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Alzheimer's disease and vascular biology – A focus on the procoagulant state

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Alzheimer's disease (AD) is characterized by a multifactorial pathophysiology. Beyond its classical hallmarks, growing evidence highlights vascular contributions, including hemostatic dysregulation and a prothrombotic state in AD. This review focuses on recent findings concerning two key blood clot components–fibrin(ogen) and platelets–and their roles in AD pathology, including fibrinogen's abnormal accumulation in the AD brain, its interaction with amyloid-β, together with the associated impacts on clot stability, vascular occlusion, and neuroinflammation; and the potential switch of platelets along the AD continuum from protective to deleterious. This review provides an update on the interplay between vascular dysfunction and AD, underscoring the need for comprehensive integrative research to address AD's complexity and advocating for personalized approaches to tackle this multifaceted disorder.

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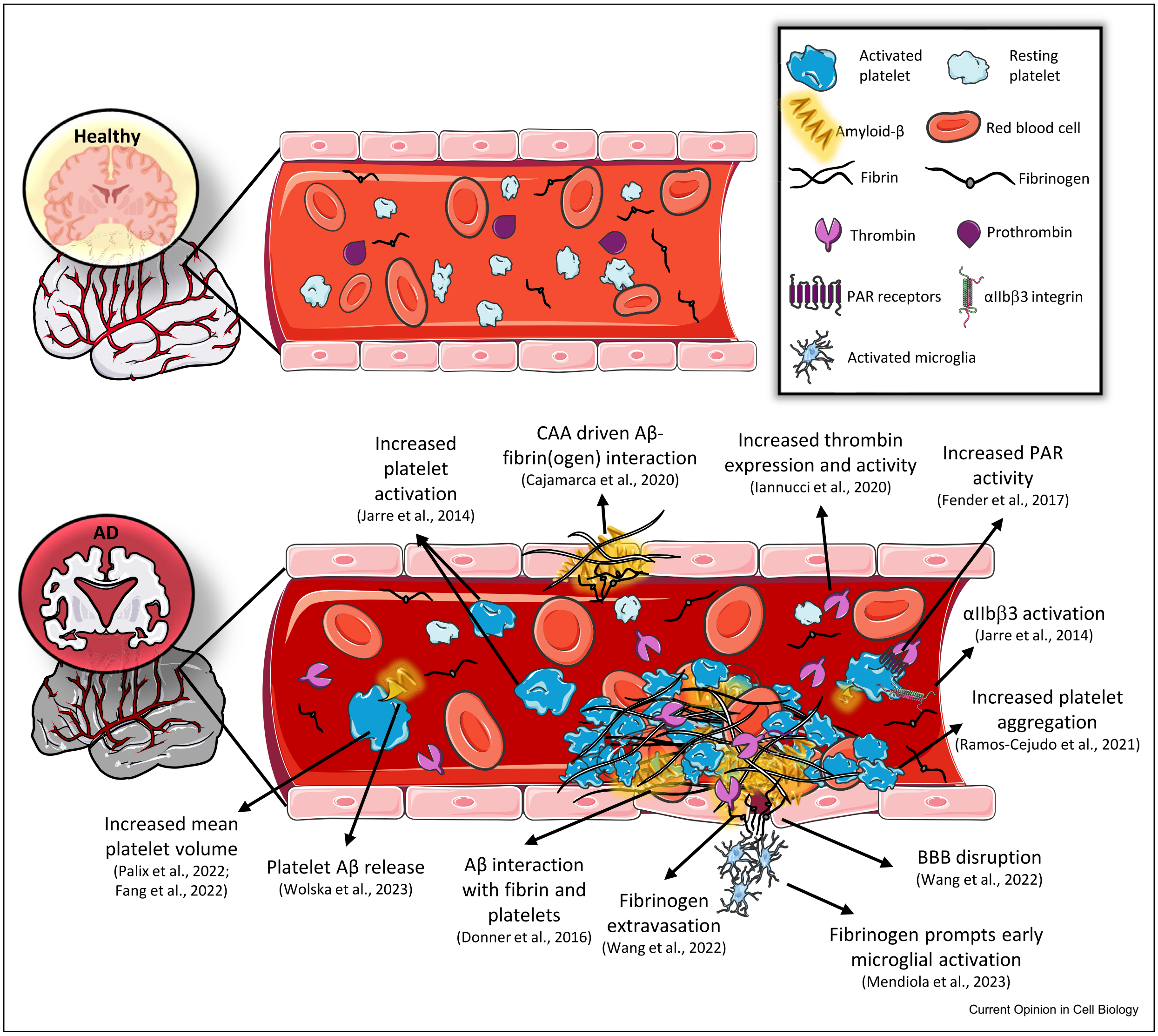
Introduction

