Focus Review

Shaping the role of mitochondria in the pathogenesis of Huntington's disease

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Intense research on the pathogenesis of Huntington's disease (HD), a genetic neurodegenerative disease caused by a polyglutamine expansion in the Huntingtin (Htt) protein, revealed multiple potential mechanisms, among which mitochondrial alterations had emerged as key determinants of the natural history of the disease. Pharmacological and genetic animal models of mitochondrial dysfunction in the striatum, which is mostly affected in HD corroborated a key role for these organelles in the pathogenesis of the disease. Here, we will give an account of the recent evidence indicating that the mitochondria-shaping machinery is altered in HD models and patients. Since its correction can counteract HD mitochondrial dysfunction and cellular damage, drugs impacting on mitochondrial shape are emerging as a new possibility of treatment for this devastating condition.

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Introduction

Huntington's disease (HD) is a genetic autosomal dominant neurodegenerative disorder for which no disease-modifying therapy currently exists. The mutation underlying HD consists in the abnormal expansion of the CAG repeats in the gene IT15 (4p16.3) (The Huntington's Disease Collaborative Research Group, 1993). Pathologic expansions contain a number of CAG repeats beyond 36, and the clinical severity directly correlates with length and dosage of the expansion. HD occurs with a frequency of ~1 in 10 000 individuals in populations of Caucasian descent (Hayden *et al*, 1981). Patients affected by HD display progressive motor dysfunctions characterized by abnormality of voluntary and involuntary movements (choreoathetosis) and psychiatric and cognitive disturbances (Martin and Gusella, 1986; Purdon

et al, 1994), which worsen over the course of the disease. While primarily apparent for the neurological picture, patients of HD suffer clearly from a multisystemic disease, as evident for several extraneurological symptoms: muscle wasting and weight loss, cardiac (Chiu and Alexander, 1982; Lanska *et al*, 1988; Sorensen and Fenger, 1992) and immunological defects (Leonardi *et al*, 1986). The main pathological feature of HD is the atrophy and gliosis in basal ganglia, supported in particular by the degeneration of GABAergic medium spiny projection neurons of the striatum (Ferrante *et al*, 1991).

The IT15 gene encodes for the protein Huntingtin (Htt) and the mutation results in the expansion of the polyglutamine domain in its first exon. Huntingtin is ubiquitously expressed, with the highest levels found in the brain and testis, and it bears no homology to any other known protein (Schilling *et al*, 1995; Sharp *et al*, 1995). Huntingtin is essential for embryogenesis and its ablation in mouse models results in early embryonic lethality (Duyao *et al*, 1995) accompanied by retarded development and increased apoptosis in the embryonic ectoderm. Interestingly, the observation that the lethal phenotype in knockout mice is rescued by expression of a mutant form of the protein (Hodgson *et al*, 1999) and that homozygous patients do not exhibit embryonic lethality (Wexler *et al*, 1987) suggests that the mutation in the polyglutamine domain does not interfere with the function of Huntingtin in the embryonic life. Huntingtin shows a broad subcellular localization and it exerts different localization-specific functions. In the cytosol it regulates vesicular and organelle trafficking (Trushina *et al*, 2004; Li and Li, 2005), endocytosis (Li *et al*, 1995) and it associates with a variety of subcellular structures: endoplasmic reticulum (ER) (Atwal and Truant, 2008), Golgi (Rockabrand *et al*, 2007) and mitochondria (Gutekunst *et al*, 1995; Panov *et al*, 2002). In the nucleus, it regulates gene transcription (Sugars and Rubinsztein, 2003). The pathological mechanisms activated by the mutation can be ascribed both to a loss of the physiological functions and gain of new toxic features. Huntingtin bearing expanded polyQ domain undergoes a conformational transition and is prone to aggregation (Scherzinger *et al*, 1997; Nagai *et al*, 2000), accumulating in the nucleus as well as in the cytoplasm (DiFiglia *et al*, 1997). These aggregates represent a major pathological hallmark of HD. The list of functions with which mutant Huntingtin in its soluble or aggregated form has been proposed to interfere is extensive, ranging from transcription (Steffan *et al*, 2000; Yu *et al*, 2002), to proteasome function (Bence *et al*, 2001; Jana *et al*, 2001), autophagic progression (Martinez-Vicente *et al*, 2010), cellular trafficking (DiFiglia *et al*, 1997; Szebenyi *et al*, 2003; Twelvetrees *et al*, 2010). In this list, changes in mitochondrial function gained a central position first when the

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group of Beal (1994) showed that rodents treated with inhibitors of mitochondrial complex II developed a selective striatal loss. The list of mitochondrial parameters altered in patients and models of HD grew considerably to include altered Ca^{2+} metabolism, production of reactive oxygen species (ROS), sensitization to apoptosis and excitotoxicity (Fan and Raymond, 2007), to the more recent discoveries of changes in mitochondrial morphology and trafficking that will be addressed in this review.

