16

Consequences of Mitochondrial Dysfunction in Huntington's Disease and Protection via Phosphorylation Pathways

Teresa Cunha-Oliveira[1]*, Ildete Luísa Ferreira[1]* and A. Cristina Rego[1,2]
[1]*CNC-Center for Neuroscience and Cell Biology, University of Coimbra,*
[2]*Faculty of Medicine, University of Coimbra,*
Portugal

1. Introduction

Huntington's Disease (HD) is an autosomal dominant neurodegenerative disorder clinically characterized by psychiatric disturbances, progressive cognitive impairment and choreiform movements. These symptoms are associated with the selective atrophy and neuronal loss in the striatum, cortex and hypothalamus. The disease is caused by a mutation at the 5′ terminal of the huntingtin (*HTT*) gene involving the expansion of CAG triplet, which encodes for glutamine. Mutant huntingtin (mHtt) may be cleaved by proteases originating neurotoxic fragments, and also undergoes conformational changes that lead to the formation of protein aggregates (Gil and Rego 2008, for review). Among several mechanisms of neurodegeneration, mHtt is related to mitochondrial dysfunction and relevant changes in energy metabolism in both central and peripheral cells, which may underlie cell death (Gil and Rego 2008, for review).

In this review chapter we emphasize the role of mitochondrial dysfunction in neurodegeneration in HD, particularly centering on loss of mitochondrial activity and the regulation of intrinsic apoptosis in central and peripheral HD human tissue or cells, and in animal models of HD. We focus on the changes in energy metabolism, oxidative stress, the link to transcriptional dysfunction and the regulation of intrinsic apoptosis. We further explore the therapeutic role of promoting phosphorylation pathways through selective inhibition of phosphatases (e.g. with FK506) and/or activation of kinase signaling cascades mediated by neurotrophins, namely brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF).

2. Mitochondrial dysfunction and apoptosis in HD

2.1 Mitochondrial dysfunction

The mechanisms by which neurons die in HD are uncertain, however, mitochondrial dysfunction and apoptosis have been implicated. Mitochondria are important organelles

*These authors contributed equally

that regulate the life and death of cells and neurons are particularly dependent on these organelles due to their high energy requirements.

Mitochondrial dysfunction is considered a common feature in the pathogenesis of neurodegenerative disorders like HD (Kim *et al.* 2010;Oliveira 2010;Parker, Jr. *et al.* 1990), and constitutes a cellular hallmark for neurodegeneration, occurring as a consequence of defective mitochondrial composition, trafficking to synapses, calcium handling, ATP production, transcription abnormalities and/or electron transport chain (ETC) impairment (Rosenstock *et al.* 2010, for review). Moreover, cell and animal models of HD exhibit mitochondrial impairment and metabolic deficits similar to those found in HD patients (reviewed in Damiano *et al.* 2010;Quintanilla and Johnson 2009). mHtt may cause mitochondrial dysfunction by directly interacting with the organelle (Panov et al. 2002) by evoking defects in mitochondrial dynamics, organelle trafficking and fission and fusion, which, in turn, may result in bioenergetic failure, or indirectly by perturbing transcription of nuclear-encoded mitochondrial proteins (Bossy-Wetzel *et al.* 2008, for review).

The hypothesis that mitochondrial dysfunction contributes to the pathogenesis of HD was first tested pharmacologically by using 3-nitropropionic acid (3-NP) and malonate, irreversible and reversible inhibitors of succinate dehydrogenase (a component of both the tricarboxylic acid cycle and the complex II of the ETC), respectively. Administration of these inhibitors to animals results in pathological characteristics of HD, such as marked increases in striatal lactate concentration, striatal lesions and motor disturbances (Beal *et al.* 1993;Brouillet *et al.* 1993;Frim *et al.* 1993), involving an immediate ATP drop and secondary increase in reactive oxygen species (ROS), which is correlated with profound mitochondrial fragmentation (Brouillet *et al.* 1999). Selective striatal neurodegeneration induced by 3-NP appears to be related to the early expression and activation of matrix metalloproteinase-9 by ROS which can digest the endothelial basal lamina, leading to the disruption of the blood–brain barrier and to progressive striatal damage (Kim *et al.* 2003). Concordant with 3-NP mimicking the disease, in 1974 a defect in succinate dehydrogenase was reported in the caudate and, to a lesser extent, in the cortex of postmortem HD brains (Stahl and Swanson 1974). Moreover, yeast expressing mHtt showed a significant reduction in oxidative phosphorylation due to a decrease in complexes II and III activities (Solans *et al.* 2006).

Furthermore, early studies of cortical biopsies obtained from patients with either juvenile or adult onset HD showed abnormal mitochondria morphology and function (Goebel *et al.* 1978;Tellez-Nagel *et al.* 1974). Functional changes in mitochondrial ETC were also observed in HD, namely decreased mitochondrial complexes II/III activity and succinate oxidation in striatal tissue from HD patients (Stahl and Swanson 1974;Gu *et al.* 1996;Browne *et al.* 1997;Benchoua *et al.* 2006). Moreover, a decrease in complex IV activity was found in HD striatum (Browne *et al.* 1997;Gu *et al.* 1996).

In skeletal muscle, mHtt was reported to affect the activity of mitochondrial complex I (Arenas *et al.* 1998) and also complexes II/III (Ciammola *et al.* 2006;Turner *et al.* 2007), along with mitochondrial depolarization, cytochrome c release and caspases activation (Ciammola *et al.* 2006;Turner *et al.* 2007). In platelets from HD patients, some authors also found a decrease in complex I activity (Parker, Jr. *et al.* 1990), whereas others reported no changes in the activity of mitochondrial complexes (Gu *et al.* 1996;Powers *et al.* 2007a). A decrease in mitochondrial complex II/III activity was also found in lymphoblasts of HD patients (Sawa *et al.* 1999). No significant differences were observed in complexes I and IV but a correlation

was found between complex II/III activity and disease duration and progress and inclusion formation in muscle (Turner *et al.* 2007).

Cybrids, an *ex-vivo* human peripheral cell model in which the contribution of mitochondrial defects from patients may be isolated, are an interesting approach to study mitochondrial dysfunction (King and Attardi 1989). Results from our laboratory showed that HD cybrids, prepared from the fusion of HD human platelets with NT2 rho0 cells, depleted of mitochondrial DNA, did not exhibit significant modifications in the activity of ETC complexes I–IV or specific mitochondrial DNA (mtDNA) sequence variations, suggestive of a primary role in mitochondrial susceptibility in the subpopulation of HD carriers studied (Ferreira et al. 2010). In accordance, Swerdlow and collaborators (1999) showed that HD cybrids did not present changes in ETC activity, oxidative stress or calcium homeostasis. Despite unchanged activity of mitochondrial complexes, this cell model presented evidences of mitochondrial dysfunction based on significant changes on mitochondrial membrane potential and increased ROS generation (Ferreira et al. 2010). The presence of mtDNA variations, including an 8656A N G variant in one patient, was previously shown in a screening study for mutations in the tRNA(leu/lys) and MTATP6 genes of 20 patients with HD (Kasraie *et al.* 2008). However, the nucleotides 8915-9207 of the same gene did not present any sequence variation in our HD cybrids (Ferreira et al. 2010). One of our HD cybrid lines carried the 3394T N C mutation with status "unclear" (Ferreira et al. 2010), previously described in cases suffering from Leber Hereditary Optic Neuropathy (LHON), which was shown to be related with HD features (Morimoto *et al.* 2004). In addition, a decrease in mitochondrial DNA content was found in cerebral cortex of HD patients (Horton *et al.* 1995).

It is accepted that mHtt not only impairs mitochondrial function, but also compromises cytosolic and mitochondrial calcium homeostasis, which contributes to neuronal dysfunction and death in HD (Damiano *et al.* 2010;Quintanilla and Johnson 2009, for review). Multiple changes in mitochondrial calcium handling (Panov *et al.* 2002;Oliveira *et al.* 2007), metabolism (Damiano *et al.* 2010), and susceptibility to apoptosis (Sawa *et al.* 1999) were suggested to be related with mitochondrial localization of mHtt (Orr *et al.* 2008). Indeed, mHtt interaction with neuronal mitochondria of YAC72 transgenic mice (Panov et al. 2002) was directly linked to mitochondrial calcium abnormalities (Choo et al. 2004;Panov et al. 2002). In this respect our group has also demonstrated changes in calcium handling linked to mitochondrial dysfunction in striatal neurons from YAC128 HD mice and cells derived from knock-in mice (Oliveira *et al.* 2006). Interestingly, increased vulnerability of striatal mitochondria to calcium loads was found to be present in both intact neurons and astrocytes, when compared with their cortical counterparts. Moreover, a lower mitochondrial calcium buffering capacity in intact striatal *versus* cortical astrocytes, associated with increased cyclosporin A-dependent permeability transition, suggested that the striatum is at higher risk for disturbed interactions between neurons and astrocytes (Oliveira and Goncalves 2009).

Various mitochondrial abnormalities observed in human patient samples, postmortem HD brains, cellular, invertebrate and vertebrate models of the disease, cooperate with mitochondrial ETC dysfunction in the genesis of HD (Pandey *et al.* 2010, for review). These include imbalance of calcium buffering capacity and oxidative stress, impaired axonal transport and abnormal fission and fusion of mitochondria, which are further described in this Chapter.

2.2 Altered mitochondrial trafficking and dynamics

Mitochondrial shape and structure are maintained by mitochondrial fission and fusion and disruption of mitochondrial dynamics was shown to be involved in HD (Chen and Chan 2009, for review). Fission is controlled by dynamin-related protein 1 (Drp1), mostly localized in the cytoplasm and in the mitochondrial outer membrane (MOM), and fission 1 (Fis1), localized to the MOM. On the other hand, mitochondrial fusion is ruled by mitofusin 1 (Mfn1) and mitofusin 2 (Mfn2), localized in the MOM, and optic atrophy-1 (Opa1), localized in the mitochondrial inner membrane (MIM) (Chen and Chan 2009, for review). In a healthy neuron, fission and fusion mechanisms balance equally and mitochondria alter their shape and size to move from cell body to the axons, dendrites, and synapses, and back to the cell body through mitochondrial trafficking. Recently, a role for abnormal mitochondrial networking in HD pathogenesis was described, involving mitochondrial fragmentation and cristae alterations, in different cellular models of HD (lymphoblasts from HD patients, striatal progenitor cell lines isolated from knock-in HdhQ111 mouse embryos and in YAC128 primary striatal neurons), explaining their increased susceptibility to apoptosis (Costa *et al.* 2010). Thus, increased cytotoxicity induced by overexpression of Htt proteins containing expanded polyglutamine (polyQ) tracts is likely mediated, at least in part, by an alteration in normal mitochondrial dynamics, which results in increased mitochondrial fragmentation (Wang *et al.* 2009). In striatal neurons from moderate-to-severe grade HD patients, both mitochondrial loss and altered mitochondrial morphogenesis have been described, with increased mitochondrial fission and reduced fusion (Kim *et al.* 2010). Indeed, mHtt was recently shown to bind the mitochondrial fission Drp-1 and increase its enzymatic activity (Song *et al.* 2011). Furthermore, overexpression of proteins that stimulate mitochondrial fusion attenuates the toxicity of Htt proteins containing expanded polyQ tracts in both HeLa cells and *C. elegans* (Wang *et al.* 2009).

Efficient mitochondrial trafficking is especially important in neurons with long axons and dendrites, to ensure high metabolic energy requirements for neuronal signaling, plasticity and neurotransmitter release. mHtt impairs axonal transport of mitochondria, decreases mitochondrial function and damages neurons in affected regions of HD patients' brains (Shirendeb *et al.* 2011). In particular, specific N-terminal fragments of mHtt (produced before aggregate formation) were shown to preferentially associate with mitochondria *in vivo*, in an age-dependent way, directly affecting the mitochondrial traffic in an HD-knock-in mouse model (Orr *et al.* 2008). In rat cortical neurons expressing full-length mHtt, an early event in HD pathophysiology is the aberrant mobility and trafficking of mitochondria caused by cytosolic Htt aggregates (Chang *et al.* 2006). Sequestration of mitochondrial proteins along with defective trafficking might lead to failure of ATP synthesis, energy depletion, and ultimately cell death in striatal neurons isolated from transgenic mice expressing mHtt with 72 glutamines (Trushina et al. 2004). Thus, disruption of mitochondrial trafficking in neurodegenerative diseases and abnormal mitochondrial dynamics, due to the perturbation of balance between fission and fusion, may mediate and amplify mitochondrial dysfunction in HD, compromising the supply of energy for normal neuronal function (Bossy-Wetzel *et al.* 2008, for review).

