The Role of Neuroinflammation in the Pathogenesis of Amyotrophic Lateral Sclerosis

September 2, 2014
BRT 105
1:00PM
VITA

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease, is a fatal neurodegenerative disease affecting motor neurons resulting in severe muscle atrophy, paralysis, and ultimately respiratory failure and death. Typically, ALS strikes people between 40-70 years old, and it is estimated that 5,600 people are diagnosed with ALS in the United States per year. Only one FDA-approved drug, Riluzole, is available for patients, which extends lifespan by only a few months. For the majority of ALS cases, there is no family history of the disease (termed sporadic ALS), making it difficult to identify genetic factors that contribute or cause disease. The remaining 5 to 10% of ALS is inherited in an autosomal dominant fashion (termed familial ALS). Sporadic and familial ALS cases are clinically indistinguishable. One of the most striking hallmarks of disease that is shared by both familial and sporadic ALS is neuroinflammation, characterized by microglial activation, astrogliosis, and infiltration of peripheral immune cells. It is unknown what role neuroinflammation plays in motor neuron (MN) death in ALS. Therefore, the aim of these studies is to identify upstream regulators of inflammation that are dysregulated with disease and to understand the role of this complex response in MN death in ALS.

Nuclear Factor-kappa B (NF-κB), a master regulator of inflammation, is upregulated in glia of both familial and sporadic ALS patients. We demonstrate that NF-κB signaling is upregulated in SOD1-G93A mice, and increases with disease progression. However, selective NF-κB inhibition in ALS astrocytes is not sufficient to rescue MN death in vitro or in vivo. Furthermore, to characterize the spacial and temporal localization of NF-κB activity in ALS, we crossed the SOD1-G93A mice to an NF-κB-GFP reporter strain. Although NF-κB activity was detected in astrocytes, we identified microglia as the predominant cell-type activating NF-κB with disease progression. To further study the potential role of NF-κB in microglial-mediated MN
death, we established the first robust and reproducible \textit{in vitro} coculture model of adult microglia and motor neurons. Utilizing this novel model, we determined NF-κB inhibition in microglia rescued MN survival. Subsequent deletion of NF-κB signaling in microglia \textit{in vivo} dampened pro-inflammatory microglial activation and extended survival in ALS mice by 20 days. Conversely, constitutive activation of NF-κB selectively in wild-type microglia \textit{in vitro and in vivo} induced pathological hallmarks of ALS, such as gliosis and MN death. Taken together, these data provide a mechanism by which microglia induce MN death in ALS, and suggest a novel therapeutic target that can be modulated to slow the progression of ALS and possibly other neurodegenerative diseases by which microglial activation plays a role.

In addition to microglia, other cell types such as motor neurons, astrocytes, and oligodendrocytes are involved in ALS pathogenesis. Therefore, we hypothesized that a successful therapeutic strategy is likely to involve targeting multiple cell types. Our laboratory previously demonstrated that a single, post-natal, intravenous injection of AAV9 encoding a shRNA against mutant SOD1 is able to traverse the blood-brain-barrier of ALS mice and reduce SOD1-expression in astrocytes and motor neurons. Reducing mutant SOD1 increased survival by 51.5 days in ALS mice. Therefore, to evaluate the benefit of a combinatorial treatment in ALS, we combined microglial NF-κB suppression with SOD1 reduction in astrocytes and motor neurons. Targeting all three cell-types resulted in an additive increase in lifespan, with maximum survival reaching 204 days, 67 days longer than the mean survival of control animals.

In summary, the data presented here are significant because we identify a novel mechanism by which microglia, but not astrocytes, induce motor neuron death in ALS. Furthermore, we demonstrate targeting two independent pathogenic mechanisms results in an additive increase in survival in the ALS mouse model. This suggests a combinatorial approach should be investigated as a therapeutic paradigm for the treatment of ALS.
## RECENT ABSTRACTS AND PRESENTATIONS

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<td>Oral presentation, Edward F. Hayes Graduate Research Forum</td>
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RECENT PUBLICATIONS

Ashley E. Frakes, Lyndsey Braun, Leah Schmelzer, Denis C. Guttridge, Brian K. Kaspar. Targeting independent pathogenic mechanisms in a familial mouse model of ALS leads to an additive increase in survival and motor function. *In preparation*


Laura Ferraiuolo, Ashley Frakes, Brian K. Kaspar. Neural stem cells as a therapeutic approach for amyotrophic lateral sclerosis. *Molecular Therapy.* 2013 Mar;21(3):503-5. PMID: 23449106


AWARDS AND HONORS

Feb. 2014 1st place in oral presentation competition
Edward F. Hayes Graduate Research Forum,
OSU, Columbus, OH.

Oct. 2013 Selected oral presentation winner and travel award recipient, Annual Retreat for The Research Institute at Nationwide Children’s Hospital, Columbus, OH.

March 2013 1st place in oral presentation competition
Edward F. Hayes Graduate Research Forum,
OSU, Columbus, OH.

Nov. 2012 1st place in poster competition and travel award recipient, Neuroscience Research Day, OSU

FUTURE PLANS

I have accepted a post-doctoral position at University of California Berkeley in Andrew Dillin’s lab, which I will start in January. In the Dillin lab I will study the molecular pathways that regulate aging. During normal aging, protein homeostasis declines, resulting in accumulations of misfolded, aggregated proteins that reduce cellular viability and can cause disease. I hope to investigate how these age-regulated mechanisms that govern protein homeostasis are altered or accelerated during age-related diseases, such as neurodegeneration.

During and after my post-doc I will be feverishly writing grants to anyone who will give me the money to (hopefully) establish my own lab! 😊