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Mitochondrial Biogenesis: A Therapeutic Target for Neurodevelopmental Disorders and Neurodegenerative Diseases

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Abstract

In the developing and mature brain, mitochondria act as central hubs for distinct but interwined pathways, necessary for neural development, survival, activity, connectivity and plasticity. In neurons, mitochondria assume diverse functions, such as energy production in the form of ATP, calcium buffering and generation of reactive oxygen species. Mitochondrial dysfunction contributes to a range of neurodevelopmental and neurodegenerative diseases, making mitochondria a potential target for pharmacological-based therapies. Pathogenesis associated with these diseases is accompanied by an increase in mitochondrial mass, a quantitative increase to overcome a qualitative deficiency due to mutated mitochondrial proteins that are either nuclear- or mitochondrial-encoded. This compensatory biological response is maladaptive, as it fails to sufficiently augment the bioenergetically functional mitochondrial mass and correct for the ATP deficit. Since regulation of neuronal mitochondrial biogenesis has been scantily investigated, our current understanding on the network of transcriptional regulators, co-activators and signaling regulators mainly derives from other cellular systems. The purpose of this review is to present the current state of our knowledge and understanding of the transcriptional and signaling cascades controlling neuronal mitochondrial biogenesis and the various therapeutic approaches to enhance the functional mitochondrial mass in the context of neurodevelopmental disorders and adult-onset neurodegenerative diseases.

Keywords

Mitochondrial DNA maintenance; adaptive mitochondrial biogenesis; mitochondrial fusion-fission; mitophagy; maternally inherited mitochondrial diseases; Parkinson's disease; Huntington's disease; small-molecule-based therapies

1. INTRODUCTION

Due to their eubacterial ancestry, mitochondria contain their own genome characterized by limited encoding capacity, making these organelles dependent on the nuclear genome for

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

their functions. Even though mitochondria are ubiquitous organelles, their mitochondrial proteome is complex and exhibits tissue-heterogeneity to meet the metabolic and energy needs specific to each cell type, to assume diverse functions tailored to specific organs, and to adapt a myriad of mitochondrial pathways to specific metabolic state of the cell [1]. Half of the mitochondrial proteins are tissue-specific, while the other half makes up the core protein components [2]. Using a combination of in-depth mass spectrometry, microscopy and computation, the mitochondrial compendium has been estimated at 1098 genes with their expression profiles analyzed across 14 distinct mouse tissues [3]. This mitochondrial protein atlas, which is constantly expanded and updated on the MitoCarta inventory available at http://www.broad.mit.edu/publications/MitoCarta, provides a platform to decipher tissue-specific programs and pathogenesis of mitochondrial diseases. This inventory highlights a lack of tissue specificity for most of the subunits of the oxidative phosphorylation (OXPHOS) system and the Krebs cycle, whereas many of the mitochondrial ribosomes, half of the subunits of complex IV, enzymes involved in the ketogenesis and urea cycle pathways exhibit some degree of tissue-specificity [3].

Mitochondrial dysfunction causes a range of diseases spanning from incurable neonatal neurodevelopmental diseases to adult-onset neurodegenerative diseases [4]. Maintenance of an adequate and functional mitochondrial population during the lifetime of neurons is critical and involves a balance between mitochondrial biogenesis and turnover. Mitochondrial quality control occurs via the process of mitophagy through the autophagy machinery, a process that is often dysregulated in many neurological diseases [5, 6]. Mitochondrial biogenesis is a complex process requiring a coordinated bigenomic regulation to execute several distinct processes: 1) inner and outer mitochondrial membrane synthesis; 2) synthesis of mitochondrial-encoded proteins; 3) synthesis and import of nuclear-encoded mitochondrial proteins; and 4) replication of mitochondrial DNA (mtDNA). Since neuronal mitochondrial biogenesis by itself has been poorly explored, the identity of the neuronal-specific regulators responsible to coordinate mitochondrial biogenesis with neural development remains unknown. In the case of the mitochondrial respiratory disorders and adult-onset neurodegenerative diseases, neurons exhibit a mixed population of healthy and defective mitochondria whose overall functionality depends on the equilibrium between mitochondrial biogenesis and mitophagy. As a result of bioenergetic deficit and sub-optimal ATP synthesis, a compensatory biological response is triggered as an attempt to produce more mitochondria- a quantitative increase to overcome a qualitative deficiency due to mutated mitochondrial proteins that are either nuclear- or mitochondrial-encoded.

This review will concentrate on mitochondrial biogenesis in the context of neuronal differentiation, its timing and regulation, the signaling pathways responsible to enhance mitochondrial mass in response to neuronal stimuli. We will discuss potential small molecule-based therapeutic strategies to boost the mitochondrial biogenic response in various animal models for mitochondrial encephalomyopathies and their implications for mitochondrial respiratory disorders and adult-onset neurodegenerative diseases (Table 1).

2. MITOCHONDRIA ARE ESSENTIAL ORGANELLES FOR DEVELOPING AND MATURE NEURONS

It has long been known that the brain is a highly energy-demanding organ that consumes more than 20% of the total energy produced by the organism, even though it only makes 2–3% of the whole body weight [7, 8]. Most of the energy produced in the form of ATP derives from OXPHOS, since glycolysis generates a small proportion of cellular ATP [9]. Thus, developing neurons are highly dependent on mitochondrial biogenesis to assume their energy need associated with cytoskeletal remodeling, axonal and dendritic growth, axonal transport of synaptic vesicles and synaptic transmission, which consume about 50% of generated ATP [10–13]. Similarly, a mature brain requires more than 50% of the brain's energy consumption to maintain synaptic homeostasis and plasticity. Therefore, a dysfunctional mitochondrial biomass and/or disturbed mitochondrial trafficking, two pathological hallmarks of neurodegenerative diseases, lead to altered neurometabolic coupling, neural processing and circuitry, and functional connectivity in mature neurons [14–16].

Aside from producing ATP, mitochondria regulate calcium (Ca^{2+}) homeostasis by modulating Ca^{2+} uptake in an energy-dependent and pulsatile manner via the mitochondrial Ca^{2+} uniporter (mCU) and by providing ATP to stimulate the plasma membrane Ca^{2+}-ATPase, thereby influencing synaptic transmission, cellular survival and metabolism [17–21]. Moreover, Ca^{2+} sequestration dictates mitochondrial motility to specific sub-cellular domains of neurons to regulate synaptic function, with defective mitochondrial movements causing neurological disorders [22, 23]. Under pathological conditions, mitochondrial Ca^{2+} overload compromises the integrity of the mitochondrial inner membrane, thereby triggering mitochondrial permeability transition (MPT), a process when sustained results in cessation of ATP production, permeability of the outer mitochondrial membrane, cytochrome c leakage and subsequent neuronal cell death [24, 25]. Thus, the mitochondrion functions as a major hub for several distinct but interconnected pathways necessary for neural development, survival, activity, connectivity and plasticity.

3. MAINTENANCE OF MITOCHONDRIAL HOMEOSTASIS

A hallmark of brain metabolism is the tight coupling between energy demand and supply, which involves constant regulation of mitochondrial homeostasis and correct localization of mitochondria in the distinct subcellular compartments of the extremely polarized neurons to address their unique regional metabolic needs in response to signaling cues [23]. Thus, mitochondria are not uniformly distributed among the subcellular domains, the soma, axon and dendrites [26]. They occupy up to 40% of the cytoplasmic volume of neuronal cells with their number oscillating from a few hundred to thousands. They are transported to specific compartments of neurons characterized by high ATP consumption and calcium dynamics, such as active growth cones, axonal branching points [27–31], nodes of Ranvier [32], myelination boundaries and demyelinated regions [33, 34].

Although mitochondria have a longer half-life in neurons than in other post-mitotic somatic cells, their renewal is essential for proper neural development and survival [35–39]. The

question of how to define mitochondrial biogenesis has been addressed in many different cellular systems, nonpathological and pathological contexts and distinct developmental stages, which led to further questions. Is this a self-sufficient or partially independent or dependent process of preexisting mitochondria? The most likely response is that the mitochondrial mass is under the control of three distinct mechanisms: fission of pre-existing mitochondria, biogenesis of newly generated mitochondria and mitochondrial quality control to dispose of dysfunctional mitochondria via two pathways, mitophagy and the ubiquitin proteasome system (UPS) (Fig. 1). While fission does not necessitate replication of mtDNA and newly synthesized mitochondrial membrane, mitochondrial biogenesis generates new mitochondria via replication of mtDNA and synthesis of mitochondrial lipids for the genesis of outer and inner mitochondrial membranes [40]. Cardiolipin is a unique phospholipid that is almost exclusively present in mitochondrial membranes and required for mitochondrial biogenesis and maintenance of the mitochondrial membrane composition [41, 42].

In neurons, mitochondrial biogenesis mainly occurs in the soma although it has been observed locally within the axon, albeit with low frequency [43]. Its regulation and timing will be discussed in subsequent sections of this review. Local increase of the mitochondrial density can be modulated by repeated cycles of fusion-fission and mitochondrial trafficking on actin and microtubules – both processes involved in maintaining functional integrity of the mitochondrial network. Mitochondria are dynamic and mobile organelles, which shuttle between “individual ” and “network ” states characterized by distinct morphologies, discrete spheres or interconnected tubules, respectively [44–46]. Mitochondrial fusion results in elongated and interconnected mitochondrial network via coordinated merging of the outer and inner mitochondrial membranes under the control of three conserved transmembrane GTPases proteins, mitofusin1 (Mfn1), mitofusin 2 (Mfn2), and optic atrophy 1 protein (OPA1) [47, 48]. Fusion allows exchanging matrix content and mtDNA molecules between mitochondria, which favors optimal mitochondrial physiology by diluting mutated mtDNA and rescuing damaged mitochondria via acquisition of key components from healthy mitochondria (Fig. 1) [49]. Mfn1 or Mfn2 knockout mice exhibit early embryonic lethality due to a placental defect [50]. However, conditional Mfn2 knockout mice display cerebellar neurodegeneration, while Mfn1 is not essential for cerebellar development [51]. Although mitochondrial fusion is a ubiquitous process, its dysregulation provokes specific neurodegenerative diseases, including autosomal-dominant optic atrophy and the Charcot-Marie-Tooth neuropathy type 2A (CMT2A) [52–54]. It is believed that certain neurons are particularly sensitive to defective mitochondrial fusion-fission, as it impacts mitochondrial distribution in neurons with long axons or extensive dendritic branching. Cerebellar Purkinje cells of Mfn2 conditional knockout mice display aggregated mitochondria in dendrites thereby preventing microtubule-dependent transport of organelles [51]. A similar occlusion in neuritic branches has been observed in mouse models of Alzheimer’s disease (AD) and is considered as a potential mechanism for neurodegeneration (Table 1) [55]. Finally, abnormal trafficking has been reported in the longest axons of sensory neurons affected in CMT2A (Table 1) [56]. In contrast, fission of preexisting mitochondria generates new mitochondria in the absence of mtDNA replication under the control of the master mediator dynamin-related protein Drp1, whose activity is regulated through post-translational modifications and interactions with specific receptor proteins, such as the Fission 1 protein (Fis1) (Fig. 1)

[57]. While mitochondrial fusion-fission influences many cellular functions, neurons critically rely on this dynamic process to ensure adequate distribution of mitochondria for supporting synaptic activity via the formation of synapses and dendritic spines [58, 59]. Moreover, imbalance of mitochondrial dynamics is predicted to lead to neurodegenerative diseases, as continuous mitochondrial fission can induce a neurodegenerative cascade [60–63].

