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Review

Interactions between Beta-Amyloid and Pericytes in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder characterized by aberrant amyloid precursor protein (APP) cleavage, pathological aggregations of beta-amyloid (Aβ) that make up Aβ plaques and hyperphosphorylation of Tau that makes up neurofibrillary tangles (NFTs). Although progress has been made in research on AD, the fundamental causes of this disease have not been fully elucidated. Recent studies have shown that vascular dysfunction especially the loss of pericytes plays a significant role in the onset of AD. Pericytes play a variety of important roles in the nervous system including the regulation of the cerebral blood flow (CBF), the formation and maintenance of the blood–brain barrier (BBB), angiogenesis, and the clearance of toxic substances from the brain. Pericytes participate in the transport of Aβ through various receptors, and Aβ acts on pericytes to cause them to constrict, detach, and die. The loss of pericytes elevates the levels of Aβ1-40 and Aβ1-42 by disrupting the integrity of the BBB and reducing the clearance of soluble Aβ from the brain interstitial fluid. The aggravated deposition of Aβ further exacerbates pericyte dysfunction, forming a vicious cycle. The combined influence of these factors eventually results in the loss of neurons and cognitive decline. Further exploration of the interactions between pericytes and Aβ is beneficial for understanding AD and could lead to the identification of new therapeutic targets for the prevention and treatment of AD. In this review, we explore the characterization of pericytes, interactions between pericytes and other cells in the neurovascular unit (NVU), and the physiological functions of pericytes and dysfunctions in AD. This review discusses the interactions between pericytes and Aβ, as well as current and further strategies for preventing or treating AD targeting pericytes.

Keywords: Alzheimer's disease; pericytes; beta-amyloid; cerebral blood flow; blood-brain barrier; neurovascular unit; cognitive decline

1. Introduction

Alzheimer's disease (AD) is an age-related progressive neurodegenerative disorder characterized by cognitive dysfunction and behavioral impairment. In addition, AD is the primary cause of dementia [1]. The two typical neuropathological changes in AD include neuritic plaques formed by the deposition of beta-amyloid (Aβ) in the brain parenchyma and intracellular Tau that makes up neurofibrillary tangles (NFTs) formed by the accumulation of hyperphosphorylated tau proteins [2,3].

The plaques of Aβ also deposit on vessel walls causing cerebral amyloid angiogenesis (CAA) [4,5]. However, the Aβ plaques in AD and CAA are distinct. Aβ1-40 and Aβ1-42 are the most common subtypes of Aβ peptide. Aβ1-42 is more prone to form insoluble aggregates in the parenchyma [6], constituting the major component of neuritic plaques in AD. In contrast, Aβ1-40 aggregates more slowly and ultimately deposits in the walls of vessels through perivascular drainage [4,7,8]. Abnormal perivascular drainage is the main pathogenesis of CAA [4,9,10], which also explains why the Aβ deposited on the vascular wall in CAA is mainly Aβ1-40. Neuron loss and synapse dysfunction caused by the toxicity of Aβ will ultimately contribute to dementia and degeneration of the central nervous system (CNS) [11,12]. Moreover, a substantial body of research has demonstrated that the occurrence of CAA and AD largely overlap [13–15]. Cerebrovascular dysfunction caused by CAA is related to severe cognitive impairment in AD patients [15–18].

The shared role of Aβ in AD and CAA is likely the most apparent interaction between neurodegenerative diseases and cerebrovascular diseases. Moreover, there is evidence indicating that vascular dysfunction plays a significant role in the onset of AD. Recent studies have demonstrated that a reduction in the cerebral blood flow (CBF) is the earliest detectable clinical change in mild cognitive impairment and AD patients [19–21] and that capillaries exhibit focal constriction. The greatest vascular resistance occurs in the capillary bed rather than in the penetrating arterioles [22]. At the capillary level, the neurovascular unit (NVU) is composed of endothelial cells (ECs), pericytes, glial cells and neurons. Pericytes are the only contractile cells responsible for regulating blood flow in capillaries. Pericytes likely plays an important role in the pathogenesis of AD. Pericytes, which are indispensable components of the NVU, play an essential role in the formation and maintenance of the blood-brain barrier (BBB), the regulation of the CBF, angiogenesis and the phagocytosis of toxic sub-

stances including Aβ from the brain. A significant loss of pericytes in AD patients has been observed, and the accumulation of Aβ may be the potential cause. Conversely, the loss of pericytes could lead to impaired clearance of Aβ, exacerbating the deposition of Aβ and leading to a vicious cycle.

Currently, there are no effective drugs that can effectively reverse cognitive decline and there are no therapeutic strategies targeting pericytes [23]. Further understanding of the pathological changes in pericytes in AD and the interactions between pericytes and Aβ may provide new therapeutic directions for the prevention and treatment of AD. In this review, we summarize the characterization of pericytes, the signaling pathways linking pericytes and other cells in the NVU, the physiological effects of pericytes, the functional changes in pericytes in AD, the pathways through which pericytes clear Aβ, the effects of Aβ on pericytes and the current strategies for preventing or treating AD targeting pericytes.

2. The Characterization of Pericytes

Pericytes were originally characterized by Eberth and Rouget in the 1870s (Eberth, 1871; Rouget, 1873) and firstly named by Zimmermann in 1923 based on their location within the vascular basement membrane (BM) and the extension of cytoplasmic processes to wrap ECs. Both pericytes and vascular smooth muscle cells (VSMCs) are called mural cells [24]. In addition to ring-shaped VSMCs with circumferential processes on arteries and arterioles [25], pericytes are classified into three subtypes based on their morphology and location: ensheathing pericytes which have more circumferential processes on precapillary arterioles; thin-strand or helical pericytes, which have protruding nuclei and longitudinal processes on the middle capillary, which is the most widely accepted morphology of pericytes; and stellated pericytes on the postcapillary space [26,27].

