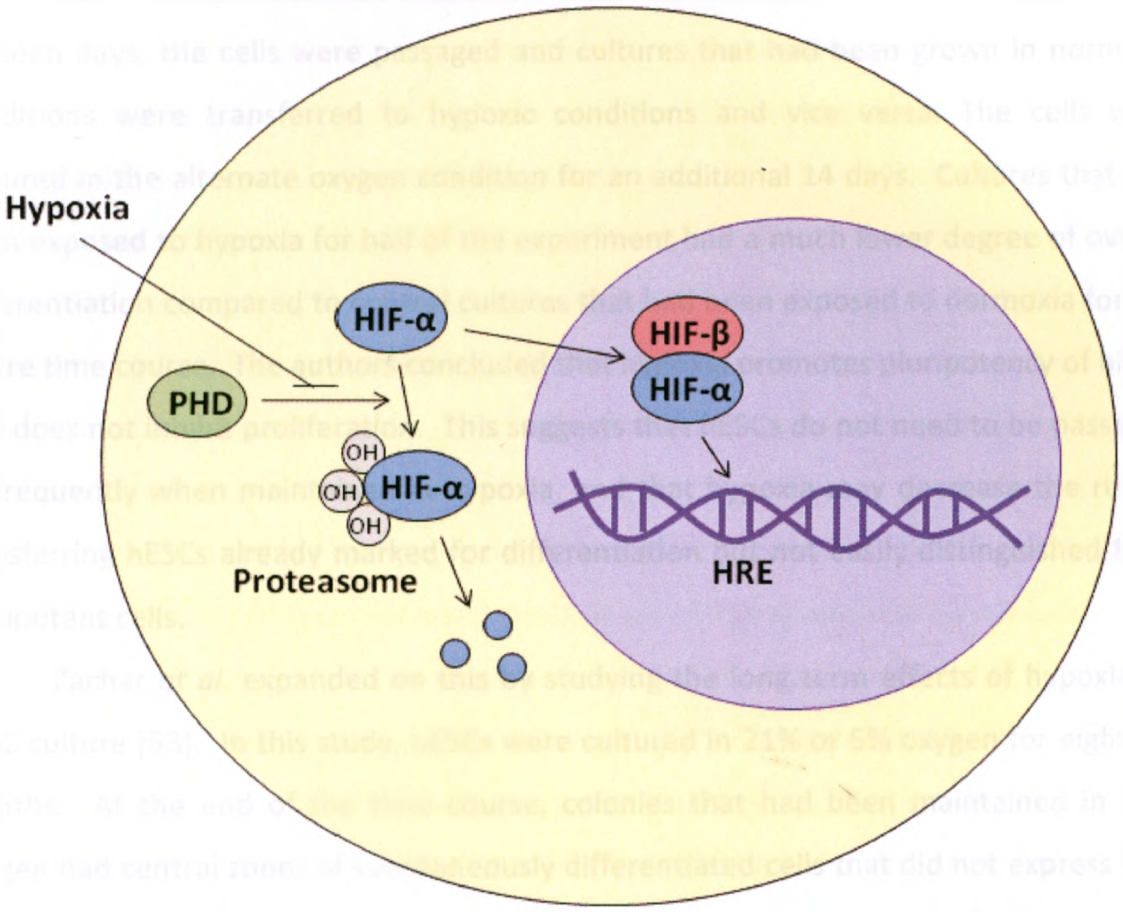

Figure 2. HIFs translate changes in oxygen concentration to changes in protein expression. Hypoxia prevents the hydroxylation of HIFα by PHD, which would result in proteosomal degradation of HIFα. Stabilized HIFα subunits travel to the nucleus and form heterodimers with the stable subunit, HIF1β. HIF heterodimers regulate transcriptional responses by binding to hypoxia-response elements (HREs) on their target genes.

differentiation of hESCs, began to increase after five days in normoxic culture; however, only low concentrations of hCG were detected in hypoxic culture beginning at day seven. Hypoxia did not appear to limit the growth of hESCs, as the number of colonies and average colony surface area did not differ between oxygen conditions, although it was noted that less DNA was recovered from the cells grown at 1% oxygen. After thirteen days, the cells were passaged and cultures that had been grown in normoxic conditions were transferred to hypoxic conditions and vice versa. The cells were cultured in the alternate oxygen condition for an additional 14 days. Cultures that had been exposed to hypoxia for half of the experiment had a much lower degree of overall differentiation compared to control cultures that had been exposed to normoxia for the entire time course. The authors concluded that hypoxia promotes pluripotency of hESCs and does not inhibit proliferation. This suggests that hESCs do not need to be passaged as frequently when maintained in hypoxia, and that hypoxia may decrease the risk of transferring hESCs already marked for differentiation but not easily distinguished from pluripotent cells.

Zachar *et al.* expanded on this by studying the long term effects of hypoxia on hESC culture [53]. In this study, hESCs were cultured in 21% or 5% oxygen for eighteen months. At the end of the time course, colonies that had been maintained in 21% oxygen had central zones of spontaneously differentiated cells that did not express Oct-4. Colonies that had been maintained in 5% oxygen consisted largely of homogeneous cells that expressed Oct-4. Only 56% of the colony area was undifferentiated in cultures maintained in 21% oxygen, while 98% of the colony area was undifferentiated in cultures maintained in 5% oxygen. Contrary to Ezashi *et al.*'s findings, measurements of colony size and incorporation of [H^3]-labeled thymidine revealed that the colonies maintained at atmospheric oxygen grew significantly faster than the colonies maintained in hypoxic conditions. After four weeks, colonies cultured in 21% oxygen had a 2.6-fold greater area than those cultured in 5% oxygen. The authors concluded that hypoxia enhances the long-term self-renewal and pluripotency of hESCs but decreases the rate of proliferation.

A study by Prasad *et al.* compared short- and long-term effects of hypoxia on hESCs [54]. To study the effect of short-term hypoxic culture, hESCs were cultured in 1%, 5%, 10%, 15% or 20% oxygen for four weeks. After two weeks, pericentral thick zones, which indicate spontaneous differentiation, became evident around colonies cultured in 10%, 15% or 20% oxygen. The cells cultured in 1% and 5% oxygen were homogeneous and did not have pericentral thickening; however, most of the colonies in 1% oxygen did not survive beyond 2 weeks. Immunofluorescence assays revealed that only 60% of the cells cultured in 10% and 15% were Oct-4 positive, undifferentiated cells after 4 weeks, while cells cultured in 1% and 5% were 100% undifferentiated at 4 weeks. In order to compare short- and long-term effects of hypoxia, some hESC cultures were maintained in 5% oxygen for 18 months prior to the 4-week experiment. Colonies that had been maintained in hypoxia for the long-term displayed similar structural development to the colonies maintained in 21% oxygen prior to the experiment. However, real time RT-PCR analysis revealed that the colonies that had been maintained in 5% oxygen for 18 months expressed lower levels of Nanog and Notch1 mNA than cells maintained in 5% oxygen for only 4 weeks. After the four week experiment, all cultures were transferred back to normoxic conditions, and after only one week, differentiation zones appeared in all cultures, except for the cultures originally maintained in 1% oxygen. By the end of four weeks, all cultures contained 60% undifferentiated cells. The authors additionally noted that the rate of proliferation was lower in 5% oxygen and especially lower 1% oxygen compared to cells cultured in higher oxygen tensions, as determined by incorporation of [H^3]-labeled thymidine.

Prompted by the finding that hypoxia promotes pluripotency in hESCs, Westfall *et al.* investigated the molecular basis of the phenomenon by studying differences in RNA transcript levels between hESCs maintained in low and high oxygen tensions [55]. RNA was collected after hESCs had been maintained in 4% or 20% oxygen for one week, at which point the colonies were indistinguishable in morphology and size, and neither culture had visible signs of differentiation. When three samples from each condition were compared, the samples from hESCs cultured in 20% oxygen exhibited greater

variance in their gene expression profile that those cultured in 4% oxygen. A total of 149 transcripts demonstrated consistent differences in expression level between the two oxygen conditions; however, the changes observed were quite small. Of these, 42 transcripts had increased expression in 20% oxygen and 107 transcripts had decreased expression in 20% oxygen compared to 4% oxygen. Several genes considered to be under the transcriptional control of the Oct4/Nanog/Sox2 complex, including LEFTY2 and endothelin receptor type B (EndRB), were expressed at much lower levels in cells cultured in 20% oxygen than cells cultured in 4% oxygen. hESCs cultured in 20% oxygen also had decreased expression of genes that are known to be regulated by Oct4, such as SALL1, Trim2, Zic2, and FGFR2. However, several genes that have been found to be associated with pluripotency in hESCs, including Oct4, Nanog, Lin28, Sox2, ZFP42/Rex1, Tert, and PodXL did not show a significant difference in transcript levels between the two oxygen conditions. In addition, there was no difference in the expression of the TDGF1 (CRIPTO) gene, which has been shown to be down-regulated during the initial steps of hESC differentiation. The authors suggest that although transcriptional profiles of the core pluripotency genes may not be greatly affected by oxygen conditions, the expression of their downstream targets might be. As one would expect, several genes associated with oxidative stress responses, such as NRF2, NQO1, AKR1C3, VCAN and CTNS, showed increased expression in 20% oxygen conditions. The biochemical pathway that had the greatest number of downregulated genes in 20% oxygen was glycolysis, which agrees with the fact that most genes encoding enzymes of the glycolytic pathway are known to be regulated by HIF1α. HIF1α mRNA was highly expressed, but the transcript concentration did not differ between the oxygen conditions. However, several genes thought to be under the control of HIF1α and that contribute to apoptosis, cellular redox regulation, and proliferation were down-regulated under 20% oxygen; for example, BNIP3, TXNIP (thioredoxin interacting protein), DDIT4 (DNA damage inducible transcript 4), IGFBP2, LGALS1 and VEGF. HIF2α was expressed at a much lower level than HIF1α, but its transcript concentration was increased at 20% oxygen, and transcripts for HIFβ were unaffected by oxygen concentration. It was not

surprising that there was no change in HIF1α mRNA expression because HIF1α is primarily regulated at the level of protein turnover. Studying the proteome by mass spectrometry may provide more insight into differences in gene expression because changes in many other proteins may exist through alterations in the rate of translation or protein degradation.

The observation that hypoxia prevents differentiation of hESCs led Yoshida *et al.* to hypothesize that hypoxia could enhance the generation of induced pluripotent stem cells (iPSCs) [56]. iPSCs are pluripotent stem cells that are artificially derived from differentiated cells by the forced expression of four transcription factors (Oct3/4, Sox2, Klf4, and c-Myc) [57]. They are nearly indistinguishable from ESCs, but the full extent of their similarity to natural pluripotent stem cells is currently being assessed. Yoshida *et al.* used retroviral vectors to introduce four or three transcription factors (Oct3/4, Sox2, Klf4, +/- c-Myc) into MEFs, and then cultured the cells in 5% or 21% oxygen from day 5 to day 14 after transduction. The percentage of pluripotent cells was greater in cultures reprogrammed in hypoxia than cells reprogrammed in atmospheric oxygen. The four transcription factors were also introduced into human dermal fibroblasts (HDFs) and the cells were maintained in 5% oxygen for 7, 14, 21, or 33 days. The efficiency of iPSC generation was increased by 4.2 fold after 14 and 21 days in hypoxia, and by 3.6 fold after 24 days in hypoxia. Interestingly, iPSCs could be generated in the presence of hypoxia when only 2 transcription factors (Oct3/4 and Klf4) were used. The authors concluded that conducting reprogramming in hypoxic conditions results in improved efficiency for both mouse and human cells and they suggested that hypoxia may contribute to the reprogramming process itself.

Recently, Lengner *et al.* derived a new hESC line in 5% oxygen [58]. Interestingly, these cells contained two active X chromosomes (XaXa). The presence of two active X chromosomes is observed in pluripotenct mESCs, whereas all previous hESC lines have undergone X chromosome inactivation (XCI) and are considered developmentally more advanced than mESCs. Using the XaXa hESC line that had been derived in hypoxia, the authors demonstrated that random XCI is induced during differentiation and that

continuous exposure to 20% oxygen induces irreversible XCI. These findings indicate that human ICM cells have two active X chromosomes, and that culturing hESCs in hypoxia preserves this state.

Collectively, these studies have demonstrated that hypoxia plays a significant role in hESC self-renewal and pluripotency and that hypoxia must therefore be carefully controlled when culturing hESCs *in vitro*. This phenomenon is not well understood, and future studies are needed to determine exactly how hypoxia exerts this effect on protein expression and activity.

1.3.3 Hypoxia can improve differentiation of stem cells

While many studies have shown that culturing hESCs in hypoxia promotes pluripotency and self renewal, other studies have shown that hypoxia is able to improve the efficiency of hESC differentiation, especially to chondrocytes and cardiomyocytes [28]. In a study by Koay *et al.*, hESCs that were differentiated to chondrocytes in 2% oxygen had significantly greater biomechanical functionality and production of cartilage matrix proteins, especially collagen, than hESCs differentiated in 20% oxygen [59]. Niegruegge *et al.* differentiated hESCs to cardiomyocytes in 4% oxygen and found that the total cell number increased by 30-47% and some cardiac markers increased compared to cardiomyocytes that had been differentiated in 20% oxygen [60].

It is not surprising that hypoxia has been shown to promote pluripotency in hESCs and also to improve the efficiency of differentiation. At the beginning of its development, the pre-implantation embryo consists largely of pluripotent cells. These cells soon begin to differentiate down particular lineages as directed by external signals. Until the embryo accesses maternal circulation, it resides in a hypoxic environment. Therefore, pluripotency and differentiation both naturally occur in hypoxia.

1.4 Fundamentals of mass spectrometry

Proteomics is a rapidly evolving field that provides unparalleled insight into a cell's biochemistry. Mass spectrometry (MS) has become a central technology for

proteomic studies because it is highly sensitive and can generate spectral information about a peptide's amino acid sequence in milliseconds [61].

In order to measure the mass-to-charge ratio (m/z) of peptides, a mass spectrometer must convert these large biomolecules to ions in the gas phase, which was a long-standing barrier to the efficacy of MS. The development of two soft ionization techniques, Matrix Assisted Laser Desorption Ionization (MALDI) and Electrospray Ionization (ESI), revolutionized this technology [61]. In the MALDI technique, a peptide is mixed with a low-molecular weight aromatic acid that forms a light-absorbing matrix. A focused laser beam irradiates the sample, causing the matrix molecules to sublime and transfer the embedded peptides into the gas phase. Generally, the peptide ions are singly charged. In the ESI technique, a peptide solution is dispersed into airborne droplets as it exits a charged needle or the tapered end of an LC column that is held at a high electrical potential with respect to the MS. This generates a high positive charge on the droplets, which undergo desorption of analyte ions and/or droplet fission as the solvent evaporates. Eventually, each droplet contains an average of one multiply-charged analyte ion [61]. ESI ionization was used in this thesis because it allows liquid separation techniques to be coupled directly to MS analysis, and because multiply-charged ions are more easily characterized by MS.

Numerous types of mass analyzers are available to measure the mass-to-charge ratio of peptide ions. These include the quadrupole (Q), time-of-flight (ToF), ion trap (IT), and the newer Orbitrap and Fourier transform ion-cyclotron-resonance (FT-ICR) analyzers. Most mass spectrometers are hybrids that contain different types of mass analyzers in a single instrument; for example, QqQ, Q-ToF, QqIT, ITqOrbitrap, and qFT-ICR. Each of these platforms has advantages and limitations, but they share the ability to generate spectra containing sequence data for thousands of species in a short period of time. Currently, FT ICR and Orbitrap instruments have the highest resolution and mass accuracy, but they are expensive and difficult to operate. Ion traps are robust and usually less expensive than other models, but their mass accuracy and effective mass range are not as great. A Q-ToF is the only type of MS used in this thesis. In this

instrument, the quadrupole is used as a mass filter because it has high efficiency in transmitting a small m/z window. The ToF is used for measuring the m/z of the selected ion because it has a higher mass accuracy.

1.4.1 Peptide sequencing by tandem mass spectrometry

The ability to interface electrospray ionization with these advanced tandem mass analyzers meant that thousands of peptides in a single sample could be analyzed in a high-throughput manner. In a tandem MS experiment, the mass spectrometer first determines the mass of peptide ions as they elute from the LC column. One at a time, abundant ions are selected and allowed to pass to the collision cell, where they are fragmented by Collision Induced Dissociation (CID) with an inert gas or Electron Transfer Dissociation (ETD). CID causes cleavage at the peptide bond, and the resulting ions are called b-ions if the charge is at the amino-terminal and y-ions if the charge is at the carboxy-terminal [61]. ETD causes cleavage between the amino group and the alpha carbon, and the resulting ions are called c-ions if the charge is at the amino-terminal and z-ions if the charge is at the carboxy-terminal. The fragmentation techniques are mild so that the peptide only fragments in one place along the backbone. The peptide fragments move to another mass analyzer, which generates a spectrum of all m/z values in the pool of fragments. The difference in mass between the fragment ions corresponds to the mass of an amino acid, and the sequence can be determined from this spectrum (Figure 3, reviewed in [62]).

1.4.2 Sample preparation for MS analysis

Even with advancements in instrument scan speed, mass spectrometers can only detect a limited number of ions in a given period of time. Proteomes are difficult to study because they are extremely complex and the dynamic range of protein concentrations can span ten orders of magnitude. To alleviate this complexity, the proteome can be fractionated by one- or two-dimensional SDS PAGE or any type of liquid chromatography to divide the sample into simpler portions (Figure 4, [63]).

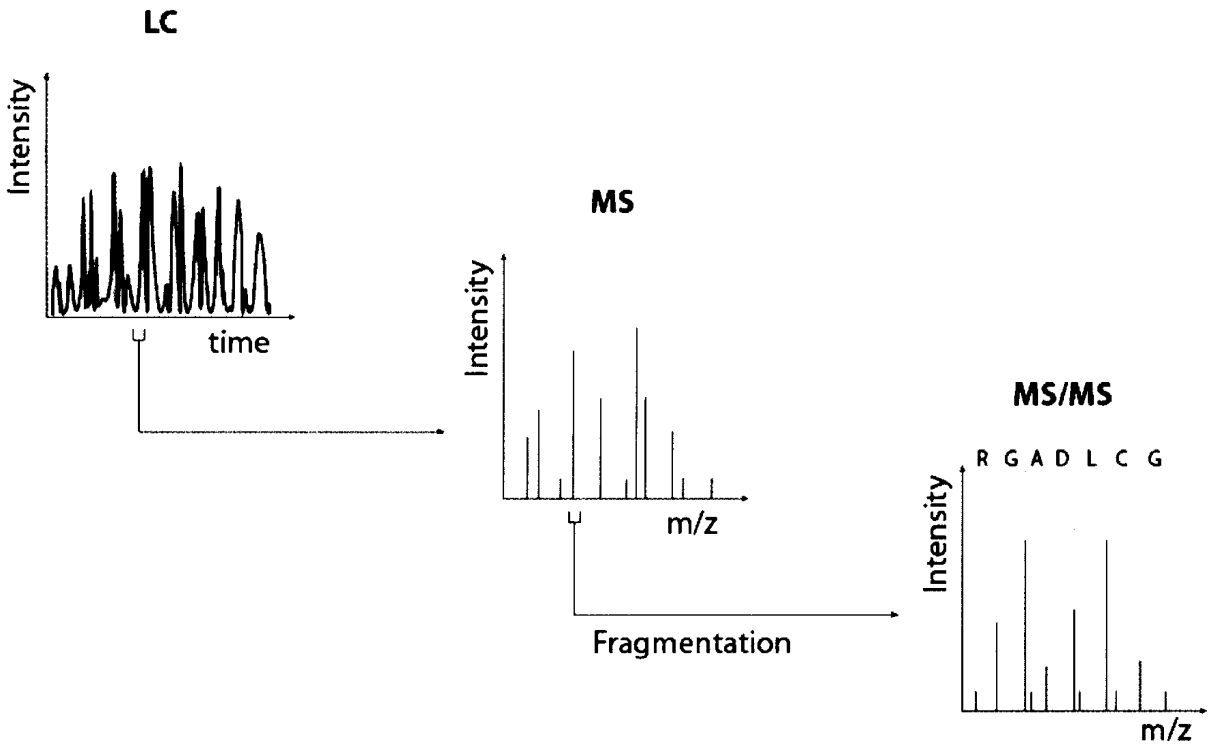

Figure 3. Liquid-chromatography tandem mass spectrometry. In an LC-MS/MS experiment, peptides ions are separated by LC, which is directly coupled to MS. At a given point in time, the *m/z* of peptides eluting from the LC column is determined by MS^1. An abundant peptide ion is selected and fragmented such that it breaks in one place along the backbone. The *m/z* of the fragments is measured in MS/MS. The sequence of the peptide can be determined because the difference in mass between the fragments is equal to the mass of the corresponding amino acid.

MS experiments are typically done in a 'bottom-up' approach, in which proteins are enzymatically digested to peptides prior to fractionation and analysis (Figure 4). An important reason for this is that it is difficult to generate sequence information from polypeptides that contain more than 20 amino acids. In addition, many proteins are difficult to solubilize and/or have multiple modification sites, which complicates the identification of the protein. Trypsin, which cleaves peptides on the C-terminal side of arginine and lysine, is a popular choice for enzymatic digestion of proteins. This is because it is stable and highly specific, and it creates appropriately sized peptides that have a charged amino acid at the C-terminus. These properties allow for generation of fragmentation spectra that are easy to interpret. Other enzymes may be used to generate peptides that are complementary to the tryptic peptides or when proteins must be solubilized in conditions that affect trypsin's activity.

It is very common to perform a second fractionation to separate the resulting peptides for MS analysis. The most popular method to identify more ions in a given sample is to interface the MS with a RP, SCX, or SAX LC device (Figure 4). Each of these column types has a different ability to separate a mixture, so the column choice depends on the sample type and proteomics application. Complementary types of fractionation can be used to increase proteome coverage; however, many peptides will not be characterized, making experiments difficult to reproduce.

1.4.3 Quantitative proteomics

Mass spectrometers are not strictly quantitative; therefore, in order to obtain accurate quantitative information in proteomic experiments, stable isotopic labeling is typically used. In techniques involving isotopic labels, such as stable isotope labeling of amino acids in culture (SILAC), one sample is labeled with a stable isotope through metabolic incorporation, and then mixed with an unlabeled sample at a 1:1 ratio of protein concentration [64]. The resolution of current mass spectrometers is high enough to resolve heavy (labeled) from light (unlabeled) peptides, and the intensities of the spectral peaks they produce can be directly compared to determine their relative

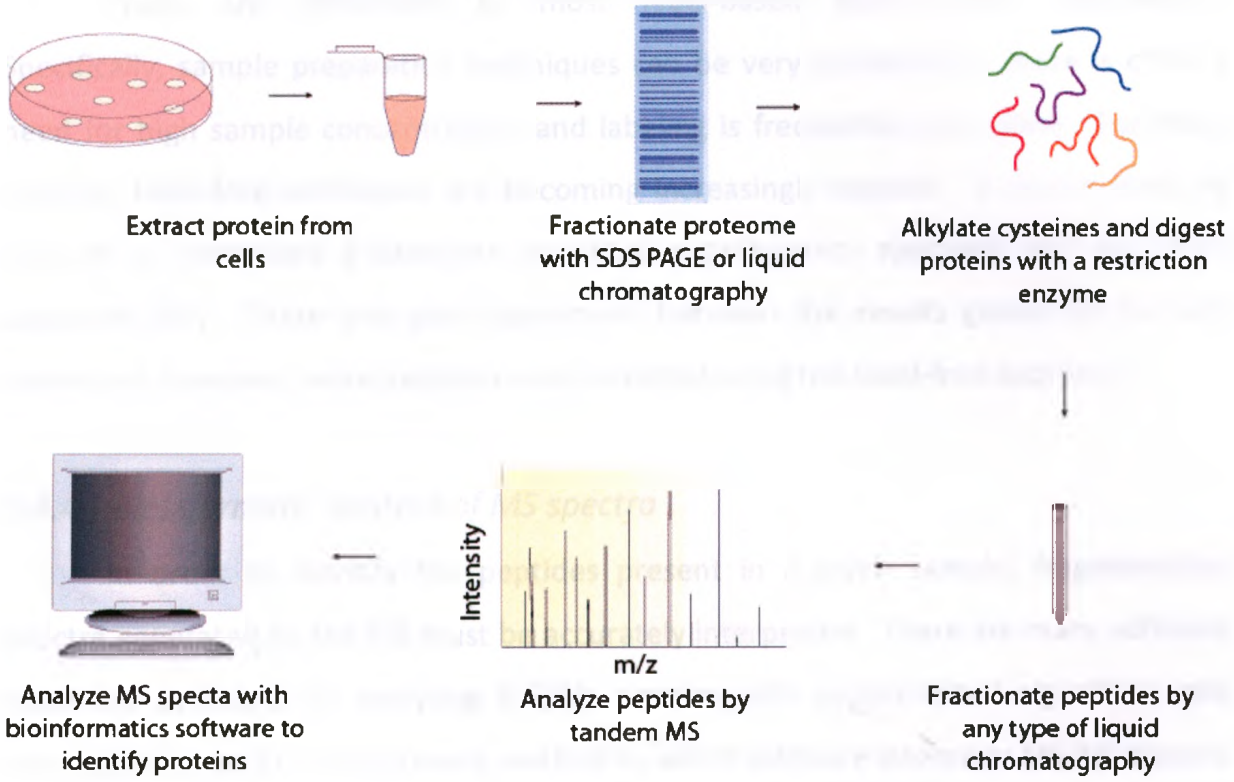

Figure 4. Overview of a general proteomics workflow. Proteins are extracted from cells and fractionated by 1D or 2D electrophoresis or some type of liquid chromatography (RP, SCX, SEC, etc.). Cysteines are often reduced and alkylated, and proteins are digested to peptides with a site specific enzyme. The resultant peptides are then fractionated by liquid chromatography, which can be coupled directly to MS. The peptides are analyzed by MS/MS, and bioinformatics software is used to identify the peptide sequences.

abundance (Figure 5; [65]). Alternatively, samples can be labeled following digestion by way of isobaric labeling techniques, such as iTRAQ. After the samples are mixed at a 1:1 ratio, the peptide abundance levels can be compared quantitatively based on the amount of tag present in the MS/MS spectrum. These methods allow minute changes between cellular states to be monitored over time.

There are limitations to most label-based quantification approaches. Specifically, sample preparation techniques can be very complicated, there is often a need for high sample concentration, and labeling is frequently incomplete. For these reasons, label-free techniques are becoming increasingly popular. A recent study by Patel *et al.* compared a label-free quantitative proteomics approach with an iTRAQ approach [66]. There was good agreement between the results generated by each technique; however, more peptides were detected using the label-free approach.

1.4.4 Bioinformatic analysis of MS spectra

In order to identify the peptides present in a given sample, fragmentation spectra generated by the MS must be accurately interpreted. There are many software platforms available for analyzing MS/MS spectra with sophisticated algorithms and scoring schemes [67]. The primary method by which software interprets MS/MS spectra is through comparison of observed spectra to *in silico* spectral databases [68]. These *in silico* databases are generated using theoretical digests of protein sequences that have been observed or predicted from genome sequencing projects [69]. By statistically matching MS/MS spectra to *in silico* databases, the actual sequence of the peptide does not need to be measured, and the peptides can be more rapidly identified. Three search engines were used to analyze data in this thesis: Mascot, X!Tandem and OMSSA. All of these tools compare observed spectra to *in silico* databases, but they use different scoring schemes to establish the best peptide match [70-72]. Although spectral interpretation software offer rapid analysis of a large number of spectra, the majority of spectra generated in a typical MS experiment will remain unidentified [73]. Background peaks can be mistaken as peptide peaks, resulting in false positive identifications and

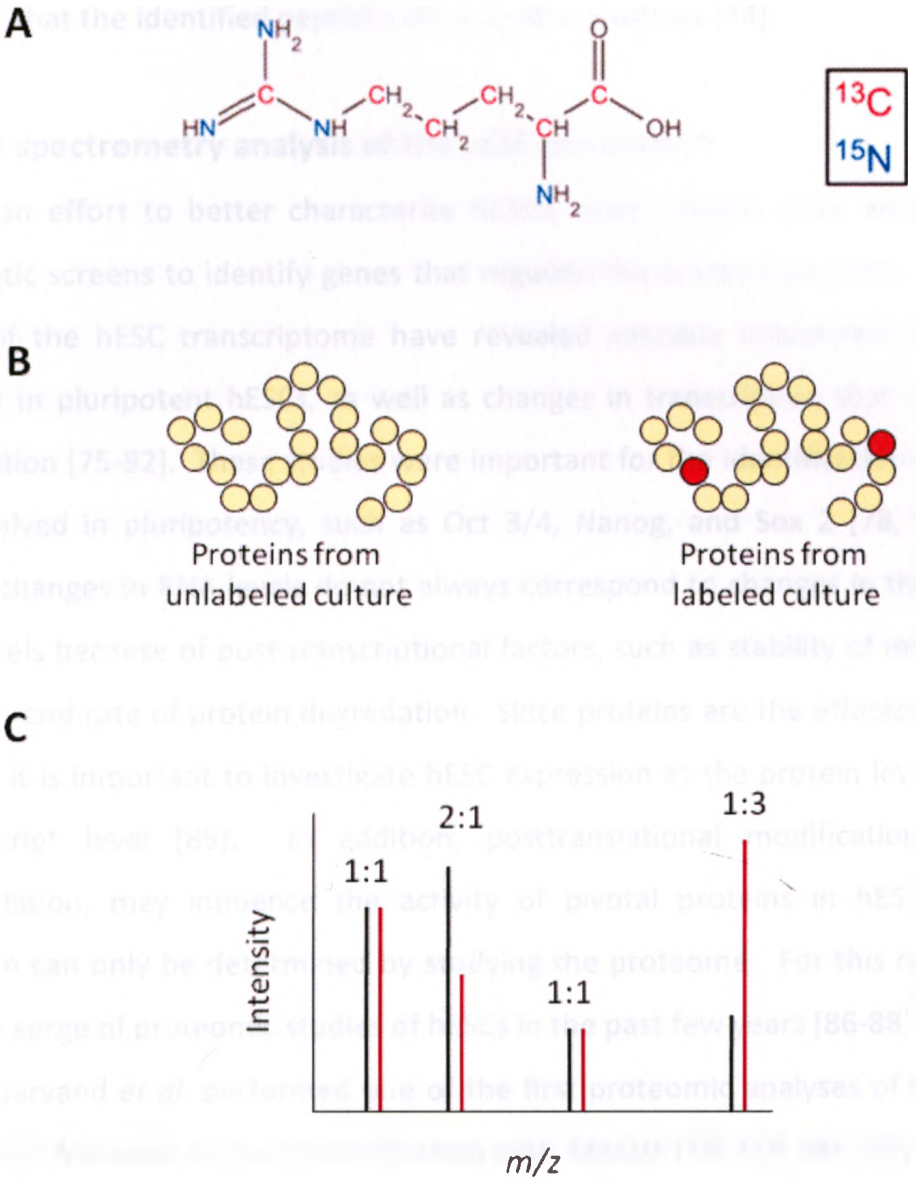

Figure 5. Stable isotope labeling of amino acids in culture. A) The amino acids, arginine and lysine are labeled with heavy isotopes, N^{15} and C^{13}, and added to culture medium that does not contain arginine and lysine. B) Labeled medium is added to a cell culture so that cells in that culture incorporate heavy isotopes into their proteins. C) Proteins from labeled and unlabeled cultures can be mixed at a 1:1 ratio and differences in abundance between particular proteins can be observed by mass spectrometry.

unpredicted posttranslational modifications (PTMs) or sequence polymorphisms can result in missed identifications. Combining results of multiple search engines can increase the percentage of peptides that are identified in a sample and increase confidence that the identified peptides are not false positives [74].

1.5 Mass spectrometry analysis of the hESC proteome†

In an effort to better characterize hESCs, many studies have employed large scale genetic screens to identify genes that regulate the pluripotent state. Large-scale analyses of the hESC transcriptome have revealed valuable information about gene expression in pluripotent hESCs, as well as changes in transcription that occur during differentiation [75-82]. These studies were important for the identification of some key genes involved in pluripotency, such as Oct 3/4, Nanog, and Sox 2 [78, 80, 83, 84]. However, changes in RNA levels do not always correspond to changes in the respective protein levels because of post-transcriptional factors, such as stability of mRNA, rate of translation, and rate of protein degradation. Since proteins are the effectors of cellular processes, it is important to investigate hESC expression at the protein level as well as the transcript level [85]. In addition, posttranslational modifications, such as phosphorylation, may influence the activity of pivotal proteins in hESCs, and this information can only be determined by studying the proteome. For this reason, there has been a surge of proteomic studies of hESCs in the past few years [86-88].

Baharvand *et al.* performed one of the first proteomic analyses of hESCs, using 2D-SDS-PAGE followed by spot identification with MALDI-TOF-TOF MS [89]. This study compared protein expression of three hESC lines: Royan H2, H3, and H5 and identified a total of 685 proteins. A significant portion of these were localized to the nucleus, which agrees with the fact that hESCs have a high nucleus to cytoplasm ratio. Of the proteins identified, many are involved in protein synthesis and regulation, which the authors suggest reflects the ability of hESCs to change phenotype rapidly. The authors also acknowledged that 2D-SDS-PAGE has limited ability to detect low abundance proteins.

† Parts of this section are excerpts from Hughes CS*, Nuhn AA*, Postovit LM, and Lajoie GA. Proteomics of human embryonic stem cells. *Proteomics*. 2011. 11(4): 675-90. (*co-first authors).

In the same year, Van Hoof *et al.*, reported a more extensive analysis of the hESC proteome, and compared the proteomes of undifferentiated mouse and human ESCs to their differentiated counterparts [90]. Using tandem MS analysis on an FT-ICR-MS, the authors identified 1871 and 1775 unique proteins from undifferentiated mESCs and hESCs respectively, 639 and 743 of which were found only in pluripotent ESCs. The proteins that were uniquely identified or enriched in mouse and human ESCs include important transcription factors such as Oct4 and UTF-1, and the ESC marker, alkaline phosphatase. The relative expression of selected proteins was determined by western blotting, and this data correlated well with the proteomics data. This validates the ability of an MS-based screen to fish out cell specific markers.

In an attempt to elucidate which proteins secreted by MEFs support pluripotency of hESCs, Lim *et al.* used MS to identify 136 unique proteins in MEF-CM [91]. The MEF-CM was concentrated, separated by 2D-SDS-PAGE, and compared to gels from media that was not conditioned. Differential spots were excised and identified by MS using a MALDI-TOF. An interesting candidate for a hESC pluripotency regulator was pigment epithelium-derived factor (PEDF), a protein with a diverse array of functions. A similar study by Chin *et al.* used 2D-SDS-PAGE and MALDI-TOF analysis of CM from MEFs (supportive of hESC growth) and ΔE-MEF (not supportive of hESC growth) [92]. Of the proteins identified as differentially abundant, they chose six growth factors including PEDF, MCP-1, PAI, IGFBP-2 and 7, and IL-6 as supplements for defined hESC media. Using this cocktail, they were able to maintain the hESCs in an undifferentiated state based on Oct4 and Tra-1-60 detection, although for only 5 passages. Gonzalez *et al.* later demonstrated that PEDF can maintain undifferentiated hESCs without the addition of other exogenous supplements [93].

Two studies by Prowse *et al.* revealed some proteins that are secreted into conditioned medium (CM) by other types of fibroblasts. The first study surveyed media conditioned by human neonatal fibroblasts [94]. A 2D-SDS PAGE gel of CM was compared to that of unconditioned media, and differential spots were analyzed by MALDI-TOF/TOF-MS. The CM was also analyzed by Q-Star tandem MS after SCX-RP-LC

fractionation. A total of 102 proteins were identified. Some of these proteins are known to function in pathways related to development, including the BMP inhibitor Gremlin, members of the insulin-like growth factor family, and ECM proteins such as SPARC and follistatin. Some of the identified proteins were also detected in the studies by Chin *et al.* and Lim *et al.*, including IGF binding proteins. The second study by Prowse *et al.* used the same fractionation and analysis techniques to identify proteins in the conditioned media of three fibroblast lines (human neonatal, human foreskin, and mouse embryonic) that are commonly used to maintain hESC pluripotency [95]. They identified a total of 175 proteins, 34 of which were common between all three cell lines. Based on previous literature and ontology classification, proteins most likely to be involved in growth, differentiation, and maintenance of hESC pluripotency were found. Many of these proteins were extracellular matrix core, binding, and remodeling proteins. Some interesting proteins that were not identified in the first study were Activin A, IGF-1, and proteins involved in TGF-β1 signaling. Activin A has been shown through supplementation in culture medium to promote the feeder-independent growth of hESCs in the absence of MEF pre-conditioning [96, 97]. TGF-β1 is known to promote hESC pluripotency, and has also been shown to promote the feeder independent growth of hESCs [27]. IGF-1 has also been shown to function with bFGF in the maintenance of hESCs [98]. These studies offered valuable insight into potential regulators of hESC pluripotency *in vitro*; however, they demonstrated the limitations of reproducibility and the inability to sample low abundance proteins.

Bendall *et al.* hypothesized that growth factors secreted by both feeder cells and hESCs themselves are involved in the microenvironment that maintains hESC pluripotency in culture [99]. A variety of fractionation and analysis methods were used in combination with an iterative exclusion technique to provide the most in-depth analysis of CM from MEFs and hESCs at the time of publication. In iterative exclusion, the first round of MS analysis identifies the most abundant proteins in the fraction. In subsequent rounds, ions that were selected in all previous rounds are ignored based on *m/z* and retention time to allow for the identification of previously uncharacterized,

lower abundance ions. This resulted in the identification of 550 and 2493 proteins in the MEF media and hESC media, respectively. Some of these proteins were also identified by Prowse *et al.*, including IGF binding protein 3, 6, and 7, follistatin, DKK3, TGF-β-binding protein, PEDF, and inhibin β A. In addition, IGF-II, TGF-β1, and over 40 new potential growth factors were identified. From this dataset, a model was proposed for *in vitro* hESC signaling with human dermal fibroblasts (hDfs), wherein bFGF in the medium signaled the production and release of IGF-II from hDfs to maintain hESCs in an undifferentiated state [98]. This model indicated that hESCs may communicate with fibroblast-like cells *in vitro* to sustain pluripotency, and highlighted the utility of proteomics analysis for this research.

Many studies have compared the protein expression of hESCs with the protein expression of differentiated derivatives of hESCs, different hESC cell lines, or other pluripotent cells. These studies have revealed hESC specific markers, proteins associated with the pluripotent state, and changes in gene expression that occur during differentiation.

To characterize the differences between hESCs and their differentiated equivalents after 3, 6, 12, and 20 days toward EB formation, Fathi *et al.* utilized a 2D-SDS-PAGE tandem-MS approach [100]. Of 979 reliably detected protein spots, 58 spots were up-regulated and 38 were down-regulated as hESCs differentiated into EBs. Functional analysis revealed that many of the down-regulated proteins are involved in cell cycle, developmental, and protein degradation processes. Some of the proteins that were more abundant in hESCs than EBs, such as NPM1, Ebp1, and Sutg1, have been shown to be down-regulated as mESCs differentiate. The researchers also acquired genomic expression data using RT-PCR to obtain mRNA levels for comparison to the proteomic data. A total of 6187 transcripts were found to be modulated upon differentiation. When the proteomic and genomic data were compared, there was minimal correlation between the two sets. While some transcripts and proteins shared the same change in expression, others displayed opposite patterns. The authors

mention limitations in the sensitivity of the proteomic assay, as well as discordance between protein and mRNA abundance levels as possible reasons for this.

1.6 Objectives of this thesis

It is known that hypoxia promotes pluripotency in hESCs, but the mechanism by which this occurs is poorly understood. A few proteins have been linked to oxygen signaling and pluripotency in hESCs, but it is believed that there are several oxygen signaling networks involved, and that many proteins are differentially expressed in hypoxia. Microarray analysis of hESCs cultured in hypoxia shed some light on global changes in protein expression in hypoxia; however, since there is little correlation between changes in RNA expression and changes in protein levels, it is important to study this problem at the proteome level for a complete picture. In this thesis, mass spectrometry is used to identify proteins that are expressed differently under low oxygen conditions. We hypothesized that hESCs alter their protein expression in response to decreased oxygen levels, and that these changes in protein expression are associated with the pluripotent state. The results of this study will improve our understanding of the mechanism by which hypoxia maintains pluripotency in hESCs *in vitro* and in ICM cells during development of embryos in the hypoxic reproductive tract. In addition, the identification of proteins associated with pluripotency of hESCs could aid the development of defined, xeno-free culture conditions for hESCs.

Chapter 2: Experimental Procedures

2.1 Maintenance of hESC cultures

H9 and CA1 hESCs were maintained on a feeder layer of MEFs because MEFs provide a growth substrate and secrete various proteins that are needed to maintain hESC pluripotency [19]. The MEFs (strain CF-1; American Type Culture Collection, Manassas, VA, http://www.atcc.org) were γ-irradiated so they could no longer proliferate, and were plated in gelatin-coated six-well polystyrene dishes at 200 000 cells per well in 2 mL of MEF medium (MM; 90% Dulbecco's modified Eagle's medium, 8% fetal bovine serum, 1% nonessential amino acids, and 1% L-Glutamine). After a minimum of 24 hours, when the MEFs had attached to the bottom of the dish, the MM was aspirated and hESCs were transferred to each well in 2.5 mL of stem cell medium (SM; 80% Dulbecco's modified Eagle's medium–F12, 20%, 1% nonessential amino acids, 1 mM L-Glutamine, and 4 ng/ml basic fibroblast growth factor (Invitrogen) and 0.1 mM mercaptoethanol). The cultures were incubated at 37°C in 5% CO_2 and the SM was changed daily. If differentiating colonies became visible, they were removed manually by scraping with a glass pick.

Cultures were passaged approximately every five days to prevent differentiation and were passaged less than 50 times to limit the risk of karyotypic abnormalities. H9 hESCs were passaged manually and CA1 hESCs were passaged enzymatically or manually. For manual passaging, small clusters of hESCs were mechanically detached from the MEF layer with a glass pick and transferred to a new six-well dish of MEFs. For enzymatic passaging, hESCs were rinsed with phosphate buffered saline (PBS) and incubated with 500 µL of 0.05% trypsin until the cells detached from the plate in small clumps. MM was added to each well to deactivate the trypsin and the suspension was centrifuged to collect the hESCs in a pellet. The supernatant was aspirated and replaced with SM, and the hESCs were transferred to a fresh six-well dish of irradiated MEFs. For both cell lines, one well of a six-well dish was split into six wells and cells were

transferred in compact colonies of at least 3 cells, as single-celled hESCs are prone to differentiation [101].

2.2 Culture of hESCs in different oxygen conditions

A feeder-free system was used for all hypoxia experiments to limit the transmission of MEF proteins into the experimental samples [21]. To create a 3D extracellular matrix for hESC attachment, each well of a six-well dish was coated in 800 µL of growth factor-reduced Matrigel® (1 mg/ml dissolved in DMEM-F12; BD Biosciences, San Diego, http://www.bdbiosciences.com) for 30 minutes. Excess Matrigel® solution was aspirated and hESCs were transferred in compact colonies from a MEF layer onto the Matrigel® coated wells. Since MEFs secrete proteins that are necessary for hESC pluripotency, special medium is needed when hESCs are maintained in the absence of a MEF feeder layer [102]. For proteomics, western blotting, and real time reverse transcription polymerase chain reaction (RT-PCR) experiments, the hESCs were cultured in mTeSR®1 medium, which is a defined, serum-free medium that contains all growth factors needed to maintain hESCs in feeder free conditions [103]. For immunofluorescence experiments, the hESCs were maintained in SM that had been preconditioned for 24 hours on irradiated MEFs seeded at a density of 2.12×10^5 MEFs per mL of medium.

Twenty-four hours after the hESCs were seeded onto Matrigel®, the medium was changed, and the cultures were placed in 1% oxygen (hypoxia) or 20% oxygen (normoxia). To establish hypoxic conditions, cells were placed in airtight chambers (BioSpherix) that were flushed with a gas mixture of 5% CO_2 and 95% N_2. Oxygen concentrations within these chambers were maintained at 1% using Pro-Ox Model 110 O_2 regulators (BioSpherix, Redfield, NY). In each oxygen condition, one plate of hESCs was incubated for 48 hours, and another was incubated for 72 hours. The medium was not changed during this time in order to accelerate differentiation and to accumulate hESC derived signals within the culture milieu. At the appropriate time points, the medium was removed and cells were washed with PBS. Phase contrast

images were taken of the hESC colonies in order to assess cell growth and morphology. The medium was then removed and culture dishes were wrapped in parafilm and frozen at -80°C until protein and RNA could be extracted.

2.3 Protein extraction and quantification

Immediately after frozen six-well dishes of hESCs were transferred from -80°C to room temperature, each well was covered with 150 µL of the nondenaturing detergent, Mammalian Protein Extraction Reagent (mPER; Thermo Scientific) mixed with 1.5 µL 100X EDTA-Free Protease Inhibitor Cocktail (Thermo Scientific) and 1.5 µL 100X Halt™ Phosphatase Inhibitor Cocktail (Thermo Scientific) for five minutes. The wells were then scraped with a disposable cell scraper (Fischer Scientific) to aid the removal of cells. The cell lysates were transferred to microcentrifuge tubes and kept on ice. Each sample was then sonicated to ensure all membranes had been lysed. The samples were centrifuged at 14 000 g for 20 minutes at 4°C to remove large cytoskeleton proteins and other cell debris. The supernatant was then aliquoted and stored at -80°C for future mass spectrometry and Western blot analysis.

A modified Bradford assay was used to quantify the protein [104]. A protein standard was prepared by diluting a solution of bovine serum albumin (BSA; Pierce) to 1 mg/mL. The protein standard and protein samples of unknown concentration were diluted with ddH_2O to a final volume of 10 µL in a 96-well flat bottom plate as shown in Figure 6. 200 µL of Coomassie Protein Assay Reagent (Thermo Scientific) was dispensed into each well. The absorbance at 595 nm was measured with a Victor^{3}V 1420 Multilabel Counter (Perkin Elmer). A standard curve was created by plotting absorbance at 595 nm versus concentration of BSA. The concentrations of the protein samples were calculated by inserting their absorbance values into the equation of the standard curve.

2.4 RNA extraction and quantification

RNA was extracted from hESCs using a Purification Column and proprietary solutions from a Perfect Pure RNA Purification Kit (5Prime). Immediately after frozen

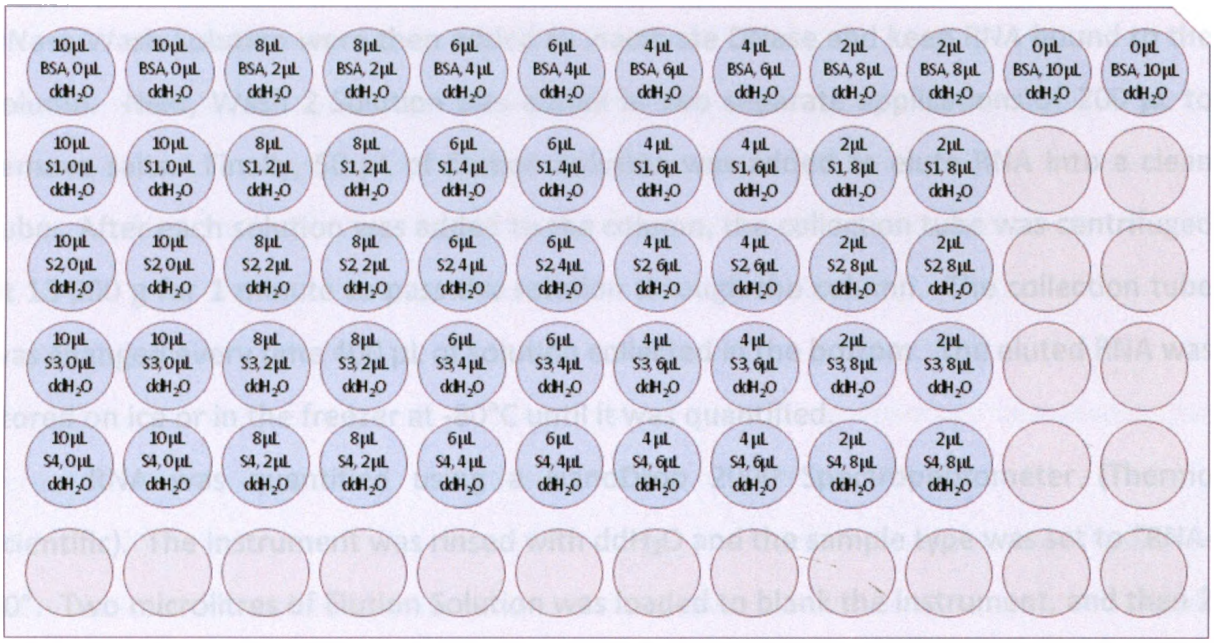

Figure 6. Modified Bradford assay setup. Various volumes of protein standard (BSA) and samples (S1, S2, S3 and S4) were brought up to 10 µL with ddH_2O. Two hundred microlitres of Coomassie Protein Assay Reagent was then added to each well.

six-well dishes of hESCs were transferred from -80°C to room temperature, each well designated to be used for RNA experiments was covered with 400 µL of Lysis Buffer. After five minutes of gentle rocking at room temperature, the solution was pipetted up and down vigorously to homogenize and lyse the cells. The solution was then transferred to a Purification Column. Four hundred microlitres of Wash 1 Solution was added to the column to wash away residual lysate, to eliminate RNase activity, and to support full DNase activity. To degrade DNA, 50 µL of DNase Solution was added to the column and incubated at room temperature for 15 minutes. Two 200 µL aliquots of DNase Wash Solution were then added to inactivate DNase and keep RNA bound to the column. Next, Wash 2 Solution was added in two separate applications of 200 µL to remove salts. Finally, 50 µL of Elution Solution was added to elute RNA into a clean tube. After each solution was added to the column, the collection tube was centrifuged at 13 000 g for 1 minute to pass the solution through the column. The collection tube was changed every time 400 µL of solution collected in the bottom. The eluted RNA was stored on ice or in the freezer at -80°C until it was quantified.

RNA was quantified using a NanoDrop 2000 Spectrophotometer (Thermo Scientific). The instrument was rinsed with ddH_2O and the sample type was set to "RNA-40". Two microlitres of Elution Solution was loaded to blank the instrument, and then 2 µL of each sample was loaded and measured. Each sample was measured twice and an average concentration was calculated. The instrument was washed with ddH_2O between measurements.

2.5 Immunofluorescence

H9 and CA1 compact hESC colonies were seeded onto Matrigel® in twelve-well dishes and cultured in 1% or 20% oxygen as described in section 2.2. After 48 or 72 hours, the wells were rinsed twice in PBS and incubated in 0.5 mL of fixing solution (4% paraformaldehyde, 4% sucrose, 300 µM $CaCl_2$ in PBS) for 20 minutes at room temperature. After the cells had been fixed, they were rinsed three times in PBS and stored at 4°C until staining was performed. Before staining for Oct-4, which is an

intracellular protein, the cells were permeabilized with 0.1% Triton X-100 in PBS for 10 minutes. After two five-minute washes in 1X Rinse Buffer (5% Tris-Cl buffer, 150 mM NaCl, 0.05% Tween 20 in ddH_2O), the cells were treated with Serum-Free Protein Block (0.25% casein in PBS, containing stabilizing protein and 0.015 M sodium azide; Dako) for 30 minutes at room temperature to inhibit non-specific staining. The cells were then incubated with 0.5 mL of a primary antibody against human Oct-4 (Oct-3/4 probe mouse monoclonal IgG; Santa Cruz Biotechnology) diluted 1:50 in Antibody Diluent (Tris-HCl buffer containing stabilizing protein and 0.015 M sodium azide; Dako) for one hour. After three five-minute washes in 1X Rinse Buffer, the cells were incubated with a secondary antibody against mouse IgG (AlexaFluor 488 goat anti-mouse IgG (H+L); Invitrogen). After another three five-minute washes in 1X Rinse Buffer, fluorescence micrographs were taken of random colonies. The total number of colonies in three wells for each time point and oxygen condition was counted. The number of colonies containing at least one region that was not expressing Oct-4 was also counted and divided by the total number of colonies to determine the percentage of colonies that contained differentiated cells. A Two Way Analysis of Variance (ANOVA) with a Student-Newman-Keuls post hoc test was performed for each cell line to determine whether there was a significant difference between time points and between oxygen availiability in the datasets. A P value < 0.05 was considered significant.

2.6 Western blotting

Twenty-five micrograms of each protein sample was mixed in a 5:1 ratio with 5X loading buffer (28% glycerol, 17% Tris-HCl buffer, pH 6.8, 0.2 M SDS, 4 mM bromophenol blue in ddH_2O) and 1 M dithiothreitol (DTT) for a final concentration of 100 mM DTT. The mixtures were heated at 100°C for five minutes to denature the proteins and reduce disulfide bonds. The samples were then loaded onto a 1.5 mm, 8% polyacrylamide mini-gel and run at 200 V. When 20 kDa proteins had run off the gel, the voltage was turned off and the gel was placed in Transfer Buffer (1.4% glycine, 0.3% Tris Base, 20% methanol in ddH_2O) for five minutes. Polyvinlyidene difluoride (PVDF)

paper was activated in methanol for five minutes and then soaked in Transfer Buffer for ten minutes. The gel and PVDF paper were clamped together and transferring was performed in Transfer Buffer on ice at 100V for 2 hours. The PVDF paper was then stained with Amido Black Staining Solution (0.1% Amido black, 50% methanol, 10% acetic acid in ddH_2O) to visualize total protein present. The paper was cut in half horizontally at 75 kDa so that HIF-1α (~120 kDa) and β-actin (~42 kDa) could be imaged at the same time.

