Review

Andrea Princz[a], Konstantinos Kounakis[a] and Nektarios Tavernarakis*

Mitochondrial contributions to neuronal development and function

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Abstract: Mitochondria are critical to tissues and organs characterized by high-energy demands, such as the nervous system. They provide essential energy and metabolites, and maintain Ca^{2+} balance, which is imperative for proper neuronal function and development. Emerging findings further underline the role of mitochondria in neurons. Technical advances in the last decades made it possible to investigate key mechanisms in neuronal development and the contribution of mitochondria therein. In this article, we discuss the latest findings relevant to the involvement of mitochondria in neuronal development, placing emphasis on mitochondrial metabolism and dynamics. In addition, we survey the role of mitochondrial energy metabolism and Ca^{2+} homeostasis in proper neuronal function, and the involvement of mitochondria in axon myelination.

Keywords: electron transport chain; ion homeostasis; mitochondrial dynamics; mitophagy; myelination; reactive oxygen species.

[a]**Andrea Princz and Konstantinos Kounakis:** These authors contributed equally to this article.
***Corresponding author: Nektarios Tavernarakis,** Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, N. Plastira 100, Vassilika Vouton, Heraklion 70013, Crete, Greece; and Department of Basic Sciences, Faculty of Medicine, University of Crete, N. Plastira 100, Vassilika Vouton, Heraklion 70013, Crete, Greece, e-mail: tavernarakis@imbb.forth.gr
Andrea Princz: Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, N. Plastira 100, Vassilika Vouton, Heraklion 70013, Crete, Greece; and Department of Biology, University of Crete, N. Plastira 100, Vassilika Vouton, Heraklion 70013, Crete, Greece
Konstantinos Kounakis: Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, N. Plastira 100, Vassilika Vouton, Heraklion 70013, Crete, Greece; and Department of Basic Sciences, Faculty of Medicine, University of Crete, N. Plastira 100, Vassilika Vouton, Heraklion 70013, Crete, Greece

Introduction

Mitochondria are often referred to as the 'powerhouses' of the cell. Their main function is considered to be energy production through the tricarboxylic acid cycle (TCA) and oxidative phosphorylation (OXPHOS) via the mitochondrial electron transport chain (ETC). Pyruvate from the cytoplasm is converted to acetyl-coenzyme A (acetyl-CoA) by the mitochondrial pyruvate dehydrogenase, which fuels the TCA cycle. Through a series of metabolic reactions, the TCA cycle is producing NADH and H^+ to aid the ATP production by the ETC (Figure 1A). The inevitable byproducts of OXPHOS are reactive oxygen species (ROS). Although disproportionate and supra-physiological ROS levels are harmful to proteins and cells (Ristow, 2014), their physiological function in differentiation, autophagy and immune response has also been demonstrated (Sena and Chandel, 2012).

Mitochondria are not static organelles. They can change shape, size, number, or localization inside the cell in order to adapt to changes in their environment and their own condition. Mitochondria possess the ability to fuse into each other or divide by fission as a means to adapt to cellular needs and facilitate quality control on their components. Mitochondrial fusion utilizes three dynamin-related GTPases: the Mitofusins 1 and 2 (Mfn1/Mfn2) that control outer membrane fusion and optic atrophy (OPA1) that controls inner membrane fusion. Mitochondrial fission is conducted by another dynamin-related GTPase, known as dynamin related protein 1 (Drp1). Drp1 can form a ring that constricts mitochondria and causes their division, after being recruited by mitochondrial outer membrane proteins, primarily mitochondrial fission 1 protein (FIS1) and mitochondrial fission factor (MFF) (Toyama et al., 2016). Mitochondrial fusion allows the sharing and redistribution of mitochondrial components, including mtDNA, throughout the entire network. Mitochondrial fission permits the isolation of damaged mitochondrial components from the remainder of their network, so that they can be effectively disposed of without disrupting cell function (Figure 1B) (Suarez-Rivero et al., 2016).

Mitochondria possess several pathways of quality control that ensure the removal or amelioration of damage before it can cause serious consequences to the cell. These mechanisms include the targeting of outer membrane proteins by the proteasome system, the mitochondrial unfolded protein response (mitoUPR) and, most importantly, mitophagy (mitochondrial specific autophagy). There are many mitophagy pathways in mammalian systems, some of which are cell/tissue specific (Fivenson et al., 2017). Mitophagy is facilitated by a series of autophagic receptor molecules that are either constitutively located on the outer mitochondrial membrane (OMM) (for instance NIX3/BNIP3L or FUNDC1) or are recruited there upon mitophagic induction (for instance NBR1). The main pathway of that induction involves PINK1, a mitochondrial kinase that is translocated to the mitochondrial matrix for deactivation by cleavage under healthy conditions. In mitochondria with disrupted membrane potential, however, PINK1 remains on the OMM, becomes active and can recruit an E3 ubiquitin ligase known as Parkin (Figure 1B). Both proteins then proceed to phosphorylate/ubiquitinate targets, enabling autophagosome recruitment (Ploumi et al., 2017).

Mitochondria are transported around the cell with the help of the cytoskeleton, motor proteins (kinesins and dyneins) and appropriate adaptors that connect the organelles to the motors. In neurons, mitochondria are primarily trafficked on microtubules spanning the entirety of the soma, dendrites and axon. Kinesins mediate anterograde transport (away from the soma), while dyneins mediate retrograde transport (towards the soma). The most notable adaptors that regulate this transport process are the Miro and Milton/TRAK proteins (Devine et al., 2016).

