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Direct reprogramming of human astrocytes to dopaminergic neurons

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Replacement of dopaminergic neurons lost in Parkinsons Disease has long been a goal in the field of regenerative medicine. Fetal midbrain tissue, pluripotent stem cells, neural stem cells, and directly reprogrammed fibroblasts all provide potentially valuable sources of replacement neurons for cell-based therapies. However, the relatively recent development of direct reprogramming strategies has opened the door for a novel approach: direct in vivo conversion of astrocytes to dopaminergic neurons. We previously demonstrated that a combination of three factors - ASCL1, LMX1B, and NURR1 - could efficiently convert mouse astrocytes to functional dopaminergic neurons via a polycistronic vector. We now report that human astrocytes, unlike their murine counterparts, require just 2 transcription factors to effect efficient conversion to dopaminergic neurons. These factors can be readily delivered to astrocytes via doxycycline-inducible bicistronic lentiviral vectors. The resulting neurons exhibit phenotypic characteristics consistent with midbrain dopaminergic neurons, as evidenced by gene and protein expression analysis, electrophysiological recording of spontaneous action potentials, and release of dopamine upon membrane depolarization. In addition, we have cloned the bicistronic expression cassette into an adeno-associated viral vector (AAV) to mediate efficient transduction of astrocytes in vivo. We present preliminary results describing the effectiveness of this AAV to transduce and reprogram astrocytes to dopaminergic neurons in a non-human primate model of Parkinsons Disease.

Biography

Russell Addis is a senior research investigator at the University of Pennsylvania Institute for Regenerative Medicine. He earned a Ph.D. in human genetics and molecular biology at Johns Hopkins University, where he studied the differentiation of embryonic stem cells into dopaminergic neurons. In his current position at Penn, he led the group that was first to report the direct conversion, or transdifferentiation, of astrocytes into functional dopaminergic neurons.

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