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ORIGINAL ARTICLE

Mitochondria in Developmental and Adult Neurogenesis

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Abstract

Generation of new neurons is a tightly regulated process that involves several intrinsic and extrinsic factors. Among them, a metabolic switch from glycolysis to oxidative phosphorylation, together with mitochondrial remodeling, has emerged as crucial actors of neurogenesis. However, although accumulating data raise the importance of mitochondrial morphology and function in neural stem cell proliferation and differentiation during development, information regarding the contribution of mitochondria to adult neurogenesis processes remains limited. In the present review, we discuss recent evidence covering the importance of mitochondrial morphology, function, and energy metabolism in the regulation of neuronal development and adult neurogenesis, and their impact on memory processes.

Keywords Mitochondria · Neurons · Development · Adult neurogenesis

Introduction

The brain is a complex organ, both structurally and functionally, composed of diverse neuronal and glial cell types, which appear during the embryonic development of the central nervous system (CNS), a process known as developmental neurogenesis. Throughout the early stages of development, brain cells are generated in the embryonic neural tube from neural stem cells (NSCs), which expand their pool by symmetrical division. At the onset of neurogenesis, the division of progenitors becomes asymmetric, allowing the generation of neurons, astrocytes and oligodendrocytes, which together will give rise to a complex and functional neural circuitry (McConnell 1995; Rao and Mayer-Proschel 1997; Paridaen et al. 2014).

Until the early 2000s, the general theory was that neurogenesis started during development and stopped immediately after birth due to depletion of the NSCs. This classical view failed to hold up to increasing evidence that originated in 1965 with the discovery of newly generated dentate granule cells (DGCs) in the adult mammalian brain (Altman and Das 1965) and have accumulated during the 1990s (Kaplan and Hinds 1977; Gross 2000). The generation of new neurons during adult life was thus defined as adult neurogenesis. In mammals, adult neurogenesis has now been undoubtedly detected in the subventricular zone (SVZ), from which neurons migrate to the olfactory bulb, and the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) (Eriksson et al. 1998; Alvarez-Buylla and Garcia-Verdugo 2002). Within a few weeks in the mouse brain, adult-born neurons acquire mature morphological and functional properties (Kempermann et al. 1997; Taupin 2007), rendering them indistinguishable from any other mature neuron (Song et al. 2012). It is now well documented that adult-born neurons integrate existing neural circuits and establish functional synaptic connections through which they participate in several cerebral functions. The ability of new neurons to connect to pre-existing neurons and rewire parts of the brain constitutes a form of neuronal

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plasticity which is particularly crucial in the hippocampus where it contributes to hippocampal-dependent memory processes (Kee et al. 2007; Aimone et al. 2011; Gu et al. 2012). As such, adult neurogenesis may provide a reservoir of plasticity that could be used in pathological contexts, such as memory impairment in Alzheimer's disease (Krezymon et al. 2013).

Neuronal activity and plasticity are based on the maintenance of membrane potentials, which conditions synaptic transmission, as well as on spine formation and pruning, signaling mechanisms and vesicular trafficking. All these phenomena require huge amounts of ATP and a tight regulation of cellular homeostasis (Vos et al. 2010; Flippo and Strack 2017). In the CNS, most of the ATP is produced by oxidative metabolism within mitochondria, through a complex oxidative phosphorylation (OxPhos) of substrates (mainly NADH in neurons), while only 10% relies on glycolysis within the cytoplasm (Rolfe and Brown 1997; Raefsky and Mattson 2017). Briefly, OxPhos is driven by the inner membrane respiratory complexes, mostly composed of nuclear genome encoded-proteins. However, 13 of them are directly encoded by the mitochondrial DNA (mtDNA), whose integrity is thus crucial for proper mitochondrial function (El-Hattab et al. 2017). OxPhos is based on an electron transport chain, ending with oxygen, coupled to an active pumping of protons from the mitochondrial matrix to the intermembrane space. This gradient provides the energy that enables activation of ATP synthase, ensuring ATP production. Moreover, mitochondrial respiration is accompanied by superoxide anion (O_2^-) production, due to oxygen reduction. Overall, O_2^- is dismuted into hydrogen peroxide (H_2O_2), mainly by superoxide dismutase 2 (SOD2) in the mitochondria or by superoxide dismutase 1 (SOD1) in the cytosol and the mitochondrial intermembrane space. In healthy cells, low levels of reactive oxygen species (ROS) are required for various signaling pathways (Ray et al. 2012), and the balance between ROS production and ROS scavenging must thus be highly regulated. An increase in net ROS generation exceeding the antioxidant scavenging capacity is defined as oxidative stress, a hallmark of most neurodegenerative diseases (Espinet et al. 2015), leading to lipid peroxidation, oxidation of proteins, and DNA damage (Buhlman 2017; Plotegher and Duchen 2017).