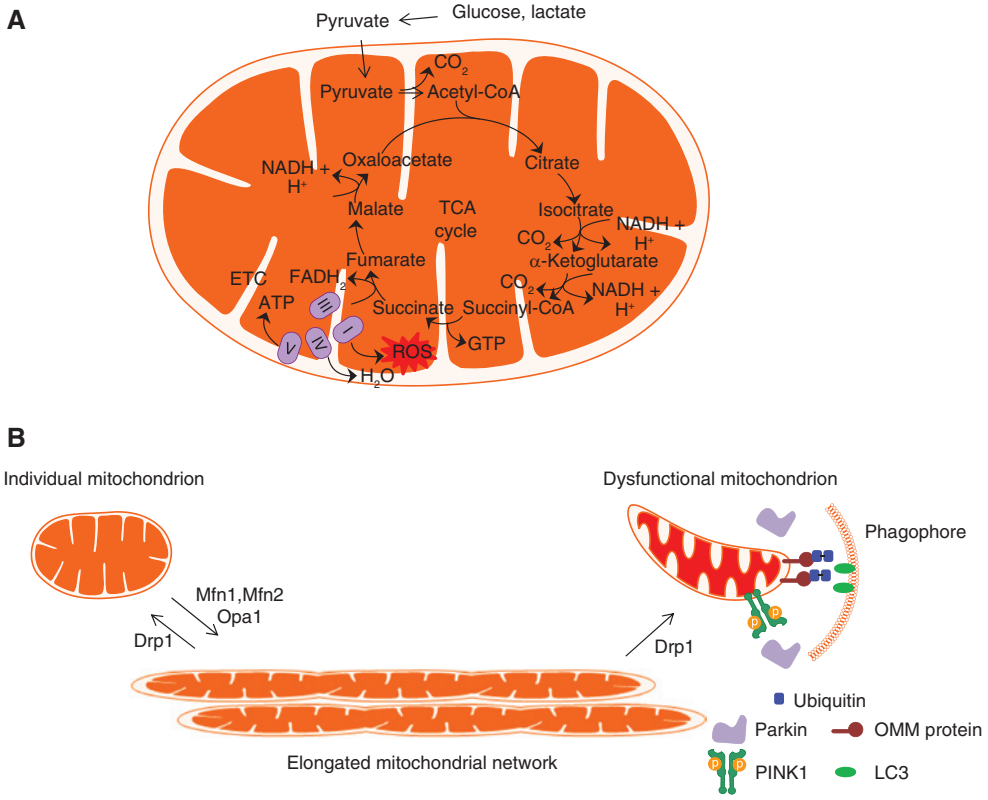

Figure 1: Mitochondrial ATP production and dynamics.
(A) The mitochondrial pyruvate dehydrogenase catalyzes pyruvate to acetyl-CoA and CO_2. The acetyl-CoA then enters the TCA cycle. The TCA cycle produces metabolites (NADH and H^+) which are then transferred to the ETC, the main ATP producing system in the cell. The ETC is composed of five membrane bound complexes, which generate NAD^+, FAD, H_2O and a proton-enriched microenvironment in the lumen between the inner and OMM. This proton imbalance will drive the synthesis of ATP. The byproducts of this process are H_2O and reactive oxygen species (ROS). (B) The mitochondrial network is under constant remodeling in healthy cells. Mitofusin 1 and 2 (Mfn1,2) and Opa1 promote the fusion of mitochondria and the formation of elongated mitochondrial network. Drp1 is responsible for the fission of healthy mitochondrion from the network, as well as the dysfunctional one. Malfunctioning mitochondria are recognized by PINK1 and Parkin. Parkin ubiquitilates a series of mitochondrial outer membrane proteins, which leads to the recruitment of phagophore and the selective degradation of mitochondria.

In the last 20 years, it has become widely accepted that neurogenesis exists not only during embryonic development but also throughout the lifespan of an organism (Bond et al., 2015). The adult mammalian brain harbors two main sites of neurogenesis: the sub ventricular zone (SVZ) along the lateral ventricles and the sub granular zone (SGZ) in the hippocampal dentate gyrus (Ming and Song, 2011). The differentiation of these neuronal stem cells (NSCs) depends on their imminent niche (Bond et al., 2015) and their metabolic state (discussed below). Cells from the SVZ give rise to transient amplifying progenitors, which will become neuroblasts after a few cell divisions (Doetsch et al., 1999). Intermediate progenitor cells (IPCs) arise from SGZ cells and after dividing a few times develop into neuroblasts (Berg et al., 2015). In this review we summarize the recent findings regarding how mitochondria influence the development, differentiation and function of neurons.

Mitochondria and neuronal development

Mitochondrial metabolism

The importance of mitochondrial functions in cell homeostasis is well established and studied; however, the involvement of mitochondria in neuronal development has just emerged recently. Stem cells in general and also NSCs depend on glycolysis as an energy producing mechanism to minimize ROS production and avoid damage to macromolecules (Ito and Suda, 2014). However, neuronal differentiation demands great amounts of energy, and the cells have to switch to oxidative phosphorylation (OXPHOS) and exit the cell cycle (Homem et al., 2014; O'Brien et al., 2015). Should they fail to shut down glycolysis with the continuing expression of hexokinase (HK2) and lactate dehydrogenase (LDHA), the neurons will undergo cell death (Zheng et al., 2016). This demonstrates that glycolysis is not neutral, but even detrimental during neuronal differentiation. In addition, the metabolic enzyme, pyruvate kinase M (PKM), undergoes a splice isoform change from PKM2 to PKM1. PKM2 is expressed in cells with high glycolytic activity, while PKM1 marks the cells, which are utilizing OXPHOS for energy production. During brain development, the alternative splicing of PKM mRNA is mediated by the splicing factor RNA Binding Motif Protein 4 (RBM4). Importantly, this isoform shift induces neuronal gene expression, enhances mitochondrial respiration capacity and promotes neuronal differentiation (Su et al., 2017). Additionally, PKM2 activity is inhibited upon elevated ROS levels (Yeo et al., 2013). This could act as a safeguard mechanism by which the cell ensures the isoform switch during differentiation, as ROS levels increase upon neuronal development as a result of OXPHOS upregulation. Although elevated ROS levels have to meet with high ATP levels in order to signal for neuronal differentiation. Pharmacological interference at mitochondrial complex III by introducing antimycin A to embryonic stem cells halts the differentiation into dopaminergic neurons. Interference with ETC leads to high ROS levels (specifically, superoxide anion was measured in this study), paired up with low ATP production and stabilization of hypoxia-inducible factor 1α (HIF-1α) which promotes glycolysis and the pluripotent state (Pereira et al., 2013). Recently, it has been shown that OXPHOS is vital as early as in the IPCs. Upon impairment of ETC by depletion of TFAM, the mitochondrial transcription factor A, IPCs undergo apoptosis, which leads to the depletion of the NSC pool (Beckervordersandforth et al., 2017). These findings emphasize the importance of adequate energy production and its need for tight regulation during neuronal differentiation.

