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Mitochondria and neuroplasticity

Aiwu Cheng*[1], Yan Hou* and Mark P Mattson*,†[1]
*Laboratory of Neurosciences, National Institute of Aging Intramural Research Program, Baltimore, MD 21224, U.S.A.
†Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD 21205, U.S.A.

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ABSTRACT

The production of neurons from neural progenitor cells, the growth of axons and dendrites and the formation and reorganization of synapses are examples of neuroplasticity. These processes are regulated by cell-autonomous and intercellular (paracrine and endocrine) programs that mediate responses of neural cells to environmental input. Mitochondria are highly mobile and move within and between subcellular compartments involved in neuroplasticity (synaptic terminals, dendrites, cell body and the axon). By generating energy (ATP and NAD^+), and regulating subcellular Ca^{2+} and redox homoeostasis, mitochondria may play important roles in controlling fundamental processes in neuroplasticity, including neural differentiation, neurite outgrowth, neurotransmitter release and dendritic remodelling. Particularly intriguing is emerging data suggesting that mitochondria emit molecular signals (e.g. reactive oxygen species, proteins and lipid mediators) that can act locally or travel to distant targets including the nucleus. Disturbances in mitochondrial functions and signalling may play roles in impaired neuroplasticity and neuronal degeneration in Alzheimer's disease, Parkinson's disease, psychiatric disorders and stroke.

Key words: neural progenitor cell, mitochondria biogenesis, mitochondria fission and fusion.

INTRODUCTION

Neuroplasticity is a term used to describe a range of adaptive changes that occur in the structure and function of cells in the nervous system in response to physiological or pathological perturbations. Examples of neuroplasticity include the sprouting and growth of axons or dendrites, synapse formation, the strengthening of synapses in response to repeated activation and neurogenesis (the production of new neurons from stem cells). The biological basis of this capacity for structural and functional adaptation encompasses a diverse set of cellular and molecular mechanisms, including the pre- and post-synaptic apparatuses for neurotransmission, cytoskeletal remodelling, membrane trafficking, gene transcription, protein synthesis and proteolysis (Shepherd and Huganir, 2007; Bramham, 2008; Greer and Greenberg, 2008; Pak et al., 2008; Tai and Schuman, 2008; Shah et al., 2010). In addition, glial cells (astrocytes, microglia and oligodendrocytes) play important roles in neuroplasticity by producing soluble and surface-bound factors that influence neurite outgrowth, synaptic plasticity and cell survival (Haydon and Carmignoto, 2006; Barres, 2008).

Among the many specialized cell types in the body, neurons are particularly marvellous because they elaborate tree-like shapes, are electrically excitable, and engage in spectacular spatiotemporal displays of signal detection, integration and storage, and generation of adaptive responses to life situations. Newly generated neurons possess an intrinsic pre-ordained sequence of events that determine at least some of their structural and functional phenotypes. For example, the dendritic morphology of cerebellar Purkinje cells is largely established independently of interactions with other cells (Sotelo and Dusart, 2009). Interestingly, the most closely related neuronal cells, mitotic sister neurons arising from a common progenitor, elaborate morphologies more similar to themselves compared with their close neighbours (Mattson et al., 1989). While the cytoarchitecture and functional capabilities of the nervous system are highly complex, several of the signalling mechanisms that control the formation and adaptive plasticity have been elucidated. Neurotransmitters, neurotrophic factors and cell adhesion molecules are three highly conserved classes of intercellular signals that regulate the genesis and adaptive plasticity of nervous systems (Mattson, 1988; Loers and Schachner, 2007; Gottmann et al., 2009). The most intensively studied representatives of

[1] Correspondence may be addressed to either of these authors (email chengai@mail.nih.gov or mattsonm@grc.nia.nih.gov).
Abbreviations: Aβ, amyloid β-peptide; AD, Alzheimer's disease; AP, adaptor protein; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; CaMK, Ca^{2+}/calmodulin-dependent protein kinase; CR, caloric restriction; CREB, cAMP-response-element-binding protein; ES, embryonic stem; ETC, electron transport chain; HD, Huntington's disease; LRRK2, leucine-rich repeat kinase 2; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; Mn-SOD, manganese superoxide dismutase; NGF, nerve growth factor; NMDA, *N*-methyl-D-aspartate; Nrf1, nuclear respiratory factor 1; OPA1, Optic Atrophy-1; PD, Parkinson's disease; PGC1α, peroxisome-proliferator-activated receptor γ co-activator 1α; PINK1, PTEN (phosphatase and tensin homologue deleted on chromosome 10)-induced kinase 1; PPAR, peroxisome-proliferator-activated receptor; UCP, uncoupling protein.

these three classes of signals are the excitatory neurotransmitter glutamate (Mattson, 2008; Newpher and Ehlers, 2008), BDNF (brain-derived neurotrophic factor; Mattson et al., 2004; Lipsky and Marini, 2007) and the NCAM (neural cell adhesion molecule; Hildebrandt et al., 2007). Details of the components of these signalling pathways will not be covered in the present paper. Instead, we focus on emerging findings regarding the interactions of the latter signalling pathways with mitochondria, an organelle increasingly recognized as not only a power station, but also as a signalling platform involved in fundamental events in the formation and plasticity of neuronal circuits.

Mitochondria are vital ATP-generating organelles present in all eukaryotic cells. In addition to converting energy substrates into ATP, mitochondria participate in ROS (reactive oxygen species) metabolism, calcium signalling and apoptosis (Mattson et al., 2008). Mitochondria are distributed throughout the length of axons and in presynaptic terminals. Mitochondria in dendrites are located mainly in the dendritic shafts and are occasionally found associated with spines (Cameron et al., 1991; Popov et al., 2005).

The application of novel imaging and molecular biology technologies to studies of mitochondria has revealed several surprising properties and functions of mitochondria in neuroplasticity. For example, we now know that mitochondria (i) move rapidly within and between subcellular compartments (e.g. dendrites, the axon shaft, presynaptic terminals) (Zinsmaier et al., 2009); (ii) undergo fission and fusion (Liesa et al., 2009); (iii) respond (e.g. move, change their energy output, take up or release calcium) to electrical activity and activation of neurotransmitter and growth factor receptors (Macaskill et al., 2009); and (iv) function as signalling outposts that contain kinases, deacetylases and other signal transduction enzymes (Stowe and Camara, 2009). Mitochondrial fission and fusion are mediated by two distinct protein complexes involving GTPase. Key molecular mechanisms involved in mitochondrial fission and fusion have recently been elucidated (Berman et al., 2008). Two key proteins, Drp (dynamin-related protein) and Fis1, mediate mitochondrial fission, whereas mitofusins (Mfn1 and Mfn2) and OPA1 (Optic Atrophy-1) mediate mitochondrial fusion (Karbowski et al., 2002; Shaw and Nunnari, 2002; Koshiba et al., 2004; Detmer and Chan, 2007). Mitochondrial fission and fusion can occur rapidly (within less than 1 min) and remodel individual mitochondria continuously. Mitochondria dynamics are important for neuronal functions since they regulate mitochondrial location, morphology, number and function (Detmer and Chan, 2007).

