Abstract: Recent research has identified ER stress as a major mechanism implicated in cytotoxicity in many neurodegenerative diseases, among them Huntington’s disease. This genetic disorder is of late-onset, progressive and fatal, affecting cognition and movement. There is presently no cure nor any effective therapy for the disease. This review focuses on recent findings that shed light on the mechanisms of the advent and development of ER stress in Huntington’s disease and on its implications, highlighting possible therapeutic avenues that are being or could be explored.

Keywords: Huntington, neurodegenerative disease, conformational disease, protein misfolding, protein aggregation, unfolded protein response, ER-associated degradation.

1 Huntington’s Disease

Huntington’s disease (HD) is a neurodegenerative disease arising from an expanded CAG repeat, coding for a polyglutamine (polyQ) tract in the huntingtin (Htt) protein. It is a member of a quite large family of polyQ diseases, such as several spinocerebellar ataxias and Machado-Joseph Disease [1, 2]. HD is a genetic, autosomal dominant disease that causes motor dysfunction and cognitive decline. These symptoms are progressive and usually of late onset, the age of onset being inversely correlated with the number of glutamine repeats, from a minimum of about 35 repeats for Htt to be pathogenic, going up to over 100 repeats in early onset patients. The mutation causes Htt aggregation [3, 4], and there is accumulating evidence that the toxic species are intermediate oligomeric associations of Htt and not the final large aggregates [5-8]. In a cell-protective pathway, the aggregates can be cleared by autophagy, and interestingly, it was recently determined that wild type Htt participates in the process of protein targeting to autophagy [9, 10]. Mutant Htt was reported to interfere with the autophagic process in several ways, one being through a deleterious effect on mTorc1 [11].

The process of aggregation of mutant Htt interferes in several other ways with normal cell metabolism [4, 6, 12, 13] and leads to cell death through a still unclear mechanism. One of the implicated pathways has been glutamate receptor overstimulation, so-called excitotoxicity, which activates calcium influx and cAMP response element-binding protein (CREB) [14-16], leading to mitochondrial dysfunction [17, 18]. Mitochondrial damage can also come about from oxidative stress in HD [19, 20]. Mutant Htt was also recently reported to inhibit protein import to mitochondria [21]. There is, in addition, interference with transport on microtubules, which affects endoplasmic reticulum (ER)-Golgi traffic [22] and axonal transport [23, 24]. There is also sequestration of transcription factors [6, 25, 26] and importantly, interference with the ubiquitin-proteasome system (UPS) as seen in cells in culture, in mouse HD models and in HD patients [27-30]. The turnover of Htt is then affected and may lead to its accumulation and aggregation [31].

Interference with the UPS by mutant Htt inhibits cytosolic protein degradation as well as ER-associated protein degradation (ERAD) [8, 32, 33]. ERAD is a pathway that normally reduces the protein load in the ER [34, 35] and inhibition of this pathway leads to the accumulation of unfolded and misfolded proteins in the ER, which is termed ER stress. ER stress causes activation of the unfolded protein response (UPR) [32, 36, 37], (reviewed in [38, 39]) as we will see later.

Despite the expression of mutant Htt in most cell types in HD patients, HD initially affects medium spiny neurons in the brain striatum [40, 41] and only later...
regions of the brain cortex. This is a common feature of many neurodegenerative diseases, where there is an unexplained high sensitivity of certain specific regions or cell types of the central nervous system. The reasons for the special sensitivity of striatal cells in HD are unclear; mechanisms have been proposed, involving enhanced expression of proteins in these cells [42] and also, recently, of long noncoding RNAs [43]. As we will see later, striatal neurons have distinct features in their UPR [44].

2 ERAD

In eukaryotic cells, the folding and assembly of nascent secretory polypeptides takes place in the ER with the assistance of chaperones. In general, only proteins that have folded or assembled correctly are able to leave the ER. Terminally misfolded/unassembled proteins, as well as many molecules with slow folding, are recognized, retrotranslocated to the cytosol, and degraded by the ubiquitin-proteasome system. This process is referred to as ERAD [34, 45-49].

The same set of factors participating in protein folding and assembly, such as immunoglobulin binding protein (BiP), calnexin, and the family of protein disulfide isomerases, is involved in recognition and retention of folding-defective products [50-52].

In mammals, misfolded or slowly folding secretory proteins are segregated into a domain referred to as the ER-derived quality control compartment (ERQC) [53-56].

Most proteins traversing the secretory pathway are glycoproteins carrying N-linked oligosaccharide modifications at asparagine residues in the context of a glycosylation sequon (Asp-Xxx-Ser/Thr). Extensive trimming of mannose residues of the precursor glycoprotein ERAD [57] and α1,2 ER mannosidase I was proposed to function as an ERAD timer in the quality control of glycoproteins [58-60], together with a family of ER degradation enhancing α-mannosidase-like proteins (EDEM), [61-65].

After crossing the ER membrane, by a still unclear mechanism, ERAD substrates undergo polyubiquitination, the attachment of one or more covalently linked ubiquitin chains to lysine residues [66]. In yeast, the Hrd1 and Doa10 E3 ubiquitin ligases are central components of the membrane-associated ERAD machinery [67, 68]. In mammals, no less than 16 E3 ligases have been implicated in the ERAD pathway, including HRD1 [69], gp78 [70], and TEB4 [71, 72]. Constituents of the HRD1 complex are similar to those in yeast and include the adaptor protein SEL1L (similar to Hrd3) [73], the rhomboid pseudoprotease Derlin-1 (a homolog of Der1) [74, 75], the scaffold protein Herp (Usa1) [76, 77] and other lumenal and cytosolic factors. Herp was found to be responsible for the recruitment of HRD1 and other ERAD components, ubiquitinated proteins and proteasomes, facilitating the assembly of the ERAD complex at the ERQC and making it a staging ground for ubiquitination and degradation [78].

A cytosolic protein complex consisting of the AAA ATPase p97/VCP and two cofactors, UFD1 and NPL4 has an important role in the release of polyubiquitinated polypeptides from the ER membrane into the cytosol [79-81]. N-glycanase (PNGase), was shown to deglycosylate a glycoprotein after its dislocation to the cytosol and prior to proteasomal degradation [82, 83].

3 ER Stress and UPR

Upon shortage of chaperone availability, nutrient deprivation, viral infections, hypoxia or oxidative stress, secretory proteins cannot be properly folded and accumulate in the ER, causing ER stress. Interference with the UPS and ERAD, which occurs in protein misfolding diseases, including neurodegenerative diseases, also causes this accumulation. To face these situations, which can be detrimental to cell survival, cells have evolved the unfolded protein response (UPR) to restore ER protein homeostasis. The basic UPR pathways in mammalian cells consist of three main signaling cascades initiated by three primary ER-localized stress sensors: IRE1 (inositol-requiring 1), PERK (double-strand RNA-activated protein kinase-like ER kinase) and ATF6 (activating transcription factor 6) [84, 85].

Upon ER stress, the chaperone BiP/GRP78 binds to unfolded proteins and its consequent dissociation from all three UPR sensors is involved in their activation. IRE1 then converts from a monomeric inactive state to an oligomeric active form [86]. In addition, IRE1 activation may involve direct binding of unfolded proteins [87]. This process is accompanied by its autophosphorylation, leading to activation of an endonuclease activity present in its C-terminal cytosolic tail. In yeast, Ire1p splices out an intron from the HAC1 precursor mRNA, which is now translated to an active basic leucine zipper (bZIP)-type transcriptional factor, Hac1p. Hac1p induces expression of genes encoding ER-resident chaperones [88]. In mammalian cells, two homologues of yeast Ire1 have been found: Ire1α and β [89, 90], which in a similar splicing reaction remove an intron from the XBP1 transcription factor mRNA [91-93]. Unlike the 252 nucleotide fragment
deleted from yeast HAC1 mRNA, the excised XBP-1 fragment is only 23 bases in C. elegans and 26 bases in mammals and its deletion produces a frame-shift in the C-terminal portion of the protein. The spliced protein has a new C-terminal transactivation domain and can activate expression of a group of ER chaperones and enzymes to help protein folding, maturation, secretion, as well as degradation of misfolded proteins [94].

