Key mechanisms identified for regeneration of neurons

July 4 2024

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Neurological disorders, such as trauma, stroke, epilepsy, and various neurodegenerative diseases, often lead to the permanent loss of neurons, causing significant impairments in brain function. Current treatment options are limited, primarily due to the challenge of replacing lost neurons.

Direct neuronal reprogramming, a complex procedure that involves changing the function of one type of cell into another, offers a promising strategy.

In cell culture and in living organisms, glial cells—the non-neuronal cells in the central nervous system—have been successfully transformed into functional neurons. However, the processes involved in this reprogramming are complex and require further understanding. This complexity presents a challenge, but also a motivation, for researchers in the field of neuroscience and regenerative medicine.

Modifications in the epigenome

Two teams, one led by Magdalena Götz, Chair of Physiological Genomics at LMU, Head of the Stem Cell Center Department at Helmholtz Munich, and researcher in the SyNergy Cluster of Excellence, and the other led by Boyan Bonev at the Helmholtz Pioneer Campus, explored the molecular mechanisms at play when glial cells are converted to neurons by a single transcription factor.

The findings are published in the journal *Nature Neuroscience*.

Specifically, the researchers focused on small chemical modifications in the epigenome. The epigenome helps control which genes are active in different cells at different times. For the first time, the teams have now shown how coordinated the epigenome rewiring is, elicited by a single transcription factor.

Using novel methods in epigenome profiling, the researchers identified that a posttranslational modification of the reprogramming neurogenic transcription factor Neurogenin2 profoundly impacts the epigenetic rewiring and neuronal reprogramming. However, the transcription factor alone is not enough to reprogram the glial cells.

In an important discovery, the researchers identified a novel protein, the transcriptional regulator YingYang1, as a key player in this process. YingYang1 is necessary to open up the chromatin for reprogramming, to which end it interacts with the transcription factor.

"The protein YingYang1 is crucial for achieving the conversion from astrocytes to neurons," explains Götz. "These findings are important to understand and improve reprogramming of glial cells to neurons, and thus bring us closer to therapeutic solutions."

More information: Allwyn Pereira et al, Direct neuronal reprogramming of mouse astrocytes is associated with multiscale epigenome remodeling and requires Yy1, *Nature Neuroscience* (2024). DOI: 10.1038/s41593-024-01677-5

Provided by Ludwig Maximilian University of Munich