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CONCISE REVIEW

STEM CELLS

Mitochondria in neurogenesis: Implications for mitochondrial diseases

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Abstract

Mitochondria are organelles with recognized key roles in cellular homeostasis, including bioenergetics, redox, calcium signaling, and cell death. Mitochondria are essential for neuronal function, given the high energy demands of the human brain. Consequently, mitochondrial diseases affecting oxidative phosphorylation (OXPHOS) commonly exhibit neurological impairment. Emerging evidence suggests that mitochondria are important not only for mature postmitotic neurons but also for the regulation of neural progenitor cells (NPCs) during the process of neurogenesis. These recent findings put mitochondria as central regulator of cell fate decisions during brain development. OXPHOS mutations may disrupt the function of NPCs and thereby impair the metabolic programming required for neural fate commitment. Promoting the mitochondrial function of NPCs could therefore represent a novel interventional approach against incurable mitochondrial diseases.

KEYWORDS
induced pluripotent stem cells, mitochondria, mitochondrial diseases, neural progenitor cells, neurogenesis

Significance statement

This study discusses the emerging role of mitochondria for neural progenitor cells and for the regulation of cell fate decisions during neurogenesis. Elucidating the importance of mitochondria in neurogenesis might be instrumental to identify interventional targets for mitochondrial diseases, a group of rare incurable disorders causing neurological and neurodevelopmental defects.

1 | INTRODUCTION

Mitochondria are dynamic double-membrane organelles that are classically considered to be the powerhouse of the cell for their production of adenosine triphosphate (ATP) through the process of oxidative phosphorylation (OXPHOS).[1] At the same time, mitochondria are involved in several additional tasks, including calcium and free radical signaling, apoptosis, and metabolite-mediated modulation of gene expression.[2] Hence, mitochondria can act as gatekeepers of cellular homeostasis and can regulate cell death pathways to preserve cellular fitness and maintain genome integrity.[3,4]

In the past few years, several works investigated the role of mitochondria in stem cell reprogramming and differentiation.[5-7]

Undifferentiated stem cells mainly rely on glycolytic metabolism for energy generation and exhibit mitochondria with a roundish morphology.[8] During the differentiation process, mitochondria acquire a fused morphology and the metabolism switches from glycolysis to OXPHOS.[9,10] Conversely, somatic cells generally depend on OXPHOS and show a fused mitochondrial network, which reverts to a stem cell-like state upon reprogramming into induced pluripotent stem cells (iPSCs).[9,11,12]

Among somatic cells, neurons are known to be highly dependent on mitochondrial function, given the high energy demand of the brain, which consumes around 20% of energy at rest despite weighting only around 2% of the entire human body.[13] Recent evidence indicates that mitochondria could play a role not only in energetically demanding mature cells like neurons, but also in governing cell fate decisions during the establishment of physiological neurogenesis.[14-17]

Here, we focus on the emerging role of mitochondria for neurogenesis and for the function of neural progenitor cells (NPCs). We discuss the impact of these recent findings in the context of mitochondrial diseases. Mitochondrial diseases are currently incurable and the mechanisms underlying their neuronal pathology remain to be fully understood.

2 | MITOCHONDRIA IN CELL FATE DECISION: BIOENERGETICS AND BEYOND

The OXPHOS process occurs at the level of the mitochondrial inner membrane through five membrane protein complexes. As mitochondrial complexes shuttle electrons from one to another, protons are pumped into the inner mitochondrial matrix. This creates a proton gradient along the inner mitochondrial membrane, known as mitochondrial membrane potential (MMP).[18] The release of protons through the mitochondrial complex V, and their conversion into water in the presence of oxygen, enables the final generation of ATP.[19]

Mitochondria dynamically regulate their structural morphology through fusion or fission of the outer and inner mitochondrial membrane in a coordinated manner.[20] This is orchestrated by the dynamin-related GTPases Mitofusin 1 (MFN1), Mitofusin 2 (MFN2), optic atrophy protein 1 (OPA1), and Dynamin-related protein 1 (DRP1).[21,22] Also cristae membranes, once thought to be static under physiological conditions, can rapidly reshape their ultrastructural morphology.[23] The coordinated modifications of mitochondrial shape and cristae architecture can play a critical role in the cellular regulation of bioenergetic outputs and in the cellular adaptation to environmental cues and changing demands.[24,25]

