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The contact activation system and vascular factors as alternative targets for Alzheimer's disease therapy

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease, affecting millions of people worldwide. Extracellular beta-amyloid (Aβ) plaques and neurofibrillary tau tangles are classical hallmarks of AD pathology and thus are the prime targets for AD therapeutics. However, approaches to slow or stop AD progression and dementia by reducing Aβ production, neutralizing toxic Aβ aggregates, or inhibiting tau aggregation have been largely unsuccessful in clinical trials. The contribution of dysregulated vascular components and inflammation is evident in AD pathology. Vascular changes are detectable early in AD progression, so treatment of vascular defects along with anti-Aβ/tau therapy could be a successful combination therapeutic strategy for this disease. Here, we explain how vascular dysfunction mechanistically contributes to thrombosis as well as inflammation and neurodegeneration in AD pathogenesis. This review provides evidence that addressing vascular dysfunction in people with AD could be a promising therapeutic strategy.

KEYWORDS
Alzheimer's disease, beta-amyloid, blood-brain barrier, coagulation factors, contact system, dementia, fibrinogen

Essentials

- Crosstalk between beta-amyloid (Aβ) and blood proteins contributes to Alzheimer's disease (AD).
- Contact system activation correlates with memory impairment in AD and mild cognitive impairment.
- Blood clots can block blood flow and cause inflammation and cell death, which contribute to AD.
- Preventing contact system activation or resistant blood clots are promising therapies for AD.

1 | INTRODUCTION

Alzheimer's disease (AD) is the most prevalent form of neurodegenerative dementia affecting nearly 30 million people worldwide.[1,2] Though beta-amyloid (Aβ) plaques and oligomers as well as aggregated phosphorylated tau tangles are the most studied therapeutic targets for AD,[3] it remains unclear how these proteinaceous inclusions lead to neuronal death and cognitive impairment. Aβ plaques are composed of aggregated Aβ peptides that are generated from the amyloid precursor protein (APP) upon a series of enzymatic cleavages. Aβ peptides can

be of various lengths, ranging from 38 to 49 amino acids in length (ie, Aβ38-Aβ49), depending on the type of APP cleavage.[4-6] Among these different lengths, Aβ42 and Aβ43 aggregates are the most neurotoxic and pathogenic.[5,6] However, approaches to prevent or slow neurodegeneration and dementia by reducing Aβ production, neutralizing toxic Aβ aggregates, or inhibiting tau aggregation have been largely unsuccessful.[7-10] There are several other factors that may play a role in neurodegeneration and cognitive decline in AD,[11-19] however, which should also be considered when defining new targets and developing effective AD therapeutics.

AD is recognized as a multifactorial disease, where numerous components, including cerebrovascular dysfunction and inflammation, drive disease pathology.[16,20,21] Cerebrovascular abnormalities, such as decreased blood flow, hemorrhage, microinfarcts, small-vessel disease, dysregulated plasma contact system, and white-matter hyperintensities, are observed in >50% of people with AD.[13,22-31] In a large data-driven study of people with late-onset AD (LOAD), imaging techniques were used to analyze brain Aβ aggregates, cerebral glucose metabolism, cerebral blood flow, and functional activity/brain structural patterns in relation to disease progression. Temporal ordering of these abnormalities was assigned using trajectory models of aging. This analysis revealed that dysregulated cerebral blood flow occurs before Aβ deposition in people with LOAD.[16] Similarly, white matter hyperintensities are an early pathological feature observed in people with early-onset AD (EOAD).[30]

The most clear-cut and classic example of crosstalk between neurodegeneration and vascular damage in AD is cerebral amyloid angiopathy (CAA). Between 80% and 95% of AD patients develop CAA, a condition characterized by deposition of Aβ aggregates in and around cerebral blood vessels.[3,32] It results in damage to endothelial cells and the blood vessel wall, which can lead to a loss in blood-brain barrier (BBB) integrity[33,34] and inflammatory activity. In animal models of CAA, Aβ can trigger structural as well as functional damage in smooth muscle cells, pericytes, and endothelial cells.[17,35-37] CAA also leads to production of superoxide radicals,[36] which impairs the perivascular drainage system, an Aβ clearance pathway, in both AD mouse models and human patients,[32,38-40] thereby augmenting Aβ-driven damage within the brain. Thus, CAA is a major contributor to cerebrovascular dysfunction, which can lead to microhemorrhage, vessel occlusion, loss of smooth muscle cells, and disruption of vasoactivity in AD.[32,41,42]

