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REVIEW

Small Heat Shock Proteins and Human Neurodegenerative Diseases

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Abstract—The review discusses the role of small heat shock proteins (sHsps) in human neurodegenerative disorders, such as Charcot–Marie–Tooth disease (CMT), Parkinson's and Alzheimer's diseases, and different forms of tauopathies. The effects of CMT-associated mutations in two small heat shock proteins (HspB1 and HspB8) on the protein stability, oligomeric structure, and chaperone-like activity are described. Mutations in HspB1 shift the equilibrium between different protein oligomeric forms, leading to the alterations in its chaperone-like activity and interaction with protein partners, which can induce damage of the cytoskeleton and neuronal death. Mutations in HspB8 affect its interaction with the adapter protein Bag3, as well as the process of autophagy, also resulting in neuronal death. The impact of sHsps on different forms of amyloidosis is discussed. Experimental studies have shown that sHsps interact with monomers or small oligomers of amyloidogenic proteins, stabilize their structure, prevent their aggregation, and/or promote their specific proteolytic degradation. This effect might be due to the interaction between the β-strands of sHsps and β-strands of target proteins, which prevents aggregation of the latter. In cooperation with the other heat shock proteins, sHsps can promote disassembly of oligomers formed by amyloidogenic proteins. Despite significant achievements, further investigations are required for understanding the role of sHsps in protection against various neurodegenerative diseases.

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Correct folding of long polypeptide chains synthesized *de novo* or renaturation of protein denatured under unfavorable conditions are very complex processes. The protein homeostasis (proteostasis) in the cell is maintained by several families of heat shock proteins (Hsps) that can interact with cell proteins and with each other in order to perform their function. Human cells contain several Hsp families: HspH (Hsp110), HspC (Hsp90), HspA (Hsp70), HspD/E (Hsp60/Hsp10), DNAJ (Hsp40), and HspB (according to the old classification, the number after Hsp corresponds to the molecular weight of protein monomer) [1, 2]. Each sHsp family is characterized by specific properties, functions, and intracellular location. Some Hsps (Hsp110, Hsp90, Hsp70, Hsp60) possess ATPase activity, whereas other Hsps (DNAJ) regulate the ATPase activity of their partner (Hsp70) or lack the ATPase activity at all (small Hsps, sHsps). Efficient folding of polypeptides chains can be achieved only by coordinated participation of all (or most) of Hsps belonging to different protein families, each family including several or even tens of Hsps. For instance, human genome contains 10 genes coding sHsps [3, 4]. sHsp monomers are composed of 150-250 amino acid residues (a.a.) and have comparatively small molecular masses [5, 6]. A characteristic feature of sHsps is the presence of highly conserved α-crystallin domain (ACD) consisting of 80-100 a.a. organized into six or seven β-strands (Fig. 1a) [7, 8]. ACD participates in the formation of sHsp dimers that can contain either identical or different monomers [9-11]. Both isolated ACDs and intact sHsps can form amyloid fibrils under specific conditions *in vitro* [12, 13]. Interestingly, short ACD fragments that can prevent aggregation of denatured proteins, i.e., possess the chaperone-like activity, tend to form amyloid fibrils [14]. In addition to the conserved ACD, sHsps contain *N*-termi-

Abbreviations: ACD, α-crystallin domain; CMT, Charcot–Marie–Tooth disease; CTD, *C*-terminal domain; NTD, *N*-terminal domain; (s)Hsp, (small) heat shock proteins.

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nal (NTD) and *C*-terminal (CTD) domains that differ in length and structure (Fig. 1a). sHsps containing conserved (I/V)P(I/V) tripeptide in the CTD (αA-crystallin (HspB4), αB-crystallin (HspB5), HspB1) are prone to the formation of very large oligomers composed of more than 20 monomers, which is due to the interaction of this conserved tripeptide with the hydrophobic groove formed by the β4-β8 strands of the neighboring ACD and leads to the generation of large oligomers composed of several dimers [15, 16]. sHsps differ in the length of poorly ordered *N*-terminal domain (NTD) that might play an important role in the stabilization of large oligomers and their interaction with partners and target proteins [11]. This NTD often contains one or several phosphorylation sites [5, 6], whose phosphorylation can affect sHsp oligomeric structure [17, 18] and interaction with partner proteins, e.g., universal 14-3-3 adapter protein [19].

As already mentioned, the main function of sHsps is the maintenance of protein homeostasis. Hsps can perform this function by different mechanisms. Firstly, sHsps bind partially denatured and misfolded proteins and prevent their aggregation [5, 6]. Formation of such complexes not only prevents aggregation of denatured proteins but keeps them in a state maximally suitable for the interaction with ATP-dependent Hsps that can renature these proteins [20]. Secondly, sHsps promote elimination of denatured proteins via degradation in proteasomes [6, 21] or autophagosomes [22, 23]. Finally, in cooperation with Hsp110, Hsp70, and Hsp40, sHsps can participate in disassembling of amyloid aggregates [24]. Therefore, sHsps play an important role in cell protection against accumulation of partially denatured or misfolded proteins.