OXPHOS is under dual genetic control.[26] The majority of mitochondrial complex proteins are encoded by the nuclear DNA, while 13 protein subunits are encoded by the mitochondrial DNA (mtDNA). mtDNA, a circular 16.5 kb-long genome, also encodes two rRNAs and 22 tRNAs for mtDNA translation.[27] mtDNA does not exhibit introns or histones, and it is present in multiple copies in mammalian cells. When an mtDNA mutation occurs, the mutation can be present in all mtDNA molecules (a situation known as homoplasmy) or only in a portion of the mtDNA molecules (a situation known as heteroplasmy).[28] Since mtDNA is inherited through the maternal lineage, mtDNA mutations can be passed from mother to offspring. However, the proportion of mutated molecules can vary dramatically among the children. This phenomenon is usually explained by the so-called mtDNA bottleneck, that is, the presence of a sudden reduction of mtDNA copies from primordial germ cells during the production of primary oocytes that changes the ratio between mutated and wild-type mtDNA molecules.[29] For this reason, a healthy mother carrying mtDNA mutations at low heteroplasmy could give birth to healthy children with low levels of heteroplasmy, as well as to affected children carrying pathogenically high levels of heteroplasmy.

The number of mtDNA copies can also vary among individual cells. Energetically demanding cells like neurons and cardiomyocytes possess elevated mtDNA copy number, while less active cells usually exhibit low amount of mtDNA copies. Undifferentiated stem cells usually contain low mtDNA copy number, which gradually increases during differentiation.[9,30] A major mechanism governing mtDNA copy number in cells is nuclear transcription-mediated mitochondrial biogenesis.[31] The master regulator of mitochondrial biogenesis is PPAR-gamma Coactivator 1 alpha (PGC-1a), a transcriptional coactivator induced in the cells by shortage of energy or by increased energy demands.[32,33] Low ATP levels are sensed by AMP-dependent kinase (AMPK), which responds by switching on mechanisms to increase energy output, including PGC-1a. AMPK can activate PGC-1a through SIRT1-mediated deacetylation or through direct phosphorylation.[34,35] Once activated, PGC-1a induces nuclear respiratory factors (NRF1 and NRF2) to promote the expression of OXPHOS-related genes.[36]

Besides bioenergetics, mitochondria perform a plethora of functions that contribute to the regulation of cellular homeostasis. Mitochondria are involved in the generation of reactive oxygen species (ROS), calcium balance, and apoptotic cells death.[3,37] ROS and calcium are important second messengers involved in cellular signaling.[38] However, excessive ROS production that cannot be counterbalanced by the antioxidant capacity of the cell can result in macromolecular damage.[39] Similarly, disproportionate intramitochondrial accumulation of calcium can cause the opening of the mitochondrial permeability transition pore, leading to the collapse of the MMP and the initiation of the apoptotic cascade.[40] In the context of stem cells, ROS are implicated in promoting differentiation through activation of a nuclear transcriptional program that alters gene expression profiles.[41-43] Indeed, ROS mediated damage and antioxidant levels increase during stem cell differentiation and decrease upon reprogramming to iPSCs.[9,44]

Mitochondrial metabolites generated in the mitochondria through the tricarboxylic (TCA) cycle can also function as cofactors or substrates for chromatin modifying enzymes. Hence, the amount of mitochondrial activity and related levels of metabolites can influence the global epigenetic landscape of the cells through the regulation of nuclear gene expression.[45] Through this crosstalk between energy metabolism and gene regulation, mitochondrial activity can thus contribute to the regulation of cell fate identity and plasticity.[6]

