



A Mitochondria-Associated Oxidative Stress Perspective on Huntington's Disease

Ju Zheng^{1,2,3}, Joris Winderickx², Vanessa Franssens^{2*} and Beidong Liu^{3,4,5*}

¹Department of Biology, Southern University of Science and Technology, Shenzhen, China, ²Department of Biology, Functional Biology, KU Leuven, Heverlee, Belgium, ³Department of Chemistry and Molecular Biology, University of Gothenburg, Gothenburg, Sweden, ⁴State Key Laboratory of Subtropical Silviculture, School of Forestry and Biotechnology, Zhejiang A&F University, Hangzhou, China, ⁵Center for Large-scale Cell-based Screening, Faculty of Science, University of Gothenburg, Gothenburg, Sweden

OPEN ACCESS

Edited by:

Ralf J. Braun,
University of Bayreuth, Germany

Reviewed by:

Johannes Herrmann,
Technische Universität
Kaiserslautern, Germany
Martin Lothar Duennwald,
University of Western Ontario,
Canada

*Correspondence:

Vanessa Franssens
vanessa.franssens@kuleuven.be
Beidong Liu
beidong.liu@cmb.gu.se

Received: 13 April 2018

Accepted: 24 August 2018

Published: 19 September 2018

Citation:

Zheng J, Winderickx J, Franssens V
and Liu B (2018)
A Mitochondria-Associated Oxidative
Stress Perspective on
Huntington's Disease.
Front. Mol. Neurosci. 11:329.
doi: 10.3389/fnmol.2018.00329

Huntington's disease (HD) is genetically caused by mutation of the Huntingtin (*HTT*) gene. At present, the mechanisms underlying the defect of *HTT* and the development of HD remain largely unclear. However, increasing evidence shows the presence of enhanced oxidative stress in HD patients. In this review article, we focus on the role of oxidative stress in the pathogenesis of HD and discuss mediators and potential mechanisms involved in mutant *HTT*-mediated oxidative stress generation and progression. Furthermore, we emphasize the role of the unicellular organism *Saccharomyces cerevisiae* in investigating mutant *HTT*-induced oxidative stress. Overall, this review article provides an overview of the latest findings regarding oxidative stress in HD and potential therapeutic targets for HD.

Keywords: Huntington's disease, Huntingtin, neurodegeneration, yeast, oxidative stress

INTRODUCTION

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disorder inherited in an autosomal dominant pattern. The symptoms in affected individuals include emotional problems, psychiatric disturbances and a decline in the ability to control movements and thinking.

Mutation of the Huntingtin (*HTT*) gene causes HD. An expansion of CAG repeats was found in the DNA sequence of mutant *HTT*, resulting in a polyQ expansion in the encoded mutant *HTT* protein (MacDonald et al., 1993). This polyQ expansion of *HTT* has been proven to trigger misfolding/aggregation of *HTT* and cytotoxicity to cells (DiFiglia et al., 1997; Penney et al., 1997; Krobitch and Lindquist, 2000). The CAG-segment in the *HTT* gene is repeated approximately 25 times in healthy individuals. In contrast, individuals with 40–50 CAG repeats in the *HTT* gene usually develop adult-onset HD and the presence of more than 60 CAG repeats of *HTT* tends to result in the development of juvenile HD (MacDonald et al., 1993; Langbehn et al., 2004). Despite the well-studied genetic cause of HD, the mechanisms by which polyQ expansion induces cytotoxicity and neuronal death are not yet fully understood. Expression of the N-terminal fragment of *HTT* with a polyQ expansion results in polyQ protein aggregation and produces neurological symptoms (Lunkes et al., 2002). Therefore, both full-length and truncated *HTT* containing a polyQ expansion exceeding 36Q are defined as mutant *HTT* (m*HTT*) in this review article. As the proline-rich region is critical for polyQ expansion-induced

toxicity in a yeast model (Dehay and Bertolotti, 2006; Duennwald et al., 2006), we will emphasize the presence/absence of the proline-rich region within a mHTT fragment in the yeast model.

In addition to the effect of polyQ-expanded HTT, CAG repeats within HTT mRNA were also identified as a toxic species. Importantly, the toxic effect of CAG repeat within mRNA are also length dependent. CAG repeats in mRNA may serve as a template for formation of RNA foci (Jain and Vale, 2017). Furthermore, expanded CAG repeats sequester functional proteins and cause gene expression perturbations (Martí, 2016). Moreover, non-polyQ-expanded homomeric proteins were reported to accumulate in the HD human brain and were demonstrated to be toxic to neural cells in a consistent, length-dependent manner (Bañez-Coronel et al., 2015).

Oxidative Stress

Cells possess complicated mechanisms to ensure their proper functioning. These mechanisms are responsible for the elimination of harmful by-products generated during biological processes. However, when these cellular systems fail to maintain the balance between generations of toxic by-products and scavenging, stress occurs, and this may result in cellular cytotoxicity. Oxidative stress is the imbalance between reactive oxygen species (ROS)/reactive nitrogen species (RNS) generation and the biological antioxidant defense system. ROS/RNS are very active species that interact with a number of cellular macromolecules, resulting in a reversible alteration of their molecular structure and function that causes a subsequent cellular response. Accumulation of ROS/RNS in cells leads to damage of proteins, DNA and lipids and further damages tissues and organs, and these changes contribute to the pathogenesis of many diseases (Sies, 1991; Yu, 1994; Weidinger and Kozlov, 2015).

Endogenous ROS mainly originates from mitochondria during the synthesis of ATP and the transfer of electrons, derived from the mitochondrial respiratory reactions, to the electron transport chain. Part of the electrons generated during this process interact with O₂, thereby generating superoxide. It was estimated that approximately 2% of the total amount of O₂ that is consumed by mitochondria is involved in ROS generation (Chance et al., 1979; Sabharwal and Schumacker, 2014). In addition, ROS is also produced by NADPH oxidase (NOX) within the cytoplasm (Valencia et al., 2012).

In this review article, we address the ROS production upon expression of mutant HTT and how this increased ROS level contributes to cytotoxicity and neuronal death.

MITOCHONDRIAL DYSFUNCTION CONTRIBUTES TO HD PATHOGENESIS

Although the mechanisms underlying HD are still unclear, there is evidence showing that mitochondrial dysfunction indeed plays a crucial role in the pathogenesis of HD (Lin and Beal, 2006; Quintanilla and Johnson, 2009; Damiano et al., 2010; Costa and Scorrano, 2012; Guedes-Dias et al., 2016; Carmo et al., 2018). Here, we highlight the major findings regarding the

