Universidade de Lisboa

Faculdade de Farmácia

PGC-1α: a metabolic regulator

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Monografia orientada pela Professora Doutora Maria João Gama, Professora Auxiliar

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

De modo a garantir a sobrevivência, os organismos vivos estão numa batalha constante para manter a homeostase energética, um processo fisiológico robusto e coordenado que pode ser definido como a regulação do equilíbrio entre a produção e o gasto de energia. Este processo requer a capacidade de os organismos adaptarem-se a mudanças ambientais, como no caso de atividades físicas extenuantes ou durante um estado de jejum. De maneira a atender às necessidades de ATP, as nossas células usam diferentes modalidades do metabolismo energético na presença ou ausência de oxigênio para produção de energia. Descoberto inicialmente como uma proteína que regulava a termogénese adaptativa na presença de frio por meio da interação com PPAR-γ, o PGC-1α foi considerado um fator central no metabolismo energético. Logo após foram também identificados dois homólogos, o PGC-1β e PRC, e várias isoformas. O PGC-1α funciona como o agente principal da biogénese mitocondrial e fosforilação oxidativa, no entanto, novos dados ao longo dos anos mostraram que o papel fisiológico do PGC-1α estende-se para além do controlo restrito do metabolismo energético, sendo um participante chave na angiogénese, músculo esquelético, gliconeogénese, função cardíaca e outros numerosos processos. A disfunção metabólica é uma característica comum observada em muitas doenças, estas geralmente acompanhadas por uma desregulação na atividade do PGC-1α. Devido a este papel fundamental na homeostase energética, revela-se assim um potencial alvo terapêutico bastante atraente em diversas doenças metabólicas e degenerativas que frequentemente acompanham o avançar da idade. Consequentemente, regular a ação de PGC-1α aumentando sua atividade em certos tecidos apresenta uma terapia adequada e interessante numa grande variedade de patologias, como a sarcopenia, doenças cardiovasculares, doenças neurodegenerativas, síndrome metabólico, diabetes tipo 2 e até mesmo no cancro. O objetivo desta revisão é elucidar como é que o PGC-1α e suas isoformas desempenham suas atividades fisiológicas no organismo, mostrar dados atuais sobre como o PGC-1α está implicado na saúde e na doença, lacunas na literatura e alguns obstáculos que poderemos enfrentar no futuro no que diz respeito ao seu uso terapêutico.

Palavras-chave: PGC-1α, homeostasia energética, biogénese mitocondrial, metabolismo oxidativo e doença metabólica.

Abstract

To assure survivability, living organisms are in a constant battle to maintain energy homeostasis, a robust and coordinated physiological process that can be defined as the regulation of the balance between energy production and expenditure. This process requires the capacity for organisms to adapt in environmental changes like in strenuous physical activity or a fasted state, to fulfill the organism's ATP needs, our cells will enroll in different modalities of energy metabolism in the presence or absence of oxygen. Initially discovered as a protein that regulated adaptive thermogenesis in the presence of cold through interaction with PPAR-γ, PGC-1α was considered a central factor in energy metabolism. Soon after two homologues, PGC-1β and PRC, were identified same with several PGC-1α isoforms. PGC-1α acts as a main driver of mitochondrial biogenesis and oxidative phosphorylation, nonetheless, new data throughout the years have showed us that PGC-1α physiological role extends beyond the strict control of energy metabolism but it is also a key participant in angiogenesis, skeletal muscle fiber-type switching, gluconeogenesis, normal heart function, and other numerous processes. Metabolic dysfunction is a common feature seen in plenty of diseases that generally are accompanied by PGC-1α impairment and dysregulation. Due to this family key role in energy homeostasis, it is unveiled a quite attractive therapeutic potential in various metabolic and degenerative diseases that commonly accompany old age. Hence regulating PGC-1α action by increasing its activity in certain tissues presents a suitable and interesting therapy in a plethora of conditions such as skeletal muscle waste and sarcopenia, cardiovascular disease, neurodegenerative conditions, metabolic syndrome, type 2 diabetes and even cancer. The goal of this review is to shed some light on how PGC-1α and its isoforms perform their physiological activities in the whole body, show novel insights of the current literature about how PGC-1α is implicated in health and disease, knowledge gaps, and some obstacles we might face in the future in regards of its therapeutic use.

Key words: PGC-1α, energy homeostasis, mitochondrial biogenesis, oxidative metabolism, and metabolic disease.

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Abbreviations

ALS - Amyotrophic lateral sclerosis

AMPK - AMP-activated protein kinase

AD – Alzheimer's disease

ApoE - apolipoprotein E

BAT- Brown adipose tissue

BFR – Blood flow restriction

cAMP - cyclic adenosine monophosphate

CaMKIV - calcium/calmodulin-dependent protein kinase type IV

CnA - calcineurin a

CREB - cAMP response element-binding protein

CRE - CREB response element

Clk2 - CDC Like Kinase 2

DMD - Duchenne muscular dystrophy

ERRα - Estrogen-related receptor alpha

eNOS - endothelial nitric oxide synthetase

FAO - Fatty acid oxidation

FOXO1 - Forkhead box protein O1

GLUT 4 - glucose transporter type 4

GSK-3β - glycogen synthase kinase 3 beta

HD - Huntington's disease

HNF4α - hepatocyte nuclear factor 4 alpha

mTOR - mammalian target of rapamycin

NLS - Nuclear localization signal

NO – Nitric oxide

NT- N terminal

NRF - nuclear respiration factor

NMJ - neuro muscular junction

OXPHOS - oxidative phosphorylation

PD - Parkinson’s disease

PGC-1α - peroxisome proliferator-activated receptor gamma coactivator 1-alpha

PPAR - peroxisome proliferator-activated receptor

PRC - PGC-1-related coactivator

RRM – RNA recognition motif

ROS - reactive oxygen species

RXR - retinoid X receptor

SIRT 1 - silent mating type information regulation homolog 1

SOD - superoxide dismutase

UCP - uncoupling protein

VEGF - vascular endothelial growth factor

WAT- White adipose tissue

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1. Introduction

Energy homeostasis is a crucial process to guaranty the survivability of living organisms, it encompasses an astonishing physiological adaptive capability towards environmental changes signaled through external stimuli that represents millions of years of life evolution on earth. To fulfill the organism's ATP needs, our cells will enroll in different modalities of energy metabolism in the presence or absence of oxygen. This means in certain occasions where there is high a demand for energy like in strenuous physical activity or a fasted state our body must quickly adapt by expanding the number of mitochondria or increase substrate utilization. Plenty of molecular pathways have been identified to be associated with the energy metabolism gene program that drives the appropriate response in catabolic states. The gene expression of this response is regulated by transcription factors such as peroxisome proliferator activated receptors (PPARs), forkhead box 01A (FOXO1), nuclear respiratory factors (NRFs), estrogen related receptors (ERRs) are the primary proteins that will ensure cellular energy homeostasis.

The goal of this review is to shed some light on how PGC-1α and its isoforms perform their physiological activities in the whole body, show novel insights of the current literature about how PGC-1α is implicated in health and disease, knowledge gaps, and some obstacles we might face in the future in regards of its therapeutic use.

2. PGC-1α: a master regulator in energy metabolism

Approximately two decades ago, while studying cold-induced adaptive thermogenesis, researchers discovered a direct link between cold exposure, regulation of mitochondrial function and biogenesis caried out by a protein that interacted with *peroxisome proliferator-activated receptor alpha* (PPAR-γ), they later identified it as *peroxisome proliferator-activated receptor gamma coactivator 1-alpha* (PGC-1α) (1). The discovery of this protein lead to profound understating of thermogenesis, skeletal muscle physiology, cellular energy homeostasis, and mitochondrial adaption pathways to different environmental changes**.** In the past few years, there is been a growing amount of data demonstrating PGC-1α's role in certain pathologies such as metabolic syndrome, heart disease, age-related illnesses and neurodegenerative disorders(2). Moreover, there has been recent literature that shed some light on how PGC-1α may be associated with carcinogenesis and neoplasia (3). As the name suggests, PGC-1α acts as a co-activator implying that this type of proteins does not interact directly with DNA and requires transcription factors (activators) to exert its varied biological

functions. Generally, these coactivators operate either by recruiting transcriptional machinery to the gene promoter region altering transcription rate or having intrinsic enzymatic activity targeting chromatin configuration. Coactivators provide complex gene transcription regulation to eukaryotic cells, offering a strong adaptable capability to environmental, physiological changes and can be associated with sensing capabilities (4,5). Some examples of PGC-1α protein-protein interactions include: nuclear respiration factor 1 (NRF1), nuclear respiration factor 2 (NRF2), glucocorticoid receptor (GR), hepatocyte nuclear factor 4 (HNF4), estrogen-related receptors (ERRs), Peroxisome proliferator-activated receptor (PPARs) and retinoid X receptor (RXR)(6).

2.1 The wide family of PGC-1's

This family consists of three homologues: PGC-1α, PGC-1β and PGC-1-related coactivator (PRC). PGC-1α assumes several isoforms such as: PGC-1α-b and c, a splice variant N-terminal (NT)-PGC-1α-a, b and c and PGC-1α2, 3, and 4. PGC-1β and PRC were both discovered by researching similar PGC-1α gene sequences through genomic databases, and seem to not have isoforms as PGC-1α (7,8). Structurally wise, they are incredibly similar, considering they are encoded by different genes. As shown in Fig.1, all three homologues share LXXLL binding motifs involved with nuclear receptor docking with other coactivators, a nuclear localization signal (NLS) and a C-terminal RNA recognition motif (RRM) (7,8). Additionally, there are short arginine/serine rich domains in PGC-1α and PRC but not in PGC-1β, these are commonly called RS domains and they are generally associated with mRNA splicing (9). In terms of biological functions, they all enroll in cellular energy metabolism and mitochondrial biogenesis. Although unlike PGC-1α, PRC was not dramatically up-regulated during thermogenesis in brown fat and it appears to be more involved in proliferative signaling(8). Despite function similarity in other tissues, PGC-1β appears to diverge from its canonical counterpart in the liver, where they seem to regulate antagonistic gene programs and biological functions. PGC-1α is responsible for hepatic gluconeogenesis regulation(10) , while PGC-1β participates in lipogenesis and synthesis of very low density lipoproteins in feed states (11).

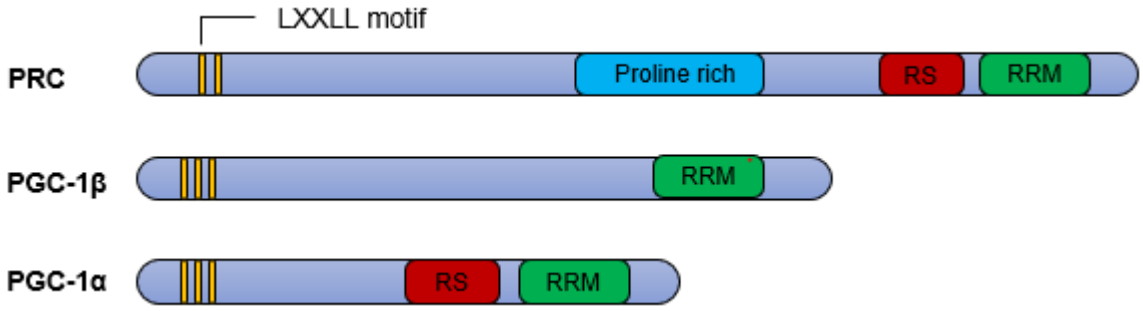

Figure 1: Structural protein domains of the PGC- 1's. LLXXL motifs mediate PGC-1α with transcription factors and other coactivators. The RS (Arginine/Serine rich) and RRM (RNA recognition motif) domains are characteristic of proteins involved in RNA splicing.

