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·Review·

# Clusterin in Alzheimer's disease: a player in the biological behavior of amyloid-beta

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Alzheimer's disease (AD) remains a major killer, and although its pathogenesis varies, one dominant feature is an increase in the expression, formation, and sedimentation of senile plaques of amyloid-beta (Aβ) peptides in the brain. The chaperone protein clusterin has, since its first discovery at the end of the 20th century, been labeled as a cytoprotector. However, epigenetic studies showing that clusterin is associated with the severity and risk of AD, especially in the hippocampus, triggered studies to clarify its role in the pathogenesis of AD. It is true that clusterin can inhibit the aggregation of Aβ and therefore prevent further formation of senile plaques in the AD brain, yet it induces the formation of soluble forms of Aβ which are toxic to neurons. Another problematic finding is that clusterin is involved in a pathway through which Aβ has neurodegenerative effects intracellularly. Although the role of clusterin in the pathogenesis of AD is still not clear, this review specifically discusses the interactions between clusterin and Aβ, to open up the possibility of a potential therapeutic approach for treating AD.

**Keywords:** clusterin; Alzheimer's disease; amyloid-beta peptides; cytotoxicity; cytoprotection

## Introduction

Although the pathogenesis of Alzheimer's disease (AD) remains shrouded in mystery, one major hypothesis concerns its pathology with the formation of senile plaques, the aggregation of amyloid-beta (Aβ) peptides. These peptides exist in the normal brain but reach particularly high levels in the AD brain[1]. The deposited plaques, comprised of polymers of low-molecular-weight protein subunits, have common physical, tinctorial, and structural (beta-pleated sheet) properties[2, 3]. These plaques were therefore named amyloid beta, and comprise a family of 39–43-residue peptides derived from the normal proteolytic processing of Aβ precursor protein (APP), a large protein coded by a single gene[4]. However, in AD pathogenesis, the cleavage of APP induces signs of malfunction, which may generally account for the accumulation of misfolded Aβ in senile plaques[5]. Still, epidemiological studies have linked non-plaque forming, soluble Aβ peptides to the risk of early-onset AD, which may seem in contradiction with a pathological presentation that features Aβ aggregation into senile plaques.

At the end of the last century, a specific chaperone protein, clusterin, was discovered. Clusterin was found initially in ram rete testis fluid in 1983, and now is believed to play roles in various cellular functions, including spermatogenesis (the first function discovered), cell–cell adhesion, and most significantly cell aggregation[5, 6]. Historically, clusterin was also named apolipoprotein J[7, 8]. In humans, clusterin is widely expressed in the kidney, liver, prostate and predominantly, in the brain. It has been shown that clusterin is highly elevated in AD and tends to colocalize with Aβ. Also, clusterin is abundantly expressed in neurons and astroglia, and is present particularly in senile plaques where diffusible Aβ aggregates[4]. However, only a handful of papers have investigated the exact mechanisms

by which clusterin influences the biological behavior of amyloid plaques. Yet since the discovery of clusterin in AD brains, its significance has become a new focus of study. This review thus discusses the interactions between clusterin and Aβ peptides and the effect of clusterin on both the triggering and inhibition of AD pathology (Fig. 1), in the hope of shedding new light on possible therapies.

## Clusterin and Its Biochemical Properties

Clusterin is encoded by the *CLU* gene that maps chromosome 8p21-p12, in a region of interest in late-onset AD (LOAD), recently defined in a genome-wide linkage study. It has been reported that variation in the *CLU* gene plays an important role in sporadic LOAD[4]. Though it has long been known that *CLU* is expressed as secreted and intracellular clusterin, CLU isoforms and SNPs have been reported in the pathogenesis of AD[9]. Moreover, whether clusterin alleviates AD remains in dispute[6].