In addition to their historical role as energy-generating organelles, mitochondria are now viewed as central hubs or signaling platforms that control and integrate several cellular processes, including proliferation, differentiation, migration, and survival. Consequently, within cells, mitochondria work as a system that adapts to environmental changes by controlling their number, shape and functions. These adaptive properties are particularly important for CNS neuronal networks. Furthermore, mitochondria are submitted to quality control processes that guarantee the fulfillment of all their functions. Particularly important in long-lived post-mitotic cells such as neurons, this mitochondrial quality control is achieved by complementary processes aiming at renewing the pool by biogenesis as well as repairing or removing damaged mitochondria. Altogether, the latter imply local action of mitochondrial chaperones, proteases, ROS scavengers, formation of mitochondrial-derived vesicles that direct distinct and damaged mitochondrial cargos for degradation in the lysosomes, and selective removal of damaged or excessive mitochondria by specific autophagy, i.e., mitophagy (Kotiadis et al. 2014).

Moreover, neurons, as polarized cells possessing a complex morphology, require mitochondria to migrate in order to populate specific neuronal compartments and support complex neuronal functions. This leads to highly orchestrated bi-directional moves and pauses along microtubules and the actin cytoskeleton (Saxton and Hollenbeck 2012; Schwarz 2013; Sheng 2014; Bertholet et al. 2016). Microtubule-based mitochondrial transport is driven by kinesin and dynein motors for anterograde and retrograde movements, respectively, whereas myosin motors are responsible for the movement of mitochondria along actin filaments. The latter allows their distribution in presynaptic boutons and axonal terminals, where metabolic and calcium homeostatic capacities are highly demanded.

One of the adaptive features of mitochondria is their long-known striking variability in shape. This morphological plasticity relies on two antagonist machineries mainly composed, on one hand, of mitofusins 1 and 2 (MFN1/2) and optic atrophy protein (OPA1) proteins involved in the fusion process, while the dynamin-related protein 1 (DRP1) is responsible for mitochondrial fission (Bertholet et al. 2016). Thus, the equilibrium between these two processes, i.e., mitochondrial dynamics, directly controls mitochondrial morphology, participating in the immediate adaptation of the organelles to energetic needs, and influences the transport of mitochondria in neurons as well as their functions (Chang et al. 2006; Baloh et al. 2007; Arnold et al. 2011; Bertholet et al. 2013). Finally, this balance has a direct impact on mitochondrial quality control: fission of mitochondria favors mitophagy and fusion leads to complementation between damaged and undamaged mitochondria (Galloway et al. 2012; Haroon and Vermulst 2016).

While numerous data accumulated in the last decade showing that many neural functions rely on mitochondria (Kann and Kovács 2007; Raefsky and Mattson 2017; Todorova and Blokland 2017), their role in neuronal development and adult neurogenesis has only recently been the focus of several emergent and interesting studies (Xavier et al. 2016; Knobloch and Jessberger 2017; Beckervordersandforth et al. 2017; Khacho et al. 2017). Herein, after introducing their role in stem cell state transition, we review mitochondrial functions in embryonic and adult neurogenesis, unraveling their impact in adult hippocampal neurogenesis-dependent processes, like memory and learning.

