Title Page

Mitochondrial dynamics and quality control in Huntington's disease

Pedro Guedes-Dias[1,2], Brígida R. Pinho[1], Tânia R. Soares[1], João de Proença[1], Michael R. Duchen[2], Jorge M. A. Oliveira[1,*]

[1]*REQUIMTE/LAQV*, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal
[2]Department of Cell and Developmental Biology, University College London, London, WC1E 6BT, UK

*Corresponding author at: Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Rua Jorge Viterbo Ferreira, 228, 4050-313 Porto, Portugal. Tel.: +351 220 428 610; E-mail: jorgemao@ff.up.pt.

Neurobiology of Disease, Special Issue:
Role of mitochondria in physiological and pathophysiological functions in the central nervous system
Guest Editors:
Dr. Giovanni Marsicano, Dr. Giovanni Bénard, Dr. Sandrine Pouvreau

Abstract

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by polyglutamine expansion mutations in the huntingtin protein. Despite its ubiquitous distribution, expression of mutant huntingtin (mHtt) is particularly detrimental to medium spiny neurons within the striatum. Mitochondrial dysfunction has been associated with HD pathogenesis. Here we review the current evidence for mHtt-induced abnormalities in mitochondrial dynamics and quality control, with a particular focus on brain and neuronal data pertaining to striatal vulnerability. We address mHtt effects on mitochondrial biogenesis, protein import, complex assembly, fission and fusion, mitochondrial transport, and on the degradation of damaged mitochondria via autophagy (mitophagy). For an integrated perspective on potentially converging pathogenic mechanisms, we also address impaired autophagosomal transport and abnormal mHtt proteostasis in HD.

Keywords:

Mitochondria; Huntington's disease; huntingtin; mitochondrial dynamics; mitophagy

Abbreviations:

Ambra1, activating molecule in Beclin1-regulated autophagy 1; Atg, autophagic related protein; BDNF, brain-derived neurotrophic factor; BNIP3, BCL2/adenovirus E1B 19 kDa interacting protein 3; CREB, cAMP response element-binding; DIC, dynein intermediate chain; Drp1, dynamin-related protein 1; FEZ1, fasciculation and elongation protein zeta-1; Fis1, mitochondrial fission protein 1; GABARAPL1, GABA(A) receptor-associated protein like 1; HAP1, huntingtin-associated protein 1; HDAC, Histone deacetylase; HD, Huntington's disease; Htt, huntingtin; iPS cells, induced pluripotent stem cells; Mff, mitochondrial fission factor; Mfn, mitofusin; mHtt, mutant huntingtin; MiD, mitochondrial dynamics protein; Miro, mitochondrial Rho GTPase; mtDNA/nDNA, mitochondrial/nuclear DNA ratio; MSNs, medium spiny neurons; NIX (BNIP3L), BNIP3-like; NMDAR, NMDA receptor; NRF, nuclear respiratory factor; OPA1, optic atrophy 1; PolyQ, polyglutamine; PPAR, peroxisome proliferator-activated receptor, PGC-1α, PPAR γ coactivator 1α; PINK1, PTEN-induced putative kinase 1; RanBP2, Ran-binding protein 2; Rhes, Ras homolog enriched in striatum; TAF4, TBP (TATA box binding protein)-associated factor 4;

TIM, translocase of the inner membrane; TOM, translocase of the outer membrane; TRAK, trafficking kinesin protein; TrkB, tyrosin-related kinase B.

1. Introduction

Huntington's disease (HD) is a dominantly inherited neurodegenerative disease characterized by motor dysfunction, cognitive decline and psychiatric disturbances (Ross et al., 2011). HD is caused by CAG trinucleotide repeat expansion mutations that encode abnormally large polyglutamine (polyQ) stretches at the N-terminal of the huntingtin (Htt) protein (HDCRG, 1993). Mutations between 36 and 40 polyQ have incomplete penetrance, whereas mutations beyond 41 polyQ are fully penetrant (Walker, 2007). Individuals express mutant Htt (mHtt) during their whole lifetime. While HD onset is most frequent in the 4th decade of life, the age of onset is inversely correlated with the polyQ expansion size, and very large expansions may cause juvenile or even infantile HD (Ross et al., 2011; Seneca et al., 2004). Significantly, despite ubiquitous expression of mHtt in the brain and peripheral tissues, preferential atrophy of the striatum is observed even prior to onset of the manifestations of disease (Aylward et al., 2011; Paulsen et al., 2010). Striatal atrophy stems from the degeneration of GABAergic medium spiny neurons (MSNs), which normally constitute approximately 95% of the striatal neuronal population (Ehrlich, 2012). The basis for the selective vulnerability of the striatal MSNs to mHtt remains an outstanding question in the field.

Several mechanisms have been proposed to contribute to HD pathogenesis involving both gain-of-function of mHtt and loss-of-function of normal Htt (Zuccato et al., 2010). These include transcriptional dysregulation (Francelle et al., 2014), synaptic dysfunction and excitotoxicity (Plotkin et al., 2015; Sepers et al., 2014), differential mHtt proteostasis (Margulis et al., 2014), defects in intracellular transport (Hinckelmann et al., 2013), and mitochondrial dysfunction (Costa et al., 2012; Oliveira, 2010a; Reddy et al., 2012).

Neurons are particularly vulnerable to mitochondrial dysfunction given their energetic dependence on oxidative phosphorylation (Bolanos et al., 2010; Oliveira, 2011), their polarized morphology which requires efficient mitochondrial distribution to provide ATP and calcium buffering to distant synapses (Leitao-Rocha et al., 2015; Schwarz, 2013), and their postmitotic nature that demands effective mitochondrial quality control mechanisms (Amadoro et al., 2014). Mitochondria differ across tissues, cell-types and even sub-cellular compartments within neurons (Dubinsky,

2009; Kuznetsov et al., 2009). Indeed, inherent differences in mitochondrial function, or in susceptibility to mitochondrial dysfunction, are proposed to mediate the differential neuronal vulnerability in several neurodegenerative disorders, including HD (Brustovetsky et al., 2003; Dubinsky, 2009; Oliveira et al., 2009; Pickrell et al., 2011).

Here we review the current evidence for disturbed mitochondrial dynamics in HD, with a particular focus on brain and neuronal data pertaining to striatal vulnerability. We use the term mitochondrial dynamics to comprise several processes from the mitochondrial life cycle that mediate mitochondrial generation (biogenesis), adoption of morphology and size (fission-fusion), transport, and degradation. We address mitochondrial dynamics together with the subject of mitochondrial quality control since these dynamics are embedded in the pathways that segregate or recognize damaged mitochondria, and assist their autophagic clearance (mitophagy) (Ni et al., 2015). For a broader perspective, the discussion of biogenesis will include changes in mitochondrial protein import and complex assembly, whereas quality control will be complemented with data on autophagosomal transport and mHtt proteostasis in HD.

2. Mitochondrial Biogenesis

Mitochondrial biogenesis requires a tight coordination between the nuclear, cytosolic and mitochondrial compartments, since only a minority (13 proteins) of the full mammalian mitochondrial proteome (about 1,100 to 1,500 proteins) is locally encoded in the mitochondrial DNA (mtDNA; (Meisinger et al., 2008; Pagliarini et al., 2008). The transcriptional co-activator PGC-1α is considered the master regulator of the mitochondrial biogenesis program, acting in concert with nuclear respiratory factors NRF1 and NRF2 (Scarpulla, 2011). Proteins translated in the cytosol may be targeted to mitochondria via positively charged N-terminal presequences recognized by the translocase of the outer membrane (TOM), and then transferred to the translocase of the inner membrane (TIM23) in a membrane potential-dependent manner (Schmidt et al., 2010). Proteins within the TIM23 complex may fully translocate to the mitochondrial matrix or insert into the inner membrane, where some will integrate into respiratory complexes (Harbauer et al., 2014; Schulz et al., 2015).