Additional confirmation for the pivotal role of mitochondria in neural differentiation was provided by Khacho and colleagues. Impairment of mitochondrial function by the depletion of the mitochondrial oxidoreductase apoptosis inducing factor (AIF) in NSCs causes differentiation failure, aberrant proliferation and defects in self-renewal. In the developing brain this leads to severe cognitive and motor deficits, while in the adult brain, the stem cell pool will be depleted, due to elevated ROS (superoxide anion) levels which are a signal for neural cell fate commitment (Khacho et al., 2017). Forkhead box O (FoxO) transcription factors are central in ROS metabolism, as they activate the transcription of ROS-scavenging enzymes (e.g. superoxide dismutase, catalase), maintaining the redox homeostasis in the cell. They also proved to be essential to sustain the NSC pool in the adult and developing brain. Depletion of FoxOs results in an initial increase in mouse brain size, coupled with decreased number of NSCs in the adult brain and their impaired capacity to differentiate into distinct neuronal lineages (Paik et al., 2009; Renault et al., 2009). In particular, FoxO3 is responsible for the regulation of glucose and glutamine metabolism and through these mechanisms, for the preservation of the proliferative state of NSCs (Yeo et al., 2013). Interestingly, there is also research showing, that not low, but high ROS levels (superoxide anion and hydrogen peroxide) are

contributing to the self-renewal capacity of NSCs through PI3K/Akt/mTOR signaling (Le Belle et al., 2011). Based on this information, it has been reported that the PR domain containing 16 (Prdm16) and peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α) are activated by higher superoxide anion levels in the progenitor cells which are required for the proper migration of multipolar neurons in the ventricular zone. Abrogation of Prdm16 expression or ROS levels cause abnormal brain morphology, due to migration defects (Inoue et al., 2017). These contradictions in the effect of ROS on the physiology of NSCs may prove to be context, cell type and ROS dependent. It is also worth noting that the methods used to measure ROS (mainly fluorescent dyes) are known to be error and artifact-prone. However, recently there has been significant improvements in this research area, and with the help of these tools and more sensitive fluorescent dyes, now we can measure the desired ROS more precisely and selectively (Woolley et al., 2013). The implementation of these methods will most probably help us understand the exact role of each ROS in neuronal self-renewal and differentiation.

NSCs also utilize the HIF-1α in order to maintain their self-renewing capacity. It is well established that stem cells reside in a hypoxic niche (Shyh-Chang et al., 2013) and under these conditions, HIF-1α is stabilized, promotes the expression of glycolytic genes and prevents (by upregulating pyruvate dehydrogenase kinase 2 and 4) mitochondrial OXPHOS by blocking pyruvate from entering mitochondria. Loss of HIF-1α in the SVZ of adult brain first leads to decreased vascularization by reduced VEGF expression. Improper vascularization eventually causes NSC pool exhaustion (Li et al., 2014). Corroborating these results, another study found that HIF-1α stabilization was essential to support neuronal stem cell renewal and high levels of glycolysis (Lange et al., 2016). It has also been shown that FUNDC1 is an essential mitophagic receptor under hypoxic conditions. Hypoxia triggers the dephosphorylation of FUNDC1 which leads to the selective removal of mitochondria (Liu et al., 2012). These results show the importance of hypoxic neuronal stem cell niche and its extent of vascularization in the regulation of mitochondrial metabolism in stem cell fate decision.

Mitochondria are crucial for the metabolism of fatty acids as well. Recently, it has been shown that *de novo* lipogenesis via Fasn (fatty acid synthase) is imperative in NSCs for neurogenesis. The process is regulated by Spot14, which is selectively expressed in NSCs and determines malonyl-CoA (an essential building block of fatty acids) availability (Knobloch et al., 2013). Fasn also mediates exercise-induced neurogenesis (Chorna et al., 2013). Intriguingly, NSCs can also use fatty acids as an energy source (Stoll et al., 2015). Fatty acid oxidation (FAO) is required for the self-renewal of NSCs. Increasing the amount of malonyl-CoA in NSCs leads to the differentiation of neurons (Knobloch et al., 2017). Defects in FAO have been linked to neuropsychiatric disorders, due to stem cell pool exhaustion (Xie et al., 2016). These findings demonstrate that yet another mitochondrial function, fatty acid metabolism is invaluable for NSC maintenance and differentiation. However, research in this area has just begun and the upcoming years will help us understand in more detail the relationship between FAO and neuron differentiation.

Given the high-energy requirements of neurons, the growth in mitochondrial number is expected. Mitochondrial mass increases during neuronal development, in accordance with the size of the cell (Zheng et al., 2016). Although, there has been evidence showing that neuronal growth factors induce the AMPK-PGC1α-NRF1 axis and this leads to the generation of new mitochondria to meet the energy requirement of a growing neuron or axon (Vaarmann et al., 2016). In the adult brain, the proliferation of mitochondria is even more pronounced in neurons upon exercise (Steib et al., 2014). Moreover, PGC-1α controls the generation and maintenance of hippocampal dendritic spines and synapses, through mitochondrial biogenesis (Cheng et al., 2012). Neurons, which fail to increase their mitochondrial number, cannot grow and develop properly, and this leads to functional and morphological deficiencies. Besides ATP production, building blocks of macromolecules are also required for the proper differentiation and development of neurons. These are mainly provided by the pentose phosphate pathway (PPP). The pathway and its implication in brain development are discussed in detail elsewhere (Stincone et al., 2015).

Mitochondrial dynamics

Mitochondrial metabolism is tightly connected to mitochondrial dynamics; the complexes of ETC are membrane bound and ROS metabolism is affected by mitochondrial network connectivity. Intriguingly, research has only recently begun to connect mitochondrial dynamics and neural differentiation during embryogenesis and in the adult brain. Mitochondrial network reshaping has been observed during the development of spinal cord in chicken and mouse embryos (Mils et al., 2015). When mitochondria are fragmented, their energy production becomes less efficient and they produce more ROS, simultaneously. During dopaminergic neuron differentiation mitochondria become elongated, and their movement and

dynamics throughout the cell increase (Fang et al., 2016a). Elongation of the mitochondrial network is mediated by Mitofusin 2 (Mfn2), as was shown in human induced pluripotent stem cells (hiPSCs). Mfn2 levels increase during differentiation and its loss causes shorter neuronal processes and decreased number of synapses, impairing neuronal function (Fang et al., 2016b). This notion was reinforced by another study, in which the absence of Opa1 and Mfn2 influenced the dynamics of mitochondria; fusion was inhibited and a fragmented network was observed. This impacted neurogenesis and cognitive function. The self-renewal capacity of NSCs was suppressed and differentiation was promoted by nuclear factor erythroid 2-related factor 2 (NRF2), due to increased ROS (superoxide anion) levels (Khacho et al., 2016). Therefore, mitochondrial fusion is essential to sustain the self-renewal capacity of NSCs and for the proper function and morphology of mature neurons.

