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Amylotrophic Lateral Sclerosis-Like Motor Impairment in Prion Diseases

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Abstract

Neurodegenerative diseases are collective diseases that affect different parts of the brain with common or distinct disease phenotype. In almost all of the Prion diseases, motor impairments that are characterized by motor derangement, apathy, ataxia, and myoclonus are documented and again are shared by motor neuron diseases (MND). Proteins such as; B-Cell lymphoma 2 (BCL2), Copper chaperone for superoxide dismutase (CCS), Amyloid beta precursor protein (APP), Amyloid Precursor-Like Protein1/2 (APLP1/2), Catalase (CAT), and Stress induced phosphoprotein 1 (STIP1), are common interactomes of Prion and superoxide dismutase 1 (SOD1). Although there is no strong evidence to show the interaction of SOD1 and Prion, the implicated common interacting proteins indicate the potential bilateral interaction of those proteins in health and disease. For example, down-regulation of Heat shock protein A (HSPA5), a Prion interactome, increases accumulation of misfolded SOD1 leading to MND. Loss of Cu uptake function disturbs normal function of CCS. Over-expressed proteasome subunit alpha 3 (PSMA3) could fatigue its normal function of removing misfolded proteins. Studies showed the increase in CAT and lipid oxidation both in Prion-knocked out animal and in catalase deficiency cases. Up regulation, down regulation or direct interaction with their interactomes are predicted molecular mechanisms by which Prion and SOD exert their effect. The loss of protective function or the gain of a novel toxic property by the principal proteins is shared in Prion and MND. Thus, it might be possible to conclude that the interplay of proteins displayed in both diseases could be a key phenomenon in motor dysfunction development.

Keywords

Prion, Super Oxide Dismutase-1, Amyotrophic Lateral Sclerosis, Motor

Neuron Diseases, Interactomes

1. Introduction

Neurodegenerative disease is a global concern and poses serious social and individual challenges. Seen in light of financial limitations and resource allocation, developing countries are specifically currently challenged by a wide variety of neurodegenerative diseases [1]. Alzheimer, Parkinson, Huntington, and dementia are the most common diseases that degenerate neurons. Apart from those, Prion diseases are characterized as the lethal form of neurodegenerative diseases with no clearly defined molecular mechanism and cure. Among the different types of Prion diseases, Kuru is one of the oldest that was discovered in New Guinea [2]. Later, Creudzfelt-Jacob Disease (CJD) was identified for the first time in the UK in late 1990s [3].

Here we attempt to focus on the predictable molecular mechanism of motor impairment which is manifested in patients of Prion diseases. The basis for the predicative pathomechanism is the absence of evidence of definite physiologic function of cellular Prion [4] [5] [6] [7]. There are knock-out and knock-down studies which show the gain and/or loss of Prion functions and its effect on the expression level of other proteins [8] [9] [10] [11]. Moreover, there is presumption that the normal physiologic function of cellular Prion depends on other proteins that interact with it [8] [12]. For example, up-regulation of superoxide dismutase (SOD) by cellular Prion is one of the many pieces of evidence to illustrate the physiologic function of Prion [13] [14]. Some of the clinical features that are implicated in Prion diseases might be because of the same molecular phenomena of other diseases which are explained by up-regulation, down-regulation or abnormal interaction with the specific protein.

2. Prion and Prion Diseases Pathogenesis

Prion protein is highly expressed in brain cells [15] by a single copy PRNP gene [16] and it is a transmembrane protein which undergoes multiple post-translational modifications [17] [18]. Cleavage of 22 aa from N terminal signal peptide, cleavage of 23 aa from C terminal and addition of GPI anchor, disulfide bond, and glycosylation are the well-documented post-translational modification which might affect its higher order structure and its interaction with its interactomes [19]. The sum total effect may contribute to species and strain specific barrier phenomenon [20] [21] [22].

Prion diseases are among the very rear lethal disease of both humans and animals [23]. Though there are a number of studies, there are still unconfirmed issues about biological structure, defined molecular pathophysiology and the mechanism how selective cross-species infections take place [24]. Despite the low rate of prevalence, its non-curability, within and cross-species transmissibility

and lethality make Prion diseases one of the most debilitating diseases of our time.

Prion diseases are principally caused by abnormally misfolded Prion proteins which are capable of replicating themselves by recruiting normal cellular Prion and later amyloidosis [25] [26]. vCJD, CJD, GSS, FFI are among the most characterized human Prion diseases classified based on whether they are sporadic, acquired or inherited [27]. In most instances, the duration of incubation varies for different variants of Prion [28]. Apart from that, the onset of the disease is the basis for classification of Prion diseases [29] [30]. Histological studies revealed that thalamus, brain stem, and cerebellum are the most affected brain parts by the majority of Prion strain [27] [31]. Almost all of the human Prion diseases share common clinical features: anxiety, depression, hyperactivity are the commonest psychiatric clinical features while dementia [32], motor derangement, apathy, ataxia, myoclonus tremor and at later stage mutism, Pyramidal, and extrapyramidal dysfunctions are the pronounced neurological disorders [32] [33] [34].

3. Development of Motor Neuron Impairment

3.1. Types and Etiology of Motor Neuron Diseases

Among the most distinct clinical symptoms of Prion diseases, motor impairment is the commonest at the different stages of disease development. The symptom resembles clinical features of motor neuron diseases where both or either of Upper motor neuron (UMN) or lower motor neuron (LMN) that arise from spine and brain innervating muscles are degenerated [35]. Based on the cause, severity, clinical presentation and onset of the disease, motor neuron disease (MND) are classified as amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), hereditary spastic paraplegias (HSP), and progressive bulbar palsy (PBP) [36] [37]. ALS is the most common that affect both UMN and LMN neurons. Majority of ALS cases are sporadic though it can also be familial [35]. ALS is caused by a number of mutations in Cu/Zn superoxide dismutase-1 gene, ALS, cytoplasmic dynein and dynactin, D-amino acid oxidase DAO and Optineurin OPTN, Chromosome 9 open reading frame 72C9ORF72 and others [38] [39]. Mutation to superoxide dismutase1 (SOD) is the main cause of ALS next to mutation to C9ORF72 hexanucleotide repeat in the promoter region [38] [40] [41]. One of the most notable pathogenesis of this disease is glutamate-induced excitotoxicity that disrupts Ca^{2+} homeostasis to cause motor neuron death [42] [43] [44]. Apart from that, oxidative distress and axonal transport dysfunction cause neural injury through metal (Cu, iron, Zn) homeostatic disturbance [33] [45] [46]. BCL2-mediated Apoptosis, protein aggregation and autophagy are also part of pathomechanisms of ALS disease development [47] [48] [49]. As in familial Prion diseases, ALS is autosomal dominant [50]. The other type of MDN which mostly arises in the medulla is progressive bulbar palsy. Among inheritable MDN disease, spinal muscular atrophy (SMA) is autosomal recessive that af-

fects LMN [51] where its molecular basis is an alteration in the survival motor neuron gene [52].