Impaired BBB integrity can lead to abnormal levels of Aβ in the plasma as well as extravasation of blood proteins, such as fibrin(ogen), into the brain. In the circulation, Aβ can activate the plasma contact system, which induces coagulation and inflammation.[13,43-46] Extravasation of fibrin(ogen) into the brain can lead to its persistent accumulation as well as neuroinflammation. Below, we provide detailed evidence of the role of vascular dysfunction in AD pathogenesis. Table 1 summarizes the human and animal model evidence for vascular dysfunction and contact system activation in AD pathophysiology discussed herein. This review emphasizes the importance of better understanding the mechanistic link between Aβ and components of the contact system and the vasculature in AD, as it could provide alternative therapeutic strategies for many people with AD.

2 | Aβ ACTIVATES FACTOR XII-DRIVEN INTRINSIC COAGULATION

The plasma contact system is comprised of a group of plasma proteins, including factor XII (FXII), factor XI (FXI), prekallikrein (PK), and high molecular weight kininogen (HK). The role of the plasma contact system is to (i) promote thrombin generation and fibrin clotting via activated FXI (FXIa) and (ii) induce inflammation upon cleavage of HK and release of bradykinin (Figure 1). When FXII is activated (FXIIa) by its binding to a negatively charged surface, both of these pathways can be triggered.[47] Though it is primarily produced in the liver and found in the blood,[48] FXII has been found in the brain and even localized with Aβ plaques in the postmortem brain tissue of people with AD.[49,50]

Aβ42 can bind to and activate FXII and thus trigger the contact system.[43-46] Addition of Aβ42 to normal human plasma accelerates the generation of FXIIa.[45] To trigger intrinsic clotting, FXIIa cleaves FXI. This activated coagulation factor, FXIa, sets off a series of activation events that eventually result in fibrin clot formation.[51] The level of FXI is significantly lower in the plasma of people with AD compared to age-matched nondemented individuals,[43] suggesting increased FXIa levels and increased activation of the intrinsic clotting system in AD. Furthermore, using both human plasma and purified protein systems, it has been shown that Aβ can promote thrombin generation required for fibrin clot formation.[43] Additionally, the procoagulant effect of Aβ42 is specifically via FXII activation since Aβ42 has no effect on thrombin generation in FXII-deficient human plasma.[43] Moreover, antibody-mediated blocking of FXII activation abolishes Aβ42-induced thrombin generation in plasma.[43] Increased FXIIa levels are also reported in the plasma of people with AD.[13] Together, these findings support the hypothesis that Aβ42-induced FXIIa generation promotes fibrin production. These fibrin deposits, which aggregate with Aβ and are resistant to degradation (discussed in detail below), may not only increase the number of occlusive thrombi in vessels but could also drive inflammation associated with AD pathology.[52-56] Therefore, blocking Aβ42-induced FXII activation could be a therapeutic strategy to reduce vascular pathologies in AD.

AD patient plasma also often shows prolonged activated partial thromboplastin time (aPTT), a test that measures intrinsic clotting, compared to age-matched healthy control plasma.[57] Prolonged aPTT correlates with cognitive impairment in people with AD,[57] suggesting that a coagulation defect could affect memory. Extrinsic clotting is not significantly altered in these patients with AD,[57] indicating that the issue lies within the intrinsic clotting pathway. Moreover, analysis of plasma from an AD mouse model (5XFAD) that overexpresses human APP also shows significantly prolonged intrinsic clotting time compared to that of their wild-type littermates.[57] It should be noted that although Aβ42 is a procoagulant,[58] its precursor APP possesses an anticoagulant property.[59,60] Furthermore, AD is a heterogeneous disease, and it is possible that depletion of coagulation factors over time due to a continuously activated contact system or the presence of some other protease inhibitors could also affect intrinsic clotting in AD.