Mitochondria in Stem Cell Self-Renewal, Differentiation, and Reprogramming

Increasing number of studies in embryonic stem cells (ESC) as well as in reprogrammed induced pluripotent stem cells (iPSC) have demonstrated that mitochondria have a critical role in cell state maintenance and transition, not only through metabolism and ROS signaling but also biogenesis, mitochondrial dynamics and mitophagy.

Unambiguously, ESCs are characterized by a high activity of glycolytic enzymes accompanied by a low mitochondrial biomass and mtDNA content (Facucho-Oliveira and St. John 2009). This maintenance of a glycolytic state protects from oxidative damages and contributes to differentiation blockade (Chen et al. 2008; Van Blerkom 2011). Reciprocally, differentiation of pluripotent ESCs into specific cell types is controlled by the balance between glycolytic and respiratory metabolism as well as mtDNA replication, together with an increase in the mitochondrial biogenesis co-activator peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) (Facucho-Oliveira et al. 2007; Chen et al. 2010; Folmes and Terzic 2014; Maryanovich et al. 2015; O'Brien et al. 2015; Noguchi and Kasahara 2017; Chen and Chan 2017). Altogether, differentiation is thus associated with mitochondrial maturation, the switch to oxidative phosphorylation better fitting the high-energy demand of differentiating cells (Chen et al. 2010). Consequently, inhibition of mitochondrial respiration leads to the impairment of differentiation and the enhancement of stem cell pluripotency (Varum et al. 2009). Furthermore, either repression of oxidative metabolism or glycolysis activation are obligatory steps for the reprogramming of somatic cells into iPSCs (Armstrong et al. 2010; Prigione et al. 2010; Folmes et al. 2012).

Aside from increased oxidative phosphorylation, differentiation is characterized by an upregulation of mitochondrial biomass and mtDNA, together with improved respiration capacity (Vayssière et al. 1992). The resulting increase in ROS production should render mtDNA vulnerable to oxidation damage, potentially affecting the differentiation process since mtDNA integrity is essential for the mitochondrial maturation that occurs during differentiation of NSC (Wang et al. 2010). However, high levels of ROS are not persistent along the process because antioxidant enzymes are immediately upregulated to limit ROS production and to promote mitochondrial maturation (Cho et al. 2006; Chen et al. 2008, 2010).

Reversible metabolic adaptations of pluripotent and differentiated cells are concomitant with mitochondrial morphology changes and subjected to mitochondrial dynamics contingencies (Wilkerson and Sankar 2011; Wang et al. 2017). Indeed, the mitochondriome appears rather simple both in ESCs, hematopoietic stem cells and in iPSCs, with a limited number of perinuclear organelles with immature morphology, i.e., round elements containing little cristae. During differentiation, it gains structural maturity by becoming a complex network of elongated cristae-rich mitochondria with a dense matrix, while returning to an underdeveloped morphology during reprogramming (Folmes et al. 2011; Bukowiecki et al. 2014; Prieto et al. 2016a, 2016b). Interestingly, in an increasing number of studies, mitochondrial dynamics appear instrumental in state transition. Impairing fission through knock-down of DRP1 promotes ESC differentiation whereas overexpression of constitutively active DRP1 mutant, mimicking its mitotic phosphorylation-activated state, increases pluripotency (Son et al. 2013). Reciprocally, pharmacological inhibition of DRP1 was shown to cause loss of stem cell properties in the progeny cells (Katajisto et al. 2015). Moreover, DRP1 is required in somatic cell reprogramming to pluripotency in numerous studies (Vazquez-Martin et al. 2012; Son et al. 2013; Prieto et al. 2016a, 2016b) and impairments of mitochondrial fusion, by MFN1/2 depletion, increase reprogramming and maintenance of pluripotency, while facilitating the glycolytic metabolic transition (Son et al. 2015). On the other hand, impaired mitochondrial fusion in ESC, by MFN2 or OPA1 ablation, affects differentiation into cardiomyocytes (Kasahara et al. 2013). Moreover, MFN2 overexpression enhances mitochondrial bioenergetics and functions, and promotes iPSC differentiation to neurons, and their maturation, while MFN2 knock-out in iPSC results in deficits in mitochondrial metabolism and network, neurogenesis and synapse formation (Fang et al. 2016). However, contradictory results are bringing complexity in this duality: (i) DRP1 was shown dispensable for reprogramming and pluripotency maintenance (Wang et al. 2014), (ii) downregulation of the growth factor erv1 (like in ESCs)—that leads to increased DRP1 and fission levels—impairs pluripotency (Todd et al. 2010), (iii) DRP1-null ESCs maintain their proliferative capacity (Ishihara et al. 2009), and (iv) DRP1-mediated fission was also shown to be required for the myogenic differentiation of myoblasts (Kim et al. 2013), as well as for the terminal differentiation of ESCs in neuronal lineages (Wang et al. 2014). Altogether, these data suggest that a proper balance between mitochondrial fission-fusion is critical for ESC differentiation even if the relationship of mitochondrial dynamics to cell state is not straightforward.