Impaired PGC-1α signalling and defective mitochondrial biogenesis were suggested to contribute for striatal vulnerability in HD following data from PGC-1α knockout mice. These PGC-1α$^{-/-}$ mice exhibited behavioural changes consistent with neurodegeneration, presenting spongiform lesions primarily in the striatum and, less prominently, in the motor cortex and hippocampus (Lin et al., 2004). More recently, PGC1α suppression in cultured neurons was found to contribute to mHtt-induced increases in extrasynaptic NMDAR activity and vulnerability to excitotoxic insults (Puddifoot et al., 2012). In wild-type mice, PGC-1α mRNA levels were identical in striatum and cortex, but mitochondrial/nuclear DNA ratios (mtDNA/nDNA) and citrate synthase activity were higher in the striatum (Hering et al., 2015; Pickrell et al., 2011). Interestingly, in R6/2 HD mice, PGC-1α mRNA levels were similarly decreased in the striatum and cortex; however, only the striatum presented decreased mtDNA/nDNA (Hering et al., 2015), suggesting that the striatum may be particularly susceptible to reduced PGC-1α expression.

In early-stage HD patients, PGC-1α mRNA levels were decreased in the striatum (caudate nucleus), but not in the hippocampus or cerebellum (Cui et al., 2006; Weydt et al., 2006). Within the striatum, data from CAG140 knock-in mice showed that PGC-1α mRNA levels were decreased in MSNs and increased in cholinergic interneurons, which are mostly spared in HD (Cui et al., 2006). The mechanism by which striatal PGC-1α transcription is differently affected in MSNs and interneurons is unknown. Nevertheless, mHtt is thought to repress PGC-1α transcription by associating with the promoter region and interfering with the activation functions of the transcription factors CREB and TAF4 (Cui et al., 2006) (Figure 1A).

It was recently reported that mHtt inhibits protein import into mitochondria *in vitro* (isolated mouse forebrain mitochondria and HdhQ111 striatal cell line) and *in vivo* (R6/2 mice) (Jonas, 2014; Yano et al., 2014). Using immunoprecipitation and TIM23 overexpression experiments, the authors suggest that mitochondrial protein import is inhibited by the direct interaction of mHtt with the TIM23 complex (Yano et al., 2014) (Figure 1B). Although the association between mHtt and mitochondria has been previously reported (reviewed in (Oliveira, 2010b), its sub-mitochondrial localization remains unsettled. Indeed, full-length mHtt was found associated with the mitochondrial outer membrane in HdhQ111 cells (Choo et al., 2004), whereas N-terminal mHtt in R6/2 mice was found associated with the surface of the

mitochondrial membrane, but also clustered within degenerating mitochondria (Yu et al., 2003). As the direct interaction between mHtt and TIM23 was reported for both HdhQ111 cells and R6/2 mice (Yano et al., 2014), this recent data suggests that both full-length and N-terminal mHtt are associated with the mitochondrial inner membrane. Moreover, since the deficit in protein import was more pronounced in synaptosomal versus non-synaptosomal or liver mitochondria, and was present in pre-symptomatic R6/2 mice without significant changes in mitochondrial respiratory control, the authors hypothesize that import impairment might be an early abnormality intrinsic to neurons (Yano et al., 2014). It would thus be interesting to assess whether this import defect might be particularly pronounced or detrimental to striatal MSNs.

In addition to protein import, TIM23 assists the assembly of respiratory complexes (Mick et al., 2012), thus opening the possibility that mHtt-TIM23 interactions would disturb such assembly. It is presently unclear whether defective complex assembly contributes for HD pathology. Indeed, whereas one study reported defective complex II assembly and activity in striatal mitochondria from mice injected with N-terminal mHtt (Damiano et al., 2013), another study reported normal assembly and activity of respiratory complexes in striatal and cortical mitochondria from R6/2 mice (Hering et al., 2015). Nevertheless, other lines of evidence suggest that the direct interaction between mHtt and neuronal mitochondria is a relevant component of HD pathology, contributing to calcium handling defects (Panov et al., 2002), disrupted mitochondrial trafficking (Orr et al., 2008) and excessive mitochondrial fission (Song et al., 2011).

3. Mitochondrial fission and fusion

Fission and fusion events modulate mitochondrial morphology, number and size. Fission allows isolation of defective mitochondria, partition during mitosis, and distribution along neuronal processes (Otera et al., 2011). Drp1, a GTPase, is the main mediator of mitochondrial fission, forming constricting spirals that split both outer and inner mitochondrial membranes (Smirnova et al., 2001); whereas Fis1, Mff, MiD49 and MiD51 are key effector proteins that mediate Drp1 recruitment and assembly on the outer membrane of mammalian mitochondria (DuBoff et al., 2013). Fusion allows functional complementation, mixing mtDNA, RNA, proteins and lipids

between mitochondria (Youle et al., 2012). Mitofusins Mfn1 and Mfn2 mediate the fusion of mitochondrial outer membranes, whereas OPA1 mediates the fusion of inner membranes (Mishra et al., 2014).

In HD, evidence suggests that mitochondrial dynamics is unbalanced towards fission (Costa et al., 2010; Oliveira et al., 2010). Advanced stage HD patients exhibited elevated mRNA and protein levels of the fission-associated Drp1 and Fis1, together with decreased levels of mitofusins in striatal and cortical regions (Kim et al., 2010; Shirendeb et al., 2011). Similarly, the cortex of BACHD mice also exhibited increased mRNA levels of Drp1 and Fis1, together with decreased levels for Mfn1 and Mfn2; being consistent with the increased mitochondrial fragmentation found in cultured cortical neurons from these HD mice (Shirendeb et al., 2012). The mechanisms by which mHtt alters the expression of mitochondrial fission-fusion genes remain uncertain. Mitochondria in striatal neurons may be particularly prone to mHtt-induced fragmentation given that they show an intrinsically higher balance towards fission than cortical mitochondria (Guedes-Dias et al., 2015). Moreover, mHtt may promote mitochondrial fission via direct interaction with Drp1 (Song et al., 2011) or by promoting post-translational modifications that enhance Drp1 activity (Chang et al., 2010), as addressed below and illustrated in Figure 2.

Increased levels of S-nitrosylated Drp1 were found in the brain of HD patients, and also in the striatum but not in the cerebellum of BACHD mice (Haun et al., 2013). S-nitrosylation of Drp1 was reported to enhance its GTPase activity (Cho et al., 2009), whereas expression of S-nitrosylation-resistant Drp1 prevented mitochondrial fragmentation in neurons expressing mHtt (Haun et al., 2013). Mechanistically, mHtt expression increases neuronal nitric oxide (NO) production and is more extensively nitrosylated than wild-type Htt, leading to the hypothesis that mHtt-Drp1 interaction facilitates the transfer of NO to Drp1, thereby enhancing mitochondrial fragmentation in HD (Haun et al., 2013).

The affinity of mHtt for Drp1 is higher than that of wild-type Htt, as judged from immunoprecipitation experiments with brain homogenates from HD patients and mouse models (Song et al., 2011). The interaction of mHtt with Drp1 increased its GTPase activity *in vitro*, suggesting that this interaction could promote mitochondrial fragmentation in HD (Song et al., 2011). In agreement with this hypothesis, Drp1 GTPase activity was increased in the cortex of HD patients, and also in the striatum and cortex of BACHD mice (Shirendeb et al., 2012). Significantly, upregulation of

Drp1 GTPase activity was stronger in the striatum than in the cortex of BACHD mice (Shirendeb et al., 2012).

