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Authors
Desikan, RS
Thompson, WK
Holland, D

et al.

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The Role of Clusterin in Amyloid-β-Associated Neurodegeneration

Rahul S. Desikan, MD, PhD; Wesley K. Thompson, PhD; Dominic Holland, PhD; Christopher P. Hess, MD, PhD; James B. Brewer, MD, PhD; Henrik Zetterberg, MD, PhD; Kai Blennow, MD, PhD; Ole A. Andreassen, MD, PhD; Linda K. McEvoy, PhD; Bradley T. Hyman, MD, PhD; Anders M. Dale, PhD; for the Alzheimer’s Disease Neuroimaging Initiative Group

**IMPORTANCE** Converging evidence indicates that clusterin, a chaperone glycoprotein, influences Alzheimer disease neurodegeneration. However, the precise role of clusterin in Alzheimer disease pathogenesis is still not well understood.

**OBJECTIVE** To elucidate the relationship between clusterin, amyloid-β (Aβ), phosphorylated tau (p-tau), and the rate of brain atrophy over time among nondemented older individuals.

**DESIGN, SETTING, AND PARTICIPANTS** This longitudinal cohort included cognitively normal older participants and individuals with mild cognitive impairment assessed with baseline lumbar puncture and longitudinal structural magnetic resonance imaging. We examined 241 nondemented older individuals from research centers across the United States and Canada (91 participants with a Clinical Dementia Rating score of 0 and 150 individuals with a Clinical Dementia Rating score of 0.5).

**MAIN OUTCOMES AND MEASURES** Using linear mixed-effects models, we investigated interactions between cerebrospinal fluid (CSF) clusterin, CSF Aβ1-42, and CSF p-tau at threonine 181 (p-tau181p) on the atrophy rate of the entorhinal cortex and hippocampus.

**RESULTS** Across all participants, we found a significant interaction between CSF clusterin and CSF Aβ1-42 on the entorhinal cortex atrophy rate but not on the hippocampal atrophy rate. Cerebrospinal fluid clusterin was associated with the entorhinal cortex atrophy rate among CSF Aβ1-42-positive individuals but not among CSF Aβ1-42-negative individuals. In secondary analyses, we found significant interactions between CSF Aβ1-42 and CSF clusterin, as well as CSF Aβ1-42 and CSF p-tau181p, on the entorhinal cortex atrophy rate. We found similar results in subgroup analyses within the mild cognitive impairment and cognitively normal cohorts.

**CONCLUSIONS AND RELEVANCE** In nondemented older individuals, Aβ-associated volume loss occurs in the presence of elevated clusterin. The effect of clusterin on Aβ-associated brain atrophy is not confounded or explained by p-tau. These findings implicate a potentially important role for clusterin in the earliest stages of the Alzheimer disease neurodegenerative process and suggest independent effects of clusterin and p-tau on Aβ-associated volume loss.
Converging genetic, cellular, molecular, and biomarker evidence indicates that clusterin, a chaperone glycoprotein also known as apolipoprotein J, influences Alzheimer disease (AD) pathogenesis. Clusterin levels are increased in AD-affected brain regions\(^1-3\) and elevated in the cerebrospinal fluid (CSF) of patients with AD.\(^4\) Several genomewide association studies have identified clusterin gene variants as AD susceptibility loci.\(^5\) Elevated plasma clusterin levels are associated with disease prevalence and severity of AD\(^6\) and with increased amyloid deposition and brain atrophy.\(^7\) Still, experimental findings suggest that clusterin increases both amyloid-\(\beta\) (A\(\beta\)) aggregation and clearance,\(^5\) leading to the question of whether elevated clusterin levels are beneficial or harmful.

