

# Molecular Chaperones in Neurodegenerative Diseases: A Short Review

Catherine Bobori, Georgia Theocharopoulou, and Panayiotis Vlamos

**Abstract** Stress and misfolded proteins result to dysfunction in the cell, often leading to neurodegenerative diseases and aging. Misfolded proteins form toxic aggregates that threaten cell's stability and normal functions. In order to restore its homeostasis, the cell activates the UPR system. Leading role in the restoration play the molecular chaperones which target the misfolded proteins with the purpose of either helping them to unfold and refold to their natural state or lead them degradation. This paper aims to present some of the most known molecular chaperones and their relation with diseases associated to protein misfolding and neurodegeneration, as well as the role of chaperones in proteostasis.

**Keywords** Molecular chaperones • Neurodegenerative diseases • Alzheimer disease • Huntington's disease • Misfolded proteins • UPR • Protein folding

## 1 Introduction

The concept of proteostasis maintenance involves the biological pathways which are critical for post-mitotic cells, such as neurons. Disruption of the mechanisms of proteostasis is increasingly referred in many studies, to be involved in neurodegenerative diseases. Dysregulation of some of the key mechanisms which have been evolved to maintain cellular homeostasis, such as protein folding, as well as the presence of molecular chaperones and degradation mechanisms, are implicated as pathological hallmark of these diseases.

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C. Bobori  
Bioinformatics and Human Electrophysiology Laboratory (BiHELab), Department of Informatics, Ionian University, 7 Tsirigoti Square, Corfu, Greece  
e-mail: [p12bobo@ionio.gr](mailto:p12bobo@ionio.gr)

G. Theocharopoulou (✉)  
Department of Informatics, Ionian University, Corfu, Greece  
e-mail: [zeta.theo@ionio.gr](mailto:zeta.theo@ionio.gr)

P. Vlamos  
Department of Informatics, Bioinformatics and Human Electrophysiology Laboratory, Ionian University, Corfu, Greece  
e-mail: [vlamos@ionio.gr](mailto:vlamos@ionio.gr)

Protein misfolding and formation of toxic aggregates within affected neurons are thought to be involved in the pathogenesis many age-related diseases, such as Alzheimer's disease. Whilst neurodegenerative diseases differ in the proteins which appear to misfold, one common feature is the disruption of the protein quality control system.

Chaperone machinery is involved in the assembly of the unique three-dimensional structure of proteins. Chaperones play a ubiquitous role in the cytoplasmic meshwork: they are highly abundant, they form a complex with all the elements of the cytoskeleton and they also attach to a plethora of other proteins [1]. Molecular chaperones serve to prevent protein misfolding, participate in the loose folding procedure, assist in folding and refolding of damaged proteins and target severely damaged proteins to degradation and sequester them to larger aggregates. Therefore, chaperones are key components to this protein quality control system [2].

The native folding of proteins can be disrupted by stress, molecular crowding and mutations [3]. Driven by ATP, chaperones gradually convert toxic misfolded protein substrates, into non-toxic, natively refolded. Stress and protein damages can lead to cellular dysfunction, causing degenerative diseases and aging [4]. These conditions activate cellular stress-response pathways, including the UPR, which counteract stress and help restore homeostasis to protein folding in the ER [5].

Chaperone complex disruption results in instability and incorrect subcellular localization of the signaling protein [6]. Besides the major role of chaperones, which is to target all misfolded proteins with hydrophobic surfaces, there are also specialized chaperones that stabilize several signal transduction networks important to cancer cells [7].

## 2 Why Proteins Misfold?

Misfolding may originate from improper interactions between regions of the folding polypeptide chain. Another factor is the crowded nature of the intracellular environment that may prevent folding from proceeding at a biologically relevant time scale [8]. Incompletely folded proteins, often tend to inappropriate interactions with other molecules [9] and aggregate in the cell due to high local concentration of nascent chains [10]. There may be several kinds of aggregates, including disordered or 'amorphous' aggregates, but amyloid fibrils are the most characteristic [11]. Deposition of abnormal protein aggregation characterizes most neurodegenerative disorders, not just AD and Parkinson's, but also motor neuron diseases, as well as diseases of peripheral tissue like familial amyloid polyneuropathy, Charcot-Marie-Tooth [12–15].

