Molecular Mechanisms Underlying the Role of HSPB8 in Neurodegeneration

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Abstract

Heat shock proteins (HSPs) regulate protein quality control and are responsible for protein aggregation and disaggregation. Molecular chaperones are members of the small heat shock protein (sHSP) family that maintains cellular homeostasis during unfavorable conditions. The sHSPs due to their chaperone properties avert protein aggregation. The sHSP dysregulation turns out to be an important pathological factor in numerous conditions including neurodegenerative disorders. Recent studies suggest the broad and diversified role of sHSPs in neuroprotection, but the mechanism of sHSPs with the neurodegeneration-promoting signaling pathway is still not clear. Some harmful events like proteasome inhibition induce the chaperone, sHSP-B8 (HSPB8). Misfolded protein toxicity is associated with motor neuron diseases (MNDs) exhibiting expression of HSPB8. Concerning this, HSPs may be considered as a feasible target for the development of drugs that can reduce protein aggregates associated with pathogenic conditions contributing to the development of neurodegenerative disorders. This chapter explores the role of HSPB8 in the regulation of neurodegenerative disorders.

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8.1 Introduction

Heat shock proteins (HSPs) are the family of cellular protein, which protects against the stresses responsible for cell injury. As a defense mechanism, organisms significantly increase the synthesis of HSPs against multiple stressors, thus conserving the function of the cell. Based on molecular masses, different families of human HSPs have been identified, and HSP70 superfamily includes HSPA (HSP70) and HSPH (HSP110); the DNAJ family includes HSP40; the HSPB family includes small heat shock protein (sHSP); HSPC family includes HSP90; and human chaperonin families include HSPD/E and CCT (Kampinga et al. 2009). Molecular chaperones are the members of the sHSP family, which participates in cellular homeostasis and maintains cellular functions under unfavorable conditions. The sHSPs provide chaperone specificity and inhibit protein aggregation by binding to misfolded proteins at the hydrophobic domain (Jakob et al. 1993). The different members of the sHSP family may exist in multimeric complexes attributed to variations in subunit numbers (12 to >48) (Candido 2002; McDonald et al. 2012; van Montfort et al. 2001).

In the sHSP family, more attention has been provided to HSPB8, as it is involved in important physiological and pathological conditions. These are the intrinsically disordered proteins (IDPs), which in the process partly retain their structure and are also characterized by structural flexibility via reversible changes in folding (Kazakov et al. 2009). Though other members of this family exist as hetero-oligomers or homo-oligomer, HSPB8 exists mainly as equilibrium mixtures of monomers and dimers (Vos et al. 2008). Numerous studies have presented the involvement of HSPB8 in cellular protein quality control mechanisms, supported by its mutations resulting in the development of motor neuropathy. Besides, it participates in the process of apoptosis, autophagy, and cell proliferation. Based on protein expression level and cell type, HSPB8 also modulates apoptotic signaling (Gober et al. 2003; Hase et al. 2005; Li et al. 2006; Depre et al. 2006). Thus, many diseases, including ischemia, myopathy, diabetes, cataract, and neurodegenerative disorders, may involve sHSP dysregulation due to its involvement in physiological processes (Bakthisaran et al. 2015; Kampinga and Garrido 2012; Sun and MacRae 2005; Kannan et al. 2012).

Native state by substrate refolding may not be achieved after binding of sHSPs (Friedrich et al. 2004; Haslbeck et al. 2005; Mogk et al. 2003). The complex of sHSP and substrate acts as an intermediate, which is processed by the chaperonin family (HSP90) and HSP70 (Lee and Vierling 2000; Nillegoda et al. 2015; Nillegoda and Bukau 2015). An overabundance of HSPB8 in cellular function shows effects on different pathological states, viz. cancers (Modem et al. 2011; Li et al. 2014; Suzuki

et al. 2015; Yamamoto et al. 2016), myocardial ischemia (Danan et al. 2007), autoimmune disease (Roelofs et al. 2006; Peferoen et al. 2015), and neurological diseases (Irobi et al. 2004; Rusmini et al. 2015; Crippa et al. 2013; Crippa et al. 2016b; Yang et al. 2015).

The sHSP also provides neuroprotection mediated via diverse mechanisms. Being a chaperone protein, HSPB8 is also highly expressed in the brain and exhibits protection in the neurophysiological state. Also, the levels of HSP8 are elevated during various neuropathological conditions including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Vicario et al. 2014). Environmental, metabolic, and pathophysiological stress continuously affects both organisms and cells disturbing the integrity of proteome and cell functioning causing the death of the cell. The protective mechanism of the heat shock response pathway mediated via molecular HSP chaperone families helps to counteract the damaging effect of stress produced due to extrinsic and intrinsic factors (Akerfelt et al. 2010; Gomez-Pastor et al. 2018). Within these HSPs, the important ATP-dependent molecular chaperones with small molecular mass (12–42 kDa) (Haslbeck and Vierling 2015) and alpha-crystalline domain are sHSPs (Franck et al. 2004).

This chapter explains the current state of knowledge about the structure and role of HSPB8 in various neurodegenerative diseases, highlighting its involvement in neuropathological conditions, thus presenting a promising novel target in neurodegenerative disease for probing the underlying processes.

