Universidade de Lisboa

Faculdade de Farmácia

PGC-1α: a target for neurodegenerative disorders

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Monografia orientada pela Professora Doutora Maria João Gama, Professora Auxiliar

Mestrado Integrado em Ciências Farmacêuticas

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Obrigada.

Recomeça…
Se puderes
Sem angústia
E sem pressa.
E os passos que deres,
Nesse caminho duro
Do futuro
Dá-os em liberdade.
Enquanto não alcances
Não descanses.

Miguel Torga

Resumo

Com o aumento da esperança média de vida, também o impacto social e económico associado a problemas de saúde tem vindo a crescer. As doenças neurodegenerativas tendem a manifestar-se com a idade, principalmente devido à sua longa fase assintomática, durante a qual a doença já está em progressão, portanto a sua incidência tem aumentado e continuará a aumentar em todo o mundo, acompanhando a tendência de envelhecimento e crescimento da população.

Entretanto, os tratamentos disponíveis para a maioria destas patologias apenas aliviam os sintomas já numa fase avançada, não existindo ainda disponíveis opções que alterem ou impeçam o seu curso natural. Ora, esta falta de alternativas farmacológicas é consequência da incerteza existente em relação aos mecanismos fisiopatológicos que originam estas doenças e à enorme variabilidade registada na população afetada. No entanto, vários estudos evidenciaram que a disfunção mitocondrial e o *stress* oxidativo desempenham um papel importante na patogénese de doenças como a doença de Alzheimer, doença de Parkinson e doença de Huntington, por exemplo. Tendo em conta a grande necessidade de aporte energético do tecido cerebral, tal não é inesperado.

O *peroxisome proliferator-activated receptor γ coactivator-1α* (PGC-1α) é visto como um importante co-regulador da função mitocondrial desde a sua descoberta, há mais de 20 anos, e a sua hipotética relação com as doenças neurodegenerativas e expectável potencial terapêutico têm sido considerados e avaliados desde o início. Na verdade, vários modelos animais sem PGC-1α têm, desde então, revelado a presença de anomalias comportamentais e neurodegeneração, o que parece provar esta ligação. Assim, regular seletivamente a ação do PGC-1α (para evitar efeitos prejudiciais e indesejados noutros tecidos onde este também é expresso) poderá ser uma forma interessante e específica de mitigar a disfunção mitocondrial e o *stress* oxidativo. Contudo, ter como alvo um co-regulador da transcrição constitui um desafio a vários níveis, mas também apresenta diversas possibilidades, especialmente considerando os avanços científicos e tecnológicos recentes e futuros. Deste modo, a hipótese de usar o PGC-1α como um alvo terapêutico altamente específico para o tratamento de doenças como as neurodegenerativas não pode ser excluída e aguarda novos desenvolvimentos.

Palavras-chave: PGC-1α; Doenças Neurodegenerativas; Stress Oxidativo; Disfunção Mitocondrial; Potencial Terapêutico

Abstract

With increased life expectancy comes a greater disease burden that accounts for a gigantic social and economic impact. Neurodegenerative disorders (NDDs) are among the diseases that tend to manifest with age, especially given their long asymptomatic phase during which the disease is already progressing and leading to neurologic alterations. So, their incidence has been rising and will continue to do so worldwide, accompanying the population growth and ageing tendency.

In the meantime, the available treatments for most of them focus on symptomatic relief, with no disease-modifying options available. This lack of pharmacological alternatives is a consequence of poor established knowledge regarding the pathophysiological mechanisms of these disorders. However, several studies have reported that mitochondrial dysfunction and oxidative stress play major roles in the pathogenesis of diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), for example. This comes as no surprise given the high energy demands of the brain.

Peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) has emerged as a master co-regulator of mitochondrial function since its discovery more than 20 years ago, so its putative connection to NDDs and hypothetical therapeutic potential was considered and assessed from the start. In fact, several animal models lacking PGC-1α have since then shown behavioural abnormalities and neurodegeneration, which might prove this connection. Thus, selectively targeting PGC-1α (in order to avoid deleterious and unwanted effects in other tissues where it is also expressed) could be an appealing and fine-tuned way of mitigating mitochondrial dysfunction and related oxidative stress.

However, targeting a transcriptional co-regulator comes with significant challenges but also with a vast number of opportunities, especially considering the recent scientific and technological breakthroughs. Thus, the prospect of using PGC-1α as a highly specific therapeutic target for the treatment of NDDs and other diseases cannot be ruled out and awaits further developments.

Keywords: PGC-1α; Neurodegenerative Disorders; Oxidative Stress; Mitochondrial Dysfunction; Therapeutic Potential

Abbreviations

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
ATP	adenosine triphosphate
Aβ	amyloid-β
BAT	brown adipose tissue
cAMP	cyclic adenosine monophosphate
CAT	catalase
CBP	CREB-binding protein
CNS	central nervous system
CREB	cAMP-response element binding protein
Cyt c	cytochrome c
DA	dopamine
DNA	deoxyribonucleic acid
ERRα	oestrogen related receptor α
FAD	familial AD
FoxO1	forkhead box O1
GCN5	general control non-repressed 5 protein
GPx	glutathione peroxidase
GR	glucocorticoid receptor
GSH	glutathione
HAT	histone acetyl transferase
HCF	host cell factor
HD	Huntington's disease
HIV	human immunodeficiency virus

HNF4α	hepatocyte nuclear factor 4α
Htt	huntingtin
MAPK	mitogen-activated protein kinase
MDA	malondialdehyde
MDVs	mitochondria-derived vesicles
MEF2C	myocyte enhancer factor 2C
Mfn2	mitofusin 2
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MQC	mitochondrial quality control
mRNA	messenger RNA
mtDNA	mitochondrial DNA
mtHtt	mutant huntingtin
NT-PGC-1α	N-terminal-PGC-1α
NDDs	neurodegenerative disorders
NRs	nuclear receptors
NRFs	nuclear respiratory factors
NRF-1	nuclear respiratory factor 1
NRF-2	nuclear respiratory factor 2
Nrf2	nuclear factor (erythroid-derived 2)-like 2
OXPHOS	oxidative phosphorylation
PARIS	parkin-interacting substrate
PD	Parkinson’s disease
PGC-1α	PPARγ coactivator-1α
PGC-1β	PPARγ coactivator-1β
POLG	polymerase γ
PolyQ	polyglutamine

PPARs	peroxisome proliferator-activated receptors
PPARα	peroxisome proliferator-activated receptor α
PPARγ	peroxisome proliferator-activated receptor γ
PPARδ	peroxisome proliferator-activated receptor δ
PRC	PGC-1-related coactivator
PS1	presenilin 1
PS2	presenilin 2
RNA	ribonucleic acid
ROS	reactive oxygen species
RRM	RNA recognition motif
SR	arginine/serine-rich
RT-PCR	reverse transcription polymerase chain reaction
SIRT1	sirtuin 1 (silence information regulator 2-like 1)
SN	*substantia nigra*
SNpc	*substantia nigra pars compacta*
SOD	superoxide dismutase
Tfam	mitochondrial transcription factor A
Trx2	thioredoxin-2
UCP-1	uncoupling protein 1
WAT	white adipose tissue
YY1	yin yang
α-Syn	α-synuclein

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1. Introduction

1.1. The current paradigm of neurodegenerative disorders and the potential role of PGC-1α

The prevalence of NDDs is increasing at an alarming rate throughout the world and that is particularly noticeable because the human lifespan has been extending throughout the years, following the advances in medicine and pharmacotherapy. Estimates predict that the number of people aged 60 and over will double by 2050 and more than triple by 2100, going from 962 million in 2017 (which already represented 13% of the global population) to 2.1 billion in 2050 and then 3.1 billion in 2100 (1). Alarmingly, between 2000 and 2018, there was a reduction in the death toll due to stroke, human immunodeficiency virus (HIV) and heart disease whilst casualties associated with AD rose up to 146,2% (2). As expected, along with the increasing number of people affected by NDDs, that eventually lead to a state of disability and dependence, the social and public health implications and associated economic burden are enormous.

NDDs lead to the deterioration and irreversible impairment of the structure and function of the nervous tissue. Therefore, it is of the utmost importance to try to decipher the mechanisms behind the most common conditions associated with neurodegeneration. On that note, plenty of scientific evidence has shown that oxidative stress, mitochondrial dysfunction, neuroinflammation, autophagy and neuroapoptosis play central roles in the pathogenesis of NDDs such as AD, PD and HD (3).

There are several obstacles to discovering the pathophysiological nature of such diseases, especially since factors such as the varying age at the time of testing, the prevalence of the genotype or varying approaches to statistical modelling may hinder the proper interpretation of data from cross-sectional studies, compromising reproducibility (4).

Besides that, the actual emergence of symptoms in NDDs represents a very late stage of neuronal loss that may have been under way for many years and this fact represents another setback to the discovery of the early signs and predisposing factors. At the same time, the very existence of highly penetrant single-gene mutations associated with NDDs is a core conundrum (4).

Understanding the underpinnings of the lengthy process that leads to degeneration, on a molecular and systemic level, will be essential to developing preventative strategies and the discovery of biomarkers of such phenomenon would be a scientific breakthrough. Crucially,

this early phase probably entails different biomarkers from those that mark the late, symptomatic stage of neurodegeneration, which tells us that the therapeutic intervention and its success would most definitely vary according to the stage of the condition (4).

For the last twenty years, different potential therapeutic targets have been under analysis, and several nuclear receptors and transcriptional co-regulators have caught the eye of investigators. For instance, the peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1 (PGC-1) family of transcriptional coactivators has emerged as central metabolic regulators. Early gain- and loss-of-function studies supported the conclusion that the members of the aforementioned family take part in the control of mitochondrial biogenesis by regulating overlapping gene expression programs (5).

One particular member of that family, PGC-1α, which is the focus of the present dissertation, is involved in a bewildering array of biological responses, ranging from regulation of mitochondrial biogenesis and respiration, adaptive thermogenesis, gluconeogenesis, among others (6). Of course, this broad spectrum of physiological actions also hints at a problem: activation or inhibition must be tissue-specific to be beneficial for the particular purpose we are focusing on (7).

A common theme driving scientific investigation is PGC-1α's ability to promote patterns of gene expression that favour oxidative metabolism. For example, its capacity to stimulate mitochondrial biogenesis and respiration in skeletal muscle represents an important choice to resort to oxidative over glycolytic metabolism (7).

In view of the role of PGC-1α in several metabolic processes, it is appropriate to question whether and how its activity might be modulated with a therapeutic intent, especially when it comes to NDDs (7), as it will be discussed in this dissertation, given its role in mitochondrial dysfunction and oxidative stress, which are believed to be a part of the assortment of mechanisms behind neurodegeneration.

2. Objectives

The main purpose of this dissertation is to ponder on the possibility of viewing and actually using PGC-1α as a therapeutic target in NDDs while considering the state of the art regarding the most common of these diseases, associated pathophysiological mechanisms and PGC-1α's role as a transcriptional coactivator involved in different cellular signalling and metabolic pathways.

3. Methodology

The research that supports this dissertation was carried out in PubMed and Google Scholar databases on multiple dates mainly between last October and June of the present year.

In order to find relevant information, the following scientific descriptors were used: *PGC-1α, Neurodegenerative Diseases/Disorders, Oxidative Stress, Mitochondrial Dysfunction, Alzheimer's Disease, Parkinson's Disease* and *Huntington's Disease*. After being researched individually, the descriptors were paired and crossed, using the Boolean connector "AND". The search terms used were as follows: *PGC-1α and Neurodegenerative Disorders and Oxidative Stress*, for example.

Whenever possible, the following search limitations were used while conducting research on the listed databases: chronological filter of publication date, full text (free full text), peer review (preferably) and language (English). Despite this, the bibliographic references presented in this dissertation correspond to the original articles from which the information was initially mentioned.

4. PGC-1α as a transcriptional coactivator

4.1. The PGC-1 family

Following the discovery and cloning of its first member in the late 1990s and especially in recent years, the PGC-1 family of transcriptional coactivators, which comprises PGC-1α, PPARγ coactivator-1β (PGC-1β) and PGC-1-related coactivator (PRC), has drawn attention as pivotal regulators of metabolism, since together they regulate a wide array of metabolic functions. In order to do so, the three members of this family interact with several transcription factors and nuclear receptors to exert their biological functions. Meanwhile, it has been established that all three members have the connection to mitochondrial metabolism in common (5,8).

For context, the term coactivator refers to a protein or protein complex that increases the rate of transcription by interacting with transcription factors, but that does not bind to DNA itself in a sequence-specific manner (7).

The knowledge about the different functions of these coactivators has been acquired through gain- and loss-of-function models that demonstrated the variety of processes managed in a tissue- and cue-specific manner, such as angiogenesis, muscle fiber-specification, phospholipid synthesis, protection against oxidative stress, mitochondrial biogenesis, and even some control over immune responses (5).

The most prominent and investigated member of the PGC-1 family is PGC-1α (encoded by the *PPARGC1A* gene) (8). PGC-1α is a positive regulator of mitochondrial biogenesis and respiration, adaptive thermogenesis, gluconeogenesis, as well as many other metabolic processes, as will be discussed ahead (6). Importantly, its expression is highly inducible by physiological cues such as exercise, cold and fasting (6,8).