Adapted from Villena *et al.* (2015): "*New insights into PGC-1 coactivators: redefining their role in the regulation of mitochondrial function and beyond*" (218)

2.2 PGC-1α isoforms and gene characterization

To achieve such an astonishing protein variety with unique features and functions, eukaryotic cells have developed an elaborate gene program that allows the formation of multiple gene transcripts from a single gene, for such, our cells use intricate processes such as alternative splicing and usage of gene promoters. This ability also permits to establish different expression rates of the same gene in different tissues, one prime example of this phenomenon is *PGC-1α or* PPARGC1A gene. This gene encompasses a genomic region of roughly 67 kB long containing 13 exons. It gives rise to 2 mRNA species derived from the use of two polyadenylation signals, with 6.4 and 5.3 kb in length, respectively(12).

The gene transcription leads to a wide spectrum of proteins with distinct structures and functions, this isoform variety is ensured by use of alternative splicing and different promoter regions. PPARGC1A possess 4 promoter regions: A proximal promoter (PP), an alternative promoter (AP) , a liver promoter (LP) and a distal brain promoter (BP) located 587 kb upstream of AP (2), as shown in Fig.2.

Figure 2: Promoter regions within the PPARGC1A gene. Four promoter regions are included in the PPARGC1A gene: A proximal promoter (PP), an alternative promoter (AP), a liver promoter (LP) and a distal brain promoter (BP) located 587 kb upstream of AP. The PP and AP are separated by 14 kB.

Adapted from: Martínez-Redondo et al. (2015): *"The hitchhiker's guide to PGC-1α isoform structure and biological functions."* (219)

2.2.1 - PGC-1α-a, -b and -c

PPARGC1A proximal promoter is responsible for the transcription of canonical PGC-1α1 and its alternate splicing variant isoform, NT-PGC-1α-a. This promoter appears to have a higher basal expression, while the alternative promoter, located just 14kb upstream, and exhibits a more adaptable response to specific types of stimulation. For instance, β2-adrenergic receptor activation and exercise lead to an increase of PGC-1α-b and PGC-1α-c mRNA levels in rats, both isoforms are transcripts of the alternative promoter (13). It has also been reported that both resistance and endurance training lead to an increase of alternative promoter gene expression originating PGC-1α exon 1b and 1b' derived isoforms. It was also noted that proximal promoter derived transcripts were less inducible and were upregulated only after endurance exercise (14).

PGC-1α-b and PGC-1α-c seem to be quite similar functionally and structurally. In total of 795 amino acids just only 16 N-terminal amino acids in PGC-1α-a (PGC-1α1) are different from those in PGC-1α-b and PGC-1α-c. PGC-1α-b and PGC-1α-c is shorter by four and 13 amino acids, respectively, than PGC-1-a that covers 797 kb in length(13) (Figure 1). Transgenic mice overexpressing PGC-1α-b and PGC-1α-c in skeletal muscle increased mitochondrial biogenesis and fatty acids oxidation(13), an event that can be duplicated with PGC-1α1, although *in vitro* (15).

2.2.2. Liver-PGC-1α (L-PGC-1α) and Brain-PGC-1α (B-PGC-1α) derived isoforms

Liver promoter is located within intron 2 and encodes L-PGC-1α which is identical with the wild type transcripts apart from the deletion of the first N-terminal 127 amino acids. This is a highly conserved genomic region only seeming to be observed in humans and not in other mammals. Therefore, it looks that L-PGC-1α reflects an adaption to more complex pathways in humans (16).

This isoform is generally seen in fasted states with gene expression induced by *forkhead box 01A* (FOXO1), glucocorticoids and *cAMP-response element-binding* (CREB). L-PGC-1α co-activates PPARγ, PPARα and HNF4α but unlike PGC-1α1 it fails to coactivate Liver X receptors (LXRα). Consequence of lacking the N-terminal portion the protein it is devoid of the first LXXLL motif, responsible for recruitment of steroid receptor coactivator-1 (SRC-1)/p300 complex and CGN5, an acetyltransferase. The lack of this sites might explain why the protein does not interact with LXRα. The protein maintains its C-terminal NLS, this makes L-PGC-1α to stay in the nucleus therefore it likely has transcriptional activity. Functionally, the protein participates on an overlap of activities shared with its canonical predecessor and gluconeogenesis, perhaps on a greater extent than PGC-1α1 in the latter.

Gluconeogenesis is achieved by coactivation of HNF4 by PGC-1α. Researchers performed a ChIP assay discovering a direct interaction between the two proteins at the *Phosphoenolpyruvate Carboxykinase 1* (PCK1) promoter site and found that hepatic PCK1 mRNA levels exhibited stronger associations with the novel than with the wild-type transcript levels (16). PCK1 is an enzyme that plays an important role in gluconeogenesis and governs a rate-limiting step in the process (17).

The same group of researchers discovered brain specific isoforms derived from a distant 587kb transcription starting site upstream of the proximal promoter. It appears to be probably more abundant than PGC-1α wild type in the whole brain. Functional domains of the isoform have yet to be unraveled. An additional key fact is that this new brain promoter is located within a genome currently associated with Huntington disease age of onset (18).

2.2.3 NT-PGC-1α, a splicing variant

As stated above, besides different promoter usage, PPARGC1A gene utilizes alternative splicing to yield a wider transcript variety. N-Terminal-(NT)-PGC-1α is a truncated splicing form derived from introducing an early in-frame stop codon between exon 6 and 7 resulting in a 270 aa protein, corresponding to the first N-terminus aa of PGC-1α1 (19). This protein maintains its N-terminal transcriptional activation and nuclear receptors interacting domains but lacks all the rest of the full protein length domains. C-terminal protein components such as RS domains and NLS are missing which might explain the reason the protein is more abundant in the cytosol, although not always the case, since *in vitro* brown adipocytes stimulation with a cAMP analogue can rapidly shuttle NT-PGC-1α back into the nucleus (19).

After analyzing DNA-binding and gene expression profiles of PGC-1α and NT-PGC-1α target genes in brown adipose tissue (BAT) it was reported that they are both broadly

associated with cold exposure transcriptional activity. Besides their known gene targets of oxidative metabolism and mitochondrial biogenesis researchers found they also play a role in ubiquitin-dependent protein catabolism, ribonucleoprotein complex biosynthesis, phospholipid biosynthesis, angiogenesis, glycogen metabolism, phosphorylation, and autophagy (20).

It has been described two additional splicing isoforms named NT-PGC-1α-b, identical to PGC-1α4, and NT-PGC-1α-c.

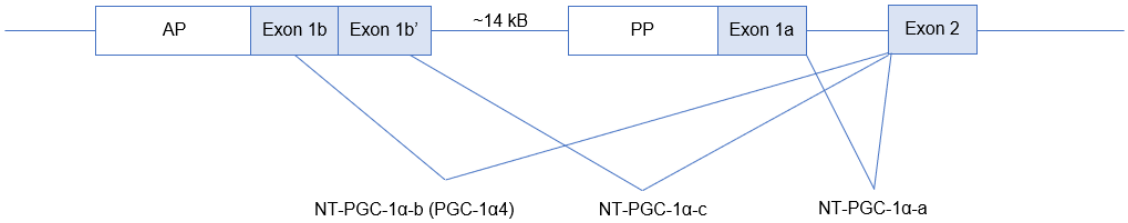

Figure 3: Transcription origins of NT-PGC-1α splice variants. NT-PGC-1α-b, also known as PGC-1α4, is derived from exon 1b and exon 2, NT-PGC-1α-c is derived from exon 1b' and exon 2 while NT-PGC-1α-a is derived from exon 1a and exon 2. Alternative promoter (AP); Proximal Promoter (PP).

Adapted from: Wen et al. (2014): "Effect of Exercise Intensity on Isoform-Specific Expressions of NT-PGC-1α mRNA in Mouse Skeletal Muscle"

Interestingly, the splicing variants are dependent on different stimuli. In mice exon 1a derived NT-PGC-1α-a was induced by both high-intensity exercise and 5' AMP-activated protein kinase (AMPK) activation but not by beta-adrenergic stimulation, whereas expression of exon 1b derived NT-PGC-1α-b and NT-PGC-1α-c were markedly elevated by low-to-high-intensity exercise, AICAR, and clenbuterol (21). This event might reinforce the promoter shift theory from basal proximal promoter PGC-1α's expression to the alternative promoter isoforms and spliced variants expression in an exercise adaptation state.

NT-PGC-1α expression is similarly regulated in both *in vivo and in vitro* models by the physiological signals that regulate full-length PGC-1α, but the truncated protein structure allows for different protein-protein interactions and protein stability and different gene targets despite some function overlap (19).

On contrary to PGC-1α1, NT-PGC-1α expression it is not suppressed by Twist-1, a negative-feedback regulator of PGC-1α in BAT, due to the absence of the C-terminal domain(22). Perhaps this splicing isoform serves a complementary tissue-specific protein that concurrently overlaps and prolongs canonical PGC-1α1 activity (19).

2.2.4 PGC-1α 2, 3 ,4

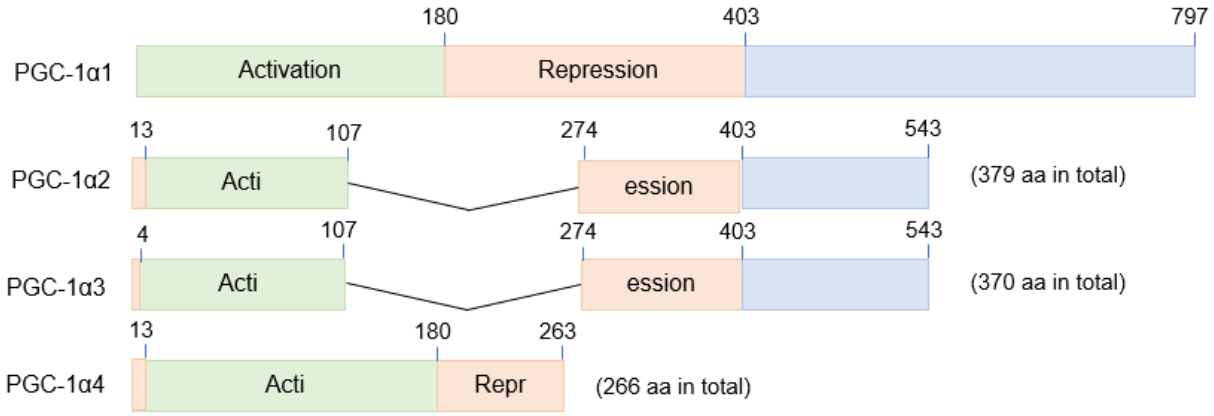

Figure 4: Protein domains and total size of the PGC-1α isoforms. Relative sizes of PGC-1α isoforms. Activation domains are represented in green and repression domains in red. Canonical PGC-1α1 is the largest of all isoforms, whereas PGC-1α4 is the smallest, PGC-1α2 and PGC-1α3 are relatively equal size.