2.3 Changes in energy metabolism

Neurons are largely dependent on ATP to perform their functions and, thus, a decrease in mitochondrial energy metabolism may highly contribute to neurodegeneration. Moreover,

mitochondria in striatal neurons, especially in the GABAergic medium-sized spiny neurons (MSNs), seem to be selectively vulnerable to metabolic stress, which may contribute to the selective loss of these neurons in HD (Jin and Johnson 2010, for review). Evidences of altered energy metabolism in HD include a decrease in glucose metabolism, observed in the caudate, putamen and cortex of symptomatic and pre-symptomatic HD patients (Kuhl *et al.* 1982;Kuwert *et al.* 1990). Modified glycolytic energy metabolism, in particular, has been described in HD patients, both in central and in peripheral tissues. This includes elevated levels of lactate in the striatum (Jenkins *et al.* 1993) and in the cortex (Jenkins *et al.* 1993;Koroshetz *et al.* 1997), and increased lactate/pyruvate ratio in the CSF (Koroshetz *et al.* 1997). However, decreased astrocytic glucose metabolism, with preserved oxygen metabolism, was described in the striatum of early symptomatic HD patients (Powers *et al.* 2007b). A significant decrease in phosphocreatine/inorganic phosphate ratio was found in resting muscle (Koroshetz *et al.* 1997) of HD patients, evidencing bioenergetic changes in HD peripheral tissues. Previous studies showed low levels of phosphocreatine/inorganic phosphate ratio in muscle of HD patients, compared to control subjects (Lodi *et al.* 2000), and a delayed recovery of phosphocreatine levels in HD patients in response to exercise (Saft *et al.* 2005). Moreover, reduced ATP production was observed in muscle of both presymptomatic and symptomatic HD patients (Lodi *et al.* 2000). In fact, the onset of energy-related manifestations at the presymptomatic stages of the disease, such as alterations in brain and muscle metabolism and weight loss, suggest that the energy deficit is likely to be an early phenomenon in the cascade of events leading to HD pathogenesis (Mochel and Haller 2011). Conversely, in HD N171-82Q mice model, increased glucose metabolism and ATP levels were found in brain tissue, suggesting that the neuronal damage in HD tissue may be associated with increased energy metabolism at the tissue level, leading to modified levels of various intermediary metabolites (Olah *et al.* 2008). Interestingly, we observed that HD cybrid lines exhibited increased glycolytic ATP levels compared to control cybrids, which were correlated with increased lactate/pyruvate levels (Ferreira *et al.* 2011). In these cybrids, the activity of G6PD, a key enzyme of the pentose phosphate pathway, was decreased (Ferreira *et al.* 2011), suggesting that glucose metabolization occurs primarily through the glycolytic pathway. Furthermore, mitochondrial NADH/NADt ratio was decreased (Ferreira *et al.* 2011), which was further correlated with a large decrease in the activity and protein levels of pyruvate dehydrogenase (PDH) (Ferreira *et al.* 2011). Nevertheless, the activity of alpha-ketoglutarate dehydrogenase (KGDH), another NADH producer in the tricarboxylic acid cycle, was increased, suggesting a compensatory mechanism to counterbalance the decrease in NADH production through the PDH. Decreased PDH activity was also previously observed in the caudate and putamen of HD patients (Sorbi *et al.* 1983), which was correlated with increasing duration of the illness (Butterworth *et al.* 1985). Moreover, PDH expression was shown to decrease with age in the striatum of R6/2 transgenic mice (Perluigi *et al.* 2005). A decrease in mitochondrial alanine and an increase in mitochondrial glutamate levels observed in these cybrids may be interpreted as an attempt to recover ketoglutarate levels and thus mitochondrial NADH (Ferreira *et al.* 2011). Alanine levels were also found to be decreased in the CSF of HD patients, along with decreased pyruvate levels and increased lactate/pyruvate ratio (Koroshetz *et al.* 1997). Our results demonstrated that HD cybrid lines possess inherent bioenergetically dysfunctional mitochondria derived from HD patients' platelets in the presence of a functional nuclear background (Ferreira et al. 2011). Mitochondrial

dysfunction at the level of PDH, upstream the oxidative phosphorylation, affected amino acid metabolic fluxes and the cellular bioenergetics through glycolysis stimulation, which assumed a greater importance in promoting ATP production (Ferreira et al. 2011).

2.4 Oxidative stress

Oxidative phosphorylation at the level of mitochondrial ETC is a major source of ROS, such as superoxide anion (the radical formed from the direct reduction of oxygen due to electron leakage at the ETC), hydrogen peroxide and hydroxyl radical (the most reactive and unstable radical). In the absence of effective antioxidants, ROS generated by dysfunctional mitochondria may attack mitochondrial components, promoting intracellular oxidative stress and leading to protein, lipid and DNA oxidation, further contributing to mitochondrial dysfunction.

Oxidative damage was shown to play an important role in the pathogenesis and progression of HD in the R6/2 transgenic mouse model (Perluigi *et al.* 2005) and also in post-mortem samples obtained from the striatum and cortex of human HD brain (Sorolla *et al.* 2010). An increase in DCF fluorescence, indicative of an increase in hydroperoxide levels, was also described in the striatum of R6/1 mice 11-35 weeks (Perez-Severiano *et al.* 2004). In accordance, we demonstrated that, under basal conditions, HD cybrids were endowed with a significant higher production of hydroperoxides when compared to control cybrids (Ferreira et al., 2010). These data differ from a previous study showing no evidence of ROS generation in untreated HD cybrids (Swerdlow *et al.* 1999); however, these authors did not exclude a subtle mitochondrial pathology in these cells. In agreement, we showed that HD cybrids are more vulnerable than control cybrids to produce superoxide upon exposure to 3-NP or staurosporine (STS), whereas increased hydroperoxide production was mainly evoked by STS, suggesting that the presence of higher amounts of hydroperoxides in untreated HD cybrids masks the effect caused by 3-NP-induced mitochondrial inhibition (Ferreira *et al.* 2010).

Several biomarkers of oxidative stress, such as oxidized macromolecules, were found in HD patients and in HD models. Oxidized DNA was found in the caudate of HD patients (Browne *et al.* 1997), whereas oxidized mtDNA was reported in the parietal cortex of late stage (grade 3-4) HD patients (Polidori *et al.* 1999). 8-Hydroxy-deoxyguanosine was also found in peripheral blood of HD patients (Chen *et al.* 2007;Hersch *et al.* 2006). Moreover, oxidized DNA markers were also found in forebrain, striatum (Tabrizi *et al.* 2000;Bogdanov *et al.* 2001), urine, plasma and striatal dialysates of R6/2 mice at 12 and 14 weeks of age (Bogdanov *et al.* 2001). An increase in lipid peroxidation markers was also found in HD human blood (Chen *et al.* 2007;Stoy *et al.* 2005) or brain (Browne *et al.* 1999) and in R6/2 mouse brain (Tabrizi *et al.* 2000;Perez-Severiano *et al.* 2000). Protein oxidation markers, such as carbonyl levels, were also found to be increased in mitochondrial enzymes, resulting in decreased mitochondrial activity in the striatum of Tet/HD94 conditional HD mice (Sorolla *et al.* 2010).

Decreased activities of the antioxidant enzymes Cu–Zn-superoxide dismutase and glutathione peroxidase in erythrocytes (Chen *et al.* 2007), and decreased catalase activity were found in skin fibroblasts from HD patients (del Hoyo *et al.* 2006). A decrease in the antioxidant enzyme Cu/Zn-superoxide dismutase was also observed in R6/1 mice at 35

weeks (Santamaria *et al.* 2001). Moreover, the antioxidant agents lipoic acid and BN-82451 are neuroprotective in HD mice (R6/2 and N171–82Q lines), increasing survival and delaying striatal atrophy in these genetic models of HD (Andreassen *et al.* 2001;Klivenyi *et al.* 2003), further evidencing participation of oxidative damage in the process of neurodegeneration in HD. However, 3-NP *in vivo* exposure induced antioxidant response element (ARE)-dependent gene expression in cultured astrocytes through the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2), leading to gene expression of antioxidant and detoxification genes (Shih *et al.* 2005).

2.5 Transcriptional deregulation

Nuclear localization of mHtt was shown to play a role in toxicity (Saudou *et al.* 1998), possibly due to interference of the mutant protein with nuclear transcription factors and co-factors (Benn *et al.* 2008;Zhai *et al.* 2005). Moreover, mitochondrial dysfunction in HD has been related to transcriptional deregulation.

Mitochondrial gene expression is regulated in the nucleus by the transcriptional co-activator peroxisome proliferative activated receptor gamma coactivator 1 alpha (PGC-1alpha) (Lin *et al.* 2004;Lin *et al.* 2005), and in the mitochondria, by the nuclear-encoded mitochondrial transcription factor A (Tfam) (Kaufman *et al.* 2007), which also regulate mitochondrial function and biogenesis.

Abnormal PGC-1alpha function was shown to result in significant mitochondrial impairment (Kim *et al.* 2010). The levels of PGC-1alpha and Tfam were found to be reduced in HD (Cui et al. 2006;Chaturvedi et al. 2009). Moreover, both proteins have been reported to be significantly reduced in brain lysates from HD patients, which was correlated with HD progression (Kim et al. 2010). A significant decrease in PGC-1alpha mRNA was found in the caudate nucleus in asymptomatic HD patients, accompanied by reduced expression of genes involved in energy metabolism (Cui *et al.* 2006). Interestingly, decreased expression of PGC-1alpha was observed in MSNs (largely affected in HD), whereas striatal interneurons showed increased mRNA levels for PGC-1alpha (Cui *et al.* 2006) which could, at least partially, explain the different vulnerability of these striatal neuronal populations. PGC-1alpha and Tfam were also reduced in muscle biopsies and myoblast cultures from HD subjects (Chaturvedi *et al.* 2009). Transcriptional repression of PGC-1alpha by mHtt leads not only to mitochondrial dysfunction, but also to neurodegeneration, suggesting a key role for PGC-1alpha in the control of energy metabolism in the early stages of HD pathogenesis (Cui *et al.* 2006). Thermoregulatory and metabolic defects in HD transgenic mice also implicate PGC-1alpha in HD neurodegeneration (Weydt *et al.* 2006), and polymorphisms at the PGC-1alpha gene modify the age at onset in HD (Weydt *et al.* 2009). In accordance, activation of PGC-1alpha/peroxisome proliferator-activated receptor gamma (PPARgamma) seems to protect against neurodegeneration (St-Pierre *et al.* 2006).

PGC-1alpha controls many aspects of oxidative metabolism, including respiration and mitochondrial biogenesis by co-activating and enhancing the expression and activity of several transcription factors, including the nuclear respiratory factors (NRF)-1 and NRF-2 (also known as GA-binding protein, GABP), PPARgamma and the estrogen related receptor alpha (ERRalpha) (Scarpulla 2002;Scarpulla 2011). It was recently shown that PGC-1alpha downstream transcription factors NRF-1 and Tfam are genetic modifiers of HD

(Taherzadeh-Fard *et al.* 2011). PGC-1alpha is indirectly involved in regulating the expression of mtDNA transcription *via* increased expression of Tfam, which is co-activated by NRF-1 (Scarpulla 2002;Kelly and Scarpulla 2004). Moreover, mitochondrial-dependent generation of ROS in HD seems to be due, at least in part, to suppression of PGC-1alpha in the presence of mHtt, as this transcription coactivator is required for the induction of ROS-detoxifying enzymes, namely Mn-superoxide dismutase and glutathione peroxidase (St-Pierre *et al.* 2006), implicating PGC-1alpha as an important protector against oxidative damage in HD. Importantly, activation of PPARgamma was recently shown to rescue mitochondrial dysfunction in HD (Chiang *et al.* 2011).

An important and key event in the signaling cascade that regulates PGC-1alpha expression is related with mitogen- and stress-activated protein kinase 1 (MSK-1) activation (Martin *et al.* 2011). MSK1 induces neuroprotection in HD, involving chromatin remodeling at the PGC-1 alpha promoter (Martin *et al.* 2011).

cAMP response element-binding (CREB) is a major transcription factor for PGC-1alpha (Cui *et al.* 2006). CREB is widely expressed and has a well-established role in neuronal protection (Lee *et al.* 2005). mHtt was shown to interfere with CREB transcriptional processes, through direct interaction with CREB-binding protein (CBP) (Steffan *et al.* 2000) and with TATA box-binding protein (TBP)-associated factor TAF4/TAFII130 (Dunah *et al.* 2002;Shimohata *et al.* 2000), leading to an increase in mHtt-induced cytotoxicity (Steffan *et al.* 2001). TAFII130 is a co-factor for CREB-dependent transcriptional activation that binds to polyQ, strongly suppressing CREB-mediated transcription (Shimohata *et al.* 2000). Reduction in cAMP levels in HD mice and HD patients likely contributes to the significant reduction in CREB activation (Gines *et al.* 2003). Moreover, CBP co-localizes with mHtt (Nucifora, Jr. *et al.* 2001), being found in nuclear inclusions in HD mice (Nucifora, Jr. *et al.* 2001;Steffan *et al.* 2001) and human brain (Nucifora, Jr. *et al.* 2001). In accordance, CRE-response genes such as corticotrophin-releasing hormone, proenkephalin, substance P were found to be reduced in brain tissue in HD patients (Augood *et al.* 1996;De Souza 1995) and R6/2 mice (Luthi-Carter *et al.* 2002).