3.2. Pathogenesis and Clinical Presentation of MND

Neurons of the spinal cord, brain stem, cerebellum, cerebral cortex, and basal ganglia are most affected by MND [53] [54]. Like in Prion diseases, histological studies revealed that there is also vastrogliosis [55] and microglial activation in MND [56]. Moreover, spongiosis-microvaculation is frequently documented in frontal and temporal cortices particularly in FTLD [57]. Progressive skeletal muscle weakness, wasting, fatigability, the difficulty of movement and gait disturbance, extrapyramidal diseases, tremor, atrophy, the difficulty of swallowing and other emotional disorders like anxiety, depression, excitability, dementia, and insomnia are all implicated in the majority of MND [58] [59] [60].

4. Motor Impairment in Prion Diseases that Resembles ALS

4.1. Prion and SOD1 Interactomes in Health and Disease

As indicated above, the function of Prion is studied in relation to loss or gain of functions. In some, in *in-vivo* studies the knocking out/knocking down of genes or challenging Prion expression had little to no effect on the normal cellular function and/or brings no known disease phenotype [30] [61]. As a result, its biological function may be through proteins that it interacts with under the normal physiologic conditions.

Prion protein is implicated in several signaling pathways having a wide range of functions from cell differentiation [30] [62] [63] to apoptosis [64] [65] [66]. Prion protein forms interaction network with a wide variety of proteins intracellularly (**Figure 1**, **Figure 2**). Findings showed that proteins such as Stress induced phosphoprotein 1 (STIP1) [67], Heat Shock Protein A4 (HSPA4) Clustrin (CLU) [68], Heat shock protein family A (HSPA5) [69], Argonaute-1 (AGO1) [70], BCL2 Associated Athanogene 6 BAG6 [71], and N-myc and STAT interactor (NML) are the most characterized interactomes of Prion [72]-[79]. B-Cell lymphoma 2 (BCL2) [80] [81], Smith-Magenis syndrome chromosome region, candidate 8 (SMCR8), Proteasome subunit alpha 3 (PSMA3), Copper chaperone for superoxide dismutase (CCS) [82], Amyloid beta precursor protein (APP) [83] [84], Amyloid Precursor-Like Protein (1APLP1/2) [85], WD repeat domain (5WDR5), Homeobox (A1HOXA1) [86], and Catalase (CAT) [87] are identified to interact with Prion with a variety of cellular function. CCS and CAT are especially involved in oxidative stress [88]. BAG6, PSMA3, and SMCR8 are involved in proteolytic degradation of misfolded protein and autophagy. Heat shock protein family A44 and HSPA5 are chaperones that are involved in the folding and refolding of misfolded proteins in response to cellular stress [89]. BCL2, NML, and CLU, are mostly known for their role in either pro or anti-apoptosis activities [90] [91]. Copper chaperone for superoxide dismutase, CAT, HSPA4, SMCR8, Cone-rod homeobox (CRX), N-myc and STAT interactor (NMI), and

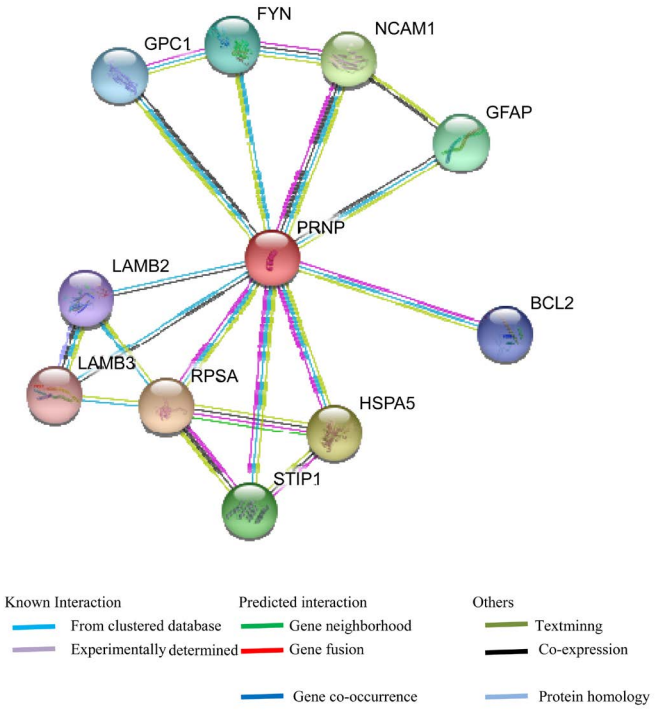

Figure 1. Interaction network based on experiment and gene co-occurrence [73].