P110 is a peptide designed to block Drp1 interaction with Fis1 and so to inhibit mitochondrial fission (Qi et al., 2013). Treatment of HdhQ111 cells and MSNs (derived from HD iPS cells) with P110 reduced mitochondrial fragmentation and superoxide formation, and increased mitochondrial membrane potential (Guo et al., 2013). Furthermore, treatment with P110 suppressed striatal neuronal loss, improved motor activity and reduced mortality in R6/2 HD mice (Guo et al., 2013), suggesting that improving mitochondrial dynamics and bioenergetics may have a beneficial effect on the disease progression. In this context, pharmacological inhibition of the tubulin deacetylase HDAC6 was found to promote mitochondrial motility and fusion in wild-type striatal neurons, reducing their intrinsic mitochondrial fragmentation and approximating their fission-fusion balance to that of the less HD-vulnerable cortical neurons (Guedes-Dias et al., 2015). Further studies are thus warranted to assess the impact of HDAC6 inhibition on the mitochondrial dynamics of HD neurons.

4. Mitochondrial and vesicle transport

Transport along microtubules is mainly mediated by two superfamilies of opposing motors: kinesins and dyneins. The kinesin-1/KIF5 family is the main mediator of mitochondrial anterograde transport and, in mammals, binds mitochondria through syntabulin, FEZ1, RanBP2 (MacAskill et al., 2010), or the Miro/TRAK1 adaptor complex (van Spronsen et al., 2013). Dynein mediates retrograde mitochondrial transport, forming a complex with dynactin that binds mitochondria through Miro and TRAK1 or TRAK2 (van Spronsen et al., 2013).

Mitochondrial transport was impaired in neurons expressing mHtt (Chang et al., 2006; Orr et al., 2008; Trushina et al., 2004), however, the mechanisms remain uncertain. Large mHtt aggregates may block axoplasmic flow, aggregates may sequester motor proteins, and diffuse mHtt may disrupt the trafficking complexes and their binding to mitochondria or microtubules (Oliveira, 2010b; Orr et al., 2008). Significantly, mitochondrial transport in cortical neurons was disrupted specifically at sites of mHtt aggregates (Chang et al., 2006), whereas in striatal neurons, impairment

occurred before mHtt aggregate formation (Orr et al., 2008). Thus, striatal neurons may be particularly vulnerable to trafficking impairment by diffuse mHtt.

In addition to mitochondria, mHtt impairs the fast axonal transport of vesicles, such as those containing BDNF, more severely in striatal than in cortical neurons (Her et al., 2008). The neurotrophin BDNF is transported in vesicles along cortical axons projecting to the striatum, using the kinesin-1 motor and the Htt/Htt-associated protein 1 (HAP1) scaffolding complex (Gauthier et al., 2004). The Htt-HAP1 complex also mediates the vesicular transport of the BDNF receptor TrkB in striatal dendrites (Xiang et al., 2014), and this TrkB transport was found impaired in striatal neurons expressing mHtt (Liot et al., 2013). Impaired BDNF signalling has been thought to contribute for selective striatal vulnerability in HD (Gauthier et al., 2004; Zuccato et al., 2007), and recent evidence suggest that a defective postsynaptic response to BDNF due to reduced TrkB transport and availability may be a more prominent cause for impaired BDNF signalling in HD than disturbed BDNF delivery to the striatum (Liot et al., 2013; Plotkin et al., 2014).

The polyQ expansion in mHtt may also impair autophagosomal transport (Wong et al., 2014). Neuronal autophagosomes are generated distally and display robust retrograde movement along the axon towards the soma, where most cargo degradation likely takes place (Lee et al., 2011; Maday et al., 2014; Maday et al., 2012). Dynein and kinesin motors are both present in autophagosomes (Maday et al., 2012), however, regulation by scaffolding complexes limits kinesin processivity to sustain the dynein-mediated retrograde transport (Fu et al., 2014). Recent evidence suggests that Htt and HAP1 form a scaffolding complex in a subpopulation of LC3-positive neuronal autophagosomes that enhances their dynein-dynactin-driven transport toward the soma (Wong et al., 2014). The polyQ expansion in mHtt enhances its affinity for HAP1 (Li et al., 1995). mHtt may thus disrupt the normal Htt-HAP1 association, impairing autophagosomal transport and limiting the clearance of cargo, such as damaged mitochondria (Wong et al., 2014) (Figure 3).

Htt and mHtt show preferential association with the neuron-specific dynein subunit DIC1A, versus the ubiquitous DIC2C (Wong et al., 2014). Although potentially contributing for neuron-selective pathology, it seems unlikely that the mHtt-DIC1A association determines striatal vulnerability as DIC1A is expressed in multiple brain regions (Kuta et al., 2010). Nevertheless, since the Htt-HAP1 scaffolding complex seems confined to a subpopulation of autophagosomes (Wong et al., 2014), it would

be interesting to address whether such subpopulation is enriched in the HD vulnerable striatal MSNs, and also if it has a prominent role in transporting defective mitochondria or mHtt for autophagic degradation.

5. Mitophagy and huntingtin proteostasis

The clearance of defective mitochondria has been proposed to rely on the activity of the PINK1/Parkin mitophagy pathway (Pickrell et al., 2015). PINK1 accumulates in the outer membrane of depolarized mitochondria, and recruits the E3-ubiquitin ligase Parkin (Burté et al., 2015). Parkin-dependent ubiquitination promotes the degradation of Miro and Mfn1/2, respectively, arresting the movement and fusion of damaged mitochondria (Ashrafi et al., 2015; Birsa et al., 2014; Tanaka et al., 2010; Wang et al., 2011). Autophagy receptors such as optineurin or p62 may then link ubiquitinated mitochondria to autophagosomal LC3, thereby mediating engulfment for mitophagic digestion after autophagosome-lysosome fusion (Martinez-Vicente et al., 2010; Rui et al., 2015; Wong et al., 2014) (Figure 3).

Several studies suggest that the removal of defective mitochondria may be compromised in HD. Impaired mitophagy was recently reported in flies expressing neuronal Htt-ex1p-Q93 and in HdhQ111 striatal cells lines, being associated with decreased targeting of ubiquitinated mitochondria to autophagosomes (Khalil et al., 2015). The same study reported that PINK1 overexpression was neuroprotective in flies and restored mitophagy in HdhQ111 cells, and the proposed mechanism was that PINK1 overexpression might lower the threshold of mitochondrial damage that must be crossed before mitophagy occurs (Khalil et al., 2015).

The hypothesis that mitochondrial loading into autophagosomes is compromised in HD has been previously suggested following data from non-neuronal models, and was proposed to stem from an abnormal interaction between mHtt and the autophagy receptor p62 (Martinez-Vicente et al., 2010). Data from neuronal HD models, however, failed to identify impaired mitochondrial loading, but rather pointed to the accumulation of undigested mitochondria due to disturbances in the autophagosomal transport, which is required for efficient fusion with lysosomes (Wong et al., 2014) (Figure 3).