The notion that mitochondria participate in neuroplasticity is not new. For example, more than four decades ago, Sotelo and Palay (1968) examined electron micrographs of the lateral vestibular nucleus and observed: ''The distal segments of some dendrites display broad expansions packed with slender mitochondria and glycogen particles. These distinctive formations are interpreted as being growing tips of dendrites, and the suggestion is advanced that they are manifestations of architectonic plasticity in the mature central nervous system.'' In the present review article, we consider the emerging roles of mitochondria in neuroplasticity.

Mitochondria and neurogenesis

Neurogenesis, the birth of new neurons from stem cells, occurs rapidly and globally during development of the nervous system, and to a much more limited extent in some regions of the adult nervous system. Adult neurogenesis is believed to be functionally important as a mechanism of brain plasticity under physiological conditions and in brain repair after injury (Kempermann et al., 2004; Ge et al., 2008; Kitamura et al., 2009). How are mitochondria involved in the process of neurogenesis? First, the mitochondria may play a role in the self-renewal capacity of neural stem cells, a defining property of all stem cells. Studies of mouse ES (embryonic stem) cells suggest that the proliferative capacity of stem cells is correlated with low mitochondrial oxygen consumption and high levels of glycolytic activity (Kondoh et al., 2007). Using typical bicarbonate buffer and a 5% CO_2/95% air atmosphere, cells are exposed to much higher levels oxygen compared with what they would be exposed to *in vivo*. Reducing the oxygen level enhances the proliferation and multipotency of neural stem cells (Rodrigues et al., 2010; Santilli et al., 2010). Human ES cells exhibit an 'anaerobic' metabolic profile, and when somatic cells are induced to revert to an ES cell-like phenotype, their mitochondria also revert to an ES cell-like state with respect to their morphology, subcellular distribution, biogenesis, and ROS and ATP production (Prigione et al., 2010). Cultured neural crest stem cells incubated in the presence of bone morphogenetic protein 2 and forskolin can be coaxed, by exposure to mild hypoxia, to differentiate into a relatively pure population of sympathoadrenal neuronal cells that produce adrenaline (norepinephrine) and dopamine (Morrison et al., 2000). A link between mitochondrial Ca handling and neurogenesis is suggested by results showing that, when neuroblastoma cells are induced to stop dividing and differentiate into neuron-like cells, there is an increase of mitochondrial fusion and an increase in intramitochondrial Ca^{2+} levels (Voccoli and Colombaioni, 2009).

The second step in neurogenesis is the differentiation of neural progenitors into postmitotic neurons. While much has been learned regarding the molecular changes involved in neuronal differentiation (Hamby et al., 2008; Zhang et al., 2008; Cane and Anderson, 2009), very little is known of the roles of mitochondria in these processes. Neuronal differentiation is associated with an increase in mitochondrial mass per cell, and the mitochondrial translation inhibitor chloramphenicol prevents differentiation, indicating participation of the mitochondrial genome and mitochondrial protein synthesis in neuronal differentiation (Vayssière et al., 1992). The increased mitochondrial biogenesis associated with differentiation provides ATP to support fundamental cellular processes involved in neurite outgrowth (cytoskeletal

dynamics, membrane turnover and transport of various RNA and protein cargos).

While mitochondrial mass increases on neuronal differentiation to increase ATP production (Figure 1), energy generation is only one mechanism by which mitochondria enable neurite outgrowth. Mitochondrial UCPs (uncoupling proteins) have received increasing attention regarding their roles in physiological processes other than heat generation in brown fat cells (Mattson and Liu, 2003). By leaking protons across the mitochondrial inner membrane, UCPs not only reduce ATP production, but also decrease the generation of ROS and modify mitochondrial and endoplasmic reticulum Ca^{2+} dynamics (Chan et al., 2006; Liu et al., 2006). UCP4 is expressed preferentially in neurons (Liu et al., 2006) and its developmental expression characteristics suggest a role for UCP4 in neuronal differentiation (Smorodchenko et al., 2009). In addition, the transcription factor NeuroD6 can induce the differentiation of the neuronal progenitor-like PC12 cells and up-regulate the expression of several mitochondria-related genes; NeuroD6-induced expression of mitochondrial genes is maximum at a very early stage of neurite outgrowth (Baxter et al., 2009). One mitochondria-related gene induced by NeuroD6 is KIF5B, a kinesin motor protein involved in mitochondrial transport.

Mitochondria and neurite outgrowth

During their differentiation, neurons extend neurites with one becoming the axon and others becoming dendrites. This polarity is important in the formation of functional neuronal circuits.

During axogenesis, mitochondria congregate at the base of the developing neurites that are destined to become axon (Mattson and Partin, 1999). Once the axon forms and accelerates its growth there is increased entry of mitochondria into the new axon where they are concentrated at the growth cone (Ruthel and Hollenbeck, 2003). Rather strikingly, depletion of mitochondria at or before the stage of axogenesis, under conditions where cellular ATP levels are maintained using pyruvate and uridine as energy sources, prevents axon formation (Mattson and Partin, 1999). Furthermore, in dorsal root ganglion cells isolated from neonatal rats, the mitochondria become reorganized to form clusters in the axonal hillock of regenerating axons (Dedov et al., 2000). These studies suggest that mitochondria play an important role in neural polarization and axonal outgrowth regulation.

The mechanisms by which mitochondria influence the establishment of neuronal polarity remain to be established. It was reported that the cytoplasmic free Ca^{2+} concentration