An immediate response to the accumulation of unfolded proteins in the ER occurs also by transient inhibition of protein synthesis, thereby preventing further accumulation of unfolded proteins. This occurs through the activation of the PERK protein kinase (after BiP dissociation from its luminal domain), which specifically phosphorylates eukaryotic translation initiation factor 2 alpha (eIF-2α) [95]. Interestingly, translation of the transcription factor ATF4 is increased upon phosphorylation of eIF2α [96, 97]. ATF4 activates genes involved in amino acid metabolism, transport, and in resistance to oxidative stress [98]. The ATF4 target-gene Growth arrest and DNA damage-inducible gene 34 (GADD34) recruits the catalytic subunit of protein phosphatase PP1 to dephosphorylate eIF2α [99], a process required for recovery from the PERK-mediated translational block.

Upon UPR activation, the third UPR sensor, ATF6, also dissociates from BiP, is released from the ER and travels to the Golgi compartment where it is cleaved by proteases. This cleavage detaches ATF6 from the Golgi membrane, producing a soluble bZIP transcription factor that activates expression of UPR target genes, involved in protein folding, secretion and degradation in the ER [100-102].

UPR induction also affects other cellular processes, activating autophagy and affecting mitochondria [103]. When adaptation of cells through the UPR is unsuccessful, due to prolonged ER stress, cell death programs are induced to eliminate the damaged cells [34, 104-106]. One of these pathways is mediated by the transcription factor GADD153/ CCAAT-enhancer-binding protein homologous protein (CHOP), which is downstream of the PERK/ eIF2α UPR pathway and is induced by ATF4 [107, 108]. Another pathway involves IRE1 association with tumor necrosis factor receptor-associated factor 2 (TRAF-2), and activation of apoptosis signal regulating kinase 1 (ASK1), which results in phosphorylation of c-Jun N-terminal kinase (JNK) [98, 109]. JNK interacts with Bcl-2 family members and/or activates several BH-3 only proteins, promoting cell death [99]. Upon ER stress there is also rapid calcium transfer from the ER to mitochondria, triggering the mitochondrial apoptotic pathway [110, 111]. This transfer is at ER-mitochondria contacts called mitochondria-associated membranes (MAMs). The calcium overload leads to a large production of reactive oxygen species and a loss of mitochondrial membrane potential [112]. Several ER chaperones and cytosolic chaperones are enriched at the MAM: BiP, calnexin, calreticulin, ERP44, ERP57, FKBP12, Grp75, and HSP60 [113-115], and regulate ER–mitochondria calcium transfer [116-119]. ER stress triggers the induction of the oxidoreductase Ero1α, which also localizes to the MAM and stimulates inositol 1,4,5-triphosphate receptor (IP3R) activity. IP3R is a ligand-gated calcium channel with high concentration at the MAM, which upon its activation releases calcium from the ER to the cytosol [120, 121].

4 Sigma-1 Receptor

One interesting UPR target is the sigma-1 receptor (Sigma-1R). The Sigma-1R is a small (25 kDa), highly conserved, transmembrane protein, which in its inactive state forms a complex with BiP [122]. Upon ER stress, or in the presence of Sigma-1R agonists, it dissociates from BiP and becomes activated [122, 123]. Its activation depends on the modulation of calcium levels [122, 124] and its expression was reported to be upregulated in response to PERK pathway activation [125]. Sigma-1R has been implicated in a large variety of cellular processes, such as cellular redox, neurotransmitter release, inflammation, cellular differentiation, neuronal survival and synaptogenesis. It seems to act as a molecular chaperone, though the characteristics of Sigma-1R interactions in each pathway are still unclear [126, 127].

Sigma-1R promotes cell survival upon ER stress [128]. Interestingly, Sigma-1R is also located predominantly at the MAMs [122]. As mentioned before, IP3R activation releases Ca²⁺ from the ER at the MAM and its chronic activation causes depletion of ER calcium, and this in turn also triggers the dissociation of Sigma-1R from BiP and its activation. Activated Sigma-1R in turn modulates IP3R activity and calcium transfer to mitochondria [122]. Activation of Sigma-1R was also shown to decrease expression levels of Bax and caspase 3, which are associated with ER stress-mediated apoptosis, and hence aids cell survival in cells affected by amyloid beta [129]. Sigma-1R activation also provides significant protection against oxidative damage by reducing ER stress [123, 124, 126, 130]. It was recently suggested that through its interaction with Rac1-GTPase at the MAMs, Sigma1R induces mild oxidative stress, preventing apoptosis [131].
5 ER Stress in Neurodegenerative Diseases

ER stress and the induction of the UPR has been reported in several neurodegenerative diseases [38].

In Alzheimer’s disease (AD), brain samples from patients showed increased BiP levels [132], spliced XBP1 mRNA [133] and activated IRE1 [134]. PERK and phosphorylated eIF2α were also upregulated [134, 135] and there was a decrease in Sigma-1R [136]. Amyloid β increases PERK activation and CHOP expression in neurons in culture [137-139]. Expression of mutant presenilin 1, linked to familial AD, also alters the PERK, IRE1 and ATF6 pathways [140, 141] and increases CHOP expression [142]. Calcium signaling, as a result of ER stress, is altered by expression of amyloid β or mutant presenilin 1 [143, 144]. Tau accumulation was shown to block ERAD and lead to UPR activation in AD model mice [145]. It was recently observed that ER stress accelerates amyloid precursor degradation [146].

ER dysfunction and ER stress have been implicated in Parkinson’s disease (PD) [147]. PERK and phosphorylated eIF2α are increased in brain samples of PD patients with α-synuclein inclusions [148]. A mutant α-synuclein that causes a familial form of PD was shown to activate the UPR with increases in the levels of BiP and CHOP [149]. Mutations in Parkin, a ubiquitin ligase, cause another familial form of PD, resulting in an impairment of its activity [150]. Parkin localizes to the ER and is upregulated by the UPR [151]. The levels of phosphorylated PERK and eIF2α were also found elevated in brain samples of patients with sporadic PD [148], whereas Sigma-1R levels decreased [136].

Increased levels of UPR markers were also found in brain samples from patients with amyotrophic lateral sclerosis (ALS) [152]. ER stress is induced in models of familial ALS [153, 154]. A Sigma-1R mutation was recently linked to another familial form of ALS [155]. The Sigma-1R mutation impairs ER-mitochondria contacts, causing ER stress and affecting calcium signaling [156]. In a mouse mutant SOD1 ALS model, Sigma-1R knockout accelerated considerably disease progression. There might be a general mitochondrial dysfunction in ALS [157].

UPR activation was also reported in brain samples of patients with prion disease [158], PERK-P and eIF2α-P levels increased as the disease progressed, inhibiting protein translation and reducing the levels of synaptic proteins [159]. Interestingly, two opposite strategies for therapy were tested with positive results reported. In one strategy, GADD34 (PPP1R15A) was inhibited, which ameliorated the conditions of mouse prion disease and ALS models [160, 161]. In the other, cytotoxicity in cells expressing mutant prion protein (PrPSc) was increased by salubrinal, an inhibitor of GADD34, whereas overexpression of GADD34 was protective [159], suggesting that the phosphorylated state of eIF2α was responsible for the toxicity. Treatment with a compound that restores translation downstream of eIF2α prevented prion-related neurodegeneration [162].

6 Genesis and Impact of ER Stress in Huntington’s Disease

As we mentioned above, interference with the UPS by mutant Htt inhibits degradation of proteins from the cytosol as well as from the ER, which are targeted to ERAD [8, 32, 33]. Inhibition of ERAD leads to the accumulation of unfolded or misfolded proteins in the ER, or in other words, causes ER stress, which in turn activates the UPR. UPR induction was observed by expression of mutant Htt in yeast and mammalian cells [8, 32, 36, 37, 44]. It has also been reported in animal models of HD [36, 163-165]. P97 depletion by mutant Htt appears to be a major cause in the inhibition of ERAD, which causes ER stress, as p97 overexpression was sufficient for complete compensation in mammalian cells (Fig. 1) [8]. Overexpression of the p97 cofactors Npl4 and Ufd1 also reduced mutant Htt toxicity in yeast [32]. It was also reported that mutant Htt interacts with the ER E3 ligase gp78, inhibiting ERAD [33]. However, gp78 is not the major pathway to ERAD, whereas p97 is an essential factor for the process. Interactions of Htt with ER membrane-bound p97 and with transmembrane gp78 may explain the finding of mutant Htt associated with the ER membrane [166]. Other mechanisms were also suggested that could lead to ER stress in HD, such as impaired ER-Golgi traffic, inhibition of autophagy and calcium deregulation [39], but evidence is scarce.