How mutant Huntingtin can affect selectively medium spiny striatal neurons despite its ubiquitous expression is a key question that remains still unanswered. One of the several theories that has been put forward points again to mitochondria, suggesting that medium spiny neurons, characterized by particularly high-energy demands, are especially susceptible to mutant Huntingtin-induced mitochondrial dysfunction and inhibition of respiration (Mitchell *et al.*, 1999; Pickrell *et al.*, 2011). Indeed, patients and animal models for the disease develop several mitochondrial defects, which range from altered calcium buffering capacity (Panov *et al.*, 2002), impaired bioenergetics (Grunewald and Beal, 1999), increased oxidative stress and abnormal trafficking (Trushina *et al.*, 2004) and dynamics (Costa *et al.*, 2010; Song *et al.*, 2011). On the other hand, it has been for long debated whether mitochondrial dysfunction represents an epiphenomenon of the cellular degeneration or if it plays a pathogenic role. This conundrum is reinforced by the discovery that a large number of hereditary and sporadic neurodegenerative disorders that differ in aetiology and clinical phenotype share similar mitochondrial alterations, challenging the specificity of the mitochondrial contribution to disease progression. In the attempt to answer these questions in the context of HD, considerable effort has been put forward to characterize the mechanisms whereby mutant Huntingtin can affect mitochondrial function and therefore to identify new potential therapeutic targets to modulate the progression of the disorder. In this review, we will discuss the evidence for a crucial role of mitochondria in HD pathogenesis, with a special focus on the recent findings that point to alterations in morphology and dynamics as a unifying mechanism for the different alterations that have been reported.

The functional side: alterations in mitochondrial bioenergetics and function in HD

Neurons are characterized by particularly high-energy demands as they must maintain expensive physiological functions like a fluctuating plasma membrane potential, the release and re-uptake of neurotransmitters at synapses, the trafficking of organelles and vesicles along extended axonal and dendritic processes. Moreover, they rely mainly on mitochondria as source of ATP production and cannot switch to glycolysis when oxidative phosphorylation is impaired. These metabolic and functional characteristics have been always evoked as the main reason to explain the predominant neurological picture of patients with specific mitochondrial diseases.

HD patients exhibit well-described metabolic defects (Leenders *et al.*, 1986; Jenkins *et al.*, 1993) that have been linked to mitochondrial dysfunction. Patients show weight loss despite adequate caloric intake already in the early stages of the disease (Djousse *et al.*, 2002) and positron emission

tomography (PET) revealed that striatal glucose uptake and consumption is reduced in gene carriers years before the onset of the motor symptoms (Kuhl *et al.*, 1982; Antonini *et al.*, 1996). Elevated lactate production in basal ganglia and cortex in HD patients revealed by proton nuclear magnetic resonance (^1H -NMR) imaging suggests defects in mitochondrial pyruvate utilization (Jenkins *et al.*, 1993). While the presence of metabolic alterations in presymptomatic carriers supports mitochondrial dysfunction as an early cause of disease progression (Jenkins *et al.*, 1993; Antonini *et al.*, 1996; Feigin *et al.*, 2001), the observation that dendritic alterations precede respiratory chain complexes defects in striatum and cortex of early stage patients might suggest that energy deficit is a consequence of neuropathological changes (Guidetti *et al.*, 2001). Interestingly, metabolic impairment is observed also in peripheral tissues. Analysis by ^{31}P magnetic resonance spectroscopy of *in vivo* muscle metabolism in HD patients showed reduced phosphocreatine to inorganic phosphate ratio and a significant delay in the recovery of phosphocreatine after exercise (Lodi *et al.*, 2000; Saft *et al.*, 2005), indicative of a decreased synthesis of ATP. An inverse correlation of ATP/ADP ratio and CAG repeat length has been observed also in HD human lymphoblastoid cells (Seong *et al.*, 2005), while the correlation between the activity of respiratory chain complexes observed in platelets and in the brain from HD patients is still controversial (Parker *et al.*, 1990; Gu *et al.*, 1996; Powers *et al.*, 2011). Weight loss, altered cerebral glucose consumption and early alterations of brain energy homeostasis have been observed also in different HD mouse models (Mangiarini *et al.*, 1996; Browne *et al.*, 1999; van der Burg *et al.*, 2008). Surprisingly, analysis of specific brain regions from different HD mouse models revealed an increase in the levels of phosphocreatine already at presymptomatic stages, preceding the ATP decrease which characterizes the advanced stages of the disease. The increased phosphocreatine/ATP ratio is likely due to an altered utilization of phosphocreatine rather than to enhanced creatine synthesis (Zhang *et al.*, 2011; Mochel *et al.*, 2012).