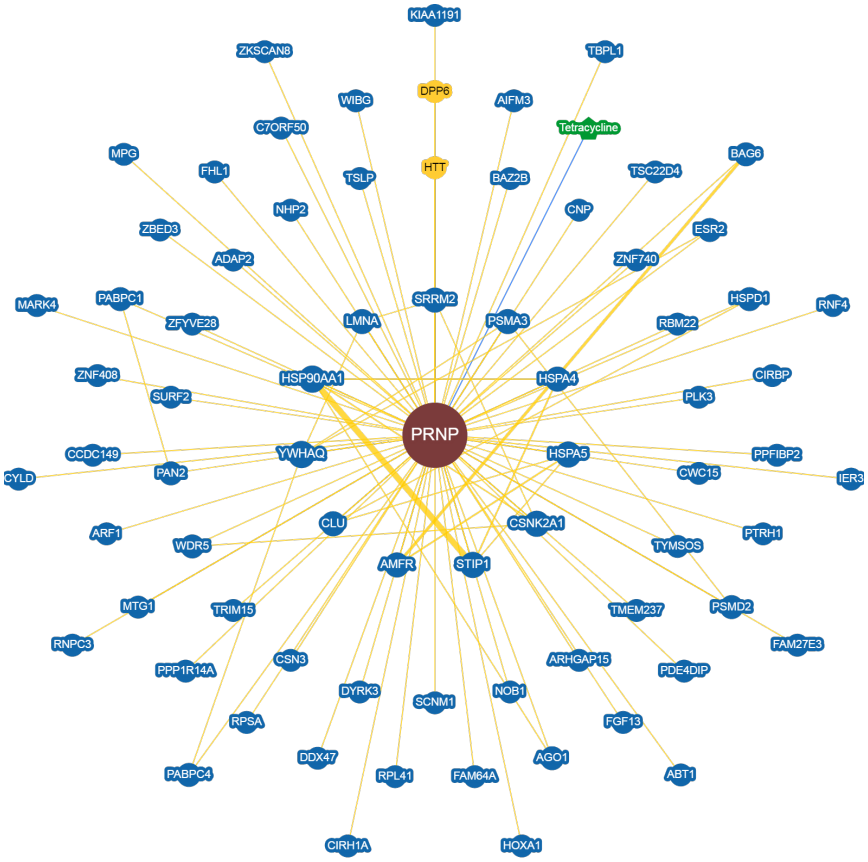

Figure 2. Interaction network with 1 - 23 evidence. Note—the thickness of the lines corresponds to the number of evidence [74].

Ubiquitin C (UBC) [79] are common proteins that interact with Prion, SOD1, and C9ORF72. Similarly, Adenylate kinase 2 AK2, HSPA5, HSPA2 [78], HSPH1, SOD2 [73] are especially known to interact with SOD1.

4.2. The Interplay of Interactomes in Motor Neuron Impairment (MNI)

Considering the presumable and potential interaction between Prion and SOD in disease pathogenesis, it is worth to take into account the interplay between Prion and SOD1 through their interacting proteins which are common for both. The expression of SOD is somehow influenced by the level of PrP^c [92]. In another way, the loss of SOD1 up-regulating property of Prion would rather exacerbate oxidative stress which results in cell death. However, there are reports that show PrP^c having no SOD activity whatsoever [93] [94]. If the loss of SOD1 upregulating function of the Prion is indeed the cause for SOD1 dysfunction, then abrupt mitochondria-based oxidative stress and cell death would be expected.

Both Prion and SOD1 have a role in metal regulation and homeostasis [94] [95] [96]. Conversions of cellular Prion to scrapie form cause derangement of Ca^{2+} homeostasis [97]. Further Ca^{2+} homeostatic imbalance continues to occur when the L-type voltage-sensitive Ca^{2+} channel is affected by oxidative stress. As part of the signaling process that Prion plays, infective form of Prion is assumed to disrupt Ca-activated K current [98] [99]. The sum total effects of electron imbalance could be the cause of impaired neural excitability which leads to motor impairment.

In some studies, Prion peptides are documented to cause down-regulation of HSPA5 expression. The same phenomenon can be extrapolated for misfolded protein to downregulate known chaperons [100]. Likewise, impaired chaperons could also lose their protective effect of firing signal under stressful condition [101]. That often could accompany with endoplasmic reticulum stress-associated cell death [102]. By the same mechanism, down-regulation of HSPA5 may increase accumulation of misfolded SOD1 leading to MND. Thus, it might be possible to conclude HSPA5 regulation in both diseases is a key phenomenon in motor dysfunction development [103].

Experimental evidence confirms CCS maintains SOD [104]. The Cu served to SOD is taken up by the Prion. Loss of Cu uptake function disturbs normal function of CCS [30]. As a result, SOD is unable to perform its normal cellular functions. Accumulation of Cu in cytosol causes up-regulation of cellular Prion under physiologic conditions [96]. Misfolded Prion seed, according to Refolding Hypothesis, recruits cellular Prions as their own substrate [105]. It is possible to predict that upon up-regulation of Prion by Cu might further potentiate misfolded aggregate to form amyloid. In addition to this effect, either physical axonal transport blockage and/or an increase in oxidative stress kills neurons. Studies showed extracellular Cu also control expression and turnover of PrP^c in neurons. The transport of Prion from neuron to astrocyte is somehow mediated by extracellular Cu [96]. In turn, PrP^c participates in Cu transport from neuron

to astrocyte. This complementary function protects the cell from Cu toxicity [106]. When PrP^c loses this protective function, the concentration of Cu might increase both in extracellular space, astrocytes and other neurons. An invitro study also showed Cu to enhance renaturation and stabilization of PrPSc, and again further boost its resistance and infectivity [107].

PrPSc cause downregulation of PSMA3. In this case, there might be the bulk removal of cells [108]. Overexpressed PSMA3 could fatigue its own normal function of removing misfolded proteins [109]. Such condition brings in a toxic gain function of Prion and loss of protective function of SOD causing motor neuron death [30] [110] [111] [112] [113]. CAT is another very important protein in processing reactive oxygen species together with SOD [114]. Protein and lipid oxidation increase in Prion knocked out and catalase deficient model animals [111] [115]. The synergetic effect of a decrease in catalytic activity and increased oxidation could result in neural death.

Under the physiologic condition, Clusterin is a ligand for PrP^c [68]. In Prion diseased sample, Clusterin is believed to form an aggregate with misfolded Prion [116]. That might suggest a structural change which challenges the interaction of Clusterin and Prion. As a result, removal of aggregates might be boldly jeopardized. Aggregates and precipitations are the prominent cause of cell death. Proteins in UPS and autophagy are the other molecular phenomenon that is frequently mentioned in trafficking and maintaining the normal cellular function of Prion [101]. These systems are important machineries playing the role of removing misfolded proteins. Dysfunctional proteins, misfolded proteins, are believed to possess structures that potentially challenge interactions with chaperones for degradation. Ub and NMI are among the many proteins that are displayed in UPS and autophagy of neurodegenerative disease [101] [116]. Those proteins are documented to interact with Prion and SOD. AGO is an interesting protein with a critical function in the regulation of miRNA. Ago regulate protein translation through its catalytic action by forming a complex called RISC with miRNA [117] [118]. It is also an interactome to Prion [119] and potentially to SOD. Any abnormal interaction with dysfunctional proteins can potentially subvert normal function of AGO and threaten cell survival. And again, the loss of interaction with those key proteins might be the reason for the development of the disease (**Figure 3**).

