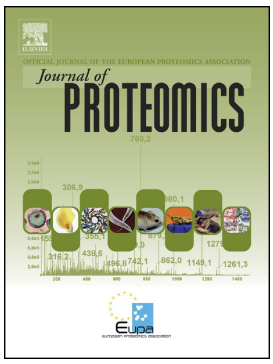

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REVIEW ARTICLE - REVISED

What if? *Mouse proteomics after gene inactivation*

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Abstract

The complex interactions among proteins and of proteins with small molecular weight protein ligands are overturned every time one of the components of the network is missing. For study purposes, animal models lacking one protein are obtained by experimental manipulation of the genome: in the knocking out approach, a gene is altered through the insertion of an artificial DNA sequence, which halts the transcription-translation sequence of events.
In this review we have compiled the research papers that analyze the effects of knocking out individual genes on the proteomes of various tissues/organs throughout the body. We have gathered and organized all the available evidence and then compared the proteomic data in order to stress the context-specificity of the outcome every time two or more organs were investigated in the same KO mice. Finally, in a symmetrical approach to the above, we surveyed whether there is any obvious overlap among the effects of different KO on the same organ, marking affection of general pathways or lacking specificity of the gene targeting. Specific attention was put on the possible involvement of cellular stress markers.

Keywords

KO mice; systemic knock-out; conditional knock-out; tissue-specific outcome

1 Foreword

Almost 15 years ago we were involved in a study with transgenic mice whose serum apolipoprotein A-I (apo A-I) had been knocked out and who instead produced the human homologue. In a proteomic study applying 2-DE, we found out that apo A-I was not the only protein altered, as serum protein levels of alpha1-acid glycoprotein, alpha1-macroglobulin, esterase, kininogen and contrapsin were significantly different between those knock-outs and their transgenic counterparts [1]. Since then, both the genetic and proteomic methods have developed further, and the use of genetically modified animals has become more widespread. Thus, knock-out (KO) mice are used as a tool to investigate the function(s) of the product(s) of each individual gene by observing the changes occurring in each one-less genetic setup.
The National Institutes of Health (NIH) launched in 2004 the Knockout Mouse Project (KOMP) with the aim of generating a comprehensive and public resource of animals containing a null mutation in every gene in the mouse genome [2]. The mouse strain C57BL/6 was selected as the common background for this catalog of mutants as its complete genome sequence is available (http://www.informatics.jax.org). An International Mouse Phenotyping Consortium (IMPC) (http://www.mousephenotype.org), which integrates 18 research institutions and 5 national funders across North America, Europe and Asia, took charge of implementing the project. One of the main actions carried out inside the Consortium is to produce and then test each mutant mouse line through a broad primary phenotyping pipeline across all the major anatomical structures in adult organisms (http://www.mousephenotype.org/impress/procedures/7).
In the inventory of the checks, collection of a standardized list of tissues is meant for fixation (and, when relevant, for microscopic examination). Assessment of gene expression pattern hence of protein synthesis in embryos and adults is not a mandatory step of the phenotyping pipeline and, when carried out, only addresses the null-mutated gene through its replacement with a reporter (*i.e.* with bacterial LacZ, to be then stained for on histological sections). Because of its cost, a wider survey on gene expression by transcriptome profiling of tissues via array technology was initially advocated “on a subset of mice, chosen by peer review” [2]; currently, however, it is included neither in the core procedures of the Consortium nor in the extra parameters some of the participating institutions are assessing (https://www.mousephenotype.org/impress/pipelines).
Within this initiative, no proteomic investigation standardized in its procedures and systematic in its scope was ever planned, or even advocated, on the knockout mouse specimens. Individual investigations were instead carried out, and still are, according to different experimental paradigms, and addressing different tissue proteomes, both in the institutions taking part in the Consortium and outside. In the following we’ll try to provide an overview on these efforts.

The first aim of our review is to gather all the available evidence and to organize it with reference to the topographic origin of the samples (organ in a system, organelle in a cell). A second aim of our writing is to compare the proteomic data and to stress the context-specificity of the outcome every time

two or more organs are investigated in the same KO mice. Finally, in a symmetrical approach to the above, a third aim is to survey whether there is any obvious overlap among the effects of different KO on the same organ, which could be a sign for 'non-specificity', *i.e.* alteration of other than the aimed-at protein, or influence on very general cellular or organ-specific reactions. As an example, we put specific attention to the possible involvement of cellular stress markers.

The title of this review echoes the name of a computer program for molecular modeling written, as a pioneer in the field, by prof. Anna Tramontano. One and a half year after her premature death, all the authors wish to dedicate this writing to the beloved memory of a great scientist and of a dear friend.

2 Gene inactivation procedures

Gene inactivation may be arrived at in several ways, which we'll shortly list in the following (outline in Figure 1).

A gene may be altered in its structure through the insertion of an artificial DNA sequence: this approach is defined *knocking out* (KO). This aim may be accomplished with either a non-specific or with a locus-specific protocol. *Gene trapping* relies on the random insertion in the genome of generic trapping cassettes; when this type of insertional mutation occurs in introns, a fusion transcript results, encoding a truncated and nonfunctional version of the cellular protein and a reporter/selectable marker; the cassette contains, in addition, a DNA tag (GTST) for the rapid identification of the disrupted gene. Conversely**,** *gene targeting* relies on homologous recombination with specific constructs that include sequences from the gene exons; the success rate of the process can be enhanced through the use of engineered endonucleases. Gene targeting can be *permanent*, or *conditional*, *e.g.* when resorting to the Cre-Lox technology [3]. In the latter case, deletions at specific sites in the DNA are obtained with the Cre protein catalyzing recombination between a direct repeat of loxP sites flanking the target gene. To limit all-body inactivation as a function of time, Cre expression is triggered by an external stimulus (*e.g.* tetracycline and tamoxifen); conversely, to limit gene inactivation as a function of space, Cre coding sequence is engineered under the control of a tissue-specific promoter. With either protocol, Cre-Lox recombination is able to circumvent embryonic lethality associated with the systemic inactivation of some genes.
All of the protocols involved in the above procedures have long been established, and were compiled in textbooks, including those of the 'Methods in Molecular Biology' series [4-6].
The expression of a gene may be reduced by interfering with the cognate RNA, or the cognate protein: this approach is defined *knocking down*.
RNA interference [7] involves two types of molecules: small interfering RNAs (siRNAs) base-pair to their target mRNA and cleave it, preventing its use as a translation template, while microRNA (miRNAs) target the 3'-untranslated region regions of mRNA, blocking the access of ribosomes for translation. Morpholinos have DNA bases attached to a backbone of

methylenemorpholine rings linked through phosphorodiamidate groups; they form heteroduplexes with mRNA and sterically block the translation machinery [8, 9]. Intracellular antibodies (*intrabodies*) are recombinant antibody fragments that bind to target proteins expressed inside the same cell that produces them: ER intrabodies interfere with membrane proteins or secretion products, cytoplasmic intrabodies with cellular components; with this approach, a graded interference can be achieved, and it becomes possible to target individual post-translationally modified protein species [10, 11].

3 Which papers to review

Definitely, gene inactivation in mice via knocking out is a central topic in current research: searching PubMed with these keywords yields >140,000 reports, and ~1,000 reviews. Focusing on proteomic investigations, as per the aim of this writing, still leaves ~650 papers. To deal with such a mass of information, we have to set some inclusion/exclusion criteria. In this account we are going to review data on single (not multiple), systemic or tissue-specific conditional KO (see, however, in Table 14 the outcome of inactivating gene families). We'll disregard investigations comparing KO mice of the same line (*e.g.* apoE KO) exposed to different experimental conditions to concentrate, instead, on comparisons between KO and wild-type animals (whether under baseline conditions or undergoing the same challenge *e.g.* ischemia/reperfusion, ionizing irradiation, oxidative stress, or receiving the same dietary or pharmacological treatment). We'll stick to proteomics proper (neglecting immunoprecipitations in which a null sample acts as a negative control, interactomics experiments and cytokine screens).
Next decision to make is how to organize the contents. In the vast majority of cases, it turns out that, even when KO was systemic, the proteome of only one tissue was actually analyzed in each null-mutant mouse: this suggests itemizing by system and organ (Section 4), and singling out the few instances in which more than one sample type was investigated (Section 5). Also, while in most cases the whole tissue was processed, in a few instances specific sub-proteomes were dealt with: again, the exceptions will be referred to in a specific section (Section 6.1). Finally, some reports compare more than one mouse model, whether to differentiate between null allele and inhibition or to monitor the dose effects between null-mutant, wild-type and transgenic animals: also these special cases will be singled out in a specific section (Section 6.4).

4 Tissues/organs, one by one

Bibliographic lists from our search are presented in tables; rows specify, for each item, type/origin of the sample, mode of gene inactivation and, under heading *KO gene*, name of the protein, name of the gene (in parentheses) and identifier of the UniProt entry. As a rule, arrangement is by sample type (by organ, or by organ region, as for brain, or by experimental treatment, as for heart) then by gene (in alphabetical order).

4.1 Cardiovascular system

Most reports, listed in Table 1, deal with heart, either under baseline conditions or after some kind of experimental injury (*e.g.* artery ligation).

sample	*geno-type*	*KO gene*	*references*
heart	S	cathepsin L1 (Ctsl) P06797	[12]
	C	cullin-3 (Cul3) Q9JLV5	[13]
	S	estrogen receptor beta (Esr2) O08537	[14][a]
	C	frataxin, mitochondrial (Fxn) Q16595	[15][b]
	S	galectin-3 (Lgals3) P16110	[16]
	C	low-density lipoprotein receptor-related protein 6 (Lrp6) O88572	[17]
	S	myoglobin (Mb) P04247	[18][c]
	S	cardiac phospholamban (Pln) P61014	[19]
	S	titin (Ttn) A2ASS6	[20]
	S	thioredoxin-interacting protein (Txnip) Q8BG60	[21]
heart (left ventricle)	S	two pore calcium channel protein 1 (Tpcn1) Q9EQJ0	[22]
heart (decellularized left ventricle tissue)	S	matrix metalloproteinase-9 (Mmp9) P41245	[23][d]
heart (infarcted regions)[e]	S	matrilysin, or matrix metalloproteinase-7 (Mmp7) Q10738	[24]
	S	matrix metalloproteinase-9 (Mmp9) P41245	[25] [26][f]

heart (ischemia-reperfusion)	S	ATP-binding cassette sub-family C member 9, or sulfonylurea receptor 2 (Abcc9) P70170	[27]
	S	glutathione peroxidase 1 (Gpx1) P11352	[28]
heart[g]	S	nitric oxide synthase, endothelial (Nos3) P70313	[29]
vessels (brain)	S	serine protease HTRA1 (Htra1) Q9R118	[30]
vascular smooth muscle cell	S	neutrophil collagenase (Mmp8) O70138	[31]

Table 1
legend for genotype: C = conditional KO; S = systemic KO
[a] control and pressure overload, male and female mice
[b] 4 and 9 weeks old mice
[c] under chronic hypoxia (10% O_2)
[d] 10-16 and 20-24-month old mice
[e] from permanent coronary artery ligation
[f] N-glycoproteomics
[g] plus or minus endothelin-1 transgene, male and female mice

4.2 Digestive system

Reports dealing with intestine (mainly colon) and pancreas are listed in Table 2A, whereas the very high number of reports dealing with liver are grouped in Table 2B.

sample	*geno-type*	*KO gene*	*references*
jejunum and colon	C	insulin receptor (Insr) P15208	[32][a]
colon	S	aquaporin-8 (Aqp8) P56404	[33, 34]
	S	glutathione peroxidase 2 (Gpx2) Q9JHC0	[35][b]
	C	retinoblastoma-like protein 1 (Rbl1) Q64701	[36]
pancreas	S	alpha-2A adrenergic receptor (Adra2a) Q01338	[37]

	S	alpha-1,3-galactosyltransferase 2 (A3galt2) Q3V1N9	[38]
	S	aquaporin-8 (Aqp8) P56404	[33]
	C	ubiquitin carboxyl-terminal hydrolase BAP1 (Bap1) Q99PU7	[39]

Table 2A
legend for genotype: C = conditional KO; S = systemic KO
[a] control chow and high-fat diet
[b] Se-deficient or Se-enriched diet (150 µg selenite / kg diet)

sample	*geno-type*	*KO gene*	*references*
liver	S	alpha-1,3-galactosyltransferase 2 (A3galt2) Q3V1N9	* ** [38]
	S	aquaporin-8 (Aqp8) P56404	[33]
	C	ubiquitin carboxyl-terminal hydrolase BAP1 (Bap1) Q99PU7	* ** [39]
	C	baculoviral IAP repeat-containing protein 5 (Birc5) O70201	* ** [40][a]
	S	bile salt export pump (Abcb11) Q9QY30	[41]
	S	catechol O-methyltransferase (Comt) O88587	* ** [42][b]
	S	cytochrome P450 2E1 (Cyp2e1) Q05421	** [43] * [44][c]
	S	cytochrome P450 2J6 (Cyp2j6) O54750	[45]
	C	endoribonuclease Dicer (Dicer1) Q8R418	* ** [46]
	C	receptor tyrosine-protein kinase erbB-4 (Erbb4) Q61527	* ** [47]

	S	fatty-acid amide hydrolase 1 (Faah) O08914	* ** [48]
	S	glucagon receptor (Gcgr) Q61606	* ** [49]
	C	growth hormone receptor (Ghr) P16882	* [50]
	C	ragulator complex protein LAMTOR2 (Lamtor2) Q9JHS3	* ** [51]
	S	hormone-sensitive lipase (Lipe) P54310	** [52]
	S	S-adenosylmethionine synthase isoform type-1 (Mat1a) Q91X83	* ** [53][d] * ** [54][e]
	C	nibrin (Nbn) Q9R207	* [55][f]
	S	nuclear factor erythroid 2-related factor 2 (Nfe2l2) Q60795	* ** [56][g]
	S	nucleoside diphosphate kinase A (Nme1) P15532	* ** [57]
	S	bile acid receptor, or farnesoid X-activated receptor (Nr1h4, or Fxr) Q60641	* ** [58][h] * ** [59][i]
	S	nitric oxide synthase, endothelial (Nos3) P70313	** [60][j]
	S	cytosolic phospholipase A2, or phospholipase A2 group IVA (Pla2g4a) P47713	* ** [61][k]
	S	peroxisome proliferator-activated receptor alpha (Ppara) P23204	[62][l]
	S	protein kinase C delta type (Prkcd), protein kinase C epsilon type (Prkce) P16054	* ** [63][m]

	-S -C[n]	phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN (Pten) O08586	-* [64] - [65]
	S	sphingomyelin phosphodiesterase (Smpd1) Q04519	* [66][o]
	S	sortilin (Sort1) Q6PHU5	* [67]
	S	signal transducer and transcription activator 6 (Stat6) P52633	* ** [68]
	S	metalloproteinase inhibitor 3 (Timp3) P39876	* ** [69]
	S	Bax inhibitor 1 (Tmbim6) Q9D2C7	[70]
hepatocytes	S	peroxisome proliferator-activated receptor alpha (Ppara) P23204	* ** [71][p]

Table 2B
legend for genotype: C = conditional KO; S = systemic KO
[a] control and after hepatectomy
[b] males and females
[c] males and females, fed isoenergetic dextrose- and ethanol-containing diet
[d] time-course
[e] hepatocellular carcinoma in KO animals
[f] after 4 Gy ionizing irradiation
[g] control and 3 mg/kg methyl-2-cyano-3,12-dioxooleana-1,9(11) dien-28-oate
[h] control and 10 mg/kg obeticholic acid (6α-ethyl-chenodeoxycholic acid)
[i] control and 100 mg/kg GW4064 (a FXR agonist)
[j] in apoE-/- mice
[k] control and high-fat high-cholesterol diet
[l] control and diethylhexylphthalate treatment
[m] control and 45% fat-containing diet
[n] knockout specific to the pancreas
[o] standard chow and high-fat diet
[p] control and 50 µM nafenopin
* affected pathways summarized in 8.2 (Overview)
** quantitative data on stress proteins in Figure 2

4.3 Endocrine system

Due to the extremely low number of reports, all dealing with tumor cell lines, we include in Table 3 both a single report on a specimen of mouse origin and a single report on a specimen of human origin. The latter is peculiar in that it exemplifies an unusual approach to gene inactivation, namely the expression at high levels of a protein with suppressor effects on the target component.

sample	*genotype*	*KO gene*	*references*
insulinoma MIN6 cells	siRNA	acyl-CoA desaturase 1 (Scd1) P13516	[72]
secretome from ***human*** anaplastic thyroid carcinoma cell line	repression[a]	nuclear factor NF-kappa-B	[73]

Table 3
legend for genotype: siRNA = knocking down with small interfering RNA in a wild type genotype
[a] stable transfection with a super-repressor form of IκBα

4.4 Hematopoietic and immune system

sample	*geno-type*	*KO gene*	*references*
mesenchymal stromal cells	siRNA	hypoxia-inducible factor 1-alpha (Hif1a) Q61221	[74][a]
hematopoietic stem/ progenitor cells	S	latexin (Lxn) P70202	[75]
bone marrow cells, thymocytes	S	cellular tumor antigen p53 (Tp53) P02340	[76][b]
macrophages (bone marrow)	C	tumor necrosis factor alpha-induced protein 3, or zinc finger protein A20 (Tnfaip3) Q60769	[77][c]
dendritic cells (bone marrow)	S	NACHT, LRR and PYD domains-containing protein 10 (Nlrp10) Q8CCN1	[78][d]
dendritic cells (bone marrow)	S	nuclear factor erythroid 2-related factor 2 (Nfe2l2) Q60795	[79][e]

T lymphocytes	S	transcription factor E2F2 (E2f2) P56931	[80]
spleen	C	ubiquitin carboxyl-terminal hydrolase BAP1 (Bap1) Q99PU7	[39]
spleen	S	ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 1 (Cd38) P56528	[81][f]

Table 4
legend for genotype: C = conditional KO; S = systemic KO; siRNA = knocking down with small interfering RNA in a wild type genotype
[a] 21% O_2 (normoxia) and 2% O_2 (hypoxia)
[b] together with a mutant p53 lacking the proline domain and a mimic for the human Δ133p53α p53 isoform (Δ122p53); control and amsacrine, 0.2 µg/mL for bone marrow cells and 1 µg/mL for thymocytes
[c] control and and after LPS or TNF treatment
[d] control and 100 ng/mL LPS
[e] 50 or 100 µM cinnamaldehyde, and 5 or 10 µM 2,4-dinitrochlorobenzene
[f] control and collagen type II-induced arthritis

4.5 Muscular system

All entries in Table 5 are listed according to the alphabetical order of the inactivated gene.

sample	*geno-type*	*KO gene*	*references*
quadriceps	S	aquaporin-4 (Aqp4) P55088	[82]
gastrocnemius	C	CDGSH iron-sulfur domain-containing protein 2 (Cisd2) Q9CQB5	[83]
diaphragm and gastrocnemius	S	collagen alpha-1(VI) chain (Col6a1) Q04857	[84][a]
gastrocnemius, plantaris, soleus	C	cullin-3 (Cul3) Q9JLV5	[13]
tibialis anterior	S	heat shock protein beta-1 (Hspb1) P14602	[85]
soleus	S	hormone-sensitive lipase (Lipe) P54310	[86]

-gastrocnemius -quadricipes	S	growth/differentiation factor 8, or myostatin (Mstn) O08689	-[87][b] -[88]
quadricipes	C	rapamycin-insensitive companion of mTOR (Rictor) Q6QI06	[89]
quadricipes	S	titin (Ttn) A2ASS6	[20]
myotubes	S	calpain-3 (Capn3) Q64691	[90]

Table 5
legend for genotype: C = conditional KO; S = systemic KO
[a] animals of different ages
[b] -/- and +/+ receiving 10 mg/kg anti-myostatin antibody twice weekly for 2 weeks via subcutaneous injection

4.6 Nervous system

Table 6 lists reports dealing with whole brains, then reports studying individual brain structures and eventually papers investigating sensory organs (ear, eye).

sample	*geno-type*	*KO gene*	*references*
brain (whole)	S	adenylate cyclase type 5 (Adcy5) P84309	[91]
	S	bleomycin hydrolase (Blmh) Q8R016	[92][a]
	S	disks large homolog 2, or postsynaptic density protein PSD-93(Dlg2) Q91XM9	[93][b]
	S	protein eva-1 homolog A, or FAM176A (Eva1a) Q91WM6	[94]
	S	isoform 3 of F-box/LRR-repeat protein 20 = scrapper (Fbxl20) Q9CZV8	[95]
	S	prosaposin receptor GPR37 (Gpr37) Q9QY42	[96]
	S	neurolysin, mitochondrial (Nln) Q91YP2	[97][c]