The other two members of the family, PGC-1β and PRC, were identified due to their similarity in sequence identity and modes of action in comparison to PGC-1α (8). However, the three coactivators display significant dissimilarities concerning the physiological setting in which each of them acts (5). As opposed to PGC-1α, even though PGC-1β shows a similar tissue-specific expression pattern, it is not stimulated by most of the physiological cues that regulate PGC-1α's expression, so it is expected to participate in the maintenance of basal mitochondrial function, while PGC-1α can increase mitochondrial mass and is involved in the adaptation of different tissues to situations of high energetic requirements (5). Functionally, PGC-1β is also

a powerful inducer of mitochondrial biogenesis and respiration and it is also involved in the expression of the lipogenic programme in the liver (9) and of type IIX fibres in muscle (10), for example. For its part, PRC remains the least well-understood member of the family and its function seems to be connected to the regulation of mitochondrial biogenesis in proliferating cells (5,11), to inflammatory programs (12) and to the regulation of the expression of components of the respiratory chain (8,13). Consequently, silencing PRC in proliferating cells prompts abnormal mitochondrial biogenesis and prevents the progression of the cell cycle (13). Also contrary to PGC-1α, high levels of PRC are not found in tissues with high energy requirements and even though it is indeed able to coactivate nuclear respiratory factor-1 (NRF-1), it is not closely linked to mitochondrial biogenesis in adipose tissue (11), and its expression is lower in the brain (14).

A pivotal feature of the PGC-1 coactivators is therefore their high versatility and capacity to interact with multiple distinct transcription factors (Figure 1), which explains their diverse functions and interactions with several biological programs in different tissues (Figure 4).

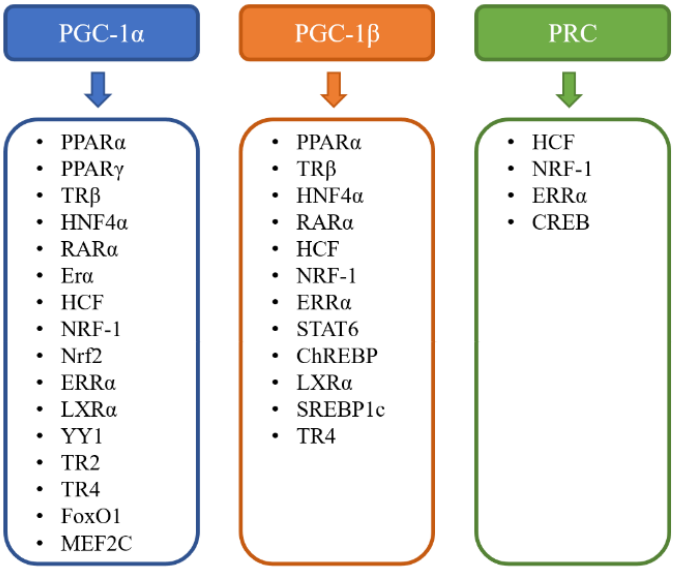

Figure 1. Transcriptional factors and nuclear receptors that interact with the different PGC-1 family members. Adapted from (5). TRβ = selective thyroid hormone receptor β; RARα = retinoic acid receptor α; Erα = oestrogen receptor α; LXRα = liver X receptor α; TR2 = testicular nuclear receptor 2; TR4 = testicular nuclear receptor 4; STAT6 = signal transducer and activator of transcription 6; ChREBP = carbohydrate response element binding protein; SREBP1c = sterol regulatory element-binding transcription factor 1c.

Seeing that ROS are generated during mitochondrial respiration, PGC-1α has emerged as a key player in the control of their removal by ruling the expression of numerous ROS-detoxifying

enzymes. Thus, PGC-1α seemingly both enhances mitochondrial functions and lessens the build-up of its by-products, guaranteeing an overall positive effect on oxidative metabolism (8), as will be addressed later on, making it a master co-regulator of mitochondrial function (15).

As it has been pointed out, PGC-1α responds to several forms of environmental stress, such as temperature and nutritional status and it also regulates mitochondrial biogenesis in response to diverse environmental *stimuli* (6). It acts by forming heteromeric complexes with an array of transcription factors, including NRF-1, nuclear factor (erythroid-derived 2)-like 2 (Nrf2), peroxisome proliferator-activated receptors (PPARs) α, δ, γ, and oestrogen related receptor α (ERRα) (Figure 1) (15–17). In turn, these complexes are able to induce gene activation by displacing repressor proteins (14).

As it turns out, the aforementioned transcription factors are able to influence the expression of many nuclear-encoded mitochondrial genes, such as cytochrome c (cyt c), complexes I-V and the mitochondrial transcription factor A (*TFAM*) (15,18). Activation of these mitochondrial genes results in an increase of enzymatic capacity for activities like fatty-acid β-oxidation, Krebs cycle, and oxidative phosphorylation (OXPHOS). Moreover, PGC-1α can stimulate the expression of genes involved in heme biosynthesis, ion transport, mitochondrial protein translation, and protein import (15).

In order to explore and understand the role of this coactivator in metabolism and thermoregulation, investigators created PGC-1α knockout mice (19), anticipating that they were going to exhibit a tendency to be obese. However, the mice turned out lean and such fact could perhaps be due to the pronounced hyperactivity that they showed. In-depth examination of PGC-1α knockout mice disclosed neurological abnormalities, notably myoclonus, dystonia, excessive startle responses, and clasping (which is a standard discovery in all polyglutamine (polyQ)-related diseases and HD mouse models) and signs of degeneration in several areas of the brain. Indeed, accompanying these abnormalities were massive gliosis and substantial neuronal loss (19,20). Noteworthy, real-time reverse transcription polymerase chain reaction (RT-PCR) analysis of hyperactive PGC-1α knockout mice revealed that the expression of mitochondrial genes was considerably reduced (19,20).

PGC-1α is commonly expressed in tissues with a high energy demand, including brown adipose tissue (BAT), skeletal muscle, and the brain (6). In the brain, impairment of the activity of PGC-1α is particularly important as it triggers the degeneration of neurons through mitochondrial dysfunction (21). Also according to clinical research, it may be a key player in multiple NDDs

since its levels appear to be lower in AD patients in comparison to those in normal individuals (22–24).

4.2. Structural characteristics of PGC-1α, PGC-1β and PRC

PGC-1α was first identified as a protein with 798 amino acids that interacts with the nuclear receptor PPARγ (7,25). Further structure-function analysis of this transcription coactivator revealed that the N-terminal 200 amino acids contain a potent transcription activation domain that is rich in acidic amino acids and that within this region there is an LXXLL sequence (amino acids 142-146) (Figure 2) (7).

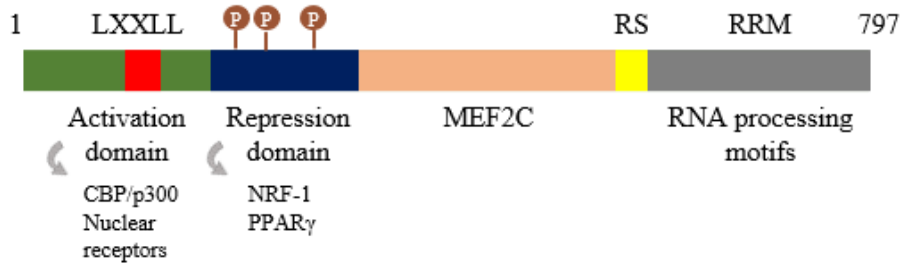

Figure 2. Representation of the structural organization of the PCG-1α protein. Adapted from (7).

Accordingly, it has been established that this LXXLL is vital for the ligand-dependent interaction with nuclear-receptors such as ER (26), PPARα (27), RXRα (28), glucocorticoid receptor (GR; (29)), and possibly other members of the nuclear hormone receptors superfamily. Furthermore, PGC-1α uses distinct non-LXXLL domains to interact with additional transcription factors: a domain rich in proline residues roughly between amino acids 180 and 403 is responsible for the interaction with PPARγ and NRF-1 (30) and a section between amino acids 403 and 570 that interacts with myocyte enhancer factor 2C (MEF2C) (7,31).

In terms of amino acid sequence homology, PGC-1β possesses a large degree of sequence identity and homology to PGC-1α, whereas PRC shares only some structural features (11). The three members of the PGC-1 family present a higher degree of homology within the amino- and carboxyl-terminal ends of the proteins, where several conserved domains have been described. It is in this amino-terminal region that all PGC-1 coactivators contain a highly conserved activation domain that serves as a surface for the recruitment of histone acyltransferase (HAT)

proteins, such as SRC-1 and CREB binding protein (CBP)/p300 (32), and that contains multiple leucine-rich LXXLL motifs, also known as nuclear receptors (NR) boxes, which are essential mediators of the interaction between PGC-1s and the hydrophobic pocket of the ligand-binding domain of different hormone NR. PGC-1α has three functional LXXLL motifs that are used for this purpose (7).

In fact, the carboxyl-terminal half shows the greatest similarity (45-46%) between the three PGC-1 coactivators (5). This C-terminal end contains a well-conserved RNA recognition motif (RRM), located between amino acids 677 and 709 in PGC-1α (25), which has been found to take part in both RNA and single-stranded DNA binding (33). In addition to this, short serine/arginine-rich regions, called RS domains, are found N-terminal to the RRM motif in PGC-1α (between amino acids 565 and 631 (25)) and PRC, but not in PGC-1β. Interestingly, given that RS and RRM motifs are commonly found in proteins engaged in RNA splicing, it makes sense to think that their presence indicates that PGC-1 coactivators may present the capacity to process RNA. Indeed, it has been shown that PGC-1α is found in a complex along with the phosphorylated form of RNA polymerase II and other factors engaged in elongation. So, this PGC-1α's C-terminal domain oversees the maintenance of these interactions (33). Accordingly, although it has been demonstrated *in vitro* that the carboxyl-terminal region of PGC-1α takes part in mRNA processing to regulate gene expression, its *in vivo* participation in the expression of target genes needs further elucidation. Mutations in these domains (RS and RRM) undermine PGC-1α's capacity to link up with RNA-processing factors, thereby hindering its ability to prompt downstream gene expression (14,33).

The carboxyl-terminal fraction also comprises two motifs whose function is unknown, but that are very well conserved among the three members of this family. One of them, consisting of a DHDY tetrapeptide, has been identified as a binding site for host cell factor (HCF), a protein that acts as a coactivator to regulate gene expression during the cell cycle progression and that acts by enhancing PGC-1 transcriptional activity (34). In addition, the carboxy-terminal halves of PGC-1 proteins have also been found to contain interaction sites for other transcription factors, such as MEF2C, yin-yang-1 (YY1) or forkhead box O1 (FoxO1) (5,25,31,35,36).

In conclusion, an uncommon characteristic of the PGC-1 family is the presence of transcriptional activation domains and RNA processing motifs in the same molecule (7) and the fact that different members of the PGC-1 family possess analogous modular structures may explain why they seem to share functions to some extent.

However, the fact that PGC-1α and β comprise different binding sites for diverse transcription factors increases the possibility of experimentally making alleles that can perform merely a portion of the functions that the full-length proteins can prompt (17).

Since the discovery of PGC-1α, multiple isoforms have been described, arising from alternative promoter usage and/or alternative mRNA splicing (37), namely PGC-1α-b, and c (38), NT-PGC-1α-a, b and c (39,40), and PGC-1α2, 3 and 4 (Figure 3) (37,41).

NT-PGC-1α isoforms a, b and c appear to preserve the full capacity to boost mitochondrial biogenesis and expression of thermogenic genes in brown adipocytes despite lacking the RNA processing motifs (39,42), which shows that RRM and RS motifs are not a requirement for correct expression of PGC-1α target genes in BAT, or at least for the genes connected to mitochondrial function. Furthermore, another functional truncated PGC-1α isoform, PGC-1α4, presents virtually the same sequence as NT-PGC-1α-a, except for a stretch of 12 amino acids in the amino-terminus (Figure 3) (41). This protein is expressed in most tissues and arises from an alternative promoter located 13 kb upstream of the first exon of the *PPARGC1A* gene. But even though it is so similar to NT-PGC-1α-a, PGC-1α4 appears to regulate a distinct group of genes (5).

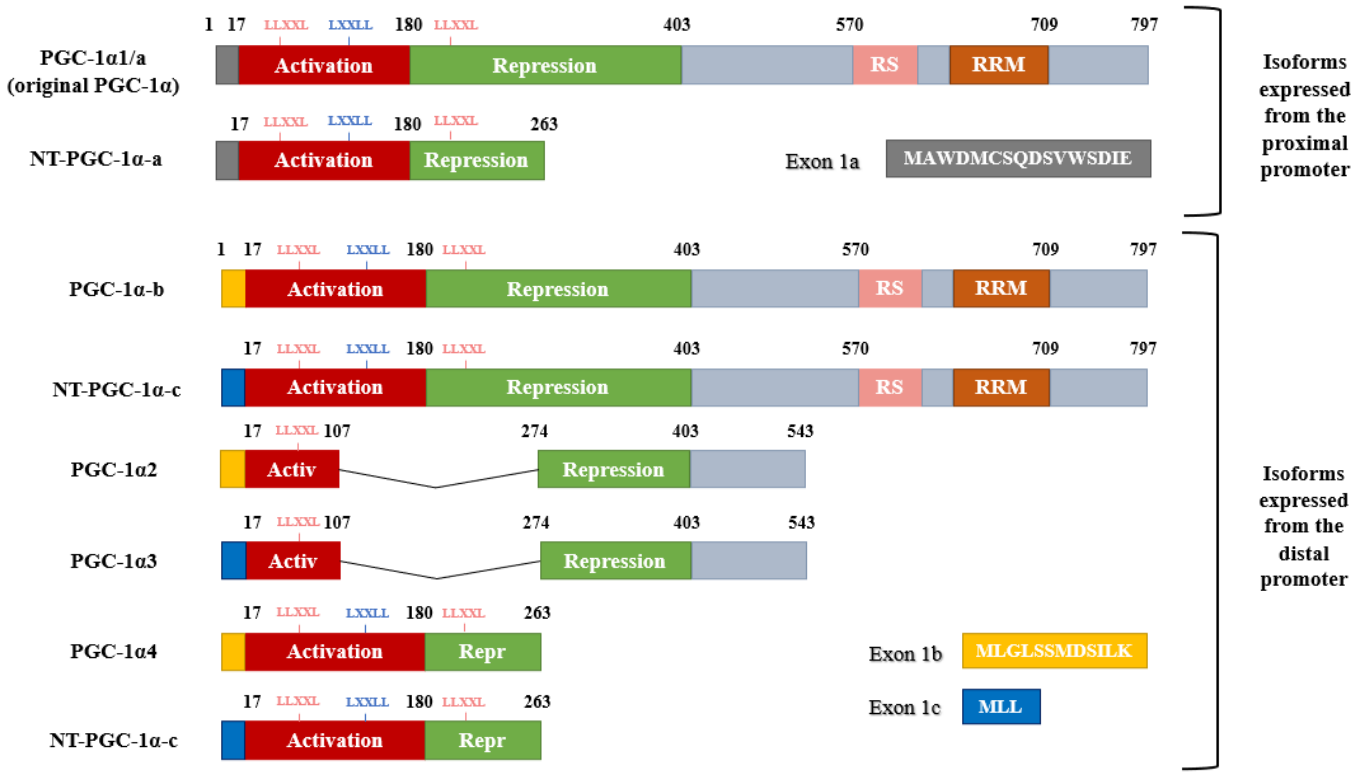

Figure 3. Representation of several identified PGC-1α isoforms. Adapted from (37).