## Clusterin as a Protector Against the Pathogenesis of AD

### *Extracellular Clusterin Inhibits the Process of Aβ Aggregation*

Clusterin, a chaperone with a globular structure, can bind to a variety of proteins. There is convincing evidence that clusterin binds to Aβ, prevents Aβ aggregation, and has neuroprotective effects under physiological conditions[10, 11]. Poon *et al.* demonstrated that clusterin does not refold or change the configuration of substrate proteins but rather stabilizes them in a state suitable for refolding by other proteins, notably the heat-shock proteins[12]. In the CLU family, extracellular clusterin binds and co-localizes with amyloid deposits. *In vivo* studies have demonstrated that clusterin effectively binds to and prevents the aggregation of soluble forms of Aβ peptides and their sedimentation into senile plaques[10]. However, in the AD brain, this neuroprotective effect may change, depending on the Aβ concentration. When the ratio of clusterin to Aβ (clusterin/Aβ) is high yet within the sub-stochiometric ratio/concentrations, clusterin has an inhibitory effect on plaque formation. But when the ratio is low, clusterin is pro-amyloidogenic and thus is cytotoxic and induces oxidative stress to some extent[13]. An explanation is that at a low ratio, there is enough clusterin to bind to the hydrophobic surfaces of the aggregates, but not enough to inhibit cytotoxicity. But when the clusterin concentration is high, it masks the hydrophobic surfaces of the aggregates, and at the same time there is also enough clusterin to bind to and mask the hydrostatic surfaces of the aggregates, a mechanism evidenced in a previous report[13].

A flaw in the conclusion of this research, nonetheless, may be that it fails to explain the toxic effects of the hydrophobic surfaces of the aggregates. Since both laboratory and clinical studies confirm that the plaque is essential in the pathogenesis of AD, it stands suspicion that the hydrophobic surface must present signs of neurotoxicity. This might be explained by the fact that soluble clusterin, with both hydrophobic and hydrophilic surfaces, is

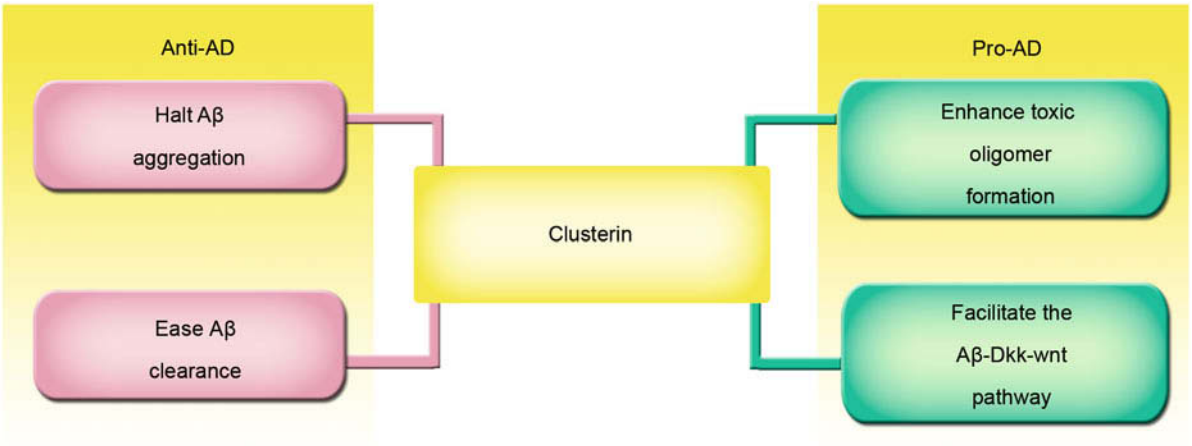


**Fig. 1. The overall effects of clusterin in AD pathogenesis.**

cytotoxic. Although data have shown a disassociation between the mass of senile plaques and the severity or the risk of disease in the AD brain[4], some reports showed a direct correlation between Aβ aggregation and AD severity, and strangely enough, the more Aβ is formed, the more clusterin is expressed, a problem that leads to the second topic: involvement of clusterin in Aβ toxicity[1].

