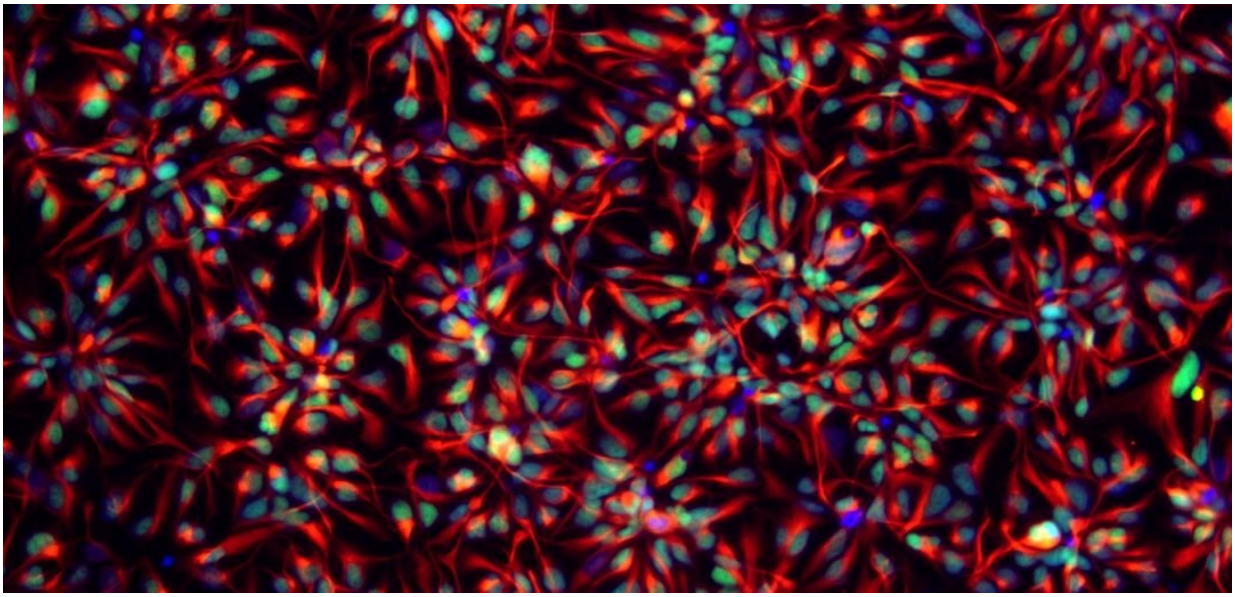
DNA methylation plays key role in stem cell differentiation

March 26 2018, by Will Doss



Neural progenitors cells differentiated from human embryonic stem cells. Credit: Northwestern University

Northwestern Medicine scientists have discovered how the process of DNA methylation regulates the development of spinal cord motor neurons, according to a study published in the journal *Cell Stem Cell*.

DNA methylation, an epigenetic mechanism that determines whether or not a gene is expressed, guides stem cells as they transform from blank slates into specialized cells, according to Evangelos Kiskinis, Ph.D.,

assistant professor of Neurology in the Division of Neuromuscular Disease and senior author of the study.

Motor neurons are highly specialized neuronal cells that connect the central nervous system to muscle and degenerate in amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

"If you look at DNA methylation patterns in ALS patients, they are all over the place," said Kiskinis, who is also a professor of Physiology. "Is it a driver of disease, or is it just a byproduct? Our study provides us with a platform to address these intriguing questions."

The investigators used a variety of cutting-edge technologies—including single cell RNA-Sequencing and a methylation-focused adaption of CRISPR-Cas9 gene editing, known as epigenetic editing—to create a series of stem cells that each lacked different enzymes that trigger DNA methylation.

After analyzing the stem cells along with the differentiating neural progenitors and the motor neuron populations, Alberto Ortega, Ph.D., senior postdoctoral fellow in Kiskinis' laboratory and lead author on the study, concluded that the enzyme DNMT3A triggered DNA methylation, which in turn repressed or counterintuitively activated the key transcription factors that controlled differentiation of stem cells into spinal cord motor neurons.

"DNA methylation governs gene expression potential and hence cell identity," Kiskinis said. "As stem cells transition from early progenitors to committed progenitors to developed neurons, DNA methylation allows for the induction or suppression of key transcription factors. In turn, those transcription factors govern cell type function and specificity."

"Our study nicely shows the importance of epigenetics on controlling different steps of the development of the human central nervous system by tuning the expression levels of transcription factors," Ortega added.

In addition, the scientists found irregular DNA methylation patterns could have downstream consequences related to the function of these neurons, according to Kiskinis.

"It seems if you don't set your DNA methylation patterns correctly, there's a cascade of irregular gene expression that results in defective cells," Kiskinis said. "This is intriguing, because people usually think about methylation in the context of cell differentiation—the role in developed neurons is largely overlooked."

Further investigation could shed light on spinal cord diseases, as patients with ALS have irregular patterns of methylation, according to Kiskinis. In addition, patients with ALS exhibit a high rate of genetic variants associated with the DMNT3A enzyme—another puzzling link.

"Whether it's causal or not, we don't know—but we're going to figure this out next," Kiskinis said.

More information: Michael J. Ziller et al. Dissecting the Functional Consequences of De Novo DNA Methylation Dynamics in Human Motor Neuron Differentiation and Physiology, *Cell Stem Cell* (2018). DOI: 10.1016/j.stem.2018.02.012

Provided by Northwestern University