In humans, structural magnetic resonance imaging (MRI) and CSF biomarkers allow for the indirect assessment of cellular changes underlying AD in vivo. Structural MRI provides measures of brain atrophy, which include loss of dendrites, synapses,\(^8\) and neurons.\(^9\) Low CSF levels of A\(\beta\) strongly correlate with intracranial amyloid plaques, and high concentrations of CSF phosphorylated-tau (p-tau) correlate with tau-associated neurofibrillary tangles.\(^10\) Here, we investigated whether interactions between increased CSF clusterin and decreased CSF A\(\beta_{1-42}\) are associated with increased brain atrophy over time in nondemented older individuals at risk for developing AD. Building on recent evidence that A\(\beta\)-associated volume loss occurs in the presence of elevated p-tau,\(^11-15\) we also examined the additive effect on volume loss of an interaction between increased CSF clusterin and decreased CSF A\(\beta_{1-42}\) in the presence of an interaction between increased CSF p-tau at threonine 181 (p-tau\(_{181p}\)) and decreased CSF A\(\beta_{1-42}\).

### Methods

The institutional review boards of all participating institutions approved the procedures of this study, and written informed consent was obtained from all participants or their surrogates.

A total of 313 nondemented older participants from the Alzheimer’s Disease Neuroimaging Initiative underwent longitudinally acquired MRI and CSF lumbar puncture. Of these, we restricted analyses to 91 cognitively normal older adults (healthy control [HC] participants) and 150 individuals with amnestic mild cognitive impairment (MCI) who had a quality-assured baseline scan and at least 1 follow-up MRI scan (6 months–3 years, 4% with 6-month follow-up, 8% with 12-month follow-up, 11% with 18-month follow-up, 42% with 24-month follow-up, and 35% with 36-month follow-up) (Table; for additional details, see eAppendix 1 and eAppendix 2 in Supplement).

We examined baseline CSF clusterin levels derived from a multiplex-based immunoassay panel based on Luminesix immunoassay technology developed by Rules-Based Medicine (MyriadRBМ).\(^16\) In brief, the Alzheimer’s Disease Neuroimaging Initiative Biomarker Core assessed CSF samples (159 analytes measured by the MyriadRBМ) from a total of 327 individuals. These baseline CSF samples had matching aliquots from 1 year, allowing evaluation of test-retest to determine analyte precision. For each analyte, a multistep quality-control procedure was implemented, which included evaluation of CSF signal characteristics (high, medium, and low), assessment for normality of distribution (abnormal values were transformed), and need for imputation (data with missing values and high/low values) (for additional details on CSF quality-control procedures, see the Biomarkers Consortium Data Primer\(^17\)). We used the quality-controlled values for CSF clusterin in all analyses. Using previously proposed CSF cutoffs,\(^17\) we examined baseline CSF A\(\beta_{1-42}\) and p-tau\(_{181p}\) levels and classified participants based on low (<192 pg/mL, positive) and high (>192 pg/mL, negative) A\(\beta_{1-42}\) levels, and high (>23 pg/mL, positive) and low (<23 pg/mL, negative) p-tau\(_{181p}\) levels. As previously described,\(^17\) CSF A\(\beta_{1-42}\) and p-tau\(_{181p}\) were measured using the multiplex xMAP Luminesix platform (Luminesix Corp) with Innogenetics (INNOBIA AlzBio3) immunoassay kit–based reagents.

We analyzed 977 T1-weighted MRI scans using a modified version of the FreeSurfer software package (http://surfer.nmr.mgh.harvard.edu). These analysis procedures have been applied, validated, and described in detail in a number of publications.\(^18\) The MRI scans were reviewed for quality, automatically corrected for spatial distortion due to gradient nonlinearity, registered, and averaged to improve the signal to noise ratio. The cortical surface was automatically reconstructed and gray matter thickness measurements were obtained at each point across the cortical mantle. Here, we primarily focused on