Alzheimer's disease (AD) is the most common form of dementia, affecting 32 million people worldwide [1]. When including all people estimated to be across the AD continuum, this number reaches 416 million: 32, 69, and 315 million people with AD dementia, prodromal AD, and preclinical AD, respectively [1]. AD is a devastating neurodegenerative disorder with a deep multifactorial and heterogenous pathophysiology, in which the formation of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain are key for disease diagnosis [2]. However, the intrinsic heterogeneity of AD is evidenced by the fact that treatments are failing, partially because of the lack of diagnostic and therapeutic approaches targeting the different contributing mechanisms [3]. This context reinforces the necessity of developing individualized strategies to address the variety of pathological factors involved.

Beyond the classic neuropathological hallmarks of AD, there is a strong vascular component contributing to disease onset and progression [4]. Part of this vascular component in AD includes an early hemostatic dysregulation that leads to abnormal accumulation of fibrinogen and/or fibrin (fibrin(ogen)) in the AD brain coupled with a procoagulant environment with increased clot formation [5] and decreased fibrinolysis [6,7]. In fact, anticoagulation proved to ameliorate AD's pathology in AD mice [8], and atrial fibrillation patients treated with anticoagulants present less incidence of dementia [9], highlighting the important role of the prothrombotic context in this disorder (Box 1). This procoagulant state further promotes both the occlusion of blood vessels and the disruption of the blood–brain barrier, therefore greatly contributing to neuroinflammation, cerebral hypoperfusion, and neurodegeneration [10].

This manuscript aims to mainly review the scientific articles published in the last two years (i.e. from 2022 until 2024) in the AD vascular field related to the main cellular and protein components of blood clots: platelets and fibrin, respectively (Central Figure). The selection was performed by searching in "PubMed" the key terms "platelet AD," "fibrin AD," and "fibrinogen AD" and setting the appropriate period of publication. Therefore, this manuscript is conceived as an update in the research field more than a systematic review of the current general knowledge about the procoagulant state in AD. Thus, despite providing here a brief contextualization, we encourage readers to consult comprehensive reviews to obtain a more detailed context (such as [9,11–17]).

Central Figure



Schematic representation of vascular prothrombotic changes in Alzheimer's disease (AD). The top panel represents a blood vessel in healthy conditions, maintaining a correct functioning with intact endothelium barrier, resting platelets, and no deposition of Aβ or fibrin(ogen). In the bottom panel, the mechanisms of fibrin(ogen) and platelet alteration in the procoagulant AD brain are summarized, particularly focusing on recent findings reviewed in this manuscript.

Fibrin(ogen)

The formation of fibrin, the main protein component of blood clots, is the final step of the coagulation cascade: fibrinogen is converted into insoluble fibrin by the action of thrombin. This is a highly regulated process instrumental for hemostasis, but important pathophysiological implications arise when it is not tightly controlled [18].