Besides the products of the classic UPR-induced genes (ATF6, BiP, protein disulfide isomerase, CHOP, etc), [8, 36, 44, 163, 164], other proteins that are induced by ER stress have recently been linked to HD pathology and are upregulated in HD patients, Rrs1 [36] and SCAMP5, the latter especially upregulated in the striatum [164].

We recently showed that the onset of ER stress is due to soluble Htt forms and correlates with the formation of Htt oligomers, preceding the formation of visible inclusions [8]. ER stress levels did not increase in response to the presence and growth of large aggregates, but ER stress was actually reduced with time, implying a protective role for these aggregates. Htt regions that bind and sequester cellular factors may be exposed in
the oligomeric state. These aggregation-prone regions could be hidden and protected inside the structure of the large amyloid aggregates (Fig. 1), similar to what has been found in other neurodegenerative diseases [167]. This is consistent with increasing evidence that Htt oligomers and not aggregates are the cytotoxic species in HD [5-7] and the reports of UPS inhibition before Htt inclusion into large aggregates [168-170]. This might explain why clinical trials of anti-aggregating molecules in HD have been so far unsuccessful [171]. The presence of toxic oligomeric forms (detected with specific antibodies), was found to predict neurodegeneration [172].

Apoptotic pathways induced through ER stress have been suggested in HD pathology through induction of CHOP and also of ASK1 [44, 163, 173, 174], leading finally to caspase activation [175]. Mutant Htt causes altered calcium signaling and apoptosis, possibly by its interference with the ER IP3R. This effect may be downstream of the UPR or by direct interaction with IP3R [176-178]. Interestingly, as mentioned before, the IP3R is mostly located at the MAM, and autophagy, which can be induced by the UPR, has also been reported to initiate at this region [179]. Apoptotic and autophagic pathways might then be induced in parallel by mutant Htt at the MAM. Sigma-1R, also at the MAM, was recently reported to have a protective effect in cells expressing mutant Htt, increasing UPS function and Htt degradation [180].

We recently showed that striatal neurons are especially sensitive to ER stress [44]. Their PERK pathway is altered, with very reduced PERK activity and low phosphorylation of eIF2α, a characteristic that we also found in WT mouse brain striatum. In contrast, a knock-in striatal cell line expressing mutant Htt and the striatum of HD model mice showed higher levels of eIF2α-P. Huntingtin toxicity in the mutant Htt expressing cells could be strongly reduced by inhibiting PERK [44]. This suggests on one hand a reason for the special sensitivity of the striatum in HD, and on the other it underscores the importance of ER stress for Htt cytotoxicity. As the dephosphorylated state of eIF2α was linked to memory and long term potentiation, possibly to maintain high translation rates [181, 182], the appearance of ER stress upon expression of mutant Htt and the consequent increase in eIF2α-P levels suggest the intriguing possibility that they are linked to the cognitive impairment observed in HD.

7 Therapeutic Targeting

Several therapeutic strategies have been proposed for HD, but so far with no successful resulting therapy. Gene therapy approaches have been suggested for the silencing of mutant Htt expression, but they are far from implementation [183]. Another strategy proposed recently is the targeting of Htt cleavage by caspase 6, which gave positive results in a BACHD mouse model [184].

As a general strategy for reducing ER stress, there are reports that chemical chaperones, including 4-PBA and TUDCA, hindered disease progression in HD mouse models, and decreased ER stress levels in HD and other disease models [185-187]. Reduction of eIF2α-P [159], or treatment with a compound that restores translation downstream of eIF2α, thwarted prion-related disease in mouse models [162]. This is consistent with our results of PERK inhibition in knock-in striatal neurons expressing mutant Htt, which considerably reduced cytotoxicity [44]. Inhibition of the PERK pathway could be a promising therapeutic strategy.

As explained above, Sigma-1R expression has a general cell protective effect and Sigma-1R agonists have proven effective in mouse models of brain disease [123, 188]. Sigma-1R activation was reported to induce neuronal re-growth and functional recovery following experimental stroke in a rat model [189] and a phase II trial was conducted with the Sigma-1R agonist cutamesine (SA4503) in patients with ischemic stroke [190]. A recent study showed that another Sigma-1R agonist, PRE084, improved behavioral symptoms in a Parkinson's disease mouse model [191]. In another study, this same agonist promoted cell viability, reduced oxidative stress and decreased cleavage of caspases in mutant Htt-expressing cells [192], suggesting a possible therapeutic benefit of Sigma-1R agonists in HD.

8 Conclusions

Many pathways could partake in mutant huntingtin cytotoxicity, but the fact that UPR modulation, such as PERK inhibition or Sigma-1R activation, reduces significantly the toxicity, implicates ER stress as a main factor. UPR modulation with novel drugs could thus be a promising therapeutic approach for HD. The onset of ER stress, as a consequence of ERAD inhibition through p97 depletion and other interferences, is linked to the formation of Htt oligomers, whereas the formation of Htt large aggregates was shown to be protective. Therefore, caution is advised in the development of inhibitors of aggregation, which might have an overall detrimental effect.
Figure 1: Model of mutant Htt aggregation and the genesis of ER stress and cytotoxicity. 1) The initial appearance of misfolded mutant Htt monomers, with exposed aggregation prone regions (blue) is initially compensated by chaperones and proteasomal degradation. 2) Misfolded monomer cleavage and association into oligomers, which are not easy to degrade, saturates the buffering capacity of the cytosolic chaperones and leads to binding and depletion of ERAD factors such as p97, inhibiting ERAD. 3) This causes accumulation of unfolded secretory proteins at the ERQC (ER stress) and activates a protective stage of the UPR, with induction of chaperone expression and transient arrest in translation. 4) Persistence of the ER stress leads to the pro-apoptotic stage of the UPR, causing upregulation of ASK1 downstream of IRE1 and CHOP downstream of PERK and Ca\textsuperscript{2+} exit from the ER through the IP3R, triggering the mitochondrial apoptotic pathway. Sigma-1R upregulation has a protective effect. 5) If the cell has not reached the apoptotic stage, Htt sequestration into large aggregates, with aggregation-prone domains buried in the core of these structures, leads to disinhibition of ERAD, reduction of ER stress and cell recovery.
Abbreviations

Alzheimer’s disease (AD), activation of apoptosis signal regulating kinase 1 (ASK1), amyotrophic lateral sclerosis (ALS), ATF6 (activating transcription factor 6), CCAAT-enhancer-binding protein homologous protein (CHOP), c-Jun N-terminal kinase (JNK), endoplasmic reticulum (ER), ER-associated protein degradation (ERAD), ER degradation enhancing α-mannosidase-like proteins (EDEM), ER-derived quality control compartment (ERQC), eukaryotic translation initiation factor 2 alpha (eIF2α), growth arrest and DNA damage-inducible gene 34 (GADD34), huntingtin (Htt), Huntington’s disease (HD), immunoglobulin binding protein (BiP), inositol 1,4,5-triphosphate receptor (IP3R), IRE1 (inositol-requiring 1), mitochondria-associated membranes (MAMs), Parkinson’s disease (PD), PERK (double-strand RNA-activated protein kinase-like ER kinase), polyglutamine (polyQ), sigma-1 receptor (Sigma-1R), ubiquitin-proteasome system (UPS), tumor necrosis factor receptor-associated factor 2 (TRAF-2), unfolded protein response (UPR).

Acknowledgments: We apologize to those authors that we have not been able to cite due to space limitations. Work related to this article was supported by grants from the Israel Science Foundation (1070/10) and German–Israeli Project Cooperation (Deutsch-Israelische Projektkooperation K 5-1).