The mitophagy process was recently shown to regulate ESC renewal as well as acquisition and maintenance of pluripotency (Liu et al. 2016). In canonical autophagy mutants (*atg3*$^{-/-}$) ESC, abnormal accumulation of mitochondria is indeed accompanied with both a decrease in clonogenic survival and in pluripotency gene expression, and with a delay in mitochondrial remodeling during embryonic body differentiation (Liu et al. 2016). Furthermore, mitophagy is key in the efficient reprogramming of somatic cells into iPSCs, since mitochondrial clearance facilitates the metabolic switch from

mitochondrial respiration to glycolysis (Ma et al. 2015; Xiang et al. 2017). In this case, the mitophagy process is driven, depending on the study, either by canonical autophagy (ATG3 and ATG5 dependent) involving the PINK-Parkin ubiquitin-mediated pathway or by non-canonical autophagy through ULK-1 and Rab9 pathway that may require outer mitochondrial membrane receptors like BNIP3L/Nix (Ma et al. 2015; Liu et al. 2016; Vazquez-Martin et al. 2016; Xiang et al. 2017).

Mitochondria in Developing Neurons

For many years, in vitro and in vivo data accumulated on the implication of mitochondria in the different stages of development of the nervous system, i.e., neural stem cells proliferation and differentiation into neurons as well as neuritogenesis and synaptogenesis.

The role of mitochondria during neurogenesis was first highlighted by the observation that mitochondrial content and respiration capacity increased during neuronal differentiation. Said process was prevented by inhibition of mitochondrial translation and shown to require both mtDNA integrity and accurate mitochondrial ATP synthesis (Vayssière et al. 1987; Vayssière et al. 1992; Wang et al. 2010, 2011; Oruganty-Das et al. 2012). Later studies further showed that neuronal differentiation is accompanied (1) by an increase in the expression of the master transcriptional regulators of mitochondrial biogenesis, peroxisome proliferator-activated receptor α (PPARα) and PGC1α, while inactivation of the latter affects dendritogenesis and synapogenesis and (2) by a metabolic switch from aerobic glycolysis in neural progenitor cell to neuronal oxidative phosphorylation (Agathocleous et al. 2012; O'Brien et al. 2015; Agostini et al. 2016; Cheng et al. 2012). This switch correlates with a decreased expression of both lactate dehydrogenase (LDHA) and hexokinase 2 (HK2). On the contrary, constitutive expression of LDHA or HK2 in neurons leads to cell death, indicating that a shutoff of aerobic glycolysis is essential for neuronal differentiation (Zheng et al. 2016). Interestingly, differentiation of glia-like central NSCs into neurons relies particularly on the integrity of the mitochondrial respiratory complex II. This was shown using an animal model with homozygous deletion of the succinate dehydrogenase subunit D gene restricted to cells of glial fibrillary acidic protein lineage, which displayed a lack of proper differentiation of glia-like central NSCs into neurons and oligodendrocytes (but not to astrocytes), leading to brain atrophy and early death (Díaz-Castro et al. 2015). Recently, Slack's team explored the consequences of severe impairments of mitochondrial functions on embryonic neurogenesis using conditional deletion of the mitochondrial oxidoreductase protein apotosis-inducing factor (*AIF*) in mouse (Khacho et al. 2017). The resulting dysfunctions of mitochondria (respiratory chain defects, aberrant mitochondrial fragmentation and increased ROS production) impair NSC self-renewal, neuronal progenitor proliferation and cell cycle exit, as well as neural differentiation. This leads to abnormal forebrain development with impaired cortical and hippocampal maturation.