The mitochondrial quality control system is essential to maintain a functional mitochondrial population in neurons, which occurs via UPS and mitophagy to clear aged and dysfunctional mitochondria (Fig. 1) [64–65]. The question of whether induction of mitochondrial biogenesis triggers the mitophagic process of older mitochondria to keep constant the overall mitochondrial content in healthy neurons remains to be answered. In contrast, dysregulation of either process has been the subject of intense studies in the context of adult-onset neurodegenerative diseases. The mitochondrial quality control system has mainly been investigated as an intrinsic mechanism to selectively sequester aberrant mitochondria as a consequence of bioenergetic deficit, accumulation of reactive oxygen species or high levels of Ca^{2+} influx, followed by degradation via the autophagy-lysosomal pathway, also referred to as mitophagy [66]. Although direct evidence for compartmentally restricted mitophagy in neurons is scant, it is speculated that the process of mitophagy occurs predominantly in the soma where mature lysosomes reside, and therefore coupled to mitochondrial retrograde movement [67]. However, the notion of retrograde movement of depolarized mitochondria is controversial given that axonal mitochondrial transport depends on the strength of the mitochondrial membrane potential [29, 30]. Recent time-lapse imaging provides new insight on neuronal mitophagy, as depolarized mitochondria were observed undergoing local mitophagy in the somatodentritic regions where lysosomes are mostly positioned [68]. Furthermore, recent studies have revealed the colocalization of lysosomal markers and autophagosomes in the distal axons of dorsal root ganglion neurons, congruent with local mitochondrial clearance [69, 70]. The surveillance pathway under the control of the serine/threonine PTEN-Induced putative Kinase 1 (PINK1) and the E3 ubiquitin ligase Parkin regulates mitophagy in various cellular contexts and systems [65, 71]. Following depolarization, PINK1 moves from the inner mitochondrial membrane (IMM) to the outer mitochondrial membrane (OMM) and phosphorylates the molecular/adaptor molecule, Mitochondrial Rho (Miro), which connects mitochondria to microtubules via its binding partner Milton and kinesin heavy chain (KHC). PINK1 also recruits Parkin to the OMM of compromised mitochondria, setting the stage for Parkin-mediated ubiquitination and degradation of Miro causing mitochondrial motility arrest and clearance via mitophagy [72, 73]. In addition, Parkin functions as a molecular link between the UPS and mitophagy pathways by ubi-quinating numerous proteins from the mitochondrial proteome, among them Mfn1 and Mfn2, to favor mitochondrial fission and fragmentation, making mitochondria more susceptible to mitophagy [74–76]. The PINK1-Parkin pathway is particularly relevant to the nervous system, as mutations in the *Parkin* and *PINK1* genes are linked to familial forms of Parkinson's disease (PD) [77, 78]. Furthermore, compelling evidence is congruent with the notion of a dysregulated mitochondrial quality control system leading to mitochondrial dysnfunction and neuronal loss, two hallmarks of numerous

neurodegenerative diseases, such as AD and Huntington's disease (HD) as discussed in the section 7 of the review [5, 64; 79–82].

4. HIGHLIGHTS OF NEURONAL MITOCHONDRIAL BIOGENESIS AND ITS REGULATORS

Little is known about neuronal mitochondrial biogenesis, as most studies have been conducted in the context of adipocyte and muscle cell differentiation [83]. However, the high degree of conservation among key transcription factors and co-activators suggests that a similar regulatory cascade should modulate the mitochondrial content in neurons [84]. Since mitochondria cannot be made *de novo*, the formation of new mitochondria occurs from preexisting mitochondria via mitochondrial biogenesis [85]. Mitochondrial biogenesis is an extremely complex process requiring replication of the mtDNA, the synthesis, import, and incorporation of proteins and lipids to the existing mitochondrial reticulum, and a certain threshold of mitochondrial membrane potential as the result of proton gradient generated during oxidative phosphorylation. Mitochondrial biogenesis requires a coordinated regulation of two distinct genomes, the nuclear and mitochondrial genomes given that the majority of mitochondrial proteins are encoded by nuclear genes. This is potentially challenging for post-mitotic neurons due to the extremely polarized architecture, forcing the majority of mitochondrial biogenesis to be confined to the soma and requiring mitochondrial renewal in the distal axons to rely on axonal transport via microtubules.

Findings over the last decade have revealed several converging signaling pathways intersecting with the basic mitochondrial regulatory machinery via a mitochondrial-nuclear crosstalk to replicate the mitochondrial genome in parallel with increase in mitochondrial mass. The circular double stranded mtDNA (16,569 bp) encodes a total of 37 genes, 13 of which encode essential protein subunits of the OXPHOS respiratory complexes, while the other genes are dedicated for synthesis of mitochondrial proteins by encoding 22 transfer RNAs and 2 ribosomal RNAs [86]. None of the mitochondrial genes encodes for proteins directly involved in mitochondrial DNA replication and maintenance. Therefore, the functional mitochondrial mass is influenced by the nuclear-mitochondrial cross talk and cellular context.

Mitochondria contain between 800 to 1000 copies of mtDNA, which are maternally inherited and packaged in high-ordered nucleo-protein structures called nucleoids [87–91]. Although nucleoids are distributed throughout the mitochondrial matrix, they are often located in proximity of the cristae, which carry the OXPHOS system. *In vitro* studies have revealed that nucleoids are packed in a sphere consisting of two components, the core center and the peripheral layer [92–94]. While the core center is composed of two to ten mtDNA copies bound to proteins responsible for mtDNA transcription, replication and maintenance, the peripheral layer contains proteins involved in diverse functions, such as protein folding and metabolism, which tether the nucleoids to the inner mitochondrial membrane of the cristae [93, 95, 96]. Although the *in vivo* structure and composition of nucleoids remain to be established, alteration in nucleoid architecture is detrimental to mitochondrial functions, as bitransgenic mice overexpressing Tfam and Twinkle, two essential regulators of mtDNA

copy number, exhibited nucleoid enlargement accompanied by mtDNA deletions due to high mtDNA copy number interfering with mtDNA replication and transcription [97].

A compilation of recent studies has provided key evidence in support of the concept of the nucleoid functioning as the mitochondrial genetic inheritance unit [98]. Our understanding of how nucleoid numbers are regulated remains elusive and the question of whether their copy number is specific to cell fate and/or the mitotic status remains to be answered. Two models for the mode of nucleoid-mediated mtDNA propagation have been postulated: the static or "faithful nucleoid" model and the "dynamic nucleoid" [99]. The faithful model implies that nucleoids do not exchange mtDNA between each other, while the "dynamic nucleoid" model states that nucleoids under go dynamic reorganization allowing mtDNA exchange. A recent study has demonstrated that the "faithful nucleoid" model appears to be the predominant mode of propagation in rapidly dividing cells [94]. By fusing two cybrid cell lines, each containing a homoplastic population of mtDNA with two distinct non-overlapping Δ mtDNA deletions, the authors found that the two distinct nucleoid populations did not exchange mtDNAs after many cell divisions, congruent with the notion of nucleoids being essentially autonomous. The packaging of mtDNA into nucleoids is believed to be the limiting factor preventing the mixing of two distinct mtDNAs populations. More importantly, the two-nucleoid populations complemented each other to restore bioenergetic functions, suggesting that mtDNA-derived transcripts and/or polypeptides involved in the assembly of OXPHOS complexes diffuse locally within the matrix. This is in agreement with the notion of the relative threshold of heteroplasmic burden observed in patients affected with maternally-inherited mitochondrial respiratory diseases. However, it remains to be determined whether *in vivo* nucleoids may exchange mtDNA between each other during specific cellular events.

The regulatory circuitry responsible to modulate mitochondrial biogenesis in response to developmental and physiological cues is composed of transcriptional coactivators, such as members of the peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1) family, and transcription factors, including the nuclear respiratory factors 1 (NRF-1) and 2 (NRF-2) (Fig. 2) [100]. PGC-1α is a ubiquitously expressed transcriptional co-activator that was initially identified as the co-activator of the nuclear receptor PPARγ, a regulator of adaptive thermogenesis in brown adipose tissue [101]. It belongs to the PGC-1 family, which is composed of three members, PGC-1α, PGC-1β, and PGC-1-related co-activator (PRC), all of them known to interact with the family of nuclear receptors PPARα, PPARβ/γ, and PPARγ [102]. PGC-1α is expressed at high levels in tissues with high metabolic demands, such as heart, skeletal muscle, kidney and brain [103, 104]. PGC-1α is expressed in the developing brain, from embryonic day 15 to postnatal day 3, with accentuated expression levels in GABAergic neurons to regulate their metabolism and survival capacity [105]. Consistent with PGC-1α critical role in the brain is the phenotype of PGC-1α null mice exhibiting striatal degeneration and small lesions in the cortical layer V/VI of the motor cortex, nucleus accumbens, substantia nigra, hippocampus and the mammalliary body, reminiscent of the neurodegenerative HD [106]. Although PGC-1α remains expressed in the mature brain, its function and activities remain elusive.

