

Astroglial Transcriptome Dysregulation at the Core of Amyotrophic Lateral Sclerosis

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Editorial

Amyotrophic lateral sclerosis (ALS) which is also known as motor neuron disease, is a neurodegenerative disorder in which upper and lower motor neuron death occurs leading to progressive neuromuscular failure, resulting in death within 3-5 years of symptom onset [1]. Despite substantial endeavors the cause of ALS remains elusive. ALS is caused by a dominant mutation in an antioxidant enzyme, superoxide dismutase 1 (SOD1) which normally protects the cell from toxic reactive oxygen species. In a recent study, it has been proposed that exposure of motor neurons to the mutant SOD1 results in increased sodium channel permeability, induction of nitroxidative stress, hyperexcitability and motor neuron excitability through dysregulation of AMPA receptors. Dysregulation of the receptors leads to sodium channel dysfunction and astroglia toxicity to motor neurons [2]. The mechanisms behind the dysregulation of neuronal signaling remain ambiguous. Current researches suggest alternations in function of motor neurons to be associated with astrocyte mediated increase neuronal excitability and failing to regulate glutamate levels.

Astroglia derived from SOD1 ALS mouse model show significant decrease in glutamatergic response, as compared to wild type astrocytes that exhibit a vigorous response when activated with lipopolysaccharides, G5 or treated with ceftriaxone [3]. A study documented astroglial potassium channel KCNK1 down regulation and an increase in sodium cotransporter Slc41a1, prior to symptomatic phase in G93A SOD1 mice of ALS mouse model. In mid symptomatic stage, there is strongest decrease of calcium binding protein, Sparc11, and a remarkable increase in lysosomal protein, Ctss. These intriguing results are suggestive of transcriptional level dysregulation in astroglia in ALS [4]. Mutant superoxide dismutase 1 (SOD1) is secreted in the exosomes and transmitted from astrocytes to motor neurons, causing neuronal cell death (Figure 1) [2].

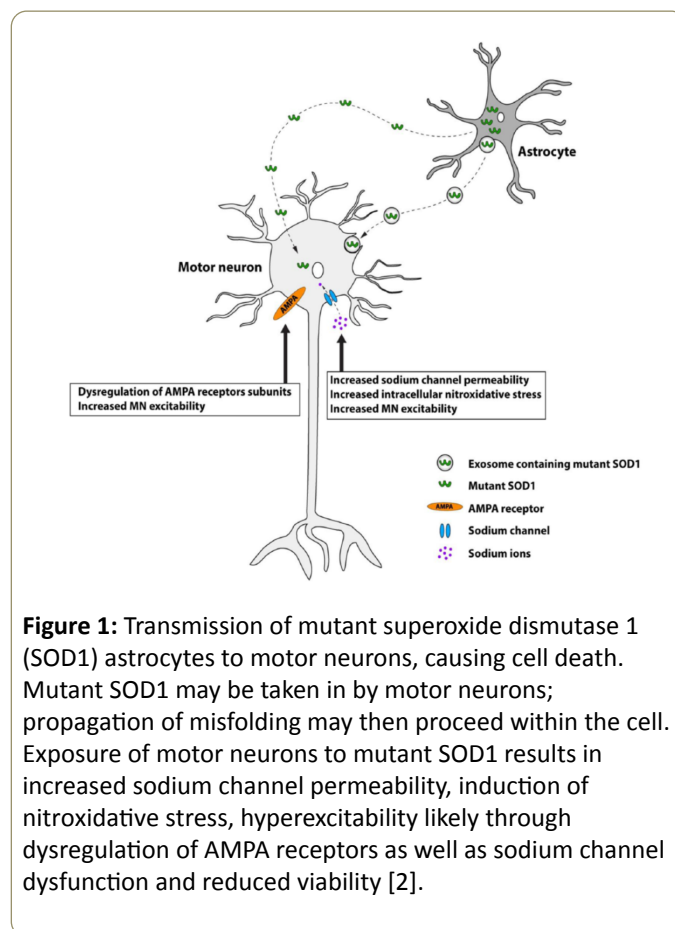


Figure 1: Transmission of mutant superoxide dismutase 1 (SOD1) astrocytes to motor neurons, causing cell death. Mutant SOD1 may be taken in by motor neurons; propagation of misfolding may then proceed within the cell. Exposure of motor neurons to mutant SOD1 results in increased sodium channel permeability, induction of nitroxidative stress, hyperexcitability likely through dysregulation of AMPA receptors as well as sodium channel dysfunction and reduced viability [2].

In a study on microRNAs (miRNAs), involved in post translational gene regulation, established that miRNAs expression of astrocytes as compared to miRNAs secreted via astroglial exosomes are vastly different and only selective miRNAs are recruited to exosomes. There is also evidence of central nervous system consequences in disturbance of expression of miRNAs abounding in astroglial exosomes [5]. Dysregulation of gene expression is recognized as one of the pathophysiological components triggering neurodegeneration in the disease. Alteration in properties of astrocytes leads to

propagation of motoneuron injury in SOD1 related ALS. Previous reports have also demonstrated that selective silencing of mutant SOD1 expression in astrocytes has significantly slowed disease progression [6]. Data from recent studies indicates that manipulation of energy supply to motoneuron may help to reduce disease progression. Results proposed that lactate supplement can completely reverse the observed toxicity particularly as metabolic dysregulation occurs to be the cause of progression of the disease. Dietary interventions are being considered as a potential therapeutic approach to ameliorate the motoneuron energy deficit in the disease [4]. We further anticipate that emerging methodologies will enable to investigate on the gene expression dysregulation and will dissect the molecular events that occurs in actively translating mRNA (i.e. translatome). These hypothesis offer new avenues for development of new therapeutic strategies targeting astrocytic dysregulation in ALS.

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