Compromising mitochondrial fission also affects the development of neurons. The first evidence came from primary hippocampal neurons, where impaired mitochondrial fission (either by Drp1 or Opa1 knockdown) reduced the number of dendritic spines. It has been shown that proper distribution of mitochondria in neurons and in its protrusions is imperative for neuronal development and function (Li et al., 2004). Since then several studies have focused on the function of Drp1 in relation to neuronal development. Depletion of Drp1 in mouse embryos leads to their death at embryonic day 11.5–12.5. However, primary cultures from neuron specific Drp1 knockout mice revealed abnormal synapse formation and reduced neurite number due to aggregated mitochondria in the cell body and their inability of successful distribution to the processes (Ishihara et al., 2009). In addition, these animals exhibited aberrant forebrain and cerebellum development (Ishihara et al., 2009; Wakabayashi et al., 2009). Various studies suggest that the function of Drp1 may be cell type dependent. Depletion of Drp1 in mouse embryonic fibroblasts (Wang et al., 2014), as well as in Purkinje cells (Kageyama et al., 2012) and forebrain neurons (Ishihara et al., 2009), results in elongated mitochondrial network. However, granule neurons (Wakabayashi et al., 2009) and embryonic stem cells (Wang et al., 2014) display normal mitochondrial morphology; nevertheless, Drp1 is still required for neurogenesis under these circumstances. Inhibition of Drp1 in adult neural stem cells leads to defects in cell migration and failure of differentiation. The mitochondrial network loses its remodeling capability in these cells, which negatively impacts neuronal function and differentiation (Kim et al., 2015). Mitochondrial distribution also determines dendrite development; nonetheless, their effect in close proximity to the dendrites seems to be cell type specific. In Purkinje cells, blocking Drp1 function results in enlarged mitochondria and uneven energy dissemination. These cells are short and have underdeveloped dendritic branches (Fukumitsu et al., 2016). On the other hand, mitochondria inhibit dendritic branching in the pyramidal neurons of the mouse neocortex (Kimura and Murakami, 2014). Drp1 activity is also regulated through phosphorylation of Ser616. Depending on the kinase and cellular context, this can result in activation or inhibition of Drp1. In differentiating NSCs, CDK1 activates Drp1 and mitochondrial fission, boosting superoxide anion production at the same time. The upstream signal for this mechanism is thyroid hormone administration, which also induces the necessary metabolic switch for neuronal differentiation (Gothie et al., 2017). However, CDK1 is no longer present in post-mitotic, mature neurons. Instead, phosphorylation by CDK5 leads to inhibition of Drp1 and mitochondrial fission (Cho et al., 2014). Together, these data show the significance of the dynamic nature of mitochondria in neural differentiation. Mitochondria are elongated in the stem cells and mature neurons, but at the early stages of differentiation, they display a fragmented network, which is imperative for adequate neuronal development. Perturbing the balance towards either side (fusion or fission) will have detrimental consequences on the cognitive and regenerative behavior of NSCs.

Interestingly, loss of wolfram syndrome 1 (WFS1), an ER membrane localized protein, disturbs mitochondrial dynamics. $WFS1^{-/-}$ mice have smaller brains due to upregulated mitophagy in the developing neurons, which leads to fewer mitochondria number. This causes an energy deficit for the developing neurons, due to their high-energy demands. Importantly, this phenotype can be reversed by the inhibition of the main mitophagy regulators, PINK1 or Parkin (Cagalinec et al., 2016). It has been shown that PINK1 deficient mice also feature aberrant neuronal development. Adult hippocampal NSCs from these mice exhibit higher levels of glycolysis and abnormal differentiation (Agnihotri et al., 2017). Interestingly, another study found that PINK1 levels increase during development and loss of PINK1 causes defects in astrogliogenesis but not in neuronal development or self-renewal (Choi et al., 2016). These data demonstrate that not just the dynamics or function of mitochondria is of importance during neuronal development, but quality control is as well. Figure 2 provides an overview of the aforementioned mitochondrial processes and their changes during the differentiation of NSC, and Table 1 summarizes the genes, which link mitochondria to neuronal maturation.

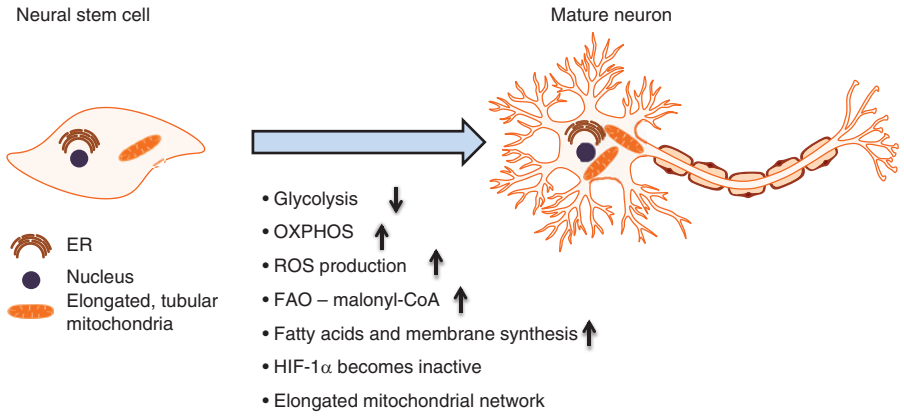

Figure 2: Changes in the main mitochondrial processes during neuronal development.
As the neuronal stem cell undergoes differentiation, a series of mitochondrial processes need to be altered. Glycolysis has to be downregulated, and OXPHOS has to serve as a major energy producing mechanism. This leads to increased reactive oxygen species (ROS) production. As the cell divides and grows, more fatty acids are needed for the synthesis of new membranes, therefore the amount of malonyl-CoA (which is the building block of fatty acids) increases in the cell; fatty acid oxidation (FAO) is also upregulated. In stem cells, HIF-1α (hypoxia-inducible factor 1α) is active and promotes glycolysis. During differentiation, HIF-1α is inhibited, in order to promote OXPHOS. In mature neurons, as well as in the stem cells, mitochondria form an elongated network. However, mitochondrial fragmentation is imperative for differentiation, as intermediate progenitor cells have a fragmented network, and this promotes the increase in ROS production as well.