Wild-type Htt has been proposed to play a physiological role in mitophagy, either by its interaction with autophagy receptors or due to its similarity with autophagy-related proteins. Specifically, the Htt C-terminal was reported to interact with p62 to facilitate p62-mediated cargo recognition, and this was considered relevant for mitophagy since Htt-deficient cells presented lower mitophagy levels (Rui et al., 2015). Further, the Htt C-terminal domain exhibits strong similarities with the yeast autophagic related protein 11 (Atg11) (Ochaba et al., 2014). Since mitophagy in yeast involves the interaction between cytosolic Atg11 and mitochondrial Atg32 (Kanki et al., 2015), and since the Htt C-terminal can interact with mammalian Atg32 homologues (BNIP3 and NIX), mammalian mitophagy is proposed to involve Htt-BNIP3/NIX interactions (Ochaba et al., 2014). Significantly, BNIP3 and NIX also interact with autophagosomal LC3, and while the BNIP3/NIX-associated mitophagy pathway has been primarily associated with reticulocyte maturation (Ney, 2015), recent evidence implicates this pathway in neuronal mitophagy (Shi et al., 2014). Thus, wild-type Htt may have a role in mitophagy that is disturbed by mHtt, nevertheless, whether and how N-terminal polyQ disturbs the interaction of the C-terminal with mitochondria remains undetermined.

In addition to changes in mitophagy, differences in mHtt proteostasis may also play a role in HD pathogenesis, namely by influencing the levels of toxic mHtt species (Margulis et al., 2014). Indeed, evidence suggests that differential mHtt proteostasis, namely the mHtt lifetime and mHtt aggregate formation, condition neuronal survival. Specifically, diffuse mHtt mean lifetime directly correlates with neuronal death and is higher in striatal than in cortical or cerebellar neurons (Tsvetkov et al., 2013). Moreover, striatal neurons form less mHtt aggregates than cortical neurons (Guedes-Dias et al., 2015; Gutekunst et al., 1999), and the survival of neurons without aggregates is inversely proportional to their levels of diffuse mHtt (Arrasate et al., 2004). High expression of the Rhes protein in the striatum supports increased mHtt lifetime in this region: Rhes binds to mHtt and promotes its sumoylation, which increases the levels of soluble mHtt and reduces mHtt ubiquitination and aggregation (Subramaniam et al., 2009). Moreover, studies in PC12 cells indicate that Rhes binds Beclin-1 and activates autophagy, and that this Rhes-induced autophagic activation is blocked by mHtt co-expression (Mealer et al., 2014). The mechanisms behind differential mHtt proteostasis in striatal and cortical neurons may thus involve differences in autophagy, being relevant that striatal

neurons with higher autophagic flux (lower LC3 mean lifetime) were found to survive longer in the presence of mHtt (Tsvetkov et al., 2013).

Although we found no published studies that directly compare autophagic flux in cortical versus striatal neurons expressing mHtt (but see (Baldo et al., 2013), data from wild-type neurons suggest that there are differences in autophagy in these neuronal populations. Indeed, lower autophagic flux (lower p62 accumulation after autophagy inhibition with bafilomycin) was detected in wild-type striatal versus cortical neurons (Guedes-Dias et al., 2015). Moreover, levels of the autophagic protein GABARAPL1 (mammalian homologue of yeast Atg8) were lower in the striatum compared to the cortex of the adult mouse brain (Le Grand et al., 2013). Furthermore, levels of Ambra1 (activating molecule in Beclin1-regulated autophagy; (Fimia et al., 2007) were lower in MSNs when compared with interneurons from the adult mouse striatum (Sepe et al., 2014). Taken together with evidence that the 'mitophagy capacity' (proportion of mitochondria in autophagosomes) was also lower in the wild-type mouse striatum versus cortex (Diedrich et al., 2011), these data support the hypothesis that striatal vulnerability in HD may involve an intrinsically lower autophagic degradation capacity, which might limit the efficient degradation of mHtt and dysfunctional mitochondria.

Pharmacological induction of autophagy is thus a potential strategy to reduce mHtt lifetime and striatal vulnerability. Treatment with the autophagy inducer 10-NCP decreased diffuse mHtt levels in striatal neurons and extended their survival (Tsvetkov et al., 2010). Tubastatin A, an inhibitor of the α-tubulin deacetylase HDAC6, was recently shown to promote neuronal autophagic flux and reduce diffuse mHtt levels in striatal neurons (Guedes-Dias et al., 2015). Encouragingly, HDAC6 inhibition in an Alzheimer's disease mouse model facilitated the autophagic degradation of amyloid-β and hyperphosphorylated tau, ameliorating behavioral and cognitive deficits (Zhang et al., 2014). Further studies will be required to assess the impact of these pharmacological strategies in mouse models of HD, and how they affect mitochondrial dynamics and quality control *in vivo*.

6. Concluding Remarks

Impaired mitochondrial dynamics and quality control pathways seem to be emerging as common themes in a number of major neurodegenerative diseases, leading to disturbed mitochondrial bioenergetics and cell death in affected neuronal populations. The literature reviewed here suggests that mHtt may impair neuronal mitochondrial dynamics and quality control by several mechanisms. Mitochondrial biogenesis may be decreased through reduced PGC-1α expression, coupled with impaired protein import attributed to mHtt interaction with TIM23. Reduced expression of fusion proteins and increased expression/activity of fission-associated Drp1 are associated with excessive mitochondrial fission in the HD striatum. Striatal neurons seem particularly vulnerable to trafficking impairment by diffuse mHtt, which may disrupt trafficking complexes such as the normal Htt-HAP1 association involved in retrograde autophagosomal transport. Together with impaired cargo loading by disturbed interactions with autophagic receptors, disturbed transport may compromise the efficient autophagic degradation of mHtt and mitochondria. These cumulative effects of mHtt on mitochondrial dynamics are predictably detrimental to mitochondrial bioenergetics and quality control, and are likely to impact neuronal homeostasis, given the high-energy requirements, postmitotic nature, and polarized morphology of the neuron.

Pharmacological strategies that modulate mitochondrial function have been showing promising results in several HD models. Approaches to upregulate the PGC-1α pathway (e.g. PPAR agonists) were neuroprotective in cellular and mouse models of HD (Johri et al., 2013), and pharmacological inhibition of mitochondrial fission with P110 prevented striatal neuronal loss and reduced mortality of R6/2 HD mice (Guo et al., 2013). Lysine deacetylases (a.k.a. histone deacetylases; HDACs) may also constitute viable targets for the modulation of mitochondrial function (Guedes-Dias et al., 2013). Significantly, pharmacological pan-inhibition of HDACs improved mitochondrial calcium handling in striatal neurons expressing mHtt (Oliveira et al., 2006), while selective inhibition of the α-tubulin deacetylase HDAC6 promoted mitochondrial motility and fusion, and also increased autophagic flux and mHtt clearance in striatal neurons ((Guedes-Dias et al., 2015).

Why mHtt expression is particularly damaging to striatal MSNs remains incompletely understood, but increased susceptibility to impaired mitochondrial dynamics and quality control may be an important piece of the HD pathogenic puzzle.

Pharmacological approaches capable of rescuing impaired mitochondrial dynamics and quality control are thus likely to hold therapeutic potential to reduce the vulnerability of striatal MSNs in HD.

Acknowledgements

JMAO acknowledges support by Fundação para a Ciência e a Tecnologia (FCT): Strategic award UID/QUI/50006/2013, and the research grant PTDC/NEU-NMC/0237/2012 (PI: JMAO), co-financed by the European Union (FEDER, QREN, COMPETE) – FCOMP-01-0124-FEDER-029649. BRP acknowledges FCT for her PostDoc Grant (SFRH/BPD/102259/2014). PGD and TRS acknowledge FCT for their PhD Grants (SFRH/BD/72071/2010 and SFRH/BD/108733/2015, respectively). MRD is a member of the UK Parkinson's Disease consortium (www.ucl.ac.uk/ukpdc) funded through a Wellcome Trust and Medical Research Council strategic grant (WT089698/Z/09/Z).

Author contributions

PGD performed the majority of literature search and wrote the manuscript draft. BRP, TRS, JdP and MRD contributed to search and writing. JMAO coordinated the work and wrote the manuscript. All authors read and approved the final version.