5. Conclusion

The molecular basis described in the review of cell death through a different mechanism in relation to either the loss of protective function or the gain of a novel toxic properties is shared by both Prion diseases and MND especially ALS. In conclusion, here we tried to show the similarity between the molecular basis of motor impairment in ALS and Prion diseases. Despite they are distinct from each other, the interplay of proteins displayed in both cases can tell a lot about pathomechanism of motor impairment in Prion diseases. Thus, with further experimental studies it is worth to confirm the molecular mechanism of motor

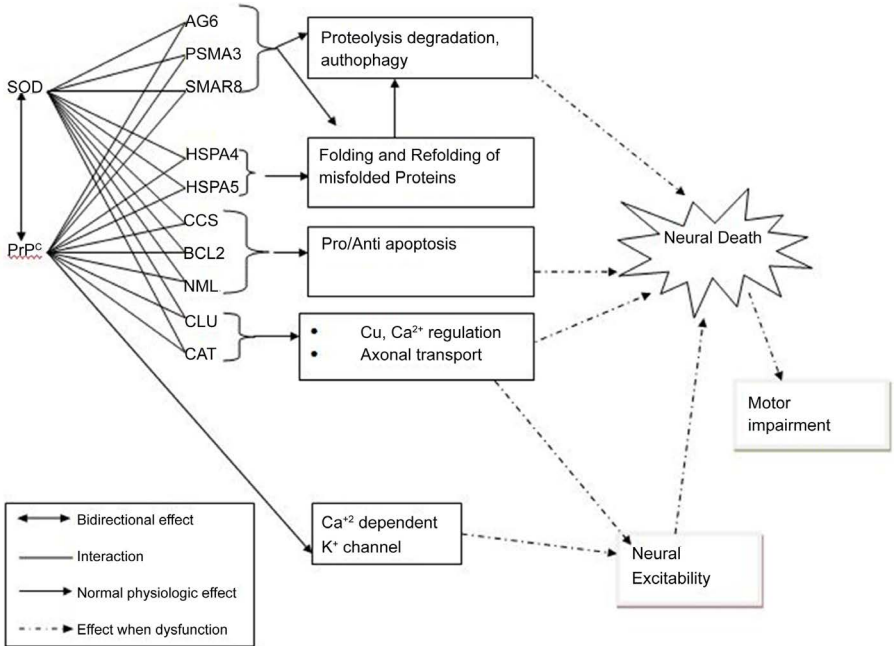

Figure 3. Predicted and experimentally supported interactions. Note-PrP^c and SOD1 are predicted to influence each other under normal and disease conditions (indicated by double-headed arrow). They both have the common interactomes with distinct cellular function (indicated by solid arrows). PrP^c and SOD1 are presumed to exert their effect through their interactomes to cause motor impairment in underlined diseases conditions when they are misfolded (indicated by broken arrows).

impairments of Prion diseases in order to identify potential therapeutic approaches.

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Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Sosso, F.A.E. and Kabore, P. (2016) The African Burden of Mental Health. *Journal of Mental Disorders and Treatment*, **2**, 1222. https://doi.org/10.4172/2471-271X.1000122

[2] Liberski, P.P. (2013) Kuru: A Papua New Guinea to the Neanderthals' Extinction. *Pathogens*, **2**, 472-505. https://doi.org/10.3390/pathogens2030472

[3] NPR.org. (2017) When People Ate People, a Strange Disease Emerged. https://www.npr.org/sections/thesalt/2016/09/06/482952588/when-people-ate-people-a-strange-disease-emerged

[4] Almond, J.W. (1998) Bovine Spongiform Encephalopathy and New Variant Creutzfeldt-Jakob Disease. *British Medical Bulletin*, **54**, 749-759. https://doi.org/10.1093/oxfordjournals.bmb.a011724

[5] Collinge, J., *et al.* (1994) Prion Protein Is Necessary for Normal Synaptic Function.

Nature, **370**, 295-297. https://doi.org/10.1038/370295a0

[6] Dormont, D. (2002) Prion Diseases: Pathogenesis and Public Health Concerns. *FEBS Letters*, **529**, 17-21. https://doi.org/10.1016/S0014-5793(02)03268-4

[7] Choi, D.K., Kim, I.S. and Do, J.H. (2014) Signaling Pathway Analysis of MPP^+-Treated Human Neuroblastoma SH-SY5Y Cells. *Biotechnology and Bioprocess Engineering*, **19**, 332-340. https://doi.org/10.1007/s12257-013-0754-x

[8] La Mendola, D., *et al.* (2008) Prion Proteins Leading to Neurodegeneration. *Current Alzheimer Research*, **5**, 579-590. https://doi.org/10.2174/156720508786898415

[9] Martins, V.R., *et al.* (2001) Insights into the Physiological Function of Cellular Prion Protein. *Brazilian Journal of Medical and Biological Research*, **34**, 585-595. https://doi.org/10.1590/S0100-879X2001000500005

[10] Lee, K.J., *et al.* (2007) Cellular Prion Protein (PrP^C) Protects Neuronal Cells from the Effect of Huntingtin Aggregation. *Journal of Cell Science*, **120**, 2663-2671. https://doi.org/10.1242/jcs.004598

[11] Westergard, L., Christensen, H.M. and Harris, D.A. (2007) The Cellular Prion Protein (PrP^C): Its Physiological Function and Role in Disease. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1772**, 629-644. https://doi.org/10.1016/j.bbadis.2007.02.011

[12] Solomon, I.H., Schepker, J.A. and Harris, D.A. (2010) Prion Neurotoxicity: Insights from Prion Protein Mutants. *Current Issues in Molecular Biology*, **12**, 51-61.

[13] Castle, A.R. and Gill, A.C. (2017) Physiological Functions of the Cellular Prion Protein. *Frontiers in Molecular Biosciences*, **4**, 19. https://doi.org/10.3389/fmolb.2017.00019

[14] Kozlowski, H., *et al.* (2009) Copper, Iron, and Zinc Ions Homeostasis and Their Role in Neurodegenerative Disorders (Metal Uptake, Transport, Distribution and Regulation). *Coordination Chemistry Reviews*, **253**, 2665-2685. https://doi.org/10.1016/j.ccr.2009.05.011

[15] Onodera, T. (2017) Dual Role of Cellular Prion Protein in Normal Host and Alzheimer's Disease. *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences*, **93**, 155-173. https://doi.org/10.2183/pjab.93.010

[16] McKinley, M.P., *et al.* (1987) Developmental Expression of Prion Protein Gene in Brain. *Developmental Biology*, **121**, 105-110. https://doi.org/10.1016/0012-1606(87)90143-6

[17] Ciric, D. and Rezaei, H. (2015) Biochemical Insight into the Prion Protein Family. *Frontiers in Cell and Developmental Biology*, **3**, 5. https://doi.org/10.3389/fcell.2015.00005