3 | MITOCHONDRIA IN NEUROGENESIS

Of all cell types in the central nervous system (CNS), neurons have the highest energy demands.[46] The majority of ATP generated in the CNS is utilized to maintain neuronal excitability and overall synaptic function.[47] In order to maximize local energy generation, mitochondria can be anchored at dendrites and synapses to synthetize ATP, thereby fueling vesicle recycling during neuronal activity.[48] However, in addition to postmitotic neurons, mitochondrial OXPHOS might also play a crucial role during neurogenesis.[16,49]

Neurogenesis is the process in which new neurons are formed from NPCs.[50,51] NPCs can be defined as the precursor cell population in the CNS giving rise to neuronal cells and glial cells that include oligodendrocytes and astrocytes.[52] Importantly, mammalian NPCs can be present not only during embryonic brain development,[53] but also in neonatal and mature adult brain.[51,54] However, to what extent neurogenesis is maintained during human adulthood still remains a matter of debate.[55-57]

In the process of generating neurons, the metabolic program undergoes critical changes. Undifferentiated stem cells mainly rely on glycolysis,[9,58] while neurons are highly dependent on mitochondrial OXPHOS.[59] Single-cell transcriptomics of adult mouse NPCs revealed the activation of an OXPHOS signature during the initiation of neurogenesis.[60] The acquisition of such metabolic program could represent an important factor for the evolution of the human brain size.[61] The human brain contains an expanded pool of progenitors compared to rodents, which could contribute to the extension of brain size, and exhibit higher basal energy expenditures compared to primates, which might provide sufficient energy for larger brains and faster reproduction while maintaining homeostatic functions and longevity .[61]

In order to acquire an OXPHOS metabolic profile, mitochondria in differentiating neuronal cells increase in number, and develop an elongated morphology with a dense network appearance.[62,63] During mouse embryonic neurogenesis, mitochondria in intermediate progenitor cells appear more fragmented than in undifferentiated neural stem cells.[64] Conversely, in adult neurogenesis mitochondria in intermediate progenitor cells show increased fused morphology compared to undifferentiated neural stem cells.[65] Despite these minor differences, it is widely accepted that mitochondria undergo changes during neurogenesis to eventually acquire an elongated morphology in neurons.[15,17]

Until recently, the above-mentioned changes in energy metabolism and mitochondrial morphology were considered as one of the by-products of neuronal differentiation, together with changes in cell cycle, communication, and signaling.[15,66] However, recent data in mouse embryonic NPCs and human iPSC-derived NPCs reveled that changes in mitochondrial dynamics are instrumental in initiating neurogenesis.[14] During cell division, NPCs can either self-renew or exit from stemness to begin neuronal differentiation. Interestingly, those NPCs with fragmented mitochondria are the ones that are poised to become neurons, while those with fused mitochondria are destined to self-renew and maintain stemness.[14] The time window for this decision point was found to be 3 to 6 hours for mouse NPCs and 6 to 12 hours for human NPCs.[14] These new findings provide a causal link between mitochondrial remodeling and mammalian neurogenesis, suggesting new potential targets for neurological diseases in which mitochondrial function is impaired.

In agreement with this new role of mitochondrial dynamics in instructing neurogenesis, recent works highlighted the importance of mitochondrial metabolism for neurogenesis. Adult neurogenesis requires mitochondrial activity, as proliferating mouse intermediate progenitors become dependent on OXPHOS, and OXPHOS disruption in mice can induce premature aging phenotypes.[65,67] Indeed, human iPSC-derived NPCs exhibit fused mitochondria, and a reduction of glycolytic metabolism coupled with increased OXPHOS.[68] Proliferating mouse adult NPCs also express high endogenous ROS levels, suggestive of elevated mitochondrial activity.[69] Redox regulation impacts physiological neurogenesis,[69] and may play a role in NPCs for balancing between stemness and differentiation.[70] Increasing the glycolytic reliance of NPCs can prevent their neuronal commitment, as seen for example in mouse embryonic NPCs expressing low levels of the RNA-binding protein Sam68.[71] Accordingly, the impairment of mitochondrial function in mouse embryonic NPCs causes calcium dyshomeostasis and delayed cortical neurogenesis.[72] Inhibition of mitochondrial function also disrupt the generation of neurons from human embryonic stem cells.[73]