Despite their dissimilarities, the majority of PGC-1α's isoforms are related to oxidative metabolism. However, PGC-1α4 is known for its ability to modulate muscle hypertrophy, while PGC-1α2 and α3 functions are yet to be described (37). Thus, the mere existence of isoforms can represent a supplementary level of regulation and specification of these transcription coactivators' activity.

Interestingly enough, the majority of coactivators amplify transcriptional activity through specific enzymatic functions necessary to remodel chromatin and initiate transcription (43), but PGC-1α not only does not comprise any identifiable HAT domain, as it does not have this intrinsic enzymatic activity that is found in other coactivators. Nevertheless, by being capable of recruiting proteins that embody HAT activity (such as CBP, p300, and SRC-1) to its N-terminal regions (32), it is implied that when not connected to a transcription factor, PGC-1α seems to be in an inactive state and that it then becomes active when bound to the transcription factor and induces the needed conformational changes that lead to the recruitment of such proteins into the complex (7). In turn, these proteins acetylate histones and alter chromatin structure to allow access to additional factors for gene activation. The PGC-1α transcriptional activator complex is then capable of dislodging repressor proteins on its target promoters, leading to increased gene transcription (17). In conclusion, the PGC-1 coactivators have powerful transcriptional activity when linked to heterologous DNA binding domains (25,29,34), or when docking on a transcriptional factor (7,17).

Contrary to the examples mentioned so far, the nature of the interactions between PGC-1α and hormone receptors can also be ligand-independent as is with PPARγ (25). In this case, PGC-1α seems to interact with the central axis region of the receptor. On the other hand, when there is a ligand regulating such interaction, PGC-1α engages with the C-terminal activation function 2 (AF-2) region of the receptor (7).

It is interesting to notice that PGC-1α co-activates synergistically both PPARγ and the thyroid receptor in the uncoupling protein 1 (UCP-1) enhancer, after stimulation of cells with cyclic adenosine monophosphate (cAMP), which is a known powerful inducer of UPC-1 gene expression. This could mean that any coactivator could be able to induce each of the target genes of certain nuclear receptors without the need for any promoter specificity. However, that is not the case since PCG-1α does not activate all promoters of endogenous genes with functional PPARγ binding sites, which shows that there is noticeable promoter specificity even when this coactivator interacts with the same nuclear receptor (7). So, transcriptional

coactivators not only enhance transcription but also take part in specifying which gene is targeted by a transcription factor (7).

A broad set of data has indicated that pre-mRNA splicing is linked to transcription *in vivo* (44). Thus, given the fact that PGC-1α encompasses domains associated with splicing and other domains that bind to transcriptional factors and other coactivators, it makes PGC-1α a great key player to explore the integration of these two processes (7).

So how does PGC-1α activate a particular target gene? Three plausible models could describe the way PGC-1α influences the activation of certain target genes. In some instances, PGC-1α could behave as a traditional transcriptional coactivator, binding to transcription factors and enhancing the rate of transcription initiation. In a second model, PGC-1α could influence several genes by affecting other RNA processing functions, such as elongation, mRNA capping, alternative mRNA splicing, or even mRNA stability. Finally, a third model would essentially be a combination of the first two. This would mean that PGC-1α would be an active participant in several circumstances of gene expression, in which case it would initially be at the promoter region by means of transcription factor attachment and recruitment of HAT complexes. Then, after the beginning of transcriptional initiation, PGC-1α would participate in the elongation step by interacting with elongation factors and the phosphorylated form of RNA polymerase II. This would presumptively impact the rate of RNA elongation and/or splicing (7).

4.3. The impact of post-translational modifications on PGC-1α's specificity

PGC-1α's activity is also modulated at a post-translational level in a way that either positively or negatively influences its ability to recruit chromatin-remodelling complexes and, therefore, its capacity to activate gene transcription. In fact, these post-translational modifications not only modulate this coactivator's activity but also its stability and cellular localization.

So, this is another mechanism that tweaks PGC-1α's activity, directing it towards certain transcriptional factors or other co-regulators, depending on a variety of factors, such as tissue nature, *stimuli*, among others (5,37).

According to different studies, summarized in Table 1, it is known that PGC-1α suffers post-translational modifications, such as phosphorylation by p38 mitogen-activated protein kinases (MAPK) (45) and AMP-activated protein kinase (AMPK) (46), which translates into improved transcriptional activity in skeletal muscle, for instance. Acetylation via acetyltransferase

general control non-repressed 5 protein (GCN5) and the deacetylase sirtuin 1 (SIRT1) represents another pathway that connects PGC-1α activity to cellular energy status (47). Methylation (48) and O-linked N-acetylglucosamination have also been described (49).

First and foremost, PGC-1α is a protein with a naturally short half-life (~2,3hr) due to its rapid degradation via the ubiquitin proteasome system (45,50). So, since its stabilization and degradation are critical for its activity (51), this is an example of where post-translational modifications can have an additional benefit for therapeutic purposes, if necessary.

The fact that PGC-1α can be found in mitochondria, where it forms nucleoid-associated complexes with SIRT1 and Tfam (52), may explain how it is able to interfere with the transcription of both nuclear and mitochondrial genes to exert its function in mitochondrial biogenesis regulation. Hence, the fact that PGC-1α can be found at a subcellular level represents another degree of regulation that can be the target for post-translational modifications that modify its transcriptional activity. For example, in contrast with the PGC-1α-full-length isoform, which is located primarily in the nuclei, it has been shown that the short NT-PGC-1α isoform is preponderantly found in the cytoplasm and translocated to the nuclei after phosphorylation by protein kinase A (53). In spite of that, additional studies are necessary to gauge if this fact has any real biological significance when it comes to its activity (5).

Since modification of the PGC-1α protein could result in a preference to bind to particular transcription factors or to recruit certain binding partners that eventually lead to more selective gene transcription (6), proteins that perform such post-translational modifications are alluring drug targets for the development of activators and inhibitors. Therefore, these enzymes upstream of PGC-1α might be pharmacologically manipulated in a way that would allow for an accurate modulation of PGC-1α in a tissue- and target-gene-precise approach. This is important because the therapeutic beneficial window might vary between tissues and physiological environment (6,54).

The main takeaway of this point is that associations of post-translational modifications of co-regulators greatly enhance the extent of specification of these proteins and that the activity of PGC-1 coactivators is therefore regulated at various levels (6).

Table 1. Post-translational modifications of PGC-1α and their biological consequences

Post-translational modifications	Biological outcome	References
Phosphorylation		
AKT	Inhibition of activity affecting the expression of gluconeogenic and lipid oxidation genes	(55)
AMPK	Increase in activity and regulation of genes involved in mitochondrial functions and glucose metabolism	(56)
CLK2	Decrease in expression of gluconeogenesis genes	(57)
GSK3β	In combination with phosphorylation of p38 MAPK, GSK3β designates PGC-1α for proteasome degradation	(58)
p38 MAPK	Increase in activity leading to the expression of mitochondrial genes	(45)
S6 kinase	Decrease in the induction of gluconeogenic genes while maintaining the expression of mitochondrial genes	(59)
Acetylation		
GCN5	Inhibition of transcriptional activity	(47)
Deacetylation		
SIRT1	Increase in expression of gluconeogenic genes	(60)
SUMOylation		
SUMO1	Decrease in transcriptional activity	(61)
Methylation		
PRMT1	Increase in activity leading to expression of mitochondrial biogenesis genes	(48)

Adapted from (8). AKT = protein kinase B; CLK2 = cdc2-like kinase 2; GSK3β = glycogen synthase kinase 3β; SUMO1 = small ubiquitin like modifier 1; PRMT1 = protein arginine methyltransferase 1.

4.4. Functions in different tissues and associated therapeutic potential

PGC-1α is highly expressed in tissues with high energy demands and mitochondrial content, such as heart, skeletal muscle, kidney, and BAT, and carries out different tasks in several cell types through the interaction with distinct transcription factors in a cell-specific manner (6). For instance, it interacts with MEF2C in skeletal muscle, while engaging with HNF4α and FoxO1 in the liver. This transcriptional coactivator has therefore been found to be a crucial broker of cellular accommodation to an assortment of *stimuli* in various tissues, such as BAT (25), liver (62), brain (19), heart (63), and skeletal muscle (37).

PGC-1α activation is not only important at a cellular level in a tissue-specific manner but also has distal effects in other tissues, contributing to an integrated systemic reaction (37), especially because several signalling pathways are involved in its regulation. But this fact might result in unwanted implications in other organs. For instance, observations from muscle-specific loss-of-function mouse lines indicate that PGC-1α ties muscle function to systemic inflammation and, eventually, the risk of developing numerous chronic diseases (54,64).

Ultimately, PGC-1α's expression and activity are narrowly controlled and related to diverse functions in different organs and tissues (Figure 4).

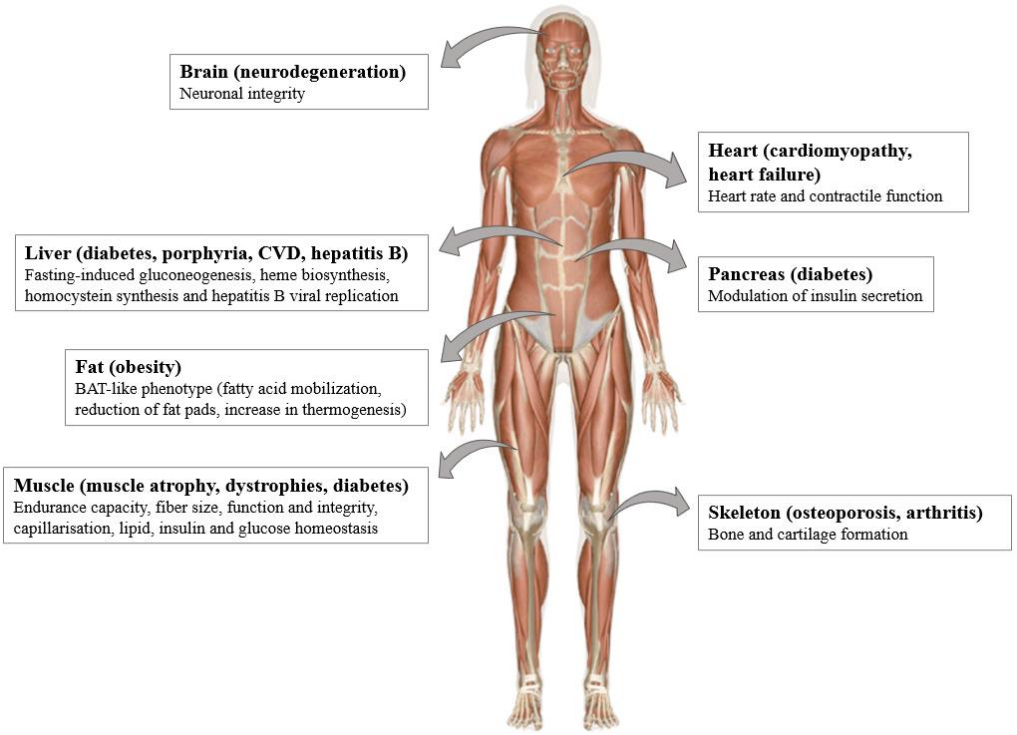

Figure 4. Functions associated with PGC-1α in different tissues. Adapted from (54) using Servier Medical Art, licensed under a Creative Common Attribution 3.0 Generic License. http://smart.servier.com/)

4.4.1. Skeletal muscle

Since their discovery, PGC-1 coactivators have been recognized as therapeutic targets in several cases involving muscle atrophy (41,65). In fact, muscle atrophy triggered by lack of use has been connected with lower skeletal muscle PGC-1α mRNA levels in humans (66). Interestingly, PGC-1α expression seems to be faulty in elderly murine and human (67) skeletal muscle, which implies a plausible part in age-related muscle decay (37).

In fact, PGC-1α's capacity to hinder muscle withering is ubiquitous in multiple pathophysiological (14,19) contexts (37). Skeletal muscle-specific PGC-1α transgenic mice are less subject to muscle atrophy caused by loss of nerve and disuse, and along with maintaining their skeletal muscle mass, they also sustain their mitochondrial function better than wild type controls (68).

On the contrary, mice devoid of PGC-1α display a decline in muscle strength and tend to be weary (69), which might be a repercussion of lower expression of genes engaged in mitochondrial functions (14,19). Additional loss-of-function studies proved that *Pgc1a*$^{-/-}$ mice show fewer mitochondria and reduced respiratory capacity in slow-twitch skeletal muscle (69,70).

In view of this, different PGC-1 proteins activate certain gene programs to regulate skeletal muscle mass, fiber-type determination, and neuromuscular junction (NMJ) properties, all of which refine the function and performance of skeletal muscle (37).