### 3 How Chaperones Prevent Aggregation

The cellular strategy to counteract the aggregation of non-native proteins is the chaperone machinery. The heat shock proteins (HSPs) are the main chaperone classes which are referred to prevent the accumulation of misfolded conformers (e.g. HSP60 and HSP70) [16]. The reversibility of protein aggregation has been first observed to be mediated by heat-shock protein Hsp104 [17]. Chaperone binding blocks intermolecular aggregation of non-native polypeptides and may also prevent, or reverse intramolecular misfolding [18, 19]. Those proteins that do not succeed to fold correctly are selected for degradation by the protein control system. This is achieved through the proteasome and the chaperone mediated autophagy [20]. Increasing evidence show that perturbation of these functions plays a key role in the pathogenesis of severe human disorders [21, 22].

Moreover, the ability of maintaining cellular proteostasis declines with aging, which results in the accumulation of misfolded proteins, deposition of aggregates, cellular toxicity and eventually cell death [23–25]. The age-related accumulation of oxidized proteins has been proposed to be due to either, or both, increased protein oxidative damage and decreased oxidized protein degradation and repair [26]. This deterioration of proteostasis is a characteristic risk factor of many human pathologies and represents a hallmark which is considered to contribute to the aging process [27].

The role of chaperone function and the simultaneous protein oxidation, misfolding and aggregation in aged organisms, suggest that preservation of protein homeostasis and long-range protein organization have a major role in neurodegeneration and aging [1, 28, 29].

### 4 ER Stress and the Unfolded Protein Response

Although differential mechanisms have been described to be involved in different neurodegenerative conditions, endoplasmic reticulum (ER) stress is increasingly implicated as a key factor relevant to pathogenesis of AD and other neurodegenerative diseases [30, 31]. The accumulation of misfolded or deficiently modified proteins within the ER, disturbs ER homeostasis, giving rise to ER stress, which results in activation of the unfolded protein response (UPR) [32, 33]. The UPR involves [31, 34]:

- up-regulation of protein chaperones to promote protein folding,
- translational attenuation to reduce the load of proteins within the ER to prevent further accumulation of misfolded proteins,
- up-regulation of ER-associated protein degradation (ERAD) and
- autophagy to promote degradation of misfolded proteins

Therefore, ER stress triggering of UPR plays a pivotal role in maintaining cell proteostasis [35, 36]. In circumstances of chronic or prolonged ER stress, however, the UPR seems to trigger apoptotic signalling cascades [37, 38]. The ER response

includes changes in specific proteins, which might cause translational attenuation, induction of ER chaperones and degradation of misfolded proteins [39]. In case of prolonged or aggravated ER stress, apoptotic signalling is stimulated, which leads to cell death [40]. The dual functions of ER stress appears to switch from pro-survival to pro-apoptosis [41–43].

## 5 Chaperones and Diseases

Molecular chaperones have a ubiquitous role in the protein quality control system. Misfolded proteins are usually refolded with the assistance of molecular chaperons and/or degraded by the ubiquitin-proteasome system. In many studied the protective effects of overexpressing chaperones in models of misfolding disease is promoted. The role of different chaperones, their function and their association in different neurological diseases is summarized in the table in Appendix section.

