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Mitochondrial support and local translation of mitochondrial proteins in synaptic plasticity and function

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Summary. Complex neural and brain functions are executed through structural and functional alterations of synapses and neurons. Neuronal compartmentalization requires neurons to allocate mitochondria and proteins in a spatiotemporal manner to allow their plasticity, function and homeostasis. Importantly, mitochondria are known to interact with and modulate synaptic activities through their ATP supply, calcium buffering and signaling abilities. Over the years, mitochondrial support and local translation (including mitochondrial proteins) at neuronal sub-compartments and their synaptic specializations have been considered critical for maintaining synaptic plasticity and function. Recently, evidence has shown that late endosomes can serve as sites for local translation of mRNAs crucial for mitochondrial integrity and mitochondrial compartments can fuel plasticity-induced local translation. Indeed, failed mitochondrial homeostasis and subsequent synaptic dysfunction are often intricately linked in the malfunction of the central nervous system in synaptic aging and diseases. In this review, I will discuss the critical role of local translation (including mitochondrial proteins) in dendrites, axons and synapses on neuronal/synaptic plasticity and function.

Key words: Mitochondria, Synapse, Neuron, Local translation, Biogenesis, Synaptic plasticity, Memory, Aging, Disease

Introduction

Brain functions including sensory perception, motor action, memory, sleep and emotion require the establishment, maintenance and adaptations of neural wiring. Neural wiring is executed through structural and functional plasticity of synapses that form the communication sites between neurons. Alterations in the strengthening or weakening of synapses in the brain with either increased or decreased synaptic activity (synaptic plasticity) are believed to represent the cellular mechanisms of learning and memory across most model organisms tested (Abbott and Nelson, 2000). Put differently, memory is believed to be stored in neuronal engrams, or specific subsets of synaptically connected, neuronal assemblies (Buzsaki, 2010; Poo et al., 2016).

Neurons are uniquely polarized and morphologically complex cells with extensive arborizations including axonal and dendritic compartments. This extreme structure of neurons poses an enormous challenge for the remodeling and homeostasis of proteome in different neuronal compartments. To safeguard the development, maintenance and homeostasis of neuronal sub-specializations, regulatory and controlling mechanisms must exist to control the trafficking and distribution of proteins and molecules to their precise sites of need in a spatial and temporal manner. It has been established that the long-distance movement of material (including organelles such as mitochondria, signaling endosomes, autophagosomes, lysosomes, mRNA granules and synaptic vesicle (SV) precursors) from the soma to presynapses (anterograde movement) and back (retrograde movement) is mainly conducted via the microtubule network and a set of motor proteins, namely dynein and kinesin (Guedes-Dias and Holzbaur, 2019). Besides, actin-based myosin motors are known to mediate short-range movement in neurons, especially in synapses (Quintero et al., 2009; Nirschl et al., 2017).

Neurons heavily rely on the essential organelle mitochondria and their trafficking to survive and perform, which is evidenced by the abundant mitochondria in neurons (Schwarz, 2013). Mitochondria are key metabolic double-membrane organelles that have the outer mitochondrial membrane (separating the mitochondrion from the cytosol) and inner mitochondrial

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membrane (separating the mitochondrial matrix from the intermembrane space). Glucose is the primary energy fuel, which is oxidized via glycolysis in the cytoplasm and oxidative phosphorylation (OXPHOS) in mitochondria to generate ATP. Static mitochondria operate as a local energy source. Motile mitochondria can become stationary or pause at metabolically active regions such as synaptic terminals, and growth cones (Sheng and Cai, 2012; Sheng, 2014). To date, the most analyzed process of mitochondrial dynamics in neurons is their trafficking along the microtubules (Schwarz, 2013; Mandal and Drerup, 2019). Mitochondrial dynamic processes refer to the distinct cell biological events, including biogenesis, turnover (via a specialized form of autophagy termed 'mitophagy'), fission and fusion and trafficking (Lee et al., 2018).

Indeed, mitochondria are dynamically regulated to change their distribution, morphology and function in response to synaptic activity that requires an array of metabolic adaptations (Rossi and Pekkurnaz, 2019). Activity-dependent regulation of mitochondrial plasticity is essential for synaptic plasticity, performance and homeostasis during both development and adulthood (Rossi and Pekkurnaz, 2019). Reciprocally, mitochondria have been shown to interact with and modulate synaptic activity by their ATP supply, calcium buffering and signaling abilities (Lee et al., 2018). Genetic or pharmacological attenuation of mitochondria has been shown to inhibit synaptic activity (Verstreken et al., 2005; Vos et al., 2010; Rangaraju et al., 2014; Pathak et al., 2015; Wong et al., 2019; Ashrafi et al., 2020). Furthermore, dysfunctional mitochondria have been implicated in compromised synaptic and neuronal function (Cai and Tammineni, 2017; Anagnostou and Hepple, 2020).

Notably, the importance of mitochondria is again stressed by their various mechanisms in powering the synapse (Rangaraju et al., 2019; Rossi and Pekkurnaz, 2019; Thomas et al., 2019). Burgeoning evidence has shown that mRNA localization and local translation, which represent the translation of mRNAs (including mitochondrial mRNAs) at axons, dendrites and synaptic terminals (Martin and Ephrussi, 2009; Holt and Schuman, 2013; Holt et al., 2019), might serve as a compensating mechanism in addition to the classic somatic translation and transport mechanism (Rangaraju et al., 2017; Fonkeu et al., 2019), and might play a pivotal role in synaptic plasticity and function. In effect, neurons overcome these distance constraints by distributing mRNAs locally to synapses and producing proteins there.