As expected, mitochondrial dynamics also take part in neuronal development. First of all, inactivation of mitochondrial dynamics has been associated with impairments of dendritic, axonal and synaptic compartments. Embryonic brain specific MFN2 KO in mice leads to severe cerebellar defects related to alteration of dendritic outgrowth, axonal morphology and loss of Purkinje cell bodies (Chen et al. 2007). MFN2 dopaminergic (DA) neuron-specific knockout mice present severe loss of dopaminergic terminals in the striatum (Lee et al. 2012), whereas cell death of $MFN2^{-/-}$ DA neurons in the midbrain is evidenced later and through a retrograde degeneration (Pham et al. 2012). Embryonic neuron-specific deletion of DRP1 in mice leads to smaller forebrain or cerebellum associated with apoptosis induction or proliferation decrease respectively (Ishihara et al. 2009; Wakabayashi et al. 2009) and post-natal depletion of DRP1 in the forebrain leads to hippocampal atrophy (Shields et al. 2015; Oettinghaus et al. 2016). Moreover, both in primary neurons from these mice models and in wild-type neurons with mitochondrial dynamic imbalance, neuritogenesis, and synaptogenesis are affected. Downregulation of OPA1 in primary cortical neurons leads to dendritic and synaptic impairments (Bertholet et al. 2013). Inactivation of DRP1 in primary hippocampal or forebrain-cultured neurons is associated to decreases in neurite numbers, in levels of synaptic markers, in spines density, in synaptic vesicles recycling and in synaptic transmission (Li et al. 2004; Wang et al. 2009; Oettinghaus et al. 2016).

More recently, mitochondrial shaping has also been shown to regulate NSC renewal and fate. In the developing neural tube of chick and mouse embryos, we described that mitochondria undergo morphological reshaping, from small and round mitochondria in the mitotic population of the ventricular zone that become thick and short in interphase cells, while ending as a dense tubular network in differentiated neurons (Mils et al. 2015). In mouse embryonic cortex, however, mitochondrial morphology of NSC of the ventricular zone appears tubular, differing from the well-documented fragmented mitochondria of ESCs (Khacho et al. 2016). However, progression to a committed neuronal progenitor in the subventricular zone is accompanied by mitochondrial fragmentation while mitochondria regain an elongated phenotype in post-mitotic neurons (Khacho et al. 2016). Furthermore, this study suggests an ATP-independent upstream action of mitochondrial dynamics, since loss of OPA1 or MFN1/2 impaired NSC self-renewal by a mechanism involving a modest increase in ROS, which act as physiological signaling molecules inducing the expression of genes that inhibit self-renewal, as the Notch-inhibitor Botch, and promoting commitment

and differentiation (Khacho et al. 2016). Interestingly, this retrograde signaling involves NRF2, a master regulator of the anti-oxidant response. Nevertheless, knock-down of MFN2 was also shown to impair differentiation of human iPSC-derived cortical neurons leading to decreased dendritic length, synapses number and synaptic transmission (Fang et al. 2016). This correlates with fragmentation of mitochondria, reduced mitochondrial mobility, and decreased mitochondrial respiratory functions and ROS levels (Fang et al. 2016).

Mitochondria quality control also contributes to neuronal development. Mitophagy is involved in neurogenesis of retinal ganglion cells (RGC) from proliferating neuroblasts in the embryonic mouse retina (Esteban-Martínez et al. 2017). In this model, the mitophagy-dependent metabolic reprogramming is linked to hypoxia, which triggers activation of HIF-1 transcription factor and one of its targets, the mitophagy receptor BNIP3L/Nix, which mediates mitochondria engulfment within autophagosomes. Moreover, developmental mitophagy was evidenced in CRMP5-dependent dendritogenesis in brain (Brot et al. 2014).