### 5.1 *Alzheimer's Disease*

Amyloid fibrils,  $A\beta$  aggregation, are a well-characterized aggregation state associated with Alzheimer's disease [44]. Several studies have investigated the role of heat shock proteins in AD [45]. Some studies suggest that the induction of small heat-shock proteins, Hsp70, protects neurons from protein aggregation and toxicity [46, 47]. In addition to HSP70 the complex of Hsp90 can also inhibit  $A\beta$  formation and slow the rate of aggregation [48]. Other studies showed that ubiquitin (a heat-shock protein, which labels damaged proteins and directs them for proteolytic degradation) is affected by Alzheimer's disease, in neurons and in surrounding astrocytes [49]. The role that HSPs may act therapeutically as neuroprotective agents, by modulating innate immune activation is reviewed in [50].

### 5.2 *Parkinson's Disease*

Parkinson's disease is the second most common movement disorder, characterized by motor impairments—bradykinesia, rigidity, and resting tremor, caused by a progressive degeneration of dopaminergic neurons in the substantia nigra [51]. An increasing number of evidence shows that endoplasmic reticulum stress and the unfolded protein response are also key elements of Parkinson's disease etiology [52]. These results suggest a proposed therapeutic strategy to ensure appropriate protein folding and to avoid ER stress. This requires an efficient chemical or molecular chaperone network to promote the appropriate folding of proteins [53]. A number of chaperone-based therapies are under development, which aim to prevent the formation of potentially toxic—synuclein oligomers and aggregates [54].

### ***5.3 Amyotrophic Lateral Sclerosis***

Amyotrophic Lateral Sclerosis also known as ALS is a neurodegenerative disease that affects the upper and lower motor neurons. Molecular analyses have shown that the disease is primarily caused due to a mutation either to SOD1 (Cu/Zn superoxide dismutase) or to FUS (fused in sarcoma) [55]. Mutant SOD1 is related to the Hsp70/Hsp90 network and its degradation seems to be regulated by CHIP, another co-chaperone [56]. Ubiquitinated SOD1 forms aggregates, that are associated with Hsc70 which might be able to protect Sod1 from degradation while Hsp70 favors it [57]. Therapeutic strategies that inhibit Hsp90 and increase Hsp70 activity are investigated in some cellular and animal ALS models [58].

### ***5.4 Huntington's Disease***

Amyloid-like inclusions have been associated also with Huntington's disease (HD), which is caused by expanded polyglutamine repeats in the Huntingtin protein [59]. HD is an autosomal, dominant and inherited neurodegenerative disease that is focused on the region of basal ganglia causing mental, emotional and motor problems to the patients. In Huntington's, the responsible gene (IT15) for the production of protein huntingtin is mutated causing expanded repetition of the trinucleotide CAG, which in turn makes the produced polyglutamine strand toxic for the brain. As a result, neurons which contain the mutant protein begin to atrophy [60, 61]. The normal function of huntingtin is to maintain brain cells in a good condition and to help in intracellular procedures. The mutation at the beginning of the huntingtin gene causes the destabilization of the protein leading to problems; it interferes with the typical function of [62]. Mutant huntingtin (m-htt) affects many cytoplasmic proteins which are related to apoptosis, transcription, mitochondrial function and other vital for the cell procedures. M-htt joins together with other proteins forming protein aggregates. Protein aggregation is the phenomenon when misfolded proteins clump together inside or outside the cell. Those forms are toxic for the cell and reduce the Ubiquitin Proteasome System function (UPS) [63, 64].

### ***5.5 Charcot-Marie-Tooth Disease***

Autosomal Dominant Demyelinating Neuropathies CMT1 (Charcot-Marie-Tooth Disease type1) is associated with an autosomal dominant duplication on a chromosome that includes the peripheral myelin protein 22 gene (PMP22) [65]. When overexpressed in cultured cells, PMP22 has been observed to form protein

aggregates [66]. In other studies were found that misfolded protein SIMPLE forms abnormal cytosolic aggregates. These findings suggest that demyelinating CMT may be a protein-misfolding disease of Schwann cells [67].