References

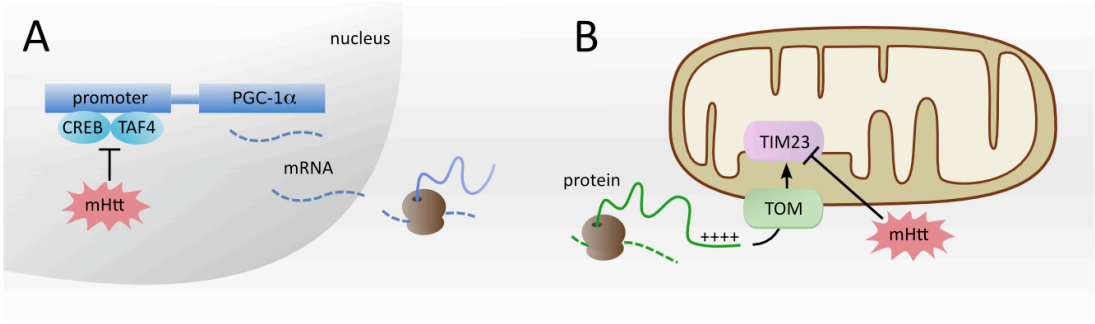

Figure 1. Impaired mitochondrial biogenesis and protein import in HD. **A**, Mutant Htt (mHtt) interference with the activation functions of the transcription factors CREB and TAF4 may reduce PGC-1α transcription (Cui et al., 2006). **B**, An interaction between mHtt and the TIM23 complex may impair mitochondrial protein import in HD (Yano et al., 2014).

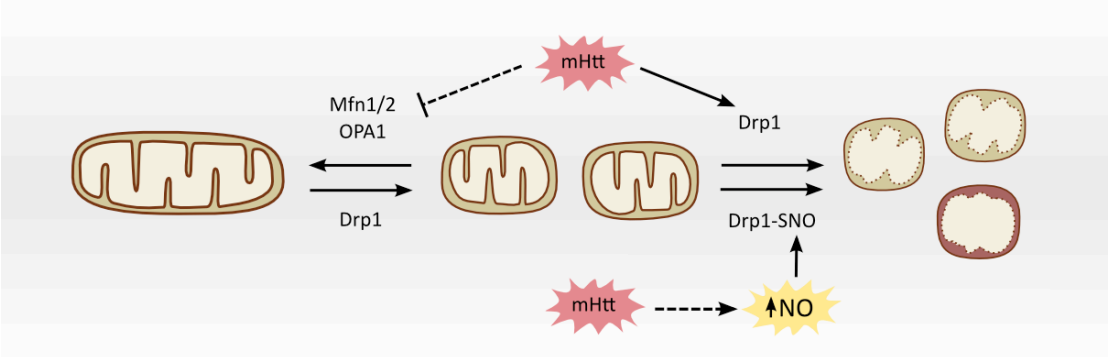

Figure 2. Excessive mitochondrial fission in HD. Mutant Htt (mHtt)-induced decreases in the expression of mitofusins (Mfn1/2); upregulation of Drp1 expression/activity (Shirendeb et al., 2011; Shirendeb et al., 2012; Song et al., 2011); and increased nitric oxide (NO) leading to Drp1 S-nitrosylation (Drp1-SNO) may promote excessive mitochondrial fission in HD (Haun et al., 2013).

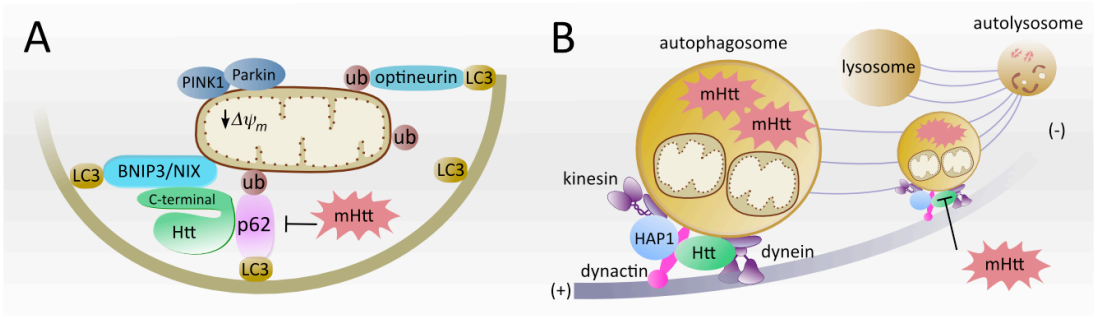

Figure 3. Impaired mitophagy and autophagosomal transport in HD. **A,** Mutant Htt (mHtt)-mediated disruption of the normal interactions between C-terminal Htt and the autophagic receptors (p62 or BNIP3/NIX) may compromise the recognition of ubiquitinated (ub) mitochondria by LC3-containing isolation membranes (Martinez-Vicente et al., 2010; Ochaba et al., 2014; Rui et al., 2015). **B**, Wild-type Htt and Htt-associated protein 1 (HAP1) form a scaffolding complex that limits kinesin processivity and sustains dynein-dynactin-driven retrograde autophagosomal transport. Impairment of this retrograde transport by mHtt may limit autophagosome-lysosome fusion and the degradation of cargo such as mHtt or dysfunctional mitochondria (Wong et al., 2014).

Amadoro G., Corsetti V., Florenzano F., Atlante A., Bobba A., Nicolin V., Nori S.L., Calissano P., 2014. Morphological and bioenergetic demands underlying the mitophagy in post-mitotic neurons: the pink-parkin pathway. Front Aging Neurosci 6, 18.

Arrasate M., Mitra S., Schweitzer E.S., Segal M.R., Finkbeiner S., 2004. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. Nature 431, 805-810.

Ashrafi G., Schwarz T.L., 2015. PINK1- and PARK2-mediated local mitophagy in distal neuronal axons. Autophagy 11, 187-189.

Aylward E.H., Nopoulos P.C., Ross C.A., Langbehn D.R., Pierson R.K., Mills J.A., Johnson H.J., Magnotta V.A., Juhl A.R., Paulsen J.S., Investigators P.-H., Coordinators of Huntington Study G., 2011. Longitudinal change in regional brain volumes in prodromal Huntington disease. J Neurol Neurosurg Psychiatry 82, 405-410.

Baldo B., Soylu R., Petersen A., 2013. Maintenance of basal levels of autophagy in Huntington's disease mouse models displaying metabolic dysfunction. PLoS One 8, e83050.

Birsa N., Norkett R., Wauer T., Mevissen T.E., Wu H.C., Foltynie T., Bhatia K., Hirst W.D., Komander D., Plun-Favreau H., Kittler J.T., 2014. Lysine 27 ubiquitination of the mitochondrial transport protein Miro is dependent on serine 65 of the Parkin ubiquitin ligase. J Biol Chem 289, 14569-14582.

Bolanos J.P., Almeida A., Moncada S., 2010. Glycolysis: a bioenergetic or a survival pathway? Trends Biochem Sci 35, 145-149.

Brustovetsky N., Brustovetsky T., Purl K.J., Capano M., Crompton M., Dubinsky J.M., 2003. Increased susceptibility of striatal mitochondria to calcium-induced permeability transition. J Neurosci 23, 4858-4867.

Burté F., Carelli V., Chinnery P.F., Yu-Wai-Man P., 2015. Disturbed mitochondrial dynamics and neurodegenerative disorders. Nat Rev Neurol 11, 11-24.

Chang C.R., Blackstone C., 2010. Dynamic regulation of mitochondrial fission through modification of the dynamin-related protein Drp1. Ann N Y Acad Sci 1201, 34-39.