Conflict of interest statement: We have no conflict of interest to declare.

References

[1] Pennuto, M., Palazzolo, I., and Poletti, A., Post-translational modifications of expanded polyglutamine proteins: impact on neurotoxicity, Hum Mol Genet, 2009; 18(R1): R40-47.
[2] Shao, J., and Diamond, M.I., Polyglutamine diseases: emerging concepts in pathogenesis and therapy, Hum Mol Genet, 2007; 16 Spec No. 2: R115-123.
[3] Hatters, D.M., Putting huntingtin “aggregation” in view with windows into the cellular milieu, Current topics in medicinal chemistry, 2012; 12(22): 2611-2622.
[4] Sakahira, H., Breuer, P., Hayer-Hartl, M.K., and Hartl, F.U., Molecular chaperones as modulators of polyglutamine protein aggregation and toxicity, Proc Natl Acad Sci U S A, 2002; 99 Suppl 4: 16412-16418.
[5] Lajoie, P., and Snapp, E.L., Formation and toxicity of soluble polyglutamine oligomers in living cells, PLoS One, 2010; 5(12): e15245.
[6] Schaffar, G., Breuer, P., Boteva, R., Behrends, C., Tzetkov, N., Strippel, N., Sakahira, H., Siegers, K., Hayer-Hartl, M., and Hartl, F.U., Cellular toxicity of polyglutamine expansion proteins: mechanism of transcription factor deactivation, Mol Cell, 2004; 15(1): 95-105.
[7] Takahashi, T., Kikuchi, S., Katada, S., Nagai, Y., Nishizawa, M., and Onodera, O., Soluble polyglutamine oligomers formed prior to inclusion body formation are cytotoxic, Hum Mol Genet, 2008; 17(3): 345-356.
[8] Leitman, J., Ulrich Hartl, F., and Lederkremer, G.Z., Soluble forms of polyQ-expanded huntingtin rather than large aggregates cause endoplasmic reticulum stress, Nat Commun, 2013; 4: 2753.
[9] Ochaba, J., Lukacsovich, T., Csikos, G., Zheng, S., Margulis, J., Salazar, L., Mao, K., Lau, A.L., Yeung, S.Y., Humbert, S., et al., Potential function for the Huntingtin protein as a scaffold for selective autophagy, Proc Natl Acad Sci U S A, 2014; 111(47): 16889-16894.
[10] Rui, Y.N., Xu, Z., Patel, B., Chen, Z., Chen, D., Tito, A., David, G., Sun, Y., Stimming, E.F., Bellen, H.J., et al., Huntingtin functions as a scaffold for selective macroautophagy, Nat Cell Biol, 2015; 17(3): 262-275.
[11] Lee, J.H., Tecedor, L., Chen, Y.H., Monteys, A.M., Sowada, M.J., Thompson, L.M., and Davidson, B.L., Reinstating aberrant mTORC1 activity in Huntington’s disease mice improves disease phenotypes, Neuron, 2015; 85(2): 303-315.
[12] Imarisio, S., Carmichael, J., KoroChuk, V., Chen, C.W., Saiki, S., Rose, C., Krishna, G., Davies, J.E., Tofli, E., Underwood, B.R., et al., Huntington’s disease: from pathology and genetics to potential therapies, Biochem J, 2008; 412(2): 191-209.
[13] Kim, S.D., and Fung, V.S., An update on Huntington’s disease: from the gene to the clinic, Current opinion in neurology, 2014; 27(4): 477-483.
[14] Andre, V.M., Cepeda, C., and Levine, M.S., Dopamine and glutamate in Huntington’s disease: A balancing act, CNS neuroscience & therapeutics, 2010; 16(3): 163-178.
[15] Estrada-Sanchez, A.M., Montiel, T., Segovia, J., and Massieu, L., Glutamate toxicity in the striatum of the R6/2 Huntington’s disease transgenic mice is age-dependent and correlates with decreased levels of glutamate transporters, Neurobiology of disease, 2009; 34(1): 78-86.
[16] Heng, M.Y., Detloff, P.J., Wang, P.L., Tsien, J.Z., and Albin, R.L., In vivo evidence for NMDA receptor-mediated excitotoxicity in a murine genetic model of Huntington disease, J Neurosci, 2009; 29(10): 3200-3205.
[17] Bossy-Wetzel, E., Petrilli, A., and Knott, A.B., Mutant huntingtin and Elusive Defects in Alzheimer’s disease transgenic mice is age-dependent and correlates with decreased levels of glutamate transporters, Neurobiology of disease, 2009; 34(1): 78-86.
[18] Quintanilla, R.A., and Johnson, G.V., Role of mitochondrial dysfunction in the pathogenesis of Huntington’s disease, Trends in neurosciences, 2008; 31(12): 609-616.
[19] Rose, C., Krishna, G., Davies, J.E., Ttofi, E., Underwood, B.R., et al., Huntington’s disease: from pathology and genetics to potential therapies, Biochem J, 2008; 412(2): 191-209.
[20] Salazar, L., Mao, K., Lau, A.L., Yeung, S.Y., Humbert, S., et al., Potential function for the Huntingtin protein as a scaffold for selective autophagy, Proc Natl Acad Sci U S A, 2014; 111(47): 16889-16894.
[21] Ochaba, J., Lukacsovich, T., Csikos, G., Zheng, S., Margulis, J., Salazar, L., Mao, K., Lau, A.L., Yeung, S.Y., Humbert, S., et al., Potential function for the Huntingtin protein as a scaffold for selective autophagy, Proc Natl Acad Sci U S A, 2014; 111(47): 16889-16894.
[22] Rui, Y.N., Xu, Z., Patel, B., Chen, Z., Chen, D., Tito, A., David, G., Sun, Y., Stimming, E.F., Bellen, H.J., et al., Huntingtin functions as a scaffold for selective macroautophagy, Nat Cell Biol, 2015; 17(3): 262-275.
[23] Lee, J.H., Tecedor, L., Chen, Y.H., Monteys, A.M., Sowada, M.J., Thompson, L.M., and Davidson, B.L., Reinstating aberrant mTORC1 activity in Huntington’s disease mice improves disease phenotypes, Neuron, 2015; 85(2): 303-315.
[24] Imarisio, S., Carmichael, J., KoroChuk, V., Chen, C.W., Saiki, S., Rose, C., Krishna, G., Davies, J.E., Tofli, E., Underwood, B.R., et al., Huntington’s disease: from pathology and genetics to potential therapies, Biochem J, 2008; 412(2): 191-209.
[25] Kim, S.D., and Fung, V.S., An update on Huntington’s disease: from the gene to the clinic, Current opinion in neurology, 2014; 27(4): 477-483.
[26] Andre, V.M., Cepeda, C., and Levine, M.S., Dopamine and glutamate in Huntington’s disease: A balancing act, CNS neuroscience & therapeutics, 2010; 16(3): 163-178.
[27] Estrada-Sanchez, A.M., Montiel, T., Segovia, J., and Massieu, L., Glutamate toxicity in the striatum of the R6/2 Huntington’s disease transgenic mice is age-dependent and correlates with decreased levels of glutamate transporters, Neurobiology of disease, 2009; 34(1): 78-86.
[28] Heng, M.Y., Detloff, P.J., Wang, P.L., Tsien, J.Z., and Albin, R.L., In vivo evidence for NMDA receptor-mediated excitotoxicity in a murine genetic model of Huntington disease, J Neurosci, 2009; 29(10): 3200-3205.
[22] Brandstaetter, H., Krupa, A.J., and Buss, F., Huntington is required for ER-to-Golgi transport and for secretory vesicle fusion at the plasma membrane, Disease models & mechanisms, 2014; 7(12): 1335-1340.

[23] Gunawardena, S., and Goldstein, L.S., Polyglutamine diseases and transport problems: deadly traffic jams on neuronal highways, Archives of neurology, 2005; 62(2): 46-51.