8.2 Protein Quality Control System in Neurodegeneration

Maintaining protein balance is essential for normal cellular viability and functioning. Different stressors such as heat, reactive oxygen species (ROS), heavy metals, and mutation can disturb the conformational flexibility of protein required for proper functioning, and even can cause misfolding of existing protein, which ultimately results in dysfunctioning or protein aggregation. Such outcomes are centered on the pathology of several neurological disorders such as AD, PD, and HD. Thus, for minimizing the production of misfolded proteins, protein quality control (PQC) mechanisms have been evolved that maintain normal proteostasis (Hartl et al. 2011). At the post-translational level, PQC involves ingenious mechanisms, which include molecular chaperones that help in maintaining proper protein conformation and/or prevent misfolding and protein aggregation by the ubiquitin–proteasome system (UPS) and autophagy–lysosome pathway (ALP), which destroys proteins that are damaged, irreversibly misfolded, or are no longer required by the cell (Amm et al. 2014). Molecular chaperones and degradative pathways are an integrated part of the PQC system. However, chaperones such as HSPs are constitutively expressed but are elevated during the action of different cell stressors (Morimoto 2006). The co-chaperones such as BCL2-associated athanogene (BAG) family act as nucleotide exchange factors (NEFs) for the molecular chaperones (Takayama and Reed 2001). Neuronal loss is a characteristic feature for chaperone and co-chaperone mutations in

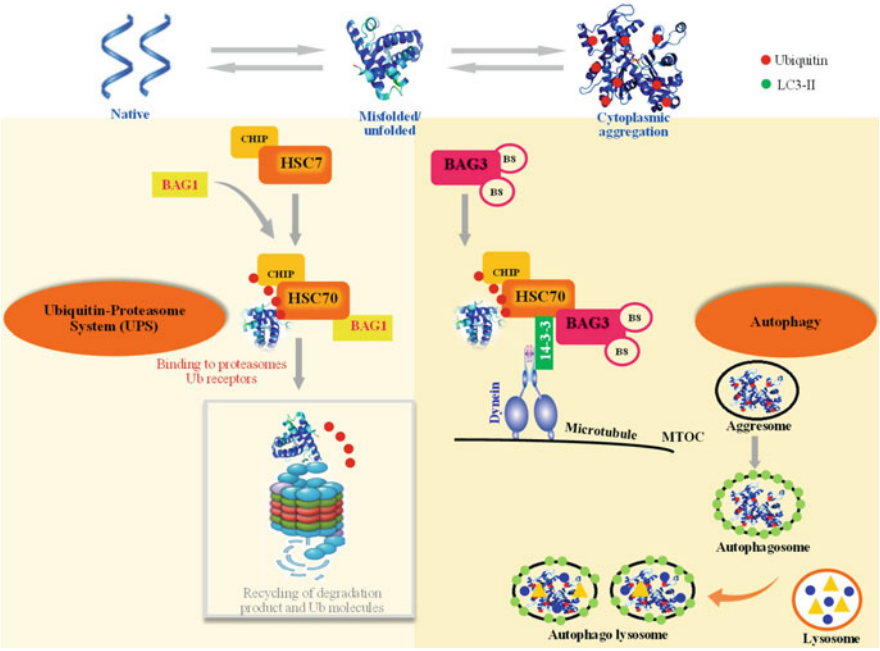

Fig. 8.1 Proteostasis mechanism in neurodegenerative disorders. Molecular chaperones direct misfolded proteins to ubiquitination for degradation. The process is mediated by the HSC70-CHIP complex, which interacts with co-chaperone HSC70 and NEF/BCL2-associated methanogens. BAG1 directs misfolded proteins to polyubiquitination by inhibiting HSP70 and thus promotes degradation via UPS. BAG3 interacts with the protein 14-3-3 and dynein and directs misfolded proteins to autophagosomes for degradation via autophagy (Rusmini et al. 2017). BAG, BCL2-associated athanogene; CHIP, co-chaperone C terminus of Hsc70-interacting protein; HSP, heat shock cognate protein

neurodegenerative diseases (NDs) or other diseases (Smith et al. 2015). This suggests their role in protective mechanism against the degeneration of neurons.

Chaperones control folding of emerging proteins or refolding of existing denatured proteins by directing unfolded, misfolded, or partially folded proteins to degradation via different pathways including UPS, autophagy, and unfolded protein response (UPR). HSPB8 prevents abnormal protein production, which may accumulate in cells escaping degradation during cell death (Cristofani et al. 2017; Minoia et al. 2014; Crippa et al. 2010b) (Fig. 8.1). The endoplasmic reticulum (ER), extensively explored at present, manages the folding and maturation of protein through the UPR signal transduction pathway, which targets the gene specific for ER-associated degradation (ERAD) by translocating the unfolded protein into the cytoplasm to proteasomes, which also participate in PQC (Ron and Walter 2007; Volpi et al. 2017), while specific chaperones and co-chaperones regulate UPS and autophagy pathways (Minoia et al. 2014; Behl 2016; Gamerdinger et al. 2011; Cristofani et al. 2017; Lilienbaum 2013).