Each half of the PVDF blot was incubated in 5% milk in Tris-Buffered Saline with Tween (TBS-T; 0.15 M NaCl, 0.05M Tris buffer (pH 7.6), 0.2% Tween in ddH_2O) for one hour. The milk was drained and the top half of the PDVF paper was incubated for one hour with 0.5 µg/mL mouse anti-human HIF-1α antibody (BD BioSciences, Lot: 06820) in 1% BSA in TBS-T. The bottom half of the PDVF paper was incubated for one hour with 20 ng/mL monoclonal mouse anti-human β-actin antibody (Santa Cruz Biotechnology, Lot: D1610) in 1% BSA in TBS-T. Excess primary antibody was rinsed away with four five-minute washes of TBS-T. The PDVF paper was then incubated for one hour with goat anti-mouse IgG antibody containing a horseradish peroxidase (HRP) conjugate (BioRad). Excess secondary antibody was rinsed away with five five-minute washes of TBS-T. The membrane was coated with a 1:1 mixture of Peroxidase Solution and Luminol/Enhancer Solution from an Immuno-Star™ Western C™ Kit (BioRad) and wrapped with Saran wrap. CL-X Posure™ Film (Thermo Scientific) was pressed against the PDVF paper in a dark room for 1 second to 5 minutes and was developed with a M35A X-OMAT Processor (Kodak).

2.7 Real-time RT-PCR

In order to make cDNA from RNA, 1 µg of RNA from each sample was mixed with 10 µL Master Medium (20% 10 RT PCR buffer, 32% RNase free ddH_2O, 8% dNTPs, 20% random primers, 10% reverse transcriptase, 10% RNase inhibitor) from a High Capacity cDNA Reverse Transcription Kit (Applied Biosystems). ddH_2O was added to bring the final volume up to 20 µL. The samples were placed in a BioRad C1000 Thermal Cycler at

25°C for 10 minutes, 37°C for 2 hours, 85°C for five minutes, and 4°C until the samples were retrieved.

For real time RT-PCR, a Master Mix solution containing specific primer probes was prepared for each gene that would be analyzed. The Master Mix contained 56% TaqMan Universal PCR Master Mix (Applied Biosystems), 4% $MgCl_2$, and 6% primer probes in RNase free ddH_2O. Primer probes were selected for the housekeeping gene, HPRT1, which served as comparison for the other genes that were analyzed: Oct 4, Nanog, Nodal and HIF-1α. In a 96-well PCR plate, 2 µL of cDNA from each sample was mixed with 18 µL of Master Mix for each primer probe, in duplicate. Two microlitres of water was mixed with 18 µL of Master Mix for each primer probe as a no template control (NTC). The plate was placed in a C1000™ Thermal Cycler (BioRad) and run at 50°C for 2 minutes, 95°C for 10 minutes, and then repeating cycles of 95°C for 15 minutes and 58°C for one minute. The following equation was used to calculate fold difference based on CT values:

$$\text{ratio} = \frac{(E_{target})^{\Delta CP_{target}\,(control\,-\,sample)}}{(E_{ref})^{\Delta CP_{ref}\,(control\,-\,sample)}}$$

Man-Whitney Rank sum tests were performed to determine whether the differences in RNA levels were significant. A P value < 0.05 was considered significant.

2.8 Fractionation and tryptic digestion of proteins for MS analysis

To reduce the complexity of samples for MS analysis, the proteomes were fractionated by 1D gel electrophoresis [104]. Eighty micrograms of each protein sample was mixed in a 5:1 ratio with 5X loading buffer (28% glycerol, 17% Tris-HCl buffer, pH 6.8, 0.2 M SDS, 4 mM bromophenol blue in ddH_2O) and 1 M DTT for a final concentration of 100 mM DTT. The mixtures were heated at 90°C for 5 minutes to denature the proteins and reduce disulfide bonds. The samples were then loaded onto a 1.5 mm, 12% SDS-PAGE mini-gel and run at 100 V. When the run was complete, the gel was fixed for one hour in Fixing Solution (50% methanol, 10% acetic acid in ddH_2O), stained for one hour with Coomassie Stain Solution (1 mM Brilliant Blue R-250 (BBR),

50% methanol, 10% acetic acid in ddH_2O), and destained overnight in Destaining Solution 1 (45% methanol, 10% acetic acid in ddH_2O).

Each lane representing the concentrated sample was then cut into fifteen fractions. Gel fractions were cut into small cubes (~1 mm^2) and placed into separate microcentrifuge tubes. The gel pieces were destained by alternating between washes in Destaining Solution 1 and Destaining Solution 2 (20% acetonitrile [ACN] in 100 mM ammonium bicarbonate [NH_4HCO3]).

The cysteines were reduced and alkylated to eliminate disulfide linkages. First, the gel pieces were dehydrated with 100% ACN and completely dried by spinning in a SpeedVac centrifuge. Then the gel pieces were rehydrated with 10 mM (DTT) in 100 mM NH_4HCO3 for 30 min. The DTT solution was removed and 100 mM iodoacetamide (IDA) in 100 mM NH_4HCO_3 was added for 30 min to alkylate the cysteines. The gel pieces were washed and dehydrated with 100% ACN, and then rehydrated with 50 mM NH_4HCO_3 twice.

For tryptic digestion, the gel pieces were first dehydrated with 100% ACN, and then rehydrated with modified procine trypsin (Promega, Madison, WI) (20 µg/mL in 50 mM NH_4HCO_3) on ice for 15 min. Fifty millimolar NH_4HCO_3 was added to cover the gel pieces and the samples were maintained at 37°C for 18 h. To extract the tryptic peptides, the supernatant was collected and the gel pieces were washed three times with 10% formic acid (FA). The samples were then placed in a Speedvac centrifuge until the volume was approximately 50 µL. The tubes were centrifuged at 10 000 g for three minutes to remove insoluble matter and the supernatant was transferred to MS tubes.

2.9 Iterative exclusion tandem mass spectrometry analysis

LC separation (5-50% ACN, 0.1% FA gradient) was performed on a NanoAcquity UPLC (Waters, Milford, MA) with a 15 cm x 75 µm C_{18} reverse phase column. Peptide ions were detected in data-dependent acquisition (DDA) mode by tandem MS (Q-ToF Ultima; Waters). To identify lower abundance proteins, each sample was injected multiple times using iterative exclusion to ignore previously selected ions [99]. Ions that

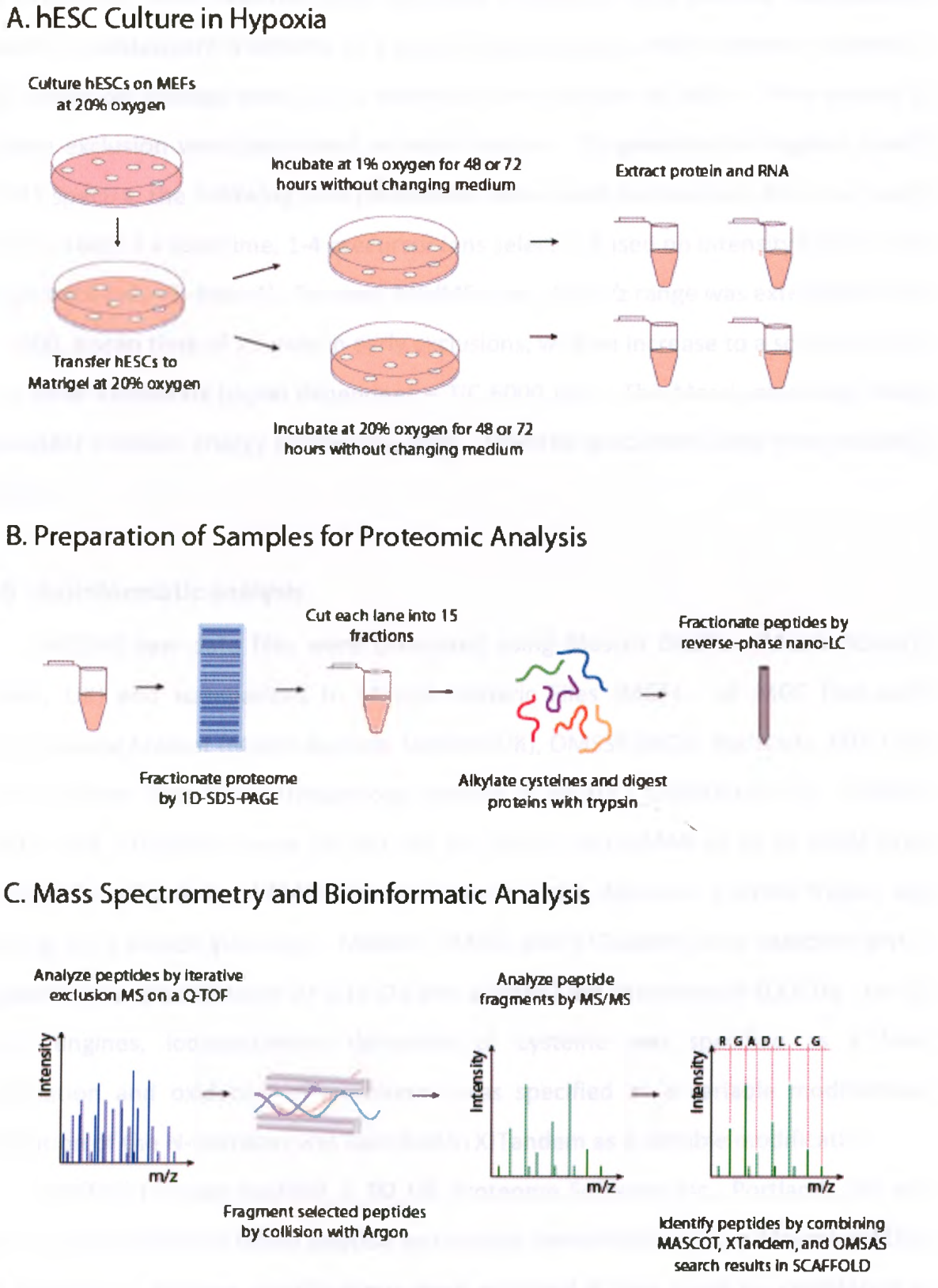

Figure 7. Proteomic analysis of hESCs cultured in hypoxia. A) hESCs were cultured in 1% or 20% oxygen for 48 or 72 hours. B) The proteome was fractionated by 1D gel electrophoresis and proteins were alkylated, digested with trypsin, and separated with reversed-phase LC. C) The peptides were analyzed by ESI tandem mass spectrometry and identified with bioinformatics software.

had previously been selected were excluded (MassLynx DDA exclude functionality; Waters) in subsequent injections of a given fraction using a *m/z* tolerance window of ±0.8, based on average mass and a retention time window of ±60 s. Five rounds of iterative exclusion were performed on each fraction. To generate the highest quality MS/MS spectra, the following DDA parameters were used: survey scan (MS only) range *m/z* 400-1800, 1 s scan time, 1-4 precursor ions selected based on intensity (30 cps) and charge state (+2, +3, and +4). For each MS/MS scan, the *m/z* range was extended to *m/z* 50 -1800, a scan time of 1 s used in early exclusions, with an increase to a scan time of 1-4 s in later exclusions (signal dependent – TIC 6000 cps). The MassLynx charge state-dependent collision energy profile was used. Selected precursors were then excluded for 45 s.

2.10 Bioinformatic analysis

MS/MS raw data files were processed using Mascot Distiller (Matrix Science, London, UK) and summarized to Mascot Generic Files (MGF). All MGF files were analyzed using Mascot (Matrix Science, London, UK), OMSSA (NCBI, Bethesda, MD, USA) and X!Tandem (The GPM, thepgm.org; version TORNADO (2009.04.01.4)). OMSSA, Mascot and X!Tandem were all set up to search ipi.HUMAN.v3.78_REVERSE.fasta (selected for All Entries, 173404 entries) assuming the digestion enzyme trypsin and allowing for 2 missed cleavages. Mascot, OMSSA and X!Tandem were searched with a fragment ion mass tolerance of 0.15 Da and a parent ion tolerance of 0.15 Da. For all search engines, iodoacetamide derivative of cysteine was specified as a fixed modification and oxidation of methionine was specified as a variable modification. Acetylation of the N-terminus was specified in X!Tandem as a variable modification.

Scaffold (version Scaffold_3_00_08, Proteome Software Inc., Portland, OR) was used to validate MS/MS based peptide and protein identifications from Mascot, OMSSA and X!Tandem. Peptide identifications were accepted if they could be established at greater than 95.0% probability as specified by the Peptide Prophet algorithm in [105]. Protein identifications were accepted if they could be established at greater than 99.0%

probability and contained at least 2 identified peptides. Protein probabilities were assigned by the Protein Prophet algorithm in [106]. Proteins that contained similar peptides and could not be differentiated based on MS/MS analysis alone were grouped to satisfy the principles of parsimony.

The results of all six replicates (three for each cell line) were combined and compared manually in Excel. Proteins were said to be up-regulated in hypoxia if they were identified in two out of three replicates in both cell lines in hypoxia but not identified in any replicates in normoxia. Some additional proteins were categorized as up-regulated in hypoxia if the number of peptide identifications for a particular protein was much higher (≥3) in hypoxia than in normoxia for four replicates. Proteins were said to be down-regulated in hypoxia if the opposite trend was observed.

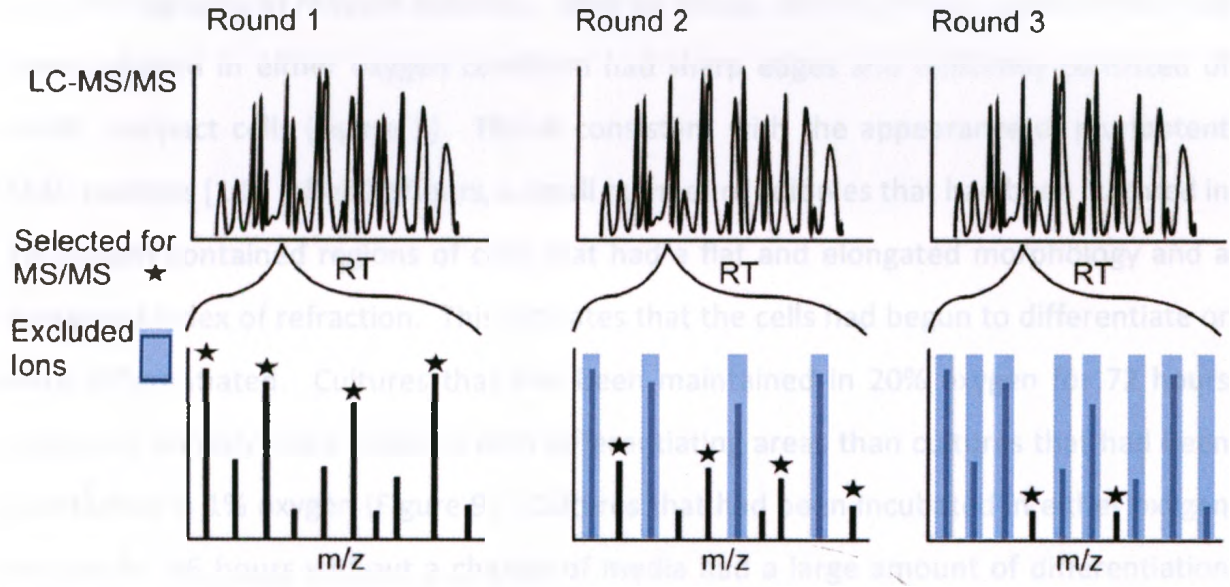

Figure 8. Iterative exclusion tandem mass spectrometry. In this technique, the first round of MS analysis identifies the most abundant proteins in the fraction. In subsequent rounds, ions that were selected in all previous rounds are ignored based on *m/z* and retention time to allow for the identification of previously uncharacterized, lower abundance ions. Image from [99].

Chapter 3: Results

3.1 Hypoxia promotes pluripotency in our experimental system

H9 and CA1 hESCs in feeder-free cultures were incubated in 1% or 20% oxygen for up to 96 hours. The medium was not changed during this time in order to promote differentiation. After 48, 72 and 96 hours, a phase contrast microscope was used to take micrographs of random colonies. After 48 hours, almost all hESC colonies that had been cultured in either oxygen condition had sharp edges and uniformly consisted of small, compact cells (Figure 9). This is consistent with the appearance of pluripotent hESC colonies [13]. After 72 hours, a small number of colonies that had been cultured in 1% oxygen contained regions of cells that had a flat and elongated morphology and a decreased index of refraction. This indicates that the cells had begun to differentiate or were differentiated. Cultures that had been maintained in 20% oxygen for 72 hours contained notably more colonies with differentiating areas than cultures that had been maintained in 1% oxygen (Figure 9). Cultures that had been incubated in either oxygen tension for 96 hours without a change of media had a large amount of differentiation (Figure 9).

Cultures that contain large numbers of differentiated cells no longer represent a hESC population. Therefore, hESCs that are beginning to differentiate in 20% oxygen but are still mostly pluripotent would provide the most insight into how hypoxia promotes pluripotency in hESCs. This is most consistent with the level of differentiation observed after 48 hours and 72 hours; therefore, these time points were chosen for all subsequent experiments. Since there was excessive differentiation after 96 hours of culture in unchanged media, no further experiments were carried out at this time point.

3.1.1 Immunofluorescence localization of Oct-4

To confirm the observation from phase contrast images that hypoxia promotes pluripotency in our system, immunofluorescence analysis was performed to detect the

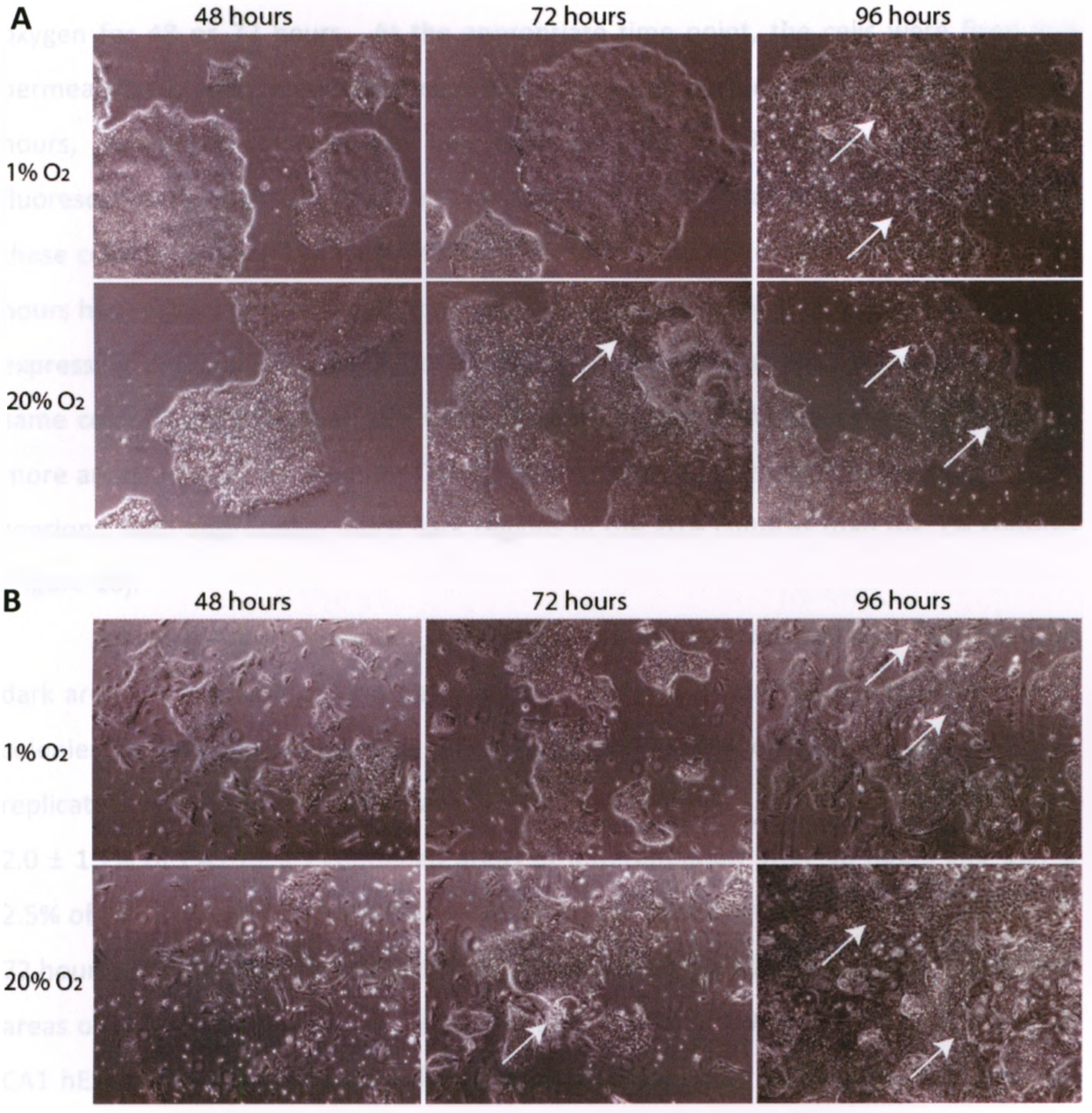

Figure 9. hESC morphology after 48 or 72 hours of culture in 1% or 20% oxygen. H9 and CA1 hESC compact colonies were seeded onto a 3D matrix comprised of growth factor-reduced Matrigel® and were cultured in the presence of conditioned stem cell medium for 48, 72 or 96 hours in 1% or 20% oxygen. The medium was not changed during this time in order to accelerate differentiation. Phase-contrast micrographs were taken of randomly selected colonies at each time point. Biological replicates were performed with (A) the H9 hESC line and (B) the CA1 hESC line. Arrows point to areas of differentiation.

presence of Oct-4, which is a transcription factor that is only present in the nucleus of pluripotent hESCs. hESC colonies in feeder-free culture were incubated in 1% or 20% oxygen for 48 or 72 hours. At the appropriate time point, the cells were fixed and permeabilized, and immunofluorescence analysis was performed for Oct-4. After 48 hours, almost all colonies that had been cultured in 1% oxygen emitted bright fluorescence throughout the colony, indicating that Oct-4 was expressed in all cells of these colonies (Figure 10). Some colonies that had been cultured in 20% oxygen for 48 hours had regions of darkness that did not fluoresce, indicating that these cells were not expressing detectable levels of Oct-4. Phase contrast micrographs were taken of the same colonies to show that cells were present in these dark regions. After 72 hours, more areas that did not stain for Oct-4 appeared in cultures maintained at both oxygen tensions, with appreciably more dark regions in the 20% cultures than the 1% cultures (Figure 10).

For each oxygen condition, the number of colonies that contained at least one dark area not expressing Oct-4 was counted. This was divided by the total number of colonies to give the percentage of colonies with areas of differentiation. Three replicates were performed with each cell line. In hypoxia, 3.0 ± 3.1% of H9 hESCs and 2.0 ± 1.7% of CA1 hESCs contained areas of differentiation after 48 hours and 11.7 ± 2.5% of H9 hESCs and 15.5 ± 5.6% of CA1 hESCs contained areas of differentiation after 72 hours. In normoxia, 20.3 ± 7.1% of H9 hESCs and 18.4 ± 5.2% of CA1 hESCs contained areas of differentiation after 48 hours and 38.7 ± 8.0% of H9 hESCs and 34.3 ± 7.4% of CA1 hESCs contained areas of differentiation after 72 hours (Figure 11). For both cell lines, there was a significant difference in the percentage of colonies with areas of differentiation between hypoxic and normoxic culture for both time points ($P<0.01$, $n=3$). For the CA1 cell line, there was a significantly higher percentage of colonies with differentiation at 72 hours than at 48 hours for cultures maintained in hypoxia. For both cell lines, there was a significantly higher percentage of colonies with differentiation at 72 hours than at 48 hours for cultures maintained in normoxia ($P < 0.05$, $n=3$).

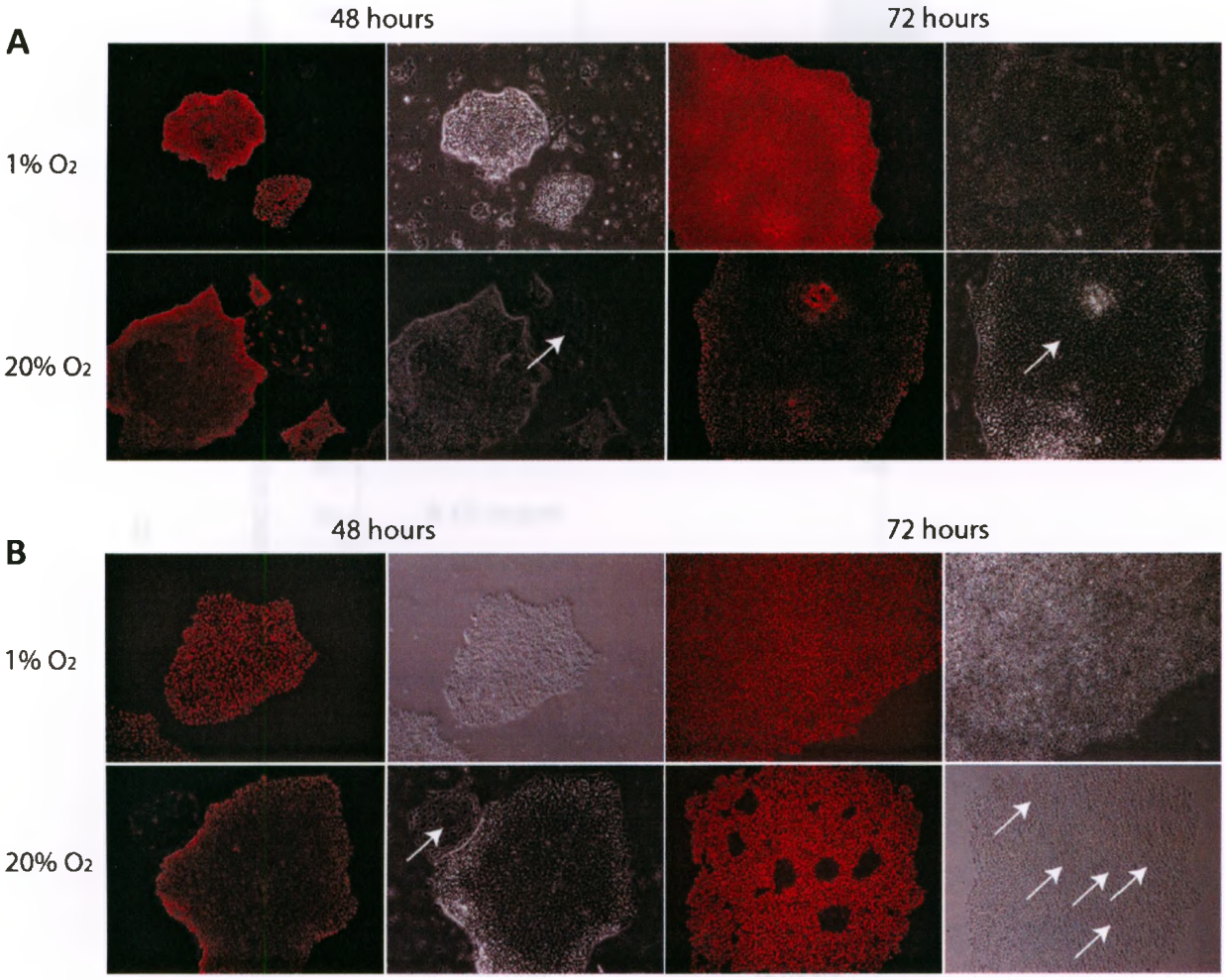

Figure 10. Immunofluorescent detection of Oct-4 in hESCs cultured in 1% or 20% oxygen for 48 or 72 hours. hESCs cultured on growth factor-reduced Matrigel® in conditioned stem cell medium were incubated in 1% or 20% oxygen for 48 or 72 hours. The medium was not changed during this time in order to accelerate differentiation. The cultures were fixed with paraformaldehyde and immunostained for Oct-4, a protein known to be expressed only in pluripotent cells. Biological replicates were performed with (A) the H9 hESC line and (B) the CA1 hESC line. Arrows point to areas of differentiation.

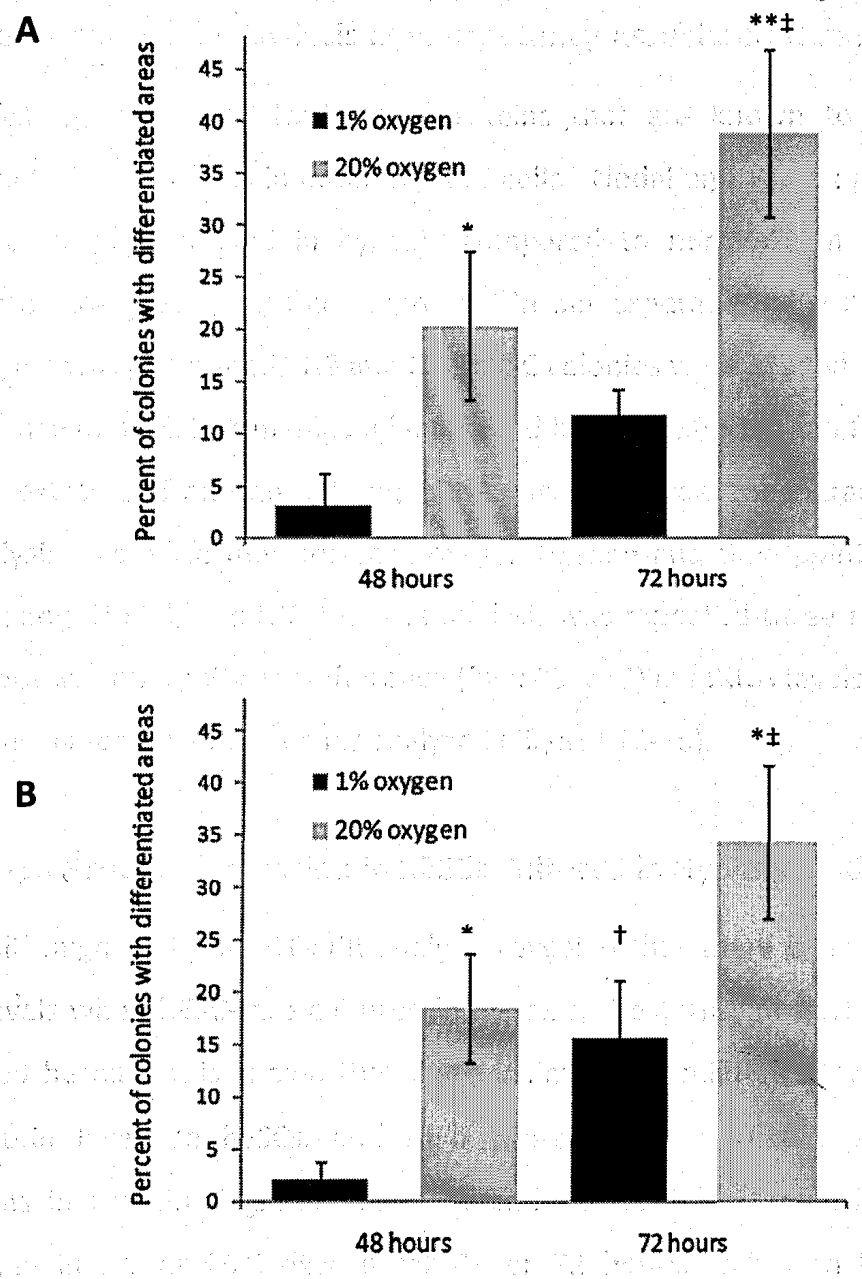

Figure 11. Percentage of colonies with areas of differentiation for hESCs cultured in 1% or 20% oxygen, as determined by Immunofluorescent detection of Oct-4. hESCs in feeder-free culture were maintained for 48 or 72 hours in 1% or 20% oxygen. The cultures were immunostained for Oct-4, a marker of pluripotency. The number of colonies containing regions that did not express Oct-4 was counted. This was divided by the total number of colonies to give the percentage of colonies with areas of differentiation. Biological replicates were performed with (A) the H9 hESC line and (B) the CA1 hESC line (mean ± SD, n=3). Values that differ significantly between oxygen tensions within a time point are shown with asterisks (*, $P < 0.01$; **, $P < 0.001$) and values that differ significantly between time points within an oxygen tension are shown with daggers (†, $P < 0.05$; ‡, $P < 0.01$).

3.2 Real-time RT-PCR Analysis of Pluripotency Associated Genes in Hypoxia

Oct-4, Nanog and Nodal are proteins that are known to be expressed in pluripotent hESCs but not in differentiated cells. Nodal and HIF-1α protein have been shown to be up-regulated in hypoxia compared to normoxia in cancer cells. To investigate how these genes are expressed in our experimental system, real-time RT-PCR anaylsis was performed. H9 and CA1 hESC colonies were seeded onto Martrigel® in the presence of mTESR®1 media and incubated in 1% or 20% oxygen for 48 or 72 hours. RNA was extracted from the cells and cDNA was made from the extracts. Real-time RT-PCR analysis was performed for each oxygen tension and time point with primers for Oct-4, Nanog, Nodal, and HIF-1α. The analysis was repeated three times for each cell line. There was no significant difference ($P > 0.05$, $n=3$) in mRNA levels between hypoxia and normoxia for any of the genes analyzed (Figures 12-15).

3.3 HIF-1α Protein Expression in hESCs Cultured in Hypoxia and Normoxia

Although real-time RT-PCR analysis revealed that there is no change in HIF-1α mRNA levels when hESCs are cultured in hypoxia, Western blot analysis of HIF-1α was performed because it is known that there is limited correlation between mRNA levels and protein levels in hESCs, and HIFα proteins are regulated predominantly via alterations in protein degradation. CA1 and H9 hESCs in feeder-free culture were maintained in 1% or 20% oxygen for 48 or 72 hours. Western blot analysis was performed with anti-HIF-1α and anti-β-actin antibodies. Distinct double bands, representing phosphorylated and unphosphorylated HIF-1α, were present around 120 kDa in all lanes containing protein from hESCs cultured in hypoxia. The same double band was much fainter or not visible in lanes containing protein from hESCs cultured in normoxia. Densitometry analysis of the plots was performed for three replicates with each cell line and results were analysed with t-tests. There was significantly greater expression of HIF-1α in hypoxic samples than in normoxic samples ($P < 0.01$, $n=3$) for both cell lines at both time points (Figure 16).

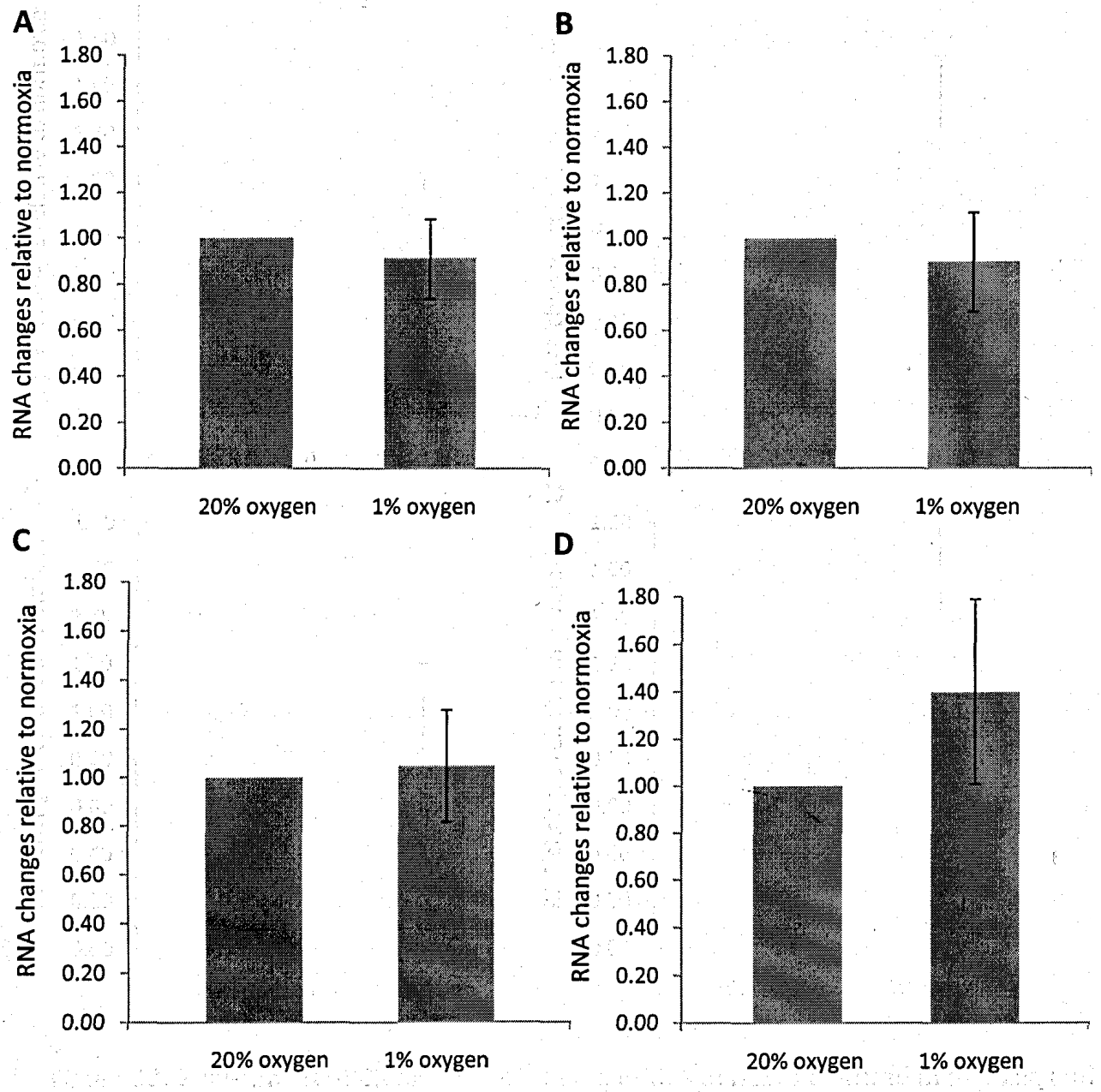

Figure 12. Real-time RT-PCR analysis of Oct-4 mRNA in hESCs cultured in hypoxia and normoxia. H9 and CA1 hESCs were cultured in 1% or 20% oxygen for 48 or 72 hours. At each time point, RNA was extracted and quantified, and real-time RT PCR was performed with a primer for the Oct-4 transcript. CT values were normalized to the housekeeping gene, HPRT1. Graphs depict relative levels of Oct-4 mRNA in hypoxia compared to normoxia for (A) H9 hESCs after 48 hours, (B) CA1 hESCs after 48 hours, (C) H9 hESCs after 72 hours and (D) CA1 hESCs after 72 hours. Values are means ± SD (n=3, $P > 0.05$).

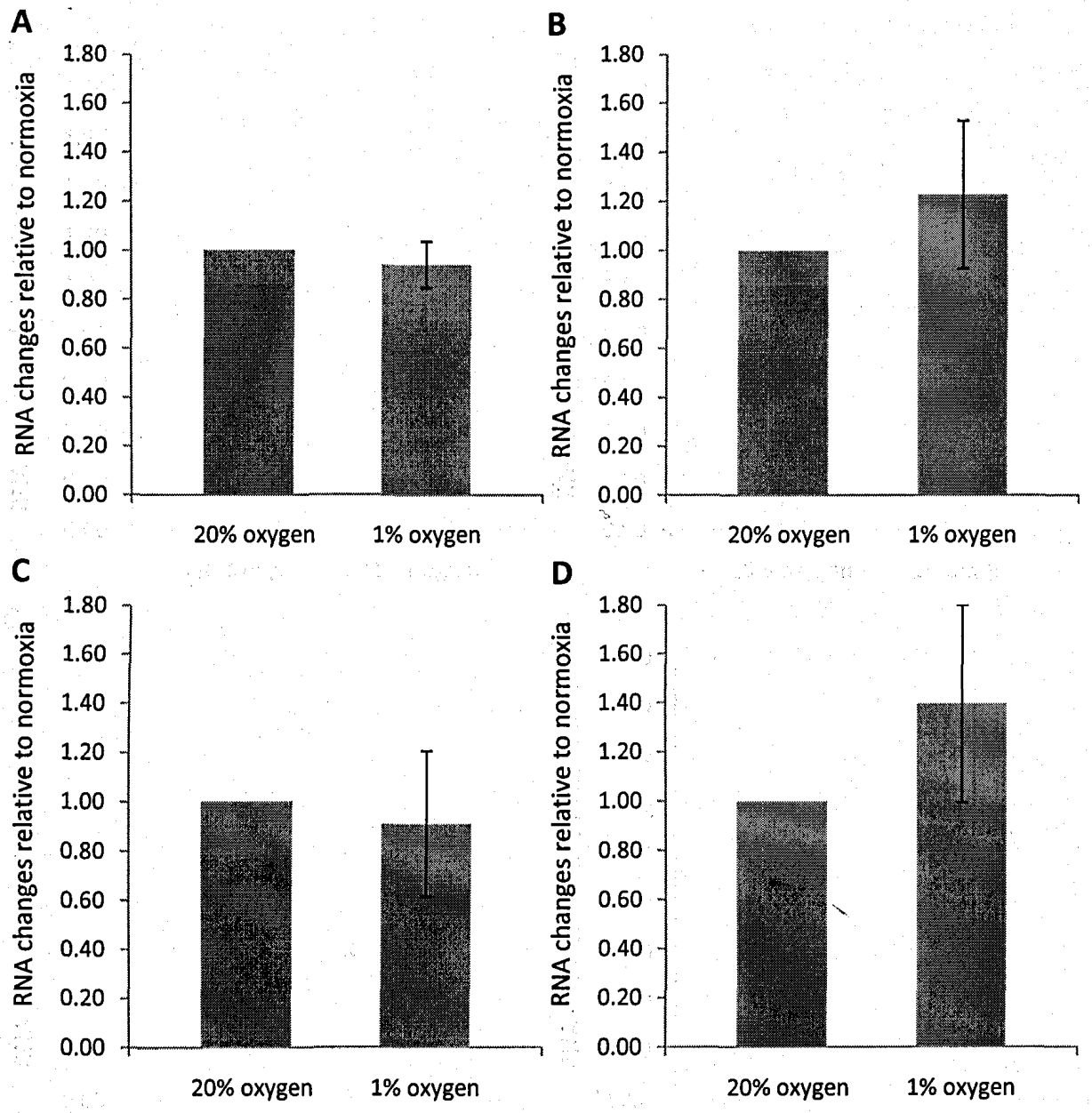

Figure 13. Real-time RT-PCR analysis of Nanog mRNA in hESCs cultured in hypoxia and normoxia. H9 and CA1 hESCs were cultured in 1% or 20% oxygen for 48 or 72 hours. At each time point, RNA was extracted and quantified, and real-time RT-PCR was performed with a primer for the Nanog transcript. CT values were normalized to the housekeeping gene, HPRT1. Graphs depict relative expression of Nanog in hypoxia compared to normoxia for (A) H9 hESCs after 48 hours, (B) CA1 hESCs after 48 hours, (C) H9 hESCs after 72 hours and (D) CA1 hESCs after 72 hours. Values are means ± SD (n=3, $P > 0.05$).

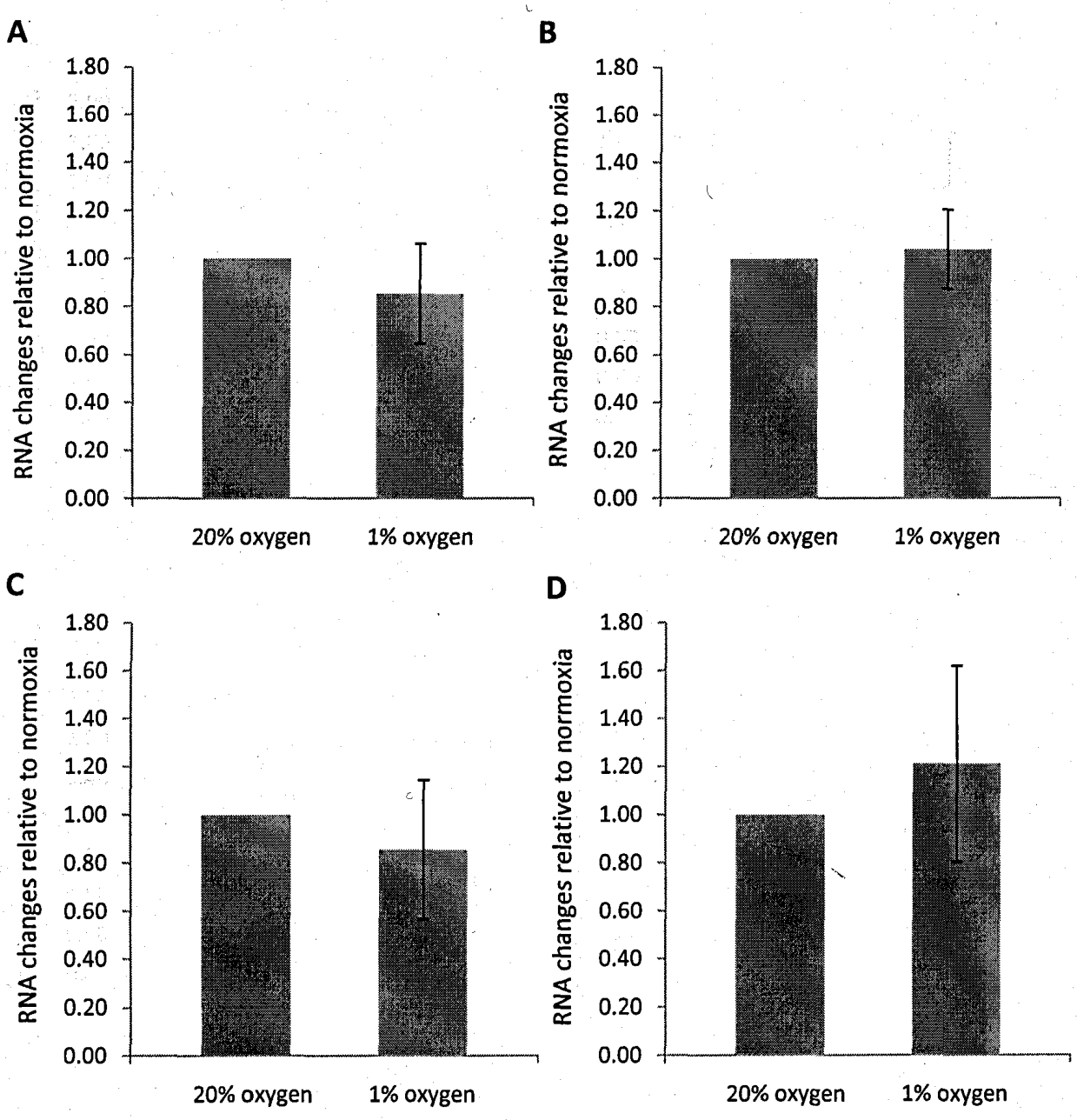

Figure 14. Real-time RT-PCR analysis of Nodal mRNA in hESCs cultured in hypoxia and normoxia. H9 and CA1 hESCs were cultured in 1% or 20% oxygen for 48 or 72 hours. At each time point, RNA was extracted and quantified, and real-time RT-PCR was performed with a primer for the Nodal transcript. CT values were normalized to the housekeeping gene, HPRT1. Graphs depict relative expression of the transcript in hypoxia compared to normoxia for (A) H9 hESCs after 48 hours, (B) CA1 hESCs after 48 hours, (C) H9 hESCs after 72 hours and (D) CA1 hESCs after 72 hours. Values are means ± SD ($n=3$, $P > 0.05$).

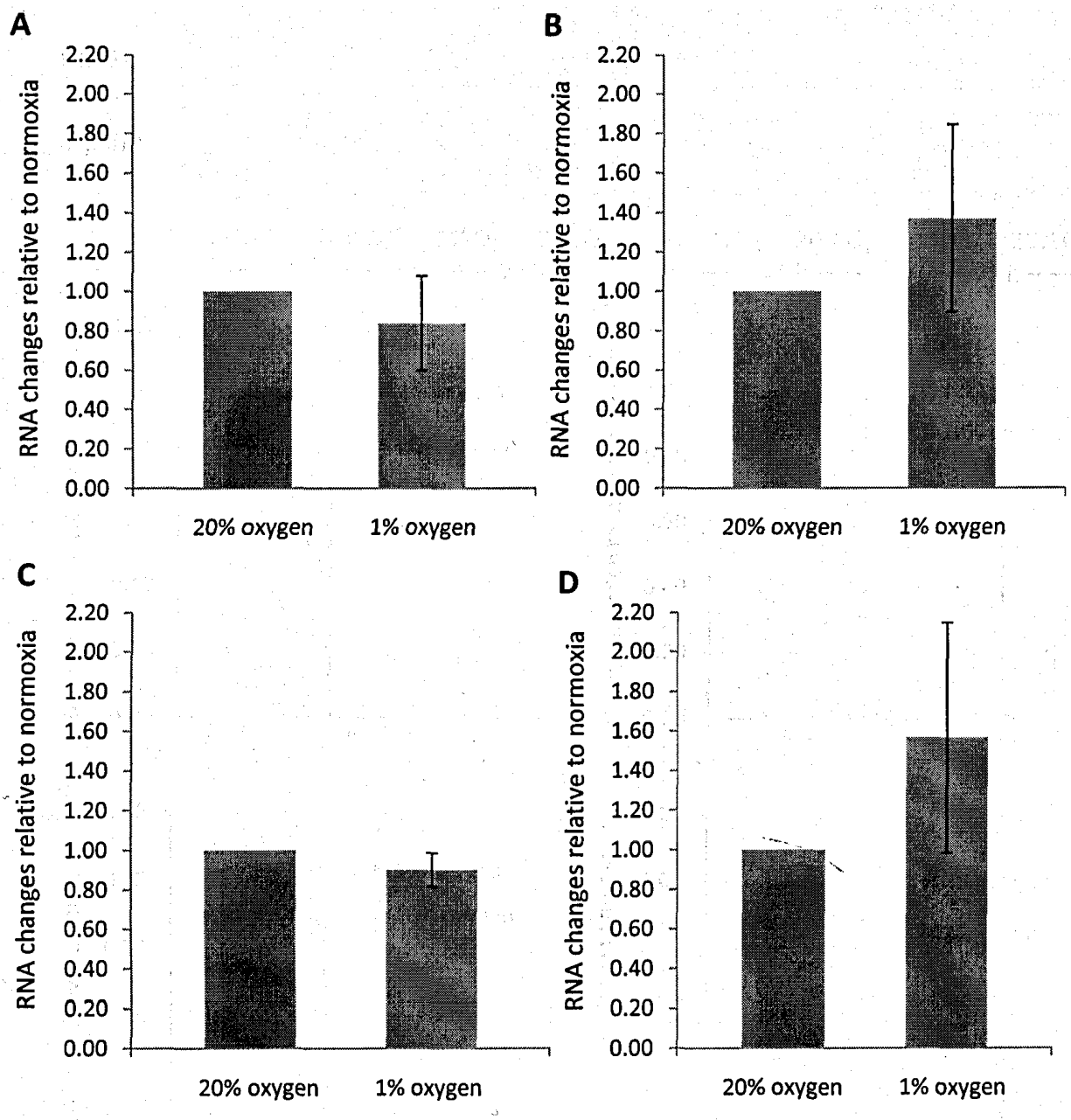

Figure 15. Real-time RT-PCR analysis of HIF-1α mRNA in hESCs cultured in hypoxia and normoxia. H9 and CA1 hESCs were cultured in 1% or 20% oxygen for 48 or 72 hours. At each time point, RNA was extracted and quantified, and real-time RT-PCR was performed with a primer for the HIF-1α transcript. CT values were normalized to the housekeeping gene, HPRT1. Graphs depict relative expression of the transcript in hypoxia compared to normoxia for (A) H9 hESCs after 48 hours, (B) CA1 hESCs after 48 hours, (C) H9 hESCs after 72 hours and (D) CA1 hESCs after 72 hours. Values are means ± SD (n=3, $P > 0.05$).