Finally, it has been increasingly recognized that mitochondria play an essential role in synaptic plasticity and mitochondrial dysfunction has been implicated in synaptic aging and neurodegenerative diseases. Strategies targeting the mitochondrial health, such as promoting mitochondrial biogenesis, function and homeostasis, might offer great therapeutical potential to synaptic and neural health.

The purpose of the review is to describe the important role of mitochondrial compartmentalization, morphology, distribution, movement and adaptation in matching the needs in different neuronal sub-compartments and how mitochondrial health and disease can modulate synaptic plasticity and function, and highlight that local translation (including local translation of mitochondrial proteins) is essential for the remodeling of dendritic/axonal and synaptic proteome and that mitochondrial compartments power plasticity-induced local translation.

Spatial compartmentalization and abundant mitochondria in neurons

Though constituting only 2% of the body mass, the brain uses around 20% of the oxygen consumption generated by the resting body in the human being (Mink et al., 1981). Thus, the brain must have evolved various bioenergetic mechanisms to adapt to an ever-changing environment, especially under conditions of high bioenergetic demands. Moreover, various brain functions depend on the functional and structural plasticity as well as the stability of neuronal processes (Sharma et al., 2013). Neurons are post-mitotic polarized cells that encompass extending neurites, namely axons and dendrites (neuropils) that constitute large parts of the cytoplasm. How neurons monitor the activity of different compartments and maintain their homeostasis are subject to complex regulatory and executive mechanisms. From a logistic perspective, neuronal compartmentalization places a formidable challenge for protein and organelle transport between the soma and axonal/dendritic areas.

Within these sub specializations in neurons, metabolic requirements and Ca^{2+} buffer demands constantly change in response to synaptic activity or homeostatic plasticity (Ohno et al., 2011). Indeed, most brain energy is known to be consumed at specialized contacts called synapses to maintain neuronal firing and synaptic neurotransmission (Harris et al., 2012; Howarth et al., 2012). Synaptic activities including synaptic transmission, firing action potentials, repeated processes of endocytosis and exocytosis and axonal growth and branching are arguably energetically the most expensive neuronal computations which pose an exceptional challenge for synaptic and neuronal maintenance, performance and plasticity. The synapse is the primary site of ATP consumption in the brain with mitochondrial OXPHOS supplying around 93% of the ATP generated, while cytoplasmic glycolysis generates only 7% of the ATP (Harris et al., 2012; Sheng, 2017). To reiterate, the mechanisms regulating synaptic plasticity are complex and multilayered and involve manifold cascades of molecular and cellular components that modulate synaptic efficacy (Baumgartel and Mansuy, 2012). Mitochondrial regulation has been shown, inter alia, to be one obvious and critical regulatory component in

modulating synaptic efficacy.

It is now clear that intact mitochondrial ATP production, together with calcium regulation, are crucial for proper synaptic function and neuroplasticity (Rangaraju et al., 2014; Vaccaro et al., 2017; Rossi and Pekkurnaz, 2019; Vanhauwaert et al., 2019). In line with their important role in neuronal performance, mitochondria are abundant in all neuronal compartments (Course and Wang, 2016; Rangaraju et al., 2019) with both motile and stationary pools of mitochondria (Sheng, 2014) (Fig. 1). Around 50% of the presynaptic terminal and dendritic length possess mitochondria (Shepherd and Harris, 1998; Li et al., 2004; Harris, 2020). Most synapses have motile mitochondria passing by to supply ATP spatiotemporally when there are no immotile mitochondria (Fig. 1); stationary mitochondria are often located at synapses for both rapid and repetitive neuronal firing (Li et al., 2004; Verstreken et al., 2005; Chang et al., 2006) (Fig. 1). At any given time, around 10-40% of mitochondria are on the move (Misgeld and Schwarz, 2017) (Fig. 1). Mitochondria move anterogradely and retrogradely, pause and reverse their direction frequently (Misgeld and Schwarz, 2017) (Fig. 1).

That said, neurons need to allocate and sustain mitochondria to provide ample energy and enough Ca^{2+} buffering capacity in their extensive arborizations to balance local autonomy and neuron-wide homeostasis. Although it is not fully understood how neurons use different mechanisms to establish and maintain an adequate distribution of healthy, functional mitochondria through their sub-compartments, a thorough picture is now emerging whereby mitochondria support synaptic activity, function and plasticity in various contexts.