Many cell surface proteins such as platelet-derived growth factor receptor-β (PDGFR-β), neural/glial antigen 2 (NG2) and CD13 [28–33] are expressed on both pericytes and VSMCs, and these two cell types can be distinguished by morphology. Additionally, vitronectin (VTN) and interferon-induced transmembrane protein 1 (Ifitm-1) label pericytes specifically [31]. However, there is currently a lack of specific markers for distinguishing subpopulations of pericytes. Pericytes and VSMCs exhibit contractile alpha-smooth muscle actin (α-SMA) and desmin expression [26,30,34]. Notably, there is a difference in the expression level of α-SMA between the subtypes of pericytes, which may be related to their distinct functions [27,30]. These markers, especially PDGFR-β, NG2 and α-SMA, are widely applied in studies. PDGFR-β can outline the contours of pericytes [35]. Because they are labeled by PDGFR-β, pericytes are easily recognized by their protruding soma. Therefore, relying solely on morphology is sufficient to reliably identify pericytes [26,27]. However, it is worth noting that adequate experience is needed for observers [36]. NG2 is the first discovered marker of pericytes that can be used to identify pericytes through combination with morphology, but not all pericyte subsets express NG2 [37]. α-SMA is not sensitive enough to identify pericytes in capillary beds, because pericytes on precapillary tubes express more α-SMA while pericytes on capillary beds may be negative [27,30].

3. The Interactions between Pericytes and other Cells in the Neurovascular Unit

The NVU is composed of endothelial cells, mural cells (vascular smooth muscle cells, pericytes), glial cells (astrocytes, microglia, oligodendrocytes) and neurons [38–40]. The cellular components vary with the branching of the cerebral vascular tree. At the capillary level, pericytes are located centrally between endothelial cells, the endfeet of pericytes and neurons, and the BM is shared with pericytes [26,41]. They communicate with their neighboring cells and generate corresponding responses which are crucial for normal functions of the CNS [26]. We reviewed the interactions between pericytes and ECs, astrocytes and neurons in Table 1 (Ref. [26,35,38,42–50]).

4. The Functions of Pericytes and Dysfunctions in AD

As pericytes are indispensable components of the BBB and NVU, we review the roles of pericytes in the CNS and their dysfunctions in AD.

4.1 Regulation of the Cerebral Blood Flow (CBF)

Mural cells are cellular components with contractile properties in the NVU, that enable them to regulate vascular tone and the CBF [22]. As pial arteries branch into arterioles and capillaries after penetrating into parenchyma, the mural cell population composed of the NVU changes [51]. Penetrating arteries consist of one to three layers of VSMCs while arterioles contain only one layer [41,51]. After descending to capillary level, pericytes replace VSMCs and embed within the endothelial BM [51]. Previously, the CBF was shown to be regulated solely by VSMCs [52]. However, with the study of pericytes, this viewpoint has been challenged.

In a series of studies, pericyte were confirmed to constrict or dilate in response to neurotransmitters [53], for example, glutamate evokes pericyte dilation, and pericytes constrict in response to a gamma-aminobutyric acid (GABA) receptor blocker suggesting that pericytes participate in the regulation of the CBF [52,54–57]. Moreover, an *in vivo* experiment in which mice expressed DsRed in pericytes, revealed that capillary dilation precedes penetrating arterioles, demonstrating that capillary dilation is a result of active relaxation of pericytes rather than a passive response to elevated blood pressure caused by arteriole dilation [52]. In ischemic stroke, capillaries constrict segmentally at re-

Table 1. The interactions between pericytes and other cells in the NVU.

Cell type	Signaling pathway with pericytes	Functions	Ref
ECs	PDGF-BB-PDGFRβ pathway	PDGF-BB secreted by ECs combines with PDGFRβ on pericytes in high affinity. PDGF-BB-PDGFRβ signaling promotes pericytes survival, proliferation and migration.	[26,35,42]
	TGF-β–TGFβR2 pathway	TGF-β is activated though interactions between ECs and pericytes to promote proliferation and differentiation of pericytes, and stabilization of vessels.	[43,44]
	Ang-Tie2 pathway	Ang1 secreted by pericytes combines with Tie2 on ECs. Ang-Tie2 signaling regulate angiogenesis and vascular permeability.	[26,35,45]
	VEGF-A-VEGFR2 pathway	VEGF-A secreted by pericytes and ECs to promote the survival and proliferation of pericytes as well as angiogenesis.	[26,38,46]
Astrocytes	CypA–NFκB–MMP-9 pathway	ApoE secreted by astrocytes interacts with LRP1 on pericytes triggering the degradation of the extracellular matrix and tight junction.	[26,47,48]
		Pericytes regulate the AQP4 distribution of astrocytes to regulate the polarization of astrocytic endfeet.	[49,50]
Neurons		Pericytes secrete neurotrophic factors to promote the survival of neurons whereas neurons secrete neurotransmitters to regulate pericytes contractility.	[26,50]

Abbreviations: NVU, neurovascular unit; EC, endothelial cells; PDGF-BB, platelet-derived growth factor-BB; PDGFRβ, platelet-derived growth factor receptor-β; TGF-β, transforming growth factor-β; TGFβR2, transforming growth factor-β receptor 2; Ang1, angiopoietin-1; Tie2, tyrosine protein kinase receptor; VEGF-A, vascular endothelial growth factor-A; VEGFR2, vascular endothelial growth factor receptor 2; CypA, cyclophilin A; NFκB, nuclear factor kappa-B; MMP-9, matrix metalloproteinase-9; ApoE, apolipoprotein E; LRP1, LDL receptor-related protein-1; AQP4, aquaporin 4.

gions near pericytes, after which pericytes contract and subsequently die rigidly [58]. Damages to pericytes contributes to long-lasting microcirculatory reflow impairment even after reperfusion [59].