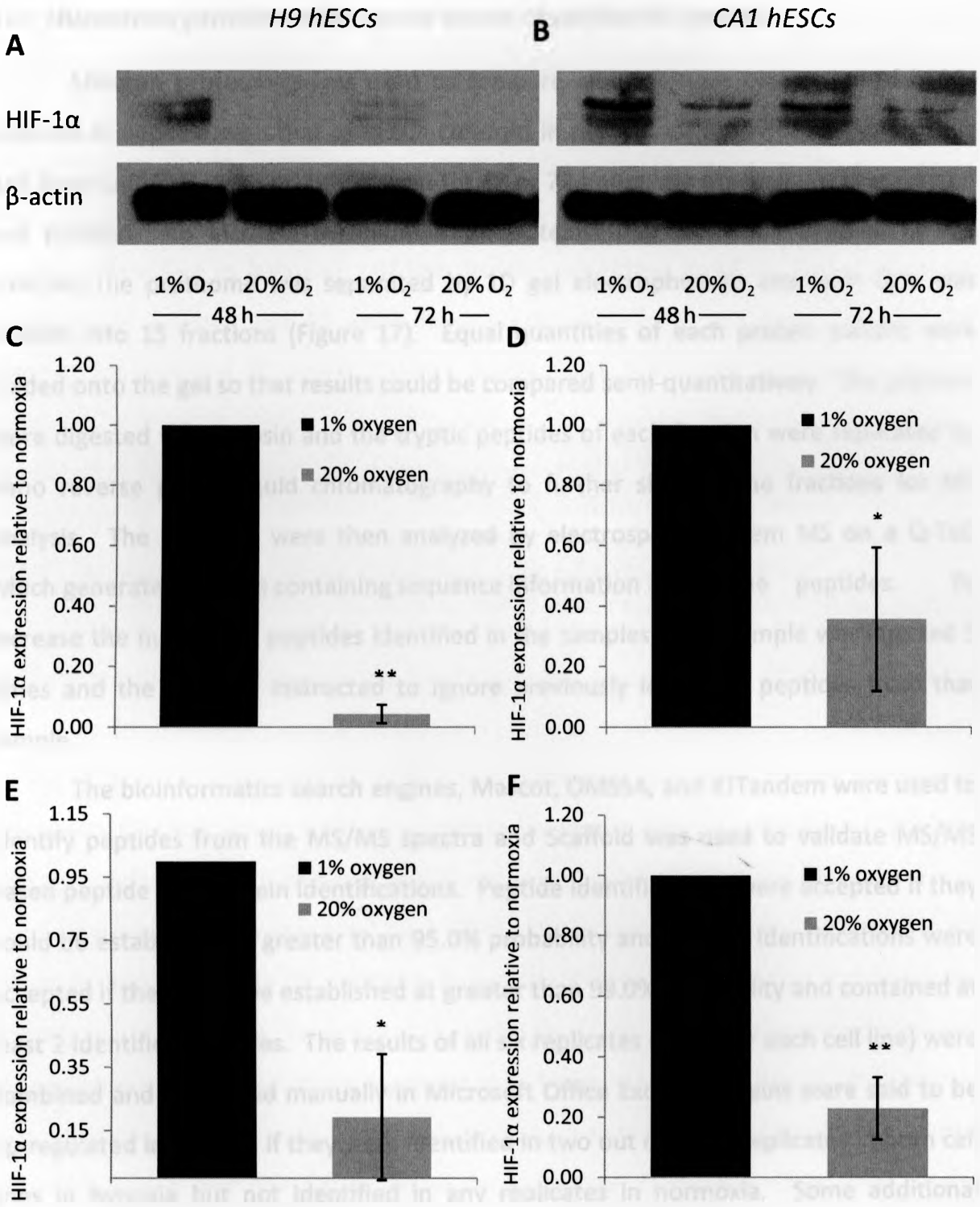

Figure 16. Expression of HIF-1α in hESCs cultured in hypoxia and normoxia. hESCs were cultured in 1% or 20% oxygen for 48 or 72 hours. Western blot analysis was performed for HIF-1α, normalized to β-actin for A) H9 hESCs and B) CA1 hESCs. Densitometry analysis was performed to compare HIF-1α expression at C) 48 hours in H9 hESCs, D) 48 hours in CA1 hESCs, E) 72 hours in H9 hESCs, and F) 72 hours in CA1 hESCs. Values (mean ± SD, n=3) that differ significantly between oxygen tensions are shown with asterisks (*, $P < 0.01$; **, $P < 0.001$).

3.4 Numerous proteins were up- or down-regulated in hypoxia

Shotgun proteomics was used to compare global protein expression of hESCs cultured in hypoxia with that of hESCs cultured in normoxia. After H9 and CA1 hESCs had been cultured in 1% or 20% oxygen for 48 or 72 hours, the proteome was extracted and purified. To increase the number of proteins that could be identified by MS analysis, the proteome was separated by 1D gel electrophoresis and each lane was divided into 15 fractions (Figure 17). Equal quantities of each protein sample were loaded onto the gel so that results could be compared semi-quantitatively. The proteins were digested with trypsin and the tryptic peptides of each fraction were separated by nano reverse phase liquid chromatography to further simplify the fractions for MS analysis. The peptides were then analyzed by electrospray tandem MS on a Q-Tof, which generated spectra containing sequence information about the peptides. To increase the number of peptides identified in the samples, each sample was injected 5 times and the MS was instructed to ignore previously identified peptides from that sample.

The bioinformatics search engines, Mascot, OMSSA, and X!Tandem were used to identify peptides from the MS/MS spectra and Scaffold was used to validate MS/MS based peptide and protein identifications. Peptide identifications were accepted if they could be established at greater than 95.0% probability and protein identifications were accepted if they could be established at greater than 99.0% probability and contained at least 2 identified peptides. The results of all six replicates (three for each cell line) were combined and compared manually in Microsoft Office Excel. Proteins were said to be up-regulated in hypoxia if they were identified in two out of three replicates in both cell lines in hypoxia but not identified in any replicates in normoxia. Some additional proteins were categorized as up-regulated in hypoxia if the number of peptide identifications for a particular protein was much higher (≥3) in hypoxia than in normoxia for four replicates. Proteins were said to be down-regulated in hypoxia if the opposite trend was observed. (See appendices A-D for lists of the number of peptide identifications in each replicate for proteins up- and down-regulated in hypoxia).

A total of 1358 distinct proteins were identified in at least two replicates in both H9 and CA1 hESCs at 48 hours from cells cultured under both oxygen conditions (see Appendix E for a complete list of proteins identified in hypoxia). A total of 1649 distinct proteins were identified in at least two replicates in both H9 and CA1 hESCs at 72 hours from cells cultured under both oxygen conditions (see Appendix F for a complete list of proteins identified in hypoxia). Of the proteins identified at 48 hours, 17 were up-regulated in hypoxia and 48 were down-regulated in hypoxia (Figure 18). Of the proteins identified at 72 hours, 27 were up-regulated in hypoxia and 32 were down-regulated in hypoxia (Figure 18). Only four of the proteins that were up- or down-regulated at 48 hours were also up- or down-regulated at 72 hours, respectively.

3.4.1 Hypoxia influenced the expression of some metabolic proteins

Several proteins involved in metabolism were either up- or down-regulated in hESCs that had been cultured in hypoxia (Figure 19). Hexokinase-2, which catalyses the first committed step of glucose metabolism [107], was up-regulated in hypoxia at both 48 and 72 hours (Table 1 and 3). Solute carrier family 2, facilitated glucose transporter member 1 (GLUT1), which transports glucose across the plasma membrane [108], was also up-regulated at both 48 hours and 72 hours in hypoxia (Table 1 and 3).

Pyruvate dehydrogenase E1α 1 (PDHA1) precursor was down-regulated at 48 hours in hypoxia (Table 2). PDHA1 is a mitochondrial enzyme that catalyzes the conversion of pyruvate to acetyl-CoA and CO_2 [109]. α-ketoglutarate-dependent dioxygenase FTO was also down-regulated at 48 hours in hypoxia (Table 2). This protein is a dioxygenase that uses molecular oxygen, α-ketoglutarate and iron to repair alkylated ssDNA and RNA by oxidative demethylation [110] and contributes to the regulation of the global metabolic rate and energy expenditure [111]. Aldose-1 epimerase, which converts D-glucose, L-arabinose, D-xylose, D-galactose, maltose and lactose to the β-anomer [112], was down-regulated at 48 hours in hypoxia (Table 2). At 48 hours, there was also down-regulation of Arginase-2, which is an inducible protein

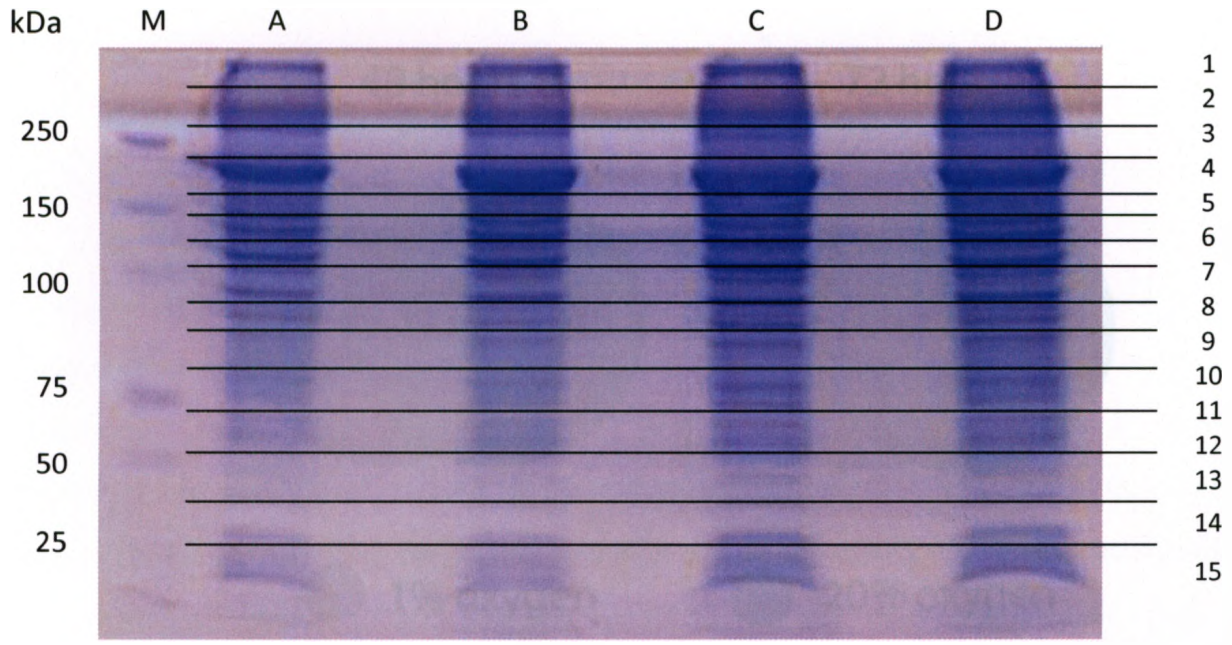

Figure 17. Fractionation of the hESC proteome by 1D gel electrophoresis. To simplify hESC proteomes for MS analysis, 1D gel electrophoresis was performed as a pre-fractionation step. Each lane was divided into 15 fractions. Regions of each lane that contained more protein as revealed by Coomassie blue staining were cut into narrower fractions so that each fraction contained approximately the same amount of protein. Proteomes were extracted from hESCs that had been cultured for (A) 48 hours in 1% oxygen, (B) 48 hours in 20% oxygen, (C) 72 hours in 1% oxygen and (D) 72 hours in 20% oxygen. Molecular weight standards are shown in Lane M.

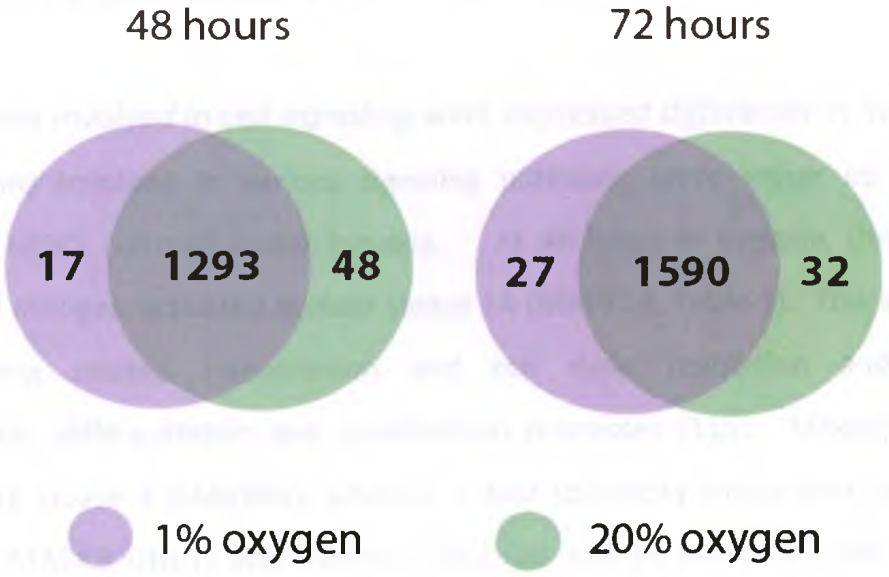

Figure 18. Number of proteins consistently identified by MS in hypoxic and normoxic hESC samples. Venn diagrams display the number of distinct proteins identified in at least two replicates in both H9 and CA1 hESCs after 48 and 72 hours of culture in either oxygen tension. ○ The number of proteins detected only in hypoxia, ○ the number of proteins detected only in normoxia, and ○ the number of proteins detected in both oxygen conditions.

that catalyzes the hydrolysis of arginine to ornithine and urea and inhibits the production of nitric oxide ([113]; Table 2).

Two components of Complex I of the electron transport chain: NADH dehydrogenase 75 kDa subunit and NADH dehydrogenase α subcomplex 5, were up-regulated at 72 hours in hypoxia (Table 3). Bifunctional coenzyme A synthase, which is a bifunctional enzyme that catalyzes two sequential steps of the CoA biosynthetic pathway [114], was down-regulated at 72 hours in hypoxia (Table 4).

3.4.2 Proteins involved in cell signaling were expressed differently in hypoxia

Proteins involved in various signaling pathways were either up- or down-regulated in hESCs cultured under hypoxia. At 48 hours in hypoxia, there was up-regulation of mitogen-activated protein kinase 14 (MAPK14; Table 1). This kinase has a role in stress related transcription and cell cycle regulation and mediates developmental, differentiation and proliferation processes [115]. Mitogen activated protein kinase kinase 4 (MAP2K4), which is a dual specificity kinase that activates the JUN kinases MAPK8 (JNK1) and MAPK9 (JNK2) as well as MAPK14 (p38) [116], was down-regulated at 48 hours in hypoxia (Table 2).

Insulin-like growth factor binding protein 2 (IGFBP-2), which modulates the action of insulin-like growth factors (IGFs) and also acts independently to affect proliferation, apoptosis, and mobility [117], was up-regulated at 72 hours in hypoxia (Table 3). PERQ amino acid-rich with GYF domain-containing protein 2 (GIGYF2), which may regulate tyrosine kinase receptor signaling at endosomes and regulate IGF-1 receptor trafficking [118], was also up-regulated at 72 hours in hypoxia.

Oxysterol-binding protein (OSBP) was down-regulated at 48 hours in hypoxia (Table 2). OSBP is a scaffold protein that binds cholesterol and other oxysterols and coordinates the activity of PP2A and a tyrosine phosphatase on the ERK signaling pathway [119]. Tetratricopeptide repeat protein 1 (TPR1), which competes with the Ras-binding domain of Raf-1 [120], was also down-regulated at 48 hours in hypoxia (Table 2).

Table 1: Proteins Up-regulated in Hypoxia at 48 Hours

Symbol	*Protein Name*	*IPI Number*
AARS	Alanyl-tRNA synthetase	IPI00910701
CSE1L	Exportin-2 (Isoform 1)	IPI00022744
DCTN1	Dynactin, subunit 1 (Isoform p150)	IPI00029485
DHX38	Pre-mRNA-splicing factor ATP-dependent RNA helicase PRP16	IPI00294211
EXOSC7	Exosome complex exonuclease RRP42	IPI00014198
FAM96B	Protein FAM96B	IPI00007024
FDPS	Farnesyl pyrophosphate synthase (Isoform B)	IPI00914971
GLUT1	Solute carrier family 2, facilitated glucose transporter, member 1	IPI00220194
HIST1H2A	Histone H2A type 1-H	IPI00081836
HK2	Hexokinase-2	IPI00102864
KIAA1524	Protein CIP2A (Isoform 1)	IPI00154283
LRBA	Lipopolysaccharide-responsive and beige-like anchor protein (Isoform 1)	IPI00002255
MAPK14	Mitogen-activated protein kinase 14 (Isoform CSBP2)	IPI00002857
PPP1CA	Serine/threonine-protein phosphatase PP1-α, catalytic subunit (Isoform 3)	IPI00027423
SMC4	Structural maintenance of chromosomes protein 4 (Isoform 2)	IPI00328298
SQLE	Squalene monooxygenase	IPI00291544
TOMM22	Mitochondrial import receptor subunit, TOM22 homolog	IPI00024976
-	Actin-like protein (Fragment)	IPI00556391

Table 2: Proteins Down-regulated in Hypoxia at 48 Hours

Symbol	*Protein Name*	*IPI Number*
ARG2	Arginase-2, mitochondrial	IPI00020332
ATG3	Ubiquitin-like-conjugating enzyme ATG3 (Isoform 1)	IPI00022254
C10orf119	UPF0557 protein C10orf119 (Isoform 2)	IPI00552546
C5orf51	UPF0600 protein C5orf51	IPI00374272
DCTD	Deoxycytidylate deaminase (Isoform 1)	IPI00296863
DCTN3	Dynactin subunit 3 (Isoform 2)	IPI00013654
DCUN1D1	DCN1-like protein 1	IPI00291893
DERA	Putative deoxyribose-phosphate aldolase	IPI00219677
DYNLRB1	Dynein, light chain, roadblock-type 1	IPI00412497
EIF2B1	Translation initiation factor eIF-2B, subunit α	IPI00221300
EML4	Echinoderm microtubule-associated protein-like 4	IPI00001466
FAM129B	Niban-like protein 1	IPI00456750
FKBP2	Peptidyl-prolyl cis-trans isomerase FKBP2	IPI00002535
FTO	α-ketoglutarate-dependent dioxygenase FTO (Isoform 1)	IPI00028277
G3BP2	Ras GTPase-activating protein-binding protein 2 (Isoform A)	IPI00009057
MAP2K4	Mitogen-activated protein kinase kinase 4 (Isoform 2)	IPI00024674
MARCKS	Myristoylated alanine-rich C-kinase substrate	IPI00219301
MNAT1	CDK-activating kinase assembly factor MAT1	IPI00294701
MRPL19	39S ribosomal protein L19, mitochondrial	IPI00027096
MRPS28	28S ribosomal protein S28, mitochondrial	IPI00022276
NAA25	N-alpha-acetyltransferase 25, NatB auxiliary subunit (Isoform 1)	IPI00025890
NAA38	N-alpha-acetyltransferase 38, NatC auxiliary subunit	IPI00219871
NLN	Neurolysin, mitochondrial	IPI00010346
NSFL1C	NSFL1 cofactor p47 (Isoform 1)	IPI00100197
NUP48	Nucleoporin 43 kDa	IPI00742943
NUP98	Nucleoporin 98 kDa	IPI00006038
OSBP	Oxysterol-binding protein 1 (Isoform 1)	IPI00024971
PCYT2	Ethanolamine-phosphate cytidylyltransferase	IPI00015285
PDCT3	Pentatricopeptide repeat domain 3 (Isoform 2)	IPI00783302
PDHA1	Pyruvate dehydrogenase E1 alpha 1 (Isoform 2) precursor	IPI00306301
PIR	Pirin	IPI00012575
PP2AC	Serine/threonine-protein phosphatase PP1-α, catalytic subunit	IPI00550451
PSMF1	Proteasome inhibitor, PI31 subunit	IPI00009949
PTCD1	Pentatricopeptide repeat domain 1	IPI00926491
RAB4A	RAB4A, member RAS oncogene family variant	IPI00480056
REEP5	Receptor expression-enhancing protein 5	IPI00024670
SLC16A1	Monocarboxylate transporter 1	IPI00024650
SMC4	Structural maintenance of chromosomes protein 4 (Isoform 1)	IPI00411559

SQSTM1	Sequestosome-1 (Isoform 1)	IPI00179473
STOML2	Stomatin-like protein 2	IPI00334190
SUGT1	Suppressor of G2 allele of SKP1 homolog (Isoform 2)	IPI00791573
TBRG4	Transforming growth factor beta regulator 4	IPI00329625
TOMM34	Mitochondrial import receptor, subunit TOM34	IPI00009946
TSFM	Elongation factor Ts, mitochondrial (Isoform 1)	IPI00021016
TTC1	Tetratricopeptide repeat protein 1	IPI00016912
XPNPEP1	xaa-Pro aminopeptidase 1 (Isoform 1)	IPI00645898
-	Protein of unknown function, DUF410 family protein	IPI00419575

Table 3: Proteins Up-regulated in Hypoxia at 72 Hours

Symbol	*Protein Name*	*IPI Number*
ACO1	Cytoplasmic aconitate hydratase	IPI00008485
AP1B1	AP-1 complex subunit beta-1 (Isoform A)	IPI00328257
ENAH	Protein enabled homolog (Isoform 2)	IPI00374054
FAM162A	Protein FAM162A	IPI00023001
FANCI	Fanconi anemia group I protein (Isoform 1)	IPI00019447
FUBP1	Far upstream element-binding protein 1 (Isoform 1)	IPI00375441
GIGYF2	PERQ amino acid-rich with GYF domain-containing protein 2 (Isoform 2)	IPI00647635
GLUT1	Solute carrier family 2, facilitated glucose transporter, member 1	IPI00220194
HK2	Hexokinase-2	IPI00102864
IDI1	Isopentenyl-diphosphate Delta-isomerase 1 (Isoform 1)	IPI00645307
IGFBP2	Insulin-like growth factor-binding protein 2 precursor	IPI00297284
LEPREL1	Prolyl 3-hydroxylase 2	IPI00217055
LUZP1	Leucine zipper protein 1 (Isoform 1)	IPI00296830
MAP4	Microtubule-associated protein 4 (Isoform 1)	IPI00396171
MLLT4	Afadin (Isoform 4)	IPI00023461
MOBKL3	Mps one binder kinase activator-like 3 (Isoform 1)	IPI00386122
MOGS	Mannosyl-oligosaccharide glucosidase	IPI00328170
NDUFAS	NADH dehydrogenase (ubiquinone) 1α, subcomplex 5	IPI00412545
NDUFS1	NADH-ubiquinone oxidoreductase, 75 kDa subunit	IPI00604664
P4HA1	Prolyl 4-hydroxylase subunit α-1 (Isoform 1)	IPI00009923
PLOD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (Isoform 2)	IPI00337495
RPL35A	60S ribosomal protein L35a	IPI00029731
RPRD1A	Regulation of nuclear pre-mRNA domain-containing protein 1A (Isoform 2)	IPI00062336
SAP18	Histone deacetylase complex subunit SAP18	IPI00011698
SNX3	Sorting nexin-3 (Isoform 4)	IPI00552276
TPD52	Tumor protein D52 (Isoform 1)	IPI00619958
YRDC	YrdC domain-containing protein, mitochondrial	IPI00384180

Table 4: Proteins Down-regulated in Hypoxia at 72 Hours

Symbol	*Protein Name*	*IPI Number*
ARPC1B	Actin-related protein 2/3 complex, subunit 1B	IPI00005160
BOLA2	BolA-like protein 2	IPI00301434
CDC73	Parafibromin	IPI00300659
CLASP1	CLIP-associating protein 1 (Isoform 1)	IPI00396279
COASY	Bifunctional coenzyme A synthase (Isoform 1)	IPI00184821
CTSA	Lysosomal protective protein	IPI00021794
DCTN1	Dynactin, subunit 1 (Isoform 4)	IPI00914026
DDX19A	ATP-dependent RNA helicase DDX19A	IPI00019918
DNAJA3	DnaJ homolog subfamily A member 3, mitochondrial (Isoform 2)	IPI00179187
FKBP2	Peptidyl-prolyl cis-trans isomerase FKBP2	IPI00002535
GLS	Glutaminase kidney isoform, mitochondrial (Isoform 3)	IPI00215687
H1FX	Histone H1x	IPI00021924
H3F3A	Histone H3.3	IPI00219038
IDI1	Isopentenyl-diphosphate Delta-isomerase 1 (Isoform 2)	IPI00220014
MINPP1	Multiple inositol polyphosphate phosphatase 1 (Isoform 1)	IPI00293748
MLLT4	Afadin (Isoform 3)	IPI00216505
MRPL15	39S ribosomal protein L15, mitochondrial	IPI00023086
MRPL19	39S ribosomal protein L19, mitochondrial	IPI00027096
MRPS9	28S ribosomal protein S9, mitochondrial	IPI00641924
MYO1C	Myosin-Ic (Isoform 2)	IPI00010418
PFDN4	Prefoldin, subunit 4	IPI00015891
POLR2G	DNA-directed RNA polymerase II, subunit RPB7	IPI00218895
PTK2	Focal adhesion kinase 1 (Isoform 1)	IPI00012885
SEC11A	Signal peptidase complex, catalytic subunit SEC11A	IPI00104128
SNX3	Sorting nexin-3 (Isoform 1)	IPI00815770
SPCS3	Signal peptidase complex, subunit 3	IPI00300299
TBPL1	TATA box-binding protein-like protein 1	IPI00032911
TMEM109	Transmembrane protein 109	IPI00031697
VPS26A	Vacuolar protein sorting-associated protein 26A	IPI00411426
YLPM1	YLP motif-containing protein 1	IPI00165434

3.4.3 Enzymes involved in steroid biosynthesis were up-regulated in hypoxia

Three proteins involved in biosynthesis of isoprenoids and steroid molecules were up-regulated in hypoxia (Figure 18). At 72 hours in hypoxia, there was up-regulation of Isoform 1 and down-regulation of Isoform 2 of Isopentenyl-diphosphate Delta-isomerase 1 (IPPI1), which catalyses the interconversion of isopentenyl pyrophosphate (IPP) and dimethylallyl diphosphate (DMAPP), which are both substrates for Farnesyl pyrophosphate synthase (FDPS) [121]. FDPS, which is a key branch point the isoprenoid biosynthesis pathway, was also up-regulated at 48 hours in hypoxia (Table 1). FDPS creates lipids that are incorporated into sterols, dolichols, ubiquinones and carotenoids or used as substrates for farnesylation and geranylgeranylation of proteins [122]. At 48 hours, there was up-regulation of squalene monooxygenase (SQLE), which catalyzes the first oxygenation step in sterol biosynthesis ([123]; Table 1).

3.4.4 Transcriptional regulatory proteins were expressed differently in hypoxia

Proteins involved in the regulation of transcription were up- or down-regulated in hypoxia. Far upstream element-binding protein 1, which stimulates the expression of c-Myc in undifferentiated cells by activating the far upstream element of c-Myc [124], was up-regulated at 72 hours in hypoxia (Table 3). Protein CIP2A, which prevents proteolytic degradation of c-Myc by inhibiting PP2A tumor suppressor activity towards it [125], was up-regulated at 48 hours in hypoxia (Table 1). DNA-directed RNA polymerase II, subunit RPB7, which is a subunit of RNA polymerase II that is dispensable under optimal growth conditions, but essential for transcription of specific genes when cells are in stressful environments [126], was down-regulated at 72 hours in hypoxia (Table 4).

Several transcription factors were down-regulated in hypoxia. CDK-activating kinase assembly factor MAT1 (MNAT1) was down-regulated at 48 hours (Table 2). MNAT1 forms a trimeric complex with CDK7 and cyclin H called the CAK complex [127], which associates with additional proteins to form the TFIIH basal transcription factor [128]. The transcription regulator, Pirin, which has been shown to be necessary for

terminal myeloid differentiation [129], was down-regulated at 48 hours in hypoxia. TATA box-binding protein-like protein 1 (TBPL1) was down-regulated at 72 hours (Table 4). TBPL1 is a promoter-specific recognition factor that can replace TATA binding protein in transcription regulation of specific genes [130].

3.4.5 Proteins involved in RNA processing were expressed differently in hypoxia

Some proteins involved in RNA splicing, processing, and export from the nucleus were differentially expressed in hypoxia. Pre-mRNA-splicing factor ATP-dependent RNA helicase PRP16, which is essential for catalytic step II in the pre-mRNA splicing process [131], was up-regulated at 48 hours in hypoxia (Table 1). Exosome complex exonuclease RRP42 (EXOSC7) was also up-regulated at 48 hours in hypoxia (Table 1). EXOSC7 is a component of the exosome 3'-5' exoribonuclease complex, which degrades unstable mRNAs that have AU-rich elements (AREs) in their 3'-untranslated region and it is also required for processing of 7S pre-RNA to the mature 5.8S rRNA [132]. N-α-acetyltransferase 38, NatC auxiliary subunit (NAA38), which binds to the 3'-terminal U-tract of U6 snRNA and is involved in mRNA processing and splicing [133], was down-regulated at 48 hours in hypoxia (Table 2). ATP-dependent RNA helicase DDX19A, which is an ATP-dependent RNA helicase involved in mRNA export from the nucleus [134], was down-regulated at 72 hours in hypoxia (Table 4).

3.4.6 Protein-processing enzymes were differentially expressed in hypoxia

Some enzymes involved in posttranslational processing of proteins were up- or down-regulated in hypoxia. Mannosyl-oligosaccharide glucosidase, which is the first enzyme in the N-linked oligosaccharide processing pathway, was up-regulated at 72 hours in hypoxia. This enzyme is found in the endoplasmic reticulum and it cleaves the distal glucose from Glc(3)-Man(9)-GlcNAc(2) glycosylated proteins [135].

Peptidyl-prolyl cis-trans isomerase FKBP2, which accelerates protein folding in the endoplasmic reticulum [136], was down-regulated at both 48 and 72 hours in hypoxia (Table 2 and 4). Signal peptidase complex catalytic subunit SEC11A and Signal

peptidase complex subunit 3, which are components of the signal peptidase complex that removes signal peptides from nascent proteins as they are translated into the endoplasmic reticulum [137, 138], were down-regulated at 72 hours in hypoxia (Table 4).

3.4.7 Proteins involved in cell trafficking were expressed differently in hypoxia

Proteins involved in trafficking and sorting of proteins through the Golgi and endosomes were up- or down- regulated in hypoxia. Lipopolysaccharide-responsive and beige-like anchor protein (LBRA) was up-regulated at 48 hours in hypoxia (Table 1). LRBA may be involved in coupling signal transduction and vesicle trafficking for polarized secretion and/or membrane deposition of immune effector molecules [139]. Isoform p150 of dynactin subunit 1 was up-regulated at 48 hours in hypoxia, isoform 2 of dynactin subunit 3 was down-regulated at 48 hours and isoform 4 of dynactin subunit 1 was down-regulated at 72 hours. Dynactin is involved in many cell functions, including ER-to-Golgi transport, centripetal movement of lysosomes and endosomes, spindle formation, and chromosome movement [140, 141].

Adaptor protein complex 1, subunit beta, which is involved in protein sorting in the Golgi and endosomes, was up-regulated at 72 hours in hypoxia. The AP complexes mediate the recruitment of clathrin to membranes and the recognition of sorting signals [142]. Isoform 4 of sorting nextin-3 (SNX3) was up-regulated at 72 hours in hypoxia (Table 3) and isoform 1 was down-regulated (Table 4). SNX3 is required for multivesicular body formation and plays a role in protein transport between cellular compartments [143]. Tumor protein D52, which is an adaptor protein that is involved in lysosomal membrane trafficking to and from the plasma membrane and regulation of vesicle trafficking [144], was also up-regulated at 72 hours in hypoxia.

Rab4A was down-regulated at 48 hours in hypoxia (Table 2). Rab4A is a member of the Rab family of small GTPases that regulates intracellular transport, and has been localized to early endosomes and dynein light intermediate chain 1 [145]. Dynein, light chain, roadblock-type 1, which links dynein to cargos and to adapter proteins that

regulate dynein function, was also down-regulated at 48 hours in hypoxia. Dynein 1 acts as a motor for the retrograde movement of vesicles and organelles along microtubules [146]. Vacuolar protein sorting-associated protein 26A (VPS26A) was down-regulated at 72 hours in hypoxia (Table 4). VPS26A is a necessary component of the retromer complex, which retrieves lysosomal enzyme receptors (IGF2R and M6PR) from endosomes to the trans-Golgi network [147].

Some proteins involved in the transport of proteins between mitochondria, the cytoplasm, and the nucleus, were differentially expressed in hypoxia. Nucleoporin 43 kDa (NUP43) and Nucleoporin 98 kDa (NUP98) were down-regulated at 48 hours in hypoxia (Table 2). NUP43 is responsible for assembly of a functional nuclear pore complex for transport of molecules between the nucleus and cytoplasm, and it is also required for normal kinetochore microtubule attachment, mitotic progression and chromosome segregation [148]. NUP98 is a component of the nuclear pore complex that contributes to nuclear-cytoplasmic trafficking, including mRNA export. In addition, it may play a role in gene expression, mitotic checkpoints, and pathogenesis [149]. At 48 hours, mitochondrial import receptor subunit TOM34, was down-regulated (Table 2) and Mitochondrial import receptor subunit TOM22 homolog was up-regulated (Table 1). TOM34 and TOM22 play roles in the import of pre-proteins that were synthesized in the cytosol into mitochondria [150].

3.4.8 Proteins involved in epigenetics were expressed differently in hypoxia

Several proteins associated with chromatin structure and epigenetic regulation were up- or down-regulated in hypoxic conditions. Histone H2A type 1-H was up-regulated at 48 hours in hypoxia (Table 1) and Histone H1X and H3.3 were downregulated in hypoxia at 72 hours (Table 4). Histones are core components of the nucleosome, which wraps DNA into chromatin, limiting the ability of transcription factors to access DNA [151]. Histone deacetylase complex subunit SAP18, which is a component of the SIN3-repressing complex that enhances transcriptional repression [152], was up-regulated in hypoxia at 72 hours (Table 3). Parafibromin (CDC73), which

was down-regulated at 72 hours in hypoxia (Table 4), is a component of the PAF1 complex, which activates transcription of specific genes by ubiquitinating and methylating histones [153, 154]. The PAF1 complex regulates transcription of genes involved in cell growth and survival and it is essential for normal embryonic development [155].

3.4.9 Some procollagen hydroxylases were up-regulated in hypoxia

Three enzymes that hydroxylate components of collagen were up-regulated at 72 hours in hypoxia: Prolyl 4-hydroxylase, subunit α-1 (P4HA1), Prolyl 3-hydroxylase 2 (LEPREL1), and Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2) (Table 3). P4HA1 and LEPREL1 hydroxylate prolyl residues and PLOD2 hydroxylates lysyl residues in collagen-like peptides [156]. P4HA1 and PLOD2 have been shown to be up-regulated in rat vascular smooth muscle cells cultured in hypoxia [156].

3.4.10 Proteins involved in proliferation or mitosis were differentially expressed

Some proteins that inhibit proliferation were up-regulated in hypoxia, and some proteins that are associated with increased proliferation or mitotic progression were down-regulated. Transforming growth factor beta regulator 4 (TBRG4), which may play a role in cell cycle progression [157], was down-regulated at 48 hours. NSFL1C cofactor p47, which is necessary for the fragmentation of Golgi stacks during mitosis and for reassembly of Golgi stacks after mitosis [158], was also down-regulated at 48 hours in hypoxia (Table 2). Deoxycytidylate deaminase, which creates the substrate for thymidylate synthetase to make dTMP for use in DNA synthesis and repair [159], was down-regulated at 48 hours in hypoxia (Table 2). Echinoderm microtubule-associated protein-like 4 (EML4) was down-regulated at 48 hours in hypoxia. EML4, which is highly expressed during mitosis and is associated with the mitotic spindle, is needed for correct microtubule formation [160]. Isoform 2 of structural maintenance of chromosomes protein 4 (SMC4) was up-regulated at 48 hours in hypoxia (Table 1) and isoform 1 was down-regulated at 48 hours (Table 2). SMC4 is a core component of the condensin

complex, which converts interphase chromatin into condensed chromosomes for mitosis [161]. Focal adhesion kinase 1, which is a tyrosine kinase that has been linked to increased proliferation and cell motility and decreased apoptosis [162, 163], was down-regulated at 72 hours in hypoxia (Table 4). Regulation of nuclear pre-mRNA domain-containing protein 1A, which may act as a negative regulator in G(1) phase by repressing translation of cyclin D1 and cyclin E, was up-regulated at 72 hours in hypoxia (Table 3).

Some proteins that are associated with mitotic progression were up-regulated in hypoxia. Microtubule associated protein 4 (MAP4), which contributes to the formation of a radial array of microtubules during mitosis [164], and Mps one binder kinase activator-like 3 (MOBKL3), which coordinates mitotic exit and cytokinesis [165], were up-regulated at 72 hours (Table 3).

3.4.11 Proteins involved in apoptosis were expressed differently in hypoxia

Some proteins that induce apoptosis were up-regulated in hypoxia and some proteins that suppress apoptosis were down-regulated. Exportin-2 was up-regulated at 48 hours in hypoxia (Table 1). This protein functions as a nuclear transport factor, but has also been shown to bind preferentially to p53 target promoters, which increases transcription of p53 target genes and causes increased apoptosis [166]. The negative regulator of p53, Ras GTPase-activating protein-binding protein 2 (G3BP2) was down-regulated at 48 hours in hypoxia. G3BP2 binds to p53, leading to the redistribution of p53 from the nucleus to the cytoplasm and a reduction in p53 induced apoptosis [167]. FAM162A (HGTD-P), which is a HIF-1α-responsive pro-apoptotic molecule [168], was up-regulated at 72 hours in hypoxia (Table 3). DnaJ homolog subfamily A member 3 (Isoform 2), which suppresses apoptosis by preventing cytochrome c release from the mitochondria and caspase 3 activation [169], was down-regulated at 72 hours in hypoxia (Table 4). DNAJA3 had also been shown to enhance the interaction between HIF-1α and pVHL, which destabilizes HIF-1α [170].

3.4.12 Proteins involved in autophagy were expressed differently

Sequestosome-1 (SQSTM1) was down-regulated at 48 hours in hypoxia (Table 2). SQSTM1 has multiple functions and participates in signal transduction, protein degradation and cell differentiation [171]. It has been shown to be degraded in hypoxia, not through HIF signaling or the proteasome, but through autophagy [171]. Ubiquitin-like-conjugating enzyme ATG3, which is involved in autophagy and mitochondrial homeostasis, was down-regulated at 48 hours in hypoxia (Table 2). Knockdown of ATG3 produces an expansion in mitochondrial mass [172], and rat APG3 mRNA is up-regulated by hypoxic preconditioning but down-regulated by prolonged hypoxia [173].

3.4.13 Proteins involved in translation were down-regulated in hypoxia

Proteins involved in translation in the cytoplasm were differentially expressed in hypoxia. Translation initiation factor eIF-2B subunit alpha was down-regulated at 48 hours (Table 2) and 60S ribosomal protein L35a was up-regulated at 72 hours (Table 3).

Some proteins involved in translation of mitochondrial proteins were down-regulated in hypoxia. At 48 hours, there was down-regulation of the mitochondrial ribosomal proteins: ribosomal protein S28 and ribosomal protein L19 (Table 2) and at 72 hours there was down-regulation of ribosomal protein S9, ribosomal protein L15, and ribosomal protein L19 (Table 4). Elongation factor Ts, which is a mitochondrial elongation factor [174], was down-regulated at 48 hours in hypoxia (Table 2). Pentatricopeptide repeat domain 1 (PTCD1) and Pentatricopeptide repeat domain 3, mitochondrial (PTCD3), were down-regulated at 48 hours in hypoxia (Table 2). PTCD1 and PTCD3 are predicted to be involved in the assembly of respiratory chain complexes [175], and PTCD3 has been shown to associate with the mitochondrial small ribosomal subunit and to activate mitochondrial translation [176, 177].

Cytoplasmic aconitrate hydratase (ACO1) was up-regulated at 72 hours in hypoxia (Table 3). ACO1 is an mRNA binding protein that regulates uptake, sequestration and utilization of iron when iron levels in the cell are low [178].

3.4.14 Proteins associated with cytoskeleton were up-regulated in hypoxia

Isoform 4 of Afadin was up-regulated in hypoxia at 72 hours (Table 3) and isoform 3 was down-regulated at 72 hours (Table 4). Afadin connects the adhesion molecule, nectin, to the actin cytoskeleton and is activated by Rap1 to regulate VEGF- and S1P-induced angiogenesis [179]. Protein enabled homolog, which induces the formation of F-actin rich outgrowths and links signal transduction pathways to localized actin cytoskeleton remodeling [180], was up-regulated at 72 hours in hypoxia (Table 3).

Myristoylated alanine-rich C-kinase substrate (MARCKS), which is an F-actin cross-linking protein [181], was down-regulated at 48 hours in hypoxia (Table 2). Actin-related protein 2/3 complex subunit 1B, which is a regulator of actin dynamics, was down-regulated in hypoxia at 72 hours (Table 4; [182]). CLASP1, which facilitates the recognition of actin filaments by the plus ends of growing microtubules, was also down-regulated at 72 hours in hypoxia (Table 4). Dynamic communication between actin filaments and microtubules is required for cell morphogenesis [183].

3.4.15 Proteasomal proteins were down-regulated in hypoxia

Several proteins involved in proteasomal degradation were down-regulated in hypoxia. For example, Suppressor of G2 allele of SKP1 homolog (SUGT1), which interacts with E3 ubiquitin ligase complexes and plays a role in ubiquitination and subsequent proteosomal degradation of target proteins [184], was down-regulated at 48 hours (Table 2). SUGT1 also activates the kinetochore core complex and is important for both the G_1/S and G_2/M transitions in the cell cycle [184]. Proteasome inhibitor PI31 subunit (PSMF1) was also down-regulated at 48 hours (Table 2). PSMF1 plays an important role in controlling proteasome function by inhibiting the 20S proteasome, and also by inhibiting activation of the proteasome by two regulatory proteins, PA700 and PA28 [185]. DCN1-like protein 1 (DCUN1D1) was down-regulated at 48 hours in hypoxia (Table 2). DCUN1D1 is part of an E3 ubiquitin ligase complex for neddylation, and is involved in nuclear localization of neddylation components [186].

Chapter 4: Discussion

Hypoxia has been shown to promote pluripotency in hESCs, but the mechanism by which this occurs in unknown [52]. To gain insight into this mechanism, we investigated differences in protein expression between hESCs cultured in 1% oxygen and hESCs cultured in 20% oxygen for 48 and 72 hours. Interesting changes were observed in the expression of proteins involved in metabolism, post-transcriptional modification, chromatin modification and regulation of the transcription factor, c-Myc.

4.1 Establishment of a model to study the effects of oxygen in the regulation of pluripotency

The experimental model used in this study was developed to investigate the effect of hypoxia versus normoxia on hESCs that were cultured in unchanged media for up to three days. The objective of leaving the media unchanged was to promote differentiation so that differences in pluripotency between hESCs cultured in hypoxia and normoxia could be observed. hESCs were studied after 48 and 72 hours in the experimental system in order to observe changes in protein expression just as the cells in normoxia were beginning to differentiate. In order to validate the experimental model, immunofluoresence localization of Oct-4 was performed to assess the pluripotency of hESCs after 48 and 72 hours in the experiment. Western blot analysis was performed for HIF-1α to confirm that a difference in protein expression between the experimental oxygen conditions could be observed for a protein known to be regulated by hypoxia.

At 48 hours, almost all hESC colonies that had been cultured in either oxygen condition were morphologically pluripotent. However, immunofluorescent detection of Oct-4 revealed that there was significantly more differentiation in cultures that had been incubated at 20% oxygen than in cultures that had been incubated in 1% oxygen. At 72 hours, cultures that had been maintained in 20% oxygen contained notably more morphologically differentiated colonies than cultures that had been maintained in 1%

oxygen. Moreover, immunofluorescent detection of Oct-4 revealed that this difference was significant. These results demonstrate that hESCs in our system survive in both oxygen concentrations, but cultures incubated in 1% oxygen contain more pluripotent cells than cultures incubated in 20% at both 48 and 72 hours. By observation with a phase-contrast microscope, there was not a qualitative difference in proliferation between hESCs cultured in 1% oxygen and hESCs cultured in 20% oxygen. This agrees with the findings of Ezashi *et al.* that hESCs cultured for 12 days in 1-5% oxygen are more pluripotent than hESCs cultured in atmospheric oxygen and that there is no difference in average colony size between the conditions [52]. However, it differs from the observations of Zachar *et al.* and Prasad *et al.*, which are that 1% oxygen inhibits hESC growth [53, 54].

Real-time RT-PCR analysis showed that there was no significant difference in mRNA levels of Oct-4, Nanog, Nodal or HIF-1α in hESCs cultured in 1% oxygen versus hESCs cultured in 20% oxygen at both 48 and 72 hours. This agrees with the findings of Westfall *et al.*, who used microarray analysis to compare mRNA expression of hESCs cultured at 4% oxygen to mRNA expression of hESCs cultured at 20% oxygen for seven days. Their results revealed that there is no change in the transcript level of Oct4, Nanog, or HIF-1α and there is no change or a mild increase in Nodal transcript levels [55]. It has been shown for many genes that there is not a direct correlation between changes in mRNA expression and changes in the corresponding protein levels during stem cell differentiation [187]. This is because protein levels are influenced by post-transcriptional factors, such as stability of mRNA, rate of translation, and rate of protein degradation. Since proteins are the effectors of cellular processes, it is important to investigate hESC expression at the protein level as well as the transcript level [85].

Although real-time RT-PCR analysis revealed that there is no change in HIF-1α mRNA levels when hESCs are cultured in hypoxia, Western blot analysis revealed that HIF-1α protein expression was up-regulated in hypoxia at both 48 and 72 hours. It is not surprising that a difference in HIF-1α expression is observed in the proteome, but not in the transcriptome, because HIF-1α is largely regulated at the protein level. In hypoxia,

HIF-1α is stabilized and forms a heterodimer with the constitutively expressed protein, HIF-1β. In the presence of increased oxygen concentration, HIF-1α is hydroxylated by prolyl-hydroxylase domain enzymes, which are only active in the presence of oxygen [47]. Hydroxylated HIF-1α is subsequently marked for proteosomal degradation.

4.2 Hypoxia influenced the expression of some metabolic proteins

When oxygen is available, most human cells rely on mitochondrial oxidative phosphorylation to produce ATP; however, in hypoxia, cells have the ability to use glycolysis as a primary source of ATP because oxygen is not available to be a terminal electron acceptor in the electron transport chain (ETC) [188]. Thus, it is not surprising that HIF-1α acts as a transcription factor for many rate-limiting glycolytic enzymes and transporters [189]. Interestingly, it only up-regulates specific isoforms of each of the glycolytic proteins that it modulates [189].

Hexokinase-2, which catalyses the first committed step of glycolysis [107], was up-regulated in hypoxia at both 48 and 72 hours. Hexokinase-1 and -2 are special isoforms of hexokinase that have the ability to bind to the external mitochondrial membrane in order to inhibit apoptosis by blocking cytochrome c release [190] and to ensure that mitochondrial ATP is used for glucose phosphorylation [191]. It is known that the Hexokinase-2 promoter contains an HRE and that its gene expression is activated by HIF-1α [192]. It is also known that Hexokinase-2 is increased at the transcript level in hESCs cultured in hypoxia [55]. Other transcription factors and growth factors that modulate hexokinase-2 expression and activity include: insulin growth factor, c-Myc, glucagon, and cAMP [193]. Hexokinase-2 is the principal regulated isoform of hexokinase in many cell types and it is up-regulated in many cancers [189]. Its depletion in cancer cells results in decreased proliferation and angiogenesis as well as diminished expression of HIF-1α and VEGF, and its over-expression leads to increased proliferation and therapeutic resistance [194].

GLUT1, which transports glucose across the plasma membrane [108], was up-regulated at both 48 hours and 72 hours in hypoxia. It is known that GLUT1 is up-

regulated at the transcript level in hESCs cultured in hypoxia [55] and its expression is directly regulated by HIF-1α [195]. GLUT1 is a rate-limiting transporter for glucose uptake [196] and it is the most widely over-expressed glucose transporter in proliferative cancer cells [197]. It has been suggested that GLUT1 is over-expressed in cancer cells because it has a higher affinity for glucose than other glucose transporters [198].

Pyruvate dehydrogenase E1α 1 (PDHA1) precursor was down-regulated at 48 hours in hypoxia. Down-regulation of PDHA1, which catalyzes the conversion of pyruvate to acetyl-CoA and CO_2, reduces the delivery of acetyl-CoA to the tricarboxylic acid cycle, thus reducing transfer of electrons to the ETC [109]. It is known that pyruvate dehydrogenase kinase 1 (PDK1) is up-regulated by HIF-1α, which results in decreased activity of PDHA1 [109]; however, it has not been shown previously that PDHA1 protein expression is decreased in hypoxia. Together, these data suggest that hypoxia triggers up-regulation of isoforms of key glycolytic enzymes that increase flux through the glycolytic pathway and it promotes down-regulation of PDHA1 to limit entry into aerobic metabolism.

Low oxygen levels cause an increase in the generation of reactive oxygen species (ROS) in mitochondria by respiratory complexes I and III [188, 199]. It has been hypothesized that the increased concentration of ROS induces oxidation of Fe^{2+} to Fe^{3+}, which cannot be used as a cofactor for PHD to hydroxylate HIF-1α for degradation [200]. In agreement with this hypothesis, HIF-1α is hydroxylated and degraded in hypoxia in cells that have been treated with anti-oxidants [201]. Two components of Complex I of the electron transport chain were up-regulated at 72 hours in hypoxia. Up-regulation of Complex I subunits may be necessary for continuous ROS production and subsequent stabilization of HIF during hypoxia.

The presence of ROS in hypoxic conditions induces phosphorylation of the protein kinase, MAPK14 [202], which was up-regulated at 48 hours in hypoxia in this proteomic analysis. A common feature of cancer cells, which tend to reside in poorly vascularized hypoxic tumors, is the increased use of glycolysis to produce ATP, even in

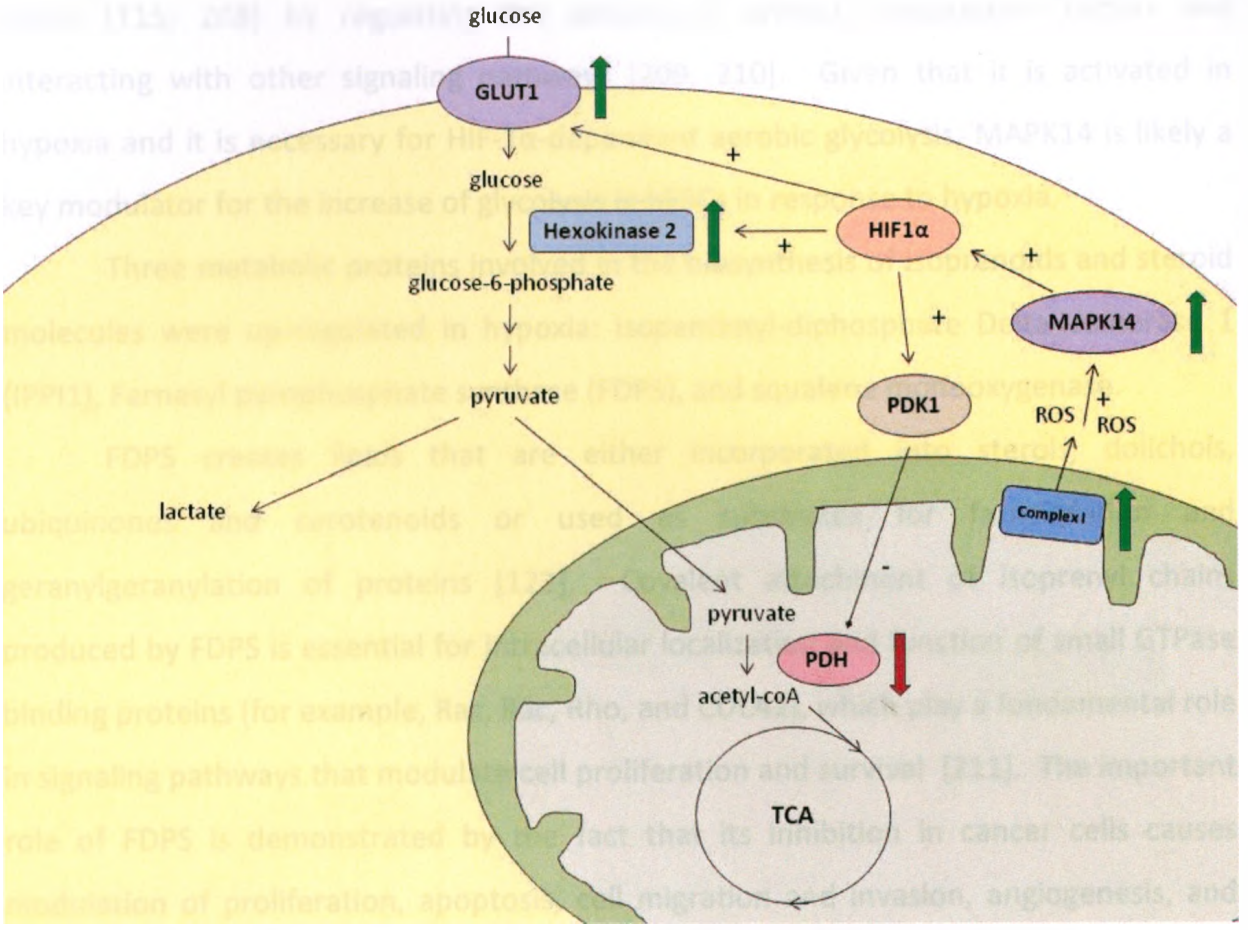

Figure 19. Metabolic proteins that were differentially expressed in hypoxia. Several proteins that play key roles in glycolysis or entry into the tricarboxylic acid cycle (TCA) showed increased (green arrows) or decreased (red arrows) expression in hypoxia. GLUT1: Solute carrier family 2, facilitated glucose transporter, member 1, PDK1: pyruvate dehydrogense kinase isozyme 1, HIF: hypoxia inducible factor, PDH: pyruvate dehydrogenase, MAPK14: mitogen activated protein kinase 14, ROS: reactive oxygen species.

the presence of oxygen [203]. This is called aerobic glycolysis, and it is largely sustained through the stabilization and activation of HIF-1α in normoxia [204]. MAPK14 is necessary for HIF-1α-dependent aerobic glycolysis, as inhibition of MAPK14 results in decreased levels of HIF-1α and HIF-1α target genes, such as GLUT1 and hexokinase 2 [205]. MAPK14 has also been shown to stabilize HIF-1α in hypoxic conditions [206, 207]. The MAPK14 pathway plays a role in proliferation, differentiation, metabolism and cell death [115, 208] by regulating the activity of several transcription factors and interacting with other signaling pathways [209, 210]. Given that it is activated in hypoxia and it is necessary for HIF-1α-dependent aerobic glycolysis, MAPK14 is likely a key modulator for the increase of glycolysis in hESCs in response to hypoxia.

Three metabolic proteins involved in the biosynthesis of isoprenoids and steroid molecules were up-regulated in hypoxia: Isopentenyl-diphosphate Delta-isomerase 1 (IPPI1), Farnesyl pyrophosphate synthase (FDPS), and squalene monooxygenase.

