REVIEW

Aging, senescence and mitochondria: the PGC-1/ERR axis

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Abstract

Aging is a degenerative process that results from the accumulation of cellular and tissue lesions, leading progressively to organ dysfunction and death. Although the biological basis of human aging remains unclear, a large amount of data points to deregulated mitochondrial function as a central regulator of this process. Mounting years of research on aging support the notion that the engendered age-related decline of mitochondria is associated with alterations in key pathways that regulate mitochondrial biology. Particularly, several studies in the last decade have emphasized the importance of the estrogen-related receptor (ERR) family of nuclear receptors, master regulators of mitochondrial function, and their transcriptional coactivators PGC-1s in this context. In this review, we summarize key discoveries implicating the PGC-1/ERR axis in age-associated mitochondrial deregulation and tissue dysfunction. Also, we highlight the pharmacological potential of targeting the PGC-1/ERR axis to alleviate the onset of aging and its adverse effects.

Key Words

- ▶ aging
- ▶ nuclear receptors
- ▶ transcription factors
- ▶ metabolism
- ▶ mitochondrion

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Introduction

During the last century or so, humans have learned to more efficiently recognize and evade pathogens, provide a continuous supply of food, lower the rate of accidental deaths and cure or manage a number of diseases. The main consequence of these accomplishments is a human population with an elevated individual lifespan marked by the progressive and inevitable deterioration of our physiological functions. Among many alterations, aging is characterized by degradation of bone and joints, cardiovascular and muscular insufficiency, weakened renal function, neurodegeneration and increased onset of cancer (Khan *et al.* 2017). Several theories have been suggested to explain the biological causes

of aging. The first link between aging and metabolism was presented by Max Rubner in 1908 who proposed the rate-of-living theory, postulating that the faster an organism's metabolism, the shorter its lifespan (Arking *et al.* 1988). Since then, aging and metabolism have been repeatedly connected from the Free Radical Theory of Aging (FRTA) by Harman in 1958 to the conception of mitohormesis in 2007 (Liochev 2013, Ristow & Schmeisser 2014). Despite certain discrepancies, all these theories agree that aging and metabolism are intrinsically linked and have one common actor, mitochondria, and one effector, reactive oxygen species (ROS) (Kauppila *et al.* 2017).

Mitochondria, the cellular powerhouse and metabolite factory, produce most of the energy required for biological processes and correspondingly consume the bulk of intracellular oxygen while generating ROS. The FRTA first implied that ROS randomly oxidize molecules such as proteins, lipids and DNA, resulting in the accumulation of molecular modifications over time, cellular dysfunctions and aging-associated disorders (Liochev 2013). While ROS can indeed oxidize their targets, decades of work on the cellular redox system have shown that variations in mitochondrial ROS production serve as an essential communication mechanism to coordinate metabolism with other cellular processes to maintain homeostasis (Finkel & Holbrook 2000). Cells act to sustain ROS production and ROS detoxification in constant equilibrium as an imbalance in mitochondrial function can result in the development of severe disorders (Gorman *et al.* 2016). In aging cells, mitochondria appear to be dysfunctional and comprise several disruptions such as DNA mutations, altered mitochondrial dynamics, elevated ROS production and impaired electron transport chain (ETC) and ATP production. As a result, these transformed mitochondria participate in inducing cellular senescence, chronic inflammation and a decline in stem cell activity (Lopez-Otin *et al.* 2013). The importance of mitochondria in aging is upheld by accumulating evidence demonstrating that cellular metabolic modifications or pathways regulating mitochondrial biology influence lifespan and the aging phenotype (Finkel 2015, Zhang *et al.* 2018).

Maintaining the proper functioning of the mitochondrial network over time involves several mechanisms including the clearance of damaged mitochondria by mitophagy, preservation of mitochondrial mass by mitochondrial biogenesis, and optimization of energy efficiency via mitochondrial fusion and fission dynamics. These processes are finely tuned by metabolic pathways that sense cellular energy needs and impinge on the activity of key transcription factors to control mitochondrial nuclear-encoded gene expression. Nuclear receptors and their cognate hormone ligands are one of the main family of transcription factors involved in the transcriptional regulation of nuclear-encoded mitochondrial genes (Alaynick 2008, Lefranc *et al.* 2018, Lapp *et al.* 2019, Klinge 2020). Notably, it is now well-recognized that the subfamily of orphan nuclear receptors referred to as estrogen-related receptors (ERRs) also plays a major role in this process. The transcriptional activity of the ERRs is tightly regulated by peroxisome proliferator-activated receptor (PPAR) coactivator 1 α (PGC-1 α) and

PGC-1 β (Eichner & Giguère 2011), themselves important regulators of mitochondrial function and biogenesis (Fernandez-Marcos & Auwerx 2011). Herein, we review findings that link the activity of the PGC-1/ERR axis with mitochondrial alterations that arise in the contexts of aging and senescence.

