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# Mitochondrial biogenesis in organismal senescence and neurodegeneration

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ABSTRACT

Mitochondrial biogenesis is indispensable for organismal homeostasis. The semi-autonomous nature of mitochondria renders their biogenesis rather complex, as it requires the contribution of the nucleus, the cytoplasm and the organelle itself. Recently, several transcription regulators, RNA binding proteins and outer mitochondrial membrane (OMM) components have been implicated in the coordination of the process. Both the expression and the abundance of several of these factors are altered during ageing, and their impairment can have diverse, yet principally detrimental, effects on lifespan. These findings converge on the notion that mitochondrial biogenesis is an age-modulated process that, when perturbed, compromises survival. Notably, core brain functions are dependent on mitochondrial metabolite availability. Indeed, emerging evidence indicates that mitochondrial biogenesis regulators play important roles in the onset and progression of severe neurodegenerative syndromes such as AD, PD and HD. These devastating human pathologies remain incurable to date. A better understanding of the mechanisms that govern mitochondrial biogenesis could facilitate the development of effective pharmaceutical interventions against these diseases.

## 1. Introduction

Mitochondria serve pivotal roles in the regulation of cellular homeostasis by controlling energy metabolism. In addition, they are tightly associated with the regulation of ion homeostasis, intermediate metabolism, apoptosis, lipid metabolism and proliferation. Among the inherent mitochondrial processes are β-oxidation, the tricarboxylic acid cycle (TCA cycle) or Krebs cycle and oxidative phosphorylation. Products of these processes such as ATP, ROS, NAD + and Acetyl-CoA are crucial modulators of disease and longevity within a broad range of eukaryotes. Sufficient ATP production is critical for the viability of cells and primarily essential for high-energy demanding organs, such as the brain. Thus, mitochondrial function has lately drawn considerable interest in the field of neurodegeneration. Mitochondrial dysfunction is a typical hallmark of neurodegenerative disorders, several of which remain incurable to date (Chaturvedi and Flint Beal, 2013; Johri and Beal, 2012). Both the number of the organelles and their protein composition designate mitochondrial functionality. Of note, organelle quality control and abundance are regulated through the two opposing functions of mitochondrial biogenesis and mitophagy (Ploumi et al., 2017). While mitochondrial biogenesis propagates a healthy mitochondrial population, mitophagy, on the other hand, eliminates the malfunctioning or superfluous organelles.

Mitochondrial biogenesis constantly occurs at basal levels and increases during cell renewal, proliferation, development, and under stress conditions such as oxidative, heat stress, exercise and caloric restriction (CR) (Antico Arciuch et al., 2012; Civitarese et al., 2007; Cuezva et al., 1997; Hood et al., 2011; Lee and Wei, 2005; Prigione and Adjaye, 2010; Vaarmann et al., 2016). Organelle biogenesis is not *de novo* but emerges from the propagation of a pre-existing pool of mitochondria and is a multi-step process, which entails multiplication of the organelle protein constituents as well as fission and fusion events (Jornayvaz and Shulman, 2010). The complexity of mitochondrial biogenesis attributes to the semi-autonomous nature of the organelles. The vestige of either the endosymbiotic or autogenous origin of mitochondria is the mitochondrial genome (Roger et al., 2017). Mitochondrial DNA (mtDNA) is a circular, double-stranded molecule located and regulated within the mitochondrial matrix. In mammals, similarly to other organisms such as *Drosophila melanogaster* and *Caenorhabditis elegans*, mtDNA encodes 13 proteins, all components of the four out of the five electron transport

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chain (ETC) complexes, two rRNAs and 22 tRNAs, (D'Souza and Minczuk, 2018). Despite its necessity, mtDNA encodes the 1% of the total protein content of mitochondria while the rest 99% is nuclear-encoded (Kotrys and Szczesny, 2019). Among the nuclear-encoded, exist the majority of the components of the five ETC complexes, as well as all mtDNA regulators (Scarpulla, 2008). Therefore, mitochondrial biogenesis requires the synchronous expression of both the mitochondrial and the nuclear genomes. Nevertheless, it was recently shown in yeast that synchronization of the expression of the two genomes is not bidirectional but unidirectional, driven exclusively from the nucleus to the mitochondrion (Couvillion et al., 2016). While evidence concerning this mechanism lacks to date, it is becoming apparent that, in general, mitonuclear communication is bidirectional and coordinated by anterograde and retrograde regulation (Quiros et al., 2016).

The fundamental steps for mitochondrial biogenesis befall in three different subcellular compartments. These are the nucleus, where the transcription of nuclear-encoded mitochondrial genes takes place, the cytoplasm, within which mRNAs are transported and locally translated close to mitochondria and last, the organelle itself, where mtDNA is expressed (D'Souza and Minczuk, 2018; Dominy and Puigserver, 2013; Hood et al., 2003; Scarpulla et al., 2012; Zhang and Xu, 2016). Perturbed mitochondrial biogenesis is closely associated with premature ageing and age-related disease onset, while strategies that enhance the process manage to, a significant extend, ameliorate deleterious phenotypes. In this review, we intend to outline current findings linked to mitochondrial biogenesis with an emphasis on nuclear and cytoplasmic regulators. Besides, we explain how and whether perturbation of these regulators is implicated in the onset and progression of organismal senescence and neurodegeneration.

## 2. Mitochondrial biogenesis regulators

### 2.1. Nuclear regulators

The mitochondrial proteome comprises more than 1000 proteins, the majority of which are nuclear-encoded, highlighting the significance of nuclear transcription for organelle homeostasis, functionality and biogenesis. Notably, studies through the past thirteen years have uncovered transcription factors, nuclear hormone receptors and transcriptional co-activators that are indispensable for mitochondrial biogenesis (Ploumi et al., 2017).

#### 2.1.1. Nuclear respiratory factors

The nuclear respiratory factors 1 and 2 (NRF1 and NRF2) are two transcription factors that positively regulate mitochondrial biogenesis. NRF1 was first identified as a positive regulator of cytochrome c transcription and since then its role in the transcription of nuclear-encoded mitochondrial transcripts has expanded (Evans and Scarpulla, 1989). Particularly, NRF1 forms homodimers and positively regulates the expression of several components of the oxidative phosphorylation pathway, the mitochondrial protein import machinery, ion channel components and heme biosynthesis enzymes (Biswas and Chan, 2010; Blesa et al., 2008b, 2007; Kiyama et al., 2018; May et al., 1995; Satoh et al., 2013; Virbasius et al., 1993). In addition, it indirectly controls mitochondrial genome expression, through binding on the promoter regions of the principal mtDNA regulators, mitochondrial transcription factor A (TFAM) and the assistant factors mitochondrial transcription factor B1 (TFB1M) and mitochondrial transcription factor B2 (TFB2M), yet results about TFAM are inconsistent (Baar et al., 2003; Gleyzer et al., 2005; Virbasius and Scarpulla, 1994). This discrepancy triggers the assumption that NRF1 could bind on diverse gene promoters in a tissue-specific manner. Moreover, NRF1 positively regulates mitochondrial ribosomal proteins and mitochondrial translation factors in a sirtuin 7 (SIRT7)-dependent manner (Mohrin et al., 2015). Intriguingly, SIRT7 binds on NRF1 and exclusively represses the transcription of mitochondrial ribosomal components and translation factors, without affecting the transcription of other NRF1 targets. In effect, *SIRT7* overexpression decreases mitochondrial mass and respiration, yet whether this mechanism is conserved among the various cell types might be addressed in future studies (Mohrin et al., 2015). Besides, NRF1 activity is regulated by posttranslational modifications, like methylation and phosphorylation (Domcke et al., 2015; Piantadosi and Suliman, 2006). Above all, *Nrf1* depletion causes elimination of mtDNA and embryonic lethality, emphasizing the crucial role of mitochondrial biogenesis in cellular and organismal homeostasis (Huo and Scarpulla, 2001).

NRF2, also known as GA-binding protein transcription factor (GABP), was first identified as a positive regulator of cytochrome oxidase subunit IV (Carter et al., 1992). NRF2/GABP consists of five-subunits (subunit α, β1, β2, γ1, γ2) of which only subunit α binds on DNA, while the rest form heterodimers with α (Gugneja et al., 1995). NRF2/GABP, similarly to NRF1, positively regulates the expression of several mitochondrial genes such as ETC components, mitochondrial import system components, as well as the expression of the transcription factors *TFAM* and *TFBs* (Blesa et al., 2008a, 2007; Gleyzer et al., 2005; Ongwijitwat et al., 2006; Villena et al., 1998; Virbasius and Scarpulla, 1994). Intriguingly, although still controversy exists, the mRNA levels of *Tfam* and *Tfb2m* are not affected by GABPα depletion, while *Tfb1m*, is classified as a novel NRF2/GABPα target (Yang et al., 2014). SIRT7, similarly to NRF1, is also involved in NRF2/GABP activation, as it targets GABPβ1 and triggers its association with GABPα, thus enhances the transcriptional activity of the complex and boosts mitochondrial function (Ryu et al., 2014). Consequently, SIRT7 differentially regulates the two NRFs, thus mitochondrial activity. Future research should shed light in the underlying mechanism and its biologic significance.