Mitochondrial function may not only be crucial for the activity and survival of postmitotic neurons and for safeguarding the ability of NPCs to commit to neuronal cell fate, but also for ensuring the physiological homeostasis of NPCs (Figure 1). Mitochondrial function in embryonic and adult mice was found essential not only for ensuring proper NPC differentiation but also for allowing their maintenance of self-renewing capacity.[74] Two recent studies identified that two proteins that are crucial for neurogenesis, and specifically for neocortex expansion, namely MCPH1 and ARHGAP11B, act in the mitochondria of NPCs.[75,76] Hence, the mitochondrial function of NPCs may play a pivotal role for mammalian neurogenesis and neocortical growth.[77]

For the proper generation of neurons, which are highly complex and polarized cells, it is essential to establish a proper morphology for dendrites, axons, and synapses. This process is known as neuronal morphogenesis.[78] Mitochondria may play an important role during neuronal morphogenesis.[79] Mitochondria are present at synaptic terminals during the time synaptic connections are formed.[80,81] Mitochondria also contribute to the coordination of axon branching sites through localized axonal protein synthesis.[82] Depletion of mitochondria during neuronal morphogenesis can lead to defects in synaptic plasticity and spine morphology.[48,83]

Taken together, dysfunctions in the regulation of mitochondrial dynamics and morphology or defective OXPHOS bioenergetics could have profound effects on physiological neurogenesis and on the proper establishment of neuronal function.

4 | NEURAL PROGENITOR CELLS AS POTENTIAL INTERVENTIONAL TARGETS FOR MITOCHONDRIAL DISEASES

One of the major causes of mitochondrial dysfunction in humans is represented by mitochondrial diseases, a group of rare genetic