The PGC-1/ERR transcriptional axis

The ERR subfamily

The ERR subfamily comprises three members: ERR α , ERR β and ERR γ . They were named after the discovery of ERR α and β using the human estrogen receptor (ER) cDNA as a hybridization probe (Giguère *et al.* 1988). However, the ERRs do not bind estrogens nor do they participate directly in classic estrogen physiology. In addition, the ERRs and ERs bind to distinct DNA sequences in the genome leading, with few exceptions, to the regulation of distinct target genes (Sladek *et al.* 1997, Deblois *et al.* 2009). Moreover, the ERRs do not require the presence of an exogenous ligand to localize to the nucleus and interact with the genome and as such is considered to be constitutively active. Characterization of the ERR cistromes identified in numerous cell types and tissues showed their propensity to control metabolic gene networks involved primarily in glucose and glutamine metabolism, mitochondrial function, lipid handling and energy sensing (Chen *et al.* 2008, Deblois *et al.* 2009, 2016, Charest-Marcotte *et al.* 2010, Dufour *et al.* 2011, Chaveroux *et al.* 2013). Taken together with their elevated expression levels in metabolic tissues and in high-energy demand settings in response to physiological or environmental challenges, the ERRs are now well-appreciated to act as major transcriptional regulators of energy metabolism (Giguère 2008, Audet-Walsh & Giguère 2015, Misra *et al.* 2017). Although the three ERR isoforms share extensive structural and functional similarities, mice deficient for each individual ERR exhibit sharply different phenotypes and display metabolic features that are tissue- and function-specific. For instance, ERR α knockout (KO) mice are alive but are metabolically deficient (Luo *et al.* 2003, Villena & Kralli 2008, Audet-Walsh & Giguère 2015, Xia *et al.* 2019), while ERR β - and ERR γ -null mice are non-viable due to impaired placental formation and abnormal heart and renal function, respectively (Luo *et al.* 1997, Alaynick *et al.* 2007, 2010). However, the ERR isoforms regulate common biological pathways and can work in concert to control cellular and physiological processes in tissues with high energy demands such as brown fat and the heart (Dufour *et al.* 2007, Wang *et al.* 2015, Gantner *et al.* 2016, Brown

et al. 2018, Sakamoto *et al.* 2020). Since ERR β is principally expressed in embryonic tissues and stem cells, its role in aging has not yet been explored, as such the remainder of the review will focus primarily on ERR α and ERR γ .

The PGC-1 family

The PGC-1 family of transcriptional coactivators which includes PGC-1 α , PGC-1 β and PRC-1, plays a critical role in the regulation of mitochondrial biogenesis and bioenergetics (Fernandez-Marcos & Auwerx 2011, Liu & Lin 2011, Scarpulla 2011). Notably, the expression of PGC-1 α is highly induced in response to physiological stressors such as exercise, cold and fasting leading to increased mitochondrial biogenesis and energy metabolism (Puigserver *et al.* 1998, Puigserver & Spiegelman 2003, Lin *et al.* 2004). Accordingly, tissues from *Ppargc1a*-null mice are characterized by decreased expression of mitochondrial genes and respiration (Austin & St-Pierre 2012). As transcriptional coregulators, members of the PGC-1 family maintain metabolic homeostasis and mitochondrial function by regulating the activity of several transcription factors involved in all aspects of cellular metabolism, including but not limited to PPAR γ , NRF-1, YY1 and GABPA (Gaillard *et al.* 2006, Hock & Kralli 2009, Liu & Lin 2011). Given the central role of mitochondria in energy homeostasis, PGC-1 α has been implicated in pathological conditions associated with mitochondrial dysfunction, including symptoms of aging, and modulation of PGC-1 α activity influences the aging phenotype (Anderson & Prolla 2009, Austin & St-Pierre 2012).

Co-dependency of PGC-1 and ERR function

The activity of the ERRs is ligand-independent but requires the presence of transcriptional coregulators, most notably that of PGC-1 α and PGC-1 β (Huss *et al.* 2002, Kamei *et al.* 2003, Schreiber *et al.* 2003, Laganière *et al.* 2004, Sonoda *et al.* 2007). Indeed, the PGC-1s are envisioned to act as proxy 'protein ligands' for the ERRs (Kamei *et al.* 2003, Handschin & Spiegelman 2006). The PGC-1 α protein encompasses a nuclear receptor-interacting motif that acts as a highly specific anchor for the ERRs (Huss *et al.* 2002, Schreiber *et al.* 2003, Gaillard *et al.* 2007). Remarkably, a PGC-1 α mutant engineered to interact exclusively with the ERRs was shown to exert a similar transcriptional readout to that of the WT protein (Stein *et al.* 2008), suggesting that the ERRs are the main effectors of PGC-1 α action (Schreiber *et al.* 2004, Gaillard *et al.* 2006, Stein *et al.* 2008). Work from numerous groups