3 | Aβ TRIGGERS INFLAMMATION THROUGH FXII-DRIVEN PK ACTIVATION AND BRADYKININ GENERATION

FXII-driven contact system activation not only produces fibrin clots but also generates proinflammatory bradykinin.[61] FXIIa cleaves PK to generate kallikrein, which in turn cleaves HK.[51,61] The proinflammatory molecule, bradykinin, is liberated upon HK cleavage (Figure 1). In addition to having increased FXIIa,[13] AD patient plasma also shows increased kallikrein-kinin activity[13,43] that leads to inflammation. It has been suggested that kallikrein could drive hemorrhagic conditions,[62,63] and therefore AD patients with increased kallikrein activity could be at greater risk of cerebral hemorrhage. Furthermore, levels of full-length/intact HK are decreased, while levels of cleaved HK (cHK) [13,64] and bradykinin are increased in the plasma of people with AD compared to that of controls.[65] This increased bradykinin not only induces inflammation but also can lead to edema, vasodilation, and increased BBB permeability.[61,66-68] Consistently, an impaired BBB is often observed in people with AD.[17] Furthermore, the addition of Aβ42 to human plasma from nondemented individuals shows significantly higher levels of bradykinin than untreated plasma.[12,65] It has also been shown that AD mice that overexpress Aβ have increased plasma cHK levels.[69] Additionally, it has been reported that intravenous injection of Aβ42 increases HK cleavage and kallikrein activity in wild-type mouse plasma.[13] The connection between a dysregulated contact system and AD is further supported by findings that people with AD have increased cHK in their cerebrospinal fluid (CSF).[70] These findings suggest that both the thrombotic (via FXI) and inflammatory (via HK cleavage and bradykinin) arms of the contact system are activated in AD.

Vascular abnormalities alone can lead to memory impairment.[71] However, the coexistence of AD and cerebrovascular pathology could exert synergistic effects on brain and memory function. If the peripheral contact activation system contributes to AD progression and pathology, there should be a correlation between these changes and memory impairment and/or AD pathologies.

TABLE 1 Human and animal model evidence of vascular dysfunction and contact system activation in AD

Symptom/Phenotype		Reference
Patients with AD		
Vascular Pathology	Vascular dysfunction is an early pathology.	[16,30]
	CAA is observed in 80%-95% of patients.	[3,32]
	Impaired BBB integrity and extravasation of fibrin(ogen) into the brain parenchyma is observed.	[17,33,34,79]
	Dutch and Iowa APP mutations increase cerebral fibrin deposits.	[55]
	Patient plasma exhibits increased aPTT.	[57]
Contact System Activation	Aβ42 activates FXII to trigger the contact system.	[43–46]
	FXII is found in Aβ plaques in postmortem brain tissue.	[50]
	FXIIa, cHK, and bradykinin levels are increased in patient plasma.	[13,64,65]
	Kallikrein activity is increased in patient plasma.	[13]
	Intact HK levels are decreased in patient plasma.	[13]
	FXI levels are decreased in patient plasma.	[43]
	cHK levels are increased in patient CSF.	[70]
	Memory impairment correlates with vascular deficits and cHK levels.	[64,65,71]
Animal models		
Vascular Pathology	Anticoagulation treatment delays AD pathogenesis.	[54]
	Fibrin(ogen) is associated with abnormal thrombosis, fibrinolysis, inflammation, neuronal damage, and cognitive impairment in AD.	[15,33,52,79]
	BBB integrity is impaired in AD.	[17,54]
	Cerebrovascular lesions induce Aβ deposition in AD.	[82,83]
Contact System Activation	Aβ42 activates FXII to trigger the contact system.	[13]
	Contact system activation is associated with BBB damage.	[62,63,66]
	Inhibition of contact system activation ameliorates AD pathology and cognitive decline.	[69]

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; APP, amyloid precursor protein; aPTT, activated partial thromboplastin time; BBB, blood-brain barrier; CAA, cerebral amyloid angiopathy; cHK, cleaved high molecular weight kininogen; CSF, cerebrospinal fluid; FXI, factor XI; FXII, factor XII; FXIIa, activated factor XII; HK, high molecular weight kininogen.

