ALZHEIMER DISEASE

Chaperone protein clusterin is involved in amyloid- β -associated entorhinal atrophy in early AD

Clusterin, a chaperone glycoprotein, could interact with amyloid- β ($A\beta$) to exacerbate entorhinal volume loss in the preclinical stage of Alzheimer disease (AD), according to new research. The effect of clusterin was independent of phosphorylated tau (p-tau), a key indicator of AD-related neuropathology. “Considerable efforts have focused on amyloid and tau, but comparatively little is known about other proteins influencing neurodegeneration in AD”, says Rahul Desikan, the lead author of the study.

Using publicly available data from the Alzheimer’s Disease Neuroimaging Initiative, Desikan and colleagues combined MRI scans with cerebrospinal fluid (CSF) levels of clusterin, $A\beta_{1-42}$ and p-tau_{181p} in 91 cognitively normal older adults (mean age 76 years) and 150 individuals with amnesic mild cognitive impairment (MCI; mean age 75.1 years).

The investigators found an interaction between $A\beta_{1-42}$ and clusterin: in individuals

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with increased $A\beta$ deposition, elevated levels of CSF clusterin at baseline were associated with increased entorhinal atrophy on the follow-up MRI scans, which took place 6–36 months later. The entorhinal cortex is known to be one of the first brain areas affected in AD.

The findings by Desikan *et al.* are in line with converging evidence for clusterin involvement in AD. Interestingly, clusterin did not contribute to entorhinal atrophy

in $A\beta$ -negative individuals. Desikan hopes that a biomarker profile comprising clusterin, $A\beta_{1-42}$ and p-tau in the CSF could aid identification of individuals who are at elevated risk of progressing to dementia.

The team also discovered that the effects of $A\beta$ and clusterin on entorhinal volume loss were stronger in individuals with MCI than in those with AD. The findings suggest that clusterin is involved in the earliest stage of AD, but the mechanism by which clusterin affects AD pathogenesis remains elusive. Further research will be required to disentangle the role of clusterin in amyloid toxicity and to find out whether modulation of the clusterin pathway could have potential for slowing down neurodegeneration in AD.

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Original article Desikan, R. S. *et al.* The role of clusterin in amyloid- β -associated neurodegeneration. *JAMA Neurol.* doi:10.1001/jamaneurol.2013.4560