

# Amylotrophic Lateral Sclerosis-Like Motor Impairment in Prion Diseases

Eden Yitna Teferedegn<sup>1</sup>, Dawit Tesfaye<sup>2</sup>, Eyualem Abebe<sup>3</sup> , Cemal Un<sup>1</sup>

<sup>1</sup>Department of Biology, Molecular Biology Division, Ege University, Izmir, Turkey

<sup>2</sup>Institute for Animal Science, University of Bonn, Bonn, Germany

<sup>3</sup>Department of Natural Sciences, Elizabeth City State University, Elizabet City, NC, USA

Email: Edenyitna@gmail.com, Dtes@itz.uni-bonn.de, Ebabebe@ecu.edu, Cemaluen@gmail.com

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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

## 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, Creutzfeldt-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 rare 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 astrocytosis [55] and microglial activation in MND [56]. Moreover, spongiosis-microvacuolation is frequently documented in frontal and temporal cortices particularly in FTLN [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



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<sup>c</sup> [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<sup>c</sup> 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<sup>2+</sup> homeostasis [97]. Further Ca<sup>2+</sup> homeostatic imbalance continues to occur when the L-type voltage-sensitive Ca<sup>2+</sup> 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<sup>c</sup> in neurons. The transport of Prion from neuron to astrocyte is somehow mediated by extracellular Cu [96]. In turn, PrP<sup>c</sup> participates in Cu transport from neuron

to astrocyte. This complementary function protects the cell from Cu toxicity [106]. When PrP<sup>c</sup> 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].

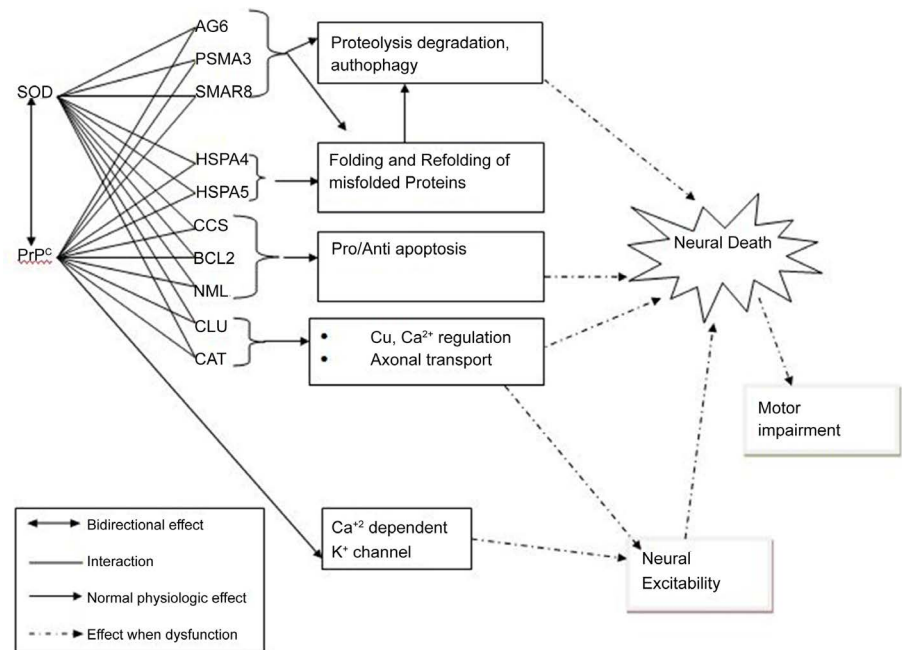
PrPSc cause downregulation of PSMA3. In this case, there might be the bulk removal of cells [108]. Overexpressed PSMA3 could fatigue its own normal function of removing misfolded proteins [109]. Such condition brings in a toxic gain function of Prion and loss of protective function of SOD causing motor 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<sup>c</sup> [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<sup>c</sup> 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<sup>c</sup> 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.

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