### Table. Demographic, Clinical, and Imaging Data for All Participants in This Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cognitively Normal ((n = 91))</th>
<th>Mild Cognitive Impairment ((n = 150))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>76.0 (0.6)</td>
<td>75.1 (0.7)</td>
</tr>
<tr>
<td>Female, %</td>
<td>51</td>
<td>33</td>
</tr>
<tr>
<td>Education, y</td>
<td>15.6 (0.3)</td>
<td>16.1 (0.2)</td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.1 (0.1)</td>
<td>26.7 (0.1)</td>
</tr>
<tr>
<td>CDR-SB score</td>
<td>0.03 (0.01)</td>
<td>1.5 (0.07)</td>
</tr>
<tr>
<td>APOE ε4 carriers, %</td>
<td>24</td>
<td>54</td>
</tr>
<tr>
<td>CSF clusterin level, μg/mL</td>
<td>1.39 (0.02)</td>
<td>1.42 (0.01)</td>
</tr>
<tr>
<td>CSF A(\beta_{1-42}) level, pg/mL</td>
<td>207.8 (5.6)</td>
<td>157.5 (4.1)</td>
</tr>
<tr>
<td>CSF p-tau(_{181p}) level, pg/mL</td>
<td>24.7 (1.4)</td>
<td>36.8 (1.3)</td>
</tr>
<tr>
<td>Baseline LP-MRI interval, mo</td>
<td>0.07 (0.007)</td>
<td>0.08 (0.006)</td>
</tr>
<tr>
<td>Time between baseline and last available MRI scans, y</td>
<td>2.37 (0.08)</td>
<td>2.17 (0.05)</td>
</tr>
<tr>
<td>Annualized percentage change</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entorhinal cortex</td>
<td>−0.84 (0.11)</td>
<td>−2.37 (0.12)</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>−0.95 (0.08)</td>
<td>−2.42 (0.13)</td>
</tr>
<tr>
<td>Amygdala</td>
<td>−0.99 (0.10)</td>
<td>−2.65 (0.15)</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>−0.70 (0.09)</td>
<td>−1.97 (0.12)</td>
</tr>
</tbody>
</table>

Abbreviations: A\(\beta_{1-42}\), amyloid-\(\beta\)-1-42; APOE ε4, apolipoprotein E ε4 allele; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; LP, lumbar puncture; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; p-tau\(_{181p}\), phosphorylated tau at threonine 181.
on the entorhinal cortex and hippocampus, 2 medial temporal lobe regions that are affected in the earliest stages of AD (Figure 1).\(^\text{19}\) We additionally evaluated the amygdala and middle temporal gyrus, 2 temporal lobe regions that are also affected in AD.\(^\text{19}\) The entorhinal cortex and middle temporal gyrus were delineated using an automated, surface-based cortical parcellation atlas.\(^\text{20}\) The hippocampus and amygdala were identified using an automated, subcortical segmentation atlas.\(^\text{21}\) For the analysis of the longitudinal gray matter volume change, we used Quarc (quantitative anatomical regional change), a method developed from our laboratory.\(^\text{22,23}\) Briefly, each participant’s follow-up image was affine aligned to the baseline scan and locally intensity normalized. Using nonlinear registration, a deformation field was then calculated to locally register the images with high fidelity for both large- and small-scale structures including those with low boundary contrast. From the deformation field, a volume change field (atrophy) can directly be calculated. Using the baseline subcortical and cortical regions of interest, the volume change field can be sampled at points across the cortical surface or averaged over subcortical regions to give the percentage volume change for those regions of interest (Figure 1).

We asked whether statistical interactions between CSF clusterin and CSF Aβ\(_{1-42}\) and between CSF clusterin and CSF p-tau\(_{181}\) are associated with brain atrophy over time (Figure 2). Using a linear mixed-effects model, we concurrently examined the main and interactive effects of CSF clusterin, CSF Aβ\(_{42}\), and CSF p-tau\(_{181}\) on the atrophy rate of the temporal lobe regions (entorhinal cortex, hippocampus, amygdala, and middle temporal gyrus), covarying for age, sex, carrier status for the ε4 allele of apolipoprotein E, group status (MCI vs HC), and disease severity (assessed using Clinical Dementia Rating-
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Sum of Boxes, a composite measure that characterizes 6 domains of cognitive and functional performance\(^{29}\). Of note, the main effects of all variables (the 3 CSF analytes and all covariates) were also included in these analyses. For brevity, we focused on the effects of interest. Specifically:

\[ \Delta v = \beta_0 + \beta_1 \Delta t + \beta_2 CSF_{\text{clusterin}} \times \Delta t + \beta_3 CSF_{A\beta1-42} \times \Delta t + \beta_4 [CSF_{\text{clusterin}} \times CSF_{\text{A\beta1-42}}] \times \Delta t + \beta_5 [CSF_{\text{clusterin}} \times CSF_{p\text{-tau181p}}] \times \Delta t + \text{covariates} \times \Delta t + \epsilon. \]