Mitochondria and neuronal function

Mitochondrial TCA/OXPHOS and neuronal metabolic requirements

Neurons have disproportionately high-energy demands compared to other cell types. For instance, human brain neurons can consume as much as 20% of the organism's total daily energy production, despite comprising only about 2% of its total body mass. These unusual energy demands are imposed by neurotransmission and its associated cellular processes (maintenance of resting membrane potential, recovery of ion balance at post synaptic receptors, recovery after action potentials via Na^+ and Ca^{2+} pumping), as well as a series of other indirectly associated housekeeping processes (such as lipid and protein synthesis and turnover, vesicle transport, or microtubule and actin dynamics) (Harris et al., 2012; Engl and Attwell, 2015). These extensive energetic demands are primarily covered by ATP production through the TCA cycle and OXPHOS in the mitochondria (Hall et al., 2012).

Consequently, disorders that affect these pathways can be particularly impactful on neurons. For instance, diabetes, one of the most prominent metabolic diseases is associated with neuropathy of the peripheral nervous system (PNS) in over 50% of its patients (Fernyhough, 2015). This involves loss of unmyelinated and myelinated neural fibers (Malik et al., 2005; Christianson et al., 2007) with additional sensory loss, reduction in branch density, and defects in axonal regeneration and sprouting (Ebenezer et al., 2011). Mitochondria in diabetes exhibit reduced levels of TCA and ETC components, reduced respiratory activity and membrane depolarization (Chowdhury et al., 2010; Akude et al., 2011; Zhang et al., 2012). This is most likely a consequence of defunct PGC-1α and AMPK signaling, as experimental models of diabetes exhibit downregulation of these factors and their targets and their complete disruption enhances the diabetic neuropathy phenotype (Roy Chowdhury et al., 2012; Dugan et al., 2013; Choi et al., 2014). These defects force the neurons away from aerobic metabolism through OXPHOS and towards significantly less efficient methods of ATP production, such as glycolysis, and thus deny cells of the ATP they need to support their needs (Fernyhough, 2015). A similar metabolic switch is believed to occur in Parkinson's disease (PD) (Requejo-Aguilar and Bolanos, 2016). Another example is amyotrophic lateral sclerosis (ALS), a neurodegenerative disease associated with loss of motor neurons in the central nervous system (CNS) that can also be derived from abnormal energy metabolism (Tefera and Borges, 2016). Indeed mitochondrial respiration gene expression is altered in ALS patients and mouse models of the disease (Ferraiuolo et al., 2007; Lederer et al., 2007) while TCA anaplerosis via triheptanoin supplementation improves the motor functions of mouse carrying mutant human superoxide dismutase 1 (SOD1) (the protein that is considered primarily responsible for ALS) (Tefera et al., 2016). Additionally, in Huntington's disease (HD), a neurodegenerative disorder associated with loss

Table 1: Key proteins that regulate mitochondria in neuronal development.

Protein	Function	Reference(s)
HK2 (hexokinase 2)	Outer mitochondrial membrane protein; phosphorylates glucose	Zheng et al., 2016
LDHA (lactate dehydrogenase)	Converts pyruvate to lactate	Zheng et al., 2016
PKM (pyruvate kinase M)	Produces pyruvate from phosphoenolpyruvate. PKM1 is expressed in neurons, while neuronal stem cells express PKM2	Yeo et al., 2013; Zheng et al., 2016; Su et al., 2017
HIF-1α (hypoxia-inducible factor-1α)	Transcription factor, promotes the expression of glycolytic genes	Pereira et al., 2013; Shyh-Chang et al., 2013; Li et al., 2014; Lange et al., 2016
TFAM (mitochondrial transcription factor A)	Transcription factor; also required for mitochondrial genome replication	Beckervordersandforth et al., 2017
FOXOs (forkhead box O transcription factors)	Transcription factors; promote the expression of ROS scavenging enzymes	Paik et al., 2009; Renault et al., 2009; Yeo et al., 2013
Prdm16 (PR domain containing 16)	Zinc finger transcription factor; required for neuronal differentiation	Inoue et al., 2017
PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-α)	Transcriptional coactivator; crucial for mitochondrial biogenesis	Vaarmann et al., 2016; Inoue et al., 2017
Fasn (fatty acid synthase)	Promotes synthesis of fatty acids	Chorna et al., 2013; Knobloch et al., 2013
Mfn1,2 (mitofusin 1,2)	GTPases; essential for outer mitochondrial membrane fusion	Fang et al., 2016b; Khacho et al., 2016
Opa1 (optic atrophy 1)	GTPase; required for inner mitochondria membrane fusion	Khacho et al., 2016
Drp1 (dynamin related protein 1)	GTPase; facilitates mitochondrial fission	Li et al., 2004; Ishihara et al., 2009; Wakabayashi et al., 2009; Kageyama et al., 2012; Cho et al., 2014; Kimura and Murakami, 2014; Wang et al., 2014; Kim et al., 2015; Fukumitsu et al., 2016; Gothie et al., 2017
WFS1 (wolfram syndrome 1)	ER localized protein; regulates cellular Ca^{2+} homeostasis and contributes to mitochondrial fission	Cagalinec et al., 2016
PINK1 (PTEN-induced putative kinase 1)	Serine/threonine protein kinase; activates Parkin and promotes mitophagy	Cagalinec et al., 2016; Choi et al., 2016; Agnihotri et al., 2017
Parkin (Parkinson juvenile disease protein 2)	E3 ubiquitin ligase; ubiquitylates outer mitochondrial membrane proteins and activates mitophagy	Cagalinec et al., 2016

of striatal GABAergic neurons due to abnormal polyglutamine expansion at the N-terminal end of the Huntingtin protein (Htt), patients exhibit reduced expression of components of complex II of the ETC, while artificial expression of mutant Htt in striatal neurons reproduces this change in expression (Benchoua et al., 2006). Finally, reduced ATP production can be observed in Alzheimer's disease (AD) mouse models (Zhang et al., 2015). It is worth noting that mitochondria transport inside neurons is partially impeded by high ADP levels, causing the organelles to occupy more time at areas of increased ATP consumption (Mironov, 2007, 2009).

In addition to ATP, the mitochondrial metabolic pathways contribute other molecules of great functional relevance to the neurons. For instance some of the intermediates that are produced by the TCA are used in the synthesis of the neurotransmitters GABA and glutamate (Nunnari and Suomalainen, 2012). Furthermore, ROS, a common byproduct of OXPHOS, can act as regulatory signals that can regulate neuron excitability. For example, hydrogen peroxide regulates membrane hyperpolarization through K_{ATP} channels in dopaminergic neurons (Avshalumov et al., 2005). Superoxide regulates synaptic plasticity by inducing the activity of CaMKII, PKA and PKC (Kim et al., 2011). Both types of ROS are suggested to affect axon myelination by neighboring oligodendrocytes via the induction of post-translational modifications in myelin proteins (Atkins and Sweatt, 1999).

