

REVIEW

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Trajectory of brain-derived amyloid beta in Alzheimer's disease: where is it coming from and where is it going?

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Abstract

Alzheimer's disease (AD) is a progressive neurological disorder that primarily impacts cognitive function. Currently there are no disease-modifying treatments to stop or slow its progression. Recent studies have found that several peripheral and systemic abnormalities are associated with AD, and our understanding of how these alterations contribute to AD is becoming more apparent. In this review, we focus on amyloid-beta ($A\beta$), a major hallmark of AD, summarizing recent findings on the source of brain-derived $A\beta$ and discussing where and how the brain-derived $A\beta$ is cleared in vivo. Based on these findings, we propose future strategies for AD prevention and treatment, from a novel perspective on $A\beta$ metabolism.

Keywords Alzheimer's disease, Amyloid- β , Periphery system, Immune clearance

Background

Alzheimer's disease (AD) is an age-related neurodegenerative disease that can lead to brain atrophy and neuronal death in the brain [1]. AD is the most common type of dementia. In the 2019 Global Status Report on the Public Health Response to Dementia, the World Health Organization (WHO) highlighted that approximately 55 million patients worldwide are suffering from AD. Without significant medical breakthroughs in the prevention, slowing, and treatment of AD, the number would reach 150 million by 2050. However, after nearly a century of research, effective preventive strategies and treatments for AD are still lacking. A deeper understanding of the pathogenesis of AD may facilitate development of therapeutic strategies for AD.

AD pathogenesis is complex, involving extracellular amyloid-beta ($A\beta$) protein plaques, intracellular tau, neurofibrillary tangles, cholinergic insufficiency, oxidative stress, mitochondrial dysfunction, inflammation, and hormonal imbalances [2]. Brain $A\beta$ plaques are the major pathological hallmark of AD [3]. Hardy et al. [4] found that amyloid precursor protein (APP) gene mutations can lead to massive $A\beta$ deposition in the brain. They further proposed the $A\beta$ cascade hypothesis, supported by the molecular genetic data of early-onset familial AD. The hypothesis states that when the amount of $A\beta$ generated is greater than the amount that is degraded, accumulation occurs, leading to plaque formation, tau tangle formation, neuronal death, and a cascade of neuroinflammatory responses [5]. The anti- $A\beta$ monoclonal antibodies Aducanumab and Lecanemab have been approved by the United States Food and Drug Administration (FDA) for brain $A\beta$ clearance.

Both human and mouse studies have demonstrated that high levels of $A\beta$ can flow from the brain to the periphery, and physiological catabolism of brain-derived $A\beta$ can occur in the peripheral system [6]. This provides

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a novel perspective for understanding the pathogenesis of AD and developing therapeutics. In this review, we focus on the systemic role of A β in AD, discussing the major source of brain A β and associations of brain-derived A β aggregates with inflammation in the brain. We also discuss the communications between peripheral and central pools of A β , the peripheral pathways of brain-derived A β clearance, and how systemic diseases might interfere with brain-derived A β clearance. Finally, we summarize therapeutic strategies targeting A β .

Where does brain-derived A β come from?

The generation and spread of A β

A β is a peptide of 38–43 amino acids generated from sequential cleavage of β -APP by β -secretase (BACE1) and γ -secretase [7]. BACE1 is an aspartyl protease that cleaves APP primarily at a single site, β -site1, whereas the γ -secretase complex cleaves the C-terminal fragment (CTF) at multiple sites, with preference for positions 40 and 42, forming the A β_{40} and A β_{42} peptides [8] (Fig. 1a). Previous studies have indicated that A β_{38} and A β_{3-40} are more amyloidogenic than other forms of A β , such as A β_{4-40} [8]. APP is a transmembrane protein widely expressed in brain neurons and various peripheral tissues, including blood (platelets) and peripheral organs (skin, intestines, and liver) [9, 10] (Fig. 1a). Alternative splicing of exons 7 and 8 of *APP* leads to generation of three major isoforms of APP, APP₆₉₅, APP₇₅₁, and APP₇₇₀, comprising 695, 751 and 770 amino acids, respectively [11]. The APP₆₉₅ isoform is predominantly expressed in neurons and lacks two exons. APP₇₅₁ and APP₇₇₀ possess a Kunitz-type serine protease inhibitor domain encoded by exon 7, while APP₇₇₀ contains an additional immunoregulatory OX-2 antigen domain encoded by exon 8 in its extracellular region. Both APP₇₅₁ and APP₇₇₀ are expressed in both the brain and peripheral tissues [12, 13]. Therefore, AD is a disorder of both the central nervous system (CNS) and the peripheral system. Moreover, studies in animal models and cell cultures demonstrate that peripheral A β seeds accelerate plaque formation in a prion-like manner via templated seeding and intercellular propagation [14]. One study found that hepatogenic A β can enter the bloodstream through triglyceride-rich lipoproteins and further deposit in the brain to result in AD-like pathology, including neurodegeneration and brain atrophy [15]. Similarly, A β plaques have also been detected in the gastrointestinal tracts of AD patients and mice [16]. Additionally, when fluorescence-labeled A β is injected into the intestines of C57BL/6J mice, the fluorescence-labeled A β could spread to the hippocampus, resulting in brain disorder [17]. In another study, AD patient brain lysates were injected into the colons of wild-type (WT) mice, and induced AD-like pathology in

the mice [18]. These studies suggest that A β in the gastrointestinal tract can also enter the brain parenchyma, resulting in A β deposition in the brain. However, it is still unclear how gastrointestinal tract A β is transmitted from the intestines to the brain and how A β deposition is induced.

Brain-derived A β can enter the peripheral blood through the blood–brain barrier (BBB) or cerebrospinal fluid (CSF) [9]. Given the bidirectional relationship between the brain and the periphery, the question arises concerning whether peripheral A β is the primary source of brain A β . Bu and colleagues used a parabiosis model between APP^{swE}/PS1^{dE9} (APP/PS1) transgenic AD mice and their WT littermates, and found that the blood-derived A β can enter the brain and induce AD-like pathologies in WT mice, suggesting that the blood-derived A β may contribute to AD pathogenesis [19]. Lam and colleagues generated hepatocyte-specific human amyloid transgenic mice that produce pathogenic A β specifically in the liver. They found that the liver-derived A β travels through the circulatory system and crosses the BBB to enter the brain. The accumulation of A β in the brain drives the pathology associated with AD, including capillary dysfunction, inflammation and neurodegeneration [15]. Platelets are the primary source of A β in the peripheral circulation, and transplantation of bone marrow cells from APP/PS1 mice into WT mice leads to a continuous increase of human A β in the blood and A β deposition in the brain [20]. These findings suggest that AD is not simply a result of brain A β deposition.

A β aggregation

Under normal physiological conditions, brain A β production and clearance are maintained at a dynamic balance and confer neuroprotection [9]. However, this balance can be disrupted by excessive production or decreased clearance of A β . Microglia dysfunction, low expression of low-density lipoprotein receptor-related protein-1 (LRP-1), apolipoprotein E (ApoE) overexpression, and ApoE binding to LPR-1 in competition with A β , can affect the clearance of A β [21, 22] (Fig. 1b). In addition, A β (especially A β_{42}) is a hydrophobic peptide that is prone to aggregation. When A β_{42} exceeds a certain level, its monomers would aggregate into soluble oligomers, fibrils, and even insoluble plaques [23]. The brain A β_{42} patches will continuously recruit A β_{42} monomers and oligomers to form larger plaques [24]. A β oligomers are considered as the main neurotoxic components, and there is a negative correlation between the degree of oligomer aggregation and the level of toxicity [25]. The Osaka and Arctic mutations in *APP* can increase A β hydrophobicity, enabling aggregate formation [25, 26]. Studies have shown that the E693Delta *APP* mutation produces an A β variant