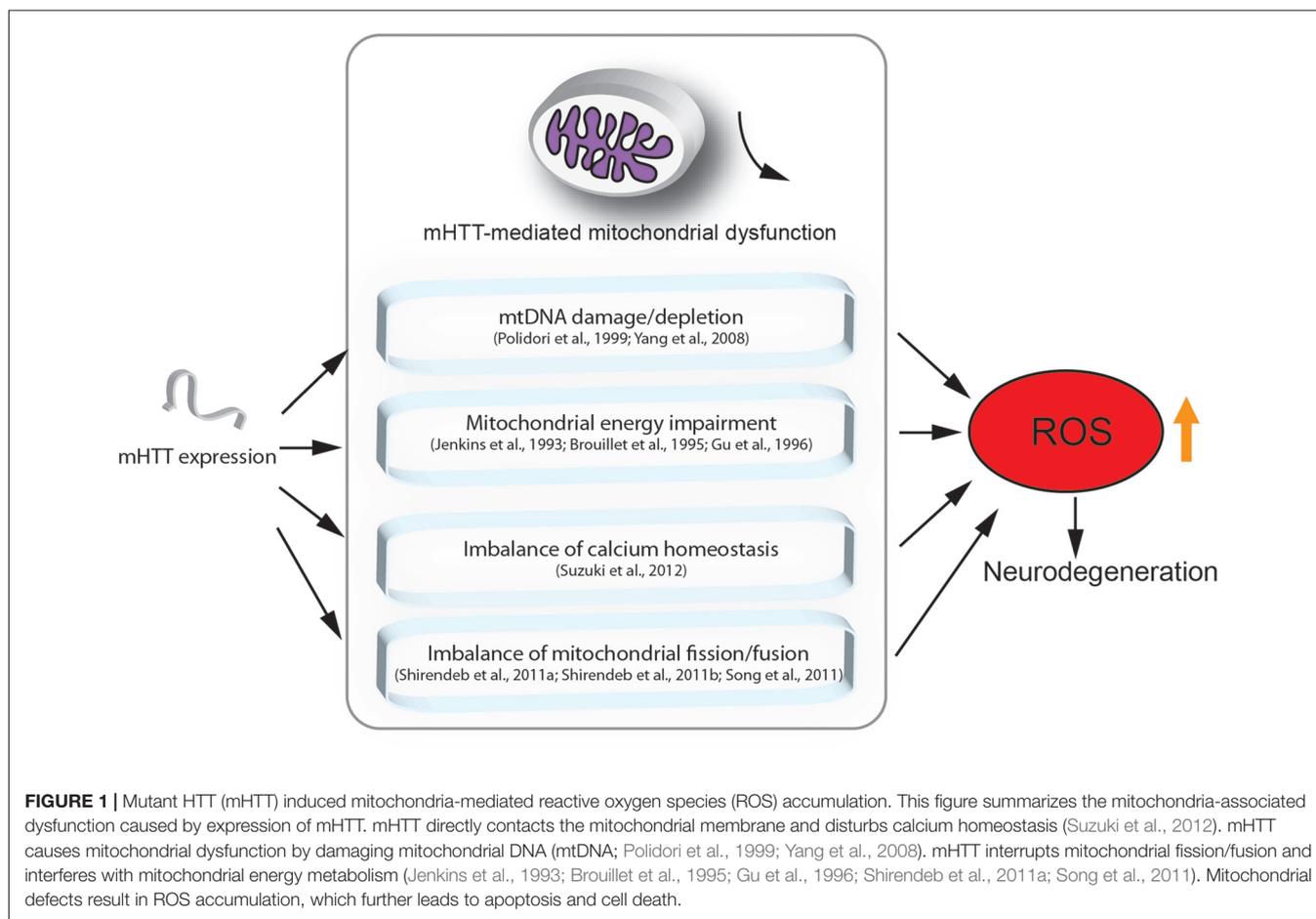
role of mitochondrial loss or dysfunction in HD pathogenesis (Figure 1).

Evidence for Mitochondrial Dysfunction in HD Pathology

Oxidative stress causes damage to mitochondrial DNA (mtDNA) during ageing. In addition, researchers have provided evidence that mtDNA damage is implicated in the pathogenesis of HD (Polidori et al., 1999; Yang et al., 2008). In this respect, an increase in both the basal levels of mitochondria-generated ROS and mtDNA lesions and a simultaneous decrease in spare respiratory capacity were observed in striatal cells expressing mHTT. As mtDNA is a major target of the oxidative stress associated with mHTT, researchers found that the abundance of mtDNA decreases dramatically in mHTT cells compared to wild-type cells (Siddiqui et al., 2012). In addition, mtDNA depletion in leukocytes was reported in patients with polyQ diseases, and the level of mtDNA content was negatively correlated to the number of polyQ repeats in the mHTT (Liu et al., 2008). A mitochondrial biology study showed that a selective mtDNA depletion coincides with an increased vulnerability of the striatum in transgenic HD mice (Hering et al., 2015). In addition, the copy number of mtDNA is significantly lower in peripheral HD leukocytes and transgenic HD R6/2 mice (Petersen et al., 2014). Moreover, expression of mHTT impairs the mitochondrial disulfide relay system (MDRS), which is accompanied by a decreased copy number of mtDNA and the accumulation of mtDNA deletions (Napoli et al., 2013).

Mitochondria are key organelles that participate in the regulation of intracellular Ca²⁺ homeostasis (Giacomello et al., 2007). When the Ca²⁺ level in the cytosol is high, the extra Ca²⁺ is sequestered into inactive calcium-phosphate complexes. On the other hand, when the Ca²⁺ level is low, Ca²⁺ is released back into the cytosol (Nicholls and Budd, 2000; Nicholls, 2005). Researchers found that calcium transport between the mitochondria and cytoplasm occurs through the ryanodine receptor (RyR), an endoplasmic reticulum-resident Ca²⁺ channel. Inhibitors of the RyR attenuated cell death induced by mHTT, while co-expression of the RyR enhanced HTT toxicity (Figure 2). Furthermore, Ca²⁺ leakage was observed in striatal and cortical neurons from R6/2 HD model mice (Suzuki et al., 2012). These observations show that maintaining an appropriate Ca²⁺ concentration within the cytoplasm is vital for cell viability. However, failure of the Ca²⁺ homeostasis buffering system or an overload of Ca²⁺ can lead to the opening of a non-specific pore in the inner mitochondrial membrane, known as the mitochondrial permeability transition pore (mPTP). The opening of the mPTP can disturb the ATP level within mitochondria. Since a proper ATP level is critical for cells to function properly, opening the mPTP potentially kills the cell (Krieger and Duchen, 2002; Halestrap, 2006; Rasola et al., 2010).

Increasing evidence shows that a defect in mitochondrial Ca²⁺ handling contributes to HD pathogenesis (Brustovetsky, 2016). Lower membrane potential and higher sensitivity to calcium loads were found in lymphoblast mitochondria from



HD patients and brain mitochondria from transgenic mice expressing mHTT (Panov et al., 2002). Another study showed that mHTT interacts with the outer mitochondrial membrane and directly induces opening of the mPTP, which is accompanied by a significant release of cytochrome *c* (Choo et al., 2004). This release of cytochrome *c* has been shown to initiate apoptosis (Green and Reed, 1998). Addition of cyclosporin A, an inhibitor of the mPTP, prevented the release of cytochrome *c* (Figure 2). Moreover, a defect in calcium handling not only resulted in the opening of the mPTP but also caused higher levels of mtDNA damage in HD cells. The same effect was observed with elevated superoxide production, suggesting a new link between an imbalance in mitochondrial Ca^{2+} signaling and elevated oxidative DNA damage in HD (Wang et al., 2013). In addition, it was also shown that the first 17 amino acids and the polyQ repeat region of HTT, cause mitochondrial dysfunction in a calcium-homeostasis disrupted manner (Rockabrand et al., 2007). Furthermore, loss of mitochondrial integrity was observed during ageing and disease progression (Hughes and Gottschling, 2012; Szklarczyk et al., 2014), and the integrity of the mitochondrial cristae were found to be disrupted in HD, which was potentially caused by the oligomerization of OPA1, an optic atrophy protein (Hering et al., 2017). Overall, these results indicate that the imbalance in

calcium homeostasis and mitochondrial dysfunction contribute to HD pathogenesis.

Mediators of mHTT-Mediated Mitochondrial Dysfunction

It has been hypothesized that the cytotoxicity mediated by polyQ expansion of mHTT is caused by altering the expression level of cellular factors (McCampbell et al., 2000; Schaffar et al., 2004). The tumor suppressor protein, p53, was found to interact with mHTT, and the mHTT-p53 interaction represses the transcription of genes regulated by p53 (Steffan et al., 2000). Furthermore, activation of p53 increased both mHTT mRNA and protein expression, thereby suggesting that p53 is a modulator of the processes involved in HD development (Feng et al., 2006). On the other hand, suppression of p53 reversed the mHTT-induced mitochondrial depolarization and cytotoxicity in HD cells (Bae et al., 2005), indicating that p53 plays an important role in mediating mitochondrial dysfunction caused by mHTT. Moreover, an interaction between mHTT and the mitochondrial protein import complex TIM23 was reported. This mHTT-TIM23 interaction causes a mitochondrial protein import defect and induces neuronal death (Yano et al., 2014).