FDPS creates lipids that are either incorporated into sterols, dolichols, ubiquinones and carotenoids or used as substrates for farnesylation and geranylgeranylation of proteins [122]. Covalent attachment of isoprenyl chains produced by FDPS is essential for intracellular localization and function of small GTPase binding proteins (for example, Ras, Rac, Rho, and CDC42), which play a fundamental role in signaling pathways that modulate cell proliferation and survival [211]. The important role of FDPS is demonstrated by the fact that its inhibition in cancer cells causes modulation of proliferation, apoptosis, cell migration and invasion, angiogenesis, and tumor-mediated immunosuppression. Inhibition of FDPS is known to cause a reduction is several signaling pathways, including TGF-β signaling [212]. FDPS inhibition has also been shown to suppress the accumulation of HIF-1α in response to IGF-1 stimulation in part by increasing degradation of HIF-1α [213]. This suggests a potential role for the isoprenoid biosynthesis pathway, particularly FDPS, in modulating the cell's response to hypoxia by slowing degradation of HIF-1α.

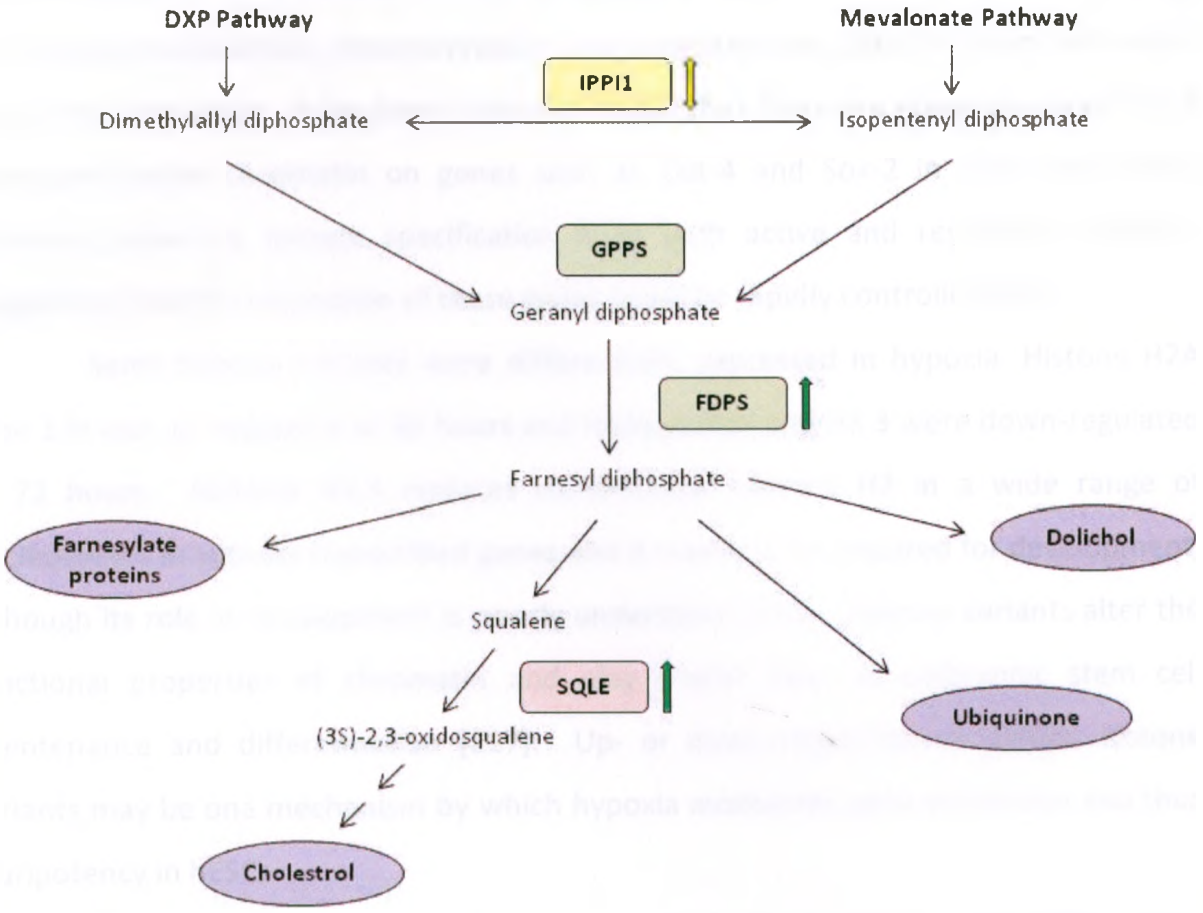

Figure 20. Hypoxic up-regulation of proteins involved in steroid biosynthesis. Several proteins involved in isoprenoid and steroid biosynthesis showed increased expression (green arrows) or differential expression of isoforms (yellow arrows) in hypoxia. IPPI1: isopentenyl diphosphate isomerase, GPPS: geranyl diphosphate synthase, FDPS: farnesyl pyrophosphate synthase, SQLE: squaline monooxygenase.

4.3 Hypoxia influenced the expression of some proteins involved in chromatin modification

Pluripotent hESCs maintain a wide open chromatin structure, which is selectively condensed as differentiation down a particular lineage progresses [214]. This process is directed by epigenetic modifications, which control gene expression without changing DNA sequence. The histone family of proteins, which can be modified through acetylation, methylation, phosphorylation, and ubiquitination, plays an important role in epigenetic regulation. It has been shown in mESCs that there are epigenetic markers of open and active chromatin on genes such as Oct-4 and Sox-2 in early replication, whereas genes for lineage specification have both active and repressive markers, suggesting that the expression of these genes could be rapidly controlled [215].

Some histone variants were differentially expressed in hypoxia. Histone H2A type 1-H was up-regulated at 48 hours and Histone H1X and H3.3 were down-regulated at 72 hours. Histone H3.3 replaces conventional Histone H3 in a wide range of nucleosomes in actively transcribed genes and it seems to be required for development, although its role in development is poorly understood [216]. Histone variants alter the functional properties of chromatin and play crucial roles in embryonic stem cell maintenance and differentiation [217]. Up- or down-regulation of specific histone variants may be one mechanism by which hypoxia modulates gene expression and thus pluripotency in hESCs.

Two proteins that modify epigenetic labels of histones were differentially expressed in hypoxia. Histone deacetylase complex subunit SAP18, which is a component of the SIN3-repressing complex that enhances transcriptional repression [152], was up-regulated at 72 hours. Parafibromin was down-regulated at 72 hours in hypoxia. Parafibromin is a component of the PAF1 complex, which activates transcription of specific genes by ubiquitinating and methylating histones [153, 154]. The PAF1 complex regulates transcription of genes involved in cell growth and survival and it is essential for normal embryonic development [155]. The differential expression of these proteins may promote pluripotency in hypoxia by adjusting epigenetic marks in such a way as to reduce transcription of genes associated with differentiation.

The actin cytoskeleton has an essential role in cell migration, determination of cell shape and polarity, and protein and organelle trafficking [218]. It is now generally accepted that actin also has a role in transcription and transcriptional regulation through several mechanisms [219]. Actin is a member of several chromatin remodeling and HAT complexes and is essential for the function of these complexes in transcriptional activation [218, 220]. It also physically interacts with all three RNA polymerases and this interaction is necessary for transcription *in vitro* and *in vivo* [218, 220]. Monomeric actin regulates gene transcription by binding to specific transcription factors and targeting them for the cytoplasm. It is suggested that actin polymerization may regulate gene transcription by affecting the concentration of monomeric actin that is available to interact with nuclear components.

The highly dynamic organization of actin is controlled by environmental signals that activate signaling pathways and actin-regulatory proteins [221]. In hypoxia, there was up-regulation of protein enabled homolog, which induces the formation of F-actin rich outgrowths and links signal transduction pathways to localized actin cytoskeleton remodeling [180]. There was also down-regulation of MARCKS, which is an F-actin cross-linking protein [181], and Actin-related protein 2/3, which is a regulator of actin dynamics [182]. This suggests that hypoxia may promote pluripotency in hESCs in part by up-regulating actin regulatory proteins, which in turn affect chromatin remodeling and transcription in the nucleus. Very little is known about actin function in nuclear processes and more research must be done to confirm this idea.

4.4 Some proteins that regulate c-Myc expression or activity were up-regulated in hypoxia

As cells progress through the multistage process of differentiation, they selectively activate and silence sets of genes in order to acquire specific functions and lose self-renewal capacity. These changes in gene expression are coordinated by the action of many transcription factors that have temporal and cell-type specific expression [222]. The transcription factor, c-Myc has been implicated in the modulation of many

cell functions, including cell cycle regulation, proliferation, growth, differentiation, and metabolism [223]. It acts as a transcription factor for an extremely large number of genes – perhaps 15% of genes in the genome [224]. Two proteins that are associated with increased levels of c-Myc were up-regulated in hypoxia. Protein CIP2A, which prevents proteolytic degradation of c-Myc by inhibiting PP2A tumor suppressor activity towards it [125], was up-regulated at 48 hours. Over-expression of CIP2A promotes Ras-elicited cell growth and knock-down of CIP2A correlates with differentiation of neural progenitor cells [225]. FUBP1, which stimulates the expression of c-Myc in undifferentiated cells by activating the far upstream element of c-Myc [124], was up-regulated at 72 hours. c-Myc is one of only four proteins needed to reprogram differentiated cells to iPSCs, indicating its important role in promoting the pluripotent state of human cells. Therefore, the up-regulation of Protein CIP2A and FUBP1 in hypoxia may result in the maintenance of pluripotency through up-regulation of c-Myc.

4.5 Proteins involved in post-transcriptional modification were differentially expressed in hypoxia

Protein expression and activity are regulated at many levels beyond transcription, including RNA splicing, translation, protein trafficking, and proteasomal degradation. Alternative splicing, a process in which the exons of an RNA transcript are connected in different combinations during RNA splicing, provides a flexible mechanism through which cells can generate proteins with different properties [226]. The resulting mRNAs may be translated into different isoforms of a protein. For example, a change in splice isoforms from the adult pyruvate kinase muscle 1 (PKM1) to the fetal PKM2, is observed in lung cancer cell lines and this change is believed to promote aerobic glycolysis and tumor growth [227]. Many human genes are known to be alternatively spliced in response to hypoxia, and in some cases this has been shown to be regulated by HIF-1α [228-231]. In this study, some proteins involved in RNA splicing were differentially expressed in hypoxia. PRP16, which is essential for catalytic step II in the pre-mRNA splicing process [131], and EXOSC7, which is a component of the exosome 3'-

5' exoribonuclease complex that degrades unstable mRNAs [132], were up-regulated at 48 hours. NAA38, which binds to the 3'-terminal U-tract of U6 snRNA and is involved in mRNA processing and splicing [133], was down-regulated at 48 hours. NAA38 has been shown to be regulated by hypoxia in human retina cells [232]. In response to environmental stress, cells use alternative splicing to rapidly and specifically alter gene expression [233]. It is possible that these RNA splicing proteins were up- or down-regulated in response to hypoxia in order to facilitate splicing of genes that mediate the cell's response to hypoxia.

Several proteins that were differentially expressed in hypoxia in this study displayed up-regulation of one isoform alongside down-regulation of another isoform (see Tables 1-4). One example is serine/threonine-protein phosphatase PP1-α, catalytic subunit, which has three different isoforms that are generated through alternative splicing. For most of the proteins that had differential expression of isoforms, little information is available on differences in function between the isoforms. It would be interesting to investigate whether these proteins are spliced differently in response to hypoxia, and whether these changes promote pluripotency.

In order to survive in hypoxia, cells must suppress their metabolic rate to a level that can be sustained with the ATP produced through glycolysis alone [234]. The most energy consuming process in cells is translation of mRNA into protein; therefore, it is not surprising that protein synthesis is globally reduced in hypoxia [235]. In addition, cells can respond to environmental stimuli more rapidly when changes in gene expression are targeted at translation rather than transcription, as protein synthesis is thought to be the rate limiting step in gene expression [236, 237]. Severe hypoxia has been shown to cause a rapid decline in protein synthesis from about 30% of the cell's energy expenditure to about 7% [238]. Global regulation of protein synthesis is largely accomplished through the modification of translation initiation factors [239]. In hypoxia, short term inhibition of translation occurs through phosphorylation eIF-2α, which inhibits GDP-GTP exchange catalyzed by eIF-2B, thus halting initiation of translation [240, 241]. In this proteomic analysis, translation initiation factor eIF-2B

subunit α was down-regulated at 48 hours in hypoxia. This result suggests that hypoxia may also decrease global protein expression through down-regulation of eIF-2B.

Some proteins involved in translation of mitochondrial proteins were down-regulated in hypoxia. At 48 hours, there was down-regulation of the mitochondrial ribosomal proteins: S28 and L19 and at 72 hours there was down-regulation of S9, L15, and L19. Elongation factor Ts, which is a mitochondrial elongation factor [174], and PTCD1 and PTCD3, which are predicted to be involved in the assembly of respiratory chain complexes [175], were down-regulated at 48 hours. PTCD3 can additionally associate with the mitochondrial small ribosomal subunit to activate mitochondrial translation [176, 177]. These results complement the theory that protein expression is globally decreased in hypoxia and also suggest that there may be a particularly large decrease in expression of proteins associated with mitochondria, which are mostly inactive in hypoxia. Anaerobic energy production in a human cell causes the production of lactic acid, which is secreted from the cell and causes extracellular acidosis. Increased production of H^+ ions during hypoxia promotes interactions between the von Hippel-Lindau tumor suppressor protein and rRNA genes, resulting in a reduction of rRNA synthesis [242].

Numerous proteins involved in cell trafficking through endosomes, vesicles, and the Golgi aparatus were differentially expressed in hypoxia. Little is known about the role of these proteins in the response to hypoxia or differentiation of stem cells. They may have a role in the response to hypoxia by processing, degrading, secreting, localizing, and endocytosing proteins that have a role in pluripotency or differentiation. For example, Rab4A, which is a member of the Rab family of small GTPases that regulates intracellular transport [145], was down-regulated at 48 hours. Rab4A has an interesting role in the activity of plasma membrane receptors. After activation, many receptors are endocytosed and sorted through endosomes to the lysosome for proteolytic degradation. However, some receptors in Rab4a-positive endosomes are recycled back to the plasma membrane, rather than sent to the lysosome [243-245]. Additionally, VEGF receptor 2 has been shown to stimulate MAPK signaling from the

endosome during this recycling process [243]. Therefore, down-regulation of Rab4A in hypoxia may result in decreased signaling from the receptors that are recycled in a Rab4A dependent manner.

Several proteins involved in proteasomal degradation were down-regulated at 48 hours in hypoxia. These include: SUGT1, which plays a role in ubiquitination and subsequent proteosomal degradation of target proteins [184], PSMF1, which controls proteasome function by inhibiting the 20S proteasome, and also by inhibiting activation of the proteasome by two regulatory proteins, PA700 and PA28 [185], and DCUN1D1, which is part of an E3 ubiquitin ligase complex for neddylation of target proteins [186]. The proteasome ultimately degrades most intracellular proteins in a highly regulated fashion; therefore, it has a crucial role in the regulation of cellular processes such as cell cycle progression, proliferation, differentiation, angiogenesis and apoptosis [246].

The fact that proteins that regulate translation, protein trafficking, and protein degradation were expressed differently in hypoxia strengthens the notion that changes in protein expression in hypoxia do not directly correlate with changes in transcript levels. This highlights the necessity of looking for changes in gene expression at the level of the proteome in addition to the transcriptome.

4.6 Some proteins that require oxygen as a substrate were differentially expressed in hypoxia

The synthesis of collagen deposits involves many steps, including procollagen protein synthesis, prolyl hydroxylation, lysyl hydroxylation, and covalent cross-bridging between collagen fibres [247]. Two enzymes that hydroxylate prolyl residues in collagen, P4HA1 and LEPREL1, were up-regulated at 72 hours in hypoxia. Although prolyl hydroxylation is required for both collagen synthesis and for the stability of HIF-1α protein, different prolyl hydroxylases perform these functions [248], and P4HA1 and LEPREL1 do not accept HIF1-α as a substrate [249]. P4HA1 is essential for triple helix formation and has been shown to be up-regulated in hypoxia in fetal lung fibroblasts in a HIF-1α-dependent manner [250]. The prolyl hydroxylase, LEPREL1, has not previously been shown to be up-regulated in hypoxia.

During the maturation of procollagen, lysine residues must also be hydroxylated, and this is performed by procollagen lysyl-hydroxylases [251]. The procollagen lysyl-hydroxylase, PROD2 was up-regulated at 72 hours in hypoxia. Hypoxia has been shown to stimulate the expression of several hydroxylases, including P4HA1 and PROD2, in a HIF-1α dependent mechanism in rat vascular smooth muscle cells [156].

All of the collagen hydroxylases use oxygen directly as a substrate [252]. These enzymes may be up-regulated in hypoxia because (a) collagen formation must be increased in hypoxic tissues, or (b) because the concentration of enzyme must increase in order to maintain a normal rate of procollagen hydroxylation in the presence of decreased oxygen substrate. The latter hypothesis is supported by the observation that only components of collagen synthesis that depend on oxygen as a substrate are up-regulated in hypoxia, whereas other components, such as procollagen (Iα) are not up-regulated by hypoxia [156]. Together, these results suggest that hypoxia stimulates the expression of a group of hydroxylases that are essential for collagen fiber formation in order to compensate for the lack of oxygen molecules available for use as substrates.

In hypoxia, the high affinity of cytochrome oxidase for oxygen means that the majority of available oxygen is sequestered by the ETC, leaving little in the cytosol for dioxygenases, such as prolyl hydroxylases, which require oxygen as a substrate [253]. The consumption of oxygen by the ETC may be regulated by the endogenous gas, nitric oxide (NO). NO competitively inhibits cytochrome oxidase by competing for binding with molecular oxygen [254]. Arginase-2, which is an inducible mitochondrial protein that inhibits the production of NO [113], was down-regulated at 48 hours in hypoxia. Reduction of Arginase 2 may allow for the production of NO, which can limit binding of oxygen to the ETC in hypoxic conditions.

4.7 Proteins associated with proliferation and apoptosis were differentially expressed in hypoxia

Some proteins that inhibit proliferation were up-regulated in hypoxia, and some proteins that are associated with increased proliferation or mitotic progression were

down-regulated. Regulation of nuclear pre-mRNA domain-containing protein 1A, which may act as a negative regulator in G(1) phase by repressing translation of cyclin D1 and cyclin E, was up-regulated at 72 hours in hypoxia. EML4, which is highly expressed during mitosis and is needed for proper microtubule formation [160], was down-regulated at 48 hours. TBRG4, which may play a role in cell cycle progression [157], was also down-regulated at 48 hours in hypoxia. Other proteins that were down-regulated at 48 hours include: NSFL1C cofactor p47, which is necessary for the fragmentation of Golgi stacks during mitosis and for reassembly of Golgi stacks after mitosis [158], and deoxycytidylate deaminase, which creates the substrate for thymidylate synthetase to make dTMP for use in DNA synthesis and repair [159]. At 48 hours, isoform 2 of SMC4 was up-regulated and isoform 1 was down-regulated. SMC4 is a core component of the condensin complex, which converts interphase chromatin into condensed chromosomes for mitosis [161]. Focal adhesion kinase 1, which is a tyrosine kinase that has been linked to increased proliferation and cell motility and decreased apoptosis [162, 163], was down-regulated at 72 hours.

These results correspond with the findings of two studies of the long term culture of hESCs in hypoxia, which showed that the rate of proliferation of hESCs is significantly higher in normoxia than in hypoxia [53, 54]. Since hESCs must switch from aerobic metabolism to glycolysis in hypoxia, which results in significantly less ATP production per glucose molecule, they must also suppress their metabolic rate and growth to a level that can be sustained with the ATP produced through glycolysis alone [234].

Most genes that are up-regulated by HIF-1α promote cell survival in hypoxic conditions, such as genes that increase oxygen availability or ATP production through glycolysis. Paradoxically, HIF-1α also participates in hypoxic cell death through interaction with the pro-apoptotic transcription factor, p53 and by up-regulating other pro-apoptotic factors [255, 256]. In tolerable hypoxia, anti-apoptotic Bcl-2 family proteins prevent cell death by stabilizing mitochondria or inhibiting caspase activation;

however, in the case of severe cell damage caused by hypoxia beyond the cell's adaptive capacity, apoptosis-promoting genes are expressed [257].

Some proteins that promote apoptosis were up-regulated in hypoxia, and some proteins that inhibit apoptosis were down-regulated. The pro-apoptotic molecule, FAM162A, was up-regulated at 72 hours in hypoxia. FAM162A facilitates cell death by induction of the mitochondrial permeability transition (PT), and its transcription is known to be up-regulated by the binding of HIF-1α to its promoter [168]. Exportin-2, which binds to p53 target promoters to increase transcription of p53 target genes and increase apoptosis [166], was up-regulated at 48 hours in hypoxia. The negative regulator of p53, Ras GTPase-activating protein-binding protein 2 (G3BP2) [167], was down-regulated at 48 hours and DNAJA3, which suppresses apoptosis by preventing cytochrome c release and caspase 3 activation [169], was down-regulated at 72 hours. DNAJA3 had also been shown to enhance the interaction between HIF-1α and VHL, leading to HIF-1α degradation [170].

These results suggest that there may have been increased apoptosis in the hESCs cultured at 1% oxygen, although no cell death was observed by phase contrast microscopy. In a study that compared the effects of hypoxia on hESCs cultured in 1%, 5%, 10%, 15% or 20% oxygen for four weeks, most of the colonies in 1% oxygen did not survive beyond 2 weeks [54]. Since hypoxia up to 5% oxygen has been shown to promote pluripotency in hESCs [52] , and the natural environment of hESCs is closer to 2% [28], culture of hESCs above 1% oxygen but below 5% oxygen may be ideal to promote pluripotency, but prevent apoptosis.

4.8 Suggestions for future experiments

In this study, immunofluoresence localization of Oct-4 was used to determine the percentage of colonies that were differentiating in each oxygen condition. This technique gave an approximate estimation of the percentage of cells that had differentiated, but since some colonies may have had larger patches of differentiation than others, it would be more accurate to determine the percentage of differentiated

cells by measuring the cells individually. This could be achieved by incubating the cells with an antibody against SSEA-4, which is a cell surface marker of pluripotency, and then performing flow cytometry.

Some studies have shown that hypoxia does not affect the rate of proliferation of stem cells, while others have shown that it does (discussed in section 1.3). Proliferation is likely affected by the degree of hypoxia, duration of incubation, and whether the cells are occasionally exposed to oxygen when the incubator door is opened. In order to determine the best culture conditions for hESCs, a study should be performed to determine whether hypoxia does in fact slow proliferation, and under what circumstances this happens.

Dramatic changes were observed in the number of peptides identified for some proteins. For example, Far upstream element-binding protein 1 was not detected in any replicates of hESCs that had been cultured in normoxia, but 8, 3, 9, 8, 10, and 6 peptides were identified in the six replicates of hESCs cultured in hypoxia for 72 hours. For other proteins, the changes in number of peptides were more subtle. For example, RRP4S was not detected in any replicates of hESCs that had been cultured in normoxia, but 2, 1, 2, 1, 1, and 2 peptides were identified in the six replicates of hESCs cultured in hypoxia for 48 hours. Further experiments that utilize Western blotting, selected reaction monitoring, or shotgun MS/MS with isotopic labeling should be performed to confirm that some of the proteins identified in this study are in fact differentially expressed.

Selected reaction monitoring (SRM) is a highly selective and sensitive MS technique that can be used for precise and accurate quantification of low-abundance proteins in complex proteomics samples [258]. In this technique, specific precursor ions are selected and fragmented and a few specific fragments are monitored for detection and quantification purposes [259]. SRM is emerging in proteomics as an excellent method to complement shotgun qualitative studies [259].

As discussed in section 1.5.3, accurate quantitative information can be obtained in shotgun proteomics experiments through stable isotopic labeling using SILAC or iTRAQ. These methods allow minute changes between cellular states to be monitored

over time. Since label free MS was used in this study, changes in protein expression were only detected if the difference was large. In future experiments, SILAC or iTRAQ should be used to quantitatively compare protein expression so that more subtle changes in protein expression can be identified.

The importance of candidate proteins such as FUBP1, CIP2A, and MAPK14 in the maintenance of pluripotency can be determined through genetic knock-down of each protein of interest, followed by culture in hypoxia and normoxia.

A major challenge in shotgun proteomics is to identify as many peptides as possible in an LC-MS/MS run. Many proteins known to be present in the hESC proteome, such as Oct-4, Nanog, Nodal and HIF-1α were not identified by MS/MS in this study. Primary reasons for missed peptide identifications are limitations in sequencing speed and sensitivity of mass spectrometers and the very high complexity of proteomics samples [73]. Another major factor is that the resolution of quadrupoles and ion traps is not high enough to separate all precursor ions, which leads to cofragmentation of precursor ions that are present in the same window [260]. Because of these limitations, even state-of-the-art mass spectrometers do not identify a large percentage of peptides in complex proteomics samples [73]. It is likely that proteins in addition to the ones identified in this study are differentially expressed in hypoxia, but were not identified due to limitations of the experimental technology.

There was little overlap between the proteins expressed differently at 48 hours and the proteins expressed differently at 72 hours, which may be in part due to dynamic regulation of gene expression in the first 72 hours of exposure to hypoxia. Another possibility is that the protein was differentially expressed at both time points, but this change was only detected at one time point due to aforementioned limitations of shotgun proteomics. Since the regulation of gene expression in hESCs after exposure to hypoxia is dynamic, it would be useful to measure protein expression at more frequent time points in future studies, for example every 12 hours for 72 hours over the course of the experiment.

Another important extension of this experiment would be to measure differences in posttranslational modifications, such as phosphorylation of proteins expressed in hESCs cultured under hypoxia versus normoxia. This would provide more insight into the mechanism by which hypoxia promotes pluripotency in hESCs as posttranslational modifications play an important role in the activity or localization of proteins. It would also be interesting to investigate which proteins are up-regulated in hypoxia from specific protein fractions, such as extracellular proteins or nuclear proteins.

4.9 Conclusion

In this study, shotgun proteomics was used for the first time to investigate changes in protein expression that occur when hESCs are cultured in hypoxia. In addition, a new experimental system was developed to compare the pluripotency of hESCs cultured in hypoxia to that of hESCs cultured in normoxia. Many changes in protein expression were observed in hypoxia, particularly in proteins involved in metabolism, chromatin remodeling, post-transcriptional modification, and regulation of c-Myc.

Many experiments and therapeutic applications of hESCs require the cells to be pluripotent [261]. Knowing which proteins are expressed differently in hypoxia and therefore, which proteins may promote pluripotency is important for the development of methods to maintain hESC pluripotency and prevent differentiation in culture [262]. In addition, cancer cells are often exposed to a hypoxic microenvironment due to poor vascularisation of tumors, which is associated with increased invasion and metastatic potential of the cells. The identification of proteins that are expressed differently under hypoxic conditions may be useful for the development of therapeutic strategies to target invasive cells in tumors. This knowledge will also improve our understanding of the ability of hESCs to remain pluripotent during their pre-implantation development in the hypoxic reproductive tract.

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Appendix A *Proteins up-regulated in hypoxia at 48 hours*

Protein Name	Peptide IDs, H9 replicates, 1% O_2			Peptide IDs, CA1 replicates, 1% O_2			Peptide IDs, H9 replicates, 20% O_2			Peptide IDs, CA1 replicates, 20% O_2		
Actin-like protein (Fragment)	2	2	1	2	1	0	0	0	0	0	0	0
Alanyl-tRNA synthetase	0	2	1	5	3	2	0	0	0	0	0	0
Dynactin, subunit 1 (Isoform p150)	7	2	4	2	7	4	3	0	1	0	0	0
Exosome complex exonuclease RRP42	2	1	2	1	1	2	0	0	0	0	0	0
Exportin-2 (Isoform 1)	2	1	0	4	2	0	0	0	0	0	0	0
Farnesyl pyrophosphate synthase	7	4	10	6	7	2	0	0	0	4	4	5
Hexokinase-2	10	12	5	5	3	1	3	3	1	1	1	2
Histone H2A type 1-H	1	4	12	11	5	2	0	0	0	0	0	0
Lipopolysaccharide-responsive and beige-like anchor protein (Isoform 1)	2	2	2	1	4	0	0	0	0	0	0	0
Mitochondrial import receptor subunit, TOM22 homolog	2	0	1	2	5	2	0	0	0	0	0	0
Mitogen-activated protein kinase 14 (Isoform CSBP2)	3	2	0	5	0	1	0	0	0	0	0	0
Pre-mRNA-splicing factor ATP-dependent RNA helicase PRP16	2	1	0	2	0	1	0	0	0	0	0	0
Protein CIP2A (Isoform 1)	3	1	0	2	2	0	0	0	0	0	0	0
Protein FAM96B	3	0	1	2	1	0	0	0	0	0	0	0
Serine/threonine-protein phosphatase PP1-α, catalytic subunit (Isoform 3)	12	8	9	10	10	7	0	0	0	0	0	0
Solute carrier family 2, facilitated glucose transporter, member 1	6	4	3	4	3	1	2	0	0	2	2	0
Squalene monooxygenase	2	1	2	1	4	0	0	0	0	0	0	0
Structural maintenance of chromosomes protein 4 (Isoform 2)	1	2	4	2	4	0	0	0	0	0	0	0

Note: "Peptide IDs" means the number of unique peptides that were identified from the corresponding protein during one replicate of the experiment. Three replicates are shown for each cell line and each oxygen concentration.

Appendix B *Proteins down-regulated in hypoxia at 48 hours*

Protein Name	Peptide IDs, H9 replicates, 1% O_2			Peptide IDs, H9 replicates, 1% O_2			Peptide IDs, CA1 replicates, 1% O_2			Peptide IDs, H9 replicates, 1% O_2		
28S ribosomal protein S28, mitochondrial	0	0	0	0	0	0	2	0	5	1	0	2
39S ribosomal protein L19, mitochondrial	0	0	0	0	0	0	2	0	1	2	1	0
Arginase-2, mitochondrial	0	0	0	0	0	0	2	2	2	0	2	1
CDK-activating kinase assembly factor MAT1	0	0	0	0	0	0	1	0	2	2	0	1
DCN1-like protein 1	0	0	0	0	0	0	2	0	1	1	2	0
Deoxycytidylate deaminase (Isoform 1)	0	0	0	0	0	0	1	0	2	3	0	1
Dynactin subunit 3 (Isoform 2)	0	0	0	0	0	0	1	2	0	2	2	2
Dynein, light chain, roadblock-type 1	0	0	0	0	0	0	0	2	2	5	1	2
Echinoderm microtubule-associated protein-like 4	0	0	0	0	0	0	1	0	3	1	3	0
Elongation factor Ts, mitochondrial (Isoform 1)	0	0	0	0	0	0	2	0	1	1	3	0
Ethanolamine-phosphate cytidylyltransferase	0	0	0	0	0	0	1	0	2	1	2	0
Mitochondrial import receptor, subunit TOM34	0	0	0	0	0	0	1	0	2	2	1	0
Mitogen-activated protein kinase kinase 4 (Isoform 2)	0	0	0	0	0	0	2	1	2	1	2	1
Monocarboxylate transporter 1	0	0	0	0	0	0	3	3	1	1	2	0
Myristoylated alanine-rich C-kinase substrate	0	0	0	0	0	0	0	1	4	1	0	2
N-alpha-acetyltransferase 25, NatB auxiliary subunit (Isoform 1)	0	0	0	0	0	0	1	0	2	2	1	0
N-alpha-acetyltransferase 38, NatC auxiliary subunit	0	0	0	0	0	0	2	1	2	3	0	1
Neurolysin, mitochondrial	0	0	0	2	2	0	5	5	9	5	5	2
Niban-like protein 1	0	0	0	0	0	0	2	0	1	4	4	1
NSFL1 cofactor p47 (Isoform 1)	0	0	0	0	0	0	3	1	2	5	5	0
Nucleoporin 43 kDa	0	0	0	0	0	0	1	4	2	1	2	1
Nucleoporin 98 kDa	0	0	0	0	0	0	2	2	2	2	1	1
Oxysterol-binding protein 1 (Isoform 1)	0	0	0	0	0	0	1	0	2	2	2	0
Pentatricopeptide repeat domain 1	0	0	0	0	0	0	2	2	2	3	1	2
Pentatricopeptide repeat domain 3 (Isoform 2)	0	0	0	0	0	0	0	1	2	1	2	0
Peptidyl-prolyl cis-trans isomerase FKBP2	0	0	0	0	0	0	2	1	1	2	1	1
Pirin	0	0	0	0	0	0	3	2	2	1	3	1
Proteasome inhibitor, PI31 subunit	0	0	0	0	0	0	1	0	2	2	1	0
Protein of unknown function, DUF410 family protein	0	0	0	0	0	0	3	1	2	2	3	1

Putative deoxyribose-phosphate aldolase	0	0	0	0	0	0	3	1	1	1	4	0
Pyruvate dehydrogenase E1 alpha 1 (Isoform 2) precursor	0	0	0	0	0	0	1	0	3	1	4	1
RAB4A, member RAS oncogene family variant	0	0	0	0	0	0	2	0	1	2	2	0
Ras GTPase-activating protein-binding protein 2 (Isoform A)	0	0	0	0	0	0	4	1	3	4	6	0
Receptor expression-enhancing protein 5	0	0	0	0	0	0	2	0	2	2	2	1
Sequestosome-1 (Isoform 1)	0	0	0	0	0	0	1	0	3	1	2	0
Serine/threonine-protein phosphatase PP1-α, catalytic subunit	0	0	0	0	0	0	9	7	12	12	7	9
Stomatin-like protein 2	0	0	0	2	4	3	5	2	5	3	7	2
Structural maintenance of chromosomes protein 4 (Isoform 1)	0	0	0	0	0	0	1	1	3	4	3	0
Suppressor of G2 allele of SKP1 homolog (Isoform 2)	6	2	5	4	9	5	11	5	9	9	10	7
Tetratricopeptide repeat protein 1	0	0	0	0	0	0	4	0	4	1	6	0
Transforming growth factor beta regulator 4	0	0	0	0	0	0	1	0	2	4	1	0
Translation initiation factor eIF-2B, subunit α	2	0	2	3	2	0	6	1	5	7	3	0
Ubiquitin-like-conjugating enzyme ATG3 (Isoform 1)	0	0	0	0	0	0	2	1	1	1	3	1
UPF0557 protein C10orf119 (Isoform 2)	0	0	0	0	0	0	2	1	3	2	1	0
UPF0600 protein C5orf51	0	0	0	0	0	0	0	1	2	3	1	0
xaa-Pro aminopeptidase 1 (Isoform 1)	0	0	0	0	0	0	4	0	2	3	2	1
α-ketoglutarate-dependent dioxygenase FTO (Isoform 1)	0	0	0	0	0	0	2	0	1	2	1	0

Note: "Peptide IDs" means the number of unique peptides that were identified from the corresponding protein during one replicate of the experiment. Three replicates are shown for each cell line and each oxygen concentration.

Appendix C *Proteins up-regulated in hypoxia at 72 hours*

Protein Name	Peptide IDs, H9 replicates, 1% O_2			Peptide IDs, CA1 replicates, 1% O_2			Peptide IDs, H9 replicates, 20% O_2			Peptide IDs, CA1 replicates, 20% O_2		
60S ribosomal protein L35a	1	3	3	2	1	2	0	0	0	0	0	0
Afadin (Isoform 4)	4	1	1	3	1	0	0	0	0	0	0	0
AP-1 complex subunit beta-1 (Isoform A)	12	4	8	5	7	4	0	0	0	0	3	5
Cytoplasmic aconitate hydratase	11	8	6	7	9	7	4	0	5	3	2	1
Fanconi anemia group I protein (Isoform 1)	4	0	1	3	3	1	0	0	0	0	0	0
Far upstream element-binding protein 1 (Isoform 1)	8	3	9	8	10	6	0	0	0	0	0	0
Hexokinase-2	7	6	12	6	8	4	4	1	5	1	0	4
Histone deacetylase complex subunit SAP18	2	1	0	5	1	1	0	0	0	0	0	0
Insulin-like growth factor-binding protein 2 precursor	4	2	7	1	2	2	0	0	2	0	0	0
Isopentenyl-diphosphate Delta-isomerase 1 (Isoform 1)	6	5	9	4	5	4	0	0	0	0	0	0
Leucine zipper protein 1 (Isoform 1)	2	0	1	3	2	1	0	0	0	0	0	0
Mannosyl-oligosaccharide glucosidase	1	2	1	6	3	3	0	0	0	0	0	0
Microtubule-associated protein 4 (Isoform 1)	6	6	4	11	9	12	3	4	3	0	0	0
Mps one binder kinase activator-like 3	2	0	1	0	3	2	0	0	0	0	0	0
NADH dehydrogenase (ubiquinone) 1α, subcomplex 5	1	0	2	1	1	2	0	0	0	0	0	0
NADH-ubiquinone oxidoreductase, 75 kDa	4	4	2	1	1	3	0	0	0	0	0	0
PERQ amino acid-rich with GYF domain-containing protein 2 (Isoform 2)	2	0	1	0	3	1	0	0	0	0	0	0
Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (Isoform 2)	7	1	1	2	6	1	0	0	0	0	0	0
Prolyl 3-hydroxylase 2	2	1	1	2	1	0	0	0	0	0	0	0
Prolyl 4-hydroxylase subunit α-1 (Isoform 1)	4	1	3	11	14	3	0	0	0	6	3	1
Protein enabled homolog (Isoform 2)	1	0	5	2	2	0	0	0	0	0	0	0
Protein FAM162A	1	3	0	3	1	1	0	0	0	0	0	0
Regulation of nuclear pre-mRNA domain-containing protein 1A (Isoform 2)	2	0	6	1	2	0	0	0	0	0	0	0
Solute carrier family 2, facilitated glucose transporter, member 1	5	5	4	7	9	5	3	1	3	1	3	0
Sorting nexin-3 (Isoform 4)	3	0	3	2	2	1	0	0	0	0	0	0
Tumor protein D52 (Isoform 1)	3	3	3	5	5	4	0	0	0	0	0	0
YrdC domain-containing protein	2	0	2	2	1	0	0	0	0	0	0	0

Note: "Peptide IDs" means the number of unique peptides that were identified from the corresponding protein during one replicate of the experiment. Three replicates are shown for each cell line and each oxygen concentration.

Appendix D *Proteins down-regulated in hypoxia at 72 hours*

Protein Name	Peptide IDs, H9 replicates, 1% O_2			Peptide IDs, CA1 replicates, 1% O_2			Peptide IDs, H9 replicates, 20% O_2			Peptide IDs, CA1 replicates, 20% O_2		
28S ribosomal protein S9, mitochondrial	0	0	0	0	0	0	1	0	4	3	1	1
39S ribosomal protein L15, mitochondrial	0	0	0	0	0	0	1	1	3	2	3	0
39S ribosomal protein L19, mitochondrial	0	0	0	0	0	0	1	1	3	1	3	0
Actin-related protein 2/3 complex, sub 1B	0	0	0	0	0	0	1	1	2	2	0	1
Afadin (Isoform 3)	0	0	0	0	0	0	6	0	3	2	4	1
ATP-dependent RNA helicase DDX19A	0	0	0	0	0	0	0	1	4	4	1	3
Bifunctional coenzyme A synthase	0	0	0	0	0	0	2	0	1	2	2	2
BolA-like protein 2	0	0	0	0	0	0	0	1	2	0	1	2
CLIP-associating protein 1 (Isoform 1)	0	0	0	0	0	0	5	0	3	1	4	0
DNA-directed RNA polymerase II, subunit RPB7	0	0	0	0	0	0	2	1	4	3	2	2
DnaJ homolog subfamily A member 3, mitochondrial (Isoform 2)	0	0	0	0	0	0	2	0	1	2	1	0
Dynactin, subunit 1 (Isoform 4)	4	1	1	0	0	0	8	0	4	9	2	3
Focal adhesion kinase 1 (Isoform 1)	0	0	0	0	0	0	1	1	3	1	2	0
Glutaminase kidney isoform, mitochondrial	0	0	0	0	0	0	3	2	3	1	0	3
Histone H1x	0	0	0	0	0	0	0	1	4	1	2	1
Histone H3.3	0	0	0	0	0	0	3	1	3	0	2	3
Isopentenyl-diphosphate Delta-isomerase 1	0	0	0	0	0	0	4	2	7	4	5	4
Lysosomal protective protein	0	0	0	0	0	0	1	0	2	2	2	1
Multiple inositol polyphosphate phosphatase 1 (Isoform 1)	0	0	0	0	0	0	2	1	3	1	2	0
Myosin-Ic (Isoform 2)	0	0	0	0	0	0	3	1	1	6	0	3
Parafibromin	0	0	0	0	0	0	1	0	2	1	2	0
Peptidyl-prolyl cis-trans isomerase FKBP2	0	0	0	0	0	0	2	1	0	1	2	1
Prefoldin, subunit 4	0	0	0	0	0	0	1	0	3	1	2	1
Signal peptidase complex, subunit SEC11A	0	0	0	0	0	0	0	1	2	1	2	1
Signal peptidase complex, subunit 3	0	0	0	0	0	0	2	1	0	1	1	2
Sorting nexin-3 (Isoform 1)	0	0	0	0	0	0	2	0	3	3	3	2
TATA box-binding protein-like protein 1	0	0	0	0	0	0	1	1	4	2	1	1
Transmembrane protein 109	0	0	0	0	0	0	2	1	1	1	2	1
Vacuolar protein sorting-associated 26A	0	0	0	0	0	0	1	0	5	2	0	2
YLP motif-containing protein 1	0	0	0	0	0	0	1	0	2	2	1	0

Note: "Peptide IDs" means the number of unique peptides that were identified from the corresponding protein during one replicate of the experiment. Three replicates are shown for each cell line and each oxygen concentration.

Appendix E *All proteins identified at 48 hours in hypoxia*

Protein Name	IPI Number	Peptide IDs, H9 replicates			Peptide IDs, CA1 replicates		
10 kDa heat shock protein, mitochondrial	IPI00220362	8	8	13	9	1	2
116 kDa U5 small nuclear ribonucleoprotein component	IPI00003519	14	7	7	11	16	10
14-3-3 protein epsilon	IPI00000816	28	22	19	23	25	17
14-3-3 protein eta	IPI00216319	14	8	13	11	7	8
14-3-3 protein gamma	IPI00220642	8	9	6	5	6	5
14-3-3 protein theta	IPI00018146	16	10	14	12	11	8
14-3-3 protein zeta/delta	IPI00021263	19	14	21	25	13	12
15 kDa selenoprotein isoform 1 precursor	IPI00030877	2	2	3	2	0	2
1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-3	IPI00010400	2	1	1	2	3	4
24-dehydrocholesterol reductase	IPI00016703	3	2	2	0	2	1
26S protease regulatory subunit 10B	IPI00021926	10	5	11	11	6	9
26S protease regulatory subunit 4	IPI00011126	4	6	4	5	4	5
26S protease regulatory subunit 6A	IPI00018398	14	10	12	10	8	10
26S protease regulatory subunit 7	IPI00021435	15	8	8	14	10	7
26S protease regulatory subunit 8	IPI00023919	13	9	7	3	1	1
26S proteasome non-ATPase regulatory subunit 14	IPI00024821	6	6	5	9	7	4
26S proteasome non-ATPase regulatory subunit 2	IPI00012268	15	16	4	22	20	9
26S proteasome non-ATPase regulatory subunit 3	IPI00011603	8	7	5	2	1	0
26S proteasome non-ATPase regulatory subunit 5	IPI00002134	6	3	5	9	3	3
26S proteasome non-ATPase regulatory subunit 6	IPI00014151	14	15	14	13	8	6
26S proteasome non-ATPase regulatory subunit 7	IPI00019927	5	6	5	10	4	4
26S proteasome non-ATPase regulatory subunit 8	IPI00937278	3	3	2	5	1	1
28 kDa heat- and acid-stable phosphoprotein	IPI00013297	2	2	2	2	1	4
29 kDa protein	IPI00453476	31	22	25	25	22	14
2-oxoglutarate dehydrogenase, mitochondrial	IPI00098902	1	2	2	6	2	2
33 kDa protein	IPI00413108	15	8	14	15	14	12
39S ribosomal protein L1, mitochondrial	IPI00549381	2	0	3	2	1	3
39S ribosomal protein L11, mitochondrial	IPI00007001	3	1	3	4	0	1
39S ribosomal protein L13, mitochondrial	IPI00022403	1	2	1	2	1	0
39S ribosomal protein L44, mitochondrial	IPI00009680	2	1	3	1	1	2
39S ribosomal protein L49, mitochondrial	IPI00013195	2	1	1	1	0	2
3-hydroxyisobutyrate dehydrogenase, mitochondrial	IPI00013860	2	0	2	3	1	0
3-ketoacyl-CoA thiolase, mitochondrial	IPI00001539	4	4	5	7	5	9
40S ribosomal protein S10	IPI00008438	3	4	5	5	2	3
40S ribosomal protein S11	IPI00025091	5	6	6	5	5	3
40S ribosomal protein S12	IPI00013917	11	10	13	15	4	4
40S ribosomal protein S13	IPI00221089	12	15	12	13	6	5
40S ribosomal protein S14	IPI00026271	7	5	10	9	5	5
40S ribosomal protein S15	IPI00479058	6	7	4	8	3	2
40S ribosomal protein S16	IPI00221092	6	6	10	6	7	3
40S ribosomal protein S17	IPI00221093	11	7	8	8	7	4
40S ribosomal protein S18	IPI00013296	16	11	11	10	10	6
40S ribosomal protein S19	IPI00215780	8	10	8	7	5	5
40S ribosomal protein S2	IPI00013485	8	7	7	9	6	7
40S ribosomal protein S20	IPI00012493	6	6	7	5	3	4
40S ribosomal protein S21	IPI00017448	7	4	4	5	2	2
40S ribosomal protein S23	IPI00218606	3	3	1	1	1	2
40S ribosomal protein S25	IPI00012750	3	5	5	4	5	3
40S ribosomal protein S26	IPI00655650	2	3	2	3	2	1
40S ribosomal protein S3	IPI00011253	15	15	19	17	10	13
40S ribosomal protein S3a	IPI00419880	18	15	17	16	10	12
40S ribosomal protein S4, X isoform	IPI00217030	16	12	8	10	7	6
40S ribosomal protein S5	IPI00008433	7	8	10	6	5	7

40S ribosomal protein S6	IPI00021840	10	9	11	6	7	3
40S ribosomal protein S7	IPI00013415	11	13	13	11	7	5
40S ribosomal protein S8	IPI00216587	8	9	10	12	8	8
40S ribosomal protein S9	IPI00221088	9	11	7	6	5	5
482 kDa protein	IPI00179298	11	10	12	9	16	0
4-trimethylaminobutyraldehyde dehydrogenase	IPI00479877	2	2	3	3	3	0
51 kDa protein	IPI00033025	4	2	0	3	4	3
59 kDa protein	IPI00302925	18	21	14	14	15	9
5'-nucleotidase domain-containing protein 1	IPI00177965	3	2	4	4	4	1
60 kDa heat shock protein, mitochondrial	IPI00784154	47	46	26	49	37	24
60S acidic ribosomal protein P0	IPI00008530	16	13	6	15	10	11
60S acidic ribosomal protein P1	IPI00008527	2	6	3	1	4	2
60S acidic ribosomal protein P2	IPI00008529	7	9	4	10	6	6
60S ribosomal protein L10	IPI00554723	7	8	6	9	9	4
60S ribosomal protein L10a	IPI00412579	10	12	8	10	7	6
60S ribosomal protein L13	IPI00465361	5	3	5	7	2	2
60S ribosomal protein L13a	IPI00304612	4	5	3	4	3	3
60S ribosomal protein L15	IPI00470528	3	6	6	4	6	2
60S ribosomal protein L17	IPI00413324	10	7	7	10	5	3
60S ribosomal protein L18	IPI00215719	9	9	8	5	4	4
60S ribosomal protein L18a	IPI00026202	4	4	2	2	4	2
60S ribosomal protein L19	IPI00025329	3	4	2	7	4	2
60S ribosomal protein L21	IPI00247583	6	6	4	9	7	3
60S ribosomal protein L22	IPI00219153	5	3	4	9	3	4
60S ribosomal protein L22-like 1	IPI00856049	3	2	0	1	2	0
60S ribosomal protein L23	IPI00010153	5	4	4	4	4	2
60S ribosomal protein L23a	IPI00021266	11	13	9	12	3	4
60S ribosomal protein L24	IPI00306332	4	1	3	4	4	2
60S ribosomal protein L26	IPI00027270	9	14	8	7	5	4
60S ribosomal protein L27	IPI00219155	8	6	5	5	5	5
60S ribosomal protein L27a	IPI00456758	4	4	4	5	5	3
60S ribosomal protein L28	IPI00182533	7	7	6	6	2	5
60S ribosomal protein L3	IPI00550021	7	8	7	12	9	6
60S ribosomal protein L30	IPI00219156	6	4	3	5	4	4
60S ribosomal protein L31	IPI00026302	4	5	3	5	3	2
60S ribosomal protein L32	IPI00395998	5	3	4	5	3	1
60S ribosomal protein L35	IPI00412607	3	2	5	5	2	2
60S ribosomal protein L35a	IPI00029731	1	3	0	1	3	1
60S ribosomal protein L36	IPI00216237	2	3	4	5	1	3
60S ribosomal protein L36a-like	IPI00056494	3	0	2	2	2	1
60S ribosomal protein L38	IPI00215790	2	1	3	3	2	2
60S ribosomal protein L4	IPI00003918	15	12	12	20	16	7
60S ribosomal protein L5	IPI00000494	11	12	5	11	9	8
60S ribosomal protein L6	IPI00329389	12	18	8	14	6	4
60S ribosomal protein L7	IPI00030179	13	9	13	10	9	6
60S ribosomal protein L7a	IPI00299573	13	9	10	8	9	8
60S ribosomal protein L8	IPI00012772	8	2	8	8	5	3
60S ribosomal protein L9	IPI00031691	6	9	5	8	2	7
6-phosphofructokinase type C	IPI00009790	4	2	3	7	9	7
6-phosphogluconate dehydrogenase, decarboxylating	IPI00219525	22	17	17	12	11	11
6-phosphogluconolactonase	IPI00029997	8	4	10	5	7	8
AARS cDNA FLJ61339, highly similar to Alanyl-tRNA synthetase	IPI00910701	0	2	1	5	3	2
Acidic leucine-rich nuclear phosphoprotein 32 family member A	IPI00025849	6	6	5	11	2	8
Acidic leucine-rich nuclear phosphoprotein 32 family member E	IPI00165393	6	6	2	4	1	5
Aconitate hydratase, mitochondrial	IPI00017855	5	2	3	5	3	3
Actin, alpha cardiac muscle 1	IPI00023006	11	7	9	9	7	12
Actin, cytoplasmic 2	IPI00021440	52	70	58	55	48	33
Actin-like protein (Fragment)	IPI00556391	2	2	1	2	1	0

Actin-related protein 2	IPI00005159	8	5	4	5	8	6
Actin-related protein 2/3 complex subunit 2	IPI00005161	10	4	6	7	4	5
Actin-related protein 2/3 complex subunit 3	IPI00005162	7	4	4	5	5	2
Actin-related protein 2/3 complex subunit 4	IPI00554811	3	6	4	3	2	2
Actin-related protein 3	IPI00028091	6	3	6	8	8	6
Activated RNA polymerase II transcriptional coactivator p15	IPI00221222	2	1	4	7	1	2
Activator of 90 kDa heat shock protein ATPase homolog 1	IPI00030706	3	3	5	3	2	2
Acyl-protein thioesterase 2	IPI00027032	4	2	7	4	3	3
Adenine phosphoribosyltransferase	IPI00218693	8	12	10	9	4	4
Adenosylhomocysteinase	IPI00012007	15	11	16	11	13	5
Adenylate kinase isoenzyme 4, mitochondrial	IPI00016568	4	5	6	6	5	3
Adenylosuccinate synthetase isozyme 2	IPI00026833	11	7	7	6	5	3
ADP/ATP translocase 2	IPI00007188	5	4	4	4	5	4
ADP-ribosylation factor 1	IPI00215914	8	12	8	11	10	5
ADP-ribosylation factor 4	IPI00215918	4	3	1	5	1	4
ADP-ribosylation factor 5	IPI00215919	4	4	3	3	3	0
ADP-ribosylation factor 6	IPI00215920	2	1	2	3	3	2
ADP-ribosylation factor-like protein 2	IPI00003326	4	4	3	4	5	0
ADP-ribosylation factor-like protein 3	IPI00003327	4	3	6	6	3	3
Aflatoxin B1 aldehyde reductase member 2	IPI00305978	2	1	1	3	2	2
A-kinase anchor protein 12 isoform 2	IPI00217683	8	3	7	5	6	0
Alanyl-tRNA synthetase, cytoplasmic	IPI00027442	18	12	14	16	22	14
Alcohol dehydrogenase [NADP+]	IPI00220271	7	7	7	8	8	3
Alcohol dehydrogenase class-3	IPI00746777	4	3	5	6	8	5
Aldehyde dehydrogenase X, mitochondrial	IPI00103467	5	5	5	4	3	1
Aldehyde dehydrogenase, mitochondrial	IPI00006663	3	3	2	7	5	4
Aldose reductase	IPI00413641	3	3	2	7	3	4
Alkaline phosphatase, tissue-nonspecific isozyme	IPI00419916	1	3	2	4	3	3
Alpha-actinin-1	IPI00013508	38	23	19	43	37	25
Alpha-actinin-4	IPI00013808	16	11	6	21	22	13
Alpha-aminoadipic semialdehyde synthase, mitochondrial	IPI00033217	17	14	15	10	10	11
Alpha-centractin	IPI00029468	6	2	2	4	2	1
Alpha-soluble NSF attachment protein	IPI00009253	5	5	7	1	2	1
Amidophosphoribosyltransferase	IPI00029534	1	3	1	6	2	1
Aminoacyl tRNA synthase complex-interacting multifunctional protein 1	IPI00006252	3	2	4	4	5	3
Aminoacyl tRNA synthase complex-interacting multifunctional protein 2	IPI00011916	2	2	3	2	2	2
Annexin A1	IPI00218918	4	3	4	16	9	7
Annexin A3	IPI00024095	10	9	6	14	8	6
annexin A4	IPI00793199	3	2	1	7	3	2
Annexin A5	IPI00329801	26	19	18	20	17	16
Annexin A6	IPI00221226	15	5	1	20	8	3
Apolipoprotein E	IPI00021842	11	2	14	8	7	3
Argininosuccinate synthase	IPI00020632	6	2	2	2	1	1
Asparagine synthetase [glutamine-hydrolyzing]	IPI00554777	8	4	7	7	7	0
Asparaginyl-tRNA synthetase, cytoplasmic	IPI00306960	5	2	0	7	10	1
Aspartate aminotransferase, cytoplasmic	IPI00219029	9	6	8	9	9	8
Aspartate aminotransferase, mitochondrial	IPI00018206	10	9	9	10	7	5
Aspartyl-tRNA synthetase, cytoplasmic	IPI00216951	8	6	6	8	9	4
Astrocytic phosphoprotein PEA-15	IPI00014850	3	3	2	3	1	2
Ataxin-10	IPI00001636	8	2	2	2	6	0
ATP synthase subunit alpha, mitochondrial	IPI00440493	16	16	14	17	12	7
ATP synthase subunit b, mitochondrial	IPI00029133	8	5	8	7	6	5
ATP synthase subunit beta, mitochondrial	IPI00303476	26	24	22	32	27	23
ATP synthase subunit O, mitochondrial	IPI00007611	7	8	7	8	4	2
ATPase ASNA1	IPI00013466	4	4	3	4	2	3
ATP-binding cassette sub-family E member 1	IPI00303207	5	1	3	3	10	0