[18] Harris, D.A. (1999) Cellular Biology of Prion Diseases. *Clinical Microbiology Reviews*, **12**, 429-444. https://doi.org/10.1128/CMR.12.3.429

[19] Otvos, L. and Cudic, M. (2002) Post-Translational Modifications in Prion Proteins. *Current Protein & Peptide Science*, **3**, 643-652. https://doi.org/10.2174/1389203023380440

[20] Duan, G. and Walther, D. (2015) The Roles of Post-Translational Modifications in the Context of Protein Interaction Networks. *PLoS Computational Biology*, **11**, e1004049. https://doi.org/10.1371/journal.pcbi.1004049

[21] Tessier, P.M. and Lindquist, S. (2009) Unraveling Infectious Structures, Strain Variants and Species Barriers for the Yeast Prion [*PSI*$^+$]. *Nature Structural & Molecular Biology*, **16**, 598-605. https://doi.org/10.1038/nsmb.1617

[22] Woodsmith, J., Kamburov A. and Stelzl, U. (2013) Dual Coordination of Post

Translational Modifications in Human Protein Networks. *PLoS Computational Biology*, **9**, e1002933. https://doi.org/10.1371/journal.pcbi.1002933

[23] Holman, R.C., *et al.* (2010) Human Prion Diseases in the United States. *PLoS ONE*, **5**, e8521. https://doi.org/10.1371/journal.pone.0008521

[24] Grizel, A.V., Rubel, A.A. and Chernoff, Y.O. (2016) Strain Conformation Controls the Specificity of Cross-Species Prion Transmission in the Yeast Model. *Prion*, **10**, 269-282. https://doi.org/10.1080/19336896.2016.1204060

[25] Cobb, N.J. and Surewicz, W.K. (2009) Prion Diseases and Their Biochemical Mechanisms. *Biochemistry*, **48**, 2574-2585. https://doi.org/10.1021/bi900108v

[26] Marin-Moreno, A., *et al.* (2017) Transmission and Replication of Prions. *Progress in Molecular Biology and Translational Science*, **150**, 181-201. https://doi.org/10.1016/bs.pmbts.2017.06.014

[27] Gambetti, P., *et al.* (2003) Sporadic and Familial CJD: Classification and Characterisation. *British Medical Bulletin*, **66**, 213-239. https://doi.org/10.1093/bmb/66.1.213

[28] Morales, R. (2017) Prion Strains in Mammals: Different Conformations Leading to Disease. *PLoS Pathogens*, **13**, e1006323. https://doi.org/10.1371/journal.ppat.1006323

[29] Wadsworth, J.D.F., Kong, Q., Zou, W., Parchi, P. and Chen, S.G. (2003) Molecular and Clinical Classification of Human Prion Disease. *British Medical Bulletin*, **66**, 241-254. https://doi.org/10.1093/bmb/66.1.241

[30] Chen, C. and Dong, X.P. (2016) Epidemiological Characteristics of Human Prion Diseases. *Infectious Diseases of Poverty*, **5**, 47. https://doi.org/10.1186/s40249-016-0143-8

[31] Reiniger, L., *et al.* (2013) Filamentous White Matter Prion Protein Deposition Is a Distinctive Feature of Multiple Inherited Prion Diseases. *Acta Neuropathologica Communications*, **1**, 8. https://doi.org/10.1186/2051-5960-1-8

[32] Takada, L.T. and Geschwind, M.D. (2013) Prion Diseases. *Seminars in Neurology*, **33**, 348-356. https://doi.org/10.1055/s-0033-1359314

[33] Rodriguez, M.M., *et al.* (2005) A Novel Mutation (G114V) in the Prion Protein Gene in a Family with Inherited Prion Disease. *Neurology*, **64**, 1455-1477. https://doi.org/10.1212/01.WNL.0000158618.39527.93

[34] Nakatani, E. (2016) Specific Clinical Signs and Symptoms Are Predictive of Clinical Course in Sporadic Creutzfeldt-Jakob Disease. *European Journal of Neurology*, **23**, 1455-1462. https://doi.org/10.1111/ene.13057

[35] Wijesekera, L.C. and Leigh, P.N. (2009) Amyotrophic Lateral Sclerosis. *Orphanet Journal of Rare Diseases*, **4**, 3. https://doi.org/10.1186/1750-1172-4-3

[36] Desai, M.S.J. (2000) Motor Neuron Disease: Classification and Nomenclature. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, **1**, 105-112. https://doi.org/10.1080/14660820050515403

[37] Statland, J.M., *et al.* (2015) Patterns of Weakness, Classification of Motor Neuron Disease & Clinical Diagnosis of Sporadic ALS. *Neurologic Clinics*, **33**, 735-748. https://doi.org/10.1016/j.ncl.2015.07.006

[38] Chen, S., Barohn, R.J., McVey, A.L., Katz, J.S. and Dimachkie, M.M. (2013) Genetics of Amyotrophic Lateral Sclerosis: An Update. *Molecular Neurodegeneration*, **8**, 28. https://doi.org/10.1186/1750-1326-8-28

[39] Parakh, S. and Atkin, J.D. (2016) Protein Folding Alterations in Amyotrophic Lateral Sclerosis. *Brain Research*, **1648**, 633-649.

https://doi.org/10.1016/j.brainres.2016.04.010

[40] Renton, A.E., *et al.* (2011) A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD. *Neuron*, **72**, 257-268. https://doi.org/10.1016/j.neuron.2011.09.010

[41] Van Blitterswijk, M., DeJesus-Hernandez, M. and Rademakers, R. (2012) How Do *C9ORF72* Repeat Expansions Cause ALS and FTD: Can We Learn from Other Non-Coding Repeat Expansion Disorders? *Current Opinion in Neurology*, **25**, 689-700. https://doi.org/10.1097/WCO.0b013e32835a3efb

[42] Shaw, R. (2005) Molecular and Cellular Pathways of Neurodegeneration in Motor Neurone Disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **76**, 1046-1057. https://doi.org/10.1136/jnnp.2004.048652

[43] Foran, E. and Trotti, D. (2009) Glutamate Transporters and the Excitotoxic Path to Motor Neuron Degeneration in Amyotrophic Lateral Sclerosis. *Antioxidants & Redox Signaling*, **11**, 1587-1602. https://doi.org/10.1089/ars.2009.2444

[44] Zarei, S., *et al.* (2015) A Comprehensive Review of Amyotrophic Lateral Sclerosis. *Surgical Neurology International*, **6**, 171. https://doi.org/10.4103/2152-7806.169561

[45] Roos, P., Vesterberg, O. and Nordberg, M. (2006) Metals in Motor Neuron Diseases. *Experimental Biology and Medicine*, **231**, 1481-1487. https://doi.org/10.1177/153537020623100906

[46] Chen, X., Guo, C. and Kong, J. (2012) Oxidative Stress in Neurodegenerative Diseases. *Neural Regeneration Research*, **7**, 376-385.