#### 2.1.2. Nuclear factor erythroid 2-related factor 2 (Nrf2)

Nuclear factor erythroid 2-related factor 2 (NRF2) belongs to the Nrf/cap "n" collar (CNC) subfamily of the leucine zipper (bZIP) transcription factors (Moi et al., 1994). NRF2 positively regulates mitochondrial biogenesis, apart from its role in cytoprotection and detoxification. Its role in mitochondrial biogenesis was introduced in a study performed in the mouse heart, where it was shown that heme oxygenase (HO)-1 overexpression (also regulated by NRF2), triggers H2O2 and superoxide dismutase-2 (SOD2). Upregulation of the latter, triggers protein kinase B (PKB/Akt) which in turn, blocks glycogen synthase kinase 3β (GSK3β), an NRF2 inhibitor and creates a positive feedback loop that enables NRF2 to activate *Nrf1* transcription in a tissue-specific manner (Hota et al., 2012; Joe et al., 2015; Merry and Ristow, 2016; Piantadosi et al., 2008; Zhang et al., 2013). Consequently, indirectly through NRF1, it activates the transcription of downstream mitochondrial genes encoded by the nuclear genome. Besides, GSK3β inhibits NRF2 by phosphorylating Fyn kinase, which next phosphorylates NRF2 at Tyr568 and triggers its nuclear export (Jain and Jaiswal, 2007; Salazar et al., 2006). Moreover, AMP-activated protein kinase (AMPK)-mediated phosphorylation of NRF2 at Ser550, blocks its nuclear export and concomitantly inhibits GSK3β, thus activates NRF2 (Joo et al., 2016). Another critical negative regulator of NRF2 is Keap1, which drives polyubiquitination and proteasomal degradation of NRF2, an effect blocked by Keap1 oxidation (Zhang and Hannink, 2003). The E3 ubiquitin ligase Hrd1 is the third negative regulator of Nrf2, as it triggers, similarly to Keap1, Nrf2 ubiquitination and subsequent degradation (Wu et al., 2014). Further, *Nrf2* depletion reduces the total mitochondrial mass and impairs ATP production (Chen et al., 2014; Zhang et al., 2013).

Of note, the finding that NRF2 binds on mtDNA, suggests a novel regulatory function of NRF2 that needs to be further validated (Malhotra et al., 2010). The function of NRF2 is conserved also in *C. elegans*. Its orthologue, SKiNhead-1 (SKN-1), is a positive regulator of mitochondrial biogenesis in this model organism. SKN-1 triggers the transcription of several mitochondrial genes such as ETC components, proteins of the mitochondrial import machinery and mitochondrial genome regulators, while its depletion significantly reduces mtDNA (Palikaras et al., 2015).

To avoid confusion, the nuclear respiratory factor 2 will be referred as "NRF2/GABP" and the nuclear factor erythroid 2-related factor 2 as "NRF2".

### 2.1.3. Nuclear hormone receptors

*2.1.3.1. Peroxisome proliferator-activated receptors (PPARs).* Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor superfamily. PPARs initially form a heterodimer complex with the retinoid X receptor (RXR) on DNA, which is inactive (Chandra et al., 2008). Subsequent binding of a PPAR ligand activates the complex by inducing a conformational change, facilitating the dissociation of corepressors and the recruitment of coactivators on the heterodimer, thus enabling it to initiate transcription. PPARs contain three isotypes, PPARα, PPARβ/PPARδ and PPARγ with cell type-specific expression and function (Dubois et al., 2017).

PPARs are fundamental regulators of energy homeostasis. They regulate the expression of genes related to fatty acid oxidation, glucose and lipid metabolism and play an essential role in the regulation of mitochondrial biogenesis (Lee et al., 2017; Watanabe et al., 2000). Administration of the PPAR panagonist, bezafibrate, similarly to the PPARγ activators, rosiglitazone and troglitazone, induces mitochondrial biogenesis (Wenz et al., 2008). In turn, treatment with GW9662, a PPARγ antagonist, reverses this phenotype (Quintanilla et al., 2008). What is more, rosiglitazone raised the expression of Proliferator-activated receptor γ coactivator-1 α (PGC-1α), effect reversed by GW9662, and increased ATP levels, mtDNA copy number and total mitochondrial mass in a PPARγ-dependent manner (Chiang et al., 2014). Notably, the role of PPARγ in mitochondrial biogenesis is conserved among various cell types (Miglio et al., 2009; Rong et al., 2011).

PPARβ/δ triggers mitochondrial biogenesis during the late hepatic cell maturation phase, while PPARα in the initial steps of the process (Zhu et al., 2010). Besides, treatment with GW1516, in combination with exercise, triggers mitochondrial biogenesis through selective activation of PPARβ/δ (Narkar et al., 2008). Moreover, PPARβ/δ binds and protects PGC-1α from degradation, while *PGC-1α* mRNA levels remained unaffected upon PPARβ/δ depletion, confirming that PPARβ/δ acts on *PGC-1α* post-transcriptionally. Another line of work, suggests that *Nrf1* is a direct target of PPARβ/δ, thus overexpression of the second triggers the initiation of a global mitochondrial biogenesis program (Koh et al., 2017). In contrast, conditional knockout of PPARβ/δ in mouse heart decreased total mitochondrial abundance. This drop was coupled to a reduction in mtDNA copy number, the mRNA and protein levels of positive core regulators of mitochondrial biogenesis such as PGC-1α and PGC-1β, NRF1 and NRF2/GABP and the mRNA levels of several nuclear-encoded mitochondrial genes (Wang et al., 2010). PPARα does not affect mitochondrial biogenesis, but only when in complex with PGC-1α. In this complex it targets genes of the mitochondrial fatty acid oxidation which are elevated upon induction of mitochondrial biogenesis (Vega et al., 2000). Finally, evidence suggests that a shorter, PPARγ-related protein is localised inside the mitochondrial matrix (mt-PPAR). mt-PPAR binds on mtDNA, possibly to regulate mtDNA expression. Expression of mt-PPAR has been detected in many tissues, such as the heart, brown adipose tissue (BAT), white adipose tissue (WAT), liver, kidney and muscle, but not in the brain (Casas et al., 2000).

*2.1.3.2. Thyroid receptor (TR).* The thyroid receptor (TR) belongs to the superfamily of nuclear hormone receptors. Thyroid hormones (THs) and more specifically, T3, which is the active TH, control gene expression by binding on TRs. TRs consist of two nuclear receptors, TRα and TRβ and one mitochondrial TH receptor, p43 (Sterling et al., 1984). TRs positively regulate mitochondrial biogenesis in a tissue-specific manner (Sterling et al., 1977). Further, it is established to date, that TH triggers mitochondrial protein synthesis and increases total mitochondrial volume (Jakovcic et al., 1978; Yau et al., 2019). The latter, combined with the finding that both mitochondrial and nuclear TH receptors exist, raises the hypothesis that TRs can co-regulate the expression of the nuclear and mitochondrial genome. Indeed TH binding on TRα and TRβ, triggers transcription of their downstream target genes such as *Nrf1*, *Nrf2/GABP* and *PGC-1α* (Rodriguez-Pena et al., 2002; Weitzel et al., 2001; Wulf et al., 2008). Finally, p43 is imported inside mitochondria in a translocase of the outer membrane (TOM)-independent manner and localizes inside the matrix where it binds mtDNA and increases its expression in a T3-dependent manner. Thus, it increases mitochondrial content and respiration (Casas et al., 1999; Enriquez et al., 1999; Wrutniak et al., 1995). In contrast, depletion of p43 in skeletal muscles impaired mitochondrial function (Pessemesse et al., 2012). A TH receptor is also found in the inner mitochondrial membrane (IMM) while its role there is undefined to date (Sterling et al., 1978).

*2.1.3.3. Estrogen receptors (ERs).* Estrogen receptors (ERs) belong to the superfamily of nuclear hormone receptors and positively regulate mitochondrial biogenesis. Estrogen receptors (ERα and ERβ) are detected in an inactive form, bound by chaperons and are activated exclusively after binding of estradiol on their ligand-binding domain, followed by chaperone dissociation (Yasar et al., 2017). The conformational change of ERs after estradiol binding triggers their binding on DNA estrogen response elements (EREs) and transcription of target genes. Examination of ERα and ERβ gene targets revealed their selective binding on non-overlapping targets (O'Lone et al., 2007). ERa and ERβ are detected in several tissues, but their expression within tissues differs (Gustafsson, 1999; Shi et al., 2013). Also within the brain, their expression differs among the various brain regions, yet stimulation of either of the two ERs increases mitochondrial respiration and mitochondrial protein expression (Irwin et al., 2012; Rettberg et al., 2014).

In the subcellular level, while ERα is mostly nuclear, both receptors have also been found in the mitochondrial matrix (Chen and Yager, 2004; Milanesi et al., 2008; Solakidi et al., 2005; Stirone et al., 2005). However, in primary cardiomyocytes and HT-22 cells, ERβ was found solely inside mitochondria (Yang et al., 2004). Their mitochondrial localization is further supported by findings showing that mitochondrial ERs bind on mtEREs and trigger the expression of mtDNA in an estradiol-dependent manner (Chen et al., 2004a, b). Hence, estradiol can successfully coordinate the synchronized production of ETC complexes from both genomes.

In the nucleus, ERs bind on the promoter region of *Nrf1*, activate *Tfam* and ETC components, and induce mitochondrial biogenesis (Ivanova et al., 2013; Mattingly et al., 2008). Of note, among the ER-targets are *Pgc-1* and *Nrf2/GABP*. Because PGC-1 functions as an ER co-activator of transcription, activation of ERs can trigger a positive feedback loop that further enhances their activity (Hsieh et al., 2005; Tcherepanova et al., 2000).