### *Clusterin Mediates the Clearance of Aβ Peptides outside the Brain*

Amyloid toxicity within the brain has been well studied. Under physiological conditions, Aβ is cleared at a rate of 8.3% per hour, showing that the peptides are actively cleared from the brain[14, 15]. Although the results of therapies targeting clusterin, whether increasing or decreasing its formation, remain debatable, some workers have focused the therapeutic aim on the clearance of Aβ from the brain[16]. Transport of Aβ indeed sheds light on the treatment of AD, and this directly involves the protein clusterin.

Aβ levels remain low in healthy individuals and high in AD patients, leading to the hypothesis that the concentration of Aβ is under delicate regulation – its formation and clearanceare balanced in healthy individuals. But in AD, this balance is somehow disrupted. Under normal conditions, Aβ travels from the cerebrospinal fluid to the choroid plexus in a concentration-dependent manner[17], then moves into the bloodstream. However, this gradient pathway only transports 10–15% of the Aβ produced. The bulk of this protein is transported *via* the lipoprotein receptor-related protein (also named megalin), a protein responsible for the transport of a number of lipoproteins in the brain, including apolipoprotein E (ApoE) and clusterin (apolipoprotein J)[17]. Megalin is expressed in the blood vessels of the CNS including the choroid plexus, the blood-brain barrier (BBB) endothelium, and the ependyma. However, when coupled with Aβ, clusterin may undergo elevated transport *via* megalin. The same phenomenon applies to ApoE, a carrier of peptides including Aβ. Megalin is involved in the transport of amyloid through a linkage to clusterin[16, 18].

In fact, in the absence of Aβ, clusterin is transported *via* megalin under physiological conditions. However, since both clusterin and amyloid are elevated in the AD brain, the plaque-forming Aβ, once binds to clusterin, is transported faster than clusterin alone[15]. ELISA shows that Aβ alone does not bind to megalin, but in the presence of clusterin it does[15]. However, evidence has shown that under physiological conditions, megalin is saturated by clusterin, suggesting that this may not be the main pathway for Aβ depletion from the AD brain. However, little is known about the biological behavior of megalin. In an ischemic brain mouse model, the clusterin-amyloid complex is sequestered in the BBB and is prone to exacerbated amyloid aggregation, suggesting a change in the biological behavior of megalin[19]. In another experiment, the guinea pig brain was perfused with clusterin under physiological conditions, and yielded satisfactory results for Aβ transport[19]. This result, however, fails to explain the fact that clusterin saturates megalin under physiological conditions. In spite of this, clusterin-mediated transport of Aβ has little influence on Aβ influx into the brain[16]. These contradictory results clearly demand further studies on the pathological and physiological roles of clusterin and megalin, and more work needs to be done to clarify their mechanism in pathological conditions and especially in AD[19].

### *Megalin-mediated Endocytotic Degradation of the Amyloid-clusterin Complex by Lysosomes*

In addition to the BBB transport of Aβ, megalin is responsible for the endocytosis and subsequent lysosomal degradation of Aβ, which binds with clusterin to form a complex[16, 18]. This was demonstrated in the study of Bell *et al.* showing that degradation is blocked by anti-megalin antibody, and Aβ uptake is upregulated by the co-introduction of clusterin[18]. Interestingly, when vacuoles containing amyloid peptides are exposed to astrocytes that secrete clusterin, the intracellular expression of clusterin increases in parallel[7]. This finding strikingly corresponds with the phenomena discussed above, and the mechanism of clusterin-mediated Aβ neurotoxicity can thus be explained. Also, exposure to Aβ stimulates astrocyte function and this is followed by a dramatic decrease of extracellular clusterin in the culture medium, while the intracellular clusterin simultaneously increases[15]. These findings suggest that there may be an unknown mechanism for the inflow of clusterin during endocytosis[16]. However, as has been discussed, clusterin is expressed in parallel in the process, so more work needs to be done to determine the exact changes of both the intracellular and extracellular

clusterin, because its intracellular or nuclear expression is detrimental to neurons and thus, may be involved in the pathogenesis of AD.