In this equation, \( \Delta v \) indicates entorhinal cortex or hippocampal atrophy (millimeters) and \( \Delta t \) indicates change in time from baseline MRI scan (years). Intercept and slope (\( \beta_0 \) and \( \beta_1 \)) were entered as mixed effects.

Prior findings from our laboratory indicate that A\( \beta \)-associated neurodegeneration occurs in the presence of elevated p-tau.\(^{11 - 13}\) To test whether the effect of clusterin on A\( \beta \)-associated neurodegeneration is independent of the effect of p-tau on A\( \beta \)-associated neurodegeneration, we performed secondary analyses and fit the following linear mixed-effects model:

\[ \Delta v = \beta_0 + \beta_1 \Delta t + \beta_2 CSF_{\text{clusterin}} \times \Delta t + \beta_3 CSF_{A\beta1-42} \times \Delta t \]

In contrast, there was no significant CSF clusterin by time interaction on the entorhinal cortex atrophy rate either among CSF p-tau181p-positive (\( \beta \) coefficient = 0.01; \( P = .49 \)) individuals (Figure 3) or among CSF p-tau181p-negative (\( \beta \) coefficient = 0.001; \( P = .66 \)) individuals (Figure 4). Similar results were obtained when CSF p-tau181p and CSF A\( \beta \) were treated as continuous rather than categorical variables (eAppendix 2 in Supplement).

To determine whether these effects differed by group status (MCI vs HC), we performed additional analyses fitting interactions between group status and the main effects of interest (for additional details, see eAppendix 1 and eAppendix 2 in Supplement). These analyses showed a significant interaction between group status, time, CSF clusterin, and CSF A\( \beta \)-status on the entorhinal cortex atrophy rate (\( \beta \) coefficient = 0.031; \( SE = 0.009 \); \( P = .001 \)). Follow-up subgroup analyses revealed that although both the MCI and HC cohorts demonstrated a significant 3-way interaction of time, CSF clusterin, and CSF A\( \beta \)-status on the entorhinal cortex atrophy rate, whereby entorhinal cortex volume loss was significantly associated with CSF clusterin only among CSF A\( \beta \)-positive individuals, the slopes of change over time were steeper among the MCI cohort than the HC cohort (MCI: \( \beta \) coefficient = 0.076; \( SE = 0.03 \); \( P = .008 \); HC: \( \beta \) coefficient = 0.047; \( SE = 0.01 \); \( P = .001 \)).

To determine whether similar associations could be observed in other temporal lobe areas affected later in the disease process, we repeated these analyses using atrophy rates of the hippocampus, amygdala, and middle temporal gyrus.

Results

Results from the primary analyses revealed a significant 3-way interaction between CSF clusterin, CSF A\( \beta \)-status, and time (\( \beta \) = −0.032; \( SE = 0.01 \); \( P = .01 \)), indicating that increased CSF clusterin and positive CSF A\( \beta \)-status were associated with an elevated entorhinal cortex atrophy rate. In contrast, the interaction between CSF clusterin, CSF p-tau181p-status, and time was not significant (\( \beta \) = 0.01; \( SE = 0.01 \); \( P = .54 \)). With both of these 3-way interaction terms in the model, only the effect of CSF A\( \beta \)-status by time was significantly associated with the entorhinal atrophy cortex rate (\( \beta \) = 0.04; \( SE = 0.02 \); \( P = .02 \)); the effect of time by CSF clusterin and CSF p-tau181p-status was not associated with the entorhinal cortex atrophy rate. None of the main effects of CSF clusterin, CSF A\( \beta \)-status, and CSF p-tau181p-status were significant.

