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The chaperone Clusterin in neurodegeneration—friend or foe?

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Abstract

Fibrillar protein aggregates are the pathological hallmark of a group of age-dependent neurodegenerative conditions, including Alzheimer's and Parkinson's disease. Aggregates of the microtubule-associated protein Tau are observed in Alzheimer's disease and primary tauopathies. Tau pathology propagates from cell to cell in a prion-like process that is likely subject to modulation by extracellular chaperones such as Clusterin. We recently reported that Clusterin delayed Tau fibril formation but enhanced the activity of Tau oligomers to seed aggregation of endogenous Tau in a cellular model. In contrast, Clusterin inhibited the propagation of α-Synuclein aggregates associated with Parkinson's disease. These findings raise the possibility of a mechanistic link between Clusterin upregulation observed in Alzheimer's disease and the progression of Tau pathology. Here we review the diverse functions of Clusterin in the pathogenesis of neurodegenerative diseases, focusing on evidence that Clusterin may act either as a suppressor or enhancer of pathology.

KEYWORDS
Alzheimer's disease, Clusterin, extracellular chaperone, neurodegeneration, protein aggregation, tau, tauopathies

INTRODUCTION

The formation of protein aggregates within and around neurons is a signature of age-dependent neurodegenerative diseases (NDs) and dementias. Insoluble fibrillar (amyloid-like) deposits together with soluble, oligomeric aggregate species are considered major toxic agents driving pathology.[1,2] The aggregates consist of specific disease proteins as the main component: α-Synuclein in Parkinson's disease (PD) and other synucleinopathies, mutant Huntingtin in Huntington's disease, amyloid-β (Aβ) in Alzheimer's disease (AD), and Tau in tauopathies including AD.[1] Aggregate pathology typically initiates in disease-specific brain regions, such as the substantia nigra in PD or the hippocampus in AD. Extensive evidence indicates that the aggregates of certain disease proteins (e.g., α-Synuclein and Tau) may then propagate from cell to cell in a prion-like process that underlies disease progression.[3,4] In this process, preexistent aggregate seeds catalyze the aggregation of normal versions of the same protein through a templating mechanism[5] (Figure 1), resulting in a disease-specific pattern of aggregate propagation through interconnected regions of the brain.[6] However, unlike the human prion disease, there is currently no evidence to suggest that the aggregates found in other NDs are infectious and transmissible between individuals or species, hence the use of the term "prion-like".[7]

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-β; ApoER2, apolipoprotein E receptor 2; ApoJ, apolipoprotein J; CNS, central nervous system; CSF, cerebrospinal fluid; HSPG, heparan sulfate proteoglycan; iClu, intracellular Clusterin; iPSC, induced pluripotent stem cells; KO, Knock out; LOAD, late-onset Alzheimer's disease; LRP, low density lipoprotein receptor-related protein; ND, neurodegenerative disease; PD, Parkinson's disease; psClu, pre-secretory Clusterin; TREM2, triggering receptor expressed on myeloid cells 2; VLDLR, very low density lipoprotein receptor.

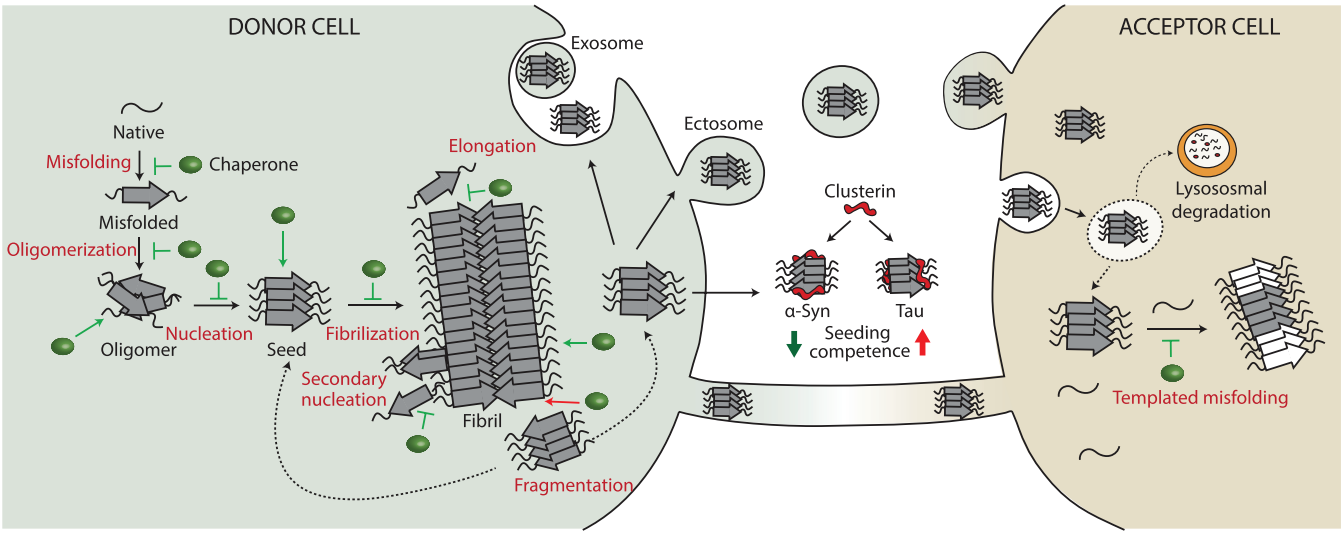

FIGURE 1 Role of chaperones in amyloid protein aggregation and prion-like, transcellular aggregate propagation. Native proteins in the donor cell (left) unfold or misfold, populating aggregation-prone states. Primary nucleation of amyloid fibril formation may involve oligomer formation. Oligomers are also generated at the surface of preexistent fibrils through secondary nucleation. Intracellular molecular chaperones (green) interfere with amyloid aggregation at different stages, by preventing misfolding, oligomerization, primary and secondary nucleation, fibrilization and fibril elongation. Chaperones may bind to oligomers or fibrils neutralizing their interactive surfaces (green thin arrows), suppressing aggregate toxicity. Chaperones can also promote fibril fragmentation, forming seeds that can further propagate and template aggregation (red thin arrow). Transcellular aggregate propagation may involve the release of aggregates by donor cells directly into the extracellular space, secretion in exosomes or ectosomes, or transport through intercellular nanotubes. Free seed material in the extracellular space is substrate of extracellular chaperones such as Clusterin, with different outcomes: Clusterin may neutralize seeds of α-Synuclein (α-Syn), but stabilize seeds of Tau.[14] Aggregate seeds can be internalized from the extracellular space by recipient cells (right) through endocytosis, possibly in complex with chaperone.[14] Aggregate seeds may damage endolysosomal membranes and escape to the cytosol to induce aggregation of endogenous, native protein. This templating process may be interfered with by intracellular chaperones

The prion-like spreading of pathological aggregates involves the transport of seed aggregates between cells, either through tubular intercellular connections, by secretion of seeds in exosome vesicles or upon release into the extracellular space and uptake by recipient cells[3,8] (Figure 1). Multiple mechanisms of aggregate spreading may coexist, but the appearance of seeding-competent aggregates in free form in the extracellular space is well documented through their detection in cerebrospinal fluid (CSF).[9–12] Thus, it is plausible that aggregate propagation is subject to modulation by extracellular chaperones and quality control factors.[13] Using a cellular model of Tau aggregate propagation, we recently found that the abundant extracellular chaperone Clusterin, while delaying Tau fibril formation, markedly enhanced Tau aggregate seeding by stabilizing highly potent, soluble seed species.[14] The pathophysiological relevance of these findings remains to be established, but given its frequent upregulation in AD,[15–17] Clusterin may conceivably contribute to promoting Tau pathology.

Here we review possible roles of the extracellular chaperone Clusterin in the pathogenesis and progression of neurodegeneration with a focus on AD and tauopathies. We discuss the effects of Clusterin on protein aggregation and toxicity, as well as its functions in aggregate clearance by glial cells and in suppressing neuroinflammation. As proposed previously,[18–20] Clusterin appears to be a Janus-faced chaperone, acting either as a suppressor or enhancer of pathology, dependent on specific disease context.

CLUSTERIN, AN UNUSUAL CHAPERONE

Clusterin (also known as ApoJ), encoded by the *CLU* gene, is a ubiquitously expressed extracellular chaperone and apolipoprotein in all vertebrates. It is abundant in plasma (~100 to 200 μg/ml; 2 to 4 μM) and CSF (~ 2 to 6 μg/ml; 50 to 100 nM).[13,15,17,21–23] The name Clusterin derives from its identification as a cell-aggregating factor in ram rete testis.[24] Clusterin is translated as a precursor protein of 449 amino acids containing a 22 amino acid signal peptide that is cleaved during translocation into the endoplasmic reticulum (ER) (Figure 2A). Once in the oxidizing environment of the ER, formation of five disulfide bonds followed by N-glycosylation generates pre-secretory Clusterin (psClu). psClu is then transferred to the Golgi apparatus where it is further processed and cleaved by a furin-like protease resulting in two chains (α and β) of~ 35 kDa, which remain disulfide-linked.[19,25] The mature heterodimeric Clusterin is then secreted to the extracellular space, with glycans comprising~ 30% of its mass[19] (Figure 2A). Experimental structure determination of Clusterin has not succeeded thus far, probably due to heterogeneity in glycosylation state and a

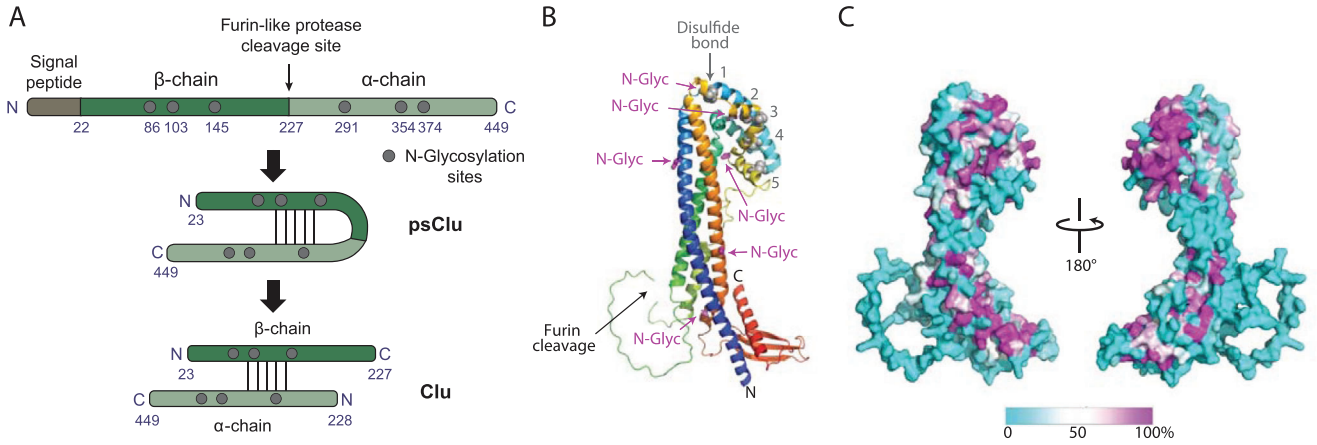

FIGURE 2 Biogenesis of Clusterin and predicted structure. (A) Clusterin is synthesized as a precursor protein of 449 amino acids containing a 22 amino acid signal peptide (brown) that is cleaved during translocation into the endoplasmic reticulum (ER). Once in the ER, N-glycosylation (gray circles) and formation of five intramolecular disulfide bonds (black lines) is thought to occur, resulting in pre-secretory Clu (psClu). Subsequently, psClu is transferred to the Golgi apparatus where the N-glycans are further processed and psClu is cleaved by a furin-like protease, resulting in two chains of similar size (α and β chains, light and dark green, respectively), which remain linked by the disulfide bonds. The mature glycosylated heterodimeric Clusterin is then secreted to the extracellular space. Numbers represent amino acid positions. Modified from ref.[14] (B) Predicted 3D-structure of Clusterin[27,28] (https://alphafold.ebi.ac.uk/entry/P10909). The structural model predicted with AlphaFold2 is shown in ribbon representation in rainbow colors. The signal peptide is not represented. N- and C-termini are indicated. Disulfide bonds are represented as spheres (silver, 1–5), N-glycosylation sites (N-Glyc) as sticks (magenta) and the Furin-like protease cleavage site in white. (C) Surface conservation of the predicted Clusterin structure. The similarity score was calculated with the program ESPript[140] based on the alignment of 10 representative Clu sequences and is shown as a color gradient from magenta (invariant residue) to cyan (no conservation). Mainly structurally important residues appear to be conserved