Other studies also demonstrated that ROS production in HD is mediated by PGC-1 α , a transcriptional co-regulator of

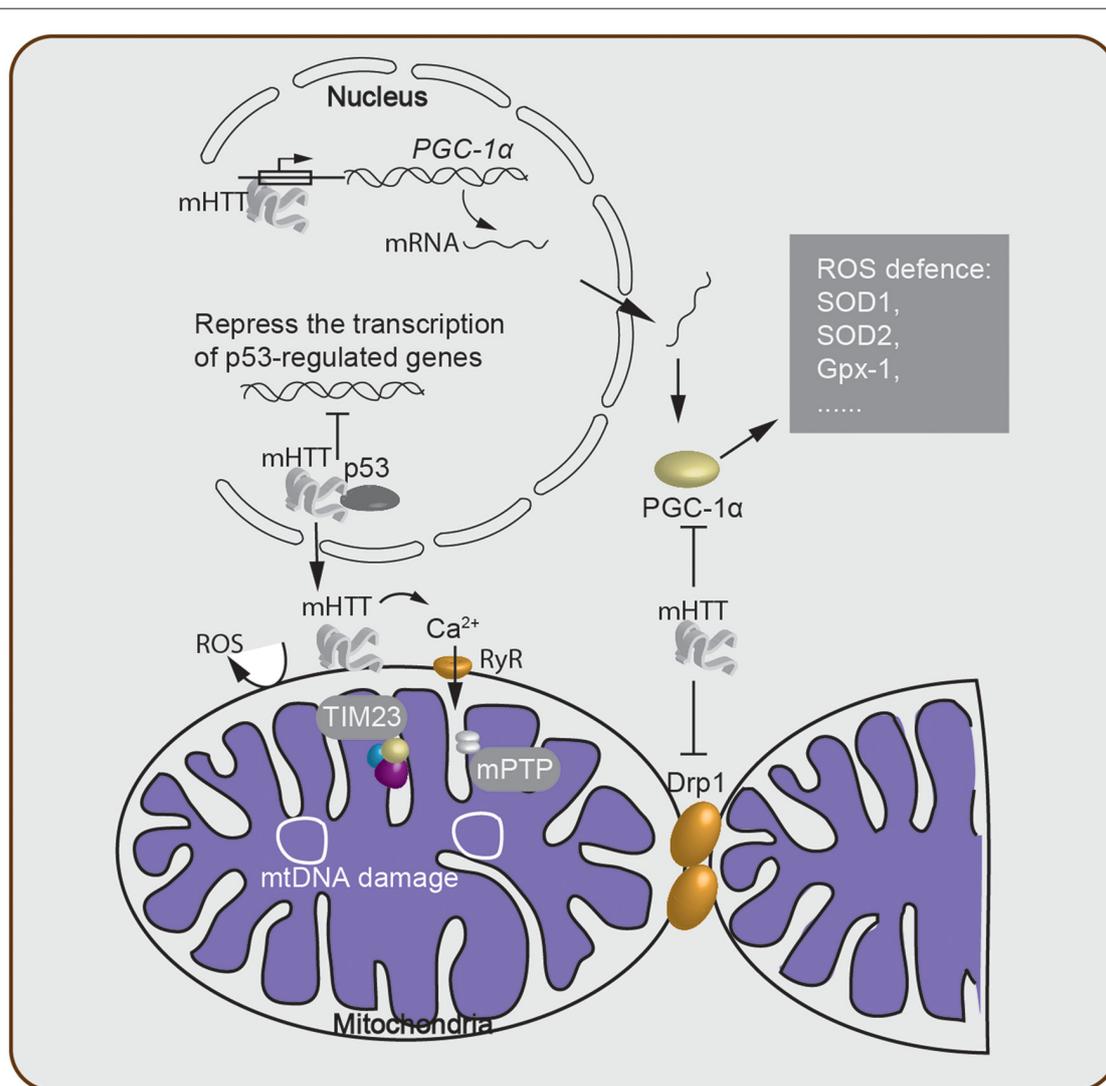


FIGURE 2 | Oxidative stress-associated cellular processes involved in Huntington's disease (HD) pathogenesis. mHTT acts within the nucleus and either suppresses transcription of critical genes and downregulates mitochondrial function or directly alters the expression level of mitochondrial biogenesis-associated proteins such as PGC-1 α . This alteration of the PGC-1 α protein level then further regulates the ROS defense system in the cytosol. The mHTT-mitochondria interaction generates ROS through many processes, including Ca²⁺ leakage through the ryanodine receptor (RyR). Failure of Ca²⁺ homeostasis triggers the opening of the mitochondrial permeability transition pore (mPTP), which disturbs the ATP level and enables release of cytochrome c. Meanwhile, mitochondrial protein import is impaired due to the binding of mHTT to the TIM23 complex. mtDNA damage and depletion within the mitochondria elevate ROS production. Lastly, cytosolic mHTT inhibits mitochondrial fission–fusion by interacting with Drp1.

mitochondrial biogenesis, metabolism, and antioxidant defenses (Johri et al., 2013). mHTT caused an increase in PGC-1 α -mediated oxidative stress via multiple mechanisms (**Figure 2**): (1) mHTT binds to the promoter sequences of PGC-1 α and reduces the transcription level of PGC-1 α (Chaturvedi et al., 2012). (2) mHTT binds directly to PGC-1 α , suppresses the activity of PGC-1 α , which in turn, reduces the expression level of downstream targets of PGC-1 α , including mitochondrial uncoupling proteins and antioxidants such as copper/zinc superoxide dismutase (SOD1), manganese SOD (SOD2), and glutathione peroxidase (Gpx-1; St-Pierre et al., 2006). SODs are major antioxidant enzymes that scavenge O₂⁻ radicals in the

antioxidant system (Gandhi and Abramov, 2012; Kim et al., 2015). Thus, the lower expression level of SOD1, the more SOD2 and Gpx-1 contribute to the mitochondrial dysfunction, which enhances the pathology of HD. (3) mHTT interacts with Drp1 (Shirendeb et al., 2011b), thereby interfering with the mitochondrial dynamics by disrupting the balance of the mitochondrial fission–fusion processes (Shirendeb et al., 2011a; Song et al., 2011). Indeed, overexpression of PGC-1 α rescued HD neurodegeneration partially by attenuating oxidative stress (Tsunemi et al., 2012). A recent study revealed that a variant of PGC-1 α is associated with an earlier age onset of HD (Weydt et al., 2014). Furthermore, mice lacking PGC-1 α show

mitochondrial function impairment and HD features such as uncontrolled movement and striatal degeneration (Lin et al., 2004). Taken together, this evidence indicates that PGC-1 α is a key factor in mediating neuronal death through oxidative stress induced by mHTT.

mHTT-INDUCED OXIDATIVE STRESS AND POTENTIAL THERAPEUTIC TARGETS FOR HD

Multiple pathways that contribute to oxidative stress in HD have been described, including elevated NOX activity, oxidation of mitochondrial enzymes, the disturbance of active vitamin B6 and the activation of the antioxidant defense system (Table 1).

NOX, which produces ROS, has been used as an indicator for the ROS level *in vivo*. Researchers detected higher levels of brain NOX activity in post mortem HD cortex and striatum than in controls, particularly, NOX2, which localizes at plasma membrane lipid rafts, directly responsible for ROS level and survival in HD mice (Valencia et al., 2012). Conversely, NOX activity, ROS level and neuronal cell death were significantly reduced when cells were treated with NOX inhibitors (Valencia et al., 2012).