ATP-citrate synthase	IPI00021290	32	23	30	14	19	15
ATP-dependent RNA helicase A	IPI00844578	25	27	20	22	24	16
ATP-dependent RNA helicase DDX1	IPI00293655	10	11	4	3	1	7
ATP-dependent RNA helicase DDX18	IPI00301323	2	4	1	2	1	1
ATP-dependent RNA helicase DDX19A	IPI00019918	2	0	3	3	4	2
ATP-dependent RNA helicase DDX3X	IPI00215637	11	7	6	13	1	4
Band 4.1-like protein 2	IPI00015973	3	1	1	5	7	0
Barrier-to-autointegration factor	IPI00026087	2	2	2	4	1	2
Basic leucine zipper and W2 domain-containing protein 2	IPI00022305	4	3	1	4	2	2
B-cell receptor-associated protein 31	IPI00218200	2	1	0	2	4	0
Beta-actin-like protein 2	IPI00003269	2	1	2	1	1	2
Bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthase 1	IPI00011619	5	2	0	3	3	0
Bifunctional aminoacyl-tRNA synthetase	IPI00013452	10	3	13	14	22	10
Bifunctional methylenetetrahydrofolate dehydrogenase/cyclohydrolase, mitochondrial	IPI00011307	4	4	0	1	2	1
Bifunctional protein NCOAT	IPI00477231	3	3	2	3	1	0
Bifunctional purine biosynthesis protein PURH	IPI00289499	25	16	14	24	19	7
Branched-chain-amino-acid aminotransferase	IPI00382412	5	5	5	3	1	2
Brefeldin A-inhibited guanine nucleotide-exchange protein 1	IPI00002188	2	1	3	1	5	0
C-1-tetrahydrofolate synthase, cytoplasmic	IPI00218342	19	19	18	18	15	14
CAD protein	IPI00301263	21	17	19	7	13	5
Cadherin-1	IPI00025861	5	1	3	0	3	1
Calcium-regulated heat stable protein 1	IPI00304409	4	3	2	5	4	2
Calmodulin	IPI00075248	14	8	2	10	0	5
Calpain small subunit 1	IPI00025084	3	1	2	3	3	5
Calpain-1 catalytic subunit	IPI00011285	2	3	0	7	3	1
Calponin-2	IPI00015262	8	4	3	4	4	4
Calponin-3	IPI00216682	6	1	5	7	6	6
Calreticulin	IPI00020599	12	9	8	12	19	8
Carbonic anhydrase 2	IPI00218414	2	1	1	3	2	2
Carbonyl reductase [NADPH] 1	IPI00295386	6	1	7	5	3	6
Casein kinase II subunit alpha'	IPI00020602	3	1	4	2	1	0
Casein kinase II subunit beta	IPI00010865	2	2	1	2	1	2
Caspase-3	IPI00292140	2	1	4	5	2	2
Cation-independent mannose-6-phosphate receptor	IPI00289819	3	1	5	1	4	0
CCR4-NOT transcription complex subunit 7	IPI00006552	4	1	3	3	1	1
cDNA FLJ25678 fis, clone TST04067, highly similar to PURINE NUCLEOSIDE PHOSPHORYLASE	IPI00017672	14	11	9	11	7	9
cDNA FLJ35809 fis, clone TESTI2006016, highly similar to Eukaryotic translation initiation factor 3 subunit 3	IPI00647650	4	4	4	3	4	1
cDNA FLJ36192 fis, clone TESTI2027450, highly similar to Eukaryotic translation initiation factor 3 subunit 5	IPI00654777	7	8	6	6	2	4
cDNA FLJ44436 fis, clone UTERU2019706, highly similar to T-complex protein 1 subunit gamma	IPI00290770	18	10	9	18	14	10
cDNA FLJ51909, highly similar to Serine-threonine kinase receptor-associatedprotein	IPI00294536	8	9	4	8	12	5
cDNA FLJ52712, highly similar to Tubulin beta-6 chain	IPI00908469	3	0	2	1	1	2
cDNA FLJ53193, highly similar to Homo sapiens caldesmon 1 (CALD1), transcript variant 5, mRNA	IPI00218696	4	4	6	10	6	3
cDNA FLJ53975, highly similar to Acetyl-CoA acetyltransferase, cytosolic	IPI00291419	10	14	18	6	6	1
cDNA FLJ54365, highly similar to DNA replication licensing factor MCM4	IPI00795318	23	12	8	17	12	8
cDNA FLJ54536, highly similar to Mitochondrial 28S ribosomal protein S27	IPI00022002	4	2	1	1	1	2
cDNA FLJ54957, highly similar to Transketolase	IPI00643920	28	28	17	32	22	7
cDNA FLJ55382, highly similar to Hsp70-binding protein 1	IPI00100748	4	3	3	4	1	2
cDNA FLJ55482, highly similar to Annexin A11	IPI00414320	2	1	0	2	2	0

cDNA FLJ55574, highly similar to Calnexin	IPI00020984	10	8	4	10	9	9
cDNA FLJ55586, highly similar to MMS19-like protein	IPI00154451	5	3	2	8	3	2
cDNA FLJ55599, highly similar to DNA replication licensing factor MCM3	IPI00013214	18	13	12	8	10	15
cDNA FLJ56307, highly similar to Ubiquitin thioesterase protein OTUB1	IPI00000581	4	7	4	5	4	3
cDNA FLJ59211, highly similar to Glucosidase 2 subunit beta	IPI00026154	4	5	8	4	8	7
cDNA FLJ59367, highly similar to Adenylosuccinate lyase	IPI00026904	10	6	7	10	7	5
cDNA FLJ59758, highly similar to S-methyl-5-thioadenosine phosphorylase	IPI00011876	7	6	8	2	0	1
cDNA FLJ60076, highly similar to ELAV-like protein 1	IPI00301936	10	5	5	8	6	3
cDNA FLJ60097, highly similar to Tubulin alpha-ubiquitous chain	IPI00792677	30	33	30	32	36	19
cDNA FLJ60424, highly similar to Junction plakoglobin	IPI00789324	9	4	6	3	4	3
cDNA FLJ60607, highly similar to Acyl-protein thioesterase 1	IPI00007321	5	3	4	3	3	3
cDNA FLJ61162, highly similar to Ras-related protein R-Ras2	IPI00012512	4	1	2	4	2	3
cDNA FLJ75085, highly similar to Homo sapiens glutaminyl-tRNA synthetase (QARS), mRNA	IPI00026665	8	7	3	3	1	3
cDNA FLJ77177, highly similar to Homo sapiens arginine-rich, mutated in early stage tumors (ARMET), mRNA	IPI00328748	1	2	0	1	2	1
cDNA FLJ77422, highly similar to Homo sapiens RNA binding protein, autoantigenic (hnRNP-associated with lethal yellow homolog (mouse)), transcript variant 1, mRNA (Fragment)	IPI00011268	2	1	2	2	2	1
cDNA, FLJ79184, highly similar to Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1	IPI00027192	2	1	0	1	2	0
cDNA, FLJ96508, Homo sapiens SH3-domain GRB2-like 1 (SH3GL1), mRNA	IPI00019169	3	1	3	2	1	0
Cell division protein kinase 2	IPI00031681	2	2	1	1	2	1
Cellular retinoic acid-binding protein 1	IPI00219930	6	7	6	10	8	5
Cellular retinoic acid-binding protein 2	IPI00216088	5	1	1	5	3	2
Chloride intracellular channel protein 1	IPI00010896	9	5	10	11	10	8
Chloride intracellular channel protein 4	IPI00001960	15	11	9	9	8	8
Chromobox protein homolog 3	IPI00297579	6	4	4	5	3	6
Citrate synthase, mitochondrial	IPI00025366	5	5	3	7	4	1
Claudin-6	IPI00011084	4	3	3	2	2	2
Cleavage and polyadenylation specificity factor subunit 5	IPI00646917	6	4	6	2	0	1
Cleavage stimulation factor subunit 3	IPI00015195	2	2	1	5	1	0
Coactosin-like protein	IPI00017704	1	2	1	3	1	2
Coatomer subunit beta	IPI00295851	8	4	4	13	13	7
Coatomer subunit beta'	IPI00220219	7	1	6	2	10	5
Coatomer subunit delta variant 2	IPI00298520	9	4	7	9	8	3
Coatomer subunit epsilon	IPI00465132	6	2	2	4	4	4
Coatomer subunit gamma	IPI00783982	11	7	3	11	12	10
Coatomer subunit gamma-2	IPI00002557	3	4	2	8	2	2
Coatomer subunit zeta-1	IPI00032851	3	5	6	3	3	4
Cofilin-1	IPI00012011	12	19	17	18	12	7
Coiled-coil domain-containing protein 58	IPI00046828	2	0	2	2	1	0
Cold-inducible RNA-binding protein	IPI00180954	2	0	2	3	2	2
Collapsin response mediator protein 4 long variant	IPI00029111	20	9	8	15	10	7
Complement component 1 Q subcomponent-binding protein, mitochondrial	IPI00014230	11	12	5	7	6	7
Condensin complex subunit 1	IPI00299524	5	3	3	3	5	1
COP9 signalosome complex subunit 4	IPI00171844	6	4	6	5	3	4
COP9 signalosome complex subunit 5	IPI00009958	0	1	2	2	2	3
COP9 signalosome complex subunit 6	IPI00163230	3	2	1	4	0	1
COP9 signalosome complex subunit 7a	IPI00301419	3	3	2	3	4	3
COP9 signalosome complex subunit 8	IPI00009480	3	1	4	4	1	1
Creatine kinase B-type	IPI00022977	11	14	10	16	15	11
CSE1L Isoform 1 of Exportin-2	IPI00022744	2	1	0	4	2	0

CSNK2A1 protein	IPI00016613	10	7	10	1	2	2
CTP synthase 1	IPI00290142	6	2	3	8	4	2
Cullin-1	IPI00014310	4	1	1	3	0	2
Cystatin-B	IPI00021828	3	2	3	3	2	2
Cysteine and glycine-rich protein 2	IPI00002824	3	3	2	5	6	2
cysteinyl-tRNA synthetase, cytoplasmic isoform c	IPI00027443	4	6	7	3	4	0
cytochrome b5 type B precursor	IPI00303954	4	2	2	2	4	2
Cytochrome c	IPI00465315	5	4	6	6	1	3
Cytochrome c oxidase subunit 2	IPI00017510	3	3	1	4	1	1
Cytochrome c oxidase subunit 4 isoform 1, mitochondrial	IPI00006579	2	1	0	1	2	0
Cytochrome c oxidase subunit 5A, mitochondrial	IPI00025086	3	1	0	2	0	2
Cytoplasmic aconitate hydratase	IPI00008485	7	6	1	1	2	1
Cytoplasmic dynein 1 heavy chain 1	IPI00456969	64	37	36	14	33	0
Cytosolic Fe-S cluster assembly factor NUBP2	IPI00644674	3	1	3	0	2	2
D-3-phosphoglycerate dehydrogenase	IPI00011200	16	11	15	14	13	9
dCTP pyrophosphatase 1	IPI00012197	0	4	2	3	0	1
D-dopachrome decarboxylase	IPI00293867	4	3	6	6	2	2
Destrin	IPI00473014	1	4	3	3	3	1
Developmental pluripotency-associated protein 4	IPI00018878	2	0	1	2	1	0
Diablo homolog, mitochondrial precursor	IPI00008418	3	3	1	2	3	0
Dihydrolipoyl dehydrogenase, mitochondrial	IPI00015911	3	1	3	5	5	2
Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	IPI00021338	6	1	3	3	4	0
Dihydropteridine reductase	IPI00014439	3	2	0	2	2	1
Dihydropyrimidinase-related protein 2	IPI00257508	17	5	8	13	10	7
Diphosphomevalonate decarboxylase	IPI00022745	1	2	7	1	2	1
DNA damage-binding protein 1	IPI00293464	6	2	2	6	10	1
DNA ligase 1	IPI00219841	5	3	0	2	1	1
DNA mismatch repair protein Msh2	IPI00017303	9	7	6	8	5	3
DNA replication licensing factor MCM2	IPI00184330	19	14	13	12	16	14
DNA replication licensing factor MCM5	IPI00018350	10	16	9	7	8	10
DNA replication licensing factor MCM6	IPI00031517	15	12	8	13	9	6
DNA-(apurinic or apyrimidinic site) lyase	IPI00215911	5	4	5	9	11	10
DNA-directed RNA polymerase II subunit RPB1	IPI00031627	2	2	2	4	2	0
DNA-directed RNA polymerase II subunit RPB3	IPI00018288	4	3	2	6	2	1
DNA-directed RNA polymerases I, II, and III subunit RPABC1	IPI00291093	2	1	2	1	2	3
DnaJ homolog subfamily A member 1	IPI00012535	10	10	4	5	8	4
DnaJ homolog subfamily A member 2	IPI00032406	7	2	4	5	4	5
DnaJ homolog subfamily B member 11	IPI00008454	1	1	2	0	1	2
DnaJ homolog subfamily C member 7	IPI00329629	3	0	2	2	5	0
DnaJ homolog subfamily C member 8	IPI00003438	6	1	2	4	4	4
Dolichol-phosphate mannosyltransferase	IPI00022018	2	1	3	3	2	0
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1 precursor	IPI00025874	3	1	3	10	11	1
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 2	IPI00028635	5	1	1	2	8	3
Dual specificity mitogen-activated protein kinase kinase 1	IPI00219604	2	0	3	2	2	1
Dual specificity protein phosphatase 3	IPI00018671	2	3	1	4	1	1
dynactin subunit 2	IPI00220503	4	1	5	1	2	0
Dynein light chain Tctex-type 1	IPI00019495	3	0	2	2	0	1
E3 SUMO-protein ligase RanBP2	IPI00221325	5	2	5	2	1	0
E3 ubiquitin-protein ligase KCMF1	IPI00306661	2	2	1	2	1	1
Electron transfer flavoprotein subunit alpha, mitochondrial	IPI00010810	5	3	6	7	3	8
Elongation factor 1-alpha 1	IPI00396485	24	31	28	19	23	16
Elongation factor 1-beta	IPI00178440	4	4	4	2	5	5
Elongation factor 1-gamma	IPI00937615	17	12	8	13	14	14
Elongation factor 2	IPI00186290	53	50	29	50	40	33
Emerin	IPI00032003	1	1	2	1	3	1

Endoplasmic reticulum resident protein 29	IPI00024911	8	5	9	8	7	5
Endoplasmic reticulum resident protein 44	IPI00401264	3	0	2	5	2	0
Endoplasmin	IPI00027230	34	22	21	32	29	23
Enhancer of rudimentary homolog	IPI00029631	4	3	0	4	2	2
Enoyl-CoA hydratase, mitochondrial	IPI00024993	9	4	4	10	8	6
Epiplakin	IPI00010951	3	4	2	2	3	1
Epithelial cell adhesion molecule	IPI00296215	1	2	5	3	5	3
ERO1-like protein alpha	IPI00386755	1	0	3	1	2	0
Estradiol 17-beta-dehydrogenase 12	IPI00007676	10	9	11	10	7	5
Eukaryotic initiation factor 4A-I	IPI00025491	27	24	26	20	23	15
Eukaryotic initiation factor 4A-III	IPI00009328	13	4	6	3	8	6
eukaryotic peptide chain release factor GTP-binding subunit ERF3A isoform 2	IPI00909083	4	4	0	4	2	1
Eukaryotic peptide chain release factor subunit 1	IPI00429191	5	3	4	7	7	4
Eukaryotic translation elongation factor 1 epsilon-1	IPI00003588	5	4	4	4	3	2
Eukaryotic translation initiation factor 2 subunit 1	IPI00219678	6	3	4	5	7	7
Eukaryotic translation initiation factor 2 subunit 2	IPI00021728	3	0	2	4	3	1
Eukaryotic translation initiation factor 2 subunit 3	IPI00297982	10	6	2	8	7	5
Eukaryotic translation initiation factor 3 subunit A	IPI00029012	24	22	16	23	19	15
Eukaryotic translation initiation factor 3 subunit C	IPI00016910	10	10	5	9	10	7
Eukaryotic translation initiation factor 3 subunit D	IPI00006181	3	1	1	4	10	1
Eukaryotic translation initiation factor 3 subunit E	IPI00013068	13	5	6	7	9	6
Eukaryotic translation initiation factor 3 subunit G	IPI00290460	5	3	7	4	4	3
Eukaryotic translation initiation factor 3 subunit I	IPI00012795	7	3	3	0	3	1
Eukaryotic translation initiation factor 3 subunit K	IPI00033143	4	3	6	6	1	3
Eukaryotic translation initiation factor 3 subunit M	IPI00102069	8	11	7	4	7	7
Eukaryotic translation initiation factor 3, subunit E interacting protein	IPI00465233	7	5	5	6	12	0
eukaryotic translation initiation factor 4 gamma 1 isoform 1	IPI00479262	11	6	8	10	10	7
Eukaryotic translation initiation factor 5	IPI00022648	3	2	5	5	4	2
Eukaryotic translation initiation factor 5B	IPI00299254	4	4	2	5	0	2
Eukaryotic translation initiation factor 6	IPI00010105	5	5	4	3	6	6
Exosome complex exonuclease MTR3	IPI00073602	2	2	2	1	2	2
Exosome complex exonuclease RRP4	IPI00015905	3	2	2	3	3	4
Exosome complex exonuclease RRP41	IPI00745613	2	2	2	2	1	2
Exosome complex exonuclease RRP42	IPI00014198	2	1	2	1	1	2
Exosome complex exonuclease RRP43	IPI00552920	2	0	1	1	2	1
Exportin-1	IPI00298961	26	16	13	18	16	20
Exportin-4	IPI00028357	5	0	1	1	2	3
Exportin-5	IPI00640703	17	7	7	6	14	5
Exportin-7	IPI00302458	5	6	7	6	3	2
Exportin-T	IPI00306290	5	3	4	1	4	1
Ezrin	IPI00843975	9	15	6	19	13	10
FACT complex subunit SPT16	IPI00026970	5	1	1	11	10	5
FACT complex subunit SSRP1	IPI00005154	3	3	1	5	3	5
F-actin-capping protein subunit alpha-1	IPI00005969	8	3	5	5	8	5
F-actin-capping protein subunit alpha-2	IPI00026182	5	3	3	3	5	3
farnesyl pyrophosphate synthase isoform b	IPI00914971	7	4	10	6	7	2
Fascin	IPI00163187	12	11	5	16	14	10
Fatty acid synthase	IPI00026781	89	93	99	47	45	37
Fatty acid-binding protein, epidermal	IPI00007797	9	3	8	13	9	8
Ferritin heavy chain	IPI00554521	1	0	2	2	1	0
Flap endonuclease 1	IPI00026215	2	2	2	2	4	2
Fructose-bisphosphate aldolase	IPI00418262	9	6	11	7	4	3
Fructose-bisphosphate aldolase A	IPI00465439	30	26	31	29	26	17
G2/mitotic-specific cyclin-B1	IPI00745793	3	0	1	2	2	0
Gamma-enolase	IPI00216171	7	4	4	4	7	3
Glia maturation factor, beta	IPI00412987	4	3	3	6	2	0
Glucosamine 6-phosphate N-acetyltransferase	IPI00061525	4	1	3	5	4	3

Glucosamine-6-phosphate isomerase 1	IPI00009305	5	2	5	1	2	1
Glucose-6-phosphate isomerase	IPI00027497	21	14	9	17	15	6
Glutamate dehydrogenase 1, mitochondrial	IPI00016801	2	2	1	6	5	3
Glutaredoxin-3	IPI00008552	13	7	9	15	6	6
Glutathione S-transferase omega-1	IPI00019755	3	1	1	2	1	0
Glutathione S-transferase P	IPI00219757	18	15	17	22	14	9
Glyceraldehyde-3-phosphate dehydrogenase	IPI00219018	52	60	50	57	37	25
Glycogen phosphorylase, brain form	IPI00004358	3	5	3	8	5	2
Glypican-4	IPI00232571	11	5	9	7	5	8
GMP synthase [glutamine-hydrolyzing]	IPI00029079	25	9	6	16	12	3
G-rich sequence factor 1	IPI00478657	2	1	1	2	2	2
GTP:AMP phosphotransferase, mitochondrial	IPI00465256	3	1	2	1	2	1
GTPase NRas	IPI00000005	1	1	2	5	2	2
GTP-binding nuclear protein Ran	IPI00643041	11	10	10	11	5	5
GTP-binding protein Rheb	IPI00016669	4	2	3	1	2	0
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1	IPI00026268	7	2	6	8	7	6
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2	IPI00003348	2	1	3	3	4	3
Guanine nucleotide-binding protein G(k) subunit alpha	IPI00220578	3	1	0	3	6	4
Guanine nucleotide-binding protein G(q) subunit alpha	IPI00288947	1	0	2	2	2	1
Guanine nucleotide-binding protein subunit alpha-13	IPI00290928	1	0	2	2	1	0
Guanine nucleotide-binding protein subunit beta-2-like 1	IPI00848226	17	14	11	15	15	16
Heat shock 70 kDa protein 1A/1B	IPI00304925	15	3	10	6	6	0
Heat shock 70 kDa protein 4	IPI00002966	25	21	18	16	28	21
Heat shock protein 75 kDa, mitochondrial	IPI00030275	10	3	4	7	3	2
Heat shock protein beta-1	IPI00025512	7	5	3	4	2	3
Heat shock protein HSP 90-beta	IPI00414676	70	73	42	62	60	34
Heat shock-related 70 kDa protein 2	IPI00007702	2	1	2	2	1	2
Heme oxygenase 1	IPI00215893	1	0	3	3	2	1
Heme-binding protein 1	IPI00148063	5	3	2	3	3	0
Heterogeneous nuclear ribonucleoprotein A0	IPI00011913	4	2	4	7	5	3
Heterogeneous nuclear ribonucleoprotein F	IPI00003881	7	5	5	5	1	3
Heterogeneous nuclear ribonucleoprotein G	IPI00304692	7	5	6	8	6	5
Heterogeneous nuclear ribonucleoprotein H	IPI00013881	6	4	4	9	12	10
Heterogeneous nuclear ribonucleoprotein K	IPI00514561	21	16	12	19	16	11
Heterogeneous nuclear ribonucleoprotein L	IPI00027834	9	4	3	6	12	4
Heterogeneous nuclear ribonucleoprotein U-like protein 2	IPI00456887	3	2	4	3	6	2
Hexokinase-2	IPI00102864	10	12	5	5	3	1
High mobility group protein B1	IPI00419258	9	10	4	11	7	5
Histidyl-tRNA synthetase, cytoplasmic	IPI00021808	2	0	3	6	3	0
Histone H1.5	IPI00217468	5	4	7	7	4	4
Histone H2A type 1-H	IPI00081836	1	4	12	11	5	2
Histone H2A.V	IPI00018278	2	2	1	3	2	3
Histone H4	IPI00453473	6	7	17	17	10	7
Hsc70-interacting protein	IPI00032826	5	6	4	4	4	4
Hsp90 co-chaperone Cdc37	IPI00013122	7	2	5	0	2	1
HSPA5 protein	IPI00003362	35	30	23	31	19	14
Hydroxymethylglutaryl-CoA synthase, cytoplasmic	IPI00008475	23	18	17	7	12	7
Hypoxanthine-guanine phosphoribosyltransferase	IPI00218493	7	10	6	7	6	5
Hypoxia up-regulated protein 1	IPI00000877	22	16	16	15	24	15
Importin subunit alpha-2	IPI00002214	16	14	10	10	11	9
Importin subunit alpha-3	IPI00299033	5	2	1	2	0	1
Importin subunit alpha-4	IPI00012578	4	1	0	4	4	1
Importin subunit beta-1	IPI00001639	22	22	9	22	17	17
Importin-11	IPI00301107	4	0	3	2	1	4
Importin-7	IPI00007402	12	7	9	10	11	9
Importin-9	IPI00185146	7	7	7	3	11	6
Inorganic pyrophosphatase	IPI00015018	9	3	3	8	4	3
Inosine triphosphate pyrophosphatase	IPI00018783	2	0	2	3	2	1

Inosine-5'-monophosphate dehydrogenase 2	IPI00291510	11	10	8	8	10	3
inositol-3-phosphate synthase 1 isoform 2	IPI00478861	3	1	1	6	3	1
Insulin-degrading enzyme	IPI00220373	2	4	3	4	2	0
Insulin-like growth factor 2 mRNA-binding protein 1	IPI00008557	10	5	7	11	9	1
Interleukin enhancer-binding factor 2	IPI00005198	11	11	11	14	9	9
Isochorismatase domain-containing protein 1	IPI00304082	5	3	4	4	1	2
Isocitrate dehydrogenase [NADP] cytoplasmic	IPI00027223	20	17	27	20	14	7
Isocitrate dehydrogenase [NADP], mitochondrial	IPI00011107	2	1	0	4	2	0
Isoform 1 of 26S protease regulatory subunit 6B	IPI00020042	11	8	6	7	6	3
Isoform 1 of 26S proteasome non-ATPase regulatory subunit 1	IPI00299608	10	6	9	13	12	10
Isoform 1 of 3,2-trans-enoyl-CoA isomerase, mitochondrial	IPI00300567	2	3	2	5	2	1
Isoform 1 of 39S ribosomal protein L22, mitochondrial	IPI00414410	3	3	1	3	0	1
Isoform 1 of 3-hydroxyacyl-CoA dehydrogenase type-2	IPI00017726	12	7	7	9	6	4
Isoform 1 of 3-hydroxyisobutyryl-CoA hydrolase, mitochondrial	IPI00419802	3	3	0	3	1	0
Isoform 1 of 40S ribosomal protein S24	IPI00029750	5	5	4	5	4	3
Isoform 1 of 5'(3')-deoxyribonucleotidase, cytosolic type	IPI00005573	2	2	2	2	1	1
Isoform 1 of 5'-3' exoribonuclease 2	IPI00100151	8	6	3	3	5	2
Isoform 1 of 5'-nucleotidase domain-containing protein 2	IPI00009662	3	1	1	3	2	1
Isoform 1 of 60S ribosomal protein L11	IPI00376798	4	8	3	4	2	2
Isoform 1 of 60S ribosomal protein L12	IPI00024933	6	5	6	4	4	4
Isoform 1 of 6-phosphofructokinase, liver type	IPI00332371	4	2	1	4	6	3
Isoform 1 of Acetyl-CoA carboxylase 1	IPI00011569	11	9	15	0	3	3
Isoform 1 of Acidic leucine-rich nuclear phosphoprotein 32 family member B	IPI00007423	2	2	0	3	1	2
Isoform 1 of Actin-related protein 2/3 complex subunit 5	IPI00550234	3	1	1	4	2	2
Isoform 1 of Adenylate kinase 2, mitochondrial	IPI00215901	5	5	7	7	3	4
Isoform 1 of Adenylyl cyclase-associated protein 1	IPI00008274	12	12	5	14	8	7
Isoform 1 of Adipocyte plasma membrane-associated protein	IPI00031131	3	0	1	1	4	3
Isoform 1 of Annexin A7	IPI00002460	3	1	1	2	2	1
Isoform 1 of AP-2 complex subunit beta	IPI00784156	11	5	6	8	14	9
Isoform 1 of Apoptosis-associated speck-like protein containing a CARD	IPI00001699	4	5	3	4	2	0
Isoform 1 of ATP synthase subunit d, mitochondrial	IPI00220487	4	3	3	11	3	2
Isoform 1 of Basic leucine zipper and W2 domain-containing protein 1	IPI00785096	7	6	4	8	4	2
Isoform 1 of BRCA2 and CDKN1A-interacting protein	IPI00002203	3	3	1	2	1	1
Isoform 1 of Calcyclin-binding protein	IPI00395627	10	9	5	10	12	7
Isoform 1 of Caprin-1	IPI00783872	7	1	3	4	2	1
Isoform 1 of Catenin alpha-1	IPI00215948	15	7	9	20	16	16
Isoform 1 of Catenin beta-1	IPI00017292	5	5	4	10	9	4
Isoform 1 of CCR4-NOT transcription complex subunit 1	IPI00166010	5	3	6	3	6	0
Isoform 1 of Cellular nucleic acid-binding protein	IPI00430812	2	2	0	2	1	2
Isoform 1 of Chromodomain-helicase-DNA-binding protein 4	IPI00000846	2	0	1	7	3	1
Isoform 1 of Clathrin heavy chain 1	IPI00024067	46	44	31	30	40	36
Isoform 1 of Coatomer subunit alpha	IPI00295857	8	8	8	5	14	7
Isoform 1 of Coiled-coil domain-containing protein 47	IPI00024642	3	2	0	4	4	1
Isoform 1 of COP9 signalosome complex subunit 2	IPI00743825	5	4	2	2	3	3
Isoform 1 of COP9 signalosome complex subunit 7b	IPI00009301	3	1	3	4	0	2
Isoform 1 of C-terminal-binding protein 2	IPI00010120	2	1	4	4	2	2
Isoform 1 of Cullin-4A	IPI00419273	4	3	3	2	0	1
Isoform 1 of Cullin-associated NEDD8-dissociated protein 1	IPI00100160	21	19	17	12	18	18
Isoform 1 of Cystathionine beta-synthase	IPI00219352	10	8	3	4	6	2
Isoform 1 of Cysteine and histidine-rich domain-containing protein 1	IPI00015897	3	1	1	0	5	1
Isoform 1 of Cytosol aminopeptidase	IPI00419237	3	2	2	7	3	0
Isoform 1 of Cytosolic acyl coenzyme A thioester hydrolase	IPI00010415	8	6	4	5	4	3
Isoform 1 of Cytosolic non-specific dipeptidase	IPI00177728	11	14	11	16	10	9
Isoform 1 of Dipeptidyl peptidase 1	IPI00022810	2	2	1	1	3	0
Isoform 1 of Dipeptidyl peptidase 3	IPI00020672	11	9	2	11	5	2
Isoform 1 of DNA replication licensing factor MCM7	IPI00299904	17	14	9	11	14	14

Isoform 1 of DNA-dependent protein kinase catalytic subunit	IPI00296337	35	28	27	30	39	0
Isoform 1 of Drebrin	IPI00003406	8	3	7	6	10	6
Isoform 1 of Enolase-phosphatase E1	IPI00038378	3	3	2	2	2	1
Isoform 1 of Enoyl-CoA hydratase domain-containing protein 1	IPI00302688	6	0	2	1	1	2
Isoform 1 of Eukaryotic initiation factor 4A-II	IPI00328328	7	1	1	1	3	1
Isoform 1 of Eukaryotic translation initiation factor 3 subunit B	IPI00396370	13	9	6	9	16	13
Isoform 1 of Exosome complex exonuclease RRP44	IPI00746351	2	0	1	1	3	1
Isoform 1 of Exportin-2	IPI00022744	27	21	21	20	18	26
Isoform 1 of Extended synaptotagmin-1	IPI00022143	11	4	5	3	3	0
Isoform 1 of Far upstream element-binding protein 2	IPI00479786	8	9	7	10	12	6
Isoform 1 of Filamin-B	IPI00289334	32	22	24	55	59	23
Isoform 1 of Filamin-C	IPI00178352	2	2	0	29	40	10
Isoform 1 of Fragile X mental retardation syndrome-related protein 1	IPI00016249	3	2	2	2	1	0
Isoform 1 of Friend of PRMT1 protein	IPI00300990	1	0	2	2	2	1
Isoform 1 of Gamma-glutamylcyclotransferase	IPI00031564	4	4	7	8	2	1
Isoform 1 of General transcription factor II-I	IPI00054042	5	4	2	2	5	3
Isoform 1 of General vesicular transport factor p115	IPI00941161	11	6	8	10	15	8
Isoform 1 of Glucosamine--fructose-6-phosphate aminotransferase [isomerizing] 1	IPI00217952	9	4	3	7	10	4
Isoform 1 of Growth factor receptor-bound protein 2	IPI00021327	4	3	2	2	3	4
Isoform 1 of Guanine nucleotide-binding protein G(i) subunit alpha-2	IPI00748145	6	3	3	4	0	3
Isoform 1 of Heat shock cognate 71 kDa protein	IPI00003865	48	35	32	38	33	26
Isoform 1 of Hematological and neurological expressed 1-like protein	IPI00027397	2	2	3	3	1	0
Isoform 1 of Heterogeneous nuclear ribonucleoprotein D0	IPI00028888	15	8	14	12	16	9
Isoform 1 of Heterogeneous nuclear ribonucleoprotein M	IPI00171903	18	13	14	15	21	3
Isoform 1 of Heterogeneous nuclear ribonucleoprotein Q	IPI00018140	9	9	6	2	2	1
Isoform 1 of Heterogeneous nuclear ribonucleoprotein R	IPI00012074	6	4	4	5	4	3
Isoform 1 of Hexokinase-1	IPI00018246	2	3	3	8	7	6
Isoform 1 of Histone-binding protein RBBP4	IPI00328319	5	3	3	3	6	0
Isoform 1 of Importin-4	IPI00156374	11	4	11	9	8	6
Isoform 1 of Importin-5	IPI00793443	30	22	23	23	29	26
Isoform 1 of Insulin-like growth factor 2 mRNA-binding protein 3	IPI00658000	8	1	2	5	8	1
Isoform 1 of Isocitrate dehydrogenase [NAD] subunit alpha, mitochondrial	IPI00030702	2	2	2	2	4	3
Isoform 1 of KH domain-containing, RNA-binding, signal transduction-associated protein 1	IPI00008575	4	3	2	6	6	1
Isoform 1 of Kinesin heavy chain isoform 5C	IPI00028561	3	2	3	0	2	1
Isoform 1 of Large proline-rich protein BAT3	IPI00465128	3	1	1	2	1	0
Isoform 1 of Leukotriene A-4 hydrolase	IPI00219077	8	6	3	0	3	1
Isoform 1 of LIM and SH3 domain protein 1	IPI00000861	3	1	4	5	3	1
Isoform 1 of Lipopolysaccharide-responsive and beige-like anchor protein	IPI00002255	2	2	2	1	4	0
Isoform 1 of L-lactate dehydrogenase A chain	IPI00217966	46	37	26	45	30	22
Isoform 1 of Low molecular weight phosphotyrosine protein phosphatase	IPI00219861	5	2	4	3	5	2
Isoform 1 of Malignant T cell-amplified sequence 1	IPI00179026	1	3	2	5	2	1
Isoform 1 of Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	IPI00005040	3	0	2	1	2	2
Isoform 1 of Metastasis-associated protein MTA3	IPI00165357	5	2	1	5	4	0
Isoform 1 of Methyl-CpG-binding domain protein 3	IPI00439194	2	3	1	4	2	1
Isoform 1 of Microtubule-associated protein 4	IPI00396171	3	2	2	6	9	4
Isoform 1 of Mitotic checkpoint protein BUB3	IPI00013468	4	3	5	1	3	1
Isoform 1 of Myb-binding protein 1A	IPI00005024	7	8	5	1	4	2
Isoform 1 of Myosin-10	IPI00397526	34	20	38	46	36	25
Isoform 1 of Myosin-9	IPI00019502	64	53	61	63	49	45
Isoform 1 of NACHT, LRR and PYD domains-containing protein 2	IPI00016480	3	2	3	1	1	3
Isoform 1 of NADH-cytochrome b5 reductase 3	IPI00328415	3	4	4	7	5	2
Isoform 1 of N-alpha-acetyltransferase 50, NatE catalytic subunit	IPI00018627	6	3	3	6	4	3

Isoform 1 of Nuclear autoantigenic sperm protein	IPI00179953	26	17	15	23	23	15
Isoform 1 of Nuclear pore complex protein Nup155	IPI00026625	11	3	3	1	5	2
Isoform 1 of Nuclear pore complex protein Nup160	IPI00748807	5	2	3	2	2	3
Isoform 1 of Nucleolar RNA helicase 2	IPI00015953	12	10	9	2	4	4
Isoform 1 of Nucleoredoxin	IPI00304267	2	2	1	5	4	1
Isoform 1 of Nucleoside diphosphate kinase A	IPI00012048	2	2	1	1	3	1
Isoform 1 of Obg-like ATPase 1	IPI00290416	9	7	5	7	5	2
Isoform 1 of Oligoribonuclease, mitochondrial (Fragment)	IPI00032830	3	4	3	5	0	1
Isoform 1 of Paraspeckle component 1	IPI00103525	3	2	1	3	4	1
Isoform 1 of Partner of Y14 and mago	IPI00305092	2	1	1	2	1	1
Isoform 1 of Peptidyl-prolyl cis-trans isomerase-like 3	IPI00300952	2	1	2	0	3	3
Isoform 1 of Peroxidasin homolog	IPI00016112	3	2	1	1	5	0
Isoform 1 of Phosphatidylinositol transfer protein beta isoform	IPI00334907	7	3	1	3	3	1
Isoform 1 of Phosphoglucomutase-1	IPI00219526	7	4	6	14	11	0
Isoform 1 of Platelet-activating factor acetylhydrolase IB subunit α	IPI00218728	2	1	2	1	6	0
Isoform 1 of Plectin	IPI00014898	2	0	3	43	32	2
Isoform 1 of Polyadenylate-binding protein 1	IPI00008524	19	13	8	15	14	6
Isoform 1 of Polyadenylate-binding protein 2	IPI00005792	2	2	1	2	1	1
Isoform 1 of Polyadenylate-binding protein 4	IPI00012726	3	2	0	4	1	1
Isoform 1 of Polypyrimidine tract-binding protein 1	IPI00179964	14	11	10	16	12	7
Isoform 1 of Probable ATP-dependent RNA helicase DHX36	IPI00027415	3	2	1	1	3	1
Isoform 1 of Prolyl 4-hydroxylase subunit alpha-1	IPI00009923	3	0	1	2	3	1
Isoform 1 of Proteasome activator complex subunit 3	IPI00030243	9	5	6	7	6	7
Isoform 1 of Proteasome activator complex subunit 4	IPI00005260	5	2	1	1	2	0
Isoform 1 of Proteasome subunit alpha type-7	IPI00024175	15	9	7	8	10	6
Isoform 1 of Protein canopy homolog 2	IPI00443909	4	4	5	5	3	2
Isoform 1 of Protein CIP2A	IPI00154283	3	1	0	2	2	0
Isoform 1 of Protein diaphanous homolog 1	IPI00852685	4	1	3	1	3	0
Isoform 1 of Protein KIAA1967	IPI00182757	7	2	5	6	10	2
Isoform 1 of Protein LSM12 homolog	IPI00410324	3	2	1	1	2	1
Isoform 1 of Protein phosphatase 1 regulatory subunit 12A	IPI00183002	2	0	2	3	3	0
Isoform 1 of Protein phosphatase 1 regulatory subunit 7	IPI00033600	3	1	2	2	1	1
Isoform 1 of Protein SET	IPI00072377	12	11	11	4	1	1
Isoform 1 of Protein syndesmos	IPI00031650	2	3	4	5	3	1
Isoform 1 of Putative helicase MOV-10	IPI00444452	3	1	1	1	2	1
Isoform 1 of Quinone oxidoreductase PIG3	IPI00384643	2	0	1	2	2	0
Isoform 1 of Rab3 GTPase-activating protein non-catalytic subunit	IPI00554590	2	1	1	2	2	0
Isoform 1 of Ras-related protein Rab-1A	IPI00005719	4	3	4	5	1	2
Isoform 1 of Ras-related protein Rab-34	IPI00328180	5	1	0	2	2	1
Isoform 1 of Regulator of nonsense transcripts 1	IPI00034049	6	3	3	3	4	1
Isoform 1 of Replication factor C subunit 2	IPI00017412	3	1	4	3	1	2
Isoform 1 of Replication protein A 32 kDa subunit	IPI00013939	5	1	1	3	3	2
Isoform 1 of Retinol dehydrogenase 11	IPI00339384	5	0	2	2	2	2
Isoform 1 of RNA 3'-terminal phosphate cyclase	IPI00011726	2	1	2	2	1	0
Isoform 1 of RNA-binding protein 25	IPI00004273	3	0	1	3	3	0
Isoform 1 of RuvB-like 1	IPI00021187	7	8	7	11	8	8
Isoform 1 of SEC23-interacting protein	IPI00026969	0	3	1	1	2	0
Isoform 1 of Septin-2	IPI00014177	8	5	4	4	3	5
Isoform 1 of Serine/arginine-rich splicing factor 7	IPI00003377	4	3	5	7	3	0
Isoform 1 of Serine/threonine-protein phosphatase 6 catalytic subunit	IPI00012970	1	2	1	4	5	1
Isoform 1 of Spermine synthase	IPI00005102	9	4	5	5	3	3
Isoform 1 of S-phase kinase-associated protein 1	IPI00301364	6	6	4	7	3	3
Isoform 1 of Splicing factor 3B subunit 3	IPI00300371	17	6	9	8	11	5
Isoform 1 of Squamous cell carcinoma antigen recognized by T-cells 3	IPI00006025	1	0	2	2	2	0
Isoform 1 of Structural maintenance of chromosomes protein 2	IPI00007927	3	0	1	4	3	1
Isoform 1 of Surfeit locus protein 4	IPI00005737	2	2	1	3	3	2
Isoform 1 of Syntaxin-7	IPI00289876	3	1	0	4	3	2

Isoform 1 of TP53RK-binding protein	IPI00301432	1	3	2	2	0	1
Isoform 1 of Transcription elongation factor A protein 1	IPI00333215	5	2	4	4	8	3
Isoform 1 of Transcription factor BTF3	IPI00221035	8	3	6	7	3	2
Isoform 1 of Transcription intermediary factor 1-beta	IPI00438229	12	8	12	8	16	14
Isoform 1 of Transformer-2 protein homolog beta	IPI00301503	4	1	3	2	2	2
Isoform 1 of Transportin-1	IPI00024364	10	8	8	12	10	10
Isoform 1 of Tropomyosin alpha-4 chain	IPI00010779	6	7	8	6	2	5
Isoform 1 of Tryptophanyl-tRNA synthetase, cytoplasmic	IPI00295400	13	9	4	9	8	1
Isoform 1 of U2-associated protein SR140	IPI00143753	3	1	0	4	3	1
Isoform 1 of U5 small nuclear ribonucleoprotein 200 kDa helicase	IPI00420014	23	20	14	6	13	5
Isoform 1 of Ubiquitin conjugation factor E4 B	IPI00005715	1	1	2	2	1	0
Isoform 1 of Ubiquitin-conjugating enzyme E2 K	IPI00021370	6	4	7	3	4	3
Isoform 1 of Ubiquitin-like modifier-activating enzyme 6	IPI00023647	3	2	2	2	1	3
Isoform 1 of UDP-glucose:glycoprotein glucosyltransferase 1	IPI00024466	10	6	3	2	4	1
Isoform 1 of Uridine 5'-monophosphate synthase	IPI00003923	3	3	2	3	3	1
Isoform 1 of UTP--glucose-1-phosphate uridylyltransferase	IPI00329331	23	20	14	19	17	8
Isoform 1 of Vinculin	IPI00291175	56	32	43	56	36	40
Isoform 1 of WD repeat-containing protein 1	IPI00746165	5	3	2	9	6	3
Isoform 1AB of Catenin delta-1	IPI00182469	1	3	2	7	3	5
Isoform 2 of Apoptosis inhibitor 5	IPI00554742	9	6	3	2	1	1
Isoform 2 of ATP-dependent RNA helicase DDX54	IPI00152510	2	0	1	2	1	0
Isoform 2 of Basigin	IPI00019906	6	3	7	3	4	4
Isoform 2 of Cat eye syndrome critical region protein 5	IPI00011511	3	1	3	2	4	1
Isoform 2 of Cell division control protein 42 homolog	IPI00016786	6	2	8	7	3	4
Isoform 2 of Cytochrome P450 2S1	IPI00164018	5	2	4	0	3	1
Isoform 2 of Eukaryotic translation initiation factor 5A-1	IPI00376005	13	12	12	7	12	8
Isoform 2 of F-actin-capping protein subunit beta	IPI00642256	11	7	6	9	7	8
Isoform 2 of Filamin-A	IPI00302592	98	76	69	80	94	55
Isoform 2 of Golgi apparatus protein 1	IPI00414717	4	2	5	4	11	3
Isoform 2 of Golgin subfamily A member 2	IPI00413895	1	0	2	2	2	0
Isoform 2 of Heat shock protein HSP 90-alpha	IPI00382470	33	30	13	39	27	15
Isoform 2 of Heterogeneous nuclear ribonucleoprotein A/B	IPI00334587	7	6	5	7	7	5
Isoform 2 of Isochorismatase domain-containing protein 2	IPI00003031	1	1	2	3	1	0
Isoform 2 of Lysine-specific histone demethylase 1A	IPI00217540	2	1	1	3	5	2
Isoform 2 of N-alpha-acetyltransferase 15, NatA auxiliary subunit	IPI00032158	4	3	3	2	3	1
Isoform 2 of Neutral alpha-glucosidase AB	IPI00011454	13	12	9	26	15	7
Isoform 2 of Nuclear mitotic apparatus protein 1	IPI00006196	8	2	6	5	6	3
Isoform 2 of Nucleoporin NUP188 homolog	IPI00385001	2	2	1	2	2	1
Isoform 2 of Proteasome subunit alpha type-3	IPI00171199	9	10	6	5	6	1
Isoform 2 of Protein disulfide-isomerase A6	IPI00299571	21	15	19	16	10	7
Isoform 2 of Prothymosin alpha	IPI00455510	3	4	3	3	0	6
Isoform 2 of Ras-related protein Rab-6A	IPI00217943	6	3	5	6	4	1
Isoform 2 of Sarcoplasmic/endoplasmic reticulum calcium ATPase 2	IPI00177817	10	1	4	5	7	7
Isoform 2 of Serrate RNA effector molecule homolog	IPI00220038	1	2	4	1	7	0
Isoform 2 of Spliceosome RNA helicase BAT1	IPI00641829	10	7	9	15	9	11
Isoform 2 of Splicing factor 1	IPI00294627	2	2	1	5	5	1
Isoform 2 of Structural maintenance of chromosomes protein 4	IPI00328298	1	2	4	2	4	0
Isoform 2 of Succinyl-CoA ligase [ADP-forming] subunit beta	IPI00217232	2	1	1	2	1	1
Isoform 2 of Suppressor of G2 allele of SKP1 homolog	IPI00791573	6	2	5	4	9	5
Isoform 2 of TAR DNA-binding protein 43	IPI00025815	3	2	3	2	3	1
Isoform 2 of Tropomyosin alpha-3 chain	IPI00218319	27	24	24	26	19	9
Isoform 2 of Tumor protein D54	IPI00221178	3	4	5	1	3	4
Isoform 3 of Anamorsin	IPI00025333	4	0	1	3	6	1
Isoform 3 of Epithelial splicing regulatory protein 1	IPI00184262	3	1	2	2	1	2
Isoform 3 of Nucleolar and coiled-body phosphoprotein 1	IPI00908873	2	2	1	2	0	1
Isoform 3 of Protein PRRC1	IPI00217053	2	1	2	3	2	1
Isoform 3 of Protein transport protein Sec31A	IPI00305152	5	2	2	5	3	2
Isoform 3 of Ribosome-binding protein 1	IPI00215743	5	0	1	4	6	0

Isoform 3 of Serine/arginine-rich splicing factor 10	IPI00009071	1	1	2	3	2	0
Isoform 3 of Ubiquitin-conjugating enzyme E2 variant 1	IPI00472498	2	2	3	4	3	0
Isoform 4 of Tropomyosin alpha-1 chain	IPI00296039	8	9	9	9	0	3
Isoform 4 of Tubulin-specific chaperone D	IPI00030774	2	1	1	1	5	1
Isoform 5 of Dynamin-1-like protein	IPI00037283	7	7	2	2	1	3
Isoform 5 of Interleukin enhancer-binding factor 3	IPI00219330	12	13	7	17	9	8
Isoform 5 of Thioredoxin reductase 1, cytoplasmic	IPI00554786	6	4	0	3	6	1
Isoform A of Ras-related C3 botulinum toxin substrate 1	IPI00010271	3	1	1	3	3	4
Isoform A of RNA-binding protein with multiple splicing	IPI00004045	2	2	3	1	1	2
Isoform A of Trypsin-3	IPI00015614	2	0	1	1	3	2
Isoform A1 of Tight junction protein ZO-2	IPI00003843	3	2	3	1	7	0
Isoform A1-B of Heterogeneous nuclear ribonucleoprotein A1	IPI00215965	32	33	15	36	30	13
Isoform Alpha of Apoptosis regulator BAX	IPI00443773	8	4	4	7	3	4
Isoform Alpha-6X1X2B of Integrin alpha-6	IPI00010697	3	1	2	6	6	0
Isoform alpha-enolase of Alpha-enolase	IPI00465248	48	48	54	46	34	21
Isoform ASF-1 of Serine/arginine-rich splicing factor 1	IPI00215884	7	7	9	9	7	9
Isoform B of Perilipin-3	IPI00303882	8	2	4	11	10	6
Isoform B1 of Heterogeneous nuclear ribonucleoproteins A2/B1	IPI00396378	22	23	15	21	15	14
Isoform Beta of Heat shock protein 105 kDa	IPI00218993	18	9	13	16	18	19
Isoform Beta-1 of Protein phosphatase 1B	IPI00026612	1	0	3	3	4	1
Isoform C1 of Heterogeneous nuclear ribonucleoproteins C1/C2	IPI00216592	10	12	11	16	9	9
Isoform Complexed of Arginyl-tRNA synthetase, cytoplasmic	IPI00004860	10	3	4	12	8	2
Isoform CSBP2 of Mitogen-activated protein kinase 14	IPI00002857	3	2	0	5	0	1
Isoform Cytoplasmic of Lysyl-tRNA synthetase	IPI00014238	11	4	4	6	5	0
Isoform Delta-1 of Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit delta isoform	IPI00000030	1	2	2	3	1	0
Isoform DFF45 of DNA fragmentation factor subunit alpha (Fragment)	IPI00010882	2	1	0	2	0	2
Isoform Gamma-1 of Serine/threonine-protein phosphatase PP1-gamma catalytic subunit	IPI00005705	1	2	2	1	2	2
Isoform GTBP-N of DNA mismatch repair protein Msh6	IPI00384456	7	6	8	6	9	10
Isoform II of Ubiquitin-protein ligase E3A	IPI00011609	4	0	1	4	1	0
Isoform Long of 14-3-3 protein beta/alpha	IPI00216318	14	8	11	13	11	9
Isoform Long of Cold shock domain-containing protein E1	IPI00470891	4	0	3	4	4	1
Isoform Long of Delta-1-pyrroline-5-carboxylate synthase	IPI00008982	10	8	9	7	5	4
Isoform Long of Double-stranded RNA-binding protein Staufen homolog 1	IPI00000001	4	1	1	3	2	0
Isoform Long of Eukaryotic translation initiation factor 4H	IPI00014263	2	3	4	3	3	2
Isoform Long of Glucose-6-phosphate 1-dehydrogenase	IPI00216008	6	4	1	2	2	0
Isoform Long of Heterogeneous nuclear ribonucleoprotein U	IPI00883857	21	17	12	22	21	14
Isoform Long of Sodium/potassium-transporting ATPase subunit α-1	IPI00006482	15	11	10	13	13	8
Isoform Long of Spectrin beta chain, brain 1	IPI00005614	34	18	19	33	46	16
Isoform Long of Splicing factor, proline- and glutamine-rich	IPI00010740	9	11	11	13	15	7
Isoform Long of Trifunctional purine biosynthetic protein adenosine-3	IPI00025273	11	11	9	8	15	10
Isoform Long of Ubiquitin carboxyl-terminal hydrolase 5	IPI00024664	12	6	6	4	4	4
Isoform M2 of Pyruvate kinase isozymes M1/M2	IPI00479186	42	40	27	51	38	26
Isoform Mitochondrial of Peroxiredoxin-5, mitochondrial	IPI00024915	7	4	9	10	4	6
Isoform Mitochondrial of Phospholipid hydroperoxide glutathione peroxidase, mitochondrial	IPI00304814	6	4	1	4	1	0
Isoform p150 of Dynactin subunit 1	IPI00029485	7	2	4	2	7	4
Isoform p26 of 7,8-dihydro-8-oxoguanine triphosphatase	IPI00004392	2	2	3	4	2	1
Isoform p27-L of 26S proteasome non-ATPase regulatory subunit 9	IPI00010860	2	0	3	1	3	0
Isoform Rpn10A of 26S proteasome non-ATPase regulatory subunit 4	IPI00022694	3	1	3	6	7	0
Isoform Sap-mu-0 of Proactivator polypeptide	IPI00012503	3	1	2	1	1	2
Isoform Short of Proteasome subunit alpha type-1	IPI00016832	15	4	7	5	5	4
Isoform Short of RNA-binding protein FUS	IPI00221354	5	0	3	8	6	0
Isoform Short of Ubiquitin fusion degradation protein 1 homolog	IPI00218292	2	0	2	1	3	2
Isoform SM-B' of Small nuclear ribonucleoprotein-associated proteins B and B'	IPI00027285	2	4	2	4	2	2