tendency of the protein to self-associate.[24,26] AlphaFold2[27,28] predicts an elongated, mostly α-helical structure of psClu, in which the two chains are linked via five disulfide bridges in a globular domain at one end of a central, mixed anti-parallel coiled-coil bundle (Figure 2B). The regions containing the cysteines involved in disulfide bond formation are well conserved, while other parts of the protein are more variable (PFAM number PF01093)[29] (Figure 2C). The predicted structure agrees with the experimentally determined disulfide topology, and all asparagine residues known to be glycosylated[30] are exposed to the solvent. Consistently, the furin cleavage site maps to a long accessible loop segment.

Clusterin is an ATP-independent chaperone with functional properties of a "holdase", similar to so-called small heat shock proteins (sHSP).[31] Holdase chaperones bind and stabilize folding intermediates and misfolded proteins against aggregation, but do not actively promote refolding. Clusterin has been shown to prevent or slow the formation of amorphous aggregates and amyloid fibrils as demonstrated for Aβ, α-Synuclein, Tau, and several other proteins.[13,14,32–37] Clusterin has been proposed to interact with client proteins via an as yet undefined "molten globule"-like domain(s).[38] In addition to its chaperone capacity, Clusterin functions in sperm maturation,[39] cell differentiation,[40] regulation of cell death and survival mechanisms,[41] and as an anti-inflammatory inhibitor of the complement system.[42,43] Moreover, it is often overlooked that Clusterin is an apolipoprotein (ApoJ) that has been identified in plasma high-density lipoprotein particles, suggesting a role in lipid and cholesterol metabolism.[44] Indeed, together with ApoE, Clusterin is one of the major apolipoproteins in the brain parenchyma, but its role in lipid metabolism in the central nervous system (CNS) is not well understood.[45] Although Clusterin lipidation status does not seem to affect amyloid binding, it may modify the affinity of Clusterin for cell surface receptors involved in uptake.[46,47]

While Clusterin is mainly located in the extracellular space, several reports described the presence of intracellular Clusterin (iClu) under specific stress conditions.[34,41,48–50] An increase in iClu levels has been observed in neurons upon exposure to Aβ oligomers and has been suggested to play a role in mediating Aβ toxicity.[51] The biogenesis and regulation of iClu has mainly been studied in certain cancer cells where it is abundant,[41] but its biogenesis is not well understood. Although alternative splicing and alternative initiation codons have been implicated, the mRNA species for these Clusterin isoforms are of very low abundance. Rather, iClu appears to be generated predominantly by retrotranslocation from the ER or Golgi apparatus to the cytosol under stress conditions. The differences in size and glycosylation pattern found in iClu species are therefore likely to reflect different maturation stages along the secretory pathway.[50] It is possible that prematurely retro-translocated iClu retains chaperone activity, at least partially, contributing to intracellular proteostasis.[26,34,50]

Clusterin expression is regulated by hormones, growth factors, and cytokines. The *CLU* promoter contains multiple transcription factor motifs, including a heat shock element from the cytosolic heat shock response.[52,53] In addition, *CLU* is also regulated epigenetically by DNA methylation and histone deacetylation, and by micro-RNAs.[53]

The wide range of ascribed functions and its complex regulation make Clusterin a puzzling and enigmatic player in neurodegeneration.

CLUSTERIN IN ALZHEIMER'S DISEASE

Research over nearly three decades paints a complex picture of the role of Clusterin in AD with both neuroprotective and pathology-enhancing effects having been reported.[14,18–20,32,35,46,51,54–64] AD is the most common cause of dementia, characterized by two neuropathological hallmarks: the deposition of extracellular amyloid plaques mainly composed of Aβ and the formation of intracellular neurofibrillary tangles of the microtubule-associated protein Tau.[65] Clusterin has been found to colocalize with both types of deposits.[35,66–68] Indeed, the *CLU* gene ranks third among the genetic risk factors for late-onset AD (LOAD), with genome wide association studies having identified several single nucleotide polymorphisms (SNPs) linked to AD.[18,69–71] While some rare, non-synonymous mutations have been suggested to affect Clusterin secretion,[72] other variants may affect *CLU* alternative splicing[73] and regulatory elements,[74–76] with complex effects on Clusterin expression. LOAD risk variants of *CLU* have been associated with either unchanged,[16,17] increased[73,75] or decreased[22,77] Clusterin levels in the brain, plasma or CSF of AD patients when compared to AD patients with a normal *CLU* gene. Despite this complexity, there is agreement that the LOAD risk variants of *CLU* are associated with increased Aβ deposition[78] and accelerated cognitive decline.[79,80] Interestingly, *CLU* variants have also been linked to changes in brain connectivity and structure in healthy individuals, effects that could precede clinical phenotypes.[81,82] Critical insights into the mechanism by which *CLU* variants promote LOAD may be gained using patient-derived induced pluripotent stem cells (iPSCs) that can be differentiated into neurons and other brain cells.

Importantly, Clusterin levels are often increased in the brain, CSF and plasma of AD patients independent of the presence of *CLU* variants. Moreover, elevated Clusterin correlates with greater severity and more rapid disease progression.[15–17] Local Clusterin expression has been observed to be associated with regional Aβ deposition[83,84] and possibly with Tau pathology.[84] Remarkably, in healthy middle-aged adults, a high level of plasma Clusterin is associated with a lower volume of the entorhinal cortex, a brain region that atrophies early in AD, suggesting that plasma Clusterin may serve as a biomarker for preclinical AD.[85] However, these findings leave open the question whether elevated Clusterin levels are a consequence of pathology or a promoting factor. Both the chaperone function of Clusterin in modulating amyloid aggregation, toxicity and clearance, as well as its anti-inflammatory effect have the capacity to modulate neurodegenerative pathology.

EFFECTS OF CLUSTERIN ON Aβ AND TAU AGGREGATION

Clusterin has been detected in association with various disease aggregates.[13] While its colocalization with Aβ deposits in the extracellular space has been studied extensively,[66,67] the physiological consequences of these interactions are not well understood. In support of a beneficial effect, Clusterin was shown to inhibit Aβ aggregation in vitro[32,54–57] and peripheral administration or overexpression of Clusterin reduced total Aβ plaque load in AD mouse models.[46,58–60] On the other hand, *CLU* knock out (KO) mouse models of AD displayed a reduction in oligomeric Aβ aggregates and plaques,[20,61] especially at early stages of pathogenesis,[62] pointing to a possible pro-amyloidogenic role of Clusterin. However, it has not been ruled out that the lower oligomer concentration resulted from compensatory effects in response to the *CLU* KO. Indeed, upregulation of multiple pathways related to neurodegeneration has been reported in iPSC derived *CLU* KO neurons[51] and in a *CLU* KO mouse model.[86]

Amyloid fibrils form through a process of nucleation-dependent polymerization[2,87] (Figure 1). Various intermediate aggregate species have been characterized, including structurally ill-defined soluble oligomers and prefibrillar species.[2,87] A key question with particular relevance in disease is to determine which of these species exert direct cellular toxicity and/or propagate the pathological conformation as seeds in a prion-like manner. While soluble oligomers are widely considered highly interactive and cytotoxic, insoluble aggregates contribute to pathology by sequestering key cellular proteins and physically displacing organelle structures.[2,88] Chaperones, including Clusterin, can act at different stages of the aggregation pathway, thereby modulating the levels of aggregate species and their toxicity. They may interfere with primary nucleation by binding to misfolded monomers or small oligomers, or inhibit fibril elongation by blocking fibril ends. Chaperones may also block secondary nucleation, a process in which oligomer formation is catalyzed on the surface of preformed fibrils[89,90] (Figure 1). Prevention of aggregation is generally cell-protective: binding of chaperones may shield exposed hydrophobic surfaces of oligomeric or prefibrillar aggregate species, thereby impeding their ability to engage in aberrant interactions with key cellular factors or disrupt cellular membranes.[37,91,92] However, chaperone intervention in the aggregation pathway, either by binding monomers, intermediates or mature fibrils, may also shift the dynamic equilibrium between aggregation intermediates, potentially promoting the accumulation of toxic species or stabilizing seeding-competent aggregates. Clusterin has been shown to inhibit primary and secondary nucleation of Aβ oligomers, as well as fibril elongation,[32,54,57] thereby reducing toxicity.[46,58,59,63] On the other hand, Clusterin has also been reported to promote the formation of rare toxic oligomers[56,64] and to enhance fibril formation when present at a very low molar ratio relative to its substrate[32] (Figure 3).