Oxidative modification of proteins is a main aspect of ROS-mediated cytotoxicity *in vivo*, which encouraged researchers to explore the unique oxidative proteins in HD individuals. Indeed, by comparing HD and control samples, Sorolla et al. (2010) identified 13 proteins that were oxidatively modified, including mitochondrial enzymes. Modification of these enzymes decreased their catalytic activity, consistent with the observation of energy deficiency in HD (Sorolla et al., 2010). More importantly, oxidation of pyridoxal kinase and antiquitin 1 decreased the availability of pyridoxal 5-phosphate, the active form of vitamin B6, leading to neurotransmitter disturbances, which is critical in HD pathology (Sorolla et al., 2010). Another study that focused on the proteomic levels of post mortem human brain samples obtained from striatum and cortex identified a significant increase in the level of antioxidant defense proteins, including peroxiredoxins (Prxs) 1, 2 and 6 and Gpx-1 and 6 in individuals with HD (Sorolla et al., 2008). Energy metabolism defects have been consistently proposed to contribute to the pathogenesis of HD (Jenkins et al., 1993; Brouillet et al., 1995; Gu et al., 1996). These findings suggest that oxidative stress and damage to specific macromolecules are increased in HD patients and that the antioxidant defense system alleviates oxidative stress and damage during the HD progression.

Thus far, the connection between oxidative stress and HD is not yet fully understood. It has been suggested that mHTT induces cytotoxicity through the kynurenine pathway (Giorgini et al., 2005; Stoy et al., 2005). In this respect, it has been shown that inhibition of the kynurenine pathway reduces the production of quinolinic acid (QUIN), ROS level, and cytotoxicity induced by mHTT (Giorgini et al., 2005). QUIN triggers striatal neuronal death via a cascade of events including oxidative stress, which is closely related to

mitochondrial dysfunction. Recently, Jamwal et al. (2015) observed that spermidine, a molecule with free radical scavenging and anti-inflammatory properties, significantly attenuated the pathological alterations caused by QUIN treatment in rats (Jamwal et al., 2015). Similarly, sulforaphane has been proven to be effective in preventing mitochondrial dysfunction induced by QUIN in the rat striatum (Luis-García et al., 2016). Therefore, it is well worth examining the potential neuroprotective role of spermidine and sulforaphane in HD.

Furthermore, expression of mHTT triggered a decrease in the expression of the antioxidant protein Prx1. The same study also showed that treatment by dimercaptopropanol, a thiol-based antioxidant, rescued the cytotoxicity induced by mHTT and the expression level of Prx1 (Pitts et al., 2012). These results suggest that mHTT can exert its toxic effect by disturbing the ROS clearance system and document the potential of thiol-based antioxidants as drugs for HD treatment. However, some of the antioxidants do not seem to attenuate HD symptoms, which is likely because HD-induced ROS damage mainly occurs at the mitochondria. Indeed, inducing a synthetic mitochondria-specific antioxidant XJB-5-131, which targets mitochondria, remarkably suppressed oxidative mtDNA damage, restored the copy number of mtDNA, and alleviated the pathophysiology in HD animals (Xun et al., 2012; Polyzos et al., 2016). In addition, oxidation of cysteines within mHTT promoted the formation of soluble HTT oligomers, which are mediators of HD pathogenesis, and thereby interfered with the clearance of soluble mHTT, leading to enhanced mHTT cytotoxicity (Fox et al., 2011).

YEAST MODELS PROVIDE INSIGHTS INTO OXIDATIVE STRESS IN HD

Yeast lacks an HTT ortholog, and thus, its value for studying cellular communication is limited due to the absence of axonal and synaptic structures within a yeast bud (Khurana and Lindquist, 2010), as well as the lack of neural transmitters and the corresponding receptors (Khurana and Lindquist, 2010). As such, the suitability of the yeast model should be carefully taken into consideration before application to the study of HD. However, expression of mHTT fragment in yeast reproduces two major features of HD (i.e., protein aggregation and mHTT fragment-induced cytotoxicity). Moreover, many findings in yeast models were confirmed in higher model systems, such as mammalian cell lines, *C. elegans*, mice and even human patients. The insights gained from the studies in yeast have contributed greatly to our understanding of the pathogenesis of HD (Winderickx et al., 2008; Khurana and Lindquist, 2010; Mason and Giorgini, 2011; Fruhmman et al., 2017). As most mediators and pathways of energy metabolism are highly conserved in eukaryotes, it is not surprising to see that mHTT fragment induces oxidative stress in yeast. Here, we discuss the oxidative stress response of mHTT fragment and related findings in yeast models.

A toxic version of the mHTT fragment expression system lacking the proline-rich region in yeast established by the lab of Sherman and Lindquist (Krobitsch and Lindquist, 2000;

TABLE 1 | Major published oxidative stress-associated processes and mediators of Huntington's disease (HD) pathogenesis.

Processes and mediators	Model system	Type of mHTT	Description and consequence	References
mtDNA damage	Mouse; Striatal immortalized neuronal cell	Human HTT exon1: 115–150Q; 111Q	mHTT increases mitochondria-generated ROS and decreases mtDNA abundance.	Yang et al. (2008) and Siddiqui et al. (2012)
mtDNA depletion	Mouse and human HD patient	Human HTT exon1: 144Q; ~160Q	mHTT results in a lower copy number of mtDNA and increases the vulnerability of the striatum.	Petersen et al. (2014) and Hering et al. (2015)
Ca ²⁺ imbalance	Rat cortical neuron	Truncated N-terminal HTT: 150Q	mHTT induces Ca ²⁺ leakage through the Ca ²⁺ channel RyR, further resulting in opening of the mPTP, which contributes to mitochondrial oxidative stress.	Suzuki et al. (2012)
p53	HEK293 cell; Mouse and human HD patient	Human HTT exon1 ^{+/-} proline-rich region: 103Q; N-terminal HTT: 86Q	p53 promotes expression of mHTT and mediates mHTT-induced mitochondrial dysfunction; the mHTT-p53 interaction suppresses transcription of p53-regulated genes.	Steffan et al. (2000) and Bae et al. (2005)
PGC-1 α	Mouse and striatal cell culture	Human HTT exon1 and Mouse HTT: 111Q	mHTT reduces PGC-1 α transcription and activity and suppresses downstream targets of PGC-1 α , such as ROS defense factors.	Chaturvedi et al. (2012)
Drp1	Human HD patient; mouse; rat cortical neuron	Human mutant HTT; full-length human mHTT: 97Q; Human HTT exon1: 46 and 97Q	mHTT interacts with Drp1, disrupting the balance of the mitochondrial fission–fusion processes.	Shirendeb et al. (2011a,b) and Song et al. (2011)
NOX	Human HD patient and mouse	Mouse HTT: 140Q	Higher levels of brain NOX activity are observed in HD, whereas NOX inhibitors reduce the ROS level and neuronal death.	Valencia et al. (2012)
Mitochondrial enzymes	Human HD patient and mouse	Human HTT exon1: 94Q	Mitochondrial enzymes are oxidatively modified, with decreased catalytic activity and energy deficiency in individuals with HD.	Sorolla et al. (2010)
Vitamin B6	Human HD patient and mouse	Human HTT exon1: 94Q	Oxidation of pyridoxal kinase and antiquitin 1 decreased the availability of active vitamin B6, leading to the disturbances of neurotransmitters.	Sorolla et al. (2010)
Kynurenine pathway	Yeast	Human HTT exon1 lacking proline-rich region: 103Q	mHTT induces cytotoxicity through the kynurenine pathway and its intermediate product QUIN, which triggers striatal neuronal death via a cascade of events, such as oxidative stress.	Giorgini et al. (2005), Stoy et al. (2005) and Jamwal et al. (2015)
Prx1	PC12 cell	Human HTT exon1: 103Q	mHTT affects expression of the antioxidant protein Prx1, disturbing the ROS clearance system.	Pitts et al. (2012)
GPxs	Yeast	Human HTT exon1 lacking proline-rich region: 103Q	These antioxidant enzymes protect against ROS production and suppress mHTT toxicity.	Mason et al. (2013)
RQC	Yeast	Human HTT exon1 presence/absence of proline-rich region: 103Q	RQC system regulates mHTT compartmentalization and nucleocytoplasmic translocation that is associated with polyQ cytotoxicity.	Yang et al. (2016) and Zheng et al. (2017)