Despite the multilevel protection of cells against proteostasis dysregulation, impairments in the protein folding control can cause certain neurodegenerative diseases.

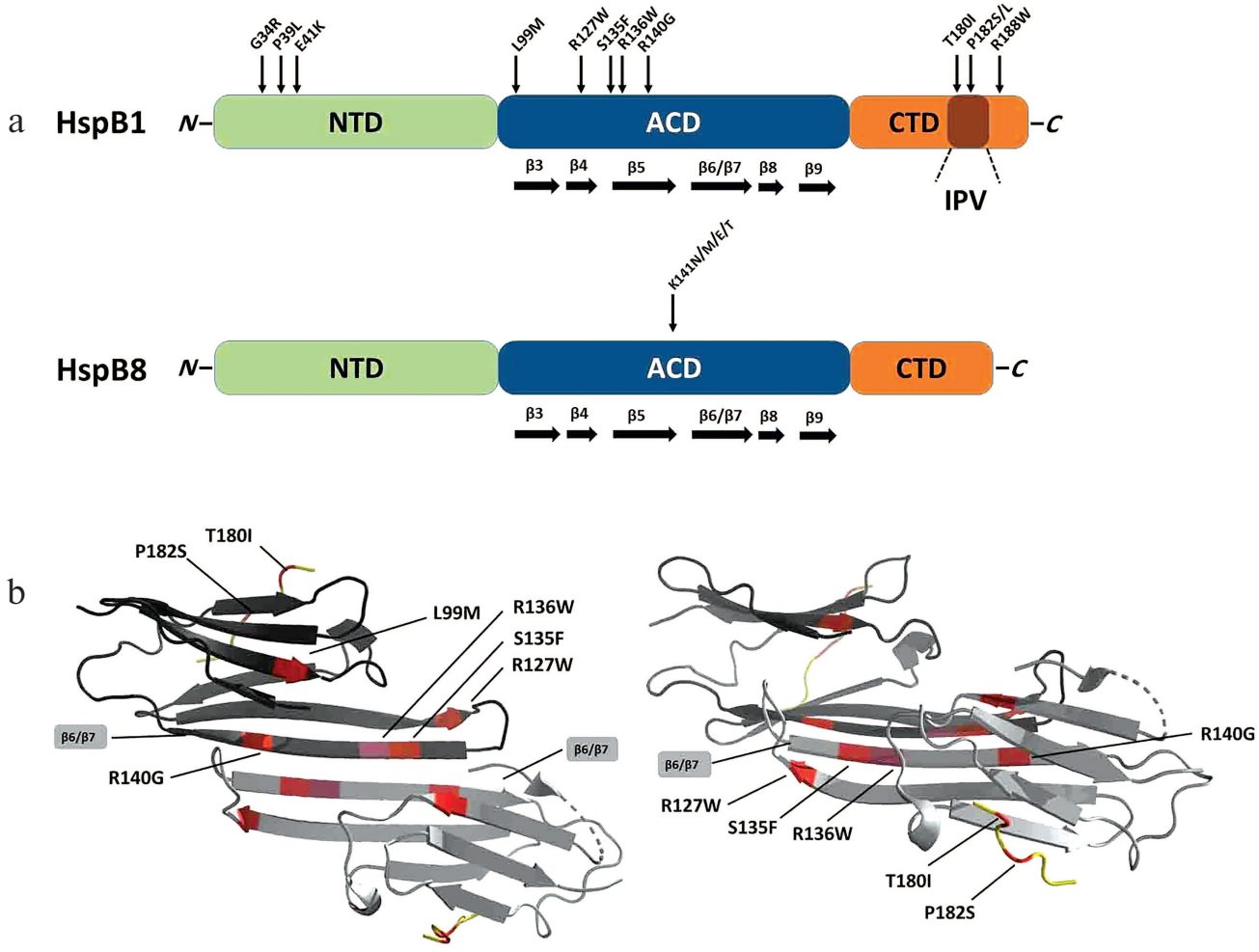

Fig. 1. a) Structures of human HspB1 and HspB8. Green, *N*-terminal domain (NTD); blue, α-crystallin domain (ACD); orange, *C*-terminal domain (CTD) with conserved IPV tripeptide. Arrows indicate positions of point mutations associated with Charcot–Marie–Tooth (CMT) disease. b) Ribbon model of the HspB1 dimer fragment containing ACD and CTD (constructed based on PDB 4MJH using PyMol program). Position of β6/β7 strands forming the intermonomer interface is indicated. Left panel, top view; right panel, side view; dimers are rotated by 90° relative to each other.

Such impairments can result from mutations in Hsps or accumulation of extremely large amounts of misfolded proteins, the renaturation or elimination of which would be beyond of the capability of the proteostasis-controlling system.