[47] Akhtar, R. (2004) Bcl-2 Family Regulation of Neuronal Development and Neurodegeneration. *Biochimica et Biophysica Acta*, **1644**, 189-203. https://doi.org/10.1016/j.bbamcr.2003.10.013

[48] Hetz, C., *et al.* (2007) The Proapoptotic BCL-2 Family Member BIM Mediates Motoneuron Loss in a Model of Amyotrophic Lateral Sclerosis. *Cell Death and Differentiation*, **14**, 1386-1389. https://doi.org/10.1038/sj.cdd.4402166

[49] Ramesh, N. and Pandey, U.B. (2017) Autophagy Dysregulation in ALS: When Protein Aggregates Get Out of Hand. *Frontiers in Molecular Neuroscience*, **10**, 263. https://doi.org/10.3389/fnmol.2017.00263

[50] Cheon, C.K., *et al.* (2017) Autosomal Dominant Transmission of Complicated Hereditary Spastic Paraplegia Due to a Dominant Negative Mutation of KIF1A, SPG30 Gene. *Scientific Reports*, **7**, Article No. 12527. https://doi.org/10.1038/s41598-017-12999-9

[51] Ninds.nih.gov (2017) Motor Neuron Diseases Fact Sheet. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Motor-Neuron-Diseases-Fact-Sheet

[52] Burghes, A.H.M. and Beattie, C.E. (2009) Spinal Muscular Atrophy: Why Do Low Levels of Survival Motor Neuron Protein Make Motor Neurons Sick? *Nature Reviews Neuroscience*, **10**, 597-609. https://doi.org/10.1038/nrn2670

[53] Sharma, K.R., Saigal, G., Maudsley, A.A. and Govind, V. (2011) 1H MRS of Basal Ganglia and Thalamus in Amyotrophic Lateral Sclerosis. *NMR in Biomedicine*, **24**, 1270-1276. https://doi.org/10.1002/nbm.1687

[54] Bede, P., *et al.* (2013) Basal Ganglia Involvement in Amyotrophic Lateral Sclerosis. *Neurology*, **81**, 2107-2115. https://doi.org/10.1212/01.wnl.0000437313.80913.2c

[55] Vargas, M.R. and Johnson, J.A. (2010) Astrogliosis in Amyotrophic Lateral Sclerosis: Role and Therapeutic Potential of Astrocytes. *Neurotherapeutics*, **7**, 471-481.

https://doi.org/10.1016/j.nurt.2010.05.012

[56] Frakes, A.E., *et al.* (2014) Microglia Induce Motor Neuron Death via the Classical NF-κB Pathway in Amyotrophic Lateral Sclerosis. *Neuron*, **81**, 1009-1023. https://doi.org/10.1016/j.neuron.2014.01.013

[57] Polvikoski, T.M., Murray, A., Harper, P. and Neal, J. (2003) Familial Motor Neurone Disease with Dementia: Phenotypic Variation and Cerebellar Pathology. *Journal of Neurology, Neurosurgery & Psychiatry*, **74**, 1516-1520. https://doi.org/10.1136/jnnp.74.11.1516

[58] Leighton, S.E., Burton, M.J., Lund, W.S. and Cochrane, G.M. (1994) Swallowing in Motor Neurone Disease. *Journal of the Royal Society of Medicine*, **87**, 801-805.

[59] Watts, C.R. and Vanryckeghem, M. (2001) Laryngeal Dysfunction in Amyotrophic Lateral Sclerosis: A Review and Case Report. *BMC Ear, Nose and Throat Disorders*, **1**, 1. https://doi.org/10.1186/1472-6815-1-1

[60] Atassi, N., *et al.* (2011) Depression in Amyotrophic Lateral Sclerosis. *Amyotrophic Lateral Sclerosis*, **12**, 109-112. https://doi.org/10.3109/17482968.2010.536839

[61] Chiesa, R. and Harris, D.A. (2009) Fishing for Prion Protein Function. *PLoS Biology*, **7**, e1000075. https://doi.org/10.1371/journal.pbio.1000075

[62] Lee, Y.J. and Baskakov, I.V. (2014) The Cellular Form of the Prion Protein Guides the Differentiation of Human Embryonic Stem Cells into Neuron-, Oligodendrocyte-, and Astrocyte-Committed Lineages. *Prion*, **8**, 266-275. https://doi.org/10.4161/pri.32079

[63] Shi, F., *et al.* (2016) Cellular Prion Protein Promotes Neuronal Differentiation of Adipose-Derived Stem Cells by Upregulating miRNA-124. *Journal of Molecular Neuroscience*, **59**, 48-55. https://doi.org/10.1007/s12031-016-0733-8

[64] Mouillet-Richard, S., *et al.* (2000) Signal Transduction through Prion Protein. *Science*, **289**, 1925-1928. https://doi.org/10.1126/science.289.5486.1925

[65] Resenberge, U.K., Winklhofer, K.F. and Tatzelt, J. (2011) Neuroprotective and Neurotoxic Signaling by the Prion Protein. *Topics in Current Chemistry*, **305**, 101-119. https://doi.org/10.1007/128_2011_160

[66] Liebert, A., Bicknell, B. and Adams, R. (2014) Prion Protein Signaling in the Nervous System—A Review and Perspective. *Signal Transduction Insights*, **3**, 11-32. https://doi.org/10.4137/STI.S12319

[67] Maciejewski, A., *et al.* (2016) Domains of STIP1 Responsible for Regulating the PrP^C-Dependent Amyloid-β Oligomer Toxicity. *Biochemical Journal*, **473**, 2119-2130. https://doi.org/10.1042/BCJ20160087

[68] Xu, F., Karnaukhova, E. and Vostal, J.G. (2008) Human Cellular Prion Protein Interacts Directly with Clusterin Protein. *Biochimica et Biophysica Acta*, **1782**, 615-620. https://doi.org/10.1016/j.bbadis.2008.08.004

[69] Cai, Y., *et al.* (2016) Interplay of Endoplasmic Reticulum Stress and Autophagy in Neurodegenerative Disorders. *Autophagy*, **12**, 225-244. https://doi.org/10.1080/15548627.2015.1121360

