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Complement C1q/C3-Microglia Axis in Alzheimer's Disease: Molecular Mechanisms, Animal Evidence and Therapeutic Implications

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive memory decline and cognitive impairment. Synapse loss shows the stronger correlation with cognitive dysfunction than amyloid plaques or neurofibrillary tangles. In recent years, the classical complement cascade, especially the C1q and C3 components, has been viewed as a critical driver of pathological synaptic pruning mediated by microglia. Complement proteins tag synapses for developmental refinement, thereby ensuring the proper formation of neural circuits. However, in AD, abnormal reactivation of this pruning program leads to inappropriate elimination of functional synapses. Animal studies demonstrate that genetic knockout or pharmacological inhibition of complement components, including C1q, C3 and their downstream receptors (C3aR, C5aR1), preserves synaptic density and improve behavioral outcomes. These findings make complement signaling as both a mechanistic insight and a therapeutic target. This paper reviews the molecular mechanisms of the C1q/C3-microglia axis, integrates evidence from animal studies, and discusses the clinical potential of complement inhibitors such as anti-C1q antibody, C3 inhibitor and C5aR1 antagonists. This paper also mentions future clinical applications and emphasize synaptic protection as a significant therapy for AD.

Keywords: Alzheimer's disease, complement system, microglia, synapse pruning

1. Introduction

At present, there are approximately 55 million AD patients worldwide, and this number is projected to double every five years, eventually reaching 152 million by 2050. AD burden affects individuals, their families and the economy. Although numerous studies have been conducted on amyloid-β (Aβ) and Tau pathologies, the clinical benefits remain limited, and many patients continue to experience cognitive decline. This suggests the urgent need for new mechanistic insights and novel therapeutic strategies [1].

Synaptic loss is an early and critical event in the pathological progression of AD. Its extent is associated with patients' cognitive dysfunction. It even reflects the severity of cognitive decline more accurately than Aβ plaques and neuronal loss [2]. In the early stages of AD, synaptic dysfunction and loss are the direct causes of impaired memory and learning abilities.

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One emerging molecular driver of synapse loss is the complement system. It is an important component of innate immunity. According to previous studies, the complement system participates in host defense and the regulation of peripheral inflammation. However, complement proteins are now recognized as critical regulators of neural development and plasticity. During postnatal brain maturation, complement component C1q binds to weak or inactive synapses, triggering deposition of C3 fragments. Microglia, the resident immune cells of the brain, recognize these tags via complement receptor 3, leading to selective phagocytosis of tagged synapses [3]. This developmental pruning ensures refinement of neural circuits.

A major breakthrough in the past two decades is the recognition that complement-mediated synaptic pruning, normally critical for developmental refinement of neural circuits, is aberrantly reactivated in AD [3, 4]. Complement components C1q and C3 tag synapses, which enable microglial phagocytosis via receptors such as C3aR and C5aR1. While it is beneficial in early brain development, this mechanism drives pathological synapse elimination in AD. Animal studies demonstrate that blockade of complement signaling prevents synaptic loss and improves behavior. This illustrates that complement signaling represents both a mechanistic insight and a therapeutic target [5-7].

This review provides a comprehensive synthesis of complement biology in synapse pruning, evidence from animal and human studies C1q/C3-microglia signaling to AD, therapeutic strategies targeting complement components and future clinical directions. By integrating mechanistic and clinical perspectives, this review highlights the complement C1q/C3-microglia axis as a promising therapeutic avenue for AD.

2. Molecular mechanisms of the C1q/C3-microglia axis

2.1. Physiological synaptic pruning by the complement system

2.1.1. Developmental function of complement

The complement system is divided into the classical, lectin and alternative pathways. All of them concentrate on the activation of C3. In the developing brain, complement proteins play an essential role in synaptic refinement.

The prior study demonstrates that C1q and C3 localize to immature synapses throughout the postnatal CNS and retina [3]. And the elimination of C1q or C3 results in excess synaptic connections, suggesting defective pruning. Importantly, microglia are identified as the effector cells carrying out phagocytosis of synapses tagged by complement.

Further studies show that microglia actively phagocytose synaptic structures during postnatal development [8]. This process depends on CR3, the microglial receptor for iC3b. Moreover, loss of CR3 disrupts phagocytosis, leading to abnormal synaptic connectivity and altered visual system function.

According to these studies, complement components serve as molecular tags for synapse elimination and microglia participate in this process.

2.1.2. Regulation of pruning

The pruning mediated by complement is regulated by neuronal activity. Synapses with lower activity are tagged with C1q and C3, while active synapses are spared. Astrocytes also contribute by

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secreting transforming growth factor-β (TGF-β), which induces neuronal C1q expression [9]. Therefore, pruning integrates multiple cell types and signaling pathways to improve neural circuits.