*2.1.3.4. Estrogen-related receptors (ERRs).* Related to ERs, are the orphan nuclear receptors, estrogen-related receptors (ERRα, ERRβ and ERRγ). Of them, ERRα and ERRγ are involved in the regulation of mitochondrial biogenesis. Both are expressed in numerous tissues such as the BAT and heart. ERRα positively auto-regulates its expression, effect further enhanced by PGC-1α binding on it (Laganiere et al., 2004; Soriano et al., 2006). Further, ERRα induces *Pgc-1α* transcription (Ramjiawan et al., 2013). The latter creates a positive feedback loop that enhances ERRα activity and mitochondrial biogenesis. ERRα/PGC-1α increase the expression of several OXPHOS genes while constitutive activation of ERRα triggers mitochondrial biogenesis independently of PGC-1α (Mootha et al., 2004; Schreiber et al., 2004). Complementary to PGC-1α, ERRα positively regulates mitochondrial biogenesis in a PGC-1β-dependent manner (Shao et al., 2010).

ERRγ functions together and shares common gene targets with ERRα (Dufour et al., 2007). Both can induce the expression of transcription factors, like PPARα and NRF2/GABP (Dufour et al., 2007; Giguere,

2008). Despite ERRα and ERRγ, a role of ERRβ in mitochondrial biogenesis is not established, to date.

#### 2.1.4. CREB

Cyclic AMP-Responsive Element-Binding Protein (CREB) is a transcription factor, which binds on a specific DNA sequence, the cAMP-response element (CRE) to activate transcription. The stimulus for its activation is the elevation of intracellular cAMP levels. Following, protein kinase A (PKA) is induced, which, among other kinases, phosphorylates CREB and activates it (Hai and Hartman, 2001; Montminy and Bilezikjian, 1987; Shaywitz and Greenberg, 1999). Creb-binding protein (CBP) is a co-activator of CREB (McManus and Hendzel, 2001). Finally, apart from PKA, the enhancer of mitochondrial biogenesis, calcium/calmodium-dependent protein kinase IV (CaMKIV), also activates CREB (Arnould et al., 2002; Wu et al., 2002).

CREB correlates with enhanced mitochondrial biogenesis and respiration and similar to TRs and ERs, CREB is detected in both the nucleus and mitochondria (De Rasmo et al., 2009). CREB lacks a canonical mitochondria-targeting sequence (MTS), and its import through the TOM complex is probably mediated by chaperones (De Rasmo et al., 2009; Lionaki et al., 2016). Inside mitochondria, CREB binds on CRE sites on mtDNA and activates its expression (Cammarota et al., 1999; De Rasmo et al., 2009; Lee et al., 2005). Activation of mitochondrial and nuclear CREB is coordinated as they are both responsive to common triggering signals. Similarly to the nuclear, PKA-mediated phosphorylation is indispensable also for the activation of the mitochondrial CREB, although the mitochondrial CREB functions independently of the nuclear (Lee et al., 2005; Ryu et al., 2005).

In the nucleus, CREB transcribes several genes needed for mitochondrial biogenesis. Amongst its most prominent targets are ETC components such as cytochrome c, PGC-1-related coactivator (*PRC*), *PGC-1* and *Nrf1* (Franko et al., 2008; Gopalakrishnan and Scarpulla, 1994; Herzig et al., 2000, 2001; Lee et al., 2005; Suliman et al., 2010; Vercauteren et al., 2006).

#### 2.1.5. Proliferator-activated receptor γ coactivator-1

Proliferator-activated receptor γ coactivator-1 alpha (PGC-1α) and Proliferator-activated receptor γ coactivator-1 beta (PGC-1β) are coactivators of transcription that belong to the PGC-1 family. The two proteins share multiple sequence and structural similarities, yet they obtain distinct, tissue-specific roles (Lin et al., 2005). Particularly, PGC-1α and PGC-1β are indispensable for the NRF1- and NRF2/GABP-mediated gene expression (Shao et al., 2010; Taherzadeh-Fard et al., 2011; Wu et al., 1999). In parallel, since NRF1 activates *Tfam* transcription, it is becoming apparent that PGC-1α and PGC-1β trigger the synchronized expression of the nuclear and mitochondrial genomes. Furthermore, both PGC-1α and PGC-1β are essential for the activation of ERRs and expression of their target genes (Deblois et al., 2013; Shao et al., 2010; Takacs et al., 2013). PGC-1α also co-activates PPARs, TRs and ERs as well as NRF2 (Bourdoncle et al., 2005; Navarro et al., 2017; Wenz et al., 2008; Wulf et al., 2008).

Overall, PGCs have been closely associated with enhanced expression of mitochondrial protein import complexes, mitochondrial genome regulators, ETC components and are sufficient to trigger elevated mitochondrial abundance and respiration rates (Choi et al., 2006; Srivastava et al., 2007; Ventura-Clapier et al., 2008). In turn, excessive mitochondrial biogenesis triggered by overexpression of *Pgc-1* caused toxicity, and overexpression of *Pgc-1β* lead to disorganization of myofibrils (Arany et al., 2007; Lehman et al., 2000). In addition, ectopic expression of *Pgc-1α* and *Pgc-1β* could enhance mitochondrial biogenesis (Haralampieva et al., 2017; Meirhaeghe et al., 2003; Wu et al., 1999). Notably, PGC-1α localizes inside mitochondria, forms a complex with TFAM and regulates the expression of the mitochondrial genome (Aquilano et al., 2010). In future work, investigating the effect of this regulation (inhibitory or activating) and the inducing conditions might prove important.

PGC-1α expression is induced by exposure to low temperatures, exercise, fasting and Nitric oxide (NO) (Lelliott et al., 2006; Lira et al., 2010a, b; Norheim et al., 2014; Puigserver et al., 1998; Teng et al., 2011). In addition, research shows that PGC-1α is regulated at both the transcriptional and the post-translational level. Among the core PGC-1α regulators are CREB, myocyte enhancer factor-2 (MEF2), activating transcription factor 2 (ATF2), sirtuin 1 (SIRT1), AMPK, NRF2, GSK3b, transcription factor E3 (TFE3), forkhead box protein O (FOXO) and Nectin (Anderson et al., 2008; Czubryt et al., 2003; Hasegawa et al., 2016; Herzig et al., 2001; Higashida et al., 2013; Kang et al., 2017; Olmos et al., 2009; Salma et al., 2015; Tufekci et al., 2011; Wan et al., 2014). A synopsis of the nuclear regulators of mitochondrial biogenesis and their functions are summarised in Table 1.

### 2.2. Cytoplasmic regulators

Following transcription, new transcripts translocate from the nucleus near mitochondria to be locally expressed and imported into the organelle. Considerable effort has been made the last years to understand how mRNAs or their encoded protein products are specifically targeted to mitochondria. Current studies support the existence of two discrete mechanisms that differentially regulate mRNA transport, translation and import into the organelles. The first mechanism comprises post-translational import of mRNAs into the organelles and the second co-translational import (Ahmed et al., 2006; MacKenzie and Payne, 2007; Neupert and Herrmann, 2007). However, why both mechanisms evolved remains obscure. Recent research suggests that mRNAs with prokaryotic origin are co-translationally imported, in contrast to the ones with eukaryotic origin, which are translated first in the cytoplasm and are next imported into the organelles (Garcia et al., 2007; Marc et al., 2002; Sylvestre et al., 2003).

According to the post-translational import mechanism, mRNAs are translated in free, cytoplasmic ribosomes (Chacinska et al., 2009; Hoseini et al., 2016). One example is *ATP16* mRNA (Saint-Georges et al., 2008). Numerous mRNAs contain a Mitochondrial Targeting Sequence (MTS) on the N-terminus of their coding sequence, which is exposed only after translation. Some mRNAs may not contain a canonical MTS, but instead, noncanonical ones (Chacinska et al., 2009). The encoded pre-proteins are “secured” by cytoplasmic chaperones that keep them in an unfolded state until they reach mitochondria. There, TOM complex components recognize the MTS of the targeted pre-proteins and allow their import into the organelle. After their import and appropriate localization, the MTS is cleaved and mitochondrial chaperones fold the pre-proteins to acquire their mature form. Full-length mitochondrial proteins found in an unfolded state within the cytoplasm, further support the post-translational import mechanism (Fig. 1, panel a) (Wienhues et al., 1991).

Conforming to the co-translational import model, nuclear-encoded mRNAs, as well as ribosomes, are present on the OMM (Gehrke et al., 2015; Gold et al., 2017; Matsumoto et al., 2012; Williams et al., 2014). mRNAs are first translocated from the nucleus to the vicinity of the organelle where they are locally translated. Overall, mRNA transport entails the binding of the mRNAs by RNA binding proteins. This binding preserves mRNAs in a translationally inactive state until they reach their final destination (Blower, 2013).

While the entire repertoire of the proteins involved in this process is still unexplored, a member of the Pumilio-Fbf (Puf) family of proteins, Puf3, binds on the 3’ untranslated regions (UTRs) of their target mRNAs, like ETC components and mitochondrial genome regulators and coordinates their expression and transport (Quenault et al., 2011 2118; Saint-Georges et al., 2008). Puf3 was detected initially in the cytoplasm, while recent studies in yeast reveal that it is also located on the OMM (Garcia-Rodriguez et al., 2007; Gerber et al., 2004).

