Characterizing TDP-43 pathology in ALS patient macrophages to facilitate early diagnosis and protect motor neurons

Amyotrophic lateral sclerosis (ALS) causes progressive paralysis due to the degeneration of motor neuron (MN) axons. Developing effective treatments has been exceptionally difficult because the earliest phases of the disease occur before the patients are diagnosed. Unfortunately, almost all cases of ALS are sporadic and lack any family history. In addition, most cases cannot be linked to a specific genetic mutation. Thus, at present, one of the most important outstanding challenges in ALS is to identify individuals in the earliest phases of the disease. Almost all ALS patients share a common pathology: mislocalization of RNA-binding proteins, particularly TDP-43, from the nucleus, where it regulates splicing, to the cytoplasm, where it aggregates. Although previous research primarily focused on MNs, recent critical advances suggest that peripheral macrophages display TDP-43 pathology years before ALS symptoms manifest. This is important because it opens the possibility that a blood test could be developed to identify individuals in the earliest phases of ALS. In addition, macrophages play an important role in regulating MN axons, raising the intriguing hypothesis that aberrant macrophages may causally contribute to MN degeneration. Thus, understanding TDP-43 pathology in macrophages may facilitate early detection of ALS using non-invasive blood samples as well as enable development of therapeutics protecting MNs against ALS pathogenesis. To accomplish these ambitious objectives we will isolate primary patient monocytes and differentiate them into macrophages. Since not all macrophages manifest ALS pathology, single cell transcriptome sequencing will identify splicing changes associated with mislocalized TDP-43, which we aim to develop into candidate biomarkers of early ALS. Next, we will characterize the impact of ALS pathology on macrophage function. Finally, we will characterize the impact of pathological macrophages on MN axons and test strategies to restore TDP-43 homeostasis in macrophages to promote axonal survival and regeneration.