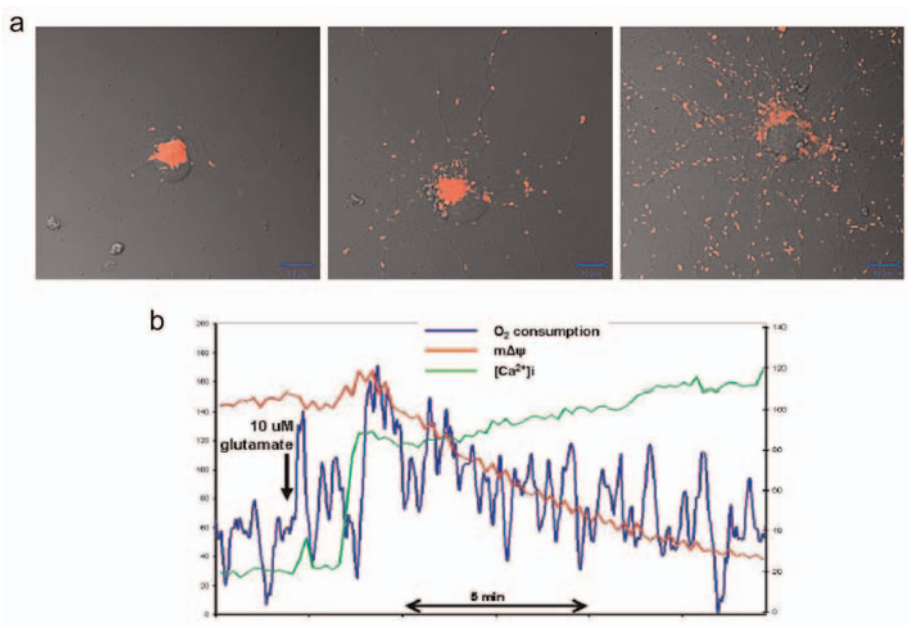

Figure 1 **Examples of methods for evaluating mitochondrial morphology, subcellular localization and functional status**
(**a**) Each panel shows a single live embryonic rat hippocampal neuron at a different stage of development in culture (1, 5 and 14 days). Mitochondria in the neurons were stained with the fluorescent probe MitoTracker Red. Note that the immature neuron has elaborated short processes, and that the vast majority of mitochondria are clustered in a perinuclear location. At 5 days in culture the neuron exhibits longer neurites that contain multiple mitochondria, and perinuclear mitochondria remain abundant. Mitochondrial numbers have increased, indicating that biogenesis has occurred. At 14 days in culture the neuron has elaborated an extensive neuritic network with each neurite containing multiple mitochondria. Relative numbers of mitochondria in a perinuclear location are reduced. (**b**) Example of the results of an experiment in which oxygen consumption, mitochondrial membrane potential and cytoplasmic Ca^{2+} levels were monitored in a single cultured embryonic rat hippocampal neuron before and during exposure to the excitatory neurotransmitter glutamate. In response to glutamate receptor activation, oxygen consumption increased and then slowly returned towards baseline levels, intracellular Ca^{2+} levels rose rapidly and remained elevated, whereas mitochondrial membrane potential declined progressively. Adapted from Gleichmann et al. (2009).

is lower surrounding the mitochondria at the base of the developing axon in cultured embryonic rat hippocampal neurons, and that exposure of the neurons to a calcium ionophore (which increases the cytoplasmic Ca^{2+} concentration throughout the cell) prevents axon formation (Mattson and Partin, 1999). One possible explanation is that mitochondria act as a calcium buffering organelle to reduce the Ca^{2+} concentration at the base of the presumptive axon, thereby promoting polymerization of microtubules and the rapid growth and differentiation of the axon (Figures 2 and 3).

In addition to playing critical roles in neural polarization and axonal outgrowth regulation, mitochondria may also be required for normal dendrite development, maintenance and plasticity. Studying the correlation between mitochondrial energy status and mitochondrial membrane potential, Overly et al. (1996) found that mitochondria in dendrites are metabolically more active than those in the axons, although the reason for this differential mitochondrial activity is unknown. Recent studies provide experimental evidence that mitochondria are important in regulating dendrite development, maintenance and plasticity. Disruption of mitochondrial protein translation in *Drosophila* olfactory projection neurons preferentially reduces dendritic arborization, while axon morphology is relatively unaltered (Chihara et al., 2007). Dendritic mitochondria also have essential roles in dendritic spine morphogenesis and plasticity.

Mechanisms by which mitochondria move within neurites are beginning to be understood; their movement is affected by energy-dependent transport along microtubules. Mitochondrial transport can occur bidirectionally; microtubule plus end-directed kinesin moves mitochondria in the anterograde direction, whereas minus end-directed dynein motors move mitochondria retrogradely (Hollenbeck and Saxton, 2005; Zinsmaier et al., 2009; Pathak et al., 2010; Figure 2). Measurements of the membrane potential of individual mitochondria in the growing axons of chick sensory neurons using the dye TMRM (tetramethylrhodamine methyl ester) revealed no major differences among mitochondria along the length of the axon, and no differences in

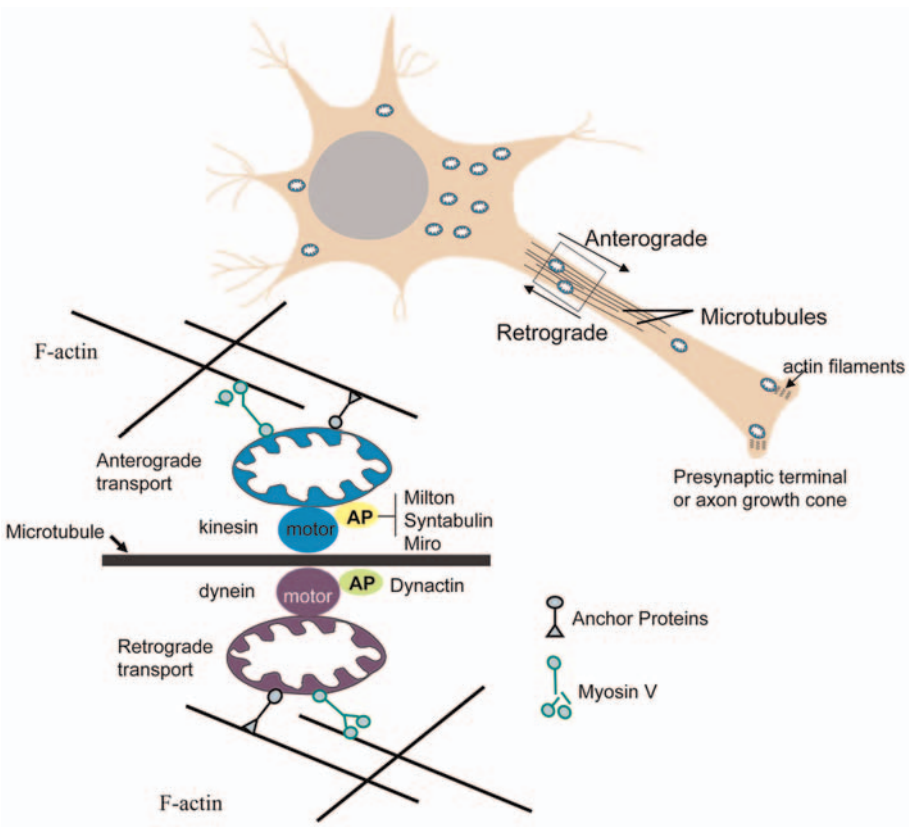

Figure 2 **Molecular machinery that actively moves mitochondria to and fro within axons**
A major mechanism by which mitochondria are transported in either anterograde or retrograde directions in axons involves their energy (ATP)-dependent movement along microtubules. ATP-dependent 'motor' proteins interact with the microtubules to generate the force that moves the mitochondria in anterograde (kinesin) or retrograde (dynein) directions respectively. Several APs (adaptor proteins) mediate the interaction of mitochondria with motor proteins, including APs that interact with kinesin (Milton, syntabulin and the Rho GTPase Miro) and APs that associate with dynein (dynactin). In addition, in synaptic terminals and growth cones, microtubules may be moved by myosin-mediated interactions with actin filaments. Myosin V can drive short-range movements along F-actin, as well as modulate long-range transport by pulling mitochondria away from microtubules by facilitating anchorage of mitochondria to F-actin by unknown actin–mitochondrion crosslinkers. Adapted from Mattson et al. (2008).