[24] Trushina, E., Dyer, R.B., Badger, J.D., 2nd, Ure, D., Eide, L., Tran, D.D., Vrieze, B.T., Legendre-Guillemin, V., McPherson, P.S., Mandavalli, B.S., et al., Mutant huntingtin impairs axonal trafficking in mammalian neurons in vivo and in vitro, Molecular and cellular biology, 2004; 24(18): 8195-8209.

[25] Becanovic, K., Pouladi, M.A., Lim, R.S., Kuhn, A., Pavlidis, P., Luthi-Carter, R., Hayden, M.R., and Leavitt, B.R., Transcriptional changes in Huntington disease identified using genome-wide expression profiling and cross-platform analysis, Hum Mol Genet, 2010; 19(8): 1438-1452.

[26] Buckley, N.J., Johnson, R., Zuccato, C., Bithell, A., and Gunawardena, S., and Goldstein, L.S., Polyglutamine diseases counteracts neuronal cell death and protein aggregation and Korhonen, L., Inhibition of endoplasmic reticulum stress response in Huntington disease, J Biol Chem, 2009; 284(27): 18167-18173.

[27] Forster, M.L., Sivick, K., Park, Y.N., Arvan, P., Lencer, W.I., and Ortega, Z., Diaz-Hernandez, M., and Lucas, J.J., Is the ubiquitin-proteasome pathway in Huntington’s disease, ScientificWorldJournal, 2008; 8: 421-433.

[28] Ortega, Z., Diaz-Hernandez, M., and Lucas, J.J., Is the ubiquitin-proteasome system impaired in Huntington’s disease?, Cell Mol Life Sci, 2007; 64(17): 2245-2257.

[29] Bennett, E.J., Shaler, T.A., Woodman, B., Ryu, K.Y., Zaitseva, T.S., Becker, C.H., Bates, G.P., Schulman, H., and Kopito, R.R., Global changes to the ubiquitin system in Huntington’s disease, Nature, 2007; 448(7154): 704-708.

[30] Hipp, M.S., Patel, C.N., Bersuker, K., Riley, B.E., Kaiser, S.E., Shaler, T.A., Brandeis, M., and Kopito, R.R., Indirect inhibition of 26S proteasome activity in a cellular model of Huntington’s disease, J Cell Biol, 2012; 196(5): 573-587.

[31] Tsvetkov, A.S., Arrasate, M., Barbadena, S., Ando, D.M., Sharma, P., Shaby, B.A., and Finkbeiner, S., Proteostasis of polyglutamine varies among neurons and predicts neurondegeneration, Nature chemical biology, 2013; 9(9): 586-592.

[32] Duennwald, M.L., and Lindquist, S., Impaired ERAD and ER stress are early and specific events in polyglutamine toxicity, Genes Dev, 2008; 22(23): 3308-3319.

[33] Yang, H., Liu, C., Zhong, Y., Luo, S., Monteiro, M.J., and Fang, S., Huntington interacts with the cue domain of gp78 and inhibits gp78 binding to ubiquitin and p97/VCP, PLoS One, 2010; 5(1): e8905.

[34] Benyair, R., Ron, E., and Lederkremer, G.Z., Protein quality control, retention, and degradation at the endoplasmic reticulum, Int Rev Cell Mol Biol, 2011; 292: 197-280.

[35] Smith, M.H., Ploegh, H.L., and Weissman, J.S., Road to ruin: targeting proteins for degradation in the endoplasmic reticulum, Science, 2011; 334(6059): 1086-1090.

[36] Carnevalotta, A., Fossale, E., Agostoni, E., Michelazzi, S., Calligaris, R., De Maso, L., Del Sal, G., MacDonald, M.E., and Persichetti, F., Rsl1 is involved in endoplasmic reticulum stress response in Huntington disease, J Biol Chem, 2009; 284(27): 18167-18173.

[37] Reijonen, S., Putkonen, N., Norremolte, A., Lindholm, D., and Korhonen, L., Inhibition of endoplasmic reticulum stress counteracts neuronal cell death and protein aggregation caused by N-terminal mutant huntingtin proteins, Exp Cell Res, 2008; 314(5): 950-960.

[38] Roussel, B.D., Krupa, A.J., Miranda, E., Crowther, D.C., Lomas, D.A., and Marciniak, S.J., Endoplasmic reticulum dysfunction in neurological disease, Lancet Neurol, 2013; 12(2): 105-118.

[39] Vidal, R., Caballero, B., Couve, A., and Hetz, C., Converging pathways in the occurrence of endoplasmic reticulum (ER) stress in Huntington’s disease, Curr Mol Med, 2011; 11(1): 1-12.

[40] Reiner, A., Albin, R.L., Anderson, K.D., D’Amato, C.J., Penney, J.B., and Young, A.B., Differential loss of striatal projection neurons in Huntington disease, Proc Natl Acad Sci U S A, 1988; 85(15): 5733-5737.

[41] Roze, E., Cahill, E., Martin, E., Bonnet, C., Vanhoupt, P., Betuing, S., and Caboche, J., Huntington’s Disease and Striatal Signaling, Front Neuroanat, 2011; 5: 55.

[42] Subramaniam, S., Six, K.M., Barrow, R., and Snyder, S.H., Rhe, a striatal specific protein, mediates mutant-huntingtin cytotoxicity, Science, 2009; 324(5932): 1327-1330.

[43] Francelle, L., Galvan, L., Gaillard, M.C., Petit, F., Bernay, B., Guillermer, M., Bonvento, G., Dufour, N., Elalouf, J.M., Hantraye, P., et al., The striatal long noncoding RNA Abhd11os is neuroprotective against an N-Terminal fragment of mutant huntingtin in vivo, Neurobiology of aging, 2015; 36(3): 1601.e1607-1616.

[44] Leitman, J., Barak, B., Benyair, R., Shenkman, M., Ashery, U., Hartl, F.U., and Lederkremer, G.Z., ER stress-induced eIF2-alpha phosphorylation underlies sensitivity of striatal neurons to pathogenic huntingtin, PLoS One, 2014; 9(3): e90803.

[45] Romisch, K., Endoplasmic reticulum-associated degradation, Annu Rev Cell Dev Biol, 2005; 21: 435-456.

[46] Hirsch, C., Gauss, R., Horn, S.C., Neuber, O., and Sommer, T., The ubiquitylation machinery of the endoplasmic reticulum, Nature, 2009; 458(7237): 453-460.

[47] Brodsky, J.L., Cleaning Up: ER-Associated Degradation to the Rescue, Cell, 2012; 151(6): 1163-1167.

[48] Sommer, T., and Wolf, D.H., The ubiquitin-proteasome-system, Biochim Biophys Acta, 2014; 1843(1): 1.

[49] Lederkremer, G.Z., Glycoprotein folding, quality control and ER-associated degradation, Curr Opin Struct Biol, 2009; 19(5): 515-523.

[50] Okuda-Shimizu, Y., and Hendershot, L.M., Characterization of an ERAD pathway for nonglycosylated BiP substrates, which require Herp, Mol Cell, 2007; 28(4): 544-554.

[51] Forster, M.L., Sivick, K., Park, Y.N., Arvan, P., Lencer, W.I., and Tsai, B., Protein disulfide isomerase-like proteins play opposing roles during retrotranslocation, J Cell Biol, 2006; 173(6): 853-859.

[52] Nakatsukasa, K., and Brodsky, J.L., The recognition and retrotranslocation of misfolded proteins from the endoplasmic reticulum, Traffic, 2008; 9(6): 861-870.

[53] Kamhi-Nesher, S., Shenkman, M., Tolchinsky, S., Fromm, S.V., Ehrlich, R., and Lederkremer, G.Z., A novel quality control compartment derived from the endoplasmic reticulum, Mol Biol Cell, 2001; 12(6): 1711-1723.

[54] Groisman, B., Shenkman, M., Ron, E., and Lederkremer, G.Z., Mannose trimming is required for delivery of a glycoprotein from EDEM1 to XTP3-B and to late endoplasmic reticulum-associated degradation steps, J Biol Chem, 2011; 286(2): 1292-1300.
[55] Kondratyev, M., Avezov, E., Shenkman, M., Groisman, B., and Lederkremer, G.Z., PERK-dependent compartmentalization of ERAD and unfolded protein response machineries during ER stress, Exp Cell Res, 2007; 313(6): 3395-3407.