have since exposed strategic functional co-dependencies between the PGC-1s and ERRs in controlling metabolic target gene expression in a variety of biological contexts (Gaillard *et al.* 2007, Sonoda *et al.* 2007, Villena & Kralli 2008, Hock & Kralli 2009, Deblois *et al.* 2013, Audet-Walsh *et al.* 2016, Bakshi *et al.* 2016, Torrano *et al.* 2016, Luo *et al.* 2017, Valcarcel-Jimenez *et al.* 2019).

The PGC-1/ERR axis and mitochondrial biology

The PGC-1/ERR axis has been implicated in modulating several aspects of mitochondrial biology. For instance, exercise promotes mitochondrial turnover in skeletal muscle, which consists of clearance of damaged mitochondria by mitophagy accompanied by the frenewal of mitochondrial mass through mitochondrial biogenesis. In PGC-1 α KO mice, both events were attenuated in response to exercise, demonstrating that PGC-1 α coordinates mitophagy with mitochondrial biogenesis (Vainshtein *et al.* 2015). ERR α was also shown to coordinate transcriptional programs essential for exercise tolerance and muscle fitness, including a large set of ERR α -dependent genes involved in mitochondrial dysfunction and energy metabolism. In accordance with changes in gene expression and concomitant alterations in energy production, ERR α -null mice exhibit decreased exercise capacity (Perry *et al.* 2014). In other tissues such as the intestinal epithelium, a SIRT1/PGC-1 pathway is activated in response to oxidative stress to promote mitophagy and maintain tissue integrity (Liang *et al.* 2020). Interestingly, a recent study showed that liver mitochondrial turnover was triggered by thyroid hormone via activation of the thyroid hormone receptor THR β 1 in mice. This study demonstrated that in response to hormone treatment, THR β 1 increases ERR α expression through the induction of PGC-1 α to promote mitochondrial fission, mitophagy and biogenesis (Singh *et al.* 2018). Thus, the PGC-1/ERR axis is a major molecular conduit that enables mitochondrial metabolic plasticity and maintenance of mitochondrial integrity and function.

Regulation of the PGC-1/ERR axis

To rapidly respond to variations in nutrient availability or energy demands, the cells have developed key signaling pathways facilitating the constant rewiring of mitochondrial metabolism. Given the major roles of PGC-1 and ERR family members in this process, a number of signaling pathways have been shown to modulate their expression and/or activity through transcriptional

effects or post-translational modifications (PTM) (Fig. 1A and B). While we focus our attention on well-described key effectors involved in aging (Fig. 1B), there are other factors known to regulate the PGC-1s and ERRs such as the kinases p38 MAPK and PKA and the corepressors NCOR1 and RIP140 to name a few. For further examples and more information on these pathways, the reader is referred to a recent review (Huss *et al.* 2015).

mTOR

As a driver of cell growth and master regulator of cell metabolism, mTOR stimulates mitochondrial respiration and ATP production through several mechanisms (Morita *et al.* 2013). Notably, nuclear mTOR controls transcription of nuclear-encoded mitochondrial genes through a YY1-PGC-1 α transcriptional complex in skeletal muscle, and treatment with rapamycin is sufficient to reduce mitochondrial function as well as mRNA levels of PGC-1 α and ERR α (Cunningham *et al.* 2007). Our laboratory has also reported the functional crosstalk between nuclear mTOR and ERR α in the regulation of mitochondrial metabolism in mouse liver and revealed that inhibition of the mTOR pathway by rapamycin induces ERR α destabilization in both hepatocytes and breast cancer cells (Chaveroux *et al.* 2013, Deblois *et al.* 2016). While the exact mechanisms of ERR α regulation by the mTOR

pathway remain to be fully elucidated, the rapamycin-mediated decrease in ERR α protein levels was shown to be triggered by the proteasome upon ubiquitination of ERR α by the ubiquitin ligase STUB1, a genomic target of nuclear mTOR (Chaveroux *et al.* 2013). Globally, in situations of high energetic demands, mTOR increases cell metabolism and mitochondrial efficiency, and the PGC-1/ERR axis plays a key role in this process. In contrast, inhibition of mTOR signaling in the context of low nutrient availability leads to the rapid degradation of ERR α and concurrent decline in mitochondrial function and energy production.