Isoform SNAP-23a of Synaptosomal-associated protein 23	IPI00010438	2	2	2	2	1	1
Isoform SRP55-1 of Serine/arginine-rich splicing factor 6	IPI00012345	2	2	4	2	1	1
Isoleucyl-tRNA synthetase, cytoplasmic	IPI00644127	20	9	6	13	25	5
Junction plakoglobin	IPI00554711	2	2	0	4	5	3
Junctional adhesion molecule A	IPI00001754	3	1	3	3	4	1
Keratin, type I cytoskeletal 10	IPI00009865	13	11	6	21	20	15
Keratin, type I cytoskeletal 18	IPI00554788	8	6	6	20	19	8
Keratin, type I cytoskeletal 9	IPI00019359	8	3	5	5	15	13
Keratin, type II cytoskeletal 1	IPI00220327	10	9	6	25	18	17
Keratin, type II cytoskeletal 2 epidermal	IPI00021304	4	4	4	17	16	9
Keratin, type II cytoskeletal 8	IPI00554648	21	7	17	42	33	16
Kinesin-1 heavy chain	IPI00012837	13	5	8	8	11	11
Kinesin-like protein KIF11	IPI00305289	4	5	3	4	5	0
Lactoylglutathione lyase	IPI00220766	5	5	5	5	3	4
Lamin-B1	IPI00217975	4	1	4	5	7	3
Laminin subunit alpha-1	IPI00375294	3	4	4	1	3	0
Laminin subunit beta-1	IPI00013976	5	2	4	1	5	6
Laminin subunit gamma-1	IPI00298281	9	2	2	3	11	4
Lanosterol synthase	IPI00009747	5	5	7	6	4	0
Leucine-rich PPR motif-containing protein, mitochondrial	IPI00783271	43	36	19	18	22	16
Leucine-rich repeat-containing protein 47	IPI00170935	5	2	4	5	3	0
Leucine-rich repeat-containing protein 59	IPI00396321	4	2	5	9	4	2
Leucyl-tRNA synthetase, cytoplasmic	IPI00103994	18	13	12	7	14	8
LINE-1 type transposase domain-containing protein 1	IPI00253050	18	9	12	17	10	14
L-lactate dehydrogenase B chain	IPI00219217	20	27	19	23	15	15
Lon protease homolog, mitochondrial	IPI00005158	5	2	3	5	1	0
Long-chain-fatty-acid--CoA ligase 3	IPI00031397	2	1	1	1	4	1
Lupus La protein	IPI00009032	17	13	14	15	8	8
Macrophage migration inhibitory factor	IPI00293276	3	2	2	3	3	2
Malate dehydrogenase	IPI00916111	11	11	8	10	8	8
Malate dehydrogenase, mitochondrial	IPI00291006	22	13	16	17	13	13
Matrin-3	IPI00017297	19	11	14	9	10	11
Membrane-associated progesterone receptor component 1	IPI00220739	4	4	3	3	3	3
Methionyl-tRNA synthetase, cytoplasmic	IPI00008240	13	7	6	11	11	10
Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1	IPI00291646	3	1	4	2	3	0
Methylosome subunit pICln	IPI00004795	2	3	2	3	3	2
Microsomal glutathione S-transferase 1	IPI00021805	4	1	2	1	3	2
Microtubule-associated protein 1B	IPI00008868	1	0	4	4	6	0
Microtubule-associated protein RP/EB family member 1	IPI00017596	8	1	8	5	5	7
Midasin	IPI00167941	17	9	11	3	8	0
Mitochondrial fission 1 protein	IPI00007052	2	2	3	3	2	3
Mitochondrial import receptor subunit TOM22 homolog	IPI00024976	2	0	1	2	5	2
Moesin	IPI00219365	18	11	5	14	8	7
mRNA turnover protein 4 homolog	IPI00106491	6	2	1	2	2	1
Multifunctional protein ADE2	IPI00217223	21	16	14	21	17	11
N(G),N(G)-dimethylarginine dimethylaminohydrolase 1	IPI00220342	4	6	3	3	3	1
Na(+)/H(+) exchange regulatory cofactor NHE-RF1	IPI00003527	3	3	4	5	6	2
N-acetyltransferase 10	IPI00300127	7	3	2	4	6	2
NADH dehydrogenase [ubiquinone] flavoprotein 2, mitochondrial	IPI00291328	2	2	2	3	1	1
NADH dehydrogenase [ubiquinone] iron-sulfur protein 3	IPI00025796	3	4	4	5	1	2
NADPH--cytochrome P450 reductase	IPI00470467	6	4	0	2	2	2
N-alpha-acetyltransferase 10, NatA catalytic subunit	IPI00013184	3	2	2	2	2	1
Nascent polypeptide-associated complex subunit alpha	IPI00023748	7	8	5	8	5	5
NEDD8-activating enzyme E1 catalytic subunit	IPI00328154	4	0	2	3	6	0
NEDD8-conjugating enzyme Ubc12	IPI00022597	1	3	4	5	4	2
Nestin	IPI00010800	16	5	9	11	25	16
NHP2-like protein 1	IPI00026167	2	0	4	3	2	3
Nicotinamide phosphoribosyltransferase	IPI00018873	6	4	3	5	4	3

Nodal modulator 1	IPI00329352	2	1	1	4	6	2
Non-POU domain-containing octamer-binding protein	IPI00304596	11	8	5	17	8	4
Nuclear migration protein nudC	IPI00550746	10	3	6	6	4	6
Nuclear pore complex protein Nup107	IPI00028005	5	1	1	2	1	2
Nuclear pore complex protein Nup133	IPI00291200	6	1	0	3	2	0
Nuclear pore complex protein Nup205	IPI00783781	11	5	2	4	6	1
Nuclear pore complex protein Nup93	IPI00397904	7	4	4	2	5	5
Nuclear transport factor 2	IPI00009901	4	1	2	2	1	4
Nuclease-sensitive element-binding protein 1	IPI00031812	8	5	6	3	13	10
Nucleobindin-1	IPI00295542	4	3	1	3	0	1
Nucleolar GTP-binding protein 1	IPI00385042	6	2	1	3	4	1
Nucleolar protein 56	IPI00411937	3	1	1	6	5	1
Nucleolar protein 58	IPI00006379	4	3	2	7	5	0
Nucleoporin 54kDa variant (Fragment)	IPI00172580	1	2	1	0	2	1
Nucleoprotein TPR	IPI00742682	13	5	18	17	10	2
Nucleoside diphosphate kinase	IPI00604590	21	14	16	16	12	8
Nucleoside-triphosphatase C1orf57	IPI00031570	2	3	2	2	2	1
Nucleosome assembly protein 1-like 1	IPI00023860	12	9	10	11	12	7
NudC domain-containing protein 2	IPI00103142	6	1	2	1	2	1
Ornithine aminotransferase, mitochondrial	IPI00022334	11	11	7	2	1	1
OTU domain-containing protein 6B	IPI00182180	1	1	3	4	2	2
PDZ and LIM domain protein 1	IPI00010414	8	3	1	12	11	9
Peptidyl-prolyl cis-trans isomerase A	IPI00419585	21	16	20	18	18	14
Peptidyl-prolyl cis-trans isomerase B	IPI00646304	11	10	11	11	11	3
Peptidyl-prolyl cis-trans isomerase FKBP4	IPI00219005	15	8	6	12	16	8
Peptidyl-prolyl cis-trans isomerase H	IPI00007346	3	0	2	3	1	0
Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	IPI00013723	5	1	1	4	2	1
Peptidyl-prolyl cis-trans isomerase-like 1	IPI00007019	2	1	4	4	1	0
Peroxiredoxin-1	IPI00000874	21	22	25	31	14	10
Peroxiredoxin-2	IPI00027350	9	13	10	9	6	3
Peroxiredoxin-4	IPI00011937	10	9	6	8	7	4
Peroxiredoxin-6	IPI00220301	20	25	26	27	17	13
Peroxisomal multifunctional enzyme type 2	IPI00019912	8	7	4	7	5	0
Phosducin-like protein 3	IPI00031629	5	0	1	2	5	4
Phosphatidylethanolamine-binding protein 1	IPI00219446	7	9	8	7	6	5
Phosphoglycerate kinase 1	IPI00169383	36	36	36	34	29	19
Phosphoglycolate phosphatase	IPI00177008	2	2	3	3	3	2
Phospholipase D3	IPI00328243	2	0	1	3	0	1
Phosphoribosylformylglycinamidine synthase	IPI00004534	20	10	11	20	18	14
Phosphoserine aminotransferase	IPI00001734	15	15	12	14	11	6
Phosphoserine phosphatase	IPI00019178	4	3	3	3	2	1
Plastin-3	IPI00216694	23	18	11	13	16	6
Platelet-activating factor acetylhydrolase IB subunit beta	IPI00026546	3	2	3	2	2	3
Platelet-activating factor acetylhydrolase IB subunit gamma	IPI00014808	1	1	3	1	0	2
Podocalyxin-like protein 1 precursor	IPI00299116	5	3	5	3	6	3
Poly [ADP-ribose] polymerase 1	IPI00449049	5	3	9	14	11	9
Poly(rC)-binding protein 1	IPI00016610	10	11	11	11	10	10
Prefoldin subunit 2	IPI00006052	5	3	3	5	2	2
Prefoldin subunit 5	IPI00015361	5	1	3	6	1	3
Pre-mRNA-processing factor 19	IPI00004968	5	2	1	7	10	0
Pre-mRNA-processing-splicing factor 8	IPI00007928	26	19	11	9	26	15
Pre-mRNA-splicing factor ATP-dependent RNA helicase PRP16	IPI00294211	2	1	0	2	0	1
Pre-mRNA-splicing factor SPF27	IPI00025178	3	3	2	3	1	2
Probable ATP-dependent RNA helicase DDX5	IPI00017617	16	11	7	14	13	7
Probable ATP-dependent RNA helicase DDX6	IPI00030320	6	2	5	2	1	2
Probable fructose-2,6-bisphosphatase TIGAR	IPI00006907	4	2	2	2	1	0
Probable ribosome biogenesis protein NEP1	IPI00025347	4	2	1	3	2	1
probable ubiquitin carboxyl-terminal hydrolase FAF-X isoform 4	IPI00003964	12	6	12	8	14	2

Profilin-1	IPI00216691	18	13	18	18	11	9
progesterone receptor membrane component 2	IPI00005202	2	2	1	4	2	1
Programmed cell death 6-interacting protein	IPI00246058	6	2	5	9	8	8
Programmed cell death protein 10	IPI00298558	2	2	2	2	2	2
Programmed cell death protein 6	IPI00025277	4	2	3	4	4	2
Prohibitin	IPI00017334	5	5	5	7	3	4
Prohibitin-2	IPI00027252	4	3	4	10	8	5
Proliferating cell nuclear antigen	IPI00021700	10	5	8	5	4	4
Proliferation-associated protein 2G4	IPI00299000	14	6	8	1	3	1
Prolyl endopeptidase	IPI00008164	3	5	2	7	5	2
Prostaglandin E synthase 3	IPI00015029	6	4	5	4	4	3
Prostaglandin reductase 1	IPI00292657	2	1	0	6	10	3
Proteasome 26S non-ATPase subunit 11 variant (Fragment)	IPI00105598	16	9	5	2	2	3
Proteasome activator complex subunit 1	IPI00479722	5	4	4	6	1	2
Proteasome subunit alpha type-2	IPI00219622	6	5	7	6	4	4
Proteasome subunit alpha type-4	IPI00299155	6	5	6	2	5	5
Proteasome subunit alpha type-5	IPI00291922	7	6	6	7	5	5
Proteasome subunit alpha type-6	IPI00029623	10	10	11	8	5	6
Proteasome subunit beta type-1	IPI00025019	8	10	8	10	6	3
Proteasome subunit beta type-2	IPI00028006	7	8	6	7	3	4
Proteasome subunit beta type-3	IPI00028004	8	9	7	9	1	3
Proteasome subunit beta type-5	IPI00479306	14	9	9	7	9	4
Proteasome subunit beta type-6	IPI00000811	4	4	4	6	4	2
proteasome-associated protein ECM29 homolog	IPI00157790	14	12	13	13	18	6
protein arginine N-methyltransferase 1 isoform 1	IPI00018522	12	7	11	3	10	10
Protein C10	IPI00016925	3	1	3	2	0	4
Protein disulfide-isomerase	IPI00010796	21	17	10	25	16	7
Protein disulfide-isomerase A3	IPI00025252	27	28	18	33	32	16
Protein disulfide-isomerase A4	IPI00009904	17	16	12	23	13	8
Protein DJ-1	IPI00298547	11	12	10	9	7	8
Protein dpy-30 homolog	IPI00028109	0	1	2	2	0	1
Protein FAM3C	IPI00334282	4	4	3	2	1	3
Protein FAM49B	IPI00303318	7	4	3	5	2	2
Protein FAM96B	IPI00007024	3	0	1	2	1	0
Protein kinase, cAMP-dependent, regulatory, type II, alpha, isoform CRA_b	IPI00063234	2	0	1	1	2	0
Protein lin-28 homolog A	IPI00002948	10	13	9	11	12	9
Protein lin-7 homolog C	IPI00019997	3	1	2	3	1	1
Protein mago nashi homolog 2	IPI00059292	5	3	7	5	2	3
Protein of unknown function DUF858, methyltransferase-like family protein	IPI00549389	3	3	0	2	1	2
Protein phosphatase 1G	IPI00006167	2	2	4	3	4	2
Protein RCC2	IPI00465044	8	3	2	7	8	5
Protein RRP5 homolog	IPI00400922	5	4	2	1	2	1
Protein S100-A11	IPI00013895	3	2	2	5	2	1
Protein transport protein Sec23A	IPI00017375	2	1	3	5	5	2
Protein transport protein Sec23B	IPI00017376	5	4	3	3	4	0
Protein transport protein Sec61 subunit beta	IPI00220835	2	2	2	1	1	3
Pseudouridylate synthase 7 homolog	IPI00044761	2	4	3	2	1	0
Puromycin-sensitive aminopeptidase	IPI00026216	10	8	6	11	8	9
Putative pre-mRNA-splicing factor ATP-dependent RNA helicase DHX15	IPI00396435	8	12	6	3	1	4
Putative RNA-binding protein 3	IPI00024320	3	2	3	2	3	3
Putative uncharacterized protein	IPI00010402	3	0	2	1	1	2
Putative uncharacterized protein DKFZp686L20222	IPI00026689	7	6	6	7	4	2
Quinone oxidoreductase	IPI00000792	3	2	2	2	2	1
Rab GDP dissociation inhibitor beta	IPI00940148	29	25	25	26	20	17
Radixin, isoform CRA_a	IPI00017367	3	2	0	6	4	2

Ran GTPase-activating protein 1	IPI00294879	11	4	6	7	4	4
Ran-specific GTPase-activating protein	IPI00414127	7	5	6	8	5	5
Ras GTPase-activating protein-binding protein 1	IPI00012442	9	5	5	9	9	3
Ras GTPase-activating-like protein IQGAP1	IPI00009342	15	7	8	25	24	21
Ras suppressor protein 1	IPI00017256	3	3	5	4	3	4
Ras-related protein Rab-10	IPI00016513	3	4	3	4	4	1
Ras-related protein Rab-11B	IPI00020436	7	6	6	6	6	4
Ras-related protein Rab-14	IPI00291928	5	5	4	3	1	1
Ras-related protein Rab-18	IPI00014577	6	3	5	4	5	3
Ras-related protein Rab-1B	IPI00008964	9	6	10	13	6	3
Ras-related protein Rab-21	IPI00007755	1	2	4	1	0	2
Ras-related protein Rab-3B	IPI00300562	4	2	3	2	2	2
Ras-related protein Rab-5C	IPI00016339	9	6	6	5	3	4
Ras-related protein Rab-7a	IPI00016342	9	5	8	2	2	1
Ras-related protein Rab-8A	IPI00028481	4	1	3	2	0	1
Replication factor C subunit 4	IPI00017381	2	2	2	0	2	1
Reticulocalbin-1	IPI00015842	5	2	2	5	1	1
Reticulocalbin-2	IPI00029628	3	3	1	2	1	2
retinol-binding protein 1 isoform a	IPI00219718	2	0	1	2	2	0
Rho GDP-dissociation inhibitor 1	IPI00003815	9	4	5	6	5	4
Rho GTPase-activating protein 1	IPI00020567	5	5	2	8	7	0
RhoA activator C11orf59	IPI00016670	1	1	2	2	2	0
Rho-related GTP-binding protein RhoC	IPI00027434	2	1	2	2	1	3
Ribonuclease inhibitor	IPI00550069	4	1	4	1	3	1
Ribonuclease UK114	IPI00005038	3	0	2	2	2	1
Ribonucleoside-diphosphate reductase large subunit	IPI00013871	6	5	2	1	0	2
ribonucleoside-diphosphate reductase subunit M2 isoform 1	IPI00011118	6	4	5	5	3	0
Ribose-phosphate pyrophosphokinase 1	IPI00219616	8	7	4	7	6	3
Ribosomal protein L14 variant	IPI00555744	4	5	3	4	3	2
Ribosome biogenesis protein WDR12	IPI00304232	3	1	1	1	5	1
RNA-binding protein with multiple splicing 2	IPI00238688	2	0	2	4	1	3
rRNA 2'-O-methyltransferase fibrillarin	IPI00025039	5	10	1	5	6	3
RuvB-like 2	IPI00009104	7	10	11	8	10	6
S-adenosylmethionine synthase isoform type-2	IPI00010157	10	5	10	4	1	4
Selenide, water dikinase 1	IPI00029056	8	7	7	6	6	7
Sentrin-specific protease 8	IPI00165616	1	0	3	2	0	1
Serine hydroxymethyltransferase, mitochondrial	IPI00002520	10	8	12	7	4	4
Serine/arginine-rich splicing factor 2	IPI00005978	0	4	2	1	2	4
Serine/arginine-rich splicing factor 3	IPI00010204	6	4	6	10	4	2
Serine/arginine-rich splicing factor 9	IPI00012340	5	6	4	4	2	3
Serine/threonine-protein kinase MST4	IPI00292827	11	1	7	3	4	0
Serine/threonine-protein kinase OSR1	IPI00010080	2	3	3	2	0	1
Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B alpha isoform	IPI00332511	5	2	4	0	2	1
Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit epsilon isoform	IPI00002853	2	2	3	2	2	0
Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform	IPI00554737	19	14	12	25	13	9
Serine/threonine-protein phosphatase 2A catalytic subunit alpha isoform	IPI00008380	4	4	4	5	7	4
serine/threonine-protein phosphatase PP1-alpha catalytic subunit isoform 3	IPI00027423	12	8	9	10	10	7
Serine/threonine-protein phosphatase PP1-beta catalytic subunit	IPI00218236	4	2	3	1	3	3
Serpin B6	IPI00413451	1	2	1	3	1	0
Serpin B9	IPI00032139	3	6	11	11	11	8
Serpin H1	IPI00032140	20	18	17	20	19	17
Seryl-tRNA synthetase, cytoplasmic	IPI00220637	3	1	2	3	2	0
SF3A2 protein (Fragment)	IPI00017341	3	1	1	1	2	1

S-formylglutathione hydrolase	IPI00411706	2	2	1	1	2	1
SH3 domain-binding glutamic acid-rich-like protein	IPI00025318	3	2	4	6	2	4
Sialic acid synthase	IPI00147874	3	4	3	4	3	3
Sideroflexin-1	IPI00009368	3	0	1	3	1	1
Signal recognition particle 72 kDa protein	IPI00215888	3	2	0	2	1	0
Signal recognition particle 9 kDa protein	IPI00642816	2	1	2	2	2	1
Single-stranded DNA-binding protein, mitochondrial	IPI00029744	6	4	7	10	5	5
Small glutamine-rich tetratricopeptide repeat-containing protein α	IPI00013949	2	5	3	7	2	3
Small nuclear ribonucleoprotein E	IPI00029266	3	2	2	3	1	2
Small nuclear ribonucleoprotein F	IPI00220528	3	2	3	2	1	1
Small nuclear ribonucleoprotein Sm D1	IPI00302850	7	3	5	2	1	2
Small nuclear ribonucleoprotein Sm D2	IPI00017963	6	3	4	6	4	3
Small nuclear ribonucleoprotein Sm D3	IPI00017964	2	2	2	1	3	2
Sodium/potassium-transporting ATPase subunit beta-3	IPI00008167	4	3	2	1	2	1
Solute carrier family 2, facilitated glucose transporter member 1	IPI00220194	6	4	3	4	3	1
Solute carrier family 2, facilitated glucose transporter member 3	IPI00003909	2	2	2	3	3	0
Sorcin	IPI00027175	4	2	5	5	3	1
Sperm-associated antigen 7	IPI00006863	4	0	3	2	0	2
Spermidine synthase	IPI00292020	7	5	4	7	3	3
Splicing factor 3A subunit 1	IPI00017451	7	5	5	6	8	3
Splicing factor 3A subunit 3	IPI00029764	4	6	1	3	1	0
Splicing factor 3B subunit 1	IPI00026089	19	10	12	13	23	10
Splicing factor 3B subunit 2	IPI00221106	3	1	4	1	3	2
Splicing factor U2AF 35 kDa subunit	IPI00005613	3	3	4	4	3	4
Squalene monooxygenase	IPI00291544	2	1	2	1	4	0
Squalene synthase	IPI00020944	9	9	14	7	6	3
SRA stem-loop-interacting RNA-binding protein, mitochondrial	IPI00009922	2	1	3	1	2	1
Staphylococcal nuclease domain-containing protein 1	IPI00140420	13	8	7	14	14	14
Stathmin	IPI00479997	4	9	6	6	1	3
Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	IPI00019407	3	3	5	2	1	1
Stress-70 protein, mitochondrial	IPI00007765	28	14	19	21	16	11
Stress-induced-phosphoprotein 1	IPI00013894	16	12	4	5	5	1
Structural maintenance of chromosomes protein 1A	IPI00291939	3	1	1	3	4	3
Structural maintenance of chromosomes protein 3	IPI00219420	5	1	3	3	6	0
SUMO-activating enzyme subunit 1	IPI00033130	5	6	6	2	1	0
SUMO-activating enzyme subunit 2	IPI00023234	6	4	3	3	6	5
SUMO-conjugating enzyme UBC9	IPI00032957	1	2	3	2	4	2
Superkiller viralicidic activity 2-like 2	IPI00647217	10	4	4	6	8	0
Superoxide dismutase [Cu-Zn]	IPI00218733	5	3	4	4	1	1
SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 5	IPI00297211	1	0	3	1	6	3
Synaptic vesicle membrane protein VAT-1 homolog	IPI00156689	8	4	7	7	8	4
Talin-1	IPI00298994	23	11	24	37	31	22
T-complex protein 1 subunit alpha	IPI00290566	17	8	9	20	16	7
T-complex protein 1 subunit beta	IPI00297779	26	26	14	26	28	15
T-complex protein 1 subunit delta	IPI00302927	13	11	11	11	17	10
T-complex protein 1 subunit epsilon	IPI00010720	19	17	6	18	17	6
T-complex protein 1 subunit eta	IPI00018465	17	15	8	13	10	10
T-complex protein 1 subunit zeta	IPI00027626	10	15	9	16	11	8
TEL2-interacting protein 1 homolog	IPI00011702	3	2	1	2	1	1
Thimet oligopeptidase	IPI00549189	2	2	1	2	1	0
Thioredoxin	IPI00216298	3	3	2	3	1	3
Thioredoxin domain-containing protein 12	IPI00026328	2	3	2	2	1	0
Thioredoxin domain-containing protein 17	IPI00646689	3	2	4	2	3	2
Thioredoxin domain-containing protein 5	IPI00171438	4	4	4	3	5	3
Thioredoxin-dependent peroxide reductase, mitochondrial	IPI00024919	9	10	9	6	5	6
Thioredoxin-like protein 1	IPI00305692	9	5	6	8	7	4
THO complex subunit 4	IPI00328840	8	3	5	4	6	7

Threonyl-tRNA synthetase, cytoplasmic	IPI00329633	15	14	12	10	11	11
THUMP domain-containing protein 1	IPI00550243	2	0	3	1	4	1
Thy-1 membrane glycoprotein	IPI00022892	1	2	3	2	1	1
Trafficking protein particle complex subunit 3	IPI00004324	1	0	2	2	0	1
Transaldolase	IPI00744692	9	8	5	12	10	6
Transcription elongation factor B polypeptide 1	IPI00300341	3	1	1	1	0	2
Transferrin receptor protein 1	IPI00022462	10	4	4	2	3	1
Transforming protein RhoA	IPI00478231	6	6	9	10	8	7
Transgelin	IPI00216138	15	16	16	19	20	10
Transgelin-2	IPI00550363	6	8	8	14	9	9
Transitional endoplasmic reticulum ATPase	IPI00022774	34	36	20	34	32	24
Translation initiation factor eIF-2B subunit alpha	IPI00221300	2	0	2	3	2	0
Translational activator GCN1	IPI00001159	18	20	12	21	4	10
Translin	IPI00018768	6	7	5	8	4	6
Translin-associated protein X	IPI00293350	5	4	3	6	2	2
Transmembrane emp24 domain-containing protein 10	IPI00028055	5	7	5	8	7	2
Transmembrane emp24 domain-containing protein 2	IPI00016608	1	2	1	3	1	0
Transmembrane emp24 domain-containing protein 9	IPI00023542	2	1	3	4	2	3
Trifunctional enzyme subunit alpha, mitochondrial	IPI00031522	8	8	1	8	4	1
triosephosphate isomerase isoform 2	IPI00465028	26	30	26	31	21	16
Tripartite motif-containing protein 71	IPI00719053	3	4	5	1	2	1
Tripeptidyl-peptidase 2	IPI00020416	8	5	4	3	7	0
tRNA (cytosine-5-)-methyltransferase NSUN2	IPI00306369	7	3	3	2	6	1
tRNA (guanine-N(7)-)-methyltransferase	IPI00290184	3	1	3	2	0	1
tRNA methyltransferase 112 homolog	IPI00009010	2	2	2	2	2	2
Tropomodulin-3	IPI00005087	4	2	4	3	5	2
Tu translation elongation factor, mitochondrial precursor	IPI00027107	11	6	8	11	7	1
TUBB6 protein	IPI00646779	2	3	4	3	2	4
Tubulin alpha-1C chain	IPI00218343	3	2	1	2	3	1
Tubulin beta-2A chain	IPI00013475	2	1	2	2	1	1
Tubulin beta-2B chain	IPI00031370	29	34	31	8	9	5
Tubulin beta-2C chain	IPI00007752	4	5	3	9	8	4
Tubulin beta-3 chain	IPI00013683	10	6	8	7	7	2
Tubulin beta-4 chain	IPI00023598	2	2	3	3	1	1
Tubulin, beta	IPI00645452	10	8	12	35	35	23
Tubulin-folding cofactor B	IPI00293126	4	2	5	5	3	2
Tubulin-specific chaperone A	IPI00217236	7	7	7	6	6	5
Tubulin-specific chaperone E	IPI00018402	4	1	2	2	1	0
Tubulin--tyrosine ligase-like protein 12	IPI00029048	5	7	0	9	8	4
Tumor protein, translationally-controlled 1	IPI00009943	8	7	3	5	7	5
Twinfilin-2	IPI00550917	1	2	1	2	2	1
Tyrosyl-tRNA synthetase, cytoplasmic	IPI00007074	10	10	4	11	8	2
U1 small nuclear ribonucleoprotein A	IPI00012382	3	0	1	3	1	0
U2 small nuclear ribonucleoprotein A'	IPI00297477	9	7	9	8	2	3
U2 small nuclear ribonucleoprotein B''	IPI00029267	2	3	2	4	1	0
U6 snRNA-associated Sm-like protein LSm2	IPI00032460	2	2	2	2	1	1
U6 snRNA-associated Sm-like protein LSm3	IPI00219229	0	1	3	2	1	0
U6 snRNA-associated Sm-like protein LSm4	IPI00294955	5	2	2	2	2	2
Ubiquitin carboxyl-terminal hydrolase 10	IPI00291946	3	1	4	2	2	1
Ubiquitin carboxyl-terminal hydrolase 11	IPI00184533	5	5	4	1	2	1
Ubiquitin carboxyl-terminal hydrolase 14	IPI00219913	8	5	2	5	8	3
Ubiquitin carboxyl-terminal hydrolase 7	IPI00003965	9	5	8	2	1	1
Ubiquitin carboxyl-terminal hydrolase isozyme L1	IPI00018352	11	8	9	13	7	6
Ubiquitin-40S ribosomal protein S27a	IPI00179330	7	3	9	10	3	5
Ubiquitin-conjugating enzyme E2 G1	IPI00219783	3	1	0	2	2	0
Ubiquitin-conjugating enzyme E2 L3	IPI00021347	6	3	5	3	4	2
Ubiquitin-conjugating enzyme E2 O	IPI00783378	4	2	2	3	5	1
Ubiquitin-like modifier-activating enzyme 1	IPI00645078	33	22	25	23	21	19

UDP-glucose 6-dehydrogenase	IPI00031420	7	2	5	2	2	0
Uncharacterized protein	IPI00022434	6	10	5	5	6	6
Uncharacterized protein C17orf25	IPI00007102	5	5	4	7	6	3
UPF0027 protein C22orf28	IPI00550689	6	3	2	1	1	2
UPF0160 protein MYG1, mitochondrial	IPI00029444	2	1	4	5	1	0
UPF0364 protein C6orf211	IPI00002270	5	2	4	4	5	1
UPF0368 protein Cxorf26	IPI00107104	4	3	1	1	3	0
UPF0568 protein C14orf166	IPI00006980	7	9	7	2	0	1
UPF0587 protein C1orf123	IPI00016605	3	1	1	3	1	0
UPF0727 protein C6orf115	IPI00855846	2	2	3	3	0	1
Uroporphyrinogen decarboxylase	IPI00301489	4	4	2	4	4	1
UV excision repair protein RAD23 homolog B	IPI00008223	2	3	1	5	4	2
Vacuolar protein sorting-associated protein 26A	IPI00411426	3	0	1	0	2	1
Vacuolar protein sorting-associated protein 35	IPI00018931	2	4	1	10	5	4
Vacuolar protein sorting-associated protein VTA1 homolog	IPI00017160	1	2	0	1	2	0
Valyl-tRNA synthetase	IPI00000873	12	5	6	10	5	9
Vesicular integral-membrane protein VIP36	IPI00009950	2	2	1	7	4	1
Vimentin	IPI00418471	33	10	18	47	40	27
Visinin-like protein 1	IPI00216313	7	3	4	3	1	0
von Hippel-Lindau binding protein 1, isoform CRA_b	IPI00334159	3	2	2	1	4	1
V-type proton ATPase catalytic subunit A	IPI00007682	8	4	2	6	2	2
V-type proton ATPase subunit C 1	IPI00007814	1	0	2	2	1	1
V-type proton ATPase subunit E 1	IPI00003856	3	1	2	3	2	1
V-type proton ATPase subunit G 1	IPI00025285	4	0	3	3	0	1
WD repeat and HMG-box DNA-binding protein 1	IPI00411614	1	1	3	1	3	0
Xaa-Pro dipeptidase	IPI00257882	4	3	2	4	4	0
X-ray repair cross-complementing protein 5	IPI00220834	28	18	11	19	20	13
X-ray repair cross-complementing protein 6	IPI00644712	26	23	13	38	26	9
Zyxin	IPI00926625	6	6	2	6	6	4

Note: "Peptide IDs" means the number of unique peptides that were identified from the corresponding protein during one replicate of the experiment. Three replicates are shown for each cell line.

Appendix F *All proteins identified at 72 hours in hypoxia*

Protein Name	IPI Number	Peptide IDs, H9 replicates			Peptide IDs, CA1 replicates		
60S ribosomal protein L35a	IPI00029731	1	3	3	2	1	2
histone deacetylase complex subunit SAP18	IPI00011698	2	1	0	5	1	1
Isoform 1 of Fanconi anemia group I protein	IPI00019447	4	0	1	3	3	1
Isoform 1 of Far upstream element-binding protein 1	IPI00375441	8	3	9	8	10	6
Isoform 1 of Isopentenyl-diphosphate Delta-isomerase 1	IPI00645307	6	5	9	4	5	4
Isoform 1 of Leucine zipper protein 1	IPI00296830	2	0	1	3	2	1
Isoform 1 of Mps one binder kinase activator-like 3	IPI00386122	2	0	1	0	3	2
Isoform 1 of Tumor protein D52	IPI00619958	3	3	3	5	5	4
Isoform 2 of PERQ amino acid-rich with GYF domain protein 2	IPI00647635	2	0	1	0	3	1
Isoform 2 of Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	IPI00337495	7	1	1	2	6	1
Isoform 2 of Protein enabled homolog	IPI00374054	1	0	5	2	2	0
Isoform 2 of Regulation of nuclear pre-mRNA domain protein 1A	IPI00062336	2	0	6	1	2	0
Isoform 4 of Afadin	IPI00023461	4	1	1	3	1	0
Isoform 4 of Sorting nexin-3	IPI00552276	3	0	3	2	2	1
Mannosyl-oligosaccharide glucosidase	IPI00328170	1	2	1	6	3	3
NADH-ubiquinone oxidoreductase 75 kDa subunit	IPI00604664	4	4	2	1	1	3
Prolyl 3-hydroxylase 2	IPI00217055	2	1	1	2	1	0
Protein FAM162A	IPI00023001	1	3	0	3	1	1
Putative uncharacterized protein DKFZp781K1356	IPI00412545	1	0	2	1	1	2
YrdC domain-containing protein, mitochondrial	IPI00384180	2	0	2	2	1	0
insulin-like growth factor-binding protein 2 precursor	IPI00297284	4	2	7	1	2	2
Solute carrier family 2, facilitated glucose transporter member 1	IPI00220194	5	5	4	7	9	5
Hexokinase-2	IPI00102864	7	6	12	6	8	4
Cytoplasmic aconitate hydratase	IPI00008485	11	8	6	7	9	7
Isoform 1 of Microtubule-associated protein 4	IPI00396171	6	6	4	11	9	12
Isoform 1 of Prolyl 4-hydroxylase subunit alpha-1	IPI00009923	4	1	3	11	14	3
Isoform A of AP-1 complex subunit beta-1	IPI00328257	12	4	8	5	7	4
116 kDa U5 small nuclear ribonucleoprotein component	IPI00003519	13	9	11	13	9	17
14-3-3 protein epsilon	IPI00000816	38	21	28	31	23	19
14-3-3 protein eta	IPI00216319	14	13	17	14	8	8
14-3-3 protein gamma	IPI00220642	6	6	7	9	5	8
14-3-3 protein theta	IPI00018146	15	9	13	22	13	14
14-3-3 protein zeta/delta	IPI00021263	22	14	23	19	12	10
15 kDa selenoprotein isoform 1 precursor	IPI00030877	1	1	2	2	1	2
1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase beta-3	IPI00010400	2	4	1	1	4	3
2,4-dienoyl-CoA reductase, mitochondrial	IPI00003482	2	0	1	0	2	0
22 kDa protein	IPI00219910	3	2	1	1	1	2
24-dehydrocholesterol reductase	IPI00016703	3	1	5	0	3	1
26S protease regulatory subunit 10B	IPI00021926	9	5	9	14	7	4
26S protease regulatory subunit 4	IPI00011126	6	4	6	8	6	9
26S protease regulatory subunit 6A	IPI00018398	12	10	12	16	10	11
26S protease regulatory subunit 7	IPI00021435	12	5	13	18	13	12
26S protease regulatory subunit 8	IPI00023919	11	6	10	9	8	6
26S proteasome non-ATPase regulatory subunit 10	IPI00003565	3	2	0	4	2	1
26S proteasome non-ATPase regulatory subunit 12	IPI00185374	7	5	8	7	11	10
26S proteasome non-ATPase regulatory subunit 14	IPI00024821	7	6	5	9	5	8
26S proteasome non-ATPase regulatory subunit 2	IPI00012268	17	10	11	21	24	13
26S proteasome non-ATPase regulatory subunit 3	IPI00011603	7	8	6	8	12	8
26S proteasome non-ATPase regulatory subunit 5	IPI00002134	5	3	2	7	5	6
26S proteasome non-ATPase regulatory subunit 6	IPI00014151	12	10	9	11	13	9
26S proteasome non-ATPase regulatory subunit 7	IPI00019927	5	5	6	6	4	4
26S proteasome non-ATPase regulatory subunit 8	IPI00937278	3	1	2	7	5	2
28 kDa heat- and acid-stable phosphoprotein	IPI00013297	2	1	2	1	1	3

28S ribosomal protein S22, mitochondrial	IPI00013146	3	1	2	1	2	0
28S ribosomal protein S29, mitochondrial	IPI00018120	2	1	0	2	2	1
29 kDa protein	IPI00453476	28	21	28	37	23	20
2-oxoglutarate dehydrogenase, mitochondrial	IPI00098902	4	2	3	6	5	6
33 kDa protein	IPI00413108	15	12	12	13	12	11
39S ribosomal protein L1, mitochondrial	IPI00549381	3	0	2	3	2	2
39S ribosomal protein L11, mitochondrial	IPI00007001	4	2	1	3	3	2
39S ribosomal protein L44, mitochondrial	IPI00009680	3	1	0	1	0	2
39S ribosomal protein L49, mitochondrial	IPI00013195	3	0	1	1	1	2
3-hydroxyisobutyrate dehydrogenase, mitochondrial	IPI00013860	2	1	3	5	5	0
3-ketoacyl-CoA thiolase, mitochondrial	IPI00001539	5	4	6	10	9	8
3-ketoacyl-CoA thiolase, peroxisomal	IPI00012828	1	0	2	3	1	1
3-mercaptopyruvate sulfurtransferase	IPI00165360	3	4	2	3	3	3
40S ribosomal protein S10	IPI00008438	2	3	3	6	4	5
40S ribosomal protein S11	IPI00025091	3	3	4	4	5	5
40S ribosomal protein S12	IPI00013917	13	7	8	12	6	4
40S ribosomal protein S13	IPI00221089	10	14	6	16	8	10
40S ribosomal protein S14	IPI00026271	11	7	4	9	3	6
40S ribosomal protein S15	IPI00479058	5	6	4	7	5	5
40S ribosomal protein S15a	IPI00221091	7	5	1	8	4	4
40S ribosomal protein S16	IPI00221092	8	6	3	8	5	8
40S ribosomal protein S17	IPI00221093	11	5	7	6	9	7
40S ribosomal protein S18	IPI00013296	13	13	7	16	9	9
40S ribosomal protein S19	IPI00215780	3	10	7	11	4	5
40S ribosomal protein S2	IPI00013485	8	7	6	9	8	9
40S ribosomal protein S20	IPI00012493	5	3	5	8	4	4
40S ribosomal protein S21	IPI00017448	0	3	1	7	4	4
40S ribosomal protein S23	IPI00218606	2	2	1	3	1	1
40S ribosomal protein S25	IPI00012750	4	5	4	5	3	3
40S ribosomal protein S26	IPI00655650	2	3	1	3	3	1
40S ribosomal protein S28	IPI00719622	0	2	1	7	2	1
40S ribosomal protein S3	IPI00011253	17	12	20	14	14	14
40S ribosomal protein S3a	IPI00419880	16	15	14	16	13	12
40S ribosomal protein S4, X isoform	IPI00217030	7	8	9	13	7	9
40S ribosomal protein S5	IPI00008433	6	6	3	8	3	6
40S ribosomal protein S6	IPI00021840	9	8	8	10	2	5
40S ribosomal protein S7	IPI00013415	9	11	5	17	3	6
40S ribosomal protein S8	IPI00216587	8	9	13	20	10	8
40S ribosomal protein S9	IPI00221088	7	6	5	11	6	4
482 kDa protein	IPI00179298	15	11	27	14	20	1
4-trimethylaminobutyraldehyde dehydrogenase	IPI00479877	1	1	5	1	2	0
51 kDa protein	IPI00033025	3	2	2	6	8	3
5'-nucleotidase domain-containing protein 1	IPI00177965	4	1	5	5	5	2
60 kDa heat shock protein, mitochondrial	IPI00784154	50	43	46	50	28	29
60S acidic ribosomal protein P0	IPI00008530	17	10	11	10	14	11
60S acidic ribosomal protein P1	IPI00008527	2	2	3	4	4	3
60S acidic ribosomal protein P2	IPI00008529	11	5	4	9	7	7
60S ribosomal protein L10	IPI00554723	9	6	5	13	8	5
60S ribosomal protein L10a	IPI00412579	12	6	7	13	9	5
60S ribosomal protein L13	IPI00465361	3	5	4	6	4	2
60S ribosomal protein L13a	IPI00304612	3	2	3	3	3	2
60S ribosomal protein L15	IPI00470528	4	4	3	7	3	5
60S ribosomal protein L17	IPI00413324	9	5	4	14	6	5
60S ribosomal protein L18	IPI00215719	9	8	4	9	8	8
60S ribosomal protein L18a	IPI00026202	5	3	1	5	4	3
60S ribosomal protein L19	IPI00025329	4	4	4	5	3	4
60S ribosomal protein L21	IPI00247583	5	6	6	8	7	4
60S ribosomal protein L22	IPI00219153	7	2	3	10	3	3

60S ribosomal protein L23	IPI00010153	4	2	4	4	4	4
60S ribosomal protein L23a	IPI00021266	8	8	9	8	5	5
60S ribosomal protein L24	IPI00306332	3	3	2	5	3	3
60S ribosomal protein L26	IPI00027270	9	8	7	9	10	4
60S ribosomal protein L27	IPI00219155	8	6	2	6	5	5
60S ribosomal protein L27a	IPI00456758	5	3	3	6	3	3
60S ribosomal protein L28	IPI00182533	6	6	7	4	3	3
60S ribosomal protein L3	IPI00550021	9	8	9	8	7	7
60S ribosomal protein L30	IPI00219156	4	4	3	5	4	5
60S ribosomal protein L31	IPI00026302	3	4	2	7	2	2
60S ribosomal protein L32	IPI00395998	5	3	5	6	3	3
60S ribosomal protein L35	IPI00412607	3	3	3	6	2	2
60S ribosomal protein L36	IPI00216237	3	2	4	3	3	4
60S ribosomal protein L36a-like	IPI00056494	2	1	2	1	2	2
60S ribosomal protein L38	IPI00215790	0	2	1	4	4	4
60S ribosomal protein L4	IPI00003918	17	9	13	26	12	13
60S ribosomal protein L5	IPI00000494	8	4	10	10	12	6
60S ribosomal protein L6	IPI00329389	6	11	9	14	7	8
60S ribosomal protein L7	IPI00030179	13	10	13	15	12	8
60S ribosomal protein L7a	IPI00299573	12	12	12	9	9	9
60S ribosomal protein L8	IPI00012772	5	5	5	8	8	8
60S ribosomal protein L9	IPI00031691	6	6	1	8	4	5
6-phosphofructokinase type C	IPI00009790	6	4	6	11	15	10
6-phosphogluconate dehydrogenase, decarboxylating	IPI00219525	23	13	22	18	13	15
6-phosphogluconolactonase	IPI00029997	12	7	10	7	8	7
Acetyl-CoA acetyltransferase, mitochondrial	IPI00030363	4	3	2	2	0	2
Acidic leucine-rich nuclear phosphoprotein 32 family member A	IPI00025849	8	3	6	11	8	7
Acidic leucine-rich nuclear phosphoprotein 32 family member E	*IPI00165393*	6	5	6	7	3	3
Aconitate hydratase, mitochondrial	IPI00017855	6	4	4	8	9	5
Actin, alpha cardiac muscle 1	IPI00023006	9	9	7	7	10	13
Actin-related protein 2	IPI00005159	7	6	6	5	8	8
Actin-related protein 2/3 complex subunit 2	IPI00005161	6	5	10	10	9	8
Actin-related protein 2/3 complex subunit 3	IPI00005162	6	6	5	5	6	6
Actin-related protein 2/3 complex subunit 4	IPI00554811	4	3	5	3	4	3
Actin-related protein 2/3 complex subunit 5-like protein	*IPI00414554*	1	2	2	1	0	2
Actin-related protein 3	IPI00028091	11	5	10	14	10	14
Activated RNA polymerase II transcriptional coactivator p15	IPI00221222	3	2	3	6	2	2
Activator of 90 kDa heat shock protein ATPase homolog 1	IPI00030706	6	5	5	4	5	4
Acylamino-acid-releasing enzyme	IPI00337741	3	4	4	6	5	6
Acyl-protein thioesterase 2	IPI00027032	4	0	1	4	1	1
Adenine phosphoribosyltransferase	IPI00218693	14	5	9	14	6	6
Adenosylhomocysteinase	IPI00012007	13	11	15	13	16	9
Adenylate kinase isoenzyme 1	IPI00018342	2	4	1	6	2	3
Adenylate kinase isoenzyme 4, mitochondrial	IPI00016568	6	4	3	5	5	6
Adenylosuccinate synthetase isozyme 2	IPI00026833	12	7	9	10	8	10
ADP/ATP translocase 2	IPI00007188	4	1	3	3	5	4
ADP-ribosylation factor 4	IPI00215918	2	2	4	2	4	5
ADP-ribosylation factor 5	IPI00215919	5	1	3	3	4	3
ADP-ribosylation factor 6	*IPI00215920*	4	2	3	2	4	4
ADP-ribosylation factor-like protein 2	*IPI00003326*	5	4	5	4	5	5
ADP-ribosylation factor-like protein 3	*IPI00003327*	5	3	4	8	5	4
ADP-sugar pyrophosphatase	IPI00296913	2	6	6	6	4	4
A-kinase anchor protein 12 isoform 2	IPI00217683	6	4	14	4	6	7
Alanyl-tRNA synthetase, cytoplasmic	IPI00027442	25	17	24	27	24	19
Alcohol dehydrogenase [NADP+]	IPI00220271	9	6	12	9	11	10
Alcohol dehydrogenase class-3	IPI00746777	4	3	7	4	9	7
Aldehyde dehydrogenase X, mitochondrial	IPI00103467	8	3	5	4	8	4
Aldehyde dehydrogenase, mitochondrial	IPI00006663	5	4	5	4	12	3

Aldose reductase	IPI00413641	4	2	7	4	5	7
Alkaline phosphatase, tissue-nonspecific isozyme	IPI00419916	3	1	3	5	3	4
Alpha-actinin-1	IPI00013508	39	22	38	45	47	43
Alpha-actinin-4	IPI00013808	22	15	20	30	26	21
Alpha-aminoadipic semialdehyde synthase, mitochondrial	IPI00033217	25	16	20	16	10	13
Alpha-centractin	IPI00029468	3	2	3	5	6	7
Alpha-mannosidase 2	IPI00003802	2	1	2	1	1	2
Alpha-soluble NSF attachment protein	IPI00009253	4	4	5	7	5	7
Amidophosphoribosyltransferase	IPI00029534	3	3	3	8	6	5
Aminoacyl tRNA synthase complex-interacting multifunctional prtn 1	IPI00006252	4	2	3	3	4	2
Aminoacyl tRNA synthase complex-interacting multifunctional prtn 2	IPI00011916	4	0	2	2	3	4
Aminopeptidase B	IPI00642211	1	1	4	2	8	2
Annexin A1	IPI00218918	4	3	5	16	11	10
Annexin A3	IPI00024095	11	5	12	10	10	13
annexin A4	IPI00793199	3	2	3	7	3	3
Annexin A5	IPI00329801	24	17	19	28	17	13
Annexin A6	IPI00221226	17	6	5	15	17	12
Apolipoprotein E	IPI00021842	9	2	17	3	6	7
Argininosuccinate synthase	IPI00020632	8	3	2	0	3	1
Asparaginyl-tRNA synthetase, cytoplasmic	IPI00306960	4	3	4	3	7	8
Aspartate aminotransferase, cytoplasmic	IPI00219029	13	10	13	9	7	7
Aspartate aminotransferase, mitochondrial	IPI00018206	13	12	13	10	10	9
Aspartyl-tRNA synthetase, cytoplasmic	IPI00216951	7	6	5	8	11	12
Astrocytic phosphoprotein PEA-15	IPI00014850	1	1	2	3	2	3
Ataxin-10	IPI00001636	7	5	4	4	10	4
ATP synthase subunit alpha, mitochondrial	IPI00440493	20	17	19	24	16	15
ATP synthase subunit b, mitochondrial	IPI00029133	13	7	3	8	5	6
ATP synthase subunit beta, mitochondrial	IPI00303476	30	25	27	31	30	26
ATP synthase subunit O, mitochondrial	IPI00007611	5	5	7	9	4	5
ATPase ASNA1	IPI00013466	4	5	4	5	5	5
ATP-binding cassette sub-family E member 1	IPI00303207	3	0	6	2	7	5
ATP-citrate synthase	IPI00021290	28	22	63	20	14	21
ATP-dependent RNA helicase A	IPI00844578	21	20	32	26	30	24
ATP-dependent RNA helicase DDX1	IPI00293655	11	7	3	12	9	6
ATP-dependent RNA helicase DDX18	IPI00301323	3	1	2	5	6	4
ATP-dependent RNA helicase DDX3X	IPI00215637	10	4	7	9	5	12
BAG family molecular chaperone regulator 2	IPI00000643	2	1	1	3	1	1
Band 4.1-like protein 2	IPI00015973	2	1	4	4	13	3
Basal cell adhesion molecule	IPI00002406	1	1	3	4	9	2
Basic leucine zipper and W2 domain-containing protein 2	IPI00022305	1	2	1	3	1	2
B-cell receptor-associated protein 31	IPI00218200	1	1	4	5	3	2
Beta-hexosaminidase subunit beta	IPI00012585	1	1	3	4	2	3
Bifunctional 3'-phosphoadenosine 5'-phosphosulfate synthase 1	IPI00011619	2	1	1	3	6	4
Bifunctional aminoacyl-tRNA synthetase	IPI00013452	20	3	15	23	21	20
Bifunctional ATP-dependent dihydroxyacetone kinase/FAD-AMP lyase	IPI00551024	2	1	1	4	6	0
Bifunctional purine biosynthesis protein PURH	IPI00289499	24	13	17	23	19	24
Bleomycin hydrolase	IPI00219575	2	1	2	2	2	1
Branched-chain-amino-acid aminotransferase	IPI00382412	9	7	5	1	1	2
Brefeldin A-inhibited guanine nucleotide-exchange protein 1	IPI00002188	3	3	2	4	6	2
C-1-tetrahydrofolate synthase, cytoplasmic	IPI00218342	21	16	20	21	21	25
CAD protein	IPI00301263	18	14	19	14	16	17
Cadherin-1	IPI00025861	3	3	7	6	6	7
Calcium-binding protein p22	IPI00218924	2	1	1	1	2	2
Calcium-regulated heat stable protein 1	IPI00304409	6	2	3	5	5	2
Calpain small subunit 1	IPI00025084	3	1	3	4	2	5
Calpain-1 catalytic subunit	IPI00011285	5	2	3	9	10	7
Calponin-2	IPI00015262	5	3	9	5	4	4
Calponin-3	IPI00216682	5	2	6	8	9	6