UPS has high selectivity and low capacity for misfolded monomeric proteins. The chaperones such as E3-ubiquitin ligase CHIP/STUB1, BAG1, and HSP70 specifically target misfolded proteins to UPS (Fig. 8.1). Autophagy shows low selectivity and high capacity for substrates causing degradation of heteromeric species and damaged organelles (Klionsky et al. 2016). The molecular chaperone actively participates in the autophagy pathway by forming chaperone-assisted selective autophagy complex (CASA), with the target misfolded protein, which is composed of BAG3, CHIP/STUB1, HSP70, and HSPB8. CASA complex activates the receptor, SQSTM1/p62, which binds with LC3 (LC3-II) protein and targets in the direction degradation toward autophagosomes (Klionsky et al. 2016). Several harmful effects in NDs are associated with an imbalance in these two systems of UPS and autophagy (Ciechanover and Kwon 2015; Xilouri and Stefanis 2015; Kakkar et al. 2014; Nikoletopoulou et al. 2015; Senft and Ronai 2015).

The molecular chaperones participate in PQC by activating UPS and thus directing misfolded protein for degradation. The process of degradative pathway involves the interaction of HSC70-CHIP complex along with co-chaperone HSC70, nucleotide exchange factor NEF/BCL2-associated methanogens. BAG1 directs misfolded proteins to polyubiquitination. The interaction of the HSC70-CHIP complex with co-chaperone BAG1 allows misfolded protein degradation via UPS. Alternatively, chaperone-assisted selective autophagy (CASA) involves chaperone HSPB8 and BAG3 complex, which directs the misfolded proteins for degradation via autophagy. HSPB8 helps to recognize misfolded protein and thus acts as a restrictive factor for the formation of a complex. These HSPB8 and BAG3 complexes together interact with HSP70, conjugated with ubiquitin ligase CHIP, whereas BAG3 interacts with the protein 14-3-3 and dynein, which assist delivery of misfolded protein with HSPB8 and BAG3 toward autophagosomes, the microtubule-organizing center (MTOC). The polyubiquitinated protein CHIP in the CASA complex gets recognized by SQSTM1/p62 receptor and inserts the misfolded proteins into autophagosomes (Corti et al. 2020; Rusmini et al. 2017).

Alterations in degradation pathways can result in aggregation of misfolded, which can block PQCS via interfering with autophagy and UPS. The saturation of proteasomes by misfolded protein triggers the expression of HSPB8, which activates the process of autophagy via interaction with HSP70 and BAG3. In the course of failure of dynein-assisted transport and formation of autophagosomes, activation of transcription of BAG1 through unknown factors can stimulate UPS, which is attached to CHIP/HSP70 and leads to misfolded or unfolded proteins to UPS (Fig. 8.2) (Rusmini et al. 2017).

8.3 Distribution of HSPB8

HSPB8 is distributed in various tissues but richly found in the heart, brain, skeletal, and smooth muscle. In human skin, it is present in keratinocytes, which control the growth. The involvement of HSPB8 in cell growth was demonstrated by the study of

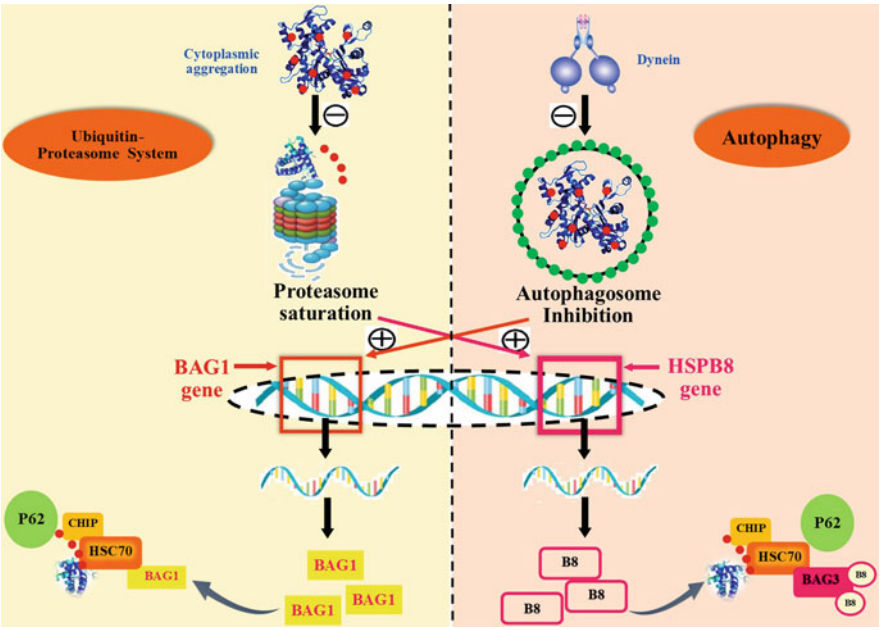

Fig. 8.2 Regulation of protein quality control system. Failure of the degradative system results in the accumulation of misfolded proteins, which blocks UPS and autophagy. As a result, the saturation of proteasomes by misfolded protein triggers the expression of HSPB8, which activates autophagy via HSP70 and BAG3. Concurrently, blockage of autophagosome action activates BAG1, which interacts with CHIP/HSP70 and assists misfolded proteins to UPS (Rusmini et al. 2017). BAG, BCL2-associated athanogene; CHIP, co-chaperone C terminus of Hsc70-interacting protein; HSP, heat shock protein

cultured human keratinocytes in which DNA synthesis and cell proliferation were blocked by inhibition of HSPB8 (Verschuure et al. 2003).