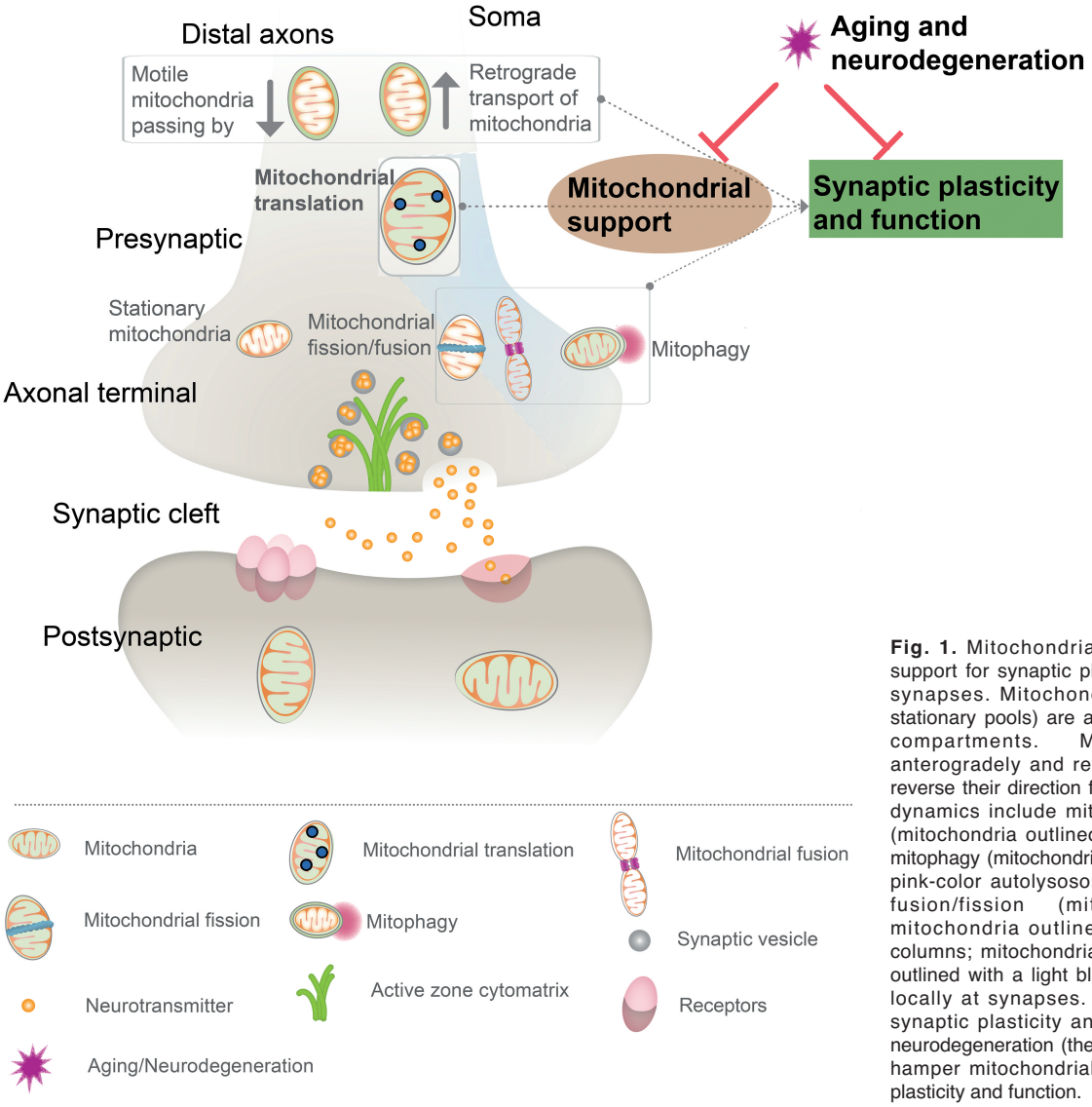

Fig. 1. Mitochondrial dynamics and their support for synaptic plasticity and function at synapses. Mitochondria (both motile and stationary pools) are abundant in all neuronal compartments. Mitochondria move anterogradely and retrogradely, pause and reverse their direction frequently. Mitochondrial dynamics include mitochondrial translation (mitochondria outlined with dark blue dots), mitophagy (mitochondria outlined with engulfed pink-color autolysosome) and mitochondrial fusion/fission (mitochondrial fusion: mitochondria outlined with two dark pink columns; mitochondrial fission: mitochondria outlined with a light blue belt) can also occur locally at synapses. Mitochondria support synaptic plasticity and function. Aging and neurodegeneration (the flash sign in dark pink) hamper mitochondrial support and synaptic plasticity and function.

Mitochondrial support in synaptic refinement, activity, function and plasticity

Mitochondria were described to reside at synaptic terminals of axons as early as 1956 in electron micrographs (Palay, 1956). Now it is clear that mitochondria are present at both the pre- and post-synapse (Chavan et al., 2015). To maintain normal neuronal circuits and synaptic physiology, mitochondria need to remain plastic and be appropriately remodeled and tailored in response to synaptic activity or homeostatic plasticity (Rossi and Pekkurnaz, 2019).

During development, mitochondria are indispensable for the correct establishment and refinement of axonal/dendritic compartments together with their synaptic specializations. In propagated axonal processes of chick sympathetic neurons, mitochondrial localization was highly skewed towards growth cones to support the high metabolic demand of their motile structures (Morris and Hollenbeck, 1993). In the assembly of presynaptic specializations in *Xenopus* spinal neurons, mitochondria are coclustered with SVs at the developing presynaptic specialization within minutes after spinal neurons are presented by synaptogenic stimulus, while inhibiting ATP synthase here blocks SV clusters induced by growth factor-coated beads, hinting at an essential role of mitochondrial ATP production in synaptogenesis (Lee and Peng, 2008). Moreover, mitochondrial activation of the caspase-3 apoptotic pathway was found to induce the pruning of dendritic spines in cultured hippocampal neurons (Erturk et al., 2014). Remarkably, a later study investigating the development of *C. elegans* RME neurons showed that caspase-3 (CED-3 as the homolog in *C. elegans*) and axonal mitochondria are also required for the removal of transient presynaptic structures (Meng et al., 2015). A recent study showed that mitochondria volumes and their synaptic localization elevate at the calyx of Held developmentally from immature postnatal day 7 to mature postnatal day 21 and might thus contribute to morphological and functional diversity at these auditory brainstem presynaptic terminals (Thomas et al., 2019). These findings suggested mitochondria may regulate the refinement of synapse connections.