Less is known about the potential role of Clusterin in Tau aggregation and toxicity, despite the fact that Tau pathology strongly correlates with the severity of AD.[93] Tau is a microtubule-associated protein encoded by the *MAPT* gene that functions in maintaining microtubule stability. Six different isoforms of Tau, generated by alternative splicing, are expressed in the human CNS. They differ in the number of N-terminal 29 amino acid inserts (0N, 1N, or 2N) and of microtubule-binding repeat domains (3R or 4R).[94] Accumulation of hyperphosphorylated Tau in neurons facilitates the formation of fibrillar aggregates associated with AD and tauopathies (so-called neurofibrillary tangles and neuropil threads). Specific tauopathies are linked with different fibril conformations in which the repeat domains and the 10 to 13 amino acids following them adopt distinct amyloid folds.[95] In healthy

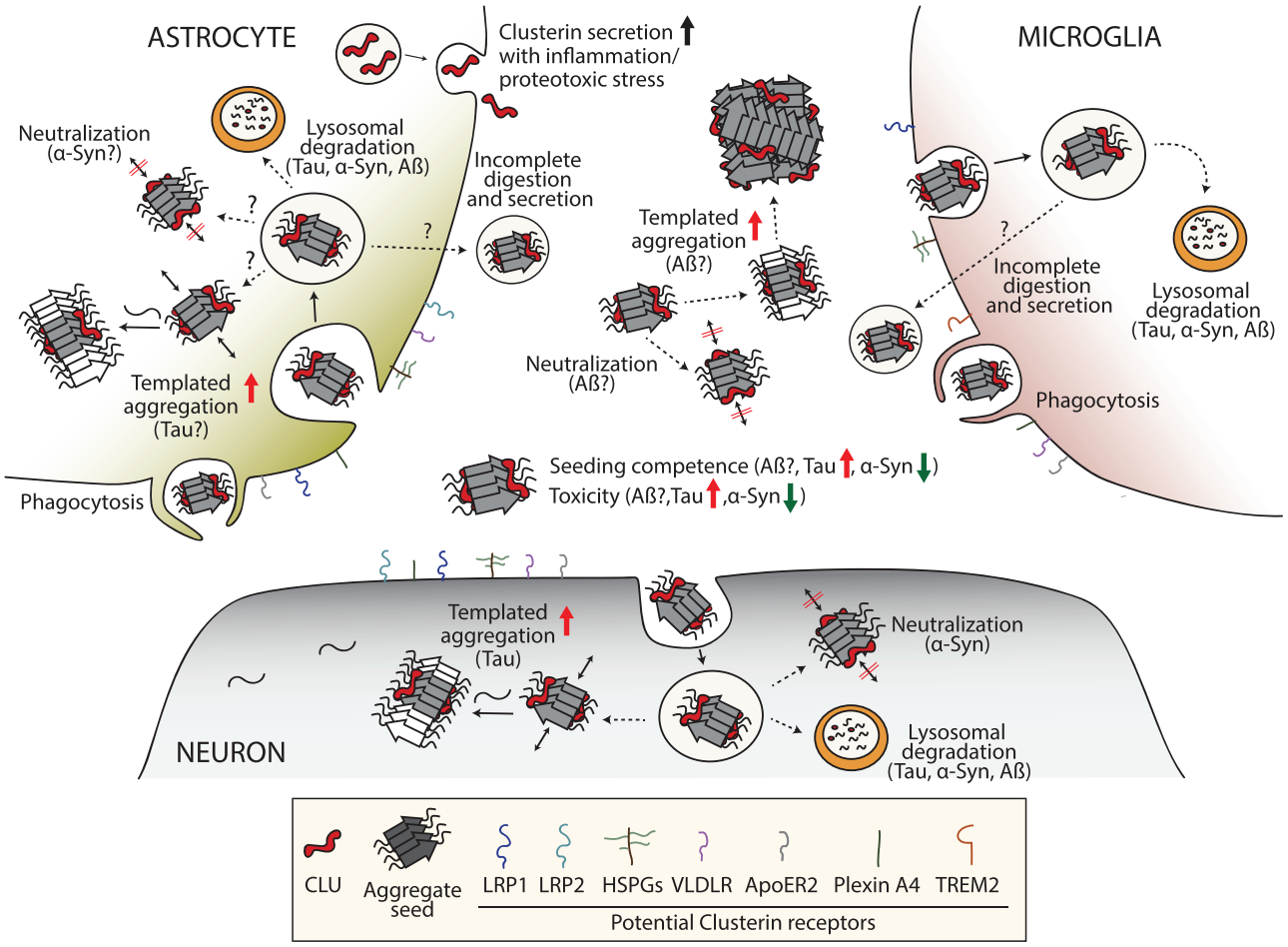

FIGURE 3 Differential effects of Clusterin on Aβ, Tau, and α-Synuclein (α-Syn) aggregates. Clusterin (CLU, red, mainly secreted by astrocytes) may interact with Aβ oligomers and deposits and with Tau and α-Synuclein aggregates that have been released into the extracellular space. Clusterin levels are elevated in AD, facilitating its interaction with these aggregates. Aβ-Clusterin complexes may be internalized by brain cells via receptor-mediated endocytosis using potential Clusterin receptors, including LRP1, HSPGs, VLDLR, ApoER2, Plexin A4 (neurons, astrocytes and microglia), LRP2 (neurons and astrocytes), and TREM2 (microglia), followed by lysosomal degradation. This function of Clusterin is mainly beneficial, but may also facilitate the uptake of potentially toxic Aβ oligomers that Clusterin is unable to neutralize.[20,32,56,61,62,64] Tau aggregates may be stabilized by Clusterin in a seeding-competent state.[14] These complexes may also be internalized in the same way as Aβ complexes by receptor-mediated endocytosis using Clusterin receptors. In addition, glial cells take up aggregates by phagocytosis. When the lysosomal system is overwhelmed, degradation of Tau-Clusterin complexes becomes inefficient. Tau seeds may escape from endocytic vesicles and template aggregation of native Tau in neurons.[14] Incomplete digestion of aggregates by glial cells can lead to their secretion via exosomes, promoting spreading. In contrast, Clusterin neutralizes α-Synuclein seeds and therefore, α-Synuclein-Clusterin complexes are unable to template aggregation of endogenous α-Synuclein[14]

cells, quality control machineries including chaperones HSP40, HSP70, HSP90, and sHSPs normally function in preventing Tau aggregation, but these mechanisms apparently fail in disease.[96]

Clusterin has been shown to interfere with Tau aggregation in vitro by extending the lag phase of fibril formation and slowing fibril elongation.[14,35,36] However, as Tau aggregation is an intracellular process, it would be unlikely to be affected by secreted Clusterin. Yet intracellular Clusterin, accumulating under stress conditions, could have a role in modulating Tau aggregation, consistent with a recent study reporting aggravated Tau pathology in *CLU* KO mice.[35] Regardless of a possible direct effect on aggregation of intracellular Tau, we have recently made the surprising observation that Clusterin can bind and stabilize Tau oligomers competent in seeding aggregates of endogenous Tau upon uptake by neurons and cells in culture.[14] This effect was specific to Tau, as Clusterin neutralized aggregate seeds of α-Synuclein.

For Clusterin acting as a possible enhancer of the prion-like spreading of Tau pathology, Tau aggregates have to be accessible in the extracellular space. Tau and other neurodegenerative disease proteins may reach the extracellular environment via release from dying cells or upon active secretion by neurons, which may occur through a trans-synaptic mechanism[8] or in a manner facilitated by chaperones, such as the HSP40 protein DnaJC5.[97,98] Indeed, seeding-competent Tau species have been detected in the CSF of AD patients[10,11] and Clusterin binding to Tau in patient brain has been reported.[68,99,100] Of note, the concentrations of Clusterin used in the in vitro experiments

demonstrating stabilization of Tau aggregate seeds[14] were substantially higher (in the micromolar range) than those in CSF (nanomolar) and thus further studies using CSF samples from AD patients will be useful in assessing the effect of Clusterin on Tau aggregation and seeding under more physiologically relevant conditions.

ROLE OF CLUSTERIN IN AGGREGATE CLEARANCE

Soluble extracellular waste, including oligomeric and prefibrillar amyloid species, is removed from the brain by various clearance systems. Extracellular proteins such as Aβ can be degraded by extracellular proteases or internalized by glial cells or neurons, followed by degradation via the lysosomal pathway. In addition, clearance of Aβ and possibly Tau through the blood brain barrier is an important mechanism to prevent aggregate accumulation in the brain.[101]

Glial cells, such as microglia and astrocytes, have a pivotal role in brain homeostasis, supporting neuronal function and survival. They are also key regulators of inflammation in the CNS, a condition often associated with neurodegenerative pathologies (see below). Reactive microglia and astrocytes are located near Aβ plaques and Tau inclusions[102] and are thought to mediate aggregate clearance through phagocytosis as well as fluid-phase and receptor mediated endocytosis, while neurons internalize oligomers and fibrillar species of Aβ and Tau only through endocytosis[103–109] (Figure 3). Notably, a fraction of internalized aggregates may escape from the endolysosomal pathway to the cytoplasm where they can act as seeds in templating aggregation of endogenous native protein[14,110,111] (Figure 1 and 3). Accordingly, glial cells are thought to be involved in propagating aggregation of Tau, Aβ and α-Synuclein.[103,112–118] The role of glial cells in aggregate propagation could relate to failed attempts at degradation, as incomplete degradation of aggregates has been suggested to promote spreading.[103,114]

Clusterin binds to extracellular aggregates and promotes their clearance via receptor mediated endocytosis.[14,99,119,120] Accordingly, high levels of Clusterin have been suggested to be beneficial in PD,[14,37,121] consistent with findings that Clusterin efficiently interferes with aggregate seeding of α-Synuclein and its toxic effects[14,37] (Figure 3). In contrast, a fraction of Clusterin-Tau complexes was found to escape from endosomes upon uptake by HEK cells and cultured neurons to induce the aggregation of endogenous Tau[14] (Figure 3). The mechanism of Clusterin internalization is not yet clear. Multiple potential receptors expressed on brain cells have been implicated in mediating Clusterin uptake, including scavenger receptors,[119] heparan sulfate proteoglycans (HSPGs),[120] apolipoprotein E receptor 2 (ApoER2), very low density lipoprotein receptor (VLDLR),[122] triggering receptor expressed on myeloid cells 2 (TREM2),[47] Plexin A4,[123] and low density lipoprotein receptor-related proteins 1 and 2 (LRP1 and LRP2)[124–127] (Figure 3). *TREM2* and *PLXNA4* (encoding Plexin A4) are both also risk factors for LOAD.[69,128] *TREM2* variants linked to LOAD present with impaired binding and uptake of Clusterin-Aβ complexes, suggesting a protective role of TREM2 in Aβ clearance via Clusterin.[47] Recent research has identified LRP1 as an endocytic receptor for Tau uptake.[108,129] Interestingly, while LRP1 was shown to efficiently bind and internalize monomeric Tau for lysosomal degradation, it promoted seeding of endogenous Tau aggregation by uptake of pathological Tau forms.[129] Stabilization of Tau seeds by Clusterin may conceivably exacerbate this effect.

In summary, receptor mediated-endocytosis of Clusterin-client protein complexes by neurons and glial cells may effectively clear α-Synuclein and Aβ aggregates, but in the case of Tau may be associated with the detrimental side effect of promoting aggregate propagation.