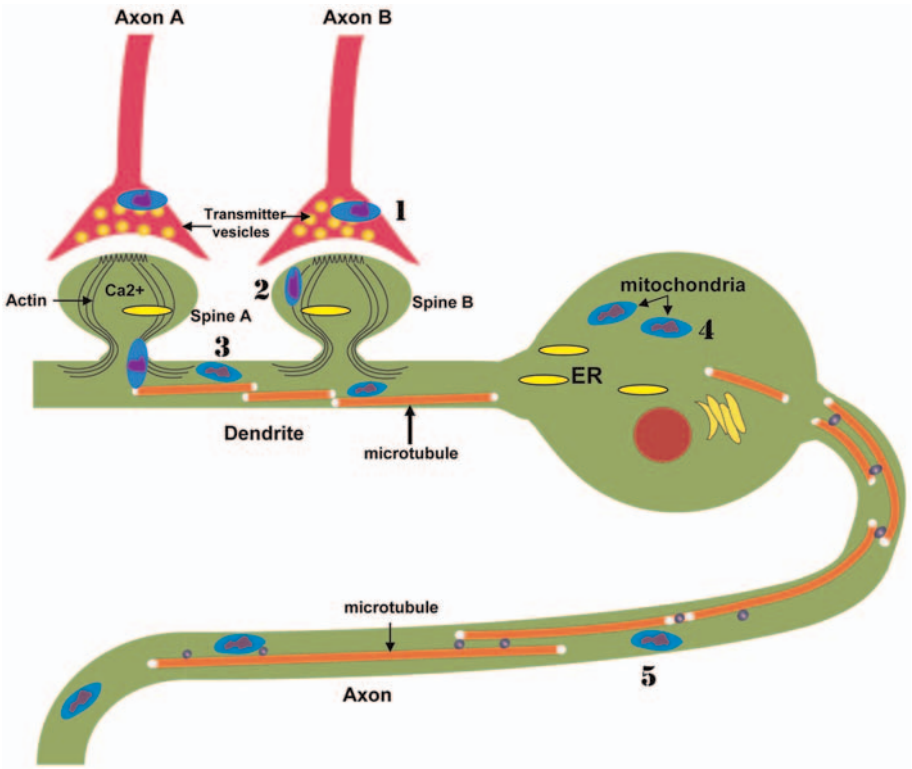

Figure 3 **The landscape of mitochondrial involvement in the plasticity of neuronal structure and information processing**
Increasing evidence suggests that mitochondria play active roles in regulating the outgrowth of axons and dendrites, synaptogenesis and morphological and functional responses to synaptic activity. Mitochondria in presynaptic terminals (**1**) provide the energy for the maintenance and restoration of membrane potential, and may modulate neurotransmitter packaging and release. Mitochondria in postsynaptic spines (**2**) and dendritic shafts (**3**) may enable/regulate both structural and functional responses of these compartments to synaptic activity. Mitochondria in the cell body (**4**) provide the energy required for numerous biochemical processes, and may also serve as signalling platforms involved in information transfer within the neuron. Mitochondria in axons (**5**) provide the energy necessary for the transport of various proteins and organelles from the axon terminal to the cell body and vice versa.

membrane potential in stationary versus moving mitochondria (Verburg and Hollenbeck, 2008). However, the membrane potential of mitochondria in the lamellipodia of growth cones is significantly greater than the membrane potential of mitochondria in the axon shaft. In another study that employed the mitochondrial membrane potential-sensing dye JC-1 to image mitochondria in growing axons of cultured chick sensory neurons, it was found that most of the mitochondria with a high potential were transported towards the growth cone, whereas most mitochondria with a low potential were transported towards the cell body (Miller and Sheetz, 2004).

Using beads coupled with signals for axon outgrowth [NGF (nerve growth factor)] or guidance (semaphoring 3A), it was shown that both of these signals cause an increase in the membrane potential of mitochondria immediately adjacent to the site of the beads (Verburg and Hollenbeck, 2008). Additional data in the latter study provided evidence that PI3K (phosphoinositide 3-kinase) and MAPK (mitogen-activated protein kinase) mediated the effects of NGF and semaphorin 3A on mitochondrial potential. Quantitative analyses of motility show that the accumulation of axonal mitochondria near a focus of NGF stimulation is due to increased movement into bead regions followed by inhibition of movement out of these regions and that anterograde movement and retrograde movement are differentially affected. In axons made devoid of F-actin by latrunculin B treatment, bidirectional transport of mitochondria continues, but they can no longer accumulate in the region of NGF stimulation. Additional experiments provided evidence that the regulation of mitochondrial movement by NGF signalling involves increased transport to the sites of stimulation in combination with retention of the mitochondria by interactions with the actin cytoskeleton (Chada and Hollenbeck, 2004).

Although most of the ATP production by mitochondria occurs in the ETC (electron transport chain), mitochondrial glycogenesis may enable or regulate physiological processes in neurons, including neurite outgrowth. It is clear that neuronal cells can survive without a functioning mitochondrial ETC, as demonstrated in cultured cells in which mitochondria are depleted of their ATP and provided lactate and pyruvate as energy substrates (Miller et al., 1996; Hyun et al., 2007). One example comes from studies in which the activity of hexokinase was manipulated in growing neurons; hexokinase is an enzyme that plays a pivotal role early in the

glycolytic pathway in which glucose is metabolized to generate ATP. When hexokinase is selectively inhibited using a hexokinase-binding peptide, the ability of NGF to stimulate neurite outgrowth in cultured adult sensory neurons is impaired (Wang et al., 2008a).

Mitochondria and synaptic plasticity

The behaviour and functional properties of mitochondria differ in axons and dendrites. For example, twice as many mitochondria are motile in the axons compared with the dendrites of cultured hippocampal neurons, and there is a greater proportion of highly charged, more metabolically active mitochondria in dendrites than in axons (Overly et al., 1996). Both presynaptic axon terminals and postsynaptic dendrites experience considerable metabolic and oxidative stress as a result of activation of membrane voltage- and ligand-gated Ca^{2+} channels (Bezprozvanny and Mattson, 2008). Mitochondrial functions in synaptic plasticity have been mostly studied at glutamatergic synapses, which are the most abundant type of excitatory synapse in the central nervous system. Activation of AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid), NMDA (*N*-methyl-D-aspartate) and metabotropic glutamate receptors results in Ca^{2+} influx through plasma membrane voltage-dependent channels and NMDA receptor channels, and Ca^{2+} release from the endoplasmic reticulum (Toresson and Grant, 2005). The mitochondria are essential components in synaptic transmission, since they are a major source of energy (ATP and NAD^+) required for maintenance and restoration of ion gradients; mitochondria are also intimately involved in the regulation of Ca^{2+} homoeostasis and Ca^{2+} signalling (Duchen, 2000; Nicholls and Budd, 2000; Toescu 2000). Presynaptic terminals typically contain several mitochondria (Sheehan et al., 1997), indicating that the local need for ATP and Ca^{2+} handling is great in this compartment. In response to neuronal stimulation, synaptic mitochondria redistribute and enhance their activity (Miller and Sheetz, 2004).