## Clusterin Plays a "Forcing" Role in the Pathogenesis of AD

### *Clusterin "Forces" the Prefibrillar, Soluble Amyloid-beta Peptides into Cytotoxic Oligomers*

Despite the cytoprotective effects of clusterin, it has also been reported that clusterin induces the formation of soluble oligomeric Aβ peptides, but the mechanisms remain unkown. These small diffusible peptides are strongly associated with neurotoxicity. Although the basis of oligomer toxicity remains mysterious, it is known that they bind to the cell surface, in particular trypsin-sensitive domains, and neurons are thus killed, especially in the hippocampus. This toxicity is effective at nanomolar concentrations, when synaptic signal transduction may be blocked. In particular, long-term potentiation, a phenomenon associated with memory-formation, is thought to bear the brunt. Some have proposed that the early memory loss and subsequent catastrophic dementia in AD are caused by oligomers formed by diffusible, non-aggregating Aβ[20]. Therefore clusterin may be regarded as the trigger for the subsequent memory loss because of its actions with oligomers, that is, the extracellular clusterin is cytotoxic when diffusible Aβ is present and forms oligomers.

Although the mechanism of clusterin and Aβ interaction is critical yet elusive in AD pathogenesis, a few studies have targeted oligomeric Aβ peptides formed in the presence of clusterin[21]. It is true that clusterin can act to prevent senile plaque formation, but the primary effect of Aβ in neurotoxicity may not be due to the mass or size of the plaque, as has been shown in epidemiological studies. Rather, in patients predisposed to the clinical signs of AD, soluble, oligomeric forms of Aβ have been detected[21]. These oligomers only form in the presence of "neuroprotective" clusterin yet show signs of elevated toxicity, initially against synapses and later against mature neurons[20]. Although numerous studies have pointed to the toxicity of senile plaques based on their positive correlation with the severity of the disease[22], little is known about the soluble form of Aβ because of its diffusible property. Also, an earlier article (1998) pinpointed the toxicity of Aβ in its diffusible or non-aggregating form and further to the derived diffusible ligands that form oligomeric ligands[10]. These aggregates may result in an early loss of memory and the subsequently catastrophic dementia[10]. Although the toxicity of these non-sedimenting forms of Aβ has been revealed, little is known about the mechanism. Also, an earlier article has pointed out that, since soluble forms of Aβ remain diffusible and are slower to aggregate in the presence of clusterin, they may diffuse within the brain and then exacerbate the pathology of AD[11]. These oligomers are thus described as slowly-sedimenting Aβ peptide complexes.

### *Clusterin Mediates the Aβ-induced Dkk-Wnt-JNK Cytotoxic Pathway*

A more recent study of Aβ and the subsequent intracellular second-messenger pathway shed new light on its relationships[23]. Aβ is known to increase the expression of Dickkopf-1 (Dkk1), an antagonist of the canonical signaling pathway (silencing Dkk1 blocks the further damage produced by Aβ). It has been shown that Aβ increases the intracellular clusterin and decreases its secretion. Further, Aβ induces the expression of several genes through wnt–planar cell-polarity (PCP)–c-Jun-N-terminal kinase (JNK) signaling, and clusterin occurs within this pathway[24].

Another aspect is that a genome-wide association study showed that clusterin may be cytoprotective[10, 11], whereas anoidal wnt/beta-catenin signaling promotes cell adaptability and thus good survival[24]. Therefore, the question was posed as to the neurotoxicity of clusterin, and it was found that Aβ causes neurotoxicity while clusterin plays a substantial role in plaque formation, in that it is needed to trigger the expression of Dkk1, the antagonist of the canonical signaling pathway[24]. Killick *et al.* found that knockdown of clusterin in primary neurons (using a penetrating peptide (Pen1)-coupled siRNA duplex with *CLU*) reduces Aβ toxicity[24]. Moreover, the *CLU* gene has recently been identified as a risk factor for AD[23]. A schematic of the toxicity pathway is shown in Fig. 2.

