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REVIEW ARTICLE

Quality Control in Huntington's Disease: a Therapeutic Target

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Abstract

Huntington's disease (HD) is a fatal autosomal dominantly inherited brain disease caused by excessively expanded CAG repeats in gene which encodes huntingtin protein. These abnormally encoded huntingtin proteins and their truncated fragments result in disruption of cellular quality mechanism ultimately triggering neuronal death. Despite great efforts, a potential causative agent leading to genetic mutation in *HTT*, manifesting the neurons more prone to oxidative stress, cellular inflammation, energy depletion and apoptotic death, has not been established yet. Current scenario concentrates on symptomatic pathologies to improvise the disease progression and to better the survival. Most of the therapeutic developments have been converged to rescue the protein homeostasis. In HD, abnormal expansion of glutamine repeats in the protein huntingtin leads to toxic aggregation of huntingtin which in turn impairs the quality control mechanism of cells through damaging the machineries involved in removal of aggregated abnormal protein. Therapeutic approaches to improve the efficiency of aggregate clearance through quality control mechanisms involve protein folding machineries such as chaperones and protein degradation machineries such as proteasome and autophagy. Also, to reduce protein aggregation by enhancing proper folding, to degrade and eliminate the aggregates are suggested to negatively regulate the HD progression associated with the disruption of protein homeostasis. This review focuses on the collection of therapeutic strategies targeting enhancement of protein quality control activity to delay the HD pathogenesis.

Keywords Huntington's disease · Autophagy · Cellular quality control · Proteasome

Introduction

Huntington's disease (HD) is a lethal dominantly inheritable progressive disease of central nervous system (CNS). HD was first described in 1872 by George Huntington (Stevenson 1934) and longitudinally observed in many generations of a family in East Hampton on Long Island by George Lee Huntington and Abel Huntington. Latest census of HD

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prevalence from 2009 reflects the variation across the ethnicity and geographical differences. The centres of origin are supposed to be in Northern European countries (Messer 2005), so it is obvious that highest prevalence is reported in these countries (Warby et al. 2009). In European countries, around 4–5 persons per 100,000 are estimated to be affected with HD (Quarrell et al. 1988; Simpson and Johnston 1989; Harper 1992; Barbeau et al. 1964). In Canada, this number is around 2.4–8.0 persons per 100,000. The proportion of people living with HD recorded in UK is around 1/8000 (Shokeir 1975; Chandler et al. 2012). On other side, the average prevalence of HD in Asian countries is much lower than that in European countries which is about 0.40/100,000 (Pringsheim et al. 2012). Current medicinal approaches majorly focus symptomatic management along with uplift the quality of life which includes medications to reduce difficulties in daily life.

HD progressively damages cells of the brain predominantly in basal nuclei and cerebral cortex. Onset of HD covers a broad range of age groups. Prevalence can be observed in people as young as 5–10 years and also in people as old as above 80 years. More than half of the HD cases have been found in the patients with age of 35–55 years. Briefly abrupt, irregular, unpredictable, non-stereotyped movements (choreiform movement) are the most common behavioural characteristics of HD which can be seen as an early sign of HD onset. Clinically, chorea is mostly developed in conjugation with uncontrolled muscular actions (dystonia), sluggish locomotion (bradykinesia) and many other abnormalities in motor coordination. Behavioural symptoms may include altered personality, lack of proper attention, stiffness in mental sets and irritability, aggression, apathy, depression and higher suicidal tendency. Cognitive deficits observed often even in premanifest period evolve into subcortical dementia in later HD stages (Killoran et al. 2013; Zielonka et al. 2018).

One of the main causative agents is *huntingtin* (*HTT*) gene which was identified in 1993 and is located on chromosome 4p16.3. This disease is connected with an unstable expansion of a CAG triplet repeat encoding polymer of glutamine residues (polyQ) in exon 1 of *HTT* gene. The normal *HTT* allele also contains 6–35 repeats of CAG triplet. The number of CAG repeats exceeding 40 is abnormal and highly penetrant in population. A gene with 36–39 CAG repeats is considered to have comparatively less penetrance. Although 27–35 CAG repeats are in the normal range, they are unstable alleles and may get more or less in number in next generation (The American College of Medical Genetics/American Society of Human Genetics Huntington Disease Genetic Testing Working Group 1998). The number of CAG repeats in *HTT* plays a crucial role in HD phenotype. Generally, the number of CAG repeats in the expanded allele is the deciding factor for the age of HD onset and accounts approximately 65–70% of the variation of age of onset (Duyao et al. 1993). A number of CAG repeats are inversely proportional to the age of onset (Lee et al. 2012b; Jiang et al. 2014). Serial MRI imaging information suggests that the Htt protein is widely expressed and is distributed almost evenly throughout the brain (Klöppel et al. 2009). Remarkable structural deformities can be observed in the striatum, especially in the caudate and putamen in early age even before the onset of cognitive and motor deficits (Harris et al. 1992). Pathologically, GABAergic medium-sized spiny neurons are poorly affected in these brain regions (Mitchell et al. 1999). This selective cellular damage is basically the result of disrupted energy metabolism, enhanced excitotoxicity and mutant htt (mHtt) induced cytotoxicity (Lin and Beal 2006). Some other brain regions are also affected in this disease like cerebral cortex (mainly layers III, V and VI), hippocampus, thalamus, globus pallidus, subthalamic nucleus, substantia nigra, white matter and cerebellum (Walker 2013; Vonsattel 2008). Localization study revealed the cytoplasmic and nuclear accumulation of wild-type and mHtt respectively, especially as N-terminal truncation fragments found in this disease (DiFiglia et al. 1995; DiFiglia et al. 1997; Davies et al. 1997; Becher et al. 1998; Van Raamsdonk et al. 2005; Landles et al. 2010). To explore the HD pathogenesis, several models have been established; *Caenorhabditis elegans* (worm), *Drosophila* (fruit fly) and *Danio rerio* (zebrafish) expressing htt have now been widely used to model polyglutamine toxicity (Faber et al. 1999; Parker et al. 2002; Gunawardena et al. 2003; Miller 2005; Marsh and Thompson 2006). Recently, mouse model was effectively used for modelling polyglutamine toxicity (Cardinale et al. 2018; Giampa' et al. 2013; Leuti et al. 2012; Fusco et al. 2012). These models recapitulate many pathological features of HD like progressive neuronal cell death, reduced lifespan, aggregation of Htt and formation of nuclear inclusions. These models are mostly exploited to explore the pathways leading HD and the screening of potential therapeutic target for HD pathology. Until now, we do not have any well-known chemical and genetic modifiers that can effectively modulate HD pathogenesis.