[56] Leitman, J., Ron, E., Ogen-Shtern, N., and Lederkremer, G.Z., Compartmentalization of Endoplasmic Reticulum Quality Control and ER-Associated Degradation Factors, DNA Cell Biol, 2012.

[57] Frenkel, Z., Gregory, W., Kornfeld, S., and Lederkremer, G.Z., Endoplasmic reticulum-associated degradation of mammalian glycoproteins involves signal chain trimming to Man6-5GlcNAc2, J Biol Chem, 2003; 278(36): 34119-34124.

[58] Helenius, A., and Aebi, M., Roles of N-linked glycans in the endoplasmic reticulum, Annu Rev Biochem, 2004; 73: 1019-1049.

[59] Avezov, E., Frenkel, Z., Ehrlich, M., Herscovics, A., and Lederkremer, G.Z., Endoplasmic reticulum (ER) mannosidase I is compartmentalized and required for N-glycan trimming to Man5-6GlcNAc2 in glycoprotein ER-associated degradation, Mol Biol Cell, 2008; 19(1): 216-225.

[60] Benyair, R., Ogen-Shtern, N., Mazkereth, N., Shai, B., Ehrlich, M., and Lederkremer, G.Z., Mammalian ER mannosidase I resides in quality control vesicles, where it encounters its glycoprotein substrates, Mol Biol Cell, 2015; 26(2): 172-184.

[61] Benyair, R., Ogen-Shtern, N., and Lederkremer, G.Z., Glycan regulation of ER-associated degradation through compartmentalization, Seminars in cell & developmental biology, 2015; 41: 99-109.

[62] Hosokawa, S., Tremblay, L.O., Sleno, B., Kamiya, Y., Wada, I., Nagata, K., Kato, K., and Herscovics, A., EDEM1 accelerates the trimming of alpha,2-linked mannose on the C branch of N-glycans, Glycobiology, 2010; 20(5): 567-575.

[63] Ninagawa, S., Okada, T., Sumitomo, Y., Kamiya, Y., Kato, K., Horimoto, S., Ishikawa, T., Takeda, S., Sakuma, T., Yamamoto, T., et al., EDEM2 initiates mammalian glycoprotein ERAD by catalyzing the first mannose trimming step, J Cell Biol, 2014; 206(3): 347-356.

[64] Olivari, S., Cali, T., Salo, K.E., Paggetti, P., Roodick, L.W., and Molinari, M., EDEM1 regulates ER-associated degradation by accelerating de-mannosylation of folding-defective polypeptides and by inhibiting their covalent aggregation, Biochemical and biophysical research communications, 2006; 349(4): 1278-1284.

[65] Ron, E., Shenkman, M., Groisman, B., Izenstein, Y., Leitman, J., and Lederkremer, G.Z., Bypass of glycane-dependent glycoprotein delivery to ERAD by up-regulated EDEM1, Mol Biol Cell, 2011; 22(21): 3945-3954.

[66] Wang, X., Herr, R.A., Chua, W.J., Lybarger, L., Wiertz, E.J., and Hansen, T.H., Ubiquitination of serine, threonine, or lysine residues on the cytosolic tail can induce ERAD of MHC-I by viral E3 ligase mK3, J Cell Biol, 2007; 177(4): 613-624.

[67] Gardner, R.G., Swarbrick, G.M., Bays, N.W., Cronin, S.R., Wilovsky, S., Seeilig, L., Kim, C., and Hampton, R.Y., Endoplasmic reticulum degradation requires lumen to cytosol signaling. Transmembrane control of Hrd1p by Hrd3p, J Cell Biol, 2000; 151(1): 69-82.

[68] Deak, P.M., and Wolf, D.H., Membrane topology and function of Der3/Hrd1p as a ubiquitin-protein ligase (E3) involved in endoplasmic reticulum degradation, J Biol Chem, 2001; 276(14): 10663-10669.

[69] Kikkert, M., Doolman, R., Dai, M., Avner, R., Hassink, G., van Voorden, S., Thedens, S., Roitelman, J., Chau, V., and Wiertz, E., Human HRD1 is an E3 ubiquitin ligase involved in degradation of proteins from the endoplasmic reticulum, J Biol Chem, 2004; 279(5): 3525-3534.

[70] Fang, S., Ferrone, M., Yang, C., Jensen, J.P., Tiwari, S., and Weissman, A.M., The tumor autocrine motility factor receptor, gp78, is a ubiquitin protein ligase implicated in degradation from the endoplasmic reticulum, Proc Natl Acad Sci U S A, 2001; 98(25): 14422-14427.

[71] Kreft, S.G., Wang, L., and Hochstrasser, M., Membrane topology of the yeast endoplasmic reticulum-localized ubiquitin ligase Doa10 and comparison with its human ortholog TEB4 (MARCH-VI), J Biol Chem, 2006; 281(18): 4646-4653.

[72] Hassink, G., Kikkert, M., van Voorden, S., Lee, S.J., Spaapen, R., van Laar, T., Coleman, C.S., Bartee, E., Fruh, K., Chau, V., et al., TEBA is a CAH3C RING-finger-containing ubiquitin ligase of the endoplasmic reticulum, Biochem J, 2005; 388(Pt 2): 647-655.

[73] Mueller, B., Lilley, B.N., and Ploegh, H.L., SEL1L, the homologue of yeast Hrd3p, is involved in protein dislocation from the mammalian ER, J Cell Biol, 2006; 175(2): 261-270.

[74] Lilley, B.N., and Ploegh, H.L., A membrane protein required for dislocation of misfolded proteins from the ER, Nature, 2004; 429(6994): 834-840.

[75] Greenblatt, E.J., Ollizm, J.A., and Kopito, R.R., Derlin-1 is a rhomboid pseudoprotease required for the dislocation of mutant alpha-1 antitrypsin from the endoplasmic reticulum, Nat Struct Mol Biol, 2011; 18(10): 1147-1152.

[76] Kokame, K., Agarwala, K.L., Kato, H., and Miyata, T., Herp, a lectin-like ERAD players in ER and cytosol, Biochimica et biophysica acta, 2010; 1800(2): 172-180.

[77] Schulze, A., Standera, S., Buenger, E., Kikkert, M., van Voorden, S., Wiertz, E., Koning, F., Kloetzel, P.M., and Seeger, M., The ubiquitin-domain protein HERP forms a complex with components of the endoplasmic reticulum associated degradation pathway, J Mol Biol, 2005; 354(5): 1021-1027.

[78] Leitman, J., Shenkman, M., Gofman, Y., Shtern, N.O., Ben-Tal, N., Hendershot, L.M., and Lederkremer, G.Z., Herp coordinates compartmentalization and recruitment of HRD1 and misfolded proteins for ERAD, Mol Biol Cell, 2014; 25(7): 1050-1060.

[79] Bays, N.W., Wilovsky, S.K., Goradia, A., Hodgkiss-Harlow, K., and Hampton, R.Y., HRD4/NPL4 is required for the proteasomal processing of ubiquitinated ER proteins, Mol Biol Cell, 2001; 12(12): 4114-4128.

[80] Ye, M., Meyer, H.H., and Rapoport, T.A., The AAA ATPase Cdc48/p97 and its partners transport proteins from the ER into the cytosol, Nature, 2001; 414(6864): 652-656.

[81] Rabinovich, E., Kerem, A., Frohlich, K.U., Diamant, N., and Bar-Nun, S., AAA-ATPase p97/Cdc48p, a cytosolic chaperone required for endoplasmic reticulum-associated protein degradation, Mol Cell Biol, 2002; 22(2): 626-634.

[82] Zhao, G., Zhou, X., Wang, L., Li, G., Schindelin, H., and Lennarz, W.J., Studies on peptide-N-glycanase-p97 interaction suggest that p97 phosphorylation modulates endoplasmic reticulum-associated degradation, Proc Natl Acad Sci U S A, 2007; 104(21): 8785-8790.