Our group has previously shown that dysregulation of CREB activation and histone acetylation occurs in 3-NP-treated cortical neurons (Almeida *et al.* 2010), an *in vitro* model of mitochondrial complex II inhibition in HD. The phosphorylation status of CREB is critical for its activity and several protein kinases, such as calcium/calmodulin-dependent kinase II and IV, protein kinase C, PI3K, Akt, MAPK, and Rsk2, have been reported to promote the activation of CREB (Yamamoto *et al.* 1988;Matthews *et al.* 1994;Du and Montminy 1998;Bito *et al.* 1996;Impey *et al.* 1998;Perkinton *et al.* 2002). Phosphorylation on Ser133 leads to CREB activation and promotes the transcription of a large number of genes, through interaction with its nuclear partner CBP (Mayr and Montminy 2001). Results from our laboratory showed that 3-NP treatment of cortical neurons decreased both CREB phosphorylation on Ser133 and CBP levels (Almeida *et al.* 2010), strongly suggesting reduced CREB-dependent gene expression/activation. The decrease in CREB phosphorylation was possibly due to the activation of phosphatases in response to 3-NP exposure. Several studies have shown that calcineurin, whose expression is regulated by 3-NP (Napolitano *et al.* 2004), also regulate the duration of CREB phosphorylation (Bito *et al.* 1996). However, the concentration of 3-NP used in our study did not significantly alter calcineurin (Almeida *et al.* 2004). The decrease in total CBP levels after 3-NP exposure could be explained by an independent mechanism,

related with caspase-3 (Almeida *et al.* 2010), but not calpain activation (Almeida *et al.* 2004). CBP has previously been reported to be specifically targeted for cleavage by caspases (and also by calpains) at the onset of neuronal apoptosis (Rouaux *et al.* 2003). A decrease in CBP was correlated with reduced acetylation of histones H3 and H4 and with a reduction in CBP/p300 HAT activity, even while total HAT activity remained unchanged (Rouaux *et al.* 2003). Similarly, we showed that 3-NP did not alter total HAT activity, but significantly decreased overall HDAC activity, likely explaining why we did not observe a reduction in H3 or H4 acetylation (Almeida *et al.* 2010). Instead, we observed an increase in both H3 and H4 acetylation in cortical neurons upon exposure to 3-NP. Because 3-NP induces caspase-3 activation (Almeida *et al.* 2004), we hypothesized that caspase-3 plays a role in inactivating HDACs. On the other hand, inhibition of HDAC may constitute a mechanism of protection of cells exposed to mild metabolic stress. Indeed, neuroprotection induced by HDAC inhibitors in HD striatal cells involves more efficient calcium handling, thus improving the neuronal ability to cope with excitotoxic stimuli (Oliveira *et al.* 2006).

mHtt was previously reported to bind p53 and upregulate its expression and transcriptional activity (Bae *et al.* 2005). It was demonstrated that some of the alterations induced by mHtt in mitochondrial homeostasis and cell death were dependent on p53 (Bae *et al.* 2005). Recently, mHtt expression was correlated with an increase in phosphorylated p53 at Ser15, a decrease in acetylation at Lys382, altered ubiquitination pattern, and oligomerization activity. The lack of a proper p53-mediated signaling cascade or its alteration in the presence of DNA damage may contribute to the slow progression of cellular dysfunction which is a hallmark of HD pathology (Illuzzi *et al.* 2011).

Specific protein-1 (Sp1) is another transcription factor that was found to bind mHtt, resulting in inhibition of Sp1-mediated transcription of genes in post-mortem brain tissue of pre-symptomatic and symptomatic HD patients (Dunah *et al.* 2002), such as NGF receptor (Li *et al.* 2002). Sp1 is a regulatory protein that binds to guanine-cytosine boxes and mediates transcription through its glutamine-rich activation domains which target components of the basal transcriptional complex, such as TAFII130 (Sugars and Rubinsztein 2003,for review). Furthermore, it has also been shown that, despite normal protein levels and nuclear binding activity, the binding of Sp1 to specific promoters of susceptible genes is significantly decreased in transgenic HD mouse brains, striatal HD cells and human HD brains, suggesting that mHtt dissociates Sp1 from target promoters, inhibiting the transcription of specific genes (Chen-Plotkin *et al.* 2006). Sequestration of Sp1 and TAFII130 into nuclear inclusions leads to the inhibition of Sp1-mediated transcription (Dunah *et al.* 2002;Li *et al.* 2002). Moreover, shorter N-terminal Htt fragments, which are more prone to misfold and aggregate, are more competent to bind and inhibit Sp1 (Cornett *et al.* 2006). Interestingly, this effect was reversed *in vitro* by HSP40, a molecular chaperone that reduces mHtt misfolding (Cornett *et al.* 2006).

mHtt may also lose the ability to bind and interact with other transcription factors regulated by wild-type huntingtin (Htt), as is the case of the neuron-restrictive silencer element (NRSE)-binding transcription factors, in which the failure of mHtt to interact with transcriptional factor complex repressor-element-1 transcription factor (REST)/neuron-restrictive silencer factor (NRSF) in the cytoplasm leads to its nuclear accumulation. There, it binds to NRSE sequences and promotes histone deacetylation, leading to the remodeling of the chromatin into a closed structure, resulting in the suppression of NRSE-containing

genes, including the bdnf gene (Zuccato *et al.* 2003). In this case, the loss of the normal Htt function may have profound effects, leading to decreased levels of BDNF, an important survival factor for striatal neurons (section 2.2). Indeed, BDNF-knockout models were shown to largely recapitulate the expression profile of human HD (Strand *et al.* 2007), suggesting that striatal MSNs suffer similar insults in HD and BDNF-deprived environments.

2.6 Regulation of mitochondrial-driven apoptosis

Neurodegeneration in HD has been associated with increased cell death by apoptosis, particularly by the intrinsic pathway, highly regulated by mitochondria. Previous studies demonstrated the presence of caspases cleavage sites in Htt, a mechanism that may also contribute to apoptotic death by generating truncated toxic fragments of this protein (Wellington *et al.* 1998), although the CAG length does not seem to modulate the susceptibility for cleavage. mHtt is a substrate for several caspases and calpains (Kim *et al.* 2001) and the polyglutamine fragments of Htt may present enhanced toxicity, promoting caspases activation by interfering with mitochondrial function, thus amplifying the generation of toxic truncated mHtt (Graham *et al.* 2010). Moreover, sequestration of pro-caspases in the aggregates is thought to promote their activation, triggering an intracellular cascade of proteolytic events (Gil and Rego 2008, for review). Interestingly, wild-type Htt was found to have antiapoptotic properties against a variety of apoptotic stimuli, including serum withdrawal, death receptors, and proapoptotic Bcl-2 homologs (Rigamonti *et al.* 2000), namely through inhibition of cytochrome c-dependent procaspase-9 processing and activity (Rigamonti *et al.* 2001). Furthermore, calpain (Gafni and Ellerby 2002), caspase-1 (Ona *et al.* 1999) and caspase-8 (Sanchez *et al.* 1999) activities are increased in HD human brains, suggesting that an apoptotic mechanism is responsible for HD neuronal loss (Gil and Rego 2008, for review). Moreover, cultured blood cells from patients homozygous for CAG repeat mutations and heterozygous with high size mutations causing juvenile onset presented significantly increased caspases -2, -3, -6, -8 and -9 activities, decreased cell viability and pronounced mitochondria morphological abnormalities, compared with cells from HD patients carrying low mutation size and controls (Squitieri *et al.* 2011).

Cell death by necrosis and apoptosis, along with energy deficiency, were previously described in striatal, cortical and hippocampal cells exposed to 3-NP (Behrens *et al.* 1995;Pang and Geddes 1997;Almeida *et al.* 2004;Almeida *et al.* 2006;Brouillet *et al.* 2005), and both processes of cell damage have been proven to involve mitochondria (Kroemer and Reed 2000). Concordantly with a higher role of intrinsic apoptosis in HD, Ferrer and collaborators (2000) found a reduction in Fas and FasL expression levels in the caudate and putamen of HD patients. Mitochondria has been largely recognized to play a critical role in cell death by releasing apoptogenic factors, such as cytochrome c and apoptosis-inducing factor (AIF), from the intermembrane space into the cytoplasm.

As described before, by directly interacting with the mitochondria (Panov *et al.* 2002), mHtt may cause mitochondrial abnormalities in HD, leading to cytochrome c release (Panov *et al.* 2002), and a decrease in mitochondrial membrane potential (Sawa *et al.* 1999). Release of cytochrome *c* along with the activation of caspases -1, -8, and -9 have been demonstrated in HD (Ona *et al.* 1999;Sanchez *et al.* 1999;Kiechle *et al.* 2002), and increased Bcl-2 and Bax were also reported in HD patients' brain, especially in the most severely affected (Vis *et al.* 2005).

Overexpression of mHtt, but not the normal protein, increases oxidative stress-induced mitochondrial fragmentation in HeLa cells, which correlates with increased caspase-3 activation and cell death (Wang *et al.* 2009). Results from our laboratory highly suggested that 3-NP induces both caspase-dependent and -independent cell death (Almeida *et al.* 2006). Our group also showed that exposure of HD cybrid cell lines to 3-NP or STS caused DNA fragmentation and moderate caspase-3 activation, evidencing an increased susceptibility of HD cybrids to apoptosis (Ferreira *et al.* 2010). In contrast, 3-NP-treated control cybrids died predominantly by necrosis, not involving caspase-3 activation (Ferreira *et al.* 2010), suggesting that HD mitochondria are endowed with pro-apoptotic machinery and thus more susceptible to this type of cell death. Moreover, preserved ATP in HD cybrids compared to control cybrids (Ferreira et al. 2011) may facilitate apoptotic cell death. Mitochondrial-dependent apoptosis in HD cybrids subjected to 3-NP was correlated with increased release of mitochondrial cytochrome c, AIF, Bax translocation, caspase-3 activation and ROS formation (Ferreira *et al.* 2010). Increased mitochondrial Bim and Bak levels, and a slight release of cytochrome c in untreated HD cybrids further explained their moderate susceptibility to mitochondrial-dependent apoptosis under basal conditions (Ferreira et al. 2010). These data appear to be consistent with possible subtle effects of mHtt in the mitochondria of HD cybrids. 3-NP has been also shown to collapse mitochondrial membrane potential and to downregulate striatal Bcl-2 levels (Zhang *et al.* 2009b), promoting cytochrome c release from mitochondria, transient caspase-9 processing, activation of calpains and subsequent striatal apoptosis (Bizat *et al.* 2003;Zhang *et al.* 2009b). 3-NP-induced decrement in Bcl-2 may also play a role in mitochondrial-dependent autophagy activation (through the release of Beclin 1 from hVps34 complex), which was also involved in striatal neuronal apoptosis (Zhang *et al.* 2009a).

Our group has also reported that 3-NP causes mitochondrial-dependent apoptotic neuronal death through the release of cytochrome c and consequent activation of caspases, or the release of AIF in cortical neurons, depending on the concentration of 3-NP (Almeida *et al.* 2004;Almeida *et al.* 2006;Almeida *et al.* 2009). Enhanced mitochondrial-dependent apoptosis was also observed in 3-NP-treated cortical neurons as a result of decreased Bim turnover (Almeida *et al.* 2004). mHtt fragments were previously shown to directly induce the opening of the mitochondrial permeability transition pore (PTP) in isolated mouse liver mitochondria, with the consequent release of cytochrome c (Choo *et al.* 2004), which evokes caspase cascade activation. Choo and collaborators (2004) also described that mitochondria from liver of knock-in mouse model of HD and from homozygous ST*Hdh*^{Q111} cells were more sensitive to calcium-induced cytochrome c release, swelling at lower calcium loads. An increased striatal mitochondrial susceptibility to the induction of permeability transition (Brustovetsky *et al.* 2003) may be responsible to the striatal selectivity for energy deficit associated with mHtt. An age- and polyQ-dependent decrease in the amount of calcium necessary to induce permeability transition in striatal mitochondria was observed in severe (R6/2 mice) and in mild (*HdhQ92* knock-in mice) HD mouse models (Brustovetsky *et al.* 2003). Moreover, increased mitochondrial calcium loading capacity, previously shown in isolated mitochondria from 12-13 week-old R6/2 and 12 month-old YAC mice brain (Oliveira *et al.* 2007) could constitute a compensatory mechanism, to extend neuronal function and survival or, alternatively, it could simply reflect an artifact resulting from mitochondria isolation, as it was not observed in neuronal *in situ* experiments following exposure to excitotoxic stimuli (Oliveira *et al.* 2007).