FUNCTION OF CLUSTERIN IN NEUROINFLAMMATION

While the neuroinflammatory response contributes to homeostasis maintenance in the brain, a turning point in AD pathology is the transition from the physiological role of inflammation to chronic, maladaptive activation triggered by Aβ and Tau aggregation.[130] Several risk genes for LOAD, including *CLU*, are involved in regulating the immune response, providing support for the critical role of neuroinflammation in AD pathogenesis.[131] An upregulation of inflammation-related genes in the brain is generally observed during normal aging, consistent with age being the primary risk factor for developing AD.[130]

Microglia and astrocytes are key mediators of neuroinflammation in the CNS. These cells undergo transcriptional, morphological, and functional changes and release pro- or anti-inflammatory cytokines in response to external stimuli, such as the presence of protein aggregates.[132] Clusterin is mainly expressed in the brain by astrocytes[133] (Figure 3) and its expression is positively regulated by several cytokines, including the anti-inflammatory TGF-β[134] and the pro-inflammatory IL-1β,[135] which are secreted by activated microglia.[132] Thus, inflammation is likely one of the triggers of Clusterin overexpression in AD. Interestingly, Clusterin in turn seems to directly activate microglia, which would result in a positive feedback loop contributing to maintaining the chronic state of microglial activation observed in AD.[136] Interestingly, activated microglia appear to be more efficient in Tau internalization and promoting spreading than quiescent microglia,[105,113] and microglial activation correlates with propagation of Tau pathology.[137]

Clusterin exerts anti-inflammatory effects mainly by suppressing complement activation.[42,43] Because synapse pruning by astrocytes and microglia during development involves the complement system,[138] upregulation of complement proteins in AD has been associated with synapse loss and cognitive decline.[139] Accordingly, inhibition of the complement system by Clusterin may be neuroprotective. In support of this interpretation, astroglial overexpression of Clusterin rescued synapse loss in *CLU* KO mice and reduced Aβ pathology and synaptic deficits in the 5x familial AD (5xFAD) mouse model.[60]

While similar basic mechanisms underlie the cellular pathology of several neurodegenerative diseases associated with protein aggregation, the specific effects of Clusterin—whether protective or potentially harmful—may vary. The general trend of Clusterin to be elevated

in these diseases and its colocalization with amyloid aggregates suggest that Clusterin is broadly involved in neurodegeneration.

CONCLUSIONS

The abundant extracellular chaperone Clusterin has become of major interest in recent years, especially due to its association with AD, a connection that remains incompletely understood. Clusterin is upregulated in AD and several other neurodegenerative diseases where it colocalizes with the pathognomonic amyloid deposits. Clusterin modulates disease mechanism in a complex manner, including aggregation prevention, promoting aggregate clearance and anti-inflammatory effects. However, these protective functions may eventually fail, for instance when clearance mechanisms are overwhelmed, then possibly allowing undesired activities of Clusterin in stabilizing seeding-competent aggregates to come to the fore. Our recent findings from cell culture models indicate that while Clusterin efficiently interferes with α-Synuclein aggregation and aggregate propagation, it can potentiate the seeding-activity of Tau aggregates, enhancing the conversion of endogenous Tau into toxic aggregates upon uptake of Clusterin-bound Tau seeds by recipient cells (Figure 3). These results in combination with previous findings support the view that Clusterin is a Janus-faced chaperone,[18–20] having both beneficial functions in suppressing aggregation and potentially detrimental activities in promoting aggregate pathology, dependent on specific disease context. Future studies employing organoids and animal models will be required to define the effect of Clusterin on Tau aggregate spreading in disease. These experimental models will also help to understand the contribution of different brain cell types, such as glial cells, to aggregate spreading. Finally, cellular and animal models combining Aβ plaques and Tau tangles would provide most relevant insight into the complex role of Clusterin in AD.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Soto, C., & Pritzkow, S. (2018). Protein misfolding, aggregation, and conformational strains in neurodegenerative diseases. *Nature Neuroscience*, *21*(10), 1332–1340. https://doi.org/10.1038/s41593-018-0235-9
2. Chiti, F., & Dobson, C. M. (2017). Protein misfolding, amyloid formation, and human disease: A summary of progress over the last decade. *Annual Review of Biochemistry*, *86*, 27–68. https://doi.org/10.1146/annurev-biochem-061516-045115
3. Peng, C., Trojanowski, J. Q., & Lee, V. M. (2020). Protein transmission in neurodegenerative disease. *Nature reviews Neurology*, *16*(4), 199–212. https://doi.org/10.1038/s41582-020-0333-7
4. Jucker, M., & Walker, L. C. (2018). Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. *Nature Neuroscience*, *21*(10), 1341–1349. https://doi.org/10.1038/s41593-018-0238-6
5. Scheckel, C., & Aguzzi, A. (2018). Prions, prionoids and protein misfolding disorders. *Nature Reviews Genetics*, *19*(7), 405–418. https://doi.org/10.1038/s41576-018-0011-4
6. Jucker, M., & Walker, L. C. (2013). Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. *Nature*, *501*(7465), 45–51. https://doi.org/10.1038/nature12481
7. Goedert, M., Eisenberg, D. S., & Crowther, R. A. (2017). Propagation of tau aggregates and neurodegeneration. *Annual Review of Neuroscience*, *40*, 189–210. https://doi.org/10.1146/annurev-neuro-072116-031153
8. Brunello, C. A., Merezhko, M., Uronen, R. L., & Huttunen, H. J. (2020). Mechanisms of secretion and spreading of pathological tau protein. *Cellular and Molecular Life Sciences*, *77*(9), 1721–1744. https://doi.org/10.1007/s00018-019-03349-1
9. Kang, U. J., Boehme, A. K., Fairfoul, G., Shahnawaz, M., Ma, T. C., Hutten, S. J., Green, A., & Soto, C. (2019). Comparative study of cerebrospinal fluid alpha-synuclein seeding aggregation assays for diagnosis of Parkinson's disease. *Movement Disorders*, *34*(4), 536–544. https://doi.org/10.1002/mds.27646
10. Takeda, S., Commins, C., Devos, S. L., Nobuhara, C. K., Wegmann, S., Roe, A. D., Costantino, I., Fan, Z., Nicholls, S. B., Sherman, A. E., Trisini Lipsanopoulos, A. T., Scherzer, C. R., Carlson, G. A., Pitstick, R., Peskind, E. R., Raskind, M. A., Li, G., Montine, T. J., Frosch, M. P., & Hyman, B. T. (2016). Seed-competent high-molecular-weight tau species accumulates in the cerebrospinal fluid of Alzheimer's disease mouse model and human patients. *Annals of Neurology*, *80*(3), 355–367. https://doi.org/10.1002/ana.24716
11. Hampel, H., Blennow, K., Shaw, L. M., Hoessler, Y. C., Zetterberg, H., & Trojanowski, J. Q. (2010). Total and phosphorylated tau protein as biological markers of Alzheimer's disease. *Experimental Gerontology*, *45*(1), 30–40. https://doi.org/10.1016/j.exger.2009.10.010
12. De, S., Whiten, D. R., Ruggeri, F. S., Hughes, C., Rodrigues, M., Sideris, D. I., Taylor, C. G., Aprile, F. A., Muyldermans, S., Knowles, T. P. J., Vendruscolo, M., Bryant, C., Blennow, K., Skoog, I., Kern, S., Zetterberg, H., & Klenerman, D. (2019). Soluble aggregates present in cerebrospinal fluid change in size and mechanism of toxicity during Alzheimer's disease progression. *Acta Neuropathologica Communications*, *7*(1), 120. https://doi.org/10.1186/s40478-019-0777-4
13. Wyatt, A. R., Yerbury, J. J., Ecroyd, H., & Wilson, M. R. (2013). Extracellular chaperones and proteostasis. *Annual Review of Biochemistry*, *82*, 295–322. https://doi.org/10.1146/annurev-biochem-072711-163904
14. Yuste-Checa, P., Trinkaus, V. A., Riera-Tur, I., Imamoglu, R., Schaller, T. F., Wang, H., Dudanova, I., Hipp, M. S., Bracher, A., & Hartl, F. U (2021). The extracellular chaperone Clusterin enhances Tau aggregate seeding in a cellular model. *Nature Communication*, *12*(1), 4863. https://doi.org/10.1038/s41467-021-25060-1
15. Hsu, J. L., Lee, W. J., Liao, Y. C., Wang, S. J., & Fuh, J. L. (2017). The clinical significance of plasma clusterin and Abeta in the longitudinal