Although it has been shown that clusterin is neurotoxic *via* activation of the wnt-PCP pathway, leading to the activation of JNK/c-Jun, the fact is that only clusterin outside the neuron can be cytoprotective. Clusterin has been shown to bind soluble Aβ fibrils and prevent their

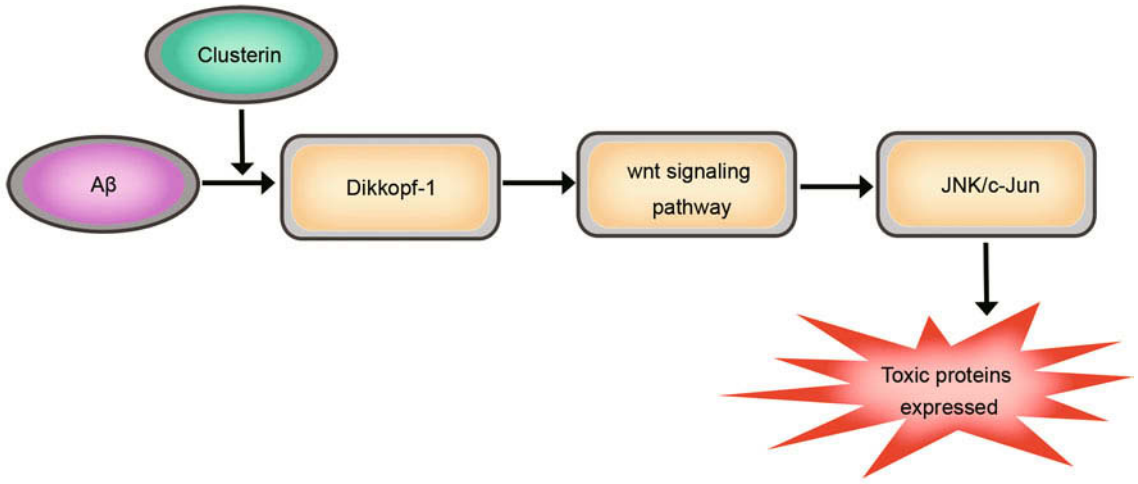


**Fig. 2. The intracellular clusterin-mediated Dik-wnt-JNK pathway to toxicity.**

aggregation and proteolysis[7, 11]; this is consistent with the hypothesis that clusterin remains balanced in and out of the cytoplasm[24]. However, this balance may be damaged by Aβ, causing increased intracellular clusterin which then triggers its cytotoxic pathways. Clusterin and Aβ form a complex that resists proteolysis, thus facilitating their movement to the cerebrospinal fluid and by this mechanism attack other neurons *via* the above pathways.

This mechanism may partially elucidate the means by which Aβ is neurotoxic, but fails to explain why its oligomeric forms are toxic. Clusterin is somehow both protective and debilitating in the pathogenesis of AD. Therefore more work is needed to determine the concentration difference between intracellular and extracellular clusterin, and whether there is a channel to shift the intracellular clusterin to the outside.

## Perspectives: Clusterin as a Therapeutic Target in the Treatment of AD

Therapeutic methods in AD treatment usually target the reduction of formation or the increase of clearance of Aβ[25]. Both seem to have a direct relationship with clusterin.

As increasing numbers of studies have demonstrated that clusterin is a cytoprotective and anti-inflammatory protein, it would be reasonable to consider it as a treatment target for AD (Fig. 3). Clusterin has been shown to be beneficial in mouse models of AD[26]. For example, injection of purified clusterin into a mouse model of cerebral ischemia reduces the formation of fibrillary tangles and plaques[7]. Injection of clusterin has anti-inflammatory and anti-apoptotic effects in the brains of AD mice[27]. Although from the previous discussion clusterin can be associated with the risk and severity of AD, it is worthwhile to make cautious attempt to apply clusterin agents as an alternative in clinical trials. In fact, Nuutinen *et al.* found that therapeutic concentrations of valproic acid, a common anti-epilepsy drug, induces clusterin expression and secretion in human astrocytes[28], which may have cytoprotective effects in the AD brain. Clinical therapeutic approaches targeting AD also find changes in the biological behavior of HDL, LDL, and lipids, and suggest a possible protective role of clusterin in vessels, especially plaque-sedimenting vessels in the brain[29].