Chang D.T., Rintoul G.L., Pandipati S., Reynolds I.J., 2006. Mutant huntingtin aggregates impair mitochondrial movement and trafficking in cortical neurons. Neurobiol Dis 22, 388-400.

Cho D.H., Nakamura T., Fang J., Cieplak P., Godzik A., Gu Z., Lipton S.A., 2009. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. Science 324, 102-105.

Choo Y.S., Johnson G.V., MacDonald M., Detloff P.J., Lesort M., 2004. Mutant huntingtin directly increases susceptibility of mitochondria to the calcium-induced permeability transition and cytochrome c release. Hum Mol Genet 13, 1407-1420.

Costa V., Giacomello M., Hudec R., Lopreiato R., Ermak G., Lim D., Malorni W., Davies K.J., Carafoli E., Scorrano L., 2010. Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli. EMBO Mol Med 2, 490-503.

Costa V., Scorrano L., 2012. Shaping the role of mitochondria in the pathogenesis of Huntington's disease. EMBO J 31, 1853-1864.

Cui L., Jeong H., Borovecki F., Parkhurst C.N., Tanese N., Krainc D., 2006. Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 127, 59-69.

Damiano M., Diguet E., Malgorn C., D'Aurelio M., Galvan L., Petit F., Benhaim L., Guillermier M., Houitte D., Dufour N., Hantraye P., Canals J.M., Alberch J., Delzescaux T., Deglon N., Beal M.F., Brouillet E., 2013. A role of mitochondrial complex II defects in genetic models of Huntington's disease expressing N-terminal fragments of mutant huntingtin. Hum Mol Genet 22, 3869-3882.

Diedrich M., Kitada T., Nebrich G., Koppelstaetter A., Shen J., Zabel C., Klose J., Mao L., 2011. Brain region specific mitophagy capacity could contribute to selective neuronal vulnerability in Parkinson's disease. Proteome Sci 9, 59.

Dubinsky J.M., 2009. Heterogeneity of nervous system mitochondria: location, location, location! Exp Neurol 218, 293-307.

DuBoff B., Feany M., Gotz J., 2013. Why size matters - balancing mitochondrial dynamics in Alzheimer's disease. Trends Neurosci 36, 325-335.

Ehrlich M.E., 2012. Huntington's disease and the striatal medium spiny neuron: cell-autonomous and non-cell-autonomous mechanisms of disease. Neurotherapeutics 9, 270-284.

Fimia G.M., Stoykova A., Romagnoli A., Giunta L., Di Bartolomeo S., Nardacci R., Corazzari M., Fuoco C., Ucar A., Schwartz P., Gruss P., Piacentini M., Chowdhury K., Cecconi F., 2007. Ambra1 regulates autophagy and development of the nervous system. Nature 447, 1121-1125.

Francelle L., Galvan L., Brouillet E., 2014. Possible involvement of self-defense mechanisms in the preferential vulnerability of the striatum in Huntington's disease. Front Cell Neurosci 8, 295.

Fu M.M., Nirschl J.J., Holzbaur E.L., 2014. LC3 binding to the scaffolding protein JIP1 regulates processive dynein-driven transport of autophagosomes. Dev Cell 29, 577-590.

Gauthier L.R., Charrin B.C., Borrell-Pages M., Dompierre J.P., Rangone H., Cordelieres F.P., De Mey J., MacDonald M.E., Lessmann V., Humbert S., Saudou F., 2004. Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell 118, 127-138.

Guedes-Dias P., de Proenca J., Soares T.R., Leitao-Rocha A., Pinho B.R., Duchen M.R., Oliveira J.M., 2015. HDAC6 inhibition induces mitochondrial fusion, autophagic flux and reduces diffuse mutant huntingtin in striatal neurons. Biochim Biophys Acta.

Guedes-Dias P., Oliveira J.M., 2013. Lysine deacetylases and mitochondrial dynamics in neurodegeneration. Biochim Biophys Acta 1832, 1345-1359.

Guo X., Disatnik M.H., Monbureau M., Shamloo M., Mochly-Rosen D., Qi X., 2013. Inhibition of mitochondrial fragmentation diminishes Huntington's disease-associated neurodegeneration. J Clin Invest 123, 5371-5388.

Gutekunst C.A., Li S.H., Yi H., Mulroy J.S., Kuemmerle S., Jones R., Rye D., Ferrante R.J., Hersch S.M., Li X.J., 1999. Nuclear and neuropil aggregates in Huntington's disease: relationship to neuropathology. J Neurosci 19, 2522-2534.

Harbauer A.B., Zahedi R.P., Sickmann A., Pfanner N., Meisinger C., 2014. The protein import machinery of mitochondria-a regulatory hub in metabolism, stress, and disease. Cell Metab 19, 357-372.

Haun F., Nakamura T., Shiu A.D., Cho D.H., Tsunemi T., Holland E.A., La Spada A.R., Lipton S.A., 2013. S-nitrosylation of dynamin-related protein 1 mediates mutant huntingtin-induced mitochondrial fragmentation and neuronal injury in Huntington's disease. Antioxid Redox Signal 19, 1173-1184.

HDCRG, 1993. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 72, 971-983.

Her L.S., Goldstein L.S., 2008. Enhanced sensitivity of striatal neurons to axonal transport defects induced by mutant huntingtin. J Neurosci 28, 13662-13672.

Hering T., Birth N., Taanman J.W., Orth M., 2015. Selective striatal mtDNA depletion in end-stage Huntington's disease R6/2 mice. Exp Neurol 266, 22-29.

Hinckelmann M.V., Zala D., Saudou F., 2013. Releasing the brake: restoring fast axonal transport in neurodegenerative disorders. Trends Cell Biol 23, 634-643.

Johri A., Chandra A., Beal M.F., 2013. PGC-1alpha, mitochondrial dysfunction, and Huntington's disease. Free Radic Biol Med 62, 37-46.

Jonas E.A., 2014. Impaired import: how huntingtin harms. Nat Neurosci 17, 747-749.

Kanki T., Furukawa K., Yamashita S.I., 2015. Mitophagy in yeast: Molecular mechanisms and physiological role. Biochim Biophys Acta.

Khalil B., El Fissi N., Aouane A., Cabirol-Pol M.J., Rival T., Lievens J.C., 2015. PINK1-induced mitophagy promotes neuroprotection in Huntington's disease. Cell Death Dis 6, e1617.

Kim J., Moody J.P., Edgerly C.K., Bordiuk O.L., Cormier K., Smith K., Beal M.F., Ferrante R.J., 2010. Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. Hum Mol Genet 19, 3919-3935.

Kuta A., Deng W., Morsi El-Kadi A., Banks G.T., Hafezparast M., Pfister K.K., Fisher E.M., 2010. Mouse cytoplasmic dynein intermediate chains: identification of new isoforms, alternative splicing and tissue distribution of transcripts. PLoS One 5, e11682.

Kuznetsov A.V., Hermann M., Saks V., Hengster P., Margreiter R., 2009. The cell-type specificity of mitochondrial dynamics. Int J Biochem Cell Biol 41, 1928-1939.

Le Grand J.N., Bon K., Fraichard A., Zhang J., Jouvenot M., Risold P.Y., Boyer-Guittaut M., Delage-Mourroux R., 2013. Specific distribution of the autophagic protein GABARAPL1/GEC1 in the developing and adult mouse brain and identification of neuronal populations expressing GABARAPL1/GEC1. PLoS One 8, e63133.

Lee S., Sato Y., Nixon R.A., 2011. Lysosomal proteolysis inhibition selectively disrupts axonal transport of degradative organelles and causes an Alzheimer's-like axonal dystrophy. J Neurosci 31, 7817-7830.