	S	protein/nucleic acid deglycase DJ-1 (Park7) Q99LX0	[98][d]
	S	L-isoaspartyl methyltransferase (Pcmt) P23506	[99]
	S	serine/threonine-protein kinase PINK1, mitochondrial (Pink1) Q99MQ3	[100]
	S	serum paraoxonase/ arylesterase 1 (Pon1) P52430	[101][a]
	S	NAD-dependent protein deacetylase sirtuin-2 (Sirt2) Q8VDQ8	[102][e]
	S	STIP1 homology and U box-containing protein 1 (Stub1) Q9WUD1	[103][f]
	S	14-3-3 protein gamma subtype, or 3-monooxygena-se/tryptophan 5-monooxyge-nase activation protein, gamma polypeptide (Ywhag) P61982	[104]
forebrain (embryonic)	C	transcription factor (specificity 2) Sp2 (Sp2) Q9D2H6	[105]
brain (*minus* olfactory bulb and cerebellum)	C	signal transducer and activator of transcription 3 (Stat3) P42227	[106][f] [107][g]
cortex	S	substance-P receptor, or NK-1 receptor (Tacr1) P30548	[108]
cortex (barrel)	S	zinc transporter 3 (Slc30a3) P97441	[109][h]
cortex (prefrontal), olfactory bulb	S	granulin (Grn) P28798	[110]
cortex (frontal)	S	interferon gamma (Ifng) P01580	[111]

	S	nuclear factor NF-kappa-B p105 subunit (Nfkb1), cleaved into p50 subunit, P25799	[112]
cortex, striatum	S	E3 ubiquitin-protein ligase parkin (Prkn) Q9WVS6	[113]
striatum	S	transient receptor potential cation channel subfamily M member 1 (Trpm1) Q2TV84	[114]
cortex (temporal), hippocampus	S	fragile X mental retardation protein, or synaptic functional regulator FMR1 (Fmr1) P35922	[115]
hippocampus	S	cytoplasmic polyadenylation element-binding protein 1 (Cpeb1) P70166	[116]
	S	nitric oxide synthase, brain (Nos1) Q9Z0J4	[117]
	S	NPC intracellular cholesterol transporter 1, or Niemann-Pick C1 protein (Npc1) O35604	[118]
	S	short transient receptor potential channel 1 (Trpc1) Q61056	[119]
hypothalamus	S	bifunctional epoxide hydrolase 2 (Ephx2) P34914	[120]
	S	orexin (Hcrt) O55241	[121]
hypothalamus, amygdala	C	androgen receptor (Ar) P19091	[122]
nucleus accumbens	S	equilibrative nucleoside transporter 1 (Slc29a1) Q9JIM1	[123][i]
cerebellum	S	ataxin-1 (Atxn1) P54254	[124]

	S	plasma membrane calcium-transporting ATPase 2 (Atp2b2) Q9R0K7	[125]
	S	protein bicaudal D homolog 2 (Bicd2) Q921C5	[126]
	S	UDP-glucuronosyltransferase 1-1 (Ugt1a1) Q63886	[127]
corpus callosum	S	serine/threonine-protein kinase DCLK2 (Dclk2) Q6PGN3	[128]
striatum	S	pleiotrophin (Ptn) P63089	[129][j]
suprachiasmatic nucleus (light stimulated)	S	pituitary adenylate cyclase-activating polypeptide type I receptor (Adcyap1r1) P70205	[130]
thalamus, cortex	S	palmitoyl-protein thioesterase 1 (Ppt1) O88531	[131]
various areas (frontal cortex; pons-medulla; *mesencephalon; temporal lobe-diencephalon*)	S	pituitary adenylate cyclase-activating polypeptide (Adcyap1) O70176	[132][k]
astrocyte (primary cultures)	S	glutamate-cysteine ligase regulatory subunit (Gclm) O09172	[133]
HT22 (neuronal cell line)	siRNA	tumor necrosis factor (Tnf) P06804	[134]
cortical neurons (embryonic, primary culture)	S	probable ubiquitin carboxyl-terminal hydrolase FAF-X (Usp9x) P70398	[135]
microglia	S	indoleamine 2,3-dioxygenase 1 (Ido1) P28776	[136][l]
meninges	S	extracellular sulfatases Sulf-1 and -2 (Sulf1, Sulf2) Q8K007, Q8CFG0	[137]

sciatic nerve	in-frame deletion	ubiquitin carboxyl-terminal hydrolase isozyme L1 (Uchl1) Q9R0P9	[138][m]
myenteric plexus	S	fibroblast growth factor 2 (Fgf2) P15655	[139]
ear (cochlea)	S	immunoglobulin-like domain containing receptor 1 (ILDR1) Q8CBR1	[140]
ear (cochlea, vestibulum)	S	cochlin (Coch) Q62507	[141]
eye (cornea)	S	transforming growth factor-beta-induced protein ig-h3 (TGFBI) P82198	[142]
eye (lens)	S	-alpha-crystallin A chain (Cryaa) P24622 and B chain (Cryab) P23927 -heat shock factor protein 4 (Hsf4) Q9R0L1	-[143] -[144]
eye (vitreous body)	S	protein-glutamine gamma-glutamyltransferase 2 (Tgm2) P21981	[145]
eye (retina)	S	cone-rod homeobox protein (Crx) O54751	[146][n]
eye (optic nerve)	C	E3 ubiquitin-protein ligase MYCBP2 (Mycbp2) Q7TPH6	[147]

Table 6
legend for genotype: C = conditional KO; S = systemic KO; siRNA = knocking down with small interfering RNA in a wild type genotype
[a] control and high-methionine diet
[b] control and transient middle cerebral artery occlusion (tMCAO)
[c] peptidomic analysis
[d] cerebrum, cerebellum, brainstem
[e] control and whole brain radiotherapy
[f] males and females
[g] males and females, control and cerebral ischemia/reperfusion
[h] control and manipulation
[i] control and acamprosate (200 mg/kg i.p. twice a day for 5 days) during chronic ethanol intake using two-bottle choice self-administration
[j] control and cocaine HCl (15 mg/kg i.p. once a day for 7 days)
[k] italics for the samples analyzed by 2-DE
[l] after recovery from peripheral Bacille Calmette-Guerin challenge

[m] gad mouse
[n] sampled at midday and midnight

4.7 Reproductive system

In Table 7, female structures are listed before male structures.

sample	*geno-type*	*KO gene*	*references*
ovary	S	factor in the germline alpha (Figla) O55208	[148]
uterus	S	cytosolic phospholipase A2 (Pla2g4a) P47713	[149]
hydrometra fluid	C	estrogen receptor alpha (Esr1) P19785	[150]
mammary gland	S	matrix metalloproteinase-14 (Mmp14) P53690	[151][a]
milk fat globule	C	xanthine dehydrogenase/oxidase (Xdh) Q00519	[152]
testis	S	fragile X mental retardation protein, or synaptic functional regulator FMR1 (Fmr1) P35922	[115]
	C	huntingtin (Htt) P42859	[153]
	S	plasma serine protease inhibitor (Serpina5) P70458	[154]
	C	ubiquitin-conjugating enzyme E2 W (Ube2w) Q8VDW4	[155]
Sertoli cells	siRNA	attractin (Atrn) Q9WU60	[156][b]
prostatic cancer cell line	siRNA	integrin beta-6 (Itgb6) Q9Z0T9	[157]

Table 7
legend for genotype: C = conditional KO; S = systemic KO; siRNA = knocking down with small interfering RNA in a wild type genotype
[a] time-course
[b] also, loss-of-function mutation $Atrn^{mg\text{-}3J}$

4.8 Respiratory system

sample	*geno-type*	*KO gene*	*references*
lung	C	cysteinyl leukotriene receptor 1 (Cysltr1) Q99JA4	[158]
	S	growth hormone receptor (Ghr) P16882	[159]
	C	retinoblastoma-like protein 1 (Rbl1) Q64701	[36]
	S	uteroglobin or Clara cell secretory protein (Scgb1a1) Q06318	[160][a]
	S	VIP peptides (Vip) P32648	[161]
lung cells (digestion with collagenase)	S	cellular tumor antigen p53 (Tp53) P02340	[76][b]
alveolar macrophages,	S	pulmonary surfactant-associated protein A (Sftpa1) P35242	[162][c] [163][d]

Table 8
legend for genotype: C = conditional KO; S = systemic KO
[a] female mice
[b] together with a mutant p53 lacking the proline domain and a mimic for the human Δ133p53α p53 isoform (Δ122p53); control and 1 µg/mL amsacrine
[c] control, KO and KO treated with surfactant, male mice
[d] control, KO and KO treated with surfactant, female mice

4.9 Skeletal system

sample	*geno-type*	*KO gene*	*references*
bone	S	chondroadherin (Chad) O55226	[164]
cartilage	S	collagen alpha-1(IX) chain (Col9a1) Q05722	[165]
chondrocytes (primary culture)	siRNA	nidogen-2 (Nid2) O88322	[166]

osteoblast	C	neuropeptide Y receptor type 1 (Npy1r) Q04573	[167]
fibroblasts	S	anaphase-promoting complex, or cyclosome cofactor Cdh	[168]
	S	FAS-associated death domain protein (Fadd) Q61160	[169]
	S	GTPase HRas and NRas (Hras, Nras) Q61411, P08556	[170]
	S	peroxisome proliferator-activated receptor delta, or beta (Ppard) P35396	[171]
	S	selenoprotein F (Selenof) Q9ERR7	[172]

Table 9
legend for genotype: C = conditional KO; S = systemic KO; siRNA = knocking down with small interfering RNA in a wild type genotype

4.10 Tegumentary system

Making reference to its topographical distribution more than to its embryological derivation, adipose tissue was referred to under this section, with reports dealing with it listed in Table 10B.

sample	*geno-type*	*KO gene*	*references*
epidermis	C	mothers against decapentaplegic homolog 4 (Smad4) Q13485	[173]
epidermis evelope	S	loricrin (Lor) P18165	[174]

Table 10 A
legend for genotype: C = conditional KO; S = systemic KO

sample	*geno-type*	*KO gene*	*references*
BAT	S	peroxisome proliferator-activated receptor alpha (Ppara) P23204	[175, 176]
WAT	S	cytochrome P450 2J6 (Cyp2j6) O54750	[45]
	S	growth hormone receptor (Ghr) P16882	[177]

	S	peroxiredoxin 3, or thioredoxin-dependent peroxide reductase, mitochondrial (Prdx3) P20108	[178]
	C, S	diamine acetyltransferase 1 (Sat1) P48026	[179]
	S	CAAX prenyl protease 1 homolog (Zmpste24) Q80W54	[180]

Table 10B
legend for tissue type: BAT = brown adipose tissue, WAT = white adipose tissue
legend for genotype: C = conditional KO, S = systemic KO

4.11 Urinary system

sample	*geno-type*	*KO gene*	*references*
kidney	S	apolipoprotein E (Apoe) P08226	[181]
	S	bleomycin hydrolase (Blmh) Q8R016	[182][a]
	S	B2 bradykinin receptor (Bdkrb2) P32299	[183][b]
	S	ubiquitin carboxyl-terminal hydrolase CYLD (Cyld) Q80TQ2	[184]
	S	klotho (Kl) O35082	[185]
	S	leucine-rich repeat serine/threonine-protein kinase 2 (Lrrk2) Q5S006	[186] [187]
	S	serum paraoxonase / arylesterase 1 (Pon1) P52430	[188][a]
	S	Regulator of cell cycle RGCC (Rgcc) Q9DBX1	[189]
	S	metalloproteinase inhibitor 3 (Timp3) P39876	[190][c]

	S	nuclear factor erythroid 2-related factor 2 (Nfe2l2) Q60795	[191][d]
	C	miR-17-92	[192][e]
kidney cortex	C	endoribonuclease Dicer (Dicer1) Q8R418	[193]
glomerulus	S	collagen alpha-3(IV) chain (Col4a3) or Alport mouse, Q9QZS0	[194]
mpkCCD$_{C11}$ cells[f]	C	cAMP-dependent protein kinase catalytic subunit alpha (Prkaca) and beta (Prkcb) P05132 and P68404	[195][g]
bladder	S	large-conductance, voltage-dependent and Ca^{2+}-dependent K^+ channel, or calcium-activated potassium channel subunit alpha-1 (Kcnma1) Q08460	[196]
urethra	S	estrogen receptor beta (Esr2) O08537	[197][h]

Table 11
legend for genotype: C = conditional KO; S = systemic KO
[a] control and 1% methionine in drinking water for 8 weeks
[b] pups from mothers on 5% NaCl diet during pregnancy
[c] control and after streptozotocin treatment
[d] control and 3 mg/kg methyl-2-cyano- 3,12-dioxooleano-1,9-dien-28-oate
[e] lesions in proximal tubules
[f] kidney epithelial cells in culture, with maximal expression of aquaporin
[g] single and double knockout
[h] female mice

5 Tissues/organs in comparison

The evidence collected over the years in the systematic transcriptomic/proteomic survey of the Human Protein Atlas Project [198-200] has shown that as many as 46% of the proteins are expressed in all tissues (14% at high, 32% at low level); in contrast, only 17% of the proteins are enriched in a tissue or tissue group (3% highly tissue-enriched, 9% moderately tissue-enriched, 5% group-enriched), and 28% of them have an intermediate behavior (17% mixed expression at high level, 11% mixed

expression at low level) [201]. On this basis, systematically knocking out a gene may be anticipated to result in significant, and even pervasive, changes in many/all districts throughout the body. It would thus seem of the utmost relevance to investigate the influence of the transcriptional milieu by comparing the outcome of the same deletion in a number of tissues/organs. Contrary to this perspective and its implications, however, comparisons between/among different samples in the same genetic background were carried out, so far, in only a handful of cases. We can list two papers studying three organs each [39, 76], six studying two organs [13, 20, 36, 45, 115, 202] plus two pairs, from a single research group, dealing with one tissue each, [101, 188] and [92, 182]. In addition, one report compares the effect of a gene KO across a single complex organ [132]; a pair of reports do it across different experimental conditions [106, 107]. One KO model has been assessed in various setups, including in different subproteomes, in four independent papers [115, 203-205]. Finally, and less to the point, the effects of knocking out two genes of the same family have been assessed in different organs [33, 82]. As may be expected, the way of presenting and analyzing the results extensively differs from one publication to the other. In the following we'll comment only on those papers in which data reduction allows a direct comparison of the effects on the proteome between/among samples.

Starting from the reports that deal with the highest number of tissues/organs, the paper by Baughman *et al.* [39] is very complex in its layout: it includes an extensive technical assessment of an unusual (neutron-encoded) *in vivo* labeling technique and records both proteomic and metabolomic data, spanning to a different depth as many as nine sample types (intestine, plasma, liver, lung, heart, brain, kidney, pancreatic islets, skeletal muscle). A further complication in this investigation is the fetal lethality of a systemic inactivation of the test gene, ubiquitin carboxyl-terminal hydrolase BAP1 (gene Bap1, UniProt entry Q99PU7), and the perinatal lethality of its liver-specific inactivation. BAP1 is ubiquitously expressed; however, after conditional knock-down, the highest drop in mRNA transcript level is measured in liver, spleen and pancreas. By comparing the effects on the proteomes of these organs, with a total of 1695 proteins varying >1.5-fold *vs* wild-type, only 3 proteins (0.06%) are common to the three samples, whereas 50 (2.95%) are shared by spleen and liver, 18 (1.06%) between spleen and pancreas, and 11 (0.65%) between liver and pancreas. The minimal overlap among organs correlates with the difference in the main processes being involved: in liver, several metabolic pathways are affected (involving glucose/hexose, lipid, cholesterol) whereas the main changes in pancreas deal with mitochondrial proteins and pancreatitis markers, and those in spleen with several factors that regulate the cell cycle.

As for the reports that compare two tissues/organs, a pair addresses the behavior of the two types of striated muscle - skeletal and cardiac. Raddatz *et al.* [20] aim at defining reference maps for the proteomes of these tissues in wild-type mice. In addition, the authors monitor the effects of the systemic KO of titin (gene Ttn, UniProt entry A2ASS6), which results in changes in the levels of 5 proteins in the heart and of 19 in the quadricipes; 3 of them (14% of the total) are common to both samples and document a cellular stress response. Conversely, Papizan *et al.* [13] study in the two tissues the effects

of the conditional inactivation of cullin-3 (gene Cul3, UniProt entry Q9JLV5). The publication records (in its Figure 4 and Figure 7) the top 10 up- and down-regulated proteins in either case. The lists overlap in 7 cases; however, only in 3 of them the changes monitored in heart and skeletal muscle are concordant (2 proteins consistently decrease, 1 consistently increases, in a KO *vs* wild-type comparison) while in the remaining 4 cases the changes are discordant.

A few other reports survey organs that are not closely related to one another. Hernández-Fernaud and Salido [202] compare the effects on liver and kidney of the inactivation of mitochondrial serine-pyruvate aminotransferase (gene Agxt, UniProt entry O35423). Out of a total of 31 affected proteins, 11 are unique to liver, 17 are unique to kidney and 3 are common to the two organs. Interestingly two of the shared items – peroxiredoxin and enolase, the third one being malic enzyme – rank first and second in the list of the 'repeatedly identified differentially expressed proteins' as worked out ten years ago by Petrak *et al.* [206] (the occurrence of the 'repeatedly identified differentially expressed proteins' among the items affected by gene inactivation is discussed at length in 8.2 Overview).

Xu *et al.* actually study three samples but taken from just two organs (hence the ordering at this point of our list), as they compare the outcome of the inactivation of fragile X mental retardation protein (synaptic functional regulator FMR1, gene Fmr1, UniProt entry P35922) in testis to that in two areas of the brain, hippocampus and temporal lobe. The differentially regulated proteins are clustered in the polyribosome and RNA-binding protein categories for brain but not for testis. The Venn diagram (in Figure 3D of the paper) shows the following: 248 proteins of the ribosome pathway in total, 88 specific to the temporal lobe and 83 to the hippocampus, 41 specific to the testis; 32 in common between the two areas of the brain, 2 between temporal lobe and testis, 1 between hippocampus and testis, and just 1 protein shared by the three sample types. These findings suggest that the different portions in such a complex organ as brain present with peculiar features. This very aspect is addressed, in principle, by Maasz *et al.* [132] for the inactivation of pituitary adenylate cyclase-activating polypeptide (gene Adcyap1, UniProt entry O70176). However, in practice, the procedures the authors select and the way they report their results definitely curtail the depth of the information their account provides. In a preliminary step, 4 brain districts are analyzed by 1-DE, KO *vs* wild-type, namely frontal cortex, pons *plus* medulla, mesencephalon, and temporal lobe *plus* diencephalon; in a second step, the two samples showing the most obvious variations - mesencephalon, and temporal lobe *plus* diencephalon - are further analyzed by 2-DE. Unfortunately, only a single list of 22 affected proteins is eventually provided, whose title just makes reference to 'brain samples'.

The four papers by the group of Suszyńska-Zajczyk deal with the effect of inactivation of two genes coding for enzymes involved in the metabolism of homocysteine – bleomycin hydrolase (gene Blmh, UniProt entry Q8R016) [92, 182] and serum paraoxonase/arylesterase 1 (gene Pon1, UniProt entry P52430) [101, 188] – on two organs – brain [92, 101] and kidney [182, 188]. The proteins affected in each organ of the KO animals are very similar irrespective of the genetic background: 11 in common between brains, *plus* 7 specific to Blmh and 1 specific to Pon1, *vs* 9 in common between kidneys,

plus 1 specific to Blmh and 2 specific to Pon1. Both with Blmh and with Pon1 inactivation, only 1 protein appears to be affected in brain and kidney, namely peroxiredoxin 2: in three of the samples from animals receiving standard chow this protein increases whereas it decreases in the brain of Pon1 -/- mice. In animals receiving a methionine-enriched diet (1%) the effect on the brain becomes an increase with both genes, with a much larger effect, however, with the KO of Blmh than with that of Pon1; the changes in kidneys are instead much lower than with control diet.

One more paper actually deals with the effects of gene KO (superoxide dismutase [Cu-Zn], gene Sod1, UniProt entry P08228) in two types of districts, skeletal muscle and peripheral nerve [207]; however, the main point in Sakellariou *et al.* investigation is the comparison between systemic and tissue-specific gene inactivation hence we are going to discuss of the evidence from their investigation at a later point of this review (8.3, Overview).

6 Special cases

In one of the introductory paragraphs (Section 3), we defined which types of reports we would review and which we wouldn't.

