

MOLECULAR AND CELL BIOLOGY

Complement gene expression profiles are altered in the AD frontal cortex

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Abstract

Background: Complement contributes significantly to pathophysiology in many neurodegenerative diseases (NDDs) including Alzheimer's Disease (AD); yet, the source of complement in the brain is poorly understood. Even multiple small changes to individual complement components can compound into significant dysregulation of the whole system. Targeting complement effectively in NDDs requires understanding complement expression in the healthy brain and how it changes in pathology.

Method: We integrated single-nucleus RNA sequencing datasets, including over 600,000 cells from 97 donor frontal cortices, 60 AD donors (36 male, 24 female) and 37 control donors (23 male, 14 female). Complement expression across nine cell types, and the impact of AD pathology, sex and age on complement gene expression was examined.

Results: Microglia are the principle source of C1Q/A/B/C and C3 expression in both the healthy and AD brain, with more microglia expressing higher levels observed in AD. Increases in C1R, C1S, C5 and C7 expression are seen in AD, predominately in fibroblasts, pericytes and astrocytes. Endothelial cells strongly expressed most complement regulators including, CD46, CD55, CD59 and CFH with greater expression observed in AD. The AD risk gene CLU demonstrated significantly higher expression in multiple cell types however, remains predominantly expressed in astrocytes. Expression of the novel complement regulator SRPX2 was markedly increased in AD in pericytes and fibroblasts, while slightly elevated expression of CSMD1/2/3 is seen in neurons. No significant differences in complement expression between sexes was observed in control donors. However, in AD donors sex-based differences were seen with female donors typically demonstrating a greater percentage of cells expressing complement. This data suggests that AD alters the normal pattern of changes in complement gene expression with age, in particular, significantly higher expression of C1R, C1S and CLU are seen in the youngest age group.

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Conclusion: Our comprehensive complement expression atlas for the AD and control frontal cortex reveals profound complement dysregulation in AD. There are sex specific trends in this dysregulation with females demonstrating greater dysregulation. Finally, most severe complement dysregulation in AD is observed in the youngest individuals highlighting a significant age-dependent factor that could inform the timing and design of therapeutic interventions.