Like other neurodegenerative diseases, HD is also characterized by impaired mechanism for protein quality control. Inefficient clearance of aggregated proteins disrupts the numerous biochemical pathways playing the integral role in maintaining protein homeostasis. Neurons are post-mitotic cell which require consistent functional quality control system to maintain proteostasis. Data from HD patients and several experimental models indicate that the accumulation and aggregation of mHtt are linked with a dysfunctional proteostasis network (Sieradzan et al. 1999). Understanding the mechanism that leads to aggregation and proteostasis disruption by damaging protein quality control and degradation pathways widens the therapeutic approaches. The functional coordination among several machineries involved in protein synthesis, protein folding and refolding, misfolding and aggregation, trafficking and degradation maintain the balanced cellular

proteins pool (Labbadia and Morimoto 2015). In recent years, the mortality rate from HD has increased and researchers have put enormous effort to solve the mystery about the pathogenesis and therapeutic option for HD. In this review, we have focused on how quality control of protein homeostasis might provide a novel therapeutic way in the treatment of HD. Various pathways like ubiquitin proteasomal system, autophagic pathways, NF-κB/pAkt1 and Akt/Erk along with immunomodulatory pathway have been discussed sequentially in this review. These vital therapeutic targets can be utilized by clinician in the treatment of this disease.

Therapeutic Strategies in HD

Protein misfolding and aggregation induce the several pathways involved in its clearance such as involvement of chaperones, proteasomal degradation system and autophagy (Hipp et al. 2014). Molecular chaperones are the large group of proteins which stabilize the unfolded protein, unfold the misfolded protein and correct them (Hartl et al. 2011; Nillegoda et al. 2018). Many classes of chaperones function in cooperative manner. Members of chaperone families are known as stress proteins or heat shock proteins. These proteins are upregulated under the stress condition. The chaperones majorly contributing in protein unfolding and refolding are Hsp90, Hsp70 and chaperonins (Hsp60) which act together in a multiprotein complex and form proteostasis network (Pratt et al. 2014). When aggregated proteins bypass the chaperone control, they are usually targeted for degradation, either through the ubiquitin-proteasome system (UPS) or by autophagy (Hipp et al. 2014). The UPS is the main route of protein degradation in mammalian cells, acting in both cytoplasm and nucleus, whereas autophagy functions mainly in the cytoplasm (Li and Li 2011; Hipp et al. 2014).

The UPS is a complex mechanism which prepares the misfolded protein for degradation through ubiquitinylation, a process which is catalysed by a triple enzymatic cascade, involving an E1ubiquitin activating enzyme, an E2 conjugating enzyme and an E3 ligase (Dantuma and Bott 2014); finally, ubiquitylated proteins are proteolysed by the proteasome (McKinnon and Tabrizi 2014). Polyubiquitylated proteins are recognized by the 26S proteasome. The 26S proteasome is an ATP-dependent proteolytic complex constituted by one or two 19S regulatory particles and a 20S core particle. The regulatory particle recognizes deubiquitinates and unfolds the substrate, which is then translocated to the cavity of the core particle, where multiple catalytic sites mediate its degradation (Li and Li 2011; McKinnon and Tabrizi 2014; VerPlank and Goldberg 2017). Autophagy is another pathway for the clearance of cytosolic substrates converging on liposomal degradation and is broadly categorized as micro-, macro- and chaperone-mediated autophagy (CMA) (Cortes and Spada 2014). In micro-autophagy, cytosolic components are directly engulfed by the lysosome (Shpilka and Elazar 2011). In CMA, soluble proteins are directly translocated into the lysosome after recognition of a KFERQ-like motif by the molecular chaperone Hsc70. In macro-autophagy (hereafter referred to as autophagy), cytosolic substrates are engulfed by a double membrane structure, the autophagosome, which subsequently fuses with lysosomes (Cortes and Spada 2014). A more recent concept is that of selective autophagy, meaning the selective degradation of substrates recognized by specific autophagic receptors, such as p62 (Menzies et al. 2015; Wong and Holzbaur 2015).

The nuclear or perinuclear inclusion bodies consisted of aggregated mHtt resides at the core of HD pathogenesis. How do these inclusion bodies form and impact on HD pathology is still unclear (Margulis and Finkbeiner 2014). Several groups of investigators have uncovered that inclusion bodies are prominently observable in HD affected brains; mostly, cortical and striatal brain areas seemed to have more and bigger sized inclusion bodies (DiFiglia et al. 1997). Some compounds like trehalose and many other are supposed to reduce number and size of polyQ inclusion bodies in HD mouse brains and also improve behavioural and cognitive abnormalities. Suppression of aggregates clearly reflects the toxicity mediated by inclusion bodies (Katsuno et al. 2004; Tanaka et al. 2004). In early stage, polyQ is reported to be in defused form, but over time, diffused polyQ converts into aggregated form (inclusion bodies) which in turn reduces the concentration of diffused polyQ. Interestingly, conversion into inclusion bodies seemed to recover UPS functions in cellular models of HD (Arrasate et al. 2004; Mitra et al. 2009). Like many other aggregates, polyQ inclusions are also immunoreactive with antibodies detecting ubiquitin, which reflects the ubiquitinylation and degradation of UPS system (Davies et al. 1997). Jana et al. have shown the co-localization of UPS machineries like Ube3a, a ubiquitin E3 ligase with inclusion bodies in cellular model of polyQ aggregation and also knocking Ube3a in R6/2 mice enhance the aggregate loads and deteriorates the symptomatic behaviours (Maheshwari et al. 2014a). Same group in other studies has also reported that elevation in Ube3a reduced the polyQ bodies and improved life span and motor functions in transgenic mouse models (Menzies et al. 2011). All these studies revealed the relationship between protein aggregation and UPS functions. A series of studies have tried to explain the mechanism underlying the accumulation of Ub with polyQ inclusion bodies. The most prominent models explain the involvement of cellular quality control system in the disease. It was suggested that diffused polyQ interacts to protein folding machineries such as several chaperones and saturate them. Excess misfolded polyQ are targeted to ubiquitinylation machineries which then divert to the UPS. Excessive ubiquitylated and misfolded polyQ adversely impact on proteasome and leads in its dysfunction