The fact that the 3’ UTR is an untranslated region is supportive of the co-translational import model. Indeed, mRNAs contain conserved sequences that guide their exact translocation to mitochondria. For example,

**Table 1**
Synopsis of mitochondrial biogenesis nuclear regulators.

| Full name | Abbreviation | Transcriptional targets | Regulators | Implication in mitochondrial biogenesis | Mitochondrial localization |
|---|---|---|---|---|---|
| Nuclear respiratory factor 1 | NRF1 | ETC components<br>Mitochondrial import regulators<br>Ion channel components<br>Heme biosynthesis enzymes<br>Mitochondrial genome regulators<br>Mitochondrial ribosome components | SIRT7<br>PGC-1α<br>PGC-1β | Elevated mtDNA levels | No |
| Nuclear respiratory factor 2 | NRF2/GABP | ETC components<br>Mitochondrial import regulators<br>Mitochondrial genome regulators | SIRT7<br>PGC-1α<br>PGC-1β | Increased mitochondrial mass<br>Induced electron transport chain efficiency | No |
| Nuclear factor erythroid 2-related factor 2 | NRF2 | *NRF1*<br>Heme oxygenase 1<br>ETC components<br>Mitochondrial genome regulators<br>Mitochondrial import regulators | GSK3β<br>Fyn<br>AMPK<br>Keap1<br>Hrd1<br>PGC-1α | Increased mitochondrial mass<br>Elevated ATP levels<br>Elevated mtDNA levels | Yes |
| Peroxisome proliferator-activated receptor α | PPARα | Genes related to glucose and lipid homeostasis and fatty acid oxidation and mitochondrial biogenesis | PPAR ligands<br>PGC-1α | Increased mitochondrial biogenesis (when in complex with PGC-1α) | No |
| Peroxisome proliferator-activated receptor β | PPARβ/ PPARδ | Genes related to glucose and lipid homeostasis and fatty acid oxidation and mitochondrial biogenesis<br>*Nrf1* | PPAR ligands<br>PGC-1α | Increased mitochondrial mass<br>Elevated mtDNA levels<br>Induced PGC-1α, PGC-1β, Nrf1 and Nrf2 expression<br>Increased Mitochondrial biogenesis | No |
| Peroxisome proliferator-activated receptor γ | PPARγ | Genes related to glucose and lipid homeostasis and fatty acid oxidation and mitochondrial biogenesis<br>*PGC-1α* | PPAR ligands<br>PGC-1α | Increased mitochondrial biogenesis<br>Increased mitochondrial mass<br>Elevated ATP levels<br>Elevated mtDNA levels | Yes, a shorter, PPARγ-related protein |
| Thyroid receptor α | TRα | *NRF1*<br>*NRF2/GABP*<br>*PGC-1α* | T3<br>PGC-1α | – | No |
| Thyroid receptor β | TRβ | *NRF1*<br>*NRF2/GABP*<br>*PGC-1α* | T3<br>PGC-1α | – | No |
| Estrogen receptor α | ERα | *NRF1*<br>*PGC-1*<br>*NRF2/GABP* | Estradiol<br>PGC-1α | Increased mitochondrial respiration<br>Increased mitochondrial protein expression | Yes |
| Estrogen receptor β | ERβ | *NRF1*<br>*PGC-1*<br>*NRF2/GABP* | Estradiol<br>PGC-1α | Increased mitochondrial respiration<br>Increased mitochondrial protein expression | Yes |
| Estrogen-related receptor α | ERRα | *ERRα*<br>ETC subunits<br>*PGC-1α*<br>*PPARα*<br>*NRF2/GABP* | PGC-1α<br>PGC-1β | Increased mitochondrial biogenesis | No |
| Estrogen-related receptor β | ERRβ | – | PGC-1α<br>PGC-1β | – | No |
| Estrogen-related receptor γ | ERRγ | *ERRα*<br>ETC subunits<br>ETC components<br>Mitochondrial import regulators<br>Ion channel components<br>Heme biosynthesis enzymes<br>Mitochondrial genome regulators<br>Mitochondrial ribosome components | PGC-1α<br>PGC-1β | – | No |
| Cyclic AMP-Responsive Element-Binding Protein | CREB | ETC subunits<br>*PRC*<br>*NRF1*<br>*PGC-1* | PKA<br>cAMP<br>CBP<br>CaMKIV | Increased mitochondrial biogenesis<br>Increased mitochondrial mass | Yes |
| Proliferator-activated receptor γ coactivator-1 α | PGC-1α | The same gene targets with the transcription factors it binds and co-activates | CREB<br>MEF2<br>ATF2<br>SIRT1<br>AMPK<br>NRF2<br>GSK3b<br>TFE3<br>FOXO<br>Nectin<br>Exercise<br>Fasting | Increased mitochondrial biogenesis<br>Increased mitochondrial mass | Yes |

(*continued on next page*)

**Table 1** (*continued*)

| Full name | Abbreviation | Transcriptional targets | Regulators | Implication in mitochondrial biogenesis | Mitochondrial localization |
|---|---|---|---|---|---|
| Proliferator-activated receptor γ coactivator-1 β | PGC-1β | The same gene targets with the transcription factors it binds and co-activates | Temperature<br>NO<br>– | Increased mitochondrial mass<br>Increased oxygen consumption | No |

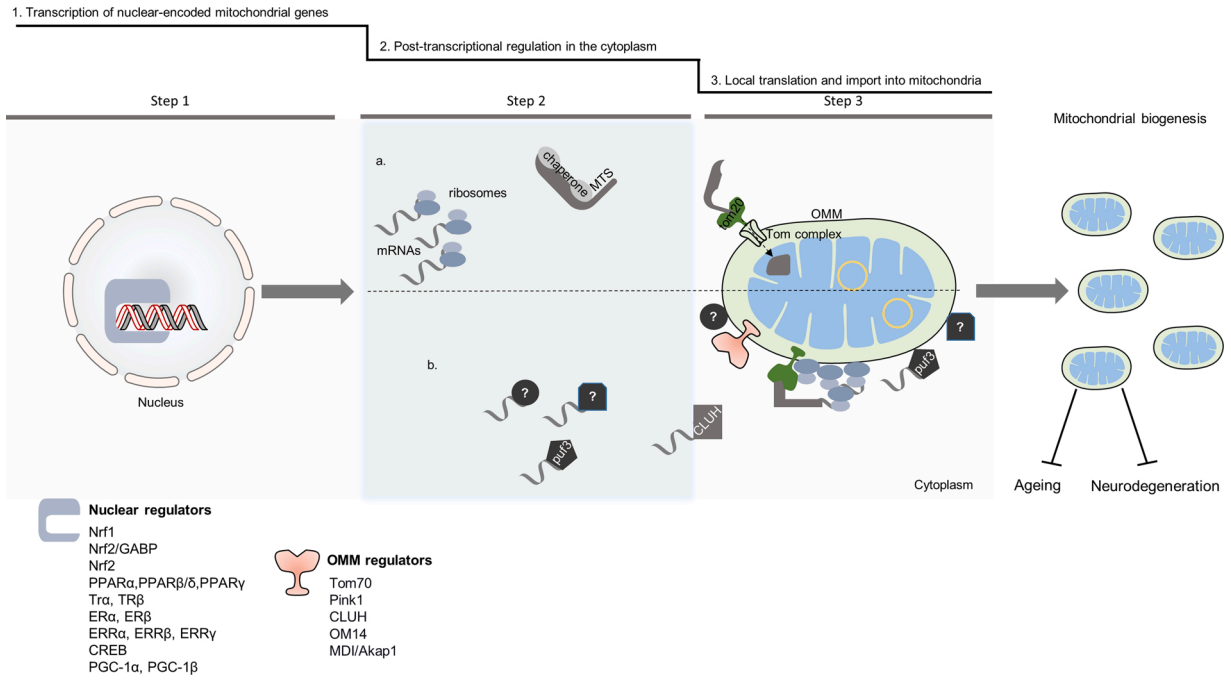


**Fig. 1. Schematic representation of the three critical steps required for proper mitochondrial biogenesis.** The first step for mitochondrial biogenesis is the transcription of nuclear-encoded mitochondrial genes. Next (step 2), the newly transcribed mRNAs exit the nucleus and in the cytoplasm are either (a.) translated by free, cytoplasmic ribosomes and bound by chaperones that keep them in an unfolded state until they reach the OMM where Tom20 recognizes their MTS and drives their import into the organelle (according to the post-translational import model) or (b.) bound by Puf3 or other, unknown factors, which keep them in a translationally silent state until they reach the vicinity of the organelles where they are translated by OMM bound ribosomes and are concomitantly harboured by OMM receptors that facilitate their local translation and import into the organelle (according to the co-translational import model). In the end, successful mitochondrial biogenesis propagates a healthy mitochondrial population. Increased mitochondrial biogenesis is beneficial and acts protectively against ageing and neurodegeneration among model organisms.

proper translocation of the *ATP2*mRNA, requires both its 3' UTR and translation of its open reading frame (ORF) (Gadir et al., 2011). Nevertheless, Puf3 deletion only partially affected the localization of *ATP2*and *OXA1*while the localization of other mitochondrial-targeted ETC component-mRNAs remained unaltered (Gadir et al., 2011). Collectively, Puf3 may be dispensable for mitochondrial biogenesis, raising the need for identification of novel cytoplasmic components that may play a role.

Proper mRNA localization next to mitochondria requires several factors. For example, the presence of ribosomes is required for the associations of *ATP2*mRNA with mitochondria (Garcia et al., 2010). Whether this is the case for the rest of the mRNAs, needs further investigation. It is suggested though, that active translation participates but is not essential for the localization of mRNAs to mitochondria, while their 3' UTR is. However, abrogation of both has an additive effect on mRNA mislocalization (Saint-Georges et al., 2008). Besides, diverse TOM components (i.e. Tom70, Tom6, Tom7, Tom20) may be critical for mRNA targeting to mitochondria (Gadir et al., 2011). It is notable that, Puf3 depletion did not alter the mitochondrial localization of mRNAs, while Tom20 did. Notably, double depletion of Tom20 and Puf3 was detrimental for organismal physiology in contrast to the single depletions, implying that the two mechanisms function either in an independent or compensatory manner (Eliyahu et al., 2010).

