Neural regeneration through cell fate reprogramming in vivo

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Neural injury or neurodegeneration frequently leads to irreversible loss of neurons; however, the adult mammalian central nervous system (CNS) has largely lost the ability to produce new neurons. A key question in the regeneration field is how to generate new neurons for functional reconstruction in the adult CNS. Our lab has taken an in vivo reprogramming approach, which is to engineer the fate of resident glial cells to let them become neurogenic.

Methods: Astrocytes and their progenies were genetically traced with a fluorescence reporter in transgenic mice. They were then transduced with virus expressing fate-determining transcription factors. New neurons were detected with cell type-specific markers and were traced with BrdU, a thymidine analog that could incorporate into newly synthesized DNA during cell replication. Transition from glial cells to neurons were examined by genetic lineage tracing. It was further analyzed through single cell RNA-seq and pseudotime trajectory.

Results: After in vivo screens, we revealed that astrocytes can be in vivo reprogrammed by specific transcription factors to generate new neurons in the adult mouse brain. Genetic lineage tracing confirmed their astrocyte origin. Immunohistochemistry and electrophysiology indicated that these neurons could become functionally mature. scRNA-seq revealed key signaling pathways and regulators during reprogramming, whereas pseudotime analysis identified the transitional cell types from glia to neurons.

Discussion: Our results showed the ability to reengineer cell fates in vivo. Further development of this reprogramming approach may lead to a regeneration-based therapeutic strategy for many of the neurological diseases.

References:

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