Mitochondria and neuronal calcium regulation

Another major way in which mitochondria contribute to proper neuronal function is their involvement in Ca^{2+} homeostasis. Ca^{2+} is a secondary messenger of critical importance to the regulation of eukaryotic cell processes. Its role is particularly significant in neurons, where it can control synaptic vesicle release via synaptotagmin, or facilitate long-term changes in post-synaptic neuron response (in the form of Long Term Potentiation or Long Term Depression) by activating enzymes such as CaMKII or changing the activity of transcriptional factors such as CREB or DREAM (Brini et al., 2014). Mitochondria often localize close to areas of high Ca^{2+} concentration in the cell such as the ER or the plasma membrane and can quickly import significant quantities of the ion into their matrix (Young et al., 2008; Rizzuto et al., 2012) (Figure 3A). The transport is facilitated by the electrochemical proton gradient that also drives ATP production, and utilizes voltage-dependent anion channels (VDACs) in the OMM (Rapizzi et al., 2002; Tan and Colombini, 2007) and the mitochondrial Ca^{2+} uniporter (MCU) in the inner one (Baughman et al., 2011; De Stefani et al., 2011). The stored Ca^{2+} can be released via ion exchange through the Na^+/Ca^{2+} exchanger NCLX (Palty et al., 2010) or through the mitochondrial permeability transition pore (PTP) (Elrod et al., 2010; Barsukova et al., 2011). LETM1, a more recently discovered inner membrane Ca^{2+}/H^+ exchanger,

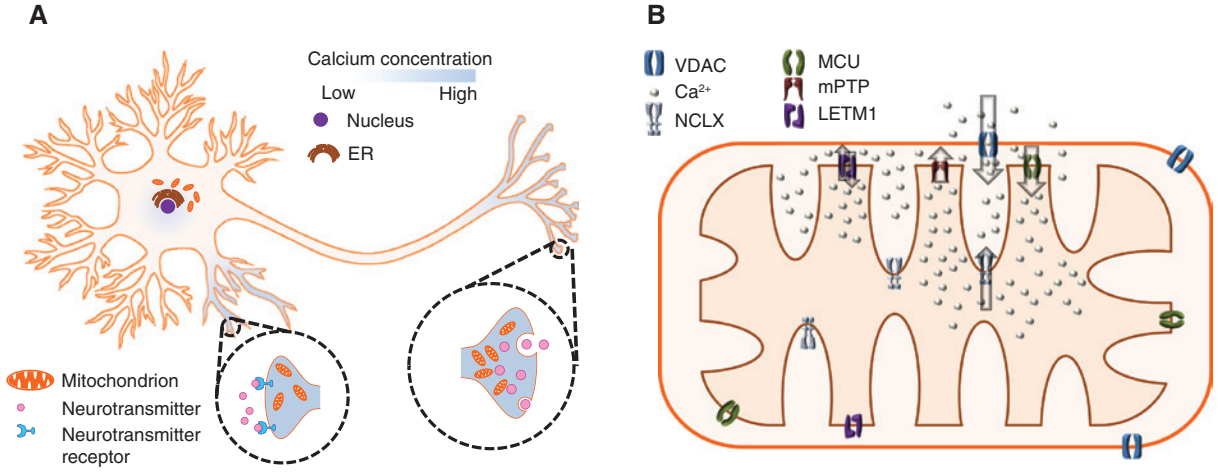

Figure 3: Mitochondria contribute to Ca^{2+} homeostasis.
(A) Mitochondria localize to areas of high Ca^{2+} concentration, such as close to the ER and nucleus or at pre- and post-synaptic terminals, to assist in regulating its levels. This affects neurotransmission by controlling the rate of pre-synaptic transmitter release and reuptake, by altering the response of post-synaptic terminals, or even by inducing transcriptional changes at the nucleus. (B) Mitochondrial Ca^{2+} transport channels. Ca^{2+} can enter the mitochondria through voltage-dependent anion channels (VDAC), the mitochondrial Ca^{2+} uniporter (MCU) and the Ca^{2+}/H^+ exchanger LETM1. It can be released through the mitochondrial permeability transition pore (mPTP), the Na^+/Ca^{2+} exchanger NCLX and LETM1.

is involved in both Ca^{2+} import and export (Doonan et al., 2014) (Figure 3B). Mitochondria can utilize all these channels to greatly affect local Ca^{2+} concentration and thus modulate neuronal processes. For instance, in retinal amacrine neurons mitochondria act as Ca^{2+} buffers that prevent the inactivation of presynaptic Ca^{2+} channels, thus ensuring normal signal transmission (Medler and Gleason, 2002). Disruption of mitochondrial Ca^{2+} storage in rats reduces neurotransmitter release in the calyx of Held (Billups and Forsythe, 2002). Mitochondrial Ca^{2+} uptake in mouse motor neurons is required for neurotransmission to muscle fibers to remain phasic, and for proper synaptic plasticity (disrupting it turns LTP into LTD) (David and Barrett, 2003). It is also necessary for neuronal plasticity in the spinal cords of mice (Kim et al., 2011). In the mouse olfactory bulb, mitochondria shape olfactory sensory neuron Ca^{2+} dynamics and are necessary for OSNs to be able to distinguish stimulus intensity (Fluegge et al., 2012). Recent findings suggest that mitochondrial Ca^{2+} regulation affects the rate of synaptic vesicle endocytosis after transmission (Marland et al., 2016). Finally, mitochondrial Ca^{2+} control has implications in general neuron survival, as it is connected with apoptotic and necrotic pathways (Nagley et al., 2010). For example, glutamate excitotoxicity is attributed to excessive Ca^{2+} through the NMDA receptor channel that, as the cell's ways to extrude Ca^{2+} gradually fail (Bano et al., 2005), causes Ca^{2+} overload in the mitochondria, triggering a series of events that leads to neuronal death (Nicholls, 2009).