[70] Gibbings, D., *et al.* (2012) Human Prion Protein Binds Argonaute and Promotes Accumulation of microRNA Effector Complexes. *Nature Structural & Molecular Biology*, **19**, 517-524. https://doi.org/10.1038/nsmb.2273

[71] David, R. (2011) BAG6 & Mislocalized Proteins. *Nature Reviews Molecular Cell Biology*, **12**, 550. https://doi.org/10.1038/nrm3167

[72] Das, J. and Yu, H. (2012) HINT: High-Quality Protein Interactomes and Their Applications in Understanding Human Disease. *BMC Systems Biology*, **6**, 92.

https://doi.org/10.1186/1752-0509-6-92

[73] Szklarczyk, D., *et al.* (2015) STRING v10: Protein–Protein Interaction Networks, Integrated over the Tree of Life. *Nucleic Acids Research*, **43**, D447-D452. https://doi.org/10.1093/nar/gku1003

[74] Stark, C., *et al.* (2006) BioGRID: A General Repository for Interaction Datasets. *Nucleic Acids Research*, **34**, D535-D539. https://doi.org/10.1093/nar/gkj109

[75] Keshava Prasad, T.S., *et al.* (2009) Human Protein Reference Database—2009 Update. *Nucleic Acids Research*, **37**, D767-D772. https://doi.org/10.1093/nar/gkn892

[76] Chatr-aryamontri, A., *et al.* (2007) MINT: The Molecular INTeraction Database. *Nucleic Acids Research*, **35**, D572-D574. https://doi.org/10.1093/nar/gkl950

[77] Peri, S., *et al.* (2003) Development of Human Protein Reference Database as an Initial Platform for Approaching Systems Biology in Humans. *Genome Research*, **13**, 2363-2371. https://doi.org/10.1101/gr.1680803

[78] Warde-Farley, D., *et al.* (2010) The GeneMANIA Prediction Server: Biological Network Integration for Gene Prioritization and Predicting Gene Function. *Nucleic Acids Research*, **38**, W214-W220. https://doi.org/10.1093/nar/gkq537

[79] Rolland, T., *et al.* (2014) A Proteome-Scale Map of the Human Interactome Network. *Cell*, **159**, 1212-1226. https://doi.org/10.1016/j.cell.2014.10.050

[80] Kurschner, C. and Morgan, J.I. (1995) The Cellular Prion Protein (PrP) Selectively Binds to Bcl-2 in the Yeast Two-Hybrid System. *Molecular Brain Research*, **30**, 165-168. https://doi.org/10.1016/0169-328X(95)00013-I

[81] Ferreiro, E., *et al.* (2007) Bcl-2 Overexpression Protects Against Amyloid-Beta and Prion Toxicity in GT1-7 Neural Cells. *Journal of Alzheimer*'s *Disease*, **12**, 223-228. https://doi.org/10.3233/JAD-2007-12303

[82] Kralovicova, S., *et al.* (2009) The Effects of Prion Protein Expression on Metal Metabolism. *Molecular and Cellular Neuroscience*, **41**, 135-147. https://doi.org/10.1016/j.mcn.2009.02.002

[83] Kaiser, D.M., *et al.* (2012) Amyloid Beta Precursor Protein and Prion Protein Have a Conserved Interaction Affecting Cell Adhesion and CNS Development. *PLoS ONE*, **7**, e51305. https://doi.org/10.1371/journal.pone.0051305

[84] McHugh, P.C., *et al.* (2012) Prion Protein Expression Alters APP Cleavage without Interaction with BACE-1. *Neurochemistry International*, **61**, 672-680. https://doi.org/10.1016/j.neuint.2012.07.002

[85] Bai, Y., *et al.* (2008) The *in Vivo* Brain Interactome of the Amyloid Precursor Protein. *Molecular & Cellular Proteomics*, **7**, 15-34. https://doi.org/10.1074/mcp.M700077-MCP200

[86] Satoh, J., *et al.* (2008) Protein Microarray Analysis Identifies Human Cellular Prion Protein Interactors. *Neuropathology and Applied Neurobiology*, **35**, 16-35. https://doi.org/10.1111/j.1365-2990.2008.00947.x

[87] Klamt, F., *et al.* (2001) Imbalance of Antioxidant Defense in Mice Lacking Cellular Prion Protein. *Free Radical Biology & Medicine*, **30**, 1137-1144. https://doi.org/10.1016/S0891-5849(01)00512-3

[88] Spee, B., *et al.* (2006) Copper Metabolism and Oxidative Stress in Chronic Inflammatory and Cholestatic Liver Diseases in Dogs. *Journal of Veterinary Internal Medicine*, **20**, 1085-1092. https://doi.org/10.1111/j.1939-1676.2006.tb00706.x

[89] Stetler, R.A., *et al.* (2010) Heat Shock Proteins: Cellular and Molecular Mechanisms in the CNS. *Progress in Neurobiology*, **92**, 184-211.

https://doi.org/10.1016/j.pneurobio.2010.05.002

[90] Kelly, P.N. and Strasser, A. (2011) The Role of Bcl-2 and Its Pro-Survival Relatives in Tumourigenesis and Cancer Therapy. *Cell Death and Differentiation*, **18**, 1414-1424. https://doi.org/10.1038/cdd.2011.17

[91] Brown, D.R. and Besinger, A. (1998) Prion Protein Expression and Superoxide Dismutase Activity. *Biochemical Journal*, **334**, 423-429. https://doi.org/10.1042/bj3340423

[92] Hutter, G., Heppner, F.L. and Aguzzi, A. (2003) No Superoxide Dismutase Activity of Cellular Prion Protein *in Vivo*. *Biological Chemistry*, **384**, 1279-1285. https://doi.org/10.1515/BC.2003.142

[93] Jones, S., *et al.* (2005) Recombinant Prion Protein Does Not Possess SOD-1 Activity. *Biochemical Journal*, **392**, 309-312. https://doi.org/10.1042/BJ20051236

[94] Choi, C.J., *et al.* (2006) Interaction of Metals with Prion Protein: Possible Role of Divalent Cations in the Pathogenesis of Prion Diseases. *Neurotoxicology*, **27**, 777-787. https://doi.org/10.1016/j.neuro.2006.06.004

[95] Toni, M., Massimino, M.L., Griffoni, C., Salvato, B., Tomasi, V. and Spisni, E. (2005) Extracellular Copper Ions Regulate Cellular Prion Protein (PrP^{C}) Expression and Metabolism in Neuronal Cells. *FEBS Letters*, **579**, 741-744. https://doi.org/10.1016/j.febslet.2004.12.053

