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Single nucleus transcriptome analysis of human reactive astrocytes

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Reactive astrocytes are a feature of many neurodegenerative diseases, including Alzheimer's disease and frontotemporal dementia. These pathologic glia are canonically associated with increases in cytoskeletal proteins. However, it is not fully understood how astrocytes are changed in disease.

Data from normal, pathologic aging, and Alzheimer's disease single nucleus RNA sequencing datasets were analyzed to identify the transcriptomic changes associated with reactive astrocytes. Deep learning algorithms denoised gene expression data and clustered astrocytic nuclei. RNA trajectory, linear regressions, and Gene Ontology analyses were used to characterize reactive astrocytes.

Deep learning-based clustering algorithms denoised gene expression data for 17,012 genes and clustered 15,529 astrocyte nuclei, enabling identification of gray matter (GM) and white matter (WM) astrocyte clusters. RNA trajectory analyses revealed distinct transcriptional differences between GM and WM astrocytes as well as a spectrum within the GM astrocytes. Reactive astrocyte markers (GFAP, VIM) increased along this spectrum, while homeostatic markers (LSAMP, NRXN1) decreased, consistent with graded amounts of reactivity of GM astrocytes. To identify reactivity-associated genes, linear regressions of gene expression versus reactivity were used to identify 52 upregulated and 144 downregulated genes. Gene Ontology analysis revealed that upregulated genes were associated with responses to metal ions, immune responses, and protein refolding. Downregulated genes were involved in cellular/neuronal development and maintenance. Transcription factors were significantly enriched among the downregulated genes ($p = 0.013$).

In neurodegenerative disease, GM astrocytes exist within a spectrum of reactivity that is marked by a modest upregulation of reactive genes and a strong downregulation of homeostatic genes.

Conflicts of interest

Authors have nothing to disclose.