4.4.2. Liver

In the liver, the expression of PGC-1α and PGC-1β is modulated by divergent nutritional signals, with fasting boosting PGC-1α expression while lipid intake increments PGC-1β mRNA levels. Thus, despite the fact that both PGC-1α and PGC-1β are able to modulate mitochondrial gene expression in the liver (19,69), it is precisely in this tissue that their dissimilar functions are highlighted since they regulate opposing pathways (5).

PGC-1α triggers the transcription of gluconeogenic genes in the liver, namely phosphoenolpyruvate, carboxykinase or glucose 6-phosphatase (5,36,62). The inherent activity of PGC-1α at a transcriptional level is additionally positively regulated after deacetylation by SIRT1, whose hepatic expression is higher during fasting (5,60). It is interesting to note that even though this post-translational modification instigates the expression of gluconeogenic

genes, it does not affect mitochondrial ones, which could mean that this process represents a specification of PGC-1α's activity (5,60).

Predictably, the knockdown of PGC-1α in hepatocytes leads to a lower expression of genes connected to both fatty acid oxidation and gluconeogenesis (14,71). Meanwhile, even though mitochondria of PGC-1α null hepatocytes show no particular differences in number or morphology, oxygen intake is substantially attenuated (14,19).

So what is the hepatic role of PGC-1α? It triggers a metabolic transition from the use of glucose to glycogenolysis, gluconeogenesis, oxidation of fatty acids and ketone body exploitation since several of these pathways are controlled through the interplay of PGC-1α with liver-enriched transcription factors, which are pivotal for the tissue-specific transcriptional regulation of genes (14,17).

4.4.3. Heart

PGC-1α reaches high expression levels in this organ, in accordance with the high mitochondria content and oxidative capacity of cardiac cells. Appropriately, *stimuli* demanding higher energy production, like exercise (72) and fasting (63), prompt the expression of PGC-1α in the heart. Thus, PGC-1α is important to the maintenance of adequate cardiac function following stress signals (5) and PGC-1α's expression is lower in several animal models of heart disease (73).

Accordingly, hearts from PGC-1α knockout animals seem normal at baseline but are unable to respond to an increase in their workload (6), showing reduced treadmill running times and declined cardiac function following exercise (69). These results suggest that diminished PGC-1α expression in heart disease is indicative of a failure to respond to physiological cues that gives rise to contractile modifications, lower heart rate and to a decreased reactivity upon beta-adrenergic stimulation (14,69). Predictably, these modifications tend to assume greater importance upon stimulation or in stressful circumstances (74).

As opposed to what happens in skeletal muscle of mice devoid of PGC-1α, there are no structural anomalies or variations in number in mitochondria of PGC-1α null cardiac muscle (14,69) but there was nevertheless a noticeable decrease in the transcription of genes connected with OXPHOS, fatty acid oxidation, and ATP synthesis (14). So, this functional disability is due to an inability to produce enough ATP to fulfil the energy requirements to support regular cardiac cell function and capacity to adapt (5). Therefore, PGC-1α not only controls mitochondrial biogenesis, but also liaises production of ATP (mainly through oxidation of fatty

acids) in cardiac muscle during development and following transient fasting (63). Also, studies have shown that despite being crucial for heart maturation during the perinatal period (5,75), PGC-1 coactivators are unnecessary for the upkeep of mitochondria mass and dynamics in the heart of adult mice (5,76).

On the contrary, PGC-1α above the physiological expression levels in the heart results in mitochondrial proliferation, myofibrillar displacement and, ultimately, cardiac dilation and heart failure in mice (6,63). Consequently, therapeutic regulation of PGC-1α in heart failure ought to obtain a normalization of PGC-1α so that it remains within a medically advantageous window (6).

Today, cardiovascular diseases contribute greatly to the worldwide death rate (77). It has become clear that mitochondrial dysfunction and inherent bioenergetics deviations and marked oxidative stress are preponderant characteristics of this type of condition (77,78). Thus, the scrutiny surrounding the impact of PGC-1α in the vasculature (78) has intensified.

4.4.4. Adipose tissue

Two different types of adipose tissue with distinct mitochondrial oxidative capacity can be found in mammals. On one hand, there is white adipose tissue (WAT) that is distinguished by its lipid storing capacity and endocrine functions. On the other hand, BAT is linked to non-shivering adaptive thermogenesis, a tissue-specific mechanism crucial to maintain body temperature in answer to cold (25). Since this adaptive mechanism depends on the capacity of mitochondria to oxidize substrates to generate heat, it comes as no surprise that brown adipocytes have an appropriate mitochondrial apparatus and high levels of PGC-1α and PGC-1β (34), which is not the case in WAT (5). In the latter, expression of PGC-1α is lower and its role in this tissue is yet to be fully understood (25). In support of the importance of PGC-1α's role in thermogenesis regulation, PGC-1α knockout mice quickly become hypothermic and tend to die after being forced to tolerate low temperatures for extended periods of time (19,54).

Taking this into account, it has been contemplated whether increasing the function of BAT in adult humans or even forcing WAT towards displaying an expression pattern more like the one seen in BAT, via heightened PGC-1α expression, could optimize energy use and lessen obesity as a result. Despite the existence of some studies on this topic, this theory has not been proven and there is a good chance that other factors would need to be involved in this kind of regulation (54).

4.4.5. Neural tissue

Lack of PGC-1α in animal models has been described to give rise to behavioural abnormalities and neurodegeneration (19). Accordingly, PGC-1α knockout mice present a pronounced spongiform lesion in the striatum, the brain region most affected in human HD and crucial for control of movement. Irregular lesions were also seen in the cortex of PGC-1α knockout mice, including in the *substantia nigra* (SN) and hippocampus, two regions that are gravely damaged in PD and AD, respectively (19).

PGC-1α null mice manifest strong motor disability, loss of neurofilament expression (19) and intensified weakness to the harmful impact of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and kainic acid (21). Meanwhile, mice with vestigial expression of an N-terminal truncation product (69) display comparable, albeit milder, neuropathological and transcriptional alterations (14). Awhile back, researchers have shown that selective deletion of PGC-1α in GABAergic neurons can generate sensorimotor deficits along with hyperactivity (14,79).

Deletion of PGC-1α in glutamatergic neurons of the hippocampus furthermore diminishes the density of mitochondria and dendritic spine (80) and decreases the expression of several mitochondrial respiration related genes and cyt c oxidase subunit I, which implies a negative impact on mitochondria biogenesis and/or related transcription (81). In fact, impaired mitochondrial function and lower expression of genes implicated in mitochondrial OXPHOS have been associated with multiple NDDs (6,82).

When the *Rgs9*-cre line was used to represent PGC-1α depletion, slight changes in transcription were noted, in accordance with the relative lack of PGC-1α spiny projection neurons (SPNs) from the striatum (14). When it comes to dopaminergic neurons, which also express somewhat modest levels of PGC-1α, no decline of dopaminergic terminals were seen in PGC-1α whole body null mice (83). Nevertheless, a recent investigation revealed that viral-mediated knockdown of PGC-1α in dopaminergic neurons of old mice prompts cell loss (84).

Additionally, mitochondrial genes dependent on PGC-1α were attenuated in whole body PGC-1α null mice (14). Nonetheless, the expression of genes regulated by PGC-1α in peripheral tissues, such as *TFAM,* is not diminished in various regions of brains of PGC-1α null mice, even though Tfam is lower in cardiac tissue from the same animals (14,85). This indicates that despite being essential for some elements of the mitochondrial respiratory chain and Krebs cycle, PGC-1α is unnecessary to support regular mitochondrial transcription in the brain (14). However, PGC-1α overexpression enhances mitochondrial density in neurons, as seen in

peripheral tissues and other cells (80), improves mitochondrial function (8) and promotes the production of ATP (80), presumably by the upregulation of Tfam and mitofusin 2 (Mfn2) (86) and other factors (14).

Meanwhile, brain-specific splice variants of PGC-1α have been reported (87) and seem to respond to cellular *stimuli*, such as hypoxia (88). Nevertheless, the distribution of these variants by cell type has not yet been established (14).

5. PGC-1α and ageing

Ageing is a complex process essentially characterized by a failure to meet energetic requirements, dysfunctions in multiple physiological pathways and accumulated oxidative stress. Consequently, it comes as no surprise that mitochondria have been at the core of ageing theories for a long time, given that it is known that their ability to function properly tends to decline with time (8). Thus, a rise in ROS levels combined with a decline in antioxidants disrupt cellular homeostasis and may be the root of several age-related health problems such as cancer, cardiovascular disease, and NDDs (89).

The alterations associated with ageing are, for example: loss of protein homeostasis that results in aggregates and inclusion bodies, DNA damage, lysosomal dysfunction, epigenetic modifications and disrupted immune response. Moreover, genetic predisposition and environmental factors have a substantial impact on the incidence and prevalence of the aforementioned changes. Other ageing hallmarks consist of: telomere shortening, mitochondrial dysfunction, stem-cell ageing, dysfunction of intercellular communication (90) and reduced tissue regeneration (91). Combined, variations in inflammation and intercellular communication are key factors of regular brain ageing and neurodegeneration (92).

Another major alteration during ageing is the decline in irreplaceable cells, especially in the skeletal muscles, heart, and brain. In fact, by the time someone is 80 years old, striated muscles will have decreased by around half and, once they vanish, they are substituted by fat cells and fibrous connective tissue. In turn, the cardiac cell reduction leads to modifications in heart function. In the brain, neurons shrivel and perish, which causes changes in neuronal synapses and circuits. The loss of neurons, specifically those found in the hypothalamus, a vulnerable area, might partake in physiological alterations, such as changed metabolism and circadian rhythm, and is closely linked to mental and emotional abnormalities in the geriatric population,

a population that naturally registers a downturn in dopamine, norepinephrine, serotonin, tyrosine hydroxylase, and cholinesterase and a rise in the activity of monoamine oxidase (91).

In line with these findings, it has been described that the brains of individuals with 90 or more years weigh 11% less than brains of people in their fifties (92), which means that more than 150g of brain tissue is lost during those 50 years in between. This change might be caused by the loss of all types of cells, fluids and structures present in the brain and it will be critical to understand if this is connected to neurodegeneration or if it is just a part of the normal ageing process (91).

On that note, even though rodents and nonhuman primates are widely used as models for NDDs, it has become increasingly necessary to take into account other factors such as ageing, that are almost certainly covariant in the progression of such diseases (93). For example, mitochondrial function, along with the expression of PGC-1α and PGC-1β, are diminished during telomere dysfunction, which is a condition commonly associated with ageing (94).

The mitochondrial polymerase γ (POLG) mouse model (95) has been crucial to understand the relevance of mitochondria in ageing. POLG is a DNA polymerase found in mitochondria where it is involved in the replication of mitochondrial DNA (mtDNA) and DNA repair. It became clear that mice with mutant POLG have a higher rate of mtDNA mutations and present alopecia, osteoporosis and cardiomyopathy, which are all conditions associated with age (96). So, with the intent of finding out whether an increase in PGC-1α could improve such conditions, these POLG mice were crossed with muscle creatine kinase-PGC-1α transgenic (MCK-PGC-1α Tg) mice (8). The investigators then concluded that mice with both mutant POLG and PGC-1α presented enhanced mitochondrial activity in the heart and skeletal muscle, which translated into a better function of these tissues in comparison with mice that only expressed mutant POLG. This information seems to illustrate that PGC-1α can delay the onset of conditions that tend to present with age and therefore lessen the impact of oxidative damage (8).

It is also believed that increased production of ROS by mitochondria and the resulting oxidative damage are decisive factors during this process. ROS greatly promote the deterioration of neuronal cells through modulation of the function of biomolecules (such as DNA, RNA, lipids, and proteins) and processes (nucleic acid oxidation and lipid peroxidation, for example) in the cell. Given the brain's role as the biggest consumer of oxygen in the human body (89), it is understandable that reduced antioxidant defences paired with an increased quantity of polyunsaturated lipids susceptible to oxidation in neurons will have a detrimental impact on the aforementioned biomolecules. So, modifications to these biomolecules taking place under

stress conditions might be used as markers for oxidative stress (89). There is a vast body of proof connecting ROS, ageing and several NDDs (91).

NDDs commonly present themselves in middle-aged individuals or in the elderly, prompting us to associate ageing with a functional decline of pathways vital for neuron durability. PGC-1α has been connected to ageing and its role may even go as far as exerting some level of control over telomeres, that are widely accepted as pivotal for the upkeep of chromosomal integrity. Predictably, a study has proposed that this constant shrinking of telomeres may activate p53, which then joins and quells PGC-1α's transcription, causing deterioration of mitochondrial function and biogenesis, a decline in gluconeogenesis and a rise of ROS. In turn, these ROS are important mediators in signalling pathways that lead to apoptosis (20,94).

Autopsies of the brains of elderly people who had no diagnosed NDD regularly document the presence of amyloid plaques, neurofibrillary tangles, Lewy bodies, synaptic dystrophy, loss of neurons and loss of brain volume (92). The cause of these alterations has not yet been determined and it remains to be understood whether they precede neurodegeneration and disease or are standard traits in the ageing brain. Adding to this, the rise in defective proteins and dying cells reported during ageing might lead to an overload in the phagocytic pathways which will, in turn, give rise to a build-up of material in lysosomes. Accordingly, with ageing and neurodegeneration, higher levels of lysosomal proteins and enzymes are found, and neurons and other cell types show unusual endosomes, lysosomes and autophagosomes (92).

Since neurodegenerative diseases are common in senior citizens and disease-free brains are unusual, it is plausible that regular brain ageing occurs alongside neurodegeneration, impacted by stochastic, genetic and environmental factors (92). In truth, environmental factors justify no less than 70% of the fluctuation in lifespan and mounting evidence proves that factors such as lifestyle, diet, exposure to toxins and drugs can have far-reaching implications on the quality and durability of life and on the development of NDDs (92). Accordingly, in-depth omics, genetic and epigenetic studies might help unearth the molecular mechanisms that seem to inextricably connect ageing with neurodegeneration and will also enable the recognition of new potential therapeutic targets that may have disease-modifying effects (92).