In the first part of our review, we discuss the effects of mutations in sHsps on congenital neuropathies, such as Charcot–Marie–Tooth disease (CMT) and distal hereditary motor neuropathy (dHMN). In the second part of the review, we summarize the data on the role of sHsps in preventing the accumulation of amyloids of different nature in the cells.

MUTATIONS IN sHsps AND TYPE II CHARCOT–MARIE–TOOTH DISEASE

Inherited neuropathies are commonly occurring and heterogeneous disorders. A neuropathy is classified as CMT if both sensor and motor neurons are damaged or as dHMN if only motor neurons are damaged [25]. Hence, dHMN can be considered as a particular case of CMT. Symptoms and molecular basis of CMT can be very different, thus complicating diagnosis of different forms of this disease [26]. In the simplest case, CMT is classified into two types. Type I CMT is characterized by the myelin sheath damage accompanied by reduced nerve conduction velocity. In type II CMT, the nerve conduction velocity is not changed, but the axon itself is damaged. Type II CMT is observed in 40% CMT patients; about 10% of these patients carry mutations in genes encoding three sHsps – HspB1, HspB3, and HspB8 [27]. At present, more than 30 mutations have been detected in the *HspB1* gene, one mutation in the *HspB3* gene, and nine mutations in the *HspB8* gene [28, 29]. To understand molecular mechanisms underlying the CMT pathology, it is essential to analyze changes induced in the protein structure by these mutations.

In HspB1, mutations associated with CMT has been localized to all three domains of this protein (Fig. 1a). Three point mutations, G34R, P39L, and E41K, in the NTD, lead to the increase in the size of protein oligomers and decrease in the protein thermal stability [18]. Both wild-type HspB1 and mutant proteins are phosphorylated by MAPKAP kinase 2. However, in the case of the wild-type protein, phosphorylation results in rapid (and often complete) dissociation of large oligomers, whereas phosphorylation of the mutants leads only to slight changes in the HspB1 quaternary structure [18]. It was found that phosphorylation-induced dissociation of large oligomers plays an important role in the chaperone-like activity of HspB1 [30]. Therefore, mutations in the NTD disturb phosphorylation-dependent regulation of chaperone-like activity of HspB1.

Most CMT-associated mutations are located in the ACD (Fig. 1a). This domain and especially its β6/β7 strands are involved in the formation of subunit–subunit contacts in large oligomers of sHsps (Fig. 1b) [31]. Therefore, mutations in the ACD could result in significant changes in the HspB1 quaternary structure. Indeed, mutations L99M, R127W, S135F, and R140G cause destabilization of the protein quaternary structure leading to partial dissociation of large HspB1 oligomers at low protein concentration [32-34]. At the same time, at high protein concentration, these mutants tend to form oligomers much larger than the corresponding oligomers formed by the wild-type HspB1, which can be explained by incorrect folding of the protein monomers and exposure of "sticky" regions leading to increased HspB1 aggregation. It should be mentioned that due to the overall destabilization, the L99M, R127W, and S135F mutants easily dissociate even at low phosphorylation levels, i.e., under condition when the wild-type protein remains in the form of large oligomers [32, 34]. In contrast, mutation R136W results in the formation of extremely stable oligomers with the size much larger than that of oligomers formed by the wild-type HspB1. This can be explained by changes in the monomer folding and formation of hydrophobic contacts between F138 residue of one monomer and mutated W136 residue of the neighboring monomer. All analyzed mutants of HspB1 differ from the wild-type protein in their ability to interact with HspB6 and usually demonstrate lower chaperone-like activity toward most model substrates (except insulin) [32-34]. Therefore, mutations in the ACD result in significant changes in the HspB1 quaternary structure, disturb phosphorylation-dependent regulation of protein quaternary structure, and affect HspB1 interaction with protein partners and substrates.

Mutation in the CTD can also be associated with CMT [29]. Mutations T180I, P182S, and R188W are located in close vicinity to the conserved IPV tripeptide (residues 181-183). As already mentioned, this peptide is a fragment of highly flexible CTD that interacts with the ACD domain of the neighboring monomer and stabilize the structure of large HspB1 oligomers [15]. Indeed, mutation P182S decreases protein thermal stability and leads to the formation of very large polydisperse HspB1 aggregates [35]. Mutation R188W is also accompanied by an increase in the HspB1 oligomer size, although it has no significant effect on the protein thermal stability. Mutations P182S and R188W considerably decrease the chaperone-like activity of HspB1 *in vitro* [35]. These effects can be explained by the fact that the CTD plays an important role in the interaction of sHsps with protein substrates [36].