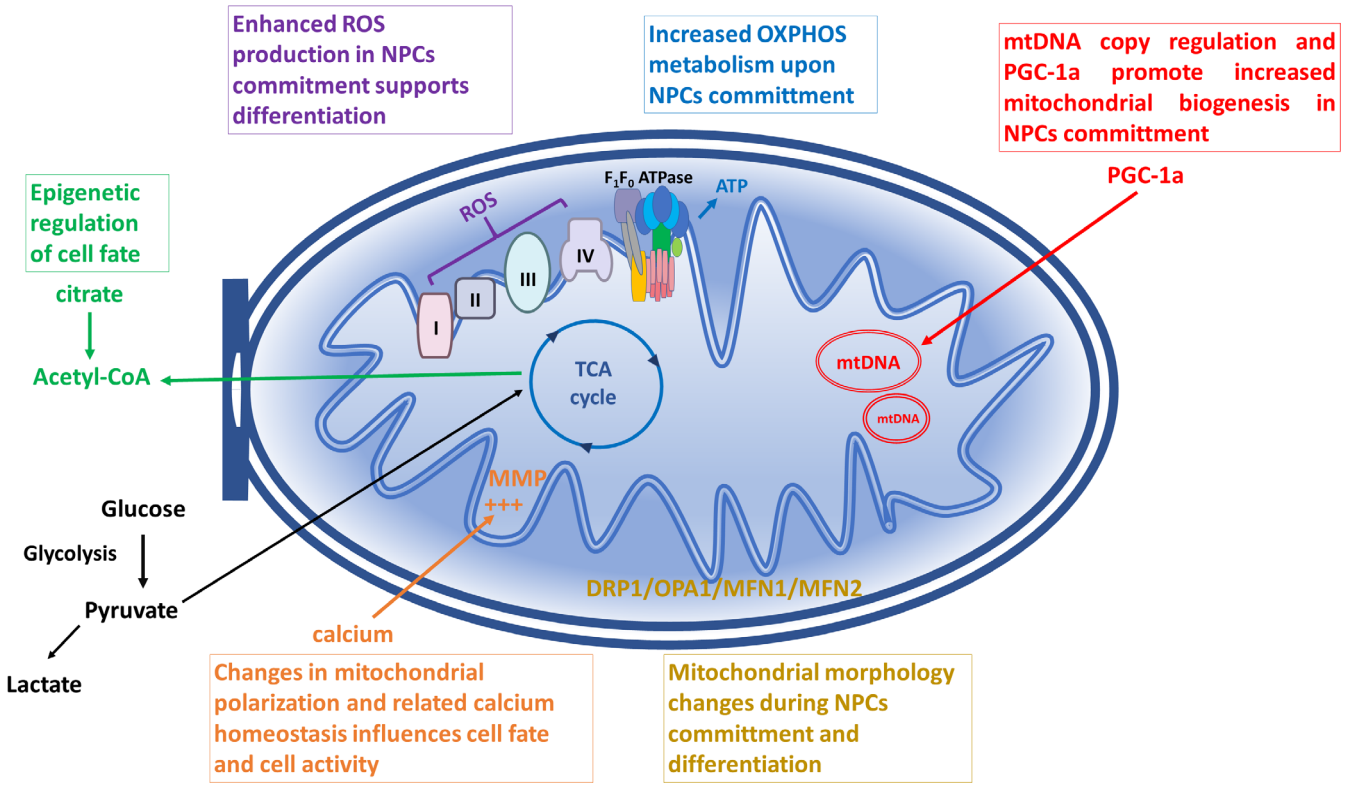

FIGURE 1 Mitochondrial pathways in cell fate decisions and neurogenesis. Mitochondria undergo changes during the commitment and differentiation of neural progenitor cells (NPCs). We here depict some of these changes highlighting distinct functions and mechanisms in different colors. MMP, mitochondrial membrane potential; ROS, reactive oxygen species

disorders caused by mutations in nuclear DNA genes or mtDNA genes encoding for proteins involved in OXPHOS functionality and structural assembly, mtDNA replication, mitochondrial transcription and translation, and mitochondrial dynamics.[26,84] Mitochondrial diseases affect approximately 1 in 4000 newborns, and typically cause neurological symptoms including psychomotor regression, stroke-like episodes, dementia, and epilepsy (Table 1).[84,85] Not only is the CNS a major target in primary genetically determined mitochondrial diseases, but mitochondrial dysfunction is also a prominent feature in many of the most prevalent neurodegenerative diseases.[86]

Although in the past 30 years mitochondrial medicine has made enormous progresses in understanding the genetic and biochemical pathomechanisms of mitochondrial disorders,[87,88] current treatments still remain focused on controlling complications and reducing the symptoms.[89,90] The lack of effective therapies for most mitochondrial diseases is due to several problems, including a specific lack of effective preclinical models for performing drug discovery.[91] The lack of disease models has limited the identifications of adequate markers and useful clinical outcomes, and it also prevented a more detailed understanding of the mechanisms underlying the neuronal pathology associated with mitochondrial diseases.

Based on the current mechanistic understanding, the neurological defects caused by mitochondrial diseases are mainly attributed to the degeneration of postmitotic neurons.[84,85] However, given the above-mentioned studies implicating mitochondria in the homeostatic regulation of NPCs and neurogenesis, it is possible that NPCs dysfunction may play an important yet underappreciated contributing role in the development of mitochondrial diseases. Accordingly, mitochondrial diseases can exhibit neurodevelopmental manifestations, such as developmental delay and cognitive impairment.[92-94]

The use of patient-derived iPSCs is providing important new insights that can shed light on the role of NPCs in the neuronal pathogenesis of mitochondrial diseases. NPCs generated from patients with mitochondrial diseases carrying mutations associated with Leigh syndrome (LS) in the mtDNA gene *MT-ATP6* (mitochondrially encoded ATP synthase membrane subunit 6) exhibited defective OXPHOS bioenergetics and aberrant calcium homeostasis.[68,95] Cerebral organoids derived from LS patients carrying mutations in the mtDNA gene *MT-ATP6* or in the nuclear genes *PDH* (pyruvate dehydrogenase) or *DLD* (dihydrolipoyl dehydrogenase) showed thinner neuronal cortical layers and abnormal organization of progenitor cells, indicative of defective neurogenesis.[96] A spinal cord organoid system obtained from patient-specific iPSCs carrying the A3243G mutation in the mtDNA gene *MT-TL1* (mitochondrially encoded TRNA-Leu [UUA/G] 1) associated with the mitochondrial disease MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) also exhibited delayed neurogenesis and neurite outgrowth defects.[97] The distribution of NPCs was affected in cerebral organoids carrying LS-related mutations in the nuclear gene *SURF1* (Surfeit locus protein 1).[98] Indeed patient organoids displayed a loss of neurogenic progenitor zones, which

