SMN dysfunction in FUS-dependent ALS

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SMN dysfunction in FUS-dependent ALS

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Research Abstract

Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are fatal neurological disorders that involve the selective degeneration of spinal motor neurons. SMA – the most common genetic cause of infant mortality – is a monogenic disorder caused by widespread deficiency in the survival motor neuron (SMN) protein due to deletion of the SMN1 gene. In contrast, ALS is predominantly a sporadic disorder, but in a minority of familial cases, mutations in over 20 different genes cause motor neuron degeneration. Genetic and molecular studies increasingly suggest that ALS and SMA may share common underlying mechanisms of disease. This project focuses on one form of familial ALS caused by mutations in the RNA binding protein fused in sarcoma (FUS) – which are associated with a broad range of clinical phenotypes including some of the most aggressive, juvenile-onset forms of the disease – and the possible role of SMN biology in the pathogenesis of FUS-dependent motor neuron

degeneration. SMN has a well-established function in the assembly of small nuclear ribonucleoproteins (snRNPs) involved in diverse mRNA processing pathways and increasing evidence links SMN-dependent RNA dysregulation with the etiology of SMA. Remarkably, recent studies in cultured mammalian cells and ALS patients' fibroblasts have shown that FUS depletion or expression of ALS-linked FUS mutations disrupt the normal localization of SMN to nuclear bodies known as Gems. Furthermore, FUS has been shown to associate with SMN as well as specific snRNPs whose biogenesis is SMN-dependent and might be disrupted by ALS-linked FUS mutations. Together, these findings suggest that FUS and SMN are functionally linked through a shared molecular pathway(s) and support the view that SMA and ALS are related motor neuron diseases. However, the normal requirement of FUS for snRNP biogenesis and the pathogenic impact of FUS mutations on SMN biology have not yet been defined mechanistically, and the contribution of SMN dysfunction to FUS-ALS pathology remains unknown. To address these outstanding questions directly, our project takes a systematic, multi-disciplinary approach involving novel mouse models of FUS-dependent ALS to explore potential SMN-dependent mechanisms of FUS-mediated motor neuron degeneration. In Aim 1, we will investigate the phenotypic effects of both reduced and increased SMN expression on FUS-dependent motor neuron pathology in mouse models of ALS. In Aim2, we will employ a comprehensive set of molecular approaches to establish the functional relevance of normal and pathogenic FUS-SMN interactions in the pathway(s) of snRNP biogenesis in motor neurons using a combination of cellular and animal model systems. Collectively, these studies aim to establish convergent mechanisms in ALS and SMA and will yield a more complete understanding of the biology of FUS and SMN that is relevant to motor neuron survival. Identification of shared molecular pathways contributing to death and dysfunction of motor neurons in SMA and ALS may also expand the range of therapeutic targets for these diseases.

Further information available at:

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