Analyses of polysome pools containing mitochondrial mRNAs provided additional supportive evidence that both models (post-translational import & co-translational import) exist. Two pools were identified, of which the first pool consisted of free, cytoplasmic ribosomes and the second of ribosomes attached on the OMM. In yeast, mRNAs such as *ATP2*, *TIM44*, *ATM1*, *COX10* and in mammalian cells *Cox1* and *ATP5b*, *ANT1*, *PiC*, *MDH2*, *COX-6c* and *CI-30* are bound to OMM ribosomes (Corral-Debrinski et al., 2000; Vardi-Oknin and Arava, 2019). Conversely, mRNAs such as *Cox4*, *Cox5* and *Cox6* are bound to free, cytoplasmic ribosomes (Corral-Debrinski et al., 2000; Su and Dowhan, 2006). Moreover, utilization of a novel technique, APEX-seq enabled identification of two types of OMM-bound mRNAs, depending on whether their localization is ribosome-dependent or not. Analysis of these mRNAs unveiled sequences important for each type of localization (Fazal et al., 2019). Collectively, upcoming findings suggest a Puf-3-independent and translation-dependent mechanism of mRNA targeting. A schematic representation of the post-translational and co-translational import model is provided in Fig. 1.

### 2.3. OMM regulators

Local translation in the vicinity of mitochondria is coupled to co-translational import. This mechanism serves several benefits for cell function and fitness. Among them are the precise regulation of a

microenvironment or even a single organelle and the prevention of ectopic misexpression. Moreover, local translation and co-translational import is less energy consuming than translation away from the organelle, as the latter requires the mRNA-chaperone binding and transport of the complex next to the organelle. Furthermore, local translation reduces the likelihood that hydrophobic proteins aggregate in the cytoplasm, causing cytotoxicity and lastly, it facilitates rapid adjustment of mitochondrial homeostasis, required upon acute stress induction (Lesnik et al., 2015).

Following their anchoring, mRNAs are translated by OMM bound ribosomes or by ribosomes found nearby mitochondria. Recently, the presence of ribosomes on the OMM was verified through electron cryotomography. Notably, ribosomes associate physically with TOM complex components, through nascent chains (George et al., 2002). In addition, mechanistic details support local translation and co-translational import of the transcripts bound by OMM ribosomes (Vardi-Oknin and Arava, 2019; Williams et al., 2014). More recently, it was shown that an OMM receptor, OM14, is specific for nascent polypeptide-associated complex (NAC) binding and that its disruption perturbs NAC and ribosome binding on mitochondria and decreases import (Lesnik et al., 2014). In addition, it has been shown that ribosomes attach on the OMM in an RNA-dependent manner, implying that mRNA transport precedes (Gold et al., 2017). This finding contradicts previous evidence that supports that mRNA transport requires active translation (Eliyahu et al., 2010). While ribosome positioning on the OMM and mRNA transport may occur concomitantly, additional temporal studies would shed light on this inconsistency.

Additional components, such as the TOM complex components, Tom20 and Tom70 are essential for local translation. These proteins function as receptors, which recognize different signals and harbour a select of translating products to drive their import through the channel. In addition, these receptors could mediate the associations of ribosomes with mitochondria (Vardi-Oknin and Arava, 2019). Ribosome-proximity biotin labelling showed that *Tom70* knockdown diminished the presence of its predicted target mRNAs on OMM ribosomes, oppositely to Tom20 targets. Tom20 depletion did not entirely abolish the import of mRNAs containing an MTS, despite the fact that it binds on most of the nuclear-encoded and mitochondrial-targeted mRNAs, raising the assumption that additional receptors act compensatory to Tom20 (Eliyahu et al., 2010).

Another important component is the RNA binding protein, Clustered Mitochondria Homologue (CLUH), which is localized mainly in the cytoplasm while a smaller portion of it is found on mitochondria. CLUH binds predominantly mitochondrial mRNAs that encode components of the ETC, TCA cycle, fatty acid metabolism and the PTEN-induced kinase 1 (*PINK1*) transcript (Gao et al., 2014). Upon its depletion, target mRNAs in the vicinity of mitochondria rise in number but are not translated since ribosomes dissociate from the organelles under this condition (Gao et al., 2014; Vardi-Oknin and Arava, 2019). Former findings established that CLUH depletion decreased the protein levels of some of its targets, suggesting a role in mitochondrial biogenesis. Although, the mechanism through which it regulates the expression of its target mRNAs remains unknown, the finding that CLUH binds on microtubules implies that it participates in RNA transport. Moreover, CLUH physically associates with Porin, TOM20, OMM ribosomes and PINK1, favouring the possibility that CLUH regulates expression of its target mRNAs locally (Sen and Cox, 2016; Sen et al., 2015).

Lately, a novel role of PINK1 in the regulation of mitochondrial biogenesis and local gene expression under basal conditions was uncovered. Particularly, the functional interplay of PINK1 with TOM20 and PUM regulates the localization and expression of a select of mRNAs encoding OXPHOS subunits in a tissue-specific manner. Mechanistic insight shows that PUM acts as a translational inhibitor and does not participate in mRNA transport in more complex eukaryotes, in contrast to yeast (Gehrke et al., 2015). However, whether PINK1 regulates mitochondrial abundance through modulating mitochondrial biogenesis, has not been shown yet. Nevertheless, complementary studies support that under normal conditions PINK1 localizes inside mitochondria and is not exposed to the OMM, raising the possibility that the localization of PINK1 on the OMM may be very dynamic or occur rarely enough to monitor (Fallaize et al., 2015).

MDI/AKAP1 is an additional OMM component that positively regulates mitochondrial biogenesis. MDI acts on the OMM as an anchor for the translation enhancer, La-related protein 1 (LARP1). Through this mechanism, MDI triggers local expression of ETC components, mitochondrial ribosome subunits and mitochondrial genome regulators. In contrast, MDI depletion blocks mtDNA replication, thus diminishes the amount of mtDNA and induces sterility, phenotypes reversed by the artificial targeting of LARP1 on the OMM. The latter reveals that the effects of MDI are mediated by LARP1 in *Drosophila melanogaster* and highlights the requirement of post-transcriptional regulation for mitochondrial biogenesis (Zhang et al., 2016). In mammals, AKAP1 directly binds on mitochondrial mRNAs. In addition, it forms physical associations with proteins such as PKA, which regulate mitochondrial biogenesis through phosphorylation events (Merrill and Strack, 2014). Nevertheless, the exact mechanism of action of MDI/AKAP1 remains elusive and the possibility that it differentially regulates mitochondrial biogenesis depending on tissue-specific interactors exists. An overview of the aforementioned mechanisms and associated factors is presented in Fig. 1.

## 3. Mitochondrial biogenesis and organismal senescence

Organismal senescence or ageing entails progressive accumulation of damage over time on molecules, organelles, cells and tissues. Accumulating damage triggers cellular senescence or death. The influence of mitochondria is unquestionable as inhibition of ETC components, availability of mitochondrial metabolites, mitochondrial network formation and organelle abundance have been implicated in the regulation of the ageing process (Morsci et al., 2016; Weir et al., 2017; Yasuda et al., 2006). Notably, understanding of the mechanisms that regulate mitochondrial biogenesis is essential, as it enables the fine-tuning of mitochondrial abundance and function with immediate implications in cellular and organismal senescence.

Ways to estimate mitochondrial biogenesis is measurement of the total mitochondrial mass, evaluation of mtDNA copy number, mitochondrial protein abundance, protein abundance and activity of mitochondrial biogenesis regulators and enzymatic activity of core mitochondrial enzymes (Miller and Hamilton, 2012). Diverse studies in young versus old organisms, tissues or cell types have tried to tackle the question of how normal ageing affects mitochondrial mass, but results are controversial. mtDNA copy number is significantly increased, or unaltered as for example in the mouse brain, depending on the tissue (Barazzoni et al., 2000; Masuyama et al., 2005; Miller et al., 2003). In accordance, the mitochondrial mass of young versus old male rat myocardium exhibited no significant difference (Schmucker and Sachs, 1985). However, most studies suggest a drop in mitochondrial abundance, enzymatic activity or mtDNA copy number during ageing (Barazzoni et al., 2000; Corsetti et al., 2008; Kushnir et al., 2012; Simsek-Duran et al., 2013; Stoll et al., 2011; Tate and Herbener, 1976). Of note, mtDNA levels drop significantly in the brain of aged rats and mitochondrial abundance drops in the cortex of aged Macaque monkeys, suggesting that this drop is conserved to primates (Burns et al., 1979; Hebert et al., 2015; Picca et al., 2013a). Also, NADH oxidase activity and the protein levels of other mitochondrial components drop significantly in the brain of old rats and humans (Dencher et al., 2007; Genova et al., 1997; Ojaimi et al., 1999).

Although the prevailing notion suggests that mitochondrial biogenesis drops during normal ageing, the reason for this and the driving mechanism remain obscure. Deeper understanding of the underlying mechanism is provided through the study of mitochondrial biogenesis regulators. Particularly, *NRF1* mRNA increases during ageing in contrast to NRF1 protein levels. Moreover, assessment of both the protein and

mRNA levels of TFAM, which is a target of NRF1, during ageing gave inconsistent results (Bori et al., 2012; Ghosh et al., 2011; Lezza et al., 2001; Picca et al., 2013b). However, recent evidence from mouse brains suggests that the mRNA levels of *TFAM*, *Nrf1* and *PGC-1α* were significantly decreased in aged particles (Reutzel et al., 2020). Although direct evidence regarding a role of NRF2/GABP in the regulation of the ageing process is still missing, it is believed that NRF2/GABP possibly has a positive but indirect role in longevity (Satterstrom et al., 2015). NRF2 levels drop during ageing, and this loss is coupled to age-related cellular deterioration (Gounder et al., 2012; Kloska et al., 2019; Li et al., 2018). It was shown in *C. elegans*, that *skn-1* downregulation shortens lifespan in contrast to its overexpression (Tullet et al., 2008). In accordance, *Nrf2* induction in mice and humans and loss of function of *keap1* in flies extends lifespan (Davinelli et al., 2012; Singh et al., 2010; Sykiotis and Bohmann, 2008). Furthermore, NRF2 influences ageing through regulating telomeres, yet whether this role interferes with its role in mitochondrial biogenesis remains to be answered (Ahmad et al., 2016).