TABLE 1 Neurological mitochondrial diseases

Mitochondrial disease	Main neurological symptoms	Mutated genes	Mitochondrial dysfunction
Leigh syndrome (LS)	Psychomotor regression, seizures, breathing problems, hypotonia, ataxia, lactic acidosis	*NDUFS1*, *NDUFS3*, *NDUFS4*, *NDUFS7*, *NDUFS8*, *NDUFA2*, *NDUFA9*, *NDUFA10*, *NDUFA12*, *NDUFV1*, *NDUFAF2*, *NDUFAF6*, *C20ORF7*, *FOXRED1*	Complex I
		SDHA	Complex II
		BCS1L	Complex III
		COX10, *COX15*	Complex IV
		SURF1	Complex IV
		TACO1	Complex IV
		LRPPRC	Complex IV
		EFG1	Multiple RC complexes
		C12orf65	Multiple RC complexes
		PDHA1	PDHC
		COQ2	CoQ
		AIF1	Multiple RC complexes
		MT-ND3, *MT-ND5*, *MT-ND6*	Complex I
Ethylmalonic encephalopathy (EE)	Microcephaly, psychomotor regression	*ETHE1*	Complex IV
Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)	Ataxia, spasticity, epilepsy, cognitive decline	*EARS2*	Multiple RC complexes
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)	Ataxia, spasticity, epilepsy, cognitive decline	*DARS2*	Multiple RC complexes
Single OXPHOS leukoencephalopathies	Encephalopathy, ataxia, psychomotor regression	*NDUFS1*, *NDUFV1*, *NUBPL*	Complex I
		SDHAF1, *SDHA*, *SDHB*	Complex II
		LYRM7	Complex III
		COX6B1, *SURF1*, *APOPT1*	Complex IV
		PDHA1	PDH
		EF-Tu, *MPV17*	Multiple RC complexes
		NFU1, *BOLA3*, *IBA57*, *ISCA2*	Multiple RC complexes
Leber's hereditary optic neuropathy (LHON)	Vision loss	*MT-ND1*, *MT-ND4*, *MT-ND5*, *MT-ND6*	Complex I
Kearns-Sayre syndrome (KSS)	Retinal degeneration, ataxia	mtDNA deletion	Complex I-III-IV-V
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	Seizures, stroke-like episodes, cognitive regression, lactic acidosis	mtDNA point mutation	Complex I-III-IV-V
Myoclonic epilepsy and ragged-red fiber disease (MERRF)	Myoclonus, epilepsy, progressive ataxia, dementia	A8344G, T8356C	Multiple RC complexes
Maternal inherited Leigh syndrome (MILS)	Psychomotor regression	*MT-ATP6* (high heteroplasmy)	Complex V
Neuropathy, ataxia, and retinitis pigmentosa (NARP)	Neuropathy, ataxia, vision loss	*MT-ATP6* (low heteroplasmy)	Complex V
Alpers disease (MSD4A)	Seizures, dementia, spasticity, blindness	*POLG1*	Isolated or multiple RC complexes

(Continues)

TABLE 1 (Continued)