6.1 Subproteomes

One of the inclusion criteria was analysis of whole tissues. Table 12 collects the cases in which, on the contrary, specific cell components have been purified and investigated.

subproteome	*sample*	*KO gene*	*references*
cytosol	brain	protein/nucleic acid deglycase DJ-1 (Park7) Q99LX0	[98]
	kidney, liver	serine-pyruvate aminotransferase, mitochondrial (Agxt) O35423	[202]
	fibroblasts (embryonic)	integrin beta-3 (Itgb3) O54890	[208]
exosomes	fibroblasts (embryonic)	arrestin domain-containing protein 1 (Arrdc1) Q99KN1	[209][a]
	endothelial progenitor cells	interleukin-10 (Il10) P18893	[210]
	serum	nuclear factor NF-kappa-B p105 subunit (Nfkb1) P25799	[211][b]

lipid rafts	brain areas	fragile X mental retardation protein, or synaptic functional regulator FMR1(Fmr1) P35922	[203]
lysosomes, mannose 6-phosphate secretome	fibroblasts	N-acetylglucosamine-1-phosphotransferase subunit gamma (Gnptg) Q6S5C2	[212]
lysosomes	fibroblasts (embryonic)	major facilitator superfamily domain-containing protein 8 (Mfsd8) Q8BH31	[213]
lysosomes	liver	lysosome-associated membrane glycoprotein 2 (Lamp2) P17047	[214]
membranes	erythrocytes	beta-adducin (Add2) Q9QYB8	[215][c]
	cerebellum (granule neurons)	major prion protein (Prnp) P04925	[216][d]
membrane vesicles	jejunal villus epithelial cell brush border	-Na^+/H^+ exchange regulatory cofactor NHE-RF1 (Slc9a3r1) P70441 -Na^+/H^+ exchange regulatory cofactor NHE-RF2 (Slc9a3r2) Q9JHL1	-[217] -[218]
microsomes	endothelium	membrane type-1 matrix metalloproteinase (Mt1mmp) P53690	[219]
microsomes	heart	cardiac phospholamban (Pln) P61014	[220]
microtubules	brain	huntingtin-associated protein-1 (Hap1) O35668	[221]
mitochondria	liver, kidney	serine-pyruvate aminotransferase, mitochondrial (Agxt) O35423	[202]
	liver	beta,beta-carotene 9',10'-oxygenase (Bco2) Q99NF1	[222]

	heart	desmin (Des) P31001	[223]
	skeletal muscle	interleukin-15 receptor subunit alpha (Il15ra) Q60819	[224]
	embryonic fibroblasts	mitogen-activated protein kinase 3 (Mapk3) Q63844	[225]
	skeletal muscle	growth/differentiation factor 8, or myostatin (Mstn) O08689	[226]
	kidney	protein kinase C epsilon type (Prkce) P16054	[227]
	heart	urea transporter 1, or B (Slc14a1) Q8VHL0	[228]
	brain	superoxide dismutase 2 (Sod2) P09671	[229]
	liver	very long-chain specific acyl-CoA dehydrogenase, mitochondrial (Acadvl) P50544	[230][e]
	brown fat	mitochondrial brown fat uncoupling protein 1 (Ucp1) P12242	[231]
	brown fat	serine/threonine-protein kinase STK11 (Stk11) Q9WTK7	[232][f]
	heart	leucine-rich PPR motif-containing protein, mitochondrial (Lrpprc) Q6PB66	[233]
	heart	transcription termination factor 4, mitochondrial (Mterf4) Q8BVN4	[233]
	heart	DNA-directed RNA polymerase, mitochondrial (Polrmt) Q8BKF1	[233]

	heart	transcription factor A, mitochondrial (Tfam) P40630	[233]
	heart	twinkle protein, mitochondrial (Twnk) Q8CIW5	[233]
myelin	from whole brain	-UDP-galactose:ceramide galactosyltransferase (CGT), galactose-3-*O*-sulfotransferase (CST) -proteolipid protein (PLP)/DM20	-[234] -[235]
nucleoli	embryonic stem cells	linker histone H1 (H1c, H1d, H1e)	[236]
peroxisomes	liver, kidney	serine-pyruvate aminotransferase, mitochondrial (Agxt) O35423	[202]
secretome	white adipocytes	aldehyde dehydrogenase 1 a1/ retinal dehydrogenase 1 (Aldh1a1) P24549	[237]
	cardiomyocytes[d]	beta-3 adrenergic receptor (Adrb3) P25962	[238][g]
	embryonic fibroblasts	-bone morphogenetic protein 1 (Bmp1) P98063 and tolloid-like protein 1 (Tll1) Q62381 -disintegrin and metalloproteinase domain-containing protein 17 (Adam17) Q9Z0F8	-[239] -[240]
synapses	hippocampus	amyloid-beta A4 protein (App) P12023	[241]
	forebrain	FERM, ARHGEF and pleckstrin domain-containing protein 1 (Farp1) F8VPU2	[242]
	-cortex -embryonic cortex (cultured cells)	fragile X mental retardation protein, or synaptic functional regulator FMR1 (Fmr1) P35922	-[204] -[205]

	prefrontal cortex	microtubule-associated protein tau (Mapt) P10637	[243]
	visual cortex	protein arginine N-methyltransferase 8 (Prmt8) Q6PAK3	[244]
	cortex	superoxide dismutase 2 (Sod2) P09671	[245]
	hippocampus	transmembrane protein 35A (Tmem35a) Q9D328	[246]
serine hydrolases	brain	NPC intracellular cholesterol transporter 1, or Niemann-Pick C1 protein (Npc1) O35604	[247]
amyloid deposits	intestinal villi	pituitary adenylate cyclase-activating polypeptide (Adcyap1) O70176	[248]

Table 12
[a] ectosomes and exosomes: ectosomes are generated by shedding of the cell surface membrane, exosomes by exocytosis of multivesicular bodies
[b] after skeletal muscle ischemia-reperfusion
[c] reticulocyte and RBC ghosts
[d] cerebellar granule neurons
[e] liver with and without 16 h fasting
[f] two temperatures
[g] control and 20 µM phenylephrine

6.2 Post-translational modifications (PTM)

Table 13 lists the cases in which the effects of gene inactivation involve the level of post-translational modifications (PTM) in addition to/instead of the very concentration of the proteins.

PTM	*sample*	*KO gene*	*references*
acetylation	fibroblasts (embryonic)	sirtuin 3 (Sirt3) Q8R104	[249]
	liver (cytoplasm)	histone deacetylase 6 (Hdac6) Q9Z2V5	[250]
	liver (mitochondria)	sirtuin 3 (Sirt3) Q8R104	[251]

citrullination	spleen	ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase 1 (Cd38) P56528	[81]
hydroxylation of lysine	liver	phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN (Pten) O08586	[64]
isoaspartylation	CNS	L-isoaspartyl methyltransferase (Pcmt) P23506	[99]
oxidation (carbonylation)	CNS (cortex)	ubiquitin carboxyl-terminal hydrolase L-1 (Uchl1) Q9R0P9	[252]
oxidation (cysteine oxidation)	erythrocytes	peroxiredoxin 2 (Prdx2) Q61171	[253]
phosphorylation	adipose tissue	cyclin-dependent kinase 5 (Cdk5) P49615	[254]
	connective tissue (spinal ligament)	chemokine (C-X-C motif) ligand 7, isoform CRA_b (Ppbp, or Cxcl7) Q9EQI5	[255]
	CNS	Ser/Thr kinase PTEN-induced kinase 1 (Pink1) Q99MQ3	[100]
	CNS (cerebellum)	cGMP-dependent protein kinase type I (Prkg1) P0C605	[256]
	CNS (striatum)	pleiotrophin and midkine (Ptn, Mdk) P63089, P12025	[257]
	liver	rapamycin-insensitive companion of mTOR (Rictor) Q6QI06	[258]

	macrophages (peritoneal)[a]	receptor interacting protein (Rip3) Q9QZL0	[259]
	testis	serine/threonine-protein phosphatase PP1-gamma catalytic subunit (Ppp1cc) P63087	[260]
succinylation of lysine	heart	NAD-dependent protein deacylase sirtuin-5, mitochondrial (Sirt5) Q8K2C6	[261] [262]

Table 13
[a] control and lipopolysaccharide- or tumor necrosis factor-treated

6.3 Gene families

Another of the inclusion criteria put forward in Section 3 was analysis of single KO. Table 14 lists on the contrary some cases in which more genes belonging to a single family, or being functionally related, were knocked down. Their number was usually 2 except with histone 1 (3 isoforms) and with MUP (21 isoforms).

sample	*KO genes*	*references*
embryonic stem cells (nucleoli)	linker histone H1 (H1c, H1d, H1e) P15864, P43277, P43274	[236]
CNS (meninges)	extracellular sulfatases Sulf-1 and -2 (Sulf1, Sulf2) Q8K007, Q8CFG0	[137]
CNS (striatum) (phosphoproteome)	pleiotrophin and midkine (Ptn, Mdk) P63089, P12025	[257]
eye (lens)	αA- and αB-crystallin (Cryaa, Cryab) P24622, P23927	[143]
fibroblasts (embryonic)	apoptosis signal-regulating kinase 1 to 3 (Ask1-3) O35099, Q9WTR2	[263][a]
fibroblasts (embryonic)	GTPase H-ras and N-ras (Hras, Nras) Q61411, P08556	[170]
fibroblasts (embryonic) (secretome)	cathepsin B and L (Ctsb, Ctsl) P10605, P06797	[264]

heart	executioner caspase-3 and -7 (Casp3, Casp7) P70677, P97864	[265]
heart (mitochondria)	creatine kinase, muscle (Ckm) and sarcomeric mitochondrial (Ckmt2) isoforms; P07310, Q6P8J7	[266]
mammary gland (stem cells)	metalloproteinase inhibitor 1 and 3 (Timp1, Timp3) P12032, P39876	[267]
penis	nitric oxide synthase, brain and endothelium (Nos1, Nos3) Q9Z0J4, P70313	[268]
platelets	transcription factor Sp1 and Sp3 (Sp1, Sp3) O89090, O70494	[269]
sperm (elongated spermatids)	polyadenylate-binding protein-interacting protein 2 (Paip2a, Paip2b) Q9D6V8, Q91W45	[270]
striated muscle	mitogen-activated protein kinase-activated protein kinases 2 and 3 (Mapkapk2, Mapkapk3) P49138, Q3UMW7	[271]
teeth (enamel)	amelogenin and ameloblastin (Amel, Ambn) P63277, O55189	[272]
urine	major urinary proteins (Mup), 21 genes and 21 pseudogenes, P11588 etcetera	[273]
conditioned media (embryonic fibroblasts)	bone morphogenetic protein 1 (Bmp1) and tolloid-like protein 1 (Tll1) P98063, O43897	[239]

Table 14
[a] control and hyperosmotic stress

6.4 Dose effects

We mention in Table 15 the few cases in which overexpression of the protein of interest, in a transgenic organism, was compared to its complete absence, in a null organism, and to its physiological levels, in a wild-type mouse. We also list the cases in which hemizygous mice were compared either to wild-type or to null animals.

sample	*KO genes*	*TG*	*+/+*	*+/-*	*-/-*	*references*
mammary gland epithelial cells	annexin A1 (Anxa1) P10107			X	X	[274]
ear (organ of Corti)	immunoglobulin-like domain containing receptor 1 (Ildr1) Q8CBR1			X	X	[140]
liver	insulin receptor (Insr) P15208			X	X	[275]
liver (mitochondria)	superoxide dismutase 2 (Sod2) P09671		X	X		[276]
CNS (visual cortex)	protein arginine N-methyltransferase 8 (Prmt8) Q6PAK3		X	X	X	[244]
CNS (prefrontal cortex)	granulin (Grn) P28798	X[a]	X		X	[110]
CNS (striatum)	pleiotrophin (Ptn) P63089	X	X		X	[129]
white adipose tissue	diamine acetyltransferase 1 (Sat1) P48026	X	X		X	[179]

Table 15
legend: +/+ = homozygous wild-type; +/- = hemizygous KO; -/- = homozygous KO; TG = transgenic; X = investigated genotype
[a] Cre recombination

7 What about research areas of our current interest

Through the years, our own proteomic investigation has most often dealt with biological fluids in animal models of disease (*e.g.* [277-280]). When initially defining reference patterns for the relevant proteomes [281, 282], we definitely analyzed specimens from both, male and female animals [283, 284]. Through the years, we have published as well review articles summarizing data on the same two topics: [285-287] on biological fluid proteomics, [288, 289] on gender proteomics. The following headings list the effects of gene inactivation as monitored in these areas.

7.1 Biological fluids

The number of reports dealing with changes in the concentration of the major proteins of plasma/serum and of the other biological fluids is very low overall, so it comes to little surprise that only very few KO murine models address this point. In two such cases the analytical matrix is serum [290, 291], in one it is apoB-depleted plasma [292], in another bronchoalveolar lavage fluid (BALF) [293] or, with the inactivation of a number of related genes, urine [273]. Two reports investigate the influence of the genetic background on the outcome of a high-fat diet. When the expression of adipocyte fatty acid-binding protein (gene Fabp4, UniProt entry P04117) is turned down, a bone morphogenetic protein from the adipose tissue, GDF-3/Vgr-2 protein, is found to circulate at higher levels than in control animals [290]. Conversely, when low-density lipoprotein receptor (gene Ldlr, UniProt entry P35951) is turned down, a number of proteins are produced at altered levels by the liver, featuring a proinflammatory remodeling of the plasma proteome. The fractional turnover rates of short-lived proteins implicated in stress-response, lipid metabolism, and transport functions are significantly increased [292]. In contrast with such an extensive rearrangement of the secretory program in Ldlr KO mice, the response to burn injury is found very similar in wild-type and in interferon-gamma (gene Ifng, UniProt entry P01580) KO animals [291]. In mice lacking the expression of pulmonary surfactant-associated protein A (gene Sftpa1, UniProt entry P35242) and exposed to 2 parts/million (ppm) ozone for 3 hours, BALF proteome is affected in a way qualitatively similar but quantitatively more extensive than wild-type mice *vs* animals exposed to filtered air [293].

7.2 Males *vs* females

As a rule, differences in the proteomes are observed between males and females already under baseline conditions (wild-type animals, no treatment) – a point documented by many reports, which we have reviewed [288, 289]; further differences are observed as a result of gene inactivation. Besides genetic background and sex, some of the experimental plans in the surveyed reports include additional variables, *e.g.* surgical procedures or exposure of the animals to toxic substances; also the outcome of such treatments differs between males and females. Data are reported in different ways from one research paper to another, sometimes featuring direct comparisons only between/among few samples from complex experimental set-ups.

Grouping the data by anatomical district, as in the main body of the review, two papers of this set deal with the cardiovascular system, and specifically with the heart: in addition to gene inactivation, either a surgical procedure is carried out to induce, or a transgene is inserted in the genome of the animals to prevent disease. One experimental plan compares wild-type to estrogen receptor beta (gene Esr2, UniProt entry O08537) KO mice of both sexes, without and with transverse aortic constriction leading to pressure overload [14]. Quantitative and qualitative differences between the proteomes of males and females are observed, with little overlap in the differential spots either in +/+ or in -/- genotypes; such a divergence is obvious not only when listing

individual proteins but also when considering protein categorization into pathways. In response to pressure overload, some of the proteins that confer cardioprotection decrease in males (*e.g*. aldehyde dehydrogenase, mitochondrial in +/+, and myosin in -/-) but increase in females (*e.g.* cytoskeletal and structural proteins, including vinculin in +/+ and cofilin in -/-). Another experimental plan includes male and female mice in four genetic backgrounds: wild-type or KO in endothelial nitric oxide synthase (gene Nos3, UniProt entry P70313), as well as wild-type or transgenic in endothelin-1 (gene Edn1, UniProt entry P22387); inactivation of Nos3 is to induce diastolic dysfunction, activation of Edn1 is to rescue it [29]. While Vignon-Zellweger *et al.* choose to not itemize the individual findings in the main body of the report, the data in their Supplementary Table 1 show that, out of a total of 77 differentially abundant protein spots, only two change in a concordant way *vs* wild-type in males and in females, namely glutathione-S-transferase Mu 2 and peroxiredoxin-6 (one species), and both of them only in the endothelin TG genotype.

Two investigations deal instead with the digestive system and specifically with the liver. One compares wild-type and catechol O-methyltransferase (gene Comt, UniProt entry O88587) KO mice [42]. Several of the observed changes are sexually dimorphic; many of the differential proteins are affected to a lesser extent in females, a few to a larger extent in males. Some changes even occur in opposite direction between the sexes: glutathione-S-transferase as well as intermediate filaments components CK-8 and CK-18 are up-regulated in females and down-regulated in males. The other paper compares wild-type and cytochrome P450 2E1 (gene Cyp2e1, UniProt entry Q05421) KO mice raised with isoenergetic liquid diets containing either dextrose or ethanol [44]. Data from the experiment are presented in different ways for the various samples (including Supplementary Tables), so that a straightforward comparison among animals and treatments is not easy. The clustering result, however, infers that, among the three factors being tested - ethanol, CYP2E1 knockout and gender - the effect of gene KO on global protein expression is the greatest. Out of 67 proteins influenced by diet in WT females and 35 in WT males, 12 are common between the sexes (one, formimidoyltransferase-cyclodeamidase, with changes in opposite directions); conversely, in KO animals, 6 of the proteins up-regulated by diet are common between males and females.

As for the nervous system/the brain, the report by Di Domenico *et al.* deals with neuron-specific KO for signal transducer and activator of transcription 3 (gene Stat3, UniProt entry P42227) [106]. Wild-type males differ from wild-type females for the concentration of 9 proteins, KO males differ from KO females for that of 9 proteins: 5 are common to both conditions. Conversely, KO males differ from wild-type males for the concentration of 8 proteins, whereas KO females differ from wild-type females for that of 7 proteins, none being in common. In both sexes the main effects of gene inactivation is on mitochondrial and oxidative metabolism, but in males both metabolic and signaling pathways are affected. In a follow up to this investigation [107], the same authors assess the effects of ischemia (through middle cerebral artery occlusion) / reperfusion by comparing the proteomic pattern of ipsilateral and

contralateral hemispheres. Once more, both number and identity of the affected proteins does vary between males and females, which emphasizes sex-specificity of repair mechanisms and ultimately of neuronal survival.

Finally, for the respiratory system, Phelps *et al.* analyze alveolar macrophages from wild-type mice in comparison with those from animals KO in pulmonary surfactant-associated protein A (gene Sftpa1, UniProt entry P35242), the latter either without any treatment or receiving a replacement therapy with surfactant. One paper from this group assesses samples from male [162], another, samples from female mice [163]. The differences between wild-type and KO are twice as many in males than in females; responses are similar for proteins related to actin function, to regulation of inflammation and to development but are different for protease balance/chaperone function. When KO mice are treated with surfactant, the pattern shifts less extensively and less rapidly in males than in females.

8 Overview

Much of what we have assembled in the previous sections amounts to lists. Indeed, each of the investigations we have reviewed appears to proceed without connection to the others. We try anyhow to present an overview on the whole material. While the main body of the text, with its many Tables, meets/fulfills the first aim of our writing, the paragraphs of the following subsections address the further aims we have set, summing up evidence from comparisons between/among the effects of the same KO in different organs (8.1) or, *vice versa*, of different KO in the same organ (8.2). A couple of further, mainly methodological, points are also dealt with (in 8.3 and 8.4).

8.1 Same KO in different organs

In section 5, we have singled out the few cases in which the effects of inactivating a single gene were studied in more than one organ. The examples we could present and discuss are few and diverse, still they allow drawing some tentative conclusions.

Definitely, the outcome of the inactivation of a given gene is context-dependent, as it varies from one tissue/organ to another and can be modulated by other experimental variables/treatments. Such differences are easily connected with the differences in the overall proteomes across the body districts: the varying protein assortment in each milieu results in a varying chance of direct interaction by protein-protein docking as well as in a varying regulation of protein biological activity through the concentration of key metabolites.

With reference to embryologic derivation, higher similarities are observed between the effects in closely related *(e.g.* striated muscles) than in distantly related samples. The latter observation agrees with the finding, in wild-type animals, of a hierarchical correlation on the same basis among the proteomes of the various tissues [201]: the tighter the relationship, the closer the clustering based in protein expression.