Biochemical studies of the brain from HD patients revealed impaired activity of respiratory chain complexes and tricarboxylic acid (TCA) cycle enzymes. Caudate and putamen from advanced grades of the disease show reduced activity of complexes II, III and IV (Brennan *et al.*, 1985; Gu *et al.*, 1996; Browne *et al.*, 1997). Complex I was affected in muscles from patients but unaltered in the brain (Parker *et al.*, 1990; Browne *et al.*, 1997; Arenas *et al.*, 1998). The particular relevance of succinate dehydrogenase (SDH) to disease progression is supported by the observation that administration of complex II inhibitors like malonate and 3-nitropropionic acid (3-NP) phenocopies in human and animal models both the biochemical lesions and clinical alterations observed in HD (Beal, 1994; Brouillet *et al.*, 1995, 1998, 2005). The SDH subunits Fp (FAD) and Ip (iron-sulphur cluster) appear reduced in HD patients brain and in rat striatal neurons in response to expression of the N-t fragment of mutant Htt and overexpression of either subunits is protective against mutant Huntingtin toxicity *in vitro* (Benchoua *et al.*, 2006). Aconitase, an iron-sulphur containing dehydratase, is one of the most affected TCA cycle enzymes in HD showing a strong inhibition in caudate, putamen and cerebral cortex (Tabrizi *et al.*, 1999) and in striatum from R6/2 mice, which overexpress exon 1 of the human *Huntingtin* gene bearing

~150 CAG repeats under the control of the human *Huntingtin* promoter (Tabrizi *et al*, 2000). Aconitase activity is particularly susceptible to regulation by ROS (Gardner *et al*, 1995) and this could represent the mechanism of its inhibition in HD, given the high level of oxidative damage observed in human HD brains and animal models. Indeed, accumulation of several markers of oxidative stress, like lipofuscin derived from peroxidation of unsaturated fatty acids (Braak and Braak, 1992), nitrated proteins (Browne *et al*, 1999) and 8-hydroxy-2-deoxyguanosine (OH8dG) in mitochondrial DNA (Polidori *et al*, 1999), is a well-described feature of HD brains. Interestingly, reduction of signalling by IRS2 (insulin receptor substrate 2) lowers oxidative stress and mitochondrial dysfunction, ameliorating motor performance and increasing life span of HD models (Sadagurski *et al*, 2011). Despite increasing research on this subject, the identification of the main sources of ROS production in HD as well as the understanding of the exact mechanisms that link oxidative damage to neuronal death are still incomplete. Moreover, the fact that oxidative stress is a hallmark of several neurodegenerative diseases suggests that there may be shared pathological mechanisms activated by independent, apical primary causes.

A HD-specific mechanism, which mediates mitochondrial dysfunction, may be represented by the interference with nuclear gene transcription by mutant Huntingtin and in particular with the activity of PGC1 α (peroxisome proliferator-activated receptor- γ coactivator 1 α), a master regulator of energy homeostasis. PGC1 α is a transcriptional coactivator involved in adaptive thermogenesis (Lin *et al*, 2005; Puigserver, 2005), β -oxidation of fatty acids, glucose metabolism (Yoon *et al*, 2001) and induction of mitochondrial biogenesis. Indeed, ectopic expression of PGC1 α in cells enhances transcription of respiratory complex subunits and increases mtDNA levels (Wu *et al*, 1999) and cardiac overexpression of PGC1 α results in increased mitochondrial mass in myocytes (Lehman *et al*, 2000). Moreover, PGC1 α expression is induced upon skeletal muscle exercise and is instrumental to mitochondrial biogenesis (Baar *et al*, 2002; Ojuka *et al*, 2003). Strikingly, mice ablated for PGC1 α show overt phenotypes in brown adipose tissue and striatum (Lin *et al*, 2004), with neuronal loss, hypothermia and motor alterations. In HD, PGC1 α levels and activity are impaired in the brain and muscles from patients and transgenic models (Cui *et al*, 2006; Weydt *et al*, 2006; Chaturvedi *et al*, 2009). Recently, alterations in the expression levels of a N-terminal truncated splice variant of PGC1 α have been reported in HD models (Johri *et al*, 2011). Moreover, polymorphisms of PGC1 α have been characterized as modifiers of age of onset of HD (Taherzadeh-Fard *et al*, 2009; Weydt *et al*, 2009). According to the findings by Weydt *et al* (2006), in brown adipose tissue mutant Htt binds to PGC1 α inhibiting the expression of its downstream target genes like UCP-1 eventually interfering with adaptive thermogenesis in response to cold in transgenic HD mice. On the other hand, mutant Htt prevents the CREB/TAF4 (cAMP responsive element-binding/TATA-binding protein-associated factor 4) transcription complex from binding to the promoter of PGC1 α inhibiting its expression and lentiviral-mediated overexpression of the factor in the brain of HD mouse model elicits a beneficial effect (Cui *et al*, 2006). Sirt1, a NAD $^{+}$ -dependent deacetylase implicated in cellular metabolism that exerts a protective role in models of neurodegenerative diseases, controls