Mitochondrial disease	Main neurological symptoms	Mutated genes	Mitochondrial dysfunction
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	Progressive external ophthalmoplegia, peripheral neuropathy	*TYMP*, *POLG1*, *RRM2B*	Nucleoside and nucleotide pool imbalance
Navajo neurohepatopathy (NNH)	Peripheral neuropathy, leukoencephalopathy	*MPV17*	dNTP pool imbalance
Charcot Marie Tooth (CMT2A)	Peripheral neuropathy	*MFN2*	Bioenergetic defects
Dominant optic atrophy (DOA)	Optic nerve degeneration	*OPA1*	Bioenergetic defects
Encephalopathy due to defect in the fission of mitochondria	Psychomotor developmental delay, peripheral neuropathy	*DRP1*	Hyperfused mitochondria
Friedreich ataxia (FA)	Cerebellar atrophy	*FXN*	Mitochondrial iron accumulation
Autosomal recessive spinocerebellar ataxia (ARCA)	Ataxia, psychosis, cognitive decline	*PITRM1*	MTS and Aβ processing defect
Spastic paraplegia	Gait and limb incoordination	*SPG7*	AAA+ complex
CoQ10 defects			
Primary Coenzyme Q deficiencies	Encephalomyopathy, seizures, ataxia	*CoQ2*, *CoQ4*, *CoQ9*, *PDSS1*, *PDSS2*, *CABC1*, *ADCK3*	Bioenergetic defects

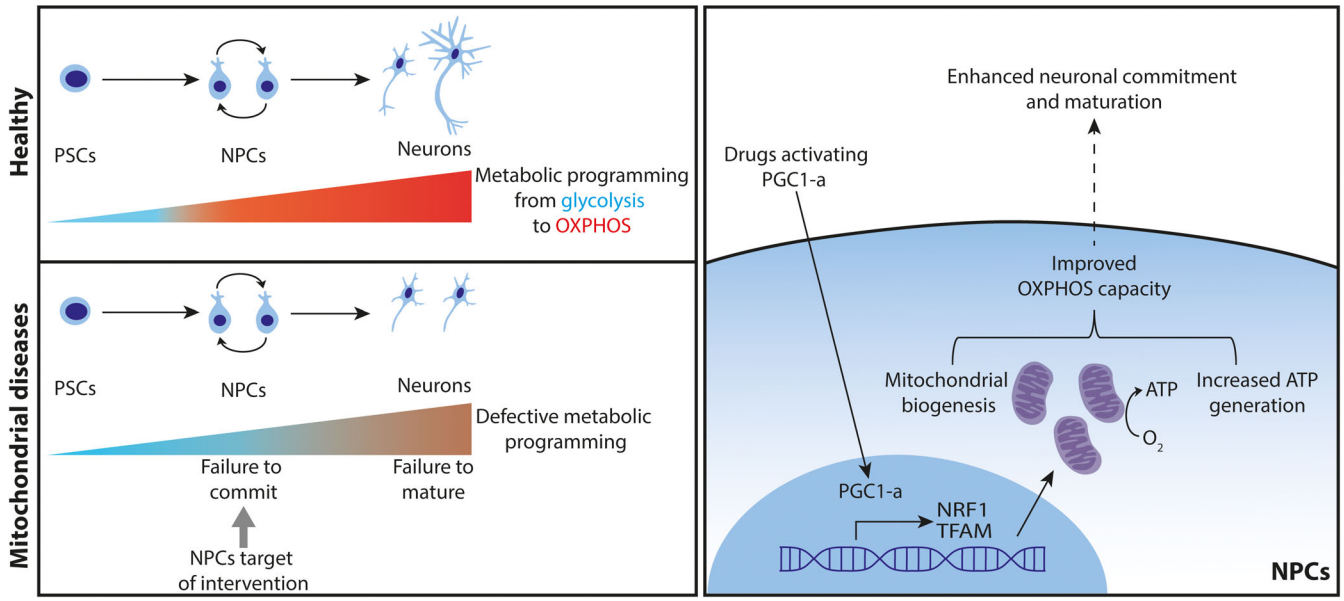

FIGURE 2 Metabolic programming during neurogenesis as a target for disease intervention. Left: In healthy conditions (above), there is an orchestrated programming of energy metabolism during the generation of neurons from pluripotent stem cells (PSCs), as neural progenitor cells (NPCs) start to shift toward oxidative phosphorylation (OXPHOS) and away from glycolysis. In patients with mitochondrial diseases (below), the metabolic shift to OXPHOS may be impaired, leading to improper generation of neurons that fail to mature and fail to generate the needed branches and connections. These NPCs defects may represent a potential target for disease intervention strategies aiming at reestablishing physiological neurogenesis. Right: An example of interventional strategies may be represented by the pharmacological activation of PGC-1a, which could promote the OXPHOS shift in NPCs by increasing mitochondrial biogenesis, ultimately leading to improved generation and maturation of neurons