(Bersuker et al. 2016). PolyQ aggregates in some studies have shown interaction with wide range of cellular proteins involved in protein homeostasis and disrupt their proper functions (Gasset-Rosa et al. 2017). A latest report has suggested that polyQ aggregates perturb the nuclear transport and accumulation of nuclear mRNA that can be seen in several brain areas of R6/2 mice (Gasset-Rosa et al. 2017). The crucial component of protein misfolded machineries Hsp40 chaperones, which interact with the diffused polyQ and insoluble polyQ and target them to proteasome for degradation, is found deficient on over expressing mHtt yeast (Park et al. 2013) and in HD patient brain as well (Seidel et al. 2016). Also, one of the major molecular chaperones, HSC70 (heat shock cognate protein 70), which is supposed to be involved in clearance of aggregated proteins and required for clathrin mediated endocytosis, is perturbed in cellular model of HD (Yu et al. 2014). In most of the cases, toxic aggregation of polyQ disrupts various sub-cellular structures such as endoplasmic reticulum (Bäuerlein et al. 2017) along with the nuclear structures (Gasset-Rosa et al. 2017). Interfering with ER and nuclear membrane, polyQ aggregates obstruct protein trafficking (Chang et al. 2006). Sub-cellular distributions of polyQ aggregates also have been reported to modulate the ribosome quality control machineries (RQC) which are also implicated in many neurodegenerative diseases, deplete many key components and promote the formation of nuclear polyQ aggregates. Same study has shown that knocking LTN1 and RQC1out enhances nuclear aggregates. These studies suggest the involvement of RQC in polyQ aggregate localization toxicity (Zheng et al. 2017). A study in yeast suggested that Ltn1, which is ubiquitin E3 ligase and a key factor in polyQ aggregation, ubiquitinylation and detoxification in HD models of study, is found impaired with formation of multiple polyQ aggregates rather than a single large aggregate. Moreover, multiple small polyQ aggregates are more toxic to cells and alter the cytoskeletal proteins such as actin (Yang et al. 2016). Though these studies suggested the contribution of RQC in polyQ aggregation and its toxicity, further study revealing the mechanism behind this is essentially needed. Emerging studies have suggested that polyQ aggregation plays a role in two ways, either being protective or by enhancing toxic effects. It is supposed that cells which express diffused mHtt extensively are more likely to go through apoptotic death, but those cells, which form polyQ aggregates and have decreased levels of diffused mHtt, are believed to convert into a quiescent state as the inclusion bodies also sequester other crucial proteins. While this process may extend survival, it also gradually disrupts cellular homeostasis and leads to cellular dysfunctions (Ramdzan et al. 2017).

HTT is an important regulator of autophagy. Autophagy is an important biological process that contributes in clearance of dead organelles, toxic and aggregated proteins. In many neurodegenerative diseases, disruptions in autophagy and accumulations of toxic autophagic cells are thought to contribute to the pathogenesis (Menzies et al. 2011; Martin et al. 2015). However, studies in human and rodents have displayed increased number of autophagosome to maintain the proteostasis (Kegel et al. 2000; Petersen 2002; Martinez-Vicente et al. 2010). mHTT has been reported to activate autophagic pathways in cell, mouse and human tissues (Ravikumar et al. 2004). Despite enhanced autophagy, aggregated proteins and dead organelles are not degraded. Such mechanistic defects in autophagic process lead to negative feedback loop and cause further accumulation of aggregated proteins. The impact of mHtt on the autophagic pathway is multiple and pleiotropic. For example, mHtt interferes with processes such as autophagosomal dynamics and initiation of autophagy (Martin et al. 2015). Mechanistic problem in the autophagic pathways in HD is further aggravated when mHtt damage the movement of autophagosome and prevents the fusion of autophagosome with lysosome (Wong and Holzbaur 2014). Overall, mHtt may disturb or fail to mimic the physiological roles of wild-type Htt (wHtt) in regulating autophagosomal transport (Wong and Holzbaur 2014), autophagosomal cargo loading, or the activity and levels of key initiators of the autophagy pathway, such as ULK1 and Beclin-1 (Rui et al. 2015; Wold et al. 2016; Ashkenazi et al. 2017).

To maintain the cellular homeostasis, continuous turnover of intracellular proteins and other components is essential. Data from HD cell models revealed that recognition and trafficking of cytosolic cargo containing autophagosomes are impaired due to mHtt (Martinez-Vicente et al. 2010). Although the reason behind how mHtt impairs ability to recognize cargo of autophagosome is still elusive, some studies suggested that mHtt interacts with p62 in abnormal manner and is supposed to fail proper engulfment of cargoes. mHtt is also associated with various cellular organelle membranes (Atwal et al. 2007). Htt interacts with the autophagy adaptor p62, affecting its affinity for substrates and for LC3, and it also interacts with and modulates the activation of ULK1—a regulatory kinase involved in autophagy activation. Htt may thus act as a scaffold that brings together the machinery required for cargo recognition and initiation of autophagy (Rui et al. 2015). Supporting this hypothesis, an independent study showed a reduced activity of ULK1 and Vsp34 kinases in HD cellular and animal models (Wold et al. 2016; Antonioli et al. 2017). Some other studies in neurons have shown that mHtt impairs the autophagosomal transport regulation exerted by wHtt and its associated protein HAP-1. In neurons, mHtt damages the axonal transport of autophagosomes and does not change the formation and loading of cargo, but reduces the fusion between autophagosome and lysosome which leads to abnormal acidification and thus degradation of cargoes (Wong and Holzbaur 2014). Beclin-1, a key modulator of autophagy, is also reported to be reduced in HD patient fibroblast cells. The

mechanistic studies have revealed that mHtt competitively inhibits a deubiquitinase enzyme called ataxin-3 for binding with beclin-1, and thus, degradation of beclin-1 through UPS increases due to enhanced ubiquitinylation. Reduced beclin-1 impairs autophagy (Ashkenazi et al. 2017). Dysfunction in the initiation of autophagy was also attributed to the loss in mHtt of a physiological function of wHtt in selective autophagy (Rui et al. 2015).