Summing up, each mutation in HspB1 leads to different alterations in its properties (Fig. 2). Nevertheless, there are some common changes in the structure and properties of HspB1 mutants associated with the CMT disease. Firstly, these mutations affect oligomeric state or stability of HspB1 oligomers. Secondly, they disturb

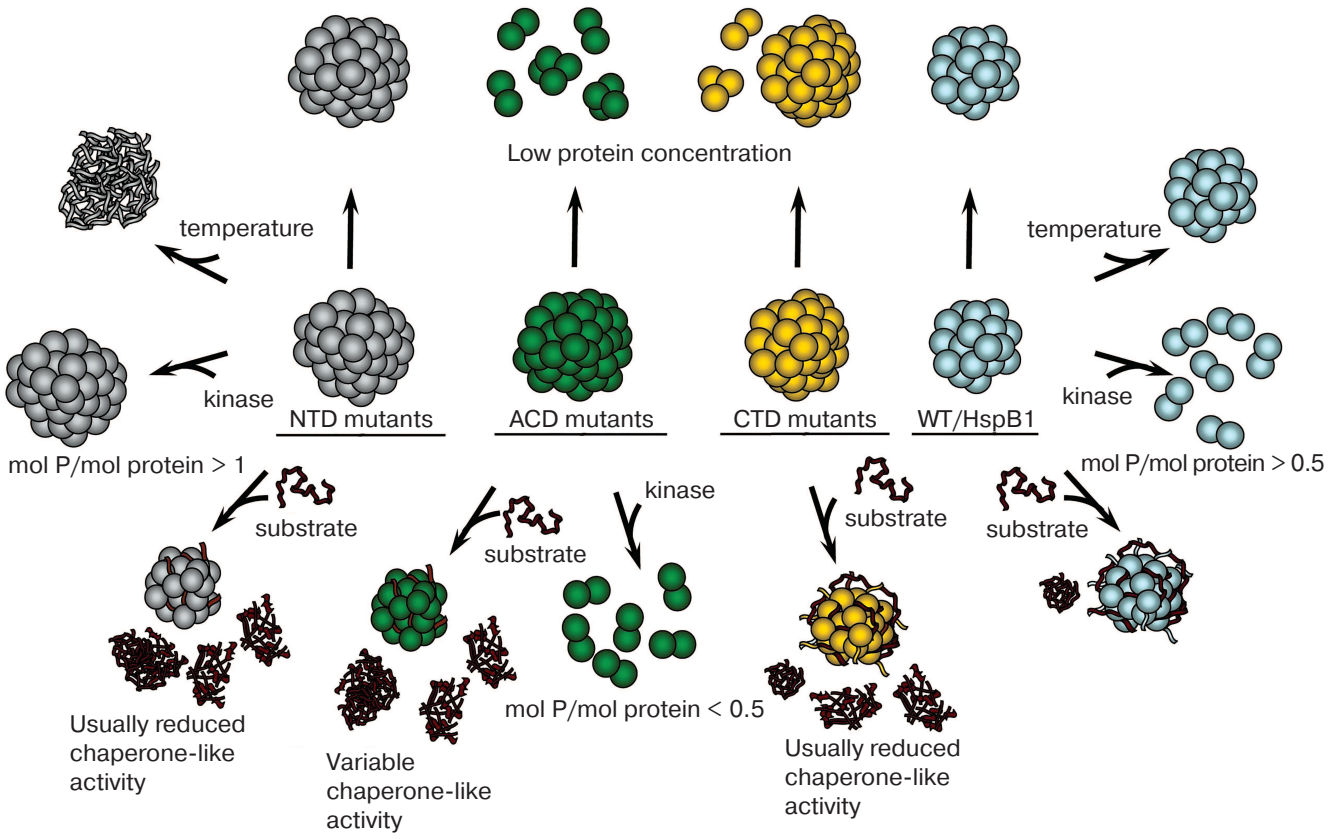

Fig. 2. Changes induced in the structure and properties of CMT-associated HspB1 mutants. Wild-type HspB1 (right column) forms oligomers stable to dissociation, possesses high chaperone-like activity, and is resistant to heat-induced aggregation. Large HspB1 oligomers dissociate to smaller oligomers when phosphorylated at a ratio more than 0.5 mol phosphate per mol protein. Mutants with amino acid substitutions in the NTD (left column) form oligomers stable to dissociation and exhibit lower thermal stability and, as a rule, decreased chaperone-like activity. Oligomers of these mutants do not dissociate after phosphorylation at a ratio of 1 mol phosphate per mol protein and higher. Mutants with amino acid substitutions in the ACD (second from the left column) form large oligomers prone to dissociation at low protein concentration, usually possess decreased chaperone-like activity, and dissociate to smaller oligomers after phosphorylation at a ratio less than 0.5 mol phosphate per mol protein (except R136W mutant). Mutants with amino acid substitutions in the CTD (second from the right column) form large oligomers prone to dissociation at low protein concentration and usually have lower chaperone-like activity.

phosphorylation-dependent regulation of protein oligomerization. Thirdly, these mutations affect HspB1 interactions with protein partners and substrates and, as a rule, are accompanied by a decrease in its chaperone-like activity. It is possible that the key factor in the effect of these mutations is the disturbance of proper assembly of HspB1 oligomeric complexes, since reversible association and dissociation of subunits is a prerequisite of normal HspB1 functioning [37].