Adapted from: Ruas et al (2012). *"A PGC-1α isoform induced by resistance training regulates skeletal muscle hypertrophy".*

Adding to the vast isoform and splicing variants repertoire, there is the inclusion of three more proteins derived from the alternative promoter named PGC-1α2, PGC-1α3 and PGC-1α4 with distinct properties. PGC-1α2 and PGC-1α3 are 379 and 370 amino acids long, respectively and PGC-1α4 is the smallest protein of all isoforms with only 266 amino acids in length (23). In a sequence of splicing events, its observed exon skipping, where exons 4, 5 and 6 of PGC-1α2 and PGC-1α3 are eliminated, together with exons 9 to 13. PGC-1α4 transcripts are smaller due to the introduction of a stop codon in exon 6. Transcriptional starting sites are also different, PGC-1α2 and PGC-1α4 (NT-PGC-1α-b) share their origin in exon 1b, while PGC-1α3 transcription starts in exon 1b'.(23) PGC-1α2 and PGC-1α3 demonstrate a short half-life similar to PGC-1α1, approximately 30 minutes, whereas PGC-1α4 is considerably more stable exhibiting an half-life of 240 minutes (24). The exon skipping event of alternative splicing leads PGC-1α2 and PGC-1α3 to, in a similarly way observed with previous isoforms, lacking some parts of the activation and repression domains and all C-terminal structural motifs in comparison to of PGC-1α1. Furthermore, PGC-1α4 protein size is less than half of PGC-1α1 protein size, only retaining the N-terminal domain (23).

Interestingly, PGC-1α4 biological role is immensely distinct from its canonical counterpart and the rest of isoforms. In fact, only 98 genes were coregulated by both PGC-1α1 and PGC-1α4, which roughly translates to approximately 15% of shared gene targets. PGC-1α4 seems to regulate muscle hypertrophy and strength adaptations in the skeletal muscle tissue upon resistance training stimuli by inducing Insulin-like growth factor 1 (IGF-1) and myostatin, a known muscle hypertrophy inhibitor (23).

Regarding PGC-1α2 and PGC-1α3, they seem to target 1638 and 1279 genes, respectively and co-regulate approximately 30% of their individual target genes. Genes regulated by PGC-1α2 in myotubes showed to be largely involved in downregulation of the cholesterol biosynthesis pathway, whereas PGC-1α3 targets genes associated with cell cycle control, proliferation, and tissue remodeling, especially, in the regulation of the epithelial adherent junction pathway (24).

3. Regulation of PGC-1α

Expression and activity of PGC-1α are tightly controlled by a plethora of nutritional and environmental signaling, ranging from hormones such as insulin and glucagon, exposure to cold, different types of physical activity and cytokines. This involves a tissue-dependent dual system of transcriptional and post-translational regulation (25).

3.1 Regulation of PGC-1α gene expression

There are 4 main transcriptional factors that directly interact with *PGC-1α gene* and subsequently control gene expression rate. These are: CREB, myocyte enhancer factor 2 (MEF2), activating transcription factor 2 (ATF2) and FOXO1 (26).

CREB serves as main driver of PGC-1α transcription in a wide variety of tissues, it binds to CREB response element (CRE), a well-conserved site in mammals, its recruitment and subsequent PGC-1α gene expression induction is phosphorylation-dependent (24,27) Depending on the tissue, we can observe distinct signal transduction pathways, for instance, in the skeletal muscle, exercise induces a cascade of intracellular calcium levels which activates Calcium/calmodulin-dependent protein kinase type IV (CaMKIV) leading to CREB activation(26,27). On the other hand, in BAT, cold exposure leads to β_3-adrenergic receptor activation triggering protein kinase A (PKA) that recruits CREB this way promoting PGC-1α gene expression.(28) (Fig 5.)

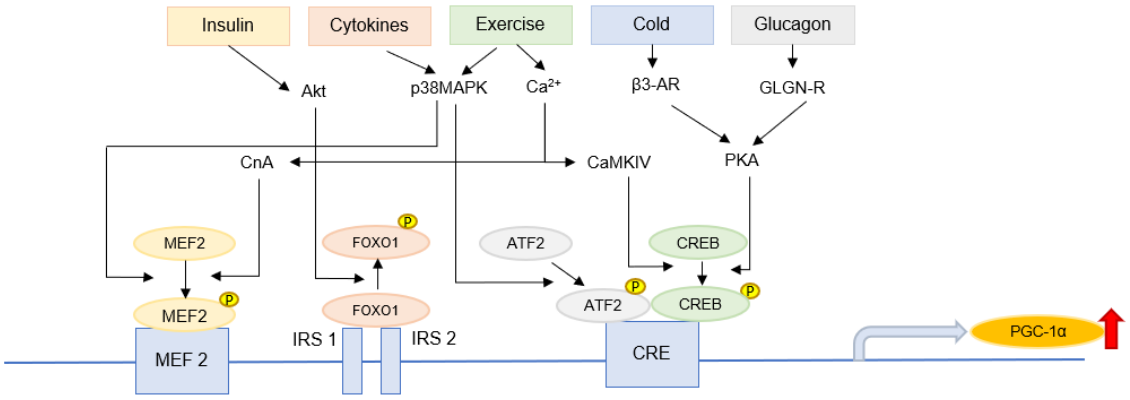

Figure 5: Schematic representation of PGC-1α gene expression in response to different stimuli. There are binding sites for transcription factors like myocyte enhancer factor 2 (MEF2), forkhead box class-O (FoxO1), activating transcription factor 2 (ATF2), and cAMP response element–binding protein (CREB), which all increase PGC-1α transcription. There are 3 identified binding sites in the PPARGC1A gene proximal promoter: a MEF2 site, insulin response sequence (IRS) and CREB response element (CRE). Multiple signaling transduction pathways are involved in PGC-1α expression. Insulin activates Akt, which leads to inhibition of FoxO1; cytokines and exercise activate p38 mitogen-activated protein kinase (p38MAPK), which activates MEF2 and ATF2; exercise also stimulates $Ca2^{+}$ signaling through calmodulin-dependent protein kinase IV (CaMKIV) and calcineurin A (CnA), inducing CREB and MEF2-mediated PGC-1α transcription. Cold activates β3-adrenergic receptors (β3-AR) in skeletal muscle and brown fat, leading to protein kinase A (PKA)–mediated activation of CREB.

Adapted from Fernandez-Marcos et al. (2011): *"Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis"*

p38 mitogen-activated protein kinase (MAPK) is as important middle agent, that in presence of cytokines and exercise, phosphorylating concomitantly ATF2 and MEF2, initiating PGC-1α transcription (28). This pathway can also be indirectly be induced by PKA, besides phosphorylating CREB, it can stimulate p38 MAPK activity and eventual PGC-1α gene expression (29).

Since it answers to cellular energy demands, transcription of PGC-1α is heavily dependent on the body nutritional state, blood-glucose regulating hormones such as insulin or glucagon can interfere with PGC-1α gene expression on a variety of ways. Insulin can inhibit PGC-1α expression through Akt-dependent FoxO1 phosphorylation, which, inactivates and

prevents FoxO1 binding to the PGC-1α promoter (30). Conversely to insulin, glucagon drives PGC-1α gene expression as part of the cellular gluconeogenic response (31).

One additional phenomenon that occurs within PGC-1α gene promoters is a quite complex series of epigenetic modifications which, in recent times, are unraveling novel ways of tissue-specific PGC-1α genetic regulation. DNA methylation is a covalent biochemical modification controlling chromatin structure and gene expression. Methylation can change the activity of a DNA segment without changing the nucleotide sequence. When located in a gene promoter, DNA methylation typically acts to repress gene transcription by making the DNA less accessible to transcription factors. In short, epigenetics modifications act as sort of an cellular on-off genetic switch (32). In the skeletal muscle, in presence of high levels of fatty acids PGC-1α promoter undergoes methylation by DNA methyltransferase 3B (DNMT3B) this way repressing PGC-1α expression (33). Methylation of the same regions has been found to increase in pathological situations such as type 2 diabetes and obesity associated with reduced PGC-1α gene expression (34,35). Hypermethylation of PGC 1α and reduced gene expression is also observed in skeletal muscle of the offspring of obese murine mothers and it was reversed (hypomethylated) by subsequent exercise of the mothers (36). On the contrary, PGC-1α promoter methylation is reduced 3 hours post-acute exercise consequently inducing its expression in muscle cells (37). Such type of modifications are described as well in white adipose tissue (WAT), promoter region of PGC-1α is enriched in lysine-specific demethylase-1 (LSD1) inhibiting PGC-1α gene expression. LSD1 represses PGC-1α transcription by removing the methyl group from mono-methylated and di-methylated lysine 4 of histone H3 (H3K4) (38,39). In absence of flavin adenosine dinucleotide, a necessary cofactor in fatty acid oxidation (FAO), it is noticed downregulation of LSD1 and induction of PGC-1α transcription (38).

3.2 PGC-1α post-translational modifications

As previously stated, an additional way PGC-1α activity is heavily controlled through a wide extent of post-translation protein modifications, which includes phosphorylation, ubiquitination, methylation, and acetylation. It can positively or negatively regulate PGC-1α whether by increasing its proteasomal degradation, therefore reducing intracellular PGC-1α levels or facilitating the recruitment of other transcriptional receptors and coactivators.

3.2.1 Regulation by phosphorylation

P38 MAPK, Akt, glycogen synthase kinase 3β (GSK3β), AMP-activated protein kinase (AMPK) are the best characterized kinases responsible for PGC-1α phosphorylation in multiple sites. AMPK induces PGC-1α biological activities not only by inducing transcription of PGC-1α but also by its direct activation, phosphorylating the threonine-177 and serine-538 residues, moderating thus the co-transcriptional activity of this co-activator in a bilateral regulation (40). P38 MAPK phosphorylates PGC-1α at residues threonine-262, serine-265 and threonine-298 resulting in increased stability (41,42) and preventing of p160 myb binding protein ($p160^{MBP}$) activity, since binding and repression of PGC-1α by p160MBP is disrupted by p38 MAPK phosphorylation of PGC-1α (43). Insulin besides inhibiting PGC-1α gene expression by inactivating FoxO1, induces phosphorylation by Akt intermediation at the serine-570 residue resulting in inhibition of the activity of the PGC-1α (44). The insulin/Akt pathway also participates in the stabilization of CDC Like Kinase 2 (Clk2), which in turn phosphorylates PGC-1α in arginine/serine rich residues leading to a decrease of PGC-1α co-transcriptional activity (45).

PGC-1α is also phosphorylated by glycogen synthase kinase 3β (GSK-3β), which inhibits PGC-1α, increasing its proteasomal degradation in situations of oxidative stress. However, this process remains poorly understood and rather paradoxical, considering that a sign of stress replenishes nuclear amounts of PGC-1α by increasing its transcription and cytoplasmic translation. It is thought that this pathway has greater weight in the regulation of PGC-1α, possibly overcoming the inhibitory pathway mediated by GSK-3β (46). Another form of phosphorylation occurs at serine-194, serine-241, and threonine-256 residues of NT-PGC-1α. This phosphorylation performed by PKA kinase (also involved in the regulation of PGC-1α transcription) blocks export of PGC-1α by inhibiting its binding to the nuclear exporter CRM1 and inducing its accumulation nuclear, thus increasing NT-PGC-1α-mediated transcription (47).

3.2.2 Regulation by acetylation

Curiously PGC-1α appears to serve as an energy-sensing protein that has the capability to react upon different cellular energy levels, adapting depending upon nutrient availability and energy needs. This role is generally associated with AMPK (48,49) which can sense increases in AMP:ATP and ADP:ATP ratios therefore restoring energy balance by inhibiting anabolic processes that consume ATP, while promoting processes that generate

ATP such as oxidative respiration and mitochondria biogenesis (49). Nevertheless, PGC-1α seems to play a complementary part in this mechanism via a quite intriguing acetylation-deacetylation negative feedback loop (Fig.6).