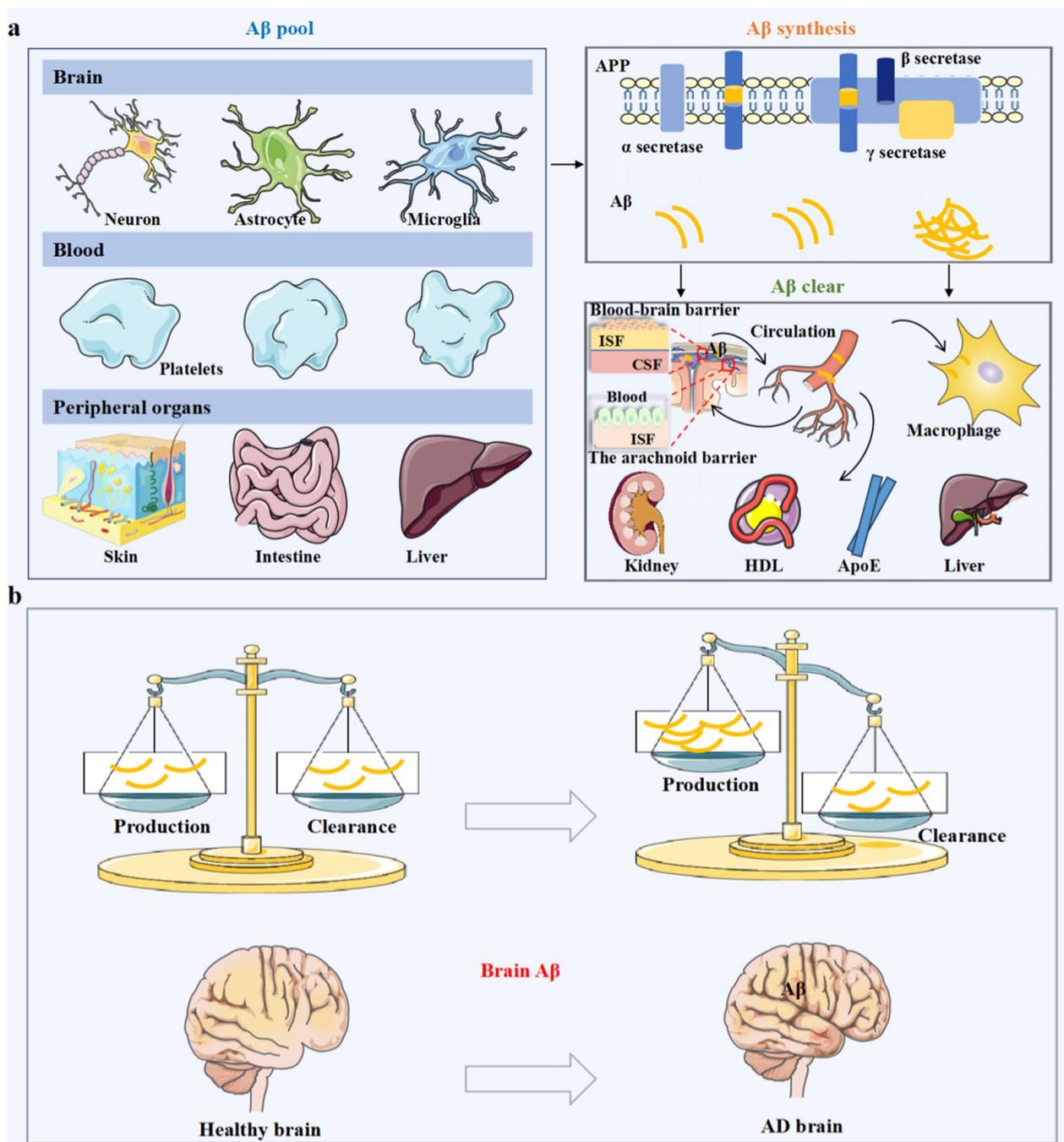


Fig. 1 The generation and clearing path of Aβ. **a** The source, synthesis, and clearance of Aβ under normal physiological condition. Aβ is produced by neurons, microglia and astrocytes in the brain, platelets in the blood, and the skin, intestine, and liver in the periphery. Some Aβ is released from the brain to the blood via the blood–brain barrier (BBB), the interstitial fluid (ISF) bulk flow or cerebrospinal fluid (CSF) leakage. Aβ can also be transported to peripheral organs or tissues by carriers, where it is degraded by macrophages or hepatocytes or excreted via the liver or kidney. Under normal physiological conditions, high-density lipoprotein (HDL) prevents Aβ vascular accumulation independently of its primary receptor, scavenger receptor class B type 1 (SR-B1). ApoE promotes Aβ clearance by activating phagocytosis and increasing Aβ migration in microglia, where ApoE4 has a reduced capacity to induce these phenotypes than ApoE3. **b** Under normal physiological conditions, there is a balance between Aβ production and clearance (healthy brain without Aβ deposits). Under pathophysiological conditions, there is a loss of the balance between Aβ production and clearance, leading to Aβ aggregation in the brain (AD brain with Aβ deposition)

more resistant to proteolytic degradation and showing enhanced oligomerization but no fibrillization, which is more likely to induce early symptoms of AD, indicating that the level of A β aggregates is closely related to the progression of AD [27].

What harmful effects can brain-derived A β induce? Brain-derived A β aggregates induce polarization of microglia

Microglia are the primary immune cells in the brain and mainly include M1 and M2 microglia. The M1 type represents the pro-inflammatory phenotype, and M2

represents the anti-inflammatory phenotype [28]. M2 microglia can exhibit both alternative activation and acquired deactivation, which are induced by interleukin (IL)-4 and IL-10, respectively. In the early stage of AD, M2 microglia phagocytose misfolded A β and exert a neuroprotective effect [29] (Fig. 2a). However, when the A β plaque enrichment exceeds the capacity of microglial phagocytosis, the microglia would shift from the M2 to the M1 type, releasing a large amount of pro-inflammatory factors such as IL-1 β and IL-6 [30, 31]. These pro-inflammatory factors can aggravate neuroinflammation, lead to neuronal damage, and further

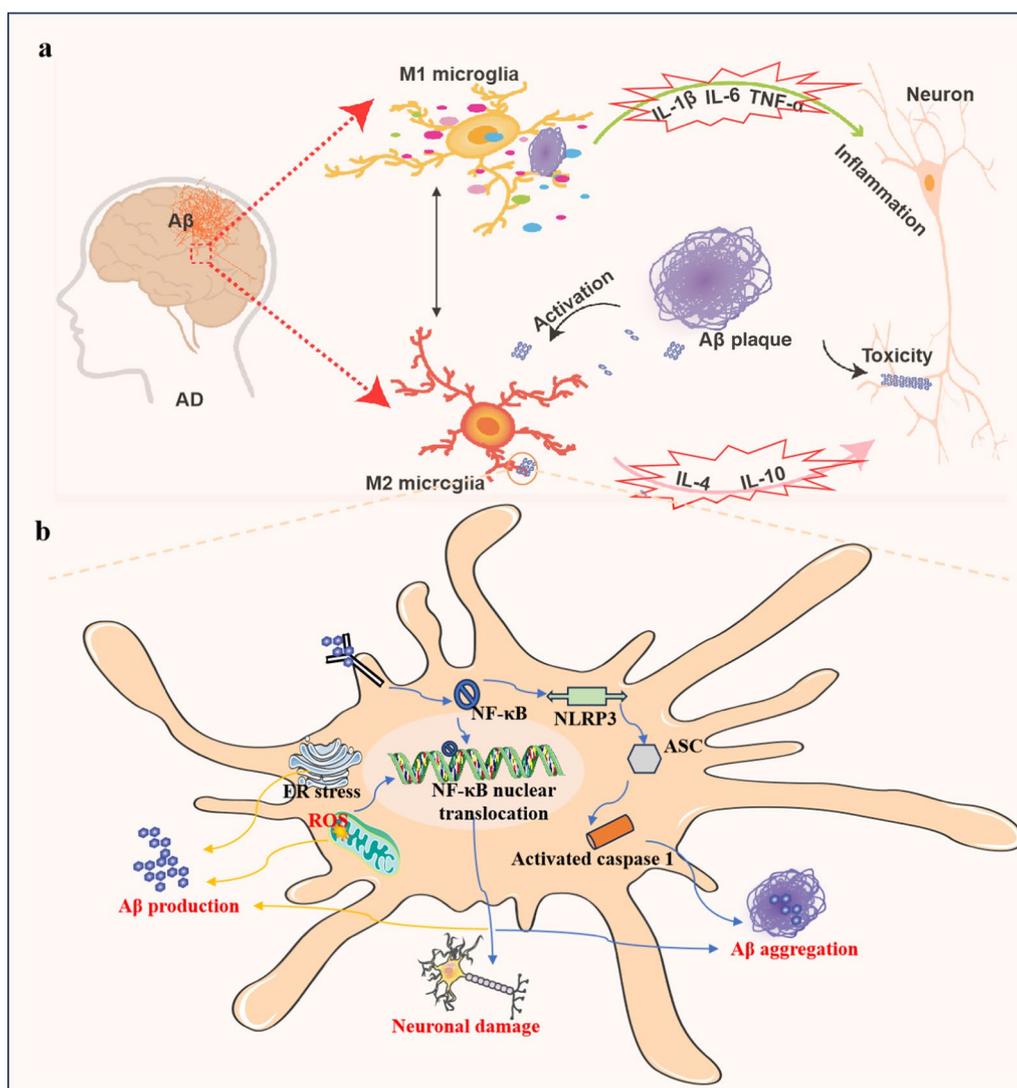


Fig. 2 The hazards of brain A β aggregates. The diagram shows the dual functions of microglia. **a** A β aggregates promote polarization of microglia from M2 to M1 phenotype in the brain. The M1 microglia promote neuroinflammation through secretion of pro-inflammatory factors, leading to neuronal damage. **b** A β stimulates neuroinflammation, with involvement of nuclear factor-kappa B (NF- κ B), endoplasmic reticulum (ER) stress, and the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome pathway