The expanding list of mitochondrial biogenesis regulators that influence the ageing process includes PPARs. Studies in *C. elegans* delineate that mutation in *nhr-49*, the most well conserved worm functional analogue of PPARα and PPARβ/δ, shortens lifespan (Van Gilst et al., 2005). Comparable results were obtained upon PPARγ deletion in mice (Argmann et al., 2009). Moreover, both the mRNA and protein levels of PPARα, PPARβ/δ and PPARγ drop during ageing (Iemitsu et al., 2002; Sung et al., 2004; Tong et al., 2019). By contrast, PPAR agonists reverse age-related phenotypes (Sung et al., 2006; Yang et al., 2009).

Regarding TH signalling, data are quite controversial to date. Particularly, while understanding is still limited, it has been found that TH signalling and TR abundance and functionality display a tissue-specific, age-related drop (De Nayer et al., 1991; Gunin and Golubtsova, 2018; Visser et al., 2016). However, decreased TH levels correlate with longer lifespan, through yet not well-understood mechanisms (Jansen et al., 2015). Moreover, it is suggested that the expression of ERs drop during normal ageing, similarly to TRs (Koenig et al., 2017; Wynne et al., 2004). Besides, inhibition of estrogen is linked to the onset of ageing-related phenotypes (Sehl and Ganz, 2018). Of note, preliminary results classify a nuclear hormone receptor responsive to estrogen in *C. elegans*, *nhr-14,* as a longevity-related gene although it is not a conserved homologue of the mammalian estrogen receptor (Hamilton et al., 2005; Mimoto et al., 2007).

Total and active CREB (pCREB), but not its mRNA levels, drop during normal ageing (Rolewska et al., 2014). CREB regulators such as PKA, cAMP or CBP also drop during ageing in various brain regions (Bach et al., 1999; Miyamoto et al., 2013; Porte et al., 2008; Xiang et al., 2019). Moreover, the age-related cognitive decline can be reversed by treatment with plasma from young mice in a CREB-dependent manner, or *Creb* overexpression in old rat hippocampus (Villeda et al., 2014). Taking into account that the levels of CREB kinases also drop in the aged, the possibility that un-phosphorylated CREB mediates part of the observed beneficial effects should be questioned. In addition, since data regarding the levels of pCREB and CREB during ageing remain inconclusive to date, it would be informative if the ratio of pCREB/CREB was tested in various brain regions and tissues (Brightwell et al., 2004; Foster et al., 2001; Monti et al., 2005; Paramanik and Thakur, 2013; Xu et al., 2010). The beneficial role of CREB in cognition is conserved in the nematode *C. elegans* (Kauffman et al., 2010). Particularly, it is uncovered that *crh-1*, the CREB mammalian homologue in *C. elegans*, also drops during ageing. Since AMPK inhibits CREB and AMPK similarly to CREB, drops during ageing, the mechanism through which *crh-1* is regulated during ageing remains obscure. Nevertheless, the lifespan of *crh-1* mutants is increased. AMPK extends lifespan through phosphorylating and de-activating the CREB-Regulated Transcription Coactivator 1 (CRTC-1) and ultimately the activity of CRH-1, while Calcineurin dephosphorylates and activates CRTC-1 having the adverse effect on lifespan (Mair et al., 2011). In turn, neuronal CRTC-1/CREB regulates mitochondrial homeostasis and metabolism in distal tissues cell-non-autonomously, acting antagonistically to *nhr-49* (Burkewitz et al., 2015). Future studies should investigate whether the role of CREB in mitochondrial biogenesis is conserved in *C. elegans*.

A considerable body of literature suggests that PGC-1 protein and mRNA levels decline during normal ageing (Ghosh et al., 2011; Gill et al., 2018; Picca et al., 2013b; Vina et al., 2009; Wenz et al., 2009). Loss of PGC-1α associates with muscle deterioration through yet not fully understood mechanisms. Besides, an age-related reduction of PGC-1α is associated with heart failure in humans and milder defects in mice, which are reversible upon moderate overexpression of *Pgc-1α* (Sihag et al., 2009; Whitehead et al., 2018; Xiong et al., 2013). In addition, overexpression of *Pgc-1α* can reverse age-dependent decline in muscles, ameliorate sarcopenia and myopathy and increase maximal lifespan (Garcia et al., 2018; Wenz et al., 2008, 2009). Similarly, *Pgc-1β* overexpression displayed beneficial anti-ageing effects in the mouse intestine (Bellafante et al., 2014). Moreover, the age-associated loss of both PGC-1α and PGC-1β, have been implicated in the shortening of telomeres, a hallmark of cellular and organismal senescence (Sahin et al., 2011; Xiong et al., 2015). Although PGC-1 does not have a *C. elegans* homologue, its role in longevity has been tested in flies. Ubiquitous overexpression of dPGC-1/*spargel* marginally lowered the lifespan of the flies, while, its overexpression gave variable, tissue-specific results (Rera et al., 2011).

Data regarding the role of cytoplasmic and OMM regulators of mitochondrial biogenesis during normal ageing are inconclusive to date. For example, Tom20 levels remain unchanged during ageing in mouse hippocampus and human muscle cells, in contrast to mouse myocardium and human cochlea in which a drop is observed (Balaker et al., 2013; Boengler et al., 2007; Buso et al., 2019; Wang et al., 2017). Nevertheless, there are no ageing studies available to provide information relative to the effect of *Tom20* overexpression or inhibition in organismal lifespan.

Moreover, the abundance of ribosomal proteins declines during ageing in human muscles, with only a few exceptions (Ubaida-Mohien et al., 2019). The same trend was also observed in *C. elegans*,highlighting the conservation of this drop across eukaryotes (Dhondt et al., 2017; Gonskikh and Polacek, 2017). Nevertheless, whether the associations of ribosomes with the OMM are modulated during ageing has not been studied.

The levels of Puf3, its mammalian orthologue PUM2, as well as its *C. elegans* orthologue, PUF-8, increase in aged animals, compared to their young counterparts (D'Amico et al., 2019). Notably, Puf3 deletion increases chronological lifespan in yeast, while it had no effect elsewhere (Chatenay-Lapointe and Shadel, 2011; Smith et al., 2016). In *C. elegans*, *puf-8* genetic inhibition increased lifespan (D'Amico et al., 2019).

PINK1 and Parkin play a role in both mitochondrial biogenesis and mitophagy. Though it is not tested to date whether the two functions are independent and can be discriminated, it is known that the activity of PINK1 increases during ageing (Fiesel et al., 2015). On the other hand, PINK1 levels significantly drop in the liver and hepatocytes of aged mice and triceps muscles of aged rats (Capitanio et al., 2016). Moreover, genetic inhibition of both *pink-1/Pink1* and *pdr-1/Parkin*, did not affect lifespan in *C. elegans* (Palikaras et al., 2015). However, in Drosophila, *PINK1* or *PARKIN* depletion shortens the lifespan of flies in contrast to *PINK1* overexpression that extends lifespan (Greene et al., 2003; Pesah et al., 2004; Si et al., 2019; Yang et al., 2006).

Finally, depletion of clu, the orthologue of CLUH in Drosophila, shortens the lifespan of the flies while no data exist to date, regarding a role of MDI during ageing or in longevity (Cox and Spradling, 2009). The alterations of mitochondrial biogenesis regulators during ageing or their effect on lifespan are outlined in Table 2.

## 4. Mitochondrial biogenesis and neurodegeneration

Mitochondria are indispensable for neuronal activity, survival, development, maturation and plasticity. Neuronal function depends on

proper regulation of energy, calcium and ROS homeostasis, all controlled by mitochondria. Thus, both hereditary and age-related neurodegeneration is closely associated with mitochondrial dysfunction. It is noted that during ageing, the number of functional mitochondria drops in the nervous system in various model organisms. Moreover, a significant drop in ETC complex abundance during ageing has been reported in the brain (Navarro and Boveris, 2007). Essential functions of neurons, like neurotransmission and excitation, require energy produced by mitochondria. Thus, it is becoming evident that mitochondrial biogenesis defects could be associated to diverse neurodegenerative disorders. Lately, several lines of work suggest that impaired mitochondrial biogenesis can even precede symptoms and be the driving force for neurodegeneration.

### 4.1. Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Typical disease features are dementia and progressive whole-brain atrophy. Its aetiology is not yet thoroughly understood while the generation of plaques and tangles have been correlated with disease progression. Typically, Amyloid precursor proteins (APPs) are embedded in the neuronal cell membrane with one terminus exposed extracellularly and the other intracellularly (O'Brien and Wong, 2011). APPs typically contribute to neuronal growth and proper neuronal cell function. Enzymatic cleavage of APPs by α-, β- and γ-secretase is crucial for their regulation and recycling (Muller and Zheng, 2012). However, when β- and γ-secretase break down APPs, they produce insoluble APP fragments. Each of these fragments comprises an Amyloid-beta monomer (Aβ peptide) (Chow et al., 2010). These monomers stick to each other creating huge aggregates, the beta-amyloid plaques, which accumulate among neurons, perturbing inter-neuronal signalling and triggering inflammatory responses that can even lead to cell death (Kinney et al., 2018). Additionally, though not yet well-understood mechanisms, the extracellular beta-amyloid plaques trigger kinases that phosphorylate tau. Hyper-phosphorylated tau (pTau) dissociates from microtubules and self-aggregates, creating the neurofibrillary tangles (NFTs) (Iqbal et al., 2010). Subsequently, microtubules lose their functionality and cause neuronal cell death.