## ***5.6 Creutzfeldt-Jakob Disease and Other Prion Encephalopathies***

Prion proteins from mammalian species, are prone to amyloid-like prion diseases, like Creutzfeld-Jakob disease [68]. In many studies it is referred that chaperones try to block the contact surfaces of prion molecules [1]. Many chaperones, such as Hsp60, Hsp70, or its co-chaperone, Hsp40 were found to fight against prion aggregation [69, 70]. The “chaperone overload” hypothesis emphasises the need for efficient ways to enhance chaperone-capacity in ageing subjects and calls for the identification and future “repair” of silent mutations [1].

## ***5.7 Conclusions***

Researches suggest that protein aggregation is part of the cellular response to an imbalanced protein homeostasis. Intense research interest to unravel the pathophysiological significance of these protein aggresome has unveiled the important role of chaperones in proteostasis, by promoting the correct folding of proteins into their native conformations. Therefore, novel therapeutic strategies should aim at the role of chaperones to prevent aberrant protein misfolding and promoting maintenance of cellular homeostasis.

## **Appendix**

Chaperone	Location	Role	Characteristics	Related disease
UPR	Lumen of ER	<p>Halting protein translation</p> <p>Degrading misfolded proteins</p> <p>Activating signaling pathways that increase the production of molecular chaperones apoptosis</p> <p>Assembly of nucleosomes form histones to DNA</p> <p>Convey folding information into some other proteins</p>		<p>Creutzfeldt-Jakob disease,</p> <p>Alzheimer's disease,</p> <p>Parkinson's disease,</p> <p>Huntington's disease</p> <p>Prion diseases</p>
First chaperone	Nucleus			
Steric chaperone				
Calnexin/Calreticulin	Lumen of ER	<p>Calnexin forms part of the quality control monitor that recognize and target abnormally folded proteins for rapid degradation</p> <p>Protein folding</p> <p>Functions as a chaperone for the folding of MHC class I <math>\alpha</math>-chain in the membrane of the ER</p> <p>Calreticulin binds to misfolded proteins and prevents them from being exported from the endoplasmic reticulum to the Golgi apparatus</p> <p>Calreticulin, an abundant ER chaperone was shown to participate in the quality control of the amyloid precursor protein</p>	<p>Lectin chaperones</p> <p>Glycan processing</p>	HD

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Chaperone	Location	Role	Characteristics	Related disease
Crystallin				AD
Hsp47/ERp29	ER	Non classical molecular chaperones	Hsp47 Procollagen chaperone	
PDI/PPI/ERp57	ER	Folding chaperones		
Transfer chaperones (Sec61 membrane protein)	Mitochondria & ER of eukaryotes	Transport across membranes		
GroEl/GroEs, DnaK/DnaJ/GrpC		Foldases	DnaK is an Hsp70 protein.  One of Hsp40 chaperones is DnaJ (75-residue protein), which interacts with DnaK (a Hsp70 chaperone) and assists in capturing substrate proteins	
DnaJ/Hsp53		Holdases	DnaJ is one of Hsp40	AD,PD
GRP78/BiP/GRP94	ER	General chaperones		
GRP170				
Erp57/BiP	ER	Quality control	Recognize misfolded proteins and help their retention in the ER allowing only correctly folded proteins to the cytosol	
Hsp60/Hsp100/Hsp90		Hsp100/Hsp90 Protein disaggregation and refolding	Heat shock proteins,ATP/ADP	HD, prion diseases
Hsp70/Hsp40		Are involved in blocking aggregation of misfolded proteins by binding to their hydrophobic segments	Hsp70 consists of ATP-binding N-terminal domain and peptide binding C-terminal domain Hsp70 works in tandem with Hsp40 co-chaperone	AD, PD, HD, prion diseases