Mitochondria in dendrites are located mainly in the dendritic shafts and are occasionally found associated with spines (Cameron et al., 1991; Popov et al., 2005). The dendritic distribution of mitochondria is regulated by neuronal activity and mitochondrial fission/fusion proteins Drp1 and OPA1. Li et al. (2004) showed that the number of dendritic spines with mitochondria increases when the dendritic spines are actively growing (embryonic rat hippocampal neurons 11–14 days in culture), or when the neurons are subjected to repeated depolarization with KCl (Li et al., 2004). Overexpressing a dominant-negative form of Drp1 (A38K) reduces the number of dendritic mitochondria and decreases the number of synapses, whereas overexpressing wild-type Drp or treating cells with creatine increases the number and/or activity of dendritic mitochondria and nearly doubles the number of synapses. Therefore mitochondria are important in dendritic spine morphogenesis and plasticity.

Changes in mitochondria have been associated with LTP (long-term potentiation) of synaptic transmission, a key event in the learning and memory process (Williams et al., 1998; Calabresi et al., 2001; Li et al., 2010). On the presynaptic side there is evidence that the protein syntaphilin is a negative regulator of mitochondrial motility in axons where it may modulate mitochondria-mediated Ca^{2+} signalling at presynaptic terminals (Kang et al., 2008). Kinesin-mediated transport of mitochondria to presynaptic terminals was demonstrated to be important for synaptic transmission as demonstrated in studies of the effects of Milton-deficient photoreceptors in *Drosophila* (Stowers et al., 2002). The GTPase dMiro is also required for axonal transport of mitochondria to *Drosophila* synapses (Guo et al., 2005). Further work will be required to establish specific and essential roles for mitochondrial recruitment to synapses in LTP and other forms of synaptic plasticity.

While changes in the location of mitochondria within axons and dendrites may play roles in synaptic plasticity, even more rapid functional changes in mitochondria are increasingly implicated. These changes may include mitochondrial Ca^{2+} uptake or release, the production of superoxide and other ROS, and the release of proteins and other factors. Post-tetanic potentiation, a form of plasticity that arises from a persistent presynaptic Ca^{2+} elevation after tetanic stimulation, is blocked by inhibitors of mitochondrial Ca^{2+} uptake and release (Tang and Zucker, 1997). Chemical blockade of mitochondrial permeability transition pores results in a reduction in mitochondrial superoxide production (Wang et al., 2008b) and an increase of basal synaptic transmission and impaired synaptic plasticity (Levy et al., 2003). Other findings suggest that presynaptic mitochondria play a role in the maintenance of synaptic transmission by sequestering Ca^{2+} and thereby accelerating recovery from synaptic transmission during periods of moderate to high synaptic activity (Billups and Forsythe, 2002). Neurons in *Drosophila* Drp1 mutants exhibit synapses devoid of mitochondria and elevations in resting cytoplasmic Ca^{2+} levels at neuromuscular junctions (Verstreken et al., 2005). Basal synaptic transmission is largely normal in Drp1 mutant flies, but during intense stimulation mutants fail to maintain normal neurotransmission. Although exo- and endo-cytosis are normal in the mutants, the ability to mobilize reserve pool vesicles is impaired as the result of reduced ATP availability. Moreover, age-related cognitive impairment in rats, and presumably the synaptic plasticity subserving learning and memory, is associated with structural abnormalities in mitochondria and oxidation of RNA and DNA (Liu et al., 2002).

Emerging findings suggest roles for mitochondria as mediators of at least some of the effects of glutamate and BDNF on synaptic plasticity. An increasing number of signalling functions for mitochondria are being discovered. For example, glutamate receptor-mediated patterned synaptic activity, such as occurs during stimulus train-induced bursting, results in slow and prolonged changes in mitochondrial potential that exhibit both temporal and spatial correlations with the intensity of the electrical activity

(Bindokas et al., 1998). The patterned changes in mitochondrial membrane potential involve glutamate receptor-mediated Ca^{2+} influx. Synaptic activation of glutamate receptors may also affect mitochondrial bioenergetics independently of Ca^{2+} influx as suggested by studies of stimulus-evoked changes in NAD(P)H fluorescence at CA1 synapses in hippocampal slices (Shuttleworth et al., 2003). Several neurotrophic factors have been shown to modify synaptic plasticity including BDNF, which plays a pivotal role in hippocampus-dependent learning and memory (Lu et al., 2009). BDNF promotes synaptic plasticity, in part, by enhancing mitochondrial energy production because it increases glucose utilization in cultured cortical neurons in response to enhanced energy demand (Burkhalter et al., 2003) and increases mitochondrial respiratory coupling at Complex I (Markham et al., 2004). Consistent with this possibility, BDNF expression and signalling is increased in response to environmental factors such as exercise, cognitive stimulation and dietary energy restriction that increase cellular energy demand (Mattson et al., 2004).

Many questions remain unanswered concerning the roles of mitochondria in synaptic plasticity. Are mitochondria in presynaptic terminals phenotypically different from those in dendrites? If and how does synaptic activity affect mitochondrial function and motility? This could be determined by combining manipulations of specific signalling components (glutamate receptors, Ca^{2+}-dependent and other kinases, cyclic nucleotides, nitric oxide etc.) with high-resolution imaging-based measurements of mitochondrial motility and functional status (membrane potential, ROS and Ca^{2+} levels etc.). Behavioural and electrophysiological evaluation of synaptic plasticity in mice with a conditional knockdown of proteins with specific roles in mitochondrial motility (Drp1, Fis1, Mfn and OPA) and function [components of the mitochondrial ETC (electron transport chain), PTP (protein tyrosine phosphatase), Ca^{2+} handling systems, for example] should help establish the roles of these proteins in synaptic plasticity.

Mitochondrial biogenesis and neuroplasticity

Mitochondrial biogenesis is defined simply as the growth and division of mitochondria. The human mitochondrial genome contains 37 genes that encode 13 polypeptides, 22 tRNAs and two rRNAs. All 13 polypeptides are subunits of electron transport protein complexes in the inner membrane of mitochondria. The vast majority of mitochondrial proteins (~1000 proteins) are encoded by nuclear genes and include proteins involved in controlling mitochondrial membrane potential and ion fluxes, ATP production, and fission and fusion. These nuclear DNA-encoded mitochondrial proteins are imported into mitochondria, wherein they are sorted to their sites of action (Figure 4). In addition, the growth of mitochondria requires the synthesis of lipid bilayers of the inner and outer mitochondrial membranes. Mitochondrial DNA replication and mitochondrial fission and fusion mechanisms must also be co-ordinated.

PGC1α (peroxisome-proliferator-activated receptor γ co-activator 1α) is a master regulator of mitochondrial biogenesis (Figure 4). PGC1α is expressed at high levels in mitochondria-rich cells with high energy demands, including cardiac myocytes, skeletal-muscle cells and neurons (Andersson and Scarpulla, 2001). It is a transcriptional co-activator that lacks DNA-binding activity; instead it interacts with and co-activates numerous transcription factors, including nuclear receptors such as PPARγ (peroxisome-proliferator-activated receptor γ), PPARα, oestrogen, thyroid hormone and retinoid receptors, and other nuclear transcription factors such as Nrf1 (nuclear respiratory factor 1). Nrf1 can activate the expression of mitochondrial target genes, including the mitochondrial transcription factor (TFAM), a factor critical for the initiation of mitochondrial DNA transcription and replication. Nrf1 can further regulate the transcription of nuclear genes encoding respiratory complex subunits and other mitochondrial proteins.

