Functional motor neuron subtypes generated from embryonic stem cells

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Scientists have devised a method for coaxing mouse embryonic stem cells into forming a highly specific motor neuron subtype. The research, published by Cell Press in the September 3rd issue of the journal *Cell Stem Cell,* provides new insight into motor neuron differentiation and may prove useful for devising and testing future therapies for motor neuron diseases.

Motor neurons in the spinal cord communicate with other neurons in the central nervous system and send long projections out to muscles, transmitting signals that are essential for proper control of movement and posture. Like other neuron classes, motor neurons are known to exhibit tremendous diversity. "The existence of dozens of muscle groups in the limbs of most mammals demands an equivalent diversity of motor neuron pool subtypes," explains the senior study author, Dr. Hynek Wichterle from Columbia University in New York.

During normal development, motor neurons settle into specific sections of the spinal cord (called columns), which correspond to the muscles that they will innervate. For example, cells in one area link up with muscles in the limbs, while cells residing in another region innervate muscles in the body wall. Although previous studies have shown that mouse and human embryonic stem cells can be converted into motor neurons, it was not clear whether these were "generic" neurons or whether they could acquire characteristics of the specific specialized subtypes.

In the current study, lead author Dr. Peljto and colleagues showed that removing a key differentiation factor allowed cultured embryonic stem cells to form motor neurons with molecular characteristics corresponding to a limb innervating subtype, without the need for genetic manipulation or added factors. Importantly, when this stem cell-derived subtype was transplanted into embryonic chick spinal cords, the motor neurons settled in the expected columnar position within the cord and had projections that mimicked the trajectory of limb innervating motor neurons.

Although encouraging from a regenerative medicine perspective, the authors caution that due to differences in limb and wing musculature, their mouse-to-chick transplantation paradigm makes it impossible to determine whether motor neurons generated in the lab exhibit subtype specific connectivity with limb muscles. However, this method for reliably generating defined motor neuron subtypes may prove to be invaluable for future disease modeling studies.

"Motor neuron subtypes exhibit differential susceptibility to neurodegeneration in two prominent motor neuron diseases, Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA)," says Dr. Wichterle. "The ability to drive the differentiation of embryonic stem cells into disease-sensitive and -resistant motor neuron subtypes could help to uncover new therapeutic strategies."

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