			<p>Proteins in a cell may experience partial unfolding due to variety of factors, such as temperature increase, pH change etc. Some proteins may also fail to reach their native states after synthesis. As result such proteins adopt aggregation-prone states. To prevent this Hsp70 binds to such proteins and act as a general "safe keeper" for misfolded proteins</p> <p>Transport substances from ER to cytoplasm</p>	
Cdc48p (valosin containing protein (VCP/p97))	ER	Ubiquitin binding protein		
PDIA3 (Protein disulfide isomeric A3)	ER	<p>Interacts with lectin chaperones</p> <p>Modulate folding of newly synthesized glycoproteins</p> <p>Correlates with the expression level of expressed proteins in order to adapt the folding capacity of the ER to the respective requirements</p>		
X-box binding protein (Xbp1)	Part of UPR			AD, Crohn's disease

## References

1. Söti, C., and P. Csermely. 2002. Chaperones and aging: role in neurodegeneration and in other civilizational diseases. *Neurochemistry International* 41(6):383–389.
2. Tirolì-Cepeda, A.O., and C.H.I. Ramos. 2011. An overview of the role of molecular chaperones in protein homeostasis. *Protein and Peptide Letters* 18(2):101–109.
3. Sharma, S.K., P. Christen, and P. Goloubinoff. 2009. Disaggregating chaperones: an unfolding story. *Current Protein and Peptide Science* 10(5):432–446.
4. Fulda, S., A.M. Gorman, O. Hori, and A. Samali. 2010. Cellular stress responses: cell survival and cell death. *International Journal of Cell Biology* 2010:214074.
5. Pincus, D., A. Aranda-Díaz, I.A. Zuleta, P. Walter, and H. El-Samad. 2014. Delayed Ras/PKA signaling augments the unfolded protein response. *Proceedings of the National Academy of Sciences* 111(41):14,800–14,805.
6. Pratt, W.B., and D.O. Toft. 2003. Regulation of signaling protein function and trafficking by the Hsp90/Hsp70-based chaperone machinery. *Experimental Biology and Medicine* 228(2):111–133.
7. Hong, D.S., U. Banerji, B. Tavana, G.C. George, J. Aaron, and R. Kurzrock. 2013. Targeting the molecular chaperone heat shock protein 90 (Hsp90): lessons learned and future directions. *Cancer Treatment Reviews* 39(4):375–387.
8. Moreno-Gonzalez, I., and C. Soto. 2011. Misfolded protein aggregates: mechanisms, structures and potential for disease transmission. In *Seminars in Cell and Developmental Biology*, vol. 22, 482–487. New York: Elsevier.
9. Dobson, C.M. 2003. Protein folding and misfolding. *Nature* 426(6968):884–890.
10. Jha, S. 2009. *Molecular Biology of Protein Folding*, vol. 84. Amsterdam: Academic.
11. Ross, C.A., and M.A. Poirier. 2004. Protein aggregation and neurodegenerative disease. *Nature Reviews Neuroscience* 5:S10–S17.
12. Berger, P., A. Niemann, and U. Suter. 2006. Schwann cells and the pathogenesis of inherited motor and sensory neuropathies (Charcot–Marie–Tooth disease). *Glia* 54(4):243–257.
13. Koo, E.H., P.T. Lansbury, and J.W. Kelly. 1999. Amyloid diseases: abnormal protein aggregation in neurodegeneration. *Proceedings of the National Academy of Sciences* 96(18):9989–9990.
14. Planté-Bordeneuve, V., and G. Said. 2011. Familial amyloid polyneuropathy. *The Lancet Neurology* 10(12):1086–1097.
15. Wood, J., T. Beaujeux, and P. Shaw. 2003. Protein aggregation in motor neurone disorders. *Neuropathology and Applied Neurobiology* 29(6):529–545.
16. Tyedmers, J., A. Mogk, and B. Bukau. 2010. Cellular strategies for controlling protein aggregation. *Nature Reviews Molecular Cell Biology* 11(11):777–788.
17. Parsell, D.A., A.S. Kowal, M.A. Singer, and S. Lindquist. 1994. Protein disaggregation mediated by heat-shock protein Hsp104. *Nature* 372(6505):475–478.
18. Bukau, B., and A.L. Horwich. 1998. The Hsp70 and Hsp60 chaperone machines. *Cell* 92(3):351–366.
19. Hartl, F.U., and M. Hayer-Hartl. 2002. Molecular chaperones in the cytosol: from nascent chain to folded protein. *Science* 295(5561):1852–1858.
20. Arias, E., and A.M. Cuervo. 2011. Chaperone-mediated autophagy in protein quality control. *Current Opinion in Cell Biology* 23(2):184–189.
21. Koga, H., and A.M. Cuervo. 2011. Chaperone-mediated autophagy dysfunction in the pathogenesis of neurodegeneration. *Neurobiology of Disease* 43(1):29–37.
22. Orenstein, S.J., and A.M. Cuervo. 2010. Chaperone-mediated autophagy: molecular mechanisms and physiological relevance. *Seminars in Cell and Developmental Biology* 21(7):719–726.
23. David, D.C., N. Ollikainen, J.C. Trinidad, M.P. Cary, A.L. Burlingame, and C. Kenyon. 2010. Widespread protein aggregation as an inherent part of aging in *C. elegans*. *PLoS Biol* 8(8):e1000450.