[96] Peggion, C., Bertoli, A. and Sorgato, M.C. (2017) Almost a Century of Prion Protein(s): From Pathology to Physiology, and Back to Pathology. *Biochemical and Biophysical Research Communications*, **483**, 1148-1155. https://doi.org/10.1016/j.bbrc.2016.07.118

[97] Herms, J.W., Tings, T., Dunker, S. and Kretzschmar, H.A. (2001) Prion Protein Affects Ca^{2+}-Activated K^{+} Currents in Cerebellar Purkinje Cells. *Neurobiology of Disease*, **8**, 324-330. https://doi.org/10.1006/nbdi.2000.0369

[98] Korte, S., *et al.* (2003) Modulation of L-Type Voltage-Gated Calcium Channels by Recombinant Prion Protein. *Journal of Neurochemistry*, **87**, 1037-1042. https://doi.org/10.1046/j.1471-4159.2003.02080.x

[99] Choi, D.K., Su Kim, I. and Do, J.H. (2014) Signaling Pathway Analysis of MPP^{+}-Treated Human Neuroblastoma SH-SY5Y Cells. *Biotechnology and Bioprocess Engineering*, **19**, 332-340. https://doi.org/10.1007/s12257-013-0754-x

[100] Macario, A.J. and Conway de Macario, E. (2005) Sick Chaperones, Cellular Stress, and Disease. *New England Journal of Medicine*, **353**, 1489-1501. https://doi.org/10.1056/NEJMra050111

[101] Goold, R., McKinnon, C. and Tabrizi, S.J. (2015) Prion Degradation Pathways: Potential for Therapeutic Intervention. *Molecular and Cellular Neurosciences*, **66**, 12-20. https://doi.org/10.1016/j.mcn.2014.12.009

[102] Hishiya, A. and Takayama, S. (2008) Molecular Chaperones as Regulators of Cell Death. *Oncogene*, **27**, 6489-6506. https://doi.org/10.1038/onc.2008.314

[103] Proescher, J.B., Son, M., Elliott, J.L. and Culotta, V.C. (2008) Biological Effects of CCS in the Absence of SOD1 Enzyme Activation: Implications for Disease in a Mouse Model for ALS. *Human Molecular Genetics*, **17**, 1728-1737. https://doi.org/10.1093/hmg/ddn063

[104] Aguzzi, A. and Calella, A.M. (2009) Prions: Protein Aggregation and Infectious Diseases. *Physiological Reviews*, **89**, 1105-1152. https://doi.org/10.1152/physrev.00006.2009

[105] Brown, D.R. (2004) Role of the Prion Protein in Copper Turnover in Astrocytes.

Neurobiology of Disease, **15**, 534-543. https://doi.org/10.1016/j.nbd.2003.11.009

[106] Desai, V. and Kaler, S.G. (2008) Role of Copper in Human Neurological Disorders. *American Journal of Clinical Nutrition*, **88**, 855s-858s. https://doi.org/10.1093/ajcn/88.3.855S

[107] Deriziotis, B. and Tabrizi, S.J. (2008) Prions and the Proteasome. *Biochimica et Biophysica Acta*, **1782**, 713-722. https://doi.org/10.1016/j.bbadis.2008.06.011

[108] Yano, M., Koumoto, Y., Kanesaki, Y., Wu, X. and Kido, H. (2004) 20S Proteasome Prevents Aggregation of Heat-Denatured Proteins without PA700 Regulatory Subcomplex like a Molecular Chaperone. *Biomacromolecules*, **5**, 1465-1469. https://doi.org/10.1021/bm049957a

[109] Rowland, L.P. and Shneider, N.A. (2001) Amyotrophic Lateral Sclerosis. *New England Journal of Medicine*, **344**, 1688-1700. https://doi.org/10.1056/NEJM200105313442207

[110] Steele, A.D., Lindquist, S. and Aguzzi, A. (2007) The Prion Protein Knockout Mouse: A Phenotype under Challenge. *Prion*, **1**, 83-93. https://doi.org/10.4161/pri.1.2.4346

[111] Winklhofer, K.F., Tatzelt, J. and Haass, C. (2008) The Two Faces of Protein Misfolding: Gain- and Loss-of-Function in Neurodegenerative Diseases. *The EMBO Journal*, **27**, 336-349. https://doi.org/10.1038/sj.emboj.7601930

[112] Saccon, R.A., Bunton-Stasyshyn, R.K.A., Fisher, E.M.C. and Fratta, P. (2013) Is SOD1 Loss of Function Involved in Amyotrophic Lateral Sclerosis? *Brain*, **136**, 2342-2358. https://doi.org/10.1093/brain/awt097

[113] Li, J., Wuliji, O., Li, W., Jiang, Z.G. and Ghanbari, H.A. (2013) Oxidative Stress and Neurodegenerative Disorders. *International Journal of Molecular Sciences*, **14**, 24438-24475. https://doi.org/10.3390/ijms141224438

[114] Onodera, T., Sakudo, A., Tsubone, H. and Itohara, S. (2014) Review of Studies That Have Used Knockout Mice to Assess Normal Function of Prion Protein under Immunological or Pathophysiological Stress. *Microbiology and Immunology*, **58**, 361-374. https://doi.org/10.1111/1348-0421.12162

[115] Freixes, M., *et al.* (2004) Clusterin Solubility and Aggregation in Creutzfeldt-Jakob Disease. *Acta Neuropathologica*, **108**, 295-301. https://doi.org/10.1007/s00401-004-0891-6

[116] Ciechanover, A. and Kwon, Y.T. (2015) Degradation of Misfolded Proteins in Neurodegenerative Diseases: Therapeutic Targets and Strategies. *Experimental and Molecular Medicine*, **47**, e147. https://doi.org/10.1038/emm.2014.117

[117] Hall, T.M. (2005) Structure and Function of Argonaute Proteins. *Structure*, **13**, 1403-1408. https://doi.org/10.1016/j.str.2005.08.005

[118] Wilczynska, A. and Bushell, M. (2015) The Complexity of miRNA-Mediated Repression. *Cell Death and Differentiation*, **22**, 22-33. https://doi.org/10.1038/cdd.2014.112

[119] Gibbings, D., *et al.* (2012) Human Prion Protein Binds Argonaute and Promotes Accumulation of microRNA Effector Complexes. *Nature Structural & Molecular Biology*, **19**, 517-524. https://doi.org/10.1038/nsmb.2273