During adulthood, proper function and plasticity processes of mature synapses also require spatiotemporal mitochondrial adaptations. Optic synapses from the suprachiasmatic nucleus of rats exposed to constant light versus those under constant darkness exhibited larger boutons with larger mitochondria, as well as more and larger mitochondria in the postsynaptic dendrites (Guldner et al., 1997). Moreover, Perkins and colleagues found the mature calyx of Held encompasses anchoring mitochondria to the presynaptic membrane near active zones and the ratio of mitochondrial cristate to outer membrane surface area is larger compared to other tissues (Perkins et al., 2010). Perhaps connected to these findings, Smith and colleagues showed that mitochondria are selectively enriched at large boutons in hippocampal neurons and that presynaptic mitochondrial proximity and widened cristate support presynaptic vesicle mobilization by applying 3D electron microscopy (Smith et al., 2016). In line with this, mitochondrially derived ATP can be rapidly dispersed between boutons to support the SV cycle, especially endocytosis which requires high ATP demands (Rangaraju et al., 2014; Pathak et al., 2015). Furthermore, cultured motor neurons, whose neuromuscular-junction (NMJ) synapses are much larger than other neuronal synapses, were shown to exhibit higher synaptic and axonal mitochondrial immobility (Altman et al., 2019). Recently, the Sheng lab uncovered a mechanistic link between the energy signaling pathway and mitochondrial anchoring in maintaining presynaptic metabolism and prolonged synaptic efficacy (Li et al., 2020). Moreover, presynaptic mitochondria have been shown to buffer Ca^{2+} signals via several mitochondrial calcium uniporters and thus downregulate neurotransmission (Kwon et al., 2016; Vaccaro et al., 2017). Furthermore, mitochondrial reactive oxygen species have been identified as signaling molecules regulating the strength of inhibitory synaptic transmission (Accardi et al., 2014).

Thus, activity-dependent mitochondrial plasticity is critical at neuronal specializations during development and adulthood (Rossi and Pekkurnaz, 2019). While the mitochondrial adaptation and support for synaptic activity are obvious, how exactly molecular alterations in mitochondria are fine-tuned and how mitochondria communicate with other proteins/organelles deserve to be studied in detail and in various contexts.

Reciprocally, investigations delving into the interaction between modulating mitochondrial activity and function and synaptic plasticity and function at various systemic levels have been performed. Early experimental evidence already demonstrated that pharmacological inhibition of mitochondrial activity results in impaired synaptic potentiation and neurotransmission (Alnaes and Rahamimoff, 1975; Tang and Zucker, 1997; Rangaraju et al., 2014; Pathak et al., 2015; Ashrafi et al., 2020). To a similar degree, acute impediment of mitochondrial function during intense stimulation was found to depress synaptic transmission (Billups and Forsythe, 2002; Medler and Gleason, 2002), whereas the number and plasticity of spines and synapses are enhanced *in vitro* via pharmacological stimulation of mitochondrial respiration (Li et al., 2004). Notably, genetic studies showed that depleting mitochondria from axonal and presynaptic terminals impairs synaptic transmission (Stowers et al., 2002; Verstreken et al., 2005; Sun et al., 2013). Recently, depletion of local mitochondria by optogenetical killerRed-photostimulation was shown to eliminate synaptic plasticity and the stimulus-induced synaptic translation (Rangaraju et al., 2019).

Taken together, these experiments suggest mitochondria not only adapt in response to synaptic activity, but also modulate and regulate synaptic function (Fig. 1). Thus, mitochondrial plasticity is obviously

tailored to match the need of synaptic activity (Rossi and Pekkurnaz, 2019). However, these findings also raised key questions as to whether the biosynthesis capacity of the cell body and the dynamics and rate of mitochondrial trafficking suffice to supply all peripheral mitochondrial compartments. Furthermore, what generic as well as specific principles might govern mitochondrial distribution, size and activity to prepare them for urgent needs in neuronal sub-compartments? Indeed, neurons not only use a sophisticated molecular machinery to transport mitochondria and anchor them in synapses and axons/dendrites (Sheng, 2014), but also employ local translation mechanisms likely for rapid needs in response to synaptic activity or homeostatic plasticity (Rangaraju et al., 2017; Biever et al., 2019).

Local translation (including mitochondrial translation) essential for the remodeling of dendritic/axonal and synaptic proteome: matching the specific needs in different neuronal sub-compartments

A fundamental question in neuroscience has been how the high bioenergetics demands at axons and dendrites together with their synaptic specializations in neurons can be met in a spatiotemporal manner to confer synaptic plasticity, maintenance and performance. All neuronal compartments require ATP. Thus, mitochondria must be properly trafficked and positioned along the axons and dendrites to power energy-consuming sites (Misgeld and Schwarz, 2017) (Fig. 2). Different physical and spatial restrictions in different neuronal compartments require mitochondria to be extremely plastic structurally. In fact, mitochondria exhibit distinct distributions and morphologies in the two main neuronal sub-specializations: the axons and dendrites (Fischer et al., 2018; Lee et al., 2018). In pyramidal neurons, dendritic mitochondria exhibit a long and tubular shape, forming a complex network occupying around 70% of the dendritic compartment, whereas axonal mitochondria are smaller, likely due to spatial restrictions and fill less than 10% of axonal volume (Kasthuri et al., 2015; Lee et al., 2018).