24. Morley, J.F., H.R. Brignull, J.J. Weyers, and R.I. Morimoto. 2002. The threshold for polyglutamine-expansion protein aggregation and cellular toxicity is dynamic and influenced by aging in *Caenorhabditis elegans*. *Proceedings of the National Academy of Sciences* 99(16):10,417–10,422.
25. Olzscha, H., S.M. Schermann, A.C. Woerner, S. Pinkert, M.H. Hecht, G.G. Tartaglia, M. Vendruscolo, M. Hayer-Hartl, F.U. Hartl, and R.M. Vabulas. 2011. Amyloid-like aggregates sequester numerous metastable proteins with essential cellular functions. *Cell* 144(1):67–78.
26. Friguet, B. 2006. Oxidized protein degradation and repair in ageing and oxidative stress. *FEBS Letters* 580(12):2910–2916.
27. López-Otín, C., M.A. Blasco, L. Partridge, M. Serrano, and G. Kroemer. 2013. The hallmarks of aging. *Cell* 153(6):1194–1217.
28. Leak, R.K. 2014. Heat shock proteins in neurodegenerative disorders and aging. *Journal of Cell Communication and Signaling* 8(4):293–310.
29. Verbeke, P., J. Fonager, B.F. Clark, and S.I. Rattan. 2001. Heat shock response and ageing: mechanisms and applications. *Cell Biology International* 25(9):845–857.
30. Pereira, C.M. 2013. Crosstalk between endoplasmic reticulum stress and protein misfolding in neurodegenerative diseases. *ISRN Cell Biology* 2013:1–22.
31. Perri, E.R., C.J. Thomas, S. Parakh, D.M. Spencer, and J.D. Atkin. 2015. The unfolded protein response and the role of protein disulfide isomerase in neurodegeneration. *Frontiers in Cell and Developmental Biology* 3:80.
32. Salminen, A., A. Kauppinen, T. Suuronen, K. Kaarniranta, and J. Ojala. 2009. ER stress in alzheimer's disease: a novel neuronal trigger for inflammation and alzheimer's pathology. *Journal of Neuroinflammation* 6(1):1.
33. Schröder, M., and R.J. Kaufman. 2005. The mammalian unfolded protein response. *Annual Review of Biochemistry* 74:739–789.
34. Rao, R.V., and D.E. Bredesen. 2004. Misfolded proteins, endoplasmic reticulum stress and neurodegeneration. *Current Opinion in Cell Biology* 16(6):653–662.
35. Manié, S.N., J. Lebeau, and E. Chevet. 2014. Cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. 3. Orchestrating the unfolded protein response in oncogenesis: an update. *American Journal of Physiology-Cell Physiology* 307(10):C901–C907.
36. Tabas, I., and D. Ron. 2011. Integrating the mechanisms of apoptosis induced by endoplasmic reticulum stress. *Nature Cell Biology* 13(3):184–190.
37. Logue, S.E., P. Cleary, S. Saveljeva, and A. Samali. 2013. New directions in ER stress-induced cell death. *Apoptosis* 18(5):537–546.
38. Rutkowski, D.T., and R.J. Kaufman. 2007. That which does not kill me makes me stronger: adapting to chronic er stress. *Trends in Biochemical Sciences* 32(10):469–476.
39. Lindholm, D., H. Wootz, and L. Korhonen. 2006. ER stress and neurodegenerative diseases. *Cell Death and Differentiation* 13(3):385–392.
40. Sano, R., and J.C. Reed. 2013. ER stress-induced cell death mechanisms. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1833(12):3460–3470.
41. Kadowaki, H., H. Nishitoh, and H. Ichijo. 2004. Survival and apoptosis signals in er stress: the role of protein kinases. *Journal of Chemical Neuroanatomy* 28(1):93–100.
42. Kim, I., W. Xu, and J.C. Reed. 2008. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nature Reviews Drug Discovery* 7(12):1013–1030.
43. Nishitoh, H. 2012. Chop is a multifunctional transcription factor in the er stress response. *Journal of Biochemistry* 151(3):217–219. doi:10.1093/jb/mvr143, <http://jb.oxfordjournals.org/content/151/3/217.abstract>.
44. Frokjaer, S., and D.E. Otzen. 2005. Protein drug stability: a formulation challenge. *Nature Reviews Drug Discovery* 4(4):298–306.
45. Asea, A.A., and I.R. Brown. 2008. *Heat Shock Proteins and the Brain: Implications for Neurodegenerative Diseases and Neuroprotection*, vol. 3. London: Springer Science and Business Media.

