Investigating the contributions of astrocyte gap junctions to ALS disease progression

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Research Abstract

? DESCRIPTION (provided by applicant): Understanding why disease progression in the majority of patients with Amyotrophic Lateral Sclerosis (ALS) occurs in contiguous anatomic regions over time is one of the fundamental limitations to designing disease modifying therapies that can be utilized after a diagnosis. Studies from chimeric mice with mosaic expression of wildtype (WT) and mutant SOD1 astrocytes surrounding motor neurons suggest that astrocytes play a role in disease propagation after onset. However, astrocyte dysfunction is not an

observation merely limited to transgenic ALS rodent models but, importantly, has been one of the most consistent observations in humans with ALS when examined in situ as well as using human cells in vitro. Astrocytes form a highly coupled intercellular network in the central nervous system (CNS) through gap junctions (GJs) and hemichannels composed of 6 connexin subunits arranged around a central pore. Connexins in astrocytes have key roles: homeostatic buffering, synchronization of astrocyte networks, metabolic support for neurons, and regulation of vascular physiology. They can also propagate Ca2+ waves and modulate synaptic events or release gliotransmitters through hemichannels. Cx43 is the predominant connexin in astrocytes and is expressed ubiquitously in the CNS. Our preliminary data show that Cx43 is upregulated in ALS models as well as in human spinal cord and cortex in patients with ALS. Yet the functional significance of this Cx43 upregulation has not been studied in ALS. Because Cx43 has a role in astrocyte connectivity and cell-cell signaling, we hypothesize that astrocyte Cx43 upregulation in ALS may contribute to neuronal loss as well as contiguous anatomical disease spread in ALS. This proposal will address the functional significance of these changes in vitro using rodent-derived astrocytes and, importantly, human iPSC-derived astrocytes from ALS patients. The specific influences of Cx43 upregulation in ALS astrocytes on wildtype motor neurons loss will also be investigated in vitro. Finally, we will utilize a variety of genetic strategies as well as focal knockdown of Cx43 in ALS animal models, to address whether reductions in Cx43 can limit disease spread. These studies will occur with an eye towards the potential for translating what is learned about Cx43-mediated astrocytic influences on disease progression and spread to the development of potential pharmacological strategies for intervention after an ALS diagnosis.

Further information available at:

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