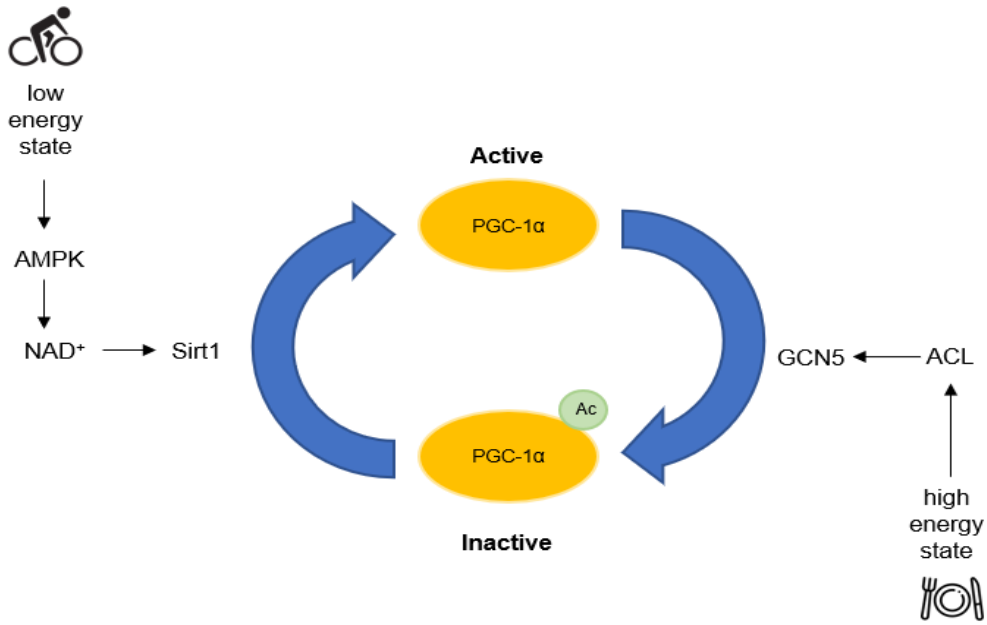

Figure 6: The acetylation-deacetylation PGC-1α negative feedback loop. PGC-1α regulates cellular energy status through a energy-sensing negative feedback loop. In low energy status, AMP-activated protein kinase (AMPK)– enhances Sirt1 activity, mediated by $NAD^{+,}$ and leads to the deacetylation of PGC-1α which, in turn, increases mitochondrial biogenesis and function. When cellular energy is plenty, GCN5 acetylates and inhibits PGC-1α; the acetyl-CoA necessary for this reaction is provided by ATP-citrate lyase (ACL).

Adapted from Fernandez-Marcos et al. (2011): *"Regulation of PGC-1α, a nodal regulator of mitochondrial biogenesis".*

In low energy levels states, like fasting, exercise or oxidative stress, AMPK leads to an increase in NAD^+, promoting Sirt1 activity that will activate PGC-1α through of its deacetylation leading to an eventual increase in energy levels through mitochondrial biogenesis and respiration (50). When energy in the cell is abundant such as in the absence of physical activity or in a postprandial state, GCN5 acetylates PGC-1α, inhibiting its activity (51). This acetylation process requires acetyl-CoA provided by ATP-citrate lyase (ACL), a rate limiting-step enzyme that converts glucose-derived citrate into the required acetyl-CoA (52).

3.2.3 Regulation by other post-translational mechanisms

As previously mentioned, GSK-3β phosphorylates PGC-1α leading to its proteasomal degradation. In addition, the Skp, Cullin, F-box containing (SCF) complex is identified as a ubiquitin E3 ligase, which directly regulates PGC-1α through the ubiquitin-mediated proteolytic system (53). PGC-1α can be methylated by the protein arginine methyltransferase 1 (PRMT1) at residues of arginine 665, 667, and 669, which greatly increases PGC-1α gene expression (54). PGC-1α can also suffer O-linked N-acetylglucosamination by O-linked N-acetylglucosamine (O-GlcNAc) transferase (OGT), which transfers the O-GlcNAc group to serine 333 (55).

4. Systemic and tissue-specific PGC-1α roles: Beyond just a metabolic regulator

PGC-1α is quite extensively characterized as being the main driver of mitochondrial biogenesis and oxidative respiration. Thus, it is commonly associated with highly oxidative tissues which an elevated demand of energy, being amply expressed in the skeletal muscle, liver, brain, heart and BAT. In these tissues PGC-1α expression and activity is regulated by distinct stimuli allowing cellular adaptations towards environmental changes or nutritional state.

Expression of nuclear respiratory factor 1 (NRF1) and nuclear respiratory factor 2 (NRF2) proteins are regulated by PGC-1α, these have been shown to regulate genes of important mitochondrial components such as COX IV, β-ATP synthase and Tfam. In addition, PGC-1α can also bind to NRF-1 and coactivate it, therefore increasing the transcription of even more mitochondrial genes (including mtTfam) (56). Estrogen related receptors (ERR) are also target of PGC-1α and participate in gene networks involved in all aspects of energy homoeostasis as well of mitochondrial biogenesis and function (57).

Additionally, PGC-1α has demonstrated to increase the expression of COXIV and cytochrome C protein levels as well as the steady-state level of mtDNA (56). PGC-1α overexpression transgenic mice also have reported massive increases of mitochondrial content in cardiac myocytes and stimulated cellular respiration (58). Furthermore, PGC-1α/β double knockout mice resulted in lower mitochondrial density in brown fat and the mitochondria exhibit diminished density of cristae coinciding with reduced expression of respiratory genes (59).

PGC-1α participates in upregulation of antioxidant enzymes such as super oxide dismutase (SOD) and mitochondrial uncoupling protein 2 (UCP2), hence increasing cellular reactive oxygen species (ROS) buffering and detoxifying capabilities limiting potential damage

associated with increased mitochondrial respiration and ROS production (60). It was also demonstrated that ROS can induce PGC-1α gene expression (61).

With advancement of current literature, it is noticeable that the scope of action of PGC-1α and its isoforms go further than a bare regulator of mitochondrial biogenesis and oxidative phosphorylation (OXPHOS), participating in important events which assure energy homeostasis and physiological adaption.

4.1 Skeletal muscle

In the skeletal muscle, PGC-1α commands numerous gene programs generally implicated with efficiently supplying myocytes with necessary oxygen and nutrients thus matching their energy needs, either by enhancing mitochondrial function or increasing fuel handling via a powerful angiogenic program.

4.1.1 Angiogenesis

Angiogenesis is a physiological process consisting of the formation of new blood vessels forms from pre-existing ones. Generally, this process occurs by action of Hypoxia-inducible factor-1 (HIF-1), which was found to be chief regulator of the angiogenic process. HIF-1 seems to participate in vasculature formation by synergistic correlations with other proangiogenic factors such as vascular endothelial growth factor (VEGF), placental growth factor (PLGF) or angiopoietins (62).

PGC-1α seems to activate angiogenesis by an HIF1-independent pathway. Overexpression of PGC-1α lead to strong induction of VEGF, angiopoietin 2 and platelet-derived growth factor subunit B (PDGFB) in both *in vivo* and *in vitro* models (63). Moreover, in the same study, overexpression of skeletal muscle PGC-1α in transgenic mice lead to increased capillary density. Conversely, knockout PGC-1α gene mice failed to induce normal neovascularization after induced limb ischemia. The authors reported that PGC-1α co-activates ERRα and leads to the expression of important angiogenic genes such as VEGF (63). PGC-1α/ERRα complex activates HIF2, which also detains angiogenic activity (64).

Remarkably, induction of VEGF alone leads to leaky, disorganized and less efficient vasculature (65). However, it was demonstrated that PGC-1α compensates such occurrence by increasing the secretion of secreted phosphoprotein 1 (SPP1), and the recruitment of macrophages. SPP1 stimulates macrophages to secrete monocyte chemoattractant protein-1 (MCP-1), which then activates adjacent endothelial cells, pericytes, and smooth muscle cells, consequently, help leading to more complete and functional blood vessels. Simultaneously,

induction of PGC-1α in SPP1 deficient mice, leads to immature capillarization and blunted angiogenesis (65). In the same study, adenoviral delivery of PGC-1α into skeletal muscle of either young or old and diabetic mice improved blood flow recovery after hind-limb ischemia. Therefore unveiling a potential therapeutical role of PGC-1α in peripheral artery disease (PAD) (65).

Basal skeletal muscle tissue capillarization does not to require PGC-1α, although it seems to dictate angiogenic training adaptations (66,67). Alternate promoter splice variants such as NTPGC-1α and PGC-1α4 participate in angiogenesis as well. Cultured cells overexpressing NT-PGC1α increased important angiogenic processes such as endothelial migration and tube formation. Transgenic expression of PGC-1α4 in skeletal muscle of mice induces angiogenesis in vivo. Simultaneously, knockout of HIF-1α and both of these isoforms nullified VEFG expression in hypoxic conditions (68).

4.1.2 Neuromuscular junction remodeling

The neuromuscular junction (NMJ) is an extremely specialized synapse which converts an electrical impulse a between a motor neuron nerve and its adjacent muscle fiber on arrival of an electrical signal, calcium will then enter the presynaptic terminal, leading to the release of acetylcholine, a neurotransmitter. Acetylcholine travels across the synaptic gap and binds to acetylcholine receptors in the muscle fibers, this leads to the endplate potential initiating the muscle action potential that results in muscle contraction (69). Among many roles of PGC-1α, one important function appears to be maintaining functional integrity and proper development of the NMJ.

It was demonstrated that there were profound pre-synaptic and post-synaptic changes in the morphology and function of the NMJ in mice overexpressing muscle-specific PGC-1α. Quantification of the nerve terminal branches within the region of the NMJ revealed a significantly higher number in nerve branches as well as an increased total length and branching complexity in the sternocleidomastoid of PGC-1α transgenic mice compared with wild type. It was additionally reported higher amount of pre-synaptic vesicles in nerve terminals together with synaptophysin, a pre-synaptic regulator of vesicle fusion, was likewise increased in the PGC-1α transgenic mice when compared with wild type. It was also noted improvement of post-synaptic morphology (70).

Neuronal function and integrity, such as neurotransmitters biosynthesis and synaptic vesicle assembly, require a highly amount of energy. In the same previous study, researchers assessed whether neuronal structural and functional changes seen were accompanied by a

metabolic adaptation. Curiously, they noted a significant increase in mitochondrial volume density in the PGC-1α transgenic mice in comparison to wild type (70), although such occurrence should be expected, taking in consideration that PGC-1α is a main driver of mitochondrial biogenesis and function.

Furthermore, it was described in a different study a process of a fiber type-specific retrograde muscle-to-motor-neuron influence of muscle fibers on their innervation, indicating a crosstalk between muscle fiber and its respective motor unit. Such hypothesis derived from the observation that PGC-1α transgenic mice have higher amounts of synaptic vesicle glycoprotein 2A (SV2A)-positive slow motor neurons. The mice in the study exhibit more motor units containing fast fibers innervated by slow motor neurons suggesting that the new slow fibers within the motor unit, converted through PGC-1α overexpression, induced retrograde conversion of fast to slow motor neurons (71).