46. Franklin, T., A. Krueger-Naug, D. Clarke, A.P. Arrigo, and R. Currie. 2005. The role of heat shock proteins Hsp70 and Hsp27 in cellular protection of the central nervous system. *International Journal of Hyperthermia* 21(5):379–392.
47. Turturici, G., G. Sconzo, and F. Geraci. 2011. Hsp70 and its molecular role in nervous system diseases. *Biochemistry Research International* 2011:1–18.
48. Ou, J.R., M.S. Tan, A.M. Xie, J.T. Yu, and L. Tan. 2014. Heat shock protein 90 in alzheimer's disease. *BioMed Research International* 2014:796869.
49. Lajtha, A., G. Gibson, and G. Dienel. 2007. *Handbook of Neurochemistry and Molecular Neurobiology: Neuroactive Proteins and Peptides*, Ed. Kriegstein, J., 123142. New York: Springer.
50. Amor, S., M. Bugiani, and J. van Noort. 2016. Heat shock proteins: old and novel roles in neurodegenerative diseases in the central nervous system. *CNS and Neurological Disorders Drug Targets*.
51. Alexander, G.E. 2004. Biology of parkinson's disease: pathogenesis and pathophysiology of a multisystem neurodegenerative disorder. *Dialogues in Clinical Neuroscience* 6:259–280.
52. Ryu, E.J., H.P. Harding, J.M. Angelastro, O.V. Vitolo, D. Ron, and L.A. Greene. 2002. Endoplasmic reticulum stress and the unfolded protein response in cellular models of parkinson's disease. *The Journal of Neuroscience* 22(24):10,690–10,698.
53. Varma, D., and D. Sen. 2015. Role of the unfolded protein response in the pathogenesis of parkinson's disease. *Acta Neurobiologiae Experimentalis* 75:1–26.
54. Ebrahimi-Fakhari, D., L.J. Saidi, and L. Wahlster. 2013. Molecular chaperones and protein folding as therapeutic targets in parkinson's disease and other synucleinopathies. *Acta Neuropathologica Communications* 1(1):1.
55. Redler, R.L., and N.V. Dokholyan. 2012. The complex molecular biology of amyotrophic lateral sclerosis (ALS). *Progress in Molecular Biology and Translational Science* 107:215.
56. Mayer, M., and B. Bukau. 2005. Hsp70 chaperones: cellular functions and molecular mechanism. *Cellular and Molecular Life Sciences* 62(6):670–684.
57. Kubota, H. 2009. Quality control against misfolded proteins in the cytosol: a network for cell survival. *Journal of Biochemistry* 146(5):609–616.
58. Carman, A., S. Kishinevsky, W.L. John Koren III, and G. Chiosis. 2013. Chaperone-dependent neurodegeneration: a molecular perspective on therapeutic intervention. *Journal of Alzheimer's Disease and Parkinsonism* 2013 (Suppl 10).