Follow-up analyses examining the 3-way interactions demonstrated that the CSF clusterin by time interaction was significantly associated with entorhinal cortex atrophy only among CSF A\( \beta \)-positive individuals (\( \beta \) coefficient = −0.20; \( SE = 0.007 \); \( P = .008 \)) but not among CSF A\( \beta \)-negative individuals (\( \beta \) coefficient = 0.007; \( SE = 0.008 \); \( P = .36 \)). In contrast, there was no significant CSF clusterin by time interaction on the entorhinal cortex atrophy rate either among CSF p-tau181p-positive (\( \beta \) coefficient = 0.01; \( SE = 0.01 \); \( P = .28 \)) or among CSF p-tau181p-negative (\( \beta \) coefficient = 0.005; \( SE = 0.007 \); \( P = .49 \)) individuals (Figure 4). Similar results were obtained when CSF p-tau181p and CSF A\( \beta \) were treated as continuous rather than categorical variables (eAppendix 2 in Supplement).

The diagram shows the main effect of clusterin (\( \beta_1 \)), the main effect of amyloid-β (A\( \beta \)) (\( \beta_2 \)), the main effect of phosphorylated tau (p-tau) (\( \beta_3 \)), an interactive effect between clusterin and A\( \beta \) (\( \beta_4 \) and circle with dot in the center), and an interactive effect between clusterin and p-tau (\( \beta_5 \) and circle with dot in the center). CSF indicates cerebrospinal fluid. The circle with the dot in the center illustrates an interactive effect.
Results revealed no significant interactions of CSF clusterin, CSF Aβ1-42 status, and time on the atrophy rate of the hippocampus (β coefficient = −0.013; SE = 0.01; P = .33), amygdala (β coefficient = −0.015; SE = 0.01; P = .24), and middle temporal gyrus (β coefficient = −0.009; SE = 0.01; P = .39). As observed for the entorhinal cortex atrophy rate, the interaction of CSF clusterin, CSF p-tau181p status, and time was not significant for the atrophy rate of the hippocampus (β coefficient = 0.004; SE = 0.01; P = .74), amygdala (β coefficient = 0.005; SE = 0.01; P = .74), and middle temporal gyrus (β coefficient = 0.016; SE = 0.01; P = .18).

To determine whether the effect of clusterin on Aβ-associated neurodegeneration is independent from the previously observed effect of p-tau on Aβ-associated neurodegeneration,11-13 we included interaction terms with CSF p-tau181p status (for additional details, see eAppendix 1 and eAppendix 2 in Supplement and equation 2 in the Methods section). These analyses on the full cohort revealed significant interactions between CSF clusterin, CSF Aβ1-42 status, and time (β coefficient = −0.026; SE = 0.01; P = .01), as well as CSF p-tau181p status, CSF Aβ1-42 status, and time (β coefficient = −0.010; SE = 0.004; P = .01), on entorhinal cortex atrophy, indicating independent effects of CSF clusterin and CSF p-tau181p on CSF Aβ1-42-associated volume loss. As in the primary analyses, with the interaction terms in the model, only the effect of CSF Aβ1-42 status by time was significant (β coefficient = 0.04; SE = 0.01; P = .009); the effects of time by CSF clusterin and CSF p-tau181p status were not significant. The main effects of CSF clusterin, CSF Aβ1-42 status, or CSF p-tau181p status were not significant.
Additional interaction analyses with group status demonstrated significant interactions between group status, time, CSF clusterin, and CSF Aβ1-42 status (β coefficient = −0.020; SE = 0.003; P = .01), as well as between group status, time, CSF p-tau181p status, and CSF Aβ1-42 status (β coefficient = −0.008; SE = 0.003; P = .009), on the entorhinal cortex atrophy rate. Subgroup analyses showed that within the MCI cohort, interactions between both CSF clusterin, CSF Aβ1-42 status, and time (β coefficient = −0.047; SE = 0.02; P = .01), as well as CSF p-tau181p status, CSF Aβ1-42 status, and time (β coefficient = −0.008; SE = 0.003; P = .009), on entorhinal cortex atrophy rate. As illustrated in parts A and B, the slopes of the red lines between the p-tau-positive and high-clusterin and p-tau-positive and low-clusterin individuals are not significantly different, corresponding to the nonsignificant interaction between cerebrospinal fluid p-tau, cerebrospinal fluid clusterin, and time (see text for further details).

