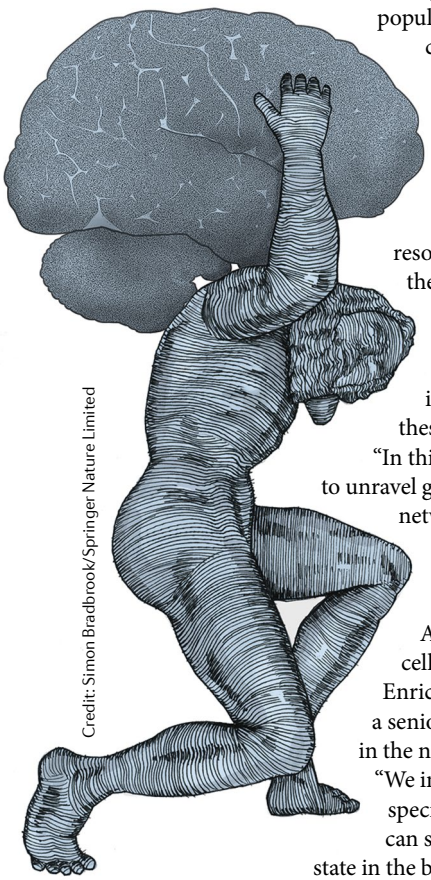
ALZHEIMER DISEASE

Single-cell atlas maps cell-specific gene changes in Alzheimer disease

> gene regulatory programmes underlying AD are highly complex and heterogeneous

Analysis of gene expression in individual cells from the brains of people with Alzheimer disease (AD) has revealed cell-type-specific changes in gene expression in a study published recently in *Nature Neuroscience*. The work provides insight into the specific cell types that mediate the effects of AD-associated genes and could help with development of therapies that target specific mechanisms.

Previous work has identified gene expression changes associated with AD, but these changes have been averaged over large populations of mixed cell types. As a result, the contributions of different cell types to these changes could not be resolved, limiting the information gained about the specific molecular implications of these changes.



Credit: Simon Bradbrook/Springer Nature Limited

"In this study, we aimed to unravel gene and gene-network expression changes in the brains of patients with AD at the single-cell level," explains Enrico Petretto, a senior investigator in the new study. "We investigated how specific, healthy cells can switch to a disease state in the brains of patients with AD and what the mechanistic underpinnings of these 'cell state transitions' in disease are."

Petretto and colleagues used RNA sequencing to analyse gene expression in individual cells in the entorhinal cortex of six patients with AD and six controls. In total, the transcriptomes of 13,214 nuclei were analysed. Reliable genetic markers were identified to classify the cells as microglia, astrocytes, neurons, oligodendrocyte progenitor cells, oligodendrocytes or endothelial cells. Gene expression patterns in cells from patients with AD were then compared with those in cells from controls.

The analysis identified nine clusters of gene expression patterns that differed between patients with AD and controls. Some of these changes were specific to certain cell types, particularly astrocytes, endothelial cells and microglia, and others were seen in multiple cell types. Furthermore, analysis of each cell type revealed multiple subclusters for each, and cells from brains with or without AD mostly segregated into different clusters.

The researchers also combined their data with data from previous genome-wide association studies to investigate the cell specificity of changes in AD-associated gene expression. Changes in expression of many of these genes were predominantly seen in one cell type, whereas others were co-ordinated between multiple subclusters. For some genes, expression changes differed between cell types. For example, in tissue from patients with AD, *APOE* was downregulated in subclusters of oligodendrocyte progenitor cells, oligodendrocytes and astrocytes, but upregulated in a microglial subcluster.

"Our study reveals that gene regulatory programmes underlying AD are highly complex and heterogeneous, demonstrating cell subtype-specific regulation and cell identity changes," explains Petretto. This insight, he continues, provides new information that could help with developing targeted therapies.

"In the past, when we have only been able to track changes over the total population of cells, it has been impossible to see how each cell type has contributed to the changes that result in AD so treatments have not been developed to target these cell type-specific processes," he explains. "Our research, along with that of others in the field, has allowed us to see which gene regulatory and functional processes in which cell types we need to target treatments to in order to get the best benefit."

The team has created the Single-cell Atlas of the Entorhinal Cortex in Human Alzheimer's Disease online to provide access to their data, which can be explored to see cell-specific gene expression, cell identities and markers. They hope that this atlas will facilitate further discoveries that reveal the functional consequences of genetic changes.

Ian Fyfe

ORIGINAL ARTICLE Grubman, A. et al. A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation. *Nat. Neurosci.* **22**, 2087–2097 (2019)

RELATED LINKS

Single-cell atlas of the Entorhinal Cortex in Human Alzheimer's Disease: http://adsn.ddnetbio.com