It is important to answer the question which cellular processes are negatively affected by HspB1 mutations. As already mentioned, mutations in HspB1 are associated with the axonal form of CMT that affects neuronal axons [27]. Therefore, it was suggested that in the case of HspB1 mutants, CMT is caused mainly by the axonal damage [38, 39]. HspB1 might directly or indirectly affect the stability of the cytoskeleton formed by microtubules and intermediate filaments (neurofilaments), which are the major components of neuronal cytoskeleton. Indeed, it was shown that HspB1 interacts with tubulin, thus increasing the stability of microtubules [40]. It is believed that mutations in the ACD promote HspB1 affinity to tubulin and stabilize microtubules [41, 42]. Under normal conditions, microtubules are dynamic structures that constantly undergo reversible polymerization/depolymerization [43]. To compensate for the stabilization of microtubules caused by HspB1 mutations, cells upregulate the activity of histone deacetylase 6 (HDAC6), an enzyme that deacetylates tubulin, thereby inducing microtubule depolymerization and causing damage of the axonal cytoskeleton [43]. In this respect, it should be mentioned that recently developed highly specific inhibitors of histone deacetylase are considered as promising drugs for the treatment of type II CMT [44].

The second important component of cytoskeleton that can be affected by HspB1 is intermediate filaments (neurofilaments). HspB1 mutations S135F and P182L are associated with the neurofilament network damage

and can lead to cell death [45, 46]. Mutations R127W, S135F, and P182L are accompanied by an increase in the extent of neurofilament phosphorylation by cdk5 protein kinase and also result in the cytoskeletal damage [47].

Experiments on transgenic mice expressing human HspB1 mutants S135F and R136W correlate with the data obtained on cell cultures. The animals demonstrated symptoms characteristic for CMT, such as locomotion impairments, axonal damage, increased level of neurofilament phosphorylation, and decreased level of tubulin acetylation [48, 49], although less pronounced than in CMT patients. There are no doubts that comprehensive understanding of molecular mechanisms underlying the association of HspB1 mutations with the CMT development requires further clinical and experimental studies.

Mutations in another Hsp, HspB8 (Hsp22), can also be associated with the CMT [29]. As in HspB1, these mutations can be located in NTD, ACD, or CTD of HspB8. However, the mutation hotspot is Lys141 residue that can be replaced by Asn, Met, Glu, or Thr. This residue is homologous to Arg140 in HspB1, Arg116 in HspB4, and Arg120 in HspB5. It is located at the interface of two monomers and participates in the stabilization of the contact between the monomers by forming a salt bridge with negatively charged residue of the neighboring monomer [31]. Unlike HspB1, HspB8 forms only small oligomers that presumably exist as an equilibrium mixture of dimers with monomers [50, 51]. Probably due to this fact, mutation K141E does not affect the quaternary structure of HspB8. However, it destabilizes the structure of HspB8 and makes it more susceptible to limited proteolysis [52]. Depending on the nature of protein substrate, the K141E mutant possesses either equal or slightly lower chaperone-like activity than the wild-type HspB8 [52]. Some experiments indicated that K141 substitution decreases HspB8 affinity to the adapter protein Bag3 [53, 54], whereas other studies demonstrated that this mutation, on the contrary, increases HspB8 affinity to Bag3 [28]. Bag3 forms heterooligomeric complex with HspB8, heat shock protein Hsc70, and chaperone-interacting ubiquitin ligase (CHIP) that catalyzes ubiquitination of denatured proteins followed by proteolytic degradation in autophagosomes [23, 29]. Mutation-induced changes in the interaction between HspB8 and Bag3 can disturb the process of proteolytic degradation of denatured proteins and lead to various neurodegenerative diseases. Recently published data indicate that certain HspB1 mutations can also affect normal processes of autophagy and phagophore formation [55].

To conclude this part of the review, mutations in sHsps are associated with the axonal form of CMT. Mutations in HspB1 shift the equilibrium between different oligomeric forms, thereby affecting HspB1 interaction with target proteins, in particular, cytoskeletal components (Fig. 3). Cytoskeleton damage can result in neuronal death. Mutations in HspB8 alter its interaction with Bag3, leading to the impairments in the chaperone-assisted ubiquitination and autophagy. This results in the accumulation of denatured proteins followed by cell death (Fig. 3). In other words, mutations in sHsps disturb proteostasis.