Myoblasts obtained from presymptomatic and symptomatic HD subjects also showed mitochondrial depolarization, cytochrome c release and increased activities of caspases -3, -8 and -9 (Ciammola *et al.* 2006). In addition, peripheral blood cells, in particularly B lymphocytes from HD patients, may reflect changes observed in HD brain. Our group previously found increased Bax expression in B and T lymphocytes, and monocytes from HD patients, with no alterations in Bcl-2 expression levels, and decreased mitochondrial membrane potential in B lymphocytes (Almeida *et al.* 2008), further suggesting that an adverse effect of mHtt is not limited to neurons. Moreover, mitochondria from lymphoblasts of HD patients have been shown to present increased susceptibility to apoptotic stimuli due to an abnormal mitochondrial transmembrane potential (Sawa et al. 1999). Lymphoblasts derived from HD patients also showed increased stress-induced apoptotic cell death associated with caspase-3 activation, abnormal calcium homeostasis and mitochondrial dysfunction (Panov *et al.* 2002;Sawa *et al.* 1999).

3. Protective effects involving modulation of phosphorylation pathways — The case of FK506 and the neurotrophins BDNF and NGF

Even though HD has a single genetic cause, the multiplicity of pathogenic mechanisms involved suggests that several different targets must be taken into account in order to slow down HD progression. Despite important advances in elucidating the molecular pathways involved in HD neurodegeneration, there is currently no therapy that delays the onset of the disease. In this respect, stimulation of phosphorylation pathways by neurotrophins or calcineurin inhibitors (such as FK506) may be a promising strategy.

3.1 FK506 — An inhibitor of calcineurin

It is well accepted that mHtt is associated with calcium handling abnormalities (Quintanilla and Johnson 2009, for review). Calcineurin can be activated by abnormal calcium levels occurring in HD. Classically, calcineurin (or protein phosphatase 3, formerly known as protein phosphatase 2B) can promote apoptosis through dephosphorylation of Bad at Ser112 and Ser136 (Wang *et al.* 1999), a proapoptotic member of the Bcl-2 family. Dephosphorylated Bad translocates from the cytosol to the mitochondria, where it inhibits antiapoptotic activity of Bcl-2 and Bcl-xL, ultimately leading to cell death. Calcineurin couples intracellular calcium to the dephosphorylation of other selected substrates, which include transcription factors [nuclear factor of activated T-cells (NFAT)], ion channels (inositol-1,4,5 triphosphate receptor), proteins involved in vesicular trafficking (amphyphysin, dynamin), scaffold proteins (AKAP79), and phosphatase inhibitors (DARPP-32 inhibitor-1) (Aramburu *et al.* 2000).

Calcineurin was recently shown to be involved in the dephosphorylation of Drp1, thus increasing Drp1 association with mitochondria and promoting fission, cristae disruption, cytochrome c release and apoptosis (Costa *et al.* 2010;Cereghetti *et al.* 2010). Concordantly, the calcineurin inhibitor PPD1 blocked Drp1 translocation to mitochondria and fragmentation of the organelle, delaying intrinsic apoptosis by preventing fragmentation and release of cytochrome ***c***, suggesting an important function of calcineurin in mitochondrial fragmentation and in the amplification of cell death (Cereghetti *et al.* 2010).

FK506, also known as tacrolimus, is a selective inhibitor of calcineurin (Griffith *et al.* 1995) that has shown to exert neuroprotective effects in several cellular and animal models of HD. Kumar and Kumar (2009) showed that systemic treatment with FK506 significantly improved cognitive function in a 3-NP rodent model. In the 3-NP neuronal model, we have previously shown that FK506 precludes cytochrome c release, activation of caspase-3 and DNA fragmentation in cultured cortical neurons (Almeida *et al.* 2004). FK506 neuroprotection against 3-NP-induced apoptosis was associated with the redistribution of Bcl-2 and Bax in the mitochondrial membrane of cortical neurons (Almeida *et al.* 2004). Moreover, FK506 significantly attenuated oxidative stress as evidenced by restoring glutathione levels and acetylcholinesterase activity in 3-NP treated animals (Kumar and Kumar 2009), highlighting the therapeutic potential of this compound. In a recent study from our laboratory FK506 has shown neuroprotective effects against apoptosis and necrosis under mild cell death stimulus, in the presence of full-length mHtt, in 3-NP-treated primary striatal neurons and immortalized striatal cells derived from HD knock-in mice (ST*Hdh*$^{Q111/Q111}$ mutant cells) (Rosenstock *et al.* 2011).

In the context of mHtt expression, intraperitoneal injection of calcineurin inhibitors was shown to accelerate the neurological phenotype in R6/2 mice (Hernandez-Espinosa and Morton 2006), which are resistant to excitotoxicity (Hansson *et al.* 1999). Interestingly, reduced calcineurin protein levels and activity were observed in this HD animal model (Xifro *et al.* 2009). In contrast, calcineurin is involved in cell death induced by activation of *N*-methyl-D-aspartate receptors (NMDARs) in knock-in striatal cells expressing full-length mHtt (Xifro *et al.* 2008). Moreover, FK506 and the genetic inactivation of calcineurin protected against mHtt toxicity through increased phosphorylation of Htt (Pardo *et al.* 2006) and further ameliorated the defect in BDNF axonal transport (Pineda *et al.* 2009).

3.2 BDNF and NGF — Activators of survival pathways

Trophic support to neurons largely influences neuronal survival and function. BDNF, a pro-survival factor that is produced by cortical neurons, is necessary for the survival of striatal neurons in the brain. This is particularly relevant in HD since its transcription (Zuccato *et al.* 2001) and axonal transport (Gauthier *et al.* 2004) are decreased by the presence of mHtt, affecting the survival of both striatal and cortical neurons. Members of the neurotrophin family, namely BDNF and NGF, have been suggested as therapeutic candidates to treat neurodegenerative disorders because they promote neuronal survival in different lesion models (Connor and Dragunow 1998). Indeed, implantation of NGF-secreting fibroblasts was found to reduce the size of adjacent striatal 3-NP lesions (Frim *et al.* 1993).

Wild-type Htt was demonstrated to promote the expression of BDNF by interacting with the REST/NRSF in the cytoplasm, preventing this complex from translocating into the nucleus and binding to NRSE present in the promoter of the bdnf gene (Zuccato *et al.* 2003). Wild-type Htt also promoted the vesicular transport of BDNF along the microtubules through a mechanism involving Htt -associated protein 1 (HAP1) and the p150 subunit of dynactin (Gauthier *et al.* 2004). Thus, wild-type Htt controls neurotrophic support and survival of striatal neurons by promoting BDNF transcription and vesicular transport along microtubules (Gauthier *et al.* 2004).

In contrast, mHtt decreases transcription of BDNF, which results in decreased production of cortical BDNF in HD (Zuccato *et al.* 2001), leading to insufficient neurotrophic support for striatal neurons, which then die. Accordingly, a reduction in cortical BDNF mRNA levels was shown to correlate with the progression of the disease in a mouse model of HD (Zuccato *et al.* 2005). In addition, BDNF-knockout models were shown to largely recapitulate the expression profiling of human HD (Strand *et al.* 2007), suggesting that striatal MSNs suffer similar insults in HD and BDNF-deprived environments. Moreover, mHtt appears to be responsible for altering the wild-type Htt /HAP1/p150 complex, causing an impaired association between motor proteins and microtubules, and attenuating BDNF transport, which results in loss of neurotrophic support (Gauthier *et al.* 2004). Thus, restoring wild-type Htt activity and increasing BDNF production are promising therapeutic approaches for treating HD (Zuccato *et al.* 2001).

BDNF was previously shown to prevent the death of different populations of striatal projection neurons in a quinolinic acid model of HD (Perez-Navarro *et al.* 2000;Kells *et al.* 2004) and in striatal neurons exposed to 3-NP (Ryu *et al.* 2004). The effects of BDNF are mainly mediated by TrkB receptor-induced activation of key signaling pathways, including phosphoinositide phospholipase C (PLC-γ), rat sarcoma GTPase (Ras)/MEK/ Ras–mitogen-activated protein kinase (MAPK) and PI3K/Akt pathways (Huang and Reichardt 2003), which have been shown to regulate apoptotic cell death by increasing the transcription of neuroprotective proteins such as Bcl-2 (Pugazhenthi *et al.* 2000) and/or by posttranslational modifications of proteins such as Bad and Bim (Scheid et al. 1999;Luciano et al. 2003). Bim phosphorylation by MAPK promotes its subsequent ubiquitination and degradation (Ley *et al.* 2003), whereas serine phosphorylation of Bad is associated with protein 14-3-3 binding and inhibition of Bad-induced cell death (Masters *et al.* 2001). Data from our laboratory support an important role for BDNF in protecting cortical neurons against apoptotic cell death caused by 3-NP through the activation of PI3K and MEK1/2 intracellular signaling pathways and the regulation of Bim turnover (Almeida et al. 2009). Moreover, signaling of BDNF and NGF culminates in the transcription of neuroprotective proteins through the activation of critical transcription factors such as CREB and nuclear factor-kB (NFkB) (Huang and Reichardt 2003). As described in section 1.5, when activated by phosphorylation, CREB binds to its co-activator CBP and the complex is competent to initiate gene transcription (Mayr and Montminy 2001). Similarly, phosphorylation of IkB releases the p65:p50 NFkB heterodimers, which then translocate to the nucleus to initiate transcription. Pro-survival proteins whose expression is dependent on these transcription factors include proteins such as Bcl-2, Mn-superoxide dismutase and BDNF (Saha et al. 2006). A recent study from our laboratory also suggested that BDNF and NGF induce positive changes in the levels and activities of CREB and NFkB, and both neurotrophins counteracted 3-NP-induced chromatin-bound histone acetylation modifications. The latter finding was correlated with BDNF-induced hyperphosphorylation of HDAC2, explaining the neuroprotective role of this neurotrophin in the context of mitochondrial dysfunction (Almeida *et al.* 2010).

4. Conclusions

In summary, biochemical studies support the view that mitochondrial dysfunction, including impaired oxidative phosphorylation, tricarboxylic acid cycle dysfunction, and

oxidative stress are important determinants of altered energy metabolism in HD. Bioenergetic changes in HD may be related with impaired intracellular transport and transcriptional deregulation in the disease (Mochel and Haller 2011). Impaired bioenergetics in HD likely represents downstream effects of both a mHtt toxic gain-of-function and a loss-of-function of the wild-type protein. Thus, therapeutic strategies designed to improve energy metabolism and survival pathways dependent on kinase signaling in the HD brain will possibly impact the course of the disease, delaying its onset and the rate of progression. BDNF support (which can be rescued by wild-type Htt) and FK506 may have important therapeutic effects as enhancers of phosphorylation pathways, preventing mitochondrial dysfunction caused by mHtt and mitochondrial-dependent apoptosis.

5. Acknowledgements

T.C.O. holds a postdoctoral fellowship from 'Fundação para a Ciência e a Tecnologia' (FCT), Portugal (SFRH/BPD/34711/2007). A.C.R. acknowledges financial support from FCT Grant PTDC/SAU-FCF/108056/2008.

6. References

Almeida S., Brett A. C., Gois I. N., Oliveira C. R. and Rego A. C. (2006) Caspase-dependent and -independent cell death induced by 3-nitropropionic acid in rat cortical neurons. *J. Cell Biochem.* 98, 93-101. ISSN: 0730-2312 (Print); ISSN: 0730-2312 (Linking)

Almeida S., Cunha-Oliveira T., Laco M., Oliveira C. R. and Rego A. C. (2010) Dysregulation of CREB activation and histone acetylation in 3-nitropropionic acid-treated cortical neurons: prevention by BDNF and NGF. *Neurotox. Res.* 17, 399-405. ISSN: 1476-3524 (Electronic); ISSN: 1029-8428 (Linking)

Almeida S., Domingues A., Rodrigues L., Oliveira C. R. and Rego A. C. (2004) FK506 prevents mitochondrial-dependent apoptotic cell death induced by 3-nitropropionic acid in rat primary cortical cultures. *Neurobiol. Dis.* 17, 435-444. ISSN: 0969-9961 (Print); ISSN: 0969-9961 (Linking)

Almeida S., Laco M., Cunha-Oliveira T., Oliveira C. R. and Rego A. C. (2009) BDNF regulates BIM expression levels in 3-nitropropionic acid-treated cortical neurons. *Neurobiol. Dis.* 35, 448-456. ISSN:1095-953X (Electronic); ISSN: 0969-9961 (Linking)

Almeida S., Sarmento-Ribeiro A. B., Januario C., Rego A. C. and Oliveira C. R. (2008) Evidence of apoptosis and mitochondrial abnormalities in peripheral blood cells of Huntington's disease patients. *Biochem. Biophys. Res. Commun.* 374, 599-603. ISSN: 1090-2104 (Electronic); ISSN: 0006-291X (Linking)

Andreassen O. A., Ferrante R. J., Dedeoglu A. and Beal M. F. (2001) Lipoic acid improves survival in transgenic mouse models of Huntington's disease. *Neuroreport* 12, 3371-3373. ISSN: 0959-4965 (Print); ISSN: 0959-4965 (Linking)

Aramburu J., Rao A. and Klee C. B. (2000) Calcineurin: from structure to function. *Curr. Top. Cell Regul.* 36, 237-295. ISSN: 0070-2137 (Print); ISSN: 0070-2137 (Linking)