8.3.1 Structure of HSPB8

The sHSPs are made up of two combined sheets of 6–8 β-strands containing conservative α-crystallin domain (ACD) (De Jong et al. 1998). The secondary structure prediction of HSPB8 specifies enrichment of β-strands along with randomly coiled structures (Kim et al. 2006). The unordered structure of HSPB8, evident from the study of far-UV CD, protects against thermal denaturation and proteolysis (Fig. 8.3) (Kazakov et al. 2009).

The approximate molecular mass of HSPB8 is around 22 kDa. It contains a protected amino acid sequence of the α-crystallin domain, which is located on the C-terminal segment (Fig. 8.3). It is also classified as an atypical serine/threonine–protein kinase (Smith et al. 2000). It is an intrinsically disordered protein (IDP) with flexible conformation, which does not have a tertiary structure. It exists in monomer

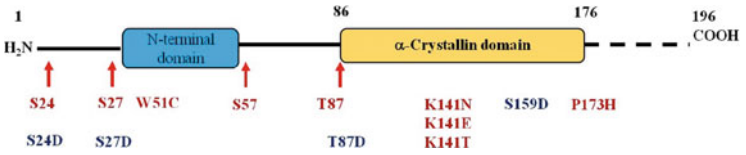

Fig. 8.3 Structure of HSPB8 protein

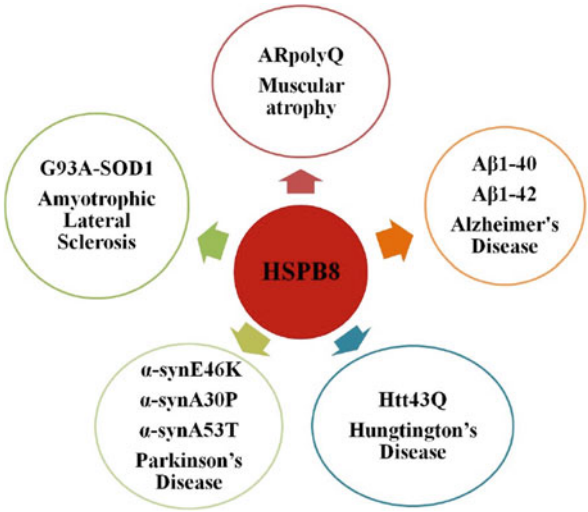

Fig. 8.4 Role of HSPB8 in various neurodegenerative disorders. G93A-SOD1, glycine 93 changed to alanine-superoxide dismutase 1; ARpolyQ, polyglutamine expansion in the androgen receptor; Aβ, amyloid-beta; Htt43Q, huntingtin gene associated with polyglutamine (polyQ) extension of 43 residues; α-syn, α-synuclein variants

form defined by the ultracentrifugation study in solvent glycerol (Chowdary et al. 2004) and differs from others by forming dimers or high-order oligomers. Besides, HSPB8 is enriched in β-strands while lacks β2-strands (Mymrikov et al. 2011).

8.4 sHSP in Neurodegenerative Disorders

Precipitation and aggregation of misfolded proteins are involved in several neurological disorders viz. AD, PD, and amyotrophic lateral sclerosis (ALS) (Fig. 8.4). Also, several studies highlighted the involvement of stress and imbalance in the physiological condition in protein misfolding, which disrupts the proteostasis mechanism. Molecular chaperones such as HSP670, HSP90, and other sHSP families are specialized ATP-dependent chaperone that executes the process of refolding and proteolysis, directing the misfolded protein to UPS and autophagy pathways.

The capability of molecular chaperones to prevent misfolding of protein aggregate formation makes them a novel target in the pathology of many diseases that involves changes in protein conformation (Mogk and Bukau 2017). Mutation and gene alteration in HSPB8 are found to be associated with neurological conditions (Hamouda et al. 2014), whereas enhanced expression of the HSPB8 gene prevents aggregation of HTT43Q in Huntington's disease. Also, HSPB8 facilitates the

exclusion of misfolded proteins via autophagy in ALS. Synucleinopathy is the installation of fibrillar α-synuclein (α-syn) in inclusion or neuronal bodies in the processes (Marti et al. 2003). The sHSP expression significantly increases in stress (Bartelt-Kirbach and Golenhofen 2014) and is also found to be co-localized with α-syn in inclusion bodies (Spillantini et al. 1997; Outeiro et al. 2006). Interestingly, HSPB8 removes misfolded proteins that contain elongated polyglutamine chains in other neurodegenerative conditions (Crippa et al. 2010b).

HSPB8 in neurodegenerative diseases may act by preventing the accumulation and aggregation of insoluble proteins. Some of the neurodegenerative conditions associated with protein conformational changes are as follows: AD is characterized by amyloid β-peptides, PD by a mutant α-synuclein forms, ALS by mutant superoxide dismutase 1, HD by mutant huntingtin protein, and muscular dystrophy by an extended CAG tract translated into an polyglutamine (polyQ) tract in the AR protein (ARpolyQ). Protein conformational changes resulting in aggregation or accumulation, and misfolding of amyloid fibrils are responsible for many neurodegenerative disorders. Molecular chaperones work as the first-line defense counter to misfolded, aggregation-prone proteins. The recent investigation suggested the importance of molecular chaperones in ALS, AD, PD, and polyglutamine repeat diseases. It provides protection against proteins prone to aggregation and misfolding and thus acts as potent suppressors of degeneration found in human disease models. Current research has found the role of molecular chaperones in ALS, AD, PD, and polyglutamine repeat diseases (Muchowski and Wacker 2005).