4.1.3 Fiber-type switching

PGC-1's is heavily involved in the formation of oxidative fibers such as type I and IIA myofibers. Transgenic mice overexpressing PGC-1α showed increasing levels of oxidative fibers type I, IIa and robustly induced the expression of genes specifically enriched in type I fibers, such as myoglobin and troponin I (72). However, its counterpart PGC-1β only seemed to induce the expression of type IIx fibers in PGC-1β overexpression transgenic mice (73).

The main transcription factor that mediates this phenomenon seems to be myocyte enhancer factor-2 (MEF2). It was demonstrated that PGC-1 α increases the expression of type I fibrillar proteins by co-activating MEF2 transcription factors, thereby coordinating the expression of both metabolic and contractile properties of type I myofibers (72). Although PGC-1α is relevant in fiber-type switching it is not the only protein responsible for it. Mice that lacked PGC-1α expression showed to still retain normal amounts of type I/IIA fibers and appropriate exercise-induced mitochondrial biogenesis, suggesting that there are more hidden compensatory mechanisms involved in the formation of oxidative fibers(74,75). Moreover, as previously stated PGC-1α coactivates ERRα, this complex leads to the expression hypoxia inducible factor 2 (HIF2) that also induces the development of slow-twitch muscle fibers (64).

4.1.4 Regulation of muscle systemic bioenergetics and organ crosstalk

Physical training PGC-1α-mediated muscle adaptations evoke a fascinating systemic action in distal organs and tissues. Reason for such derives from the fact that PGC-1α

regulates the expression of an interesting group of metabolites and small peptides named myokines, which are released from the skeletal muscle (76).

Expression of PGC-1α in the muscle increases the transcription of fibronectin type III domain-containing 5 (FNDC5), a membrane protein that is cleaved and secreted as irisin, a novel discovered myokine. Irisin acts on WAT in *vitro* and *in vivo* stimulating UCP1 expression and brown-fat-like development. Irisin is induced with exercise in mice and humans, intriguingly, mildly increased irisin levels in the blood causes an increase in energy expenditure in mice with no changes in movement or caloric intake. Besides, researchers found improvements in obesity and glucose homeostasis after irisin expression (77).

β-aminoisobutyric acid (BAIBA) is a myokine obtained from the metabolism of valine with unique properties. It reduces skeletal muscle insulin resistance and inflammation, increases WAT browning, enhances hepatic FAO and suppresses hepatic lipogenesis (78–80), consequently, upregulating and optimizing whole body energy expenditure. PGC-1α directly increases plasma BAIBA levels and its elevation is inversely correlated with cardiometabolic risk (81).

One additional benefit of skeletal muscle-PGC-1α induced by physical exercise is the expression of yet another myokine named meteorin-like (Metrnl) which is upregulated by PGC-1α4. Metrnl biological role is similar to Irisin and BAIBA, leading to improved glucose tolerance, expression of genes associated with BAT thermogenesis and anti-inflammatory action. But contrary to Irisin and BAIBA, Metrnl does not act directly on adiposities but rather through an indirect action via IL-4 and IL- 13 depend-recruitment producing eosinophils into adipose tissue (82).

Current literature shows a clear proven correlation between physical activity and the improvement of mental well-being, brain development and cognitive function (83,84). The exact molecular mechanisms behind this occurrence are still mostly unknown, but skeletal muscle PGC-1α has been recently associated with a surprising distal effect on the brain. PGC-1α participates in the modulation of the metabolism of kynurenine, a neurotoxic metabolite resulting from the degradation of tryptophan, recently emerging as one of the main mediators of induced depression by stress. This mechanism increases resistance to the development of stress-induced depressive behavior. Both PPARα/δ and PGC-1α activate the muscle expression of the kynurenine aminotransferase (KAT) genes and concomitantly the local conversion of kynurenine to kynurenic acid. Unlike kynurenine, kynurenic acid is unable to cross the blood-brain barrier and thus preventing neuroinflammation and synaptic dysfunction (85).

Concomitantly, PGC-1α can also induce hippocampal brain-derived neurotrophic factor BDNF, widely studied neurotrophin, through activation of the FNDC5 pathway (77). BDNF is commonly associated with brain health, memory, cognitive function, and synapse plasticity (86,87).

A newly discovered systemic crosstalk happens in the skeletal muscle tissue itself, between distal muscle groups. Surprisingly, it was reported that high-intensity leg cycling alters PGC-1α1, PGC-1α4 and other proteins molecular expression to resistance training in the triceps. Researchers employed a randomized cross-over design in which each subject performed one session of high-intensity interval cycling followed by upper-body resistance exercise (ER-Arm) and another session of resistance exercise only (R-Arm). The level of PGC-1α1 mRNA increased to greater extent in ER-Arm group than R-Arm after 90 min of recovery, as was PGC-1α4 mRNA after both 90 and 180 minutes (88).

4.1.5 Skeletal muscle hypertrophy and anti-atrophic effects

Exercise elicits a plethora of molecular and physiological adaptations, one of which is muscle hypertrophy, in particularly, to resistance training. The molecular pathway responsible for hypertrophy and muscle protein synthesis it is a complex system involving a great number of intervenient and signaling cascades. Current data shows that mammalian target of rapamycin complex 1 (mTORC1) is the key, but not only, mechanism that leads to hypertrophic and strength adaptations in resistance training (89).

The exact stimuli of hypertrophy it is still largely unknown although there is some compelling evidence linking PGC-1α4 to possible mediator of muscle hypertrophy (23). PGC-1α4 induces the expression of the anabolic hormone insulin growth factor 1 (IGF-1) and suppresses myostatin, a potent protein that inhibits muscle growth and differentiation (23). PGC-1α4 also induces expression of the protein-coupled receptor 56 (GPR56) and its collagen III ligand, which in turn stimulate the mammalian target of rapamycin (mTOR) in cultured myotubes promoting hypertrophy (90).

Considering that mTOR is closely related to hypertrophy, Samuelsson *et al.* hypothesized that activation of this pathway could upregulate PGC-1α4, or vice versa. Furthermore, they studied how nutritional state can influence PGC-1α4 activity and gene expression (91). Taking into consideration that mTOR activity is upregulated by leucine intake(92–94), both in humans and in mice after resistance training, we might speculate that leucine or branched chain amino acids (BCAA) could increase PGC-1α4 in sort of a similar fashion. For such, researchers selected eight male subjects and performed heavy resistance

exercise (10 sets × 8-12 repetitions at ~75% of 1 repetition maximum in the leg press machine) on four different occasions, ingesting in random order a solution containing essential amino acids (EAA), BCAA, leucine, or flavored water (placebo) during and after the exercise. They then proceeded to take biopsies from the vastus lateralis muscle before and immediately after exercise, as well as following 90 and 180 min of recovery. Contrary to the initial hypothesis, they reported that intake of EAA or BCAA attenuated the stimulatory effect of exercise on PGC-1α4 expression by 50% 3 hours after exercise, whereas intake of leucine alone did not alter this response. PGC-1α1 expression was unaltered in all 4 occasions. This results also found no activation of the mTORC1 by PGC-1α4 (91).

Another potential pathway candidate for activation or expression of PGC-1α4 could be exercise induced metabolic stress. Metabolic stress is defined as a physiological process that occurs during exercise in response to low energy that leads to metabolite accumulation such as lactate, inorganic phosphate, ions of hydrogen and ROS in muscle cells (95). It is currently theorized that this event can induce an anabolic signaling for muscle growth and adaptations on energy metabolism (96). Physical exercise performed under the condition of blood flow restriction (BFR) accentuates metabolic stress (97,98) and might concomitantly enhance training adaptations to both myogenic and mitochondrial pathways through the expression of canonical PGC-1α1 or its isoforms. Although data in this field is to some extent conflictive and contradictory.

On one hand there is some recent evidence demonstrating that endurance exercise associated with BFR (EE-BFR) indeed induced PGC-1α mRNA expression (99–101). On the other hand, a study evaluated how PGC-1α1 and its isoforms changed in moderate to high intensity endurance exercise with BFR and found that the expression of PGC-1α1, 2, 3 and 4 remain unaltered, contrary to recent evidence (102). As discussed in the previous study a possible candidate for PGC-1α expression could be lactate (88) and ROS (61), both byproducts of endurance exercise metabolism. In fact, lactate has been shown to significantly increase the level of PGC-1α in L6 myoblasts cells (103).

The data presented by these studies reinforces the need to elucidate how exactly canonical PGC-1α1 and respective isoforms are being regulated under conditions induced by physical exercise, such as metabolic stress. There is some data suggesting that BFR training can be beneficial in clinical musculoskeletal rehabilitation(104) or in bed rest patients suffering from muscle wasting (105) but it is still unknown how exactly PGC-1α is regulated in these conditions.

Finally, PGC-1α demonstrates anti-atrophic activity. Forkhead box O3 (FoxO3) is a transcription factor characterized by induction of atrophy-related ubiquitin ligases atrogin-1 and MuRF-1 therefore causing profound loss of muscle mass (106,107), transgenic mice overexpressing PGC-1α caused a much smaller decrease in muscle fiber diameter and a smaller induction of atrogin-1 and muscle RING-finger protein-1 (MuRF-1) compared to the control in denervation and fasting conditions, leaving us to assume that PGC-1α suppresses FoxO3 skeletal muscle catabolic gene program (108)

All things considered, we should highlight the importance of clarifying the molecular pathways governing PGC-1α's role in cellular metabolic stress signaling and skeletal hypertrophy, in order to possibly develop new pharmacological compounds that could mimic skeletal muscle protective effects in pathological and physiological conditions like age-related sarcopenia, cachexia or bed rest immobilization.

4.2 Liver

Regulation of PGC-1α in the liver is closely related to the organism's nutritional state, especially in fasting or postprandial conditions. The change between a fed state to a fasted condition demands a fast metabolic adaptation in the liver to nutrient deprivation to assure energy homeostasis, these changes consist in the activation of gluconeogenesis, fatty acid β-oxidation and synthesis and secretion of ketone bodies. PGC-1α has been shown both *in vitro* and *in vivo* studies to be a necessary component in the liver fasting response (109).

PGC-1α directly coactivates gluconeogenesis in fasted states via its interaction with transcription factors, such as FoxO1, and nuclear receptors, like HNF4α and glucocorticoid receptors (GR). PGC-1α will induce the expression of hepatic gluconeogenesis genes like phosphoenolpyruvate carboxykinase or glucose 6-phosphatase (110–112). This fasted state gluconeogenesis gene response is a process dependent of PGC-1α transcription by glucocorticoids and glucagon, which are the major hormonal signaling in fasting (112).

As previously stated, Sirt1 positively regulates PGC-1α by deacetylation (50) and its hepatic expression and activity is increased in fasted state (113). A quite intriguing fact is that PGC-1α deacetylation by Sirt1 upregulates hepatic gluconeogenesis without intervening with the mitochondrial gene program in the hepatocyte (113), this represents a prime example on how PGC-1α post-translational modifications can regulate specific gene programs in different tissues. In similar way, S6 kinase 1 (S6K1) phosphorylases PGC-1α in presence of insulin and nutrients downregulating its ability to regulate the expression of gluconeogenic genes without changing its capacity to regulate mitochondrial respiration and OXPHOS. The reason for this specific regulation is because S6K1 phosphorylases PGC-1α in residues S568 and S572 of

the RS domain which interfere with PGC-1α ability to bind to HNF4α failing to coactivate gluconeogenic genes while leaving uninhibited PGC-1α interaction sites of ERRα and PPARα, crucial factors for mitochondrial biogenesis (114). Additionally, insulin contributes to the phosphorylation of PGC-1α by Akt in the residue S570 leading to a decrease in gluconeogenesis (44).