[83] Yoshida, Y., and Tanaka, K., Lectin-like ERAD players in ER and cytosol, Biochimica et biophysica acta, 2010; 1802(0): 172-180.
[113] Szabadkai, G., Bianchi, K., Varnai, P., De Stefani, D., Wieckowski, M.R., Cavagna, D., Nagy, A.I., Balla, T., and Rizzuto, R., Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca2+ channels, Journal of Cell Biology, 2006; 175(6): 901-911.

[114] Myhill, N., Lynes, E.M., Nanji, J.A., Blagoveshchenskaya, A.D., Fei, H., Carmine Simmen, K., Cooper, T.J., Thomas, G., and Simmen, T., The subcellular distribution of calnexin is mediated by PACS-2, Mol Biol Cell, 2008; 19(7): 2777-2788.

[115] Hayashi, T., Rizzuto, R., Hajnoczy, G., and Su, T.P., MAM: more than just a housekeeper, Trends Cell Biol, 2009; 19(2): 81-88.

[116] Higo, T., Hattori, M., Nakamura, T., Natsume, T., Michikawa, T., and Mikoshiba, K., Subtype-specific and ER lumenal environment-dependent regulation of inositol 1,4,5-trisphosphate receptor type 1 by ERp44, Cell, 2005; 120(1): 85-98.

[117] Roderick, H.L., Lechleiter, J.D., and Camacho, P., Cytosolic phosphorylation of calnexin controls intracellular Ca(2+) oscillations via an interaction with SERCA2b, Journal of Cell Biology, 2000; 149(6): 1235-1248.

[118] Li, Y., and Camacho, P., Ca2+-dependent redox modulation of SERCA 2b by ERp57, Journal of Cell Biology, 2004; 164(3): 35-46.

[119] John, L.M., Lechleiter, J.D., and Camacho, P., Differential modulation of SERCA2 isoforms by calreticulin, Journal of Cell Biology, 1998; 142(4): 963-973.

[120] Li, G., Mongillo, M., Chinn, K.T., Harding, H., Ron, D., Marks, A.R., and Tabas, I., Role of ERO1-alpha-mediated stimulation of inositol 1,4,5-trisphosphate receptor activity in endoplasmic reticulum stress-induced apoptosis, Journal of Cell Biology, 2009; 186(6): 783-792.

[121] Gilady, S.Y., Bui, M., Lynes, E.M., Benson, M.D., Watts, R., Vance, J.E., and Simmen, T., Ero1alpha requires oxidizing and normoxic conditions to localize to the mitochondria-associated membrane (MAM), Cell Stress Chaperones, 2010; 15(5): 619-629.

[122] Hayashi, T., and Su, T.P., Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival, Cell, 2007; 131(3): 596-610.

[123] Hashimoto, K., Sigma-1 receptor chaperone and brain-derived neurotrophic factor: emerging links between cardiovascular disease and depression, Progress in neurobiology, 2013; 100: 15-29.

[124] Wang, L., Eldred, J.A., Sidaway, P., Sanderson, J., Smith, A.J., Bowater, R.P., Reddan, J.R., and Wormstone, I.M., Sigma 1 receptor stimulation protects against oxidative damage through suppression of the ER stress responses in the human lens, Mechanisms of Ageing and Development, 2012; 133(11-12): 665-674.

[125] Mitsuda, T., Omi, T., Tanimukai, H., Sakagami, Y., Tagami, S., Okochi, M., Kudo, T., and Takeda, M., Sigma-1Rs are upregulated via PERK/eIF2alpha/ATF4 pathway and execute protective function in ER stress, Biochemical and biophysical research communications, 2011; 415(3): 519-525.

[126] Hayashi, T., Tsai, S.Y., Mori, T., Fujimoto, M., and Su, T.P., Targeting ligand-operated chaperone sigma-1 receptors in the treatment of neuropsychiatric disorders, Expert opinion on therapeutic targets, 2011; 15(5): 557-577.

[127] Nguyen, L., Lucke-Wold, B.P., Mookerjee, S.A., Cavendish, J.Z., Robson, M.J., Scandinaro, A.L., and Matsumoto, R.R., Role of sigma-1 receptors in neurodegenerative diseases, Journal of pharmacological sciences, 2015; 127(1): 17-29.

[128] Hall, A.A., Herrera, Y., Ajmo, C.T., Jr., Cuevas, J., and Pennybacker, K.R., Sigma receptors suppress multiple aspects of microglial activation, Gila, 2009; 57(7): 744-754.

[129] Marrazzo, A., Caraci, F., Salinaro, E.T., Su, T.P., Copani, A., and Ronsisvalle, G., Neuroprotective effects of sigma-1 receptor agonists against beta-amyloid-induced toxicity, Neuroreport, 2005; 16(11): 1223-1226.

[130] Meunier, J., and Hayashi, T., Sigma-1 receptors regulate Bcl-2 expression by reactive oxygen species-dependent transcriptional regulation of nuclear factor kappaB, The Journal of pharmacology and experimental therapeutics, 2010; 332(2): 388-397.

[131] Natvlishvili, N., Gogudaze, N., Zhuravliova, E., and Mikeladze, D., Sigma-1 receptor directly interacts with Rac1-GTPase in the brain mitochondria, BMC biochemistry, 2015; 16(1): 11.

[132] Hoozemans, J.J., Veerhuis, R., Van Haastert, E.S., Rozemuller, J.M., Baas, F., Eikelenboom, P., and Scheper, W., The unfolded protein response is activated in Alzheimer's disease, Acta neuropathologica, 2005; 110(2): 165-172.

[133] Lee, J.H., Won, S.M., Suh, J., Son, S.J., Moon, G.J., Park, U.J., and Gwag, B.J., Induction of the unfolded protein response and cell death pathway in Alzheimer's disease, but not in aged Tg2576 mice, Experimental & molecular medicine, 2010; 42(5): 386-394.

[134] Hoozemans, J.J., van Haastert, E.S., Nijholt, D.A., Rozemuller, A.J., Eikelenboom, P., and Scheper, W., The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus, The American journal of pathology, 2009; 174(4): 1241-1251.

[135] Chang, R.C., Wong, A.K., Ng, H.K., and Hugon, J., Phosphorylation of eukaryotic initiation factor-2alpha (eIF2alpha) is associated with neuronal degeneration in Alzheimer's disease, Neuroreport, 2002; 13(18): 2429-2432.

[136] Mishina, M., Ohyama, M., Ishii, K., Kitamura, S., Kimura, Y., Oda, K., Kawamura, K., Sasaki, T., Kobayashi, S., Katayama, Y., et al., Low density of sigma1 receptors in early Alzheimer's disease, Annals of nuclear medicine, 2008; 22(3): 151-156.

[137] Lee, D., Lee, K.S., Lee, J.Y., Kim, H., Huh, Y.H., Yu, K., Jung, H.Y., Lee, S.H., Lee, J.Y., Youn, Y.C., et al., Activation of PERK signaling attenuates Abeta-mediated ER stress, PLoS One, 2010; 5(5): e10489.

[138] Seyb, K.I., Ansar, S., Bean, J., and Michaelis, M.L., beta-Amyloid and endoplasmic reticulum stress responses in primary neurons: effects of drugs that interact with the cytoskeleton, J Mol Neurosci, 2006; 28(2): 111-123.

[139] Song, S., Lee, H., Kam, T.I., Tai, M.L., Lee, J.Y., Noh, J.Y., Shim, S.M., Seo, S.J., Kong, Y.Y., Nakagawa, T., et al., E2-K52/ Hip-2 regulates caspase-12 in ER stress-mediated Abeta neurotoxicity, J Cell Biol, 2008; 182(4): 675-684.

[140] Sato, N., Imaizumi, K., Manabe, T., Taniguchi, M., Hitomi, J., Katayama, T., Noh, J., Morihara, T., Yasuda, Y., Takagi, T., et al., Increased production of beta-amyloid and vulnerability to endoplasmic reticulum stress by an aberrant spliced form of Abeta, J Mol Neurosci, 2006; 28(2): 111-123.