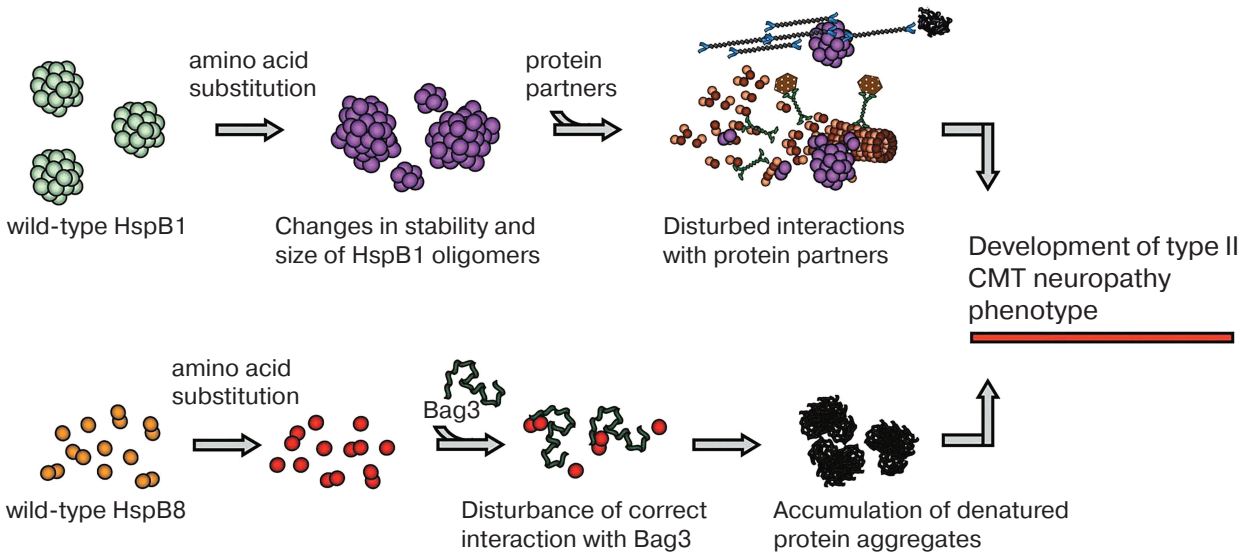

Fig. 3. Probable mechanisms underlying effects of CMT-associated mutations. Mutations in HspB1 are often associated with changes in the stability of protein oligomers or in the regulation of HspB1 oligomeric state, which disturbs HspB1 interaction with protein targets and partners resulting in cytoskeletal damage and other impairments. Mutations in HspB8 affect its interaction with the adapter protein Bag3, affecting autophagy and leading to the accumulation of denatured protein aggregates.

Let us address another problem, namely, how sHsps prevent accumulation of protein aggregates and amyloid fibrils formed by denatured proteins and proteins prone to amyloidosis.

sHsps AND AMYLOIDOSIS

Many proteins contain in their structure long stretches of amino acid sequence that can form β-strands. In addition, certain point mutations can increase the probability of β-strand formation from α-helices or random coils. When such regions are brought in close vicinity to each other and are present at high concentrations, they can interact with the formation of prefibrils due to lateral aggregation. The prefibrils can then transform into fibrils and inclusion bodies. Among proteins prone to amyloid formation are α-synuclein, amyloid peptide Aβ1-40, prions, tau protein, and many others.

The effect of sHsps on synuclein aggregation has been comprehensively studied. Synuclein, a comparatively small protein of 140 a.a., belongs to intrinsically disordered proteins. During interaction with the membrane or formation of tetramers, most of the synuclein sequence forms ordered α-helical regions. In addition, synuclein can exist as unordered monomers or misfolded monomers prone to aggregation [56]. The probability of misfolding is increased by the action of stress factors and mutations A53T, A30P, and E46K [57]. Destabilized misfolded monomers form β-amyloid prefibrils that are then transformed into fibrils or Lewy bodies detected in neurons of Parkinson's disease patients [57].

Formation of synuclein aggregates (Lewy bodies) is often accompanied by upregulation of HspB1 and HspB5 expression [58]. Detailed studies on the impact of sHsps on synuclein aggregation have led to the conclusion that HspB1 and HspB5 do not form tight complexes with synuclein monomers; however, they can stabilize the structure of the monomer and prevent its transition to the form prone to oligomerization and aggregation. These effects were observed for both intact sHsps and their isolated ACDs [59]. HspB1 and HspB5 also interact with small synuclein aggregates and even with amyloid fibrils, preventing their dissociation and induction of secondary nucleation [60]. It was shown that HspB1 can be located on the surface of synuclein fibrils, thereby decreasing their hydrophobicity and preventing their aggregation and elongation [61].

Interestingly, isolated ACD efficiently stabilizes the structure of monomeric synuclein but is unable to interact with synuclein fibrils and cannot prevent their aggregation and elongation [61]. It was suggested that the sites responsible for the prevention of amorphous aggregation of model protein substrates and for the inhibition of amyloid formation are located in different parts of the sHsp molecule. The sites responsible for the prevention of amorphous aggregation are located in the NTD, whereas the sites responsible for the prevention of amyloid peptide Aβ1-40 aggregation are located in the central ACD [62]. This is possible because of the interaction of ACD containing six or seven β-strands with β-strands of the protein target. In this respect, it should be mentioned that under *in vitro* conditions, crystallin itself can form functionally active β-amyloids with the chaperone-like activity comparable to that of intact protein [12, 13]. Moreover, recently published data indicate that β-amyloid can be accumulated in cataract eye lens [63].