Increased levels of several coagulation factors, such as fibrinogen, thrombin, D-dimer, and Factors VII, XI, and XIIa, among others, have been found to be correlated with AD pathophysiology [9]. Also, contact system activation has been described in AD [19], further inducing coagulation and inflammation. Recently, several reports added to this increasing evidence of abnormal hemostasis in AD: Fan et al. found that plasma levels of fibrinogen were positively correlated with cerebrospinal fluid (CSF) total tau, p-tau, total tau/Aβ42, and p-tau/Aβ42 in AD patients [20]; Liu et al. described a significant association of D-dimer levels with AD development in participants of the Multiethnic Study of Atherosclerosis [21]; and Rehiman et al. found that increased plasma levels of fibrinogen β and γ chains, identified by proteomics, were significantly upregulated in AD individuals [22]. These results, which are in line

BOX 1. Anticoagulation therapies for AD

Anticoagulant therapies may be promising options to address the prothrombotic state observed in AD [9]. Anticoagulants are medications that reduce blood clotting by targeting specific components of the coagulation cascade. By regulating clot formation, anticoagulants may help to reduce not only the prothrombotic state often observed in AD, but also the neuroinflammation and vascular damage, improving cognitive function. As previously reviewed by Toribio-Fernández et al. there are various classes of anticoagulants that show potential therapeutic benefits in AD patients [9]:

1. Vitamin K antagonists, such as warfarin, prevent the activation of vitamin K-dependent clotting factors, resulting in a reduced ability of blood to clot. Studies in human populations have suggested that long-term anticoagulation, particularly with vitamin K antagonists, is linked to a reduced risk of dementia, although findings vary across different studies [63].
2. Direct oral anticoagulants, include Factor Xa inhibitors (e.g. apixaban and rivaroxaban) and thrombin inhibitors (e.g. dabigatran). In AD mouse models, treatment with these anticoagulants has shown promising results. For example, treatment with dabigatran normalized cerebral perfusion, improved memory function, reduced amyloid load, mitigated neuroinflammation, and protected the blood−brain barrier in AD models [8,64]. Similarly, rivaroxaban has been shown to reduce amyloid pathology in models with pronounced cerebral amyloid angiopathy (CAA) [65].
3. Low molecular weight heparins, such as enoxaparin, inhibit Factor Xa and thrombin, preventing clot formation. In AD mouse models, treatment with enoxaparin has been associated with reduced amyloid pathology and improved spatial memory performance [66,67].
4. Emerging anticoagulant strategies, such as Factor XI inhibitors, which include antisense oligonucleotides and monoclonal antibodies, are still in early-stage clinical trials but are promising due to their potential to reduce thrombosis and inflammation with minimal bleeding risk [68]. More recently, a specific fibrin-targeting antibody, which aims to reduce the neurotoxic fibrin deposits in AD without interfering in the coagulation process, is currently being evaluated in a Phase 1 clinical trial [69].

Clinical challenges and future directions: While antithrombotic treatment offers promising avenues to address AD-associated procoagulant states, its application in clinical settings is hindered by:

- **Bleeding Risks**: Especially in patients with advanced CAA or high scores on the HAS-BLED scale [70].
- **Patient Selection**: Not all AD patients exhibit a procoagulant state, requiring the identification of biomarkers to stratify candidates.
- **Optimizing Safety**: Tailored dosing and temporal window of these therapies, and comprehensive monitoring of cerebrovascular health, are critical.

The development of specific biomarkers and well-designed clinical trials with rigorous inclusion and exclusion criteria will be crucial to determining the feasibility and safety of anticoagulant therapies in AD.

with other cohort-based studies [23,24], have led to the proposal of some of these factors as potential blood-based biomarkers for AD. However, beyond being merely fluid-based biomarkers, the underlying pathophysiology behind this altered hemostasis in AD deserves further discussion.