Mitochondria as Key Regulators of Adult Neurogenesis

New neurons are also generated during adulthood and significantly contribute to neural network plasticity. In the adult hippocampus, functionally connected new neurons originate from quiescent neural stem cells through a developmental sequence that orchestrates extensive changes in shape and activity of these cells. The contribution of mitochondria to the metabolic programs that underlie adult neurogenic processes recently started to be investigated (Steib et al. 2014; Beckervordersandforth et al. 2017). These studies demonstrated in mice that the development of adult-born neurons from stem cells is accompanied by extensive changes of mitochondrial biomass, distribution and shape (Steib et al. 2014; Beckervordersandforth et al. 2017). At the morphological level, mitochondria of hippocampal radial glia-like NSC present a mixed pattern of globular and tubular shapes, while they exhibit wider and highly elongated morphology in mature hippocampal neurons (Beckervordersandforth et al. 2017). Interestingly, the most profound changes in mitochondrial morphology and distribution were observed during the period of rapid dendritic growth and beginning of spinogenesis (Steib et al. 2014). Going further, mitochondrial remodeling along neuronal differentiation is paralleled by developmental stage-specific metabolic adaptations. Thus, from its earliest stages, adult hippocampal neurogenesis appears to critically depend on oxidative phosphorylation (Beckervordersandforth et al. 2017). Altogether, these studies provided key evidence for the central regulatory function of mitochondria in efficient lineage progression of adult neural stem cells. Accordingly, embryonic defects in mitochondrial functions through *AIF* disruption in mice impact maintenance of adult neural stem cells and ongoing neurogenesis within the adult DG (Khacho et al. 2017).

Moreover, Steib et al. (Steib et al. 2014) reported that inhibition of mitochondrial fission and distribution, mediated by dominant negative DRP1 (dnDRP1) expression in precursor cells, strongly impacts the viability and the maturation of adult-born neurons. Furthermore, physical exercise, a stimulus associated with increased mitochondrial biogenesis and accelerated neuronal maturation (van Praag 2005; Wright et al. 2007), was not able to fully prevent altered morphological development and impaired neuronal markers expression in the context of DRP1 loss of function. Indeed, under running conditions, the morphology of these dnDrp1-transduced cells remained that of immature neurons, with irregular dendritic growth and abnormal mitochondrial shape (Steib et al. 2014). Moreover, in these cells, the expression of the immature neuron-specific marker doublecortin (DCX) was greatly decreased. Conversely, overexpression of DRP1 in precursor cells accelerated running-induced neuronal maturation by increasing the tempo of dendrite growth and spinogenesis. Altogether, these data confirm that coordination of mitochondrial fission and distribution along dendrites with mitochondrial biogenesis is crucial for the stimulation of adult hippocampal neurogenesis. Mitochondrial fusion was also recently shown to be involved in adult NSC fate in mice (Khacho et al. 2016). Knockout of *MFN1/2* in NCS within the adult neurogenic niche resulted in a reduction in uncommitted ($SOX2^+$) cells in the SGZ of the adult DG and a decrease in DCX+ newborn neurons.

Very little is known about mitochondrial quality control in hippocampal adult-born neurons. A recent study, focusing on a genetic Parkinson's disease mouse model deficient in PINK1, reported mitochondrial defects associated with an impaired differentiation of NSC to neuroblasts in the dentate gyrus, as well as with a decrease in maturation of newborn neurons (Agnihotri et al. 2017).