PGC-1α is a highly versatile transcriptional co-activator that behaves as the master regulator of mitochondrial biogenesis by increasing the expression of various relevant transcription factors and cooperating with them to potentiate their transcriptional activity. In addition to mitochondrial biogenesis, PGC-1α regulates mitochondrial pathways critical for neuronal metabolism, such as fatty acid oxidation (FAO) and OXPHOS metabolism (Fig. 2) [83]. PGC-1α not only induces the expression levels of the two key transcription factors, NRF-1 and NRF-2, but also interacts with them to stimulate their transcriptional activity, resulting increased expression of genes responsible for mtDNA replication and transcription, such as the essential regulator of mtDNA copy number, mitochondrial transcription factor A (TFAM) (Fig. 2) [107]. Subsequently, TFAM stimulates the biogenesis of mitochondria via increased expression of mitochondrial-encoded polypeptides, OXPHOS respiration and intracellular ATP concentrations [108–110]. In parallel, PGC-1α stimulates the expression levels of numerous nuclear-encoded subunits of the mitochondrial respiratory complexes of the OXPHOS system via the NRF-1/NRF-2 pathway, thereby directly stimulating the mitochondrial bioenergetic output (Fig. 2). Thus, PGC-1α governs mitochondrial biogenesis, by making mitochondria more bioenergetically competent, which in turn favors biogenesis due to increased import of key nuclear-encoded mitochondrial proteins, a process that is dependent on the mitochondrial membrane potential [111–113]. Illustrating the importance of PGC-1α to control mitochondrial functions essential for neuronal survival is the decreased expression levels of PGC-1α associated with the neurodegenerative diseases, HD, PD and AD [114].

In various cellular contexts, NRF-1 and NRF-2 control multiple mitochondrial functions, most notably the oxidative phosphorylation metabolism by binding to promoter regions of nuclear genes encoding subunits of the five respiratory complexes of the OX-PHOS system (Fig. 2) [100]. Since their properties have been extensively described in numerous reviews [100, 102, 107, 108, 115–117], this review focusses on the impact of NRF-1 and NRF-2 on mitochondrial functions vis-à-vis neurogenesis. Both NRF-1 and NRF-2 regulate genes involved in assembly of the respiratory apparatus, the heme biosynthetic pathway, import of nuclear-encoded mitochondrial proteins, and mtDNA replication and transcription, most notably the *Tfam* gene. Therefore, NRF-1 and NRF-2 are transcription factors critical for modulating the nuclear-mitochondrial crosstalk in order to adapt the mitochondrial biomass and oxidative metabolism to a specific cellular context or developmental stage. Their critical roles are illustrated by the early embryonic lethality of the NRF-1 and NRF-2 null mice. NRF-1 null mice die between embryonic day E 3.5 and E6.5, as a consequence of dramatic decrease in mtDNA content and mitochondrial membrane potential in blastocysts [118]. NRF-2, which is the human homolog of the transcription factor GA-binding protein (GABP), is essential for early embryonic development in light of the peri-implantation lethal phenotype of NRF-2α homozygous null mice [119].

Unlike for other organs, such as the liver and skeletal muscle, our knowledge on the coupling signaling mechanisms between cellular activity and mitochondrial biogenesis in the brain is far from comprehensive. Moreover, most mitochondrial nuclear-encoded genes are expressed in both a pan- and neural-specific manner as demonstrated by comprehensive mitochondrial proteomic studies [2]. Our current knowledge about the integrative roles of NRF-1 and NRF-2 in linking neural activity to mitochondrial bioenergetics is derived from

extensive studies performed on the rat visual cortex [120]. The cytochrome c oxidase (COX) respiratory complex of the OXPHOS system is a critical energy-generating enzyme in glutamatergic visual cortical neurons [121]. Both NRF-1 and NRF-2 regulate the ten nuclear-encoded COX subunits by binding to regulatory elements that are conserved among the rat, mouse and human species [116–119]. Additionally, NRF-1 and NRF-2 indirectly regulate the expression of the three mitochondrial-encoded subunits of COX by binding to the Tfam promoter to activate mtDNA transcription [115]. Furthermore, NRF-1 couples mitochondrial bioenergetics to neural activity induced by KCl depolarization of visual cortical neurons via the concomitant transcriptional regulation of the 13 subunits of COX and the N-methyl-D-aspartate (NMDA) glutamate receptor subunits, thereby promoting an efficient intersection between synaptic transmission and energy metabolism [126].

TFAM, which is a direct target of NRF-1 and NRF-2, behaves as an essential regulator of embryonic development in light of the embryonic lethality of Tfam null mice coinciding with onset of neurogenesis, as a result of mtDNA depletion and severe respiratory defects [127]. The fact that this phenotype is similar to that of the DNA polymerase γ null mice infers a requirement of mtDNA replication and maintenance for early organogenesis [128]. The TFAM protein is a member of the high mobility transcription factor group that is essential for regulating transcription and replication of mtDNA, two interlinked processes given that transcription of mtDNA controls mtDNA gene expression and provides the RNA primers necessary for initiation of mtDNA replication at the origin of replication of the heavy chain [129]. TFAM binds to mitochondrial promoter sequences, the two heavy chain-specific promoters (HSP1 and HSP2) and the light chain-specific promoter (LSP) in a sequence-specific manner to initiate transcription together with the two basal mitochondrial transcription factors, TFB1M and TFB2M, and the mitochondrial RNA polymerase (POLRMT) [130, 131]. In addition, TFAM possesses histone-like properties by binding to mtDNA molecules in a non-specific manner and packaging mtDNA into nucleoids [95, 132, 133]. TFAM is a limiting determinant factor for mtDNA copy number given the tight correlation between TFAM expression levels and mtDNA copy number observed *in vitro* and *in vivo* using $Tfam^{+/-}$ heterozygous mice [127, 134–136]. Several animal models were generated to investigate the functional consequences of decreased Tfam expression levels and mtDNA copy number in neuronal cells. The mitochondrial late-onset neurodegeneration (MILON) mice were generated by crossing $Tfam\text{-}^{loxP}/Tfam^{loxP}$ mice with mice heterozygous for a transgene expressing *cre* recombinase from the calcium-dependent calmodulin kinase II promoter (+/*CaMKII-cre*) to disrupt postnatal Tfam expression in forebrain neurons [137]. Surprisingly, MILON mice exhibited adult corticohippocampal neurodegeneration associated with 40% decrease in mtDNA copy number. Since patients with PD display impaired respiratory functions due to high levels of somatic mtDNA mutations, the effect of decreased mtDNA copy number in dopaminergic (DA) neurons was investigated in the MitoPark mouse model in which Tfam is specifically deleted in DA neurons by crossing $Tfam^{loxP}/Tfam^{loxP}$ mice with mice heterozygous for a transgene expressing *cre* recombinase from the DA transporter (DAT) promoter (+/*DAT-cre*) [138]. Low mtDNA copy number in DA neurons mimics parkinsonian symptoms associated with disrupted OXPHOS [138, 139]. Collectively, these studies demonstrate the pivotal function

of TFAM in maintaining mtDNA copy number via induced mitochondrial biogenesis in developing and mature brain.

Further strengthening the functional relationship between critical mtDNA content and initiation of organogenesis, and therefore neurogenesis, is the early embryonic lethality of the Twinkle (T7 gp4-like protein with intramitochondrial nucleoid localization) null mice at E8.5 due to severe mtDNA depletion [140]. Twinkle is a nuclear-encoded mtDNA helicase with structural similarity to the bacteriophage T7 primase-helicase (T7gp4), which catalyzes hydrolysis of nucleoside triphosphates to unwind the mtDNA duplex with a 5′ to 3′ orientation [141, 142]. It is an essential component of the minimal replisome necessary for the mtDNA replication, along with the heterotrimeric mtDNA polymerase (POLG) and the tetrameric single-stranded DNA-binding protein (mtSSB) [143]. Bromodeoxyuridine (BrdU) labeling has demonstrated that Twinkle specifically regulates *de novo* mtDNA synthesis [97]. The critical role of Twinkle in regulating mtDNA copy number has been validated by its colocalization with TFAM and mtSSB in nucleoids [95, 140] and the phenotype of conditional *Twinkle* knockout mice, which display severe mtDNA depletion and reduced respiration functions in skeletal muscle and heart [140]. A similar correlation between expression levels of TWINKLE protein and mtDNA copy number was observed in human osteosarcoma (143B) cells transfected with siRNAs to reduce Twinkle expression, which caused decreased mitochondrial nucleoids [144]. Conversely, modest over-expression of Twinkle in transgenic mice under the control of the β-actin promoter or endogenous regulatory elements increased mtDNA copy number in skeletal muscle, heart and brain without provoking abnormal mitochondrial morphology [140, 144]. Interestingly, mutations in the human *Twinkle* (*C10orf2*) gene induce mtDNA deletions rather than mtDNA depletion, causing autosomal dominant progressive external opthalmoplegia (adPEO) characterized by a late-onset myopathy affecting the extraocular, limb, and facial muscles [141, 145]. These mtDNA deletions and symptoms of human PEO were recapitulated in the mouse model “Deletor” that ubiquitously expresses a mutant Twinkle cDNA carrying a dominant patient PEO mutation against a background of wild type TWINKLE [146]. More than 31 dominant mutations and 3 recessive mutations in the *Twinkle* gene cause inherited mitochondrial diseases, such as infantile-onset spinocerebellar ataxia, epileptic encephalopathy with mtDNA depletion [147, 148].

5. SIGNALING PATHWAYS MODULATING NEURONAL MITOCHONDRIAL BIOGENESIS

Mitochondrial biogenesis is tightly regulated by distinct signaling pathways in response to various physiological stimuli, such as oxygen supply, calcium levels, AMP/ATP ratio, and NAD^+/NADH (Fig. 2). The AMP-activated kinase (AMPK) and Sirtuin-1 (SIRT1) are key cellular sensors to tailor the functional mitochondrial mass to the energy needs required for sustaining brain functions by interfacing with the major transcriptional regulator of mitochondrial biogenesis PGC-1α to form the pivotal regulatory AMPK-SIRT1-PGC-1α axis (Fig. 2).