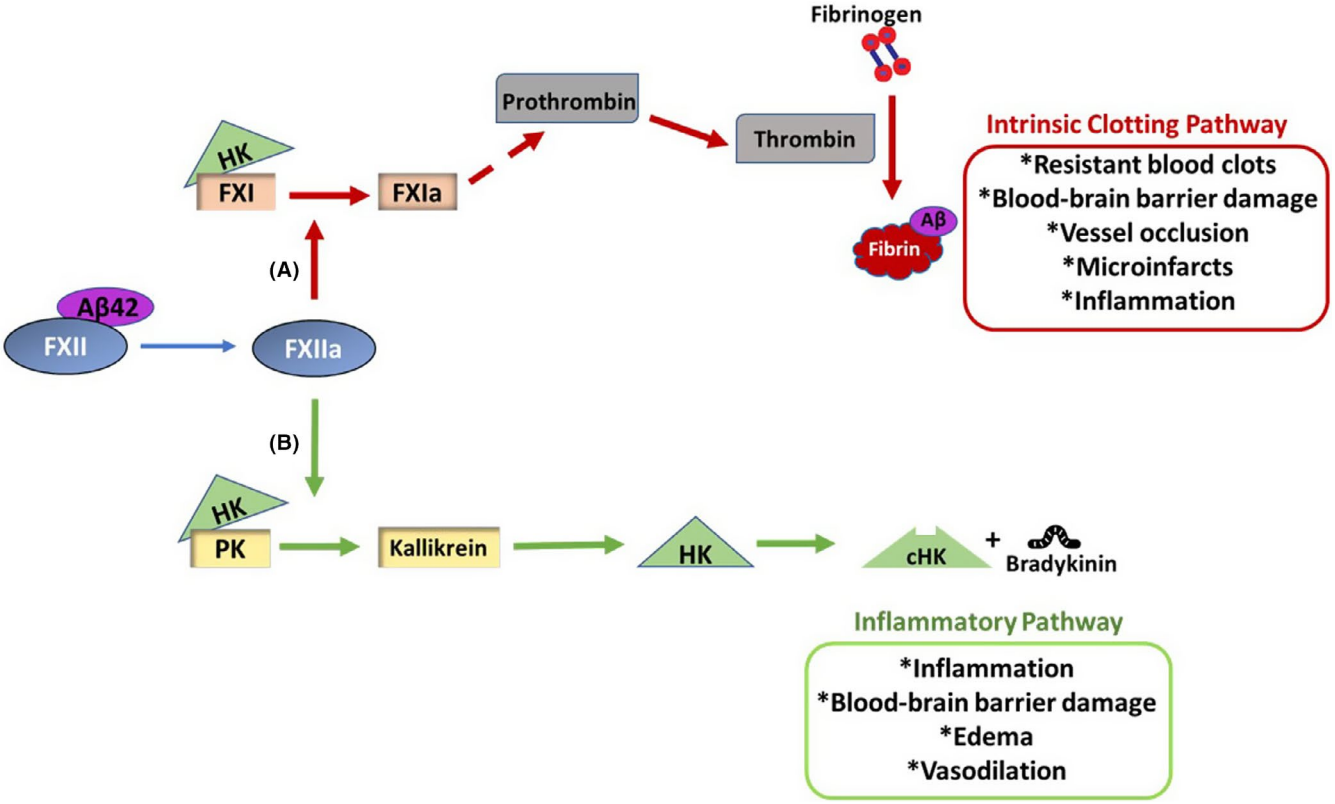

FIGURE 1 Activation of the contact system induces thrombotic and inflammatory pathways in Alzheimer's disease (AD). Activation of coagulation factor XII (FXII) by Aβ42 can trigger the intrinsic clotting pathway as well as an inflammatory pathway. A, Intrinsic clotting occurs when activated FXII (FXIIa) activates factor XI (FXI) to FXIa. Eventually, prothrombin is cleaved to thrombin, which cleaves fibrinogen into fibrin. Aβ42 can interact with fibrinogen, and fibrin clots formed in the presence of Aβ42 are resistant to degradation. These resistant blood clots can increase the incidence of vessel occlusion, leading to microinfarcts, blood-brain barrier (BBB) damage, and inflammation. Extravasated fibrin(ogen) can also induce cerebral inflammation. B, FXIIa cleaves prekallikrein (PK) to generate kallikrein. The proinflammatory peptide, bradykinin, is released upon high molecular weight kininogen (HK) cleavage by kallikrein. Bradykinin can induce vasodilation, edema, inflammation, and BBB damage. HK is essential for normal operation of both thrombotic and inflammatory pathways of the contact system, as PK and FXI need to bind HK to be activated by FXIIa