8.2 Different KO in the same organ

In a symmetrical way, we searched for possible overlaps among the effects on the proteome of a single tissue/organ out of the silencing of different genes. One of the spurs for such a search was a paper describing the outcome of the inactivation of 5 genes coding for mitochondrial proteins that regulate mtDNA gene expression in the heart (leucine-rich PPR motif-containing protein, mitochondrial (gene Lrpprc, UniProt entry Q6PB66), transcription termination factor 4, mitochondrial (gene Mterf4, UniProt entry Q9ZT96), DNA-directed RNA polymerase, mitochondrial (gene Polrmt, UniProt entry Q8BKF1), transcription factor A, mitochondrial (gene Tfam, UniProt entry P40630), twinkle protein, mitochondrial (gene Twnk, UniProt entry Q8CIW5)) [233]. Kühl *et al.* report that approximately 65% of the mitochondrial proteins are differentially abundant in all knockouts, with a concordant up-regulation of such processes as apoptosis, degradation and stress response, mitochondrial import and chaperones, and the mitochondrial 1C pathway. These results suggest that a stereotyped response may ensue from the removal of any of a number of relevant protein factors.

To evaluate this possibility, we selected the liver as test organ. Contrary to skeletal muscles, it is univocally defined; contrary to brain or kidney, its macroscopic structure is homogenous. In this evaluation, we had full access to 29 manuscripts (they are marked with * in Table 2B). General interpretation turned out not to be easy, because of the high diversity of the topics, of the applied methods, and of the format of the data actually made available by the authors (sometimes primary quantitative data and regulation effects are missing as only heatmaps or affected networks are presented). Publication date spans 19 years, which implies a dissimilar development of proteomic technology and pathway analysis from one report to the other; additionally, the reports written for very different types of journals (from biological/biochemical to proteomic or pharmacologic), which put different emphasis on data documentation and interpretation. The background of the mouse strains is most often BL/6; in 22 cases KO is systemic, in 7 cases it is conditional; in one report primary hepatocytes are used as sample. Diet may be variable – high fat or high protein diet for study of metabolic changes; in some instances the effect of a second KO gene [60] or the influence of additional treatments (*e.g.* ethanol [44]; regeneration [40]; irradiation [55]) are investigated as well.

The proteomic analysis is carried out by 2-DE in 12 papers (3 thereof with DIGE, one of them with partially depleted samples), with gel-free procedures in the other 17 cases (both with labeled, mainly iTRAQ, and label-free samples).

The number of reported changes between wild-type and KO animals varies over a wide range – from a handful (*e.g.* 5) to several hundred regulated proteins. Making reference to the 23 papers from which data on individual proteins could be retrieved (they are marked with ** in Table 2B), average number of differentially regulated components is 410, with a huge standard deviation (849).

In some cases, specific pathways are purposely targeted, *e.g.* PPAR [46, 71], collagen modifications [64], bile acids [58, 67]. Otherwise, the main affected pathways are usually "metabolic" (carbohydrate, lipid, amino acid metabolism).

Comparing proteomic and translational data results in almost equally long lists of either similarly or differently regulated genes/proteins [49].

The hypothesis of a common cellular stress response had been put forward a decade ago by the authors, Petrak *et al.* [206] and Wang *et al.* [294], who first carried out a meta-analysis of the proteomic data and found that a limited number of proteins were found affected in a very high percentage of cases, irrespective of the type of sample being analyzed as well as of the details of the experimental set-up. These papers have since been quoted in as many as 66 proteomic reports. In one of those, the commonly altered items are subtracted from the list of affected proteins to stress the specific *vs* the generic effects of the exposure to a toxic substance [295], in two other the recurrence of findings is stressed from the title ('the usual suspects revisited' [296], 'a common cellular response to different stressing stimuli' [297]). This corpus of evidence was to spur our search in this specific direction. In the 23 papers dealing with liver of KO animals in which data on individual proteins could be retrieved (marked with ** in Table 2B, see above), we manually searched for the protein families listed by Petrak *et al.* (Table 2 in [206]). The left panel of Figure 2 shows the number of their occurrences among the regulated sample components (range: 5/23-15/23; average = 5.7 ± 4.0). The right panel deals with relative values *i.e.* number of affected stress proteins/number of affected proteins, and plots the frequency of cases within specified % ranges. As marked in the inset, average relative value is close to 10% but again with a huge standard deviation (almost 12%). In the test cases some of the stress proteins are very often involved, but the variability among the situations seems to rule out 'stress' as one of the main, and common, aspects in the outcome of genetic manipulation.

8.3 Different ways, and different extent, of gene inactivation

We could retrieve only one report that compares the effects of either systemic or tissue-specific inactivation of a given gene. In their paper, Sakellariou *et al.* [207] actually do it for two types of tissues, and in both cases they observe obvious differences between the outcomes of the alternative procedures. Figure 3 shows the heatmaps from the comparison with the appropriate wild-type samples for muscle (top panels) and for peripheral nerve (bottom panels), either with systemic (left panels) or with conditional inactivation (right panels) of superoxide dismutase [Cu-Zn] (gene Sod1, UniProt entry P08228). In addition to the already reviewed effect of the context highlighted by the comparison between the two sample types (in section 5, Tissues/organs in comparison, with comments at the beginning of this section), the evaluation in parallel of the different modes of gene inactivation shows that – at least in the test case – conditional KO does not replicate the effects of systemic KO. Specifically, in the skeletal muscle, global inactivation of Sod1 results in altered redox homeostasis (increase in catalase, thioredoxin, peroxiredoxins) and mitochondrial dysfunction (including involvement of cytochrome c oxidase and ATP synthase), whereas specific deletion of the enzyme mainly affects cytoplasmic metabolism (including involvement of enolase and phosphoglucomutase). Proteolysis through the proteasome pathway (increase of both the catalytic subunits as components of the enzyme and of the

ubiquitinated proteins as its substrates) appears up-regulated in animals with the systemic but not with the conditional inactivation of Sod1. In the peripheral nerves, none of the animal models shows any induction in the antioxidant pathways; muscle-specific, but not systemic, ablation of Sod1 appears to alter the NFkB signaling pathway (IkB-alpha is reduced overall but increased in its phosphorylated form). In quantitative terms, in skeletal muscle the concentration of only 3 proteins is significantly affected by both types of gene inactivation (over a total of 25 for systemic and 17 for conditional KO) while in peripheral nerve it is so of 35 proteins (over a total of 108 affected by systemic and 92 by conditional KO); the names of these proteins are in red in Figure 3. Two of them, myosin light chain 1/3, skeletal muscle isoform (MYL1) and troponin I, fast skeletal muscle (TNNI2) are shared by both organs.
While we are discussing here the varying effect of two modes of gene inactivation, the results in Figure 3 exemplify as well what was discussed in the previous lines about the varying effect of the same procedure on different organs.

Another aspect of some interest is the effect of gene dose on the proteomic make up of a specimen. We have listed in 6.4 the reports dealing with comparisons other than +/+ vs -/- mice. Four of those are of some more interest as including the analysis of three conditions and thus allowing a detailed evaluation of the trends in protein abundance.
The one by Lee et al. compares homozygous wild-type to hemizygous and homozygous KO; the experimental protocol is LC/MS after iTRAQ labeling. Overlap between the affected proteins is observed between -/+ and -/- but it does not exceed 25% of the observed significant changes *vs* +/+ [244]. The other three reports compare instead transgenic animals to homozygous wild-type and to homozygous KO; the experimental protocol is in one case label-free LC-MS/MS [110], while in two it is 2-DE [129, 179]. In the paper by Vicente-Rodriguez et al. the authors do not discuss the quantitative aspects of their results and only report pairwise spot volume ratios; in the cases (3/26) in which both the TG and the -/- condition are significantly different from +/+, no consistent tendency (either decrease or increase) is observed [129]. Hardt *et al.* present their results in the concise and visually-oriented format of heatmaps; overall differences are obvious among the specimens, and a trend may be recognized for many of the approx. 800 proteins seen to vary from -/- to +/+ to TG [110]. Finally, in their investigation, Liu *et al.* find a total of 21 differentially abundant proteins; of the 42 pairwise comparisons they draw, 39 demonstrate a significant difference between samples, one fails to do so between KO and wild-type, two between TG and wild-type, as if in these three cases the effects of genotype manipulation were plateauing at the level achieved in the hemizygous condition [179].

8.4 Same KO, different subproteomes

Though we are focusing on whole cell/whole tissue investigations (except for listing studies on individual subproteomes in Table 12), we like to mention one report [40] that deals with the analysis of subcellular fractions, namely cytosolic proteins, nuclear soluble proteins, nuclear chromatin-bound proteins, and membrane proteins. The aim of this strategy is to increase the coverage

on the least soluble/hardly dissociable compartments, and the various findings are eventually summed up. This way, a total of 762 proteins is evaluated as differentially abundant between livers of wild-type mice and animals KO for survivin (baculoviral IAP repeat-containing protein 5, gene Birc5, UniProt entry O70201); of them, 529 are over-, and 223 under-represented in mouse liver as a result of gene inactivation. Since the enrichment in items annotated for the stated localization does not exceed 61%, 27%, 29% and 13%, respectively, of the total of proteins identified in each sample, as many as 147 components are identified in 2, or 3, of the fractions.

8.5 Conclusions

What to conclude from all the above? Very much has been done in the field – the bibliography to this writing lists little less than 300 references – but, in the absence of a comprehensive plan in any of the possible areas of research, evidence is still too scattered to provide firm clues into such biological aspects as, for instance, the tissue-specific control of gene expression or the cross-talk between metabolic and signaling pathways. Some hints in these directions surface from the few cases in which comparisons can be drawn between/among related investigations: we have compiled all the available data and added our observations and tentative comments. Unfortunately, investigations done till now deal with rather selected questions and proteins/genes, applying diverse methods of different sensitivity, and only to a limited extent offer raw data for further data-mining. A higher level of analysis, *e.g.* computer-based meta-analyses, shall become possible only if/when the primary database (*e.g.* in freely accessible public repositories) will provide comprehensive information on samples consistently defined and adequately linked to one another. Thus, we would like the reader to understand this review as a call for systematic investigation of the topic.

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All the most recent of our reviews contain some mention to music. Writing this one took a long time; notes heard while working on it are countless. One piece may be singled out, however: the salmoè aria in Vivaldi's '*Juditha triumphans*' that a friend musician was, and is, studying.

Figure legends

Figure 1 – Outline of the procedures used to selectively prevent the expression of individual gene products. Targets may be at the DNA (top: red bar for exon, gray bar for intron) or the mRNA (middle: blue bar for translated, gray bar for untranslated region) or the protein (bottom: green bar) level.

Figure 2: Evaluation of commonly affected proteins in KO mice liver.

Left: The 'repeatedly identified differentially expressed proteins' listed by Petrak *et al*. for proteomics experiments in mice [206] were manually searched for among the components significantly affected in the liver of KO animals, as reported in 23 reviewed papers (entries marked with ** in Table 2B) the number of their occurrence was recorded. The abbreviations for protein names (meant to include all proteins of a family, all species of a protein, all subunits of a protein assembly) are entered in alphabetical order: ACT = actin, ANX = annexin, APO = apolipoproteins, ATP = ATP synthase, CAH = carbonic anhydrase, ENO = enolase, GST = glutathione S-transferase, HSP = heat shock protein, PDI = protein disulfide isomerase, PRD = peroxiredoxin, TUB = tubulin, TMP = tropomyosin, 1433 = 14-3-3 protein. Right: For each of the reviewed papers, the number of items from the above list was related to the total number of significantly affected proteins. Results are plotted as number of occurrences for selected proteins/all proteins ratio as grouped into 5-unit wide ranges.

Figure 3 – Heatmaps from the comparison with the appropriate wild-type counterparts of samples from mice KO in superoxide dismutase [Cu-Zn] (gene Sod1). Top panels = skeletal muscle, bottom panels = peripheral nerve; left panels = systemic KO, right panels = conditional KO. The names (from entry names in the UniProt database https://www.uniprot.org) of the proteins affected by both types of inactivation are in red. Redrawn from Figures 3 and 6 in [207].

Bibliography

[1] Wait R, Chiesa G, Parolini C, Miller I, Begum S, Brambilla D, et al. Reference maps of mouse serum acute-phase proteins: Changes with LPS-induced inflammation and apolipoprotein A-I and A-II transgenes. Proteomics. 2005;5:4245-53.
[2] Austin CP, Battey JF, Bradley A, Bucan M, Capecchi M, Collins FS, et al. The knockout mouse project. Nat Genet. 2004;36:921-4.
[3] Friedel RH, Wurst W, Wefers B, Kühn R. Generating Conditional Knockout Mice. In: Hofker MH, van Deursen J, editors. Transgenic Mouse Methods and Protocols: Humana Press; 2011. p. 205-31.
[4] Wurst W, Kühn R. Gene Knockout Protocols. Methods in Molecular Biology. second edition ed: Humana Press; 2009.
[5] Tymms MJ, Kola I. Gene Knockout Protocols. Methods in Molecular Biology. first edition ed: Humana Press; 2010.
[6] Hofker MH, van Deursen J. Transgenic Mouse Methods and Protocols. Methods in Molecular Biology: Humana Press; 2011.
[7] Gott JM. RNA Interference, Editing, and Modification: Methods and Protocols. Methods in Molecular Biology. first edition ed: Humana Press; 2010.
[8] Blum M, De Robertis EM, Wallingford JB, Niehrs C. Morpholinos: Antisense and Sensibility. Developmental cell. 2015;35:145-9.
[9] Summerton JE. Invention and Early History of Morpholinos: From Pipe Dream to Practical Products. Methods Mol Biol. 2017;1565:1-15.
[10] Marschall AL, Dübel S, Böldicke T. Specific in vivo knockdown of protein function by intrabodies. MAbs. 2015;7:1010-35.
[11] Marschall AL, Dübel S, Böldicke T. Recent Advances with ER Targeted Intrabodies. Adv Exp Med Biol. 2016;917:77-93.
[12] Petermann I, Mayer C, Stypmann J, Biniossek ML, Tobin DJ, Engelen MA, et al. Lysosomal, cytoskeletal, and metabolic alterations in cardiomyopathy of cathepsin L knockout mice. FASEB J. 2006;20:1266-8.

[13] Papizan JB, Vidal AH, Bezprozvannaya S, Bassel-Duby R, Olson EN. Cullin-3-RING ubiquitin ligase activity is required for striated muscle function in mice. J Biol Chem. 2018;293:8802-11.
[14] Karagas G, Fliegner D, Forler S, Klein O, Schubert C, Gustafsson JA, et al. Comparative proteomic analysis reveals sex and estrogen receptor beta effects in the pressure overloaded heart. J Proteome Res. 2014;13:5829-36.
[15] Sutak R, Xu X, Whitnall M, Kashem MA, Vyoral D, Richardson DR. Proteomic analysis of hearts from frataxin knockout mice: marked rearrangement of energy metabolism, a response to cellular stress and altered expression of proteins involved in cell structure, motility and metabolism. Proteomics. 2008;8:1731-41.
[16] Ibarrola J, Arrieta V, Sadaba R, Martinez-Martinez E, Garcia-Pena A, Alvarez V, et al. Galectin-3 down-regulates antioxidant peroxiredoxin-4 in human cardiac fibroblasts: a new pathway to induce cardiac damage. Clin Sci (Lond). 2018;132:1471-85.
[17] Chen Z, Li Y, Wang Y, Qian J, Ma H, Wang X, et al. Cardiomyocyte-Restricted Low Density Lipoprotein Receptor-Related Protein 6 (LRP6) Deletion Leads to Lethal Dilated Cardiomyopathy Partly Through Drp1 Signaling. Theranostics. 2018;8:627-43.
[18] Schlieper G, Kim JH, Molojavyi A, Jacoby C, Laussmann T, Flogel U, et al. Adaptation of the myoglobin knockout mouse to hypoxic stress. Am J Physiol Regul Integr Comp Physiol. 2004;286:R786-92.
[19] Chu G, Kerr JP, Mitton B, Egnaczyk GF, Vazquez JA, Shen M, et al. Proteomic analysis of hyperdynamic mouse hearts with enhanced sarcoplasmic reticulum calcium cycling. FASEB J. 2004;18:1725-7.
[20] Raddatz K, Albrecht D, Hochgrafe F, Hecker M, Gotthardt M. A proteome map of murine heart and skeletal muscle. Proteomics. 2008;8:1885-97.
[21] Yoshioka J, Chutkow WA, Lee S, Kim JB, Yan J, Tian R, et al. Deletion of thioredoxin-interacting protein in mice impairs mitochondrial function but protects the myocardium from ischemia-reperfusion injury. J Clin Invest. 2012;122:267-79.
[22] Garcia-Rua V, Feijoo-Bandin S, Garcia-Vence M, Aragon-Herrera A, Bravo SB, Rodriguez-Penas D, et al. Metabolic alterations derived from absence of Two-Pore Channel 1 at cardiac level. Journal of biosciences. 2016;41:643-58.
[23] Padmanabhan Iyer R, Chiao YA, Flynn ER, Hakala K, Cates CA, Weintraub ST, et al. Matrix metalloproteinase-9-dependent mechanisms of reduced contractility and increased stiffness in the aging heart. Proteomics Clin Appl. 2016;10:92-107.
[24] Chiao YA, Zamilpa R, Lopez EF, Dai Q, Escobar GP, Hakala K, et al. In vivo matrix metalloproteinase-7 substrates identified in the left ventricle post-myocardial infarction using proteomics. J Proteome Res. 2010;9:2649-57.
[25] Zamilpa R, Lopez EF, Chiao YA, Dai Q, Escobar GP, Hakala K, et al. Proteomic analysis identifies in vivo candidate matrix metalloproteinase-9 substrates in the left ventricle post-myocardial infarction. Proteomics. 2010;10:2214-23.
[26] DeLeon-Pennell KY, Tian Y, Zhang B, Cates CA, Iyer RP, Cannon P, et al. CD36 Is a Matrix Metalloproteinase-9 Substrate That Stimulates Neutrophil Apoptosis and Removal During Cardiac Remodeling. Circulation Cardiovascular genetics. 2016;9:14-25.
[27] Gao J, Xu D, Sabat G, Valdivia H, Xu W, Shi NQ. Disrupting KATP channels diminishes the estrogen-mediated protection in female mutant mice during ischemia-reperfusion. Clin Proteomics. 2014;11:19.
[28] Thu VT, Kim HK, Ha SH, Yoo JY, Park WS, Kim N, et al. Glutathione peroxidase 1 protects mitochondria against hypoxia/reoxygenation damage in mouse hearts. Pflugers Arch. 2010;460:55-68.
[29] Vignon-Zellweger N, Relle K, Kienlen E, Alter M, Seider P, Sharkovska J, et al. Endothelin-1 overexpression restores diastolic function in eNOS knockout mice. J Hypertens. 2011;29:961-70.
[30] Zellner A, Scharrer E, Arzberger T, Oka C, Domenga-Denier V, Joutel A, et al. CADASIL brain vessels show a HTRA1 loss-of-function profile. Acta neuropathologica. 2018;136:111-25.
[31] Xiao Q, Zhang F, Grassia G, Hu Y, Zhang Z, Xing Q, et al. Matrix metalloproteinase-8 promotes vascular smooth muscle cell proliferation and neointima formation. Arterioscler Thromb Vasc Biol. 2014;34:90-8.
[32] Jensen SR, Schoof EM, Wheeler SE, Hvid H, Ahnfelt-Ronne J, Hansen BF, et al. Quantitative Proteomics of Intestinal Mucosa From Male Mice Lacking Intestinal Epithelial Insulin Receptors. Endocrinology. 2017;158:2470-85.