CREB/TAF4-mediated transcription by regulating the acetylation status of the coactivator TORC1 (transducer of regulated CREB activity 1) and its interaction with the transcription complex (Jeong *et al*, 2011). Mutant Htt inhibits Sirt1 deacetylase activity and overexpression of Sirt1 exerts a protective effect against mutant Htt toxicity *in vitro* and *in vivo* through the activation of multiple downstream targets and restoration of BDNF concentration, which is decreased in HD (Jeong *et al*, 2011; Jiang *et al*, 2011). Interestingly, PGC1 α has been reported to be a substrate of Sirt1 (Rodgers *et al*, 2005) and its transcription to be regulated by TORC1 (Wu *et al*, 2006). Indeed, overexpression of Sirt1 rescues PGC1 α levels and ameliorates metabolic abnormalities in HD mouse models, suggesting that the beneficial effect of Sirt1 may be at least in part mediated by PGC1 α . In HD, alteration in the transcription of nuclear encoded genes involved in cellular metabolism like PGC1 α and cytochrome *c* can be also ascribed to hyperactivation of transglutaminase 2, which can modify glutamine residues to alter intermolecular interaction of key transcription factors (McConoughey *et al*, 2010). These studies identify a molecular mechanism that could link mitochondrial dysfunction and neurodegeneration to the transcriptional alterations retrieved in HD. Moreover, treatment of HD models with the pan-PPAR (peroxisome proliferator-activated receptor) agonist bezafibrate increases PGC1 α levels and improves the neurological and extraneurological phenotypes as well as overall survival, pointing to PGC1 α as a potential therapeutic target (Johri *et al*, 2012).

The pathways whereby mutant Huntingtin influences mitochondrial function seem, however, to go beyond indirect, transcriptional mechanisms. Indeed, the protein has been demonstrated to influence the calcium handling capacity of mitochondria through direct interaction with the organelle (Panov *et al*, 2002). Besides their role in energy production, mitochondria are key spatiotemporal modulators of cellular calcium homeostasis and their buffering function is particularly important in neurons and excitable tissues (Nicholls, 2005). However, an excessive concentration of calcium in the mitochondrial matrix can lead to the opening of the permeability transition pore (PTP), a high conductance unselective channel of the inner membrane, eventually causing mitochondrial swelling and release of proapoptotic factors (Bernardi and Forte, 2007) and implicated in Ca $^{2+}$ -dependent apoptosis (Scorrano *et al*, 2003). In HD, strong evidence supports a role for mitochondrial calcium handling defects in the pathogenesis of the disease. Several studies on mitochondria from lymphoblasts from HD patients, mouse models brains and neuronal HD cell lines reported a reduction in mitochondrial membrane potential and an enhanced sensitivity to Ca $^{2+}$ -induced PTP (Panov *et al*, 2002; Choo *et al*, 2004; Gizatullina *et al*, 2006). A key study from Panov *et al* (2002) demonstrated that the reduction in mitochondrial calcium retention capacity (an index of PTP opening) correlates with the length of the polyglutamine expansion in Huntingtin. Interestingly, the physical interaction of GST fusion proteins bearing an expanded polyglutamine domain with isolated mitochondria triggers reduction of mitochondrial membrane potential and impairs calcium handling. Consistently, isolated mitochondria from mouse liver show decreased calcium threshold for PTP opening if incubated with a recombinant N-terminal fragment of Huntingtin with mutant polyglutamine domain (Choo *et al*, 2004), further

Figure 1 Functional alterations in HD mitochondria. The cartoon depicts the functional alterations occurring at the level of mitochondrial function, opening of the PTP, and morphology in the context of HD. Mutated Huntingtin can act at the transcriptional level, by inhibiting PGC1 α , directly at the mitochondrial level, by increasing the open probability of the PTP and affecting mitochondrial respiratory chain, and at the level of DRP1 causing fragmentation and remodelling of the mitochondrial cristae.

supporting the direct mechanism underlying the dysfunction. Analysis of mitochondria isolated from the brain from YAC72 HD mice, overexpressing a full-length mutant form of Htt, revealed slower clearance of extramitochondrial calcium and an inability to return to baseline calcium levels (Panov *et al*, 2002). The calcium handling alteration in the context of neuronal cells results in slower recovery rate of cytosolic calcium concentration upon NMDAR activation, which can in the long run lead to enhanced mitochondrial depolarization (Fernandes *et al*, 2007), ultimately inducing PTP-dependent apoptosis (Zeron *et al*, 2004). The multiple bioenergetic changes affecting HD mitochondria are summarized in Figure 1.

The morphology side: changes in mitochondrial shape and HD

The involvement of mitochondria in apoptosis does not depend only on Ca^{2+} , PTP-dependent mechanisms, but involves at least two interrelated aspects, the selective outer membrane permeabilization controlled by members of the Bcl-2 family (Tait and Green, 2010), and the morpho-structural changes that characterize the organelle during the progression of cell death (Wasilewski and Scorrano, 2009).