The level of CSF Aβ42 is a well-established marker of AD as the amount of CSF Aβ42 decreases with AD progression.[72-74] The concentration of plasma HK is positively correlated with the level of CSF Aβ42; as HK levels decrease in plasma, levels of Aβ42 decrease in the CSF.[13] Additionally, the level of plasma cHK is significantly correlated with memory test scores in AD patients.[64] For example, as cHK levels increase, indicating contact system activation, cognitive status decreases as defined by the Mini-Mental State Examination (MMSE) or clinical dementia rating.[64] Moreover, increased plasma bradykinin level is associated with memory impairment in people with AD.[65] Plasma cHK levels also positively correlate with Consortium to Establish a Registry for Alzheimer's Disease scores, which define the extent of Aβ plaque pathology at postmortem analysis.[64,75] As these associations were obtained in a cross-sectional analysis, a longitudinal analysis of contact activation in AD and its association with memory decline needs to be performed.

These findings suggest that a dysregulated plasma contact system could be a reliable predictor of cerebral pathology and memory impairment in AD. However, contact activation is not specific to AD, and therefore it should be used along with established fluid biomarkers (CSF Aβ42, phosphorylated tau), imaging modalities (positron emission tomography, magnetic resonance imaging), and/or memory tests [76] for diagnosing AD patients with vascular dysfunction.

4 | DYSREGULATED CONTACT SYSTEM: AN EARLY PREDICTOR OF COGNITIVE DECLINE

It has been suggested that subtle losses in cognitive function may be an early sign of AD development.[76,77] Mild cognitive impairment (MCI) refers to the intermediary stage between the cognitive decline associated with normal aging and mild dementia.[72,76] People with MCI show only slight cognitive defects, which do not significantly affect their daily functioning.[72,76,77] However, people with MCI are at a higher risk of developing AD compared to cognitively normal individuals. Specifically, each year 10% to 15% of people with MCI will develop AD, while only 1% to 2% of cognitively normal people will develop AD.[72,76] It was recently reported that the contact system is

also dysregulated in people with MCI. For example, kallikrein activity and levels of cHK and bradykinin are significantly higher in the plasma of people with MCI than age-matched cognitively normal individuals.[77] Moreover, these changes are more pronounced in MCI patients enorr with impaired short-term recall memory.[77] A significant inverse correlation is found between short-term recall scores and kallikrein activity or level of cHK in plasma.[77] Because short-term recall memory is one of the earliest cognitive changes observed in people with AD, its correlation with increased contact system activation suggests that evidence of contact activation could predict cognitive changes and AD progression.

5 | FIBRINOGEN: A SIGNIFICANT CONTRIBUTOR TO AD PATHOGENESIS

In the circulatory system, conversion of the blood protein fibrinogen into a fibrin clot by thrombin is essential to stop or prevent bleeding.[78] However, a damaged BBB allows for extravasation of fibrin(ogen) and other blood proteins into the brain parenchyma, where it can induce inflammation and neuronal damage.[15,33,54] Brains of AD mouse models and people with AD often exhibit impaired BBB integrity,[17] which can be exacerbated by coexistence of vascular disease or cerebrovascular dysfunction.[17] Extravasation of fibrinogen into the brain parenchyma also leads to the formation of fibrin deposits.[79] The extent of fibrin deposition positively correlates with neurodegeneration, suggesting that the accumulation of fibrin(ogen) directly affects cognitive function.[79]