AMPK is a heterotrimeric serine/threonine protein kinase composed of a catalytic subunit (α1 or α2) and two β (β1 or β2) and γ (γ1, γ2, or γ3) regulatory subunits [149, 150]. AMPK

activation is triggered by events increasing ATP consumption, such as rising cytoplasmic calcium levels, and pathological stresses often associated with neurodevelopmental disorders and neurodegenerative diseases, such as hypoxia, ischemia, energy crisis and glucose deprivation [151, 152]. In the nervous system, AMPK activation is controlled by two kinases, the tumor suppressor liver serine/threonine kinase B1 (LKB1, also called STK11 or Par4) and the calcium/calmodulin-dependent protein kinase β, (CAMKKβ, also known as CAMKK2) depending on the cell type (Fig. 2) [153, 154]. In immature neurons, AMPK is activated by CAMKKβ rather than by LKB1 [155–157]. The activated AMPK not only down-regulates ATP-consuming (anabolic) pathways, such as synthesis of lipids, carbohydrates, and proteins, but also up-regulates ATP-generating (catabolic) pathways, including mitochondrial biogenesis to maintain energy homeostasis [158, 159]. More specifically, mitochondrial biogenesis is enhanced via AMPK-mediated phosphorylation of PGC-1α, which is subsequently translocated into the nucleus to upregulate genes involved in mitochondrial biogenesis, FAO and ATP synthesis (Fig. 2) [160, 161]. In visual cortical neurons, AMPK integrates signaling cues to regulate the PGC-1α-NRF-1 axis to adapt the mitochondrial bioenergetic metabolism to neural activity [162]. Using KCl depolarization, the authors demonstrated that AMPK is quickly activated to increase expression levels of PGC-1α and subsequently NRF-1 and TFAM expression levels, resulting in augmented ATP levels in cultured primary visual cortical neurons. Maintenance of this expression pattern requires the presence of neural cue. Conversely, deprivation of neural activity in the *in vivo* model for monocular visual deprivation leads to a substantial reduction in AMPK activity followed by reduced PGC-1α and NRF-1 expression levels and therefore decreased mitochondrial mass and ATP levels [162]. Recent studies have suggested that activation of AMPK plays a role in the neurodegenerative disease AD [163]. In fact, amyloid-β 1-42 (Aβ42) oligomers activate AMPK in a CAMKKβ-dependent manner in neurons with activated AMPK enriched in tangle- and pretangle-bearing neurons in patients with AD [164–166]. Although the role of the CAMKKβ-AMPK pathway in the pathophysiology of AD remains unknown, some studies suggest an AMPK-mediated protective effect by diminishing Aβ production/APP cleavage or boosting Aβ clearance [167, 168]. In an animal model for PD, AMPK activation by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was also reported, which promoted neuronal survival by an unknown molecular mechanism [169]. However, it is tempting to speculate that activated AMPK may alleviate the mitochondrial complex I deficiency and altered ATP synthesis found in PD patients and inhibited upon MPTP exposure [170–174]. Given that disruption of the *Tfam* gene in dopaminergic neurons of the conditional knockout “MitoPark” mice provokes a parkinsonian phenotype, it is plausible that neuronal survival triggered by MPTP-mediated activation of AMPK may in part result from sustained mtDNA replication and therefore mitochondrial biogenesis [138, 175].

SIRT1, a NAD^+-dependent deacetylase, is another energy sensor that modulates mitochondrial biogenesis as a result of increased NAD^+/NADH ratio (Fig. 2) [176]. SIRT1 is the mammalian homolog of the yeast Silent information regulator (Sir2) belonging to the class III of histone deacetylases (HDAC), which include seven members (SIRT1-7) [177, 178]. Since brain-specific deletion of SIRT1 fails to impact brain development, SIRT1 functions in the central nervous system remain elusive [179]. However, SIRT1-deficient

mice display abnormal retinal development and sporadic exencephaly, possibly due to interference with the Hairy and Enhancer of Split-1 (Hes1)/Hairy and Enhancer of Split-related with YRPW motif protein-2 (Hey2) pathways [180]. Congruent with these observations is the SIRT1-mediated differentiation of neural precursor cells via repression of Notch1-Hes1 signaling pathway [181]. Recent studies have revealed SIRT1 impact on cognitive function and synaptic plasticity, two processes in which mitochondria play a critical role [182, 183]. In addition, emerging evidence suggests that SIRT1 confers neuroprotection in two neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and AD [184–187]. In response to increased NAD^+ levels provoked by energy stress, SIRT1 activity augments to deacetylate many protein clients, PGC-1 α being the most relevant for enhancing mitochondrial biogenesis [188–190]. However, the mechanism by which SIRT1 is activated has remained elusive until recently. Upon cellular metabolic stress causing increased NAD+/NADH ratio, SIRT1 is phosphorylated at Thr 522 residue, which subsequently modulates its oligomeric status by favoring a monomeric state and increased activity [191–195]. SIRT1 regulates the transcriptional activity of PGC-1α by deacetylating at least one of the 13 acetylated lysine residues, thereby reversing the effects of the acetyltransferase GCN5 responsible to repress PGC-1α activity via acetylation of specific lysine residues [196, 197]. Consequently, deacetylated PGC-1α cooperates with key transcription factors to stimulate expression levels of genes involved in OXPHOS, mitochondrial biogenesis, and mitochondrial metabolic pathways, including the tri-carboxylic acid (TCA) cycle and FAO [189]. Finally, the two critical energy sensors, AMPK and SIRT1, are part of an integrated signaling pathway, in which AMPK acts as the initial sensor to increase intracellular levels of NAD^+ as a consequence of fatty acid oxidation, leading to SIRT1 activation and subsequent deacetylation of PGC-1α (Fig. 2) [190, 198–200].

6. TIMING OF MITOCHONDRIAL BIOGENESIS DURING NEUROGENESIS

During pre-implantation stages of embryonic development, mitochondrial biogenesis does not occur in actively dividing pluri-potent blastomeres, resulting in fewer and fewer mtDNA molecules in the blastocyst in keeping with its reliance on anaerobic respiration for ATP production (Fig. 3) [201]. This progressive reduction in mitochondrial number is referred to as the bottleneck theory [202]. At the onset of organogenesis, increase in the number of mitochondria coincides with loss of pluripotency and cellular differentiation to promote greater levels of ATP via a metabolic shift from glycolytic to oxidative respiration (Fig. 3) [8]. During neurogenesis, the transition from neural stem cells to differentiated neurons, astrocytes, or oligodendrocytes is a high-energy demand process consuming about 50% of cellular ATP to execute key differentiation processes, including plasmalemmal biogenesis, cytoskeletal assembly associated with axonal and dendritic growth, growth cone development, synaptic functions, and organelle transport [10].

Early biochemical studies in developing neurons have revealed a biphasic augmentation in total mitochondrial proteins coinciding with growth cone formation and establishment of the neuronal network with synaptic activity [203, 204]. Despite the vital dependence of neurons on mitochondria and aerobic metabolism, little is known about the neuronal regulators responsible to tailor mitochondrial biogenesis to the onset of neuronal differentiation. And

this is particularly critical given that half of the mammalian mitochondrial proteome is tissue-specific [1]. Most studies have focused on the ubiquitously expressed transcription factors and co-factors, such as NRF-1, NRF-2 and members of the PGC-1 family, in the context of physiological adaptations and muscle and adipocyte differentiation [116].

Our studies have addressed this gap in our knowledge by demonstrating a direct link between the mitochondrial mass and the neurogenic basic helix-loop-helix (bHLH) transcription factor NeuroD6 (previously known as Nex1/MATH-2) during the early stages of neuronal differentiation [31]. NeuroD6, which contributes to the specification of multipotential progenitors towards a glutamatergic pyramidal fate during corticogenesis [205–207], links neuritogenesis to mitochondrial biogenesis by coordinating several distinct gene networks, such as cytoskeletal proteins involved in axonal outgrowth and mitochondrial trafficking, molecular chaperones essential for translocation of nuclear-encoded mitochondrial proteins, and determinants for mtDNA replication [208–211]. NeuroD6 stimulates maximal mitochondrial mass at the earliest stage of neuronal differentiation, lamellipodia stage, as defined by Dotti *et al* [212], thereby preceding axonal outgrowth (Fig. 3) [31]. Moreover, NeuroD6 synchronizes mitochondrial bioenergetics with neuritogenesis by promoting accumulation of mitochondria in axonal branching and growth cone, thereby tailoring the bioenergetic needs of these subcellular domains, an essential process for proper establishment of neural circuitry during neurogenesis [31, 208–210]. NeuroD6 modulates the mitochondrial membrane potential and expression of key subunits of OXPHOS components involved in ATP synthesis, thereby generating a bioenergetic reserve [31]. Subsequently, NeuroD6 confers cellular tolerance to mitochondrial stressors and oxidative stress, known to compromise neurogenesis and cause specific neurodevelopmental disorders and neurodegenerative diseases, including autism spectrum disorder and PD [211, 213]. Coordination of mitochondrial bioenergetics and neuritogenesis has also been demonstrated in immortalized hippocampal neuroblasts and upon local nerve groth factor (NGF) signaling in axons of cultured embryonic chick sensory neurons [30, 214]. Our collective finding of NeuroD6-mediated regulation of mitochondrial biogenesis and bioenergetics at the outset of neuronal differentiation is congruent with the concept that the network of immature mitochondria must expand via biogenesis and undergo an active process of bioenergetic maturation to fuel the needs associated with the developing brain by promoting the synthesis of greater levels of ATP and maintenance of mitochondrial homeostasis.

The link between mitochondrial biogenesis and cell fate has also been investigated in the context of neuronal differentiation of embryonic stem cells (ESCs). In undifferentiated mouse and human ESCs, mitochondria exhibit a spherical and immature morphology with a predominantly perinuclear localization, as observed in blastomeres during the early stages of mammalian embryonic development [215]. Furthermore, ESCs have low numbers of mitochondria and mtDNA copy number coinciding with low levels of regulators of mtDNA replication and transcription, such as PolG and TFAM, and high expression levels of pluripotent markers, like Oct-4, Sox2, and nanog [216–220]. Moreover, ESCs display low levels of ATP production, low oxygen consumption and modest levels of antioxidant enzymes, which are in keeping with high expression levels of glycolytic enzymes and low expression levels of TCA enzymes and specific subunits of respiratory complexes for the OXPHOS system [221, 222]. These collective observations have led to the hypothesis that

mitochondrial properties might be critical for the maintenance of pluripotency and self-renewal, supporting the notion of mitochondrial regulators being potential ESCs markers [223]. In support of this concept is the retinoic acid (RA)-induced reprogramming of mitochondria in ESCs committed to a neural fate. RA-treated ESCs cells harbor increased number of mitochondria with a tubular morphology and numerous elongated cristae, consistent with activation of a mitochondrial aerobic metabolism, OXPHOS activity, and increased mitochondrial membrane potential and ATP synthesis [215]. Consistent with this RA-mediated change in mitochondrial status is the increased number of mtDNA molecules and expression levels of regulators pivotal for mitochondrial biogenesis and bioenergetics, such as PolgA, PolgB, Tfam, and PGC-1α [219]. Expression of neural fate regulators, like the transcription factors Mash1 and Pax6 and the signaling molecule Wnt1, might also contribute to mitochondrial maturation in RA-induced ESCs [224–227]. Our studies revealed a similar mitochondrial remodelling during the transition from progenitors to neuronal-like PC12 cells in the presence of constitutive expression of the differentiation transcription factor NeuroD6 or NGF signaling [31, 211].