[33] Magdeldin S, Li H, Yoshida Y, Satokata I, Maeda Y, Yokoyama M, et al. Differential proteomic shotgun analysis elucidates involvement of water channel aquaporin 8 in presence of alpha-amylase in the colon. J Proteome Res. 2010;9:6635-46.
[34] Magdeldin S, Li H, Yoshida Y, Enany S, Zhang Y, Xu B, et al. Comparison of two dimensional electrophoresis mouse colon proteomes before and after knocking out Aquaporin 8. J Proteomics. 2010;73:2031-40.
[35] Lennicke C, Rahn J, Wickenhauser C, Lichtenfels R, Muller AS, Wessjohann LA, et al. Loss of epithelium-specific GPx2 results in aberrant cell fate decisions during intestinal differentiation. Oncotarget. 2018;9:539-52.
[36] Nicolay BN, Danielian PS, Kottakis F, Lapek JD, Jr., Sanidas I, Miles WO, et al. Proteomic analysis of pRb loss highlights a signature of decreased mitochondrial oxidative phosphorylation. Genes & development. 2015;29:1875-89.
[37] Hu X, Friedman D, Hill S, Caprioli R, Nicholson W, Powers AC, et al. Proteomic exploration of pancreatic islets in mice null for the alpha2A adrenergic receptor. J Mol Endocrinol. 2005;35:73-88.
[38] Thorlacius-Ussing L, Ludvigsen M, Kirkeby S, Vorum H, Honore B. Proteomic analysis of tissue from alpha1,3-galactosyltransferase knockout mice reveals that a wide variety of proteins and protein fragments change expression level. PLoS ONE. 2013;8:e80600.
[39] Baughman JM, Rose CM, Kolumam G, Webster JD, Wilkerson EM, Merrill AE, et al. NeuCode Proteomics Reveals Bap1 Regulation of Metabolism. Cell reports. 2016;16:583-95.
[40] Bracht T, Hagemann S, Loscha M, Megger DA, Padden J, Eisenacher M, et al. Proteome analysis of a hepatocyte-specific BIRC5 (survivin)-knockout mouse model during liver regeneration. J Proteome Res. 2014;13:2771-82.
[41] Kim KH, Choi JM, Li F, Arizpe A, Wooton-Kee CR, Anakk S, et al. Xenobiotic Nuclear Receptor Signaling Determines Molecular Pathogenesis of Progressive Familial Intrahepatic Cholestasis. Endocrinology. 2018;159:2435-46.
[42] Tenorio-Laranga J, Mannisto PT, Karayiorgou M, Gogos JA, Garcia-Horsman JA. Sex-dependent compensated oxidative stress in the mouse liver upon deletion of catechol O-methyltransferase. Biochem Pharmacol. 2009;77:1541-52.
[43] Liu H, Lou G, Li C, Wang X, Cederbaum AI, Gan L, et al. HBx inhibits CYP2E1 gene expression via downregulating HNF4alpha in human hepatoma cells. PLoS ONE. 2014;9:e107913.
[44] Wang Y, Kou Y, Wang X, Cederbaum A, Wang R. Multifactorial comparative proteomic study of cytochrome P450 2E1 function in chronic alcohol administration. PLoS ONE. 2014;9:e92504.
[45] Olona A, Terra X, Ko JH, Grau-Bove C, Pinent M, Ardevol A, et al. Epoxygenase inactivation exacerbates diet and aging-associated metabolic dysfunction resulting from impaired adipogenesis. Molecular metabolism. 2018;11:18-32.
[46] Sahasrabuddhe NA, Huang TC, Ahmad S, Kim MS, Yang Y, Ghosh B, et al. Regulation of PPAR-alpha pathway by Dicer revealed through proteomic analysis. J Proteomics. 2014;108:306-15.
[47] Liu Y, Zhou Q, He XS, Song LM, Chen L, Jiao WJ, et al. Genetic variants in ERBB4 is associated with chronic hepatitis B virus infection. Oncotarget. 2016;7:4981-92.
[48] Hamid Z, Summa M, Armirotti A. A Swath Label-Free Proteomics insight into the Faah(-/-) Mouse Liver. Scientific reports. 2018;8:12142.
[49] Yang J, MacDougall ML, McDowell MT, Xi L, Wei R, Zavadoski WJ, et al. Polyomic profiling reveals significant hepatic metabolic alterations in glucagon-receptor (GCGR) knockout mice: implications on anti-glucagon therapies for diabetes. BMC Genomics. 2011;12:281.
[50] Fan Y, Fang X, Tajima A, Geng X, Ranganathan S, Dong H, et al. Evolution of hepatic steatosis to fibrosis and adenoma formation in liver-specific growth hormone receptor knockout mice. Frontiers in endocrinology. 2014;5:218.
[51] Prokudin I, Stasyk T, Rainer J, Bonn GK, Kofler R, Huber LA. Comprehensive proteomic and transcriptomic characterization of hepatic expression signatures affected in p14 liver conditional knockout mice. Proteomics. 2011;11:469-80.
[52] Fernandez C, Krogh M, Warell K, Alm K, Oredsson S, Persson L, et al. Omics analyses reveal a potential link between hormone-sensitive lipase and polyamine metabolism. J Proteome Res. 2009;8:5008-19.

[53] Santamaria E, Avila MA, Latasa MU, Rubio A, Martin-Duce A, Lu SC, et al. Functional proteomics of nonalcoholic steatohepatitis: mitochondrial proteins as targets of S-adenosylmethionine. Proc Natl Acad Sci U S A. 2003;100:3065-70.
[54] Santamaria E, Munoz J, Fernandez-Irigoyen J, Sesma L, Mora MI, Berasain C, et al. Molecular profiling of hepatocellular carcinoma in mice with a chronic deficiency of hepatic s-adenosylmethionine: relevance in human liver diseases. J Proteome Res. 2006;5:944-53.
[55] Melchers A, Stockl L, Radszewski J, Anders M, Krenzlin H, Kalischke C, et al. A systematic proteomic study of irradiated DNA repair deficient Nbn-mice. PLoS ONE. 2009;4:e5423.
[56] Walsh J, Jenkins RE, Wong M, Olayanju A, Powell H, Copple I, et al. Identification and quantification of the basal and inducible Nrf2-dependent proteomes in mouse liver: biochemical, pharmacological and toxicological implications. J Proteomics. 2014;108:171-87.
[57] Bruneel A, Wendum D, Labas V, Mulner-Lorillon O, Vinh J, Bosselut N, et al. Proteomic analysis of NME1/NDPK A null mouse liver: evidence for a post-translational regulation of annexin IV and EF-1Balpha. Naunyn-Schmiedeberg's archives of pharmacology. 2011;384:407-19.
[58] Massafra V, Milona A, Vos HR, Ramos RJJ, Gerrits J, Willemsen ECL, et al. Farnesoid X Receptor Activation Promotes Hepatic Amino Acid Catabolism and Ammonium Clearance in Mice. Gastroenterology. 2017;152:1462-76 e10.
[59] Zhu Y, Li G, Dong Y, Zhou HH, Kong B, Aleksunes LM, et al. Modulation of farnesoid X receptor results in post-translational modification of poly (ADP-ribose) polymerase 1 in the liver. Toxicol Appl Pharmacol. 2013;266:260-6.
[60] Stachowicz A, Olszanecki R, Suski M, Wisniewska A, Kus K, Bialas M, et al. Quantitative proteomics reveals decreased expression of major urinary proteins in the liver of apoE/eNOS-DKO mice. Clinical and experimental pharmacology & physiology. 2018;45:711-9.
[61] Ishihara K, Miyazaki A, Nabe T, Fushimi H, Iriyama N, Kanai S, et al. Group IVA phospholipase A2 participates in the progression of hepatic fibrosis. FASEB J. 2012;26:4111-21.
[62] Macdonald N, Chevalier S, Tonge R, Davison M, Rowlinson R, Young J, et al. Quantitative proteomic analysis of mouse liver response to the peroxisome proliferator diethylhexylphthalate (DEHP). Arch Toxicol. 2001;75:415-24.
[63] Liao BM, Raddatz K, Zhong L, Parker BL, Raftery MJ, Schmitz-Peiffer C. Proteomic analysis of livers from fat-fed mice deficient in either PKCdelta or PKCepsilon identifies Htatip2 as a regulator of lipid metabolism. Proteomics. 2014;14:2578-87.
[64] Lai KK, Shang S, Lohia N, Booth GC, Masse DJ, Fausto N, et al. Extracellular matrix dynamics in hepatocarcinogenesis: a comparative proteomics study of PDGFC transgenic and Pten null mouse models. PLoS Genet. 2011;7:e1002147.
[65] Tong Z, Fan Y, Zhang W, Xu J, Cheng J, Ding M, et al. Pancreas-specific Pten deficiency causes partial resistance to diabetes and elevated hepatic AKT signaling. Cell research. 2009;19:710-9.
[66] Sydor S, Sowa JP, Megger DA, Schlattjan M, Jafoui S, Wingerter L, et al. Acid sphingomyelinase deficiency in Western diet-fed mice protects against adipocyte hypertrophy and diet-induced liver steatosis. Molecular metabolism. 2017;6:416-27.
[67] Li J, Woolbright BL, Zhao W, Wang Y, Matye D, Hagenbuch B, et al. Sortilin 1 Loss-of-Function Protects Against Cholestatic Liver Injury by Attenuating Hepatic Bile Acid Accumulation in Bile Duct Ligated Mice. Toxicol Sci. 2018;161:34-47.
[68] Iff J, Wang W, Sajic T, Oudry N, Gueneau E, Hopfgartner G, et al. Differential proteomic analysis of STAT6 knockout mice reveals new regulatory function in liver lipid homeostasis. J Proteome Res. 2009;8:4511-24.
[69] Fiorentino L, Vivanti A, Cavalera M, Marzano V, Ronci M, Fabrizi M, et al. Increased tumor necrosis factor alpha-converting enzyme activity induces insulin resistance and hepatosteatosis in mice. Hepatology. 2010;51:103-10.
[70] Li B, Reed JC, Kim HR, Chae HJ. Proteomic profiling of differentially expressed proteins from Bax inhibitor-1 knockout and wild type mice. Molecules and cells. 2012;34:15-23.
[71] Macdonald N, Barrow K, Tonge R, Davison M, Roberts RA, Chevalier S. PPARalpha-dependent alteration of GRP94 expression in mouse hepatocytes. Biochem Biophys Res Commun. 2000;277:699-704.
[72] Thorn K, Hovsepyan M, Bergsten P. Reduced levels of SCD1 accentuate palmitate-induced stress in insulin-producing beta-cells. Lipids in health and disease. 2010;9:108.

[73] Iannetti A, Pacifico F, Acquaviva R, Lavorgna A, Crescenzi E, Vascotto C, et al. The neutrophil gelatinase-associated lipocalin (NGAL), a NF-kappaB-regulated gene, is a survival factor for thyroid neoplastic cells. Proc Natl Acad Sci U S A. 2008;105:14058-63.
[74] Calvo-Asensio I, Dillon ET, Lowndes NF, Ceredig R. The Transcription Factor Hif-1 Enhances the Radio-Resistance of Mouse MSCs. Frontiers in physiology. 2018;9:439.
[75] Mitsunaga K, Kikuchi J, Wada T, Furukawa Y. Latexin regulates the abundance of multiple cellular proteins in hematopoietic stem cells. Journal of cellular physiology. 2012;227:1138-47.
[76] Sawhney S, Hood K, Shaw A, Braithwaite AW, Stubbs R, Hung NA, et al. Alpha-enolase is upregulated on the cell surface and responds to plasminogen activation in mice expressing a 133p53alpha mimic. PLoS ONE. 2015;10:e0116270.
[77] Van Quickelberghe E, Martens A, Goeminne LJE, Clement L, van Loo G, Gevaert K. Identification of Immune-Responsive Gene 1 (IRG1) as a Target of A20. J Proteome Res. 2018;17:2182-91.
[78] Krishnaswamy JK, Singh A, Gowthaman U, Wu R, Gorrepati P, Sales Nascimento M, et al. Coincidental loss of DOCK8 function in NLRP10-deficient and C3H/HeJ mice results in defective dendritic cell migration. Proc Natl Acad Sci U S A. 2015;112:3056-61.
[79] Mussotter F, Tomm JM, El Ali Z, Pallardy M, Kerdine-Romer S, Gotz M, et al. Proteomics analysis of dendritic cell activation by contact allergens reveals possible biomarkers regulated by Nrf2. Toxicol Appl Pharmacol. 2016;313:170-9.
[80] Azkargorta M, Arizmendi JM, Elortza F, Alkorta N, Zubiaga AM, Fullaondo A. Differential proteome profiles in E2F2-deficient T lymphocytes. Proteomics. 2006;6 Suppl 1:S42-50.
[81] Rosal-Vela A, Barroso A, Gimenez E, Garcia-Rodriguez S, Longobardo V, Postigo J, et al. Identification of multiple transferrin species in the spleen and serum from mice with collagen-induced arthritis which may reflect changes in transferrin glycosylation associated with disease activity: The role of CD38. J Proteomics. 2016;134:127-37.
[82] Basco D, Nicchia GP, D'Alessandro A, Zolla L, Svelto M, Frigeri A. Absence of aquaporin-4 in skeletal muscle alters proteins involved in bioenergetic pathways and calcium handling. PLoS ONE. 2011;6:e19225.
[83] Huang YL, Shen ZQ, Wu CY, Teng YC, Liao CC, Kao CH, et al. Comparative proteomic profiling reveals a role for Cisd2 in skeletal muscle aging. Aging cell. 2018;17.
[84] Capitanio D, Moriggi M, De Palma S, Bizzotto D, Molon S, Torretta E, et al. Collagen VI Null Mice as a Model for Early Onset Muscle Decline in Aging. Frontiers in molecular neuroscience. 2017;10:337.
[85] Picard B, Kammoun M, Gagaoua M, Barboiron C, Meunier B, Chambon C, et al. Calcium Homeostasis and Muscle Energy Metabolism Are Modified in HspB1-Null Mice. Proteomes. 2016;4.
[86] Hansson O, Donsmark M, Ling C, Nevsten P, Danfelter M, Andersen JL, et al. Transcriptome and proteome analysis of soleus muscle of hormone-sensitive lipase-null mice. J Lipid Res. 2005;46:2614-23.
[87] Salzler RR, Shah D, Dore A, Bauerlein R, Miloscio L, Latres E, et al. Myostatin deficiency but not anti-myostatin blockade induces marked proteomic changes in mouse skeletal muscle. Proteomics. 2016;16:2019-27.
[88] Chelh I, Meunier B, Picard B, Reecy MJ, Chevalier C, Hocquette JF, et al. Molecular profiles of Quadriceps muscle in myostatin-null mice reveal PI3K and apoptotic pathways as myostatin targets. BMC Genomics. 2009;10:196.
[89] Kleinert M, Parker BL, Chaudhuri R, Fazakerley DJ, Serup A, Thomas KC, et al. mTORC2 and AMPK differentially regulate muscle triglyceride content via Perilipin 3. Molecular metabolism. 2016;5:646-55.
[90] Bertipaglia I, Bourg N, Richard I, Pahlman AK, Andersson L, James P, et al. A proteomic study of calpain-3 and its involvement in limb girdle muscular dystrophy type 2a. Cell calcium. 2009;46:356-63.
[91] Yan L, Vatner DE, O'Connor JP, Ivessa A, Ge H, Chen W, et al. Type 5 adenylyl cyclase disruption increases longevity and protects against stress. Cell. 2007;130:247-58.
[92] Suszynska-Zajczyk J, Luczak M, Marczak L, Jakubowski H. Hyperhomocysteinemia and bleomycin hydrolase modulate the expression of mouse brain proteins involved in neurodegeneration. J Alzheimers Dis. 2014;40:713-26.
[93] Rong R, Yang H, Rong L, Wei X, Li Q, Liu X, et al. Proteomic analysis of PSD-93 knockout mice following the induction of ischemic cerebral injury. Neurotoxicology. 2016;53:1-11.

[94] Zhong L, Zhou J, Chen X, Liu J, Liu Z, Chen Y, et al. Quantitative proteomics reveals EVA1A-related proteins involved in neuronal differentiation. Proteomics. 2017;17.
[95] Yao I, Sugiura Y, Matsumoto M, Setou M. In situ proteomics with imaging mass spectrometry and principal component analysis in the Scrapper-knockout mouse brain. Proteomics. 2008;8:3692-701.
[96] Smith BM, Giddens MM, Neil J, Owino S, Nguyen TT, Duong D, et al. Mice lacking Gpr37 exhibit decreased expression of the myelin-associated glycoprotein MAG and increased susceptibility to demyelination. Neuroscience. 2017;358:49-57.
[97] Castro LM, Cavalcanti DM, Araujo CB, Rioli V, Icimoto MY, Gozzo FC, et al. Peptidomic analysis of the neurolysin-knockout mouse brain. J Proteomics. 2014;111:238-48.
[98] Hauser DN, Mamais A, Conti MM, Primiani CT, Kumaran R, Dillman AA, et al. Hexokinases link DJ-1 to the PINK1/parkin pathway. Molecular neurodegeneration. 2017;12:70.
[99] Zhu JX, Doyle HA, Mamula MJ, Aswad DW. Protein repair in the brain, proteomic analysis of endogenous substrates for protein L-isoaspartyl methyltransferase in mouse brain. J Biol Chem. 2006;281:33802-13.
[100] Triplett JC, Zhang Z, Sultana R, Cai J, Klein JB, Bueler H, et al. Quantitative expression proteomics and phosphoproteomics profile of brain from PINK1 knockout mice: insights into mechanisms of familial Parkinson's disease. J Neurochem. 2015;133:750-65.
[101] Suszynska-Zajczyk J, Luczak M, Marczak L, Jakubowski H. Inactivation of the paraoxonase 1 gene affects the expression of mouse brain proteins involved in neurodegeneration. J Alzheimers Dis. 2014;42:247-60.
[102] Shukla S, Shankavaram UT, Nguyen P, Stanley BA, Smart DK. Radiation-Induced Alteration of the Brain Proteome: Understanding the Role of the Sirtuin 2 Deacetylase in a Murine Model. J Proteome Res. 2015;14:4104-17.
[103] Lizama BN, Palubinsky AM, Raveendran VA, Moore AM, Federspiel JD, Codreanu SG, et al. Neuronal Preconditioning Requires the Mitophagic Activity of C-terminus of HSC70-Interacting Protein. J Neurosci. 2018.
[104] Steinacker P, Schwarz P, Reim K, Brechlin P, Jahn O, Kratzin H, et al. Unchanged survival rates of 14-3-3gamma knockout mice after inoculation with pathological prion protein. Mol Cell Biol. 2005;25:1339-46.
[105] Loziuk P, Meier F, Johnson C, Ghashghaei HT, Muddiman DC. TransOmic analysis of forebrain sections in Sp2 conditional knockout embryonic mice using IR-MALDESI imaging of lipids and LC-MS/MS label-free proteomics. Analytical and bioanalytical chemistry. 2016;408:3453-74.
[106] Di Domenico F, Casalena G, Sultana R, Cai J, Pierce WM, Perluigi M, et al. Involvement of Stat3 in mouse brain development and sexual dimorphism: a proteomics approach. Brain research. 2010;1362:1-12.
[107] Di Domenico F, Casalena G, Jia J, Sultana R, Barone E, Cai J, et al. Sex differences in brain proteomes of neuron-specific STAT3-null mice after cerebral ischemia/reperfusion. J Neurochem. 2012;121:680-92.
[108] Knowles MR, Cervino S, Skynner HA, Hunt SP, de Felipe C, Salim K, et al. Multiplex proteomic analysis by two-dimensional differential in-gel electrophoresis. Proteomics. 2003;3:1162-71.
[109] Nakashima AS, Butt RH, Dyck RH. Alterations in protein and gene expression within the barrel cortices of ZnT3 knockout mice: experience-independent and dependent changes. Neurochemistry international. 2011;59:860-70.
[110] Hardt S, Heidler J, Albuquerque B, Valek L, Altmann C, Wilken-Schmitz A, et al. Loss of synaptic zinc transport in progranulin deficient mice may contribute to progranulin-associated psychopathology and chronic pain. Biochim Biophys Acta. 2017;1863:2727-45.
[111] Kim HJ, Eom CY, Kwon J, Joo J, Lee S, Nah SS, et al. Roles of interferon-gamma and its target genes in schizophrenia: Proteomics-based reverse genetics from mouse to human. Proteomics. 2012;12:1815-29.
[112] Owen JB, Opii WO, Ramassamy C, Pierce WM, Butterfield DA. Proteomic analysis of brain protein expression levels in NF-kappabeta p50 -/- homozygous knockout mice. Brain research. 2008;1240:22-30.
[113] Periquet M, Corti O, Jacquier S, Brice A. Proteomic analysis of parkin knockout mice: alterations in energy metabolism, protein handling and synaptic function. J Neurochem. 2005;95:1259-76.

