Identifying the molecular mechanism of motor axonal degeneration in ALS

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease in which patients suffer progressive paralysis and death due to the progressive loss of MNs. Importantly, in ALS, Motor neurons (MN) axons degenerate prior to soma. Although many studies have identified neuroprotective drug candidates, these compounds have almost universally failed in clinical trials. We speculate that one of the reasons for the high attrition rate is that almost all disease models focus only MN soma. In contrast, very little is known about why axons are sensitive to ALS pathogenesis. We suggest that understanding the molecular mechanism of axonal degeneration in ALS could lead to effective therapies for patients.

MNs connect our brain and spinal cord to skeletal muscle, and they have axons up to a meter long. In order to survive and function, MN axons utilize ribonucleoprotein particles (mRNPs), which transport and store specific mRNAs. These axonal mRNAs are translated locally to support many axonal functions, including mitochondrial metabolism.

Evidence suggests an important role for axonal mRNPs in ALS, and multiple RNA-binding proteins inside axonal mRNPs are associated with ALS. One of the best studied is FUS, which causes one of the most aggressive forms of ALS. Induced pluripotent stem cells (iPSCs) are powerful tools for generating patient-specific ALS models. By reprogramming a patient's own cells, we can generate ALS MNs and characterize their axons compared with isogenic controls. Previously, our team generated iPSC-derived MNs with mutant FUS, which causes one of the most aggressive forms of ALS. Using microfluidic chambers, we were able to isolate homogenous populations of MN axons. We found profound alterations in mitochondrial function, which were associated with a risk of axonal degeneration similarly to that in patients. Here, we propose building on these findings by identifying the molecular mechanism driving this pathogenesis. We would like to use a combination of transcriptomics and proteomics data to identify ALS-associated alterations in specific mRNPs and how they are causally linked to axonal phenotypes, including mitochondrial dysfunction and degeneration. This information will then be used to develop novel therapeutic strategies such as identifying synthetic RNAs that can rescue axons from ALS-associated phenotypes.

Preferred Course of Study/Expertise of Candidate: Mammalian cell culture experience is required. Experience with iPS cells would be beneficial.