AMPK

Another effector of mitochondrial functions is AMPK, a serine/threonine kinase. AMPK is a crucial sensor of the energy status of the cell, becoming activated when the AMP/ATP ratio is high, thus triggering a wide range of catabolic pathways directed to increase cellular ATP levels (Hardie *et al.* 2012). In skeletal muscle, upon exercise, AMPK can directly phosphorylate PGC-1 α on threonine-177 and serine-538 to promote its activation, resulting in elevated expression of the glucose transporter GLUT4 and several mitochondrial genes (Jager *et al.* 2007). AMPK also regulates PGC-1 α and ERR α indirectly at the transcriptional level in this tissue, as well as in the heart, epididymal white adipose tissue, brown adipose tissue and

Figure 1

Protein structure and transcriptional control of mitochondrial functions by ERR α and PGC-1 α . (A) The most relevant structural and functional domains of ERR α and its coactivator PGC-1 α are shown. The main post-translational modifications known for ERR α and PGC-1 α including phosphorylation, acetylation and sumoylation are also indicated, along with the effectors targeting these modifications. AF-1, activation function 1; DBD, DNA-binding domain; LBD, ligand-binding domain; AD, activation domain; RD, repression domain; RS, serine/arginine-rich stretch; Ac, acetylation; P, phosphorylation; S, sumoylation. (B) Biological functions of PGC-1 α and ERR α in mitochondrial regulation. Upon fluctuations in nutrient availability or energy demands, the indicated pathways can stimulate PGC-1 α /ERR α activity to promote several aspects of mitochondrial biology. In green, are the principal effectors of PGC-1 α /ERR α signaling and factors marked in red represent known repressors of PGC-1 α and ERR α .

cancer cells, to promote mitochondrial biogenesis and increase energetic capacity (Hu *et al.* 2011, LaBarge *et al.* 2014, Wan *et al.* 2014). Interestingly, our group has recently demonstrated that the AMPK-dependent activation of the PGC-1 α /ERR α axis in breast cancer cells not only promotes mitochondrial metabolism but also represses one-carbon metabolism and nucleotide synthesis (Audet-Walsh *et al.* 2016). These findings signify that AMPK-dependent regulation of mitochondrial functions by PGC-1 α /ERR α is not limited to mitochondrial biogenesis and bioenergetic efficiency but extends to broader metabolic pathways.

Acetylation and sumoylation

Acetylation of lysine residues represents a crucial process that orchestrates cellular metabolism and signaling, and mitochondria are both generators of acetyl-CoA and targets for protein acetylation (Grevenko *et al.* 2014, Hosp *et al.* 2017). PGC-1 and ERR activities are also directly regulated by acetylation. Indeed, the histone acetyltransferase PCAF, an important sensor of the cellular energetic state, has been shown to acetylate the DNA-binding domain of ERR α on four highly conserved lysine residues *in vitro* and in mouse liver (Wilson *et al.* 2010). In a similar fashion, PGC-1 α acetylation is triggered by the homolog of PCAF, GCN5 (Lerin *et al.* 2006). Acetylation of both factors reduces their DNA binding and transcriptional activities. On the other hand, protein deacetylation increases their recruitment to DNA and transcriptional activities which is under the control of a common factor, the sirtuin SIRT1 deacetylase. SIRT1, a highly conserved protein across species, is a metabolic sensor that requires the coenzyme NAD (NAD⁺) as a substrate (Canto *et al.* 2015). In response to increased energy demand, upon exercise, for example, the NAD⁺/NADH ratio is at its highest level in skeletal muscle, resulting in SIRT1 activation, deacetylation of PGC-1 α and stimulated mitochondrial biogenesis and metabolism (Gerhart-Hines *et al.* 2007). SIRT1-dependent deacetylation of PGC-1 α and ERR α has also been demonstrated in mouse liver in response to fasting signals or after depletion of SIRT1 in Hepa1-6 mouse hepatocytes (Rodgers *et al.* 2005, Wilson *et al.* 2010). It is interesting to note that the acetyl groups required for acetylation are provided by acetyl-CoA, a metabolic intermediate derived from pyruvate during glycolysis. During periods of energy demand, acetyl-CoA is preferentially used for energy production rather than protein acetylation, adding a layer of regulation to mitochondrial bioenergetics.