follow-up of patients with Alzheimer's disease. *Alzheimer's Research & Therapy*, *9*(1), 91. https://doi.org/10.1186/s13195-017-0319-x
16. Karch, C. M., Jeng, A. T., Nowotny, P., Cady, J., Cruchaga, C., & Goate, A. M. (2012). Expression of novel Alzheimer's disease risk genes in control and Alzheimer's disease brains. *Plos One*, *7*(11), e50976. https://doi.org/10.1371/journal.pone.0050976
17. Deming, Y., Xia, J., Cai, Y., Lord, J., Holmans, P., Bertelsen, S., Holtzman, D., Morris, J. C., Bales, K., Pickering, E. H., Kauwe, J., Goate, A., Cruchaga, C., & Alzheimer's Disease Neuroimaging, I. (2016). A potential endophenotype for Alzheimer's disease: Cerebrospinal fluid clusterin. *Neurobiology of Aging*, *37*, 208.e1–208.e9. https://doi.org/10.1016/j.neurobiolaging.2015.09.009
18. Foster, E. M., Dangla-Valls, A., Lovestone, S., Ribe, E. M., & Buckley, N. J. (2019). Clusterin in Alzheimer's disease: Mechanisms, genetics, and lessons from other pathologies. *Frontiers in Neuroscience*, *13*, 164. https://doi.org/10.3389/fnins.2019.00164
19. Rohne, P., Prochnow, H., & Koch-Brandt, C. (2016). The CLU-files: Disentanglement of a mystery. *BioMolecular Concepts*, *7*(1), 1–15. https://doi.org/10.1515/bmc-2015-0026
20. Demattos, R. B., O'dell, M. A., Parsadanian, M., Taylor, J. W., Harmony, J. A. K., Bales, K. R., Paul, S. M., Aronow, B. J., & Holtzman, D. M. (2002). Clusterin promotes amyloid plaque formation and is critical for neuritic toxicity in a mouse model of Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(16), 10843–10848. https://doi.org/10.1073/pnas.162228299
21. Schrijvers, E. M., Koudstaal, P. J., Hofman, A., & Breteler, M. M. (2011). Plasma clusterin and the risk of Alzheimer disease. *JAMA*, *305*(13), 1322–1326. https://doi.org/10.1001/jama.2011.381
22. Xing, Y. Y., Yu, J. T., Cui, W. Z., Zhong, X. L., Wu, Z. C., Zhang, Q., & Tan, L. (2012). Blood clusterin levels, rs9331888 polymorphism, and the risk of Alzheimer's disease. *Journal of Alzheimer's Disease*, *29*(3), 515–519. https://doi.org/10.3233/JAD-2011-111844
23. Jongbloed, W., Herrebout, M. A., Blankenstein, M. A., & Veerhuis, R. (2014). Quantification of clusterin in paired cerebrospinal fluid and plasma samples. *Annals of Clinical Biochemistry*, *51*(Pt 5), 557–567. https://doi.org/10.1177/0004563213503456
24. Blaschuk, O., Burdzy, K., & Fritz, I. B. (1983). Purification and characterization of a cell-aggregating factor (clusterin), the major glycoprotein in ram rete testis fluid. *Journal of Biological Chemistry*, *258*(12), 7714–7720.
25. Urban, J., Parczyk, K., Leutz, A., Kayne, M., & Kondor-Koch, C. (1987). Constitutive apical secretion of an 80-kD sulfated glycoprotein complex in the polarized epithelial Madin-Darby canine kidney cell line. *Journal of Cell Biology*, *105*(6 Pt 1), 2735–2743. https://doi.org/10.1083/jcb.105.6.2735
26. Rohne, P., Prochnow, H., Wolf, S., Renner, B., & Koch-Brandt, C. (2014). The chaperone activity of clusterin is dependent on glycosylation and redox environment. *Cellular Physiology and Biochemistry*, *34*(5), 1626–1639. https://doi.org/10.1159/000366365
27. Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., … Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, *596*(7873), 583–589. https://doi.org/10.1038/s41586-021-03819-2
28. Tunyasuvunakool, K., Adler, J., Wu, Z., Green, T., Zielinski, M., Žídek, A., Bridgland, A., Cowie, A., Meyer, C., Laydon, A., Velankar, S., Kleywegt, G. J., Bateman, A., Evans, R., Pritzel, A., Figurnov, M., Ronneberger, O., Bates, R., Kohl, S. A. A., … Hassabis, D. (2021). Highly accurate protein structure prediction for the human proteome. *Nature*, *596*(7873), 590–596. https://doi.org/10.1038/s41586-021-03828-1
29. Mistry, J., Chuguransky, S., Williams, L., Qureshi, M., Salazar, G. A., Sonnhammer, E. L. L., Tosatto, S. C. E., Paladin, L., Raj, S., Richardson, L. J., Finn, R. D., & Bateman, A. (2021). Pfam: The protein families database in 2021. *Nucleic Acids Research*, *49*(D1), D412–D419. https://doi.org/10.1093/nar/gkaa913
30. Kapron, J. T., Hilliard, G. M., Lakins, J. N., Tenniswood, M. P., West, K. A., Carr, S. A., & Crabb, J. W. (1997). Identification and characterization of glycosylation sites in human serum clusterin. *Protein Science*, *6*(10), 2120–2133. https://doi.org/10.1002/pro.5560061007
31. Hoffmann, J. H., Linke, K., Graf, P. C., Lilie, H., & Jakob, U. (2004). Identification of a redox-regulated chaperone network. *The EMBO Journal*, *23*(1), 160–168. https://doi.org/10.1038/sj.emboj.7600016
32. Yerbury, J. J., Poon, S., Meehan, S., Thompson, B., Kumita, J. R., Dobson, C. M., & Wilson, M. R. (2007). The extracellular chaperone clusterin influences amyloid formation and toxicity by interacting with prefibrillar structures. *FASEB Journal*, *21*(10), 2312–2322. https://doi.org/10.1096/fj.06-7986com
33. Greene, M. J., Klimtchuk, E. S., Seldin, D. C., Berk, J. L., & Connors, L. H. (2015). Cooperative stabilization of transthyretin by clusterin and diflunisal. *Biochemistry*, *54*(2), 268–278. https://doi.org/10.1021/bi5011249
34. Gregory, J. M., Whiten, D. R., Brown, R. A., Barros, T. P., Kumita, J. R., Yerbury, J. J., Satapathy, S., Mcdade, K., Smith, C., Luheshi, L. M., Dobson, C. M., & Wilson, M. R. (2017). Clusterin protects neurons against intracellular proteotoxicity. *Acta Neuropathologica Communications*, *5*(1), 81. https://doi.org/10.1186/s40478-017-0481-1
35. Wojtas, A. M., Carlomagno, Y., Sens, J. P., Kang, S. S., Jensen, T. D., Kurti, A., Baker, K. E., Berry, T. J., Phillips, V. R., Castanedes, M. C., Awan, A., Deture, M., De Castro, C. H. F, Librero, A. L., Yue, M., Daughrity, L., Jansen-West, K. R., Cook, C. N., Dickson, D. W., … Fryer, J. D. (2020). Clusterin ameliorates tau pathology in vivo by inhibiting fibril formation. *Acta Neuropathologica Communications*, *8*(1), 210. https://doi.org/10.1186/s40478-020-01079-1
36. Mok, S.-A., Condello, C., Freilich, R., Gillies, A., Arhar, T., Oroz, J., Kadavath, H., Julien, O., Assimon, V. A., Rauch, J. N., Dunyak, B. M., Lee, J., Tsai, F. T. F., Wilson, M. R., Zweckstetter, M., Dickey, C. A., & Gestwicki, J. E. (2018). Mapping interactions with the chaperone network reveals factors that protect against tau aggregation. *Nature Structural & Molecular Biology*, *25*(5), 384–393. https://doi.org/10.1038/s41594-018-0057-1
37. Whiten, D. R., Cox, D., Horrocks, M. H., Taylor, C. G., De, S., Flagmeier, P., Tosatto, L., Kumita, J. R., Ecroyd, H., Dobson, C. M., Klenerman, D., & Wilson, M. R. (2018). Single-molecule characterization of the interactions between extracellular chaperones and toxic alpha-synuclein oligomers. *Cell Reports*, *23*(12), 3492–3500. https://doi.org/10.1016/j.celrep.2018.05.074
38. Bailey, R. W., Dunker, A. K., Brown, C. J., Garner, E. C., & Griswold, M. D. (2001). Clusterin, a binding protein with a molten globule-like region. *Biochemistry*, *40*(39), 11828–11840. https://doi.org/10.1021/bi010135x
39. Wong, P., Taillefer, D., Lakins, J., Pineault, J., Chader, G., & Tenniswood, M. (1994). Molecular characterization of human TRPM-2/clusterin, a gene associated with sperm maturation, apoptosis and neurodegeneration. *European Journal of Biochemistry*, *221*(3), 917–925. https://doi.org/10.1111/j.1432-1033.1994.tb18807.x
40. Abdallah, B. M., Alzahrani, A. M., & Kassem, M. (2018). Secreted Clusterin protein inhibits osteoblast differentiation of bone marrow mesenchymal stem cells by suppressing ERK1/2 signaling pathway. *Bone*, *110*, 221–229. https://doi.org/10.1016/j.bone.2018.02.018
41. Praharaj, P. P., Patra, S., Panigrahi, D. P., Patra, S. K., & Bhutia, S. K. (2021). Clusterin as modulator of carcinogenesis: A potential avenue for targeted cancer therapy. *Biochimica et Biophysica Acta - Reviews on Cancer*, *1875*(2), 188500. https://doi.org/10.1016/j.bbcan.2020.188500
42. Murphy, B. F., Kirszbaum, L., Walker, I. D., & d'Apice, A. J. (1988). SP-40,40, a newly identified normal human serum protein found in the SC5b-9 complex of complement and in the immune deposits

in glomerulonephritis. *Journal of Clinical Investigation*, *81*(6), 1858–1864. https://doi.org/10.1172/JCI113531