59. Melkani, G.C., A.S. Trujillo, R. Ramos, R. Bodmer, S.I. Bernstein, and K. Ocorr. 2013. Huntington's disease induced cardiac amyloidosis is reversed by modulating protein folding and oxidative stress pathways in the drosophila heart. *PLoS Genet* 9(12):e1004,024.
60. Plerou, A., and P. Vlamos. 2015. Evaluation of mathematical cognitive functions with the use of eeg brain imaging. In *Experimental Multimedia Systems for Interactivity and Strategic Innovation*, 284–306. Hershey, P.A.: IGI Global.
61. Plerou, A., C. Bobori, and P. Vlamos. 2015. Molecular basis of huntington's disease and brain imaging evidence. In *2015 IEEE International Symposium on Signal Processing and Information Technology (ISSPIT)*, 387–391. Piscataway, NJ: IEEE.
62. Schulte, J., and J.T. Littleton. 2011. The biological function of the huntingtin protein and its relevance to huntingtons disease pathology. *Current trends in neurology* 5:65.
63. Scherzinger, E., R. Lurz, M. Turmaine, L. Mangiarini, B. Hollenbach, R. Hasenbank, G.P. Bates, S.W. Davies, H. Lehrach, and E.E. Wanker. 1997. Huntingtin-encoded polyglutamine expansions form amyloid-like protein aggregates in vitro and in vivo. *Cell* 90(3):549–558.
64. Stefani, M., and C.M. Dobson. 2003. Protein aggregation and aggregate toxicity: new insights into protein folding, misfolding diseases and biological evolution. *Journal of Molecular Medicine* 81(11):678–699.
65. Lupski, J.R., R.M. de Oca-Luna, S. Slaugenhaupt, L. Pentao, V. Guzzetta, B.J. Trask, O. Saucedo-Cardenas, D.F. Barker, J.M. Killian, and C.A. Garcia, et al. 1991. DNA duplication associated with Charcot-Marie-Tooth disease type 1A. *Cell* 66(2):219–232.

66. Juárez, P., and F. Palau. 2012. Neural and molecular features on Charcot–Marie–Tooth disease plasticity and therapy. *Neural Plasticity* 2012:171636.
67. Lee, S.M., L.S. Chin, and L. Li. 2012. Protein misfolding and clearance in demyelinating peripheral neuropathies: therapeutic implications. *Communicative and Integrative Biology* 5(1):107–110.
68. Zhao, J.H., H.L. Liu, H.Y. Lin, C.H. Huang, H.W. Fang, S.S. Chen, Y. Ho, W.B. Tsai, and W.Y. Chen. 2007. Chemical chaperone and inhibitor discovery: potential treatments for protein conformational diseases. *Perspectives in Medicinal Chemistry* 1:39.
69. DebBurman, S.K., G.J. Raymond, B. Caughey, and S. Lindquist. 1997. Chaperone-supervised conversion of prion protein to its protease-resistant form. *Proceedings of the National Academy of Sciences* 94(25):13,938–13,943.
70. Newnam, G.P., R.D. Wegrzyn, S.L. Lindquist, and Y.O. Chernoff. 1999. Antagonistic interactions between yeast chaperones Hsp104 and Hsp70 in prion curing. *Molecular and Cellular Biology* 19(2):1325–1333.