A study by Ochaba et al. supports the idea that Htt acts as an autophagy-promoting scaffold. They have shown that there is high similarity between Htt and the autophagy scaffold protein Atg11 that mediates selective autophagy in yeast (Ochaba et al. 2014). A HD model mouse with deleted polyQ expansions showed improved neuronal autophagic activity which suggested that expression of expanded polyQ impairs the function of mHtt as an autophagy-promoting scaffold (Zheng et al. 2010), further suggesting that polyQ expansion in Htt disrupts its physiological role as an autophagy-promoting scaffold. Progressive loss of neuronal selective autophagy with age may increase the accumulation of protein aggregates, disruption of mitochondrial function, inflammation that are pathological features of HD and other polyQ diseases, as well as diseases such as Alzheimer's and Parkinson's diseases, frontotemporal dementia and amyotrophic lateral sclerosis.

In HD pathogenesis, motor symptoms play very important role; additionally, these motor symptoms generally influence function of female independently than males. Thus, targeting symptomatic motor symptoms is very vital in improving the HD function and quality of life in patients (Zielonka et al. 2018).

HDAC4 can also be targeted for the HD pharmacotherapy (Mielcarek et al. 2015). Last but not the least, therapeutic strategy targeting small molecules like nucleotides also provide an ultimate option for the HD treatment (Toczek et al. 2016).

Therapeutic Strategies Targeting Molecular Chaperones

Molecular chaperones are central machineries of proteostasis as they correct the protein misfolding and re-fold damaged peptides. Activation of chaperonic pathways is a primary defence mechanism that safeguards the cells from cellular stress caused by abnormal protein folding. A wide range of chaperones are reported to be reduced in HD mice brains (Yamanaka et al. 2008; Neueder et al. 2017). The levels of heat shock factor 1 (Hsf1), a key activator of the heat shock response (Anckar and Sistonen 2011), are decreased in mouse and human HD brains (Gomez-Pastor et al. 2017). The activation of HSF1 is a complex process and is not properly known. Various post-translational modifications are suggested including modulating the activity of HSF1 (Xu et al. 2012) such as acetylation (Westerheide et al. 2009), sumoylation (Westerheide et al. 2009) and hyperphosphorylation (Velichko et al. 2013). Singh et al. reported that azadiradione, a phytoextract from *Azadirachta indica*, induces the activation of HSF1 and reduces the polyQ aggregates in R6/2 mice model of HD (Singh et al. 2018). Another approach targets prevention of the degradation of HSF1 with the CK2 kinase inhibitors TID43 or emodin (Gomez-Pastor et al. 2017). Activation or suppression of particular chaperone is also a potential strategy in HD (Pratt et al. 2014; Reis et al. 2017). Overexpression of the carboxyl-terminus of HSC70-interacting protein (CHIP), which is a co-chaperone, increases the degradation of HSP90. HSP90 acts in final folding stage of proteins. It stabilizes aggregated polyQ and prevents them from UPS-mediated degradation. So, inhibition of HSP90 facilitates the recruitment of UPS components. Another chaperone known as Hsp70 works in early stage of protein folding which either corrects the folding or promotes the degradation of aggregated proteins. HSP90 and Hsp90 function in mutated Htt triage (Karagöz and Rüdiger 2015; Gomez-Pastor et al. 2017). Another idea behind involvement of Hsp90 is that some researches revealed the HSP90-assisted recruitment of Usp19, which is a deubiquitinase, to mutated Htt resulting in its accumulation and aggregation (He et al. 2017). NVP-AUY992, a HSP90 inhibitor, is found potent to increase mHtt degradation through UPS by inhibiting the formation of the Hsp90-mHtt complex, promoting the availability of mHtt for ubiquitinylation and its degradation (Baldo et al. 2012). Another pathway through which Hsp90 inhibition can also elicit the heat shock response is the dissociation of the complex Hsf1-Hsp90. Hsf1 is bound with HSP90 in inactivated form. Dissociation from the HSP90 complex enables phosphorylation and its activation which in turn increases the expression of many other chaperones to either correct mHtt conformation or target it for degradation (Jackrel and Shorter 2011). Accordingly, treatment with HSP990, a Hsp90 inhibitor, increased the levels of Hsp70 and Hsp40 and transiently ameliorated motor performance and decreased mHtt aggregate load in R6/2 mice (Labbadia et al. 2011). Previously discussed, phytocompound azadiradione also uplifts the activity of HSF1. Vinod et al. reported in their study in cellular and *Drosophila* models of HD that azadiradione activates HSF1 and increases the expression of HSP70 which results in reduced polyQ aggregate and rescue of ommatidia morphology in *Drosophila* eyes (Nelson et al. 2016). A wide range of studies on phytocompounds revealed that several compounds such as curcumin, withaferin-A, celastrol and gambogic acid potentially activate the many HSPs (Zhang and Sarge 2007; Davenport et al. 2011). Treatment of curcumin to knock-in mouse model of HD have shown the reduced HD pathology and increased motor functions (Bercovich et al. 1997; Ho et al. 2005). Some polyphenols, for example, (−) epigallocatechin gallate (EGCG) in green tea (Ehrnhoefer et al. 2008), may

elicit the similar mechanisms of action. EGCG binds to aggregates and disintegrates them which seem to be an indication of alteration in the heat shock response. In fact, similar to curcumin in other cell models, EGCG has been shown that it binds to HSP90 and impairs its association with other co-chaperones which indicate the degradation of HSP90 and activation of HSP70 (Palermo et al. 2005; Li et al. 2009). A group of Indian researchers conjugated the EGCG to nanoparticle to enhance its delivery in mouse brain. Their studies have shown that this approach increases the multifold in EGCG delivery in brain which in turn decreases aggregate load in R6/2 mouse brain (Debnath et al. 2016). Still, there is long way to go in field of discovery of the small molecules which can efficiently penetrate the blood brain barrier and potentially activate molecular chaperones that might be targeted for therapeutic approach. A detailed involvement of HSF1 in proteostasis is given in Fig. 1.

