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Genesis of ER Stress in Huntington's Disease

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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

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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 slow 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 oligosaccharide is an essential requirement for 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 (EDEMs), [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: Ire1 α and β [89, 90], which in a similar splicing reaction remove an intron from the XBP-1 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]. Interestingtly, 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 Ero1a, 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 Ca^{2+} 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.

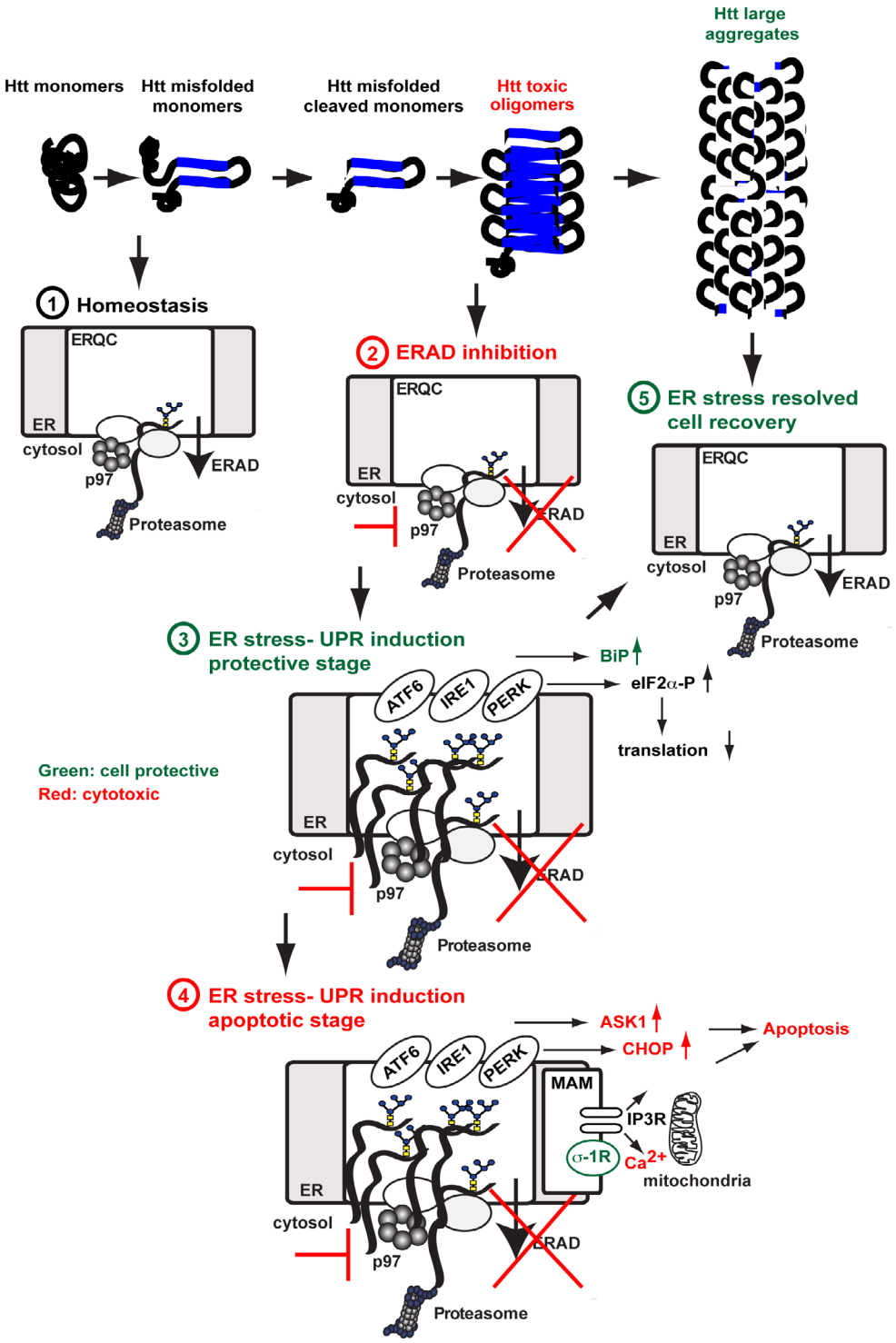

Figure 1: Model of mutant Htt aggregation and the genesis of ER stress and cytotoxicity. 1) The initial appearance of misfolded mutant Htt monomers, with exposed aggregation prone regions (blue) is initially compensated by chaperones and proteasomal degradation. 2) Misfolded monomer cleavage and association 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^{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 (EDEMs), ER-derived quality control compartment (ERQC), eukaryotic translation initiation factor 2 alpha (eIF-2α), 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).

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