promote the production, aggregation, and deposition of A β , thus forming a vicious cycle [31–33] (Fig. 2a). The M1 microglia also highly express inducible nitric oxide synthase (iNOS), while reducing iNOS in APP/PS1 mice can reduce A β plaques in the brain [34]. In AD pathology, both disease-associated microglia and down-regulation of homeostasis-associated genes are related to the upregulation of AD-related genes, including *APOE*, triggering receptors expressed on myeloid cells-2 receptor2 (*TREM2*) and *TYROB* (tyrosine protein–protein binding protein) [3]. *TREM2* is only expressed in microglia in the CNS and is a positive regulator of phagocytosis [35]. *TREM2* is a receptor for lipoproteins, and mediates clearance of lipoprotein-A β complexes by microglia [36]. *TREM2* has a dual influence on AD pathogenesis. It can form a neuroprotective barrier around A β aggregates and prevent their spreading outward, resulting in dense A β plaques in the early stage of AD. On the other hand, *TREM2* also promotes inflammation in the middle and the late stages of AD [31, 37, 38].

In addition, the nuclear factor κ B (NF- κ B)/C3/C3aR signaling can regulate A β aggregation through astrocytes and microglia [35]. Brain A β aggregates activate the NF- κ B signaling in astrocytes, which release the complement protein C3a [35]. The interaction of C3a with C3a receptors on microglia and neurons promotes A β aggregation, and blocking the interaction between C3a and microglia can reduce microglial activation and the A β load in the brain [39].

Brain-derived A β aggregates stimulate neuroinflammation

Neuroinflammation is mediated mainly by microglia and is one of the main causes of neuronal damage and necrosis [35]. Astrocytes also play an auxiliary role in neuroinflammation. Early misfolding and aggregation of A β in the brain can be cleared by binding to receptors on the surface of microglia, such as receptors for advanced glycation end product, Toll-like receptor (TLR), nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3), and formyl peptide receptor (Fig. 2b) [40]. Loss of TLR4 and NLRP3 inflammasome in mice can reduce A β accumulation and production of pro-inflammatory cytokines IL-1 β and IL-18 [41]. Additionally, when NLRP3 is activated in response to damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs), it recruits ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain [CARD]) through PYD-PYD (Pyrin domain) interactions, leading to the formation of active caspase-1 through CARD-CARD interactions. NLRP3 activation exacerbates the accumulation of A β (Fig. 2b) [42], and A β aggregates would, in turn, promote the generation of IL, mitogen-activated protein kinase, NF- κ B

and reactive oxygen species (ROS), thus aggravating neuroinflammation [34, 43, 44]. ROS production has also been identified as a mediator of A β -induced endoplasmic reticulum (ER) stress and cytotoxicity [45]. Moreover, ER stress contributes to the progression of AD pathology [46] (Fig. 2b).

Neuroinflammation can also result in the engulfment of misfolded proteins such as A β by microglia and astrocytes [47]. Although controversy exists regarding the order of occurrence of A β aggregation and neuroinflammation, it is relatively clear that A β aggregation accelerates the development of neuroinflammation, which in turn promotes the production and aggregation of A β [48]. Neuroinflammation is a chronic response of the innate immune system, resulting in the failure of A β clearance.

How can brain-derived A β be cleared?

A β clearance strategies from the brain to the periphery

Lack of A β clearance is considered the main cause of A β deposition in patients with sporadic AD [49]. Therefore, accelerating the clearance of A β is a promising strategy for treating AD. Studies using the deep cervical lymph node ligation method in AD mice have revealed that brain lymphatic clearance is a physiological mechanism for A β transport from the brain to the periphery [50].

Brain-derived A β has been detected in the periphery of AD patients and AD mice. A β flows from the brain to the periphery mainly through the BBB pathway and the brain lymphatic pathway (Fig. 1a). In the BBB pathway, the capillary lengths in mouse and human brains are approximately 0.6 km and 650 km, respectively, which account for more than 85% of the total length of cerebral blood vessels, providing a large surface area for substance exchange between the blood and the brain [24, 51]. Brain-derived A β efflux is usually mediated by brain endothelial cell surface proteins, mainly LRP-1 [52]. Previous studies have suggested that approximately 40%–60% of brain-derived A β is cleared in the periphery. A β clearance via the BBB is reduced by approximately 30% in AD patients [53, 54]. The brain lymphatic pathways include the perivascular pathway, lymphatic system, meningeal lymphatic vessels, and olfactory/cervical lymphatic drainage, which drains A β in the CSF to the deep cervical lymph nodes, allowing A β and other macromolecules to drain from the brain to the periphery [27]. The exact contribution of each mechanism to the overall A β clearance remains unclear. Nevertheless, these pathways work together to remove pathological proteins from the brain to the periphery. These findings suggest that peripheral tissues and organs are physiologically involved

Table 1 Strategies for A β clearance via the peripheral system

| Peripheral system | Mechanisms | Strategy | Research findings | References |
|-------------------|---------------------------|-------------------------------------|---|-----------------|
| Blood | Enzymatic degradation | Insulin-degrading enzyme (IDE) | Astrocyte-secreted IDE regulates A β levels; a catalytically inactive IDE aids in A β degradation | [129, 142, 143] |
| | | Nepriylisin | Reduced nepriylisin activity elevates A β oligomers, impacting cognitive function; nepriylisin administration clears plasma A β | [57, 144, 145] |
| | | Angiotensin-converting enzyme (ACE) | ACE inhibitor ramipril boosted A β in AD*ACE mice; intranasal ACE inhibitors mitigated inflammation in 5xFAD mice | [146, 147] |
| | Cell transplantation | Bone marrow | Bone marrow exosomes benefit AD behavior; young marrow preserves memory in mice | [55, 148] |
| | | Bone marrow-derived cells | Bone marrow-derived cells recruit microglia in response to A β , contributing to cognitive improvement in AD | [44, 149, 150] |
| | Immune clearance | Monocytes | A β uptake by blood monocytes is reduced with aging in AD patients and mice | [67, 151] |
| | | Macrophages | SHARPIN (Shank-associated RH domain-interacting protein) regulates A β phagocytosis and inflammation in macrophages; anti-oxidants could enhance the A β phagocytic efficacy of macrophages | [152, 153] |
| | Blood exchange | Hemodialysis | Dialysis effectively reduces A β_{42} and A β_{40} plasma levels in cognitively impaired patients | [154–156] |
| | | Peritoneal dialysis | Peritoneal dialysis reduces A β plasma levels in humans and attenuates AD-associated phenotypes in APP/PS1 mice | [157] |
| | | Whole blood therapy | Plasma exchange reduced A β in the plasma and decreased A β deposition in the cortex and hippocampus in APP/PS1 mice | [63, 158, 159] |
| Liver | Receptor regulation | Gene regulation | Enhancing hepatic A β clearance via LRP-1 overexpression attenuated cerebral A β deposition and cognitive impairments in APP/PS1 mice | [63] |
| | | Enzyme activity | Liver X receptor agonist treatment prevented memory deterioration and significantly reduced hippocampal A β . Hepatic soluble epoxide hydrolase regulates cerebral A β metabolism | [160, 161] |
| Kidney | Peripheral sink | Liver enrichment | CuxO@EM-K reduces A β burden in the blood and brain | [64] |
| | Increase urination volume | Diuretic | Chronic furosemide treatment reduced blood and brain A β levels and attenuated AD pathologies and cognitive deficits in APP/PS1 mice | [66] |
| Spleen | Peripheral sink | Monocytes/macrophages | Spleen clears A β physiologically; splenectomy worsens AD-type pathogenesis | [68] |
| Gut | Inflammation regulation | Microbial diversity | Treatment with <i>Bifidobacteria</i> or GV-971 can suppress A β accumulation and neuroinflammation | [73, 74, 162] |

in the clearance of brain-derived A β , including the blood, liver, kidney, spleen, and gut (Table 1).