However, cytoplasmic clusterin is involved in the Aβ-induced second-messenger pathway to neurotoxicity, and an intracellular clusterin increase, associated with Aβ, may exacerbate neurodegeneration. It is therefore important to test whether artificial induction increases the cytoprotective extracellular clusterin without affecting the intracellular level. Earlier studies in APP transgenic mice revealed that ApoE, a protein similar to clusterin, participates in a variety of processes in which clusterin is active, including the transport of Aβ[30]. Then, a new question arises as to whether ApoE competes with clusterin to bind megalin, or just shares the same receptor yet cooperates with

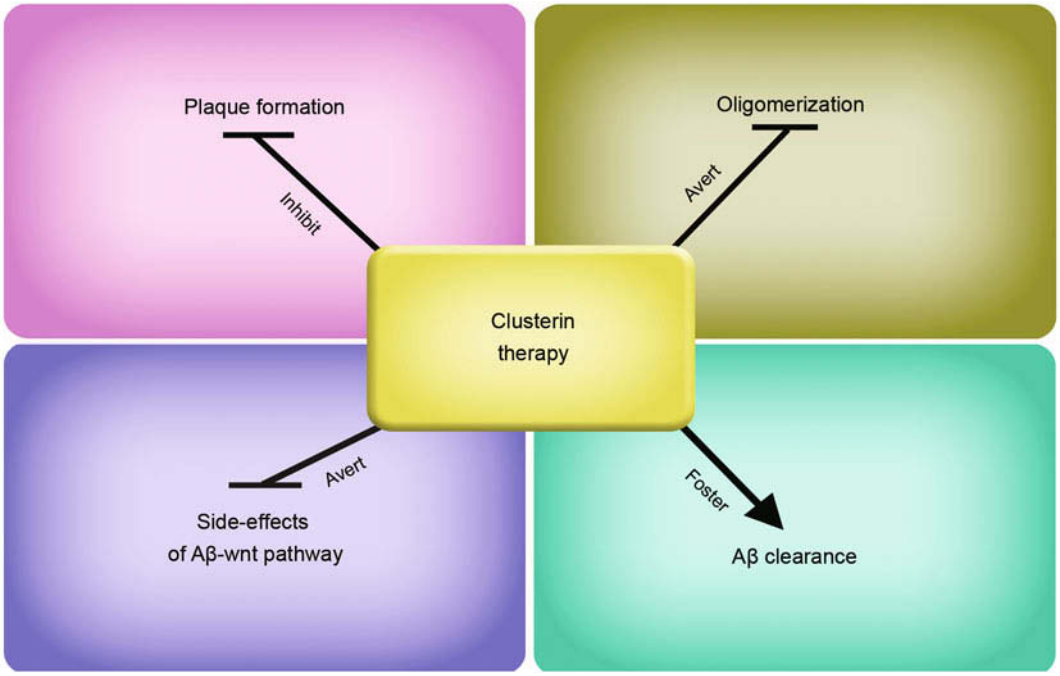


**Fig. 3. Clusterin as a potential therapeutic avenue for AD.**

clusterin in the process of Aβ clearance[30]. Further, since intra- and extracellular imbalances occur in cerebral degenerative diseases, it may be possible to find a way to remove clusterin from cells. In addition, clusterin may be detrimental for other unexpected reasons, including the megalin-mediated Aβ deposition in ischemia[19]. So how can undesired consequences in clusterin trials be avoided? These issues are worth considering in the development of clusterin-targeted drugs.

## Concluding Remarks

Clusterin, a multifunctional chaperone, interferes with neuronal activity at both the protein and gene levels. At the protein level, the secreted form of clusterin binds to and inhibits plaque formation, by preventing soluble forms of Aβ from sedimentation. However, *in vivo* experiments also show that it prevents the proteolytic degradation of Aβ, which leads to the oligomerization of soluble Aβ and triggers even worse cytotoxic effects. In terms of the gene-level intervention by clusterin, little is known about the exact mechanism, but this may provide a new perspective for the involvement of clusterin in the pathogenesis of AD.

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