Inhibition of apoptosis blocks human motor neuron cell death in a stem cell model of spinal muscular atrophy.

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Funding Grants: Use of iPS cells (iPSCs) to develop novels tools for the treatment of spinal muscular atrophy.

Public Summary:
Spinal muscular atrophy (SMA) is a genetic disorder caused by a absence of a critical gene knwon as survival motor neuron 1 (SMN1). The loss of this gene leads to loss of motor neurons through unknown mechanisms,, eventually leading the muscle wasting, paralysis and death. Using a a stem cell model we show here that induced pluripotent stem cell (iPSC) lines created from two Type I SMA subjects-one produced with viral methods and the second using a virus-free approach-recapitulate the disease phenotype and generate significantly fewer motor neurons compared to two separate control subject iPSC lines. We were able specifically show identify pathways and molecules involved the motor neuron cell death in the patient-derived motor neurons. Importantly, we are able to prevent this motor neuron death using known chemical tools that can block the activation of these cell death associated molecules, known as Fas ligand and caspase-8. Empowered with clues to to the cell death mechanisms in patient motor neurons, we plan to use this knowledge to continue developing better drugs based on the SMA patient-specific stem cell platform we have developed.

Scientific Abstract:
Spinal muscular atrophy (SMA) is a genetic disorder caused by a deletion of the survival motor neuron 1 gene leading to motor neuron loss, muscle atrophy, paralysis, and death. We show here that induced pluripotent stem cell (iPSC) lines generated from two Type I SMA subjects-one produced with lentiviral constructs and the second using a virus-free plasmid-based approach-recapitulate the disease phenotype and generate significantly fewer motor neurons at later developmental time periods in culture compared to two separate control subject iPSC lines. During motor neuron development, both SMA lines showed an increase in Fas ligand-mediated apoptosis and increased caspase-8 and-3 activation. Importantly, this could be mitigated by addition of either a Fas blocking antibody or a caspase-3 inhibitor. Together, these data further validate this human stem cell model of SMA, suggesting that specific inhibitors of apoptotic pathways may be beneficial for patients.