The synthesis, degradation and homeostasis of synaptic (mitochondrial) proteins are vital for synaptic function (Liang and Sigrist, 2018; Dorrbaum et al., 2020). Thus, a balanced action between mitochondrial protein biogenesis and mitophagy must be achieved (Misgeld and Schwarz, 2017). In fact, several groups using the SILAC- and mass-spectrometry-based proteomics found that most mitochondrial proteins are among the long-lived proteins (Cohen et al., 2013; Chan et al., 2015; Dorrbaum et al., 2018; Mathieson et al., 2018). However, it has also been shown that mitochondria and their proteins have cell-type- and tissue-specific rates of turnover (Kruse et al., 2016; Harbauer, 2017; Dorrbaum et al., 2018). Moreover, the turnover of mitochondrial proteins in specific compartments within different neuronal cell types remains largely unclear. It is now clear that mitophagy can occur locally in response to acute damage (Ashrafi et al., 2014; Ebrahimi-Fakhari et al., 2016; Palikaras and Tavernarakis, 2020) (Fig. 1). In addition to removing dysfunctional synaptic components (Liang, 2019), replenishing synapses with new proteins and/or organelles is critical for maintaining synaptic homeostasis. Mitophagy eliminates aged and dysfunctional mitochondria (Gottlieb and Stotland, 2015) and is tightly coupled to mitochondrial fusion and fission and mitochondrial biogenesis (Ashrafi and Schwarz, 2013; Misgeld and Schwarz, 2017; Pickles et al., 2018) (Fig. 1).

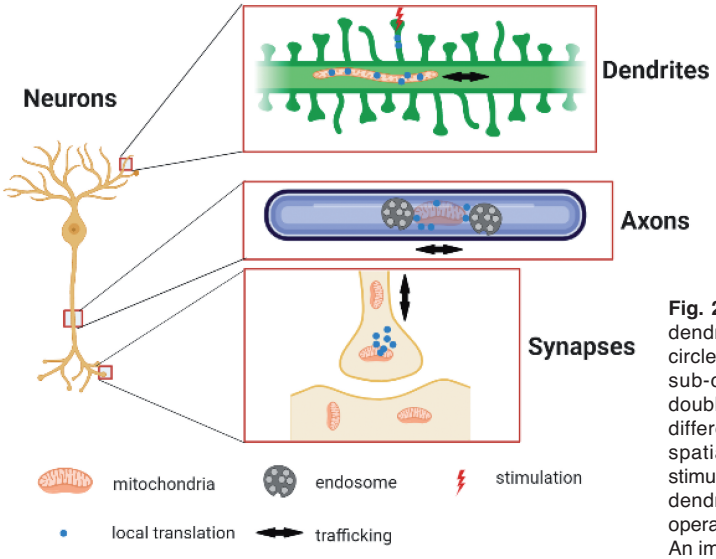

Fig. 2. Local translation and mitochondrial support for synaptic plasticity in dendrites, axons and synapses. Local translation (in blue, outlined in a circle within dendrites, axons and synapses) exists in different neuronal sub-compartments. Mitochondrial trafficking (in black, outlined in the double-sided arrow) happens frequently to match the specific needs in different neuronal specializations. Mitochondrial compartments serve as spatially (but not remote) confined energy reserves for plasticity and stimulation-induced (in red, outlined in the flash sign) synaptic translation in dendrites. Late endosomes (in gray, outlined in the oval-shaped frame) operate as local mRNA translation sites and sustain mitochondria in axons. An important pool of mitochondrial proteins is locally produced at synapses.

It's worth mentioning that mitochondrial DNA encodes 13 mitochondrial proteins (essential components of the OXPHOS complexes) in humans (Anderson et al., 1981), mRNAs transcribed from mitochondrial DNA are translated in mitochondrial ribosomes (Harbauer, 2017). Over 99% of mitochondrial proteins are still encoded in the nuclear genome in the cell body and translated in cytosolic ribosomes. Although mitochondrial proteins are long-lived in contrast to synaptic and membrane proteins (Dorrbaum et al., 2018), mitochondria themselves might rely on local synthesis of mitochondrial proteins in order to support protein synthesis at axons/dendrites (Biever et al., 2019) (Fig. 2). In recent years, mRNA localization and their local translation in axons/dendrites and synaptic terminals have been shown to play an important role in the decentralization of these neuronal sub-domains, underlying their contribution to neuronal wiring, axonal maintenance and synaptic plasticity (Ashraf et al., 2006; Holt and Schuman, 2013; Younts et al., 2016; Rangaraju et al., 2017; Cioni et al., 2019) (Fig. 2).