Blood-mediated A β clearance

The peripheral sink hypothesis suggests that by increasing A β clearance from the blood, a concentration gradient is created, which favors the efflux of A β from the brain to the bloodstream, thus facilitating A β clearance [27, 55]. As blood components, secreted enzymes are critical for the catabolism of peripheral A β . These enzymes include insulin-degrading enzyme [56], nepriylisin [57] and angiotensin-converting enzyme [58]. They have an affinity for specific domains of A β proteins and

can cleave these peptides into shorter, more benign forms. Immune cells in the blood, such as monocytes and macrophages, can recognize A β and clear A β peptides from circulation. Supplementing blood components by means of bone marrow transplantation [55] or by administering bone marrow-derived cells [44] or albumin [59] can enhance the clearance of peripheral A β . In addition, peripheral A β can be cleared by blood exchange, including hemodialysis, peritoneal dialysis, and replacement of fresh blood (whole blood therapy) [60].

Liver-mediated A β clearance

The liver plays a crucial role in systemic metabolism and detoxification, including the clearance of various substances from the blood. A study found that approximately 13.9% of A β_{42} and 8.9% of A β_{40} are removed by the liver and that LRP-1 mediates the peripheral clearance of A β in the liver. LRP-1 overexpression in hepatocytes enhances hepatic A β clearance, decreases cerebral A β deposition and attenuates cognitive impairment in AD mice [61–63]. Moreover, self-protecting biomimetic nanozymes, such as CuxO@EM-K, have been designed to test the efficacy of therapies that can enhance the peripheral sink effect, which could potentially redirect A β from the brain to the liver for clearance [64].

Kidney-mediated A β clearance

The kidney is thought to be responsible for A β clearance by filtering A β from the blood to the urine. There is a positive association between chronic kidney disease and a risk of cognitive impairment [6, 65]. Both acute kidney ligation and unilateral nephrectomy aggravate A β burdening in the blood and brain, neuroinflammation, and neurodegeneration in APP/PS1 mice. Moreover, chronic furosemide treatment can decrease brain A β deposition and ameliorate cognitive deficits in AD mice [66].

Spleen-mediated A β clearance

The spleen acts as a blood filter and an immune organ. The mononuclear phagocyte system found primarily in the spleen, has been thought to contribute to the clearance (engulfing and digesting) of A β . Splenectomy reduces the monocyte-derived periplaque macrophages and the circulating myeloid cells, and worsens amyloid pathology in APP/PS1 mice [67]. In addition, A β levels in the splenic artery are higher than those in the splenic vein, suggesting A β clearance when blood flows through the spleen. Splenectomy aggravates AD-related behaviour deficits and pathology in AD mice [68]. Therapies aimed at enhancing A β clearance through the spleen and other peripheral organs are a topic of interest. However, further studies are required to comprehensively understand the role of the spleen in A β clearance, especially the precise interplay between the peripheral immune system and brain pathology.

Gut-mediated A β clearance

Patients with AD often experience an imbalance in gut microbiota, such as an increase in pro-inflammatory gut microbes (e.g., *Shigella*) and a decrease in anti-inflammatory gut microbes (e.g., *Bifidobacterium*) [69]. This imbalance leads to abnormal secretion of secondary metabolites of gut microbes, such as lipopolysaccharides (LPS) and short-chain fatty acids (SCFAs). LPS

acts on the TLR4-CD14/TLR2 receptors on leukocytes and microglia, leading to NF- κ B-mediated increases of cytokines, resulting in elevated A β levels, damage to oligodendrocytes, and finally neuronal damage in AD brains [70]. In contrast, SCFAs, which are produced mainly by *Clostridium*, *Lactobacillus*, and *Bifidobacterium*, can cross the BBB via monocarboxylate transporters [71]. They can accelerate the clearance of brain A β by regulating the proliferation and differentiation of microglia. They can also directly bind to A β to inhibit the formation of A β plaques [72, 73]. Therefore, supplementation with probiotics can decrease the brain A β burden and ameliorate cognitive impairment in AD mice [66] (Fig. 3). In addition, the gut microflora in 5 \times FAD and APP/PS1 mice facilitate entry of peripheral immune cells into the brain, leading to microglial activation and disease progression. Treatment with GV-971 in these mice can restore the gut microbial profile, ameliorate brain immune cell infiltration and inflammation [74], reduce brain A β burden and tau hyperphosphorylation, and improve cognitive function [74]. These studies demonstrated that the brain–microbiota axis is involved in the pathogenesis of AD, and it is speculated that the gut has the potential to regulate peripheral A β clearance [75, 76].

Representative strategies for targeting A β clearance

In the past two decades, the development of AD drugs was particularly challenging. Most AD trials failed to demonstrate efficacy. However, confidence in the potential of AD drug development has not diminished [2]. In the Alzforum database, a total of 388 drugs in development for AD treatment are selected as eligible for scoring. These 388 drugs are categorized into eight therapy types and nine target classes. The largest number of drugs target A β (82, 21.19%), followed by those targeting inflammation (50, 12.92%), neurotransmitters and receptors (55, 14.21%), and tau (31, 8.01%) (Fig. 4a). At present, only 2 of the 82 A β -targeting drugs have been approved by FDA, with other 39 drugs undergoing clinical trials, 34 drugs having been discontinued, and 7 being inactive (Fig. 4a). Regarding the AD therapy type, most are classified as small-molecule drugs (222, 64.81%) or passive immunotherapy (44, 12.90%) (Fig. 4b). Among the 222 small-molecule drugs, seven have been approved by the FDA: galantamine, memantine, rivastigmine, suvorexant, brexpiprazole, donepezil, and tacrine. A further 110 drugs are undergoing clinical trials, 80 drugs have been discontinued or rejected, and only 24 are inactive. Moreover, among the 44 passive immunotherapy drugs, two have been approved by the FDA, i.e., Aducanumab

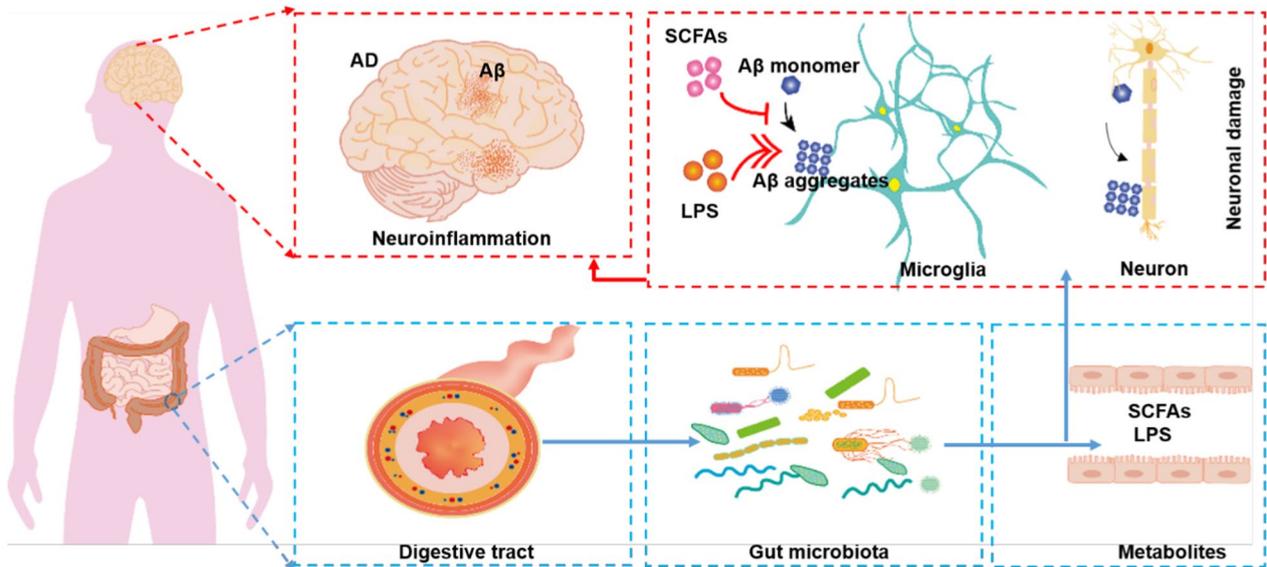


Fig. 3 The secondary metabolite lipopolysaccharides (LPS) from the gut microbiota, can affect brain Aβ via the gut-brain axis, causing neuronal damage and local inflammation, and promoting local and systemic Aβ deposition. Short-chain fatty acids (SCFAs) from the gut microbiota can enter the bloodstream and maintain BBB homeostasis, inhibiting Aβ deposition.