Mitochondria are key organelles in the process of apoptosis, amplifying cellular damage when they release cytochrome *c* and other proapoptotic factors that activate the effector caspases (Danial and Korsmeyer, 2004). To allow the complete release of cytochrome *c*, which is sequestered in the *cristae* compartment, mitochondria undergo two main morphological changes: fragmentation and *cristae* remodelling (Frank *et al*, 2001; Scorrano *et al*, 2002). Mitochondria are indeed highly dynamic organelles organized in a network whose morphology is determined by ongoing fusion and fission events finely regulated by a growing family of

‘mitochondria-shaping’ proteins. The main pro-fusion proteins are large GTPases similar to dynamins: Opa1 in the inner mitochondrial membrane and Mitofusins 1 and 2 in the outer membrane. Their action is counterbalanced by pro-fission factors like the cytoplasmic dynamin-related protein 1 (DRP1) and its molecular adaptor on the outer mitochondrial membrane Fis1 (James *et al*, 2003). Mitochondria-shaping proteins play a crucial role in the modulation of apoptotic morphological changes and the progression of cell death. Opa1, besides its role in mitochondrial fusion, keeps in check the *cristae* junctions regulating the remodelling process and the release of cytochrome *c* during apoptosis (Frezza *et al*, 2006). Moreover, DRP1 can mediate apoptotic *cristae* remodelling, its inhibition preventing apoptotic fragmentation, release of cytochrome *c*, and cell death (Germain *et al*, 2005). On the other hand, core components of the Bcl-2 family exerting both pro- and anti-apoptotic functions can modulate mitochondrial morphology and interact with mitochondria-shaping proteins (Karbowski *et al*, 2002; Brooks *et al*, 2007; Berman *et al*, 2009).

Neurons are particularly sensitive to alterations in mitochondrial dynamics and a number of genetic neurodegenerative diseases are caused by mutations in ‘mitochondria-shaping’ proteins. Two examples are the peripheral neuropathy Charcot-Marie-Tooth type 2A associated to *MFN2* mutations (Zuchner *et al*, 2004) and autosomal dominant optic atrophy (Alexander *et al*, 2000; Delettre *et al*, 2000), the most common form of optic neuropathy, caused by *OPA1* mutations. Growing evidence shows that defects in mitochondrial morphology are a hallmark of other more common sporadic and genetic neurodegenerative disorders like Parkinson’s disease (PD) and Alzheimer’s disease (AD).

The analysis of mitochondrial morphology in HD had been limited for decades to the observational level. Although mitochondrial alterations had been clearly reported in earlier

studies, only very recent work provided new insights into the molecular mechanisms responsible for the observed morphological defects. Since changes in mitochondrial morphology are intimately linked to mitochondrial ATP production (Hackenbrock, 1966; Benard and Rossignol, 2008), ROS generation (Yu *et al*, 2006), movement (Li *et al*, 2004) and apoptosis (reviewed in Wasilewski and Scorrano, 2009), a clearer understanding of the mechanisms impinging on mitochondrial morphology in the context of the disease could represent a new approach to modify the broader mitochondrial defects which are hallmarks of HD.

Early studies on brain biopsies from HD patients revealed the presence of mitochondria characterized by abnormal ultrastructure and morphology (Tellez-Nagel *et al*, 1974; Goebel *et al*, 1978). Moreover, alteration in mitochondrial *cristae* structure has been observed also in rat striata upon quinolinic acid treatment, an excitotoxic model for the disease (Portera-Cailliau *et al*, 1995). Interestingly, mitochondrial morphological alterations and dysfunction appear to characterize not only the nervous system, but also peripheral tissues in early stages of the disease (Squitieri *et al*, 2010). Indeed, electron microscopic (EM) analysis of lymphoblasts, myoblasts and fibroblasts from HD patients show that mitochondrial *cristae* appear reduced in number and altered in shape. The severity of these ultrastructural defects correlates with the genotype of the patient, being more prominent when the mutation is homozygous (Squitieri *et al*, 2006, 2010). Moreover, EM analysis of lymphoblasts from heterozygous HD patients reveal that mitochondria are abnormally clustered (Mormone *et al*, 2006), suggesting that alterations occur not only at the ultrastructural level, but mutant Huntingtin can also affect the mitochondrial network and movement. However, these studies were merely observational and did not address whether the observed changes were cause or consequence of the mitochondrial dysfunction. The next step was to dissect if mitochondria-shaping proteins were involved in the onset and in the modulation of the observed morphological defects. The overexpression of the N-terminal fragment of mutant Huntingtin (bearing a 74-aa poly Q stretch) in HeLa cells inhibited mitochondrial movement and fusion rate (Wang *et al*, 2009). Cells expressing this mutant Huntingtin undergo massive fragmentation of the mitochondrial network together with alteration in the structure and organization of *cristae*, reduction in ATP levels and enhanced apoptosis when they are exposed to pro-oxidants or when nutrient availability is reduced. Interestingly, all the morphological and functional defects can be corrected by the inhibition of the fission machinery (also in a *Caenorhabditis elegans* model of HD) or by the promotion of mitochondrial fusion by the overexpression of Mfn2, leading to the speculation that the mere promotion of mitochondrial elongation is beneficial against the mitochondrial toxicity of mutant Htt. Interestingly, Mfn2 can directly interact with the N-terminus of mutant Htt (Wang *et al*, 2009), suggesting that Htt can interfere directly with the function of Mfn2 in the promotion of mitochondrial elongation (Chen *et al*, 2003) and in the regulation of the apoptotic function of Bax (Neuspiel *et al*, 2005). Alternatively, mutant Htt might interfere with the extramitochondrial functions of Mfn2, leading to alterations in the shape of the ER, in the ER levels of Ca^{2+} , and last but not least in the tethering of mitochondria to the ER, all controlled by Mfn2 (de Brito and Scorrano, 2008). Although