The molecular machinery including mRNA molecules, ribosomes and regulatory elements for protein synthesis has been discovered in dendrites, axons and synaptic terminals (Hafner et al., 2019). Earlier work applying in-depth RNA sequencing and high-resolution imaging in the hippocampal synaptic neuropil identified 2,550 transcripts localizing to dendrites and/or axons (Cajigas et al., 2012). Recently, the Schuman group has found that presynaptic nerve terminals encompass abundant mRNAs and ribosomes and that synaptic terminals show local translation with a high frequency even in absence of stimulation (Hafner et al., 2019; Biever et al., 2020). As the cellular site of protein synthesis, ribosomes were first observed in the dendrites in neurons (Bodian, 1965; Steward and Levy, 1982). Moreover, polyribosomes (two or more ribosomes engage with mRNA clusters and are considered the active site of translation) were then found along the dendritic shafts (Steward and Levy, 1982; Ostroff et al., 2002). Furthermore, accumulating evidence shows that ribosomes are also detected in axons and terminals (Shigeoka et al., 2016; Scarnati et al., 2018; Hafner et al., 2019). In the scenario of regulatory elements, the presence of the endoplasmic reticulum and its several proteins in dendrites and axons have been described (Horton and Ehlers, 2003; Merianda et al., 2009; Cioni et al., 2019). In the context of mitochondria, once mitochondrial mRNAs are translated in the soma, they will be conveyed via fast anterograde axonal transport to their ultimate sites of function in neurite branches and synaptic terminals (Vallee and Bloom, 1991) (Fig. 2). Apparently, the decentralization of axons and dendrites in neurons makes it logistically challenging for proper amounts of proteins to be placed in the right place at the right time. That implies an alternative mechanism should exist to cope with this dilemma. It is conceivable to think that mitochondrial supply to neurites and synaptic terminals not only originates from the canonical synthesis in the soma and ensuing transport, but also might stem from a non-canonical local synthesis or transfer from adjacent cells under special conditions. Indeed, supporting evidence showed that mitochondrial mRNAs can be conveyed down the axons and presynapses (Gioio et al., 2001; Hillefors et al., 2007; Kar et al., 2014; Van Laar et al., 2018). Consistent with these notions, Kuzniewska and colleagues showed that mitochondrial proteins represent an important fraction of locally translated proteins at synapses by employing global proteomic analysis and ex vivo stimulation of isolated mouse synapses (Fig. 2). Furthermore, they established that synaptically newly translated mitochondrial proteins are imported into the mitochondria and incorporated into the functional respiratory chain complexes (Kuzniewska et al., 2020). Along these lines, Yousefi and colleagues found that mitochondrial translation occurs at both axons and dendrites as well as pre- and postsynaptic compartments using neuronal cultures (Yousefi et al., 2021). Together, these data indicated that translation of mitochondrial proteins occurs locally to maintain a functional pool of mitochondria (Kuzniewska et al., 2020; Yousefi et al., 2021) (Fig. 2).

While local translation obviously plays a critical role in axonal maintenance, how axonal mRNAs are localized and translated at specific organelles remains largely unclear. Notably, the Holt group showed that late endosomes are platforms of mRNA (including mitochondrial mRNAs) translation at axons and this translation is important for mitochondrial maintenance (Cioni et al., 2019) (Fig. 2). First, they showed that mRNA granules frequently associate with both early and late endosomes at the Xenopus retinal ganglion cell axons (Cioni et al., 2019). Then they demonstrated that ribosomes, RNA-binding proteins and mRNAs are localized to endosomes (Cioni et al., 2019). More importantly, they found out that mitochondria exist in endosomal translation sites and that mRNAs encoding mitochondrial proteins are translated on late endosomes (Cioni et al., 2019) (Fig. 2). Previously, the Holt group showed that at axons local translation of the intermediate filament protein lamin B2 mRNA, whose protein normally associates with the nuclear membrane, promotes axonal maintenance by promoting mitochondrial function (Yoon et al., 2012). Here, they presented a new mechanism distinct from the classic one whereby nascent polypeptides are directed to the mitochondrial outer membrane through the translocation translocase (Cioni et al., 2019). In a nutshell, this exciting work has revealed important intersections between RNA granules, axonal protein synthesis, late endosomes and mitochondrial function (Rossoll and Bassell, 2019). However, the close link between endosome-coupled local translation and mitochondrial integrity at axons also raises the issue of whether this connection helps power translation (Rossoll and Bassell, 2019).

It is tempting to think that local translation of mitochondrial mRNAs exists to adapt to rapidly changing demands at energy-demanding synapses, allowing for homeostatic synaptic plasticity.

Mitochondrial compartments power plasticity-induced local translation

It is known that protein synthesis-dependent plasticity occurs on a minutes to hours timescale in neurons (Huber et al., 2000; Bradshaw et al., 2003; Vickers et al., 2005). To address whether mitochondria fuel local translation during plasticity events, Rangaraju and colleagues first determined mitochondrial dynamics in neurons via a mitochondria-targeted fluorescence protein within these timescales and revealed spatially confined mitochondrial compartments in dendrites and more dynamic/motile mitochondria in axons (Rangaraju et al., 2019). Furthermore, by applying the phototoxic protein KillerRed optogenetically to the mitochondrial matrix, which in effect disables local mitochondria, they demonstrated, at basal levels of neuronal activity, mitochondrial compartments are not required to fuel local translation whose energy demands are adequately met by ambient ATP available in dendrites or ATP generated by adjacent undisturbed mitochondria. While existing ATP, as it was shown, might suffice to power protein synthesis during basal neuronal activity, a thorough picture of how the elevated energy burdens during synaptic plasticity are lifted was still lacking. To address this question, the authors developed a local synaptic stimulation protocol to induce the plasticity of spine morphology and plasticity-induced local translation, and then examined how the depletion of local mitochondria might affect plasticity-induced synaptic translation (Rangaraju et al., 2019). Indeed, they demonstrated mitochondrial compartments are essential to fuel local translation associated with synaptic plasticity and maintenance. Finally, they showed that mitochondria power plasticity-induced local translation within spatially confined domains (Fig. 2). To summarize, these findings revealed an important picture of how the tight compartment-specific regulation and optimization of mitochondrial dynamics and sizes are executed to allow for local translation and synaptic plasticity (Rangaraju et al., 2019).