Discussion

Here, we showed that in nondemented older individuals, Aβ-associated entorhinal cortex atrophy occurs in the presence of elevated clusterin. We also found that the effect of clusterin on Aβ-associated entorhinal cortex atrophy is not confounded or explained by p-tau. Taken together, this implicates a potentially important role for clusterin in the earliest stages of the Alzheimer neurodegenerative process and suggests independent effects of clusterin and p-tau on Aβ-associated volume loss (Figure 5).
Although a number of studies have evaluated the relationship between Aβ, tau, and p-tau on volume loss in the earliest stages of AD,14,15 the role of clusterin in modulating this relationship is still unknown. Our findings demonstrated that nondemented older individuals with elevated CSF clusterin and decreased Aβ (ie, increased intracranial Aβ deposition) experience increased volume loss, suggesting that clusterin may accelerate progression from amyloid deposition to neurodegeneration. These results also indicate that a biomarker profile incorporating CSF clusterin, CSF Aβ(1-42), and CSF p-tau(181) levels may better identify those older individuals who are at an elevated risk for progressing to dementia than any of these biomarkers by themselves.

These findings provide novel insights into the preclinical stage of AD. Although prior research suggests that clusterin by itself may not represent a marker of presymptomatic AD,6 our work indicated that the presence of clusterin may represent a critical link between Aβ deposition and entorhinal cortex degeneration in preclinical AD. Furthermore, in secondary analyses among HC participants, we found a significant interaction on volume loss only between clusterin and Aβ, whereas among individuals with MCI, we noted concurrent interactions of Aβ with both clusterin and p-tau, suggesting that the clusterin-related effects on Aβ-associated neurodegeneration may precede tau-related effects. Finally, in contrast to p-tau-related atrophy within the later-affected hippocampus or other temporal lobe regions, we found clusterin-associated effects only for the entorhinal cortex, a region selectively affected in the earliest stages of AD.19 Considered together, these findings indicate that the interaction between clusterin and Aβ may provide an important window into the earliest stages of the Alzheimer neurodegenerative process.

Conclusions

From a translational perspective, although considerable efforts have focused on Aβ and tau, comparatively little is known about other proteins influencing Alzheimer neurodegeneration. Our findings implicate the involvement of clusterin in the earliest stages of AD. Using experimental models, it will be essential to better delineate the differential mechanistic aspects of intracellular from extracellular clusterin. In humans, it would be helpful to understand whether CSF and plasma clusterin levels correspond to experimentally derived intracellular or extracellular clusterin. It will also be important to determine whether interactions between clusterin and other factors modulate Aβ-associated neurotoxicity. Along with our current findings, the results from these studies could provide valuable insights into whether modifying clusterin levels or blocking clusterin/Aβ interactions are likely to represent viable therapeutic approaches for individuals in the earliest phases of the disease process.
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Conflict of Interest Disclosures: Dr Brewer holds stock options in CorTechs Labs Inc and serves on its advisory board, and he receives financial support from the Eli Lilly Biomarker Unit (Amyvid). Dr Brewer also receives research support from General Electric and Janssen Alzheimer Immunotherapy. Dr Blennow has served on the advisory boards for Innogenetics, Eli Lilly, Pfizer, and Roche. Dr McEvoy’s spouse is the chief executive officer of CorTechs Labs Inc. Dr Dale is a founder and holds equity in CorTechs Labs Inc and serves on its scientific advisory board. The terms of this arrangement have been reviewed and approved by the University of California, San Diego, in accordance with its conflict of interest policies. No other disclosures were reported.

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Additional Contributions: Data used in preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this article.

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