Meriin et al., 2002; Willingham et al., 2003) revealed numerous molecular insights into mHTT fragment-induced toxicity, including findings regard to oxidative stress. In this yeast model, ROS accumulation was enhanced, and abnormal mitochondrial morphology and distribution in cells expressing mHTT fragment were observed. These findings revealed that the polyQ-mitochondria interaction interferes with mitochondrial function and increases ROS production (Solans et al., 2006). Screening the yeast deletion collection for suppressors of mHTT fragment-induced toxicity revealed that kynurenine 3-monooxygenase (Bna4) deficiency rescues cell viability (Giorgini et al., 2005). Metabolites of the kynurenine pathway have been shown to induce oxidative stress and neurological disorders (Pawlak et al., 2009; Parasram, 2018), which is associated with

HD pathophysiology (Stoy et al., 2005). Another suppressor screening with gene overexpression, instead of loss-of-function, identified GPxs as potent suppressors of mHTT fragment toxicity (Mason et al., 2013). GPx is an antioxidant enzyme that protects against ROS, thus, enhancing the GPxs capacity can alleviate mHTT fragment toxicity (Table 1). Treatment with ebselen, which mimics the antioxidant effects of GPx, showed a strong protective effect on HD model organisms (Mason et al., 2013). These findings shed light on the clinical potential of ebselen and other antioxidants for HD therapy. Another study in yeast also demonstrated a role for Sir2 in protecting cells from ROS. Sir2 levels increased dramatically when yeast cells suffer from oxidative stress from mHTT fragment expression or the environment. However, enhancing

Sir2 expression by a Sir2 activator decreased mHTT fragment aggregation and the mHTT fragment-induced stress. On the other hand, SIR2 knock-out cells showed significant oxidative stress even in the early exponential phase (Sorolla et al., 2011). Overexpression of Hap4, a protein that regulates many genes encoding mitochondrial proteins in yeast, prevented respiratory defects and ameliorated polyQ expansion-induced cytotoxicity (Ocampo et al., 2010). Together, these studies demonstrate that mHTT fragment induces oxidative stress in yeast and that preventing such oxidative stress can be a good strategy to handle mHTT fragment cytotoxicity.

Recently, a technique that combines automated yeast genetics and high-content microscopy has been applied to study mHTT fragment localization, protein-protein interaction and aggregate morphology in yeast. Taking advantage of this powerful screening approach, Yang et al identified that both the ribosome quality control (RQC) system and Hsf1 regulate the compartmentalization of mHTT fragment containing the proline-rich region (Yang et al., 2016). A follow-up study by Zheng et al. (2017) demonstrated that the RQC system indeed regulates the nucleocytoplasmic translocation of mHTT exon-1 lacking the proline-rich region and that a defective RQC system leads to enhanced cytotoxicity of mHTT fragment. Interestingly, it has been shown that oxidative stress can cause damage to rRNAs inside the ribosome, and oxidized rRNA inhibits protein synthesis in the ribosome (Willi et al., 2018). In this respect, mHTT-induced oxidative stress might be a driving force for the impairment of RQC system.

CONCLUDING REMARKS

More than two decades have passed since the first identification of the *HTT* gene, and mutation of this gene is responsible for HD pathogenesis. The mechanisms responsible for the development of the single gene mutation that induce this neurodegenerative disease are not yet fully understood, and to date, no effective therapeutic target has been developed. The major findings point towards a close relationship between HD pathogenesis and oxidative stress.

Although multiple factors are involved in regulating mHTT-mediated oxidative stress, there are indications that mitochondria play a key role. Both mtDNA damage and mtDNA depletion have been detected upon expression of mHTT (Yang et al., 2008; Napoli et al., 2013). Given the core role of mitochondria in respiration and energy production, mtDNA damage or depletion leads to increased levels of oxidative stress. Moreover, a defect in mitochondrial calcium handling was observed in HD patients (Panov et al., 2002). Failure of keeping a mitochondrial calcium balance triggers the opening of the mPTP and the subsequent events lead to the final stage of cell death. The connection between oxidative stress and

HD is also supported by the interaction of mHTT with p53 or PGC-1 α , which modulates the activity of mitochondria. NOX activity, oxidation of mitochondrial enzymes, the disturbance of active vitamin B6 and the activation of antioxidant defense system are also implicated in sensing oxidative stress from mHTT.

Increased oxidative stress is detected during HD pathogenesis, and the published literatures reviewed here favors the idea that expression of mHTT is the primary cause of HD and that mHTT induces cellular dysfunction via multiple pathways, including oxidative stress. In this aspect, oxidative stress is likely a downstream consequence of HD pathogenesis. Moreover, other neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease are controlled by multiple genes that are associated with oxidative stress (Gandhi and Abramov, 2012; Kim et al., 2015).

Despite the intensive studies on HD pathogenesis and evidence showing that oxidative stress occurs during this process, the major pathways and the sequence of oxidative stress-associated events in HD pathogenesis are still not known. Future studies that strengthen the understanding of oxidative stress in HD pathogenesis will provide insights into drug development and identification of therapeutic targets, for instance, clarifying the connections among the known pathways involved in mHTT-induced oxidative stress, identifying oxidative stress associated key factors in HD pathogenesis, and determining the major aspects as well as the order of pathologic events that contribute to HD development. Overall, this review article provides an overview of the current studies linking oxidative stress and HD development.

AUTHOR CONTRIBUTIONS

BL, VF and JW conceived and outlined the article and JZ wrote the manuscript with the help from VF, JW and BL.

FUNDING

This work was supported by the Fund for Scientific Research Flanders (FWO-Vlaanderen to JW) and an FWO postdoctoral fellowship (to VF). This work was also supported by grants from the Swedish Cancer Society (Cancerfonden, CAN 2012/601, CAN 2015/406 and CAN 2017/643, to BL), the Swedish Natural Research Council (VR 2011-5923 and VR 2015-04984, to BL), and the Carl Trygger Foundation (Carl Tryggers Stiftelse för Vetenskaplig Forskning, CTS 14: 295, to BL). Additional support came from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007–2013) under REA grant agreement n° 608743.

