

Chromatin-based somatic reprogramming to model brain disorders

Brain-enriched microRNAs (miRNAs), miR-9/9* and miR-124 (miR-9/9*-124), exert potent cellular reprogramming activity when ectopically expressed in unrelated somatic cells such as fibroblasts. In fibroblasts, these miRNAs target multiple components of chromatin remodeling machinery, including subunits of the BAF (SWI/SNF) chromatin remodeling complexes, leading to extensive reconfiguration of the chromatin landscape. This process promotes erasure of fibroblast identity and facilitates the acquisition of a stable neuronal fate. This approach is particularly important for modeling late-onset neurological disorders such as Alzheimer's disease, in which aging is the primary risk factor. Unlike induced pluripotent stem cell-based models, miRNA-induced neurons retain age-associated molecular signatures from donor fibroblasts. As a result, these neurons can recapitulate critical neuropathological features, including extracellular A β deposition, tau pathology, and progressive neuronal loss. Ongoing research efforts focus on identifying age-associated alterations in gene regulatory networks and cellular pathways that contribute to neurodegeneration in patient-derived neurons, such as those involved in autophagy and proteostasis. Here, we highlight how direct differentiation can reveal disease mechanisms and patient-specific pathology, using Alzheimer's disease as an example. We explore how this approach could be applied to substance use disorders, which follow a dynamic course marked by remission and relapse. Because directly converted neurons retain molecular signatures of prior environmental exposures, longitudinal sampling may allow these phases to be modeled and to identify patient- and stage-specific signatures. Direct differentiation therefore has the potential to provide a scalable, experimentally tractable, and temporally resolved framework for studying the gene-environment interactions that drive substance use disorders.

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