6. The role of mitochondrial dysfunction in neurodegenerative disorders and the impact of PGC-1α

Mitochondria are accountable for the production of ATP (that is vital for the all-around activities of the cell, including signalling) via electron transport chain and OXPHOS and are also involved in the production of antioxidant species, in apoptosis (i.e. programmed cell death) (97), and in the breakdown of faulty mitochondria through mitophagy, a mechanism linked with NDDs (98). Moreover, mitochondria can produce heat in BAT (25) and control calcium homeostasis by being storage units for calcium ions, a role that is particularly important in myocytes and neurons where calcium flow is closely linked to muscle contraction and action potential generation (99).

ROS have a prejudicial effect on proteins and lipids, which constrain the bioenergetic functions in mitochondria and cause damages to mtDNA, closely linked with downregulation of mitochondrial gene expression. The huge oxygen requirements, rather few antioxidant enzymes, and the large amount of catalytic transition metals in some regions of the brain make it particularly liable to oxidative damage (89).

Furthermore, mitochondrial physiological activity itself creates toxic by-products when electrons link directly to oxygen instead of finishing the entire series, creating ROS that can then lead to cellular malfunction or serve as signalling molecules in pro-growth responses connected to basic cellular signalling pathways encompassing regulation, differentiation, proliferation, and apoptosis (78,100).

These organelles are a point of intersection between neuronal survival and cell death since they have developed several mitochondrial quality control (MQC) pathways to ensure that they are qualified to keep working (16).

Mitochondria are able to intervene in neuronal death in age-related NDDs through diverse mechanisms such as the modification of mitochondrial dynamics (fission/fusion and organelle trafficking) and biogenesis or mitophagy; alterations of Ca^{2+} homeostasis; mutations on mtDNA; faulty activation of apoptosis; oxidative stress; membrane permeability and cellular metabolism modifications (Figure 5) (97,99,101).

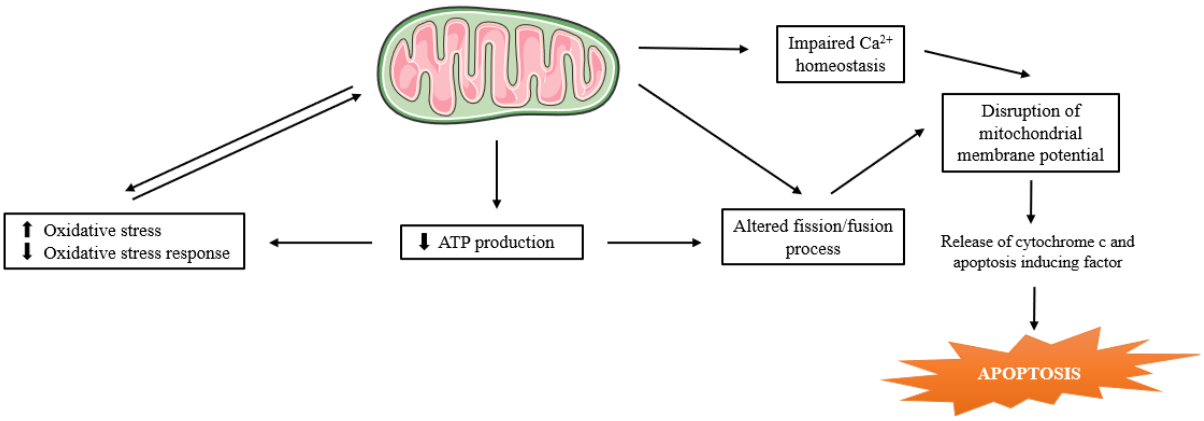

Figure 5. The connection between mitochondria, oxidative stress and apoptosis.

Adapted from (97).

Mitochondria are the only organelles in the eukaryotic cells that have their own DNA distinct from nuclear DNA. Noticeably, the mitochondrial genome is not protected by histones and its mutation rate is higher than the nuclear DNA (102). So, mtDNA mutations may be linked with the age-related decline of mitochondrial functions and with NDDs (103).

Although moderate amounts of ROS play important roles in physiologic processes (e.g. signalling pathways, induction of mitogenic response, defence against pathogens), an overproduction and failure of endogenous antioxidant defences give rise to oxidative damages such as post-translational modifications and oxidation of proteins, lipids and DNA/RNA, which are customary hallmarks of many NDDs since, as previously established, the brain is highly vulnerable to ROS (104). Collected evidence states that the oxidation products act as biomarkers in a few NDDs such as lipid peroxidation markers 4-hydroxynonenal and malondialdehyde (MDA) recognized withinside the SN, while protein nitration markers (Lewy bodies) are identified in the hippocampus and neocortex of PD patients (104).

Studies in PGC-1α-deficient mice have shown that despite not being indispensable for mitochondrial biogenesis *per se*, PGC-1α is needed for the expression of numerous mitochondrial genes (19,69). It is noteworthy that even though PGC-1β shares a myriad of target genes with PGC-1α, it is incapable of fully counterbalance the absence of PGC-1α (105). In fact, PGC-1β levels are kept in PGC-1α null mice, but the lack of PGC-1α results in a poor oxidative metabolism in multiple tissues (69). These findings emphasize the important function

of PGC-1α in the command of mitochondrial OXPHOS and general cellular energy homeostasis.

PGC-1α is one of the most well-characterised transcriptional coactivators of nuclear-encoded mitochondrial gene transcription, as are the rest of the members of its family. These elements act downstream of intracellular signalling cascades and make the connection between extracellular *stimuli* and transcription factors that is needed for both essential and energy-demanding gene expression (14,106). This transcription co-regulator modulates the expression of mitochondrial antioxidant defences, raising the levels of several antioxidant enzymes and ergo protecting cells from the consequences of mitochondrial dysfunction. This reaction is triggered when cells are under oxidative stress (78) and is vital to avoid cell death (107), to lessen mitochondrial ROS levels and to assure the integrity of mitochondria throughout cell differentiation (108).

The first indication of the participation of PGC-1α in pathophysiological pathways that lead to NDDs came from the *PPARGC1A* null mice (19,69), which presented neurodegeneration linked with a phenotype of marked hyperactivity like the one observed in HD (19). Since then, research has focused on the role of PGC-1α in dealing with oxidative stress (Appendix A2), and on how PGC-1α exerts neuroprotective effects by collaborating in the regulation of mitochondrial energy metabolism and biogenesis. Even if scarce, there are reports that activation of the PGC-1α signalling pathway can take part in MQC regulation and reduce neuronal damage (16).

Collectively, the studies exploring the impact of PGC-1α on mitochondria highlight that it causes substantial remodelling of their composition and functions. This mitochondrial remodelling works in concert with PGC-1α-mediated biogenesis of mitochondria, as well as the increase in the content of ROS-detoxifying enzymes, to establish a new state of cellular oxidative metabolism (8).

So how do mitochondria react and adapt under stress? The renowned powerhouse of the cell can restrict any anomalous mitochondrial changes that compromise cellular homeostasis through actions involving proteins and enzymes, together with mitochondrial fission, fusion, mitophagy, mitochondria-derived vesicles (MDVs) and others which are part of MQC (16).

The dynamic balance amid degradation and biogenesis (Appendix A3) regulates mitochondrial mass. Notably, these pathways respond physiologically to a rise in energetic needs and modulate the production of ROS at a mitochondrial level and consequent detoxification. They

promote the assembling of the different respiratory complexes in mitochondria and regulate any potential mutations in the mtDNA (78,109).

When confronted with the gathering of misfolded proteins, they react by improving chaperone and protease activity, for example, to correct those mistakes or to destroy the defective proteins. Considering it from an organellar level, MQC lessens damage to the organelle through fission and fusion. So, ROS trigger mitochondrial fission, leading to the disintegration of this organelle (16). These disintegrated mitochondria present a reduced membrane potential, generate smaller amounts of ATP and more ROS, and boost the discharge of pro-apoptotic mitochondrial proteins. On the other hand, mitochondrial fusion is the contrary operation (16). Still from an organelle standpoint, mitophagy helps to ensure mitochondrial integrity by selectively destroying faulty mitochondria (98), so it has been intricately connected to NDDs (16) (Appendix A4).

And what is the role of PGC-1α in this dynamic process? It is apparently a key molecule in MQC (Appendix A1). Mitochondrial biogenesis is regulated through the activation of PGC-1α and depends on mitochondrial and nuclear genes (78). Studies have demonstrated that upregulation of PGC-1α's expression in neurons can restrain mitochondrial dysfunction in some *in vivo* and *in vitro* ageing or neurodegenerative encephalopathy models, such as HD, AD, and PD. Seeing that mitochondrial dysfunction and quality control disorders are the cause of nearly all NDDs, the function of this transcriptional coactivator may be modulated with the intent of treating of such diseases (16).

In normal circumstances, the number, morphology, and function of mitochondria do not suffer relevant alterations, because of several MQC mechanisms like the degradation of proteins by mitochondrial proteases or the degradation of selected organelles in lysosomes. Therefore, when MQC fails and mitochondria malfunction, they undergo mitophagy (16).

There are two ways by which PGC-1α can increase global oxidative metabolism. Firstly, it is able to conduct cellular remodelling via organelle biogenesis (mitochondria and peroxisomes). Alternatively, PGC-1α seems to be capable of coordinating organelle remodelling, leading to a substantial modification of their individual composition and function (8). Evidence shows that PGC-1α enhances the expression of the nuclear respiratory factors (NRFs), which regulate the expression of several mitochondrial genes. On top of this, PGC-1α coactivates and boosts the transcriptional activity of NRF-1 on target genes (30), which results in a significant induction of uncoupled respiration (8). So, multiple studies recognized PGC-1α as an important player in

mitochondrial biogenesis and respiration and demonstrated that gain and loss of PGC-1α have important consequences for mitochondrial physiology *in vivo* (8).

Keeping in mind that the peroxisome is a fundamental organelle that assists mitochondria in oxidative metabolism and that, as such, its main function, in mammalian cells, is to metabolize complex fatty acids that mitochondria are unable to metabolize, a study conducted by Andrade-Navarro *et al*. demonstrated that PGC-1α is a positive regulator of peroxisome biogenesis. Therefore, mitochondria and peroxisomes cooperate in the metabolism of lipids, which are very important fuels during oxidative metabolism. The discovery of vesicles that travel between the two organelles proved this close collaboration (110).

All in all, these data show that PGC-1α coordinates alterations in cellular metabolism using organelle biogenesis. Thus, and considering that mitochondria are the principal manufacturers of ROS, cells that exhibit induced PGC-1α (in answer to physiological *stimuli*) need to adjust to the creation of even more ROS mediated by the elevated number of mitochondria and peroxisomes, or otherwise endure the repercussions of intensified oxidative metabolism (8).

Additional research has revealed that the expression of several ROS-detoxifying enzymes is regulated by PGC-1α, including mitochondrial, cytoplasmic and peroxisomal ROS-detoxifying enzymes, such as superoxide dismutase 2 (SOD2) and cyt c (8,21). In general, studies show that PGC-1α enhances mitochondrial biogenesis while simultaneously elevates the cellular ROS-detoxifying capacity (21). This way cells have reinforced respiration and ATP production but do not endure more oxidative damage. Additionally, there is also growing evidence suggesting that PGC-1α modulates the intrinsic composition of mitochondria and peroxisomes and that these changes have a major influence on cellular gene expression profiles and oxidative metabolism (8).

In conclusion, the PGC-1α-mediated impact in the respiratory capacity of mitochondria can be attributed to variations in levels or activity of several mitochondrial enzymes or a blend thereof. Several studies demonstrate that PGC-1α influences the content and activity of mitochondrial proteins that engage in varied pathways, endorsing the notion that PGC-1α has a broad effect on mitochondrial functions (8).

Remarkably, the antioxidant role of PGC-1α is attached with its part in improving the transport of mitochondrial electrons and mitochondrial mass in cells with large energy requirements. Thus, this pleiotropic part played by PGC-1α is rated as an adaptive mechanism. PGC-1α leads to the activation of numerous transcription factors, namely NRFs 1 and 2, PPARs, Tfam, and

ERRα to enhance transcription of genes that control mitochondrial biogenesis and function (78,111).

Unquestionably, mitochondria are at the helm of several critical pathways, although the magnitude of association or integration between these processes has yet to be determined, but PGC-1α has emerged as a potential target with implications in several of these pathways (Appendix A1).

7. PGC-1α and neurodegenerative disorders

PGC-1α has long been associated with neurodegeneration and NDDs such as HD and amyotrophic lateral sclerosis (ALS) (87).

PGC-1α might even be involved in myelination, as it can be found in oligodendrocytes, where it is implicated in the expression of genes that are critical for right myelination, such as myelin basic protein (MBP). In line with this assumption, PGC-1α knockout mice display irregularities in white matter in the striatum and substantially lower expression of myelin-associated oligodendrocyte basic protein (MOBP) (19).

Thus, PGC-1α disability could indeed favour NDDs, especially since lower levels of PGC-1α seem to lead to mitochondrial dysfunction and consequently to oxidative stress in the brains of patients with NDDs (24,112).

7.1. Alzheimer's disease

AD is a progressive neurodegenerative disease characterized by loss of cognitive and motor capacities, eventually leading to a level of disability that prevents patients from performing basic daily tasks. It is the most prevalent NDD globally, affecting around 45 million people and projected to affect many more in the future (89).

Even though AD is commonly seen as an age-related disease, it can also have an early onset (corresponding to less than 10% of the cases) around 40 to 60 years old in people with autosomal dominant gene mutations, most of them being on the genes encoding β-amyloid (Aβ) precursor protein (APP) and presenilins (PS1 and PS2) (103). These cases make up familial AD (FAD) (113). These mutations granted the foundation for the amyloid cascade hypothesis (114). So, Aβ and the proteases generating it have been considered prime drug targets since their

discovery and the first transgenic mice models (115) and the notion of Aβ immunotherapy (116) appeared afterwards. Eventually, apolipoprotein E (ApoE) type 4, was also identified as the primary genetic risk factor for AD (117,118).