Brain tissues of patients suffering from ailments such as AD, PD, spinocerebellar ataxia type 3 (SCA3), and HD indicate resilient upregulation of HSPB8 in astrocytes along with a minor increase in BAG3. Elevated levels of HSPB8 along with HSPB6 and HSPB1 in multiple sclerosis (MS) are associated with demyelination of white matter (WM) lesion during the active stage of the disease, found entirely in astrocytes but not in oligodendrocytes or microglia. This induction is not detected in the lesions of gray matter (GM) as well (Peferoen et al. 2015). The potential of sHSPs to avert aggregation of α-syn has also been determined by the aggregation process kinetics. The degree of aggregation increases in the presence of gene amplification, macromolecular crowding, and disease-related mutations altering the α-syn aggregation kinetics in cells. It may be associated with the devastation of the protective role due to decreased availability of aggregation contending chaperones (Cox et al. 2016; Rekas et al. 2004). HSPB8 (also known as HSP 22) is associated with the clearance of much-misfolded protein involved in neurodegenerative diseases. Clearance of protein may occur due to the upregulation of autophagy by HSPB8 acting in association with co-chaperone BAG3 (Crippa et al. 2016b). Astrocytes of cerebral areas are the main sites for HSPB8 upregulation in cases of neurodegeneration (Seidel et al. 2012) indicating the importance of astrocytic proteostasis for removal of aggregates in the neuronal microenvironment. HSPB8 restores autophagic flux and removes misfolded aggregates of androgen receptor (AR) poly to promote motor neuron survival of patients suffering from bulbar and spinal muscular atrophy with abnormally long polyQ in mutant AR (Rusmini et al. 2013). Missense mutations in HSPB1 and HSPB8 are mainly

involved in the pathogenesis of Charcot-Marie-Tooth (CMT) disease Evgrafov et al. 2004; Irobi et al. 2004; Srivastava et al. 2012).

HSPB8 knockout animals can demonstrate standard locomotor performances. The decrease in HSPB8 aggregates and autophagy were observed in modern knock-in animal models expressing HSPB8 mutant (Bouhy et al. 2018). The cytoprotective role of sHSPs is associated with inhibition of apoptotic machinery by participating in extrinsic and intrinsic apoptotic signaling pathways. HSPB8 also suppresses apoptosis via inhibiting release of cytochrome C from mitochondria (Yang et al. 2015). HSPB8 prevents protein aggregation by getting entombed inside the inclusions of polyglutamine tails with the proteins (Carra et al. 2005). Amyloidosis in the patients of hereditary cerebral hemorrhage revealed the presence of HSPB8 in senile plaques and angiopathy of cerebral amyloid (Carra et al. 2005; Wilhelmus et al. 2006; Wilhelmus et al. 2009).

Carra et al. (2005) studied the involvement of HSPB8 in preventing polyglutamine protein Htt43Q aggregation in the lung fibroblast cell line (CCL39 cells) in Chinese hamster and embryonic kidney 293 cells of humans. Generally, Htt43Q accumulates in perinuclear inclusions consisting of insoluble aggregates of SDS. HSPB8 repressed the gathering of SDS-insoluble Htt43Q. This indicates the role of HSPB8 in sustaining the soluble state of Htt43Q for speedy degradation (Carra et al. 2005; Vos et al. 2010).

8.4.1 Role of HSPB8 in Motor Neuron Diseases

A neurodegenerative disease that affects cortical and/or spinal motor neurons is collectively categorized under motor neuron diseases (MNDs) characterized by progressive muscle weakness and extensor muscle wasting (Irobi et al. 2010). They may be in familial or periodic forms. Pathogenesis of familial MNDs includes altered RNA or protein functions caused by specific gene mutations affecting synthesis or activity of RNA or protein or inducing neurotoxicity and which are specifically involving gain of functions in proteins are ALS and spinal and bulbar muscular atrophy (SBMA). They show unfolding/misfolding due to resistance to folding or conformational instability.

The major proteins affected by missense mutations are HSPB8 and HSPBl that have been reported associated with motor neuropathy (Irobi et al. 2010; Sun et al. 2010). These mutations resulted in alterations mainly at Lysl41 residue in the wild-type HSPB8 protein converting to either Asn (Kl4, NHSPB8) or Glu (K, 41EHSPB8). Numerous studies also show muHSPB8 abnormally interact with HSPB5, HSPBl, and other proteins PASSI, Hic-5 (ARA55), Sam68, BAG3, and TLR4 and act through common signaling pathway for disease progression (Badri et al. 2006; Carra et al. 2009; Fontaine et al. 2006). The sHSPs are implicated in their folding of the protein and additional functions, including protein degradation mediated via the proteasome, RNA processing, redox homeostasis, cell motility, and muscle activity. Thus, mutation in HSPB8 (muHSPB8) may have deleterious effects altering properties and possibly interacting with other proteins. Previous

studies also demonstrated that HSPB8 mutations result in protein aggregation along with the reduction in the potential of the mitochondrial membrane in early stage (Irobi et al. 2012).

