Integrating single-cell and whole-brain transcriptomes to study the progression of Alzheimer’s disease

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Alzheimer’s disease (AD) affects one in nine people of age 65 or older, and one in three above the age of 85. However, therapeutic development has been limited by an incomplete understanding of AD progression. To detect early markers of AD development, we measured gene expression profiles of whole brains from wild type (C57BL/6J) or AD-prone mouse models at multiple ages between 2 and 6 months. The AD-prone transgenic mouse model carried the human mutant APP and PSEN genes, and began developing Aβ deposit at around 5-month old. A total of 108 age-specific genes, transgene-specific, or age-transgene-interacting were identified, which were potential gene markers for the relevant sample groups. While meaningful in predicting the biological processes of AD development, marker genes provide little information in their cell type origins. Meanwhile, single cell transcriptomes measurements have advanced rapidly, which can facilitate the identification of marker cells that are relevant to AD development. To detect the marker cells in our bulk RNA-seq samples, we developed a novel method, permutation-based maximal covariance analysis (pMCA). pMCA uses the covariance of gene expression profiles from bulk and single-cell samples to detect the bulk-cell pairs that significantly covary. By integrating gene expression profiles of 48 major cell types of mouse brain, we found oligodendrocyte and microglia as significant marker cells of the five and six month old wild type mice, in that the expression pattern of the 108 marker genes in the two cell types and in the two wild type mice covary with each other. This suggests a loss-of-function of oligodendrocytes and microglia during AD progression.