Pericytes degeneration and neurovascular dysfunction have been observed in AD [51,52]. Moreover, the oxidative stress caused by Aβ leads to capillary constriction. A reduction in the CBF reduces the oxygen supply and glucose availability to the brain, resulting in the impairment of neurons and neurodegenerative changes [60]. A recent study showed that white matter lesions (WMLs) induced by persistent cerebral hypoperfusion is a driving factor for dementia [61]. Moreover, the two-hit vascular hypothesis suggests that prior to neurodegeneration and cognitive impairment, genetic, vascular and environmental factors cause vascular damage (hit1), and neurovascular dysfunction contributes to the accumulation of Aβ (hit 2) [40,41]. A previous study using APP$^{sw/0}$ Pdgfr$\beta^{+/-}$ mice found that the loss of pericytes results in a series of AD-like neurodegeneration pathological changes including accelerated Aβ deposition, tau pathology and neuronal dysfunction [62]. Notably, vascular damage (hit1) has been observed in pericyte-deficient APP$^{sw/0}$ mice, indicating that vessel damage and pericyte degeneration may be mutually causal [62]. Together, these findings suggest that pericyte degeneration is an early and key event in AD neurodegeneration.

However, due to differences in stimulation methods, transgenic mice, and other factors, the function of pericytes in regulating the CBF has not been fully elucidated.

4.2 Formation and Maintenance of the Blood-Brain Barrier (BBB)

The blood-brain barrier (BBB) is a special protective barrier that exists between capillaries and the brain, and is composed of ECs, endothelial tight junctions (TJs), the BM, pericytes and astrocyte endfeet [63,64]. The BBB protects the brain from invasion by blood-derived harmful factors, thus maintaining the homeostasis of the CNS [65]. Using quail-chick transplantation chimeras, BBB was shown to develop in response to the neural tissue environment [66]. During embryogenesis in rodents, astrocytes and pericytes are required to wrap immature vessels. It is widely accepted that immature vessels are covered preferentially by astrocytes postnatally. However, Daneman *et al*. [67] reported that pericytes were recruited during embryogenesis, more than one week before the generation of astrocytes, thus revealing the role of pericytes in the formation of the BBB. The permeability of the BBB is increased in pericyte-deficient mice, indicating the essential role of pericytes in maintaining BBB integrity [49]. Pericytes maintain the integrity of the BBB through two pathways, forming and preserving the TJs of ECs, and transcytosing in the CNS ECs.

The breakdown of the BBB has been observed in AD [68], which is attributed to the loss and detachment of pericytes destroying the integral structure of the BBB and increasing BBB permeability [69]. Interestingly, sirtuin-1 (*SIRT1*), an anti-aging gene, is markedly suppressed exposed to Aβ [70]. The decreased expression of *SIRT1* also increased the permeability of the BBB and accelerated the process of senescence [71].

4.3 Angiogenesis

Angiogenesis is the formation of new blood vessels from existing vessels. Angiogenesis involves three steps: initiation, sprouting/migration, and maturation. In angiogenesis, the complex signaling pathways between ECs and pericytes which include the platelet-derived growth factor (PDGF)-BB/PDGF receptor beta (PDGFRβ) pathway [72,73], the angiopoitin1/tyrosine protein kinase receptor (Tie2) signaling pathway [74], the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway [46], the sphingosine-1-phosphate (S1P) signaling pathway [75], transforming growth factor beta (TGF-β) [76] are the foundation for the formation and stabilization of new blood vessels. Pericytes regulate the expression of VEGF, resulting in the instability of blood vessels and initiating the angiogenesis [77]. Pericytes detach from blood vessels to pave the way for endothelial sprouting [78]. The migrating ECs secrete VEGF to stabilize nascent vessels and signal to pericytes to recruit VEGF. Moreover, the recruited pericytes communicate with ECs to promote the stabilization and maturation of new blood vessels [78]. The coverage of pericytes is a marker of vascular maturation and a lack of pericytes results in vascular hyperplasia [79].

5. Mechanisms through which Pericytes Regulate Aβ

Aβ is continuously generated by neurons and other cells in the healthy brain, and is subsequently cleared through various pathways [80–82] including receptor-dependent transport [80,83–86], cytosolic protease-mediated intracellular degradation [87] and glymphatic clearance [88]. In AD, the clearance of Aβ is impaired, and an imbalance between Aβ production and clearance leads to the aberrant accumulation of Aβ [7]. Moreover, pericytes play a considerable role in the clearance of Aβ, while the loss of pericytes in AD exacerbates the deposition of Aβ in the parenchyma.

5.1 Pericytes Clear Aβ by LDL Receptor-Related Protein-1 (LRP-1)

LDL receptor-related protein-1 (LRP-1) is an apoE receptor that mediates the clearance of Aβ. Using freshly isolated cortical slices incubated with Aβ, Ma *et al.* [80] showed that pericytes rapidly remove Cy3-Aβ42. In addition, in AD and APP$^{swe/0}$ mice, the abundant accumulation of Aβ in pericytes indicates the important role of these cells in clearing Aβ at the BBB. Additionally, in an LRP-1 conditional knockout model, Cy3-Aβ42 uptake by pericytes was reduced by 80% compared with that in the control group. The process of clearing Aβ by pericytes can be inhibited by antibodies against LRP-1 [80,84], further confirming that the clearance of Aβ is mediated by LRP-1 (Fig. 1A). Compared with that in adult wild-type mice, clearance in apoE knockout mice is substantially reduced, indicating that LRP-1-mediated transport can be influenced by apoE, a definite risk factor for AD [85]. ApoE is required for Aβ clearance and is isoform- specific. A study revealed that apoE3, but not apoE4, normalizes Aβ clearance in mouse pericytes with silenced mouse apoE [80], while another study revealed that the binding of Aβ to apoE3 reduces its clearance rate at the BBB. It has also been reported that Aβ binding to apoJ significantly accelerates the BBB clearance rate [86,89].

The expression of LRP-1 is downregulated in AD patients exacerbating Aβ pathology [90]. By injecting pericytes into APP/PS1 mice, Tachibana *et al.* [91] showed that microcirculation improved in the pericyte-injected hemisphere and that the deposition of Aβ decreased in a manner dependent on the expression of LRP-1 on pericytes. However, in a recent phase I clinical trial in which mesenchymal stem cells (MSCs) were stereotactically injected to the brains of AD patients, no significant effects on cognitive function were observed. The use of transplanted pericytes or MSCs in the brain to prevent or treat AD has not been validated [92].