Therapeutic Strategies Targeting UPS

The UPS is major machinery which degrades the abnormal proteins. Large numbers of studies have established that the UPS is impaired in HD which was monitored using different technologies to label polyglutamine aggregates with antibodies raised against ubiquitin and proteasome subunits in cellular models (Cummings et al. 1998; Wyttenbach et al. 2000), HD mouse model (Davies et al. 1997) and also in human post-mortem brain samples (DiFiglia et al. 1997). Impairment of the UPS in HD has been reported to elevate the inefficiency to target soluble mHtt for proteasomal degradation and accumulation within cells as inclusion bodies. Overexpression of activated domain PA28γ of proteasome enhances the viability of mHtt expressing striatal neurons when exposed to pathological stresses like MG132 which is proteasome inhibitor (Seo et al. 2007). Studies in YAC128 suggested that overexpression of PA28γ reduced the HD pathologies (Jeon et al. 2016), whereas studies in *C. elegans* showed that overexpression of pbs-5 catalytic subunit of proteasome increased survival under proteotoxic stress and also improved motor phenotypes (Chondrogianni et al. 2015). In another strategy to promote ubiquitinylation, people targeted ubiquitinases such as Rpn11, Uch37 and Usp14. Uch37 and Usp14 may directly interact to polyubiquitine chain and shorten them. Utilizing this idea, some studies have shown that suppression of Usp14 using its inhibitor IU1 decreased the polyQ aggregates associated

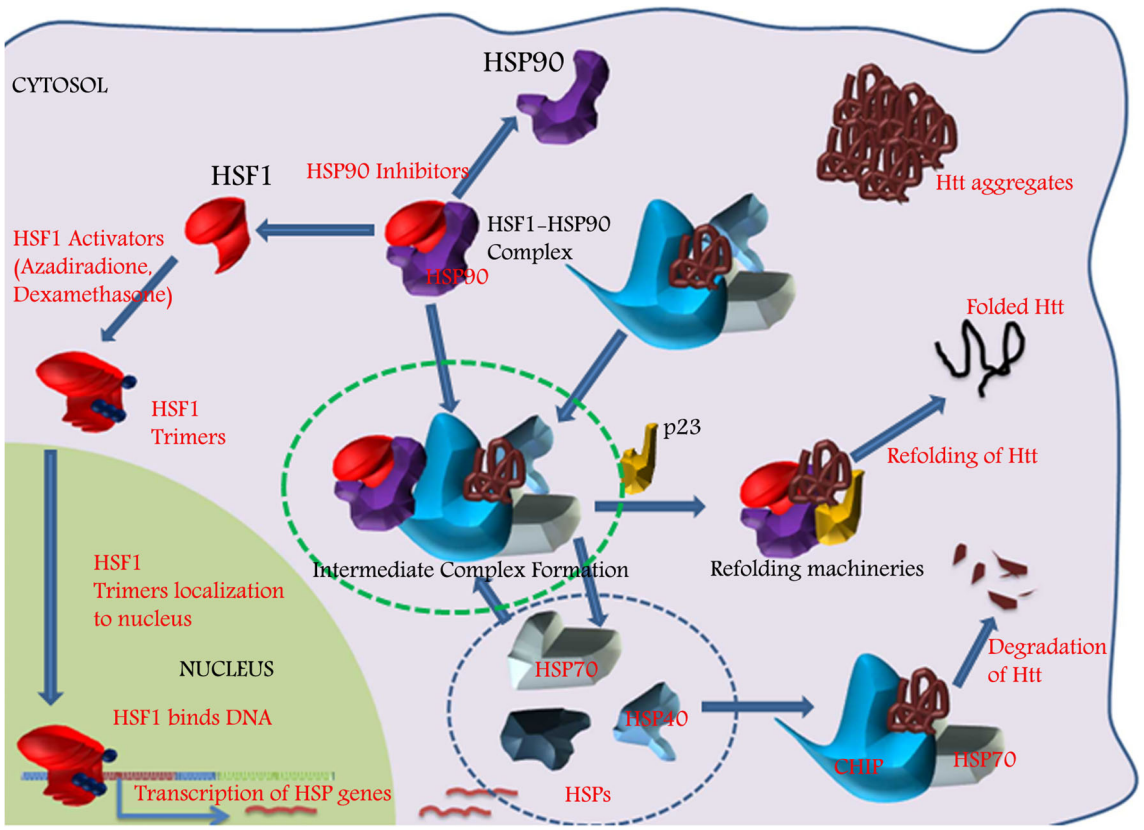

Fig. 1 Involvement of HSF1 in proteostasis. Aggregation-induced toxicity dissociates HSP90-HSF1 complexes which in turn leads phosphorylation of HSF1 and its trimerization. Trimerized HSF1 translocates in to nucleus and upregulates the expression of HSP genes. Co-chaperone CHIP along with HSP70 interacts with mHtt and promotes its degradation through proteasome. HSF1 bound to HSP90 also form intermediate complex which either initiates refolding of misfolded proteins or directs them to degradations

with disease pathologies (Lee et al. 2010; McKinnon et al. 2016). Immature deubiquitination allows aggregated protein to escape UPS-mediated degradation, while overexpression of Usp14, which leads to mature deubiquitination, makes the aggregates more available to proteasome degradation (Hyrskyluoto et al. 2014). Some other studies have also explored the impact of overexpression of Usp14 on ER stress and found that Usp14 inhibits IRE1α phosphorylation, which in turn prevents mHtt from inducing the ER stress pathway that may impair autophagy and promote mHtt accumulation (Lee et al. 2012a; Hyrskyluoto et al. 2014).