2.2. Pathological reactivation of complement in AD

2.2.1. Early complement activation in AD

In AD, complement proteins actively participate in pathogenesis. C1q and C3 deposition at synapses has been detected in multiple AD mouse models, even before obvious formation of amyloid plaque [10].

The previous study demonstrates that C1q deposition is on hippocampal synapses in early plaque stages of AD models [4]. This deposition triggers microglial phagocytosis, leading to synapse loss. Importantly, pharmacological inhibition of complement or microglial phagocytic activity could preserve synaptic density and rescue synaptic function. These findings suggest that microglial pruning depending on complement is reactivated abnormally in AD.

2.2.2. Amyloid-β and complement interactions

Aβ aggregates can induce complement activation. Neurons exposed to Aβ upregulate C1q expression, while Aβ oligomer can directly bind C1q to start the classical pathway. Once activated, disruption of C3 generates opsonins (iC3b) and anaphylatoxins (C3a, C5a), which drive microglial activation and synaptic phagocytosis.

However, a study shows that genetic deletion of C3 in APP/PS1 mice preserve synaptic density and cognitive performance with increasing amyloid plaque burden [11]. This finding indicates that amyloid pathology alone may not cause synapse loss; and it is the complement-mediated response to amyloid that accelerates synaptic dysfunction.

2.2.3. Tau pathology and complement

Tau pathology also activates complement pathways. The study shows that the deletion of C3a receptor (C3aR) reduce Tau aggregation, neuroinflammation, and synapse loss [12]. Meanwhile, another study discovers that blocking C1q with monoclonal antibodies could protect synaptic structures [13]. These results suggest that complement reactivation contributes to synaptopathy.

2.2.4. Astrocyte and microglia interactions

In response to inflammatory cues, astrocytes play a critical role by producing C3. Then these C3 act on microglial C3aR. The study demonstrates that C3 secretion of astrocytes drive microglial activation and synaptic damage, while C3aR inhibition could alleviate these effects [14]. Thus, the complement represents a multicellular network involving neurons, astrocytes, and microglia.

2.2.5. Emerging evidence on aging and proteostasis

A recent study has expanded our understanding of complement function in the adult brain. The researchers discovered that C1q derived from microglia integrates into neuronal ribonucleoprotein complexes. This process will alter mRNA stability and proteostasis [15]. This finding suggests complement activity extends beyond synapse elimination, potentially contributing to neuronal dysfunction in aging and AD

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2.3. Molecular mechanistic integration

2.3.1. Upstream triggers

In AD, there are multiple factors that can trigger complement reactivation. Aβ oligomer induces neuronal C1q expression and activates the classical pathway, while Tau aggregates stimulate astrocytic C3 release and start the C3aR signaling axis. Inflammatory mediators TGF-β further enhance complement gene expression. In addition, damage-associated molecular patterns (DAMPs) are released from damaged or dying cells. This provides additional danger signals that converge on complement activation. In conclusion, these diverse upstream triggers create a permissive environment for abnormal complement activity in the AD brain.

2.3.2. Complement cascade dynamics

Once C1q binds to synaptic or aggregated structures, the C1r/s complex disrupts C4 and C2 to form the C3 convertase (C4b2a). This enzyme disrupts C3 into C3b/iC3b, which opsonizes synapses. Microglial CR3 recognize these tags and then execute phagocytosis. Parallel disruption generates C3a and C5a that bind C3aR and C5aR1, promoting microglial activation and pro-inflammatory cytokine release [16].

2.3.3. A model in systemic level

AD pathology can be viewed as an inappropriate recurrence of developmental pruning, with pathological enlargement by Aβ, Tau and neuroinflammatory signals. Complement acts as a center connecting misfolded proteins, microglial activation and synaptic degeneration.

3. Evidence from human and animal studies

Postmortem AD brains show increased expression of C1q and C3, as well as downstream terminal pathway components. Complement proteins are found in cerebrospinal fluid and plasma, correlating with disease severity [17].

Evidence from multiple AD mouse models demonstrates complement-mediated synaptic loss and they are listed in Table 1 [5, 6, 18-21].

Table 1. Evidence from animal studies

Model	Intervention	Main Results	Conclusion
AD mice	Analysis of C1q-dependent synapse elimination (astrocyte/microglia)	Excitatory vs. inhibitory synapse profiling; phagocytosis evidence	C1q-dependent cross-cellular pruning contributes to early synapse loss in AD
Arctic48, Tg2576	C5aR1 knockout/ PMX205 antagonist	VGlut1/synapse density; LTP	Inhibiting C5aR1 rescues synapses and LTP
Arctic48	PMX205	Single-cell transcriptomics; pathology; behavior	C5aR1 antagonism reduces inflammatory polarization and improves memory
AppNL-G-F	Anti-C7 antibody / genetic blockade	MAC deposition; dendritic spine density	Blocking MAC preserves spines and modulates synapse loss near plaques
AD mice	Blocking mGluR5-C1q tagging	Synapse density; behavior	Preventing upstream tagging reverses synapse loss

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Table 1. (continued)

P301S Tau	C3aR antagonist	Tau pathology; synapse density; cognition	Blocking C3aR alleviates tau pathology and improves synaptic and behavioral outcomes

Complement inhibition improves electrophysiological measures (LTP), calcium imaging of neuronal activity and behavioral tests such as Morris water maze, Y-maze and novel object recognition [22]. These data demonstrate a relationship between complement activity and synaptic pathology.