Impaired cellular functions in misfolded proteins lead to the development of aggregate and cause neurotoxic, which subsequently leads to cell death. PQC system prevents misfolded protein toxicity by reviewing protein folding and clearing damaged substrates. HSPB8 confines to stress granules that get molded after proteotoxic stress and sequester ribonucleoprotein complexes. The intensive accomplishment of the HSPB8-BAG3-HSP70 complex determines the disassembly of stress granules indicating the role of these stress granules in the pathology of ALS. ALS involves the brain motor cortex, brain stem, and anterior horn spinal cord motor neurons (Mateju et al. 2017; Ganassi et al. 2016).

8.4.2 Role of HSPB8 in Amyotrophic Lateral Sclerosis and Muscular Atrophy

Clinically, sporadic ALS (sALS) and familial ALS (fALS) are indistinguishable. The fALS are only 15% of the affected population. It is mainly associated with specific gene mutations involving TAR DNA-binding protein 43 (TDP-43), sequestosome-1 (SQSTM1/p62), superoxide dismutase-1 (SOD-1), fused in sarcoma/translocated in liposarcoma (FUS/TLS), ubiquilin (UBQLN-2), optineurin (OPTN-1), TANK-binding kinase 1 (TBK1), and valosin-containing protein (VCP) (Taylor et al. 2016). These genes play important role in the PQC system and are autophagy-related proteins or mislodge and aggregate applying proteotoxicity (Ju et al. 2009; Taylor et al. 2016; Seguin et al. 2014). The SBMA involves lower motor neurons, neurons of dorsal root ganglia (DRG), distinct androgen target cells in germline tissues, and muscle cells. It varies from ALS by a rate of progression and no involvement of glial or microglia (La Spada et al. 1991; Cortes et al. 2014; Malena et al. 2013; Lieberman et al. 2014; Sorarù et al. 2008). The SBMA is associated with the expansion of a CAG repeat in the androgen receptor (AR) gene that leads to elongation of ARpolyQ (La Spada et al. 1991).

ARpolyQ acquires neurotoxic properties by misfolding (Poletti 2004) after binding to testosterone, which acts as its ligand (Katsuno et al. 2002, 2003; Simeoni et al. 2000; Stenoien et al. 1999). Testosterone stimulates conformational changes essential for AR activation possibly damaged by the polyQ. Degradative pathways get altered by the accumulation of misfolded proteins in SBMA, sALS, or fALS. The UPS is possibly flooded by more amount of misfolded/unfolded proteins or inhibited by the poly (Rusmini et al. 2016; Ciechanover and Kwon 2015). Though misfolded protein aggregates could block autophagic flux (Rusmini et al. 2013), the molecular steps that are distorted by the misfolded proteins in these pathways are not tacit. Many chaperones enhance removal of misfolded proteins by aiding proteasomal dilapidation and/or restrictive alterations in autophagic flux (Rusmini et al. 2016; Charmpilas et al. 2017; van Noort et al. 2017).

Chaperone HSPB8 is extensively distributed in many human tissues, at different expression levels. The upregulation of HSPB8 gives protection in the ALS and SBMA (Rusmini et al. 2013; Carra et al. 2013; Crippa et al. 2010b). Mutations in HSPB8 may be responsible for diseases like hereditary motor neuropathy type II (dHMN-II), CMT type 2L, or myopathy, which involve motor neurons and/or muscle cells (Fontaine et al. 2006; Ghaoui et al. 2016). HSPB8 has a vital role in the preservation of motor neuron function and viability, and its mutation impairs the activity of HSPB8 (Kwok et al. 2011). Motor neurons become more susceptible to toxicity induced via misfolded proteins, with age and countenance of HSPB8 in the region of spinal cord that declines with age (Crippa et al. 2010b). HSPB8 mRNA expression is high in the spinal cord sample of ALS patients than in individuals of the same age (Anagnostou et al. 2010). Proteasome impairment is a condition mainly occurring in MNDs and induces HSPB8 expression in cultured motoneurons (Crippa et al. 2010a, b) in the anterior horn spinal cord remaining at end stages of disease in transgenic (Tg) ALS SOD1-G93A mice when compared with wild variety of mice.

Throughout disease development in ALS (Carra et al. 2013) and SBMA (Rusmini et al. 2015), expression of HSPB8 increased drastically in skeletal muscle in mice, contributing to augment the unusual protein removal from muscle to advance cell survival. HSPB8 removes the obstruction of autophagic flux in many NDs. At cellular levels, HSPB8 facilitates misfolded protein autophagic degradation at cellular levels (Rusmini et al. 2013). Recent studies also suggested that enhanced transcription of the C9ORF72 gene results in the expansion of G4C2 hexanucleotide repeats, which form aggregation-prone conformational protein that is difficult to remove via PQC. The molecular chaperones, HSPB8, recognize different peptide repeats (DPRs) generated via transcription alteration and facilitate the degradation of misfolded DPRs responsible for different neurodegenerative diseases (Cristofani et al. 2018). According to increasing genetic and experimental pieces of evidence, translation of ribonucleoprotein complexes and stress granules (SGs) into amyloid-like masses may be responsible for the accumulation of RNA–protein additions in ALS and analogous NDs. Accumulation of misfolded proteins in SGs endorses their transformation into aggregates. The HSPB8-BAG3-HSP70 complex is one of the key factors of granulomatosis (Carra et al. 2017; Ganassi et al. 2016; Mateju et al. 2017).