Arenas J., Campos Y., Ribacoba R., Martin M. A., Rubio J. C., Ablanedo P. and Cabello A. (1998) Complex I defect in muscle from patients with Huntington's disease. *Ann. Neurol.* 43, 397-400. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Augood S. J., Faull R. L., Love D. R. and Emson P. C. (1996) Reduction in enkephalin and substance P messenger RNA in the striatum of early grade Huntington's disease: a detailed cellular in situ hybridization study. *Neuroscience* 72, 1023-1036. ISSN: 0306-4522 (Print); ISSN: 0306-4522 (Linking)

Bae B. I., Xu H., Igarashi S., Fujimuro M., Agrawal N., Taya Y., Hayward S. D., Moran T. H., Montell C., Ross C. A., Snyder S. H. and Sawa A. (2005) p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. *Neuron* 47, 29-41. ISSN: 0896-6273 (Print); ISSN: 0896-6273 (Linking)

Beal M. F., Brouillet E., Jenkins B., Henshaw R., Rosen B. and Hyman B. T. (1993) Age-dependent striatal excitotoxic lesions produced by the endogenous mitochondrial inhibitor malonate. *J. Neurochem.* 61, 1147-1150. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Behrens M. I., Koh J., Canzoniero L. M., Sensi S. L., Csernansky C. A. and Choi D. W. (1995) 3-Nitropropionic acid induces apoptosis in cultured striatal and cortical neurons. *Neuroreport* 6, 545-548. ISSN: 0959-4965 (Print); ISSN: 0959-4965 (Linking)

Benchoua A., Trioulier Y., Zala D., Gaillard M. C., Lefort N., Dufour N., Saudou F., Elalouf J. M., Hirsch E., Hantraye P., Deglon N. and Brouillet E. (2006) Involvement of mitochondrial complex II defects in neuronal death produced by N-terminus fragment of mutated huntingtin. *Mol. Biol. Cell* 17, 1652-1663. ISSN: 1059-1524 (Print); ISSN: 1059-1524 (Linking)

Benn C. L., Sun T., Sadri-Vakili G., McFarland K. N., DiRocco D. P., Yohrling G. J., Clark T. W., Bouzou B. and Cha J. H. (2008) Huntingtin modulates transcription, occupies gene promoters in vivo, and binds directly to DNA in a polyglutamine-dependent manner. *J. Neurosci.* 28, 10720-10733. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Bito H., Deisseroth K. and Tsien R. W. (1996) CREB phosphorylation and dephosphorylation: a Ca(2+)- and stimulus duration-dependent switch for hippocampal gene expression. *Cell* 87, 1203-1214. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Bizat N., Hermel J. M., Boyer F., Jacquard C., Creminon C., Ouary S., Escartin C., Hantraye P., Kajewski S. and Brouillet E. (2003) Calpain is a major cell death effector in selective striatal degeneration induced in vivo by 3-nitropropionate: implications for Huntington's disease. *J. Neurosci.* 23, 5020-5030. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Bogdanov M. B., Andreassen O. A., Dedeoglu A., Ferrante R. J. and Beal M. F. (2001) Increased oxidative damage to DNA in a transgenic mouse model of Huntington's disease. *J. Neurochem.* 79, 1246-1249. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Bossy-Wetzel E., Petrilli A. and Knott A. B. (2008) Mutant huntingtin and mitochondrial dysfunction. *Trends Neurosci.* 31, 609-616. ISSN: 0166-2236 (Print); ISSN: 0166-2236 (Linking)

Brouillet E., Conde F., Beal M. F. and Hantraye P. (1999) Replicating Huntington's disease phenotype in experimental animals. *Prog. Neurobiol.* 59, 427-468. ISSN: 0301-0082 (Print); ISSN: 0301-0082 (Linking)

Brouillet E., Jacquard C., Bizat N. and Blum D. (2005) 3-Nitropropionic acid: a mitochondrial toxin to uncover physiopathological mechanisms underlying striatal degeneration in Huntington's disease. *J. Neurochem.* 95, 1521-1540. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Brouillet E., Jenkins B. G., Hyman B. T., Ferrante R. J., Kowall N. W., Srivastava R., Roy D. S., Rosen B. R. and Beal M. F. (1993) Age-dependent vulnerability of the striatum to the mitochondrial toxin 3-nitropropionic acid. *J. Neurochem.* 60, 356-359. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Browne S. E., Bowling A. C., MacGarvey U., Baik M. J., Berger S. C., Muqit M. M., Bird E. D. and Beal M. F. (1997) Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. *Ann. Neurol.* 41, 646-653. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Browne S. E., Ferrante R. J. and Beal M. F. (1999) Oxidative stress in Huntington's disease. *Brain Pathol.* 9, 147-163. ISSN: 1015-6305 (Print): ISSN: 1015-6305 (Linking)

Brustovetsky N., Brustovetsky T., Purl K. J., Capano M., Crompton M. and Dubinsky J. M. (2003) Increased susceptibility of striatal mitochondria to calcium-induced permeability transition. *J. Neurosci.* 23, 4858-4867. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Butterworth J., Yates C. M. and Reynolds G. P. (1985) Distribution of phosphate-activated glutaminase, succinic dehydrogenase, pyruvate dehydrogenase and gamma-glutamyl transpeptidase in post-mortem brain from Huntington's disease and agonal cases. *J. Neurol. Sci.* 67, 161-171. ISSN: 0022-510X (Print); ISSN: 0022-510X (Linking)

Cereghetti G. M., Costa V. and Scorrano L. (2010) Inhibition of Drp1-dependent mitochondrial fragmentation and apoptosis by a polypeptide antagonist of calcineurin. *Cell Death. Differ.* 17, 1785-1794. ISSN: 1476-5403 (Electronic); ISSN: 1350-9047 (Linking)

Chang D. T., Rintoul G. L., Pandipati S. and Reynolds I. J. (2006) Mutant huntingtin aggregates impair mitochondrial movement and trafficking in cortical neurons. *Neurobiol. Dis.* 22, 388-400. ISSN: 0969-9961 (Print); ISSN: 0969-9961 (Linking)

Chaturvedi R. K., Adhihetty P., Shukla S., Hennessy T., Calingasan N., Yang L., Starkov A., Kiaei M., Cannella M., Sassone J., Ciammola A., Squitieri F. and Beal M. F. (2009) Impaired PGC-1alpha function in muscle in Huntington's disease. *Hum. Mol. Genet.* 18, 3048-3065. ISSN: 1460-2083 (Electronic); ISSN: 0964-6906 (Linking)

Chen C. M., Wu Y. R., Cheng M. L., Liu J. L., Lee Y. M., Lee P. W., Soong B. W. and Chiu D. T. (2007) Increased oxidative damage and mitochondrial abnormalities in the peripheral blood of Huntington's disease patients. *Biochem. Biophys. Res. Commun.* 359, 335-340. ISSN: 0006-291X (Print); ISSN: 0006-291X (Linking)

Chen H. and Chan D. C. (2009) Mitochondrial dynamics--fusion, fission, movement, and mitophagy--in neurodegenerative diseases. *Hum. Mol. Genet.* 18, R169-R176. ISSN: 1460-2083 (Electronic); ISSN: 0964-6906 (Linking)

Chen-Plotkin A. S., Sadri-Vakili G., Yohrling G. J., Braveman M. W., Benn C. L., Glajch K. E., DiRocco D. P., Farrell L. A., Krainc D., Gines S., MacDonald M. E. and Cha J. H. (2006) Decreased association of the transcription factor Sp1 with genes downregulated in Huntington's disease. *Neurobiol. Dis.* 22, 233-241. ISSN: 0969-9961 (Print); ISSN: 0969-9961 (Linking)

Chiang M. C., Chern Y. and Huang R. N. (2011) PPARgamma rescue of the mitochondrial dysfunction in Huntington's disease. *Neurobiol. Dis.* ISSN: 1095-953X (Electronic); ISSN: 0969-9961 (Linking)

Choo Y. S., Johnson G. V., MacDonald M., Detloff P. J. and 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. ISSN: 0964-6906 (Print); ISSN: 0964-6906 (Linking)

Ciammola A., Sassone J., Alberti L., Meola G., Mancinelli E., Russo M. A., Squitieri F. and Silani V. (2006) Increased apoptosis, Huntingtin inclusions and altered differentiation in muscle cell cultures from Huntington's disease subjects. *Cell Death. Differ.* 13, 2068-2078. ISSN: 1350-9047 (Print); ISSN: 1350-9047 (Linking)

Connor B. and Dragunow M. (1998) The role of neuronal growth factors in neurodegenerative disorders of the human brain. *Brain Res. Brain Res. Rev.* 27, 1-39. ISSN: 0165-0173

Cornett J., Smith L., Friedman M., Shin J. Y., Li X. J. and Li S. H. (2006) Context-dependent dysregulation of transcription by mutant huntingtin. *J. Biol. Chem.* 281, 36198-36204. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Costa V., Giacomello M., Hudec R., Lopreiato R., Ermak G., Lim D., Malorni W., Davies K. J., Carafoli E. and 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. ISSN: 1757-4684 (Electronic); ISSN: 1757-4676 (Linking)

Cui L., Jeong H., Borovecki F., Parkhurst C. N., Tanese N. and Krainc D. (2006) Transcriptional repression of PGC-1alpha by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. *Cell* 127, 59-69. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Damiano M., Galvan L., Deglon N. and Brouillet E. (2010) Mitochondria in Huntington's disease. *Biochim. Biophys. Acta* 1802, 52-61. ISSN: 0006-3002 (Print); ISSN: 0006-3002 (Linking)

De Souza E. B. (1995) Corticotropin-releasing factor receptors: physiology, pharmacology, biochemistry and role in central nervous system and immune disorders. *Psychoneuroendocrinology* 20, 789-819. ISSN: 0306-4530 (Print); ISSN: 0306-4530 (Linking)

del Hoyo P., Garcia-Redondo A., de B. F., Molina J. A., Sayed Y., Alonso-Navarro H., Caballero L., Arenas J. and Jimenez-Jimenez F. J. (2006) Oxidative stress in skin fibroblasts cultures of patients with Huntington's disease. *Neurochem. Res.* 31, 1103-1109. ISSN: 0364-3190 (Print); ISSN: 0364-3190 (Linking)

Du K. and Montminy M. (1998) CREB is a regulatory target for the protein kinase Akt/PKB. *J. Biol. Chem.* 273, 32377-32379. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Dunah A. W., Jeong H., Griffin A., Kim Y. M., Standaert D. G., Hersch S. M., Mouradian M. M., Young A. B., Tanese N. and Krainc D. (2002) Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. *Science* 296, 2238-2243. ISSN: 1095-9203 (Electronic); ISSN: 0036-8075 (Linking)

Ferreira I. L., Cunha-Oliveira T., Nascimento M. V., Ribeiro M., Proenca M. T., Januario C., Oliveira C. R. and Rego A. C. (2011) Bioenergetic dysfunction in Huntington's disease human cybrids. *Exp. Neurol.* 231, 127-134. ISSN: 1090-2430 (Electronic); ISSN: 0014-4886 (Linking)

Ferreira I. L., Nascimento M. V., Ribeiro M., Almeida S., Cardoso S. M., Grazina M., Pratas J., Santos M. J., Januario C., Oliveira C. R. and Rego A. C. (2010) Mitochondrial-dependent apoptosis in Huntington's disease human cybrids. *Exp. Neurol.* 222, 243-255. ISSN: 1090-2430 (Electronic); ISSN: 0014-4886 (Linking)

Ferrer I., Blanco R., Cutillas B. and Ambrosio S. (2000) Fas and Fas-L expression in Huntington's disease and Parkinson's disease. *Neuropathol. Appl. Neurobiol.* 26, 424-433. ISSN: 0305-1846 (Print); ISSN: 0305-1846 (Linking)

Frim D. M., Simpson J., Uhler T. A., Short M. P., Bossi S. R., Breakefield X. O. and Isacson O. (1993) Striatal degeneration induced by mitochondrial blockade is prevented by biologically delivered NGF. *J. Neurosci. Res.* 35, 452-458. ISSN: 0360-4012 (Print); ISSN: 0360-4012 (Linking)

Gafni J. and Ellerby L. M. (2002) Calpain activation in Huntington's disease. *J. Neurosci.* 22, 4842-4849. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Gauthier L. R., Charrin B. C., Borrell-Pages M., Dompierre J. P., Rangone H., Cordelieres F. P., De M. J., MacDonald M. E., Lessmann V., Humbert S. and Saudou F. (2004) Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. *Cell* 118, 127-138. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Gil J. M. and Rego A. C. (2008) Mechanisms of neurodegeneration in Huntington's disease. *Eur. J. Neurosci.* 27, 2803-2820. ISSN: 1460-9568 (Electronic); ISSN: 0953-816X (Linking)

Gines S., Seong I. S., Fossale E., Ivanova E., Trettel F., Gusella J. F., Wheeler V. C., Persichetti F. and MacDonald M. E. (2003) Specific progressive cAMP reduction implicates energy deficit in presymptomatic Huntington's disease knock-in mice. *Hum. Mol. Genet.* 12, 497-508. ISSN: 0964-6906 (Print); ISSN: 0964-6906 (Linking)