REFERENCES

- Bae, B.-I., Xu, H., Igarashi, S., Fujimuro, M., Agrawal, N., Taya, Y., et al. (2005). p53 mediates cellular dysfunction and behavioral abnormalities in Huntington's disease. *Neuron* 47, 29–41. doi: 10.1016/j.neuron.2005.06.005
- Bañez-Coronel, M., Ayhan, F., Tarabochia, A. D., Zu, T., Perez, B. A., Tusi, S. K., et al. (2015). RAN translation in Huntington disease. *Neuron* 88, 667–677. doi: 10.1016/j.neuron.2015.10.038
- Brouillet, E., Hantraye, P., Ferrante, R. J., Dolan, R., Leroy-willig, A., Kowall, N. W., et al. (1995). Chronic mitochondrial energy impairment

- produces selective striatal degeneration and abnormal choreiform movements in primates. *Proc. Natl. Acad. Sci. U S A* 92, 7105–7109. doi: 10.1073/pnas.92.15.7105
- Brustovetsky, N. (2016). Mutant huntingtin and elusive defects in oxidative metabolism and mitochondrial calcium handling. *Mol. Neurobiol.* 53, 2944–2953. doi: 10.1007/s12035-015-9188-0
- Carmo, C., Naia, L., Lopes, C., and Rego, A. C. (2018). Mitochondrial dysfunction in Huntington's disease. *Adv. Exp. Med. Biol.* 1049, 59–83. doi: 10.1007/978-3-319-71779-1_3
- Chance, B., Sies, H., and Boveris, A. (1979). Hydroperoxide metabolism in mammalian organs. *Physiol. Rev.* 59, 527–605. doi: 10.1152/physrev.1979.59.3.527
- Chaturvedi, R. K., Hennessey, T., Johri, A., Tiwari, S. K., Mishra, D., Agarwal, S., et al. (2012). Transducer of regulated CREB-binding proteins (TORCs) transcription and function is impaired in Huntington's disease. *Hum. Mol. Genet.* 21, 3474–3488. doi: 10.1093/hmg/dds178
- 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. doi: 10.1093/hmg/ddh162
- Costa, V., and Scorrano, L. (2012). Shaping the role of mitochondria in the pathogenesis of Huntington's disease. *EMBO J.* 31, 1853–1864. doi: 10.1038/emboj.2012.65
- Damiano, M., Galvan, L., Déglon, N., and Brouillet, E. (2010). Mitochondria in Huntington's disease. *Biochim. Biophys. Acta* 1802, 52–61. doi: 10.1016/j.bbdis.2009.07.012
- Dehay, B., and Bertolotti, A. (2006). Critical role of the proline-rich region in Huntingtin for aggregation and cytotoxicity in yeast. *J. Biol. Chem.* 281, 35608–35615. doi: 10.1074/jbc.m605558200
- DiFiglia, M., Sapp, E., Chase, K. O., Davies, S. W., Bates, G. P., Vonsattel, J. P., et al. (1997). Aggregation of huntingtin in neuronal intranuclear inclusions and dystrophic neurites in brain. *Science* 277, 1990–1993. doi: 10.1126/science.277.5334.1990
- Duenwald, M. L., Jagadish, S., Giorgini, F., Muchowski, P. J., and Lindquist, S. (2006). A network of protein interactions determines polyglutamine toxicity. *Proc. Natl. Acad. Sci. U S A* 103, 11051–11056. doi: 10.1073/pnas.0604548103
- Feng, Z., Jin, S., Zupnick, A., Hoh, J., De Stanchina, E., Lowe, S., et al. (2006). p53 tumor suppressor protein regulates the levels of huntingtin gene expression. *Oncogene* 25, 1–7. doi: 10.1038/sj.onc.1209021
- Fox, J. H., Connor, T., Stiles, M., Kama, J., Lu, Z., Dorsey, K., et al. (2011). Cysteine oxidation within N-terminal mutant huntingtin promotes oligomerization and delays clearance of soluble protein. *J. Biol. Chem.* 286, 18320–18330. doi: 10.1074/jbc.m110.199448
- Fruhmman, G., Seynnaeve, D., Zheng, J., Ven, K., Molenberghs, S., Wilms, T., et al. (2017). Yeast buddies helping to unravel the complexity of neurodegenerative disorders. *Mech. Ageing. Dev.* 161, 288–305. doi: 10.1016/j.mad.2016.05.002
- Gandhi, S., and Abramov, A. Y. (2012). Mechanism of oxidative stress in neurodegeneration. *Oxid. Med. Cell. Longev.* 2012, 1–11. doi: 10.1155/2012/428010
- Giacomello, M., Drago, I., Pizzo, P., and Pozzan, T. (2007). Mitochondrial Ca²⁺ as a key regulator of cell life and death. *Cell Death Differ.* 14, 1267–1274. doi: 10.1038/sj.cdd.4402147
- Giorgini, F., Guidetti, P., Nguyen, Q., Bennett, S. C., and Muchowski, P. J. (2005). A genomic screen in yeast implicates kynurenine 3-monooxygenase as a therapeutic target for Huntington disease. *Nat. Genet.* 37, 526–531. doi: 10.1038/ng1542
- Green, D. R., and Reed, J. C. (1998). Mitochondria and apoptosis. *Science* 281, 1309–1312. doi: 10.1126/science.281.5381.1309
- Gu, M., Gashc, M. T., Mann, V. M., Javoy-Agid, F., Cooper, J. M., and Schapira, A. H. V. (1996). Mitochondrial defect in Huntington's disease caudate nucleus. *Annals of Neurol.* 39, 385–389. doi: 10.1002/ana.4103.90317
- Guedes-Dias, P., Pinho, B. R., Soares, T. R., De, P. J., Duchon, M. R., and Oliveira, J. M. (2016). Mitochondrial dynamics and quality control in Huntington's disease. *Neurobiol. Dis.* 90, 51–57. doi: 10.1016/j.nbd.2015.09.008
- Halestrap, A. P. (2006). Calcium, mitochondria and reperfusion injury: a pore way to die. *Biochem. Soc. Trans.* 34, 232–237. doi: 10.1042/bst20060232
- Hering, T., Birth, N., Taanman, J.-W., and Orth, M. (2015). Selective striatal mtDNA depletion in end-stage Huntington's disease R6/2 mice. *Exp. Neurol.* 266, 22–29. doi: 10.1016/j.expneurol.2015.02.004
- Hering, T., Kojer, K., Birth, N., Hallitsch, J., Taanman, J.-W., and Orth, M. (2017). Mitochondrial cristae remodeling is associated with disrupted OPA1 oligomerisation in the Huntington's disease R6/2 fragment model. *Exp. Neurol.* 288, 167–175. doi: 10.1016/j.expneurol.2016.10.017
- Hughes, A. L., and Gottschling, D. E. (2012). An early-age increase in vacuolar pH limits mitochondrial function and lifespan in yeast. *Nature* 492, 261–265. doi: 10.1038/nature11654
- Jain, A., and Vale, R. D. (2017). RNA phase transitions in repeat expansion disorders. *Nature* 546, 243–247. doi: 10.1038/nature22386
- Jamwal, S., Singh, S., Kaur, N., and Kumar, P. (2015). Protective effect of spermidine against excitotoxic neuronal death induced by quinolinic acid in rats: possible neurotransmitters and neuroinflammatory mechanism. *Neurotox. Res.* 28, 171–184. doi: 10.1007/s12640-015-9535-y
- 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. doi: 10.1212/wnl.43.12.2689
- Johri, A., Chandra, A., and Beal, M. F. (2013). PGC-1 α , mitochondrial dysfunction and Huntington's disease. *Free Radic. Biol. Med.* 62, 37–46. doi: 10.1016/j.freeradbiomed.2013.04.016
- Khurana, V., and Lindquist, S. (2010). Modelling neurodegeneration in *Saccharomyces cerevisiae*: why cook with baker's yeast? *Nat. Rev. Neurosci.* 11, 436–449. doi: 10.1038/nrn2809
- Kim, G. H., Kim, J. E., Rhie, S. J., and Yoon, S. (2015). The role of oxidative stress in neurodegenerative diseases. *Exp. Neurobiol.* 24, 325–340. doi: 10.5607/en.2015.24.4.325
- Krieger, C., and Duchon, M. R. (2002). Mitochondria, Ca²⁺ and neurodegenerative disease. *Eur. J. Pharmacol.* 447, 177–188. doi: 10.1016/S0014-2999(02)01842-3
- Krobitsch, S., and Lindquist, S. (2000). Aggregation of huntingtin in yeast varies with the length of the polyglutamine expansion and the expression of chaperone proteins. *Proc. Natl. Acad. Sci. U S A* 97, 1589–1594. doi: 10.1073/pnas.97.4.1589
- Langbehn, D. R., Brinkman, R. R., Falush, D., Paulsen, J. S., and Hayden, M. R. (2004). A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clin. Genet.* 65, 267–277. doi: 10.1111/j.1399-0004.2004.00241.x
- Lin, J., Wu, P.-H., Tarr, P. T., Lindenberg, K. S., St-Pierre, J., Zhang, C.-Y., et al. (2004). Defects in adaptive energy metabolism with CNS-linked hyperactivity in PGC-1 α null mice. *Cell* 119, 121–135. doi: 10.1016/j.cell.2004.09.013
- Lin, M. T., and Beal, M. F. (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature* 443, 787–795. doi: 10.1038/nature05292
- Liu, C.-S., Cheng, W.-L., Kuo, S.-J., Li, J.-Y., Soong, B.-W., and Wei, Y.-H. (2008). Depletion of mitochondrial DNA in leukocytes of patients with poly-Q diseases. *J. Neurol. Sci.* 264, 18–21. doi: 10.1016/j.jns.2007.07.016
- Luis-García, E. R., Limón-Pacheco, J. H., Serrano-García, N., Hernández-Pérez, A. D., Pedraza-Chaverri, J., and Orozco-Ibarra, M. (2016). Sulforaphane prevents quinolinic acid-induced mitochondrial dysfunction in rat striatum. *J. Biochem. Mol. Toxicol.* 31, 1–7. doi: 10.1002/jbt.21837
- Lunkes, A., Lindenberg, K. S., Ben-Haiem, L., Weber, C., Devys, D., Landwehrmeyer, G. B., et al. (2002). Proteases acting on mutant huntingtin generate cleaved products that differentially build up cytoplasmic and nuclear inclusions. *Mol. Cell* 10, 259–269. doi: 10.1016/s1097-2765(02)00602-0
- MacDonald, M. E., Ambrose, C. M., Duyao, M. P., Myers, R. H., Lin, C., Srinidhi, L., et al. (1993). A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell* 72, 971–983. doi: 10.1016/0092-8674(93)90585-e
- Marti, E. (2016). RNA toxicity induced by expanded CAG repeats in Huntington's disease. *Brain Pathol.* 26, 779–786. doi: 10.1111/bpa.12427
- Mason, R. P., and Giorgini, F. (2011). Modeling Huntington disease in yeast: perspectives and future directions. *Prion* 5, 269–276. doi: 10.4161/pri.18005
- Mason, R. P., Casu, M., Butler, N., Breda, C., Campesan, S., Clapp, J., et al. (2013). Glutathione peroxidase activity is neuroprotective in models of Huntington's disease. *Nat. Genet.* 45, 1249–1254. doi: 10.1038/ng.2732

