Smad Signaling in Skeletal Muscle as a Biomarker of Disease Progression in ALS

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Country

USA

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Smad Signaling in Skeletal Muscle as a Biomarker of Disease Progression in ALS

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NIH (NINDS)

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5

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic Lateral Sclerosis, Skeletal Muscle, Disease Progression, Muscle, MicroRNAs

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a degenerative disease of motor neurons that inexorably leads to progressive weakness and death. There is no

specific biomarker for this disease, thus often delaying the diagnosis for more than a year. Furthermore, once a diagnosis is established, the current tools to track patients are insensitive for the timely detection of disease improvement or worsening. A biomarker that can facilitate diagnosis, track disease progression, or both, would fill a large clinical gap in ALS management, and expedite clinical trials of novel therapies. A workshop of ALS researchers came to a consensus that biomarkers are critically and urgently needed for this disease, especially those that can track disease progression. In an exploratory R21 grant, using an RNA sequencing approach, we identified members of the Smad family as promising muscle biomarkers of ALS (Si et al., 2014). Smads mediate TGF? and BMP signal transduction by modulating gene transcription and miRNA maturation. We found these markers to be significantly elevated in ALS muscle samples, and they tracked disease progression in the G93A mouse model starting at very early (preclinical) stages. From our preliminary RNA sequencing and validation data, we have found: 1) early upregulation of specific TGF ligands that activate Smads and parallel disease progression, and 2) upregulation of specific miRNAs that are targets of Smad modulation. These novel findings form the basis of our overarching hypothesis in this proposal that the Smad axis of signaling in muscle is a biomarker of ALS. The long term goal is to develop this axis as a biomarker of ALS to track the disease and to provide insight into disease mechanisms at the level of muscle. We propose 3 specific aims to address this hypothesis: 1) Characterize the TGF ligands involved in the Smad axis of signaling in ALS muscle using human and mouse ALS muscle tissues and cultured muscle cells. 2) Correlate miRNA expression patterns in human and mouse ALS muscle samples (as determined by miRNA sequencing) to disease progression. We will assess the impact of Smad induction/activation on these patterns. 3) Characterize the Smad axis of signaling as a biosensor of ALS disease progression. In this aim we will prospectively study the Smad axis of signaling in muscle from a cohort of ALS patients and correlate the molecular patterns of Smad induction/activation and miRNA expression with disease progression. This bench-to-bedside proposal represents an entirely novel direction with compelling translational implications. It vertically integrates basic and clinical approaches, capitalizing on the collaborative spirit at UAB, to address a major gap in our ability to manage patients with ALS.

Lay Summary
PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS) is a fatal degenerative disease of motor neurons. There are currently no biomarkers that can facilitate early diagnosis or track progression of the disease. This application will investigate a promising set of biomarkers (Smads) in muscle of ALS patients which may fill this clinical void and improve disease diagnosis and treatment.

Further information available at:

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Investments > €500k

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United States of America

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Motor neurone diseases

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