p-241

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Single-cell epigenomics identifies shared changes in Alzheimer's and Pick's disease

Vivek Swarup, Zechuan Shi, Sudeshna Das, Samuel Morabito, Emily Miyoshi, Elizabeth Head

Tauopathies of the brain are characterized by tau aggregates, yet they differ vastly in clinical manifestations. In this regard, Pick's disease (PiD), a behavioral variant of frontotemporal dementia, have distinct tau aggregations compared with Alzheimer's disease (AD), and yet the similarities in cognitive and behavioral impairments during the progression of the disease make their diagnosis challenging. Recent advancement in single-cell epigenomic profiling methods, Assay for Transposase-Accessible Chromatin (ATAC) combined with high throughput sequencing, will enable us to map the chromatin-regulatory landscapes of disease brains at a single-cell resolution and enable us to understand underlying molecular changes in these diseases.

In the present study, we have isolated single nucleus from postmortem human frontal cortex and performed single-nucleus ATAC sequencing (snATAC-seq) of 198,722 nuclei to generate cell-type specific chromatin accessibility profiles of postmortem brains of PiD and AD patients and to uncover their cellular heterogeneity and similarity. We constructed chromatin accessibility profiles from PiD patients, late-stage AD and healthy controls. We applied UMAP dimensionality reduction and clustered nuclei through open chromatin region to the batch-corrected epigenomic datasets. We identified seven distinct cell types, including astrocyte, excitatory neurons, inhibitory neurons, microglia, oligodendrocytes, OPC, and pericyte/endothelial cells, and we applied pseudotime analysis to characterize disease-associated cell-states in both tauopathies. Our data identified the cell-type-specific open chromatin accessible regions in AD and PiD brains. Although the causative molecular mechanisms of AD and PiD remain unknown, our work helps to identify shared epigenomic changes in AD and PiD, especially identifying cell-type-specific genomic loci with disease risk.

Conflicts of interest

No disclosure