4. Therapeutic targeting of complement

Therapeutic strategies targeting complement in AD span multiple levels from upstream initiation to downstream effectors, as shown in Table 2 below [6, 7, 18, 21-26].

ANX005 is a humanized monoclonal antibody against C1q and blocks initiation of the classical pathway. It has shown safety and tolerability in Phase I human trials, with preclinical studies supporting its ability to prevent early synaptic loss [22, 23].

At the level of C3, pegcetacoplan inhibits cleavage and has proven efficacy in other diseases, although its application to AD faces challenges of blood brain barrier penetration and potential broad immunosuppression [24, 25].

Small-molecule antagonists of C3aR and C5aR1, such as SB290157 and PMX205, demonstrate preclinical efficacy, with PMX205 in particular reducing inflammation, rescuing synapses and improving cognition across multiple AD models [7, 18, 21, 26].

Terminal complement inhibitors such as anti-C7 antibodies prevent formation of the membrane attack complex (MAC), thus preserving dendritic spine density. However, inhibition of terminal complement may carry an increased risk of infection [6].

Table 2. Therapeutic agents targeting complement in AD

Target	Representative Agent	Type/ Development Stage	Evidence in AD	Risks / Considerations
C1q	ANX005	Humanized antibody; early clinical trials (multiple indications); Phase 1 RCT safety data (2025)	Theoretically blocks initiation of the classical pathway; animal evidence; AD specific clinical validation pending	Infection risk, BBB delivery challenges, optimal dosing window undefined
C3	Pegcetacoplan	Antibody fragment; approved for other diseases; Phase II in progress	Upstream blockade with broad complement inhibition; cross-disease safety known; direct AD evidence limited	Potential interference with physiological repair; BBB penetration remains a challenge
C3aR	SB290157	Small molecule; preclinical tool compound	Some models show improved synaptic and behavioral outcomes, but issues with C5aR2 partial agonism and specificity	Limited translational potential; requires next-generation compounds
C5aR1	PMX205	Cyclic peptide; multiple preclinical studies	Reduces inflammation and plaque-associated pathology; rescues synapses, LTP, and cognition	Long-term safety, dosing, and clinical translation need further evaluation

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Table 2. (continued)

C7 / MAC	Anti-C7 antibody	Experimental; research-stage	Prevents MAC formation; alleviates spine loss near plaques	Risk of systemic complement suppression; infection concerns

5. Discussion

Over the past two decades, clinical trials targeting Aβ or Tau alone have resulted in limited clinical benefit. Synaptic pruning mediated by complement interacts with Aβ and Tau pathology, which can trigger complement activation. While complement signaling in turn aggravates neuroinflammation and accelerates protein aggregation and spread [4, 17, 27].

Therefore, a combination approach that blocks complement activity and targets Aβ or Tau could generate synergistic effects. Complement inhibition would protect functional synapses from abnormal pruning, while anti-Aβ or anti-Tau therapies would reduce the upstream pathological triggers.

About the future clinical applications, during early stage intervention, researchers could apply complement blockade in AD patients, prioritizing synaptic preservation as a primary target. Moreover, researchers could apply a combination therapy. They combine complement inhibitors with anti-Aβ or anti-tau drugs to reduce pathological protein load and preserve synaptic integrity. Also, safety monitoring is essential. It is necessary to implement long-term follow-up for infection risk and systemic immune suppression, as well as explore low-dose combination strategies.

6. Conclusion

AD remains an area of urgent unmet medical need. Synapse loss is viewed as the strongest pathological correlate of cognitive decline. The complement C1q/C3-microglia axis are designed for developmental synaptic refinement, but pathologically reactivated in AD, leading to excessive synaptic pruning and network dysfunction.

Animal models provide evidence that genetic deletion or pharmacological inhibition of complement components protects synapses and improves cognition. There are several candidate therapeutics, some of which are in or nearing clinical trials.

In the future, therapeutic targeting of complement may not act alone but will be a part of the combinatorial therapy targeting Aβ, Tau, and inflammation.

By regarding AD as a disorder characterized by abnormal synaptic elimination, the complement system emerges not only as a mechanistic driver but also as a key therapeutic target.

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