According to the prevailing concept, sHsps, including HspB1 and HspB5, prevent aggregation of synuclein by stabilizing its monomers and/or suppressing fibril formation. Unexpectedly, it was found that overexpression of HspB5 in human glioblastoma cells promotes accumulation of synuclein aggregates in astrocytes [64], which may be due to the competition between overexpressed HspB5 and HspB8 for the interaction with Bag3 and inhibition of autophagy.

Apart from synuclein, sHsps (HspB1, HspB5, HspB6, HspB8) can interact with Aβ-amyloid peptides. Different sHsps were found to accumulate in senile plaques formed mostly by amyloid peptides in the cells of Alzheimer's disease patients [65, 66]. sHsps (HspB1, HspB5, HspB6, HspB8) detected in these aggregates can be covalently linked to the amyloid peptide by transglutaminase [65]. sHsps not only co-localize with amyloid peptide aggregates but can also prevent their formation [67-69]. It is suggested that depending on the nature of amyloid peptide (Aβ1-42 or D-Aβ1-40), sHsps can affect interaction of its monomers (or small peptide oligomers) with the outer cell membrane, while HspB5 can prevents transition of protofibrils into mature fibrils [69]. Addition of amyloid peptide to the culture of cortical rat astrocytes was accompanied by the HspB1 release and binding of the added peptide [68]. HspB6 was found to protect neuroblastoma SH-SY5Y cells from the accumulation of Aβ-amyloid peptide aggregates [70]. HspB6 interacts with the peptide site responsible for its polymerization and aggregation. Phosphorylation of HspB6 promotes its interaction with the low-molecular-weight forms of amyloid peptide and increases its efficiency in preventing amyloidosis. Even small *N*-terminal peptide of HspB6 (25 a.a.) phosphorylated at Ser residue prevents aggregation of amyloid peptide fibrils [70].

Tau is another aggregation-prone protein that forms neurofibrillary tangles in the cells of Alzheimer's disease patients. Tau is a multifunctional intrinsically disordered protein that stabilizes microtubules [71] and can be phosphorylated by many protein kinases. Tau hyperphosphorylation decreases its interaction with tubulin and increases the probability of tau aggregation with the formation of inclusion bodies, which results in the development of various tauopathies [72, 73].

HspB1 predominantly interacts with hyperphosphorylated tau protein, thereby decreasing the amount of protein available for aggregation. Moreover, HspB1 increases the rate of dephosphorylation of paired helical filaments formed by the hyperphosphorylated tau [74]. It is believed that HspB1 recognizes the phosphorylation sites in tau structure, thus preventing its aggregation and promoting proteolytic degradation of this protein [75]. Experimental data indicate that hyperphosphorylation leads to further tau destabilization. This highly destabilized protein tends to aggregate, while HspB1 inhibits this process. In parallel, destabilized tau protein can undergo renaturation or proteolytic degradation, while HspB1 promotes both these processes [76]. The peptide corresponding to a.a. 244-369 of tau protein tends to form fibrils; HspB1 transiently interacts with this peptide and decreases the rate of fibril formation [77]. It was suggested that the VQI sequence twice repeated in the 244-369 a.a. peptide interacts with the hydrophobic groove formed by the ACD β4-β8 strands in HspB1, i.e., the sites occupied by the CTD (I/V)X(I/V) peptide in the absence of substrates [77, 78].

sHsps can affect tau aggregation both directly and indirectly. For instance, it was found that the adapter protein 14-3-3 transiently and weakly interacts with the nonphosphorylated tau; phosphorylation of the latter strongly increases the binding affinity of 14-3-3 protein [79-82]. Depending on the conditions and location of phosphorylation sites, 14-3-3 can either promote further tau phosphorylation and aggregation and/or stabilize tau aggregates, i.e., prevent their disassembly and emergence of especially deleterious small oligomers serving as new oligomerization seeds [83]. Phosphorylated HspB6 forms tight complexes with 14-3-3 [84] and, therefore, can efficiently compete with tau for the interaction with 14-3-3. Hence, phosphorylated HspB6 can indirectly modulate the effect of 14-3-3 on tau aggregation.

Experimental data on the impact of sHsps on prion aggregation are controversial. Introduction of the scrapie-inducing prion (scrapie 263 agent) into the hamster brain upregulated HspB5 synthesis; however, the authors failed to demonstrate HspB5 co-localization with PrP^{Sc} aggregates. The brain levels of HspB5 are significantly increased in various prion diseases, although it is unlikely that this increase affects pathogenesis of prion infections [85]. At the same time, yeast Hsp26 and Hsp42 were found to prevent prionogenesis of the yeast prion Sup35. Hsp42 suppressed the growth of fibrils from the ends, whereas Hsp26 inhibited self-association of prion fibrils. Moreover, by cooperating with Hsp40, Hsp70, and Hsp104, sHsps can destabilize prion fibrils and promote their disassembly [86].