An interesting aspect of mitochondrial biogenesis is that it is influenced by dietary energy intake and expenditure. CR (caloric restriction) and exercise stimulate mitochondrial biogenesis in muscle and nerve cells by a PGC1α-mediated mechanism (Puigserver et al., 1998; Yoon et al., 2001; Baar et al., 2002; Lin et al., 2004; Norrbom et al., 2004; Nisoli et al., 2005; López-Lluch et al., 2006). As described above, PGC1α activates several transcription factors involved in the regulation of mitochondrial biogenesis, lipid metabolism and antioxidant response. PGC-lα protein is very abundant in neural progenitor cells and newly generated neurons in the embryonic and early postnatal brain, suggesting a role for PGC-lα in the dynamic processes of neuroplasticity occurring during this time period (Cowell et al., 2007). PGC1α-knockout mice exhibit behavioral abnormalities and progressive cellular vacuolization in various brain regions (Lin et al., 2004). Both CR and exercise can stimulate adult neurogenesis and enhance synaptic plasticity, which may enhance cognitive function and the ability of the brain to resist aging (Ingram et al., 1987; Pitsikas and Algeri, 1992; van Praag et al., 1999; Eckles-Smith et al., 2000; Kempermann et al., 2000; Mattson et al., 2003). It is conceivable that CR can enhance neural plasticity during aging by maintaining PGC-1α-and mitochondrial turnover, as has been described in muscle cells of animals maintained on CR (Hepple et al., 2006). CR can enhance mitochondrial bioenergetics in neurons by increasing cellular NAD^+ levels and increasing the activity of the NAD^+-dependent histone deacetylase sirtuin-1 (Liu et al., 2008). Mild mitochondrial uncoupling and CR exert hormetic effects by stimulating bioenergetics in neurons, thereby increasing tolerance of neurons to metabolic stress and facilitating plasticity.

Several signalling molecules known to regulate neural plasticity also modify mitochondrial biogenesis; examples include nitric oxide, oestrogen, and growth factors, including BDNF, EGF (epidermal growth factor) and bFGF (basic

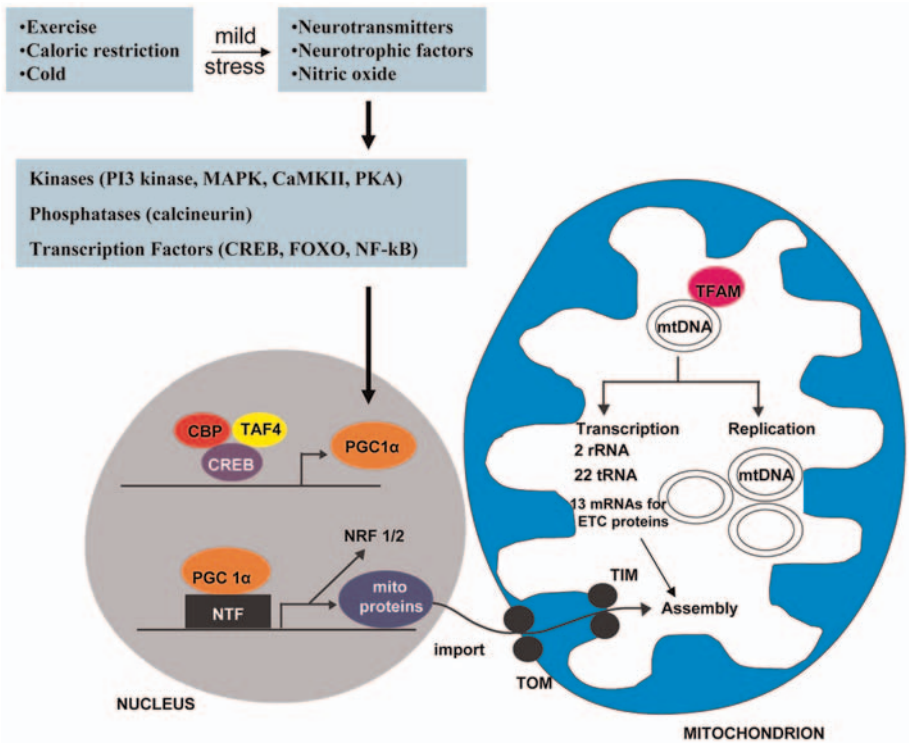

Figure 4 **Mechanisms that regulate the growth and function of mitochondria**

The vast majority of mitochondrial proteins are encoded by nuclear genes, whereas only 13 proteins that are all components of the ETC are encoded by mitochondrial genes. Proteins are imported into mitochondria by translocases of the outer membrane (TOM) and inner membrane (TIM) in a mitochondrial membrane potential-dependent manner. Mitochondrial DNA transcription is mediated by an RNA polymerase, the transcription factor A (TFAM), TFB1M or TFB2M for transcription initiation, and mTERE for transcription termination. Neurons contain particularly high levels of PGC1α, apparently because of their high energy utilization. PGC1α is a transcriptional co-activator that interacts with various transcription factors, including the nuclear receptors PPARγ, PPARα, oestrogen, thyroid hormone and retinoid receptors and Nrf1/2. Nrf1/2 induces the transcription of nuclear genes that encode ETC proteins, TFAM and proteins critical for mitochondrial biogenesis. Environmental factors (exercise, energy restriction and cold temperature, for example) activate signalling pathways involving neurotransmitters, neurotrophic factors and nitric oxide (for example), and intracellular cascades involving Ca^{2+}, CaMKII (Ca^{2+}/calmodulin-dependent protein kinase II), the phosphatase calcineurin, and the transcription factor CREB (cAMP-response-element-binding protein). In this manner, PGC1α is activated and mitochondrial biogenesis is stimulated. Modified from Mattson et al. (2008).

fibroblast growth factor; Barsoum et al., 2006; Gutsaeva et al., 2008; Klinge, 2008; Hebert et al., 2009; Renton et al., 2010). Oestrogen, BDNF and nitric oxide each play critical roles in modulating neurogenesis, hippocampal synaptic plasticity and learning and memory (Cheng et al., 2003; Foy et al., 2008; Hojo et al., 2008; Nikonenko et al., 2008; Brinton, 2009; Harooni et al., 2009; Minichiello, 2009; Vincent, 2009). Thus there are several prominent signalling pathways that stimulate mitochondrial biogenesis and energy metabolism, while simultaneously regulating neuroplasticity. However, in most cases the data linking mitochondrial biogenesis to neuronal plasticity are associational in nature, and cause–effect relationships remain to be established. It will be of considerable interest to selectively inhibit mitochondrial biogenesis using molecular genetic approaches that target PGC-1α to establish roles for mitochondrial biogenesis in experimental models of neuroplasticity.

