

Public Abstract

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Title:Utilizing Gene Therapy Methods to Probe the Genetic Requirements to Prevent Spinal Muscular Atrophy.

Spinal Muscular Atrophy (SMA) causes death of motor neurons that control muscle movement, progressive weakness, and death by age two in most patients. Low levels of a protein called SMN are the root cause of SMA. Using a well established mouse model, we delivered versions of SMN from other species as well as versions that we specifically altered. By monitoring whether each version of SMN improved survival and strength in mice, we determined the regions of SMN that seem to be important for it to function to prevent SMA.

Our findings indicate that one region in the middle of SMN is important for SMN function. This region is involved in SMN's interaction with profilin, implying that disruption of this interaction may be partially responsible for motor neuron loss in SMA.

We used similar gene therapy methods to determine which cell types require SMN and found that both SMN expressed in both motor neurons and astrocytes is beneficial in mice. Among many other functions, astrocytes provide nutrients and antioxidants to motor neurons. We tested whether addition of a regulator of antioxidant genes could also be of benefit. This treatment had a mild effect, implying that the role of astrocytes in SMA is likely not due to antioxidant regulation.

Finally, we characterized neuromuscular junctions in a variety of SMA treated and untreated conditions. As neuromuscular junctions are the contact point between motor neurons and the muscles they control, this analysis is essential in understanding SMA disease progression.