Leitao-Rocha A., Guedes-Dias P., Pinho B.R., Oliveira J.M., 2015. Trends in mitochondrial therapeutics for neurological disease. Curr Med Chem.

Li X.J., Li S.H., Sharp A.H., Nucifora F.C., Jr., Schilling G., Lanahan A., Worley P., Snyder S.H., Ross C.A., 1995. A huntingtin-associated protein enriched in brain with implications for pathology. Nature 378, 398-402.

Lin J., Wu P.H., Tarr P.T., Lindenberg K.S., St-Pierre J., Zhang C.Y., Mootha V.K., Jager S., Vianna C.R., Reznick R.M., Cui L., Manieri M., Donovan M.X., Wu Z., Cooper M.P., Fan M.C., Rohas L.M., Zavacki A.M., Cinti S., Shulman G.I., Lowell B.B., Krainc D., Spiegelman B.M., 2004. Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. Cell 119, 121-135.

Liot G., Zala D., Pla P., Mottet G., Piel M., Saudou F., 2013. Mutant Huntingtin alters retrograde transport of TrkB receptors in striatal dendrites. J Neurosci 33, 6298-6309.

MacAskill A.F., Kittler J.T., 2010. Control of mitochondrial transport and localization in neurons. Trends Cell Biol 20, 102-112.

Maday S., Holzbaur E.L., 2014. Autophagosome biogenesis in primary neurons follows an ordered and spatially regulated pathway. Dev Cell 30, 71-85.

Maday S., Wallace K.E., Holzbaur E.L., 2012. Autophagosomes initiate distally and mature during transport toward the cell soma in primary neurons. J Cell Biol 196, 407-417.

Margulis J., Finkbeiner S., 2014. Proteostasis in striatal cells and selective neurodegeneration in Huntington's disease. Front Cell Neurosci 8, 218.

Martinez-Vicente M., Talloczy Z., Wong E., Tang G., Koga H., Kaushik S., de Vries R., Arias E., Harris S., Sulzer D., Cuervo A.M., 2010. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. Nat Neurosci 13, 567-576.

Mealer R.G., Murray A.J., Shahani N., Subramaniam S., Snyder S.H., 2014. Rhes, a striatal-selective protein implicated in Huntington disease, binds beclin-1 and activates autophagy. J Biol Chem 289, 3547-3554.

Meisinger C., Sickmann A., Pfanner N., 2008. The mitochondrial proteome: from inventory to function. Cell 134, 22-24.

Mick D.U., Dennerlein S., Wiese H., Reinhold R., Pacheu-Grau D., Lorenzi I., Sasarman F., Weraarpachai W., Shoubridge E.A., Warscheid B., Rehling P., 2012. MITRAC links mitochondrial protein translocation to respiratory-chain assembly and translational regulation. Cell 151, 1528-1541.

Mishra P., Chan D.C., 2014. Mitochondrial dynamics and inheritance during cell division, development and disease. Nat Rev Mol Cell Biol 15, 634-646.

Ney P.A., 2015. Mitochondrial autophagy: Origins, significance, and role of BNIP3 and NIX. Biochim Biophys Acta.

Ni H.M., Williams J.A., Ding W.X., 2015. Mitochondrial dynamics and mitochondrial quality control. Redox Biol 4, 6-13.

Ochaba J., Lukacsovich T., Csikos G., Zheng S., Margulis J., Salazar L., Mao K., Lau A.L., Yeung S.Y., Humbert S., Saudou F., Klionsky D.J., Finkbeiner S., Zeitlin S.O., Marsh J.L.,

Housman D.E., Thompson L.M., Steffan J.S., 2014. Potential function for the Huntingtin protein as a scaffold for selective autophagy. Proc Natl Acad Sci U S A 111, 16889-16894.

Oliveira J.M., 2010a. Mitochondrial bioenergetics and dynamics in Huntington's disease: tripartite synapses and selective striatal degeneration. J Bioenerg Biomembr 42, 227-234.

Oliveira J.M., 2010b. Nature and cause of mitochondrial dysfunction in Huntington's disease: focusing on huntingtin and the striatum. J Neurochem 114, 1-12.

Oliveira J.M., 2011. Techniques to investigate neuronal mitochondrial function and its pharmacological modulation. Curr Drug Targets 12, 762-773.

Oliveira J.M., Chen S., Almeida S., Riley R., Goncalves J., Oliveira C.R., Hayden M.R., Nicholls D.G., Ellerby L.M., Rego A.C., 2006. Mitochondrial-dependent Ca2+ handling in Huntington's disease striatal cells: effect of histone deacetylase inhibitors. J Neurosci 26, 11174-11186.

Oliveira J.M., Goncalves J., 2009. In situ mitochondrial Ca2+ buffering differences of intact neurons and astrocytes from cortex and striatum. J Biol Chem 284, 5010-5020.

Oliveira J.M., Lightowlers R.N., 2010. Could successful (mitochondrial) networking help prevent Huntington's disease? EMBO Mol Med 2, 487-489.

Orr A.L., Li S., Wang C.E., Li H., Wang J., Rong J., Xu X., Mastroberardino P.G., Greenamyre J.T., Li X.J., 2008. N-terminal mutant huntingtin associates with mitochondria and impairs mitochondrial trafficking. J Neurosci 28, 2783-2792.

Otera H., Mihara K., 2011. Molecular mechanisms and physiologic functions of mitochondrial dynamics. J Biochem 149, 241-251.

Pagliarini D.J., Calvo S.E., Chang B., Sheth S.A., Vafai S.B., Ong S.E., Walford G.A., Sugiana C., Boneh A., Chen W.K., Hill D.E., Vidal M., Evans J.G., Thorburn D.R., Carr S.A., Mootha V.K., 2008. A mitochondrial protein compendium elucidates complex I disease biology. Cell 134, 112-123.

Panov A.V., Gutekunst C.A., Leavitt B.R., Hayden M.R., Burke J.R., Strittmatter W.J., Greenamyre J.T., 2002. Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci 5, 731-736.

Paulsen J.S., Nopoulos P.C., Aylward E., Ross C.A., Johnson H., Magnotta V.A., Juhl A., Pierson R.K., Mills J., Langbehn D., Nance M., Investigators P.-H., Coordinators of the Huntington's Study G., 2010. Striatal and white matter predictors of estimated diagnosis for Huntington disease. Brain Res Bull 82, 201-207.

Pickrell A.M., Fukui H., Wang X., Pinto M., Moraes C.T., 2011. The striatum is highly susceptible to mitochondrial oxidative phosphorylation dysfunctions. J Neurosci 31, 9895-9904.

Pickrell A.M., Youle R.J., 2015. The roles of PINK1, parkin, and mitochondrial fidelity in Parkinson's disease. Neuron 85, 257-273.

Plotkin J.L., Day M., Peterson J.D., Xie Z., Kress G.J., Rafalovich I., Kondapalli J., Gertler T.S., Flajolet M., Greengard P., Stavarache M., Kaplitt M.G., Rosinski J., Chan C.S., Surmeier D.J., 2014. Impaired TrkB receptor signaling underlies corticostriatal dysfunction in Huntington's disease. Neuron 83, 178-188.

Plotkin J.L., Surmeier D.J., 2015. Corticostriatal synaptic adaptations in Huntington's disease. Curr Opin Neurobiol 33C, 53-62.

Puddifoot C., Martel M.A., Soriano F.X., Camacho A., Vidal-Puig A., Wyllie D.J., Hardingham G.E., 2012. PGC-1alpha negatively regulates extrasynaptic NMDAR activity and excitotoxicity. J Neurosci 32, 6995-7000.