Today, through genetic research, results show that common forms of late-onset AD have a probability of heritability ranging from 56 to 79% (119). In turn, forms of early-onset have a heritability that exceeds 90% (120).

AD presents a long prodromal phase and evidence suggests that the pathological process begins up to 20 years before the onset of symptomology (120,121). Clinically, AD presents itself through the deposition of protein agglomerates, extracellular amyloid plaques, intracellular tau or neurofibrillary tangles, and loss of synaptic connections, loss of cholinergic nerves, neurotransmitter unbalance, neuronal loss, dendritic alterations, and so on in certain sections of the brain (89). So, the neuropathological diagnostic hallmark of AD is the build-up of neurotoxic Aβ oligomer peptides and tau protein that cause neurodegeneration and neuroinflammation.

AD is a complex disease and several metabolic pathways and cellular processes have been related to it, such as immunity, endocytosis, cholesterol transport, ubiquitination, amyloid-β and tau processing (120). Defective mitochondrial function and biogenesis in neuronal cells in AD patients cause synapse dysfunction, cellular damage (122) and further cognitive decline (24). Additionally, insulin resistance is also seen in the AD affected brain and contributes to the drastic advance of AD pathophysiology (24). This insulin resistance derives from impaired insulin signalling in the brain, as seen in some studies (123) along with reduced insulin receptor sensitivity. PGC-1α intervenes in counteracting this insulin resistance through its influence on mitochondria (124), lessening insulin resistance-related cognitive impairment in the AD brain (24).

Many reports show that ROS and consequent oxidative stress play crucial parts in AD through their detrimental impact on biomolecules, in particular on proteins, and suggest that there is a connection between Aβ-induced oxidative instability and high level of by-products of lipid peroxidation, protein oxidation, and DNA/RNA oxidation (89,125).

It has been established that deposition of amyloid plaques takes part in oxidative stress (89), affecting mitochondria via disruption of the electron transport chain (125). Therefore, the association between mitochondrial dysfunction, tau phosphorylation, and Aβ deposition attracts

great interest in the investigation and development of ground-breaking therapeutic interventions (89).

A decline in the expression and activity of proteins engaged in mitochondrial bioenergetics have been observed. Proving this point, Yao *et al*. demonstrated that mitochondrial dysfunction appeared before the beginning of plaque formation in a triple transgenic mouse model for AD (126).

Multiple studies have shown that the level of PGC-1α is clearly reduced in the brain of AD patients (22,24). So, the idea that increased levels of PGC-1α can protect neural cells from apoptosis motivated by oxidative stress through the triggering of antioxidant genes has been studied (21,24). Nevertheless, the molecular mechanism that induces mitochondrial dysfunction in AD remains undetermined. Given their role, it has been proposed that the presenilins/APP processing pathway may modulate mitochondrial performance. In one study, the investigators found that PS1 seems to modulate the expression of PGC-1α through the γ-secretase-dependent APP cleavage product APP intracellular domain (AICD). Consequently, lack of presenilins results in a lower ATP level, oxygen utilisation rate, and expression of PGC-1α target genes and proteins. Moreover, PS1-FAD mutation diminishes PS1's capacity to modulate PGC-1α mRNA levels (127).

The influence of PS1 on mitochondria was also evaluated and several conclusions were drawn, such as: PS1 upregulates protein and mRNA levels of PGC-1α; PS1 upregulates PGC-1α's target genes; inhibition of γ-secretase activity decreases PGC-1α mRNA levels; APP and AICD, but not Aβ, regulate PGC-1α mRNA levels; AICD upregulates PGC-1α promoter activity; regulation of PGC-1α expression by APP/AICD also occurs *in vivo* in mouse brains (127). These results imply that PS1 regulates PGC-1α expression via APP/AICD and that impairment in this connection may lead to mitochondrial dysfunction (127). In short, the findings of previous studies indicate that PS1 modulates PGC-1α's expression through its γ-secretase cleavage of APP and generation of AICD (127).

The impression that PS1 might upregulate the expression of PGC-1α is also supported by the fact that mRNA levels of PGC-1α and its target genes (e.g. NRF-2) were raised in mouse embryonic fibroblasts (MEFs) that expressed PS1 compared with PS1/2$^{-/-}$ MEFs and this also denotes that PS1 can regulate mitochondrial function since PGC-1α and NRF-2 collaborate to enhance nuclear-encoded mitochondrial gene expression (128). Noticeably, PS1 can control the expression of mitochondrial proteins in a PGC-1α-independent manner (127). So, the impairment in PGC-1α modulation seen in PS1-FAD mutants implies that PGC-1α may

participate in the pathology of said form of the disease and possibly in sporadic forms of AD. This theory is backed by studies that showed decreased mRNA levels of PGC-1α in the hippocampus of the AD brain (22).

Damaged mitochondria result in a severe deficit in energy metabolism and ATP generation, and also in a shortcoming in the cleansing of free radicals which causes excessive oxidative damage in the AD brain (24,129). Furthermore, mitochondria are sites of Aβ accumulation in AD neurons and that eventually leads to the death of the cell (130).

Despite being well established that oxidative stress is related to the manifestation of AD (24), the use of antioxidants as a way of preventing it is still debatable. This uncertainty is due to the permeability limitations that these molecules display since they are unable to cross the blood-brain barrier. With the emergence of nanotechnology, nanoparticles could overcome this issue and be a vehicle for drug delivery into the central nervous system (CNS) (131).

PGC-1α controls mitochondrial density in neurons (132) and PGC-1α knockout mice exhibited a higher sensitivity to the decay of dopaminergic and glutamatergic neurons in the brain (21). Another study proved that a diminished expression of mitochondrial genes in PGC-1α-knockout mice ignites neuronal dysfunction (19,24).

In June of the present year, the FDA authorized Aducanumab, which is not only the first new therapeutic option targeting AD in 18 years but also the first drug directed at a putative pathological mechanism of the disease. The approval of this Aβ-directed antibody was controversial and went against the opinion of several experts that continue to not see a benefit or how to insert this new drug into a patient's therapeutic regimen, especially given its risks (133,134).

In the meantime, the quest for a better understanding of the cellular processes that cause AD will continue in order to try to link the biochemical modifications to the clinical manifestations of AD since this is a field where disease-modifying and successful new therapeutic tools are imperative and where personalized medicine might be useful (118).

7.2. Parkinson's disease

PD is the second most common NDD in older people (89), affecting over 10 million people worldwide with an estimated economic impact of $51.9 billion in the United States of America alone (135).

PD is a disorder distinguished by motor symptoms such as: tremor, bradykinesia/akinesia, muscular rigidity, resting tremor, and postural instability (136) and non-motor symptoms like dementia, hyposmia, depression, and emotional alterations (135). These motor problems are a manifestation of an advanced loss of neurons from the *pars compacta* of the SN that produce dopamine. Even though several clinical conditions present themselves with "parkinsonism" as a characteristic, a typical PD diagnosis is established by the presence of Lewy bodies (137,138). The mechanism leading to the formation of these aggregates remains unidentified, but there are multiple theories on the table encompassing oxidative stress and mitochondrial dysfunction as catalysts (14,101,139).

The majority of PD cases are sporadic (82), but there are rare familial forms that have been found to account for up to 15% of all cases. Despite this, both forms of the disease share clinical, pathological and biochemical characteristics, so studying the function and dysfunction of gene products associated with PD has helped enlightening common PD pathological pathways (140). Today, at least nine nuclear genes have been connected to or to the risk of developing PD: *α-synuclein* (*α-Syn*), *parkin*, *ubiquitin carboxy-terminal hydrolase L1 (UCHL1)*, *DJ-1*, *phosphatase and tensin homolog (PTEN)-induced kinase 1* (*PINK1*), *leucine-rich repeat kinase 2 (LRRK2)*, *nuclear receptor-related 1 (NURR1)*, *HTRA2* and *microtubule-associated protein tau (MAPT)* (102,104).

Up until recently investigation efforts focused solely on treating symptoms with early gene therapy targeting the expression of central enzymes in the dopamine biosynthetic pathway, restitution of inhibitory control of subthalamic nucleus, and delivery of neurotrophic factor (93).

As seen in AD, PD pathogenesis is also thought to be influenced by not only genetic factors (recent surveys point to a heritability between 16 and 36%) but also by environmental factors (141). In the meantime, gathered evidence suggests a correlation between oxidative stress and resultant mitochondrial dysfunction and PD in both sporadic and familial cases (142). In fact, not only oxidative stress related mitochondrial dysfunction and dopaminergic cell damage but also mutations in mtDNA have been associated with this condition (104). So, the rise in ROS combined with a downregulation in the expression of endogenous antioxidant systems, namely SOD, catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx), leads to a selective loss of neurons in PD, especially because dopaminergic neurons are particularly susceptible to the effect of ROS since dopamine is rather unstable and suffers auto-oxidative metabolism in the nigrostriatal system, resulting in the production of more ROS (104,143).

The most convincing link between PD and mitochondrial dysfunction emerged in the 1980s after an accident involving exposure of drug abusers to an illicit drug contaminated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), an inhibitor of mitochondrial complex I, which manifested as a parkinsonism syndrome (144). Shortly after that, research results showed complex I deficiency, decreased immunoreactivity for this complex and oxidative damage in the SN of people suffering from PD. Since complex I is responsible for the production of a large amount of free radicals in the cell, changes in this complex's function in the *substantia nigra pars compacta* (SNpc) may be accountable for the intensified DNA damage and lipid peroxidation seen in the PD brain (142).

Where does PGC-1α fit in PD progression? Another study connected PD caused by a recessive mutation in the parkin-coding gene with a disrupted PGC-1α activation. Parkin-interacting substrate (PARIS) was recognized as a substrate capable of engaging with parkin and with a tendency to accumulate in models where there is deactivation of parkin and in the brains of individuals suffering from PD. PARIS inhibits PGC-1α and NRF-1's (a PGC-1α target gene) expression at a transcriptional level (145,146). Furthermore, knocking out parkin in adult animals resulted in a reduction of mitochondrial mass and respiration dependent on PARIS and selective dopaminergic neuronal death reversible through either parkin or PGC-1α co-expression (147).

Additionally, in studies focusing on the effect of this coactivator following exposure to MPTP, PGC-1α knockout mice revealed an increased tendency to SN neuronal loss while overexpression of PGC-1α seemed to exert a protective effect that counterbalanced oxidative stress *in vitro*. In fact, transgenic mice with higher levels of PGC-1α in dopaminergic neurons were not susceptible to MPTP-induced cell degeneration and exhibited increased levels of mitochondrial antioxidants SOD2 and Trx2 (148). In other words, reduced PGC-1α considerably aggravates MPTP-motivated cell death (21) and α-Syn-induced cell death (149) in models of PD. On the contrary, enhanced expression of PGC-1α intensifies autophagy and decreases toxicity related to α-Syn in cell culture (23,150). So, overexpression of PGC-1α (21,148,151) or stabilization can also hinder neurotoxicity caused by MPTP *in vivo* (14). In accordance with these findings, the sensitivity of SH-SY5Y cells (a human-derived cell line) to N-methyl-4-phenylpyridinium ions was enhanced through silencing of PGC-1α, which also resulted in a suppression of mitochondrial function (151).

The *SNCA* gene codes for the α-Syn protein and point mutations (A53T and A30P) in that same gene (*PARK1* locus) are closely linked to an escalation in the expression of said protein

(14,152). Studies using human induced pluripotent stem cells (iPSCs) with A53T *SNCA* mutations show that a MEF2C/PGC-1α transcriptional pathway favours neuronal damage. In these neurons, MEF2C and PGC-1α were reduced due to oxidative stress that obstructs MEF2C's ability to modulate PGC-1α, hindering its neuroprotective effects (14,153).

In turn, *LRRK2* mutations generate a form of PD that is clinically indiscernible from idiopathic PD (154) and since *LRRK2* controls mitochondrial motility and works in conjunction with parkin and *PINK1* to regulate mitophagy, these mutations have been associated with mitochondrial dysfunction (155). Dozens of mutations in the gene coding for parkin (an E3 ubiquitin ligase that participates in the regulation of MQC by ubiquitination of toxic substrates for breakdown by the proteasome (156)) have been related to early-onset PD with an average age of onset at 31 years old (157). Thus, parkin shortage causes the build-up of toxic substrates, as in the case of PARIS/*ZNF746*/*Zfp746*, causing cellular stress (145). The build-up of PARIS disrupts the expression of PGC-1α and NRF-1 through an insulin response element found in the *PPARGC1A* promoter (145), imitating the decrease in the expression of *PPARGC1A* and *NRF1* mRNA in *postmortem* SNpc from PD patients (14).

So, the better proof of a connection between PD and the dysregulation of the transcription of nuclear-encoded mitochondrial genes arises from two lines of research: recognition of the fundamental mechanisms of neuronal vulnerability with parkin loss-of-function models (145,147,158) and the transcriptional profiling of dopaminergic neurons from *postmortem* tissues of patients with Lewy pathology (23).

Laser capture microdissection of dopaminergic neurons from *postmortem* tissue of patients with Lewy pathology disclosed that several PGC-1α-responsive genes were downregulated, particularly genes encoding proteins for respiratory complexes of the electron transport chain. Even though this study did not show a decrease in *PPARGC1A* mRNA levels of PGC-1α protein, the generated evidence proposes that there is a disturbance in OXPHOS in PD, possibly ahead of cell loss (14). The fact that a decrease in the expression of PGC-1α is seen in several brain regions in patients with advanced-stage PD and in animal models of PD further supports this evidence (145,150). Investigations suggest that polymorphisms in the *PPARGC1A* gene may affect the age of PD onset (159).