Fibrin(ogen) in the AD brain

During the past two decades, different labs have found fibrin(ogen) abnormally deposited in the brain of human AD patients and mouse models of AD, not only lining and even blocking blood vessels but also being extravasated into the brain parenchyma [6,9]. This abnormal presence of fibrin(ogen) in the AD brain is causally linked to the cerebral hypoperfusion [8], spine elimination [25], neurodegeneration [5], neuroinflammation [7,8,25], amyloid deposition [7,8], and cognitive deficits [7,8,25] present in AD. Besides fibrinogen's essential role as the key clotting molecule, fibrinogen is an important mediator of inflammation as well. Indeed, Mendiola et al. recently discovered, performing a thorough multiomic profiling, that genetic elimination of the CD11b-CD18 binding motif on fibrinogen is able to ablate microglia polarization toward neurotoxicity in the AD brain [26]. This study suggests that fibrinogen getting into the brain may be one of the first alterations happening in AD, preceding neuroinflammation and widespread microglial transcriptional changes, including changes involving oxidative stress and neurodegeneration. In line with that, Wang et al. detected fibrin(ogen) extravasation early in AD pathology, in 4-month-old APP/PS1 AD mice, and identified perivascular accumulation of fibrin(ogen) accompanied by decreased tight junction proteins in the hippocampus and cortex of AD patients [27]. Fibrinogen's extravasation into the brain is often related to increased leakiness of the blood−brain barrier, but, since fibrinogen is a rather large molecule (i.e. 340 kDa), other specific molecular mechanisms may be involved to mediate fibrinogen's transport inside the AD brain.

Aβ interaction with fibrinogen

One could argue that extravasation of fibrin(ogen) through a leaky blood−brain barrier may not be specific to AD, but rather a general mechanism contributing to different neurological diseases [6]. However, Aβ interacts specifically with fibrinogen [28], making fibrinogen's involvement in AD quite intriguing. The interaction of Aβ with fibrinogen induces fibrinogen's oligomerization [28] and blocks the access of fibrinolytic enzymes to the clot mesh, hence preventing fibrinolysis [29,30]. This interaction contributes to AD pathology since interfering with it rescues cognitive decline in AD mice [31]. Fibrinogen's interaction with Aβ may have important implications in the context of the AD brain vasculature, a vasculature that, in many cases, has been exposed to the detrimental effects of years of hypertension and other vascular risk factors [32], which results in an endothelium prone to activation and clotting. Additionally, the deposition of Aβ in the brain vessels, known as CAA, serves as the perfect hot spot for the fibrinogen-Aβ encounter. Indeed, decreasing fibrinogen levels lessens CAA pathology [7] and CAA-linked Aβ mutations are known to possess higher binding affinity for fibrinogen [33]. Interestingly, Singh et al. recently showed that lecanemab, a Food and Drug Administration-approved Aβ antibody, was able to block fibrinogen's binding to Aβ and ameliorate clot abnormalities *in vitro*, pointing to an additional protective mechanism of this AD therapeutic agent [34].

Platelets

Platelets, the main cellular components responsible for blood clot formation, appear as well as key players in the interplay between vascular dysfunction and prothrombosis in AD. Platelets are the main source of Aβ in the human blood [35–37], are responsible for its accumulation in blood clots in the brain vessels [38], and its hyperactivation in AD patients has been reported in the literature [16,39,40]. Additionally, the contact of platelets with Aβ stimulates further Aβ release and aggregation, possibly contributing to CAA [41]. However, platelets may also be protective in AD since platelet depletion in 1-year-old female AD mice led to a significant worsening in the pathology, promoting Aβ deposition and hampering its microglial elimination [42]. Hence, the specific contribution of platelets to AD is not entirely clear, probably due to its multifaceted nature, the elevated interindividual variability in platelet function and the variety of methodologies and outcomes measured in the different reports [16,35]. Additionally, as pointed out throughout this review, platelets may play differential roles across the AD continuum, complicating even more the interpretation of the data. This dichotomy is also present in other features such as neuroinflammation, where the scientific community calls for precise temporal therapeutic approaches and biomarkers to track disease progression along the more than a decade-long course of AD [43]. Hence, despite being necessary to fully characterize the role of platelets along the AD pathology, their involvement in the disorder merits careful consideration as a potential therapeutic approach to delay disease progression (Box 2) [44–46].