Goebel H. H., Heipertz R., Scholz W., Iqbal K. and Tellez-Nagel I. (1978) Juvenile Huntington chorea: clinical, ultrastructural, and biochemical studies. *Neurology* 28, 23-31. ISSN: 0028-3878 (Print); ISSN: 0028-3878 (Linking)

Graham R. K., Deng Y., Carroll J., Vaid K., Cowan C., Pouladi M. A., Metzler M., Bissada N., Wang L., Faull R. L., Gray M., Yang X. W., Raymond L. A. and Hayden M. R. (2010) Cleavage at the 586 amino acid caspase-6 site in mutant huntingtin influences caspase-6 activation in vivo. *J. Neurosci.* 30, 15019-15029. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Griffith J. P., Kim J. L., Kim E. E., Sintchak M. D., Thomson J. A., Fitzgibbon M. J., Fleming M. A., Caron P. R., Hsiao K. and Navia M. A. (1995) X-ray structure of calcineurin inhibited by the immunophilin-immunosuppressant FKBP12-FK506 complex. *Cell* 82, 507-522. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Gu M., Gash M. T., Mann V. M., Javoy-Agid F., Cooper J. M. and Schapira A. H. (1996) Mitochondrial defect in Huntington's disease caudate nucleus. *Ann. Neurol.* 39, 385-389. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Hansson O., Petersen A., Leist M., Nicotera P., Castilho R. F. and Brundin P. (1999) Transgenic mice expressing a Huntington's disease mutation are resistant to quinolinic acid-induced striatal excitotoxicity. *Proc. Natl. Acad. Sci. U. S. A* 96, 8727-8732. ISSN: 0027-8424 (Print); ISSN: 0027-8424 (Linking)

Hernandez-Espinosa D. and Morton A. J. (2006) Calcineurin inhibitors cause an acceleration of the neurological phenotype in a mouse transgenic for the human Huntington's disease mutation. *Brain Res. Bull.* 69, 669-679. ISSN: 0361-9230 (Print); ISSN: 0361-9230 (Linking)

Hersch S. M., Gevorkian S., Marder K., Moskowitz C., Feigin A., Cox M., Como P., Zimmerman C., Lin M., Zhang L., Ulug A. M., Beal M. F., Matson W., Bogdanov M., Ebbel E., Zaleta A., Kaneko Y., Jenkins B., Hevelone N., Zhang H., Yu H., Schoenfeld D., Ferrante R. and Rosas H. D. (2006) Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. *Neurology* 66, 250-252. ISSN: 1526-632X (Electronic); ISSN: 0028-3878 (Linking)

Horton T. M., Graham B. H., Corral-Debrinski M., Shoffner J. M., Kaufman A. E., Beal M. F. and Wallace D. C. (1995) Marked increase in mitochondrial DNA deletion levels in the cerebral cortex of Huntington's disease patients. *Neurology* 45, 1879-1883. ISSN: 0028-3878 (Print); ISSN: 0028-3878 (Linking)

Huang E. J. and Reichardt L. F. (2003) Trk receptors: roles in neuronal signal transduction. *Annu. Rev. Biochem.* 72, 609-642. ISSN: 0066-4154 (Print); ISSN: 0066-4154 (Linking)

Illuzzi J. L., Vickers C. A. and Kmiec E. B. (2011) Modifications of p53 and the DNA Damage Response in Cells Expressing Mutant Form of the Protein Huntingtin. *J. Mol. Neurosci.* 45, 256-268. ISSN: 1559-1166 (Electronic); ISSN: 0895-8696 (Linking)

Impey S., Obrietan K., Wong S. T., Poser S., Yano S., Wayman G., Deloulme J. C., Chan G. and Storm D. R. (1998) Cross talk between ERK and PKA is required for Ca2+ stimulation of CREB-dependent transcription and ERK nuclear translocation. *Neuron* 21, 869-883. ISSN: 0896-6273 (Print); ISSN: 0896-6273 (Linking)

Jenkins B. G., Koroshetz W. J., Beal M. F. and Rosen B. R. (1993) Evidence for impairment of energy metabolism in vivo in Huntington's disease using localized 1H NMR spectroscopy. *Neurology* 43, 2689-2695. ISSN: 0028-3878 (Print); ISSN: 0028-3878 (Linking)

Jin Y. N. and Johnson G. V. (2010) The interrelationship between mitochondrial dysfunction and transcriptional dysregulation in Huntington disease. *J. Bioenerg. Biomembr.* 42, 199-205. ISSN: 1573-6881 (Electronic); ISSN: 0145-479X (Linking)

Kasraie S., Houshmand M., Banoei M. M., Ahari S. E., Panahi M. S., Shariati P., Bahar M. and Moin M. (2008) Investigation of tRNA(Leu/Lys) and ATPase 6 genes mutations in Huntington's disease. *Cell Mol. Neurobiol.* 28, 933-938. ISSN: 1573-6830 (Electronic); ISSN: 0272-4340 (Linking)

Kaufman B. A., Durisic N., Mativetsky J. M., Costantino S., Hancock M. A., Grutter P. and Shoubridge E. A. (2007) The mitochondrial transcription factor TFAM coordinates the assembly of multiple DNA molecules into nucleoid-like structures. *Mol. Biol. Cell* 18, 3225-3236. ISSN: 1059-1524 (Print): ISSN: 1059-1524 (Linking)

Kells A. P., Fong D. M., Dragunow M., During M. J., Young D. and Connor B. (2004) AAV-mediated gene delivery of BDNF or GDNF is neuroprotective in a model of Huntington disease. *Mol. Ther.* 9, 682-688. ISSN: 1525-0016 (Print); ISSN: 1525-0016 (Linking)

Kelly D. P. and Scarpulla R. C. (2004) Transcriptional regulatory circuits controlling mitochondrial biogenesis and function. *Genes Dev.* 18, 357-368. ISSN: 0890-9369 (Print); ISSN: 0890-9369 (Linking)

Kiechle T., Dedeoglu A., Kubilus J., Kowall N. W., Beal M. F., Friedlander R. M., Hersch S. M. and Ferrante R. J. (2002) Cytochrome C and caspase-9 expression in Huntington's disease. *Neuromolecular. Med.* 1, 183-195. ISSN: 1535-1084 (Print); ISSN: 1535-1084 (Linking)

Kim G. W., Gasche Y., Grzeschik S., Copin J. C., Maier C. M. and Chan P. H. (2003) Neurodegeneration in striatum induced by the mitochondrial toxin 3-nitropropionic acid: role of matrix metalloproteinase-9 in early blood-brain barrier disruption? *J. Neurosci.* 23, 8733-8742. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Kim J., Moody J. P., Edgerly C. K., Bordiuk O. L., Cormier K., Smith K., Beal M. F. and Ferrante R. J. (2010) Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. *Hum. Mol. Genet.* 19, 3919-3935. ISSN: 1460-2083 (Electronic); ISSN: 0964-6906 (Linking)

Kim Y. J., Yi Y., Sapp E., Wang Y., Cuiffo B., Kegel K. B., Qin Z. H., Aronin N. and DiFiglia M. (2001) Caspase 3-cleaved N-terminal fragments of wild-type and mutant huntingtin are present in normal and Huntington's disease brains, associate with membranes, and undergo calpain-dependent proteolysis. *Proc. Natl. Acad. Sci. U. S. A* 98, 12784-12789. ISSN: 0027-8424 (Print); ISSN: 0027-8424 (Linking)

King M. P. and Attardi G. (1989) Human cells lacking mtDNA: repopulation with exogenous mitochondria by complementation. *Science* 246, 500-503. ISSN: 0036-8075 (Print); ISSN: 0036-8075 (Linking)

Klivenyi P., Ferrante R. J., Gardian G., Browne S., Chabrier P. E. and Beal M. F. (2003) Increased survival and neuroprotective effects of BN82451 in a transgenic mouse model of Huntington's disease. *J. Neurochem.* 86, 267-272. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Koroshetz W. J., Jenkins B. G., Rosen B. R. and Beal M. F. (1997) Energy metabolism defects in Huntington's disease and effects of coenzyme Q10. *Ann. Neurol.* 41, 160-165. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Kroemer G. and Reed J. C. (2000) Mitochondrial control of cell death. *Nat. Med.* 6, 513-519. ISSN: 1078-8956 (Print); ISSN: 1078-8956 (Linking)

Kuhl D. E., Phelps M. E., Markham C. H., Metter E. J., Riege W. H. and Winter J. (1982) Cerebral metabolism and atrophy in Huntington's disease determined by 18FDG and computed tomographic scan. *Ann. Neurol.* 12, 425-434. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Kumar P. and Kumar A. (2009) Neuroprotective effect of cyclosporine and FK506 against 3-nitropropionic acid induced cognitive dysfunction and glutathione redox in rat: possible role of nitric oxide. *Neurosci. Res.* 63, 302-314. ISSN: 0168-0102 (Print); ISSN: 0168-0102 (Linking)

Kuwert T., Lange H. W., Langen K. J., Herzog H., Aulich A. and Feinendegen L. E. (1990) Cortical and subcortical glucose consumption measured by PET in patients with Huntington's disease. *Brain* 113 (Pt 5), 1405-1423. ISSN: 0006-8950 (Print); ISSN: 0006-8950 (Linking)

Lee J., Kim C. H., Simon D. K., Aminova L. R., Andreyev A. Y., Kushnareva Y. E., Murphy A. N., Lonze B. E., Kim K. S., Ginty D. D., Ferrante R. J., Ryu H. and Ratan R. R. (2005) Mitochondrial cyclic AMP response element-binding protein (CREB) mediates mitochondrial gene expression and neuronal survival. *J. Biol. Chem.* 280, 40398-40401. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Ley R., Balmanno K., Hadfield K., Weston C. and Cook S. J. (2003) Activation of the ERK1/2 signaling pathway promotes phosphorylation and proteasome-dependent degradation of the BH3-only protein, Bim. *J. Biol. Chem.* 278, 18811-18816. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Li S. H., Cheng A. L., Zhou H., Lam S., Rao M., Li H. and Li X. J. (2002) Interaction of Huntington disease protein with transcriptional activator Sp1. *Mol. Cell Biol.* 22, 1277-1287. ISSN: 0270-7306 (Print); ISSN: 0270-7306 (Linking)

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. and Spiegelman B. M. (2004) Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1alpha null mice. *Cell* 119, 121-135. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Lin J., Yang R., Tarr P. T., Wu P. H., Handschin C., Li S., Yang W., Pei L., Uldry M., Tontonoz P., Newgard C. B. and Spiegelman B. M. (2005) Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP. *Cell* 120, 261-273. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Lodi R., Schapira A. H., Manners D., Styles P., Wood N. W., Taylor D. J. and Warner T. T. (2000) Abnormal in vivo skeletal muscle energy metabolism in Huntington's disease and dentatorubropallidoluysian atrophy. *Ann. Neurol.* 48, 72-76. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Luciano F., Jacquel A., Colosetti P., Herrant M., Cagnol S., Pages G. and Auberger P. (2003) Phosphorylation of Bim-EL by Erk1/2 on serine 69 promotes its degradation via the proteasome pathway and regulates its proapoptotic function. *Oncogene* 22, 6785-6793. ISSN: 0950-9232 (Print); ISSN: 0950-9232 (Linking)

Luthi-Carter R., Hanson S. A., Strand A. D., Bergstrom D. A., Chun W., Peters N. L., Woods A. M., Chan E. Y., Kooperberg C., Krainc D., Young A. B., Tapscott S. J. and Olson J. M. (2002) Dysregulation of gene expression in the R6/2 model of polyglutamine disease: parallel changes in muscle and brain. *Hum. Mol. Genet.* 11, 1911-1926. ISSN: 0964-6906 (Print); ISSN: 0964-6906 (Linking)

Martin E., Betuing S., Pages C., Cambon K., Auregan G., Deglon N., Roze E. and Caboche J. (2011) Mitogen- and stress-activated protein kinase 1-induced neuroprotection in Huntington's disease: role on chromatin remodeling at the PGC-1-alpha promoter. *Hum. Mol. Genet.* 20, 2422-2434. ISSN: 1460-2083 (Electronic); ISSN: 0964-6906 (Linking)

Masters S. C., Yang H., Datta S. R., Greenberg M. E. and Fu H. (2001) 14-3-3 inhibits Bad-induced cell death through interaction with serine-136. *Mol. Pharmacol.* 60, 1325-1331. ISSN: 0026-895X (Print); ISSN: 0026-895X (Linking)

Matthews R. P., Guthrie C. R., Wailes L. M., Zhao X., Means A. R. and McKnight G. S. (1994) Calcium/calmodulin-dependent protein kinase types II and IV differentially regulate CREB-dependent gene expression. *Mol. Cell Biol.* 14, 6107-6116. ISSN: 0270-7306 (Print); ISSN: 0270-7306 (Linking)

Mayr B. and Montminy M. (2001) Transcriptional regulation by the phosphorylation-dependent factor CREB. *Nat. Rev. Mol. Cell Biol.* 2, 599-609. ISSN: 1471-0072 (Print); ISSN: 1471-0072 (Linking)