Mitochondria localization can be directly affected by intracellular Ca^{2+} levels, as the adaptor protein Miro possesses EF-hands domain that can directly bind Ca^{2+}, thus inducing detaching of the organelles from the microtubule and stopping transport (Sheng and Cai, 2012). In this way, mitochondria can localize in high activity areas of the neuron, and mediate long-term changes in signaling behavior (Vaccaro et al., 2017). Abnormalities in mitochondrial Ca^{2+} regulation have been linked with neuronal disease. In ALS, disease model animals exhibit defective mitochondrial Ca^{2+} buffering (Son et al., 2008; Jaiswal and Keller, 2009; Jaiswal et al., 2009). SOD1, the primary ALS protein, can localize to the mitochondria, and in its mutant form disrupt their function (Ferri et al., 2006). ALS neurons are vulnerable to AMPA receptor mediated excitotoxicity, probably due to excessive Ca^{2+} levels (Carriedo et al., 2000; Guatteo et al., 2007). In HD, mitochondria are more prone to releasing Ca^{2+} via the PTP (Lim et al., 2008), due to direct interaction of mutant Htt with the organelles (Panov et al., 2002; Choo et al., 2004). NMDA receptor excitotoxicity is also observed in HD (Fan and Raymond, 2007). Double knock out of presenilins, major players in AD, in hippocampal mossy fibers has been demonstrated to block mitochondrial Ca^{2+} efflux (Lee et al., 2017). In PD, excessive intracellular Ca^{2+} import by L-type channels in dopaminergic substantia nigra neurons induces oxidative stress and mitochondrial uncoupling (Guzman et al., 2010). Defects in PINK1, a mitochondrial outer membrane kinase that is closely associated with PD, induce mitochondrial Ca^{2+} depletion and render cells vulnerable to Ca^{2+} induced cell death (Gautier et al., 2012). LETM1, previously associated with Wolf-Hirschhorn disease (Jiang et al., 2013), has recently been suggested as the mediator of Ca^{2+} deregulation under PINK1 loss (Huang et al., 2017). Mutations in LRRK2, another kinase associated with PD also alter mitochondrial Ca^{2+} dynamics (Verma et al., 2017).

Mitochondria and myelination

Mitochondria can contribute to proper neuronal function even from outside the actual neurons, by affecting the myelination of their axons. Myelin is a formation created by the plasma membrane of neighboring cells [oligodendrocytes in the CNS and Schwann cells (SCs) in the PNS], which encircles the majority of the neuronal axon surface. This encirclement changes the electrochemical properties of the axonal membrane and thus limits action potentials to only a few unmyelinated segments, known as the nodes of Ranvier. This causes accelerated neuronal conductance, compared to unmyelinated axons (Nave and Werner, 2014). There is significant evidence indicating that mitochondria exert a regulatory role in myelination by SCs in the PNS (Ino and Iino, 2017). Disruption of mitochondrial DNA transcription and replication by inhibiting TFAM in mice SCs leads to gradual axon demyelination and degeneration in the PNS, even though the SCs themselves survive normally (Viader et al., 2011). It was later shown that this is due to a shift in lipid metabolism that results in the depletion of necessary myelin constituents and the production and release of byproducts that are toxic to axons (Viader et al., 2013). Disrupting the formation of the mitochondrial cytochrome c oxidase (complex IV of the ETC) in SCs induced a similar phenotype (Funfschilling et al., 2012). Recently mitochondria were shown to be a part of a signaling cascade from neurons to SCs that is necessary for the proper development of the latter (Ino et al., 2015).

The involvement of mitochondria in PNS myelination is more evident when one considers the wide range of human disorders that exhibit a demyelinating neuropathy

Table 2: Proteins associated with mitochondrial regulation of neuronal function.

Protein	Function	Reference(s)
PGC-1α (peroxisome proliferator-activated receptor-gamma co-activator 1α)	Transcriptional regulator of mitochondrial biogenesis	Roy Chowdhury et al., 2012; Choi et al., 2014
AMPK (adenosine monophosphate-activated protein kinase)	Ser/Thr kinase regulated by energy sensing (activated by binding of AMP at high AMP/ATP ratio)	Roy Chowdhury et al., 2012; Dugan et al., 2013
SOD1 (Zn/Cu superoxide-dismutase 1)	Zn/Cu superoxide-dismutase, both cytosolic and mitochondrial localization	Ferraiuolo et al., 2007; Lederer et al., 2007; Tefera et al., 2016
ETC Complex II (Fp, Ip, SDH-D, SDH-C)	Components of the tricarboxylic acid cycle and the mitochondrial respiratory chain	Benchoua et al., 2006
HTT (Huntigtin)	Unspecified	Panov et al., 2002; Choo et al., 2004; Benchoua et al., 2006
K_{ATP} channels	Plasma membrane K^+ channels primarily regulated bycytosolic ATP/ADP ratio	Avshalumov et al., 2005
CaMKII (Ca^{2+}/calmodulin-dependent protein kinase 2)	Ca^{2+} sensitive kinase associated with synaptic plasticity	Hongpaisan et al., 2004
PKA (c-AMP-dependent protein kinase A)	Ca^{2+} sensitive kinase associated with synaptic plasticity	Hongpaisan et al., 2004
PKC (Ca^{2+}/phospholipid-dependent protein kinase)	Ca^{2+} sensitive kinase associated with synaptic plasticity	Hongpaisan et al., 2004
CREB (cAMP response element-binding protein)	Plasticity associated transcription factor	Brini et al., 2014
Calsenilin/DREAM/KChIP3 protein	Neuronal Ca^{2+} sensor; transcriptional repressor	Brini et al., 2014
VDAC (voltage dependent anion channels)	Mitochondrial outer membrane ion channels	Rapizzi et al., 2002; Tan and Colombini, 2007
MCU (mitochondrial Ca^{2+} uniporter)	Mitochondrial inner membrane Ca^{2+} channel	Baughman et al., 2011; De Stefani et al., 2011
NCLX	Mitochondrial Na^+/Ca^{2+} exchanger	Palty et al., 2010
PTP (mitochondrial permeability transition pore)	Multifunctional mitochondrial inner membrane channel	Elrod et al., 2010; Barsukova et al., 2011
LETM1 (leucine zipper EF-hand containing transmembrane protein 1)	Mitochondrial inner membrane Ca^{2+}/H^+ exchanger	Doonan et al., 2014; Huang et al., 2017
Miro	Rho GTPase; adaptor of mitochondrial transport on microtubules	Sheng and Cai, 2012; Vaccaro et al., 2017
Presenilins	Components of intermembrane protease	Lee et al., 2017
PINK1 (phosphatase and tensin homolog-induced kinase 1)	Mitochondrial kinase; regulator of mitophagy	Gautier et al., 2012
LRRK2 (leucine-rich repeat kinase 2)	PD associated kinase	Verma et al., 2017
COX/complex IV/cytochrome c oxidase	Component of the tricarboxylic acid cycle and the mitochondrial respiratory chain	Funfschilling et al., 2012
AGC1 (aspartate-glutamate carrier isoform 1)	Mitochondrial Ca^{2+} stimulated aspartate/glutamate exchanger	Profilo et al., 2017
Cytochrome c	Component of ETC, caspase activator	Smith et al., 2008; Nagley et al., 2010
IAP (inhibitors of apoptosis) inhibitors: Smac/DIABLO and HtrA2/Omi	Proapoptotic factors that inhibit IAPs, permitting caspase activation	Smith et al., 2008; Nagley et al., 2010
BCL-2 family proteins	Key regulators of intrinsic apoptosis pathway	Youle and Strasser, 2008
Cyclophilin D	Regulator of mitochondrial permeability transition pore	Marshall and Baines, 2014
AIF (apoptosis inducing factor)	Mitochondria IMS factor involved in apoptosis (caspase independent) and parthanatos. Recruits the nuclease MIF (macrophage migration inhibitory factor) to genomic DNA	Wang et al., 2016