[141] Katayama, T., Imaizumi, K., Honda, A., Yoneda, T., Kudo, T., et al., Disturbed activation of endoplasmic reticulum stress transducers by familial Alzheimer's disease-linked
Genesis of ER Stress in Huntington's Disease
expression in inducible mouse model unravels ubiquitin/proteasome system impairment and permanent recovery attributable to aggregate formation, J Neurosci, 2010; 30(10): 3675-3688.

[170] Bennett, E.J., Bence, N.F., Jayakumar, R., and Kopito, R.R., Global impairment of the ubiquitin-proteasome system by nuclear or cytoplasmic protein aggregates precedes inclusion body formation, Mol Cell, 2005; 17(3): 351-365.

[171] Landwehrmeyer, G.B., Dubois, B., de Yébenes, J.G., Kremer, B., Gaus, W., Kraus, P.H., Przuntek, H., Dib, M., Doble, A., Fischer, W., et al., Riluzole in Huntington's disease: a 3-year, randomized controlled study, Annals of neurology, 2007; 62(3): 262-272.

[172] Miller, J., Arrasate, M., Brooks, E., Libeu, C.P., Legleiter, J., Hatters, D., Curtis, J., Cheung, K., Krishnan, P., Mita, S., et al., Identifying polyglutamine protein species in situ that best predict neurodegeneration, Nature chemical biology, 2011; 7(12): 925-934.

[173] Kouroku, Y., Fujita, E., Jimbo, A., Kikuchi, T., Yamagata, T., Momoi, M.Y., Kominami, E., Kuida, K., Sakamaki, K., Yonehara, S., et al., Polyglutamine aggregates stimulate ER stress signals and caspase-12 activation, Hum Mol Genet, 2002; 11(13): 1505-1515.

[174] Nishitoh, H., Matsuzawa, A., Tobiume, K., Saegusa, K., Takeda, K., Inoue, K., Hori, S., Kakizuka, A., and Ichijo, H., ASK1 is essential for endoplasmic reticulum stress-induced neuronal cell death triggered by expanded polyglutamine repeats, Genes Dev, 2002; 16(11): 1345-1355.

[175] Ueda, M., Li, S., Itoh, M., Hayakawa-Yano, Y., Wang, M.X., Hayakawa, M., Hasebe-Matsubara, R., Ohta, K., Ohta, E., Mizuno, A., et al., Polyglutamine expansion disturbs the endoplasmic reticulum formation, leading to caspase-7 activation through Bax, Biochemical and biophysical research communications, 2014; 443(4): 1232-1238.

[176] Higo, T., Hamada, K., Hisatsune, C., Nakuma, N., Hashikawa, T., Hattori, M., Nakamura, T., and Mikoshiba, K., Mechanism of ER stress-induced brain damage by IP3 receptor, Neuron, 2010; 68(3): 865-878.

[177] Tang, T.S., Tu, H., Chan, E.Y., Maximov, A., Wang, Z., Wellington, C.L., Hayden, M.R., and Bezprozvanny, I., Huntington and huntingtin-associated protein 1 influence neuronal calcium signaling mediated by inositol(1,4,5) triphosphate receptor type 1, Neuron, 2003; 39(2): 227-239.

[178] Zhang, H., Li, Q., Graham, R.K., Slow, E., Hayden, M.R., and Bezprozvanny, I., Full length mutant huntingtin is required for altered Ca2+ signaling and apoptosis of striatal neurons in the YAC mouse model of Huntington's disease, Neurobiology of disease, 2008; 31(1): 80-88.

[179] Hamasaki, M., Furuta, N., Matsuda, A., Nezu, A., Yamamoto, A., Fujita, N., Oomori, H., Noda, T., Haraguchi, T., Hiraoka, Y., et al., Autophagosomes form at ER-mitochondria contact sites, Nature, 2013; 495(7441): 389-393.

[180] Miki, Y., Tanji, K., Mori, F., and Wakabayashi, K., Sigma-1 receptor is involved in degradation of intranuclear inclusions in a cellular model of Huntington's disease, Neurobiology of disease, 2015; 74: 25-31.

[181] Costa-Mattioli, M., Gobert, D., Stern, E., Gamache, K., Colina, R., Cuello, C., Sossin, W., Kaufman, R., Pelletier, J., Rosenblum, K., et al., elf2alpha phosphorylation bidirectionally regulates the switch from short- to long-term synaptic plasticity and memory, Cell, 2007; 129(1): 195-206.

[182] Sidrauski, C., Acosta-Alvear, D., Khoutorsky, A., Vedantham, P., Hearn, B.R., Li, H., Gamache, K., Gallagher, C.M., Ang, K.K., Wilson, C., et al., Pharmacological brake-release of mRNA translation enhances cognitive memory, Elife, 2013; 2: e00498.

[183] Godinho, B.M.D.C., Malhotra, M., O’Driscoll, C.M., and Cryan, J.F., Delivering a disease-modifying treatment for Huntington’s disease, Drug Discovery Today, 2015; 20(1): 50-64.

[184] Abrahay, I., Ehrnhofer, D.E., Shruste, A., Qiu, X., Franciosi, S., Hayden, M.R., and Offen, D., A Huntingtonin-based peptide inhibitor of caspase-6 provides protection from mutant Huntingtin-induced motor and behavioral deficits, Hum Mol Genet, 2015; 24(9): 2604-2614.

[185] Ferrante, R.J., Kubilus, J.K., Lee, J., Ryu, H., Breenes, A., Zucker, B., Smith, K., Kowall, N.W., Ratan, R.R., Luthi-Carter, R., et al., Histone deacetylase inhibition by sodium butyrate chemotheraphy ameliorates the neurodegenerative phenotype in Huntington’s disease mice, J Neurosci, 2003; 23(28): 9418-9427.

[186] Keene, C.D., Rodrigues, C.M., Eich, T., Chhabra, M.S., Steer, C.J., and Low, W.C., Tau-rods of a ball, is neuroprotective in a transgenic animal model of Huntington’s disease, Proc Natl Acad Sci U S A, 2002; 99(16): 10671-10676.

[187] Wei, H., Kim, S.J., Zhang, Z., Tsai, P.C., Wisniewski, K.E., Ferrante, R.J., Kubilus, J.K., Lee, J., Ryu, H., Beesen, A., Aharony, I., Ehrnhoefer, D.E., Shruster, A., Qiu, X., Franciosi, S., and Mukherjee, A.B., ER and oxidative stresses are common mediators of apoptosis in both neurodegenerative and non-neurodegenerative lysosomal storage disorders and are alleviated by chemical chaperones, Hum Mol Genet, 2008; 17(4): 469-477.

[188] Maurice, T., Urani, A., Pah, V.L., and Romieu, P., The interaction between neuroactive steroids and the sigma1 receptor function: behavioral consequences and therapeutic opportunities, Brain research reviews, 2001; 37(1-3): 116-132.

[189] Ruscher, K., Shamloo, M., Rickhag, M., Ladunga, I., Soriano, L., Gisselsson, L., Toresson, H., Ruslim-Litrus, L., Oksenberg, D., Urfer, R., et al., The sigma-1 receptor enhances brain plasticity and functional recovery after experimental stroke, Brain : a journal of neurology, 2011; 134(Pt 3): 732-746.

[190] Urfer, R., Moebius, H.J., Skoloudik, D., Santamarina, E., Sato, W., Mita, S., and Muir, K.W., Phase II trial of the Sigma-1 receptor agonist cutamessine (SA6503) for recovery enhancement after acute ischemic stroke, Stroke; a journal of cerebral circulation, 2014; 45(11): 3304-3310.

[191] Francardo, V., Bez, F., Wieloch, T., Nissbrandt, H., Ruscher, K., and Cenci, M.A., Pharmacological stimulation of sigma-1 receptors has neurorestorative effects in experimental Parkinsonism, Brain : a journal of neurology, 2014; 137(Pt 7): 1998-2014.

[192] Hyrskyluoto, A., Pulli, I., Tortqvist, K., Ho, T.H., Korhonen, L., and Lindholm, D., Sigma-1 receptor agonist PREG084 is protective against mutant huntingtin-induced cell degeneration: involvement of calpastatin and the NF-kappaB pathway, Cell Death Dis, 2013; 4: e646.