Post-translational covalent addition of ubiquitin residues to the substrate is to be degraded, i.e. ubiquitinylation residues at the core of UPS-mediated proteostasis (Li and Ye 2008). Ubiquitinylation is the process in which ubiquitin is added to the substrate lysine by a three-enzyme cascade comprised of an ubiquitin activating enzyme (E1), a ubiquitin-conjugating enzyme (E2) and an ubiquitin ligase (E3). E3 ligases are believed to be involved in substrate recognition. Several E3 ligases have been reported to be involved in HTT ubiquitinylation, including WWP (Garbaccio and Parmee 2016), UBE3A (Bhat et al. 2014), HACE (Bové et al. 2011), CHIP (Jana et al. 2005), Hrd (Bunnage et al. 2013) and Parkin (Rubio et al. 2009) in mammals. In a study in R6/2 mice, knocking out Ube3a enhanced the aggregate load in mouse brain (Maheshwari et al. 2014b). In another study, topotecan induced expression of Ube3a in mice which reduced aggregate load and improved motor functions (Shekhar et al. 2017). Another E3 ligase known as UBR5 is also suggested to be involved in proteostasis in iPSCs. Deficiency of UBR5 increases the polyQ-expanded aggregation and neurotoxicity in invertebrate models. Interestingly, overexpression of UBR5 promotes ubiquitination and degradation of mutated Htt and reduces polyQ aggregates in HD-cell models (Koyuncu et al. 2018). Following the overexpression strategy, overexpression of NUB1 (negative regulator of ubiquitin-like protein 1), which recruits ubiquitin E3 ligases, enhances the ubiquitination and reduces aggregate toxicity in drosophila (Aron et al. 2013; Lu et al. 2013). Some researchers aimed on ubiquitin-2 which is proteasomal shuttle and cooperates with the Hsp70-Hsp110 disaggregated machinery and mediates the delivery of Hsp70-bound mutated Htt to the proteasome for degradation (Hjerpe et al. 2016).

UPS-mediated decrease in aggregate load and cellular toxicity is a potential therapeutic approach which deteriorates the HD pathology. While genetic modifiers have been the predominant approach to modulate the UPS, pharmacological approaches and also better strategies to deliver in brains are likely to increase with the recent development of chemical modulators of the UPS pathway (Collins et al. 2017; Leestemaker et al. 2017; Khan and Nelson 2018). Mechanism of action of involvement of UPS in proteostasis is given in Fig. 2.

Therapeutic Strategies Targeting Autophagy

Autophagy is a synonym of self-eating. This process is tightly regulated and dependent on various cellular factors such as cellular energy status and nutrient supply along with the availability of growth factors. Autophagy induction may occur via one of the two pathways: one is mediated by ULK1 (unc51-like autophagy activating kinase 1), and another is the PI3KC3–C1 (class III phosphatidylinositol 3-kinase complex I) lipid kinase complex. ULK1 activity is driven by two major upstream kinases—mTORC1 (mammalian target of rapamycin—mTOR, complex 1) and AMPK (AMP-activated kinase) (Hurley and Young 2017). Under normal conditions, ULK1 is phosphorylated by mTOR at Ser-757 and is kept inactivated which suppresses autophagosome formation. On the other hand, when condition generates stress, AMPK phosphorylates at Ser-317 and Ser-777 and activates ULK1. Indirectly, inhibition of mTORC1 also activates ULK1 (Kim et al. 2011). Regulating the activation and deactivation of ULK1 provides the clues about the modulation of autophagy. The most extensively studied strategies have focused to target pharmacological modulation of mTORC1 and AMPK to regulate autophagy in HD models (Vingtdeux et al. 2010; Crino 2016).

Some contradictory studies have also shown that inhibition of mTORC1 may have positive impact on HD, but in recent years, studies in post-mortem brain tissue have reported that activity of mTORC1 is reduced in the striatum of HD patient which suggests that the restoration of mTORC1 activity might improve brain pathology in HD (Lee et al. 2015). Mostly, mTORC1 activity does not promote autophagic induction, but to maintain homeostasis, a basal level of autophagy is important for cellular function and survival. At least, basal autophagic activity is critical for clearance of aggregate formation in HD. Further study on HD mice suggests that the basal level of autophagy in wild-type mice is lower than that in HD mice. Same group of researchers has also shown that Rheb (Ras homologue enriched in brain, which is activator of mTORC1) increases the induction of autophagy and depletes mHtt aggregate pathology (Lee et al. 2015). They have also shown that exogenous expression of Rhes (Ras homologue enriched in striatum) rescued the disease phenotypes in HD mice (Lee et al. 2015). Taken as a whole, the exact role of mTORC1 activity is not properly known.

Apart from the regulation of autophagy through mTORC1, various mTORC1-indepndent pathways of autophagy are amenable to aggregate clearance. Pharmacological activation or expression of active AMPK induces autophagy in an mTOR-independent manner, reduced mHtt aggregates and improved cell viability (Walter et al. 2016). Tsvetkov et al. proposed that 10-[4′-(*N*-diethylamino)butyl]-2-chlorophenoxazine (10-NCP) which is an Akt inhibitor decreases the mHtt aggregates in HD mice striatum and reduces the striatal neuronal death