Platelets & Aβ

In the last years, the interaction between platelets and Aβ has been in the spotlight. A recent work by Wolska et al. aimed to identify the mechanisms that regulate $A\beta_{1-42}$ and $A\beta_{1-40}$ release by platelets from healthy donors. In addition to finding proof of different mechanisms involved in the release of each of the peptides, platelet stimulation with thrombin showed a faster release of Aβ peptides than that induced by lipopolysaccharide [47]. Furthermore, thrombin activation led to a higher and more sustained release of $A\beta_{1-42}$, considered more toxic, than $A\beta_{1-40}$ over time [47]. In the case of lipopolysaccharide stimulation, the release of $A\beta_{1-42}$ was significantly increased in cooccurrence with hypoxia [47]. This is particularly interesting given that, as Wolska et al. propose, "infection and inflammatory conditions may trigger platelet release of considerable amounts of pathogenic Aβ peptides if combined with hypoperfusion," a condition notably promoted by a

BOX 2. Antiplatelet therapies for AD

Vascular dysfunction associated with platelet hyperactivity significantly impacts AD pathophysiology. As reviewed extensively by others, antiplatelet therapies [71] may be promising options to address the pro-thrombotic state observed in AD. Beura et al. categorized synthetic antiplatelet drugs into five intervention levels based on their molecular targets [71]. These therapies primarily aim to reduce platelet activity and aggregation, counteracting excessive platelet hyperactivity. Despite the promising perspectives, the proposed strategies are based on experimental works in *in vitro* or animal models, requiring further research to confirm their efficacy and safety in clinical settings.

1. Cyclooxygenase inhibitors: Cyclooxygenase enzymes catalyze the production of prostaglandins and thromboxane, key inflammatory mediators. Drugs like aspirin [72,73] or ibuprofen [74,75] reduce platelet aggregation while also mitigating oxidative stress, neuroinflammation, and Aβ accumulation, contributing to cognitive preservation.
2. ADP receptor $P2Y_{12}$ inhibitors: $P2Y_{12}$ enhances ADP-induced platelet aggregation and granular secretion in response to platelet activators. Clopidogrel, as a direct blocker of this receptor, irreversibly inhibits platelet aggregation and offers neuroprotective and antiinflammatory benefits, including decreasing Aβ aggregation [45,76,77].
3. Thrombin receptor protease-activated receptors $(PAR)_1$ antagonists: PAR_1 regulates αIIbβ3-mediated platelet activation and calcium mobilization, promoting platelet activity. SCH-79797, a PAR_1 antagonist, inhibits thrombin-derived platelet activation, reducing neuroinflammation and apoptosis while improving synaptic plasticity and spatial learning and memory [78].
4. Phosphodiesterase inhibitors: Phosphodiesterase enzymes catalyze platelet inhibitors cAMP and cGMP, leading to platelet activation. Antioxidants like dipyridamole [79] and cilostazol [80,81] inhibit the phosphodiesterase, reducing platelet activity. Additionally, cilostazol enhances Aβ intracellular clearance via autophagy [81] and prevents its accumulation [81] and oligomerization [82].
5. Integrin αIIbβ3 blockers: αIIbβ3 integrins are membrane receptors essential for platelet activation and aggregation. Blockers targeting this pathway directly prevent platelet aggregation and exhibit neuroprotective effects by inhibiting inflammasome assembly [83,84].

prothrombotic state in the AD brain [5]. Finally, these authors also suggested that the platelet Aβ release after stimulation seems to respond to a storage and release mechanism, seeing Aβ loads in α-granules and other places inside the platelet rather than an increased production of *de novo* peptides [47]. Beyond their role in Aβ release, increasing evidence in the literature reported that different Aβ forms promote platelet activation, adhesion, and aggregation [11], reinforcing the presence of a prothrombotic state in AD.