Interestingly, the liver is probably the tissue that best exemplifies PGC-1α and PGC-1β opposing roles by regulating antagonistic gene programs and physiological processes. Contrary to PGC-1α, PGC-1b does not regulate the expression of gluconeogenic genes, instead it serves as a central regulator of hepatic lipogenesis and lipoprotein secretion in response to dietary intake of fatty acids, in particularly, saturated and trans-fatty acids (115).

Notably liver PGC-1α might also integrate the circadian rhythm energy metabolism regulation. PGC-1α is rhythmically expressed in the liver and induces through coactivation of the ROR family of orphan nuclear receptors expression of clock genes, like *Bmal1* (Arntl) and *Rev-erbα* (Nr1d1), via coactivation of the ROR family of orphan nuclear receptors. In addition, PGC-1α null mice unveil abnormal diurnal rhythms of activity, body temperature and metabolic rate (116).

4.3 Heart and cardiovascular functions

The heart, like in skeletal muscle tissue, is an incredible dynamic tissue with a high demand for ATP. Most of its energy supply is derived mainly from lipids. In matter of fact, more than 70% of all substrates used for ATP generation are derived from fatty acids, with the remaining sources being glucose, lactate, ketone bodies, and amino acids (117). Considering this, control of mitochondrial function and OXPHOS is crucial for cardiac health, making PGC-1α a critical regulatory protein in the control of cardiac mitochondrial number and function in response to energy demands, being strongly induced in the neonatal heart of mice, for instance (117).

A great body of data regarding PGC-1α role in the heart has been obtained through extensive gain-of-functions studies, which have allowed us to understand how PGC-1α is involved in the regulation of cardiac function and the role in the etiology of cardiomyopathies. In PGC-1α deficient mice, the heart showed damage to mitochondrial respiratory function and reduced expression of important mitochondrial genes (118–120). PGC-1α knockout mice showed reductions in mitochondrial enzymatic activities and ATP levels, despite retaining mitochondrial volume (120). These mice heart are much less capable of increasing work output in response to chemical or electrical stimulation and demonstrated an increase in

circulating atrial natriuretic peptide, a hallmark of cardiomyopathy (120). The same research group have additionally showed PGC-1α knockout are also more susceptible to develop heart failure in response to transverse aortic constriction (TAC) although, surprisingly, induction of PGC-1α in cells via catecholamine treatment can reverse the mitochondrial genes inhibition (119), indicating PGC-1α as a promising therapeutic target in heart failure. By contrast, overexpressing PGC-1α a modest increase in mitochondrial number but at the cost of disturbance in the mitochondrial ultrastructure and development of cardiomyopathy (121). Another study reported that supraphysiological expression of PGC-1α in murine heart induces severe cardiomyopathy from unconstrained mitochondrial proliferation that results in premature death (122).

The dysfunctional and hypertrophic heart shift its energy substrate from dependence on FAO to anaerobic glycolysis (123,124). This metabolism shift is generally associated with PGC-1α and PPARα downregulation, therefore decreased ability to upregulate genes involved in FAO and OXPHOS(125). It is observed decreased PGC-1α transcription and activity in mice models of hypertrophic heart(126) and ischemic cardiomyopathy (127).

Additionally, PGC-1α contributes to mitochondrial biogenesis by regulating cardiac phospholipid synthesis. Mice lacking PGC-1α revealed reduced expression of the gene encoding CDP-diacylglycerol synthase 1, an enzyme involved in cardiolipin synthesis, important component of the inner mitochondrial membrane, and other phospholipid species synthesis (128).

Cardiovascular health is closely correlated with heart disease. The normal function and maintenance of the vascular system is key for a normal heart condition and prolonged life expectancy. The endothelium is responsible for regulating blood flow, largely through agonist and shear-mediated mechanisms. Shear stress on the vascular endothelium releases vasodilatory nitric oxide (NO) and stimulates the production of PGC-1α (129). NO and PGC1α are known to independently combat ROS production, thereby limiting endothelial dysfunction (130).

Supporting this, recent data indicate PGC-1α role in dictating endothelial function through regulation of endothelial NOS (eNOS) expression. Craige *et al.* used mice with endothelial specific loss or gain of function, reporting that endothelial PGC-1α is suppressed in angiotensin-II (ATII) induced hypertension (131). Mice with endothelial PGC-1α knockout were more exposed to hypertension in response to ATII, whereas overexpressed endothelial PGC-1α protected the vasculature from dysfunction. They demonstrated endothelial PGC-1α

expression protects from vascular dysfunction by promoting nitric oxide bioactivity through ERRα induced expression of eNOS (131).

There has been a growing amount of data linking PGC-1α in the prevention of atherosclerosis, one of the most prevalent cardiovascular disease in the western society. In short, the atherosclerotic process involves the invasion of the arterial wall by bone marrow–derived inflammatory monocytes, where then they differentiate into macrophages. The macrophages then ingest circulating lipids and transform in the so-called foam cells. The foam cells are responsible for formation of the atherosclerotic plaque. A recent study reported that skeletal muscle-specific PGC-1α overexpression suppresses atherosclerosis. In the study researchers divided rats into two groups, one group of apolipoprotein E-knockout mice (the deletion of Apo E gene leads to the development of atherosclerosis) and a second group of Apo E-knockout mice but overexpressing skeletal muscle PGC-1α. They found the atherosclerotic lesions in ApoE-KO/PGC-1α mice were 40% smaller than those in ApoE-KO mice, concomitant with the reduction in vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1) mRNA and protein levels in the aorta. Furthermore, they reported PGC-1α-dependent muscle myokines, Irisin and BAIBA were responsible for the inhibition tumor necrosis factor α (TNFα) induced VCAM-1 gene and protein expression. BAIBA also inhibited TNFα-induced MCP-1 gene expression (132) . These findings reinforce skeletal muscle PGC-1's powerful systemic activity. On the other hand, PGC-1α is also found in macrophages inhabiting atherosclerotic plaques, and PGC-1α overexpression such as conjugated linoleic acid treatment can inhibit foam cell development by preventing oxidized lipid uptake into macrophages (133).

4.4 Brain

A large quantity of ATP is consumed by the neural tissue using glucose as its primary energy source (134) and seems to moderately express PGC-1α when compared to other organs (135). Regardless, a high amount of ATP is consumed by neurons to preserve their axonal transport and ionic membrane gradient, depending on oxidative metabolism to obtain energy for this function (136). Considering such, it is reasonable to expect that PGC-1α dysfunction could potentially lead to neurodegeneration and poor neurological prognosis. Besides regulating neuronal energy metabolism, PGC-1α engages in the formation of important neuronal structural components such as the α2 subunit of sodium pumps in astrocytes and neurofilament proteins (137). Moreover, brains of PGC-1α knockout mice showed loss of neurons and critical structural disturbances like neuronal microvacuolation (138), a pathophysiological process found in a great quantity of neurodegenerative diseases

such as Lewy body disease, frontotemporal dementia, cortico-basal degeneration and Alzheimer's disease (139).

Neuronal mitochondrial ROS production must be constantly recycled to protect neurons from free radicals and oxidative damage. ROS accumulation has been linked to neurodegeneration and loss of neuronal function (140). PGC-1α drives neuronal mitochondrial antioxidative capabilities and reduces inflammation. Nijland *et al*. performed *in vitro* studies in human primary astrocytes that overexpressed PGC-1α showing that they produce less ROS and were more resistant to ROS-induced cell death when compared with the control group. Interestingly, neuronal cells co-cultured with PGC-1α overexpressing astrocytes were protected against oxidative stress compared to neuronal cells co-cultured with control astrocytes (140). This phenomenon might be explained by PGC-1α upregulating ROS detoxifying enzymes like, superoxide dismutase and UCP2 (60).

At last, PGC-1α overexpressing astrocytes drastically reduced the production and secretion of the pro-inflammatory mediators like interleukin-6 and chemokine ligand 2 (141), hence possibly limiting neuronal damage induced by inflammation.

4.5 Adipose tissue

BAT and WAT are two main types of adipose tissue, which are morphologically and metabolically distinct from each other, partially exerting opposite physiological roles. WAT is characterized by mainly lipid storage and some endocrine function, whereas BAT is set apart by maintaining body temperature homeostasis through adaptive thermogenesis, containing less and smaller triglyceride-filled droplets and much higher number of mitochondria when compared to WAT. PGC-1α induces uncoupling protein 1 (UCP1) expression in response to cold exposure through adrenergic activation, thus driving adaptive thermogenesis (1). One remarkable event occurrence in adipose tissue is WAT brown-differentiation, a process where WAT can convert to a “brown-like” state with prolonged cold exposure or exposure to certain β-adrenergic compounds. This event is completely induced via the PGC-1α–UCP-1 axis.

4.6 Kidney

In recent times a new organ that was found to be heavily regulated by PGC-1α is the kidney. Renal solute reabsorption, removal of waste in the blood and maintaining electrolyte homeostasis are physiological processes with a high demand for energy. Thus, the kidney, particularly, proximal tubular and medullary thick ascending limb cells exhibit high mitochondrial density for ATP generation (142). FAO in tubular cell mitochondria is the main

source of renal energy a process regulated by carnitine palmitoyl-transferase 1 (CPT1) as the limiting-step enzyme (142,143). Importantly, tubular cells are quite prone to kidney injury and mitochondria serve as crucial organelle preventing apoptotic cell death and renal stress (144). PGC-1α being an important mitochondrial regulator, is therefore, ultimately involved in normal physiological renal tissue function and disease prevention.

In renal tissue, PGC-1α seems to be mostly expressed in the proximal tubules. *In vitro* overexpression of PGC-1α in primary cultures of proximal tubular cells increased the number of mitochondria , respiratory capacity, and mitochondrial proteins, indicating the role of PGC-1α in proximal tubular homeostasis (145). Even though genetically PGC-1α deficient mice showed no signs of altered kidney size (118) they reveal increased serum blood urea nitrogen and creatinine levels, possible indicators lower renal filtration rate and kidney function. A recent study by Zhang *et al.* used diabetic mice to model diabetic kidney disease (DKD) and administered rosiglitazone, a PPARγ agonist, to induce endogenous PGC-1α expression. They revealed that endogenous PGC-1α expression exhibited protective effects against renal oxidative stress, glomerulosclerosis and tubulointerstitial fibrosis in experimental DKD (146). Furthermore, numerous *in vitro and in vivo* studies demonstrate that PGC-1α expression levels are increased in both acute and chronic kidney injury, possibly serving as a compensatory mechanism in these pathologies (142). Zhang *et al.* additionally revealed yet another quite intriguing cell-specific PGC-1α regulation. Podocytes are less metabolically active and have a less PGC-1α tolerance. Increasing PGC-1α levels in podocytes induce podocyte proliferation and collapsing glomerulopathy development, characterized by segmental and global collapse of the glomerular capillaries, marked hypertrophy and hyperplasia of podocytes (146).

5. How PGC-1α is implicated in cancer metabolism: A foe or an ally in tumor growth?

To survive and grow in nutrient-starved, hypoxic and oxidative environments cancer cells go through a process termed metabolic reprogramming, considered one of the many hallmarks of cancer, this includes a metabolic shift to glycolysis, this being the preferable source of energy (147). Besides, increases in amino acid and lipid metabolism and mitochondrial biogenesis have all been observed in cancer development and tumorigenesis(147). All these adaptations offer the tumor an enhanced ability to proliferate, migrate and invade other tissues, while being resistant to apoptosis. Lately a great amount of data showed that PGC-1α plays an important role in cancer, therefore it is relevant to understand how its action is implicated in tumor metabolism and metastasis, allowing for potential new therapeutic targets to be unveiled.