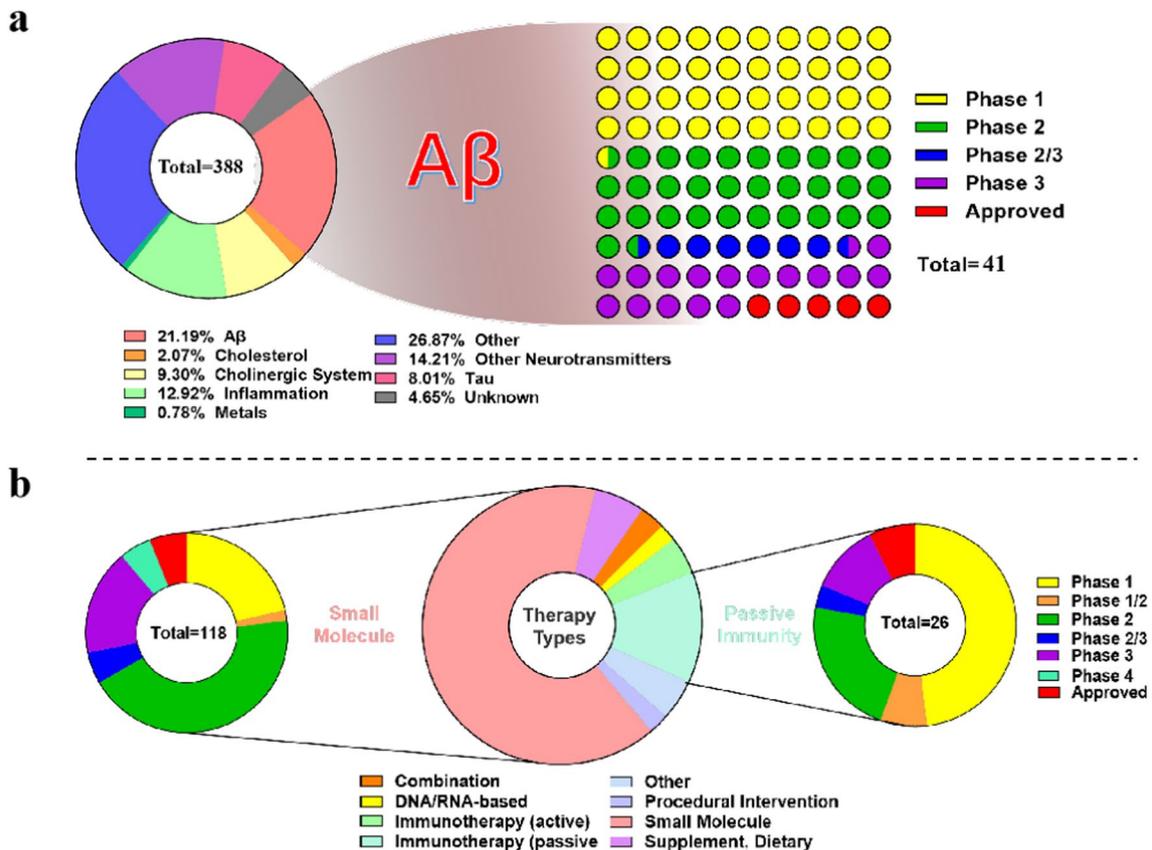


Fig. 4 Therapeutic targets and therapy types for AD (<https://www.alzforum.org/therapeutics>. Accessed March 28, 2024). **a** There are 388 drugs in development for AD. They are categorized into nine target classes. Of the 82 drugs targeting Aβ, only 39 are under clinical validation and 2 have obtained FDA approval. **b** The 388 drugs are categorized into eight therapy types. Among them, 118 small-molecule drugs and 27 passive immunotherapy drugs are in clinical validation or have obtained FDA approval

and Lecanemab, for use as A β -clearing drugs, and 24 drugs are undergoing clinical trials (Fig. 4b). Therefore, A β -targeting drugs are an important focus of research attention. In the following, we will elaborate on small-molecule drugs and passive immunotherapy.

Small molecules for A β clearance

When considering small molecules as an A β clearance strategy in AD, the goal is to reduce A β peptide accumulation in the brain (Table 2).

Secretory enzyme regulators The regulatory control of enzymes involved in A β secretion, such as BACE and γ -secretase, is an essential area for AD drug development. Drugs that regulate A β secretion include the β -secretase inhibitor Lanabecestat [77, 78] and the γ -secretase inhibitor Semagacestat [62], which can inhibit the BACE1 enzyme and the γ -secretase enzyme complex, respectively, further reducing A β production [62]. However, these drugs were discontinued in clinical trials because of ineffectiveness or liver toxicity. Several experimental small-molecule inhibitors and modulators targeting secretase enzymes and A β aggregation are under clinical trials or preclinical studies (Table 2). While these therapies offer promise, their development is complex, and identifying compounds that can effectively and safely regulate A β secretion remains a significant challenge.

A β aggregation inhibitors A β aggregation inhibitors encompass many chemical structures, including small molecules and peptides that can bind to A β and interfere with its aggregation process. These compounds are designed to target specific regions of A β , such as the

hydrophobic core involved in aggregation, to inhibit the formation of toxic A β oligomers and fibrils. The main A β small-molecule inhibitors that have entered clinical trials are 3-APS (III) [79] and 8-HQ (II/III) [80], both of which were discontinued because they did not consistently inhibit A β aggregation in the brain to improve cognitive performance in AD patients [81]. In contrast, ALZ-801 has shown good gastrointestinal absorption and stable plasma concentrations, with significant clinical effects in the *APOE4/4* high-risk population and dose-dependent preservation of the hippocampal volume [82]. Developing effective A β aggregation inhibitors is facing substantial challenges, including BBB penetration, target selectivity, and metabolic stability. Moreover, the potential off-target effects and the safety are crucial issues to be addressed.

Intestinal microbiota regulators In the process of AD, the imbalance of gut microbiota leads to an abnormal increase in phenylalanine and isoleucine in peripheral blood, which in turn induces the differentiation and proliferation of peripheral pro-inflammatory Th1 cells and promotes their brain invasion [74]. Th1 cells infiltrating the brain and the intrinsic M1 microglia in the brain are activated together, leading to AD-related neuroinflammation [74]. Probiotics, prebiotics, synbiotics, and dietary interventions represent potential regulators of the intestinal microbiota, and their effects on A β metabolism and clearance have been investigated [83]. These interventions aim to modulate the composition and activity of the gut microbiota to promote a healthy microbial community and enhance A β clearance. However, perhaps because of the widespread use of oral probiotics as supplements, no

Table 2 Representative small-molecule drugs for A β clearance (<https://clinicaltrials.gov/>; <https://www.alzforum.org/therapeutics>. Accessed January 28, 2024)

| Agent | Clinical trial phase | Study population | Parameter | Adverse event | NCT identifier |
|----------------|----------------------|---------------------------|-----------------------------------|---------------------------------|----------------|
| Acitretin | II | Mild to moderate AD | MMSE | Gastrointestinal disorders | NCT01078168 |
| ALZ-801 | III | Early to mild AD | CDR-SB, MMSE | Mild nausea and vomiting | NCT04693520 |
| ALZT-OP1 | III | Early AD | CDR-SOB | Not specified | NCT02547818 |
| Buntanetap | II | Mild AD | ADAS-Cog11, ADSC-CGIC | Dizziness, nausea, and vomiting | NCT02925650 |
| CT1812 | II | Mild to moderate AD | ADAS-Cog13, CDR-SOB | Encephalitis | NCT03493282 |
| Lenalidomide | II | Mild cognitive impairment | ADAS-Cog, ADCS-ADL, CDR-SOB, MMSE | Not specified | NCT06177028 |
| Levetiracetam | II | Patients with AD | ADCS-ADL, CDR | Somnolence | NCT01044758 |
| Nasal Insulin | III | Mild AD | ADAS-Cog | Not specified | NCT02462161 |
| NIC5-15 | II | Mild to moderate AD | ADAS-Cog | Dizziness | NCT00470418 |
| Varoglutamstat | II | Mild to moderate AD | ADNI | Not specified | NCT04498650 |

ADAS-cog, Alzheimer's Disease Assessment Scale for cognition; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living scale; CDR-SOB, Clinical Dementia Rating Sum of Boxes; ADAS-Cog 11, Alzheimer's Disease Assessment Scale-cognitive subscale 11; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-cognitive subscale 13; MMSE, Mini-Mental State Examination

probiotics are currently in clinical trials. Moreover, the strong acids and bile salts in the gastrointestinal tract may induce leakage of ions and other cellular components that may kill probiotics, resulting in their low efficacy or even ineffectiveness [73]. This poses a challenge to developing methods to effectively transport probiotics around the gastrointestinal barrier to the intestine so that they can exert their biological functions.

