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Impaired neuromuscular signalling is a feature of Motor Neuron Disease

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Motor Neuron Disease (**MND**) is a devastating disorder with death occurring in approximately 80% of patients within 3-5 years of symptom onset. A key feature of lower motor neuron involvement is the loss of connections between alpha motor neurons and their target muscle cells leading to progressive muscle weakness and death. Whether abnormalities in Motor Neuron Disease (**MND**) muscle contribute to the loss of nerve-muscle connections in MND remains uncertain and settling this issue may be important to developing effective treatments. What we do know is that the neural agrin-Muscle Specific Kinase signalling system plays a vital role in the development of neuromuscular connections, and their maintenance throughout life. Neural agrin from the motor nerve acts via Muscle Specific Kinase (**MuSK**) on the muscle fiber surface to stabilize the neuromuscular synapse. We have employed a combination of molecular-cellular pathology and in vitro human cell-based bioassays to show that neural agrin-MuSK signaling may be faulty in MND muscle, potentially contributing to loss of nerve-muscle connections in MND.

In MND muscles, we observed a 50% drop in apposition between motor nerve terminals and motor endplates, and diffuse postsynaptic acetylcholine receptors. Importantly, we also show that muscle cells cultured from MND biopsies fail to respond to motor nerve terminal signals (human motor axons or neural agrin) to form the large clusters of acetylcholine receptors that are essential for neuromuscular synaptic transmission. Moreover, we show altered levels of expression of MuSK, and MuSK-complex components: LRP4, Caveolin-3, and Dok7 differed between muscle cells cultured from MND patients compared to those from non-MND controls. Our results highlight this signaling pathway as a potential therapeutic target to prolong muscle function in MND and provides strong support to the growing body of evidence that muscle is a viable therapeutic target to help treat MND.