Further evidence of the importance of mitochondrial biogenesis for neurogenesis arises from the timing of embryonic lethality of homozygous Tfam and PolgA null mice. *PolgA*$^{-/-}$ knockout embryos display developmental arrest at the onset of organogenesis, causing early embryonic lethality between embryonic day E7.5 and E8.5 due to severe mtDNA depletion and loss of cytochrome oxidase activity [128]. Similarly, *Tfam*$^{-/-}$ knockout embryos show early embryonic lethality at the onset of neurogenesis between E8.5 and E11.5 due to mtDNA depletion and severe respiratory deficiency [127]. Such timing of embryonic lethality illustrates that mtDNA replication and maintenance are required for development beyond late gastrulation and early organogenesis to ensure adequate mitochondrial biogenesis and bioenergetics upon activation of the aerobic mitochondrial metabolism associated with differentiation of neural stem cells during neurogenesis.

7. COMPENSATORY MITOCHONDRIAL BIOGENESIS ASSOCIATED WITH SPECIFIC NEURODEVELOPMENTAL AND NEURODEGENERATIVE DISEASES

Mitochondrial dysfunction contributes to a range of neurodevelopmental and neurodegenerative diseases, making mitochondria a potential target for pharmacological-based therapies [228–230]. More specifically, disruption of mitochondrial biogenesis, turnover and functions can lead to primary or secondary type of mitochondrial diseases. Primary mitochondrial diseases are caused by mutation(s) or deletion in a mitochondrial or nuclear gene encoding a mitochondrial protein, while secondary mitochondrial diseases result from pathological events initiated outside mitochondria (Table 1).

The first pathogenic mtDNA mutations were discovered in 1988, which led to the classification of mitochondrial diseases [231, 232]. Maternally inherited mutations affect either mitochondrial protein synthesis when mapped in a mt-tRNA or mt-rRNA gene, or the OXPHOS system when mapped in one of the 13 genes encoding a subunit of the respiratory complexes [233]. In contrast, mutations in nuclear genes exhibit Mendelian inheritance

patterns and compromise mitochondrial bioenergetics or mitochondrial biogenesis [234]. Most maternally-inherited pathogenic mtDNA mutations only affect a subset of mtDNA copies, resulting in heteroplasmy, a mixture of mutant and wild type mtDNA copies [235, 236]. Nevertheless, there are rare mtDNA mutations that solely exist in a homoplasmic state, as exemplified in Leber's hereditary optic neuropathy (LHON) [237]. In a heteroplasmic state, there is a threshold effect, which ranges from 60 to 90% of mutated mtDNA depending on the tissue and mutation, resulting in OXPHOS defect, insufficient ATP levels and a diseased phenotype [238, 239]. In fact, one of the prevalent therapeutic strategies involves shifting herero-plasmy toward wild type mtDNA via increased mitochondrial biogenesis and/or turnover of mutated mitochondria to attenuate the OXPHOS deficit and therefore somatic manifestations in patients [240, 241].

The mitochondrial respiratory disorders represent the largest subset of primary mitochondrial diseases, with a frequency of 1:5000, making them the most common inborn error of metabolism [242]. They are incurable, progressive and multisystemic diseases with clinical heterogeneity and phenotypic variability, which share a defective oxidative phosphorylation and disruption of ATP synthesis. Although the age of onset defines the severity of the disease, most patients face significant disability, poor prognosis and premature death [243]. The mitochondrial respiratory disorders are commonly referred to as mitochondrial encephalomyoptahies, as they affect both the skeletal muscle and central nervous system with manifestations often including epilepsy, stroke-like episodes, cognitive impairment, ataxia, hearing loss, and progressive dementia [244]. To illustrate the concept of adaptive mitochondrial biogenesis in response to mitochondrial dysfunction, we will focus on the two most prevalent maternally inherited mitochondrial respiratory disorders, mitochondrial encephalopathy lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy and ragged-red fiber disease (MERRF) (Table 1).

MELAS is caused by a common A to G substitution at position 3243 of the mitochondrial genome, corresponding to the mitochondrial gene encoding the $tRNA^{Leu(UUR)}$ [245, 246]. This A3243G MELAS mutation is present in a heteroplasmic state, causing a severe respiratory chain deficiency with complex I being the most affected [247]. The MELAS patients also present hypertrophic cardiomyopathy, myopathy and diabetes (Table 1) [248, 249]. They exhibit a high glycolytic rate, increased lactate production, impaired NADH response, a reduced mitochondrial membrane potential and ATP production [250]. As an attempt to overcome this chronic bioenergetic crisis, MELAS patients display a compensatory biological response of producing more mitochondria, albeit maladaptive, as it fails to sufficiently augment the bioenergetically functional mitochondrial mass and compensate for the ATP deficit [242]. Accumulation of abnormal mitochondria in dendrites of Purkinje cells and endothelial and smooth muscle cells of cerebral small arteries is suspected to contribute to ataxia and stroke-like episodes [251].

MERRF is another example of maternally inherited mitochondrial respiratory disorder provoked by a common A to G substitution in the mitochondrial genome at position 8344, corresponding to the mitochondrial gene encoding the $tRNA^{Lys}$ (Table 1) [232, 252]. As an attempt to mitigate the energy deficit, enlarged and abnormal mitochondria proliferate and accumulate in the sub-sarcolemmal region of muscle cells, resulting in ragged-red fibers

visualized by the Gomori trichrome stain [253]. Abnormal large mitochondria are also present in the dentate nucleus leading to severe neuronal loss [254]. Collectively, this pattern of aggregated mitochondria may in part contribute to the diverse symptoms displayed by MERFF patients, which include myoclonus, myopathy with spasticity, cardiomyopathy, recurrent seizures, ataxia, peripeheral neuropathy, dementia and potential hearing loss or optic atrophy [255, 256].

Recent studies have provided new insight on a major contributor of neuropathogenesis for several neurodegenerative diseases with an underlying mitochondrial dysfunction, including HD, PD, and AD (Table 1) [114]. The common denominator among these neurodegenerative diseases is impaired function of the master regulator for mitochondrial biogenesis PGC-1α. PGC-1α null and conditional knock-out mice display neurological abnormalities usually associated with HD mouse models, such as myoclonus, dystonia and neurodegeneration in the cortex, thalamus, basal ganglia, hippocampus and striatum, the latter exhibiting the highest degree of degeneration [106, 257, 258]. Autoptic HD tissue samples revealed significant OXPHOS deficit due to decreased enzymatic activities of the respiratory complexes II, III, and IV, in two regions of the striatum, caudate and putamen, known to be involved in the uncontrollable dance-like movement, a hallmark of HD [259, 260]. Further evidence of the underlying mitochondrial dysfunction associated with HD was provided by studies on HD patient-derived lymphoblastoid cell lines revealing a reduced ATP/ADP ratio, a bioenergetic response inversely proportional to the length of the CAG repeat tract in the huntingtin (htt) protein [261]. Several lines of evidence support the concept that the link between transcriptional abnormalities and mitochondrial dysfunction is the central node responsible for HD neuropathology. Both expression levels and transcriptional activities of PGC-1α are reduced in medium spiny striatal neurons from HD patients and knock-in HD mice [262]. Furthermore, genome-wide microarray studies using human striatum samples documented a down-regulation of PGC-1α target genes involved in mitochondrial biogenesis and bioenergetics [263]. The authors could prevent striatal atrophy in HD-like mice by restoring PGC-1α expression using a lentiviral approach. Finally, recent studies have highlighted a link between sequence variants of PGC-1α and severity of the symptoms for HD [264, 265]. PGC-1α dysfunction extends beyond the neuronal lineage to oligodendrocytes where PGC-1α regulates the expression of several genes required for proper myelination, such as myelin basic protein (MBP), in keeping with the observed deficient myelination in HD transgenic mice [266].

Abnormal PGC-1α-mediated mitochondrial biogenesis also interfaces with PD, the second most common neurodegenerative disease [267, 268]. A meta-analysis of independent microarray analyses using microdissected human DA neurons from PD patients has documented a down-regulation of PGC-1α-regulated target genes, congruent with the concept of altered PGC-1α expression being the cause rather than the consequence of PD pathogenesis [267]. In support of this notion is the discovery of the molecular link between PGC-1α-mediated mitochondrial dysregulation, parkin inactivation and neurodegeneration of dopaminergic neurons in the substantia nigra of PD human samples and PD mouse models [268]. The authors discovered a substrate of parkin, called PARIS (ZNF746), which represses the expression of PGC-1α and its target gene NRF-1, both regulating mitochondrial biogenesis and OX-PHOS [116]. PARIS functions as a Kruppel-associated

box (KRAB) zing finger transcriptional repressor [269]. It accumulates in DA neurons upon Parkin inactivation as a result of a mutation associated with the familial form of PD, or in the presence of excessive reactive oxygen species (ROS) production, or upon dopaminergic stress, which caused reduced expression levels of PGC-1α and NRF-1. Considering that conditional knockout of *parkin* results in a PARIS-dependent loss of DA neurons, the authors argue that the Parkin-PARIS-PGC-1α pathway is one probable causal mechanism to PD pathogenesis.

Recent studies have demonstrated that reduction in mitochondrial number and impaired mitochondrial gene expression contribute to mitochondrial dysfunction associated with AD [270]. Morphometric analyses performed on hippocampal neurons of autoptic brains from patients with AD have revealed a significant decrease in intact mitochondria [271]. The correlation between the mitochondrial mass and expression of the amyloid precursor protein carrying the Swedish mutation (APPswe) was confirmed in the *in vitro* M17 cellular model [272]. Decreased expression levels of PGC-1α in AD brains imply abnormal mitochondrial biogenesis as a key event for reduction of mitochondrial mass and bioenergetic functions [273]. A recent study has demonstrated that the network of transcription factors regulating mitochondrial biogenesis, including NRF-1, NRF-2 and TFAM, was altered in AD brains suggesting a deficiency in the process of mitochondrial biogenesis [274]. The causal relationship between deficient mitochondrial biogenesis and AD was confirmed in APPswe M17 cells overexpressing PGC-1α, which displayed restored expression levels of NRF-1, NRF-2 and TFAM along with increased mtDNA content and mitochondrial mass [274]. Thus, the authors postulate that induction of mitochondrial biogenesis may alleviate mitochondrial dysfunction in AD patients. However, the pharmacological approach to improve mitochondrial biogenesis remains elusive. Activation of the protein kinase A (PKA)-CREB pathway may enhance mitochondrial biogenesis via increased expression of the PGC-1α, as the PGC-1α promoter is upregulated by the transcription factor CREB phosphorylated at Ser133 by PKA [275]. A functional correlation between CREB activity, PGC-1α expression and PKA activity was observed in the *in vitro* M17 cellular model for the familial form of AD [274]. Moreover, postmortem AD brains exhibit decreased CREB protein and phosphorylation levels as a result of inactivation of PKA [276].