8.4.3 Role of HSPB8 in Alzheimer's Disease

It is the most common detrimental neurodegenerative condition that leads to dementia and progressive alteration in behavior and learning ability. Pathological factors for disease progression include extracellular protein deposition, and intracellular neurofibrillary tangles (NFTs) result in the formation of senile plaques. With the advancement in research, various pathologies leading to neurodegeneration have been discovered, which majorly includes amyloidal plaque formation and hyperphosphorylation of NFTs (Kumar et al. 2015). Several hypotheses were constructed based on the involvement of causative factors such as the amyloid and

tau hypothesis, neurochemical (cholinergic) hypothesis, and inflammation hypothesis (Kurz and Perneczky 2011). In addition to knowing pathology, different studies have also demonstrated the occurrence of α-syn or Lewy related in more than 50% of AD brains, also termed as non-Aβ peptide fragment or non-amyloid-β component of α-syn. Similarly enhanced α-syn levels have been found in cerebrospinal fluid (CSF) of AD patients with cognitive impairment. Further, α-syn also enhances tau hyperphosphorylation. Recent studies suggest that higher α-syn levels are associated with the asymptomatic accumulation of Aβ plaques (Twohig and Nielsen 2019).

One of the distinguishing factors in AD includes senile plaques (SPs) and amyloid angiopathy, which includes deposition protein mainly amyloid-β (Aβ) protein and other proteins such as sHSP and apolipoprotein E, which indirectly interact with them form aggregates. These proteins associated with Aβ result in accumulation and also affect the rate of clearance (Wisniewski and Frangione 1992). The sHSP is involved in the PQC system and thus prevents others from adopting incorrect conformation. Among sHSP, direct interaction between HSP27, actively expressed in astrocytes, and Aβ has been demonstrated (Liang 2000). Furthermore, HSP20 and HSPB2 bind with Aβ and therefore participate in the process of aggregation. HSPB8 has recently gained attention as it contains an α-crystallin domain and it interacts with chaperon HSP27 (Benndorf et al. 2001; Sun et al. 2004). Also, HSPB8 has been demonstrated to prevent protein aggregation during different stress conditions and is expressed in different types of neuronal cells. Furthermore, studies reported that HSPB8 has a higher affinity for Aβ and DAb1–40, and causes reduction in the formation of β-sheet and also inhibits cerebrovascular cytotoxicity mediated by Aβ aggregation (Wilhelmus et al. 2006).

Besides, the HSPB8-BAG3 complex is found to be overexpressed during neurodegenerative conditions and facilitates the clearance of mutated protein prone to aggregation. Postmortem brain studies reported upregulated HSPB8-BAG3 expression in protein conformation disorders such as AD, PDD, and HD. Therefore, the upregulation of HSPB8-BAG3 may contribute to protein homeostasis and in the remodeling of astrocytes during astrogliosis in the above conditions (Seidel et al. 2012). Also, HSP20 and HSP27 prevent Aβ deposition and associated toxicity (Lee et al. 2006). The expression of HSP22 is upregulated with aging and in neurodegenerative conditions like AD, due to deficiency in regulatory mechanism during proteostasis, which can result in misfolded proteins. Numerous studies identified lower expression of HSP22 in excitatory neurons, and also, excitatory glutaminergic neurons are highly susceptible to tau toxicity, thus indicating HSP22 levels are inappropriately being upregulated causing tau activation and making it resistant to proteolytic degradation. In vitro studies have reported that HSP22 significantly reduces tau protein levels, making it a novel target in neurodegenerative conditions (Webster et al. 2020). The miR-425-5p has been recently linked with the pathology of AD and found to be upregulated in AD and also increases tau phosphorylation in HEK293/tau cells. Heat shock protein B8 (HSPB8) has been reported to be targeted by these microRNAs and thus indirectly involved in targeting phosphorylation of tau (Yuan et al. 2020).

8.4.4 Role of HSPB8 in Parkinson's Disease

PD is associated with damage to the dopaminergic network precisely in the substantia nigra. Neuropathologically, PD is characterized by intraneuronal protein aggregates viz. Lewy bodies and Lewy neurites indicating the involvement of alteration in protein handling (Spillantini et al. 1997). The α-syn is an important factor in the pathology of Lewy bodies. Point mutations in α-syn gene is responsible for familial forms of PD, also it can be caused due to an enhanced level of α-syn protein (Olanow and Brundin 2013). Formation of α-syn protein aggregates is a multi-step process that begins with the α-syn misfolding leading to the formation of insoluble oligomers complex and finishes with insoluble fibril formation and aggregates (Ebrahimi-Fakhari et al. 2014). The interaction of HSPB8 with α-syn was found to inhibit the maturation and aggregation of misfolded protein and fibril formation (Bruinsma et al. 2011a).

Based on in vitro studies by Bruinsma et al. (2011a), the most compelling sHSP is HSPB8 in stopping matured fibril development of both mutant and wild-type α-syn (A30P, A53T, and E46K). This study suggests that optimization of the collaboration of α-syn with HSP22 acts as a preparatory point in the expansion of an innovative outcome for involvement in the α-synucleinopathy pathogenesis (Fig. 8.1).