Sumoylation is another post-translational modification involved in the regulation of both PGC-1 α

and ERR activities. Sumoylation is analogous to ubiquitylation in terms of the reaction scheme and enzyme classes used, but rather than conjugation by ubiquitin, sumoylation involves the addition of small ubiquitin-like modifiers (SUMOs). The transcriptional activities of ERR α and γ have been shown to be repressed by sumoylation at a conserved phospho-sumoyl switch motif embedded in the ERR amino-terminal domain. Importantly, SUMO modification of ERR was triggered by protein inhibitor of activated signal transducer and activator of transcription PIASy with a pre-requisite for phosphorylation of ERR α on serine 19 in mouse liver (Tremblay *et al.* 2008). Although the molecular basis for ERR sumoylation in the regulation of mitochondrial function is unknown, we can infer that sumoylation would inhibit ERR-driven mitochondrial biogenesis. In line with this notion, PGC-1 α sumoylation on lysine 183 by PIAS1 or PIAS3 attenuates its transcriptional activity and negatively regulates mitochondrial biogenesis (Rytinki & Palvimo 2009). In contrast, the sumoylase sentrin-specific protease 1 (SEN1) is capable of removing SUMO conjugates from both PGC-1 α and ERR α , resulting in the upregulation of their transcriptional activities and expression of mitochondrial genes (Vu *et al.* 2007, Cai *et al.* 2012).

ROS

Mitochondria themselves can directly influence PGC-1 and ERR functions through ROS-dependent mechanisms. For instance, we recently demonstrated that ROS elevation in breast cancer cells promotes ERR α and ERR γ transcriptional activities to rewire mitochondrial metabolism, increase ROS detoxification and maintain cellular homeostasis (Vernier *et al.* 2020). In skeletal muscle, ROS production is increased in response to exercise, leading to PGC-1 α activation via phosphorylation by p38 MAPK (Thirupathi & De Souza 2017). In this context, ROS also activates Ca²⁺ signaling, promoting autoregulation of PGC-1 α through the transcription factor MEF2.

Interestingly, activation of the PGC-1/ERR axis promotes mitochondrial metabolism which, in theory, would increase the amount of ROS production. To avoid an imbalance in redox homeostasis and oxidative stress, the PGC-1/ERR axis also drives the expression of antioxidant gene programs. For example, ectopic expression of PGC-1 α in muscle increases the expression of superoxide dismutase SOD2 and glutathione peroxidase GPx1, which removes superoxide and hydrogen peroxide, respectively (St-Pierre *et al.* 2003). On the contrary, PGC-1 α KO mice display

reduced expression of several key detoxifying enzymes in skeletal muscle (Thirupathi & De Souza 2017). Recently, ROS has been shown to act as physiological activators of AMPK which, in return, activates a PGC-1 α -dependent antioxidant program to maintain cellular metabolic homeostasis (Rabinovitch *et al.* 2017). ERRs also activate antioxidant mechanisms as observed in breast cancer cells resistant to the tyrosine kinase inhibitor lapatinib, where ERR α utilizes glutamine to synthesize the powerful cellular antioxidant glutathione. In this setting, ERR α inhibition restored cancer cell sensitivity to the drug by blunting ROS detoxification thereby leading to oxidative stress and cell death (Deblois *et al.* 2016).

The PGC-1/ERR axis and mitochondria in aging

PGC-1 α /ERR α and mitochondrial defects in aging

Among the diverse factors that contribute to aging, mitochondrial dysfunction has become a key hallmark of aging and is associated with the development of numerous age-related pathologies (Srivastava 2017). Interestingly, altered mitochondrial function and tissue integrity strongly correlate with an age-dependent gradual decline in PGC-1 α and ERR α expression in numerous tissues such as skeletal muscle, nervous system, bone and kidneys (Cui *et al.* 2006, Sheng *et al.* 2012, Chan & Arany 2014, Tran *et al.* 2016, Huang *et al.* 2017, Tang *et al.* 2018). The important consequences of PGC-1 α /ERR α loss in aging are demonstrated by work with *in vivo* models. For instance, whole body PGC-1 α KO mice fail to protect from the age-associated decrease in mitochondrial function and sarcopenia, display neurodegeneration associated with hyperactivity reminiscent of symptoms of Huntington's disease and exhibit worse kidney function than wild-type mice (Cui *et al.* 2006, Chan & Arany 2014, Tran *et al.* 2016). More specifically, the reduction of PGC-1 α levels in skeletal muscle accelerated several aspects of muscle aging in old mice (21 months) under endurance exercise training (Gill *et al.* 2018). Similarly, muscle-specific ERR α KO mice exhibit decreased oxidative capacity, mitochondrial biogenesis and impaired regeneration in response to injury (Huss *et al.* 2015). In the brain, PGC-1 α has been involved in Parkinson's disease (PD) and PGC-1 α -null mice are more sensitive to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a neurotoxin causing permanent symptoms of PD (St-Pierre *et al.* 2006, Zheng *et al.* 2010).