this work provides for the first time evidence for a role of mitochondria-shaping proteins in cellular processes linked to Huntingtin toxicity, whether the observed changes are specific, or caused by the toxic overexpression of mutant full-length and N-terminal fragment Htt, remained unclear, calling for further investigation in models that express mutant Htt at physiological levels. In particular, this question of specificity was reinforced since fragmentation of the mitochondrial network had been also observed in a pharmacological model for HD, where the outstanding lesion was clearly at the level of mitochondrial function. Primary cortical neurons treated with 3-NP show an immediate drop in ATP levels and a mild rise in ROS followed by a NMDA activation-dependent more pronounced rise in ROS. Unexpectedly, mitochondrial fragmentation appears not to be an immediate consequence of the bioenergetic defect caused by 3-NP, but occurs in response to the secondary excitotoxic event and is upstream of neuronal cell death (Liot *et al*, 2009). A direct mechanism linking the well-known correlation between increase in oxidative and nitrosative stress and changes in mitochondrial dynamics (Bossy-Wetzel and Lipton, 2003; Barsom *et al*, 2006; Yuan *et al*, 2007) has been identified in a work from the group of Lipton and colleagues who showed that S-nitrosylation of Drp1 in its GTPase effector domain increases Drp1 oligomerization and GTPase activity, ultimately leading to mitochondrial fragmentation and neuronal damage in response to β -amyloid protein, a key mediator of AD (Cho *et al*, 2009). In a recent report, authors from the same group (Nakamura *et al*, 2010) state that NO-mediated modifications of Drp1 have been observed also in HD, proposing that this could be a common pathogenic mechanism in both neurodegenerative disorders. However, this view has been recently challenged since the nitrosylation of Drp1 apparently has no effect on the activity of the protein (Bossy *et al*, 2010), suggesting that it might be a late epiphenomenon of the diseases cellular context of AD and HD. These results leave open the question of whether, and how Drp1 is activated in HD.

In order to address the mechanisms and the relevance of mitochondrial morphology changes in HD, we recently studied cellular and mouse models of the disease and identified Drp1 as a key molecular player at the crossroad between modulation of mitochondrial structure and death of HD neurons (Costa *et al*, 2010). Different cellular models of HD that express mutant Htt at physiological levels (lymphoblasts from HD patients and immortalized neurons from knockin mice bearing an expansion of 111 CAG repeats in the *Hdh* locus), and primary striatal neurons from YAC128 mice (overexpressing the mutated full-length form of the human protein) are characterized by fragmentation of the mitochondrial network that could be genetically corrected by the pro-fusion proteins Opa1 and Mfn1 and by reducing Drp1 activity and translocation to mitochondria. Interestingly, genetic and pharmacological inhibition of the phosphatase calcineurin, which promotes the translocation of Drp1 to mitochondria (Cereghetti *et al*, 2008), can also correct the disrupted network of HD mitochondria. Consistently, the calcium-dependent phosphatase calcineurin is more active in HD models, and dephosphorylated Drp1 accumulates on HD mitochondria where it oligomerizes, leading to the observed fragmentation of the network. How can mutant Htt influence the activity of calcineurin? Constitutive activation of calcineurin

Figure 2 Morphological alterations in HD mitochondria. Top, normal mitochondrial morphology (immunofluorescence image of TOM20 in mouse striatal precursor cells) and ultrastructure (electron microscopy of mitochondria in the same striatal precursors) in healthy striatal precursors. Bottom, fragmentation and cristae disorganization in striatal precursor cells from a mouse model of knockin of a 111 repeat polyglutamine, triggered by the cascade of events depicted. For details, please refer to Costa *et al* (2010).

has been observed in various models of HD and several mechanisms have been proposed to explain it, from decreased expression of endogenous inhibitors (Ermak *et al*, 2009) to increased expression levels of the phosphatase subunits (Xifro *et al*, 2008), to an increase in the intracellular levels of Ca^{2+} , the proximal activator of calcineurin, whose dyshomeostasis has been largely described in HD (Tang *et al*, 2005). Moreover, the *cristae* of HD mitochondria appear deranged and undergo faster and more extensive remodelling when mitochondria are challenged with apoptotic stimuli, leading to faster release of cytochrome *c* and ultimately increased cell death (Figure 2). Interestingly, the correction of mitochondrial morphology through overexpression of Opa1 and inhibition of the calcineurin–Drp1 pathway can also confer protection towards cell death, while overexpression of Mfn1, which does not interfere with the remodelling of *cristae* (Frezza *et al*, 2006), does not exert any beneficial effect. These genetic manoeuvres demonstrate that promotion of mitochondrial elongation *per se* is not sufficient to confer protection towards cell death, which conversely correlates with the modulation of the internal structure of the organelle. Moreover, they link alteration in the morphology of mitochondrial network with *cristae* remodelling and apoptosis, originally proposed in a different context by Germain *et al* (2005). These results open the interesting possibility to further investigate whether correction of the ultrastructural defects could improve, besides the sensitivity to cell death, other physiological neuronal functions impaired in the disease. Indeed, in cells undergoing nutrient deprivation, the inhibition of the pro-fission activity of Drp1 leads to an