8. PUTATIVE THERAPEUTIC OPTIONS TO MODULATE NEURONAL MITOCHONDRIAL BIOGENESIS

Currently, mitochondrial respiratory disorders are a group of incurable, genetically and clinically heterogeneous diseases. Most often, they are caused by inherited mutations in the mitochondrial or nuclear genome that induce defects in the mitochondrial OX-PHOS system, resulting in impaired ATP synthesis. Treatment of these mitochondrial diseases has remained challenging due to polyploidy of the mitochondrial genome, heteroplasmy, and the influence of the nuclear background of the patients. Thus far, palliative therapies available to patients, which consist of various cocktails of vitamins, anti-oxidants and nutrient supplements, have been ineffective further underscoring the need to design novel pharmacological interventions [277].

One of the main therapeutic avenues to overcome maladaptive mitochondrial biogenesis is to efficiently boost mitochondrial biogenesis via pharmacological means to compensate for the OXPHOS deficit associated with mitochondrial respiratory disorders and neurodegenerative diseases, with the objective to enrich the wild type mitochondrial population. This shift in heteroplasmy would optimize OXPHOS functions and alleviate symptomatic manifestations of these diseases [240, 278]. In support of this strategy are studies demonstrating that induction of mitochondrial biogenesis via transgenic overexpression of PGC-1α using a genetic approach was able to rescue ATP levels in cybrid cell lines harboring nuclear or mitochondrial mutations derived from patients with oxidative phosphorylation defects [279, 280]. Endurance exercise has also mimicked the beneficial effect of PGC-1α overexpression in terms of mitochondrial biogenesis, thereby improving OXPHOS functions and slowing down progression of mitochondrial myopathy due to cytochrome c oxidase deficiency [281]. Similar improvement has also been observed in patients affected with mitochondrial diseases [282, 283].

To develop novel and efficient pharmacological approaches for inducing mitochondrial biogenesis, several animal models were engineered to mimic distinct human mitochondrial encephalopathies [284, 285]. The “deletor” mouse carries dominant mutations in the nuclear gene encoding the mitochondrial helicase, Twinkle, responsible for human adult-onset progressive external ophtalmoplegia due to multiple mtDNA deletions [141, 145]. This mouse exhibits progressive OXPHOS deficit in the skeletal muscle and in specific neuronal populations, including cerebellar Purkinje cells and hippocampal neurons, making it a useful model to investigate therapeutic strategies to treat adult-onset mitochondrial myopathy and neurodegeneration [146]. Another widely used mouse model to investigate mitochondrial myopathy is the muscle-specific knockout of the assembly factor of the respiratory complex IV, COX10 [286], which mimics human infantile fatal COX deficiency [287, 288]. The conditional knockout mouse for COX15, a key enzyme for the synthesis of heme A, exhibits severe myopathy in skeletal muscle, making it another useful mouse model for the fatal infantile hypertrophic cardiomyopathy and myopathy [289–292]. However, not all mouse models closely mimic human mitochondrial diseases, as exemplified by the Surf1 null mice. Although mutations of Surf1, another assembly factor for COX, cause Leigh syndrome in humans, Surf1 knockout mice fail to exhibit histo-pathological hallmarks of Leigh syndrome, such as neurodegeneration, even though they display mild COX deficiency [293].

The current therapeutic modalities for patients with mitochondrial respiratory disorders aim at increasing expression levels of PGC-1α via increased activity of the nuclear PPAR receptors and/or boosting its activity via modulation of the energy sensors AMPK and SIRT1 [116, 190, 294, 295]. Bezafibrate, an effective cholesterol-lowering drug [296], and rosiglitazone, a thiazolodinedione drug used to reduce insulin resistance in type II diabetes [297, 298], act as pharmacological activators of PGC-1 α expression levels by functioning as pan-agonists of the three PPAR nuclear receptor isoforms α, β/δ, and γ (Fig. 2). Given the limited blood-brain barrier permeability of rosiglitazone, its efficacy for neurodegenerative disorders and neurodegenerative diseases is limited [289]. Therefore, most studies investigated the impact of bezafibrate on mitochondrial biogenesis. Exposure to bezafibrate yielded conflicting results for mitochondrial biogenesis in various animal models. In skeletal muscle of the *Cox10*$^{-/-}$ mouse model, bezafibrate increased levels of PGC-1α, mtDNA and

ATP levels, thereby slowing down the progression of mitochondrial myopathy [300]. However, this response could not be achieved in other mouse models for different mitochondrial myopathies. In the *Surf1*$^{-/-}$ mouse model, bezafibrate failed to modulate the levels of PGC-1α and mtDNA as well as the enzymatic activities of OXPHOS respiratory complexes despite increased expression levels of PPARs α, β/δ, and γ [292]. Similarly, a lack of bezafibrate-induced mitochondrial biogenesis was observed in the muscle-specific *Cox15*$^{-/-}$ mouse model [292]. The "deletor" mice treated with bezafibrate failed to alter expression levels of PGC-1α while down-regulating mtDNA copy number and expression levels of OXPHOS genes [301]. Interestingly, a recent study showed that bezafibrate improved the phenotype and survival in the R6/2 transgenic mouse model of Huntington's disease by increasing expression levels of PGC-1α, OXPHOS genes and PPARs α, β/δ, and γ, along with increased mitochondrial density in medium spiny striatal neurons [302]. In contrast, *in vitro* studies using cultured fibroblasts isolated from patients affected with mitochondrial respiratory disorders due to complex I, complex III, or complex IV deficiency showed that bezafibrate concomitantly induced PGC-1α expression levels and rescued OXPHOS activities [303]. In cybrid cells carrying the human A3243G MELAS mutation or the A8344G MERFF mutation, bezafibrate also induced expression levels of PGC-1 and mitochondrial biogenesis accompanied by enhanced OXPHOS activity [304]. The underlying mechanisms responsible for these conflicting results on mitochondrial biogenesis remain unclear, which may favor a personalized therapeutic approach for patients with mitochondrial respiratory diseases. Furthermore, bezafibrate efficacy remains to be established in humans.

Another pharmacological mean to induce mitochondrial biogenesis is to modulate the activity of PGC-1α, by posttranslational modifications, such as phosphorylation or deacetylation under the control of AMPK or NAD-dependent deacetylase Sirt1, respectively (Fig. 2) [176]. As a consequence of low energy reserve resulting in inverse ATP and AMP levels, PGC-1α is phosphorylated by activated AMPK and subsequently translocated to the nucleus to upregulate genes involved in mitochondrial biogenesis and FAO [166]. Mimicking increased AMP levels is 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), which acts as an AMPK agonist and therefore activates PGC-1α (Fig. 2) [305, 306]. A recent *in vitro* study has demonstrated the potential benefit of AICAR to correct the ATP deficit due to congenital deficiency of the mitochondrial respiratory complex I by inducing mitochondrial biogenesis rather than stimulating the mitochondrial membrane potential [307]. Moreover, AICAR activated the AMPK-PGC-1α axis in diverse genotypic and nuclear backgrounds from patients' fibroblasts with different complex I defects. Surprisingly, AICAR ameliorated OXPHOS activity by increasing transcription and translation of key OXPHOS genes instead of increased mitochondrial biogenesis in three COX-defective mouse models, *Cox15*$^{-/-}$, *Surf1*$^{-/-}$ and *Sco2*$^{KO/KI}$ [292]. These conflicting results between human- and murine-based studies imply that the nuclear background most likely plays an important role in dictating the efficacy and the gene pathways triggered by pharmacological drugs.

Metformin, an anti-type 2 diabetes mellitus drug, activates AMPK and modulates PGC-1 α activity [308]. However, metformin-mediated activation of AMPK is not direct as in the case of AICAR, but rather linked to the inhibition of mitochondrial respiratory complex I,

thereby decreasing ATP synthesis while increasing ADP levels and subsequently AMP levels [309, 310]. A recent study showed that metformin also activates AMPK, independently of inhibition of complex I, via repression of the AMP deaminase enzyme, resulting in increased AMP levels [311]. Thus, metformin enhances the mitochondrial retrograde pathway controlling AMPK activity (Fig. 2). Due to its indesirable inhibition of complex I, the therapeutic potential of metformin cannot be exploited in the context of mitochondrial respiratory disorders, which are characterized by severe complex I deficiency [242]. However, studies in the roundworm *Caenorhabditis elegans* and the fruitfly *Drosophila melanogaster* may suggest otherwise given their extended lifespan upon RNA-interference-mediated knockdown of specific components of the OXPHOS system [312–314].

In light of the fact that sirtuins, more specifically SIRT1 and SIRT3, play a central role in regulating mitochondrial biogenesis, a strong emphasis has been placed on developing pharmacological strategies to activate the NAD-SIRT1-mitochondrial axis [315]. Upon SIRT1 activation in response to energy depletion, PGC-1α is deacetylated and activated in a NAD^+-dependent manner (Fig. 2) [188, 196, 316]. Manipulation of the SIRT1-mediated pathway via overexpression successfully improved energy expenditure in several animal models for neurodegenerative diseases associated with mitochondrial dysfunction by unknown molecular mechanisms [317]. For example, SIRT1 transgenic expression in distinct HD mouse models attenuated brain atrophy and ameliorated brain and motor functions through activation of several SIRT1 targets in a manner similar to that of calorie restriction [318–320]. In the context of PD, SIRT1 overexpression suppressed the formation of α-synuclein by activating molecular chaperones involved in mitochondrial functions [321]. Likewise, modulation of SIRT1 expression levels and activity conferred neuroprotection and improved learning and memory deficits in various AD models [186, 322]. Based on these collective findings, it is reasonable to speculate that altering SIRT1 activity could be a valid therapeutic strategy to alleviate somatic manifestations in patients affected with inherited metabolic diseases, such as mitochondrial respiratory disorders.

The recently identified small molecule SIRT1 agonists, SRT1720 (N-[2-[3-(piperazin-1-ylmethyl)imidazo[2,1-b][1,3]thiazol-6-yl]phenyl]quinoxaline-2-carboxamide) and isoflavone-derived compounds, such as daidzein, formononetin, DCHC (3-(2′,4′-dicholorphenyl)-7-hydroxy-4H-chromen-4-one) and 7-C (7-hydroxy-4H-chromen-4-one) have been tested in non-neuronal cellular paradigms for their impact on mitochondrial biogenesis [323–327]. Mice treated with the pharmacological activator of SIRT1, SRT1720, which is structurally unrelated to resveratrol, exhibited enhanced SIRT1 activity and mitochondrial biogenesis via direct deacetylation of PGC-1α and indirect stimulation of AMPK (Fig. 2) [328]. *In vitro* studies using primary cultures of renal proximal tubule cells, SRT1720 rapidly induced mitochondrial biogenesis in a SIRT1-dependent manner via deacetylation of PGC-1α, causing increased mtDNA content and ATP levels [327]. However, SRT1720 direct activation of SIRT1 remains disputed due to artifacts derived from the use of the nonphysiological fluorescent “Fluor de Lys” substrate for measuring *in vitro* SIRT1 activity [329].