5.2 Aβ40 is Degraded into Aβ34 in Pericytes through β-Site Amyloid Precursor Protein (APP) Cleaving Enzyme 1 (BACE1)

Amyloid precursor protein (APP) is cleaved by β-Site Amyloid Precursor Protein (APP) Cleaving Enzyme 1 (BACE1) and γ-secretase, which sequentially results in the formation of Aβ peptides, including Aβ40 and Aβ42 [93]. In addition to "amyloidogenic" activity, BACE1 also possesses "amyloidolytic" activity, whereby it degrades longer Aβ isoforms at position 34 into Aβ34 intermediates [94] (Fig. 1A). A previous study demonstrated that BACE1 is expressed in pericytes [95]. Treating pericytes with a BACE inhibitor resulted in a dose-dependent decrease in Aβ34 levels, indicating the role of BACE1 in the cleavage of Aβ peptides and the formation of Aβ34 in pericytes [95]. Notably, the substrate of BACE1 is Aβ40, but not Aβ42 [94,95].

In AD, the Aβ34/Aβ40 ratio is decreased significantly, and the level of Aβ34 is correlated with disease progression [96]. The progression of AD can be divided into six stages. AD in Braak stage I-II is clinically silent, AD in Braak stage III–IV is incipient and AD in Braak stage V–VI is fully developed [97–99]. Kirabali *et al.* [95] revealed that in Braak stage II, Aβ34 levels peak, while in Braak stages III and IV, the immunoactivity of Aβ34 signif-

icantly decreases which explains the dysfunction and loss of brain pericytes in AD pathogenesis. Moreover, analysis of PDGFRβ immunoactivity revealed that the loss of pericytes had already occurred at Braak stage II [37].

5.3 Pericytes Regulate Aβ Clearance via RAGE

AGEs (advanced glycation end-products) are the final products of the nonenzymatic glycation of proteins (Maillard reaction) [100], which is irreversible. AGEs can bind and destroy various histocytes through a process called cross linking. A series of studies have shown that AGEs accelerate aging and cause neurodegenerative disorders including AD [101–103]. Receptors for advanced glycation end products (RAGE), a multiligand receptor of the immunoglobulin family, can not only specifically bind to AGEs, but also bind to various ligands such as high-mobility group box-1 (HMGB1), S100 and Aβ [104,105], and play vital roles in the occurrence and development of various diseases. RAGE plays a critical role in regulating the influx of circulating Aβ into the brain via the BBB as a transporter [106]. Moreover, RAGE promotes the generation and accumulation of Aβ by enhancing the activity of β-secretase and γ-secretase [107]. In addition, RAGE induces dysfunction of synapses and neuronal circuits, which is the structural foundation of cognition [108,109]. According to its structure, RAGE is classified into three isoforms: N-truncated, and C-truncated, which are also called endogenous secretory RAGE (esRAGE) [110]. Moreover, RAGE can be cleaved by proteolytic enzymes to form cRAGE. The soluble form of RAGE (sRAGE) is composed of esRAGE and cRAGE. Notably, sRAGE can interact with Aβ to form sRAGE-Aβ interactions which can inhibit the neurotoxicity of RAGE and promote Aβ clearance from the brain [110].

It has been proven that RAGE is expressed on pericytes [111]. Using small interfering RNA (siRNA) technology to suppress the expression of the pericyte *RAGE* gene, Lue *et al.* [111] showed that the level of Aβ dramatically decreased, indicating that the Aβ (1-42)-RAGE interaction may function by tethering Aβ to the cell surface of pericytes, advancing the Aβ-Aβ interaction and further promoting fibrillogenesis. By blocking RAGE with an anti-RAGE antibody, the levels of Aβ-induced VEGF and monocyte chemoattractant protein-1 (MCP-1) were decreased, indicating that RAGE-Aβ interactions in pericytes contribute to the vascular remodeling that is observed in AD (Fig. 1A). The combination of Aβ and pericyte RAGE can induce oxidative stress and a subsequent inflammatory response by activating a variety of signaling pathways, including mitogen-activated protein kinase (MAPK), glycogen synthase kinase 3 (GSK-3) and nuclear factor kappa-B (NF-κB) [112]. Oxidative stress and inflammatory reactions can thicken the BM and increase the deposition of Aβ, eventually leading to vascular amyloidosis and disruption of the BBB [111]. In addition, the Aβ-RAGE interaction results in cognitive impairment by accelerating the aging process and inducing oxidative stress [113]. In AD, elevated RAGE levels may account for neuronal death and cognitive impairment. However, the level of sRAGE is lower [114]. In view of this, RAGE inhibitors may be potential targets for treating AD and these agents have been proven to be effective in preclinical and clinical studies [115], although the results have been unsatisfactory.

5.4 Pericytes Efflux Aβ via P-Glycoprotein (P-gp)

P-gp, a subtype of the ATP binding cassette (ABC) transporter family, is an ATP-dependent transporter responsible for the efflux of various substrates from the brain to the blood [116,117]. Using an immunogold technique with monoclonal anti-P-gp antibodies, Bendayan *et al.* [118] showed that gold particles are present in ECs, astrocytes and pericytes, suggesting that pericytes can express P-gp. In human studies, the expression level of P-gp was shown to be negatively correlated with the accumulation of Aβ [119,120].

Moreover, it has been proven that inhibiting P-gp leads to increased intracellular deposition of Aβ in brain capillaries [121,122], suggesting that P-gp plays a crucial role in the clearance of Aβ. However, the mechanism by which P-gp affects Aβ transport remains controversial. A variety of studies support the notion that Aβ stimulates the ATPase activity of P-gp [123,124]. However, Bello *et al.* [125] reported that Aβ has no effect on the adenosine triphosphate (ATP) hydrolysis activity of P-gp. In previous research, McCormick *et al.* [123] noted that the activation of P-gp ATPase by Aβ depends on the lipid environment, which may account for the differences between those studies. In addition, Aβ can affect P-gp conversely. By treating transgenic human amyloid precursor protein (hAPP) overexpressing mice with an irreversible inhibitor of the ubiquitin-activating enzyme E1, Hartz *et al.* [126] showed that retained P-gp results in a decreased level of Aβ, suggesting that Aβ induces P-gp degeneration through the ubiquitination pathway. In addition, the brains of AD patients exhibit marked decrease in P-gp and a significant increase in Aβ deposition and ubiquitinated Aβ [126–128].