Inherited neurodegenerative disorders provide clues to the functions of mitochondria in neuroplasticity

PD (Parkinson's disease) is characterized by the progressive degeneration of dopaminergic and noradrenergic neurons that control motor and autonomic nervous system function respectively (Halliday et al., 1990). Mitochondrial dysfunction is believed to be an early and pivotal event in PD, because (i) the activities of enzymes involved in mitochondrial energy production are reduced early in the disease process (Schulz and Beal, 1994); (ii) toxins that selectively inhibit mitochondrial Complex I can induce PD-like pathology and symptoms in rodents, monkeys and humans (Greenamyre et al., 1999); and (iii) some cases of inherited PD result from mutations in genes encoding proteins involved in mitochondrial physiology (Nuytemans et al., 2010). Recessively inherited

loss-of-function mutations in three such genes, *Parkin*, *DJ-1* and *Pink1*, compromise mitochondrial biogenesis and function (Figure 5). Parkin mutations result in impaired mitochondrial Complex I activity and abnormalities in mitochondrial structure and fusion (Mortiboys et al., 2008; Park et al., 2009). Studies of Parkin-deficient neurons suggest that this E3 ubiquitin ligase plays a role in synaptic plasticity, possibly by suppressing neurotransmitter release. Studies of nigrostriatal neurons in Parkin-null mice suggest that Parkin is a negative regulator of dopamine release (Goldberg et al., 2003). Knockdown of endogenous Parkin in cultured hippocampal neurons enhances glutamatergic transmission and increases neuronal vulnerability to synaptic excitotoxicity (Helton et al., 2008). DJ-1, which localizes to mitochondria in neurons (Zhang et al., 2005), plays an essential role in long-term decrease of synaptic transmission (Wang et al., 2008c), suggesting that impaired synaptic plasticity plays an early role in the pathogenesis of PD.

Further evidence that perturbed mitochondrial function is sufficient to cause synaptic dysfunction and PD comes from studies of PINK1 [PTEN (phosphatase and tensin homologue deleted on chromosome 10)-induced kinase 1; Figure 5]. PINK1 deficiency or PD-causing PINK1 mutations impair mitochondrial Complex I activity, resulting in mitochondrial membrane depolarization and increased vulnerability to stress (Morais et al., 2009). An early functional abnormality in PINK1 mutant animals is impaired neurotransmitter release from presynaptic terminals, a problem that can be corrected by increasing cellular ATP levels (Morais et al., 2009).

Mutations in LRRK2 (leucine-rich repeat kinase 2) are responsible for some cases of autosomal dominantly inherited PD; LRRK2 associates with the mitochondrial outer membrane and interacts with Parkin (Mata et al., 2006). LRRK2 has been shown to modify the vulnerability of cells to mitochondrial dysfunction, with PD mutant forms of LRRK2 promoting mitochondrial dysfunction (Saha et al., 2009). Primary cultured neurons derived from LRRK2 G2019S mutant transgenic mice exhibit increased growth cone size and reduced neurite outgrowth characterized by increased levels of F-actin in the growth cones (Parisiadou et al., 2009), suggesting an adverse gain-of-function effect of this LRRK2 mutation on neuronal plasticity. The evidence that multiple genetic aberrancies cause PD by adversely affecting mitochondrial function and biogenesis suggests that the earliest impairments of synaptic plasticity in this disease are the result of mitochondrial abnormalities.

Some cases of AD (Alzheimer's disease) are inherited in an autosomal dominant manner as the result of mutations in APP (amyloid precursor protein) or presenilin-1 (Mattson, 2004). Both APP and presenilin-1 are believed to play roles in developmental and synaptic plasticity, and mutations in these proteins have been reported to alter neurogenesis and synaptic plasticity (Mattson, 1997). There is evidence that the secreted form of APP generated by α-secretase cleavage of APP enhances neurogenesis (Caillé et al., 2004) and synaptic plasticity (Ishida et al., 1997). On the other hand, the Aβ (amyloid β-peptide) generated by β- and γ-secretases can impair neurogenesis (Haughey et al., 2002a, 2002b) and synaptic plasticity (Chapman et al., 1999). Inasmuch as Aβ impairs mitochondrial function (Keller et al., 1998), there may be a role for perturbed mitochondrial function in the adverse effects of Aβ on neural plasticity (Mattson et al., 1998), although this remains to be established. In the case of presenilin-1 there is a well-established mechanism by which this protease regulates neurogenesis and adult neuroplasticity, namely presenilin-1 cleaves Notch to generate the NICD (Notch intracellular domain), which then translocates to the nucleus where it modulates the transcription of genes involved in regulating neuroplasticity (Lathia et al., 2008). Studies of *Drosophila* (Presente et al., 2004) and mice with reduced Notch levels (Costa et al., 2003; Wang et al., 2004) have demonstrated a critical role for Notch signalling in synaptic plasticity and learning and memory. Presenilin-1 mutations that cause AD have been reported to impair neurogenesis by perturbing Notch signalling (Veeraraghavalu et al., 2010) and may also impair some forms of synaptic plasticity (Auffret et al., 2010). Whether there is a role for mitochondrial changes in the actions of Notch signalling on neuroplasticity is unknown; however, it has been reported that Notch signalling interacts with mitochondrial remodelling proteins (Perumalsamy et al., 2010), suggesting a potential role for mitochondria in some biological effects of Notch signalling.

Perturbed mitochondrial behaviours are also implicated in the impaired synaptic plasticity, and motor and cognitive deficits, in HD (Huntington's disease). Polyglutamine repeat expansions in the huntingtin protein cause HD, and several lines of transgenic mice expressing such mutant huntingtin proteins develop neurodegenerative changes in the striatum and cerebral cortex, and motor and cognitive deficits similar to HD. In one HD mouse model, layer II/III neurons in the perirhinal cortex exhibit impaired LTP, which is associated with nuclear accumulation of mutant huntingtin and membrane depolarization (e.g. Cummings et al., 2006). LTP at hippocampal synapses is impaired in HD mutant mice (Usdin et al., 1999). Accumulating data point to mitochondrial abnormalities as an early consequence of mutant huntingtin that contributes to impaired neural plasticity. Early events may include defective mitochondrial calcium handling, ATP production and trafficking (Oliveira, 2010). Mutant huntingtin can impair transcription of nuclear genome-encoded mitochondrial proteins, and may also inhibit biogenesis and subcellular trafficking of mitochondria.

The kinds of findings described in the preceding paragraphs suggest that impaired neural plasticity occurs in the earliest stages of neurodegenerative disorders, and abnormalities in mitochondrial function, motility and biogenesis may contribute to the early dysfunction of neurons. The complexity of the architecture and signalling processes in neuronal circuits provides the basis for sophisticated behaviours including higher cognitive functions

