REST and neural gene network Dysregulation in iPSC models of Alzheimer's disease

ABSTRACT

The molecular basis of the earliest neuronal changes that lead to Alzheimer's disease (AD) is unclear. Here, we analyze neural cells derived from sporadic AD (SAD), APOE4 gene-edited and control induced pluripotent stem cells (iPSCs). We observe major differences in iPSC-derived neural progenitor (NP) cells and neurons in gene networks related to neuronal differentiation, neurogenesis, and synaptic transmission. The iPSC-derived neural cells from SAD patients exhibit accelerated neural differentiation and reduced progenitor cell renewal. Moreover, a similar phenotype appears in NP cells and cerebral organoids derived from APOE4 iPSCs. Impaired function of the transcriptional repressor REST is strongly implicated in the altered transcriptome and differentiation state. SAD and APOE4 expression result in reduced REST nuclear translocation and chromatin binding, and disruption of the nuclear lamina. Thus, dysregulation of neural gene networks may set in motion the pathologic cascade that leads to AD.

Keyword: Alzheimer's disease; REST; Apolipoprotein E; Epigenetic; Induced pluripotent stem cell; Neural differentiation; Neural progenitor; Neurogenesis; Organoid; Polycomb