In cerebral blood vessels, fibrin(ogen) can interact directly with Aβ, which leads to degradation-resistant blood clots, vessel occlusion, and subsequently ischemic conditions and neuronal death.[52-56] The inflammatory response caused by vessel occlusion can also increase the production of Aβ and lead to greater Aβ plaque deposition, which has been shown in animal models.[80-83] Accordingly, it was recently shown that long-term treatment with dabigatran, a direct thrombin inhibitor and anticoagulant,[84] prevents occlusive thrombi formation in an AD mouse model.[54] This reduction of occlusive thrombi/fibrin deposits also prevents neuroinflammation, BBB damage, and cognitive impairment in an AD mouse model.[54] Similar correlations are observed when fibrinogen itself is pharmacologically or genetically reduced in AD mouse models, as these strategies result in less neuronal death, synaptic dysfunction, and amyloid pathology as well as improved cognition compared to AD control mice.[54,79] Anticoagulant treatment has been found to slow cognitive dysfunction in people with dementia.[85,86] Oral anticoagulant treatment was also associated with a lower risk of cognitive decline in people with atrial fibrillation.[87] Despite these findings, anticoagulant therapy is controversial since elderly patients are at higher risk of bleeding.[88]

Fibrinogen can directly drive disease pathology via activating microglial inflammatory responses and increasing the generation of reactive oxygen species.[15] Fibrinogen-mediated microglial activation via CD11b receptor binding leads to cognitive deficits in an AD mouse model through elimination of dendritic spines, tiny extensions on neurons that harbor synaptic receptors of excitatory connections in the brain and are critical for memory and cognitive function.[89] Genetic disruption of the fibrinogen domain that binds to and activates the CD11b receptor on microglia results in reduced neurodegeneration and memory impairment in AD mice.[15] Cerebral injection of fibrinogen itself can induce neuronal injury such as spine elimination and dendritic loss,[15] and in the presence of Aβ, the deleterious effect of fibrinogen is much more pronounced.[15] Aβ42 can directly interact with fibrinogen and reduce its clearance.[52,53,56] Microscopic analysis of fibrin clots formed in the presence of Aβ42 demonstrates significant structural abnormalities.[52] Radiographic crystallography analysis revealed that the central region of Aβ binds to the outer D domain of fibrinogen, which alters its structure and blocks its cleavage by plasmin.[56] This Aβ42-induced structural change could also be responsible for increased levels of a plasmin-resistant fibrin degradation fragment.[56] These results suggest that both vascular and extravasated fibrin(ogen) could synergize the Aβ-induced pathology in AD. In line with these results, a prospective population-based study that measured plasma fibrinogen levels in 2835 individuals longitudinally found that high fibrinogen levels were associated with increased risk of AD and dementia.[90] Furthermore, a meta-analysis involving 3649 patients with dementia had significantly higher plasma fibrinogen levels than nondemented individuals.[91]

It is important to note that some Aβ mutations that are associated with EOAD, particularly the Dutch (E22Q) and Iowa (D23 N) mutations, increase Aβ's toxicity as well as its vascular deposition.[55,92-97] More specifically, the Dutch and Iowa Aβ mutations have a 50-fold higher binding affinity for fibrinogen.[55] It has been suggested that this stronger affinity leads to greater structural clot abnormalities and further delayed fibrinolysis compared to wild-type Aβ.[55] Furthermore, AD patients who harbor the Dutch or Iowa mutations have significantly more fibrin deposits and Aβ-fibrin(ogen) codeposits in postmortem brain tissue compared to patients without these mutations.[55] Taken together, these findings reveal that the Aβ-fibrin(ogen) interaction is instrumental in driving cerebrovascular pathologies and cognitive decline in AD. Thus, inhibiting the interaction between fibrinogen and Aβ could be a promising therapeutic strategy in AD.