phenotype in the PNS and are associated with defects in genes associated with mitochondrial metabolism, regulation, maintenance or dynamics (Pareyson et al., 2013), especially in cases where mitochondrial abnormalities cannot be identified in the actual axons of the patients (Ino and Iino, 2017). Demyelinating variations of Charcot-Marie-Tooth disease are the most notable example of such disorders, and may be attributed to defects in mitochondrial fission in both neurons and SCs (Niemann et al., 2005, 2014). Disruption of SCs can provide an additional explanation for the aforementioned diabetic associated neuropathy (Mizisin et al., 2007; Ebenezer et al., 2011; Fernyhough, 2015).

In addition to their role in the PNS, there is growing evidence that mitochondria might also affect CNS myelination. Disruption of AGC1, a mitochondrial membrane transporter, prevents the production of N-acetylaspartate, a myelin precursor (Profilo et al., 2017). Lack of activation of the neuroprotective anticoagulant protein C in mice is associated with impaired mitochondrial function and CNS myelination (Wolter et al., 2016). Finally, there are some instances of leukoencephalopathy where mitochondrial mutations are linked with hypomyelination (Wong, 2012; Taft et al., 2013).

Mitochondria in neuronal cell death and survival

It is important to point out the contribution of mitochondria as core regulators of neuronal survival through their involvement in pathways that facilitate cell death. A variety of internal or external death triggers (for instance, ER stress, oxidative stress, ischemic injury, accumulation of toxic protein aggregates) are capable of also inducing the termination of a neuronal cell. These triggers activate signaling cascades that converge at the mitochondria and then re-diverge into one or more cell death pathways, depending on the type of trigger and the condition of the cell (Kroemer et al., 2009; Nagley et al., 2010). The most prominent example of this is the intrinsic apoptosis pathway, which involves the release of apoptogenic factors such as cytochrome c and the IAP inhibitors from the mitochondrial intermembrane space (IMS) to the cytosol, where they can act as activators of caspases (Smith et al., 2008; Nagley et al., 2010). This event is controlled by a complex network of pro- and anti-apoptotic proteins belonging to the Bcl-2 family (Youle and Strasser, 2008). Mitochondria are also associated with some non-apoptotic forms of cell death (Nakagawa et al., 2005). Necroptosis, a pathway involving TNFa, the kinases RIP1/RIPK1, RIP3/RIPK3 and the pseudokinase MLKL has been shown to occasionally (but not always) require the opening of the mitochondrial PTP and is attenuated by the loss of the transition regulator Cyclophilin-D (Marshall and Baines, 2014). Another pathway known as parthanatos involves the poly(ADP-ribose) polymerase-1 (PARP-1) induced release of the AIF from the mitochondrial IMS and its translocation to the nucleus, where it helps recruit the nuclease MIF (macrophage migration inhibitory factor) to cleave genomic DNA (Wang et al., 2016). A summary of all the genes that have been referenced in this section and link mitochondria to neuronal function is provided at Table 2.

Concluding remarks

The true extent of the importance mitochondria hold for neurons becomes more apparent when one considers the consequences of faults in the dynamic processes that mitochondria use to adapt to the cellular environment and preserve their proper function. Fully addressing this issue is beyond the scope of this review; however, we feel it is important to at least point out that defects in genes involved in mitochondrial fusion, fission, transport or mitophagy are intrinsically connected with neurodegenerative disease (Devine et al., 2016; Suarez-Rivero et al., 2016; Gao et al., 2017; Martinez-Vicente, 2017). Additionally, sometimes genes with previously known involvement in disease unexpectedly end up implicated in the regulation of mitochondrial dynamics (Moller et al., 2017; Pozo Devoto and Falzone, 2017).

Impaired mitochondrial dynamics in NSCs can drive different diseases. The severe cognitive dysfunction associated with Down syndrome was linked to defects in mitochondrial network in neural progenitors. These cells have higher levels of Drp1, coupled with low levels of Mfn2 and Opa1. Restoring the balance in dynamics in the mouse model of the disease improves neuronal function, which gives a possible, promising therapeutic intervention point in this genetic condition (Valenti et al., 2017). Increased mitochondrial fragmentation is present in cerebellar granule neuron precursors in medulloblastoma, which is a common pediatric brain tumor. Sonic hedgehog signaling initiates the upregulation of glycolysis in these cells and pushing the fatty acid metabolism balance towards synthesis. Restoring the expression of Mfn1 and 2 improves the phenotype of the disease: mitochondrial membrane potential and dynamics are recovered and malignant proliferation is decreased (Malhotra et al., 2016).

For every benefit mitochondria provide to neuronal cells, it seems that they also provide many points of failure, and this makes pinpointing the exact cause of each instance of disease difficult. What is more, as all the aforementioned systems are so closely entwined, it is most likely that one initial problem can give rise to several more. This inevitably makes phenotypes much more complex and reduces our ability to properly identify what is happening and intervene appropriately. Neuronal regeneration was initially thought to occur from stem cell pools. Intriguingly, two recent studies found that after olfactory epithelium injury, regeneration happens via dedifferentiation of neurons (Lin et al., 2017) and the activation of quiescent olfactory stem cells (Gadye et al., 2017), and both mechanisms require Sox2. These observations, however, do not consider the role of mitochondria and their need of plasticity in regenerative processes. It would, thus, be important to elucidate how and to what degree mitochondria play a role in different regenerative mechanisms in different parts of the nervous system.

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