expansion of the *cristae* surface, and to a parallel increase in mitochondrial ATP production (Gomes *et al*, 2011). It is tempting to speculate that correction of mitochondrial dysfunction in the context of HD can be achieved by modulation of mitochondrial shape, boosting ATP production to ameliorate the overall bioenergetic parameters of the cell. Importantly, the increased fragmentation of HD mitochondria has been confirmed in patients where alterations in mitochondrial dynamics and function appear to correlate with the progression of the disease. The analysis of post-mortem brain tissues in two independent studies (Kim *et al*, 2010; Shirendeb *et al*, 2011) shows a decrease in the expression levels of pro-fusion mitofusins, and an increase in Drp1 and Fis1 levels, more severe when the disease is more advanced (grades III–IV). This is accompanied by decreased detection of other core mitochondrial proteins, like COX1 and COX2, suggesting impaired mitochondrial function and organelle loss.

A recent work from the group of Bossy-Wetzel further confirmed that mitochondrial fission is a hallmark of HD, proposing a direct mechanism of Drp1 activation by mutant Htt (Song *et al*, 2011). Increased fission of mitochondria is observed in fibroblasts from HD patients, primary neurons from YAC128 mice and neurons where N-t mutant Htt is exogenously expressed. This defect correlates with reduced mitochondrial motility and increased neuronal cell death. Consistently, mitochondrial *cristae*, whose number is increased in mitochondria from YAC128 mice neurons, display reduced volume and surface area, indicative of their disorganization. A GFP-tagged N-t fragment of mutant Htt

accumulates on mitochondria where it appears to colocalize with YFP-Drp1. Co-immunoprecipitation experiments revealed that the mild interaction of Drp1 with wt Htt turns to be highly increased in the presence of the expanded polyQ domain. Moreover, the N-t fragment of mutant Htt slightly increases the GTPase activity of Drp1 *in vitro*, altering its assembly in homooligomers. Whether the accumulation of mutant Htt on mitochondria is sufficient to drive the increased recruitment of Drp1 on the organelle, working for example as a docking receptor, or whether the Htt-Drp1 interaction alters the cycling of Drp1 between mitochondria and the cytoplasm remains unclear. In contrast to Drp1, Mfn2 interacts with wt and mutant Htt to a similar extent. Importantly, the overexpression of a dominant negative form of Drp1 could restore the morphological phenotype and protect against mutant Htt toxicity. This effect appears to be further reinforced by concomitant expression of constitutively active mutant of MFN2 (RasG12V) (Neuspiel *et al*, 2005). Although possibly consistent with the one previously described by us (Costa *et al*, 2010), the mechanism by which inhibition of Drp1 protects against cell death in HD was not investigated by Bossy-Wetzel and colleagues. The contribution of CA Mfn2 could, on the other hand, be ascribed to the ability of this mutant to interfere with the Bax-mediated pathway of apoptosis (Karbowski *et al*, 2002, 2006; Jahani-Asl *et al*, 2007).

Multiple mechanisms have been put forward to explain the hyperactivation of the fission GTPase Drp1 in the context of HD. At this point, it is unclear if they are mutually exclusive, or if they co-exist; clearly, their relative contribution to neuropathology is similarly unknown and their validation *in vivo* represents an obligatory step to assign a role for mitochondrial dynamics in the progression of HD and to test if Drp1 can be a therapeutic target. However, therapeutic modulation of mitochondrial morphology in neurons shall be performed with extreme care: complete inhibition of fission causes developmental neurological alterations and reduces synaptic plasticity and function (Li *et al*, 2004; Ishihara *et al*, 2009; Wakabayashi *et al*, 2009), suggesting that Drp1 inhibition could in the long run even worsen the clinical picture of the disease. At least partially, the adverse outcomes observed upon the impairment of mitochondrial fission in neurons might be related to the downstream changes in mitochondrial motility, essential to transport the organelles along axons and dendrites and that is also affected in HD.

(Im)motile mitochondria in HD?

The concept of altered axonal transport in HD is well established: several pathways converge on an alteration of trafficking of vesicles in neurons bearing mutated Htt. Mitochondria, as well as other organelles like lysosomes, peroxisomes, ER, are actively transported along cytoskeletal elements towards the cell regions where their function is required. In neurons, long-range movement on microtubules are of key importance to transport the organelle in the dendritic and axonal cell processes. The dynein/dynactin and the kinesins motors are responsible for retrograde and anterograde transport, respectively (Hollenbeck, 1996). While no specific mitochondrial adaptors seem to exist for dynein-mediated retrograde

movement, a subset of the large Kinesin superfamily associates specifically with mitochondria (Zinsmaier *et al*, 2009).