Alzheimer's disease is mostly sporadic and increases with age while the rare, early-onset AD is familial (Liu et al., 2013). Mitochondrial dysfunction and impaired energy metabolism are evident from the first steps of the disease. Complex I, III and IV deficiency have been associated with AD (Holper et al., 2019; Kim et al., 2000). Notably, Tau triggers Complex I dysfunction and AD patients exhibit Aβ plaque accumulation within their brain mitochondria (Chen and Yan, 2007; Rhein et al., 2009). Mitochondrial Aβ causes ETC impairment, ATP shortage, excessive ROS production and correlates with greater cognitive impairment (Rhein et al., 2009). Intriguingly, recent evidence suggests that it is not the Aβ plaques that drive diesease progression, but mitochondrial dysfunction instead (Morris et al., 2018; Swerdlow et al., 2014).

Notably, the hippocampus and the cerebral cortex are the brain regions preliminary affected in AD. AD patients and mouse models of AD exhibit reduced mtDNA copy numbers and mitochondrial content, which combined with the drop in the levels of PGC-1α, NRF1, NRF2 and TFAM document compromised mitochondrial biogenesis, specific to these brain regions (Hirai et al., 2001; Sheng et al., 2012; Song et al., 2018). However, mitochondrial biogenesis was not impaired in the cerebellum, a brain region not involved in AD pathogenesis (Sheng et al., 2012). Moreover, Aβ plague formation correlates with decreased abundance of both PGC-1α and NRF2 in the brains of AD patients (Qin et al., 2009; Ramsey et al., 2007). PGC-1α regulates the expression of α- and β-secretase, thus could affect AD through this mechanism (Katsouri et al., 2011; Qin et al., 2009). Moreover, PGC-1α obtains a potentially significant, antioxidant role against AD, considering AD is highly associated with increased ROS levels in the brain. Nevertheless, the precise role of mitochondrial biogenesis in AD is not yet clear as levels of mitochondrial biogenesis regulators such as pCREB, PGC-1α, NRF1, NRF2/GABP and TFAM are reduced, while mtDNA and distinct ETC protein levels increased (Sheng et al., 2012).

Of note, the levels of mitochondrial biogenesis regulators drop even before AD onset, suggesting that mitochondrial dysfunction and diminished mitochondrial biogenesis have an active role in promoting disease progression and are not a consequence of AD. Intriguingly, the mRNA and protein levels of PGC-1α were unaffected in the hippocampus of patients with mild cognitive impairment (MCI), a state of mildly decreased cognition that precedes AD, whereas TFAM levels dropped (Delbarba et al., 2016; Qin et al., 2009). In addition, treatment of MCI patients with PPAR-γ agonists did not significantly improve their cognition performance, while resveratrol (which induces mitochondrial biogenesis among other functions) administration preserved hippocampal integrity and function (Kobe et al., 2017; Yu et al., 2010). While the interplay of mitochondrial biogenesis and MCI is still largely unexplored, future studies are required to verify whether mitochondrial biogenesis impairment is also evident in MCI patients and provide the temporal window within which administration of pharmaceutical agents that increase mitochondrial biogenesis can effectively improve cognition and delay AD progression. Moreover, mitochondrial biogenesis deficiency in young age correlates with mitochondrial dysfunction in AD (Singulani et al., 2020). Notably, *Nrf2/GABP* overexpression decreased the detrimental effects of Aβ aggregation in neuronal cells and the accumulation of hyper-phosphorylated Tau evident in an NRF2/GABP-mutant background (Jo et al., 2014; Kanninen et al., 2008). Additionally, PPAR-γ agonists can diminish Aβ aggregation (Heneka et al., 2011). Additional mitochondrial biogenesis related factors such as SIRT1 or AMPK can ameliorate the AD-related neuropathogenesis (Sun et al., 2019). Notably, VEGF-treated AD mice, displayed increased mitochondrial biogenesis and diminished levels of Aβ plaques and better

**Table 2**
Mitochondrial biogenesis regulators and ageing.

| Factor | Expression levels[a] | Lifespan[b] |
|---|---|---|
| NRF1 | Increased mRNA<br>Decreased protein | – |
| NRF2/ GABP | – | Extension (mice) |
| NRF2 | Decreased protein | Extension (mice, worm, flies) |
| PPARα | Decreased mRNA<br>Decreased protein | Extension (worms) |
| PPARβ/δ | Decreased mRNA<br>Decreased protein | Extension (worms) |
| PPARγ | Decreased mRNA<br>Decreased protein | Extension (mice) |
| TRα | Decreased protein | – |
| TRβ | Decreased protein | – |
| ERα | Decreased protein | Extension (worms) |
| ERβ | Decreased protein | Extension (worms) |
| CREB | Unaltered mRNA<br>Decreased protein | Shortening (worms) |
| PGC-1α | Decreased mRNA<br>Decreased protein | Extension (mice)<br>Tissue-specific (flies) |
| PGC-1β | Decreased protein | Tissue-specific (flies) |
| TOM20 | Unaltered protein (mouse hippocampus and human muscle cells)<br>Decreased protein (mouse myocardium and human colchlea) | – |
| CLUH | – | Extension (flies) |
| PINK1 | Decreased protein | Unaltered (worms)<br>Extension (flies) |
| Parkin | – | Unaltered (worms)<br>Extension (flies) |
| Puf3/ PUM | Increased protein | Controversial (yeast)<br>Shortening (worms) |

[a] The impact of ageing on mitochondrial biogenesis factor mRNA or protein levels is indicated.

[b] The effect of mitochondrial biogenesis factors on lifespan is indicated.

memory, while neither mitophagy nor autophagy were implicated (Liu et al., 2020). In turn, PINK1 obtains an upcoming, beneficial role in AD, although it remains unclear whether its function in mitochondrial biogenesis mediates the beneficial effects (Du et al., 2017). Besides, prior activation of ERs to pathology onset, could rescue several disease-related phenotypes such as Aβ plague formation (Bryant and Dorsa, 2010; Lan et al., 2015; Zhao et al., 2013). Perturbed estrogen signalling observed in AD could be the result of ERα binding by pTau as observed in M17 cells (Wang et al., 2016).

### 4.2. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder, characterized by impaired movement and cognition. PD patients have low levels of dopamine in basal ganglia owing to a severe loss of dopaminergic neurons in the substantial nigra pars compacta (SNpc) (Giguere et al., 2018). Additionally, PD patients exhibit accumulation of α-synuclein Lewy bodies (LBs) in substantial nigra neurons (Prymaczok et al., 2016). While the aetiology of the disease is still unknown, it is regularly idiopathic and rarely familial. Both environmental factors such as age, obesity and brain trauma as well as genetic contributors generate the various forms of PD. Notably, protein aggregation, oxidative stress and mitochondrial impairment are significant contributors to PD pathogenesis (McNaught and Olanow, 2006; Niranjan, 2014). Prominently, the levels of the master regulator of mitochondrial biogenesis, PGC-1α are decreased in PD patients while other regulators of mitochondrial biogenesis, such as PPARγ, are also affected (Chaturvedi and Beal, 2008; Su et al., 2015).

It has often been noticed in PD brains, similarly to AD, that ETC components are less functional or lower in abundance (i.e. Complex I and IV). Complex I has attracted much attention as its inhibition has been linked to perturbed proteasome activity and subsequent α-synuclein accumulation (Hoglinger et al., 2003; Parker et al., 2008). Complex I levels drop in several brain areas and peripheral tissues of PD patients (Schapira et al., 1989). Utilization of Complex I inhibitors (such as the neurotoxins MPTP, MPP + or rotenone) in the substantial nigra, triggers loss of dopaminergic neurons (Langston et al., 1983). Besides, the finding that α-synuclein can bind complex I and complex V and associate with mitochondria to perturb their function raises the hypothesis that a vicious cycle that accelerates disease progression exists (Chinta et al., 2010; Devi et al., 2008; Di Maio et al., 2016; Ludtmann et al., 2018; Reeve et al., 2015).

Familial PD is associated with mutations in genes encoding mitochondrial proteins such as PINK1 and Parkin. Depletion of *Parkin* in PD patients triggers diminished ETC Complex I and IV activities while in flies it additionally causes locomotor defects and loss of dopaminergic neurons (Muftuoglu et al., 2004; Saini et al., 2011). Furthermore, *Pink1* mutation leads to decreased energy production and mitochondrial impairment in a cell-type-specific manner (Abramov et al., 2011; Gehrke et al., 2015). Moreover, Parkin ubiquitinates PARIS and targets it for proteasomal degradation. In PD, where Parkin is mutant or absent, PARIS represses PGC-1α expression thus blocks mitochondrial biogenesis. Similarly, PARIS overexpression can itself trigger loss of dopaminergic neurons in mouse substantia nigra (Shin et al., 2011). Intriguingly, PARIS overexpression in the substantial nigra decreased mitochondrial number specifically in this brain region, as the same manipulation in the cortex did not affect cortical mitochondria (Stevens et al., 2015). Induction of mitochondrial biogenesis in a PGC-1α-dependent manner, could rescue PD-induced loss of dopaminergic neurons (Ciron et al., 2015). Moreover, in flies, mutation of *spargel* triggers PD-related pathophysiology while overexpression of the normal protein or treatment with its inducers is neuroprotective in genetic models of PD (Hasegawa et al., 2016; Merzetti and Staveley, 2015; Ng et al., 2017; Sasaki and Mochizuki, 2017). The contribution of impaired PINK1/Parkin-mediated mitochondrial biogenesis in PD needs to be explored in the future.