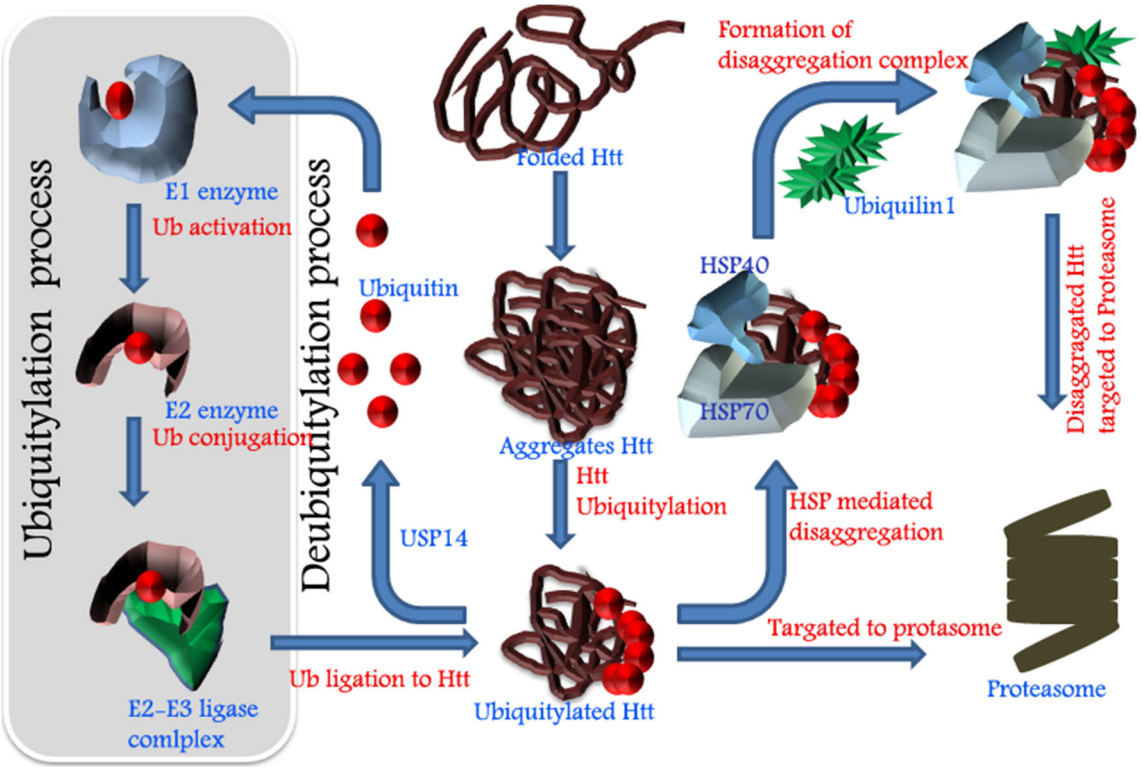

Fig. 2 Involvement of UPS in proteostasis. UPS functions are based on dynamic balance between ubiquitinylation and deubiquitylation of wide range of proteins. Ubiquitinylation of targeted protein involves three enzymes—E1 (Ubiquitin activating enzyme), E2 (conjugating enzyme) and E3 (ubiquitin ligase). E3 ligases add 8–10 ubiquitin molecules to lysine residues which signal for degradation. Ubiquitylated aggregated/misfolded proteins are targeted to proteasome for degradation. Some HSPs like HSP40 and HSP70 also interact to ubiquitylated protein to disaggregate into small pieces that finally target to proteasome. On other side, deubiquitylating enzymes like USP14 remove ubiquitin to prevent protein from degradation

(Tsvetkov et al. 2010). In another study, researchers suggested that pharmacologically enhanced autophagic activity by tubastatin A which suppresses the alpha-tubulin deacetylase HDAC6 decreased the aggregated mutated Htt levels in striatal neurons (Guedes-Dias et al. 2015).

Modulating the mTORC1 independent pathway has shown promising results in reducing HD pathogenesis. Despite this, there is another direct target which modulates autophagy more directly which is autophagy initiation complex ULK1. ULK1 and vsp34 lipid kinase are two major key regulators of autophagy. ULK1 phosphorylates ATG14 which regulates ATG14-Vps34 lipid kinase activity to control autophagy. It has been reported that ATG14-associated Vps34 activity and ULK1-mediated phosphorylation of ATG14 and Beclin 1 are compromised in the Q175 HD mouse model. These findings suggested that reduced phosphorylation of Beclin-1 and Atg14 is caused by shifting of ULK1 towards aggregated proteins (Wold et al. 2016). On the other hand, overexpression of ULK1 increased the clearance of mHtt aggregates in HD cell models (Wold et al. 2016). Modulation of ULK1 activity through activators (Zhang et al. 2017) and inhibitors (Egan et al. 2015; Lazarus and Shokat 2015; Lazarus et al. 2015; Petherick et al. 2015) might be a direct approach to pharmaceutically induced activation of autophagy. Some proposed small molecule activators, like LYN-1604, may be the best candidate for an ULK1 agonist which can be activated by some three amino residues such as LYS-50, LEU-53 and TYR-89 (Zhang et al. 2017). SBI-0206965, MRT67307 and MRT68921 are reported as potent inhibitor of ULK1 (Egan et al. 2015; Lazarus and Shokat 2015; Lazarus et al. 2015; Petherick et al. 2015).

Finally, available evidence has revealed that clearance of mHtt aggregate may also be regulated by chaperone-mediated autophagy (CMA) (Thompson et al. 2009; Bauer et al. 2010; Koga et al. 2011; Qi et al. 2012). Modulation of retinoic acid–mediated pathways gives insight into activator of this pathway which plays a significant role in CMA. Activator or inhibitor of CMA may downregulate or upregulate autophagy, respectively (143). Many threads of evidences have shown that autophagy and CMA decline with age in degenerative diseases (Kaushik and Cuervo 2015). Rescuing the CMA could be possible approach for strategies to modulate the Htt proteostasis network in HD. It has been widely demonstrated that natural bioactive molecules (such as polyphenols) and other anti-oxidant molecules can play an important role in the modulation of autophagic pathways in HD (Vidoni et al. 2017; Vidoni et al. 2016; Squillaro et al. 2018). Similar to Parkinson's disease (PD), mitophagy and chaperone-

mediated autophagy (CMA) can also be targeted for HD therapy (Tripathi et al. 2019; Corti 2019). These findings indicate that their inclusion in a therapeutic regimen can contribute to slow down neurodegeneration and HD progression. Mechanism of autophagic activity in proteostasis is given in Fig. 3.

Targeting NF-κB/pAkt1, Akt/Erk and Immunomodulatory Pathways

Reijonen et al. have reported that mHtt downregulates the transcription factor NF-κB and ultimately causes the oxidative stress which progresses the pathology of HD (Reijonen et al. 2010). Similar to Parkinson's disease (PD), NF-κB/pAkt1 might also be targeted for the therapy of HD (Rai et al. 2017b; Rai et al. 2019a; Yadav et al. 2017; Birla et al. 2019) along with Akt/Erk pathway which may also be targeted for HD therapy (Rai et al. 2019b). As like PD, immunomodulatory pathway also plays a very critical role in HD pathology and can be a prominent therapeutic option for HD (Rai et al. 2017a; Ellrichmann et al. 2013).