43. Menny, A., Lukassen, M. V., Couves, E. C., Franc, V., Heck, A. J. R., & Bubeck, D. (2021). Structural basis of soluble membrane attack complex packaging for clearance. *Nature Communication*, *12*(1), 6086. https://doi.org/10.1038/s41467-021-26366-w
44. De Silva, H. V., Stuart, W. D., Duvic, C. R., Wetterau, J. R., Ray, M. J., Ferguson, D. G., Albers, H. W., Smith, W. R., & Harmony, J. A. (1990). A 70-kDa apolipoprotein designated ApoJ is a marker for subclasses of human plasma high density lipoproteins. *Journal of Biological Chemistry*, *265*(22), 13240–13247.
45. Suzuki, T., Tozuka, M., Kazuyoshi, Y., Sugano, M., Nakabayashi, T., Okumura, N., Hidaka, H., Katsuyama, T., & Higuchi, K. (2002). Predominant apolipoprotein J exists as lipid-poor mixtures in cerebrospinal fluid. *Annals of Clinical and Laboratory Science*, *32*(4), 369–376.
46. De Retana, S. F., Marazuela, P., Solé, M., Colell, G., Bonaterra, A., Sánchez-Quesada, J. L., Montaner, J., Maspoch, D., Cano-Sarabia, M., & Hernández-Guillamon, M. (2019). Peripheral administration of human recombinant ApoJ/clusterin modulates brain beta-amyloid levels in APP23 mice. *Alzheimer's Research & Therapy*, *11*(1), 42. https://doi.org/10.1186/s13195-019-0498-8
47. Yeh, F. L., Wang, Y., Tom, I., Gonzalez, L. C., & Sheng, M. (2016). TREM2 binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. *Neuron*, *91*(2), 328–340. https://doi.org/10.1016/j.neuron.2016.06.015
48. Nizard, P., Tetley, S., Le Drean, Y., Watrin, T., Le Goff, P., Wilson, M. R., & Michel, D. (2007). Stress-induced retrotranslocation of clusterin/ApoJ into the cytosol. *Traffic (Copenhagen, Denmark)*, *8*(5), 554–565. https://doi.org/10.1111/j.1600-0854.2007.00549.x
49. Leskov, K. S., Araki, S., Lavik, J.-P., Gomez, J. A., Gama, V., Gonos, E. S., Trougakos, I. P., Matsuyama, S., & Boothman, D. A. (2011). CRM1 protein-mediated regulation of nuclear clusterin (nCLU), an ionizing radiation-stimulated, Bax-dependent pro-death factor. *Journal of Biological Chemistry*, *286*(46), 40083–40090. https://doi.org/10.1074/jbc.M111.252957
50. Satapathy, S., & Wilson, M. R. (2021). The dual roles of clusterin in extracellular and intracellular proteostasis. *Trends in Biochemical Sciences*, *46*(8), 652–660. https://doi.org/10.1016/j.tibs.2021.01.005
51. Robbins, J. P., Perfect, L., Ribe, E. M., Maresca, M., Dangla-Valls, A., Foster, E. M., Killick, R., Nowosiad, P., Reid, M. J., Polit, L. D., Nevado, A. J., Ebner, D., Bohlooly-Y, M., Buckley, N., Pangalos, M. N., Price, J., & Lovestone, S. (2018). Clusterin is required for beta-amyloid toxicity in human iPSC-derived neurons. *Frontiers in Neuroscience*, *12*, 504. https://doi.org/10.3389/fnins.2018.00504
52. Loison, F., Debure, L., Nizard, P., le Goff, P., Michel, D., & le Drean, Y. (2006). Up-regulation of the clusterin gene after proteotoxic stress: Implication of HSF1-HSF2 heterocomplexes. *Biochemical Journal*, *395*(1), 223–231. https://doi.org/10.1042/BJ20051190
53. Garcia-Aranda, M., Serrano, A., & Redondo, M. (2018). Regulation of clusterin gene expression. *Current Protein & Peptide Science*, *19*(6), 612–622. https://doi.org/10.2174/1389203718666170918155247
54. Scheidt, T., Łapińska, U., Kumita, J. R., Whiten, D. R., Klenerman, D., Wilson, M. R., Cohen, S. I. A., Linse, S., Vendruscolo, M., Dobson, C. M., Knowles, T. P. J., & Arosio, P. (2019). Secondary nucleation and elongation occur at different sites on Alzheimer's amyloid-beta aggregates. *Science Advances*, *5*(4), eaau3112. https://doi.org/10.1126/sciadv.aau3112
55. Narayan, P., Orte, A., Clarke, R. W., Bolognesi, B., Hook, S., Ganzinger, K. A., Meehan, S., Wilson, M. R., Dobson, C. M., & Klenerman, D. (2011). The extracellular chaperone clusterin sequesters oligomeric forms of the amyloid-beta (1-40) peptide. *Nature Structural & Molecular Biology*, *19*(1), 79–83. https://doi.org/10.1038/nsmb.2191
56. Oda, T., Wals, P., Osterburg, H. H., Johnson, S. A., Pasinetti, G. M., Morgan, T. E., Rozovsky, I., Stine, W. B, Snyder, S. W., Holzman, T. F., Krafft, G. A., & Finch, C E. (1995). Clusterin (apoJ) alters the aggregation of amyloid beta-peptide (A beta 1–42) and forms slowly sedimenting A beta complexes that cause oxidative stress. *Experimental Neurology*, *136*(1), 22–31. https://doi.org/10.1006/exnr.1995.1080
57. Beeg, M., Stravalaci, M., Romeo, M., Carrá, A. D., Cagnotto, A., Rossi, A., Diomede, L., Salmona, M., & Gobbi, M. (2016). Clusterin binds to Abeta1-42 oligomers with high affinity and interferes with peptide aggregation by inhibiting primary and secondary nucleation. *Journal of Biological Chemistry*, *291*(13), 6958–6966. https://doi.org/10.1074/jbc.M115.689539
58. Wojtas, A. M., Sens, J. P., Kang, S. S., Baker, K. E., Berry, T. J., Kurti, A., Daughrity, L., Jansen-West, K. R., Dickson, D. W., Petrucelli, L., Bu, G., Liu, C.-C., & Fryer, J. D. (2020). Astrocyte-derived clusterin suppresses amyloid formation in vivo. *Molecular Neurodegeneration*, *15*(1), 71. https://doi.org/10.1186/s13024-020-00416-1
59. Qi, X. M., Wang, C., Chu, X. K., Li, G., & Ma, J. F. (2018). Intraventricular infusion of clusterin ameliorated cognition and pathology in Tg6799 model of Alzheimer's disease. *Bmc Neuroscience [Electronic Resource]*, *19*(1), 2. https://doi.org/10.1186/s12868-018-0402-7
60. Chen, F., Swartzlander, D. B., Ghosh, A., Fryer, J. D., Wang, B., & Zheng, H. (2021). Clusterin secreted from astrocyte promotes excitatory synaptic transmission and ameliorates Alzheimer's disease neuropathology. *Molecular Neurodegeneration*, *16*(1), 5. https://doi.org/10.1186/s13024-021-00426-7
61. Wojtas, A. M., Kang, S. S., Olley, B. M., Gatherer, M., Shinohara, M., Lozano, P. A., Liu, C.-C., Kurti, A., Baker, K. E., Dickson, D. W., Yue, M., Petrucelli, L., Bu, G., Carare, R. O., & Fryer, J. D. (2017). Loss of clusterin shifts amyloid deposition to the cerebrovasculature via disruption of perivascular drainage pathways. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(33), E6962–E6971. https://doi.org/10.1073/pnas.1701137114
62. Oh, S.-B., Kim, M. S., Park, S., Son, H., Kim, S.-Y., Kim, M.-S., Jo, D.-G., Tak, E., & Lee, J.-Y. (2019). Clusterin contributes to early stage of Alzheimer's disease pathogenesis. *Brain Pathology*, *29*(2), 217–231. https://doi.org/10.1111/bpa.12660
63. Narayan, P., Ganzinger, K. A., Mccoll, J., Weimann, L., Meehan, S., Qamar, S., Carver, J. A., Wilson, M. R., St George-Hyslop, P., Dobson, C. M., & Klenerman, D. (2013). Single molecule characterization of the interactions between amyloid-beta peptides and the membranes of hippocampal cells. *Journal of the American Chemical Society*, *135*(4), 1491–1498. https://doi.org/10.1021/ja3103567
64. Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., Morgan, T. E., Rozovsky, I., Trommer, B., Viola, K. L., Wals, P., Zhang, C., Finch, C. E., Krafft, G. A., & Klein, W. L. (1998). Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(11), 6448–6453. https://doi.org/10.1073/pnas.95.11.6448
65. Nelson, P. T., Braak, H., & Markesbery, W. R. (2009). Neuropathology and cognitive impairment in Alzheimer disease: A complex but coherent relationship. *Journal of Neuropathology and Experimental Neurology*, *68*(1), 1–14. https://doi.org/10.1097/NEN.0b013e3181919a48
66. Choi-Miura, N. H., Ihara, Y., Fukuchi, K., Takeda, M., Nakano, Y., Tobe, T., & Tomita, M. (1992). SP-40,40 is a constituent of Alzheimer's amyloid. *Acta Neuropathologica*, *83*(3), 260–264. https://doi.org/10.1007/BF00296787
67. Giannakopoulos, P., Kovari, E., French, L. E., Viard, I., Hof, P. R., & Bouras, C. (1998). Possible neuroprotective role of clusterin in Alzheimer's disease: A quantitative immunocytochemical study. *Acta Neuropathologica*, *95*(4), 387–394. https://doi.org/10.1007/s004010050815
68. Drummond, E., Pires, G., Macmurray, C., Askenazi, M., Nayak, S., Bourdon, M., Safar, J., Ueberheide, B., & Wisniewski, T. (2020). Phosphorylated tau interactome in the human Alzheimer's disease brain. *Brain*, *143*(9), 2803–2817. https://doi.org/10.1093/brain/awaa223

69. Jansen, I. E., Savage, J. E., Watanabe, K., Bryois, J., Williams, D. M., Steinberg, S., Sealock, J., Karlsson, I. K., Hägg, S., Athanasiu, L., Voyle, N., Proitsi, P., Witoelar, A., Stringer, S., Aarsland, D., Almdahl, I. S., Andersen, F., Bergh, S., Bettella, F., … Posthuma, D. (2019). Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nature Genetics*, *51*(3), 404–413. https://doi.org/10.1038/s41588-018-0311-9
70. Lambert, J.-C., Heath, S., Even, G., Campion, D., Sleegers, K., Hiltunen, M., Combarros, O., Zelenika, D., Bullido, M. J., Tavernier, B., Letenneur, L., Bettens, K., Berr, C., Pasquier, F., Fiévet, N., Barberger-Gateau, P., Engelborghs, S., De Deyn, P., Mateo, I., …, Amouyel, P. (2009). Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nature Genetics*, *41*(10), 1094–1099. https://doi.org/10.1038/ng.439
71. Harold, D., Abraham, R., Hollingworth, P., Sims, R., Gerrish, A., Hamshere, M. L., Pahwa, J. S., Moskvina, V., Dowzell, K., Williams, A., Jones, N., Thomas, C., Stretton, A., Morgan, A. R., Lovestone, S., Powell, J., Proitsi, P., Lupton, M. K., Brayne, C., … Williams, J. (2009). Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nature Genetics*, *41*(10), 1088–1093. https://doi.org/10.1038/ng.440
72. Bettens, K., Vermeulen, S., Van Cauwenberghe, C., Heeman, B., Asselbergh, B., Robberecht, C., Engelborghs, S., Vandenbulcke, M., Vandenberghe, R., De Deyn, P. P., Cruts, M., Van Broeckhoven, C., & Sleegers, K. (2015). Reduced secreted clusterin as a mechanism for Alzheimer-associated CLU mutations. *Molecular Neurodegeneration*, *10*, 30. https://doi.org/10.1186/s13024-015-0024-9
73. Szymanski, M., Wang, R., Bassett, S. S., & Avramopoulos, D. (2011). Alzheimer's risk variants in the clusterin gene are associated with alternative splicing. *Translational Psychiatry*, *1*, e18–e18. https://doi.org/10.1038/tp.2011.17
74. Rosenthal, S. L., Barmada, M. M., Wang, X., Demirci, F. Y., & Kamboh, M. I. (2014). Connecting the dots: Potential of data integration to identify regulatory SNPs in late-onset Alzheimer's disease GWAS findings. *Plos One*, *9*(4), e95152. https://doi.org/10.1371/journal.pone.0095152
75. Padhy, B., Nanda, G. G., Chowdhury, M., Padhi, D., Rao, A., & Alone, D. P. (2014). Role of an extracellular chaperone, Clusterin in the pathogenesis of Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma. *Experimental Eye Research*, *127*, 69–76. https://doi.org/10.1016/j.exer.2014.07.005
76. Padhy, B., Hayat, B., Nanda, G. G., Mohanty, P. P., & Alone, D. P. (2017). Pseudoexfoliation and Alzheimer's associated CLU risk variant, rs2279590, lies within an enhancer element and regulates CLU, EPHX2 and PTK2B gene expression. *Human Molecular Genetics*, *26*(22), 4519–4529. https://doi.org/10.1093/hmg/ddx329
77. Allen, M., Zou, F., Chai, H. S., Younkin, C. S., Crook, J., Pankratz, V. S., Carrasquillo, M. M., Rowley, C. N., Nair, A. A., Middha, S., Maharjan, S., Nguyen, T., Ma, L., Malphrus, K. G., Palusak, R., Lincoln, S., Bisceglio, G., Georgescu, C., Schultz, D., … Ertekin-Taner, N. (2012). Novel late-onset Alzheimer disease loci variants associate with brain gene expression. *Neurology*, *79*(3), 221–228. https://doi.org/10.1212/WNL.0b013e3182605801
78. Tan, L., Wang, H.-F., Tan, M.-S., Tan, C.-C., Zhu, X.-C., Miao, D., Yu, W.-J., Jiang, T., Tan, L., & Yu, J.-T., & Alzheimer's Disease Neuroimaging, I. (2016). Effect of CLU genetic variants on cerebrospinal fluid and neuroimaging markers in healthy, mild cognitive impairment and Alzheimer's disease cohorts. *Science Reports*, *6*, 26027. https://doi.org/10.1038/srep26027
79. Green, A. E., Gray, J. R., Deyoung, C. G., Mhyre, T. R., Padilla, R., Dibattista, A. M., & William Rebeck, G. (2014). A combined effect of two Alzheimer's risk genes on medial temporal activity during executive attention in young adults. *Neuropsychologia*, *56*, 1–8. https://doi.org/10.1016/j.neuropsychologia.2013.12.020
80. Chen, L. H., Heng Mak, T. S., Fan, Y., Yin Ho, D. T., Sham, P. C., Chu, L. W., & Song, Y. Q. (2020). Associations between CLU polymorphisms and memory performance: The role of serum lipids in Alzheimer's disease. *Journal of Psychiatric Research*, *129*, 281–288. https://doi.org/10.1016/j.jpsychires.2020.07.015
81. Lancaster, T. M., Brindley, L. M., Tansey, K. E., Sims, R. C., Mantripragada, K., Owen, M. J., Williams, J., & Linden, D. E. J. (2015). Alzheimer's disease risk variant in CLU is associated with neural inefficiency in healthy individuals. *Alzheimer's & Dementia*, *11*(10), 1144–1152. https://doi.org/10.1016/j.jalz.2014.10.012
82. Qiu, L., He, Y., Tang, H., Zhou, Y., Wang, J., Zhang, W., Chen, G., Zhao, F., Ouyang, T., Ju, B., Li, Z., Wang, L., Zou, L., & Gong, Q. (2016). Genetically-mediated grey and white matter alteration in normal elderly individuals with the CLU-C allele gene. *Current Alzheimer Research*, *13*(11), 1302–1310. https://doi.org/10.2174/1567205013666160703180531
83. Sepulcre, J., Grothe, M. J., D'oleire Uquillas, F., Ortiz-Terán, L., Diez, I., Yang, H.-S., Jacobs, H. I. L., Hanseeuw, B. J., Li, Q., El-Fakhri, G., Sperling, R. A., & Johnson, K. A. (2018). Neurogenetic contributions to amyloid beta and tau spreading in the human cortex. *Nature Medicine*, *24*(12), 1910–1918. https://doi.org/10.1038/s41591-018-0206-4
84. Shepherd, C. E., Affleck, A. J., Bahar, A. Y., Carew-Jones, F., & Halliday, G. M. (2020). Intracellular and secreted forms of clusterin are elevated early in Alzheimer's disease and associate with both Abeta and tau pathology. *Neurobiology of Aging*, *89*, 129–131. https://doi.org/10.1016/j.neurobiolaging.2019.10.025
85. Haight, T., Bryan, R. N, Meirelles, O., Tracy, R., Fornage, M., Richard, M., Nasrallah, I., Yaffe, K., Jacobs, D. R., Lewis, C., Schreiner, P., Sidney, S., Davatzikos, C., & Launer, L. J. (2018). Associations of plasma clusterin and Alzheimer's disease-related MRI markers in adults at midlife: The CARDIA Brain MRI sub-study. *Plos One*, *13*(1), e0190478. https://doi.org/10.1371/journal.pone.0190478
86. Kwon, M. J., Ju, T.-J., Heo, J.-Y., Kim, Y.-W., Kim, J.-Y., Won, K.-C., Kim, J.-R., Bae, Y. K., Park, I.-S., Min, B.-H., Lee, I.-K., & Park, S.-Y. (2014). Deficiency of clusterin exacerbates high-fat diet-induced insulin resistance in male mice. *Endocrinology*, *155*(6), 2089–2101. https://doi.org/10.1210/en.2013-1870
87. Arosio, P., Knowles, T. P., & Linse, S. (2015). On the lag phase in amyloid fibril formation. *Physical Chemistry Chemical Physics*, *17*(12), 7606–7618. https://doi.org/10.1039/c4cp05563b
88. Hipp, M. S., Kasturi, P., & Hartl, F. U. (2019). The proteostasis network and its decline in ageing. *Nature Reviews Molecular Cell Biology*, *20*(7), 421–435. https://doi.org/10.1038/s41580-019-0101-y
89. Arosio, P., Michaels, T. C. T., Linse, S., Månsson, C., Emanuelsson, C., Presto, J., Johansson, J., Vendruscolo, M., Dobson, C. M., & Knowles, T. P. J. (2016). Kinetic analysis reveals the diversity of microscopic mechanisms through which molecular chaperones suppress amyloid formation. *Nature Communication*, *7*, 10948. https://doi.org/10.1038/ncomms10948
90. Linse, S. (2017). Monomer-dependent secondary nucleation in amyloid formation. *Biophysical Reviews*, *9*(4), 329–338. https://doi.org/10.1007/s12551-017-0289-z
91. Rüdiger, S., Germeroth, L., Schneider-Mergener, J., & Bukau, B. (1997). Substrate specificity of the DnaK chaperone determined by screening cellulose-bound peptide libraries. *The EMBO Journal*, *16*(7), 1501–1507. https://doi.org/10.1093/emboj/16.7.1501
92. Ungelenk, S., Moayed, F., Ho, C.-T., Grousl, T., Scharf, A., Mashaghi, A., Tans, S., Mayer, M. P., Mogk, A., & Bukau, B. (2016). Small heat shock proteins sequester misfolding proteins in near-native conformation for cellular protection and efficient refolding. *Nature Communication*, *7*, 13673. https://doi.org/10.1038/ncomms13673
93. Braak, H., Thal, D. R., Ghebremedhin, E., & Del Tredici, K. (2011). Stages of the pathologic process in Alzheimer disease: Age categories from 1 to 100 years. *Journal of Neuropathology and Exper-*