Passive immunotherapy for A β clearance

Anti-A β immunity includes active immunity and passive immunity. Active immunity strategies involve stimulating the immune system to produce anti-A β antibodies by administering A β or its fragments. This approach has the advantages of long duration and low cost, but adverse immune reactions are difficult to predict [84]. For example, the A β vaccines UB-311 and ACC-001 have been discontinued because they led to meningoencephalitis in AD patients [85, 86].

Passive immunotherapy accelerates A β clearance by peripheral injection of humanized anti-A β monoclonal immunoglobulins. A β passive immunotherapy mainly promotes A β clearance in the following three ways [87]. (1) The antibody directly binds to A β in peripheral blood to reduce the A β content in the blood. This leads to an imbalance of A β in the periphery and the brain, promotes the outflow of soluble A β from the CNS via LRP-1 expressed on the BBB, and indirectly reduces the A β load in the brain [88, 89]. (2) The antibody Fc segment binds to the Fc receptor on microglia, which stimulates microglial activation, promoting A β clearance [90, 91]. (3) The antibody acts directly on A β plaques, fibers, or oligomers in the brain after crossing the BBB, and then degrades and clears A β [92].

Targeting soluble A β The aim of targeting soluble A β with antibodies is to prevent the aggregation of A β peptides into larger, more toxic oligomeric and fibrillar forms. By retaining A β in a soluble state, these antibodies may mitigate A β -induced neurotoxicity and reduce the formation of A β plaques. Several monoclonal antibodies targeting soluble A β have been developed and investigated in clinical trials. These antibodies are engineered to specifically recognize and bind to soluble A β peptides while avoiding binding to insoluble aggregates. The potential of these antibodies to slow the progression of AD by promoting A β clearance has been evaluated in clinical trials (Table 3). Solanezumab is a humanized monoclonal immunoglobulin G (IgG) antibody that recognizes the intermediate domain of A β peptides and can specifically recognize soluble A β monomers and prevent the formation of A β aggregates [93]. A clinical phase III study found that Solanezumab did not improve the cognition of AD patients using the Alzheimer's Disease Assessment Scale (ADAS), which can be used to evaluate the severity of dementia [94]. Lecanemab is a humanized IgG1 form of a mouse monoclonal antibody (mAb), mAb158, that can selectively bind large, soluble A β protofibrils and promote their clearance [92]. The results of the latest phase III clinical trial (1795 patients) also showed that compared with the placebo-treated group, the Clinical Dementia Rating Scale (CDR) sum of boxes scores of AD patients treated with Lecanemab for 18 months decreased by 27%, the decline in cognitive level decreased by 26%, and the decline in daily activity function decreased by 36% [95, 96]. Moreover, a significant decrease in A β deposition was observed in the brains of AD patients treated with Lecanemab.

Table 3 Representative A β antibodies for A β clearance (<https://clinicaltrials.gov/>; <https://www.alzforum.org/therapeutics>. Accessed January 28, 2024)

| Agents | Clinical trial phase | Study population | Conformations recognized by antibody | Parameter | NCT identifier |
|-------------|----------------------|---------------------|---------------------------------------|-------------------------------------|----------------|
| ABBV-916 | II | Early AD | N3pG-A β | PET, MRI | NCT05291234 |
| ACU193 | I | Mild AD | Soluble A β oligomers | MRI | NCT04931459 |
| MEDI1814 | I | Mild to moderate AD | Monomeric A β_{42} | MRI, CSF total A β_{42} | NCT02036645 |
| Remternetug | III | Patients with AD | N3pG-A β | PET | NCT04451408 |
| Solanezumab | III | Mild AD | Soluble A β monomeric | CDR-SOB, MMSE | NCT02760602 |
| Trontinemab | I/II | Mild to moderate AD | A β fibrils | PET | NCT04639050 |
| Leqembi | Approved | Early AD | Large, soluble A β protofibrils | ADAS-cog14 | NCT03887455 |
| Aducanumab | Approved | Mild AD | A β aggregates | CDR-SOB, MMSE, ADAS-Cog13, ADCS-ADL | NCT02484547 |

PET, positron emission tomography; MRI, magnetic resonance imaging; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living scale; CDR-SOB, Clinical Dementia Rating Sum of Boxes; ADAS-Cog 14, Alzheimer's Disease Assessment Scale-cognitive subscale 14; ADAS-Cog 13, Alzheimer's Disease Assessment Scale-cognitive subscale 13; MMSE, Mini-Mental State Examination

Targeting insoluble A β Monoclonal antibodies that target insoluble A β have been developed to specifically recognize and bind to insoluble A β aggregates. These antibodies are designed to facilitate the clearance of existing plaques through mechanisms such as opsonization and activation of microglia-mediated phagocytosis. These approaches seek to reduce the neurotoxic effects associated with A β aggregation and improve cognitive function in individuals with AD. Several monoclonal antibodies targeting insoluble A β have been investigated in clinical trials (Table 3). These trials have assessed the safety and efficacy of immunotherapies to clear existing amyloid plaques from the brains of individuals with AD. Gantenerumab is a humanized anti-A β monoclonal antibody that recognizes A β fibers [97]. Roche currently has a phase I/II trial ongoing with a redesigned version of gantenerumab called trontinemab. Trontinemab is gantenerumab linked to Roche's "brain shuttle" technology to enhance brain delivery via the TfR. Clinical trial results show that Trontinemab is safe at high doses [98]. At present, Trontinemab is in a Phase I trial that began evaluating multiple doses in 120 people with prodromal or mild-to-moderate AD and a positive amyloid positron emission tomography (PET) scan. Aducanumab is a high-affinity human monoclonal antibody against A β that selectively binds to A β aggregates and does not bind to A β monomers [84]. After intravenous injection, Aducanumab preferentially binds to A β in the peripheral blood and brain parenchyma rather than to A β on the vascular walls [92]. In a phase III clinical trial, the AD patients treated with Aducanumab showed a 22% reduction in CDR-SB score decline from baseline compared with the placebo group in the 78th week [99].

The binding strength of Lecanemab to 75–300 kDa A β fibers was 100 times higher than that of Aducanumab, and the binding strength to 300–500 kDa A β fibers was 25 times higher than that of Aducanumab [100]. The clinical cognitive impairment scores of patients taking Lecanemab (27%) were 4% higher than those of individuals taking Aducanumab (23%) [100].

Challenges in clinical trials for passive immunity

BBB penetration

For antibodies that are used to specifically clear A β , only 0.1% of them can enter the brain after intravenous injection [101–103]. The poor penetration of the BBB by anti-A β antibodies results in an antibody level in the brain lower than the concentration needed to continuously inhibit the formation of A β aggregates or effectively degrade and clear A β . Therefore, improved efficiency of antibody entry in the brain is required to enhance A β clearance. Currently, there are three main methods for delivering brain-targeted drugs (Fig. 5a, b). (1)

Bypassing the BBB to deliver drugs to the brain, which mainly includes invasive and non-invasive administration. The invasive routes of administration (intraparenchyma administration, convection-enhanced delivery, and intrathecal administration) are performed primarily using specific devices that directly penetrate the skull or lumbar spine [104]. The non-invasive administration is typically performed directly via nasal administration. (2) Enhancing the permeability of the BBB. This method mainly includes high heat [105], high permeability, and focused ultrasound [106]. However, when the BBB is opened, the effect is local, temporary, and non-invasive, and the degree of BBB opening and the amount of medication administered are challenging to evaluate. (3) Crossing the BBB. Receptor-mediated transcytosis is one of the most common strategies for BBB crossing, through TfR, insulin receptors (IR), and LRP-1. The anti-TfR antibody 8D3 is the most commonly used method [107–109].

Low complement response

Although antibodies are well tolerated in vivo, they may also be recognized as a foreign component by the recipient, thus causing an adverse immune response. The adverse reactions caused by peripheral injection of antibodies can be classified into hypersensitivity types I, II, and III according to their pathogenesis [110]. Among them, the type I hypersensitivity is mostly mediated by immunoglobulin E (IgE) antibodies, which react quickly and usually cause physiological function disruption [111]. The type II hypersensitivity is mainly caused by IgG or IgM, which causes hemolysis with the participation of macrophages, natural killer cells, and the complement system [111]. The type III hypersensitivity is mainly caused by the deposition of soluble immune complexes formed by antibodies and antigens in blood vessels, which causes local necrosis, tissue hyperemia, and edema by activating the complement system [111, 112] (Fig. 5d).