Recent work in rodents showed that adult-born neurons, at their critical age (4- to 6-week old), play an important role in hippocampus-dependent memory. In particular, these new neurons contribute to complex forms of contextual knowledge and spatial relational memory (Sahay et al. 2011; Anacker and Hen 2017). In turn, the reduction of hippocampal neurogenesis that is observed during normal or pathological aging, may contribute to cognitive deficits. Accordingly, animals subjected to neurogenesis reduction display impaired capacities in hippocampal-dependent tasks such as fine discrimination pattern separation tasks (Clelland et al. 2009; Tronel et al. 2012; Nakashiba et al. 2012; Clemenson and Stark 2015). Conversely, an increase of hippocampal neurogenesis leads to pattern separation improvement (Creer et al. 2010; Sahay et al. 2011).

Since mitochondria are important organelles for neurogenesis and synaptic plasticity, modulation of their status in new neurons should translate into behavioral consequences, particularly regarding learning and memory performances.

Very recently, it was reported that mitochondrial activity, modeling and turn-over regulate memory processes. Disruption of mitochondrial dynamics in murine adult NSC through deletion of MFN1–2 within the adult neurogenic niche impaired hippocampus-dependent learning and memory (Khacho et al. 2016) as did global mitochondrial dysfunctions induced by the embryonic disruption of *AIF* (Khacho et al. 2017). Memory deficits were also previously reported in mice bearing DRP1 ablation in adult forebrain neurons (Oettinghaus et al. 2016; Shields et al. 2015). On the other hand, the team of G. Marsicano showed that acute cannabinoid-induced memory impairment in mice requires the activation of type-1 mitochondrial cannabinoid receptors (mtCB) (Hebert-Chatelain et al. 2014), which in turn decrease mitochondrial activity and neuronal energy metabolism (Bénard et al. 2012). Genetic ablation of mtCB prevents memory impairments (Hebert-Chatelain et al. 2016). Furthermore, in the hippocampus of aged rats, long-term exercise-induced improvement of cognitive function is associated with increased markers of mitochondrial dynamics and biogenesis but also markers of mitophagy process (Luo et al. 2017).

These recent findings confirmed the suggestions that were raised by previous studies (Fride et al. 1989; Martínez et al. 2000). In the past, Fride et al. (Fride et al. 1989) indeed demonstrated that formation of long-term memory required two phases of protein synthesis. The first one takes place in the cytoplasm and is initiated by training, while the second phase occurs in mitochondria and starts approximately 25 min after training onset, depending on newly formed mRNA (Fride et al. 1989). In addition, antioxidant diet delayed age-associated memory impairments in mice, probably by impacting mitochondrial bioenergetics action at synaptic terminals (Martínez et al. 2000).

In line with this, our recent work pointed out the crucial role of mitochondria from adult-born neurons for hippocampal-dependent memory (Richetin et al. 2017). In Alzheimer's disease (AD) patients (Jin et al. 2004; Crews et al. 2010) and in mouse models of the disease (Faure et al. 2011; Krezymon et al. 2013), it has consistently been reported that adult hippocampal neurogenesis is strongly impaired. Altered spinogenesis and connectivity of new neurons appears as a robust feature in the hippocampus of AD mouse models and could be responsible for the memory deficits reported in these animals. Supporting this idea, we demonstrated that overexpression of the pro-neural transcription factor Neurod1 into dividing NSC of AD mice in vivo, restores morphological development and synaptic integration of hippocampal new neurons, which was in turn, sufficient to abolish memory impairments in these animals (Richetin et al. 2015). Furthermore, we observed that mitochondria biogenesis and function were dramatically disturbed in hippocampal adult-born neurons of these AD mice, two features that were rescued upon Neurod1 overexpression (Richetin et al. 2017).

