Volume 12

Washington University
Undergraduate Research Digest

Spring 2017

Defining Neuronal Subtype Specification in Reprogrammed Striatal Neurons

Hannah Olsen
Washington University in St. Louis

Defining Neuronal Subtype Specification in Reprogrammed Striatal Neurons

Hannah Olsen

Mentor: Andrew Yoo

The ability to reprogram human skin cells into neurons has greatly enhanced our understanding of human neuronal function and disease processes. We recently developed a protocol to reprogram human skin fibroblasts directly into striatal medium spiny neurons (MSNs). This class of neuronal subtype is further specified into DRD1- (dopamine receptor 1) or DRD2-expressing MSNs, which are differentially affected in Huntington's disease (HD). In our study, ectopically expressing brain enriched microRNAs, miR-9/9* and miR-124 and striatum transcription factors CTIP2, DLX1/2, MYT1L (referenced hereafter collectively as miR-9/9*-124+CDM), converted human fibroblasts into MSNs comprised in the majority by DRD1-expressing cells, with approximately 70% of MSNs expressing DRD1. DRD2-MSNs are of great clinical interest as they are amongst the first cells to die in HD, with the number of DRD2-MSNs rapidly reducing with increasing pathology severity. In addition, other studies have shown that the cellular expression of DRD2 mRNA is dramatically reduced in HD while DRD1 mRNA levels are relatively stable. Therefore, the ability to generate a homogenous population of DRD2-expressing MSNs from HD patients would give us an unprecedented platform to model HD in culture. Through a comprehensive screening of over 30 genes, I found the transcription factor LHX8, when transduced in conjunction with miR-9/9*-124+CDM, consistently produced an approximately ten-fold increase in transcript levels of DRD2 without affecting DRD1 expression. Similar results were observed in both wild type and HD cell lines, indicating that LHX8 robustly affects cellular fate specification independently of disease status.