imental Neurology, *70*(11), 960–969. https://doi.org/10.1097/NEN.0b013e318232a379

94. Wang, Y., & Mandelkow, E. (2016). Tau in physiology and pathology. *Nature Reviews Neuroscience*, *17*(1), 22–35. https://doi.org/10.1038/nrn.2015.1
95. Shi, Y., Zhang, W., Yang, Y., Murzin, A. G., Falcon, B., Kotecha, A., Van Beers, M., Tarutani, A., Kametani, F., Garringer, H. J., Vidal, R., Hallinan, G. I., Lashley, T., Saito, Y., Murayama, S., Yoshida, M., Tanaka, H., Kakita, A., Ikeuchi, T., … Scheres, S. H. W. (2021). Structure-based classification of tauopathies. *Nature*, *598*(7880), 359–363. https://doi.org/10.1038/s41586-021-03911-7
96. Ryder, B. D., Wydorski, P. M., Hou, Z., & Joachimiak, L. A. (2022). Chaperoning shape-shifting tau in disease. *Trends in Biochemical Sciences*, 301–313. https://doi.org/10.1016/j.tibs.2021.12.009
97. Fontaine, S. N., Zheng, D., Sabbagh, J. J., Martin, M. D., Chaput, D., Darling, A., Trotter, J. H., Stothert, A. R., Nordhues, B. A., Lussier, A. J., Shelton, L., Kahn, M., Blair, L. J., Stevens, S. M., & Dickey, C. A. (2016). DnaJ/Hsc70 chaperone complexes control the extracellular release of neurodegenerative-associated proteins. *The EMBO Journal*, *35*(14), 1537–1549. https://doi.org/10.15252/embj.201593489
98. Wu, S., Sirkis, D. W., & Schekman, R. (2022). Unconventional secretion of α-synuclein mediated by palmitoylated DNAJC5 oligomers. *bioRxiv*. 2022.027.477991. https://doi.org/10.1101/2022.01.27.477991
99. Hsieh, Y.-C., Guo, C., Yalamanchili, H. K., Abreha, M., Al-Ouran, R., Li, Y., Dammer, E. B., Lah, J. J., Levey, A. I., Bennett, D. A., De Jager, P. L., Seyfried, N. T., Liu, Z., & Shulman, J. M. (2019). Tau-mediated disruption of the spliceosome triggers cryptic RNA splicing and neurodegeneration in Alzheimer's disease. *Cell Reports*, *29*(2), 301–316.e10.e310. https://doi.org/10.1016/j.celrep.2019.08.104
100. Zhou, Y., Hayashi, I., Wong, J., Tugusheva, K., Renger, J. J., & Zerbinatti, C. (2014). Intracellular clusterin interacts with brain isoforms of the bridging integrator 1 and with the microtubule-associated protein Tau in Alzheimer's disease. *Plos One*, *9*(7), e103187. https://doi.org/10.1371/journal.pone.0103187
101. Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., Axel, L., Rusinek, H., Nicholson, C., Zlokovic, B. V., Frangione, B., Blennow, K., Ménard, J., Zetterberg, H., Wisniewski, T., & De Leon, M. J. (2015). Clearance systems in the brain-implications for Alzheimer disease. *Nature Reviews Neurology*, *11*(8), 457–470. https://doi.org/10.1038/nrneurol.2015.119
102. Serrano-Pozo, A., Mielke, M. L., Gomez-Isla, T., Betensky, R. A., Growdon, J. H., Frosch, M. P., & Hyman, B. T. (2011). Reactive glia not only associates with plaques but also parallels tangles in Alzheimer's disease. *American Journal of Pathology*, *179*(3), 1373–1384. https://doi.org/10.1016/j.ajpath.2011.05.047
103. Amro, Z., Yool, A. J., & Collins-Praino, L. E. (2021). The potential role of glial cells in driving the prion-like transcellular propagation of tau in tauopathies. *Brain, Behavior, and Immunity - Health*, *14*, 100242. https://doi.org/10.1016/j.bbih.2021.100242
104. Ries, M., & Sastre, M. (2016). Mechanisms of abeta clearance and degradation by glial cells. *Frontiers in Aging Neuroscience*, *8*, 160. https://doi.org/10.3389/fnagi.2016.00160
105. Majerova, P., Zilkova, M., Kazmerova, Z., Kovac, A., Paholikova, K., Kovacech, B., Zilka, N., & Novak, M. (2014). Microglia display modest phagocytic capacity for extracellular tau oligomers. *Journal of Neuroinflammation*, *11*, 161. https://doi.org/10.1186/s12974-014-0161-z
106. Takeda, S., Wegmann, S., Cho, H., Devos, S. L., Commins, C., Roe, A. D., Nicholls, S. B., Carlson, G. A., Pitstick, R., Nobuhara, C. K., Costantino, I., Frosch, M. P., Müller, D. J., Irimia, D., & Hyman, B. T. (2015). Neuronal uptake and propagation of a rare phosphorylated high-molecular-weight tau derived from Alzheimer's disease brain. *Nature Communication*, *6*, 8490. https://doi.org/10.1038/ncomms9490
107. Holmes, B. B., Devos, S. L., Kfoury, N., Li, M., Jacks, R., Yanamandra, K., Ouidja, M. O., Brodsky, F. M., Marasa, J., Bagchi, D. P., Kotzbauer, P. T., Miller, T. M., Papy-Garcia, D., & Diamond, M. I. (2013). Heparan sulfate proteoglycans mediate internalization and propagation of specific proteopathic seeds. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(33), E3138–3147. https://doi.org/10.1073/pnas.1301440110
108. Rauch, J. N., Luna, G., Guzman, E., Audouard, M., Challis, C., Sibih, Y. E., Leshuk, C., Hernandez, I., Wegmann, S., Hyman, B. T., Gradinaru, V., Kampmann, M., & Kosik, K. S. (2020). LRP1 is a master regulator of tau uptake and spread. *Nature*, *580*(7803), 381–385. https://doi.org/10.1038/s41586-020-2156-5
109. Morozova, V., Cohen, L. S., Makki, A. E., Shur, A., Pilar, G., El Idrissi, A., & Alonso, A. D. (2019). Normal and pathological tau uptake mediated by M1/M3 muscarinic receptors promotes opposite neuronal changes. *Frontiers in Cellular Neuroscience*, *13*, 403. https://doi.org/10.3389/fncel.2019.00403
110. Chen, J. J., Nathaniel, D. L., Raghavan, P., Nelson, M., Tian, R., Tse, E., Hong, J. Y., See, S. K., Mok, S.-A., Hein, M. Y., Southworth, D. R., Grinberg, L. T., Gestwicki, J. E., Leonetti, M. D., & Kampmann, M. (2019). Compromised function of the ESCRT pathway promotes endolysosomal escape of tau seeds and propagation of tau aggregation. *Journal of Biological Chemistry*, *294*(50), 18952–18966. https://doi.org/10.1074/jbc.RA119.009432
111. Flavin, W. P., Bousset, L., Green, Z. C., Chu, Y., Skarpathiotis, S., Chaney, M. J., Kordower, J. H., Melki, R., & Campbell, E. M. (2017). Endocytic vesicle rupture is a conserved mechanism of cellular invasion by amyloid proteins. *Acta Neuropathologica*, *134*(4), 629–653. https://doi.org/10.1007/s00401-017-1722-x
112. Asai, H., Ikezu, S., Tsunoda, S., Medalla, M., Luebke, J., Haydar, T., Wolozin, B., Butovsky, O., Kügler, S., & Ikezu, T. (2015). Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nature Neuroscience*, *18*(11), 1584–1593. https://doi.org/10.1038/nn.4132
113. Maphis, N., Xu, G., Kokiko-Cochran, O. N., Jiang, S., Cardona, A., Ransohoff, R. M., Lamb, B. T., & Bhaskar, K. (2015). Reactive microglia drive tau pathology and contribute to the spreading of pathological tau in the brain. *Brain*, *138*(Pt 6), 1738–1755. https://doi.org/10.1093/brain/awv081
114. Sollvander, S., Nikitidou, E., Brolin, R., Soderberg, L., Sehlin, D., Lannfelt, L., & Erlandsson, A. (2016). Accumulation of amyloid-beta by astrocytes result in enlarged endosomes and microvesicle-induced apoptosis of neurons. *Molecular Neurodegeneration*, *11*(1), 38. https://doi.org/10.1186/s13024-016-0098-z
115. Xia, Y., Zhang, G., Kou, L., Yin, S., Han, C., Hu, J., Wan, F., Sun, Y., Wu, J., Li, Y., Huang, J., Xiong, N., Zhang, Z., & Wang, T. (2021). Reactive microglia enhance the transmission of exosomal alpha-synuclein via toll-like receptor 2. *Brain*, *144*(7), 2024–2037. https://doi.org/10.1093/brain/awab122
116. Guo, M., Wang, J., Zhao, Y., Feng, Y., Han, S., Dong, Q., Cui, M., & Tieu, K. (2020). Microglial exosomes facilitate alpha-synuclein transmission in Parkinson's disease. *Brain*, *143*(5), 1476–1497. https://doi.org/10.1093/brain/awaa090
117. Rostami, J., Mothes, T., Kolahdouzan, M., Eriksson, O., Moslem, M., Bergström, J., Ingelsson, M., O'callaghan, P., Healy, L. M., Falk, A., & Erlandsson, A. (2021). Crosstalk between astrocytes and microglia results in increased degradation of alpha-synuclein and amyloid-beta aggregates. *Journal of Neuroinflammation*, *18*(1), 124. https://doi.org/10.1186/s12974-021-02158-3
118. Brelstaff, J. H., Mason, M., Katsinelos, T., McEwan, W. A., Ghetti, B., Tolkovsky, A. M., & Spillantini, M. G. (2021). Microglia become hypofunctional and release metalloproteases and tau seeds when phagocytosing live neurons with P301S tau aggregates. *Science Advances*, *7*(43), eabg4980. https://doi.org/10.1126/sciadv.abg4980