[114] Wang D, Yu H, Xu B, Xu H, Zhang Z, Ren X, et al. TRPC1 Deletion Causes Striatal Neuronal Cell Apoptosis and Proteomic Alterations in Mice. Frontiers in aging neuroscience. 2018;10:72.
[115] Xu B, Zhang Y, Zhan S, Wang X, Zhang H, Meng X, et al. Proteomic Profiling of Brain and Testis Reveals the Diverse Changes in Ribosomal Proteins in fmr1 Knockout Mice. Neuroscience. 2018;371:469-83.
[116] Zearfoss NR, Alarcon JM, Trifilieff P, Kandel E, Richter JD. A molecular circuit composed of CPEB-1 and c-Jun controls growth hormone-mediated synaptic plasticity in the mouse hippocampus. J Neurosci. 2008;28:8502-9.
[117] Kirchner L, Weitzdoerfer R, Hoeger H, Url A, Schmidt P, Engelmann M, et al. Impaired cognitive performance in neuronal nitric oxide synthase knockout mice is associated with hippocampal protein derangements. Nitric Oxide. 2004;11:316-30.
[118] Byun K, Kim J, Cho SY, Hutchinson B, Yang SR, Kang KS, et al. Alteration of the glutamate and GABA transporters in the hippocampus of the Niemann-Pick disease, type C mouse using proteomic analysis. Proteomics. 2006;6:1230-6.
[119] Xing R, Zhang Y, Xu H, Luo X, Chang RC, Liu J, et al. Spatial memory impairment by TRPC1 depletion is ameliorated by environmental enrichment. Oncotarget. 2016;7:27855-73.
[120] Zhong L, Zhou J, Wang D, Zou X, Lou Y, Liu D, et al. Proteomics and bioinformatics analysis of mouse hypothalamic neurogenesis with or without EPHX2 gene deletion. International journal of clinical and experimental pathology. 2015;8:12634-45.
[121] Azzam S, Schlatzer D, Nethery D, Saleh D, Li X, Akladious A, et al. Proteomic profiling of the hypothalamus in two mouse models of narcolepsy. Proteomics. 2017;17.
[122] Zettergren A, Karlsson S, Studer E, Sarvimaki A, Kettunen P, Thorsell A, et al. Proteomic analyses of limbic regions in neonatal male, female and androgen receptor knockout mice. BMC Neurosci. 2017;18:9.
[123] Germany CE, Reker AN, Hinton DJ, Oliveros A, Shen X, Andres-Beck LG, et al. Pharmacoproteomics Profile in Response to Acamprosate Treatment of an Alcoholism Animal Model. Proteomics. 2018;18:e1700417.
[124] Sanchez I, Balague E, Matilla-Duenas A. Ataxin-1 regulates the cerebellar bioenergetics proteome through the GSK3beta-mTOR pathway which is altered in Spinocerebellar ataxia type 1 (SCA1). Hum Mol Genet. 2016;25:4021-40.
[125] Hu J, Qian J, Borisov O, Pan S, Li Y, Liu T, et al. Optimized proteomic analysis of a mouse model of cerebellar dysfunction using amine-specific isobaric tags. Proteomics. 2006;6:4321-34.
[126] Jaarsma D, van den Berg R, Wulf PS, van Erp S, Keijzer N, Schlager MA, et al. A role for Bicaudal-D2 in radial cerebellar granule cell migration. Nature communications. 2014;5:3411.
[127] Bortolussi G, Codarin E, Antoniali G, Vascotto C, Vodret S, Arena S, et al. Impairment of enzymatic antioxidant defenses is associated with bilirubin-induced neuronal cell death in the cerebellum of Ugt1 KO mice. Cell death & disease. 2015;6:e1739.
[128] Fu X, Brown KJ, Rayavarapu S, Nagaraju K, Liu JS. The use of proteomic analysis to study trafficking defects in axons. Methods in cell biology. 2016;131:151-62.
[129] Vicente-Rodriguez M, Herradon G, Ferrer-Alcon M, Uribarri M, Perez-Garcia C. Chronic Cocaine Use Causes Changes in the Striatal Proteome Depending on the Endogenous Expression of Pleiotrophin. Chem Res Toxicol. 2015;28:1443-54.
[130] Fahrenkrug J, Hannibal J, Honore B, Vorum H. Altered calmodulin response to light in the suprachiasmatic nucleus of PAC1 receptor knockout mice revealed by proteomic analysis. J Mol Neurosci. 2005;25:251-8.
[131] Tikka S, Monogioudi E, Gotsopoulos A, Soliymani R, Pezzini F, Scifo E, et al. Proteomic Profiling in the Brain of CLN1 Disease Model Reveals Affected Functional Modules. Neuromolecular medicine. 2016;18:109-33.
[132] Maasz G, Pirger Z, Reglodi D, Petrovics D, Schmidt J, Kiss P, et al. Comparative protein composition of the brains of PACAP-deficient mice using mass spectrometry-based proteomic analysis. J Mol Neurosci. 2014;54:310-9.
[133] Pehar M, Ball LE, Sharma DR, Harlan BA, Comte-Walters S, Neely BA, et al. Changes in Protein Expression and Lysine Acetylation Induced by Decreased Glutathione Levels in Astrocytes. Mol Cell Proteomics. 2016;15:493-505.
[134] Jensen P, Myhre CL, Lassen PS, Metaxas A, Khan AM, Lambertsen KL, et al. TNFalpha affects CREB-mediated neuroprotective signaling pathways of synaptic plasticity in neurons as revealed by proteomics and phospho-proteomics. Oncotarget. 2017;8:60223-42.

[135] Homan CC, Kumar R, Nguyen LS, Haan E, Raymond FL, Abidi F, et al. Mutations in USP9X are associated with X-linked intellectual disability and disrupt neuronal cell migration and growth. Am J Hum Genet. 2014;94:470-8.
[136] Rodriguez-Zas SL, Wu C, Southey BR, O'Connor JC, Nixon SE, Garcia R, et al. Disruption of microglia histone acetylation and protein pathways in mice exhibiting inflammation-associated depression-like symptoms. Psychoneuroendocrinology. 2018;97:47-58.
[137] Okada T, Keino-Masu K, Nagamine S, Kametani F, Ohto T, Hasegawa M, et al. Desulfation of Heparan Sulfate by Sulf1 and Sulf2 Is Required for Corticospinal Tract Formation. Scientific reports. 2017;7:13847.
[138] Goto A, Wang YL, Kabuta T, Setsuie R, Osaka H, Sawa A, et al. Proteomic and histochemical analysis of proteins involved in the dying-back-type of axonal degeneration in the gracile axonal dystrophy (gad) mouse. Neurochemistry international. 2009;54:330-8.
[139] Hagl CI, Klotz M, Wink E, Kranzle K, Holland-Cunz S, Gretz N, et al. Temporal and regional morphological differences as a consequence of FGF-2 deficiency are mirrored in the myenteric proteome. Pediatric surgery international. 2008;24:49-60.
[140] Sang Q, Li W, Xu Y, Qu R, Xu Z, Feng R, et al. ILDR1 deficiency causes degeneration of cochlear outer hair cells and disrupts the structure of the organ of Corti: a mouse model for human DFNB42. Biology open. 2015;4:411-8.
[141] Robertson NG, Cremers CW, Huygen PL, Ikezono T, Krastins B, Kremer H, et al. Cochlin immunostaining of inner ear pathologic deposits and proteomic analysis in DFNA9 deafness and vestibular dysfunction. Hum Mol Genet. 2006;15:1071-85.
[142] Poulsen ET, Runager K, Nielsen NS, Lukassen MV, Thomsen K, Snider P, et al. Proteomic profiling of TGFBI-null mouse corneas reveals only minor changes in matrix composition supportive of TGFBI knockdown as therapy against TGFBI-linked corneal dystrophies. The FEBS journal. 2018;285:101-14.
[143] Andley UP, Malone JP, Hamilton PD, Ravi N, Townsend RR. Comparative proteomic analysis identifies age-dependent increases in the abundance of specific proteins after deletion of the small heat shock proteins alphaA- and alphaB-crystallin. Biochemistry. 2013;52:2933-48.
[144] Mou L, Xu JY, Li W, Lei X, Wu Y, Xu G, et al. Identification of vimentin as a novel target of HSF4 in lens development and cataract by proteomic analysis. Invest Ophthalmol Vis Sci. 2010;51:396-404.
[145] Markus B, Pato Z, Sarang Z, Albert R, Tozser J, Petrovski G, et al. The proteomic profile of a mouse model of proliferative vitreoretinopathy. FEBS open bio. 2017;7:1166-77.
[146] Moller M, Rath MF, Ludvigsen M, Honore B, Vorum H. Diurnal expression of proteins in the retina of the blind cone-rod homeobox (Crx(-/-)) mouse and the 129/Sv mouse: a proteomic study. Acta ophthalmologica. 2017;95:717-26.
[147] Lee AR, Lamb RR, Chang JH, Erdmann-Gilmore P, Lichti CF, Rohrs HW, et al. Identification of potential mediators of retinotopic mapping: a comparative proteomic analysis of optic nerve from WT and Phr1 retinal knockout mice. J Proteome Res. 2012;11:5515-26.
[148] Hu W, Gauthier L, Baibakov B, Jimenez-Movilla M, Dean J. FIGLA, a basic helix-loop-helix transcription factor, balances sexually dimorphic gene expression in postnatal oocytes. Mol Cell Biol. 2010;30:3661-71.
[149] Burnum KE, Tranguch S, Mi D, Daikoku T, Dey SK, Caprioli RM. Imaging mass spectrometry reveals unique protein profiles during embryo implantation. Endocrinology. 2008;149:3274-8.
[150] Antonson P, Nalvarte I, Varshney M, Xu L, Windahl SH, Humire P, et al. Identification of proteins highly expressed in uterine fluid from mice with hydrometra. Biochem Biophys Res Commun. 2015;466:650-5.
[151] Mori H, Bhat R, Bruni-Cardoso A, Chen EI, Jorgens DM, Coutinho K, et al. New insight into the role of MMP14 in metabolic balance. PeerJ. 2016;4:e2142.
[152] Monks J, Dzieciatkowska M, Bales ES, Orlicky DJ, Wright RM, McManaman JL. Xanthine oxidoreductase mediates membrane docking of milk-fat droplets but is not essential for apocrine lipid secretion. The Journal of physiology. 2016;594:5899-921.
[153] Yan J, Zhang H, Liu Y, Zhao F, Zhu S, Xie C, et al. Germline deletion of huntingtin causes male infertility and arrested spermiogenesis in mice. Journal of cell science. 2016;129:492-501.

[154] Yang H, Wahlmuller FC, Uhrin P, Baumgartner R, Mitulovic G, Sarg B, et al. Proteome analysis of testis from infertile protein C inhibitor-deficient mice reveals novel changes in serpin processing and prostaglandin metabolism. Electrophoresis. 2015;36:2837-40.
[155] Wang B, Merillat SA, Vincent M, Huber AK, Basrur V, Mangelberger D, et al. Loss of the Ubiquitin-conjugating Enzyme UBE2W Results in Susceptibility to Early Postnatal Lethality and Defects in Skin, Immune, and Male Reproductive Systems. J Biol Chem. 2016;291:3030-42.
[156] Li J, Yang J, Cheng D, Shen SL, Xiong CL. New clues to identify proteins correlated with Attractin. Andrologia. 2014;46:796-804.
[157] Lu H, Bowler N, Harshyne LA, Craig Hooper D, Krishn SR, Kurtoglu S, et al. Exosomal alphavbeta6 integrin is required for monocyte M2 polarization in prostate cancer. Matrix biology : journal of the International Society for Matrix Biology. 2018;70:20-35.
[158] Mao J, Hu X, Pang P, Zhou B, Zhang Y, Li D, et al. Establishment of a CRISPR/Cas9-Mediated Cysltr1 Knockout Mouse Model and iTRAQ-Based Proteomic Analysis. Proteomics Clin Appl. 2018;12:e1700087.
[159] Beyea JA, Sawicki G, Olson DM, List E, Kopchick JJ, Harvey S. Growth hormone (GH) receptor knockout mice reveal actions of GH in lung development. Proteomics. 2006;6:341-8.
[160] Reynolds SD, Reynolds PR, Snyder JC, Whyte F, Paavola KJ, Stripp BR. CCSP regulates cross talk between secretory cells and both ciliated cells and macrophages of the conducting airway. Am J Physiol Lung Cell Mol Physiol. 2007;293:L114-23.
[161] Szema AM, Hamidi SA, Koller A, Martin DW. Vasoactive Intestinal Peptide Knockout (VIP KO) mouse model of sulfite-sensitive asthma: up-regulation of novel lung carbonyl reductase. BMC immunology. 2011;12:66.
[162] Phelps DS, Umstead TM, Quintero OA, Yengo CM, Floros J. In vivo rescue of alveolar macrophages from SP-A knockout mice with exogenous SP-A nearly restores a wild type intracellular proteome; actin involvement. Proteome science. 2011;9:67.
[163] Phelps DS, Umstead TM, Floros J. Sex differences in the response of the alveolar macrophage proteome to treatment with exogenous surfactant protein-A. Proteome science. 2012;10:44.
[164] Hessle L, Stordalen GA, Wenglen C, Petzold C, Tanner E, Brorson SH, et al. The skeletal phenotype of chondroadherin deficient mice. PLoS ONE. 2014;8:e63080.
[165] Brachvogel B, Zaucke F, Dave K, Norris EL, Stermann J, Dayakli M, et al. Comparative proteomic analysis of normal and collagen IX null mouse cartilage reveals altered extracellular matrix composition and novel components of the collagen IX interactome. J Biol Chem. 2013;288:13481-92.
[166] Schminke B, Frese J, Bode C, Goldring MB, Miosge N. Laminins and Nidogens in the Pericellular Matrix of Chondrocytes: Their Role in Osteoarthritis and Chondrogenic Differentiation. Am J Pathol. 2016;186:410-8.
[167] Lee NJ, Ali N, Zhang L, Qi Y, Clarke I, Enriquez RF, et al. Osteoglycin, a novel coordinator of bone and glucose homeostasis. Molecular metabolism. 2018;13:30-44.
[168] Eguren M, Alvarez-Fernandez M, Garcia F, Lopez-Contreras AJ, Fujimitsu K, Yaguchi H, et al. A synthetic lethal interaction between APC/C and topoisomerase poisons uncovered by proteomic screens. Cell reports. 2014;6:670-83.
[169] Zhuang H, Gan Z, Jiang W, Zhang X, Hua ZC. Functional specific roles of FADD: comparative proteomic analyses from knockout cell lines. Mol Biosyst. 2013;9:2063-78.
[170] Ferreira L, Fuentes-Calvo I, Munoz-Felix JM, Muniz-Martin C, Sanchez-Juanes F, Raposo C, et al. Functional specific roles of H-ras and N-ras. A proteomic approach using knockout cell lines. Electrophoresis. 2012;33:1385-96.
[171] Adamkiewicz J, Kaddatz K, Rieck M, Wilke B, Muller-Brusselbach S, Muller R. Proteomic profile of mouse fibroblasts with a targeted disruption of the peroxisome proliferator activated receptor-beta/delta gene. Proteomics. 2007;7:1208-16.
[172] Yim SH, Everley RA, Schildberg FA, Lee SG, Orsi A, Barbati ZR, et al. Role of Selenof as a Gatekeeper of Secreted Disulfide-Rich Glycoproteins. Cell reports. 2018;23:1387-98.
[173] Yuan C, Jiao L, Yang L, Ying W, Hu Z, Liu J, et al. The up-regulation of 14-3-3 proteins in Smad4 deficient epidermis and hair follicles at catagen. Proteomics. 2008;8:2230-43.
[174] Rice RH, Durbin-Johnson BP, Ishitsuka Y, Salemi M, Phinney BS, Rocke DM, et al. Proteomic Analysis of Loricrin Knockout Mouse Epidermis. J Proteome Res. 2016;15:2560-6.
[175] Tong Y, Hara A, Komatsu M, Tanaka N, Kamijo Y, Gonzalez FJ, et al. Suppression of expression of muscle-associated proteins by PPARalpha in brown adipose tissue. Biochem Biophys Res Commun. 2005;336:76-83.

[176] Komatsu M, Tong Y, Li Y, Nakajima T, Li G, Hu R, et al. Multiple roles of PPARalpha in brown adipose tissue under constitutive and cold conditions. Genes to cells : devoted to molecular & cellular mechanisms. 2010;15:91-100.
[177] Sackmann-Sala L, Berryman DE, Lubbers ER, Zhang H, Vesel CB, Troike KM, et al. Age-related and depot-specific changes in white adipose tissue of growth hormone receptor-null mice. J Gerontol A Biol Sci Med Sci. 2014;69:34-43.
[178] Huh JY, Kim Y, Jeong J, Park J, Kim I, Huh KH, et al. Peroxiredoxin 3 is a key molecule regulating adipocyte oxidative stress, mitochondrial biogenesis, and adipokine expression. Antioxid Redox Signal. 2012;16:229-43.
[179] Liu C, Perez-Leal O, Barrero C, Zahedi K, Soleimani M, Porter C, et al. Modulation of polyamine metabolic flux in adipose tissue alters the accumulation of body fat by affecting glucose homeostasis. Amino Acids. 2014;46:701-15.
[180] Peinado JR, Quiros PM, Pulido MR, Marino G, Martinez-Chantar ML, Vazquez-Martinez R, et al. Proteomic profiling of adipose tissue from Zmpste24-/- mice, a model of lipodystrophy and premature aging, reveals major changes in mitochondrial function and vimentin processing. Mol Cell Proteomics. 2011;10:M111 008094.
[181] Lv X, Ai J, Li M, Wang H, Chen T, Fang Y, et al. Comparative proteomics and correlated signaling network of kidney in ApoE deficient mouse. Proteomics Clin Appl. 2013;7:829-38.
[182] Suszynska-Zajczyk J, Utyro O, Jakubowski H. Methionine-induced hyperhomocysteinemia and bleomycin hydrolase deficiency alter the expression of mouse kidney proteins involved in renal disease. Molecular genetics and metabolism. 2014;112:339-46.
[183] Fan H, Harrell JR, Dipp S, Saifudeen Z, El-Dahr SS. A novel pathological role of p53 in kidney development revealed by gene-environment interactions. American journal of physiology Renal physiology. 2005;288:F98-107.
[184] Zhao Y, Zhang Y, Song HB, Wu F, Wang XL, Sun SC, et al. Proteomic analysis revealed the altered kidney protein profile of a Cyld knockout mouse model. Genetics and molecular research : GMR. 2015;14:5970-8.
[185] Fujino Y, Minamizaki T, Hayashi I, Kawakami A, Miyaji T, Sakurai K, et al. Comparative proteome analysis of wild-type and klotho-knockout mouse kidneys using a combination of MALDI-IMS and LC-MS/MS. Proteomics Clin Appl. 2017;11.
[186] Boddu R, Hull TD, Bolisetty S, Hu X, Moehle MS, Daher JP, et al. Leucine-rich repeat kinase 2 deficiency is protective in rhabdomyolysis-induced kidney injury. Hum Mol Genet. 2015;24:4078-93.
[187] Pellegrini L, Hauser DN, Li Y, Mamais A, Beilina A, Kumaran R, et al. Proteomic analysis reveals co-ordinated alterations in protein synthesis and degradation pathways in LRRK2 knockout mice. Hum Mol Genet. 2018.
[188] Suszynska-Zajczyk J, Sikora M, Jakubowski H. Paraoxonase 1 deficiency and hyperhomocysteinemia alter the expression of mouse kidney proteins involved in renal disease. Molecular genetics and metabolism. 2014;113:200-6.
[189] Hu YJ, Zhou Q, Li ZY, Feng D, Sun L, Shen YL, et al. Renal proteomic analysis of RGC-32 knockout mice reveals the potential mechanism of RGC-32 in regulating cell cycle. American journal of translational research. 2018;10:847-56.
[190] Rossi C, Marzano V, Consalvo A, Zucchelli M, Levi Mortera S, Casagrande V, et al. Proteomic and metabolomic characterization of streptozotocin-induced diabetic nephropathy in TIMP3-deficient mice. Acta diabetologica. 2018;55:121-9.
[191] Shelton LM, Lister A, Walsh J, Jenkins RE, Wong MH, Rowe C, et al. Integrated transcriptomic and proteomic analyses uncover regulatory roles of Nrf2 in the kidney. Kidney Int. 2015;88:1261-73.
[192] Song T, Chen M, Rao Z, Qiu Y, Liu J, Jiang Y, et al. miR-17-92 ameliorates renal ischemia reperfusion injury. The Kaohsiung journal of medical sciences. 2018;34:263-73.
[193] Fiumara CV, Scumaci D, Iervolino A, Perri AM, Concolino A, Tamme L, et al. Unraveling the Mechanistic Complexity of the Glomerulocystic Phenotype in Dicer Conditional KO Mice by 2D Gel Electrophoresis Coupled Mass Spectrometry. Proteomics Clin Appl. 2018;12:e1700006.
[194] Steenhard BM, Vanacore R, Friedman D, Zelenchuk A, Stroganova L, Isom K, et al. Upregulated expression of integrin alpha1 in mesangial cells and integrin alpha3 and vimentin in podocytes of Col4a3-null (Alport) mice. PLoS ONE. 2012;7:e50745.