6 | NOVEL THERAPEUTIC STRATEGIES FOR AD

6.1 | Inhibiting the plasma contact system

If a dysregulated contact system is contributing to AD pathology, blocking or inhibiting this system should show beneficial effects in AD. It has been shown that peripheral reduction of FXII (by FXII antisense oligonucleotide, FXII-ASO) in an AD mouse model not only prevents contact activation in plasma, but also significantly reduces microglial and astrocytic activation in the brain parenchyma.[69] Furthermore, AD mice treated with FXII-ASO show reduced

neuronal loss and less extravasated fibrin(ogen) compared to control AD mice. More importantly, FXII-ASO treated AD mice perform significantly better in cognitive tests compared to vehicle-treated AD mice.[69] Collectively, these results suggest that dysregulation of the contact system contributes to AD pathology and memory impairment and that inhibiting this system could prove beneficial in AD. Further studies are needed to establish whether AD pathology initially triggers the contact system or an activated contact system exacerbates AD progression.

Contact system activation could also be a significant contributor to the inflammation observed in AD, both via fibrin(ogen) and bradykinin. Directly blocking HK cleavage to prevent bradykinin generation is another promising strategy to reduce the contact system-driven inflammatory response in AD. We have recently shown that a monoclonal anti-HK antibody, 3E8, can block Aβ42-induced HK cleavage and bradykinin generation in human plasma.[98] Also, an oral PK-targeting therapy, another promising approach for blocking contact system activation, is undergoing clinical trial testing.[99,100] It should be noted that people who lack contact system components (FXII-, HK-, or PK-deficient individuals) are not prone to bleeding,[101-108] since intrinsic clotting is not the main coagulation pathway in the body.[61,109,110] Therefore, blocking the contact system in patients would not increase the risk of hemorrhage. The 3E8 anti-HK antibody or other contact system inhibitors could be effective at ameliorating not only vascular and inflammatory pathologies in AD but also other diseases and vascular pathologies in which the contact system is also dysregulated, such as hereditary angioedema,[111] sickle cell anemia,[112] lupus,[113] rheumatoid arthritis,[114] multiple sclerosis–associated neuroinflammation,[66,115] infection (sepsis/endotoxemia),[116,117] and colitis.[118]

6.2 | Blocking the Aβ-fibrinogen interaction

Treatment of AD mice with RU-505, a small molecule that inhibits the Aβ42-fibrinogen interaction, leads to reduced cerebral inflammation, less vascular Aβ deposition, and improved cognitive function compared to untreated AD mice.[14] The inhibition of the Aβ-fibrinogen interaction also prevents the Aβ-induced structural abnormalities of fibrin clots and the altered thrombosis and fibrinolysis observed in AD mice.[14] These findings suggest that blocking the Aβ-fibrinogen interaction not only reduces thrombotic abnormalities but also lessens neuroinflammation, cognitive impairment, and other AD pathologies. Moreover, some of the Aβ aggregation inhibitors simultaneously inhibit the Aβ-fibrinogen interaction, and their inhibitory activity could be further increased by making chemical modifications.[119] Collectively, these data suggest that the interaction between vascular fibrinogen and pathogenic Aβ could be extremely detrimental and that minimizing this crosstalk could be beneficial in AD.

7 | CONCLUSION AND FUTURE DIRECTIONS

AD is a multifactorial condition in which various pathways may synergize to produce the deleterious effects on brain function. Therefore, targeting various pathways in a combination therapy could maximize the beneficial outcome in AD treatment. Treating vascular dysregulation in AD could also improve brain function and memory along with minimizing vascular defects. We have provided evidence to support a mechanistic link between vascular components and AD pathologies. The crosstalk between pathogenic Aβ and circulatory fibrinogen as well as between Aβ and components of contact or intrinsic pathway (FXII, HK, PK) could dramatically affect the numerous pathologies found in people with AD. Targeting the contact system and amyloid pathology together or targeting contact system activation alone could improve cognitive function in people with AD with vascular deficits. Moreover, a monoclonal anti-HK antibody could be a promising drug candidate to treat thrombotic and inflammatory conditions in AD. Markers of contact activation—cHK, kallikrein activity, FXIIa, delayed intrinsic clotting (aPTT)—could be used to quickly diagnose people with MCI and AD with a vascular component to their pathology, and preventive or therapeutic care could be provided before severe AD onset.

RELATIONSHIP DISCLOSURE

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AUTHOR CONTRIBUTIONS

PKS reviewed the literature and wrote the first draft of the review; AB, ZLC, SS, and EHN edited the review and designed the figure and table; EHN supervised the process.

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