PGC-1α can intervene in oncogenesis by increasing the expression of antioxidant genes which protect cancer cells from intrinsic ROS production or from chemotherapy induced oxidative stress (148), enhancing the catabolism of glucose and fatty acids, and promoting gluconeogenesis and lipogenesis in tumor cells (149). PGC-1α expression is indeed altered in biopsies and *in vitro* studies in a great quantity of tumors including breast cancer (150), melanoma (151), pancreatic adenocarcinoma (152), ovarian cancer (153), prostate cancer (154), colon cancer (155) and more recently gallbladder cancer (156).

Surprisingly there are two phenotypes of melanomas with different metabolic and phenotypic profiles, one with increased PGC-1α expression and the other with low levels of PGC-1α transcription, both with distinct tumor progression outcomes (151). Oncogenic overexpression of PGC-1α occurs through microphthalmia-associated transcription factor (MITF) which confers an increase in proliferative and survival capacity, mainly by protecting the tumor of oxidative stress, but simultaneously, suppresses the invasive properties of this oncogenic phenotype (151). Oncogenic PGC-1α induces transcription of inhibitor of DNA binding 2 protein (ID2), which in turn inactivates Transcription factor 4 (TCF4), an important pro-metastatic program activator. Conversely lack of PGC-1α transcription results in decreased melanoma cell proliferation, however, with ability to form metastases more aggressively (151).

In the case of breast cancer, Cai *et al.* conducted a prospective long-term follow up study, observing increased levels of PGC-1α plasma concentrations of breast cancer patients when compared to the control group and it was generally correlated with clinicopathological features and worse prognosis (157). The PGC-1α / ERRα axis pathway appears to be a positive regulator in breast cancer cells enhancing the expression of glutamine metabolism (158), promoting pro-metastatic cell migration and invasion *in vitro* and lung metastasis *in vivo* (159). Another study showed that oncogenic PGC-1α can induce neovascularization in mammary tumors, possibly through HIF1-independent induction of VEGF, therefore increasing tumor nutrient supply (63,160). Furthermore, the PGC-1α / ERRα axis is implicated in the proliferation and invasion of NOZ cells, a cellular model of gallbladder carcinoma.

The c-MYC oncogene is a known cancer metabolism regulator, one of many participants responsible for metabolic reprograming. Sancho *et al.* reported that c-MYC/PGC-1α ratio determines pancreatic cancer stem cells (CSC) metabolic phenotype. MYC seems to downregulate PGC-1α transcription in CSC, thus dictating a more glycolytic phenotype. Contrastingly, CSC expressing higher levels of PGC-1α and lower levels of c-MYC demonstrate increased OXPHOS and mitochondrial numbers, rendering this phenotype a perfect target for metformin by mitochondrial complex I inhibition (152).

Similarly, to melanoma, prostate cancer has two subpopulation types with opposite PGC-1α expression. PGC-1α induces tumor growth in a subpopulation of androgen-dependent prostatic cancer cells, by activation of the androgen receptor and its target genes, concurrently, the same study showed that inhibition of PGC-1α in this cancer subtype led to cell-cycle arrest at G1 phase repressing tumor growth (154). In contrary, injection of cells overexpressing PGC-1α into an androgen-independent prostate cancer mouse model reduced metastases formation and progression (161).

PGC-1α suggests having a tumor suppressing role in some tumors. Overexpression of PGC-1α in human epithelial ovarian cancer cell line Ho-8910 induced the expression of pro-apoptotic proteins such as of B-cell lymphoma 2 (Bcl-2) and Bcl2-associated X protein (Bax)(162), thus halting neoplastic progression. Induction of PGC-1α in HT29 and HCT116 colorectal cancer cells induced apoptosis, but this time via ROS accumulation (155).

In conclusion, tracing neoplastic metabolic profile is proving to be a valuable theragnostic tool in cancer. Besides, as data above suggests, PGC-1α can serve multiple roles in cancer, depending on tumor phenotype. Firstly, it can function as a biomarker, such as in the case of breast cancer, where changes in PGC-1α cellular expression can help predicting tumor severity and prognosis. Secondly, it can assist in the correct therapy selection considering tumors with high PGC-1α expression generally prefer OXPHOS as their main source of energy and have high mitochondrial density. We can select mitochondrial inhibitors like metformin disrupting neoplastic energy production, such in the case of pancreatic cancer with low levels of c-MYC/PGC-1α ratio.

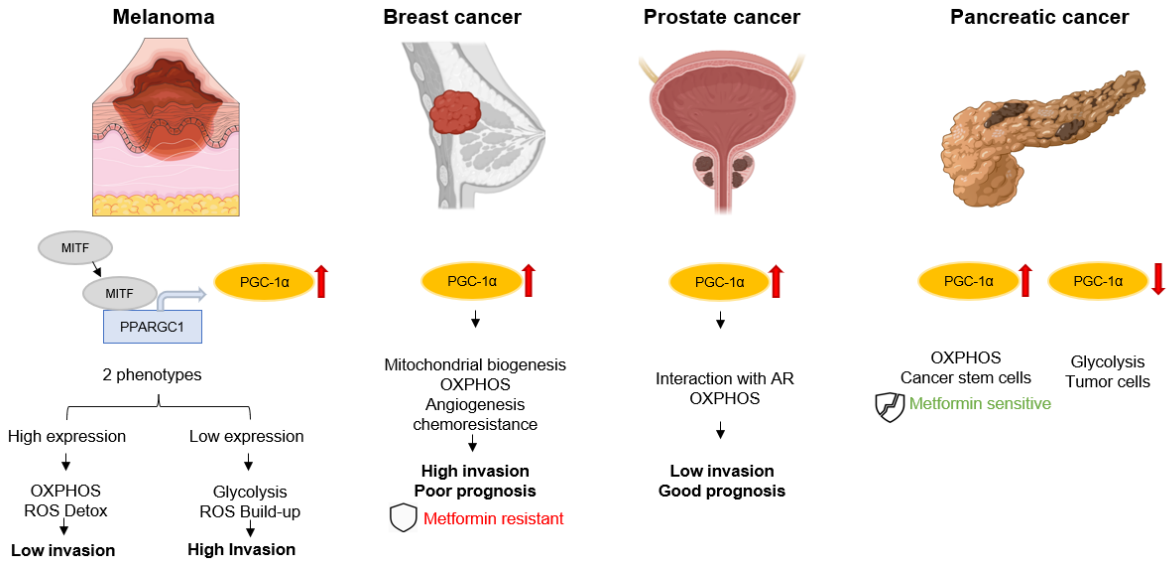

Figure 7: Visual representation on how PGC-1α is implicated in various cancers. In melanoma, microphthalmia-associated transcription factor (MITF) can lead to PGC-1α transcription, we also observe two different phenotypes: one with PGC-1α high expression levels resulting in a low tissue invasion, whereas the phenotype with PGC-1α low expression leads to metastasis. In breast cancer, high PGC-1α expression leads to an aggressive tumor phenotype with a high invasion rate and poor prognosis. On the contrary, in prostate cancer high PGC-1α expression can reduce invasion rate. Similarly to melanoma, it is reported two phenotypes with different PGC-1α expression rates in pancreatic cancer. High PGC-1α expression renders the cancer sensible to metformin, but low PGC-1α expression leads to a more glycolytic tumor phenotype. Oxidative phosphorylation (OXPHOS); reactive oxygen species (ROS); androgen receptors (AR).

Adapted from Bost et al. (2019) *"The metabolic modulator PGC-1α in cancer."*

6. Therapeutic value of PGC-1α: how is it implicated in disease?

Considering its broad function in energy homeostasis and overall importance, PGC-1α constitutes an attractive therapeutic target in numerous types of diseases ranging from metabolic syndrome, cardiovascular disease, sarcopenia to neurodegenerative pathologies. Manipulating and targeting PGC-1α tissue-specific gene expression or improving its transcriptional, half-life and co-activation activities might reveal a quite attractive therapy.

6.1. Catabolic states, sarcopenia and muscle wasting diseases

Conditions and diseases that result in significant loss of muscle mass and strength such as cancer treatment or cachexia, post-surgery bed rest, renal failure or age-related sarcopenia are all possible targets for PGC-1α intervention. It was reported *in vivo* that in catabolic states involving disuse and denervation like, cancer cachexia, renal failure, diabetes PGC-1α expression in skeletal muscle was diminished (163). Ectopic expression of skeletal muscle canonical PGC-1α1 has been demonstrated to improve muscle atrophy associated with aging, starvation or denervation (164). It has also been reported that transgenic mice overexpressing PGC-1α lead to the suppression of skeletal muscle atrophy and myofiber-type composition during hindlimb unloading (165) . As previously discussed, PGC-1α engages in the remodeling of neuromuscular junction (NMJ) by activating broad neuromuscular gene program and improving postsynaptic NMJ architecture (70,166). The NMJ plays a paramount role in maintaining skeletal muscle activity and normal function, its disruption occurs during aging or neuromuscular diseases, including Duchenne muscular dystrophy (DMD) and amyotrophic lateral sclerosis (ALS). Thus, maintaining proper and healthy neuromuscular activity will lead to skeletal muscular protection from catabolic and atrophic signals (166).

DMD is a progressive muscular pathology caused by a mutation in the dystrophin gene. The absence of this protein leads to progressive muscle degeneration eventually leading to loss of independent ambulation by early adolescence, scoliosis, cardiomyopathy, respiratory insufficiency, and reduced life expectancy (167). Overexpression of PGC-1α mdx rats, a rat model used to study DMD by causing a point mutation in the dystrophin gene, lead to positive results when compared to the control, at 6 weeks of age transgenic mice overexpressing PGC-1α had 37% less muscle injury compared with placebo treated muscles, resistance to contraction induced injury improved 10% likely driven by a five-fold increase in utrophin, a known dystrophin homologue, and an increase in dystrophin-associated complex members (168). The reported data illustrates that the PGC-1α pathway might serve as a valuable rescue and suppression in the progression of this disease.

Increasing PGC-1α expression may be an excellent way to combat drug-induced myopathies, a common and serious side effects of popular drug classes like statins(169,170). It was reported that statins increase the expression atrogin-1, MuRF1 and myostatin, all known and powerful atrophic proteins(171,172). Two recent studies demonstrate that overexpressing skeletal muscle PGC-1α does, in fact, prevents statin-induced myopathies (173,174), while decreased skeletal muscle PGC-1α expression further exacerbated statin toxicity (173).

6.2. Cardiovascular disease

One characteristic that generally co-occurs in cardiovascular disease is metabolic dysfunction. PGC-1α serves in the adaptation of increased cardiac workload and vascular maintenance, thus we could hypothesize that some degree of PGC-1α abnormal expression might accompany cardiovascular disease. As previously stated, PGC-1α deficient mice are prone to develop heart failure in response to transverse aortic constriction and induction of PGC-1α in cells via catecholamine treatment can reverse the mitochondrial genes inhibition (119).