- McC Campbell, A., Taylor, J. P., Taye, A. A., Robitschek, J., Li, M., Walcott, J., et al. (2000). CREB-binding protein sequestration by expanded polyglutamine. *Hum. Mol. Genet.* 9, 2197–2202. doi: 10.1093/hmg/9.14.2197
- Meriin, A. B., Zhang, X., He, X., Newnam, G. P., Chernoff, Y. O., and Sherman, M. Y. (2002). Huntingtin toxicity in yeast model depends on polyglutamine aggregation mediated by a prion-like protein Rnq1. *J. Cell. Biol.* 157, 997–1004. doi: 10.1083/jcb.200112104
- Napoli, E., Wong, S., Hung, C., Ross-Inta, C., Bomdica, P., and Giulivi, C. (2013). Defective mitochondrial disulfide relay system, altered mitochondrial morphology and function in Huntington's disease. *Hum. Mol. Genet.* 22, 989–1004. doi: 10.1093/hmg/ddt503
- Nicholls, D. G. (2005). Mitochondria and calcium signaling. *Cell Calcium* 38, 311–317. doi: 10.1016/j.ceca.2005.06.011
- Nicholls, D. G., and Budd, S. L. (2000). Mitochondria and neuronal survival. *Physiol. Rev.* 80, 315–360. doi: 10.1152/physrev.2000.80.1.315
- Ocampo, A., Zambrano, A., and Barrientos, A. (2010). Suppression of polyglutamine-induced cytotoxicity in *Saccharomyces cerevisiae* by enhancement of mitochondrial biogenesis. *FASEB J.* 24, 1431–1441. doi: 10.1096/fj.09-148601
- Panov, A. V., Gutekunst, C.-A., Leavitt, B. R., Hayden, M. R., Burke, J. R., Strittmatter, W. J., et al. (2002). Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. *Nat. Neurosci.* 5, 731–736. doi: 10.1038/nn884
- Parasram, K. (2018). Phytochemical treatments target kynurenine pathway induced oxidative stress. *Redox Rep.* 23, 25–28. doi: 10.1080/13510002.2017.1343223
- Pawlak, K., Domaniewski, T., Mysliwiec, M., and Pawlak, D. (2009). The kynurenines are associated with oxidative stress, inflammation and the prevalence of cardiovascular disease in patients with end-stage renal diseases. *Atherosclerosis* 204, 309–314. doi: 10.1016/j.atherosclerosis.2008.08.014
- Penney, J. B. Jr, Vonsattel, J. P., Macdonald, M. E., Gusella, J. F., and Myers, R. H. (1997). CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann. Neurol.* 41, 689–692. doi: 10.1002/ana.410410521
- Petersen, M. H., Budtz-Jørgensen, E., Sørensen, S. A., Nielsen, J. E., Hjermin, L. E., Vinther-Jensen, T., et al. (2014). Reduction in mitochondrial DNA copy number in peripheral leukocytes after onset of Huntington's disease. *Mitochondrion* 17, 14–21. doi: 10.1016/j.mito.2014.05.001
- Pitts, A., Dailey, K., Newington, J. T., Chien, A., Arseneault, R., Cann, T., et al. (2012). Dithiol-based compounds maintain expression of antioxidant protein peroxiredoxin 1 that counteracts toxicity of mutant huntingtin. *J. Biol. Chem.* 287, 22717–22729. doi: 10.1074/jbc.m111.334565
- 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. doi: 10.1016/s0304-3940(99)00578-9
- Polyzos, A., Holt, A., Brown, C., Cosme, C., Wipf, P., Gomezmarin, A., et al. (2016). Mitochondrial targeting of XJB-5-131 attenuates or improves pathophysiology in HdhQ150 animals with well-developed disease phenotypes. *Hum. Mol. Genet.* 25, 1792–1802. doi: 10.1093/hmg/ddw051
- 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. doi: 10.1016/j.brainresbull.2009.07.010
- Rasola, A., Sciacovelli, M., Pantic, B., and Bernardi, P. (2010). Signal transduction to the permeability transition pore. *FEBS Lett.* 584, 1989–1996. doi: 10.1016/j.febslet.2010.02.022
- Rockabrand, E., Slepko, N., Pantalone, A., Nukala, V. N., Kazantsev, A., Marsh, J. L., et al. (2007). The first 17 amino acids of Huntingtin modulate its sub-cellular localization, aggregation and effects on calcium homeostasis. *Hum. Mol. Genet.* 16, 61–77. doi: 10.1093/hmg/ddl440
- Sabharwal, S. S., and Schumacker, P. T. (2014). Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel? *Nat. Rev. Cancer* 14, 709–721. doi: 10.1038/nrc3803
- Schaffar, G., Breuer, P., Boteva, R., Behrends, C., Tzvetkov, N., Strippel, N., et al. (2004). Cellular toxicity of polyglutamine expansion proteins: mechanism of transcription factor deactivation. *Mol. Cell* 15, 95–105. doi: 10.1016/j.molcel.2004.06.029
- Shirendeb, U., Reddy, A. P., Manczak, M., Calkins, M. J., Mao, P., Tagle, D. A., et al. (2011a). Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington's disease: implications for selective neuronal damage. *Hum. Mol. Genet.* 20, 1438–1455. doi: 10.1093/hmg/ddr024
- Shirendeb, U. P., Calkins, M. J., Manczak, M., Anekonda, V., Dufour, B., McBride, J. L., et al. (2011b). Mutant huntingtin's interaction with mitochondrial protein Drp1 impairs mitochondrial biogenesis and causes defective axonal transport and synaptic degeneration in Huntington's disease. *Hum. Mol. Genet.* 21, 406–420. doi: 10.1093/hmg/ddr475
- Siddiqui, A., Rivera-Sánchez, S., Castro, M. d. R., Acevedo-Torres, K., Rane, A., Torres-Ramos, C. A., et al. (2012). Mitochondrial DNA damage is associated with reduced mitochondrial bioenergetics in Huntington's disease. *Free Radic. Biol. Med.* 53, 1478–1488. doi: 10.1016/j.freeradbiomed.2012.06.008
- Sies, H. (1991). Oxidative stress: from basic research to clinical application. *Am. J. Med.* 91, S31–S38. doi: 10.1016/0002-9343(91)90281-2
- Solans, A., Zambrano, A., Rodríguez, 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. doi: 10.1093/hmg/ddl248
- Song, W., Chen, J., Petrilli, A., Liot, G., Klinglmayr, E., Zhou, Y., et al. (2011). Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. *Nat. Med.* 17, 377–382. doi: 10.1038/nm.2313
- Sorolla, M. A., Nierga, C., Rodríguez-Colman, M. J., Reverter-Branchat, G., Arenas, A., Tamarit, J., et al. (2011). Sir2 is induced by oxidative stress in a yeast model of Huntington disease and its activation reduces protein aggregation. *Arch. Biochem. Biophys.* 510, 27–34. doi: 10.1016/j.abb.2011.04.002
- Sorolla, M. A., Reverter-Branchat, G., Tamarit, J., Ferrer, I., Ros, J., and Cabiscol, E. (2008). Proteomic and oxidative stress analysis in human brain samples of Huntington disease. *Free Radic. Biol. Med.* 45, 667–678. doi: 10.1016/j.freeradbiomed.2008.05.014
- Sorolla, M. A., Rodríguez-Colman, M. J., Tamarit, J., Ortega, Z., Lucas, J. J., Ferrer, I., et al. (2010). Protein oxidation in Huntington disease affects energy production and vitamin B6 metabolism. *Free Radic. Biol. Med.* 49, 612–621. doi: 10.1016/j.freeradbiomed.2010.05.016
- Steffan, J. S., Kazantsev, A., Spasic-Boskovic, O., Greenwald, M., Zhu, Y.-Z., Gohler, H., et al. (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. doi: 10.1073/pnas.100110097
- Stoy, N., Mackay, G. M., Forrest, C. M., Christofides, J., Egerton, M., Stone, T. W., et al. (2005). Tryptophan metabolism and oxidative stress in patients with Huntington's disease. *J. Neurochem.* 93, 611–623. doi: 10.1111/j.1471-4159.2005.03070.x
- St-Pierre, J., Drori, S., Uldry, M., Silvaggi, J. M., Rhee, J., Jäger, S., et al. (2006). Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell* 127, 397–408. doi: 10.1016/j.cell.2006.09.024
- Suzuki, M., Nagai, Y., Wada, K., and Koike, T. (2012). Calcium leak through ryanodine receptor is involved in neuronal death induced by mutant huntingtin. *Biochem. Biophys. Res. Commun.* 429, 18–23. doi: 10.1016/j.bbrc.2012.10.107
- Szklarczyk, R., Nootboom, M., and Osiewacz, H. D. (2014). Control of mitochondrial integrity in ageing and disease. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 369:20130439. doi: 10.1098/rstb.2013.0439
- Tsunemi, T., Ashe, T. D., Morrison, B. E., Soriano, K. R., Au, J., Roque, R. A. V., et al. (2012). PGC-1 α rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. *Sci. Transl. Med.* 4:142ra97. doi: 10.1126/scitranslmed.3003799
- Valencia, A., Sapp, E., Kimm, J. S., McClory, H., Reeves, P. B., Alexander, J., et al. (2012). Elevated NADPH oxidase activity contributes to oxidative stress and cell death in Huntington's disease. *Hum. Mol. Genet.* 22, 1112–1131. doi: 10.1093/hmg/ddt516
- Wang, J.-Q., Chen, Q., Wang, X., Wang, Q.-C., Wang, Y., Cheng, H.-P., et al. (2013). Dysregulation of mitochondrial calcium signaling and superoxide flashes cause mitochondrial genomic DNA damage in Huntington disease. *J. Biol. Chem.* 288, 3070–3084. doi: 10.1074/jbc.m112.407726
- Weidinger, A., and Kozlov, A. V. (2015). Biological activities of reactive oxygen and nitrogen species: oxidative stress versus signal transduction. *Biomolecules* 5, 472–484. doi: 10.3390/biom5020472