Qi X., Qvit N., Su Y.C., Mochly-Rosen D., 2013. A novel Drp1 inhibitor diminishes aberrant mitochondrial fission and neurotoxicity. J Cell Sci 126, 789-802.

Reddy P.H., Shirendeb U.P., 2012. Mutant huntingtin, abnormal mitochondrial dynamics, defective axonal transport of mitochondria, and selective synaptic degeneration in Huntington's disease. Biochim Biophys Acta 1822, 101-110.

Ross C.A., Tabrizi S.J., 2011. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol 10, 83-98.

Rui Y.N., Xu Z., Patel B., Chen Z., Chen D., Tito A., David G., Sun Y., Stimming E.F., Bellen H.J., Cuervo A.M., Zhang S., 2015. Huntingtin functions as a scaffold for selective macroautophagy. Nat Cell Biol 17, 262-275.

Scarpulla R.C., 2011. Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. Biochim Biophys Acta 1813, 1269-1278.

Schmidt O., Pfanner N., Meisinger C., 2010. Mitochondrial protein import: from proteomics to functional mechanisms. Nat Rev Mol Cell Biol 11, 655-667.

Schulz C., Schendzielorz A., Rehling P., 2015. Unlocking the presequence import pathway. Trends Cell Biol 25, 265-275.

Schwarz T.L., 2013. Mitochondrial trafficking in neurons. Cold Spring Harb Perspect Biol 5.

Seneca S., Fagnart D., Keymolen K., Lissens W., Hasaerts D., Debulpaep S., Desprechins B., Liebaers I., De Meirleir L., 2004. Early onset Huntington disease: a neuronal degeneration syndrome. Eur J Pediatr 163, 717-721.

Sepe S., Nardacci R., Fanelli F., Rosso P., Bernardi C., Cecconi F., Mastroberardino P.G., Piacentini M., Moreno S., 2014. Expression of Ambra1 in mouse brain during physiological and Alzheimer type aging. Neurobiol Aging 35, 96-108.

Sepers M.D., Raymond L.A., 2014. Mechanisms of synaptic dysfunction and excitotoxicity in Huntington's disease. Drug Discov Today 19, 990-996.

Shi R.Y., Zhu S.H., Li V., Gibson S.B., Xu X.S., Kong J.M., 2014. BNIP3 interacting with LC3 triggers excessive mitophagy in delayed neuronal death in stroke. CNS Neurosci Ther 20, 1045-1055.

Shirendeb U., Reddy A.P., Manczak M., Calkins M.J., Mao P., Tagle D.A., Reddy P.H., 2011. Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington's disease: implications for selective neuronal damage. Hum Mol Genet 20, 1438-1455.

Shirendeb U.P., Calkins M.J., Manczak M., Anekonda V., Dufour B., McBride J.L., Mao P., Reddy P.H., 2012. Mutant huntingtin's interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington's disease. Hum Mol Genet 21, 406-420.

Smirnova E., Griparic L., Shurland D.L., van der Bliek A.M., 2001. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Mol Biol Cell 12, 2245-2256.

Song W., Chen J., Petrilli A., Liot G., Klinglmayr E., Zhou Y., Poquiz P., Tjong J., Pouladi M.A., Hayden M.R., Masliah E., Ellisman M., Rouiller I., Schwarzenbacher R., Bossy B., Perkins G., Bossy-Wetzel E., 2011. Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Nat Med 17, 377-382.

Subramaniam S., Sixt K.M., Barrow R., Snyder S.H., 2009. Rhes, a striatal specific protein, mediates mutant-huntingtin cytotoxicity. Science 324, 1327-1330.

Tanaka A., Cleland M.M., Xu S., Narendra D.P., Suen D.F., Karbowski M., Youle R.J., 2010. Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. J Cell Biol 191, 1367-1380.

Trushina E., Dyer R.B., Badger J.D., 2nd, Ure D., Eide L., Tran D.D., Vrieze B.T., Legendre-Guillemin V., McPherson P.S., Mandavilli B.S., Van Houten B., Zeitlin S., McNiven M., Aebersold R., Hayden M., Parisi J.E., Seeberg E., Dragatsis I., Doyle K., Bender A., Chacko C., McMurray C.T., 2004. Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro. Mol Cell Biol 24, 8195-8209.

Tsvetkov A.S., Arrasate M., Barmada S., Ando D.M., Sharma P., Shaby B.A., Finkbeiner S., 2013. Proteostasis of polyglutamine varies among neurons and predicts neurodegeneration. Nat Chem Biol 9, 586-592.

Tsvetkov A.S., Miller J., Arrasate M., Wong J.S., Pleiss M.A., Finkbeiner S., 2010. A small-molecule scaffold induces autophagy in primary neurons and protects against toxicity in a Huntington disease model. Proc Natl Acad Sci U S A 107, 16982-16987.

van Spronsen M., Mikhaylova M., Lipka J., Schlager M.A., van den Heuvel D.J., Kuijpers M., Wulf P.S., Keijzer N., Demmers J., Kapitein L.C., Jaarsma D., Gerritsen H.C., Akhmanova A., Hoogenraad C.C., 2013. TRAK/Milton motor-adaptor proteins steer mitochondrial trafficking to axons and dendrites. Neuron 77, 485-502.

Walker F.O., 2007. Huntington's disease. Lancet 369, 218-228.

Wang X., Winter D., Ashrafi G., Schlehe J., Wong Y.L., Selkoe D., Rice S., Steen J., LaVoie M.J., Schwarz T.L., 2011. PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell 147, 893-906.

Weydt P., Pineda V.V., Torrence A.E., Libby R.T., Satterfield T.F., Lazarowski E.R., Gilbert M.L., Morton G.J., Bammler T.K., Strand A.D., Cui L., Beyer R.P., Easley C.N., Smith A.C., Krainc D., Luquet S., Sweet I.R., Schwartz M.W., La Spada A.R., 2006. Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. Cell Metab 4, 349-362.

Wong Y.C., Holzbaur E.L., 2014. The regulation of autophagosome dynamics by huntingtin and HAP1 is disrupted by expression of mutant huntingtin, leading to defective cargo degradation. J Neurosci 34, 1293-1305.

Xiang J., Yang H., Zhao T., Sun M., Xu X., Zhou X.F., Li S.H., Li X.J., 2014. Huntingtin-associated protein 1 regulates postnatal neurogenesis and neurotrophin receptor sorting. J Clin Invest 124, 85-98.

Yano H., Baranov S.V., Baranova O.V., Kim J., Pan Y., Yablonska S., Carlisle D.L., Ferrante R.J., Kim A.H., Friedlander R.M., 2014. Inhibition of mitochondrial protein import by mutant huntingtin. Nat Neurosci 17, 822-831.

Youle R.J., van der Bliek A.M., 2012. Mitochondrial fission, fusion, and stress. Science 337, 1062-1065.

Yu Z.X., Li S.H., Evans J., Pillarisetti A., Li H., Li X.J., 2003. Mutant huntingtin causes context-dependent neurodegeneration in mice with Huntington's disease. J Neurosci 23, 2193-2202.

Zhang L., Liu C., Wu J., Tao J.J., Sui X.L., Yao Z.G., Xu Y.F., Huang L., Zhu H., Sheng S.L., Qin C., 2014. Tubastatin A/ACY-1215 improves cognition in Alzheimer's disease transgenic mice. J Alzheimers Dis 41, 1193-1205.

Zuccato C., Cattaneo E., 2007. Role of brain-derived neurotrophic factor in Huntington's disease. Prog Neurobiol 81, 294-330.

Zuccato C., Valenza M., Cattaneo E., 2010. Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiol Rev 90, 905-981.