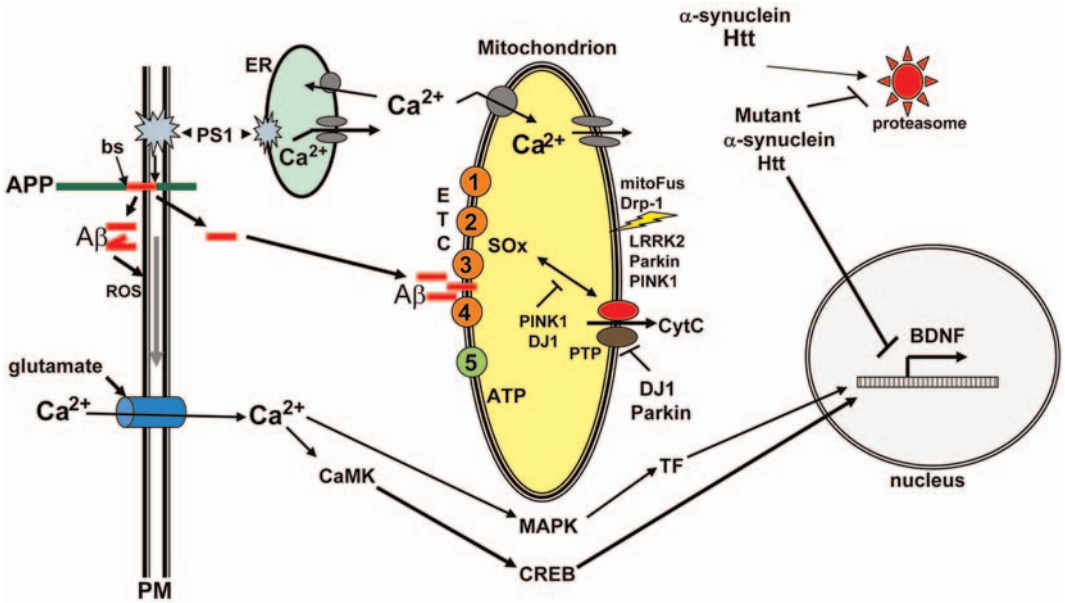

Figure 5 **Influence of neurodegenerative disease-related proteins proteins on mitochondrial function and plasticity**
The AD APP is a single-pass transmembrane protein that includes the 42-amino-acid Aβ (red). Aβ is liberated upon sequential cleavages of APP by β-secretase (bs) at the N-terminus of Aβ and γ-secretase at the C-terminus of Aβ; the latter cleavage is executed by presenilin-1 (PS1; an integral membrane protein that is the enzymatic component of the γ-secretase protein complex). An alternative cleavage of APP within the Aβ sequence by the α-secretase enzyme produces a secreted form of APP that is believed to play important roles in developmental and synaptic plasticity, and neuron survival. Whereas Aβ is normally cleared from the brain, in AD it self-aggregates to form oligomers and during this process ROS are generated and propagated to the cell membrane, resulting in lipid peroxidation, impairment of membrane ion (Na^+ and Ca^{2+}) transporters and excessive Ca^{2+} influx through glutamate receptor (NMDA) channels. In addition to increasing Aβ production, mutations in PS1 that cause AD perturb endoplasmic reticulum (ER) Ca^{2+}, resulting in excessive Ca^{2+} release. Mitochondrial Ca^{2+} homoeostasis and energy production may be impaired in neurons in AD as the result of cellular Ca^{2+} overload and increased oxidative stress possibly involving direct actions of Aβ on mitochondrial membranes. The pathological scenario just described involves perturbations in signalling pathways normally involved in adaptive neuroplasticity, with glutamate signalling being a well-established example. Glutamate-induced Ca^{2+} is normally transient with the Ca^{2+} activating kinases such as CaMK and MAPK. The kinases in turn activate transcription factors (TF) that induce the expression of nuclear genes that encode proteins involved in effecting adaptive morphological and functional responses of the neurons. CREB is one such synaptic activity-responsive transcription factor that induces the expression of BDNF, a protein critically involved in synaptic plasticity and neuronal survival. The successive discoveries of genes-linked inherited forms of PD placed mitochondrial alterations at centre stage in the pathogenesis of PD, and also revealed novel proteins that regulate mitochondrial functional and structural plasticity. A feature of all cases of PD is the intracellular accumulation of α-synuclein, apparently as the result of impaired degradation by the proteasome. Parkin (an E3 ubiquitin ligase), DJ-1, PINK1 and LRRK2 have each been shown to modify mitochondrial function (ATP and ROS production), and some findings suggest that Parkin, PINK1 and LRRK2 also influence mitochondrial fission and fusion. PINK1 and DJ-1 may suppress intramitochondrial oxidative stress, whereas Parkin and DJ-1 inhibit the opening of mitochondrial permeability transition pores, thereby protecting neurons against apoptotic cell death that can be triggered by release of cytochrome *c* (CytC) from the mitochondria. Finally, in HD, mutant huntingtin (Htt) self-aggregates and impairs CREB-mediated transcription of BDNF, thereby compromising a pathway critical for neuronal plasticity and survival. See the text of this paper and the following references for additional information and discussion (Mattson, 1997; Mattson, 2004; Mattson et al., 2004; Cattaneo et al., 2005; Cookson, 2005; Nuytemans et al., 2010).

(language, decision making, creativity etc.). However, this cellular complexity increases the demands on the networks and the potential for 'weak links' (neurons that are particularly prone to faltering under adverse conditions such as traumatic injury, stroke, diabetes and aging). The development of therapeutic interventions aimed at enhancing mitochondrial function and plasticity in vulnerable neurons is an active area for preclinical and translational research for many neurological disorders (Mattson et al., 2008). Indeed, preclinical studies have demonstrated beneficial effects of creatine (a chemical that facilitates regeneration of ATP in mitochondria) in animal models of neurodegenerative disorders (Adhihetty and Beal, 2008) and traumatic brain injury (Sullivan et al., 2000). Additional mitochondria-focused treatments that show promise in preclinical studies include Mn-SOD (manganese superoxide dismutase) mimetics (Brazier et al., 2008), mitochondrial uncoupling agents (Liu et al., 2006; Pandya et al., 2007) and coenzyme Q10 (Chaturvedi and Beal, 2008).

FUTURE DIRECTIONS

While considerable data have accrued regarding the localization of mitochondria at subcellular sites where plasticity occurs and the movement and fission or fusion of

mitochondria in response to signals that induce plasticity, questions remain just correlative and/or unanswered concerning the roles of mitochondria in neuroplasticity. To establish roles of mitochondrial energy production, redox and Ca^{2+} signalling, motility and biogenesis in neuroplasticity, several approaches may be employed: (i) use RNA interference technology to knock down the expression or function of proteins involved in specific mitochondrial events such as fission/fusion, biogenesis or targeted inhibition of mitochondrial mobility and functions selectively in subcellular compartments such as synapse, dendrites or axons. This could be accomplished in both cell culture and *in vivo* models. (ii) Perform time lapse analysis of mitochondrial movements within subcellular compartments in response to physiological stimuli, and in combination with selective ablation and/or artificial movement of mitochondria may establish the requirement of mitochondria for specific physiological events (neurite outgrowth and dendritic remodelling). (iii) Behavioural and electrophysiological evaluation of synaptic plasticity in mice with conditional knockout of proteins with specific roles in mitochondrial motility (Drp1, Mfn1/2 and OPA1) and biogenesis (PGC1α and TFAM). (iv) Utilization of novel fluorescent probes for mitochondrial superoxide, in combination with superoxide scavengers (Mn-SOD mimetics, for example). As such technologies are becoming widely available, it is very likely that there will be a rapid acceleration of our knowledge of how, where and why mitochondria respond to and regulate neural plasticity and how abnormalities in such mechanisms contribute to the pathogenesis of neurological disorders.

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