In conclusion, sHsps predominantly interact with monomers (or small oligomers) of intrinsically disordered proteins prone to amyloid formation. By binding to these proteins, sHsps stabilize their structure, prevent their aggregation, and/or facilitate their proteolytic degradation (Fig. 4). It is highly probable that this type of interaction occurs with the participation of amyloidogenic β4-β8 strands of the ACDs of sHsps [62]. The binding of sHsps results in the formation of mixed structures, in which β-strands of sHsps interact with β-strands of amyloidogenic protein monomers. The similarity between the structures formed by amyloidogenic proteins and sHsps is supported

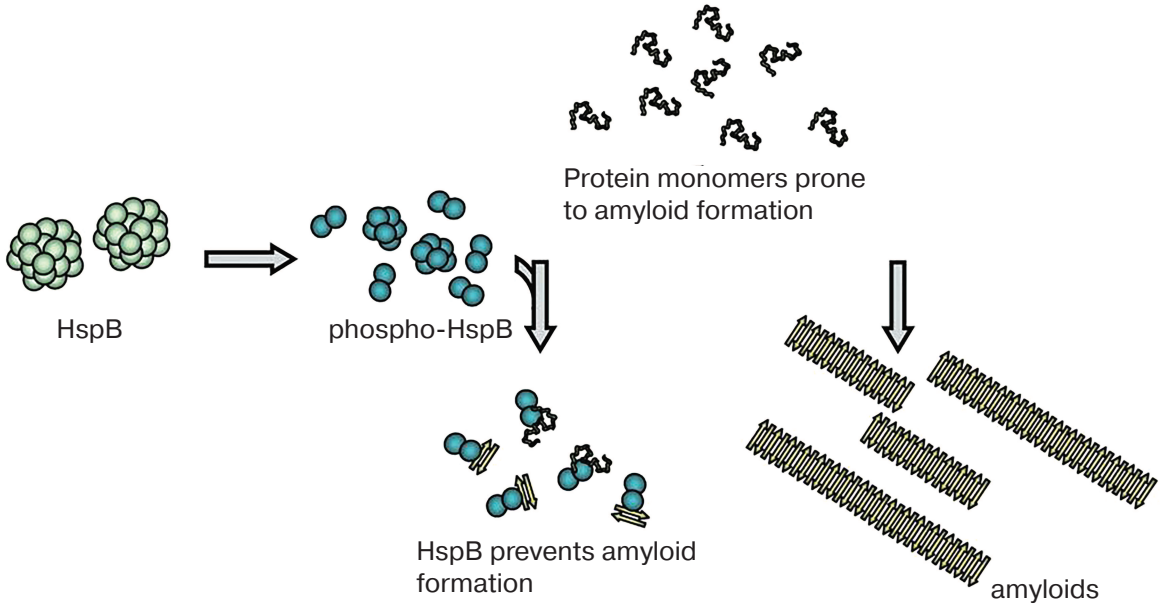

Fig. 4. Small oligomers formed upon sHsp phosphorylation at different sites can prevent amorphous aggregation of partially denatured proteins and accumulation of amyloid fibrils by binding monomers (or small oligomers) of amyloidogenic proteins.

by the fact that both sHsps (HspB5) and amyloids of tau protein interact with α7 nicotine acetylcholine receptors, inducing signal transmission through Stat3, activation of autophagy, and suppression of secretion of proinflammatory interleukins [87, 88]. It was hypothesized that in large sHsps oligomers, the β4-β8 strands responsible for the interaction with amyloidogenic proteins are occupied with the CTD tripeptide (I/V)P(I/V). Because of this, large sHsp oligomers interact poorly with amyloidogenic proteins. Stress factors and associated phosphorylation cause large sHsp oligomers to dissociate to small oligomers. This results in the exposure of hydrophobic β4-β8 strands that become available for the interaction with amyloidogenic proteins. After this, sHsps can efficiently prevent aggregation of protein substrates [89].

sHsps are important components of a complex chaperone system that ensure correct protein folding and prevent accumulation of partially denatured proteins in the cell. Certain sHsps (such as HspB1, HspB4, HspB5) exist in a form of labile large oligomers that are in the equilibrium with small oligomers. Mutations can affect the equilibrium between different oligomeric forms, thermal stability, chaperone-like activity, and interactions of sHsps with protein partners. Mutations in HspB8 can influence its interaction with the adapter protein Bag3 and autophagy regulation, ensuring selective proteolysis of misfolded proteins. Therefore, mutations in sHsps can lead to neurodegenerative disorders, such as CMT. Under certain conditions, ACD β-strands can interact with β-strands of amyloidogenic proteins and stabilize the structure of the latter, prevent their aggregation, and/or promote their proteolytic degradation. Hence, sHsps can prevent or delay the development of neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases, different forms of tauopathies, and prion diseases.

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Conflict of interest. The authors declare no conflict of interest in financial or any other area.

Compliance with ethical norms. This article does not contain studies with human participants or animals performed by any of the authors.

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