Calreticulin	IPI00020599	19	9	15	11	17	13
Carbonic anhydrase 2	IPI00218414	2	1	1	3	3	2
Carbonyl reductase [NADPH] 1	IPI00295386	7	5	8	10	9	7
Carboxypeptidase D	IPI00027078	4	0	1	1	2	0
Casein kinase II subunit alpha'	IPI00020602	4	1	4	2	4	2
Casein kinase II subunit beta	IPI00010865	2	1	0	3	5	4
Caspase-3	IPI00292140	3	2	5	5	2	4
Cathepsin D	IPI00011229	8	5	10	8	6	5
Cation-independent mannose-6-phosphate receptor	IPI00289819	3	1	6	1	5	3
CD2-associated protein	IPI00412771	2	1	1	5	2	2
CDGSH iron-sulfur domain-containing protein 2	IPI00166865	2	1	1	2	2	1
cDNA FLJ25678 fis, highly similar to purine nucleoside phosphorylase	IPI00017672	11	12	17	15	8	11
cDNA FLJ31776 fis, highly similar to calumenin	IPI00789155	4	0	3	3	1	0
cDNA FLJ35809 fis, highly similar to eukaryotic translation initiation factor 3 subunit 3	IPI00647650	3	4	3	5	4	6
cDNA FLJ36192 fis, highly similar to Eukaryotic translation initiation factor 3 subunit 5	IPI00654777	6	7	8	8	3	5
cDNA FLJ44436 fis, highly similar to T-complex protein 1 subunit γ	IPI00290770	18	14	9	18	19	18
cDNA FLJ50992, highly similar to Coronin-1C	IPI00798401	3	0	1	1	5	4
cDNA FLJ51909, highly similar to Serine-threonine kinase receptor-associated protein	IPI00294536	8	7	8	7	9	10
cDNA FLJ53193, highly similar to Homo sapiens caldesmon 1 (CALD1), transcript variant 5, mRNA	IPI00218696	7	2	10	8	8	9
cDNA FLJ53229, highly similar to Importin alpha-7 subunit	IPI00747764	5	0	2	5	3	2
cDNA FLJ53975, highly similar to Acetyl-CoA acetyltransferase	IPI00291419	13	8	18	6	6	7
cDNA FLJ54365, highly similar to DNA replication licensing factor MCM4	IPI00795318	20	8	9	21	22	17
cDNA FLJ54492, highly similar to Eukaryotic translation initiation factor 4B	IPI00012079	3	2	2	3	2	2
cDNA FLJ54536, highly similar to mitochondrial 28S ribosomal protein S27	IPI00022002	2	2	1	2	0	1
cDNA FLJ54710, highly similar to Target of Myb protein 1	IPI00023191	1	0	2	1	1	2
cDNA FLJ55382, highly similar to Hsp70-binding protein 1	IPI00100748	4	3	6	0	5	2
cDNA FLJ55482, highly similar to Annexin A11	IPI00414320	1	1	4	4	3	2
cDNA FLJ55543, highly similar to Phosphoacetylglucosamine mutase	IPI00030116	2	0	1	2	2	4
cDNA FLJ55574, highly similar to Calnexin	IPI00020984	10	6	7	13	19	9
cDNA FLJ55586, highly similar to MMS19-like protein	IPI00154451	9	3	4	10	7	4
cDNA FLJ55599, highly similar to DNA replication licensing factor MCM3	IPI00013214	15	14	14	17	14	14
cDNA FLJ56285, highly similar to ADP-ribosylation factor-like protein 8B	IPI00018871	3	0	1	2	2	1
cDNA FLJ56357, highly similar to Homo sapiens apolipoprotein A-I binding protein (APOA1BP), mRNA	IPI00168479	3	3	1	4	1	2
cDNA FLJ56370, highly similar to Homo sapiens FK506 binding protein 8, 38kDa (FKBP8), mRNA	IPI00328161	2	0	2	2	2	0
cDNA FLJ56414, highly similar to Homo sapiens proline-, glutamic acid-, leucine-rich protein 1 (PELP1), mRNA	IPI00006702	2	0	1	1	3	1
cDNA FLJ56420, highly similar to Aspartyl aminopeptidase	IPI00015856	1	0	2	0	5	0
cDNA FLJ59142, highly similar to Epididymal secretory protein E1	IPI00301579	1	0	2	1	4	0
cDNA FLJ59211, highly similar to Glucosidase 2 subunit beta	IPI00026154	6	5	8	8	9	9
cDNA FLJ59367, highly similar to Adenylosuccinate lyase	IPI00026904	9	4	7	11	8	9
cDNA FLJ59758, highly similar to S-methyl-5-thioadenosine phosphorylase	IPI00011876	10	8	8	9	7	8
cDNA FLJ60076, highly similar to ELAV-like protein 1	IPI00301936	11	5	7	9	7	6
cDNA FLJ60097, highly similar to Tubulin alpha-ubiquitous chain	IPI00792677	32	27	26	32	36	27
cDNA FLJ60124, highly similar to Mitochondrial dicarboxylate carrier	IPI00005537	3	1	3	2	1	0
cDNA FLJ60424, highly similar to Junction plakoglobin	IPI00789324	9	5	11	2	5	3
cDNA FLJ60607, highly similar to Acyl-protein thioesterase 1	IPI00007321	3	3	1	6	3	2

cDNA FLJ61162, highly similar to Ras-related protein R-Ras2	IPI00012512	4	3	2	8	4	3
cDNA FLJ75085, highly similar to Homo sapiens glutaminyl-tRNA synthetase (QARS), mRNA	IPI00026665	9	5	6	6	12	8
cDNA FLJ77177, highly similar to Homo sapiens arginine-rich, mutated in early stage tumors (ARMET), mRNA	IPI00328748	3	1	3	4	3	0
cDNA FLJ77422, highly similar to Homo sapiens RNA binding protein, autoantigenic, transcript variant 1, mRNA (Fragment)	IPI00011268	2	2	3	2	1	1
cDNA, FLJ96508, Homo sapiens SH3-domain GRB2-like 1 (SH3GL1)	IPI00019169	2	2	5	4	1	3
Cell differentiation protein RCD1 homolog	IPI00023101	5	0	1	3	5	4
Cell division cycle protein 123 homolog	IPI00005670	2	1	1	0	1	2
Cellular retinoic acid-binding protein 1	IPI00219930	11	10	6	12	9	8
Cellular retinoic acid-binding protein 2	IPI00216088	2	2	6	9	8	5
Centromere protein H	IPI00009668	1	0	2	2	1	1
Centromere/kinetochore protein zw10 homolog	IPI00011631	2	0	2	4	2	1
Charged multivesicular body protein 4b	IPI00025974	3	1	3	4	3	2
Charged multivesicular body protein 5	IPI00100796	2	1	2	2	3	1
Chloride intracellular channel protein 1	IPI00010896	10	6	11	10	14	12
Chloride intracellular channel protein 4	IPI00001960	11	7	12	12	11	12
Chromobox protein homolog 1	IPI00010320	5	2	1	3	2	2
Chromobox protein homolog 3	IPI00297579	6	5	5	5	6	6
Chromobox protein homolog 5	IPI00024662	1	0	2	3	5	3
Citrate synthase, mitochondrial	IPI00025366	4	4	5	5	3	4
Claudin-6	IPI00011084	3	3	3	3	2	2
Cleavage and polyadenylation specificity factor subunit 1	IPI00026219	2	1	1	4	4	3
Cleavage and polyadenylation specificity factor subunit 2	IPI00419531	2	0	1	2	3	2
Cleavage and polyadenylation specificity factor subunit 5	IPI00646917	8	6	6	12	6	7
Cleavage stimulation factor subunit 3	IPI00015195	3	1	4	4	5	7
Coactosin-like protein	IPI00017704	5	1	1	4	1	2
Coatomer subunit beta	IPI00295851	13	2	5	15	15	11
Coatomer subunit beta'	IPI00220219	4	3	6	7	10	8
Coatomer subunit delta variant 2	IPI00298520	6	6	4	8	7	6
Coatomer subunit epsilon	IPI00465132	9	3	3	6	4	8
Coatomer subunit gamma	*IPI00783982*	*11*	*4*	*4*	*16*	*18*	*12*
Coatomer subunit gamma-2	*IPI00002557*	*5*	*1*	*4*	*9*	*9*	*6*
Coatomer subunit zeta-1	IPI00032851	6	4	6	6	6	4
Cofilin-1	IPI00012011	13	16	16	16	9	14
Coiled-coil domain-containing protein 58	IPI00046828	2	0	1	3	2	2
Cold-inducible RNA-binding protein	IPI00180954	2	1	5	5	2	3
Collapsin response mediator protein 4 long variant	IPI00029111	13	12	20	16	19	17
Complement component 1 Q subcomponent-binding protein	IPI00014230	15	8	8	10	8	7
Condensin complex subunit 1	IPI00299524	1	2	1	5	6	4
Condensin complex subunit 3	IPI00106495	2	1	0	2	0	2
COP9 signalosome complex subunit 3	IPI00025721	2	0	2	2	5	3
COP9 signalosome complex subunit 4	IPI00171844	6	5	8	8	7	3
COP9 signalosome complex subunit 5	IPI00009958	3	0	2	2	2	5
COP9 signalosome complex subunit 6	IPI00163230	1	1	4	1	2	1
COP9 signalosome complex subunit 7a	IPI00301419	2	2	3	6	1	1
COP9 signalosome complex subunit 8	IPI00009480	5	2	3	5	2	0
Copine-1	IPI00018452	2	1	0	2	6	5
Copper chaperone for superoxide dismutase	IPI00021389	2	0	1	3	2	1
Coproporphyrinogen-III oxidase, mitochondrial	IPI00093057	2	2	2	1	3	1
Creatine kinase B-type	IPI00022977	13	11	8	23	17	13
Crk-like protein	IPI00004839	3	3	3	5	2	2
CSNK2A1 protein	IPI00016613	9	6	5	7	7	5
CTP synthase 1	IPI00290142	6	2	4	3	3	8
CTP synthase 2	IPI00645702	2	1	3	2	0	1
Cullin-1	IPI00014310	3	0	3	3	4	4
Cystatin-B	IPI00021828	4	1	3	2	4	2

Cysteine and glycine-rich protein 2	IPI00002824	2	1	5	2	3	3
cysteinyl-tRNA synthetase, cytoplasmic isoform c	IPI00027443	7	6	7	7	7	9
cytochrome b5 type B precursor	IPI00303954	4	3	5	4	3	2
Cytochrome b-c1 complex subunit 1, mitochondrial	IPI00013847	3	0	1	0	2	2
Cytochrome c	IPI00465315	7	2	4	7	5	3
Cytochrome c oxidase subunit 5A, mitochondrial	IPI00025086	2	0	1	1	1	5
Cytoplasmic dynein 1 heavy chain 1	IPI00456969	52	40	37	51	74	5
Cytoplasmic dynein 1 light intermediate chain 1	IPI00007675	2	0	1	3	2	0
Cytosolic Fe-S cluster assembly factor NUBP2	IPI00644674	4	2	1	5	2	0
D-3-phosphoglycerate dehydrogenase	IPI00011200	16	13	23	14	13	14
DCN1-like protein 5	IPI00165361	4	1	0	2	3	1
dCTP pyrophosphatase 1	IPI00012197	1	2	3	2	1	1
D-dopachrome decarboxylase	IPI00293867	3	3	4	7	3	4
Delta(3,5)-Delta(2,4)-dienoyl-CoA isomerase, mitochondrial	IPI00011416	4	5	9	7	4	1
Delta-1-pyrroline-5-carboxylate dehydrogenase, mitochondrial	IPI00217871	3	1	1	4	3	2
Density-regulated protein	IPI00306280	1	1	2	2	3	1
Desmoglein-2	IPI00028931	2	0	5	2	6	3
Destrin	IPI00473014	3	1	1	3	5	4
Developmental pluripotency-associated protein 4	IPI00018878	1	1	2	0	2	2
Developmentally-regulated GTP-binding protein 1	IPI00031836	6	6	2	6	4	6
Developmentally-regulated GTP-binding protein 2	IPI00022697	1	1	3	3	4	1
Diablo homolog, mitochondrial precursor	IPI00008418	4	2	4	4	4	2
Dihydrofolate reductase	IPI00030357	1	2	0	1	3	4
Dihydrolipoyl dehydrogenase, mitochondrial	IPI00015911	3	1	2	2	4	5
Dihydrolipoyllysine-residue acetyltransferase component of pyruvate dehydrogenase complex, mitochondrial	IPI00021338	4	1	4	3	5	3
Dihydrolipoyllysine-residue succinyltransferase component of 2-oxoglutarate dehydrogenase complex, mitochondrial	IPI00420108	2	3	3	2	3	2
Dihydropteridine reductase	IPI00014439	2	1	3	2	5	3
Dihydropyrimidinase-related protein 1	IPI00414123	4	2	3	1	3	3
Dihydropyrimidinase-related protein 2	IPI00257508	14	12	15	10	16	17
Diphosphoinositol polyphosphate phosphohydrolase 1	IPI00009148	1	2	0	2	1	1
DNA damage-binding protein 1	IPI00293464	3	3	12	6	4	12
DNA ligase 1	IPI00219841	6	1	1	4	2	2
DNA mismatch repair protein Msh2	IPI00017303	10	5	5	11	14	8
DNA polymerase delta catalytic subunit	IPI00002894	6	0	2	4	9	8
DNA replication complex GINS protein PSF1	IPI00032387	3	0	1	3	2	2
DNA replication licensing factor MCM2	IPI00184330	15	12	15	16	20	22
DNA replication licensing factor MCM5	IPI00018350	13	8	7	7	12	11
DNA replication licensing factor MCM6	IPI00031517	14	10	13	14	14	14
DNA-(apurinic or apyrimidinic site) lyase	IPI00215911	6	3	6	7	13	12
DNA-directed RNA polymerase II subunit RPB1	IPI00031627	2	0	4	4	3	2
DNA-directed RNA polymerase II subunit RPB2	IPI00027808	2	1	1	2	6	6
DNA-directed RNA polymerase II subunit RPB3	IPI00018288	3	4	5	2	4	3
DNA-directed RNA polymerases I, II, and III subunit RPABC1	IPI00291093	2	2	1	1	2	3
DNA-directed RNA polymerases I, II, and III subunit RPABC3	IPI00003309	4	4	5	7	3	3
DnaJ homolog subfamily A member 1	IPI00012535	6	5	7	6	4	4
DnaJ homolog subfamily A member 2	IPI00032406	7	3	5	3	5	7
DnaJ homolog subfamily B member 1	IPI00015947	2	1	0	1	3	0
DnaJ homolog subfamily B member 11	IPI00008454	3	0	2	2	3	0
DnaJ homolog subfamily C member 7	IPI00329629	2	1	1	2	5	4
DnaJ homolog subfamily C member 8	IPI00003438	3	2	5	4	5	3
Dolichol-phosphate mannosyltransferase	IPI00022018	3	1	1	4	1	2
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase 48 kDa subunit	IPI00297084	5	3	1	1	5	5
Dolichyl-diphosphooligosaccharide--protein glycosyltransferase subunit 1 precursor	IPI00025874	3	1	3	7	11	7
D-tyrosyl-tRNA(Tyr) deacylase 1	IPI00152692	1	1	2	1	2	1

Dual specificity mitogen-activated protein kinase kinase 1	IPI00219604	3	1	1	2	6	2
Dual specificity protein phosphatase 3	IPI00018671	1	1	3	3	3	1
dynactin subunit 2	IPI00220503	2	4	4	3	4	1
Dynein light chain Tctex-type 1	IPI00019495	2	1	2	3	2	3
E3 SUMO-protein ligase RanBP2	IPI00221325	6	1	2	2	6	2
Early endosome antigen 1	IPI00329536	2	0	1	1	6	0
EF-hand domain-containing protein D2	IPI00060181	0	1	3	6	1	0
Electron transfer flavoprotein subunit alpha, mitochondrial	IPI00010810	8	6	2	7	6	9
Elongation factor 1-alpha 1	IPI00396485	21	17	24	24	21	14
Elongation factor 1-beta	IPI00178440	4	3	5	5	3	4
Elongation factor 1-gamma	IPI00937615	21	8	10	10	18	17
Elongation factor 2	IPI00186290	60	41	42	51	52	42
Elongator complex protein 1	IPI00293735	2	1	0	3	10	1
Emerin	IPI00032003	3	0	3	3	4	2
Endoplasmic reticulum resident protein 29	IPI00024911	8	9	10	16	6	7
Endoplasmic reticulum resident protein 44	IPI00401264	3	0	3	6	2	3
Endoplasmin	IPI00027230	43	25	41	34	39	28
Enoyl-CoA hydratase, mitochondrial	IPI00024993	12	6	9	13	10	7
Epiplakin	IPI00010951	6	4	4	6	5	0
Epithelial cell adhesion molecule	IPI00296215	2	2	3	5	4	2
Epoxide hydrolase 1	IPI00009896	5	3	3	2	5	1
ERO1-like protein alpha	IPI00386755	2	0	4	3	5	3
Estradiol 17-beta-dehydrogenase 12	IPI00007676	13	10	13	10	5	6
Eukaryotic initiation factor 4A-I	IPI00025491	24	23	22	18	24	19
Eukaryotic initiation factor 4A-III	IPI00009328	9	3	4	4	9	6
eukaryotic peptide chain release factor GTP-binding subunit ERF3A isoform 2	IPI00909083	3	1	1	6	6	6
Eukaryotic peptide chain release factor subunit 1	IPI00429191	6	2	5	3	6	5
Eukaryotic translation elongation factor 1 epsilon-1	IPI00003588	5	4	6	6	4	6
Eukaryotic translation initiation factor 2 subunit 1	IPI00219678	4	5	3	5	6	7
Eukaryotic translation initiation factor 2 subunit 3	IPI00297982	9	8	6	2	9	8
Eukaryotic translation initiation factor 3 subunit A	IPI00029012	25	15	17	22	22	19
Eukaryotic translation initiation factor 3 subunit C	IPI00016910	9	6	7	7	7	12
Eukaryotic translation initiation factor 3 subunit D	IPI00006181	3	1	1	3	4	5
Eukaryotic translation initiation factor 3 subunit E	IPI00013068	12	3	8	13	10	7
Eukaryotic translation initiation factor 3 subunit G	IPI00290460	4	3	5	6	4	2
Eukaryotic translation initiation factor 3 subunit I	IPI00012795	7	3	4	3	6	6
Eukaryotic translation initiation factor 3 subunit K	IPI00033143	4	3	2	5	5	3
Eukaryotic translation initiation factor 3 subunit M	IPI00102069	5	9	7	11	6	8
Eukaryotic translation initiation factor 3, subunit E interacting protein	IPI00465233	5	3	7	4	10	11
Eukaryotic translation initiation factor 5	IPI00022648	2	2	5	5	7	5
Eukaryotic translation initiation factor 5B	IPI00299254	4	2	0	6	4	2
Eukaryotic translation initiation factor 6	IPI00010105	6	4	6	7	7	7
Exosome complex exonuclease MTR3	IPI00073602	3	2	2	2	2	1
Exosome complex exonuclease RRP4	IPI00015905	3	3	1	2	6	3
Exosome complex exonuclease RRP40	IPI00015956	3	1	1	1	2	0
Exosome complex exonuclease RRP41	IPI00745613	3	3	2	6	3	1
Exosome complex exonuclease RRP43	IPI00552920	2	0	1	0	1	2
Exportin-1	IPI00298961	22	17	21	27	23	21
Exportin-4	IPI00028357	2	1	1	1	0	5
Exportin-5	IPI00640703	13	7	5	13	13	12
Exportin-7	IPI00302458	9	3	11	10	11	9
Exportin-T	IPI00306290	7	3	4	6	9	6
Ezrin	IPI00843975	12	6	10	26	22	17
FACT complex subunit SPT16	IPI00026970	2	2	9	11	9	10
FACT complex subunit SSRP1	IPI00005154	4	0	1	9	7	5
F-actin-capping protein subunit alpha-1	IPI00005969	9	4	8	4	10	8
F-actin-capping protein subunit alpha-2	IPI00026182	3	3	4	4	6	7

Farnesyltransferase, CAAX box, alpha, isoform CRA_a	IPI00026813	2	1	0	0	2	1
Fascin	IPI00163187	16	14	16	17	17	11
Fatty acid synthase	IPI00026781	85	76	110	61	60	55
Fatty acid-binding protein, epidermal	IPI00007797	11	6	12	11	9	8
Fatty acid-binding protein, heart	IPI00219684	3	3	7	2	2	2
F-box only protein 2	IPI00007087	2	0	1	1	4	1
Ferritin heavy chain	IPI00554521	3	1	1	4	1	0
Flap endonuclease 1	IPI00026215	3	2	0	3	3	3
Fructose-bisphosphate aldolase	IPI00418262	12	7	17	11	13	7
Fructose-bisphosphate aldolase A	IPI00465439	33	29	26	31	28	19
Gamma-enolase	IPI00216171	9	6	8	9	7	7
GDP-L-fucose synthase	IPI00014361	2	1	0	2	1	0
GDP-mannose 4,6 dehydratase	IPI00030207	3	1	1	1	2	1
Gem-associated protein 5	IPI00291783	0	1	2	3	4	1
General transcription factor 3C polypeptide 4	IPI00016725	2	0	1	2	2	0
Glia maturation factor, beta	IPI00412987	3	4	4	7	3	2
Glucosamine 6-phosphate N-acetyltransferase	IPI00061525	4	2	2	3	4	4
Glucosamine-6-phosphate isomerase 1	IPI00009305	4	2	4	3	8	4
Glucosamine--fructose-6-phosphate aminotransferase [isomerizing] 2	IPI00216159	4	1	2	2	2	3
Glucose-6-phosphate isomerase	IPI00027497	27	18	22	21	20	19
Glutamate dehydrogenase 1, mitochondrial	IPI00016801	2	2	2	5	5	0
Glutamate--cysteine ligase regulatory subunit	IPI00010090	2	0	2	1	3	0
Glutaredoxin-3	IPI00008552	15	16	7	10	9	7
Glutathione peroxidase 1	IPI00927606	3	2	0	4	3	3
Glutathione S-transferase Mu 2	IPI00219067	1	2	2	3	1	2
Glutathione S-transferase omega-1	IPI00019755	3	2	4	7	3	2
Glutathione S-transferase P	IPI00219757	18	19	9	20	18	14
Glyceraldehyde-3-phosphate dehydrogenase	IPI00219018	58	47	42	54	29	29
Glycine dehydrogenase [decarboxylating], mitochondrial	IPI00843789	5	3	5	5	6	5
Glycogen phosphorylase, brain form	IPI00004358	6	2	5	13	9	5
Glycogen phosphorylase, liver form	IPI00783313	1	1	2	2	4	1
Glyoxylate reductase/hydroxypyruvate reductase	IPI00037448	3	4	5	2	4	2
Glypican-4	IPI00232571	7	6	14	4	3	8
GMP synthase [glutamine-hydrolyzing]	IPI00029079	16	11	7	12	15	15
Golgi phosphoprotein 3	IPI00005490	4	2	2	4	1	2
Golgi phosphoprotein 3-like	IPI00012313	2	1	1	2	1	0
GrpE protein homolog 1, mitochondrial	IPI00029557	1	4	2	5	4	2
GTP:AMP phosphotransferase, mitochondrial	IPI00465256	3	2	4	5	4	5
GTPase NRas	IPI00000005	2	1	5	7	2	3
GTP-binding nuclear protein Ran	IPI00643041	9	9	10	14	7	8
GTP-binding protein Rheb	IPI00016669	1	2	2	3	2	1
GTP-binding protein SAR1a	IPI00015954	4	4	2	8	4	2
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-1	IPI00026268	8	6	7	7	10	7
Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2	IPI00003348	3	1	3	2	3	6
Guanine nucleotide-binding protein G(q) subunit alpha	IPI00288947	4	3	3	5	6	2
Guanine nucleotide-binding protein subunit beta-2-like 1	IPI00848226	16	9	17	15	18	14
HEAT repeat-containing protein 1	IPI00024279	1	1	4	4	9	4
Heat shock 70 kDa protein 1A/1B	IPI00304925	10	10	11	6	11	12
Heat shock 70 kDa protein 4	IPI00002966	30	26	30	26	28	23
Heat shock protein 75 kDa, mitochondrial	IPI00030275	12	9	4	5	8	9
Heat shock protein beta-1	IPI00025512	4	3	4	5	3	4
Heat shock protein HSP 90-beta	IPI00414676	78	71	60	72	61	40
Heat shock-related 70 kDa protein 2	IPI00007702	2	1	2	2	3	6
Heme-binding protein 1	IPI00148063	8	3	2	2	4	3
Hepatoma-derived growth factor	IPI00020956	5	2	4	6	6	3
Heterogeneous nuclear ribonucleoprotein A0	IPI00011913	8	2	4	9	5	7
Heterogeneous nuclear ribonucleoprotein F	IPI00003881	6	5	6	5	5	5

Heterogeneous nuclear ribonucleoprotein G	IPI00304692	11	4	8	9	8	5
Heterogeneous nuclear ribonucleoprotein H	IPI00013881	6	6	5	7	13	9
Heterogeneous nuclear ribonucleoprotein H2	IPI00026230	2	0	1	1	4	0
Heterogeneous nuclear ribonucleoprotein K	IPI00514561	25	15	21	16	19	17
Heterogeneous nuclear ribonucleoprotein L	IPI00027834	9	9	7	11	9	12
Heterogeneous nuclear ribonucleoprotein U-like protein 2	IPI00456887	2	1	3	6	5	5
High mobility group protein B1	IPI00419258	5	5	6	10	8	8
High mobility group protein B3	IPI00217477	2	0	1	4	1	4
Histidine triad nucleotide-binding protein 1	IPI00239077	1	0	2	4	1	4
Histidine triad nucleotide-binding protein 2, mitochondrial	IPI00000335	2	1	1	2	2	2
Histidyl-tRNA synthetase, cytoplasmic	IPI00021808	6	2	5	3	4	4
Histone acetyltransferase type B catalytic subunit	IPI00024719	3	2	3	2	3	3
Histone deacetylase 2	IPI00289601	5	3	3	3	7	6
Histone H1.2	IPI00217465	1	3	13	7	4	3
Histone H1.5	IPI00217468	2	5	10	6	3	4
Histone H2A.V	IPI00018278	1	1	2	4	1	3
Histone H4	IPI00453473	7	7	15	22	10	10
Histone-binding protein RBBP7	IPI00395865	6	3	3	0	2	2
Hsc70-interacting protein	IPI00032826	4	3	5	11	5	6
Hsp90 co-chaperone Cdc37	IPI00013122	9	4	9	8	6	5
HSPA5 protein	IPI00003362	31	27	21	40	30	28
HSPC027	IPI00549672	7	8	12	16	8	6
huntingtin	IPI00002335	1	1	3	2	1	0
Hydroxymethylglutaryl-CoA synthase, cytoplasmic	IPI00008475	23	16	31	10	12	11
Hypoxanthine-guanine phosphoribosyltransferase	IPI00218493	6	6	4	8	8	7
Hypoxia up-regulated protein 1	IPI00000877	24	19	19	28	29	24
Importin subunit alpha-2	IPI00002214	17	9	13	11	14	17
Importin subunit alpha-3	IPI00299033	6	0	4	4	2	1
Importin subunit alpha-4	IPI00012578	3	1	3	4	4	2
Importin subunit beta-1	IPI00001639	25	15	17	26	24	16
Importin-11	IPI00301107	5	1	4	6	1	2
Importin-7	IPI00007402	15	11	14	16	7	11
Importin-9	IPI00185146	8	8	12	12	9	12
Inorganic pyrophosphatase	IPI00015018	5	2	9	7	8	11
Inosine triphosphate pyrophosphatase	IPI00018783	2	2	0	3	1	0
Inosine-5'-monophosphate dehydrogenase 2	IPI00291510	14	10	13	8	11	13
Inositol monophosphatase 1	IPI00020906	1	1	3	2	3	2
inositol-3-phosphate synthase 1 isoform 2	IPI00478861	5	5	4	5	5	7
Insulin-degrading enzyme	IPI00220373	9	4	5	3	4	1
Insulin-like growth factor 2 mRNA-binding protein 1	IPI00008557	7	5	7	13	13	10
Interleukin enhancer-binding factor 2	IPI00005198	14	9	12	12	11	9
Isochorismatase domain-containing protein 1	IPI00304082	3	5	4	2	2	3
Isocitrate dehydrogenase [NADP] cytoplasmic	IPI00027223	20	20	24	25	17	14
Isocitrate dehydrogenase [NADP], mitochondrial	IPI00011107	3	1	2	5	8	0
Isoform 1 of 182 kDa tankyrase-1-binding protein	IPI00304589	4	1	3	4	3	0
Isoform 1 of 1-phosphatidylinositol-4,5-bisphosphate phosphodiesterase gamma-1	IPI00016736	8	1	3	2	5	7
Isoform 1 of 26S protease regulatory subunit 6B	IPI00020042	11	6	6	15	7	5
Isoform 1 of 26S proteasome non-ATPase regulatory subunit 1	IPI00299608	11	10	12	14	13	11
Isoform 1 of 3,2-trans-enoyl-CoA isomerase, mitochondrial	IPI00300567	3	2	3	3	3	3
Isoform 1 of 3-hydroxyacyl-CoA dehydrogenase type-2	IPI00017726	10	5	5	10	8	10
Isoform 1 of 3-hydroxybutyrate dehydrogenase type 2	IPI00607799	3	0	4	5	1	2
Isoform 1 of 3-hydroxyisobutyryl-CoA hydrolase, mitochondrial	IPI00419802	1	1	3	4	6	2
Isoform 1 of 5'(3')-deoxyribonucleotidase, cytosolic type	IPI00005573	2	4	1	3	4	2
Isoform 1 of 5'-3' exoribonuclease 2	IPI00100151	11	5	8	9	9	2
Isoform 1 of 5'-nucleotidase domain-containing protein 2	IPI00009662	2	1	3	2	2	2
Isoform 1 of 60S ribosomal protein L11	IPI00376798	4	6	3	3	3	2
Isoform 1 of 60S ribosomal protein L12	IPI00024933	5	6	6	4	5	5

Isoform 1 of 6-phosphofructokinase, liver type	IPI00332371	3	2	3	5	10	8
Isoform 1 of Acetyl-CoA carboxylase 1	IPI00011569	6	8	19	3	11	6
Isoform 1 of Acid sphingomyelinase-like phosphodiesterase 3b	IPI00550115	2	1	4	1	4	1
Isoform 1 of Acidic leucine-rich nuclear phosphoprotein 32 family member B	IPI00007423	3	1	3	4	2	2
Isoform 1 of Actin-like protein 6A	IPI00003627	1	1	3	5	4	1
Isoform 1 of Actin-related protein 2/3 complex subunit 5	IPI00550234	2	1	4	5	1	3
Isoform 1 of Adenylate kinase 2, mitochondrial	IPI00215901	5	5	8	11	5	5
Isoform 1 of Adipocyte plasma membrane-associated protein	IPI00031131	2	4	3	3	3	4
Isoform 1 of Alpha-adducin	IPI00019901	5	0	2	4	6	2
Isoform 1 of Alpha-aminoadipic semialdehyde dehydrogenase	IPI00221234	8	5	13	11	14	12
Isoform 1 of Alpha-ketoglutarate-dependent dioxygenase FTO	IPI00028277	3	1	1	2	1	1
Isoform 1 of AP-1 complex subunit mu-2	IPI00002552	3	1	1	0	5	2
Isoform 1 of AP-2 complex subunit beta	IPI00784156	6	1	2	10	16	10
Isoform 1 of AP-3 complex subunit beta-1	IPI00021129	2	1	1	2	5	1
Isoform 1 of Apoptosis-associated speck-like protein containing a CARD	IPI00001699	4	5	3	3	1	0
Isoform 1 of Armadillo repeat-containing protein 6	IPI00020196	3	0	1	2	2	2
Isoform 1 of ATP synthase subunit d, mitochondrial	IPI00220487	4	4	5	8	1	3
Isoform 1 of ATP-dependent RNA helicase DDX42	IPI00409671	4	3	2	7	8	3
Isoform 1 of Axin interactor, dorsalization-associated protein	IPI00303602	1	0	2	3	1	4
Isoform 1 of Basic leucine zipper and W2 domain-containing protein 1	IPI00785096	8	5	4	7	6	4
Isoform 1 of Beta-enolase	IPI00218474	2	2	3	3	1	2
Isoform 1 of Beta-galactosidase	IPI00441344	3	1	1	3	1	1
Isoform 1 of BH3-interacting domain death agonist	IPI00413587	2	0	1	3	1	0
Isoform 1 of BRCA1-A complex subunit BRE	IPI00149276	2	1	2	2	2	1
Isoform 1 of BRCA2 and CDKN1A-interacting protein	IPI00002203	3	2	1	3	3	3
Isoform 1 of Calcyclin-binding protein	IPI00395627	10	10	15	18	11	9
Isoform 1 of Caprin-1	IPI00783872	5	3	7	7	5	5
Isoform 1 of Catenin alpha-1	IPI00215948	22	14	17	23	19	23
Isoform 1 of Catenin beta-1	IPI00017292	8	6	5	7	10	6
Isoform 1 of CCR4-NOT transcription complex subunit 1	IPI00166010	6	2	6	2	8	3
Isoform 1 of Cellular nucleic acid-binding protein	IPI00430812	1	2	2	0	2	1
Isoform 1 of Clathrin heavy chain 1	IPI00024067	37	36	48	54	52	40
Isoform 1 of Cleavage and polyadenylation specificity factor subunit 6	IPI00012998	3	3	4	4	4	4
Isoform 1 of Cleavage and polyadenylation specificity factor subunit 7	IPI00550821	1	1	2	2	2	0
Isoform 1 of Coatomer subunit alpha	IPI00295857	9	5	6	12	10	14
Isoform 1 of Coiled-coil domain-containing protein 47	IPI00024642	2	0	1	0	4	1
Isoform 1 of COP9 signalosome complex subunit 1	IPI00156282	1	1	2	2	4	5
Isoform 1 of COP9 signalosome complex subunit 7b	IPI00009301	3	3	5	3	1	1
Isoform 1 of C-terminal-binding protein 2	IPI00010120	3	3	3	1	3	4
Isoform 1 of Cullin-3	IPI00014312	7	4	6	9	6	5
Isoform 1 of Cullin-4A	IPI00419273	6	1	3	3	2	3
Isoform 1 of Cullin-associated NEDD8-dissociated protein 1	IPI00100160	24	18	26	30	20	21
Isoform 1 of Cystathionine beta-synthase	IPI00219352	12	6	6	6	8	5
Isoform 1 of Cystathionine gamma-lyase	IPI00031557	6	5	4	0	5	3
Isoform 1 of Cysteine and histidine-rich domain-containing protein 1	IPI00015897	4	0	6	1	4	3
Isoform 1 of Cytoskeleton-associated protein 4	IPI00141318	0	1	2	10	5	3
Isoform 1 of Cytosol aminopeptidase	IPI00419237	5	1	4	6	10	8
Isoform 1 of Cytosolic acyl coenzyme A thioester hydrolase	IPI00010415	5	6	9	6	8	7
Isoform 1 of Cytosolic non-specific dipeptidase	IPI00177728	18	14	14	11	16	12
Isoform 1 of DAZ-associated protein 1	IPI00165230	4	2	5	1	1	2
Isoform 1 of Deoxycytidylate deaminase	IPI00296863	0	1	2	3	3	1
Isoform 1 of Dipeptidyl peptidase 3	IPI00020672	15	7	8	14	7	10
Isoform 1 of DNA primase large subunit	IPI00027705	2	2	2	3	2	1
Isoform 1 of DNA replication complex GINS protein PSF3	IPI00748700	1	0	4	2	1	2
Isoform 1 of DNA replication licensing factor MCM7	IPI00299904	13	9	10	18	16	16
Isoform 1 of DNA-binding protein A	IPI00031801	1	0	2	1	4	2

Isoform 1 of DNA-dependent protein kinase catalytic subunit	IPI00296337	36	20	39	40	47	36
Isoform 1 of DNA-directed RNA polymerases I and III subunit RPAC1	IPI00005179	3	0	2	1	0	2
Isoform 1 of Electron transfer flavoprotein subunit beta	IPI00004902	2	2	2	6	2	3
Isoform 1 of Elongation factor G, mitochondrial	IPI00154473	3	1	1	1	3	6
Isoform 1 of Elongation factor Ts, mitochondrial	IPI00021016	2	1	1	2	2	3
Isoform 1 of Elongation factor Tu GTP-binding domain-containing protein 1	IPI00293026	4	1	1	1	3	2
Isoform 1 of Enolase-phosphatase E1	IPI00038378	5	2	2	7	2	4
Isoform 1 of Enoyl-CoA hydratase domain-containing protein 1	IPI00302688	4	2	1	0	2	2
Isoform 1 of Erlin-2	IPI00026942	4	3	2	5	4	0
Isoform 1 of Eukaryotic initiation factor 4A-II	IPI00328328	8	2	5	2	5	2
Isoform 1 of Eukaryotic translation initiation factor 3 subunit B	IPI00396370	17	11	13	13	22	15
Isoform 1 of Exportin-2	IPI00022744	31	14	30	32	28	23
Isoform 1 of Extended synaptotagmin-1	IPI00022143	10	3	5	7	14	14
Isoform 1 of FAD synthase	IPI00220299	2	1	2	3	1	2
Isoform 1 of Far upstream element-binding protein 2	IPI00479786	17	8	8	20	13	14
Isoform 1 of Fermitin family homolog 2	IPI00000856	2	3	5	4	6	5
Isoform 1 of Filamin-B	IPI00289334	43	27	44	65	72	59
Isoform 1 of Filamin-C	IPI00178352	1	4	4	38	42	25
Isoform 1 of Fragile X mental retardation syndrome-related protein 1	IPI00016249	2	1	2	2	7	5
Isoform 1 of Gamma-glutamylcyclotransferase	IPI00031564	4	3	8	9	3	1
Isoform 1 of Gelsolin	IPI00026314	4	1	1	9	13	4
Isoform 1 of General transcription factor II-I	IPI00054042	7	4	2	7	4	3
Isoform 1 of General vesicular transport factor p115	IPI00941161	13	7	15	17	16	16
Isoform 1 of Glucosamine--fructose-6-phosphate aminotransferase [isomerizing] 1	IPI00217952	10	8	5	12	14	16
Isoform 1 of Glycerol-3-phosphate dehydrogenase, mitochondrial	IPI00017895	3	1	0	1	3	2
Isoform 1 of Growth factor receptor-bound protein 2	IPI00021327	4	5	2	4	4	3
Isoform 1 of Guanine nucleotide-binding protein G(i) subunit alpha-2	IPI00748145	5	3	3	4	8	6
Isoform 1 of Heat shock cognate 71 kDa protein	IPI00003865	46	37	39	38	39	31
Isoform 1 of Hematological and neurological expressed 1-like protein	IPI00027397	2	2	3	1	3	0
Isoform 1 of Heterogeneous nuclear ribonucleoprotein A3	IPI00419373	10	6	8	15	17	10
Isoform 1 of Heterogeneous nuclear ribonucleoprotein D0	IPI00028888	16	10	15	13	13	6
Isoform 1 of Heterogeneous nuclear ribonucleoprotein H3	IPI00013877	4	4	3	4	4	5
Isoform 1 of Heterogeneous nuclear ribonucleoprotein M	IPI00171903	13	11	14	13	22	19
Isoform 1 of Heterogeneous nuclear ribonucleoprotein Q	IPI00018140	9	6	4	11	12	14
Isoform 1 of Heterogeneous nuclear ribonucleoprotein R	IPI00012074	9	7	8	8	7	6
Isoform 1 of Heterogeneous nuclear ribonucleoprotein U-like protein 1	IPI00013070	2	0	2	3	4	1
Isoform 1 of Hexokinase-1	IPI00018246	2	2	10	9	7	5
Isoform 1 of Histone-binding protein RBBP4	IPI00328319	2	1	4	2	6	7
Isoform 1 of Hydroxyacyl-coenzyme A dehydrogenase, mitochondrial	IPI00294398	5	5	3	4	0	5
Isoform 1 of Importin-4	IPI00156374	11	8	13	11	8	10
Isoform 1 of Importin-5	IPI00793443	36	24	35	34	25	28
Isoform 1 of Inorganic pyrophosphatase 2, mitochondrial	IPI00301109	2	1	2	1	2	0
Isoform 1 of Insulin-like growth factor 2 mRNA-binding protein 2	IPI00179713	7	1	3	4	6	0
Isoform 1 of Insulin-like growth factor 2 mRNA-binding protein 3	IPI00658000	7	6	11	7	10	7
Isoform 1 of Integrin alpha-V	IPI00027505	1	0	2	2	8	5
Isoform 1 of Intraflagellar transport protein 27 homolog	IPI00872292	2	0	2	3	1	0
Isoform 1 of Isocitrate dehydrogenase [NAD] subunit alpha	IPI00030702	3	3	1	3	3	3
Isoform 1 of IST1 homolog	IPI00024660	2	1	2	2	1	1
Isoform 1 of KH domain-containing, RNA-binding, signal transduction-associated protein 1	IPI00008575	5	4	3	8	7	3
Isoform 1 of Kinectin	IPI00328753	3	1	4	7	12	2
Isoform 1 of Kinesin heavy chain isoform 5C	IPI00028561	5	3	2	3	3	2
Isoform 1 of Kinesin-like protein KIF1A	IPI00604711	3	2	6	1	4	4
Isoform 1 of Kynurenine--oxoglutarate transaminase 3	IPI00465373	3	1	2	2	2	0
Isoform 1 of Large proline-rich protein BAT3	IPI00465128	4	4	2	7	5	3

Isoform 1 of LETM1 and EF-hand domain-containing protein 1, mitochondrial	IPI00017592	3	0	2	4	2	3
Isoform 1 of Leukotriene A-4 hydrolase	IPI00219077	14	7	8	4	10	7
Isoform 1 of LIM and SH3 domain protein 1	IPI00000861	3	1	4	4	6	4
Isoform 1 of L-lactate dehydrogenase A chain	IPI00217966	50	37	42	32	26	30
Isoform 1 of Low molecular weight phosphotyrosine protein phosphatase	IPI00219861	4	2	3	4	5	5
Isoform 1 of Magnesium-dependent phosphatase 1	IPI00337556	0	1	2	2	1	0
Isoform 1 of Malignant T cell-amplified sequence 1	IPI00179026	2	1	1	5	3	3
Isoform 1 of Medium-chain specific acyl-CoA dehydrogenase, mitochondrial	IPI00005040	3	1	0	2	1	1
Isoform 1 of Melanoma-associated antigen D2	IPI00009542	3	0	1	0	4	5
Isoform 1 of Metastasis-associated protein MTA3	IPI00165357	5	2	1	1	4	0
Isoform 1 of Methionine adenosyltransferase 2 subunit beta	IPI00002324	2	3	3	4	3	2
Isoform 1 of Methyl-CpG-binding domain protein 3	IPI00439194	1	1	2	4	1	1
Isoform 1 of Mitotic checkpoint protein BUB3	IPI00013468	3	4	6	5	2	2
Isoform 1 of Mps one binder kinase activator-like 1B	IPI00301518	3	3	1	3	0	1
Isoform 1 of Myb-binding protein 1A	IPI00005024	6	2	5	8	6	5
Isoform 1 of Myosin-10	IPI00397526	33	26	58	48	39	37
Isoform 1 of Myosin-9	IPI00019502	67	54	88	77	66	61
Isoform 1 of Myosin-Ib	IPI00376344	5	2	1	3	5	2
Isoform 1 of NACHT, LRR and PYD domains-containing protein 2	IPI00016480	7	2	8	9	5	12
Isoform 1 of NADH-cytochrome b5 reductase 2	IPI00008234	1	1	4	3	0	1
Isoform 1 of NADH-cytochrome b5 reductase 3	IPI00328415	5	2	4	6	5	5
Isoform 1 of N-alpha-acetyltransferase 50, NatE catalytic subunit	IPI00018627	6	0	6	12	5	7
Isoform 1 of Neurochondrin	IPI00549543	2	2	2	2	4	4
Isoform 1 of Nicastrin	IPI00021983	1	1	2	1	1	2
Isoform 1 of Nicotinate phosphoribosyltransferase	IPI00465085	3	0	1	2	2	2
Isoform 1 of NIF3-like protein 1	IPI00604624	3	1	1	2	5	2
Isoform 1 of NSFL1 cofactor p47	IPI00100197	4	0	4	4	4	2
Isoform 1 of Nuclear autoantigenic sperm protein	IPI00179953	27	19	21	23	27	26
Isoform 1 of Nuclear pore complex protein Nup155	IPI00026625	9	4	5	5	8	7
Isoform 1 of Nuclear pore complex protein Nup160	IPI00748807	1	2	5	7	6	4
Isoform 1 of Nuclear pore complex protein Nup98-Nup96	IPI00006038	2	1	1	1	2	1
Isoform 1 of Nucleolar protein 6	IPI00152890	2	0	3	2	1	0
Isoform 1 of Nucleolar RNA helicase 2	IPI00015953	11	9	9	9	12	11
Isoform 1 of Nucleoredoxin	IPI00304267	3	1	3	2	6	6
Isoform 1 of Nucleoside diphosphate kinase A	IPI00012048	2	2	2	2	2	1
Isoform 1 of Obg-like ATPase 1	IPI00290416	5	6	11	7	7	7
Isoform 1 of Oligoribonuclease, mitochondrial (Fragment)	IPI00032830	2	2	2	4	2	2
Isoform 1 of Paraspeckle component 1	IPI00103525	5	2	2	3	4	2
Isoform 1 of PC4 and SFRS1-interacting protein	IPI00028122	2	0	3	3	2	2
Isoform 1 of Peroxidasin homolog	IPI00016112	3	1	1	1	3	1
Isoform 1 of Peroxisomal acyl-coenzyme A oxidase 1	IPI00296907	3	0	1	2	0	1
Isoform 1 of Phosphatidylinositol transfer protein beta isoform	IPI00334907	6	2	4	2	5	2
Isoform 1 of Phosphoenolpyruvate carboxykinase [GTP]	IPI00797038	5	3	5	5	6	6
Isoform 1 of Phosphoglucomutase-1	IPI00219526	14	13	14	13	12	7
Isoform 1 of Phosphoribosyl pyrophosphate synthase-associated protein 1	IPI00291578	3	1	1	2	4	1
Isoform 1 of Platelet-activating factor acetylhydrolase IB subunit α	IPI00218728	1	0	4	3	4	5
Isoform 1 of Polyadenylate-binding protein 1	IPI00008524	17	7	10	16	16	13
Isoform 1 of Polyadenylate-binding protein 2	IPI00005792	1	3	3	3	1	2
Isoform 1 of Polyadenylate-binding protein 4	IPI00012726	3	1	3	5	3	4
Isoform 1 of Polypyrimidine tract-binding protein 1	IPI00179964	15	11	13	17	15	13
Isoform 1 of Polypyrimidine tract-binding protein 2	IPI00514064	1	1	3	5	3	3
Isoform 1 of Porphobilinogen deaminase	IPI00028160	2	1	2	3	0	2
Isoform 1 of Pre-mRNA-processing factor 40 homolog A	IPI00337385	4	1	1	2	5	3
Isoform 1 of Probable ATP-dependent RNA helicase DHX36	IPI00027415	1	1	3	2	2	1

Isoform 1 of Proteasome activator complex subunit 3	IPI00030243	8	6	9	8	10	6
Isoform 1 of Proteasome activator complex subunit 4	IPI00005260	5	4	3	2	7	3
Isoform 1 of Proteasome assembly chaperone 1	IPI00030770	1	1	2	1	3	2
Isoform 1 of Proteasome subunit alpha type-7	IPI00024175	16	8	12	16	11	12
Isoform 1 of Protein canopy homolog 2	IPI00443909	5	4	3	6	5	6
Isoform 1 of Protein diaphanous homolog 1	IPI00852685	2	2	7	7	6	2
Isoform 1 of Protein KIAA1967	IPI00182757	7	5	9	7	13	11
Isoform 1 of Protein LSM12 homolog	IPI00410324	2	2	2	1	0	2
Isoform 1 of Protein phosphatase 1 regulatory subunit 12A	IPI00183002	4	1	3	3	3	0
Isoform 1 of Protein phosphatase 1 regulatory subunit 7	IPI00033600	3	1	4	1	4	1
Isoform 1 of Protein phosphatase methylesterase 1	IPI00007694	2	3	4	4	2	2
Isoform 1 of Protein SET	IPI00072377	14	9	10	15	5	10
Isoform 1 of Protein syndesmos	IPI00031650	2	2	0	3	4	2
Isoform 1 of Protein transport protein Sec24A	IPI00873472	4	1	0	3	3	1
Isoform 1 of Protein unc-45 homolog A	IPI00072534	2	2	4	5	1	0
Isoform 1 of Protein virilizer homolog	IPI00036742	1	1	2	3	1	1
Isoform 1 of Putative ATP-dependent RNA helicase DHX30	IPI00411733	2	2	0	0	5	1
Isoform 1 of Putative deoxyribonuclease TATDN1	IPI00012463	2	1	1	3	6	1
Isoform 1 of Putative helicase MOV-10	IPI00444452	2	1	2	2	2	0
Isoform 1 of Putative RNA-binding protein Luc7-like 1	IPI00071318	1	0	2	1	3	0
Isoform 1 of Pyridoxal kinase	IPI00013004	4	1	3	6	2	3
Isoform 1 of Pyruvate dehydrogenase E1 component subunit beta	IPI00003925	8	6	8	8	8	6
Isoform 1 of Quinone oxidoreductase PIG3	IPI00384643	3	0	3	1	0	2
Isoform 1 of Ras-related protein Rab-1A	IPI00005719	3	2	3	4	2	1
Isoform 1 of Ras-related protein Rab-34	IPI00328180	3	1	1	1	5	5
Isoform 1 of Regulator of nonsense transcripts 1	IPI00034049	6	5	3	8	7	6
Isoform 1 of Replication factor C subunit 2	IPI00017412	4	1	1	3	3	1
Isoform 1 of Replication protein A 32 kDa subunit	IPI00013939	4	2	5	3	2	3
Isoform 1 of Reticulon-4	IPI00021766	3	3	4	2	5	4
Isoform 1 of Retinol dehydrogenase 11	IPI00339384	3	1	3	2	4	2
Isoform 1 of Rho guanine nucleotide exchange factor 2	IPI00291316	2	0	2	4	2	0
Isoform 1 of Ribonucleoside-diphosphate reductase subunit M2 B	IPI00100213	4	2	4	4	4	2
Isoform 1 of RNA polymerase II subunit A C-terminal domain phosphatase SSU72	IPI00023556	2	0	2	2	3	3
Isoform 1 of RNA-binding protein 8A	IPI00001757	3	2	0	2	5	2
Isoform 1 of RRP12-like protein	IPI00101186	4	3	4	2	3	2
Isoform 1 of RuvB-like 1	IPI00021187	9	8	6	14	17	11
Isoform 1 of Septin-2	IPI00014177	8	5	7	6	7	5
Isoform 1 of Serine/arginine-rich splicing factor 7	IPI00003377	3	2	4	6	1	3
Isoform 1 of Serine/threonine-protein phosphatase 4 regulatory subunit 3A	IPI00217013	3	1	1	1	3	0
Isoform 1 of Serine/threonine-protein phosphatase 6 catalytic subunit	IPI00012970	6	2	3	4	3	2
Isoform 1 of Sodium/potassium-transporting ATPase subunit beta-1	IPI00747849	1	0	2	1	4	0
Isoform 1 of Spectrin alpha chain, brain	IPI00844215	38	24	38	53	52	44
Isoform 1 of Spermine synthase	IPI00005102	9	7	8	5	6	6
Isoform 1 of S-phase kinase-associated protein 1	IPI00301364	5	6	6	8	5	5
Isoform 1 of Splicing factor 3B subunit 3	IPI00300371	11	5	8	17	19	14
Isoform 1 of Splicing factor U2AF 65 kDa subunit	IPI00031556	3	2	2	2	6	6
Isoform 1 of Squamous cell carcinoma antigen recognized by T-cells 3	IPI00006025	2	1	2	2	7	4
Isoform 1 of Structural maintenance of chromosomes protein 2	IPI00007927	7	2	1	3	4	2
Isoform 1 of Surfeit locus protein 4	IPI00005737	2	2	1	2	3	2
Isoform 1 of Syntaxin-7	IPI00289876	2	0	3	0	3	3
Isoform 1 of Thyroid receptor-interacting protein 13	IPI00003505	5	2	0	2	2	0
Isoform 1 of TIP41-like protein	IPI00745568	2	0	5	3	2	2
Isoform 1 of Transcription elongation factor A protein 1	IPI00333215	4	3	10	3	5	4
Isoform 1 of Transcription intermediary factor 1-beta	IPI00438229	12	13	15	20	16	16
Isoform 1 of Transformer-2 protein homolog beta	IPI00301503	4	1	2	3	5	2