Amyloid-related imaging abnormalities (ARIA), including ARIA-edema/effusion (ARIA-E) and ARIA-hemosiderosis/microhemorrhages (ARIA-H), may occur, often during early anti-A β monoclonal antibody treatment [113]. In the phase III study of Aducanumab in AD patients, ARIA occurred in 425 (41.3%) of 1029 patients in the 10 mg/kg group [114]. Similarly, in the phase III clinical trial of Lecanemab in AD patients, 12.6% of AD patients developed ARIA, and 17.3% of AD patients had intracranial hemorrhage [114] (Fig. 5c). ARIA is caused by a classical complement reaction activated by antibodies. Therefore, the antibody-mediated adverse immune response is a critical factor that limits the efficacy of passive immunotherapy.

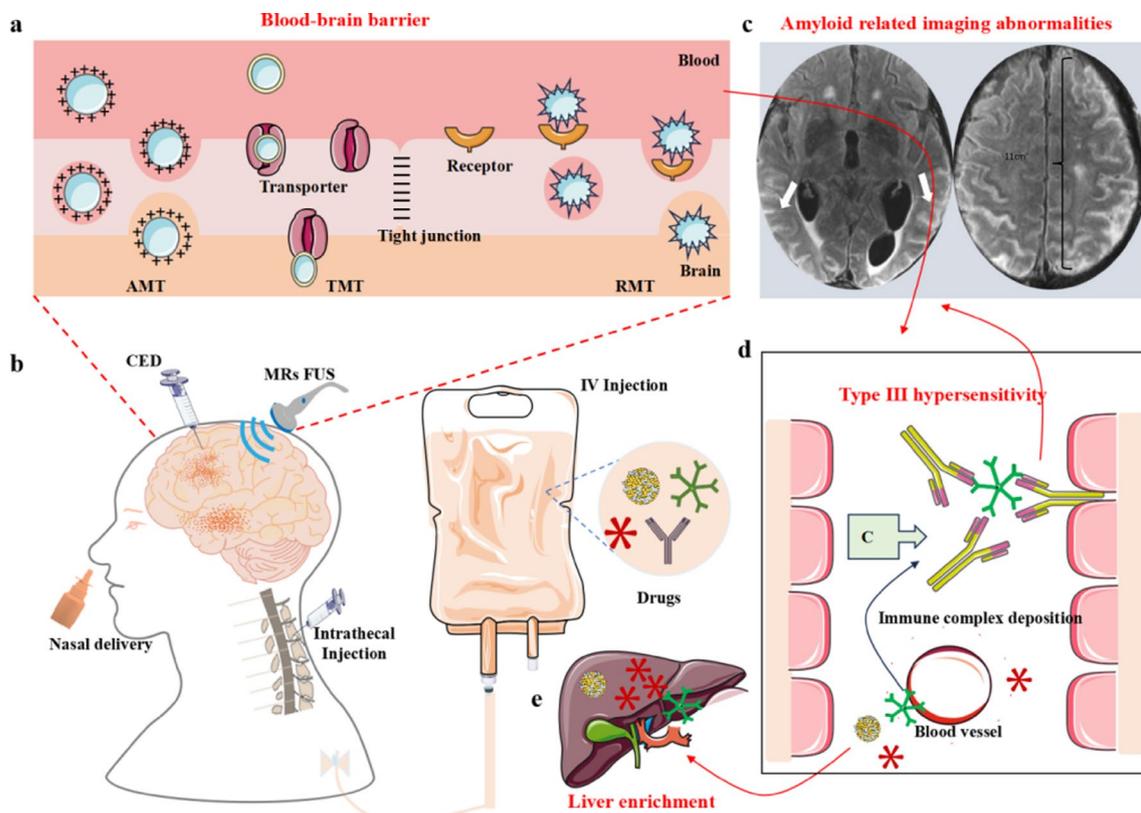


Fig. 5 Strategies and shortcomings of passive immunotherapy. **a** The drugs are mainly enriched in the brain by crossing the BBB through adsorptive-mediated transcytosis (AMT), transporter-mediated transcytosis (TMT), and receptor-mediated transcytosis (RMT). **b** Methods of drug administration to improve drug entry in the brain. The methods include nasal delivery, convection-enhanced delivery (CED), magnetic resonance-guided focused ultrasound (MRs FUS), intrathecal injection, and intravenous (IV) injection. **c** Most antibodies induce amyloid-related imaging abnormalities in clinical trials. **d** Antibody-mediated type III hypersensitivity reactions. **e** Intravenous injection of antibodies or other drugs via liver metabolism

High liver enrichment

Recent studies have shown that AD is associated with abnormal liver function [115]. Anti-A β antibodies and antibody-modified nanoparticles are enriched by approximately 33% in the liver after intravenous injection, which will mediate adverse immune reactions and increase the liver burden [116] (Fig. 5e). Moreover, neurotoxic A β in the liver also induces and accelerates the pathogenesis of AD [117]. Therefore, in AD immunotherapy, when clearing brain A β , reducing the non-specific enrichment of antibodies in the liver is an urgent issue to be addressed [118].

Lower specificity

In AD, A β plaques in the brain continuously recruit A β monomers and oligomers to form larger plaques [24, 119]. A β oligomers are considered to be the main form of neurotoxicity, and A β toxicity is negatively correlated with the degree of aggregation [25]. Therefore, an excellent anti-A β antibody should have high specificity for

soluble A β and exhibit strong and continuous inhibition and depolymerization of A β aggregates.

Systemic diseases

AD may be a heterogeneous disorder with involvement of biological and psychosocial factors, including immune system dysfunction, hepatic dysfunction, renal insufficiency and diabetes mellitus [120]. First, the immune system dysfunction is considered the most crucial pathological factor in AD. Microglia and macrophages express the class A1 scavenger receptors (Scara1) to bind and phagocytose fibrillar A β aggregates. Mononuclear phagocytes also express several A β -degrading enzymes, such as insulin-degrading enzyme and neprilysin. In AD, the expression of these phagocytic A β receptors and A β -degrading enzymes decreases significantly in microglia, resulting in reduced A β phagocytosis [121, 122]. In addition, chronic systemic inflammation, such as rheumatoid arthritis and periodontitis, can accelerate the development of AD [123]. Second, the liver is the body's

most crucial organ for protein synthesis and metabolism. Peripheral A β is degraded directly in the hepatocytes or indirectly via liver-mediated albumin and A β -associated lipoproteins [61]. Studies have shown that the elevated aspartate transaminase/alanine transaminase (ALT) ratio and lower ALT levels are associated with AD pathology (A β , Tau) in the brain and poor cognitive performance in participants [124]. Therefore, liver dysfunction is closely related to the pathogenesis of AD. In addition, ApoE is synthesized and secreted in the liver, which regulates A β clearance by transport across the BBB, enzymatic degradation, and other pathways [125]. Third, the kidney plays a critical role in the peripheral clearance of A β , and soluble A β is a normal component of human urine [126]. Clinical studies have shown that patients with chronic kidney disease are more susceptible to cognitive impairment and abnormal deposition of A β in the brain [66]. Fourth, diabetes affects the development of AD probably through the disruption of A β metabolism in the brain and the periphery [127]. In people with diabetes, excess insulin inhibits IDE-mediated A β degradation. In addition, A β clearance is also impaired by other mechanisms such as oxidative stress, BBB dysfunction, activation of inflammatory pathways, and hypercholesterolemia [128–130].

Conclusion and perspectives

Insoluble A β plaques act as a reservoir for soluble A β , and the potential removal of insoluble A β from the brain could offer several advantages by eliminating all toxic forms of A β (oligomers and fibrils) compared to the removal of soluble A β . Currently, passive immunotherapy with intravenous monoclonal anti-A β antibodies is a promising strategy for AD treatment to remove neurotoxic insoluble A β from the brain via the peripheral system. However, this method faces challenges such as antibody-mediated adverse immune responses, limited efficiency in brain penetration, and significant non-specific accumulation in the liver.