Mitochondrial disturbances implicated in synaptic aging and diseases

Normal brain aging is associated with an age-induced impairment in memory performance and mitochondrial function (Toescu and Verkhratsky, 2004; Morrison and Baxter, 2012; Mattson and Arumugam, 2018; Lautrup et al., 2019). Importantly, subtle age-related changes in synaptic ultrastructure, morphology and function, rather than the loss of neurons, are linked to impairments in cognitive function during normal aging (Morrison and Baxter, 2012; Liang and Sigrist, 2018) (Fig. 1). Concurrently, changes in mitochondrial dynamics in aging have also been implicated (Stauch et al., 2014; Grimm and Eckert, 2017; Rango and Bresolin, 2018) (Fig. 1). Notably, different forms of long-term synaptic plasticity exist to structure the neural circuits. The most well-studied synaptic plasticity is NMDA receptor-dependent long-term potentiation (LTP) that represents a persistent increase in synaptic strength (Sudhof, 2017).

Examining the differences between young and old rat brains, researchers have found that LTP maintenance is impaired in older animals (Burgdorf et al., 2011). Promisingly, administrating the polyamine spermidine whose levels normally decline with age (Casti et al., 1982; Gupta et al., 2013), has been shown to largely restore mossy fiber-CA3 LTP in mice (Maglione et al., 2019). Moreover, dietary spermidine can prevent the age-induced loss of neuronal mitochondria (Maglione et al., 2019), hinting at the possibility of mitochondrial abundance in restoring LTP via spermidine supplementation during brain aging (Maglione et al., 2019). Perhaps relevant in this context, Puleston and colleagues discovered that spermidine and hypusination (a posttranslational modification seemingly enhanced by spermidine) of the eukaryotic initiation factor 5A (eIF5A) maintains the TCA cycle and electron transport chain integrity in macrophage activation (Puleston et al., 2019). Mechanistically, hypusination of eIF5A can boost efficient expression of some mitochondrial enzymes involved in OXPHOS (Puleston et al., 2019). Thus, it would be very tempting to see whether the spermidine-eIF5A hypusination axis promotes mitochondrial performance in the aging brain via translational mechanisms in future. Along these lines, a recent study presented an increasing synaptic localization of mitochondria with the aging of presynaptic boutons, implying that mitochondria might accumulate locally at presynaptic boutons to increase presynaptic structural stability (Lees et al., 2019). In the *Drosophila Melanogaster* fruit fly model, the authors showed that upregulated energy metabolism in the fly learning center mushroom body can trigger long-term memory formation, which is in turn already sensitive to an impairment in mitochondrial flux (Placais et al., 2017).

Apart from sheer aging, deregulation of energy homeostasis, defective mitochondrial transport and synaptic dysfunction have also been implicated in the failed axonal regeneration after injury and the pathogenesis of several neurological disorders, including Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and autism spectrum disorder (ASD) (Chen and Chan, 2009; Sheng and Cai, 2012; Baldwin et al., 2016; Zhou et al., 2016; Rose et al., 2018; Rossi and Pekkurnaz, 2019; Frye, 2020; Wang et al., 2020) (Fig. 1). In fact, most neurodegenerative diseases start with synaptic terminal degeneration along with bioenergetic deficits at early disease stages (Pathak et al., 2013; Gonzalez-Sanchez et al., 2019). The fact that ATP has a limited effectiveness in diffusion in the intracellular

environment and particularly over the long-distance neuronal processes adds another layer of complexity (Sun et al., 2013; Chamberlain and Sheng, 2019).

Perhaps not so surprisingly, mutations involved in the mitochondrial fission/fusion enzymes, such as *Opa1, Drp1* or *mitofusin 2* have been shown to cause neurological defects (Alexander et al., 2000; Zuchner et al., 2004; Vos et al., 2010; Chapman et al., 2013; Sandoval et al., 2014; Keogh and Chinnery, 2015; Sarzi et al., 2017; Wilkins et al., 2017; Longo et al., 2019) (Fig. 1). Conversely, excessive mitochondrial fusion/fission activities can also promote synaptic dysfunction and neuronal death, underscoring the importance of mitochondrial dynamics in the homeostasis of the nervous system (Fig. 1). Moreover, mutations in genes (such as *Parkin, PINK1* and *LRRK2*) have been shown to cause familial forms of Parkinson's disease (Kitada et al., 1998; Valente et al., 2004; Exner et al., 2012; Hsieh et al., 2016), underlining the importance of functional mitochondria in midbrain dopaminergic neurons. Furthermore, in an Alzheimer's disease mouse model, an impairment in presynaptic mitochondrial Ca^{2+} handling was observed as an early deficit and caused post-tetanic potentiation at mossy fiber synapses (Lee et al., 2012). Recently, the Perlson lab showed that in motor neurons and NMJs of a mouse model with TDP-43 mislocalization (known to be pathogenic in amyotrophic lateral sclerosis) (Mackenzie and Rademakers, 2008) the axonal and synaptic levels of nuclear-encoded mitochondrial proteins are reduced.. Interestingly, the Frye lab showed that lymphoblastoid cell lines derived from children with ASD exhibit elevated oxygen consumption and higher glycolysis compared to lymphoblastoid cell lines derived from unaffected siblings (Rose et al., 2017). Indeed, accumulating evidence shows that synaptic mitochondria that are highly relevant for synaptic activity have been implicated in ASD (Rojas-Charry et al., 2021). Furthermore, the Charcot-Marie-Tooth disease type 2B (CMT2B) refers to sensory and motor neuropathy of the distal extremities and is characterized by a chronic muscle weakness followed by muscular atrophy (Zuchner et al., 2004; Leal et al., 2018). The CMT2B-linked Rab7a mutations (missense mutations of 4 amino acids) disrupt axonal translation of proteins essential for mitochondrial integrity (Cogli et al., 2009; Cioni et al., 2019). Lastly, an extreme form of metabolic stress caused by brain ischemia can lead to tissue damage and severe neurological deficits, and brain ischemia represents one of the leading causes of disability and death in the aging human population (Ooboshi et al., 2001; Sandu et al., 2017). In short, mitochondrial disturbance has been manifested in synaptic aging and diseases.