Reactivation of the PGC-1 α /ERR α axis in some of these contexts have shown beneficial effects, as in

skeletal muscle where elevated PGC-1 α levels delayed some aging features in old mice under exercise (Gill *et al.* 2018). Also, in cell culture models of Alzheimer's disease (AD) where both the expression of PGC-1 α and ERR α are found decreased, ectopic expression of one or the other was sufficient to protect against certain characteristics of the disease (Sheng *et al.* 2012, Tang *et al.* 2018). Finally, pharmacological reactivation of the PGC-1 α /ERR axis with a pan-ERR activator was enough to increase PGC-1 α /ERR α transcriptional activity, ameliorate mitochondrial dysfunction and improve kidney performance of aged mice (Wang *et al.* 2020).

Importantly, two recent studies observed that PGC-1 α and ERR α are also decreased in aged bone (Huang *et al.* 2017, Yu *et al.* 2018). In one study, the authors demonstrated that ERR α drives glutamine anaplerosis which is essential for osteogenic differentiation of mesenchymal stem cell (MSC) and bone formation (Huang *et al.* 2017). In this context, loss of ERR α expression contributed to bone resorption and osteoporosis, and compensation of ERR α loss potentiated glutamine anaplerosis and osteogenic capability of elderly mouse MSCs *in vitro*. In the other study, loss of PGC-1 α promoted adipogenic differentiation of MSCs at the expense of osteogenesis, while induction of PGC-1 α attenuated the adipogenic shift in osteoporosis and promoted bone formation *in vivo* (Yu *et al.* 2018). Here, the authors indicate that MSC osteogenic differentiation induced by PGC-1 α depends on the activation of TAZ, a key transcriptional coactivator in the Hippo signaling pathway and an important inducer of MSC osteogenic differentiation.

Altogether, these studies demonstrate that the activity of the PGC-1 α /ERR α axis is gradually lost during aging, resulting in mitochondrial deficiency, organ dysfunction and stem cell fate deregulation (Fig. 2). Interestingly, several observations also suggest that reactivation of the PGC-1 α /ERR α in old organisms may represent a therapeutic avenue for defective tissues in the elderly. In fact, several strategies shown to promote healthy aging, protect against age-related diseases and mediate longevity, involve enhancement of mitochondrial functions and the PGC-1/ERR axis, as discussed in the next section (Fig. 3).

The PGC-1/ERR axis and mitochondria in anti-aging strategies

According to the rate-of-living theory, energy metabolism maintains homeostasis in the organism whereas excessive consumption of energy enhances the aging process. In other words, restricting calorie intake would

Figure 2

Biological implication of the PGC-1 α /ERR α axis in aging. PGC-1 and ERR isoform expression and their activities generally decrease with age in numerous tissues, resulting in mitochondrial deregulation and organ dysfunction.

decrease metabolic rate and increase lifespan. Indeed, calorie restriction (CR) is well-recognized as a non-pharmacological approach capable of delaying aging in diverse species, and this effect is AMPK-dependent (Gillespie *et al.* 2016). Many other studies involving direct manipulation of AMPK activity also confirmed the central role of AMPK in lifespan regulation: overexpression of AMPK or treatment with AMPK activators such as

metformin extends lifespan of *Caenorhabditis elegans* and *Drosophila melanogaster* (Apfeld *et al.* 2004, Onken & Driscoll 2010, Funakoshi *et al.* 2011). On the other hand, loss of AMPK α 2 in mice disrupts metabolism, compromising health and lifespan (Viollet *et al.* 2003). As noted previously, AMPK activation induces mitochondrial biogenesis to maintain ATP production achieved notably by upregulating the PGC-1 α /ERR α axis. Noteworthy, CR is able to induce ERR α expression and activity, further confirming the concept that AMPK coordinates the activation of both PGC-1 α and ERR α in the context of energy deprivation (Ranhotra 2009, Cui *et al.* 2015). It will be interesting to test whether CR can prolong lifespan in mice depleted of ERR α or PGC-1 α in order to validate their role in this context.

Like CR, maintaining a constant exercise regimen is also a known non-pharmacological approach to increase lifespan (Li *et al.* 2018). However, while CR increases PGC-1/ERR α while decreasing the metabolic rate, exercise increases PGC-1/ERR α but concomitantly increases the metabolic rate (Speakman & Selman 2003, Redman *et al.* 2018). This discrepancy might come from a technical point of view. Indeed, both CR and exercise lead the organism to a lack of energy that requires metabolic adaptations. On one side, long-term CR decreases the resting metabolic rate, which corresponds to the minimum energy required by the body to perform basic functions. Exercise, on the other side, demands an acute and rapid increase in energy production. Intuitively, the need for energy in this context explains the increase of PGC-1/ERR α and mitochondrial activity, but why PGC-1 and ERR α are increased upon CR might be counterintuitive. One explanation is that increased ERR α expression and activity may potentially strengthen the metabolic and biochemical adaptation in tissues, which is necessary for animal survival under long-term CR. Further investigation is necessary to completely understand the different mechanisms involved in these physiological settings. Strikingly, there is a large debate on the benefits of combining calorie restriction with exercise, which tends to globally increase healthspan and reduce the risk of metabolic disorders (Mercken *et al.* 2012, Oh *et al.* 2018, Broskey *et al.* 2019), and the fact that they both activate the PGC-1/ERR axis underscores the importance of this pathway in health span and lifespan regulation.