8.4.5 Role of HSPB8 in Huntington's Disease

HD is a common disease inherited by autosomal dominant mutant expansion in the trinucleotide CAG repeats in Htt (huntingtin) gene. HD is associated with polyglutamine (PolyQ). It is characterized by damage in the striatum and cortex neurons resulting in progressive disruption of voluntary motor coordination. The protein that contains a polyglutamine extension of 43 residues (Htt43Q) is unstable. The Htt comprising more than 37 successive glutamines forms insoluble aggregates, a phenotype linked with HD (Ross et al. 2003). In 90% of cells, the development of perinuclear masses takes place as a result of transfection via plasmid encoding an HA-labeled form of Htt43Q and pHDQ43-HA (Wyttenbach et al. 2002). The coexpression of HSPB8 and Htt43Q, intensely reduces aggregation of Htt43Q as >90% of CCL39 cells expressing both Htt43Q and HSPB8 presented with no aggregate in diffuse staining. In the cells wherever inclusion bodies are detected instead of the occurrence of HSPB8, HSPB8 together with the Htt43Q aggregates. HSPB8 actions are similar to that of the chaperones HSP40 and HSP70, which can stop the formation of inclusion of polyglutamine proteins but are often found confined in refractory aggregates (Chai et al. 1999).

8.4.6 Role of HSPB8-BAG3 Induction in Motor Neuron Diseases

HSPB8 is a restrictive element for the autophagic degradation of misfolded proteins. Restoration of autophagy may be achieved by overexpression of HSPB8. The

HSPB8 inducers such as selective estrogen receptor modulators (SERMs) and estrogens (physiological inducers) govern its expression differentially (Piccolella et al. 2017). Doxorubicin and colchicine are powerful HSPB8 inducers. They are autophagy architects of the deduction of insoluble TDP-43 species (Crippa et al. 2016a, b). Trehalose also showed affirmative results in numerous animal models of NDs (Rusmini et al. 2013; Sarkar et al. 2014; He et al. 2016). It also upregulates the expression of BAG3 (Lei et al. 2015). The HSPB2, HSP20 (HSPB6), and HSPB8 are linked to cerebral amyloid angiopathy (CAA) in hereditary cerebral hemorrhage with amyloidosis of the Dutch type (HCHWA-D). Prominently, these sHSPs stimulate interleukin-6 in the cultured neuronal cell, astrocytes, and pericytes, proposing an anti-inflammatory response of sHSPs in HCHWA-D (Wilhelmus et al. 2009).

The majority of AD patients are characterized by HSP20, CAA, HSPB2B3, and HSPB8 that co-localize with CAA and persuade production of intercellular adhesion molecule 1 (ICAM-1), interleukin-8, and monocyte chemoattractant protein by astrocytes in the human brain, strengthening their role in neuroinflammation in AD (Bruinsma et al. 2011b). According to these findings, the exogenous administration of sHSPs shows a defensive role in several diseases having inflammation, protein aggregation, and cell death.

8.5 Recent Development and Future Perspectives

Mechanisms related to the regulation of sHSPs in neurodegeneration by nucleosome remodeling, transcription factor synergy, need to be revealed. Considering the role of HSPB8 in cell physiology, they represent an important target for the treatment of a wide variety of neuronal diseases. The beneficial role of sHSPs in animal models and in clinical trials related to neurodegeneration needs to be explored by interpreting the meticulous regulation and precise targets of these chaperones. Numerous animal models have been developed based on a mutation in the HSPB8 gene in mice to study progressive motor neuropathy via definite neurite degeneration (Bouhy et al. 2018; Ganassi et al. 2016; Irobi et al. 2010).

The protective role of HSPB8 has been explored against TDP43 aggregates in motor neurons, and it also extends survival of hSOD-1G93A mice (Aurelian et al. 2012; Cortese et al. 2018; Rusmini et al. 2017). Trehalose was found to induce HSPB8 expression, thereby reducing ER stress to improve autophagy, delaying disease progression, and prolonging motor neuron survival (Li et al. 2015; Zhang et al. 2014). A potent HSPB8 inducer, colchicine, was found to facilitate autophagy for removal of insoluble TDP-43 in phase II clinical trial in ALS (NCT03693781) (Mandrioli et al. 2019; Rusmini et al. 2017). Recently, surveillance role of HSPB8 in maintaining integrity and dynamism has been explored (Ganassi et al. 2016).

8.6 Conclusion

Though HSPB8 is a type of sHSPs, they differ in many aspects from other sHSPs. The HSPB8 is involved in various neurological disorders including ALS, SBMA, AD, PD, and HD. The chaperone HSPB8 enables the removal of misfolded proteins through autophagy by showing pro-degradative activity and prevents their intracellular accumulation. Activation and recruitment of autophagic machinery in protein folding disorders involve HSPB8 along with co-chaperone BAG3. Astrocytes of cerebral areas undergoing neurodegeneration show upregulation of HSPB8 in the brains of patients with a disease like HD, PD, AD, and SCA3. It also inhibits protein synthesis through the P-eIF2a-stimulating autophagy. The HSPB8 restores autophagic instability and removes misfolded ARpolyQ in spinal and bulbar muscular atrophy to promote motor neuron survival of patients. Induction of HSPB8 in cells affected by MND may be considered as a potential approach to inhibit the onset and progression of the disease.

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