Mochel F. and Haller R. G. (2011) Energy deficit in Huntington disease: why it matters. *J. Clin. Invest* 121, 493-499. ISSN: 1932-6203 (Electronic); ISSN: 1932-6203 (Linking)

Morimoto N., Nagano I., Deguchi K., Murakami T., Fushimi S., Shoji M. and Abe K. (2004) Leber hereditary optic neuropathy with chorea and dementia resembling Huntington disease. *Neurology* 63, 2451-2452. ISSN: 1526-632X (Electronic); ISSN: 0028-3878 (Linking)

Napolitano M., Centonze D., Gubellini P., Rossi S., Spiezia S., Bernardi G., Gulino A. and Calabresi P. (2004) Inhibition of mitochondrial complex II alters striatal expression of genes involved in glutamatergic and dopaminergic signaling: possible implications for Huntington's disease. *Neurobiol. Dis.* 15, 407-414. ISSN: 0969-9961 (Print); ISSN: 0969-9961 (Linking)

Nucifora F. C., Jr., Sasaki M., Peters M. F., Huang H., Cooper J. K., Yamada M., Takahashi H., Tsuji S., Troncoso J., Dawson V. L., Dawson T. M. and Ross C. A. (2001) Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. *Science* 291, 2423-2428. ISSN: 0036-8075 (Print); ISSN: 0036-8075 (Linking)

Olah J., Klivenyi P., Gardian G., Vecsei L., Orosz F., Kovacs G. G., Westerhoff H. V. and Ovadi J. (2008) Increased glucose metabolism and ATP level in brain tissue of Huntington's disease transgenic mice. *FEBS J.* 275, 4740-4755. ISSN: 1742-464X (Print); ISSN: 1742-464X (Linking)

Oliveira J. M. (2010) Nature and cause of mitochondrial dysfunction in Huntington's disease: focusing on huntingtin and the striatum. *J. Neurochem.* 114, 1-12. ISSN: 1471-4159 (Electronic); ISSN: 0022-3042 (Linking)

Oliveira J. M., Chen S., Almeida S., Riley R., Goncalves J., Oliveira C. R., Hayden M. R., Nicholls D. G., Ellerby L. M. and Rego A. C. (2006) Mitochondrial-dependent Ca2+ handling in Huntington's disease striatal cells: effect of histone deacetylase inhibitors. *J. Neurosci.* 26, 11174-11186. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Oliveira J. M. and Goncalves J. (2009) In situ mitochondrial Ca2+ buffering differences of intact neurons and astrocytes from cortex and striatum. *J. Biol. Chem.* 284, 5010-5020. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Oliveira J. M., Jekabsons M. B., Chen S., Lin A., Rego A. C., Goncalves J., Ellerby L. M. and Nicholls D. G. (2007) Mitochondrial dysfunction in Huntington's disease: the bioenergetics of isolated and in situ mitochondria from transgenic mice. *J. Neurochem.* 101, 241-249. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Ona V. O., Li M., Vonsattel J. P., Andrews L. J., Khan S. Q., Chung W. M., Frey A. S., Menon A. S., Li X. J., Stieg P. E., Yuan J., Penney J. B., Young A. B., Cha J. H. and Friedlander R. M. (1999) Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. *Nature* 399, 263-267. ISSN: 0028-0836 (Print); ISSN: 0028-0836 (Linking)

Orr A. L., Li S., Wang C. E., Li H., Wang J., Rong J., Xu X., Mastroberardino P. G., Greenamyre J. T. and Li X. J. (2008) N-terminal mutant huntingtin associates with mitochondria and impairs mitochondrial trafficking. *J. Neurosci.* 28, 2783-2792. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Pandey M., Mohanakumar K. P. and Usha R. (2010) Mitochondrial functional alterations in relation to pathophysiology of Huntington's disease. *J. Bioenerg. Biomembr.* 42, 217-226. ISSN: 1573-6881 (Electronic); ISSN: 0145-479X (Linking)

Pang Z. and Geddes J. W. (1997) Mechanisms of cell death induced by the mitochondrial toxin 3-nitropropionic acid: acute excitotoxic necrosis and delayed apoptosis. *J. Neurosci.* 17, 3064-3073. ISSN: 0270-6474 (Print); ISSN: 0270-6474 (Linking)

Panov A. V., Gutekunst C. A., Leavitt B. R., Hayden M. R., Burke J. R., Strittmatter W. J. and Greenamyre J. T. (2002) Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. *Nat. Neurosci.* 5, 731-736. ISSN: 1097-6256 (Print); ISSN: 1097-6256 (Linking)

Pardo R., Colin E., Regulier E., Aebischer P., Deglon N., Humbert S. and Saudou F. (2006) Inhibition of calcineurin by FK506 protects against polyglutamine-huntingtin toxicity through an increase of huntingtin phosphorylation at S421. *J. Neurosci.* 26, 1635-1645. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Parker W. D., Jr., Boyson S. J., Luder A. S. and Parks J. K. (1990) Evidence for a defect in NADH: ubiquinone oxidoreductase (complex I) in Huntington's disease. *Neurology* 40, 1231-1234. ISSN: 0028-3878 (Print); ISSN: 0028-3878 (Linking)

Perez-Navarro E., Canudas A. M., Akerund P., Alberch J. and Arenas E. (2000) Brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4/5 prevent the death of striatal projection neurons in a rodent model of Huntington's disease. *J. Neurochem.* 75, 2190-2199. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Perez-Severiano F., Rios C. and Segovia J. (2000) Striatal oxidative damage parallels the expression of a neurological phenotype in mice transgenic for the mutation of Huntington's disease. *Brain Res.* 862, 234-237. ISSN: 0006-8993 (Print); ISSN: 0006-8993 (Linking)

Perez-Severiano F., Santamaria A., Pedraza-Chaverri J., Medina-Campos O. N., Rios C. and Segovia J. (2004) Increased formation of reactive oxygen species, but no changes in glutathione peroxidase activity, in striata of mice transgenic for the Huntington's disease mutation. *Neurochem. Res.* 29, 729-733. ISSN: 0364-3190 (Print); ISSN: 0364-3190 (Linking)

Perkinton M. S., Ip J. K., Wood G. L., Crossthwaite A. J. and Williams R. J. (2002) Phosphatidylinositol 3-kinase is a central mediator of NMDA receptor signalling to MAP kinase (Erk1/2), Akt/PKB and CREB in striatal neurones. *J. Neurochem.* 80, 239-254. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Perluigi M., Poon H. F., Maragos W., Pierce W. M., Klein J. B., Calabrese V., Cini C., De M. C. and Butterfield D. A. (2005) Proteomic analysis of protein expression and oxidative modification in r6/2 transgenic mice: a model of Huntington disease. *Mol. Cell Proteomics.* 4, 1849-1861. ISSN: 1535-9476 (Print); ISSN: 1535-9476 (Linking)

Pineda J. R., Pardo R., Zala D., Yu H., Humbert S. and Saudou F. (2009) Genetic and pharmacological inhibition of calcineurin corrects the BDNF transport defect in Huntington's disease. *Mol. Brain* 2, 33. ISSN: 1756-6606 (Electronic); ISSN: 1756-6606 (Linking)

Polidori M. C., Mecocci P., Browne S. E., Senin U. and Beal M. F. (1999) Oxidative damage to mitochondrial DNA in Huntington's disease parietal cortex. *Neurosci. Lett.* 272, 53-56. ISSN: 0304-3940 (Print); ISSN: 0304-3940 (Linking)

Powers W. J., Haas R. H., Le T., Videen T. O., Hershey T., McGee-Minnich L. and Perlmutter J. S. (2007a) Normal platelet mitochondrial complex I activity in Huntington's disease. *Neurobiol. Dis.* 27, 99-101. ISSN: 0969-9961 (Print); ISSN: 0969-9961 (Linking)

Powers W. J., Videen T. O., Markham J., McGee-Minnich L., Antenor-Dorsey J. V., Hershey T. and Perlmutter J. S. (2007b) Selective defect of in vivo glycolysis in early Huntington's disease striatum. *Proc. Natl. Acad. Sci. U. S. A* 104, 2945-2949. ISSN: 0027-8424 (Print); ISSN: 0027-8424 (Linking)

Pugazhenthi S., Nesterova A., Sable C., Heidenreich K. A., Boxer L. M., Heasley L. E. and Reusch J. E. (2000) Akt/protein kinase B up-regulates Bcl-2 expression through cAMP-response element-binding protein. *J. Biol. Chem.* 275, 10761-10766. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Quintanilla R. A. and Johnson G. V. (2009) Role of mitochondrial dysfunction in the pathogenesis of Huntington's disease. *Brain Res. Bull.* 80, 242-247. ISSN: 1873-2747 (Electronic); ISSN: 0361-9230 (Linking)

Rigamonti D., Bauer J. H., De-Fraja C., Conti L., Sipione S., Sciorati C., Clementi E., Hackam A., Hayden M. R., Li Y., Cooper J. K., Ross C. A., Govoni S., Vincenz C. and Cattaneo E. (2000) Wild-type huntingtin protects from apoptosis upstream of caspase-3. *J. Neurosci.* 20, 3705-3713. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Rigamonti D., Sipione S., Goffredo D., Zuccato C., Fossale E. and Cattaneo E. (2001) Huntingtin's neuroprotective activity occurs via inhibition of procaspase-9 processing. *J. Biol. Chem.* 276, 14545-14548. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Rosenstock T. R., de Brito O. M., Lombardi V., Louros S., Ribeiro M., Almeida S., Ferreira I. L., Oliveira C. R. and Rego A. C. (2011) FK506 ameliorates cell death features in Huntington's disease striatal cell models. *Neurochem. Int.* ISSN: 1872-9754 (Electronic); ISSN: 0197-0186 (Linking)

Rosenstock T. R., Duarte A. I. and Rego A. C. (2010) Mitochondrial-associated metabolic changes and neurodegeneration in Huntington's disease - from clinical features to the bench. *Curr. Drug Targets.* 11, 1218-1236. ISSN: 1873-5592 (Electronic); ISSN: 1389-4501 (Linking)

Rouaux C., Jokic N., Mbebi C., Boutillier S., Loeffler J. P. and Boutillier A. L. (2003) Critical loss of CBP/p300 histone acetylase activity by caspase-6 during neurodegeneration. *EMBO J.* 22, 6537-6549. ISSN: 0261-4189 (Print); ISSN: 0261-4189 (Linking)

Ryu J. K., Kim J., Cho S. J., Hatori K., Nagai A., Choi H. B., Lee M. C., McLarnon J. G. and Kim S. U. (2004) Proactive transplantation of human neural stem cells prevents degeneration of striatal neurons in a rat model of Huntington disease. *Neurobiol. Dis.* 16, 68-77. ISSN: 0969-9961 (Print); ISSN: 0969-9961 (Linking)

Saft C., Zange J., Andrich J., Muller K., Lindenberg K., Landwehrmeyer B., Vorgerd M., Kraus P. H., Przuntek H. and Schols L. (2005) Mitochondrial impairment in patients and asymptomatic mutation carriers of Huntington's disease. *Mov Disord.* 20, 674-679. ISSN: 0885-3185 (Print); ISSN: 0885-3185 (Linking)

Saha R. N., Liu X. and Pahan K. (2006) Up-regulation of BDNF in astrocytes by TNF-alpha: a case for the neuroprotective role of cytokine. *J. Neuroimmune. Pharmacol.* 1, 212-222. ISSN: 1557-1904 (Electronic); ISSN: 1557-1890 (Linking)

Sanchez I., Xu C. J., Juo P., Kakizaka A., Blenis J. and Yuan J. (1999) Caspase-8 is required for cell death induced by expanded polyglutamine repeats. *Neuron* 22, 623-633. ISSN: 0896-6273 (Print); ISSN: 0896-6273 (Linking)

Santamaria A., Perez-Severiano F., Rodriguez-Martinez E., Maldonado P. D., Pedraza-Chaverri J., Rios C. and Segovia J. (2001) Comparative analysis of superoxide dismutase activity between acute pharmacological models and a transgenic mouse model of Huntington's disease. *Neurochem. Res.* 26, 419-424. ISSN: 0364-3190 (Print); ISSN: 0364-3190 (Linking)

Saudou F., Finkbeiner S., Devys D. and Greenberg M. E. (1998) Huntingtin acts in the nucleus to induce apoptosis but death does not correlate with the formation of intranuclear inclusions. *Cell* 95, 55-66. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Sawa A., Wiegand G. W., Cooper J., Margolis R. L., Sharp A. H., Lawler J. F., Jr., Greenamyre J. T., Snyder S. H. and Ross C. A. (1999) Increased apoptosis of Huntington disease lymphoblasts associated with repeat length-dependent mitochondrial depolarization. *Nat. Med.* 5, 1194-1198. ISSN: 1078-8956 (Print); ISSN: 1078-8956 (Linking)

Scarpulla R. C. (2002) Nuclear activators and coactivators in mammalian mitochondrial biogenesis. *Biochim. Biophys. Acta* 1576, 1-14. ISSN: 0006-3002 (Print); ISSN: 0006-3002 (Linking)