[195] Isobe K, Jung HJ, Yang CR, Claxton J, Sandoval P, Burg MB, et al. Systems-level identification of PKA-dependent signaling in epithelial cells. Proc Natl Acad Sci U S A. 2017;114:E8875-E84.
[196] Sprossmann F, Pankert P, Sausbier U, Wirth A, Zhou XB, Madlung J, et al. Inducible knockout mutagenesis reveals compensatory mechanisms elicited by constitutive BK channel deficiency in overactive murine bladder. The FEBS journal. 2009;276:1680-97.
[197] Chen YH, Chen CJ, Yeh S, Lin YN, Wu YC, Hsieh WT, et al. Urethral dysfunction in female mice with estrogen receptor beta deficiency. PLoS ONE. 2014;9:e109058.
[198] Uhlen M, Bjorling E, Agaton C, Szigyarto CA, Amini B, Andersen E, et al. A human protein atlas for normal and cancer tissues based on antibody proteomics. Mol Cell Proteomics. 2005;4:1920-32.
[199] Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, et al. Proteomics. Tissue-based map of the human proteome. Science. 2015;347:1260419.
[200] Omenn GS, Lane L, Lundberg EK, Overall CM, Deutsch EW. Progress on the HUPO Draft Human Proteome: 2017 Metrics of the Human Proteome Project. J Proteome Res. 2017;16:4281-7.
[201] Fagerberg L, Hallstrom BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Mol Cell Proteomics. 2014;13:397-406.
[202] Hernandez-Fernaud JR, Salido E. Differential expression of liver and kidney proteins in a mouse model for primary hyperoxaluria type I. The FEBS journal. 2010;277:4766-74.
[203] Kalinowska M, Castillo C, Francesconi A. Quantitative profiling of brain lipid raft proteome in a mouse model of fragile X syndrome. PLoS ONE. 2015;10:e0121464.
[204] Tang B, Wang T, Wan H, Han L, Qin X, Zhang Y, et al. Fmr1 deficiency promotes age-dependent alterations in the cortical synaptic proteome. Proc Natl Acad Sci U S A. 2015;112:E4697-706.
[205] Liao L, Park SK, Xu T, Vanderklish P, Yates JR, 3rd. Quantitative proteomic analysis of primary neurons reveals diverse changes in synaptic protein content in fmr1 knockout mice. Proc Natl Acad Sci U S A. 2008;105:15281-6.
[206] Petrak J, Ivanek R, Toman O, Cmejla R, Cmejlova J, Vyoral D, et al. Deja vu in proteomics. A hit parade of repeatedly identified differentially expressed proteins. Proteomics. 2008;8:1744-9.
[207] Sakellariou GK, McDonagh B, Porter H, Giakoumaki, II, Earl KE, Nye GA, et al. Comparison of Whole Body SOD1 Knockout with Muscle-Specific SOD1 Knockout Mice Reveals a Role for Nerve Redox Signaling in Regulation of Degenerative Pathways in Skeletal Muscle. Antioxid Redox Signal. 2018;28:275-95.
[208] Bush JA, Kitaura H, Ma Y, Teitelbaum SL, Ross FP, Smith JW. Comparative proteomic analysis of a cytosolic fraction from beta3 integrin-deficient cells. Cancer genomics & proteomics. 2012;9:1-13.
[209] Anand S, Foot N, Ang CS, Gembus KM, Keerthikumar S, Adda CG, et al. Arrestin-Domain Containing Protein 1 (Arrdc1) Regulates the Protein Cargo and Release of Extracellular Vesicles. Proteomics. 2018:e1800266.
[210] Yue Y, Garikipati VNS, Verma SK, Goukassian DA, Kishore R. Interleukin-10 Deficiency Impairs Reparative Properties of Bone Marrow-Derived Endothelial Progenitor Cell Exosomes. Tissue engineering Part A. 2017;23:1241-50.
[211] Yang JC, Lin MW, Rau CS, Jeng SF, Lu TH, Wu YC, et al. Altered exosomal protein expression in the serum of NF-kappaB knockout mice following skeletal muscle ischemia-reperfusion injury. J Biomed Sci. 2015;22:40.
[212] Di Lorenzo G, Velho RV, Winter D, Thelen M, Ahmadi S, Schweizer M, et al. Lysosomal Proteome and Secretome Analysis Identifies Missorted Enzymes and Their Nondegraded Substrates in Mucolipidosis III Mouse Cells. Mol Cell Proteomics. 2018;17:1612-26.
[213] Danyukova T, Ariunbat K, Thelen M, Brocke-Ahmadinejad N, Mole SE, Storch S. Loss of CLN7 results in depletion of soluble lysosomal proteins and impaired mTOR reactivation. Hum Mol Genet. 2018;27:1711-22.
[214] Schneider JL, Suh Y, Cuervo AM. Deficient chaperone-mediated autophagy in liver leads to metabolic dysregulation. Cell metabolism. 2014;20:417-32.
[215] Wooden JM, Finney GL, Rynes E, Maccoss MJ, Lambert AJ, Robledo RF, et al. Comparative proteomics reveals deficiency of SLC9A1 (sodium/hydrogen exchanger NHE1) in beta-adducin null red cells. British journal of haematology. 2011;154:492-501.

[216] Stella R, Cifani P, Peggion C, Hansson K, Lazzari C, Bendz M, et al. Relative quantification of membrane proteins in wild-type and prion protein (PrP)-knockout cerebellar granule neurons. J Proteome Res. 2012;11:523-36.
[217] Donowitz M, Singh S, Singh P, Salahuddin FF, Chen Y, Chakraborty M, et al. Alterations in the proteome of the NHERF1 knockout mouse jejunal brush border membrane vesicles. Physiol Genomics. 2010;42A:200-10.
[218] Donowitz M, Singh S, Singh P, Chakraborty M, Chen Y, Murtazina R, et al. Alterations in the proteome of the NHERF2 knockout mouse jejunal brush border membrane vesicles. Physiol Genomics. 2011;43:674-84.
[219] Koziol A, Gonzalo P, Mota A, Pollan A, Lorenzo C, Colome N, et al. The protease MT1-MMP drives a combinatorial proteolytic program in activated endothelial cells. FASEB J. 2012;26:4481-94.
[220] Pan Y, Kislinger T, Gramolini AO, Zvaritch E, Kranias EG, MacLennan DH, et al. Identification of biochemical adaptations in hyper- or hypocontractile hearts from phospholamban mutant mice by expression proteomics. Proc Natl Acad Sci U S A. 2004;101:2241-6.
[221] Huang PT, Chen CH, Hsu IU, Salim SA, Kao SH, Cheng CW, et al. Huntingtin-associated protein 1 interacts with breakpoint cluster region protein to regulate neuronal differentiation. PLoS ONE. 2015;10:e0116372.
[222] Wu L, Guo X, Hartson SD, Davis MA, He H, Medeiros DM, et al. Lack of beta, beta-carotene-9', 10'-oxygenase 2 leads to hepatic mitochondrial dysfunction and cellular oxidative stress in mice. Mol Nutr Food Res. 2017;61.
[223] Fountoulakis M, Soumaka E, Rapti K, Mavroidis M, Tsangaris G, Maris A, et al. Alterations in the heart mitochondrial proteome in a desmin null heart failure model. J Mol Cell Cardiol. 2005;38:461-74.
[224] O'Connell GC, Nichols C, Guo G, Croston TL, Thapa D, Hollander JM, et al. IL-15Ralpha deficiency in skeletal muscle alters respiratory function and the proteome of mitochondrial subpopulations independent of changes to the mitochondrial genome. Mitochondrion. 2015;25:87-97.
[225] Srivastava A, McGinniss J, Wong Y, Shinn AS, Lam TT, Lee PJ, et al. MKK3 deletion improves mitochondrial quality. Free Radic Biol Med. 2015;87:373-84.
[226] Puddick J, Martinus RD. Comparative proteomics of skeletal muscle mitochondria from myostatin-null mice. Cell biology international reports. 2011;18:e00013.
[227] Nowak G, Takacsova-Bakajsova D, Megyesi J. Deletion of protein kinase C-epsilon attenuates mitochondrial dysfunction and ameliorates ischemic renal injury. American journal of physiology Renal physiology. 2017;312:F109-F20.
[228] Du Y, Meng Y, Zhu J, Kang L, Jia X, Guo L, et al. Quantitative proteomic study of myocardial mitochondria in urea transporter B knockout mice. Proteomics. 2014;14:2072-83.
[229] Hinerfeld D, Traini MD, Weinberger RP, Cochran B, Doctrow SR, Harry J, et al. Endogenous mitochondrial oxidative stress: neurodegeneration, proteomic analysis, specific respiratory chain defects, and efficacious antioxidant therapy in superoxide dismutase 2 null mice. J Neurochem. 2004;88:657-67.
[230] Wang W, Palmfeldt J, Mohsen AW, Gregersen N, Vockley J. Fasting induces prominent proteomic changes in liver in very long chain Acyl-CoA dehydrogenase deficient mice. Biochemistry and biophysics reports. 2016;8:333-9.
[231] Kazak L, Chouchani ET, Stavrovskaya IG, Lu GZ, Jedrychowski MP, Egan DF, et al. UCP1 deficiency causes brown fat respiratory chain depletion and sensitizes mitochondria to calcium overload-induced dysfunction. Proc Natl Acad Sci U S A. 2017;114:7981-6.
[232] Masand R, Paulo E, Wu D, Wang Y, Swaney DL, Jimenez-Morales D, et al. Proteome Imbalance of Mitochondrial Electron Transport Chain in Brown Adipocytes Leads to Metabolic Benefits. Cell metabolism. 2018;27:616-29 e4.
[233] Kuhl I, Miranda M, Atanassov I, Kuznetsova I, Hinze Y, Mourier A, et al. Transcriptomic and proteomic landscape of mitochondrial dysfunction reveals secondary coenzyme Q deficiency in mammals. eLife. 2017;6.
[234] Fewou SN, Fernandes A, Stockdale K, Francone VP, Dupree JL, Rosenbluth J, et al. Myelin protein composition is altered in mice lacking either sulfated or both sulfated and non-sulfated galactolipids. J Neurochem. 2010;112:599-610.
[235] Werner HB, Kuhlmann K, Shen S, Uecker M, Schardt A, Dimova K, et al. Proteolipid protein is required for transport of sirtuin 2 into CNS myelin. J Neurosci. 2007;27:7717-30.

[236] Szerlong HJ, Herman JA, Krause CM, DeLuca JG, Skoultchi A, Winger QA, et al. Proteomic characterization of the nucleolar linker histone H1 interaction network. J Mol Biol. 2015;427:2056-71.
[237] Yang K, Adin C, Shen Q, Lee LJ, Yu L, Fadda P, et al. Aldehyde dehydrogenase 1 a1 regulates energy metabolism in adipocytes from different species. Xenotransplantation. 2017;24.
[238] Hermida N, Michel L, Esfahani H, Dubois-Deruy E, Hammond J, Bouzin C, et al. Cardiac myocyte beta3-adrenergic receptors prevent myocardial fibrosis by modulating oxidant stress-dependent paracrine signaling. European heart journal. 2018;39:888-98.
[239] Pappano WN, Steiglitz BM, Scott IC, Keene DR, Greenspan DS. Use of Bmp1/Tll1 doubly homozygous null mice and proteomics to identify and validate in vivo substrates of bone morphogenetic protein 1/tolloid-like metalloproteinases. Mol Cell Biol. 2003;23:4428-38.
[240] Kawahara R, Lima RN, Domingues RR, Pauletti BA, Meirelles GV, Assis M, et al. Deciphering the role of the ADAM17-dependent secretome in cell signaling. J Proteome Res. 2014;13:2080-93.
[241] Lassek M, Weingarten J, Wegner M, Neupartl M, Array TN, Harde E, et al. APP Deletion Accounts for Age-Dependent Changes in the Bioenergetic Metabolism and in Hyperphosphorylated CaMKII at Stimulated Hippocampal Presynaptic Active Zones. Frontiers in synaptic neuroscience. 2017;9:1.
[242] Cheadle L, Biederer T. The novel synaptogenic protein Farp1 links postsynaptic cytoskeletal dynamics and transsynaptic organization. The Journal of cell biology. 2012;199:985-1001.
[243] Lopes S, Teplytska L, Vaz-Silva J, Dioli C, Trindade R, Morais M, et al. Tau Deletion Prevents Stress-Induced Dendritic Atrophy in Prefrontal Cortex: Role of Synaptic Mitochondria. Cerebral cortex. 2017;27:2580-91.
[244] Lee PK, Goh WW, Sng JC. Network-based characterization of the synaptic proteome reveals that removal of epigenetic regulator Prmt8 restricts proteins associated with synaptic maturation. J Neurochem. 2017;140:613-28.
[245] Flynn JM, Czerwieniec GA, Choi SW, Day NU, Gibson BW, Hubbard A, et al. Proteogenomics of synaptosomal mitochondrial oxidative stress. Free Radic Biol Med. 2012;53:1048-60.
[246] Kennedy BC, Dimova JG, Dakoji S, Yuan LL, Gewirtz JC, Tran PV. Deletion of novel protein TMEM35 alters stress-related functions and impairs long-term memory in mice. Am J Physiol Regul Integr Comp Physiol. 2016;311:R166-78.
[247] van Rooden EJ, van Esbroeck ACM, Baggelaar MP, Deng H, Florea BI, Marques ARA, et al. Chemical Proteomic Analysis of Serine Hydrolase Activity in Niemann-Pick Type C Mouse Brain. Frontiers in neuroscience. 2018;12:440.
[248] Reglodi D, Jungling A, Longuespee R, Kriegsmann J, Casadonte R, Kriegsmann M, et al. Accelerated pre-senile systemic amyloidosis in PACAP knockout mice - a protective role of PACAP in age-related degenerative processes. The Journal of pathology. 2018;245:478-90.
[249] Sol EM, Wagner SA, Weinert BT, Kumar A, Kim HS, Deng CX, et al. Proteomic investigations of lysine acetylation identify diverse substrates of mitochondrial deacetylase sirt3. PLoS ONE. 2012;7:e50545.
[250] Zhang L, Liu S, Liu N, Zhang Y, Liu M, Li D, et al. Proteomic identification and functional characterization of MYH9, Hsc70, and DNAJA1 as novel substrates of HDAC6 deacetylase activity. Protein & cell. 2015;6:42-54.
[251] Fritz KS, Galligan JJ, Hirschey MD, Verdin E, Petersen DR. Mitochondrial acetylome analysis in a mouse model of alcohol-induced liver injury utilizing SIRT3 knockout mice. J Proteome Res. 2012;11:1633-43.
[252] Castegna A, Thongboonkerd V, Klein J, Lynn BC, Wang YL, Osaka H, et al. Proteomic analysis of brain proteins in the gracile axonal dystrophy (gad) mouse, a syndrome that emanates from dysfunctional ubiquitin carboxyl-terminal hydrolase L-1, reveals oxidation of key proteins. J Neurochem. 2004;88:1540-6.
[253] Yang HY, Kwon J, Choi HI, Park SH, Yang U, Park HR, et al. In-depth analysis of cysteine oxidation by the RBC proteome: advantage of peroxiredoxin II knockout mice. Proteomics. 2012;12:101-12.
[254] Banks AS, McAllister FE, Camporez JP, Zushin PJ, Jurczak MJ, Laznik-Bogoslavski D, et al. An ERK/Cdk5 axis controls the diabetogenic actions of PPARgamma. Nature. 2015;517:391-5.

[255] Tsuru M, Ono A, Umeyama H, Takeuchi M, Nagata K. Ubiquitin-dependent proteolysis of CXCL7 leads to posterior longitudinal ligament ossification. PLoS ONE. 2018;13:e0196204.
[256] Corradini E, Vallur R, Raaijmakers LM, Feil S, Feil R, Heck AJ, et al. Alterations in the cerebellar (Phospho)proteome of a cyclic guanosine monophosphate (cGMP)-dependent protein kinase knockout mouse. Mol Cell Proteomics. 2014;13:2004-16.
[257] Gramage E, Herradon G, Martin YB, Vicente-Rodriguez M, Rojo L, Gnekow H, et al. Differential phosphoproteome of the striatum from pleiotrophin knockout and midkine knockout mice treated with amphetamine: correlations with amphetamine-induced neurotoxicity. Toxicology. 2013;306:147-56.
[258] Lamming DW, Demirkan G, Boylan JM, Mihaylova MM, Peng T, Ferreira J, et al. Hepatic signaling by the mechanistic target of rapamycin complex 2 (mTORC2). FASEB J. 2014;28:300-15.
[259] Wu X, Tian L, Li J, Zhang Y, Han V, Li Y, et al. Investigation of receptor interacting protein (RIP3)-dependent protein phosphorylation by quantitative phosphoproteomics. Mol Cell Proteomics. 2012;11:1640-51.
[260] Henderson H, Macleod G, Hrabchak C, Varmuza S. New candidate targets of protein phosphatase-1c-gamma-2 in mouse testis revealed by a differential phosphoproteome analysis. International journal of andrology. 2011;34:339-51.
[261] Sadhukhan S, Liu X, Ryu D, Nelson OD, Stupinski JA, Li Z, et al. Metabolomics-assisted proteomics identifies succinylation and SIRT5 as important regulators of cardiac function. Proc Natl Acad Sci U S A. 2016;113:4320-5.
[262] Hershberger KA, Abraham DM, Liu J, Locasale JW, Grimsrud PA, Hirschey MD. Ablation of Sirtuin5 in the postnatal mouse heart results in protein succinylation and normal survival in response to chronic pressure overload. J Biol Chem. 2018;293:10630-45.
[263] Imamura K, Yoshitane H, Hattori K, Yamaguchi M, Yoshida K, Okubo T, et al. ASK family kinases mediate cellular stress and redox signaling to circadian clock. Proc Natl Acad Sci U S A. 2018;115:3646-51.
[264] Tholen S, Biniossek ML, Gansz M, Ahrens TD, Schlimpert M, Kizhakkedathu JN, et al. Double deficiency of cathepsins B and L results in massive secretome alterations and suggests a degradative cathepsin-MMP axis. Cell Mol Life Sci. 2014;71:899-916.
[265] Cardona M, Lopez JA, Serafin A, Rongvaux A, Inserte J, Garcia-Dorado D, et al. Executioner Caspase-3 and 7 Deficiency Reduces Myocyte Number in the Developing Mouse Heart. PLoS ONE. 2015;10:e0131411.
[266] Kernec F, Unlu M, Labeikovsky W, Minden JS, Koretsky AP. Changes in the mitochondrial proteome from mouse hearts deficient in creatine kinase. Physiol Genomics. 2001;6:117-28.
[267] Jackson HW, Waterhouse P, Sinha A, Kislinger T, Berman HK, Khokha R. Expansion of stem cells counteracts age-related mammary regression in compound Timp1/Timp3 null mice. Nature cell biology. 2015;17:217-27.
[268] La Favor JD, Fu Z, Venkatraman V, Bivalacqua TJ, Van Eyk JE, Burnett AL. Molecular Profile of Priapism Associated with Low Nitric Oxide Bioavailability. J Proteome Res. 2018;17:1031-40.
[269] Meinders M, Kulu DI, van de Werken HJ, Hoogenboezem M, Janssen H, Brouwer RW, et al. Sp1/Sp3 transcription factors regulate hallmarks of megakaryocyte maturation and platelet formation and function. Blood. 2015;125:1957-67.
[270] Delbes G, Yanagiya A, Sonenberg N, Robaire B. PABP interacting protein 2A (PAIP2A) regulates specific key proteins during spermiogenesis in the mouse. Biology of reproduction. 2012;86:95.
[271] Scharf M, Neef S, Freund R, Geers-Knorr C, Franz-Wachtel M, Brandis A, et al. Mitogen-activated protein kinase-activated protein kinases 2 and 3 regulate SERCA2a expression and fiber type composition to modulate skeletal muscle and cardiomyocyte function. Mol Cell Biol. 2013;33:2586-602.
[272] Hatakeyama J, Fukumoto S, Nakamura T, Haruyama N, Suzuki S, Hatakeyama Y, et al. Synergistic roles of amelogenin and ameloblastin. Journal of dental research. 2009;88:318-22.
[273] Yang H, Zhang W, Lu S, Lu G, Zhang H, Zhuang Y, et al. Mup-knockout mice generated through CRISPR/Cas9-mediated deletion for use in urinary protein analysis. Acta biochimica et biophysica Sinica. 2016;48:468-73.
[274] Swa HL, Blackstock WP, Lim LH, Gunaratne J. Quantitative proteomics profiling of murine mammary gland cells unravels impact of annexin-1 on DNA damage response, cell adhesion, and migration. Mol Cell Proteomics. 2012;11:381-93.