119. Wyatt, A. R., Yerbury, J. J., Berghofer, P., Greguric, I., Katsifis, A., Dobson, C. M., & Wilson, M. R. (2011). Clusterin facilitates in vivo clearance of extracellular misfolded proteins. *Cellular and Molecular Life Sciences*, *68*(23), 3919–3931. https://doi.org/10.1007/s00018-011-0684-8
120. Itakura, E., Chiba, M., Murata, T., & Matsuura, A. (2020). Heparan sulfate is a clearance receptor for aberrant extracellular proteins. *Journal of Cell Biology*, *219*(3), . https://doi.org/10.1083/jcb.201911126
121. Prikrylova Vranova, H., Mares, J., Nevrly, M., Stejskal, D., Zapletalova, J., Hlustik, P., & Kanovsky, P. (2010). CSF markers of neurodegeneration in Parkinson's disease. *Journal of Neural Transmission (Vienna)*, *117*(10), 1177–1181. https://doi.org/10.1007/s00702-010-0462-z
122. Leeb, C., Eresheim, C., & Nimpf, J. (2014). Clusterin is a ligand for apolipoprotein E receptor 2 (ApoER2) and very low density lipoprotein receptor (VLDLR) and signals via the Reelin-signaling pathway. *Journal of Biological Chemistry*, *289*(7), 4161–4172. https://doi.org/10.1074/jbc.M113.529271
123. Kang, S. S., Kurti, A., Wojtas, A., Baker, K. E., Liu, C.-C., Kanekiyo, T., Deming, Y., Cruchaga, C., Estus, S., Bu, G., & Fryer, J. D. (2016). Identification of plexin A4 as a novel clusterin receptor links two Alzheimer's disease risk genes. *Human Molecular Genetics*, *25*(16), 3467–3475. https://doi.org/10.1093/hmg/ddw188
124. Gil, S. Y, Youn, B.-S., Byun, K., Huang, H., Namkoong, C., Jang, P.-G., Lee, J.-Y., Jo, Y.-H., Kang, G. M., Kim, H.-K., Shin, M.-S., Pietrzik, C. U., Lee, B., Kim, Y.-B., & Kim, M.-S. (2013). Clusterin and LRP2 are critical components of the hypothalamic feeding regulatory pathway. *Nature Communication*, *4*, 1862. https://doi.org/10.1038/ncomms2896
125. Bartl, M. M., Luckenbach, T., Bergner, O., Ullrich, O., & Koch-Brandt, C. (2001). Multiple receptors mediate apoJ-dependent clearance of cellular debris into nonprofessional phagocytes. *Experimental Cell Research*, *271*(1), 130–141. https://doi.org/10.1006/excr.2001.5358
126. Bell, R. D., Sagare, A. P., Friedman, A. E., Bedi, G. S., Holtzman, D. M., Deane, R., & Zlokovic, B. V. (2007). Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse central nervous system. *Journal of Cerebral Blood Flow and Metabolism*, *27*(5), 909–918. https://doi.org/10.1038/sj.jcbfm.9600419
127. Tian, Y., Wang, C., Chen, S., Liu, J., Fu, Y., & Luo, Y. (2019). Extracellular Hsp90alpha and clusterin synergistically promote breast cancer epithelial-to-mesenchymal transition and metastasis via LRP1. *Journal of Cell Science*, *132*(15), . https://doi.org/10.1242/jcs.228213
128. Jun, G., Asai, H., Zeldich, E., Drapeau, E., Chen, C., Chung, J., Park, J.-H., Kim, S., Haroutunian, V., Foroud, T., Kuwano, R., Haines, J. L., Pericak-Vance, M. A., Schellenberg, G. D., Lunetta, K. L., Kim, J.-W., Buxbaum, J. D., Mayeux, R., Ikezu, T., … Farrer, L. A. (2014). PLXNA4 is associated with Alzheimer disease and modulates tau phosphorylation. *Annals of Neurology*, *76*(3), 379–392. https://doi.org/10.1002/ana.24219
129. Cooper, J. M., Lathuiliere, A., Migliorini, M., Arai, A. L., Wani, M. M., Dujardin, S., Muratoglu, S. C., Hyman, B. T., & Strickland, D. K. (2021). Regulation of tau internalization, degradation, and seeding by LRP1 reveals multiple pathways for tau catabolism. *Journal of Biological Chemistry*, *296*, 100715. https://doi.org/10.1016/j.jbc.2021.100715
130. De Strooper, B., & Karran, E. (2016). The cellular phase of Alzheimer's disease. *Cell*, *164*(4), 603–615. https://doi.org/10.1016/j.cell.2015.12.056
131. Hampel, H., Caraci, F., Cuello, A. C, Caruso, G., Nisticò, R., Corbo, M., Baldacci, F., Toschi, N., Garaci, F., Chiesa, P. A., Verdooner, S. R., Akman-Anderson, L., Hernández, F., Ávila, J., Emanuele, E., Valenzuela, P. L., Lucía, A., Watling, M., Imbimbo, B. P., … Lista, S. (2020). A path toward precision medicine for neuroinflammatory mechanisms in Alzheimer's disease. *Frontiers in Immunology*, *11*, 456. https://doi.org/10.3389/fimmu.2020.00456
132. Leng, F., & Edison, P. (2021). Neuroinflammation and microglial activation in Alzheimer disease: Where do we go from here? *Nature Reviews Neurology*, *17*(3), 157–172. https://doi.org/10.1038/s41582-020-00435-y
133. Zhang, Y., Sloan, S. A., Clarke, L. E., Caneda, C., Plaza, C. A., Blumenthal, P. D., Vogel, H., Steinberg, G. K., Edwards, M. S. B., Li, G., Duncan, J. A., Cheshier, S. H., Shuer, L. M., Chang, E. F., Grant, G. A., Gephart, M. G. H, & Barres, B. A. (2016). Purification and characterization of progenitor and mature human astrocytes reveals transcriptional and functional differences with mouse. *Neuron*, *89*(1), 37–53. https://doi.org/10.1016/j.neuron.2015.11.013
134. Morgan, T. E., Laping, N. J., Rozovsky, I., Oda, T., Hogan, T. H., Finch, C. E., & Pasinetti, G. M. (1995). Clusterin expression by astrocytes is influenced by transforming growth factor beta 1 and heterotypic cell interactions. *Journal of Neuroimmunology*, *58*(1), 101–110. https://doi.org/10.1016/0165-5728(94)00194-s
135. Zwain, I. H., Grima, J., & Cheng, C. Y. (1994). Regulation of clusterin secretion and mRNA expression in astrocytes by cytokines. *Molecular and Cellular Neuroscience*, *5*(3), 229–237. https://doi.org/10.1006/mcne.1994.1027
136. Xie, Z., Harris-White, M. E., Wals, P. A., Frautschy, S. A., Finch, C. E., & Morgan, T. E. (2005). Apolipoprotein J (clusterin) activates rodent microglia in vivo and in vitro. *Journal of Neurochemistry*, *93*(4), 1038–1046. https://doi.org/10.1111/j.1471-4159.2005.03065.x
137. Pascoal, T. A., Benedet, A. L., Ashton, N. J., Kang, M. S., Therriault, J., Chamoun, M., Savard, M., Lussier, F. Z., Tissot, C., Karikari, T. K., Ottoy, J., Mathotaarachchi, S., Stevenson, J., Massarweh, G., Schöll, M., De Leon, M. J., Soucy, J.-P., Edison, P., Blennow, K., … Rosa-Neto, P. (2021). Microglial activation and tau propagate jointly across Braak stages. *Nature Medicine*, *27*(9), 1592–1599. https://doi.org/10.1038/s41591-021-01456-w
138. Stephan, A. H., Barres, B. A., & Stevens, B. (2012). The complement system: An unexpected role in synaptic pruning during development and disease. *Annual Review of Neuroscience*, *35*, 369–389. https://doi.org/10.1146/annurev-neuro-061010-113810
139. Schartz, N. D., & Tenner, A. J. (2020). The good, the bad, and the opportunities of the complement system in neurodegenerative disease. *Journal of Neuroinflammation*, *17*(1), 354. https://doi.org/10.1186/s12974-020-02024-8
140. Gouet, P., Courcelle, E., Stuart, D. I., & Metoz, F. (1999). ESPript: Analysis of multiple sequence alignments in PostScript. *Bioinformatics*, *15*(4), 305–308. https://doi.org/10.1093/bioinformatics/15.4.305

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