Furthermore, impaired NRF2 signalling is associated with PD pathogenesis while several drugs used against PD are in parallel NRF2 activators (such as apomorphine and deprenyl). Moreover, the NRF2 activators dimethylfumarate (DMF) and monomethylfumarate (MMF) could reverse the MPTP-induced, PD-related neurotoxicity in mice (Ahuja et al., 2016). Likewise, memory enhancement was observed when *Nrf2/GABP* was injected in the brain of a mouse model of PD (Kanninen et al., 2009). Further supportive evidence of a role of mitochondrial biogenesis in PD is provided in a mouse model of PD, where the mRNA levels of *NRF1*, *Parkin* and *PPARγ* were significantly decreased in the early stages of the disease (Rudenok et al., 2020). Finally, ERβ activation has a beneficial role against PD but whether this effect is mediated through its function in mitochondrial biogenesis is not yet known (Kim et al., 2017; Westberg et al., 2004).

### 4.3. Huntington's disease

Huntington's disease is a neurodegenerative disorder, characterized by locomotor problems, psychiatric and cognitive deficiencies. It is an autosomal dominant disorder, and its onset is triggered by the expression of abnormal Huntingtin (HTT). While normal HTT contains 10–35 glutamine repeats in a row, mutant HTT contains this amino acid more than 36 times and for this reason, Huntington's is a polyglutamine (polyQ) disease (Kay et al., 2016; Warby et al., 2009). Glutamine repeats increase even more during DNA replication, and their number inversely correlates with the age of disease onset (the more the replications, the earlier the disease onset) (Langbehn et al., 2004). While the precise mechanism of toxicity of mutant HTT is still unexplored, it is believed that insoluble aggregation of mutant HTT in dorsal striatum neuronal cells might cause neuronal cell death.

Besides, mitochondrial dysfunction and impaired mitochondrial biogenesis are closely linked to HD pathogenesis and progression. It has been shown that HD patients exhibit decreased levels of PGC-1α and TFAM. In addition, a 30% decrease in PGC-1α levels since the early stages of the disease suggests that mitochondrial biogenesis impairment contributes to disease onset, while elimination of PGC-1α enhances HD pathogenesis. Intriguingly, this decrease was specifically detected in the striatum, which is the region most affected in HD, and not in the cerebellum or the hippocampus (Chaturvedi et al., 2009; Cui et al., 2006; Kim et al., 2010). In agreement, the mitochondrial content in striatal neurons of HD mouse models is decreased compared to their healthy counterparts (Guo et al., 2016). Moreover, PGC-1α promotes the removal of mutant HTT aggregates in a transcription factor EB (TFEB)-dependent manner (La Spada, 2012).

Mutant HTT can also block the activity and expression of PPARγ in a mouse model of HD. Evidence shows that apart from their lower expression in HD, PPARγ and PGC-1α are also mislocalised within mutant HTT aggregates, limiting further their presence in the nucleus (Chiang et al., 2012). Contrary, activation of PPAR-γ can rescue mitochondrial dysfunction and reduce mutant HTT aggregation (Chiang et al., 2012; Quintanilla et al., 2008). Furthermore, treatment with PPARγ agonists elevates oxidative phosphorylation levels, boosts mitochondrial biogenesis and increases mitochondrial mass in HD-striatal cells (Chiang et al., 2012; Quintanilla et al., 2008).

Furthermore, pCREB was significantly decreased in a mouse model of HD. CREB loss of function exacerbated disease pathogenesis while CREB gain of function mutation could mitigate damage (Choi et al., 2009). Besides, mutant HTT can be cleaved, and its amino terminus fragment translocate to the nucleus where it aggregates with CBP in vitro, suggesting that mutant HTT can intervene with the activity of transcription factors such as CREB (Steffan et al., 2000). On the other hand, in vivo studies in a mouse model of PD revealed that mutant HTT increased the transcriptional activity of CREB in the cortex, the hippocampus and the striatum. This increase was accompanied by elevated levels of pCREB, while mutant HTT inclusions in HD mice did not affect CBP localization (Obrietan and Hoyt, 2004). Future research should

consider this inconsistency and shed light on the implication of CREB in HD. Finally, PINK1 overexpression has a protective role against HD, while whether this is mediated through its role in mitochondrial biogenesis or mitophagy has not been investigated to date (Khalil et al., 2015).

Activation of other mitochondrial biogenesis regulators such as AMPK, NRF2 and SIRT1 also attenuates HD pathogenesis (Duan, 2013; Joshi and Johnson, 2012; Vazquez-Manrique et al., 2016). The finding that NRF2/GABP is decreased in HD mouse models also supports this idea. Besides, polymorphisms of NRF1 and TFAM have been associated with the age of disease onset (Taherzadeh-Fard et al., 2011). Furthermore, there is evidence that HD may alter the transcriptional activity of nuclear hormone receptors. For example, mutant HTT with 103Q repeats enhances the NCoR-mediated suppression of TR transcription in the absence of a ligand. On the other hand, the expression of this mutant HTT in PC12 cells enhanced the activation of TR in the presence of its ligand (Astapova and Hollenberg, 2013). This preliminary evidence suggests the implication of nuclear hormone receptors in HD. Future studies could explore their implication in disease progression.

In turn, ETC activity (impaired activity of Complex II, III and IV) and mitochondrial ATP levels are significantly reduced in striatal neurons and the neostriatum of HD patients as well as in mice models of HD while ROS levels increase significantly (Jin and Johnson, 2010). Particularly, Complex III perturbation induces mutant HTT aggregation, most probably through proteasome inhibition. Nevertheless, this was not the case in fibroblasts where HD did not affect ETC complex abundance, or mitochondrial mass, revealing that the effects of HD on mitochondria are cell-type-specific (Jedrak et al., 2018). Although the mechanism by which mutant HTT impairs mitochondrial function is still unknown, its impact on mitochondria could be direct as mutant HTT can physically associate with the OMM (Choo et al., 2004). Additionally, mutant HTT blocks PGC-1α transcription specifically in the striatum, obstructs protein import and decreases total mitochondrial abundance in the striatum and cortex of HD patients (Cui et al., 2006; Yablonska et al., 2019).

Information about the interplay of mitochondrial biogenesis regulators and neurodegeneration is summarized in Table 3.

**Table 3**
Mitochondrial biogenesis regulators and neurodegeneration.

| Factor | Levels (AD) | Levels (PD) | Levels (HD) | Therapeutic role |
|---|---|---|---|---|
| NRF1 | Decreased | Decreased | – | – |
| NRF2/GABP | Decreased | – | Decreased | Yes (AD, HD) |
| NRF2 | Decreased | Decreased | – | Yes (AD, PD) |
| PPARγ | – | Decreased | Decreased | Yes (AD, HD) |
| TRα | – | – | Dependent on the presence of a ligand | – |
| TRβ | – | – | Dependent on the presence of a ligand | – |
| ERβ | – | – | – | Yes (PD) |
| CREB | Decreased | – | Inconclusive | Yes (HD) |
| PGC-1α | Decreased | Decreased | Decreased | Yes (AD, PD, HD) |
| Pink1 | – | Decreased | – | Yes (AD, PD, HD) |
| Parkin | – | Decreased | – | Yes (PD) |

## 5. Conclusions and future prospects

Mitochondria are critical regulators of cellular and organismal homeostasis. Their abundance and metabolite availability are closely regulated by mitochondrial biogenesis. The prevailing notion suggests that mitochondrial biogenesis declines during ageing and in age-associated neurodegenerative syndromes, while controversy still exists. While current evidence proposes that several mitochondrial biogenesis regulators obtain anti-ageing and neuroprotective roles, further research on how these factors modulate cellular and organismal senescence in needed. Regulators of transcription, mRNA transport and stability and regulators of local protein synthesis on the OMM can regulate the ageing process and are themselves tightly controlled during ageing.

Notably, their activation exhibits anti-ageing phenotypes, while their uncontrolled expression can reduce healthspan and lifespan, suggesting that only when mitochondrial biogenesis is tightly controlled, it can exert its beneficial role.

Moreover, functional mitochondria are crucial for the high-energy demanding brain. Upcoming evidence suggests that mitochondrial dysfunction is the trigger for the most common incurable neurodegenerative syndromes such as AD, PD, and HD. Interestingly, perturbation of mitochondrial biogenesis regulators correlates with disease progression while activation or mild overexpression of these factors, with neuroprotection. Since mitochondrial biogenesis propagates functional mitochondria, triggering the process is expected to rescue mitochondrial dysfunction evidenced in neurodegenerative syndromes and ameliorate disease phenotypes. Nevertheless, our understanding of the mechanisms that govern mitochondrial biogenesis is still obscure and many regulators remain unexplored. Identification of brain-specific mitochondrial biogenesis-regulators and delineation of their expression pattern is essential. Mapping of their expression pattern per brain region and correlation of these findings with mitochondrial abundance and the stage of the disease could highly increase our understanding of the interplay of mitochondrial biogenesis with AD, PD and HD. In addition, complete characterization of mitochondrial biogenesis regulators and a holistic understanding of their function would provide important pharmaceutical targets that could be utilized towards the development of therapeutic strategies aimed at battling severe neurodegenerative diseases.

## Author contributions

ID summarized the literature, wrote the paper and created the initial figure and tables. NT edited the paper, revised the figures and contributed to the writing.

## Declaration of Competing Interest

The authors report no declarations of interest.

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