Mitochondrial transport and morphology seem to be intimately linked. For example, ablation of Mfn2 causes the disorganization of the movement of the organelle (Chen *et al*, 2003). Consistently, mutants of Mfn2 that are retrieved in patients with Charcot-Marie-Tooth IIa, and the lack of Mfn2 impair both anterograde and retrograde movement of mitochondria in dorsal root ganglion cells. Mfn2 (as well as Mfn1) interacts with the adaptor machinery composed of Trak1 (the mammalian homologue of *Drosophila melanogaster* Milton) and the GTPase Miro (Misko *et al*, 2010).

Interestingly, mutant Htt affects mitochondrial movement when expressed in primary rat cortical neurons (Chang *et al*, 2006) or in a transgenic mouse model where it also impairs trafficking of other vesicles (Trushina *et al*, 2004). Mutant Htt affects both anterograde and retrograde movement, in a fashion that depends on the N-terminus polyQ expansion (Orr *et al*, 2008). Several mechanisms have been proposed to explain the effect of the mutant Htt on mitochondrial movement. First, the Htt-binding partner huntingtin-associated protein (HAP1) can interact with kinesin and dynein to regulate the transport of cargo on microtubules (Bossy-Wetzel *et al*, 2008). Milton/Trak1 is a HAP1 homologue and binds Htt (Stowers *et al*, 2002), suggesting a specific mechanism for the impairment of mitochondrial trafficking. Full-length mutant Htt is more effective than N-terminal mutant Htt in blocking mitochondrial movement, in a dose-dependent manner. One possibility is that aggregates sterically impair the passage of mitochondria along neuronal processes. Chang *et al* (2006) suggested that in cortical neurons, an early event in HD pathophysiology may be the aberrant mobility and trafficking of mitochondria caused by cytosolic Htt aggregates (Chang *et al*, 2006). Another possibility can be inferred from some very recent findings connecting mitochondria quality control with regulation of mitochondrial trafficking. The PD-associated proteins pink1 and parkin participate in the regulation of mitochondrial movement by phosphorylating the GTPase Miro and targeting it to proteasomal degradation. Upon degradation of Miro, the adaptor protein kinesin detaches from mitochondria, resulting in the arrest of the organelle. It is tempting to speculate that a similar pathway can be activated in HD neurons, where mitochondria arrest as a consequence of the degradation of Miro triggered by the organellar dysfunction. This hypothesis that deserves to be tested experimentally could explain the link between mitochondrial dysfunction and movement arrest in HD. In perspective, it could clarify if disruption of movement is a primary event in HD, or if it is an epiphenomenon of the multiple mitochondrial dysfunctions that occur in the context of the disease.

Conclusion and perspectives

Changes in mitochondrial fusion and fission, as well as alterations in organelle movement, are consistently identified as causally linked to the neuronal dysfunction and increased susceptibility of HD neurons to death. However, the precise mechanism by which these changes can lead to cellular dysfunction are still poorly understood. One possibility is that the hyperactivation of Drp1 leads to *cristae* remodelling, leaving several viable therapeutic avenues open to

exploration. Indeed, Drp1 can be targeted by specific inhibitors that exist (Cassidy-Stone *et al*, 2008) and have been used successfully *in vivo* to ameliorate acute conditions like renal ischaemia (Brooks *et al*, 2009). However, whether such a treatment can be used chronically without side effects in neurons is questionable, especially given the fact that constitutive inhibition of Drp1 in neurons leads to loss of spines (Li *et al*, 2004). Conversely, if the activation of Drp1 by mutated Htt is not direct, but mediated by the calcineurin phosphatase, the therapeutic strategies can target the upstream activator with drugs such as tacrolimus (FK506) that crosses the blood–brain barrier and has been reported to be efficacious in animal models of HD (Pardo *et al*, 2006). Alternatively, a more biological therapeutic approach could capitalize on the discovery that at least in heart Drp1 and calcineurin are under the control of the same miRNA whose

expression protects from ischaemia reperfusion (Wang *et al*, 2011). Shall the same miRNA be efficacious in the striatum and cortex, it could be tested for its ability to delay cell loss in models of HD. Finally, if disruption of mitochondrial *cristae* is a key process in HD pathogenesis, stabilization of Opa1 could be an approach to be tested. Interestingly, chronic administration of the histone deacetylase 1-specific inhibitor MS-275 specifically upregulates Opa1 in the brain (Engmann *et al*, 2011), rescuing a mouse model of schizophrenia and offering a proof of principle for the efficacy of a therapy of a neuronal pathology achieved by upregulating mitochondrial *cristae* biogenesis.

Conflict of interest

The authors declare that they have no conflict of interest.

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