Sirtuins have been shown to carry out lifespan prolonging effects and to promote the beneficial outcome of CR on health and longevity in yeast, worms and flies (Chang & Guarente 2014). In mice, brain-specific SIRT1-overexpression extends lifespan in both males and females and aged mice exhibit phenotypes consistent

Figure 3

The PGC-1 α /ERR α axis as an anti-aging strategy. Metabolic anti-aging strategies, such as calorie restriction or resveratrol, activate the PGC-1 α /ERR α axis, restore mitochondrial function and ameliorate the aging condition in old organisms. Pharmacological activation of the PGC-1/ERR axis is a potential therapeutic approach to improve the function of aged tissues through the restoration of mitochondrial function.

with delayed aging (Sato *et al.* 2013). These examples illustrate well the critical role of SIRT1 in the metabolic regulation of aging and the conservation of this pathway between mammals and other species. Resveratrol (RSV) is a natural polyphenolic compound found in grapes and other fruits, made famous for its beneficial effects on lifespan and aging through activation of sirtuins (Lee *et al.* 2019). While investigating the mechanisms of action of RSV, Lagouge *et al.* clearly demonstrated that RSV promotes mitochondrial biogenesis through PGC-1 α /ERR α activation (Lagouge *et al.* 2006). Further analysis revealed that PGC-1 α , whose acetylation impedes its transcriptional activity (Rodgers *et al.* 2005), is deacetylated by SIRT1 upon RSV treatment. Importantly, SIRT1 was found essential for PGC-1 α /ERR α activation since RSV could not induce mitochondrial gene expression in SIRT1-null mouse embryonic fibroblasts. Years later, Price *et al.* made a crucial connection between AMPK and SIRT1 using an adult-inducible SIRT1 KO mouse model showing that RSV promotes the positive crosstalk between both factors, where a low dose of RSV activates SIRT1, leading to LKB1 deacetylation and activation of AMPK, while a high dose of RSV promotes AMPK phosphorylation which, in turn, modulates NAD⁺ levels and SIRT1 activation (Price *et al.* 2012). In both cases, RSV treatment increases PGC-1 α activity and mitochondrial function.

The mTOR pathway is another important metabolic pathway associated with longevity. The involvement of mTOR in longevity has first been described in non-vertebrates where impairment of the mTOR pathway through genetic manipulation increased lifespan (Antikainen *et al.* 2017). Similarly, pharmacological inhibition of mTOR by the natural compound rapamycin further confirmed that decreasing the activity of mTOR promotes longevity in *Saccharomyces cerevisiae*, *C. elegans*, *D. melanogaster* and in mice (Antikainen *et al.* 2017). The positive effect of mTOR inhibition on aging is in accordance with the notion that decreasing the metabolic rate favors longevity. However, this is in contradiction with other findings showing that an increase in lifespan is associated with activation of the PGC-1/ERR axis and increased mitochondrial biogenesis. Interestingly, CR has been shown to promote the biogenesis of mitochondria that consume less oxygen, have a reduced membrane potential and generate less ROS while maintaining their critical ATP production, essentially mitochondria with a greater bioenergetic efficiency (Lopez-Lluch *et al.* 2006). Thus, it seems that CR induces a rewiring of cellular metabolic pathways where mTOR no longer influences the PGC-1 α /ERR α axis, which would rather be under the

control of AMPK and SIRT1 to promote mitochondrial biogenesis and function. This hypothesis is in accord with the fact that mTOR inhibition appears to promote lifespan extension through mechanisms other than mitochondrial regulation, such as nutrient sensing (Papadopoli *et al.* 2019). Shedding light on the mechanisms regulating and regulated by the PGC-1/ERR axis in this context will undoubtedly answer many questions regarding the metabolic adaptations triggered by strategies enhancing lifespan and health.