The plant polyphenol, resveratrol, may be another potential pharmacological tool given that it confers neuroprotection in mouse model of AD [186]. The *in vivo* molecular mechanism, by which it induces mitochondrial biogenesis, remains controversial. Although resveratrol was identified in a screen for Sir2 deacetylase activity as a potent agonist of Sir2 activity, it appears not to act as a direct activator of Sir2 protein [323, 330]. In cultured primary dorsal root ganglion neurons, cortical neurons and Neuro2a neuronal cells, resveratrol rapidly induces mitochondrial biogenesis via increased expression levels of TFAM and PGC-1α in a SIRT1-independent pathway [331]. Within two hours, it triggered neuritogenesis and mitochondrial biogenesis via AMPK activation under the influence of the LKB1 and CaMKKβ kinases. Such rapid response is therapeutically advantageous in the context of CNS injury and ischemic or hypoxic insults [332]. Other studies confirmed that SIRT1 is not essential for immediate resveratrol-induced AMPK activity and stimulation of PGC-1α expression, but rather behaves as a downstream mediator of AMPK actions to activate PGC-1α via deacetylation [200, 333]. Moreover, it is postulated that resveratrol may promote mitochondrial biogenesis by initially creating an energy stress via its mild inhibition of the OXPHOS system. Subsquently, it activates AMPK and stimulates SIRT1 through enhanced NAD^+ levels as a result of increased FAO (Fig. 2) [190, 198, 199, 334, 335]. However, this regulatory link between resveratrol, AMPK and SIRT1 may be adapted to cellular environment, physiological conditions and stressors, which may explain the current conflicting findings on the dependence of SIRT1 and AMPK upon resveratrol exposure in skeletal muscle versus neurons [200, 331, 336, 337].

8. CONCLUSION AND PERSPECTIVES

Mitochondrial biogenesis and functions are intertwined, as they influence each other and impact diverse neuronal functions in a developing or mature brain, thereby making mitochondrial dysfunction the prime source for specific neurodevelopmental disorders or adult neurodegenerative diseases. Although mitochondrial biogenesis is a key determinant of neuronal differentiation, its regulation has not been extensively studied. Therefore, a comprehensive and integrated analysis of the molecular mechanisms controlling mitochondrial biogenesis in the context of a developing or mature neuron is worth pursuing to develop novel therapeutic approaches tailored to the nervous system. Furthermore, it is essential to elucidate the dynamic balance between mitochondrial biogenesis, fusion-fission cycles and mitophagy, as it is a key determinant of the overall mitochondrial health and density, thereby influencing the overall energetic homeostasis within the cell. In addition, the crosstalk between these distinct but interdependent biological processes is constantly tuned by shared effectors and regulators [338–340]. During establishment of CNS connectivity, fusion-fission combined with mitochondrial trafficking is critical to locally modulate the mitochondrial population to sites with increased energy needs in response to growth factors, guidance cues, synaptic activity and axonal branching [341]. This functional interlink between mitochondrial distribution and synaptic activity is well documented at the presynaptic and the postsynaptic elements of dendritic spines of hippocampal neurons [58, 342]. In a mature brain, maintenance of an adequate functional mitochondrial mass is vital to ensure synaptic activity and plasticity and relies on a balance between the rate of biogenesis and clearance of dysfunctional or old mitochondria. Thus, adult

neurodegenerative diseases may result from either impaired mitochondrial biogenesis, or inability to compensate for declined impaired mitochondrial functions, or a defective mitophagic process. In neurodegenerative diseases with a childhood onset, increased mitochondrial abundance is observed in tissues of patients affected with specific mitochondrial respiratory disorders, a quantitative increase to overcome a qualitative deficiency due to mutated mitochondrial proteins that are either nuclear- or mitochondrial-encoded.

Thus, the strategy for designing small molecules to manipulate the endogenous pathways controlling mitochondrial content and activity has been explored with the objective to potentiate the endogenous mitochondrial biogenic response. Promising results from mouse models have been obtained with various pharmacological tools acting as effectors of the AMPK-SIRT1-PGC-1α axis. However, these pharmacological interventions produced mixed results depending on the animal model for mitochondrial respiratory disorders. This mixed response may in part result from the role played by the nuclear background, a key modulator of mitochondrial biogenesis. Finally, it is important to highlight that none of the existing small molecules drugs have been tested in patients affected with mitochondrial respiratory diseases. In conclusion, improving our understanding of neuronal mitochondrial biogenesis and generating animal models mimicking diverse human mitochondrial diseases are essential to aggressively pursue the development of novel therapeutic strategies and pharmacological agents, as the field of mitochondrial pharmacology is nascent but auspicious.

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ABBREVIATIONS

AD	Alzheimer Disease
adPEO	Autosomal Dominant Progressive External Opthalmoplegia
AICAR	5-Aminoimidazole-4-carboxamide ribonucleoside
ALS	Amyotrophic Lateral Sclerosis
AMPK	AMP-activated Kinase
APP	Amyloid Precursor Protein
APPswe	Amyloid Precursor Protein carrying the Swedish mutation
bHLH	Basic Helix-Loop-Helix
BrdU	Bromodeoxyuridine
CaMMK	Calcium/calmodulin-dependent protein Kinase
CMT2A	Charcot-Marie-Tooth neuropathy type 2A

COX	Cytochrome c Oxidase
DA	Dopaminergic
DAT	Dopaminergic Transporter
DRP1	Dynamin Related Protein 1
ETC	Electron Transfer Chain
ESC	Embryonic Stem Cells
FAO	Fatty Acid Oxidation
GABP	GA-Binding Protein
HD	Huntington Disease
HDAC	Histine Deacetylase
HES1	Hairy and Enhancer of Split-1
HEY2	Hairy and Enhancer of split-related with YRPW motif protein-2
HSP	Heavy Strand Promoter
Htt	Huntingtin
IMM	Inner Mitochondrial Membrane
KRAB	Kruppel-Associated Box
LHON	Leber’s Hereditary Optic Neuropathy
LSP	Light Strand Promoter
MBP	Myelin Basic Protein
MELAS	Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes
MERRF	Myoclonic Epilepsy and Ragged-Red Fiber
Mfn	Mitofusin
MILON	Mitochondrial Late-Onset Neurodegeneration
Miro	Mitochondrial Rho
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
mtDNA	Mitochondrial DNA
mtSSB	Mitochondrial Single Stranded Protein
NAD	Nicotinamide Adenine Dinucleotide
NGF	Nerve Growth Factor
NMDA	N-methyl-D-aspartate
NRF	Nuclear Respiratory Factor
OMM	Outer Mitochondrial Membrane

OPA1	Optic Atrophy 1
OXPHOS	Oxidative Phosphorylation
PARIS	Parkin Interacting Substrate
PD	Parkinson Disease
PINK1	PTEN INducing Kinase 1
PKA	Protein Kinase A
PGC1	Peroxisome Proliferator-Activated Receptor γ Coactivator-1
POLG	Polymerase Gamma
POLRMT	Mitochondrial RNA Polymerase
PPAR	Peroxisome Proliferator-Activated Receptor
PRC	PGC-1-Related Co-activator
RA	retinoic acid
ROS	Reactive Oxygen Species
Sir	Silent Information Regulator
SIRT1	Sirtuin 1
TCA	Tricarboxylic Acid
TFAM	Mitochondrial Transcription Factor A
TFB1M	Mitochondrial Basal Transcription Factor 1
Twinkle	T7 gp4-like protein With Intramitochondrial Nucleoid Llocalization
UPS	Ubiquitin Proteasome System

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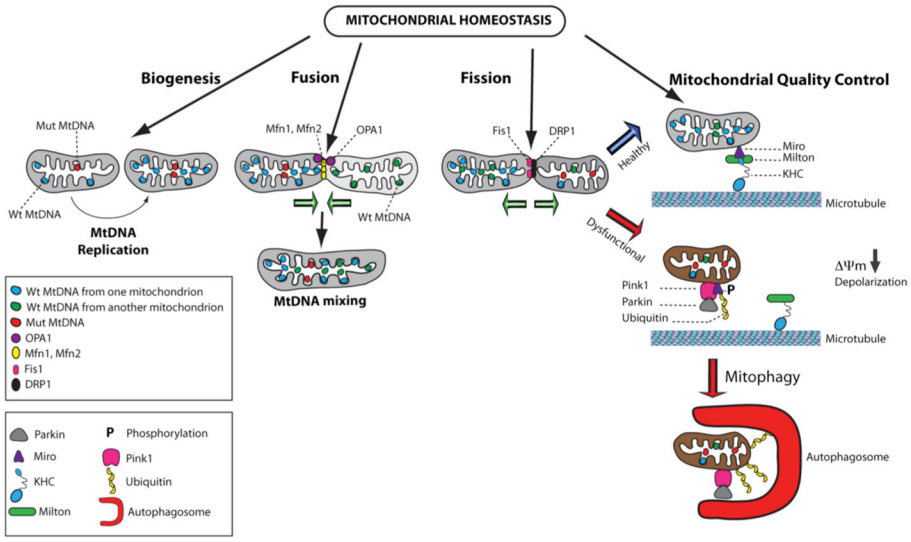

Fig. 1.

Maintenance of mitochondrial homeostasis. Mitochondrial number and health are under the control of three pathways: biogenesis, fusion-fission cycles and mitochondrial quality control. In healthy cells, these pathways are well balanced. Mitochondrial biogenesis involves mtDNA replication, while fusion promotes mtDNA mixing. Wild type mtDNA is illustrated in blue or green, while mutated mtDNA is indicated in red. Execution of the fusion process requires merging of the outer and inner mitochondrial membranes via the sequential action of the GTPase proteins, OPA1 (purple circles) and the mitofusins, Mfn1 and Mfn2 (yellow circles). Mitochondrial mass is also influenced by the process of fission, a process during which one mitochondrion gives rise to two healthy mitochondria. Fission is controlled by the dynamin-related protein DRP1 protein (black circles) and its receptors, such as Fis1 protein (pink circles), which together constrict the membranes to cause separation of mitochondria. The mitochondrial quality control prevents accumulation of dysfunctional mitochondria exhibiting mitochondrial membrane depolarization, which are targeted by the autophagic machinery for clearance. Healthy mitochondria are attached to microtubules via the kinesin heavy chain (KHC in blue) and the Miro-Milton adaptor complex illustrated by purple and green symbols, respectively. Following mitochondrial membrane depolarization provoked by various insults or increased mutated mtDNA population, PINK1 (pink symbol) accumulates in the outer mitochondrial membrane to recruit Parkin (grey symbol). Subsequently, Miro is phosphorylated resulting in detachment from Milton and microtubules. Parkin promotes ubiquitination (yellow symbol) of Miro and additional mitochondrial proteins, thereby inducing mitophagy with the assistance of autophagosomes (red symbol).