Isoform 1 of Translation initiation factor eIF-2B subunit delta	IPI00005979	1	3	1	1	2	0
Isoform 1 of Transportin-1	IPI00024364	9	4	11	13	12	8
Isoform 1 of tRNA-nucleotidyltransferase 1, mitochondrial	IPI00289807	2	0	1	2	1	1
Isoform 1 of Tropomyosin alpha-4 chain	IPI00010779	6	7	17	15	6	9
Isoform 1 of Tryptophanyl-tRNA synthetase, cytoplasmic	IPI00295400	16	10	13	8	11	6
Isoform 1 of Tyrosine-protein kinase-like 7	IPI00298292	4	1	2	2	3	0
Isoform 1 of U5 small nuclear ribonucleoprotein 200 kDa helicase	IPI00420014	15	15	17	23	27	22
Isoform 1 of Ubiquitin carboxyl-terminal hydrolase 28	IPI00045496	2	1	0	3	5	1
Isoform 1 of Ubiquitin conjugation factor E4 B	IPI00005715	1	1	4	2	4	1
Isoform 1 of Ubiquitin-conjugating enzyme E2 D3	IPI00026965	2	1	1	3	2	2
Isoform 1 of Ubiquitin-conjugating enzyme E2 K	IPI00021370	8	5	3	10	5	6
Isoform 1 of Ubiquitin-like-conjugating enzyme ATG3	IPI00022254	3	1	0	1	4	1
Isoform 1 of UBX domain-containing protein 1	IPI00027378	1	3	2	0	3	4
Isoform 1 of UDP-glucose:glycoprotein glucosyltransferase 1	IPI00024466	11	3	9	12	14	8
Isoform 1 of Uridine 5'-monophosphate synthase	IPI00003923	2	2	1	6	4	5
Isoform 1 of Uridine-cytidine kinase 2	IPI00065671	2	3	0	4	3	3
Isoform 1 of UTP--glucose-1-phosphate uridylyltransferase	IPI00329331	28	18	25	20	24	14
Isoform 1 of Vacuolar protein sorting-associated protein 29	IPI00170796	2	1	3	5	2	1
Isoform 1 of Vesicle-associated membrane protein-associated prtn A	IPI00170692	1	0	2	3	5	3
Isoform 1 of Vesicle-associated membrane protein-associated protein B/C	IPI00006211	1	1	3	2	2	1
Isoform 1 of Vinculin	IPI00291175	58	48	65	51	40	48
Isoform 1 of WD repeat-containing protein 1	IPI00746165	7	3	4	8	12	11
Isoform 1 of Zinc finger protein 326	IPI00373877	0	1	2	2	3	2
Isoform 1 of Zinc phosphodiesterase ELAC protein 2	IPI00396627	6	2	2	1	5	1
Isoform 1AB of Catenin delta-1	IPI00182469	3	2	1	4	7	5
Isoform 2 of 6-phosphofructokinase, muscle type	IPI00219585	1	3	1	2	11	7
Isoform 2 of Annexin A2	IPI00418169	20	17	11	40	23	20
Isoform 2 of AP-1 complex subunit gamma-1	IPI00293396	4	2	0	4	5	2
Isoform 2 of AP-2 complex subunit alpha-2	IPI00016621	2	0	1	4	5	1
Isoform 2 of Apoptosis inhibitor 5	IPI00554742	6	5	4	8	6	3
Isoform 2 of ATP-binding cassette sub-family F member 1	IPI00013495	4	1	1	4	3	6
Isoform 2 of ATP-dependent RNA helicase DDX54	IPI00152510	2	1	2	1	2	1
Isoform 2 of Basigin	IPI00019906	8	7	9	7	7	6
Isoform 2 of Cat eye syndrome critical region protein 5	IPI00011511	4	2	2	4	5	5
Isoform 2 of Cell division control protein 42 homolog	IPI00016786	4	2	5	7	5	3
Isoform 2 of Cullin-4B	IPI00179057	2	0	2	5	3	3
Isoform 2 of Cytochrome P450 2S1	IPI00164018	7	3	4	3	6	3
Isoform 2 of Deoxyuridine 5'-triphosphate nucleotidohydrolase	IPI00375015	5	3	6	4	8	7
Isoform 2 of Eukaryotic translation initiation factor 5A-1	IPI00376005	16	9	9	12	9	8
Isoform 2 of F-actin-capping protein subunit beta	IPI00642256	13	8	13	12	11	7
Isoform 2 of Filamin-A	IPI00302592	101	75	79	94	101	89
Isoform 2 of Golgi apparatus protein 1	IPI00414717	4	0	6	5	10	6
Isoform 2 of HD domain-containing protein 2	IPI00386751	1	2	1	5	2	0
Isoform 2 of Heat shock protein HSP 90-alpha	IPI00382470	35	27	25	40	32	20
Isoform 2 of Heterogeneous nuclear ribonucleoprotein A/B	IPI00334587	5	7	7	7	7	7
Isoform 2 of Isochorismatase domain-containing protein 2	IPI00003031	2	2	0	3	1	1
Isoform 2 of Lysine-specific histone demethylase 1A	IPI00217540	1	0	2	3	5	0
Isoform 2 of Microtubule-actin cross-linking factor 1	IPI00256861	19	11	11	13	26	0
Isoform 2 of mRNA cap guanine-N7 methyltransferase	IPI00410657	1	0	3	1	2	2
Isoform 2 of Nitrilase homolog 1	IPI00023779	1	1	2	2	2	0
Isoform 2 of Nuclear mitotic apparatus protein 1	IPI00006196	6	2	13	9	14	3
Isoform 2 of Nucleoporin NUP188 homolog	IPI00385001	0	1	3	2	2	0
Isoform 2 of Phosphatidylinositol-binding clathrin assembly protein	IPI00216184	1	1	2	3	3	2
Isoform 2 of Proteasome subunit alpha type-3	IPI00171199	10	9	6	8	5	5
Isoform 2 of Protein disulfide-isomerase A6	IPI00299571	19	13	19	26	12	15
Isoform 2 of Ras-related protein Rab-6A	IPI00217943	4	3	5	7	4	1
Isoform 2 of Sarcoplasmic/endoplasmic reticulum calcium ATPase 2	IPI00177817	5	6	2	9	11	8

Isoform 2 of Serrate RNA effector molecule homolog	IPI00220038	1	3	7	4	5	5
Isoform 2 of Spliceosome RNA helicase BAT1	IPI00641829	13	7	10	18	13	14
Isoform 2 of Structural maintenance of chromosomes protein 4	IPI00328298	3	0	3	5	3	2
Isoform 2 of Suppressor of G2 allele of SKP1 homolog	IPI00791573	6	6	7	4	8	5
Isoform 2 of TAR DNA-binding protein 43	IPI00025815	4	2	7	6	7	4
Isoform 2 of Transportin-3	IPI00395694	8	2	5	10	7	6
Isoform 2 of tRNA pseudouridine synthase A, mitochondrial	IPI00001716	2	1	4	1	3	0
Isoform 2 of Tropomyosin alpha-3 chain	IPI00218319	22	26	29	32	17	12
Isoform 2 of Tumor protein D54	IPI00221178	4	2	8	5	7	3
Isoform 2 of U1 small nuclear ribonucleoprotein 70 kDa	IPI00219483	3	4	2	5	5	4
Isoform 2 of Ubiquilin-1	IPI00071180	3	0	1	1	1	2
Isoform 2 of UPF0557 protein C10orf119	IPI00552546	2	1	2	3	3	1
Isoform 2 of Valacyclovir hydrolase	IPI00003990	2	1	1	2	1	0
Isoform 2 of Voltage-dependent anion-selective channel protein 2	IPI00024145	1	0	3	2	4	3
Isoform 2C of Cytoplasmic dynein 1 intermediate chain 2	IPI00216348	2	1	1	2	4	3
Isoform 3 of Anamorsin	IPI00025333	2	3	3	3	3	3
Isoform 3 of DNA topoisomerase 2-alpha	IPI00218753	1	0	6	3	9	7
Isoform 3 of Epithelial splicing regulatory protein 1	IPI00184262	4	0	2	2	2	4
Isoform 3 of Prolyl 3-hydroxylase 1	IPI00045839	2	0	1	2	2	2
Isoform 3 of Protein DDI1 homolog 2	IPI00031618	5	0	2	1	2	0
Isoform 3 of Protein transport protein Sec31A	IPI00305152	4	1	3	5	4	3
Isoform 3 of Reticulon-3	IPI00028946	1	3	2	1	4	0
Isoform 3 of Ribosome-binding protein 1	IPI00215743	1	0	9	7	10	1
Isoform 3 of Serine/threonine-protein phosphatase 2A activator	IPI00217296	4	4	2	1	3	2
Isoform 3 of Ubiquitin-conjugating enzyme E2 variant 1	IPI00472498	6	4	3	2	1	1
Isoform 4 of E3 ubiquitin-protein ligase UBR4	IPI00640981	8	9	14	7	13	1
Isoform 4 of Probable ATP-dependent RNA helicase DDX17	IPI00889541	9	2	4	15	11	11
Isoform 4 of Tropomyosin alpha-1 chain	IPI00296039	5	3	17	13	4	6
Isoform 4 of Tubulin-specific chaperone D	IPI00030774	6	0	4	6	8	7
Isoform 5 of Interleukin enhancer-binding factor 3	IPI00219330	8	9	13	14	18	16
Isoform 5 of Thioredoxin reductase 1, cytoplasmic	IPI00554786	8	3	8	5	10	6
Isoform 6 of Protein quaking	IPI00385562	2	0	2	2	4	0
Isoform A of Protein CutA	IPI00034319	4	1	1	2	2	2
Isoform A of Ras GTPase-activating protein-binding protein 2	IPI00009057	2	1	2	1	3	2
Isoform A of Ras-related C3 botulinum toxin substrate 1	IPI00010271	3	2	2	5	4	4
Isoform A of RNA-binding protein with multiple splicing	IPI00004045	1	0	3	7	3	3
Isoform A of Trypsin-3	IPI00015614	1	1	2	1	2	1
Isoform A1-B of Heterogeneous nuclear ribonucleoprotein A1	IPI00215965	34	28	23	34	28	22
Isoform Alpha of Apoptosis regulator BAX	IPI00443773	7	6	5	5	6	3
Isoform Alpha of Signal transducer and activator of transcription 1α/β	IPI00030781	7	0	1	3	8	1
Isoform Alpha-6X1X2B of Integrin alpha-6	IPI00010697	2	2	4	7	10	6
Isoform alpha-enolase of Alpha-enolase	IPI00465248	50	45	63	72	30	25
Isoform APP770 of Amyloid beta A4 protein (Fragment)	IPI00006608	2	2	3	2	3	0
Isoform ASF-1 of Serine/arginine-rich splicing factor 1	IPI00215884	7	8	10	14	9	10
Isoform B of AP-2 complex subunit alpha-1	IPI00256684	8	1	4	7	12	8
Isoform B of Arfaptin-1	IPI00021258	2	1	1	2	3	0
Isoform B of Perilipin-3	IPI00303882	9	6	7	14	12	6
Isoform B1 of Heterogeneous nuclear ribonucleoproteins A2/B1	IPI00396378	23	14	18	23	20	18
Isoform Beta of Heat shock protein 105 kDa	IPI00218993	22	10	22	19	20	14
Isoform Beta-1 of Protein phosphatase 1B	IPI00026612	2	1	2	2	7	3
Isoform C1 of Heterogeneous nuclear ribonucleoproteins C1/C2	IPI00216592	11	11	13	20	14	10
Isoform Complexed of Arginyl-tRNA synthetase, cytoplasmic	IPI00004860	8	4	7	9	10	10
Isoform Crk-II of Adapter molecule crk	IPI00004838	5	1	2	3	3	2
Isoform Cytoplasmic of Lysyl-tRNA synthetase	IPI00014238	8	5	6	9	9	8
Isoform Del-701 of Signal transducer and activator of transcription 3	IPI00306436	4	1	3	3	6	3
Isoform Delta-1 of Serine/threonine-protein phosphatase 2A 56 kDa regulatory subunit delta isoform	IPI00000030	2	0	1	3	3	3
Isoform DFF45 of DNA fragmentation factor subunit alpha (Fragment)	IPI00010882	3	0	1	2	1	1

Isoform Gamma-1 of Serine/threonine-protein phosphatase PP1-gamma catalytic subunit	IPI00005705	2	1	2	2	2	2
Isoform GTBP-N of DNA mismatch repair protein Msh6	IPI00384456	9	7	3	6	10	6
Isoform Heart of ATP synthase subunit gamma, mitochondrial	IPI00395769	5	2	3	5	3	2
Isoform II of Ubiquitin-protein ligase E3A	IPI00011609	3	1	3	3	3	0
Isoform Long of 14-3-3 protein beta/alpha	IPI00216318	13	9	14	18	11	7
Isoform Long of 60 kDa SS-A/Ro ribonucleoprotein	IPI00019450	4	2	2	4	3	1
Isoform Long of Cold shock domain-containing protein E1	IPI00470891	3	1	2	5	5	4
Isoform Long of Delta-1-pyrroline-5-carboxylate synthase	IPI00008982	11	6	4	8	6	10
Isoform Long of Double-stranded RNA-binding protein Staufen homolog 1	IPI00000001	3	1	2	2	4	2
Isoform Long of ES1 protein homolog, mitochondrial	IPI00024913	2	2	1	4	5	4
Isoform Long of Eukaryotic translation initiation factor 4H	IPI00014263	6	2	6	5	3	5
Isoform Long of Glucose-6-phosphate 1-dehydrogenase	IPI00216008	2	2	7	9	10	5
Isoform Long of Glycylpeptide N-tetradecanoyltransferase 1	IPI00329692	2	0	3	2	4	3
Isoform Long of Heterogeneous nuclear ribonucleoprotein U	IPI00883857	20	12	25	23	11	19
Isoform Long of Sodium/potassium-transporting ATPase subunit α-1	IPI00006482	17	15	12	14	20	14
Isoform Long of Spectrin beta chain, brain 1	IPI00005614	30	24	38	58	49	40
Isoform Long of Splicing factor, proline- and glutamine-rich	IPI00010740	14	6	8	17	18	11
Isoform Long of Tight junction protein ZO-1	IPI00216219	4	1	3	1	6	6
Isoform Long of Trifunctional purine biosynthetic protein adenosine-3	IPI00025273	14	8	9	14	12	13
Isoform Long of Ubiquitin carboxyl-terminal hydrolase 5	IPI00024664	11	5	9	7	11	7
Isoform M2 of Pyruvate kinase isozymes M1/M2	IPI00479186	44	36	38	51	35	36
Isoform Mitochondrial of Fumarate hydratase, mitochondrial	IPI00296053	9	4	7	5	5	3
Isoform Mitochondrial of Glutathione reductase, mitochondrial	IPI00016862	7	5	2	3	4	1
Isoform Mitochondrial of Phospholipid hydroperoxide glutathione peroxidase, mitochondrial	IPI00304814	5	3	4	4	5	2
Isoform Non-brain of Clathrin light chain A	IPI00216393	3	1	4	1	2	2
Isoform Non-muscle of Myosin light polypeptide 6	IPI00335168	12	5	6	9	11	9
Isoform p26 of 7,8-dihydro-8-oxoguanine triphosphatase	IPI00004392	3	1	4	6	3	4
Isoform p27-L of 26S proteasome non-ATPase regulatory subunit 9	IPI00010860	0	1	2	5	2	1
Isoform Rpn10A of 26S proteasome non-ATPase regulatory subunit 4	IPI00022694	6	6	3	5	9	5
Isoform Short of Proteasome subunit alpha type-1	IPI00016832	10	2	12	10	8	7
Isoform Short of RNA-binding protein FUS	IPI00221354	3	2	5	6	6	5
Isoform SM-B' of Small nuclear ribonucleoprotein-associated proteins	IPI00027285	2	2	4	4	2	4
Isoform SNAP-23a of Synaptosomal-associated protein 23	IPI00010438	3	1	2	3	2	3
Isoform SRP55-1 of Serine/arginine-rich splicing factor 6	IPI00012345	1	2	3	3	2	1
Isoleucyl-tRNA synthetase, cytoplasmic	IPI00644127	25	14	10	18	25	20
Junction plakoglobin	IPI00554711	2	0	1	6	6	5
Junctional adhesion molecule A	IPI00001754	2	0	3	3	6	2
Keratin, type I cytoskeletal 10	IPI00009865	10	5	8	10	24	16
Keratin, type II cytoskeletal 8	IPI00554648	16	13	21	51	31	13
Kinesin-1 heavy chain	IPI00012837	15	4	14	18	12	12
Kinesin-like protein KIF11	IPI00305289	4	4	1	8	6	3
Kinetochore-associated protein 1	IPI00001458	1	2	1	2	5	2
Lactoylglutathione lyase	IPI00220766	5	4	3	9	3	5
Lamin-B1	IPI00217975	3	0	6	5	7	5
Lamin-B2	IPI00009771	1	0	3	2	1	0
Laminin subunit alpha-1	IPI00375294	2	3	4	2	2	0
Laminin subunit beta-1	IPI00013976	3	0	2	7	8	1
Laminin subunit gamma-1	IPI00298281	6	3	5	2	10	6
L-aminoadipate-semialdehyde dehydrogenase-phosphopantetheinyl transferase	IPI00250297	3	0	2	1	0	2
lanosterol 14-alpha demethylase isoform 1	IPI00295772	11	6	11	4	8	6
Lanosterol synthase	IPI00009747	5	3	12	4	7	4
Large neutral amino acids transporter small subunit 1	IPI00008986	5	0	4	0	5	2
LDLR chaperone MESD	IPI00399089	2	1	0	1	2	3
Leucine-rich PPR motif-containing protein, mitochondrial	IPI00783271	28	27	27	29	23	30

Leucine-rich repeat-containing protein 40	IPI00152998	2	1	2	1	3	3
Leucine-rich repeat-containing protein 47	IPI00170935	5	4	2	7	5	4
Leucine-rich repeat-containing protein 59	IPI00396321	3	4	3	5	6	5
Leucyl-tRNA synthetase, cytoplasmic	IPI00103994	20	11	13	17	19	21
LINE-1 type transposase domain-containing protein 1	IPI00253050	16	10	12	15	18	14
L-lactate dehydrogenase B chain	IPI00219217	27	19	23	22	18	14
Lon protease homolog, mitochondrial	IPI00005158	9	5	5	10	7	9
Long-chain-fatty-acid--CoA ligase 3	IPI00031397	2	0	2	1	10	2
Lupus La protein	IPI00009032	22	13	18	19	14	13
L-xylulose reductase	IPI00448095	2	1	3	2	1	0
Lysophosphatidylcholine acyltransferase 1	IPI00171626	4	2	3	2	5	1
Lysosome-associated membrane glycoprotein 1	IPI00884105	3	3	4	3	1	1
Macrophage-capping protein	IPI00027341	2	1	2	6	7	4
MAGUK p55 subfamily member 6	IPI00303280	2	0	2	3	2	1
Malate dehydrogenase	IPI00916111	12	10	11	10	10	9
Malate dehydrogenase, mitochondrial	IPI00291006	20	15	20	16	14	12
Malectin	IPI00029046	2	1	2	2	4	2
maleylacetoacetate isomerase isoform 1	IPI00556579	1	1	2	2	1	1
MARCKS-related protein	IPI00641181	1	2	2	0	1	2
Matrin-3	IPI00017297	14	14	13	18	15	15
Membrane-associated progesterone receptor component 1	IPI00220739	8	3	3	8	3	3
Methionyl-tRNA synthetase, cytoplasmic	IPI00008240	17	12	12	15	18	17
Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	IPI00291646	5	3	3	3	4	3
Methylosome protein 50	IPI00012202	3	0	2	2	4	2
Methylosome subunit pICln	IPI00004795	2	2	2	3	0	1
Microsomal glutathione S-transferase 1	IPI00021805	3	1	1	0	2	2
Microtubule-associated protein 1B	IPI00008868	6	3	17	5	5	6
Microtubule-associated protein RP/EB family member 1	IPI00017596	10	4	10	15	13	9
Midasin	IPI00167941	15	5	3	5	11	0
Mitochondrial fission 1 protein	IPI00007052	3	3	1	2	3	0
Mitochondrial import inner membrane translocase subunit TIM44	IPI00306516	6	3	5	5	3	4
Mitochondrial-processing peptidase subunit alpha	IPI00166749	2	0	1	2	3	1
Mitochondrial-processing peptidase subunit beta	IPI00927892	4	2	4	4	4	3
Mitogen-activated protein kinase 1	IPI00003479	3	2	4	4	4	1
Mitogen-activated protein kinase scaffold protein 1	IPI00030919	1	0	2	1	1	2
MLL1/MLL complex subunit C17orf49 isoform 1	IPI00373869	2	0	2	3	1	2
Moesin	IPI00219365	15	12	11	22	18	14
Monocarboxylate transporter 1	IPI00024650	2	1	1	2	1	1
mRNA turnover protein 4 homolog	IPI00106491	7	2	3	5	4	4
Multifunctional protein ADE2	IPI00217223	23	17	26	24	14	15
Myosin-Ie	IPI00329672	2	1	1	1	3	2
Myotrophin	IPI00924816	1	0	2	5	1	3
Myristoylated alanine-rich C-kinase substrate	IPI00219301	0	1	5	0	4	1
N(G),N(G)-dimethylarginine dimethylaminohydrolase 1	IPI00220342	4	6	5	4	2	2
N(G),N(G)-dimethylarginine dimethylaminohydrolase 2	IPI00000760	3	0	3	4	6	3
Na(+)/H(+) exchange regulatory cofactor NHE-RF1	IPI00003527	4	4	9	7	3	3
N-acetyl-D-glucosamine kinase	IPI00296526	3	0	5	1	3	2
N-acetyltransferase 10	IPI00300127	3	5	4	6	7	5
NAD-dependent malic enzyme, mitochondrial	IPI00011201	2	0	3	1	3	0
NADH dehydrogenase [ubiquinone] iron-sulfur protein 3	IPI00025796	4	3	6	5	5	2
NADPH--cytochrome P450 reductase	IPI00470467	7	6	6	6	6	10
N-alpha-acetyltransferase 10, NatA catalytic subunit	IPI00013184	1	1	2	0	4	1
N-alpha-acetyltransferase 38, NatC auxiliary subunit	IPI00219871	1	1	2	6	0	4
nardilysin isoform a	IPI00243221	4	0	3	0	4	6
Nascent polypeptide-associated complex subunit alpha	IPI00023748	6	7	8	8	5	6
NEDD8-activating enzyme E1 catalytic subunit	IPI00328154	4	0	4	3	5	2
NEDD8-activating enzyme E1 regulatory subunit	IPI00018968	5	1	2	4	2	4

NEDD8-conjugating enzyme Ubc12	IPI00022597	3	1	6	4	3	2
Nestin	IPI00010800	18	5	22	13	22	27
Neurolysin, mitochondrial	IPI00010346	7	7	5	8	10	9
Neutral amino acid transporter B(0)	IPI00019472	7	5	6	3	4	7
NHP2-like protein 1	IPI00026167	2	1	3	5	3	3
Niban-like protein 1	IPI00456750	2	1	1	5	5	4
Nicotinamide phosphoribosyltransferase	IPI00018873	8	4	5	7	7	8
Nicotinate-nucleotide pyrophosphorylase [carboxylating]	IPI00300086	2	0	2	1	3	2
Non-POU domain-containing octamer-binding protein	IPI00304596	9	5	9	15	12	8
Nuclear cap-binding protein subunit 1	IPI00019380	7	2	5	10	5	5
Nuclear migration protein nudC	IPI00550746	7	5	6	8	10	7
Nuclear pore complex protein Nup107	IPI00028005	7	3	2	2	4	3
Nuclear pore complex protein Nup133	IPI00291200	2	2	3	5	8	2
Nuclear pore complex protein Nup205	IPI00783781	2	8	4	10	14	10
Nuclear pore complex protein Nup50	IPI00026940	0	1	4	1	3	0
Nuclear pore complex protein Nup93	IPI00397904	8	8	3	8	9	7
Nuclear receptor-binding protein	IPI00604756	2	1	1	2	1	1
Nuclear transport factor 2	IPI00009901	2	0	3	4	3	5
Nuclease-sensitive element-binding protein 1	IPI00031812	6	1	13	0	11	14
Nucleobindin-1	IPI00295542	5	1	4	6	2	1
Nucleolar GTP-binding protein 1	IPI00385042	3	1	1	3	7	3
Nucleolar protein 56	IPI00411937	3	1	2	5	7	6
Nucleolar protein 58	IPI00006379	5	2	2	7	8	6
Nucleoporin 54kDa variant (Fragment)	IPI00172580	3	0	2	3	6	2
Nucleoporin Nup37	IPI00171665	1	0	2	1	2	1
Nucleoprotein TPR	IPI00742682	15	12	25	21	23	14
Nucleoside diphosphate kinase	IPI00604590	18	17	10	19	17	11
Nucleoside-triphosphatase C1orf57	IPI00031570	3	2	1	6	4	2
Nucleosome assembly protein 1-like 1	IPI00023860	14	10	14	10	9	12
NudC domain-containing protein 2	IPI00103142	4	0	1	4	3	3
Ornithine aminotransferase, mitochondrial	IPI00022334	12	9	10	7	5	7
Osteoclast-stimulating factor 1	IPI00414836	2	1	0	3	2	2
OTU domain-containing protein 6B	IPI00935722	3	4	2	3	0	3
Paladin	IPI00297212	2	0	1	3	0	1
Palmitoyl-protein thioesterase 1	IPI00002412	4	1	4	1	2	2
PDZ and LIM domain protein 1	IPI00010414	11	4	6	16	10	12
Peptidyl-prolyl cis-trans isomerase A	IPI00419585	23	16	14	21	14	15
Peptidyl-prolyl cis-trans isomerase B	IPI00646304	12	6	13	10	9	8
Peptidyl-prolyl cis-trans isomerase D	IPI00003927	1	0	2	6	2	3
Peptidyl-prolyl cis-trans isomerase FKBP3	IPI00024157	4	3	6	9	5	4
Peptidyl-prolyl cis-trans isomerase FKBP4	IPI00219005	13	11	16	17	19	15
Peptidyl-prolyl cis-trans isomerase H	IPI00007346	3	0	4	4	3	1
Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1	IPI00013723	3	2	0	5	0	2
Peptidyl-prolyl cis-trans isomerase-like 1	IPI00007019	2	1	3	4	3	3
Peroxiredoxin-1	IPI00000874	16	19	16	30	12	11
Peroxiredoxin-2	IPI00027350	8	15	8	12	4	3
Peroxiredoxin-4	IPI00011937	10	7	9	10	3	5
Peroxiredoxin-6	IPI00220301	22	16	20	32	21	18
Peroxisomal multifunctional enzyme type 2	IPI00019912	15	9	16	7	9	9
Phenylalanyl-tRNA synthetase alpha chain	IPI00031820	3	1	3	3	4	3
Phenylalanyl-tRNA synthetase beta chain	IPI00300074	2	0	5	3	6	2
Phosducin-like protein 3	IPI00031629	5	0	3	0	4	2
Phosphatidylethanolamine-binding protein 1	IPI00219446	8	9	9	10	7	8
Phosphoglycerate kinase 1	IPI00169383	41	40	41	45	35	27
Phosphoglycolate phosphatase	IPI00177008	4	3	4	2	4	2
Phosphomannomutase 2	IPI00006092	2	0	1	4	5	1
Phosphomevalonate kinase	IPI00220648	4	2	1	3	2	1
Phosphoribosyl pyrophosphate synthase-associated protein 2	IPI00003168	6	3	5	8	6	3

Phosphoribosylformylglycinamidine synthase	IPI00004534	16	15	20	18	16	15
Phosphoserine aminotransferase	IPI00001734	17	13	18	12	12	12
Phosphoserine phosphatase	IPI00019178	4	1	5	2	2	3
Plastin-1	IPI00032304	2	3	2	1	1	3
Plastin-3	IPI00216694	22	18	16	20	18	19
Platelet-activating factor acetylhydrolase IB subunit beta	IPI00026546	1	1	2	4	2	1
Platelet-activating factor acetylhydrolase IB subunit gamma	IPI00014808	1	0	4	5	4	1
Podocalyxin-like protein 1 precursor	IPI00299116	4	4	5	5	6	3
Poly [ADP-ribose] polymerase 1	IPI00449049	6	3	11	28	25	19
Poly(rC)-binding protein 1	IPI00016610	13	7	10	9	13	12
Polymerase delta-interacting protein 2	IPI00165506	4	2	2	1	1	3
Prefoldin subunit 2	IPI00006052	3	2	3	5	5	3
Prefoldin subunit 5	IPI00015361	4	4	4	7	3	3
Pre-mRNA branch site protein p14	IPI00032827	3	2	2	3	3	3
Pre-mRNA-processing factor 19	IPI00004968	7	2	4	5	5	5
Pre-mRNA-processing-splicing factor 8	IPI00007928	17	15	13	24	30	24
Pre-mRNA-splicing factor SPF27	IPI00025178	2	0	2	4	3	2
Prenylcysteine oxidase 1	IPI00384280	1	0	2	1	5	1
Pre-rRNA-processing protein TSR1 homolog	IPI00292894	6	4	3	3	3	2
PRKC apoptosis WT1 regulator protein	IPI00001871	2	1	2	2	2	1
PRMT3 protein (Fragment)	IPI00103026	1	0	2	3	1	1
Probable ATP-dependent RNA helicase DDX27	IPI00293078	2	1	0	2	1	2
Probable ATP-dependent RNA helicase DDX47	IPI00023972	2	1	2	2	4	1
Probable ATP-dependent RNA helicase DDX5	IPI00017617	15	7	10	9	12	10
Probable ATP-dependent RNA helicase DDX6	IPI00030320	5	2	5	3	8	3
Probable fructose-2,6-bisphosphatase TIGAR	IPI00006907	3	0	4	5	4	2
Probable ribosome biogenesis protein NEP1	IPI00025347	2	2	4	1	0	5
Probable RNA-binding protein EIF1AD	IPI00298618	2	1	2	1	1	2
probable ubiquitin carboxyl-terminal hydrolase FAF-X isoform 4	IPI00003964	11	6	10	21	24	16
Profilin	IPI00107555	2	1	2	5	3	3
Profilin-1	IPI00216691	21	17	19	18	11	12
progesterone receptor membrane component 2	IPI00005202	2	1	2	2	3	2
Programmed cell death 6-interacting protein	IPI00246058	12	5	10	13	13	9
Programmed cell death protein 10	IPI00298558	2	0	1	3	4	3
Programmed cell death protein 5	IPI00023640	3	3	4	4	1	3
Programmed cell death protein 6	IPI00025277	6	2	2	4	3	0
Prohibitin	IPI00017334	5	2	5	7	5	6
Prohibitin-2	IPI00027252	5	2	6	7	5	8
Proliferating cell nuclear antigen	IPI00021700	8	7	8	7	8	7
Proliferation-associated protein 2G4	IPI00299000	9	6	13	8	9	9
Proline synthetase co-transcribed homolog (Bacterial), isoform CRA_b	IPI00016346	2	2	4	3	2	1
Prolow-density lipoprotein receptor-related protein 1	IPI00020557	2	1	3	4	2	0
Prolyl endopeptidase	IPI00008164	9	5	3	10	11	15
Prostaglandin E synthase 3	IPI00015029	4	3	5	4	4	5
Proteasomal ubiquitin receptor ADRM1	IPI00033030	2	0	2	1	3	1
Proteasome 26S non-ATPase subunit 11 variant (Fragment)	IPI00105598	14	7	10	7	15	9
Proteasome activator complex subunit 1	IPI00479722	3	3	6	7	8	5
Proteasome assembly chaperone 3	IPI00031106	3	1	2	2	2	0
Proteasome inhibitor PI31 subunit	IPI00009949	1	0	3	3	1	1
Proteasome subunit alpha type-2	IPI00219622	9	8	6	11	6	4
Proteasome subunit alpha type-4	IPI00299155	6	5	9	8	5	7
Proteasome subunit alpha type-5	IPI00291922	8	4	7	9	8	6
Proteasome subunit alpha type-6	IPI00029623	5	7	11	10	9	9
Proteasome subunit beta type-1	IPI00025019	8	5	4	15	5	5
Proteasome subunit beta type-2	IPI00028006	6	3	6	9	5	6
Proteasome subunit beta type-3	IPI00028004	8	6	1	9	4	4
Proteasome subunit beta type-4	IPI00555956	7	4	6	6	5	4
Proteasome subunit beta type-5	IPI00479306	15	7	4	11	10	6

Proteasome subunit beta type-6	IPI00000811	3	1	2	5	2	3
Proteasome subunit beta type-7	IPI00003217	2	2	2	4	2	2
proteasome-associated protein ECM29 homolog	IPI00157790	15	4	10	14	16	9
protein arginine N-methyltransferase 1 isoform 1	IPI00018522	5	5	14	4	13	12
Protein arginine N-methyltransferase 5	IPI00441473	5	0	3	1	5	5
Protein C10	IPI00016925	3	1	3	2	1	2
Protein disulfide-isomerase	IPI00010796	24	21	22	32	22	19
Protein disulfide-isomerase A3	IPI00025252	39	25	29	37	35	27
Protein disulfide-isomerase A4	IPI00009904	21	14	16	21	29	22
Protein DJ-1	IPI00298547	8	11	3	11	8	6
Protein FAM3C	IPI00334282	5	4	1	4	3	1
Protein FAM49B	IPI00303318	7	6	8	6	6	4
Protein FAM96B	IPI00007024	2	1	1	2	1	0
Protein flightless-1 homolog	IPI00031023	2	0	1	2	5	2
Protein KIAA0664	IPI00939707	5	5	3	1	5	3
Protein kinase, cAMP-dependent, regulatory, type II, alpha	IPI00063234	3	1	2	3	3	1
Protein lin-28 homolog A	IPI00002948	12	9	7	13	15	11
Protein lin-7 homolog C	IPI00019997	3	1	0	2	2	1
Protein mago nashi homolog 2	IPI00059292	4	6	1	6	4	4
Protein NipSnap homolog 1	IPI00304435	3	3	2	5	3	3
Protein of unknown function DUF410 family protein	IPI00419575	2	1	2	2	6	2
Protein of unknown function DUF858, methyltransferase-like family	IPI00549389	3	1	0	3	1	4
Protein phosphatase 1G	IPI00006167	7	2	4	6	5	11
Protein RCC2	IPI00465044	6	0	7	0	10	7
Protein RRP5 homolog	IPI00400922	2	2	1	2	7	7
Protein SEC13 homolog	IPI00375370	3	0	1	0	5	2
Protein transport protein Sec23A	IPI00017375	2	0	1	6	10	8
Protein transport protein Sec23B	IPI00017376	3	3	4	6	5	3
Protein transport protein Sec24C	IPI00024661	3	3	4	5	2	2
Protein transport protein Sec61 subunit beta	IPI00220835	2	1	3	2	3	2
Pseudouridylate synthase 7 homolog	IPI00044761	6	3	3	5	7	5
Pumilio domain-containing protein KIAA0020	IPI00791325	3	4	1	3	3	4
Puromycin-sensitive aminopeptidase	IPI00026216	14	6	15	15	15	18
Putative ATP-dependent Clp protease proteolytic subunit	IPI00003870	2	0	1	1	2	1
Putative deoxyribose-phosphate aldolase	IPI00219677	1	1	2	0	3	1
Putative phospholipase B-like 2	IPI00169285	1	0	2	2	2	0
Putative pre-mRNA-splicing factor ATP-dpendent RNA helicase DHX15	IPI00396435	9	6	9	16	15	15
Putative RNA-binding protein 3	IPI00024320	4	2	1	4	1	3
Putative uncharacterized protein	IPI00010402	0	1	2	2	3	4
Putative uncharacterized protein GARS	IPI00915808	15	14	9	20	15	12
Pyridoxal phosphate phosphatase	IPI00025340	1	3	2	2	4	1
Pyrroline-5-carboxylate reductase 2	IPI00470610	2	3	0	0	2	2
pyruvate dehydrogenase E1 alpha 1 isoform 2 precursor	IPI00306301	2	1	3	2	3	0
Quinone oxidoreductase	IPI00000792	3	4	3	5	4	2
Rab GDP dissociation inhibitor alpha	IPI00010154	1	0	3	4	8	4
Radixin, isoform CRA_a	IPI00017367	8	4	2	7	5	5
Ran GTPase-activating protein 1	IPI00294879	12	5	6	10	8	5
Ran-specific GTPase-activating protein	IPI00414127	7	9	8	12	5	8
Ras GTPase-activating protein-binding protein 1	IPI00012442	6	5	7	4	9	7
Ras GTPase-activating-like protein IQGAP1	IPI00009342	17	9	22	33	37	28
Ras suppressor protein 1	IPI00017256	4	2	4	3	3	4
Ras-related protein Rab-10	IPI00016513	4	3	1	4	7	2
Ras-related protein Rab-11B	IPI00020436	7	7	6	9	7	7
Ras-related protein Rab-14	IPI00291928	4	7	6	6	3	5
Ras-related protein Rab-18	IPI00014577	4	0	2	2	5	5
Ras-related protein Rab-1B	IPI00008964	11	10	6	10	7	7
Ras-related protein Rab-21	IPI00007755	1	1	2	4	3	1
Ras-related protein Rab-2A	IPI00031169	5	3	4	9	6	5

Ras-related protein Rab-3B	IPI00300562	1	1	3	1	4	1
Ras-related protein Rab-5A	IPI00023510	4	3	3	6	3	5
Ras-related protein Rab-5B	IPI00017344	2	2	2	1	2	1
Ras-related protein Rab-5C	IPI00016339	7	6	8	6	6	7
Ras-related protein Rab-7a	IPI00016342	9	6	7	12	7	8
Ras-related protein Rab-8A	IPI00028481	4	1	1	1	1	2
Ras-related protein Ral-A	IPI00217519	1	2	2	1	2	2
Ras-related protein Rap-1b	IPI00015148	2	4	3	6	6	3
Regulation of nuclear pre-mRNA domain-containing protein 1B	IPI00009659	1	0	5	4	4	1
Replication factor C subunit 4	IPI00017381	4	3	1	4	3	5
Replication factor C subunit 5	IPI00031514	1	0	2	1	3	2
Replication protein A 14 kDa subunit	IPI00017373	3	0	4	4	1	5
Replication protein A 70 kDa DNA-binding subunit	IPI00020127	5	2	6	5	6	4
Reticulocalbin-1	IPI00015842	4	1	4	4	3	2
Retinal rod rhodopsin-sensitive cGMP 3',5'-cyclic phosphodiesteraseδ	IPI00015161	3	1	1	2	0	2
Retinol-binding protein 1	IPI00940513	3	1	2	4	4	1
Rho GDP-dissociation inhibitor 1	IPI00003815	6	6	8	7	6	6
Rho GTPase-activating protein 1	IPI00020567	7	2	7	7	11	4
RhoA activator C11orf59	IPI00016670	1	2	1	4	1	1
Ribonuclease inhibitor	IPI00550069	3	1	5	1	6	3
Ribonuclease UK114	IPI00005038	3	1	5	5	1	2
Ribonucleoside-diphosphate reductase large subunit	IPI00013871	4	4	2	11	9	3
Ribose-phosphate pyrophosphokinase 1	IPI00219616	7	6	7	8	3	3
Ribosomal L1 domain-containing protein 1	IPI00008708	5	4	2	5	8	4
Ribosomal protein L14 variant	IPI00555744	5	2	3	3	2	4
Ribosome biogenesis protein WDR12	IPI00304232	2	2	1	1	4	2
Ribosome maturation protein SBDS	IPI00427330	0	2	1	2	2	1
RNA-binding protein EWS isoform 1	IPI00009841	1	1	2	2	3	1
rRNA 2'-O-methyltransferase fibrillarin	IPI00025039	5	4	2	10	5	5
RuvB-like 2	IPI00009104	8	7	8	12	10	7
S-adenosylmethionine synthase isoform type-2	IPI00010157	8	6	5	7	3	5
SAP domain-containing ribonucleoprotein	IPI00014938	2	0	4	3	3	1
SDHA protein	IPI00217143	2	0	1	2	2	2
Sec1 family domain-containing protein 1	IPI00165261	1	0	3	4	3	1
Secernin-1	IPI00289862	1	2	2	2	3	3
Secreted frizzled-related protein 1	IPI00749245	2	1	2	1	3	1
Selenide, water dikinase 1	IPI00029056	8	7	7	10	10	8
Sepiapterin reductase	IPI00017469	2	2	1	3	0	1
septin-9 isoform e	IPI00455033	3	3	4	2	3	1
Serine hydroxymethyltransferase, mitochondrial	IPI00002520	11	7	13	6	6	9
Serine palmitoyltransferase 1	IPI00005745	3	0	1	2	3	0
Serine/arginine-rich splicing factor 2	IPI00005978	2	1	4	1	2	4
Serine/arginine-rich splicing factor 3	IPI00010204	9	2	5	9	5	3
Serine/arginine-rich splicing factor 9	IPI00012340	4	3	3	8	6	4
Serine/threonine-protein kinase MST4	IPI00292827	9	4	7	3	4	5
Serine/threonine-protein kinase OSR1	IPI00010080	4	2	3	4	5	4
Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B alpha isoform	IPI00332511	2	2	5	5	4	5
Serine/threonine-protein phosphatase 2A 65 kDa regulatory subunit A alpha isoform	IPI00554737	16	14	17	16	18	17
Serine/threonine-protein phosphatase 2A catalytic subunit α isoform	IPI00008380	6	2	7	6	5	5
Serine/threonine-protein phosphatase 4 catalytic subunit	IPI00012833	2	1	1	0	4	2
Serine/threonine-protein phosphatase PP1-beta catalytic subunit	IPI00218236	3	4	1	5	2	3
Serpin B6	IPI00413451	2	2	2	4	7	3
Serpin B9	IPI00032139	7	3	14	13	8	12
Serpin H1	IPI00032140	21	12	18	22	21	18
Seryl-tRNA synthetase, cytoplasmic	IPI00220637	2	1	5	7	12	5
SF3A2 protein (Fragment)	IPI00017341	6	1	0	2	2	2

S-formylglutathione hydrolase	IPI00411706	2	2	2	3	2	2
SH3 domain-binding glutamic acid-rich-like protein	IPI00025318	3	2	5	7	3	4
Sialic acid synthase	IPI00147874	5	4	5	5	5	3
Sideroflexin-1	IPI00009368	2	1	0	3	2	0
Signal recognition particle 14 kDa protein	IPI00293434	4	4	4	7	5	3
Signal recognition particle 19 kDa protein	IPI00295889	3	1	1	2	0	1
Signal recognition particle 72 kDa protein	IPI00215888	4	2	3	5	6	5
Similar to Protein SAAL1. Isoform 2	IPI00304935	2	1	1	2	1	1
Single-stranded DNA-binding protein, mitochondrial	IPI00029744	6	4	7	8	5	6
Small glutamine-rich tetratricopeptide repeat-containing protein α	IPI00013949	1	1	5	4	5	3
Small nuclear ribonucleoprotein E	IPI00029266	0	2	1	3	1	3
Small nuclear ribonucleoprotein Sm D1	IPI00302850	5	2	2	2	2	3
Small nuclear ribonucleoprotein Sm D2	IPI00017963	6	4	7	5	5	6
Small nuclear ribonucleoprotein Sm D3	IPI00017964	1	2	2	1	3	2
Sodium/potassium-transporting ATPase subunit beta-3	IPI00008167	3	4	5	5	3	4
Solute carrier family 2, facilitated glucose transporter member 3	IPI00003909	5	4	3	4	2	3
Sorbitol dehydrogenase	IPI00216057	5	5	5	4	4	3
Sorcin	IPI00027175	6	2	4	5	7	5
Sorting nexin-2	IPI00299095	2	1	2	4	6	2
Sorting nexin-5	IPI00295209	1	0	2	2	2	0
Spartin	IPI00430622	2	0	2	2	3	1
Sperm-associated antigen 7	IPI00006863	3	2	5	3	3	3
Spermidine synthase	IPI00292020	6	4	5	5	6	7
Splicing factor 3A subunit 1	IPI00017451	4	3	6	7	7	7
Splicing factor 3A subunit 3	IPI00029764	8	3	5	7	5	4
Splicing factor 3B subunit 1	IPI00026089	19	12	20	29	27	16
Splicing factor 3B subunit 2	IPI00221106	7	1	4	6	9	10
Splicing factor 3B subunit 4	IPI00017339	3	1	0	1	1	4
Splicing factor U2AF 35 kDa subunit	IPI00005613	2	3	3	2	4	3
Squalene synthase	IPI00020944	9	8	14	5	8	4
SRA stem-loop-interacting RNA-binding protein, mitochondrial	IPI00009922	3	2	3	2	3	6
Src substrate cortactin	IPI00029601	3	1	3	3	5	3
Staphylococcal nuclease domain-containing protein 1	IPI00140420	18	12	17	14	17	18
Stathmin	IPI00479997	5	3	6	8	2	2
Sterol-4-alpha-carboxylate 3-dehydrogenase, decarboxylating	IPI00019407	3	2	5	4	1	2
Stomatin-like protein 2	IPI00334190	2	1	3	2	8	2
Stress-70 protein, mitochondrial	IPI00007765	32	23	22	19	20	18
Stress-induced-phosphoprotein 1	IPI00013894	20	10	11	18	16	15
Structural maintenance of chromosomes protein 1A	IPI00291939	2	0	2	0	4	1
Succinyl-CoA:3-ketoacid-coenzyme A transferase 1, mitochondrial	IPI00026516	3	1	2	2	1	1
SUMO-activating enzyme subunit 1	IPI00033130	6	4	8	5	7	4
SUMO-activating enzyme subunit 2	IPI00023234	7	3	6	7	11	7
SUMO-conjugating enzyme UBC9	IPI00032957	2	3	3	6	3	3
Superkiller viralicidic activity 2-like 2	IPI00647217	6	3	7	10	8	6
Superoxide dismutase [Cu-Zn]	IPI00218733	3	5	6	9	2	2
Superoxide dismutase [Mn], mitochondrial	IPI00022314	2	2	3	3	2	1
Synaptic vesicle membrane protein VAT-1 homolog	IPI00156689	6	3	6	6	7	7
Synaptic vesicle membrane protein VAT-1 homolog-like	IPI00030578	4	0	3	1	2	0
Talin-1	IPI00298994	25	23	40	48	49	34
T-complex protein 1 subunit alpha	IPI00290566	14	9	8	11	21	19
T-complex protein 1 subunit beta	IPI00297779	29	23	27	23	19	23
T-complex protein 1 subunit delta	IPI00302927	18	9	12	20	19	19
T-complex protein 1 subunit epsilon	IPI00010720	21	11	15	24	17	16
T-complex protein 1 subunit eta	IPI00018465	19	9	17	16	17	10
T-complex protein 1 subunit zeta	IPI00027626	17	12	13	21	10	10
Telomere length regulation protein TEL2 homolog	IPI00016868	2	1	2	2	1	2
Testis-expressed sequence 10 protein	IPI00549664	5	3	1	3	5	3
Tetratricopeptide repeat protein 35	IPI00014149	2	1	0	3	1	1

Thimet oligopeptidase	IPI00549189	6	1	1	3	6	3
Thioredoxin	IPI00216298	2	4	4	4	2	4
Thioredoxin domain-containing protein 12	IPI00026328	2	2	3	3	3	2
Thioredoxin domain-containing protein 17	IPI00646689	4	1	3	2	2	3
Thioredoxin domain-containing protein 5	IPI00171438	5	3	8	9	5	4
Thioredoxin-dependent peroxide reductase, mitochondrial	IPI00024919	10	10	4	12	6	6
Thioredoxin-like protein 1	IPI00305692	6	4	9	6	9	8
Thioredoxin-related transmembrane protein 1	IPI00395887	1	2	5	4	1	6
THO complex subunit 2	IPI00158615	2	1	1	1	2	1
THO complex subunit 4	IPI00328840	7	2	5	6	7	8
Threonyl-tRNA synthetase, cytoplasmic	IPI00329633	17	11	10	11	16	19
THUMP domain-containing protein 1	IPI00550243	2	0	4	2	4	2
Thy-1 membrane glycoprotein	IPI00022892	2	2	3	3	3	2
Thymidylate kinase	IPI00013862	1	2	0	3	3	1
Trafficking protein particle complex subunit 3	IPI00004324	2	1	0	3	3	3
Trafficking protein particle complex subunit 4	IPI00007691	2	1	2	2	2	2
Transaldolase	IPI00744692	10	7	11	16	15	7
Transcription elongation factor B polypeptide 2	IPI00026670	2	1	0	3	1	2
Transferrin receptor protein 1	IPI00022462	12	6	5	7	13	6
Transforming protein RhoA	IPI00478231	5	6	11	12	10	7
Transgelin	IPI00216138	13	9	11	19	12	13
Transgelin-2	IPI00550363	7	6	7	14	8	7
Transitional endoplasmic reticulum ATPase	IPI00022774	41	28	39	41	32	33
Translation initiation factor eIF-2B subunit alpha	IPI00221300	4	1	5	5	6	2
Translational activator GCN1	IPI00001159	14	11	15	21	20	15
Translational activator of cytochrome c oxidase 1	IPI00019903	2	0	1	2	1	1
Translin	IPI00018768	10	7	5	14	7	8
Translin-associated protein X	IPI00293350	7	3	5	5	6	4
Translocon-associated protein subunit delta precursor	IPI00019385	3	3	3	4	3	3
Transmembrane emp24 domain-containing protein 10	IPI00028055	6	8	4	7	7	3
Transmembrane emp24 domain-containing protein 9	IPI00023542	2	2	2	3	3	3
Trifunctional enzyme subunit alpha, mitochondrial	IPI00031522	8	6	4	7	6	10
Tripartite motif-containing protein 71	IPI00719053	5	5	3	5	5	3
Tripeptidyl-peptidase 2	IPI00020416	8	6	10	5	15	9
tRNA (cytosine-5-)-methyltransferase NSUN2	IPI00306369	7	2	4	6	11	5
tRNA (guanine-N(7)-)-methyltransferase	IPI00290184	2	2	3	2	1	1
tRNA methyltransferase 112 homolog	IPI00009010	2	2	4	4	2	3
Tropomodulin-3	IPI00005087	4	3	2	4	2	2
Tu translation elongation factor, mitochondrial precursor	IPI00027107	11	6	11	13	10	11
TUBB6 protein	IPI00646779	3	2	6	4	6	6
Tubulin alpha-1C chain	IPI00218343	3	1	3	1	2	2
Tubulin beta-2A chain	IPI00013475	2	1	2	4	1	1
Tubulin beta-2B chain	IPI00031370	32	26	32	42	33	31
Tubulin beta-2C chain	IPI00007752	4	4	4	6	6	5
Tubulin beta-3 chain	IPI00013683	7	7	8	11	5	7
Tubulin beta-4 chain	IPI00023598	3	3	1	2	4	2
Tubulin, beta	IPI00645452	11	10	14	15	11	9
Tubulin-folding cofactor B	IPI00293126	5	4	8	7	6	5
Tubulin-specific chaperone A	IPI00217236	8	5	6	5	8	7
Tubulin-specific chaperone E	IPI00018402	3	0	5	2	3	0
Tubulin--tyrosine ligase-like protein 12	IPI00029048	11	8	4	9	5	11
Tumor protein, translationally-controlled 1	IPI00009943	8	4	1	7	8	6
Twinfilin-2	IPI00550917	3	0	3	3	4	4
Tyrosyl-tRNA synthetase, cytoplasmic	IPI00007074	8	14	10	8	12	8
U1 small nuclear ribonucleoprotein A	IPI00012382	2	0	1	4	2	4
U2 small nuclear ribonucleoprotein A'	IPI00297477	8	7	8	9	5	5
U2 small nuclear ribonucleoprotein B''	IPI00029267	1	2	2	5	2	2
U6 snRNA-associated Sm-like protein LSm4	IPI00294955	3	1	2	5	4	2

U8 snoRNA-decapping enzyme	IPI00783497	2	1	1	3	1	2
Ubiquilin-2	IPI00409659	1	0	2	0	4	2
Ubiquitin carboxyl-terminal hydrolase 10	IPI00291946	2	3	2	2	2	5
Ubiquitin carboxyl-terminal hydrolase 11	IPI00184533	3	1	6	5	0	2
Ubiquitin carboxyl-terminal hydrolase 14	IPI00219913	6	4	5	9	7	9
Ubiquitin carboxyl-terminal hydrolase 7	IPI00003965	7	5	5	16	10	8
Ubiquitin carboxyl-terminal hydrolase isozyme L1	IPI00018352	17	8	10	13	11	11
Ubiquitin carboxyl-terminal hydrolase isozyme L3	IPI00011250	4	1	2	3	5	4
Ubiquitin-40S ribosomal protein S27a	IPI00179330	5	3	4	10	6	7
Ubiquitin-conjugating enzyme E2 C	IPI00013002	3	2	3	0	2	2
Ubiquitin-conjugating enzyme E2 L3	IPI00021347	7	4	5	3	4	4
Ubiquitin-conjugating enzyme E2 O	IPI00783378	5	1	5	3	4	4
Ubiquitin-conjugating enzyme E2 variant 2	IPI00019600	2	0	2	3	6	2
Ubiquitin-like modifier-activating enzyme 1	IPI00645078	41	30	42	30	31	28
Ubiquitin-like protein 4A	IPI00005658	1	1	2	1	2	1
UDP-glucose 6-dehydrogenase	IPI00031420	9	4	8	11	10	10
UMP-CMP kinase isoform a	IPI00219953	3	1	1	8	0	2
Uncharacterized protein	IPI00022434	5	7	5	6	14	5
Uncharacterized protein C11orf73	IPI00410091	1	1	2	1	2	0
Uncharacterized protein C17orf25	IPI00007102	7	3	7	4	3	3
Uncharacterized protein C2orf79	IPI00430803	2	2	2	3	2	1
UPF0027 protein C22orf28	IPI00550689	5	6	6	8	6	8
UPF0160 protein MYG1, mitochondrial	IPI00029444	2	1	2	2	3	1
UPF0364 protein C6orf211	IPI00002270	7	3	4	3	2	2
UPF0368 protein Cxorf26	IPI00107104	6	2	3	4	6	2
UPF0468 protein C16orf80	IPI00001655	2	2	1	1	2	1
UPF0556 protein C19orf10	IPI00056357	3	1	1	2	4	1
UPF0568 protein C14orf166	IPI00006980	6	5	7	9	7	6
UPF0587 protein C1orf123	IPI00016605	2	2	0	2	1	0
UPF0609 protein C4orf27	IPI00016532	1	0	2	2	2	0
UPF0727 protein C6orf115	IPI00855846	0	2	3	5	0	2
UPF0765 protein C10orf58	IPI00296190	2	3	2	5	2	2
Uroporphyrinogen decarboxylase	IPI00301489	5	3	2	4	2	4
UV excision repair protein RAD23 homolog B	IPI00008223	3	1	2	7	3	5
Vacuolar protein sorting-associated protein 35	IPI00018931	6	1	1	11	9	5
Valyl-tRNA synthetase	IPI00000873	16	11	15	10	20	14
Vasodilator-stimulated phosphoprotein	IPI00301058	1	1	6	5	3	4
Vesicle-trafficking protein SEC22b	IPI00006865	2	1	0	4	2	1
Vesicular integral-membrane protein VIP36	IPI00009950	4	2	1	2	2	1
Vigilin	IPI00022228	4	4	4	10	14	6
Vimentin	IPI00418471	33	17	25	65	33	26
Visinin-like protein 1	IPI00216313	8	7	6	2	4	2
von Hippel-Lindau binding protein 1, isoform CRA_b	IPI00334159	5	4	0	5	4	2
V-type proton ATPase catalytic subunit A	IPI00007682	4	3	3	5	6	4
V-type proton ATPase subunit B, brain isoform	IPI00007812	3	2	6	5	4	3
V-type proton ATPase subunit D	IPI00001568	3	1	0	3	2	0
V-type proton ATPase subunit E 1	IPI00003856	4	3	3	4	2	1
V-type proton ATPase subunit G 1	IPI00025285	1	1	3	2	2	3
WASH complex subunit strumpellin	IPI00029175	1	1	2	1	1	2
WD repeat and HMG-box DNA-binding protein 1	IPI00411614	2	1	0	4	5	2
WD repeat-containing protein 61	IPI00019269	2	2	2	1	2	2
Xaa-Pro dipeptidase	IPI00257882	6	3	3	3	4	3
X-ray repair cross-complementing protein 5	IPI00220834	29	18	12	29	28	24
X-ray repair cross-complementing protein 6	IPI00644712	27	23	15	28	34	22
Zyxin	IPI00926625	5	1	5	5	3	10

Note: "Peptide IDs" means the number of unique peptides that were identified from the corresponding protein during one replicate of the experiment. Three replicates are shown for each cell line.