However, Mizutani et al. recently suggested that Aβ alone not only did not induce platelet activation but negatively regulated thrombin-activated receptors of the PAR family, which are important mediators of the platelet-mediated clot-formation process [48,49]. In line with this, Donner et al. found defective platelet activation in middle-aged male APP23 AD mice (i.e. with parenchymal but no vascular amyloid deposits as CAA) after stimulation of PAR4, which led to reduced thrombus stability under flow conditions and protection against thrombosis [50]. However, these results were not consistent neither in females, where no differences were observed [50], nor in old APP23 mice (i.e. with parenchymal Aβ plaques and CAA), which in fact expressed a preactivated platelet state [51]. These apparent contradictory results need to be interpreted under their unique context. On the one hand, Mizutani et al. used platelet samples donated from healthy human participants [48], which showed very high heterogeneity and that were not pressed by the multiple factors involved in an AD pathophysiological context. On the other hand, Donner et al. acknowledged two very interesting points: 1) sex-specific differences in the AD platelet activation pattern and 2) a possible “switch” in the platelet activation pattern before the development of CAA [50]. According to this, Ramos-Cejudo et al. recognized the possible existence of different platelet aggregation phenotypes associated with dementia [52]. In fact, they observed that individuals from the Framingham Heart Study with a higher platelet response were at increased dementia risk later in life, highlighting its potential prognostic value [52].

Platelet activation in AD

In line with Donner et al.’s platelet activation “switch” in the AD course, studies in the Framingham Heart Study described age-dependent associations of mean platelet volume (MPV) with cognitive performance [53]. The MPV is a key indicator of the platelet size and reflects the functional status of the platelets, although results tend to be highly heterogeneous among patients and studies. In this sense, larger platelets are the young ones (i.e. those most recently released from megakaryocytes in the bone marrow), hence showing higher metabolic and enzymatic activity and being more prone to activation and aggregation. Therefore, larger MPVs serve as a surrogate marker of elevated platelet activation, reflecting increased platelet production, and a potential for a pro-thrombotic milieu. In the Framingham Heart Study, Fang et al. found that higher MPV was associated with poorer performance in the Hooper Visual Organization Test, a test intended to detect cognitive deficits by evaluating visuoperceptual skills, in participants younger than 60 years old [53]. On the contrary, this association shifted toward a positive correlation in participants older than 60 years old, although this tendency did not reach statistical significance [53]. Beyond the cognitive implication, a recent cross-sectional study aimed to uncover potential neuropathological correlates with vascular risk factors [54]. In this investigation, Palix et al. revealed higher MPV and lower platelet count in Aβ-positive patients compared to Aβ-negative controls. Interestingly, such differences only remained in the Aβ-positive mild cognitive impairment (MCI) group and not in the Aβ-positive AD sample [54]. This *a priori* controversy may indeed support the platelet activation switch proposed by Donner et al. [50] if MCI is considered an early stage for a yet undiagnosed AD. Additionally, these authors also discovered an association between increased MPV and atrophy in entorhinal and perirhinal cortices in Aβ-positive patients, which are brain regions sensitive to neurodegeneration in AD, but not with amyloid burden [54]. Previous clinical studies showed both increased [55,56] and reduced [57,58] MPV values in AD patients compared to cognitively unimpaired participants. In an attempt to solve this puzzle, Huang et al. recently performed a meta-analysis aiming to quantify the association of peripheral blood cell counts with AD and MCI incidence [59]. These authors did not find differences between AD or MCI and healthy controls in platelet count or MPV, although they found a reduction in the platelet distribution width (another proxy of platelet size) in AD in the limited number of studies that included this parameter (4 studies involving 791 subjects) [59]. As previously mentioned, technical challenges linked to platelet function, activation, and morphology, together with significant heterogeneity among studies, may have precluded finding consistent results deciphering the involvement of platelets in dementia development.