Taking into account the considerably reduced basal expression of *PPARGC1A* and *TFAM* mRNA in dopaminergic neurons in mice, it is likely that any stress factors that hinder the expression and, consequently, the function of those genes will overcome the ability of compensatory mechanisms of mitochondria, resulting in cell loss (14).

Considering this, PGC-1α has emerged as a rather appealing target for a possible intervention in the early stages of PD, given its apparent neuroprotective role in these circumstances (139).

However, considerably altering PGC-1α expression also had deleterious effects in due course. A particular study proved that, after a while, along with enhanced basal respiration, OXPHOS, and mitochondrial biogenesis, PGC-1α affected mitochondrial polarization. In the end, it was proved that continued overexpression of PGC-1α eventually caused substantial deviations in the metabolic activity of neurons, which significantly weakened dopaminergic function *in vivo* (160).

These data emphasize the importance of preserving physiological levels of PGC-1α to ensure normal metabolic and neuronal pathways. PD is seen as a paradigm target for gene therapy since it is characterized by selective degeneration of dopaminergic neurons in the SNpc; sharp reduction in striatal dopamine content that ignites motor manifestations and, finally, due to its progressive nature that demands ongoing treatment to maintain dopaminergic neuron longevity and function (93).

The comprehensive understanding of dopamine biosynthesis and of the inner works of basal ganglia integrated circuits has opened and will continue to open the doors to discerning the molecular basis of PD which continuously allows us to ponder on the possibility of using several targets, such as PGC-1α, and strategies for a breakthrough clinical intervention.

7.3. Huntington's disease

HD is a fatal autosomal dominant inherited NDD marked by motor (with involuntary movements, abnormal gait and posture) and cognitive deterioration, along with a certain level of personality and psychiatric alterations, cortical atrophy and loss of SPNs of the caudate-putamen (20,161,162). This disease may start manifesting in people as young as 35 years old (161) and once again studies indicate that cortical atrophy starts 15 years prior to onset (163).

HD has been the focus of investigation since it was first described, and it is one of many disorders caused by protein misfolding. In this case, the culprit is a protein called huntingtin (Htt) that cooperates with several other proteins and intervenes in a wide variety of biological functions. The causal mutation is a trinucleotide repeat expansion in exon 1 that encodes an elongated glutamine tract in Htt (164). HD is thereby one of several hereditary NDDs caused by CAG trinucleotide repeats that result in disease by enciphering extended polyQ tracts since

it has been shown that tracts that transcend the mid-30s result in a harmful conformation (103).

Several *in vitro* and *in vivo* models have been created with the intention of studying the grounds for Htt polyQ neurotoxicity. One major conclusion is that polyQ-elongated misfolded proteins tend to gather into large "aggregates" or "inclusions". It also seems that proteolytic cleavage plays its part when it comes to it and studies indicate that this kind of enzymatic hydrolysis of the Htt protein is a hallmark of neurotoxicity spotted in HD. Meanwhile, several other processes beyond protein misfolding and aggregation have been linked to the disorder and the inherent neuronal death, such as anomalous proteolysis, transcriptional dysfunction, excitotoxic and oxidative stress, and glial activation action (164).

Studies have revealed the implication of oxidative stress and mitochondrial dysfunction in neurodegeneration in HD (103), especially since a decrease in mitochondrial complex activity is a replicable discovery in HD patient's samples (165).

Given that mitochondrial metabolism enables the work of ion exchange pumps, which are essential to keep an electrochemical gradient across the mitochondrial membrane, an inadequate energy supply could increase the rate of depolarization of mitochondria in HD. Scientific research has shown that mitochondria from people suffering from HD are extremely susceptible to depolarizing stresses. Accordingly, Sawa *et al*. demonstrated that, following treatment with complex IV inhibitors, HD lymphoblasts suffered depolarization of mitochondria and subsequent apoptosis through the caspase cascade (166). In fact, this caspase cascade activation seems involved in the pathogenic cleavage of mutant Htt (mtHtt), so it is understandable to assume that mitochondrial dysfunction is part of the early stages of HD neurotoxicity and knowing the role that PGC-1α plays in this field, it is worth pondering if whether or not it might be a target for therapeutic interventions in HD (20).

The presence of ambulatory hyperactivity and striatal vacuolation in PGC-1α null mice attracted more attention to a connection between PGC-1α dysfunction and HD etiology (19). Accordingly, expression of *PPARGC1A* mRNA was found to be diminished in HD patient's brain as well as in cell cultures and mouse models of HD (112,167). Most importantly, these studies showed that PGC-1α overexpression dampens cellular toxicity induced by mtHtt (112,167).

Still on the same topic, Cui *et al*. and Weydt *et al*. described compelling proof connecting PGC-1α malfunction to HD neurodegeneration. As a matter of fact, PGC-1α transcriptional activity was found to be impaired in the striatum (167) and defects in striatal energy metabolism are a

significant portion of the early pathogenesis of this disease (168). Striatal metabolism is lowered in pre-symptomatic HD patients years before any clinical symptoms arise, which means that neurons found in the striatum are especially susceptible to disturbances in mitochondrial function (168). Supporting this evidence is the fact that, upon analysis of microarray data from human striatum, the largest share of PGC-1α target genes is consistently down-regulated in RNAs from striatum in both HD patients with and without symptomatology (20,112). Moreover, the expression of this transcriptional coactivator was lowered in medium spiny neurons from HD patients and also from a knock-in mouse model, and in *postmortem* human striatum (167).

Cui *et al.* demonstrated that mtHtt disrupts energy metabolism via transcriptional repression of PGC-1α through association with the promoter and meddling with the CREB/TAF4-dependent transcriptional pathway, which is crucial for the modulation of PGC-1α gene expression (167).

Also noteworthy is the fact that mtHtt has been found to interact with multiple transcription factors, indicating that this abnormal protein might be related to the regulation of gene transcription (169). Meanwhile, mtHtt alone can meddle with mitochondrial respiration, calcium buffering capacity, and the with production of ATP (14,170). Importantly, the expression of PGC-1α in the striatum offers neuroprotection in the transgenic HD mice (167).

All things considered, ever since it was first suggested that PGC-1α might be involved in HD pathogenesis, many studies have been conducted with the purpose of proving and understanding this connection and have demonstrated that impaired expression of PGC-1α's target genes and associated mitochondrial dysfunction are indeed part of HD pathogenesis.

8. PGC-1α as a therapeutic target and inherent challenges

Dysregulation of gene expression and polymorphisms of the gene encoding PGC-1α have been found in a wide variety of pathological contexts and the therapeutic efficacy of PGC-1α modulation has been demonstrated in animal models for different diseases. Thus, pharmacological regulation of PGC-1α expression and activity might be a promising novel approach for the treatment and/or prevention of several pathologies despite the inherent difficulties of targeting a coactivator.

Selective manipulation of PGC-1α could potentially result in a fine-tuned and highly specific response that is unattainable by modulation of transcription factors. However, modulation of PGC-1α in one tissue might trigger distal effects in other organs. As an example, findings from muscle-specific loss-of-function mouse lines suggest that PGC-1α links muscle function to systemic inflammation and, ultimately, is connected to the risk of developing many chronic diseases. If these findings are corroborated, modulation of PGC-1α might have a far greater therapeutic applicability (54,64,171).

As previously seen, PGC-1α's overexpression can be neuroprotective in several mouse models of, namely, HD and PD. Nonetheless, said overexpression comes with the risk of undesirable adverse effects, particularly in cell types that do not usually express it and where it could therefore meddle with regular transcriptions patterns and/or trigger ones with a detrimental repercussion (14). For example, heightened levels of PGC-1α may induce excessive mitochondrial biogenesis and consequent hypertrophy in heart tissue (172), uncoupling of mitochondrial respiration and lessen the quantity of available ATP in skeletal muscle (173). It may also lead to a repression of transcription factors engaged in the preservation of phenotype and survival in dopaminergic neurons of the SNpc, resulting in cell death (160).

Thus, a pharmacological intervention should try to obtain a normalization or no more than a moderate improvement of the expression of this transcriptional co-regulator. Another important point to take into account is the fact that the therapeutic window might vary depending on the tissue and physiological framework (54). Variations in the level of PGC-1α in whatever direction are prone to be equally deleterious. To cite one example, cardiomyopathy and heart failure tend to arise with both sub- and supraphysiological levels of this particular coactivator (74).

Ideally, any kind of treatment intended for the proposed effect would act in a tissue-specific fashion to avoid unwelcome effects connected to the modification of the expression of PGC-1α in another tissue (54).

Another issue to overcome is the difficulty of activating PGC-1α in the CNS (174). One strategy to enhance PGC-1α expression and function is through viral delivery (167). An alternative approach would be to modulate the upstream regulators of PGC-1α activation, such as SIRT1 or AMPK (Appendix A1). SIRT1 is able to stimulate PGC-1α by deacetylating it in certain lysine residues (60) and thereby enhancing the expression of PGC-1α's target genes. In fact, there are compounds that are likely to activate SIRT1 (175), namely resveratrol. So, it might be

interesting to explore other compounds able to activate SIRT1 in the context of NDDs and evaluate if PGC-1α's induction leads to any beneficial therapeutic response (20).

Alternatively, the activation of a PGC-1α target nuclear receptor could be an interesting line of work. Being a transcriptional coactivator, PGC-1α does not have DNA- and ligand-binding domains so it cannot be subject to direct pharmacological interference. Bearing this in mind, any attempt to modify PGC-1α's expression must be directed at regulation of the gene transcription, proteins' alterations or at the interaction with binding partners (54).

Similarly, solutions addressed to the assembly of the PGC-1α-containing transcriptional complex that comprises HAT enzymes (32), members of the thyroid hormone receptor-associated proteins (TRAP)/vitamin D receptor-interacting proteins (DRIP) mediator complex (176) and other proteins are alternative ideas with therapeutic potential.

In conclusion, we can think of several hypothetical approaches suitable for the modulation of PGC-1α, which explains the attractiveness of studying this budding coactivator as a therapeutic target for NDDs (20). All this work on PGC-1α has asserted the relevance of metabolic processes behind neurological disorders.

Meanwhile, precisely thirty years have passed since the discovery of the first CAG-polyQ repeat expansion and since then investigators have tried to and will continue to try to uncover the cause of the most common NDDs, with the ultimate goal being the development of interventions capable of preventing or at least slowing down the progression of these diseases.

One major limitation for drug development in NDDs has been the absence of attested criteria and strong biological markers of disease that can be used as clinical endpoints and efficacy benchmarks. This, adding to the lengthy, symptom-free prodromal phase that marks these diseases, limits clinical trials success, because most of the times patients enrol when they are already in the advanced stages of the disease. Thus, the timing of the treatment must be studied as a pivotal element in the (un)success rate of these drugs and emphasizes the absence of finer diagnostic and predictive tools. Accordingly, the latest developments regarding novel biomarkers, genetic risk factor analysis and imaging strategies with high predictive capacity in predementia stages have incited new optimism (177).

Over the last ten years, gene delivery and safety barriers have been remarkably overcome. However, clinical trials tend to fall between phase 2 and phase 3 due to failure to provide sufficient and unequivocal data regarding efficacy to support its continuation (93). Nowadays,

drug trials based on evidence with a genetic basis seem to have a better chance of succeeding (178).

These discernible challenges do not diminish the potential prospect of using the regulation of PGC-1α expression as an instrument to prevent and/or ameliorate several clinical conditions. Notwithstanding the already known inherent obstacles, coactivators display a few qualities that could be taken advantage of for clinical purposes, such as their kinetic behaviour and capacity to interact with several pathways concurrently (179).

Meanwhile, increased insight into the predisposing factors associated with the onset and advance of the disorders is essential for the creation of disease-modifying therapies (101).

PGC-1α was regarded since the beginning as an excellent prospect to achieve upregulation of genes related to antioxidant defences, along with enhancement of the Krebs cycle and OXPHOS capacity (14). So, therapeutic options to enhance mitochondrial function have been up for debate for a while, but with minor success in clinical trials (180), even after manifest optimistic conclusions in animal models (14).

It should be noted that almost all of these studies exploring PGC-1α's expression and PGC-1α-dependent genes in the brain have neither employed cell type-specific methods, nor assessed neuron-enriched PGC-1α-responsive genes (14). Up until recently, it was difficult to use culture models of differentiated neurons with a naturally high level of PGC-1α for new drug screening (181,182). Screening methods have, in recent years, begun to avoid conventional ones like luciferase reporter assays, finally acknowledging that the behaviour of cell lines is likely to be influenced by cell type and setting (183). Given the recent scientific breakthroughs that enable the culture of cells with neuronal traits, neurons developed from iPSCs or directly induced from fibroblasts are used as launching pads for the development of new drugs targeting NDDs (14,184). However, these cell cultures presumably do not accurately replicate the metabolic or mitochondrial environment (185), but a few studies denote that patient iPSC can retain metabolic modifications linked with disease (181) and evidence indicates that neurons derived from fibroblasts can evade rejuvenation effects of the culture technique (184).

Thus, studies involving direct protein-protein interaction succeeded by a meticulous evaluation of potential off-target effects might lead to a fruitful identification of strong and specific compounds (14) for many diseases, including NDDs.

New cell and gene therapies and their hypothetical yet conceivable applications symbolize a tremendous transformation from traditional medical care, especially since they may enable the

treatment or even the reversal of the underlying pathological mechanisms of the diseases, which would be a paradigmatic shift from symptomatic treatment in the management of NDDs.

9. Conclusions and future perspectives

The need for effective treatments for NDDs remains unmet due to the complexity and multifactorial nature of the molecular mechanisms that underlie these disorders. Additionally, the diversity of the affected population hampers the development of early diagnostic tools and, consequently, innovative disease-modifying therapies.