[275] Capuani B, Della-Morte D, Donadel G, Caratelli S, Bova L, Pastore D, et al. Liver protein profiles in insulin receptor-knockout mice reveal novel molecules involved in the diabetes pathophysiology. Am J Physiol Endocrinol Metab. 2015;308:E744-55.
[276] Lee YH, Boelsterli UA, Lin Q, Chung MC. Proteomics profiling of hepatic mitochondria in heterozygous Sod2+/- mice, an animal model of discreet mitochondrial oxidative stress. Proteomics. 2008;8:555-68.
[277] Eberini I, Agnello D, Miller I, Villa P, Fratelli M, Ghezzi P, et al. Proteins of rat serum: V. Adjuvant arthritis and its modulation by non steroidal antiinflammatory drugs. Electrophoresis. 2000;21:2170-9.
[278] Sironi L, Tremoli E, Miller I, Guerrini U, Calvio AM, Eberini I, et al. Acute-phase proteins before cerebral ischemia in stroke-prone rats: Identification by proteomics. Stroke. 2001;32:753-60.
[279] Veber D, Mutti E, Sironi L, Guerrini U, Gianazza E, Scalabrino G. Cobalamin deficiency-induced changes in magnetic resonance imaging of cerebrospinal fluid volume in the cervical tract in the rat. Neurosci Lett. 2008;440:202-5.
[280] Gelosa P, Pignieri A, Gianazza E, Criniti S, Guerrini U, Cappellini MD, et al. Altered iron homeostasis in an animal model of hypertensive nephropathy: stroke-prone rats. J Hypertens. 2013;31:2259-69.
[281] Wait R, Gianazza E, Eberini I, Sironi L, Dunn MJ, Gemeiner M, et al. Proteins of rat serum, urine and cerebrospinal fluid: VI. Further protein identifications and interstrain comparison. Electrophoresis. 2001;22:3043-52.
[282] Haynes P, Miller I, Aebersold R, Gemeiner M, Eberini I, Lovati MR, et al. Proteins of rat serum: I. Establishing a reference 2-DE map by immunodetection and microbore high performance liquid chromatography - electrospray mass spectrometry. Electrophoresis. 1998;19:1484-92.
[283] Miller I, Haynes P, Gemeiner M, Aebersold R, Manzoni C, Lovati MR, et al. Proteins of rat serum: II. Influence of some biological parameters on the 2-DE pattern. Electrophoresis. 1998;19:1493-500.
[284] Miller I, Haynes P, Eberini I, Gemeiner M, Aebersold R, Gianazza E. Proteins of rat serum: III. Gender-related differences in protein concentration under baseline conditions and upon experimental inflammation. Electrophoresis. 1999;20:836-45.
[285] Gianazza E, Eberini I, Villa P, Fratelli M, Pinna C, Wait R, et al. Monitoring the effects of drug treatment in rat models of disease by serum protein analysis. JChromatogr B. 2002;771:107-30.
[286] Gianazza E, Wait R, Eberini I, Sensi C, Sironi L, Miller I. Proteomics of rat biological fluids – The tenth anniversary update. J Proteomics. 2012;75:3113-28.
[287] Gianazza E, Vegeto E, Eberini I, Sensi C, Miller I. Neglected markers: Altered serum proteome in murine models of disease. Proteomics. 2012;12:691-707.
[288] Gianazza E, Miller I, Guerrini U, Palazzolo L, Parravicini C, Eberini I. Gender proteomics - I. Which proteins in non-sexual organs. Journal of Proteomics. 2018;178:7-17.
[289] Gianazza E, Miller I, Guerrini U, Palazzolo L, Parravicini C, Eberini I. Gender proteomics - II. Which proteins in sexual organs. Journal of Proteomics. 2018;178:18-30.
[290] Witthuhn BA, Bernlohr DA. Upregulation of bone morphogenetic protein GDF-3/Vgr-2 expression in adipose tissue of FABP4/aP2 null mice. Cytokine. 2001;14:129-35.
[291] Duan X, Yarmush DM, Jayaraman A, Yarmush ML. Dispensable role for interferon-gamma in the burn-induced acute phase response: a proteomic analysis. Proteomics. 2004;4:1830-9.
[292] Li L, Bebek G, Previs SF, Smith JD, Sadygov RG, McCullough AJ, et al. Proteome Dynamics Reveals Pro-Inflammatory Remodeling of Plasma Proteome in a Mouse Model of NAFLD. J Proteome Res. 2016;15:3388-404.
[293] Haque R, Umstead TM, Freeman WM, Floros J, Phelps DS. The impact of surfactant protein-A on ozone-induced changes in the mouse bronchoalveolar lavage proteome. Proteome science. 2009;7:12.
[294] Wang P, Bouwman FG, Mariman EC. Generally detected proteins in comparative proteomics--a matter of cellular stress response? Proteomics. 2009;9:2955-66.
[295] Berg K, Puntervoll P, Klungsoyr J, Goksoyr A. Brain proteome alterations of Atlantic cod (Gadus morhua) exposed to PCB 153. Aquatic toxicology. 2011;105:206-17.
[296] Rocher B, Bultelle F, Chan P, Foll FL, Letendre J, Monsinjon T, et al. 2-DE Mapping of the Blue Mussel Gill Proteome: The Usual Suspects Revisited. Proteomes. 2015;3:3-41.

[297] Tortelli TCJ, de Godoy LMF, de Souza GA, Bonatto D, Otake AH, de Freitas Saito R, et al. Accumulation of prohibitin is a common cellular response to different stressing stimuli and protects melanoma cells from ER stress and chemotherapy-induced cell death. Oncotarget. 2017;8:43114-29.

Highlights

- Gene inactivation may help understand the function of a protein in an organism.
- Proteomics on specimens from KO animals is an expedite way to obtain relevant data.
- So far, the outcome of inactivation was most often addressed in individual tissues.
- The outcome is organ-specific and influenced by the mode of gene inactivation.
- While often affected, stress proteins only feature a weak association with KO.

procedures for gene inactivation

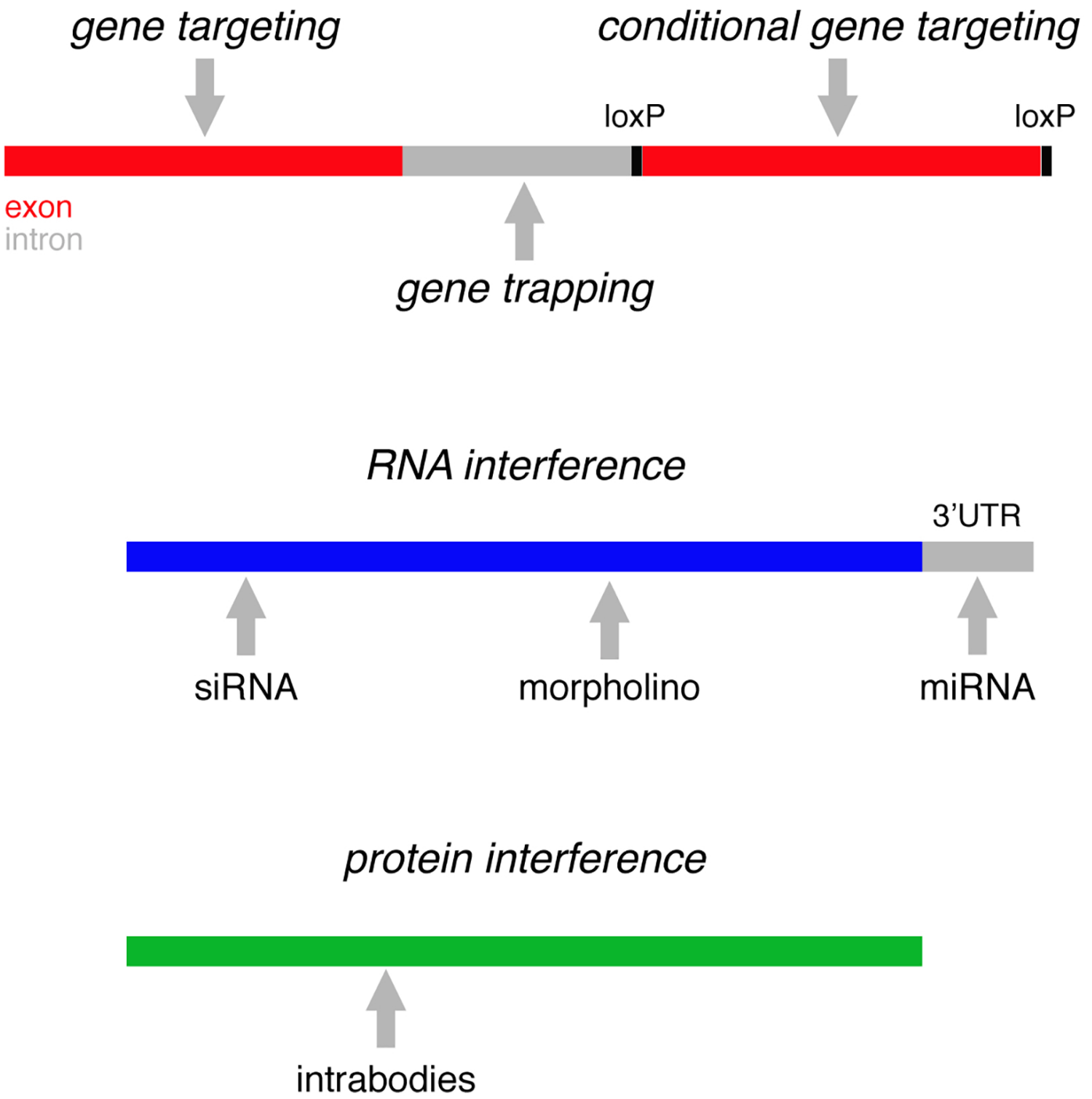

Figure 1

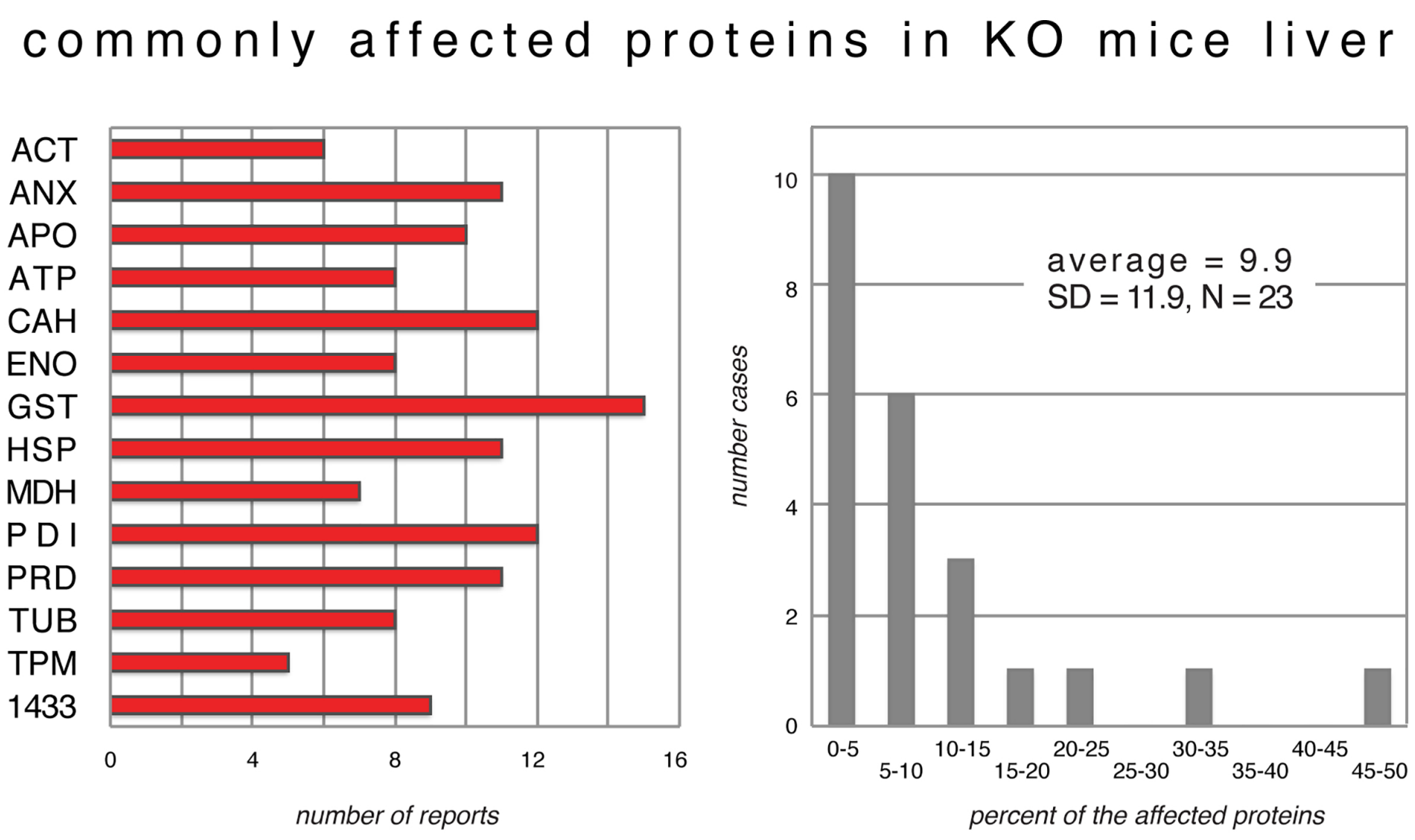
commonly affected proteins in KO mice liver
ACT
ANX
APO
ATP
CAH
ENO
GST
HSP
MDH
P D I
PRD
TUB
TPM
1433
0
4
8
12
16
number of reports
number cases
10
8
6
4
2
0
average = 9.9
SD = 11.9, N = 23
0-5
5-10
10-15
15-20
20-25
25-30
30-35
35-40
40-45
45-50
percent of the affected proteins

Figure 2

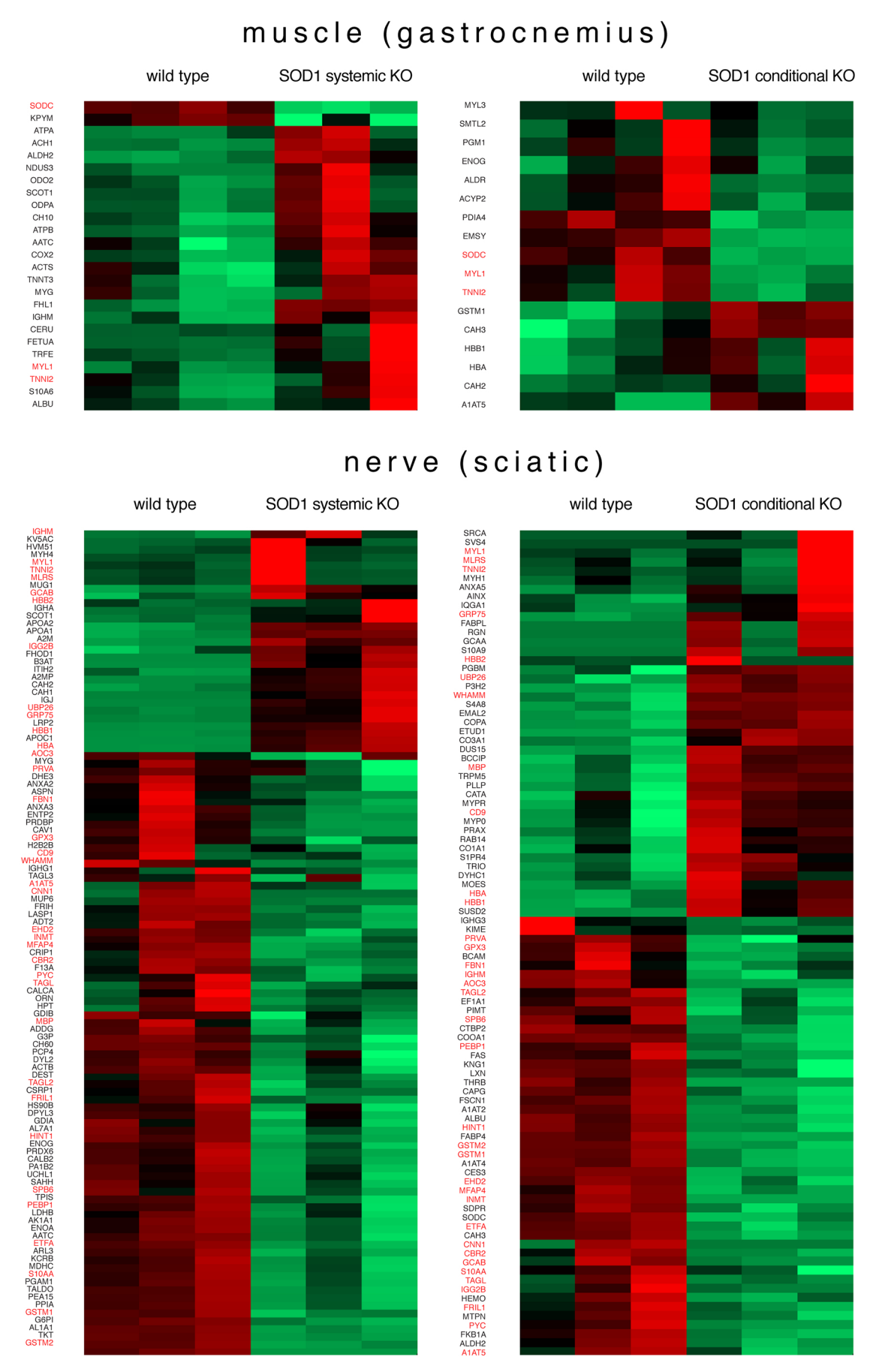
muscle (gastrocnemius)
wild type
SOD1 systemic KO
wild type
SOD1 conditional KO
SODC
KPYM
ATPA
ACH1
ALDH2
NDUS3
ODO2
SCOT1
ODPA
CH10
ATPB
AATC
COX2
ACTS
TNNT3
MYG
FHL1
IGHM
CERU
FETUA
TRFE
MYL1
TNNI2
S10A6
ALBU
MYL3
SMTL2
PGM1
ENOG
ALDR
ACYP2
PDIA4
EMSY
SODC
MYL1
TNNI2
GSTM1
CAH3
HBB1
HBA
CAH2
A1AT5
nerve (sciatic)
wild type
SOD1 systemic KO
wild type
SOD1 conditional KO
IGHM
KV5AC
HVM51
MYH4
MYL1
TNNI2
MLRS
MUG1
GCAB
HBB2
IGHA
SCOT1
APOA2
APOA1
A2M
IGG2B
FHOD1
BSAT
ITIH2
A2MP
CAH2
CAH1
IGJ
UBP26
GRP75
LRP2
HBB1
APOC1
HBA
AOC3
MYG
PRVA
DHE3
ANXA2
ASPN
FBN1
ANXA3
ENTP2
PRDBP
CAV1
GPX3
H2B2B
CD9
WHAMM
IGHG1
TAGL3
A1AT5
CNN1
MUP6
FRIH
LASP1
ADT2
EHD2
INMT
MFAP4
CRIP1
CBR2
F13A
PYC
TAGL
CALCA
ORN
HPT
GDIB
MBP
ADDG
G3P
CH60
PCP4
DYL2
ACTB
DEST
TAGL2
CSRP1
FRIL1
HS90B
DPYL3
GDIA
AL7A1
HINT1
ENOG
PRDX6
CALB2
PA1B2
UCHL1
SAHH
SPB6
TPIS
PEBP1
LDHB
AK1A1
ENOA
AATC
ETFA
ARL3
KCRB
MDHC
S10AA
PGAM1
TALDO
PEA15
PPIA
GSTM1
G6PI
AL1A1
TKT
GSTM2
SRCA
SVS4
MYL1
MLRS
TNNI2
MYH1
ANXA5
AINX
IQGA1
GRP75
FABPL
RGN
GCAA
S10A9
HBB2
PGBM
UBP26
P3H2
WHAMM
S4A8
EMAL2
COPA
ETUD1
CO3A1
DUS15
BCCIP
MBP
TRPM5
PLLP
CATA
MYPR
CD9
MYP0
PRAX
RAB14
CO1A1
S1PR4
TRIO
DYHC1
MOES
HBA
HBB1
SUSD2
IGHG3
KIME
PRVA
GPX3
BCAM
FBN1
IGHM
AOC3
TAGL2
EF1A1
PIMT
SPB6
CTBP2
COOA1
PEBP1
FAS
KNG1
LXN
THRB
CAPG
FSCN1
A1AT2
ALBU
HINT1
FABP4
GSTM2
GSTM1
A1AT4
CES3
EHD2
MFAP4
INMT
SDPR
SODC
ETFA
CAH3
CNN1
CBR2
GCAB
S10AA
TAGL
IGG2B
HEMO
FRIL1
MTPN
PYC
FKB1A
ALDH2
A1AT5

Figure 3