5.5 Pericytes Uptake Aβ1-40 via CD36

CD36, a glycosylated membrane protein, is widely expressed in the nervous system, including in pericytes [129]. CD36 is involved in a variety of pathological processes, such as vascular oxidative stress, the inflammatory response, mitochondrial dysfunction and neurovascular uncoupling [129–131].

Immunofluorescence staining revealed that, CD36 and Aβ1-40 colocalize with PDGFRβ, a marker of pericytes, suggesting that CD36 may be involved in the clearance of Aβ1-40 by pericytes [132]. In transgenic mice lacking CD36, Li *et al.* [132] showed a reduction in Aβ1-40 and cerebral amyloid angiopathy (CAA), suggesting that CD36 promotes the deposition of Aβ1-40 resulting in vas-

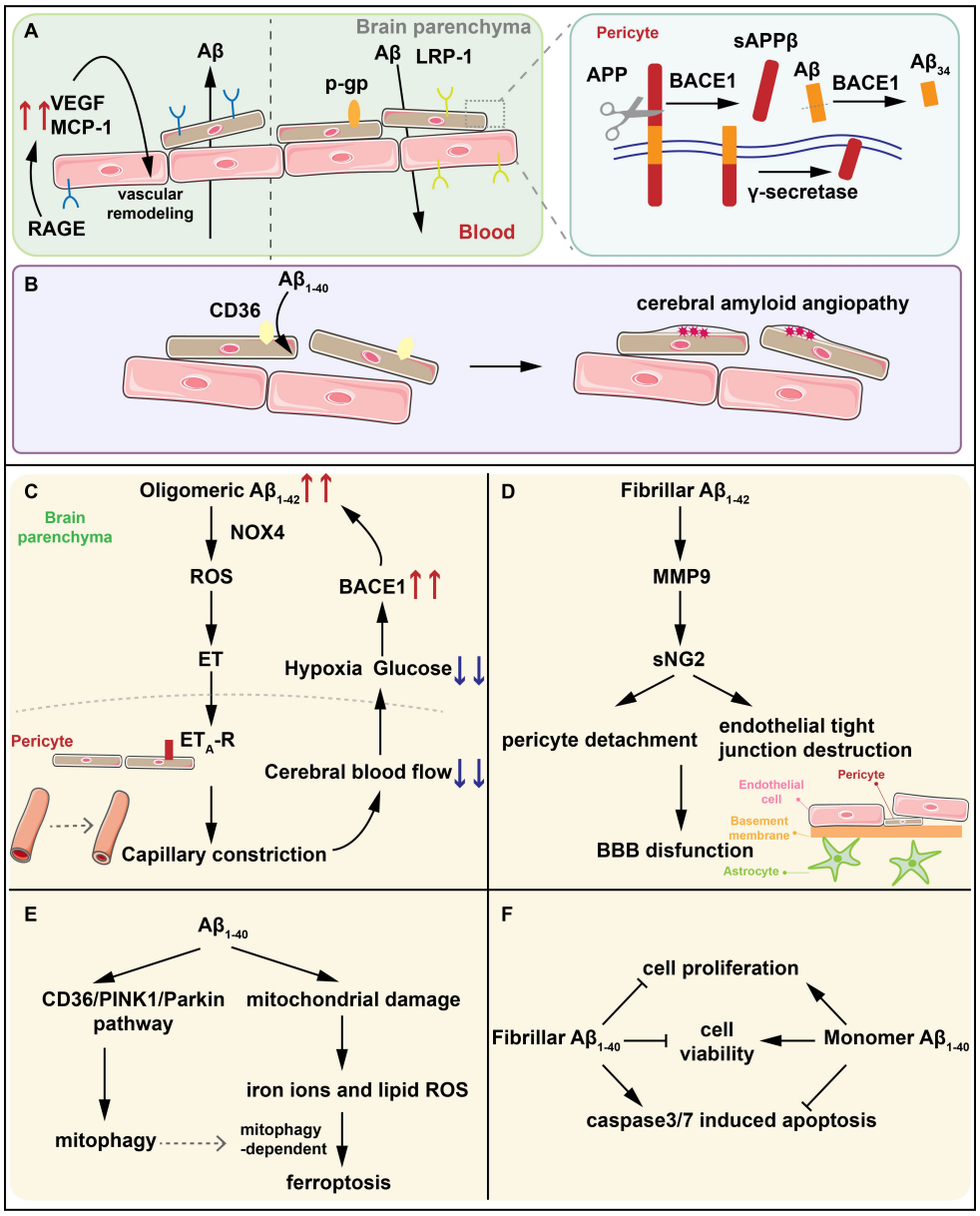

Fig. 1. The interactions between Aβ and pericytes. (A) LRP-1 and P-gp mediate the efflux of Aβ while RAGE regulate the influx of Aβ into brain parenchyma. BACE1 on pericytes degrades Aβ1-40 into Aβ34 intermediates and the Aβ (1-42)-RAGE interaction induces the generation of VEGF and MCP-1 contributing to the vascular remodeling. (B) CD36 mediates the clearance of Aβ1-40 by pericytes. The reduced expression of CD36 promotes the deposition of Aβ1-40 resulting in CAA. (C) Oligomeric Aβ1-42 activates NOX4 in pericytes to produce ROS and ET in sequence, and ET binds to ET_A-R on pericytes, triggering capillary constriction. Capillary constriction results in the reduction of CBF and the glucose and oxygen it contains. Hypoxia in turn upregulates the expression of BACE1, further increasing the generation of Aβ and forming an amplified positive loop, ultimately leading to synapse dysfunction and neuron loss. (D) Fibrillar Aβ1-42 activates MMP-9 to induce NG2 sheds from pericytes leading to the detachment of pericytes and the destruction of endothelial TJs which is the significant part of BBB. (E) Aβ1-40 induces pericytes mitophagy through the CD36/PINK1/Parkin pathway and increases oxidative stress in pericytes. The increased lipid ROS and iron ions caused by oxidative stress in pericytes inducing pericytes ferroptosis dependent on mitochondrial autophagy. (F) Fibrillar Aβ1-40 reduces the viability and proliferation of pericytes, and increases the activity of the key apoptotic proteins caspase3/7 while the effects of monomer Aβ1-40 are completely opposite. LRP-1, LDL receptor-related protein-1; RAGE, receptors for advanced glycation end products; Aβ, beta-amyloid; BACE1, β-site amyloid precursor protein (APP) cleaving enzyme 1; VEGF, vascular endothelial growth factor; CAA, cerebral amyloid angiogenesis; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; ROS, reactive oxygen species; ET, endothelin; CBF, cerebral blood flow; MMP-9, matrix metalloproteinase-9; NG2, neural/glial antigen 2; TJs, endothelial tight junctions; BBB, blood–brain barrier; PINK1, PTEN-induced putative kinase 1; sAPPβ, soluble amyloid precursor protein beta; MCP-1, monocyte chemoattractant protein-1; ET_A-R, endothelin receptor type A.

cular dysfunction (Fig. 1B). Moreover, the transcription and expression levels of CD36 in pericytes treated with Aβ1-40 increased in a concentration-dependent manner aggravating vascular dysfunction [132]. Aβ1-40 increases the permeability of the BBB *in vitro*, which can be reversed by inhibiting the expression of CD36 in pericytes, suggesting that inhibiting the expression of CD36 increases BBB tightness [133], providing a new therapeutic target for preventing BBB destruction during AD progression.

6. The Effects of Aβ on Pericytes

Aβ exerts toxic effects on pericytes through various pathways, and a significant loss of pericytes has been observed in AD patients. We have summarized the pathological effects of interactions among targets of pericytes and different species of Aβ, as well as the pathological changes observed in AD, in Table 2 (Ref. [36,37,128,134–141]).

6.1 Aβ1-42 Evokes the Constriction of Pericytes

