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Mechanisms underlying direct programming of stem cells into motor neurons could lead to cell-replacement therapies

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A team of scientists has uncovered details of the cellular mechanisms that control the direct programming of stem cells into motor neurons. The scientists analyzed changes that occur in the cells over the course of the reprogramming process. They discovered a dynamic, multi-step process in which multiple independent changes eventually converge to change the stem cells into motor neurons.

"There is a lot of interest in generating motor neurons to study basic developmental processes as well as human diseases like ALS and spinal muscular atrophy," said Shaun Mahony, assistant professor of biochemistry and molecular biology at Penn State and one of the lead authors of the paper. "By detailing the mechanisms underlying the direct programing of motor neurons from stem cells, our study not only informs the study of motor neuron development and its associated diseases, but also informs our understanding of the direct programming process and may help with the development of techniques to generate other cell types."

The direct programming technique could eventually be used to regenerate missing or damaged cells by converting other cell types into the missing one. The research findings, which appear online in the journal *Cell Stem Cell* on December 8, 2016, show the challenges facing current cell-replacement technology, but they also outline a potential pathway to the creation of more viable methods.

"Despite having a great therapeutic potential, direct programming is generally inefficient and doesn't fully take into account molecular complexity," said Esteban Mazzoni, an assistant professor in New York University's Department of Biology and one of the lead authors of the study. "However, our findings point to possible new avenues for enhanced gene-therapy methods."

The researchers had shown previously that they can transform mouse embryonic stem cells into motor neurons by expressing three transcription factors—genes that control the expression of other genes—in the stem cells. The transformation takes about two days. In order to better understand the cellular and genetic mechanisms responsible for the transformation, the researchers analyzed how the transcription factors bound to the genome, changes in gene expression, and modifications to chromatin at 6-hour intervals during the transformation.

"We have a very efficient system in which we can transform stem cells into motor neurons with something like a 90 to 95 percent success rate by adding the cocktail of transcription factors," said Mahony. "Because of that efficiency, we were able to use our system to tease out the details of what actually happens in the cell during this transformation."

"A cell in an embryo develops by passing through several intermediate stages," noted Uwe Ohler, senior researcher at the Max Delbrück Center for Molecular Medicine (MDC) in Berlin and one of the lead authors of the work. "But in direct programming we don't have that: we replace the gene transcription network of the cell with a completely new one at once, without the progression through intermediate stages. We asked, what are the timing and kinetics of chromatin changes and transcription events that directly lead to the final cell fate?"

The research team found surprising complexity—programming of these

stem cells into neurons is the result of two independent transcriptional processes that eventually converge. Early on in the process, two of the transcription factors—Isl1 and Lhx3—work in tandem, binding to the genome and beginning a cascade of events including changes to chromatin structure and gene expression in the cells. The third transcription factor, Ngn2, acts independently making additional changes to gene expression. Later in the transformation process, Isl1 and Lhx3 rely on changes in the cell initiated by Ngn2 to help complete the transformation. In order for direct programming to successfully achieve cellular conversion, it must coordinate the activity of the two processes.

"Many have found direct programming to be a potentially attractive method as it can be performed either in vitro—outside of a living organism—or in vivo—inside the body and, importantly, at the site of cellular damage," said Mazzoni. "However, questions remain about its viability to repair cells—especially given the complex nature of the biological process. Looking ahead, we think it's reasonable to use this newly gained knowledge to, for instance, manipulate cells in the spinal cord to replace the neurons required for voluntary movement that are destroyed by afflictions such as ALS."

Provided by New York University

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