Several PGC-1α partners and physiological effects have been pinpointed throughout the years, confirming its pleiotropic properties and role as an inducible promoter of gene transcription with great potential to be modulated in multiple disease states. In fact, the evidence gathered suggests that it might be an interesting therapeutic target for several NDDs, given its ability to mitigate mitochondrial dysregulation, which plays a central role in these conditions.

All things considered, even though the interconnection between PGC-1α's regulation and mode of action has yet to be fully deciphered, it is well established that this transcriptional coactivator has emerged as a pivotal intersection between metabolic regulation, redox control and so on. Thus, further studies designed with the intent to understand the mechanisms behind PGC-1α's specific target patterns across different tissues and in diverse physiological environments are required to convert it into a therapeutic target without risking off-target and undesirable results.

Considering the recent advances of genetic therapy and nanotechnology, for example, there is hope for the development of precise and effective new disease-modifying therapies that will be life-changing for people suffering from NDDs and PGC-1α might play a direct or indirect role when that happens, because it certainly has the potential to do so.

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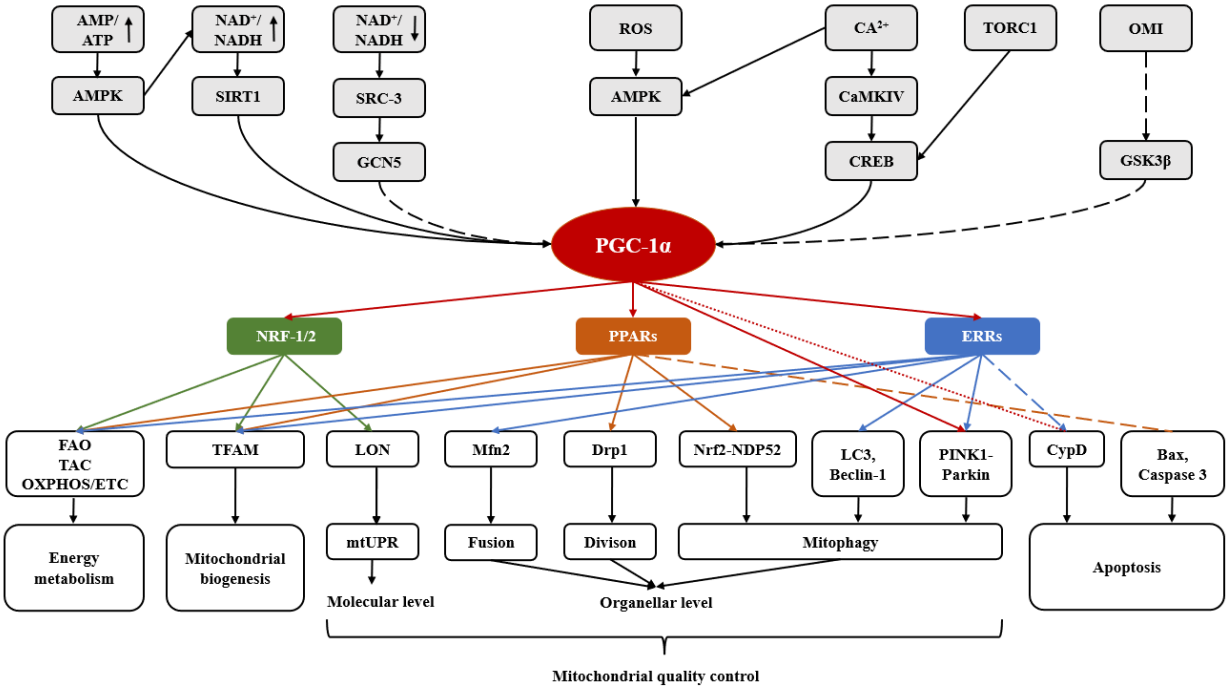
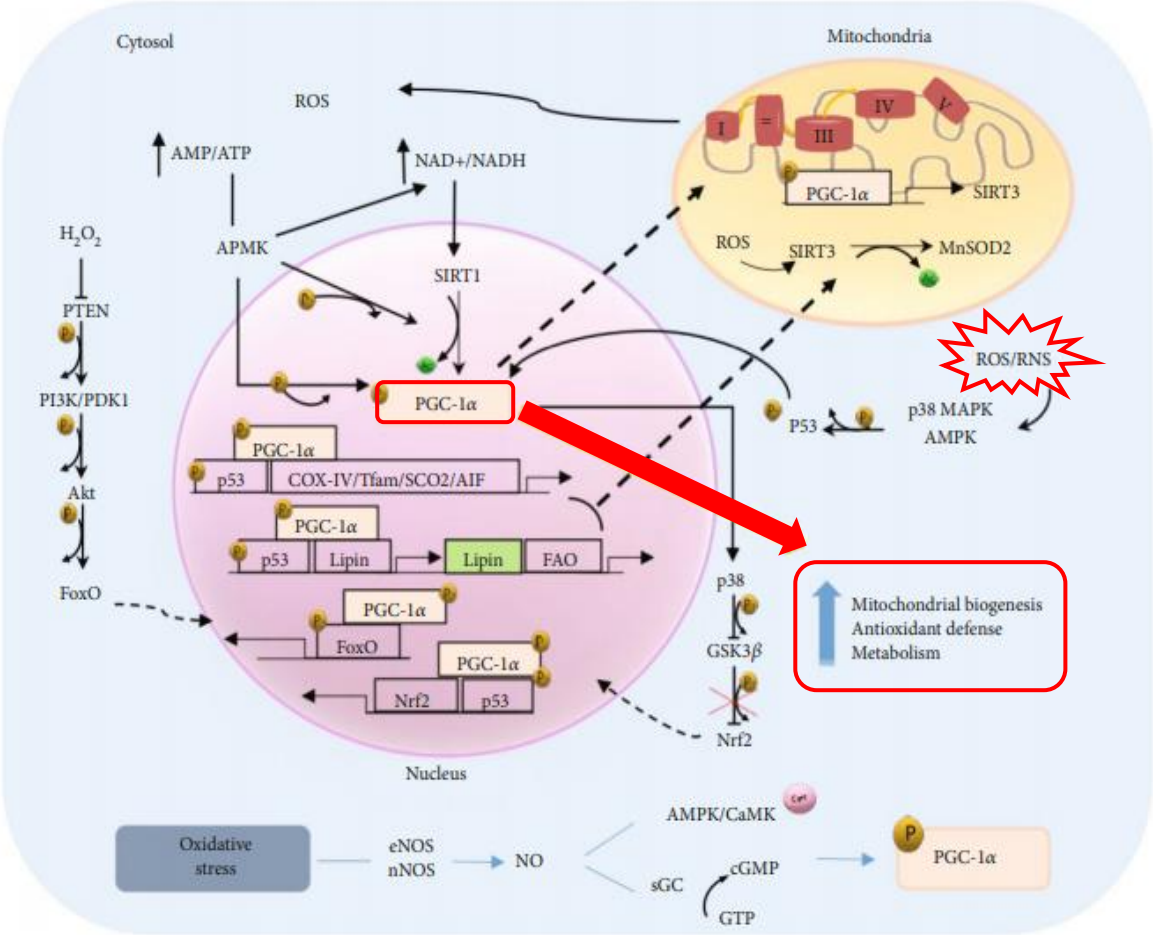
Appendix

A1. PGC-1α and mitochondrial quality control



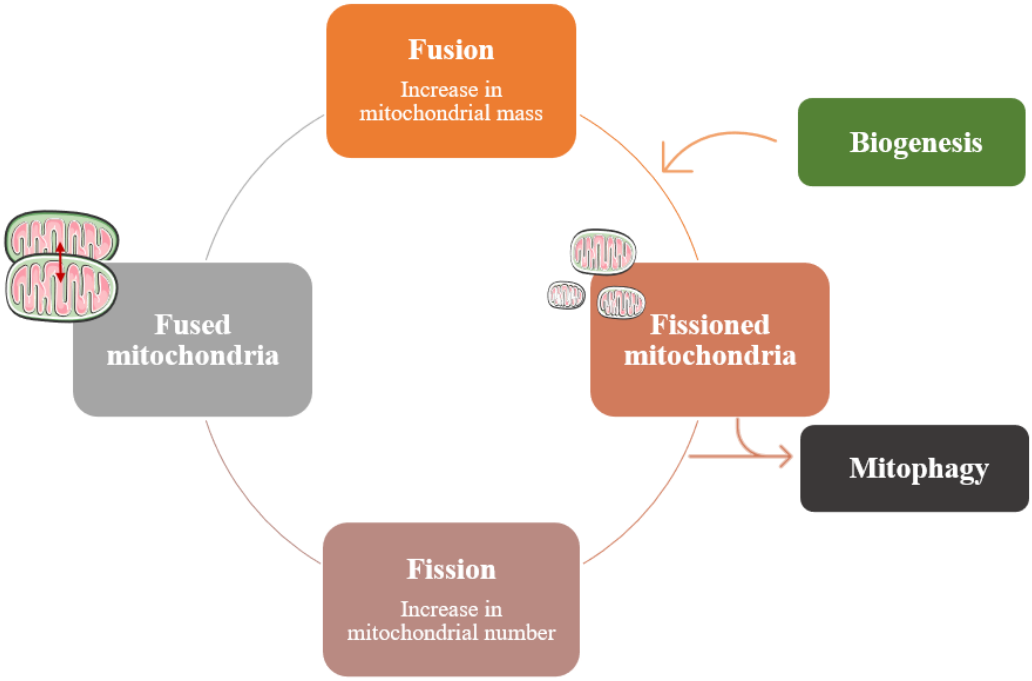
In this figure it is possible to see the connection between different signalling pathways downstream and upstream of PGC-1α and the biologic results of such interactions. Dashed lines = inhibitory pathways; regular lines with arrows = activation pathways; dotted line = mechanism not fully understood. Adapted from (16). AMP = adenosine monophosphate; NADH = nicotinamide adenine dinucleotide (reduced form); NAD^+ = nicotinamide adenine dinucleotide (oxidized form); SRC-3 = steroid receptor coactivator-3; CaMKIV = calcium/calmodulin-dependent protein kinase IV; TORC1 = target of rapamycin complex 1; OMI/HtrA2 = pro-apoptotic serine protease; FAO = fatty acid β-oxidation; TAC = tricarboxylic acid cycle; ETC = electron transport chain; MtUPR = mitochon- drial unfolded protein response; Drp1 = dynamin-related protein 1; Nrf2-NDP52 = Nrf2-nuclear dot protein 52 kDa; LC3 = microtubule-associated protein light chain 3; CypD = cyclophilin D; Bax = Bcl-2-associated X protein.

A2. PGC-1α's signalling pathway in reaction to ROS



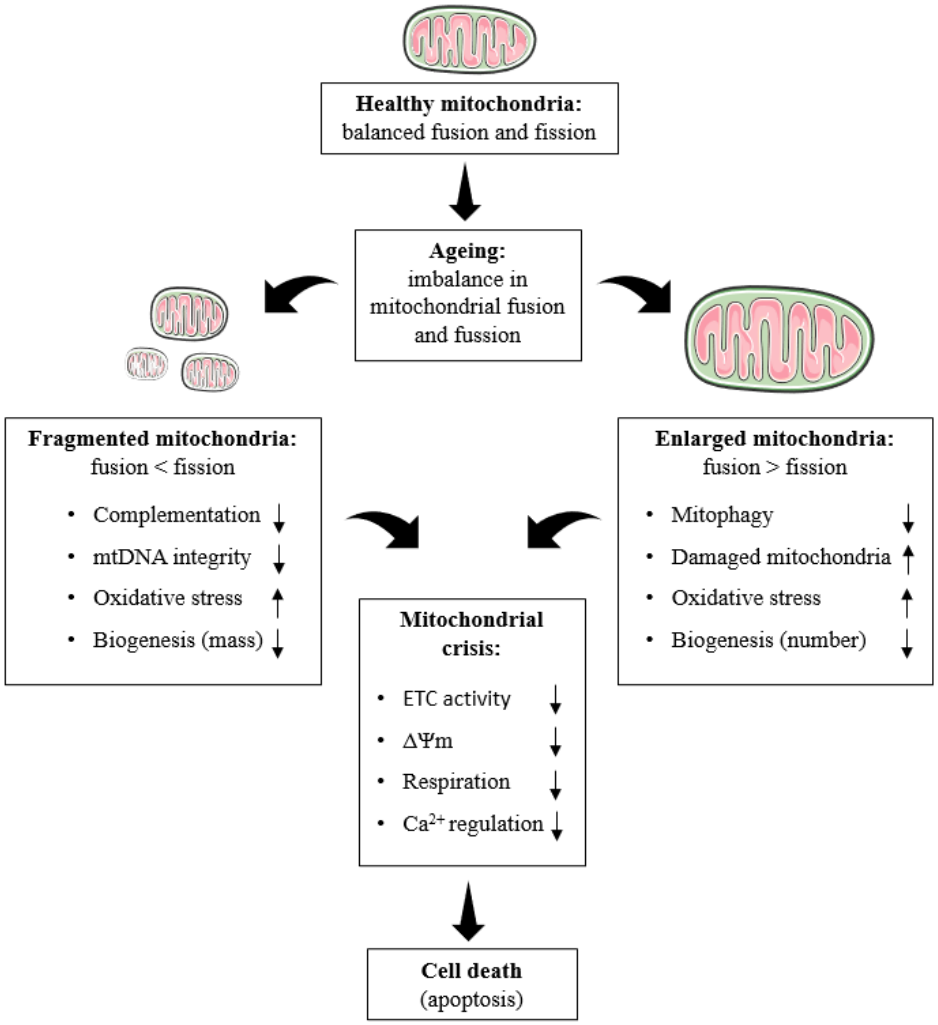
Adapted from (78).

A3. Dynamic between mitochondrial fusion, fission, biogenesis and degradation



Adapted from (98).

A4. Systematic representation of the impact of dysregulation of mitochondrial dynamics on ageing



Adapted from (98).