Modeling late-onset neurodegeneration via direct somatic reprogramming

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Aging is a major risk factor for neurodegenerative disorders, including late-onset Alzheimer's disease (LOAD). To understand how aging contributes to neurodegenerative vulnerability in human neurons, it is essential to develop neuronal models that retain age-associated molecular and epigenetic features. Direct neuronal reprogramming of easily obtainable somatic cells such as fibroblasts to neurons, offers an approach of generating human neurons bypassing the pluripotent stem cell stage while preserving the aging signatures. An advance in this method is the use of brain-enriched microRNAs (miR-9/9* and miR-124), which remodel the chromatin landscape, erasing the fibroblast identity, and sequentially evoking the neuronal identity. For LOAD modeling, combining miR-9/9*-124 with NEUROD2 and MYT1L drives fibroblast conversion into excitatory cortical neurons. Notably, these neurons express all six human tau isoforms in a 1:1 ratio of 3R- to 4R-tau, mimicking adult human brain composition, a key feature for studying tau pathology as both isoforms are present in AD tau tangles. When LOAD patient-derived fibroblasts are reprogrammed in a 3D environment, the resulting neurons recapitulate hallmark AD features, including β-amyloid (Aβ) deposition, insoluble tau accumulation, and neuronal loss. These LOAD neurons thus offer a tractable platform for investigating age-related neurodegeneration and associated molecular pathways. One such pathway involves dysregulation of retrotransposable elements (RTEs). LOAD neurons exhibit elevated RTE activity, which is mitigated by treatment with lamivudine (3TC), a reverse transcriptase inhibitor, resulting in reduced neurodegenerative phenotypes. Therefore, the miRNA-based direct neuronal reprogramming platform provides valuable mechanistic insights and facilitates the discovery of age-associated drivers of late-onset neurodegeneration.

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