Previous studies have shown that a decrease in the CBF is the earliest change in AD patients [19], and capillaries exhibit focal constriction [142]. Vascular resistance in the brain mainly occurs in capillaries, and the CBF is regulated by pericytes, indicating that pericytes dysfunction contributes to vascular disturbances in AD [22]. One of the most characteristic changes in AD is the aberrant deposition of Aβ, which results in the formation of Aβ plaques in the brain parenchyma, suggesting that Aβ may be the latent culprit.

In human brain slices, Aβ1-42 (oligomeric and monomeric) can trigger a slowly progressive constriction of capillaries near pericytes, suggesting that Aβ1-42 induces the constriction of human pericytes in a concentration-dependent manner within limits [36]. Reactive oxygen species (ROS) are generated by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and can be removed by superoxide dismutase 1 (SOD1) [134]. Recently, Nortley *et al*. [36] discovered that oligomeric Aβ1-42 evoked capillary constriction could be blocked by endothelin receptor type A (ET_A-R), SOD1 and NADPH oxidase inhibitors, suggesting that ROS and endothelin (ET) participate in the constriction induced by Aβ1-42. Moreover, evidence has shown that ROS in pericytes are produced by reduced nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4) [135] rather than other isoforms. After ET was applied along with SOD1, the capillaries remained constricted, demonstrating that ET functions downstream of ROS. Moreover, ET combined with ET_A-Rs on pericytes triggers intense constriction [143]. In summary, Aβ1-42 activates NOX4 in pericytes to generate ROS, and these ROS induce the generation of downstream ETs, which then interact with ET_A-Rs on pericytes, triggering strong capillary constriction [36,144]. The constriction of capillaries increases vascular resistance, causing a reduction in the CBF, which leads to a decrease in glucose and oxygen supplies, ultimately leading to synapse dysfunction and neuron loss [145]. In addition, hypoxia in turn upregulates the expression of BACE1, further increasing the generation of Aβ and forming an amplified positive loop [143] (Fig. 1C). The discovery of this mechanism overturns the previous view that the reduction in the CBF is the result of arteriole constriction.

It has been observed that the level of ET increases in AD with the upregulation of enzymes responsible for synthesizing ET [136]. Similarly, compared to those in nondemented controls, Sengillo *et al*. [69] reported a remarkable loss of pericytes in the cortex and hippocampus of AD patients, which may be attributed to the fact that chronic exposure to Aβ1-42 results in the constriction and rigid death of pericytes. Fortunately, blocking NOX4 and ET_A-Rs prevent further contraction caused by Aβ, although the capillary diameter does not return to baseline levels. Moreover, C-type natriuretic peptide (CNP) successfully reverses the Aβ-evoked constriction [136] and may be applied in the treatment of AD in the future.

6.2 Aβ1-42 Induces the Detachment of Pericytes by Activating MMP-9 to Induce NG2 Shedding from Pericytes

Neural/glial antigen 2 (NG2), a transmembrane proteoglycan, is an original marker of pericytes [30]. NG2 not only plays a significant role in the proliferation and motility of pericytes, but also promotes the formation and maturation of endothelial TJs [38].

Aβ1-42 is the principal component of neuritic plaques characterized in AD. Different aggregated forms of Aβ1-42 have been proven to influence the shedding of NG2 from pericytes differently. NG2 sheds pericytes to form soluble NG2 (sNG2). Fibrillar Aβ1-42 decreases the level of sNG2, while the level of sNG2 increases after exposure to oligomer-enriched preparations of Aβ1-42 [137]. After exerting inhibitors of matrix metalloproteinase (MMP, an angiogenic factor secreted by pericytes) [138], the consequences of fibrillar Aβ1-42 remain, while increase in sNG2 resulting from oligomeric Aβ1-42 is eliminated, suggesting that the shedding of NG2 induced by Aβ is mediated by MMP-9. Moreover, fibrillar Aβ1-42 decreases the activity of MMP-9 while oligomeric Aβ1-42 increased MMP-9 activity [137]. However, oligomeric Aβ1-42 does not alter the concentration of MMP-9, indicating that Aβ1-42 affects the activity rather than the secretion of MMP-9.