Scarpulla R. C. (2011) Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. *Biochim. Biophys. Acta* 1813, 1269-1278. ISSN: 0006-3002 (Print); ISSN: 0006-3002 (Linking)

Scheid M. P., Schubert K. M. and Duronio V. (1999) Regulation of bad phosphorylation and association with Bcl-x(L) by the MAPK/Erk kinase. *J. Biol. Chem.* 274, 31108-31113. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Shih A. Y., Imbeault S., Barakauskas V., Erb H., Jiang L., Li P. and Murphy T. H. (2005) Induction of the Nrf2-driven antioxidant response confers neuroprotection during mitochondrial stress in vivo. *J. Biol. Chem.* 280, 22925-22936. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

Shimohata T., Nakajima T., Yamada M., Uchida C., Onodera O., Naruse S., Kimura T., Koide R., Nozaki K., Sano Y., Ishiguro H., Sakoe K., Ooshima T., Sato A., Ikeuchi T., Oyake M., Sato T., Aoyagi Y., Hozumi I., Nagatsu T., Takiyama Y., Nishizawa M., Goto J., Kanazawa I., Davidson I., Tanese N., Takahashi H. and Tsuji S. (2000) Expanded polyglutamine stretches interact with TAFII130, interfering with CREB-dependent transcription. *Nat. Genet.* 26, 29-36. ISSN: 1061-4036 (Print); ISSN: 1061-4036 (Linking)

Shirendeb U., Reddy A. P., Manczak M., Calkins M. J., Mao P., Tagle D. A. and 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. ISSN: 1460-2083 (Electronic); ISSN: 0964-6906 (Linking)

Solans A., Zambrano A., Rodriguez M. and Barrientos A. (2006) Cytotoxicity of a mutant huntingtin fragment in yeast involves early alterations in mitochondrial OXPHOS complexes II and III. *Hum. Mol. Genet.* 15, 3063-3081. ISSN: 0964-6906 (Print); ISSN: 0964-6906 (Linking)

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. and 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. ISSN: 1546-170X (Electronic); ISSN: 1078-8956 (Linking)

Sorbi S., Bird E. D. and Blass J. P. (1983) Decreased pyruvate dehydrogenase complex activity in Huntington and Alzheimer brain. *Ann. Neurol.* 13, 72-78. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Sorolla M. A., Rodriguez-Colman M. J., Tamarit J., Ortega Z., Lucas J. J., Ferrer I., Ros J. and Cabiscol E. (2010) Protein oxidation in Huntington disease affects energy production and vitamin B6 metabolism. *Free Radic. Biol. Med.* 49, 612-621. ISSN: 1873-4596 (Electronic); ISSN: 0891-5849 (Linking)

Squitieri F., Maglione V., Orobello S. and Fornai F. (2011) Genotype-, aging-dependent abnormal caspase activity in Huntington disease blood cells. *J. Neural Transm.* ISSN: 1435-1463 (Electronic); ISSN: 0300-9564 (Linking)

St-Pierre J., Drori S., Uldry M., Silvaggi J. M., Rhee J., Jager S., Handschin C., Zheng K., Lin J., Yang W., Simon D. K., Bachoo R. and Spiegelman B. M. (2006) Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* 127, 397-408. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Stahl W. L. and Swanson P. D. (1974) Biochemical abnormalities in Huntington's chorea brains. *Neurology* 24, 813-819. ISSN: 0028-3878 (Print); ISSN: 0028-3878 (Linking)

Steffan J. S., Bodai L., Pallos J., Poelman M., McCampbell A., Apostol B. L., Kazantsev A., Schmidt E., Zhu Y. Z., Greenwald M., Kurokawa R., Housman D. E., Jackson G. R., Marsh J. L. and Thompson L. M. (2001) Histone deacetylase inhibitors arrest polyglutamine-dependent neurodegeneration in Drosophila. *Nature* 413, 739-743. ISSN: 0028-0836 (Print); ISSN: 0028-0836 (Linking)

Steffan J. S., Kazantsev A., Spasic-Boskovic O., Greenwald M., Zhu Y. Z., Gohler H., Wanker E. E., Bates G. P., Housman D. E. and Thompson L. M. (2000) The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. *Proc. Natl. Acad. Sci. U. S. A* 97, 6763-6768. ISSN: 0027-8424 (Print); ISSN: 0027-8424 (Linking)

Stoy N., Mackay G. M., Forrest C. M., Christofides J., Egerton M., Stone T. W. and Darlington L. G. (2005) Tryptophan metabolism and oxidative stress in patients with Huntington's disease. *J. Neurochem.* 93, 611-623. ISSN: 0022-3042 (Print); ISSN: 0022-3042 (Linking)

Strand A. D., Baquet Z. C., Aragaki A. K., Holmans P., Yang L., Cleren C., Beal M. F., Jones L., Kooperberg C., Olson J. M. and Jones K. R. (2007) Expression profiling of Huntington's disease models suggests that brain-derived neurotrophic factor depletion plays a major role in striatal degeneration. *J. Neurosci.* 27, 11758-11768. ISSN: 1529-2401 (Electronic); ISSN: 0270-6474 (Linking)

Sugars K. L. and Rubinsztein D. C. (2003) Transcriptional abnormalities in Huntington disease. *Trends Genet.* 19, 233-238. ISSN: 0168-9525 (Print); ISSN: 0168-9525 (Linking)

Swerdlow R. H., Parks J. K., Cassarino D. S., Shilling A. T., Bennett J. P., Jr., Harrison M. B. and Parker W. D., Jr. (1999) Characterization of cybrid cell lines containing mtDNA from Huntington's disease patients. *Biochem. Biophys. Res. Commun.* 261, 701-704. ISSN: 0006-291X (Print); ISSN: 0006-291X (Linking)

Tabrizi S. J., Workman J., Hart P. E., Mangiarini L., Mahal A., Bates G., Cooper J. M. and Schapira A. H. (2000) Mitochondrial dysfunction and free radical damage in the Huntington R6/2 transgenic mouse. *Ann. Neurol.* 47, 80-86. ISSN: 0364-5134 (Print); ISSN: 0364-5134 (Linking)

Taherzadeh-Fard E., Saft C., Akkad D. A., Wieczorek S., Haghikia A., Chan A., Epplen J. T. and Arning L. (2011) PGC-1alpha downstream transcription factors NRF-1 and TFAM are genetic modifiers of Huntington disease. *Mol. Neurodegener.* 6, 32. ISSN: 1750-1326 (Electronic); ISSN: 1750-1326 (Linking)

Tellez-Nagel I., Johnson A. B. and Terry R. D. (1974) Studies on brain biopsies of patients with Huntington's chorea. *J. Neuropathol. Exp. Neurol.* 33, 308-332. ISSN: 0022-3069 (Print); ISSN: 0022-3069 (Linking)

Trushina E., Dyer R. B., Badger J. D., Ure D., Eide L., Tran D. D., Vrieze B. T., Legendre-Guillemin V., McPherson P. S., Mandavilli B. S., Van H. B., Zeitlin S., McNiven M., Aebersold R., Hayden M., Parisi J. E., Seeberg E., Dragatsis I., Doyle K., Bender A., Chacko C. and McMurray C. T. (2004) Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro. *Mol. Cell Biol.* 24, 8195-8209. ISSN: 0270-7306 (Print); ISSN: 0270-7306 (Linking)

Turner C., Cooper J. M. and Schapira A. H. (2007) Clinical correlates of mitochondrial function in Huntington's disease muscle. *Mov Disord.* 22, 1715-1721. ISSN: 0885-3185 (Print); ISSN: 0885-3185 (Linking)

Vis J. C., Schipper E., de Boer-van Huizen RT, Verbeek M. M., de Waal R. M., Wesseling P., ten Donkelaar H. J. and Kremer B. (2005) Expression pattern of apoptosis-related markers in Huntington's disease. *Acta Neuropathol.* 109, 321-328. ISSN: 0001-6322 (Print); ISSN: 0001-6322 (Linking)

Wang H., Lim P. J., Karbowski M. and Monteiro M. J. (2009) Effects of overexpression of huntingtin proteins on mitochondrial integrity. *Hum. Mol. Genet.* 18, 737-752. ISSN: 1460-2083 (Electronic); ISSN: 0964-6906 (Linking)

Wang H. G., Pathan N., Ethell I. M., Krajewski S., Yamaguchi Y., Shibasaki F., McKeon F., Bobo T., Franke T. F. and Reed J. C. (1999) Ca2+-induced apoptosis through calcineurin dephosphorylation of BAD. *Science* 284, 339-343. ISSN: 0036-8075 (Print); ISSN: 0036-8075 (Linking)

Wellington C. L., Ellerby L. M., Hackam A. S., Margolis R. L., Trifiro M. A., Singaraja R., McCutcheon K., Salvesen G. S., Propp S. S., Bromm M., Rowland K. J., Zhang T., Rasper D., Roy S., Thornberry N., Pinsky L., Kakizuka A., Ross C. A., Nicholson D. W., Bredesen D. E. and Hayden M. R. (1998) Caspase cleavage of gene products associated with triplet expansion disorders generates truncated fragments containing the polyglutamine tract. *J. Biol. Chem.* 273, 9158-9167. ISSN: 0021-9258 (Print); ISSN: 0021-9258 (Linking)

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. and 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. ISSN: 1550-4131 (Print); ISSN: 1550-4131 (Linking)

Weydt P., Soyal S. M., Gellera C., Didonato S., Weidinger C., Oberkofler H., Landwehrmeyer G. B. and Patsch W. (2009) The gene coding for PGC-1alpha modifies age at onset in Huntington's Disease. *Mol. Neurodegener.* 4, 3.ISSN: 1750-1326 (Electronic); ISSN: 1750-1326 (Linking)

Xifro X., Garcia-Martinez J. M., Del T. D., Alberch J. and Perez-Navarro E. (2008) Calcineurin is involved in the early activation of NMDA-mediated cell death in mutant huntingtin knock-in striatal cells. *J. Neurochem.* 105, 1596-1612. ISSN: 1471-4159 (Electronic); ISSN: 0022-3042 (Linking)

Xifro X., Giralt A., Saavedra A., Garcia-Martinez J. M., Diaz-Hernandez M., Lucas J. J., Alberch J. and Perez-Navarro E. (2009) Reduced calcineurin protein levels and activity in exon-1 mouse models of Huntington's disease: role in excitotoxicity. *Neurobiol. Dis.* 36, 461-469. ISSN: 1095-953X (Electronic); ISSN: 0969-9961 (Linking)

Yamamoto K. K., Gonzalez G. A., Biggs W. H., III and Montminy M. R. (1988) Phosphorylation-induced binding and transcriptional efficacy of nuclear factor CREB. *Nature* 334, 494-498. ISSN: 0028-0836 (Print); ISSN: 0028-0836 (Linking)

Zhai W., Jeong H., Cui L., Krainc D. and Tjian R. (2005) In vitro analysis of huntingtin-mediated transcriptional repression reveals multiple transcription factor targets. *Cell* 123, 1241-1253. ISSN: 0092-8674 (Print); ISSN: 0092-8674 (Linking)

Zhang X. D., Wang Y., Wang Y., Zhang X., Han R., Wu J. C., Liang Z. Q., Gu Z. L., Han F., Fukunaga K. and Qin Z. H. (2009a) p53 mediates mitochondria dysfunction-triggered autophagy activation and cell death in rat striatum. *Autophagy.* 5, 339-350. ISSN: 1554-8635 (Electronic); ISSN: 1554-8627 (Linking)

Zhang X. D., Wang Y., Wu J. C., Lin F., Han R., Han F., Fukunaga K. and Qin Z. H. (2009b) Down-regulation of Bcl-2 enhances autophagy activation and cell death induced by mitochondrial dysfunction in rat striatum. *J. Neurosci. Res.* 87, 3600-3610. ISSN: 1097-4547 (Electronic); ISSN: 0360-4012 (Linking)

Zuccato C., Ciammola A., Rigamonti D., Leavitt B. R., Goffredo D., Conti L., MacDonald M. E., Friedlander R. M., Silani V., Hayden M. R., Timmusk T., Sipione S. and Cattaneo E. (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* 293, 493-498. ISSN: 0036-8075 (Print); ISSN: 0036-8075 (Linking)

Zuccato C., Liber D., Ramos C., Tarditi A., Rigamonti D., Tartari M., Valenza M. and Cattaneo E. (2005) Progressive loss of BDNF in a mouse model of Huntington's disease and rescue by BDNF delivery. *Pharmacol. Res.* 52, 133-139. ISSN: 1043-6618 (Print); ISSN: 1043-6618 (Linking)

Zuccato C., Tartari M., Crotti A., Goffredo D., Valenza M., Conti L., Cataudella T., Leavitt B. R., Hayden M. R., Timmusk T., Rigamonti D. and Cattaneo E. (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. *Nat. Genet.* 35, 76-83. ISSN: 1061-4036 (Print); ISSN: 1061-4036 (Linking)