The molecular characterization of platelet activation in AD has shed some light on this controversy with recent exploratory studies using omic approaches. First, Yu et al. conducted an integrative study of brain and platelet omics from the AlzData (brain) and HUST (platelets) databases and found platelet activation as a disordered network linked to AD [60]. Moreover, leveraging machine learning algorithms, they identified several platelet proteins that could be used as promising biomarkers of cognitive decline [60]. Moreover, De Sousa et al. evaluated platelet activation, along with their proteome and transcriptome, in AD patients, cognitively unimpaired elderly, and young controls [61]. Both the AD and elder controls showed a specific proteomic signature indicative of activated platelets in comparison to the younger ones [61]. Differences between AD and elder controls appear at the transcriptomic level, pointing toward dysregulation of proteasomal degradation in AD and autophagy in aging, both processes essential for platelet function [61]. Although the exact implication of such deregulation remains unclear, these comprehensive analyses, together with the extensive review work carried out by Burnouf and Walker [15] as well as a recent metaanalysis performed by Fu et al. [62], support the notion that the brain pathological mechanisms in AD are well reflected in certain molecular changes that occur systemically in platelets [60].

Conclusions

The findings reviewed in this manuscript emphasize the pivotal roles of fibrin(ogen) and platelets in the vascular contributions to AD pathology (Central Figure). Abnormal fibrin(ogen) deposition and its interactions with Aβ create a vicious cycle of impaired fibrinolysis, vascular occlusion, and neuroinflammation, exacerbating neurodegeneration. Platelets, with their dual roles in AD, demonstrate functional variability across disease stages, potentially switching from protective to deleterious phenotypes as pathology progresses.

The heterogeneity in study outcomes reflects two key challenges: the immense complexity and variability of AD and the occasional misalignment between experimental designs and research objectives, which can lead to misinterpretations. For instance, extrapolating findings from healthy donors to AD pathology may underestimate the disease's impact on platelet physiology. The possibility of undiscovered phenotypic variations contributing to hemostatic alterations further emphasizes the need for more comprehensive investigations.

Future research should prioritize context-specific, longitudinal studies that integrate clinical, molecular, and phenotypic data. This approach would enable the stratification of patients not only by cognitive decline, Aβ, and p-tau levels but also by individual characteristics, such as vascular implications, that may influence therapeutic responses. Developing a multifocal, personalized strategy could pave the way for innovative diagnostic methods and targeted interventions, significantly enhancing treatment efficacy, and patient outcomes.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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Mendiola et al., 2023, aimed to explore how blood proteins induce microglial activation and their role in neurodegeneration by utilizing multiomic and genetic loss-of-function approaches. Their findings showed that fibrinogen plays a central role in promoting oxidative stress and neurodegenerative pathways in microglia through CD11b-mediated signaling. Importantly, they discovered that genetic elimination of the CD11b-CD18 binding motif on fibrinogen prevents microglial polarization towards neurotoxicity, abolishing widespread transcriptional changes involving oxidative stress and neurodegenerative genes. This study suggests that fibrinogen infiltration into the brain may be one of the earliest events in AD, preceding neuroinflammation and microglial activation. Comparative analyses with AD and multiple sclerosis models further demonstrated that fibrin-induced gene signatures overlap with disease-associated microglial profiles. Overall, the study establishes fibrinogen as a critical regulator of microglial-driven neuroinflammation and a potential therapeutic target in AD.

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Wang et al., 2022, investigated the mechanisms of blood–brain barrier dysfunction in AD and its potential therapeutic targets. They observed early blood–brain barrier disruption in 4-month-old APP/PS1 mice, marked by fibrin(ogen) extravasation into the brain parenchyma. In human AD brain samples, fibrin(ogen)'s perivascular accumulation in the hippocampus and cortex was accompanied by decreased levels of tight junction proteins, such as Claudin-5 and Glut-1. Using a trans-well permeability assay, they demonstrated that Aβ oligomers suppress the Wnt/β-catenin signaling pathway in brain endothelial cells, leading to blood–brain barrier dysfunction. They further explored therapeutic strategies by employing optogenetic activation of the Wnt/β-catenin pathway in brain endothelial cells, recovering tight junction integrity and improving permeability.

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