Taken together, in the early stage of AD, Aβ1-42 exists as oligomers and activates MMP-9, which subsequently increases the level of sNG2. The finding coincides with the discovery of increased MMP-9 in cerebrospinal fluid (CSF) during early AD pathogenesis [139]. sNG2 has been demonstrated to promote angiogenesis, resulting in unstable blood vessels and dysfunction of the BBB [146], and the level of sNG2 is increased in the CSF of AD patients [147]. In addition, the release of NG2 from the cell surface of pericytes drives pericyte detachment and contributes to

Table 2. Interactions among targets in pericytes and different species of Aβ (f: fibrillar; o: oligomeric; m: monomeric), pathological effects and pathological changes in AD.

Study type	Markers of pericytes	Targets	The species of Aβ	Pathological effects	Pathological changes in AD	Ref.
In vitro	PDGFRβ	NOX4	oAβ1-42	NOX4 activated by Aβ1-42 induce oxidative stress in pericytes. ROS trigger the generation of ET, which interact with ET_A-R on pericytes, triggering strong capillary constriction.	The level of ET increases.	[36,134–136]
In vitro	NG2, PDGFRβ and αSMA	MMP-9	fAβ1-42	f Aβ1-42 decreases the activity of MMP-9, preventing the detachment of pericytes.	In early stage of AD, the level of MMP-9 and sNG2 in CSF are increased.	[137–139]
			oAβ1-42	oAβ1-42 increases the activity of MMP-9, promoting the detachment of pericytes.		
Both *in vitro* and *vivo*	PDGFRβ and NG2	CD36/PINK/Parkin	Aβ1-40	Aβ1-40 induces ferroptosis of pericytes by activating mitochondrial autophagy.	Pericytes exposed to Aβ1-40 exhibit ferroptosis in TEM.	[128,140]
In vitro	PDGFRβ and NG2	Caspase3/7	fAβ1-40	f Aβ1-40 reduces the viability and proliferation of pericytes by increasing the activity of caspase 3/7.	Aggregated Aβ1-40, the major component of deposition in CAA may account for the loss of pericytes in AD.	[37,141]
			mAβ1-40	m Aβ1-40 decreasing the mortality of pericytes by decreasing the activity of caspase 3/7.		

Abbreviations: AD, Alzheimer's disease; PDGFRβ, platelet-derived growth factor receptor-β; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; ROS, reactive oxygen species; ET, endothelin; NG2, neural/glial antigen 2; αSMA, alpha-smooth muscle actin; MMP-9, matrix metalloproteinase-9; CSF, cerebrospinal fluid; TEM, transmission electron microscopy; CAA, cerebral amyloid angiogenesis.

the loss and dysfunction of TJs. Even worse, this effect could be aggravated by the enhanced degradation of the extracellular matrix and TJs caused by increased MMP-9 activity [148]. The detachment of pericytes and destruction of endothelial TJs destroy the integral structure of the BBB and increase the permeability of the BBB (Fig. 1D). Subsequently, the hazardous substances enter the brain and neurotoxicity caused by Aβ could cause neuronal loss and cognitive decline. As the disease progresses, fibrillar Aβ1-42 accumulates, which may be the protective mechanism of the body [149].

Researchers found that the *SIRT1* activator, resveratrol, reduced serum MMP-9 levels in AD patients, thus reducing neuro-inflammation [141]. Additionally, resveratrol was able to slow down the progressive decline in daily living scores (ADLs) in AD patients [141]. In spite of this, the relationship between the delay in cognitive decline and the decrease in MMP-9 remains unknown. The discovery that Aβ1-42 influences the shedding of NG2 on pericytes via MMP-9 may explain the pathology of AD and provide a new therapeutic strategy, such as specifically inhibiting MMP-9, to prevent AD dysfunction.

6.3 Aβ1-40 Induces Pericyte Mitophagy-Dependent Ferroptosis through the CD36/PINK/Parkin Pathway

Aβ1-42 (<10%) and Aβ1-40 (<80%) are two typical soluble monomeric subtypes of Aβ [49]. Aβ1-42 is more likely to form insoluble aggregates than Aβ1-40 [6], but Aβ1-40 can be deposited in the vascular system to form CAA [150]. Recently, it has been reported that more than 90% of patients with AD have CAA and CAA usually precedes the formation of neuritic plaques that are composed mainly of Aβ1-42 [151]. Aβ1-40 is presumed to have a particular toxicity to pericytes [152] and could accelerate the disruption of the BBB.

A recent study showed that pericytes treated with Aβ1-40 exhibit a prominent decrease in proliferation and a marked increas in mitochondrial ROS (Mito SOX) in a manner dependent on both time and concentration [132]. The results also demonstrated that Aβ1-40 activates mitochondrial autophagy through the CD36/PINK/Parkin pathway (PINK, PTEN-induced putative kinase) [132]. Mitochondrial damage and autophagy induced by Aβ1-40 often lead to apoptosis [140]. Notably, Aβ1-40 rather than apoptosis increases oxidative stress in pericytes. An increase in lipid ROS is accompanied by an increase in the concentration of iron ions, indicating that Aβ1-40 may induce pericyte ferroptosis [153]. The morphological features of pericytes exposed to Aβ1-40 according to transmission electron microscopy (TEM) also correspond with ferroptosis. Moreover, inhibiting mitochondrial autophagy prevents pericyte ferroptosis and ferroptosis inhibitors could prevent mitochondrial autophagy evoked by Aβ1-40, suggesting that ferroptosis is dependent on mitochondrial-related autophagy [132] (Fig. 1E).