Conclusion

Protein misfolding and aggregation are widely accepted causes of several neurodegenerative diseases and provide a therapeutic opportunity to target protein homeostasis. Increased prevalence of HD and limited treatment option remains an attractive avenue to the development of therapeutic strategies for this disease. Cellular response to damaged proteostasis is governed by various cellular stress controlling mechanisms such as clearance of toxic protein through chaperone mediated actions; UPS mediates degradation and autophagic engulfment of abnormal proteins. In HD pathogenesis, mHtt is the major causing agent which damages proteostatic activity of cells, so mHtt-associated proteostatic system are among the most intensively tested therapeutic targets. Ribosome-associated quality control (RQC) also provides new therapeutic opportunities to rescue the impact of the unfolded protein.

Intriguingly, the question remains unanswered what mechanism lies behind the preferential neuronal death across the brain regions, for example, mostly medium spiny striatal neurons die when HD progress due to mHtt toxicity (Margulis and Finkbeiner 2014). Some threads of evidences suggest that various cellular intrinsic factors which vary across the various cell populations may affect the disease progression rate and resistance to protein toxicity which makes some type of cells more vulnerable to death. For example, in astrocytes and striatal neurons, clearance of toxic protein is slow compared to cortical neurons (Zhao et al. 2016). Importantly, clearance of mHtt in neuronal process is more than that in cell bodies. Variation in UPS activity across the cell types and subcellular compartment explains how mHtt accumulates differentially in cells and affect some brain parts more severely (Zhao et al. 2016). Such findings strongly support that enhancing the UPS

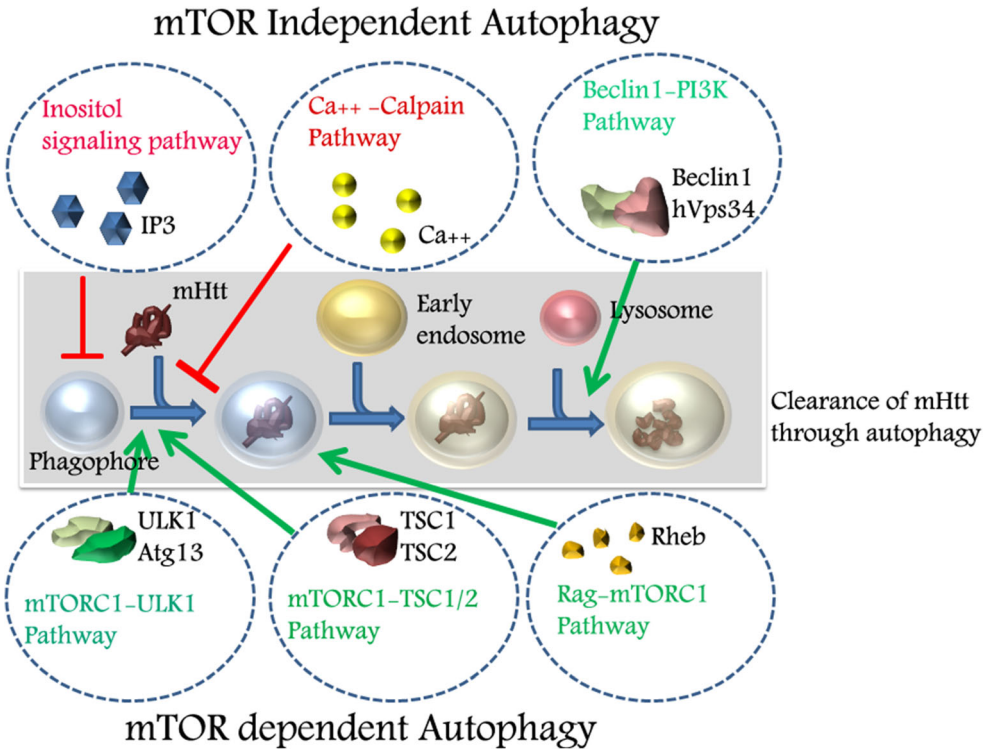

Fig. 3 Autophagic activity in proteostasis. Clearance of mHTT aggregates is regulated by various cellular mechanisms through m-TOR dependent and independent pathways. Calcium and IP3 are major factors which suppress autophagic clearance of mHTT through m-TOR independent pathway. On the other hand, Beclin1 positively regulated autophagy and thus clearance of mHTT. ULK1, TSC1/2 and Rheb follow the m-TOR-dependent pathway and promote mHTT clearance through upregulation of autophagy

activity might be the potential way to reduce the accumulation of aggregates and delay the HD pathophysiology.

Enhancing autophagic activity has been supposed as one of the most efficient ways to remove aggregated proteins. A recent report has revealed the role of Htt as positive regulator of selective autophagy. Htt physically interacts with p62 and ULK1, an autophagic cargo receptor and facilitates the induction of autophagy (Rui et al. 2015). Long-lasting question is how differently wild type and mHtt regulate autophagy induction. A study on interactor of Htt suggested that mHtt interacts with more numbers of proteins involved in autophagy than the wHtt does (Culver et al. 2012). The question still remains unanswered: how enhanced interaction impacts on autophagic activities. Further study is required to differentiate the function of wHtt and mHtt. This may provide a strong clue to suppress particularly mHtt aggregation and enhance autophagy.

Extensive effort has already put into modulating the activity of heat shocked proteins in order to enhance the clearance of mHtt aggregates. The commonest approach is to target the activation of HSF1 which in turn switch many HSP genes on (Singh et al. 2018). Many groups of researcher have focused to elevate HSF1activity using natural compounds such as azadiradione and dexamethasone (Maheshwari et al. 2014a). Most of the compounds do not cross blood-brain barrier (BBB). Enhancing the delivery across the BBB may increase the availability of compound in brain and potentiate the aggregate clearance. Polyphenols can also be utilized as vital therapeutic agent in HD. Targeting various signalling pathways like NF-κB/pAkt1, Akt/Erk and immunomodulatory pathway can also provide an efficient therapeutic option for HD.

Since HD is genetic disorder, it thus remains incurable so far. Understanding the proteostasis network and modulating them might reduce the neuronal damage and slow down the HD progression. Though numerous molecules are rapidly emerging which directly or indirectly impact the protein homeostasis and bring new hope for therapeutics.

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