Capturing initial molecular events in the pathogenesis of motor neuron disease: the roles of RNA metabolism and cellular autonomy.

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Research Abstract

Motor neuron disease (MND) is rapidly progressive, untreatable and fatal. Mutations causing MND disrupt RNA-binding proteins (RBPs) such as TDP-43 or FUS, resulting in their mislocalisation to the cytoplasm from the nucleus and raising the hypothesis that deregulated RNA networks are a primary pathogenic mechanism. We desperately need to understand RNA-RBP interactions in MND to discover disease mechanisms. Against this background, my key goals are to answer the following questions: 1) Is loss of nuclear function the earliest pathogenic event in MND? 2) Alternatively, is aberrant cytoplasmic function the earliest pathogenic event? 3) Do aberrant RBP-RNA complexes sequester RBPs away from their normal RNA targets? 4) Does deregulated RNA metabolism differentially impact neurons, astrocytes and/or oligodendrocytes? I will use my existing expertise to generate motor neurons and glia from control, TDP-43 and FUS MND human induced pluripotent stem cell (hiPSC) lines. I will next utilize a variety of state-of-the art but fully validated functional genomic methods centered on resolving RBP-RNA interactions to robustly address the core questions above. Significant findings will next be validated in different established model systems. This integrated approach will robustly elucidate the molecular pathogenesis of MND and guide new molecular therapies.

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