6.4 Aβ1-40 Affects Pericytes in an Aggregation-Dependent Manner

The expression of pericyte markers is dynamic, and depends on the functional state of pericytes; for example, PDGFRβ labels relatively immature pericytes [33], NG2 stimulates the proliferation and migration of pericytes [34], and laminin is expressed in active or mature subsets of pericytes [154]. In the hippocampus of AD patients, a significant reduction in the number of pericytes expressing NG2 [37], CD13 and PDGFRβ [70] is observed, while the number of pericytes expressing other markers is not affected. It can be concluded that the subsets of pericytes that participate in activation, migration, and proliferation are affected by the pathology of AD. A previous study demonstrated that the CAA formed by Aβ1-40 is associated with pericyte degenerative changes [150]. Interestingly, Aβ1-40 levels are associated with the number of pericytes [37]. Since aggregated Aβ1-40 is toxic [150], it is speculated that monomeric Aβ1-40 may be beneficial.

Schultz *et al*. [37] showed that fibrillar Aβ1-40 reduces the viability and proliferation of pericytes *in vitro*, and increases the activity of the key apoptotic proteins caspase3/7. These findings are consistent with the discovery of pericyte degeneration near fibrillar Aβ1-40 [150]. Moreover, the monomer Aβ1-40 decreases the mortality of pericytes by decreasing the activity of caspase3/7, and promoting pericyte proliferation, which could explain the positive correlation between the levels of monomeric Aβ1-40 and the number of pericytes (Fig. 1F).

The occurrence of CAA and AD largely overlap [13–15] and the occurrence of advanced CAA is related to more severe cognitive impairment in patients with AD [15,16]. Aggregated Aβ1-40, the major component of deposition in the CAA may account for the loss of pericytes in AD patients [155].

7. Strategies to Prevent or Treat AD via Pericytes

Further understanding of the interactions between pericytes and Aβ could lead to new insights for the treatment of AD. Superoxide dismutase-1 (SOD1) can eliminate ROS generated by NOX4 activated by Aβ [36]. Using SOD1 to eliminate ROS may be effective at preventing the constriction of pericytes. Indeed, overexpression of SOD1 or topical application of exogenous SOD could reverse vascular dysfunction and premature mortality in transgenic mice overexpressing APP [156]. Pterostilbene (PTE), the natural dimethylated analog of resveratrol, can upregulate the expression of *SIRT1* and SOD to exert neuroprotective effects [157]. Moreover, since Aβ cannot induce the constriction of pericytes without ET [143], reducing the generation of ET or blocking the combination of ET and ET_A-R may be effective. It has been proven that blocking NOX4 or ET_A-Rs could prevent further constriction of capillaries evoked by Aβ and CNPs could successfully reverse the

constriction of capillaries mediated by ET [36]. In addition, Aβ induces endothelial dysfunction characterized by attenuated endothelium-dependent relaxation and increased endothelium-dependent constriction since Aβ inactivates vasodilators produced by the endothelium and increases the production and release of ET [158]. In APP overexpressing mice, bosentan, an antagonist of both ET_A and the ET_B receptor, was shown to preserve the endothelial function of the aorta and carotids [159]. Autopsy evidence has shown that the majority of Alzheimer's disease patients suffer from vascular diseases such as CAA [13,15]. Several ET receptor antagonists, including bosentan have been applied to treat pulmonary hypertension, and recent studies have demonstrated the beneficial effects of bosentan in restoring the cerebrovascular function of diabetic rats and preventing coronary endothelial functions in hypercholesterolemic pigs [160–162]. The ability of bosentan to preserve endothelial functions in Aβ overexpressing Tg2576 mice demonstrated the potential of ET receptor antagonists for the prevention and treatment of AD.

Another promising approach might be to implant pericytes or mesenchymal stem cells (MSCs) into the brain. In APP/PS1 mice, the CBF was increased and Aβ plaques were significantly reduced in the pericyte-injected hemisphere [91]. However, no significant effects on cognitive function were observed in a recent phase I clinical trial in which stereotactically injected MSCs were administered to the brains of AD patients [92]. Many studies have shown that RAGE inhibitors may be potential targets for treating AD [107,163,164]. Recently, PF-04494700, an oral inhibitor of RAGE has attracted widespread attention. However, two clinical trials on PF-04494700 have shown that although PF-04494700 is safe and well-tolerated, it has no apparent benefit in improving cognitive decline [165,166]. Notably, high-dose PF-04494700 could also increase adverse reactions and exacerbate cognitive impairment [165].

8. Conclusion

Pericytes are multifunctional cells of the vascular system and important components of the BBB and NVU. Pericytes regulate the CBF in response to neurotransmitters and neuronal activity and are essential for endothelial TJs and they are necessary for the formation and maintenance of the BBB. Bidirectional communication between ECs and pericytes is necessary for angiogenesis. Moreover, pericytes mediate phagocytosis to maintain homeostasis in the brain.

The aberrant deposition of Aβ is the predominant pathological change in AD. Pericytes can clear Aβ via LRP-1, RAGE, P-gp, and CD36, and Aβ is degraded in pericytes via BACE1. The impairment of these pathways may account for the pathogenesis of AD. Aβ1-42 evokes the constriction of pericytes and causes death after chronic exposure. A decrease in the CBF caused by capillary constriction leads to hypoxia and glucose deficiency, contributing to the neuronal dysfunction and cognitive decline. Aβ1-42 also induces the detachment of pericytes. Aβ1-40 induces pericyte mitophagy-dependent ferroptosis through the CD36/PINK/Parkin pathway. The loss of pericytes exacerbates the aggregation of Aβ in AD. Conversely, the loss of pericytes is a result of the action of Aβ. Further exploration of the interactions between pericytes and Aβ is beneficial for understanding AD and provides new therapeutic targets for the prevention and treatment of AD.

Author Contributions

YYL—literature collection, literature analysis and drafting the manuscript; DDG—literature collection and literature analysis; RND—editing, preparing the figures, reviewing and giving final approval of the version; YL—editing, preparing the figures, reviewing and giving final approval of the version. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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