formed around cavities resembling embryonic-like ventricles in healthy organoids.[98] The NPC defects found in *SURF1*-mutant human organoids are in agreement with findings in *SURF1* knockout piglets, which displayed significant reduction of the cortical thickness of the cerebral cortex gray matter at early postnatal ages and a disorganized cortical structure.[99]

These findings collectively suggest that mutations associated with mitochondrial diseases could impair neurogenesis by disrupting the physiological function of NPCs. In particular, mitochondrial defects may prevent the establishment of the OXPHOS metabolic program of NPCs, which is necessary for orchestrating mammalian neurogenesis (see chapter above). NPCs from mitochondrial patients might not be able to shift their metabolism to OXPHOS, thereby causing a failure to commit to mature neurons (Figure 2). In addition, mitochondrial defects could hamper the establishment of neuronal morphogenesis and synaptogenesis that are essential for physiological brain development (see chapter above). Indeed, early neurons generated from patient-derived NPCs carrying *SURF1* mutations exhibited reduced branching outgrowth capacity and functional synaptic deficits.[98] These developmental-related disruptions in neurogenesis and morphogenesis might potentially explain the cognitive impairment that can be observed in mitochondrial patients.[92] Hence, the mitochondrial state of NPCs may potentially represent an innovative target for interventional strategies aiming at reestablishing the physiological process of metabolic programming and the consequent instruction of human neurogenesis (Figure 2).

One potential treatment strategy targeting NPCs could be to use measures capable of promoting their metabolic shift toward OXPHOS. For example, pharmacological activation of PGC-1a might be exploited to activate mitochondrial biogenesis, which in turn may improve the mitochondrial bioenergetic output of NPCs, thereby enhancing their ability to commit to neuronal fate and grow complex branches (Figure 2). Accordingly, genetic overexpression of PGC-1a or pharmacological activation of PGC-1a using the drug bezafibrate promoted OXPHOS metabolism in patient-derived NPCs carrying *SURF1* mutations, leading to improved neuronal branching formation in nascent neurons.[98] Genetic overexpression of PGC-1a in *Surf1* knockout mice also enhanced OXPHOS activity and improved motor abilities.[100] PGC-1a activation may promote synaptogenesis also by supporting astrocyte maturation.[101] Treating human and mouse NPCs with an inductor of oxidative metabolism (called α5 mixture) composed by TCA cycle precursors and amino acids, also led to increased branching outgrowth and neuronal maturation.[102]

This shifted view of therapeutic approaches to mitochondrial diseases might lead to novel interventions aiming at promoting the reestablishment of physiological neurogenesis rather than merely preventing the degeneration of mature neurons. The interpretation that the neuronal pathology of mitochondrial diseases is caused by neurodegeneration influenced treatment schemes centered on antioxidants to prevent the buildup of damaging ROS.[87] However, antioxidants, which may dampen physiological ROS signaling,[103] failed to consistently improve the patient symptomatology.[88,90] Conversely, gene augmentation therapy based on the expression of a healthy copy of *SURF1* in patient NPCs improved early neuronal morphogenesis.[98] These latter results suggest that, at least in this case, the neuronal pathology of mitochondrial diseases might be caused by loss of function defects affecting neurogenesis that could be potentially restored if targeted early on.

Taken together, mitochondrial function may be crucial for the homeostasis and commitment of NPCs during the establishment of neurogenesis. We suggest that innovative strategies of intervention against disorders impairing mitochondrial function could thus focus on enhancing the OXPHOS metabolic program of NPCs in order to promote neurogenesis and the downstream generation of functional neurons.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

D.B., W.D., S.L.: manuscript writing; A.P., D.B., A.Z.: figure generation. A.P.: conception, manuscript writing, final approval of manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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