- Weydt, P., Soyak, S. M., Landwehrmeyer, G. B., and Patsch, W. (2014). A single nucleotide polymorphism in the coding region of PGC-1 α is a male-specific modifier of Huntington disease age-at-onset in a large European cohort. *BMC Neurol.* 14:1. doi: 10.1186/1471-2377-14-1
- Willi, J., K pfer, P., Ev quoz, D., Fernandez, G., Katz, A., Leumann, C., et al. (2018). Oxidative stress damages rRNA inside the ribosome and differentially affects the catalytic center. *Nucleic. Acids Res.* 46, 1945–1957. doi: 10.1093/nar/gkx1308
- Willingham, S., Outeiro, T. F., DeVit, M. J., Lindquist, S. L., and Muchowski, P. J. (2003). Yeast genes that enhance the toxicity of a mutant huntingtin fragment or α -synuclein. *Science* 302, 1769–1772. doi: 10.1126/science.1090389
- Winderickx, J., Delay, C., De Vos, A., Klinger, H., Pellens, K., Vanh lmont, T., et al. (2008). Protein folding diseases and neurodegeneration: lessons learned from yeast. *Biochim. Biophys. Acta* 1783, 1381–1395. doi: 10.1016/j.bbamcr.2008.01.020
- Xun, Z., Rivera-S nchez, S., Ayala-Pe a, S., Lim, J., Budworth, H., Skoda, E. M., et al. (2012). Targeting of XJB-5-131 to mitochondria suppresses oxidative DNA damage and motor decline in a mouse model of Huntington's disease. *Cell Rep.* 2, 1137–1142. doi: 10.1016/j.celrep.2012.10.001
- Yang, J., Hao, X., Cao, X., Liu, B., and Nystr m, T. (2016). Spatial sequestration and detoxification of Huntingtin by the ribosome quality control complex. *Elife* 5:e11792. doi: 10.7554/elife.11792
- Yang, J.-L., Weissman, L., Bohr, V. A., and Mattson, M. P. (2008). Mitochondrial DNA damage and repair in neurodegenerative disorders. *DNA Repair* 7, 1110–1120. doi: 10.1016/j.dnarep.2008.03.012
- Yano, H., Baranov, S. V., Baranova, O. V., Kim, J., Pan, Y., Yablonska, S., et al. (2014). Inhibition of mitochondrial protein import by mutant huntingtin. *Nat. Neurosci.* 17, 822–831. doi: 10.1038/nn.3721
- Yu, B. P. (1994). Cellular defenses against damage from reactive oxygen species. *Physiol. Rev.* 74, 139–162. doi: 10.1152/physrev.1994.74.1.139
- Zheng, J., Yang, J., Choe, Y.-J., Hao, X., Cao, X., Zhao, Q., et al. (2017). Role of the ribosomal quality control machinery in nucleocytoplasmic translocation of polyQ-expanded Huntingtin exon-1. *Biochem. Biophys. Res. Commun.* 493, 708–717. doi: 10.1016/j.bbrc.2017.08.126

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright   2018 Zheng, Winderickx, Franssens and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.