Unsolved questions and perspectives

There is a longstanding argument that translation occurs mainly in polysomes which are surprisingly scarce in small synaptic volumes, while monosomes remain translationally inactive (Holt and Schuman, 2013; Heyer and Moore, 2016). However, the emerging role of monosomes in favoring the translation of axonal/dendritic proteins over somatic proteins in neurons have been described (Biever et al., 2020). The preference for monosome translation in neuropils likely helps to copy with space limitations and diversify the local proteome (Biever et al., 2020). In this scenario, it would be relevant to find out whether the localization of specific translational regulators might influence this pattern and whether this pattern might be subject to changes in response to synaptic stimulations. Moreover, it remains elusive as to what mRNAs are actually translated into proteins at neuropils and the cell bodies in various contexts. Furthermore, as mitochondria represent one of the most abundant categories of locally translated proteins (Kuzniewska et al., 2020), it might be tempting to apply mitochondrial ribosome profiling to monitor mitochondrial translation during synaptic aging and diseases where synaptic translation is implicated. Lastly, investigating the translational landscapes in different neuronal cell types (including those from patients with neurodegenerative diseases) might allow for a clearer understanding of the pathology/cure associated with local translation.

Conclusions

In this review, I described the extended cellular architectures of post-mitotic neurons and how this spatial compartmentalization in neurons might pose great challenges for monitoring the activity of different compartments (including the synapses, axons and dendrites) and maintaining their homeostasis. Specifically, neuronal compartmentalization poses a logistic threat for the transport of proteins/organelles between the cell body and axonal/dendritic areas. Additionally, neurons have huge metabolic demands that are mainly fulfilled by mitochondria, whose ATP production and calcium buffering abilities are critical for neuroplasticity (Vos et al., 2010; Rossi and Pekkurnaz, 2019). Neuronal compartmentalization obviously becomes bioenergetically challenging for mitochondria to support axon/dendrite/synapse-specific activities in a timely manner. To adapt to altered neuronal energy states, mitochondria become abundant in different neuronal compartments and can dynamically change their morphology, position and function (Course and Wang, 2016).

Although how mitochondrial activities are tailored in synapses, axons and dendrites in various contexts deserves to be studied, a clear picture is emerging that mitochondrial functions and synaptic activities operate closely to shape synaptic plasticity, performance and homeostasis. Thus, mitochondria are entangled in the complex regulation of synaptic plasticity and function (Todorova and Blokland, 2017).

Neurons have evolved local mechanisms (both

biogenesis and degradation) to meet the need of extensive activities in their sub specializations. As aforementioned, burgeoning evidence has uncovered local translation of mRNAs at axons, dendrites and synapses (Martin and Ephrussi, 2009; Holt and Schuman, 2013; Holt et al., 2019). Local translation can rapidly respond to physiological cues and supply proteins essential for synaptic activity and/or homeostasis. Local translation is an important source for synaptic proteins and operates as a ubiquitous feature in mature dendrites and axons in mammals. Furthermore, Mitochondrial energy compartments can power plasticity-induced synaptic translation (Rangaraju et al., 2019). Conversely, locally depleting mitochondrial compartments leads to impaired plasticity-induced local translation and spine morphological plasticity (Rangaraju et al., 2019). How neurons establish and maintain an adequate distribution of healthy, functional mitochondria through their sub-compartments remains largely unclear. Thus, it would be of importance to explore their interactions and local/other mechanisms in greater detail, such as in physiological and various pathological conditions. In short, deepening our understanding of how the synaptic metabolism intersects with synaptic plasticity might help identify new therapeutic targets of neurological disorders stemming from mitochondrial dysfunction and impaired protein synthesis.

Longstanding evidence showed that neurons are especially sensitive to perturbations of mitochondrial health (Mattson and Arumugam, 2018; Zhou et al., 2018). Moreover, accumulating evidence has indicated that synaptic dysfunction is related to mitochondrial dysfunction (compromised biogenesis, dysfunctional transport of mitochondria and defective mitophagy function) during synaptic aging and disease (Morrison and Baxter, 2012; Mattson and Arumugam, 2018). The importance of mitochondria for proper neuronal function is emphasized by the occurrence of neurological defects in patients suffering from a great variety of diseases caused by mutations in mitochondrial genes (Kausar et al., 2018). Thus, further investigations into local translation of mitochondrial proteins in different neuronal cell types are needed. Strategies promoting mitochondrial biogenesis, function and homeostasis in neurons might pave the way for maintaining synaptic plasticity and neuronal health. Although we have made a step forward, mechanistic understandings remain to be investigated to understand more deeply how mitochondrial support and local translation of mitochondrial proteins might safeguard synaptic plasticity and neuronal homeostasis.

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