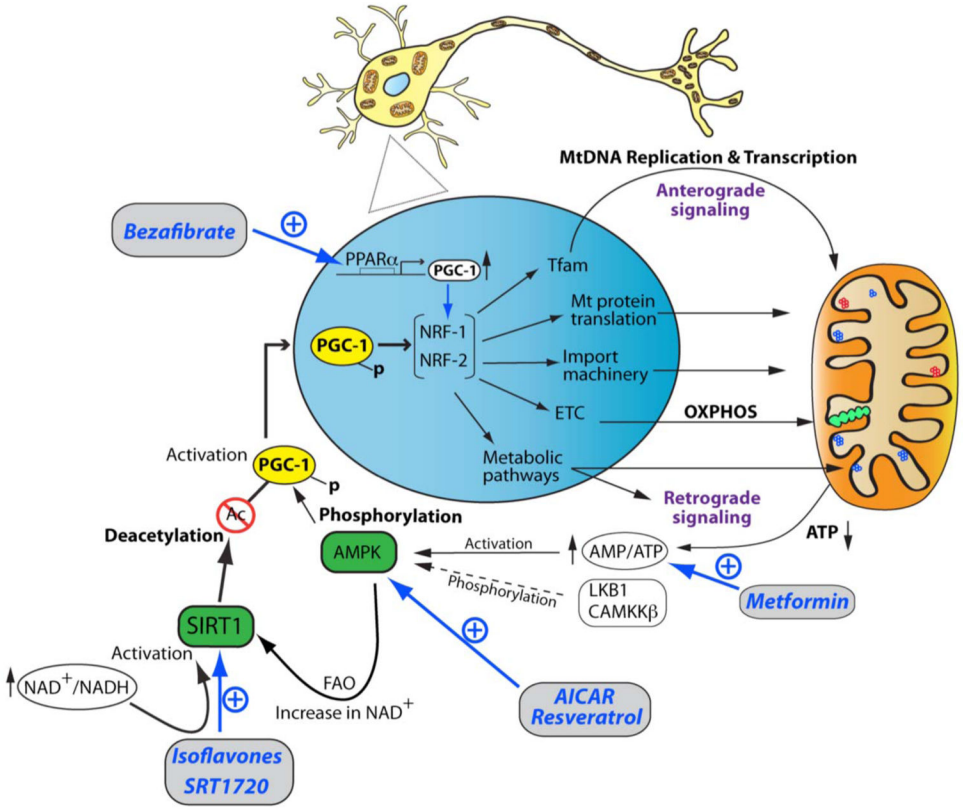

Fig. 2.

An integrated view of therapeutic strategies targeting the transcriptional network and signaling pathways promoting neuronal mitochondrial biogenesis. Diagrammed are the anterograde and retrograde signaling crosstalks between the nucleus (blue) and mitochondria (orange). The OXPHOS system is depicted with green circles, while wild type and mutated mtDNA molecules are illustrated with blue and red circles, respectively. The signaling and transcriptional cascades are limited to the PGC-1α-NRF-1-NRF-2 axis, given its important regulatory role for neuronal mitochondrial biogenesis. Pharmacological manipulations of key regulators for mitochondrial biogenesis and bioenergetics are illustrated in blue in the diagrammatic summary. PGC-1α expression can be pharmacologically enhanced by bezafibrate, an agonist of PPARα, which leads to increased expression of the *NRF-1* and *NRF-2* genes. In addition, PGC-1α directly stimulates the transcriptional activity of the NRF-1 and NRF-2 transcription factors via protein-protein interactions. Consequently, PGC-1α-mediated increased expression levels and activity of NRF-1 and NRF-2 lead to stimulation of gene expression relevant to mtDNA replication via the TFAM protein, OXPHOS activity (ETC), import of nuclear-encoded proteins, the mitochondrial translation machinery, and diverse mitochondrial and cellular metabolic pathways. The major retrograde signaling pathway is under the control of the AMP/ATP ratio, which augments upon decreased ATP levels. Increased AMP/ATP ratio activates AMPK, which subsequently phosphorylates the PGC-1α protein. In neuronal cells, activation of AMPK is also under the control of the LKB1 and CAMMKβ kinase. Phosphorylated PGC-1α migrates to the nucleus, where it stimulates the expression levels of the *NRF-1* and *NRF-2* genes as well as

their transcriptional activities. In a neuronal context, AMPK activity can be modulated via several pharmacological means, such as AICAR, resveratrol, and metformin, which are depicted in blue in the diagrammatic summary. AMPK also influences the activity of the NAD+-dependent deacetylase SIRT1 via fatty acid oxidation (FAO), resulting in increased NAD+ levels. Subsequently, SIRT1 is activated via phosphorylation, which can occur independently of AMPK upon increase of the NAD+/NADH ratio. Isoflavones and the pharmacological agent SRT1720 also activate SIRT1, which in turn deacetylate PGC-1α, thereby linking the cellular metabolic status to a network of gene expression relevant for mitochondrial biogenesis.

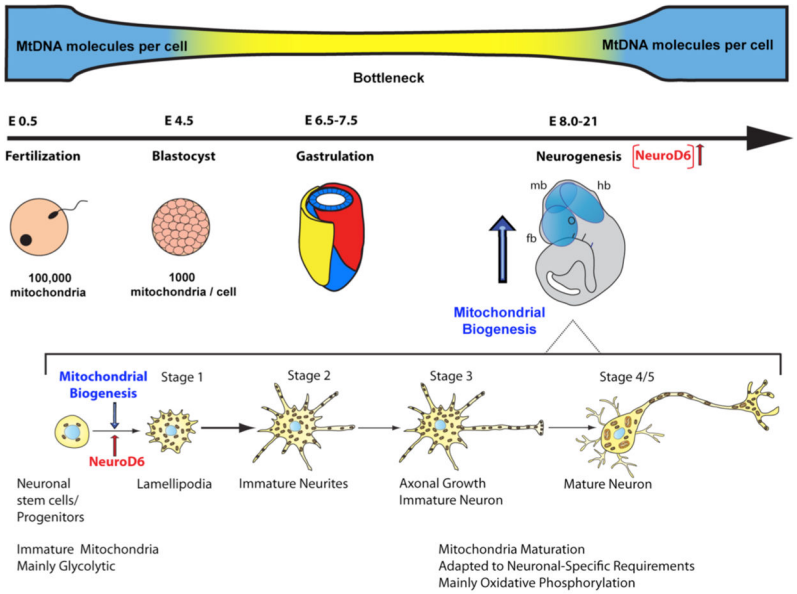

Fig. 3.

Timing of mitochondrial biogenesis during embryogenesis and neuronal differentiation. Depicted are key developmental stages during embryogenesis during which the mitochondrial genetic bottleneck occurs. Initiation of mitochondrial biogenesis coincides with increased expression of NeuroD6 and precedes neurogenesis as indicated by a blue or red arrow, respectively. The early stages of neuronal differentiation are illustrated as defined by Dotti *et al.*, 1988. Onset of mitochondrial biogenesis coincides with the transition from neural/progenitor cells to the lamellipodial stage. The degree of mitochondrial maturity and metabolism is indicated throughout neuronal differentiation. (fb) forebrain; (mb) midbrain; (hb) hindbrain.

Table 1

Discussed Neurodevelopmental and Neurodegenerative Diseases

Disease	Clinical features	Age of onset	Mt or nuclear mutations	Pattern of Inheritance	Primary or secondary mitochondrial disorders	Impaired mitochondrial biogenesis	Impaired OXPHOS activities	Aberrant mitochondrial dynamics
MELAS	stroke-like, seizures, cortical blindness, migraines, lactic acidosis, dystonia, progressive mental retardation, diabetes, hemiparesis, cardiomyopathy	Childhood or early adulthood	Mt	M	Primary	Yes	Yes	ND
MERRF	myoclonus, myopathy with ragged-red fibers, spasticity, cardiomyopathy, seizures, ataxia, dementia, peripheral neuropathy	Childhood or early adulthood	Mt	M	Primary	Yes	Yes	ND
AdPEO	Cataract, deafness, depression, myopathy with ragged-red fibers, parkinsonism, sensory ataxic neuropathy, ptosis,	Childhood	Nuclear	AD	Primary	Yes	Yes	ND
Leigh	Ataxia, intellectual retardation, hypotonia, nystagmus, cardiomyopathy, brainstem dysfunction, demylelination, vascular proliferation	Childhood	Mt or nuclear	M or AR or X-linked	Primary	Yes	Yes	ND
COX deficiency	Developmental regression, ataxia, nystagmus, hypotonia, lactic acidosis, kidney problems, respiratory failure	Childhood	Mt or nuclear	M or AR	Primary	Yes	Yes	ND
CMT2A	Progressive motor and sensory neuropathy in lower limbs, hypotonia	Childhood or adulthood	Nuclear	AD	Secondary	No	No	Yes
Parkinson’s disease	Bradykinesia, rigidity, resting tremor, balance problems, cognitive and speech impairment, degeneration of DA neurons of the substantia nigra	Adulthood	Nuclear	AR	Secondary	Yes	Yes	Yes
Huntington’s disease	Cognitive impairment, choreoathetotic movements, dementia, selective degeneration of striatal neurons, atrophy of caudate and putamen	Adulthood	Nuclear	AD	Secondary	Yes	Yes	Yes
Alzheimer’s disease	Selective memory impairment, dementia	Adulthood	Nuclear	Sporadic or AD	Secondary	Yes	Yes	Yes

Abbreviations: AD: Autonomic Dominant; AdPEO: Autonomic dominant Progressive external Ophtalmoplaegia; AR: Autonomic Recessive; COX: Cytochrome c Oxidase; CMT2A: Charcot-Marie-Tooth Type 2A; DA: Dopaminergic; M: Maternal; MELAS: Mitochondrial Encephalopathy Lactic Acidosis Stroke-like episode; MERRF: Myoclonic Epilepsy Ragged-Red Fibers; Mt; Mitochondrial; ND: Not Determined.