Cyclin-dependent kinases-9 (CDK9) is a kinase implicated in cardiac hypertrophy in mice myocardium (175), CDK9 can inhibit PGC-1α expression leading to decreased mitochondrial gene expression and predisposes heart failure in mice (176). It has been reported cardiac energy metabolism dysfunction in the pathogenesis of diabetic cardiomyopathy (177). Curiously, the diabetic heart relies exclusively on mitochondrial FAO (178) and it can be driven by PGC-1α in the heart of insulin-resistant mice (179). Simultaneously, overexpression of PPAR-α exclusively in mice heart resulted in increased PGC-1α expression, increased myocardial FAO and decreased glucose uptake and oxidation, a metabolic phenotype similar to that of the diabetic heart (180). Contrary to the previous data, Bugger *et al.* studied Akita mice, a mouse model of type 1 diabetes, and found that their heart demonstrated decreased PGC-1α expression, together with reduced OXPHOS, ATP synthesis, and mitochondrial cristae density (181). Reinforcing the need to better elucidate how exactly is metabolism dysfunction and PGC-1α implicated in diabetic cardiomyopathy.

PGC-1α notable angiogenic program promotes cardiovascular protection and improved function. PGC-1α plays a role regulating vascular endothelial homeostasis (182). The endothelium is responsible for regulating blood flow, largely through shear-mediated mechanisms. Shear stress on the vascular endothelium releases vasodilatory nitric oxide (NO) and stimulates the production of PGC-1α (129). Moreover, PGC-1α expression protects from vascular dysfunction by promoting nitric oxide bioactivity through ERRα induced expression of eNOS (131). Additionally, NO and PGC1α are known to independently combat ROS production, thereby limiting endothelial dysfunction (130) .

6.3. Neurodegenerative diseases

Sufficient energy production is paramount for overall proper neural tissue function and survival. Impairment of mitochondrial and OXPHOS gene program consequently leads to neurodegeneration and neuroinflammation by ATP deficiency, oxidative stress and failure of

ROS detoxification (183). Thus, it is reasonable to expect that some mutations in mitochondrial function genes are present in neuronal degeneration. In fact, mitochondrial and oxidative metabolism dysfunction is a common feature reported in multiple pathologies such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD).

Briefly speaking, AD is mainly characterized for accumulation of neurofibrillary tangles of Tau protein and amyloid plaques, the latter consisting of aggregated β amyloid peptides (Aβ). Qin *et al*. collected postmortem samples of AD patients brain showing decreased PGC1α expression (184). They also overexpressed PGC1α in Tg2576 neurons, reporting inhibition of hyperglycemic-mediated Aβ production (184). Likewise, another study found decreased levels of secreted Aβ in PGC-1α overexpressing n2a neuroblastoma cells (185). Moreover, the expression of PGC-1α seems to downregulate BACE1, a key enzyme involved in Aβ synthesis (186). Besides BACE1 downregulation, it was recently demonstrated that PGC-1α reduces Aβ deposition via increased vitamin D receptor expression (187).

The progressive loss of dopaminergic neurons in the *substantia nigra* is a hallmark of PD. The exact cause of PD is still mostly unknow, but it is generally associated with the aggregation of α-synuclein protein and to some extent mitochondrial dysfunction and neuroinflammation(188). In samples acquired from symptomatic PD patients, Zheng *et al.* observed genes like PGC-1α had decreased expression when compared with healthy controls (189). This occurrence derives from downregulation of PGC-1α by Parkin-Interacting Substrate (PARIS). In the absence of Parkin, PARIS is bound to PGC-1α gene promoter and suppresses its expression, although in the presence of Parkin, PARIS suffers proteasomal degradation leading to transcription of PGC-1α and subsequently, neuroprotection (190). In addition, overexpression of PARIS results in a decrease in PGC1α expression and selective death of dopaminergic neurons, which can be prevented by co-expression of either Parkin or PGC-1α (191). Intriguingly and contrary to expectations, two studies using adenoviral vector-mediated overexpression of PGC-1α lead to dopaminergic neuron impairment and loss (192,193). Previous data might suggest that supraphysiological expression seen in these types of studies results in harmful neuron adaptions like excessive mitochondrial activity, proliferation, and ROS toxicity.

Whereas increasing PGC-1α using pharmacological agents yields considerable better results. PPARα agonists like rosiglitazone confers protection in cultured human neuroblastoma SH-SY5Y cells against mitochondrial dysfunction produced by MPTP, a complex I inhibitor and neurotoxin used to study PD (194). This highlights the need for performing studies that externally express PGC-1α like with pharmacological agents other that transgenic PGC-1α overexpression, considering that the later might mislead us in *in vivo* and *in vitro* studies.

Similarly to PD and AD, HD is a genetic disease caused by accumulation of a mutated toxic form of a protein named huntingtin. This accumulation leads to harmful interaction with normal neuron activity, eventually resulting in neurodegeneration that clinically manifests with psychiatric disturbances, cognitive deterioration, and motor impairment (195). Notably, it is observed that PGC-1α levels are reduced in HD model mice and lentiviral-mediated delivery of PGC-1α in these type of mice provides neuroprotection (196). Furthermore, it has been identified PPARGC1A gene polymorphisms associated with age of HD onset (18,197,198).

One surprising finding was that it has recently been considered that PGC-1α could be associated with neuropsychiatric conditions like in bipolar disorder (BD) (199) despite much limited evidence. Currently the only genetic correlation with the PPAR family in BD is with the PPARD, the gene related to PPARδ receptor, that is associated with PGC-1α (200). Geoffroy *et al.* performed a pharmacogenetic study on the clock genes in patients suffering from BD. Although using a modest sample size, preliminary results associate lithium's response, a common drug used to treat BD with an undefined mechanism of action, with the RAR-related orphan receptor-a gene (RORA) and the PPARGC1A gene. It should be highlighted that researchers found that the link between the response of lithium and the PPARGC1A gene did not remain significant after Bonferroni correction possibly due to the small sample size (201). Moreover, primary neuronal cultures treated with valproate, a drug used to treat mood symptoms in BD, intriguingly showed that PPARδ activity was reduced (202). All things considered, previous data simply shows, if not, an indirect way that PGC-1α could be involved in BD, more evidence is required to demonstrate a more robust association of PGC-1α and BD if there is any.

6.4. Metabolic syndrome, obesity, and the insulin sensitivity "dilemma"

In current years, it has been observed a profound change in dietary habits, more precisely, we see an increase in sedentary lifestyles and poor food choices resulting in a prevalence of obesity throughout western societies. Obesity is generally correlated with type 2 diabetes, cardiovascular disease and hepatic steatosis in a condition denominated metabolic syndrome (203). This condition is usually accompanied by a state of chronic low-grade inflammation and oxidative stress which most likely contributes for metabolic disturbances. For such reasons, faulty or even absent PGC-1α activity might serve as one of numerous causes for metabolic syndrome (204), besides, It can be observed a single nucleotide polymorphism in the PPARGC1A gene correlated with relative risk of obesity and insulin resistance (205).

Heinonen *et al*. measured PGC-1α and OXPHOS genes expression levels in isolated primary mature adipocytes of obese co-twins and found they were downregulated when

compared to lean counterparts which might suggest obesity influence on metabolic complications (206). Remarkably in a different study, the same research team reported epigenetic modifications in the PPARGC1A gene, more specifically, hypermethylation in two CpG sites of obese co-twins that equates to repressed gene expression (207). As previous data indicates, PGC-1α has a prevalent position in the development and progression of obesity, thus, emphasizing the need for studying possible new molecular pathways where PGC-1α can be involved in weight gain.

Considering PGC-1's broad metabolic functions and pivot role in energy homeostasis it is expectable to speculate a promising role regarding PGG-1 action in insulin sensitivity and contribution towards new therapies in patients suffering from type 2 diabetes, a disease characterized by glucose metabolic disturbance.

The decrease in mitochondrial mass and gene expression in tissues of diabetic patients has been associated with a reduction in the levels of PGC-1α and/or PGC-1β. Two studies demonstrated that PGC-1α induced Glucose transporter type 4 (GLUT-4) which is the primary receptor responsible for glucose uptake in skeletal muscle (208,209). Furthermore, in experimental models of diabetes, Sirt3 and FOXO3a expression levels were significantly reduced and, consequently, decreased PGC-1α expression due to reduced FOXO3a bidding to PGC-1α canonical promoter. Conversely, overexpression of Sirt3 in these models could increase FOXO3a deacetylation and PGC-1α upregulation, allowing for ROS detoxification and improved insulin sensitivity. Oxidative stress is implicated in the progression of diabetes complications, in fact, *in vitro* high glucose treatment of rat glomerular mesangial cells leads to downregulation of PGC-1α, mitochondrial fragmentation accompanied by ROS and mesangial cell hypertrophy. These pathological alterations were reversed by transfecting mesangial cells with pcDNA3-PGC-1α, therefore suggesting PGC-1α as plausible protective player in diabetic nephropathy (210). More surprisingly is that there are various genetic studies that point out polymorphisms in the PPARGC1A gene associated with type 2 diabetes (211–213) .

In reality and despite past studies, current literature reports contrary and paradoxical data. Mice with skeletal muscle-specific deletion of PGC-1α, PGC-1β or both simultaneously do not show any signs of insulin resistance, despite a variable degree of mitochondrial dysfunction (209,214,215). Astoundingly, a study showed that transgenic mice overexpressing PGC-1α specifically in muscle develop peripheral insulin resistance, although with an increase in mitochondrial content and oxidative metabolism (216). Likewise, there is contradictory data in regards PGC-1's regulation of GLUT-4 since considering that there is one study

demonstrating that overexpressing PGC-1α actually leads to lower mRNA levels compared to the control group (214).

Finally, it was recently reported that overexpression of PGC-1α does not improve insulin sensitivity. To reach that conclusion, researchers performed a glucose tolerance test administrating 2 g/kg of D-glucose solution and measured blood glucose levels at 15, 30, 60, and 120 minutes to evaluate the impact of muscle PGC-1α overexpression on insulin resistance in aged animals. The results showed transgenic PGC-1α and wildtype mice had similar glucose excursions, and similar kinetics of glucose clearance, after glucose administration (217).

7. Closing remarks and future perspectives

Over the years it has been observed that PGC-1α action in our body extends beyond the strict control of mitochondrial biogenesis and oxidative phosphorylation but also in the regulation of angiogenesis, immune response, skeletal muscle exercise adaptions and a remarkable cross-systemic effect. These are all prime examples of new cellular and physiological processes that have been described to be regulated by canonical PGC-1α1 and its isoforms. Furthermore, we have learnt how PGC-1α is implicated in a plethora of diseases such as in cardiovascular dysfunction, sarcopenia, neurodegeneration and even cancer. Despite current advances, there are clear knowledge gaps in the literature especially in regards on how exactly each isoform is regulated and their specific physiological functions.

PGC-1α is a very powerful regulator in various gene programs but there is still yet a lot to learn on how to correctly manipulate its activity to yield the best possible outcomes. We do see improved results of its manipulation in plenty of metabolic and degenerative conditions, however supraphysiological expression of this protein can lead to undesirable consequences. A recent study reported that the overexpression of PGC-1α in old, aged mice had beneficial effects on muscle fatigability and protected from sarcopenia but at the cost of strength and age-related trabecular bone loss. Studies have also reported that supraphysiological expression of PGC-1α in the heart or in neurons can result in adverse results.

The main caveat to all this is to proceed with caution and understand how to correctly manipulate PGC-1α activity with respect to maintaining its level within the proper physiological range, therefore preventing the stated undesirable consequences. For that we ought to learn on how to moderately increase their action in the respective tissue either by regulating its expression or post-transduction activity via pharmacological activation, for instance. An

example of such might include the regulation of isoforms like PGC-1α4 or NT-PGC-1α that promote angiogenesis without excessively promoting oxidative metabolism.

8. References

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