The fundamental goal of AD research is to stop and eventually cure the disease. A better understanding of the pathophysiology of AD is critical for AD treatment. A β peptides are metabolized (anabolized and catabolized) in both the brain and peripheral tissues. Significantly, abnormal metabolism of A β peptides which could communicate bidirectionally between the two regions, could cause both central and systemic abnormalities, which in turn can generate feedback loops. Indeed, this close interaction between the brain and periphery, particularly about A β peptide metabolism, offers new insights into the pathogenesis of AD. Therefore, AD can be considered both a disease of the brain and a systemic disease. Understanding the pathophysiology of AD beyond the CNS is essential for the use of different therapeutic

approaches or multi-target therapies, learning from unsuccessful clinical trials with A β and non-amyloid-based approaches (metabolic and anti-tau therapies). However, clarifying how peripheral processes influence AD pathogenesis, determining the interactions between the brain and the peripheral systems during AD progression, and investigating plasma A β as a blood-based biomarker for AD diagnosis, remain challenging. Future studies should explicitly consider systemic therapeutic strategies for prevention, including (1) improving peripheral A β peptide clearance (enhancing phagocytosis, proteolytic degradation, and excretion), (2) identifying and managing systemic abnormalities or developing a comprehensive strategy that targets both brain and peripheral abnormalities, and (3) developing rejuvenation factors/A β -peptide sequestrants in the blood for systemic rejuvenation therapies. In summary, this review provides new insights into the pathogenesis of AD and potential diagnostic and therapeutic advances.

AD still faces three significant challenges (Fig. 6). First, the etiology of the disease remains unclear and hinders scientific prevention efforts. Second, there is a need for more simple and reliable methods for early diagnosis. Current clinical diagnosis relies heavily on neuropsychological tests and imaging techniques. Due to the low accuracy of cognitive assessments and the high cost of brain imaging, most AD patients receive a diagnosis at late stages. Third, the lack of effective therapeutic drugs complicates treatment and rehabilitation. Early prevention and treatment are crucial for comprehensive improvement of AD.

In terms of prevention, research has shown that specific strategies can reduce the risk or delay the onset of the disease (Fig. 6). (1) Physical activity can improve blood flow to the brain and promote overall well-being [131]. (2) A healthy diet rich in fruits, vegetables, whole grains, lean proteins, and healthy fats is recommended. Some studies suggest that following the Mediterranean diet can positively impact brain health [111]. (3) Mentally stimulating activities such as playing games, reading, learning new skills, or practicing hobbies can keep the brain active and improve cognitive health. A large-scale clinical trial, the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study, has shown that cognitive training improves the cognitive performance of healthy older adults aged 65 and over [132]. (4) Managing chronic conditions like high blood pressure, diabetes, obesity, and high cholesterol can help prevent or delay AD [133]. (5) Exposure to polluted air, especially PM_{2.5}, can lead to inflammation, oxidative stress, and damage to blood vessels, which can affect brain health and potentially contribute to neurodegenerative diseases

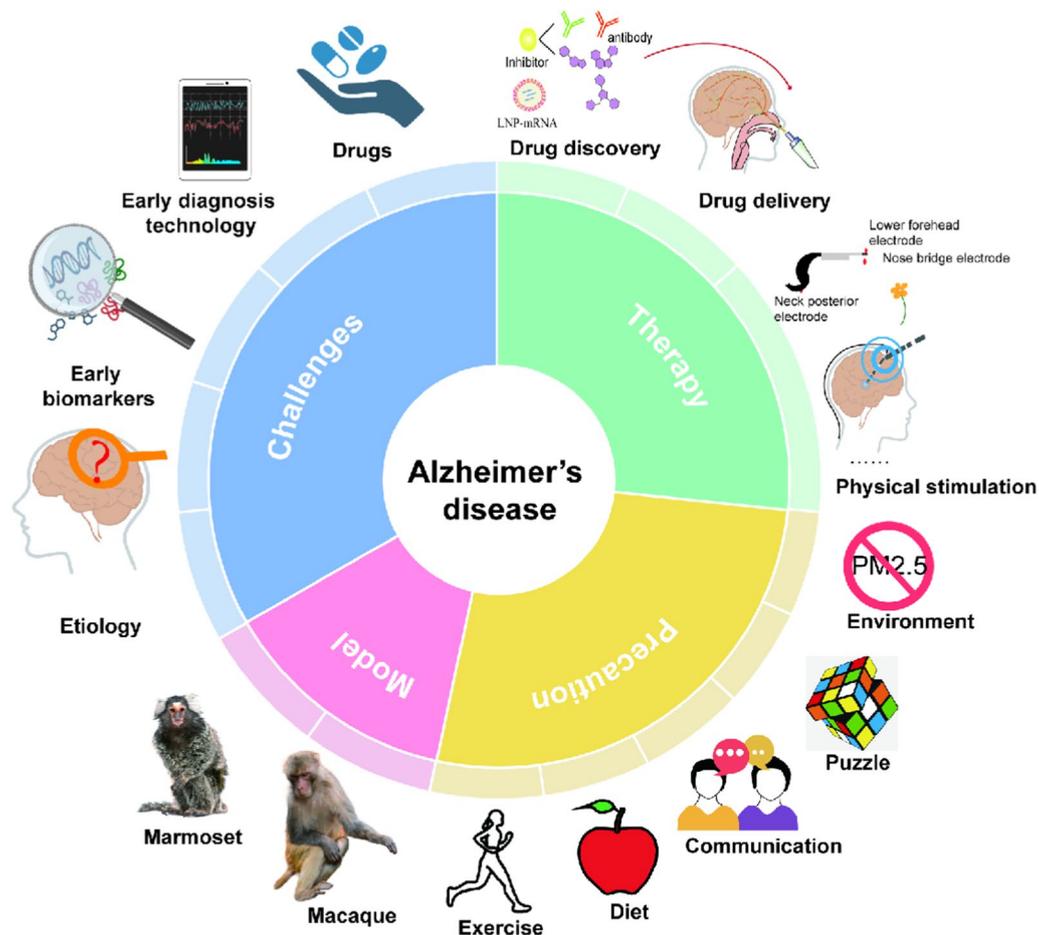


Fig. 6 The prospects of AD prevention and therapy. Challenges remain in understanding AD etiology and pathologic mechanisms, finding early biomarkers, and developing early diagnostic techniques and effective drugs. Promising research directions for AD treatment include model establishing, drug discovery and delivery, and physical stimulation. Preventive strategies focus on lifestyle modifications, including improving the living environment, playing puzzle games, promoting communication with others, maintaining a healthy diet, and physical exercise

[134, 135]. Therefore, limiting exposure to polluted air can reduce the risk of AD.

Although currently there is no cure for AD, there are several therapeutic strategies and interventions aimed at alleviating symptoms and improving the general well-being of patients (Fig. 6). Among them, FDA-approved cholinesterase inhibitors and anti-A β antibodies are effective in treating emotional and cognitive symptoms in patients, although they may not halt or reverse the progression of AD. There is ongoing research on the use of mRNAs to stimulate specific proteins or molecules in the brain, using lipid nanoparticles to encapsulate mRNA molecules and deliver them into cells to produce target proteins [136]. Drug delivery methods are critical for treatment efficacy. Researchers are investigating nanotechnology to develop nanoparticles that can cross the BBB and deliver drugs directly to the brain. These nanoparticles can improve drug solubility and stability

and increase brain uptake [137]. In addition, light [138], sound [139], and gamma wave [140] are increasingly used as non-invasive therapies to improve cognitive function. The efficacy and safety of these therapies for AD need to be thoroughly investigated in well-designed clinical trials. In addition, research is underway to develop various models to understand, diagnose, and treat AD, using biological, animal, cellular, and computational approaches. Each model has its strengths and weaknesses [141] (Fig. 6). Much work is being done to characterize animal models of AD, from rodents to primates, to improve our understanding of the pathophysiology of the disease and to find models suitable for studying potential treatments.

Abbreviations

| | |
|-----------|---------------------------|
| AD | Alzheimer's disease |
| A β | Amyloid-beta |
| APP | Amyloid precursor protein |
| CNS | Central nervous system |

| | |
|----------------|---|
| BBB | Blood–brain barrier |
| CSF | Cerebrospinal fluid |
| LRP-1 | Low density lipoprotein receptor related protein-1 |
| ApoE | Apolipoprotein E |
| IL-1 β | Interleukin-1 β |
| IL-6 | Interleukin-6 |
| iNOS | Inducible nitric oxide synthase |
| TREM2 | Triggering receptor expressed on myeloid cells-2 receptor2 |
| Tyrob | Tyrosine protein–protein binding |
| NF- κ B | Nuclear factor κ B |
| NLRP3 | Nucleotide binding oligomerization domain-like receptor protein 3 |
| ROS | Reactive oxygen species |
| TLR4 | Toll-like receptor 4 |
| TfR | Transferrin receptors |
| ARIA | Amyloid related imaging abnormalities |

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LN: Conceptualization, methodology, data curation, visualization, investigation, writing-original draft preparation, and funding; HA and ZW: software, data curation, visualization and validation. CY: methodology, software, visualization, investigation, supervision, and funding. CH: conceptualization, validation, writing-review & editing, and funding.

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Ethics approval and consent to participate

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Consent for publication

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The authors declare that they have no competing interests.

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