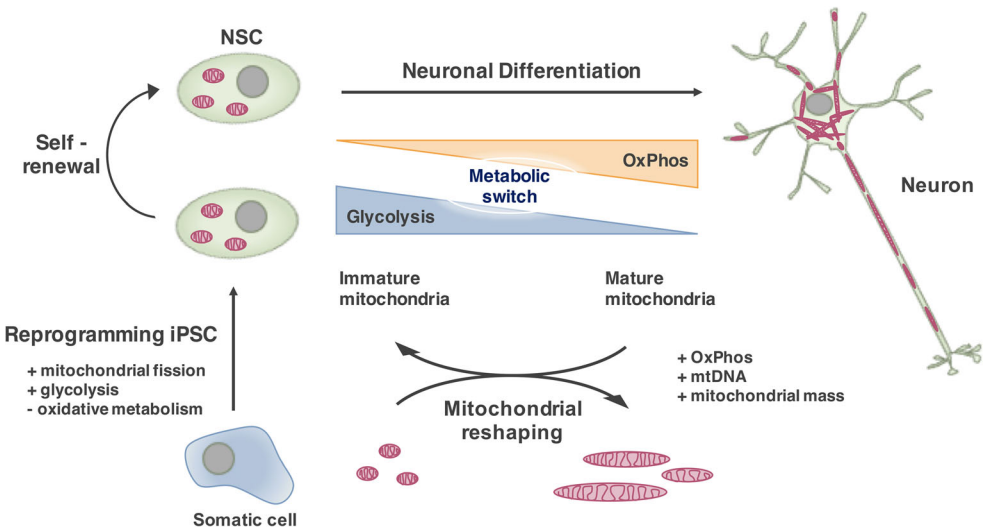

Fig. 1 Schematic representation of mitochondrial development along differentiation of NSC to neurons. Mitochondria in stem cells are smaller and functionally less mature compared with differentiated neurons, which are characterized by larger mitochondrial biomass and mtDNA as well as elongated mitochondria. The main source of energy in neurons depends on oxidative metabolism from mitochondria (OxPhos), while stem cells are characterized by a high activity of glycolytic enzymes, accompanied by a low mitochondrial biomass and DNA content. This metabolic switch between proliferative and differentiated states is also observed in iPSC reprogrammed from somatic cells

Conclusions and Futures Directions

Searching to integrate these newly observed complex organelles that were to be named mitochondria within the cellular theory, Lewis and Lewis asked, as soon as 1914: "are they concerned in the routine metabolism which takes place in all living cells or are they concerned with the process of differentiation of such structures as the myofibrillae, neurofibrillae, white fibrous tissue, etc…?" (Lewis and Lewis 1914). Long considered exclusively as the cells' powerhouses, mitochondria now appear as crucial in numbers of cellular processes. Although the growing number of mitochondria-related medical publications could be viewed to be due to increased fortuitous encounters with these pleiotropic organelles, a thorough survey definitely shows bona fide mitopathogenic mechanisms (Picard et al. 2016). The same is true in the field of developmental and adult neurogenesis. First, based on studies in stem cells self-renewal, differentiation and reprogramming, we have seen how crucial mitochondrial plasticity is during differentiation, tightly linking function and structure, in terms of mitochondrial reshaping, increased mass and mtDNA and, above all, a metabolic shift from glycolysis to oxidative phosphorylation (Fig. 1). Similarly, an increasing body of data now shows that neuronal differentiation depends on mitochondrial dynamics' contingencies, which, beyond energy supply, tightly link mitochondrial functions and structure (Fig. 1). Consequently, the central role for these organelles in adult neurogenesis and hippocampal-dependent memory formation and maintenance is of newly acknowledged significance. As a correlate of their wide-ranging functions, mitochondrial impairments have been systematically observed in neurodegenerative pathologies, whichever the targeted neuronal populations, and are associated with a large range of neurological and cognitive deficiencies (Itoh et al. 2013). An interesting and direct consequence is that manipulating mitochondrial content in adult-generated neurons could be used as a therapeutic strategy against neurodegenerative diseases associated with impaired synaptic transmission and cognitive functions.

In the future, we expect further demonstrations of the crucial role of mitochondria as signaling and integrative platforms, not only from their elective affinity for other organelles like the endoplasmic reticulum (Paillusson et al. 2016), or the puzzling communication with the nucleus, or from membranes and lipids exchanges (Dakik and Titorenko 2016) but also from the actual transfer of mitochondria from one cell type to another (Vignais et al. 2017). Occurring between astrocytes and neurons (Zhang and Yang 2018), such transports are a fascinating perspective of further understanding brain development and function.

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