The PGC1/ERR axis and mitochondria in senescence

Cellular senescence is a cell autonomous behavior first described by Leonard Hayflick in 1961 who demonstrated that a normal human fetal cell population can divide between 40 and 60 times in cell culture conditions before entering a state of permanent growth arrest (Hayflick & Moorhead 1961). Since then, senescence was shown to be essential for several biological functions such as tumor suppression, embryonic development and wound healing (McHugh & Gil 2018). It is believed that the physiological role of senescent cells is to recruit the immune system when necessary, including for their own elimination (Prata *et al.* 2018, Fafian-Labora & O'Loghlen 2020). Senescent cells secrete inflammatory cytokines, a hallmark called senescence-associated secretory phenotype (SASP). However, the decline of the immune system over time results in the accumulation of senescent cells in older organisms, causing chronic inflammation that leads to tissue disruption and dysfunction, culprits in the onset of aging and the development of age-associated disorders (McHugh & Gil 2018). As a proof of concept, clearance of senescent cells in a transgenic mouse model of premature aging attenuated age-related pathologies (Baker *et al.* 2011). Alongside other studies, this discovery sparked the race toward the development of a new class of drugs targeting these cells, called senolytics. Although senescence can be induced by a variety of stressors, it is defined by a high metabolic rate with increased mitochondrial biogenesis and altered mitochondrial metabolism and dynamics. This specificity has led researchers to believe that senescent cellular metabolism is a targetable vulnerability (Nacarelli & Sell 2017).

Senescent metabolic characteristics still remain incompletely understood. This being said, it is well accepted that mitochondria's role in senescence is associated with elevated ROS production, which regulates key senescent-associated pathways (Wei & Ji 2018).

As such, one study reported that mitochondrial depletion is enough to reduce ROS levels and some senescence-associated changes including the SASP, in multiple models of senescence induction in fibroblasts (Correia-Melo *et al.* 2016). Interestingly, the authors showed that both PGC-1 α and PGC-1 β mRNAs were increased upon senescence provocation. Notably, the induction of senescence in PGC-1 β KO MEFS resulted in lower mitochondrial mass, ROS generation and senescence markers. PGC-1 α and PGC-1 β mRNAs were also found increased in senescent primary alveolar epithelial AE2 cells purified from the lungs of 18-month-old mice compared to young mice, as well as following bleomycin-induced senescence in rat lung epithelial L2 cells (Summer *et al.* 2019). In this study, the authors found that PGC-1 activation was mTOR-dependent, and rapamycin was sufficient to dramatically reduce the expression of cellular senescence markers in bleomycin-exposed cells, illustrating the potential to target cell metabolism as a therapeutic approach. Finally, ectopic expression of PGC-1 α in human fibroblasts increases mitochondrial mass and prompts a more rapid senescent-like growth arrest (Xu & Finkel 2002).

The role of the ERRs in premature senescence is currently unknown. However, given their close functional relationship with PGC-1 and their implication in the regulation of mitochondrial aging, it is conceivable to think that this subfamily of nuclear receptors is also involved in the metabolic rewiring that occurs during senescence. This hypothesis is also supported by the intimate link between ERR activity and ROS levels, at least in breast cancer cells where the ERRs have been proposed as potential therapeutic targets (Deblois *et al.* 2016, Park *et al.* 2016, 2019, Vernier *et al.* 2020).

Concluding remarks

Aberrant mitochondrial function is a hallmark of aging and the studies reviewed herein indicate that changes in the activity of the PGC-1/ERR transcriptional axis likely plays a major role in the mitochondrial deregulation that arises in aging cells. Whether the decline in the activity of the PGC-1/ERR axis over time is a cause or consequence of aging is still an open question that needs to be addressed. Nevertheless, anti-aging strategies that attempt to rejuvenate mitochondrial functions or improve mitochondrial quality control have been proven effective to slow down the onset of aging or increase longevity, and many of these strategies implicate known activities of the PGC1/ERR axis. Importantly, targeting the activity of the PGC-1/ERR axis directly has already

been proven successful as a therapeutic approach to relieve age-associated tissues dysfunctions through genetic manipulation or pharmacological treatment (Sheng *et al.* 2012, Gill *et al.* 2018, Tang *et al.* 2018). The significant role of senescence in aging raises also some important questions. Indeed, senescent cells seem to possess high PGC-1 activity concomitant with increased mitochondrial function and targeting senescent cellular metabolism has been shown to effectively promote their elimination and increase the quality of life of old organisms (Nacarelli & Sell 2017). Thus, one might wonder whether the best anti-aging strategy would be to rejuvenate the mitochondrial function of aged cells or to inhibit the elevated mitochondrial metabolism of senescent cells, which would likely require modulation of the PGC-1/ERR axis in both situations. The field of senescence is still relatively new but evolves very rapidly. The next decade holds promise for providing a better understanding of the molecular facets of aging as well as the development of a wide range of effective mitochondria-targeted therapies. Notably, the ERRs possess a functional ligand-binding domain in their structure, rendering these proteins easily targetable with small molecules, such as C29 and GSK5182 that respectively target ERR α and ERR γ (Willy *et al.* 2004, Kallen *et al.* 2007, Patch *et al.* 2017, Vernier *et al.* 2020). Therefore, we can now test the theory that influencing mitochondrial function will attenuate, or even reverse, the rate at which we age.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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