https://doi.org/10.5607/en23014
Exp Neurobiol. 2023 Aug;32(4):216-246.
pISSN 1226-2560 • eISSN 2093-8144

Review Article

Experimental Neurobiology

Advances in Amyloid-β Clearance in the Brain and Periphery: Implications for Neurodegenerative Diseases

Rahat Ullah[1,2] and Eun Jeong Lee[3*]

[1]Neuroregeneration and Stem Cell Programs, Institute for Cell Engineering, School of Medicine, The Johns Hopkins University, Baltimore, MD 21205, USA, [2]Department of Neurology, School of Medicine, The Johns Hopkins University, Baltimore, MD 21205, USA, [3]Department of Brain Science, Ajou University School of Medicine, Suwon 16499, Korea

This review examines the role of impaired amyloid-β clearance in the accumulation of amyloid-β in the brain and the periphery, which is closely associated with Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA). The molecular mechanism underlying amyloid-β accumulation is largely unknown, but recent evidence suggests that impaired amyloid-β clearance plays a critical role in its accumulation. The review provides an overview of recent research and proposes strategies for efficient amyloid-β clearance in both the brain and periphery. The clearance of amyloid-β can occur through enzymatic or non-enzymatic pathways in the brain, including neuronal and glial cells, blood-brain barrier, interstitial fluid bulk flow, perivascular drainage, and cerebrospinal fluid absorption-mediated pathways. In the periphery, various mechanisms, including peripheral organs, immunomodulation/immune cells, enzymes, amyloid-β-binding proteins, and amyloid-β-binding cells, are involved in amyloid-β clearance. Although recent findings have shed light on amyloid-β clearance in both regions, opportunities remain in areas where limited data is available. Therefore, future strategies that enhance amyloid-β clearance in the brain and/or periphery, either through central or peripheral clearance approaches or in combination, are highly encouraged. These strategies will provide new insight into the disease pathogenesis at the molecular level and explore new targets for inhibiting amyloid-β deposition, which is central to the pathogenesis of sporadic AD (amyloid-β in parenchyma) and CAA (amyloid-β in blood vessels).

Key words: Amyloid-β clearance, Brain and periphery, Alzheimer's disease (AD), Cerebral amyloid angiopathy (CAA)

AMYLOID-β: A PEPTIDE INVOLVED IN TWO PATHOLOGIES - ALZHEIMER'S DISEASE (AD) AND CEREBRAL AMYLOID ANGIOPATHY (CAA)

Amyloid-β is generated during neuronal activity by the amyloid precursor protein (APP), a transmembrane protein [1, 2]. In non-pathological conditions, APP is first cleaved by α-secretase, preventing the formation of amyloid-β, and the subsequent carboxy-terminal fragment is then cleaved by γ-secretase [3], resulting in non-aggregating products [4]. However, under pathological conditions, APP is first cleaved by β-secretase instead of α-secretase, and the subsequent γ-secretase cleavage results in the formation of soluble, monomeric amyloid-β. The most commonly reported soluble monomeric isoforms of amyloid-β are amyloid-$\beta_{1\text{-}38}$ (<20%), amyloid-$\beta_{1\text{-}40}$ (<80%), and amyloid-$\beta_{1\text{-}42}$ (10%) [5, 6]. Amyloid-$\beta_{1\text{-}40}$ is more likely to be deposited in the vascular walls, as seen in Cerebral amyloid angiopathy (CAA) [7], whereas amyloid-$\beta_{1\text{-}38}$ is less likely to aggregate in either the vessel walls or the brain [8, 9]. Amyloid-$\beta_{1\text{-}42}$, with two extra amino acids, is more hydrophobic than amyloid-$\beta_{1\text{-}40}$, making it prone to forming insoluble aggregates that lead to plaque formation [10, 11]. These plaques differ in location, composition, and distribution. CAA plaques are perivascular and composed of amyloid-$\beta_{1\text{-}40}$, while parenchymal plaques are diffuse and composed of amyloid-$\beta_{1\text{-}42}$. CAA plaques increase

Submitted April 20, 2023, Revised July 25, 2023,
Accepted August 23, 2023

*To whom correspondence should be addressed.
TEL: 82-31-219-4529, FAX: 82-31-219-4530
e-mail: elee@ajou.ac.kr

Copyright © Experimental Neurobiology 2023.
www.enjournal.org

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

the risk of hemorrhage, while parenchymal plaques contribute to cognitive decline in Alzheimer's disease (AD). Understanding these differences is essential for effective treatment strategies. These distinct plaque formations are considered major characteristics of AD and CAA, respectively [12, 13].

Amyloid-β in AD: risk factors and genetics

AD is a slowly progressive neurological disorder that poses significant health-care challenges in the twenty-first century [14, 15]. This disease is characterized by a range of symptoms, including memory loss, cognitive decline, personality changes, and impaired daily functioning. These symptoms are associated with the accumulation of extracellular amyloid-β (diffuse or insoluble plaques) and intraneuronal neurofibrillary tangles, which can trigger processes like necroptosis and ferroptosis, as well as neuroinflammation [16-18] (Fig. 1). Amyloid-$\beta_{1\text{-}42}$ is the main component of amyloid plaques in AD brains, while amyloid-$\beta_{1\text{-}40}$ is the main component of vascular amyloid deposits found in CAA [19, 20]. The risk factors for developing AD include aging, sex, low educational and occupational status, low mental and physical activity, cardiovascular risk factors, hyperhomocysteinemia, smoking, obesity, and diabetes mellitus [19, 21]. Additionally, a typical hereditary risk factor for AD is apolipoprotein E (ApoE) gene mutation [22]. While sporadic AD, which is commonly referred to as late-onset AD, is seen in people over the age of 65 [23] and was previously thought to have no clear genetic component, recent Genome-Wide Association Studies have identified several genetic risk factors that are associated with the disease [24]. In contrast, early-onset familial AD, which affects those under the age of 65 [23], is caused by mutations in the presenilin-1 and 2 (PS1/PS2) and APP genes [25, 26]. The most common amyloid-β mutations that cause familial AD include English (H6R), A2V (A2V), Tottori (D7N), K16N (K16N), Osaka (E22Δ), Flemish (A21G), Italian (E22K), Arctic (E22G), Dutch (E22Q), Iowa (D23N), Swedish (KM670/671NL), Piedmont (L34V), and Indiana (V717F) [27, 28]. The familial forms of AD are mostly noticeable by increased

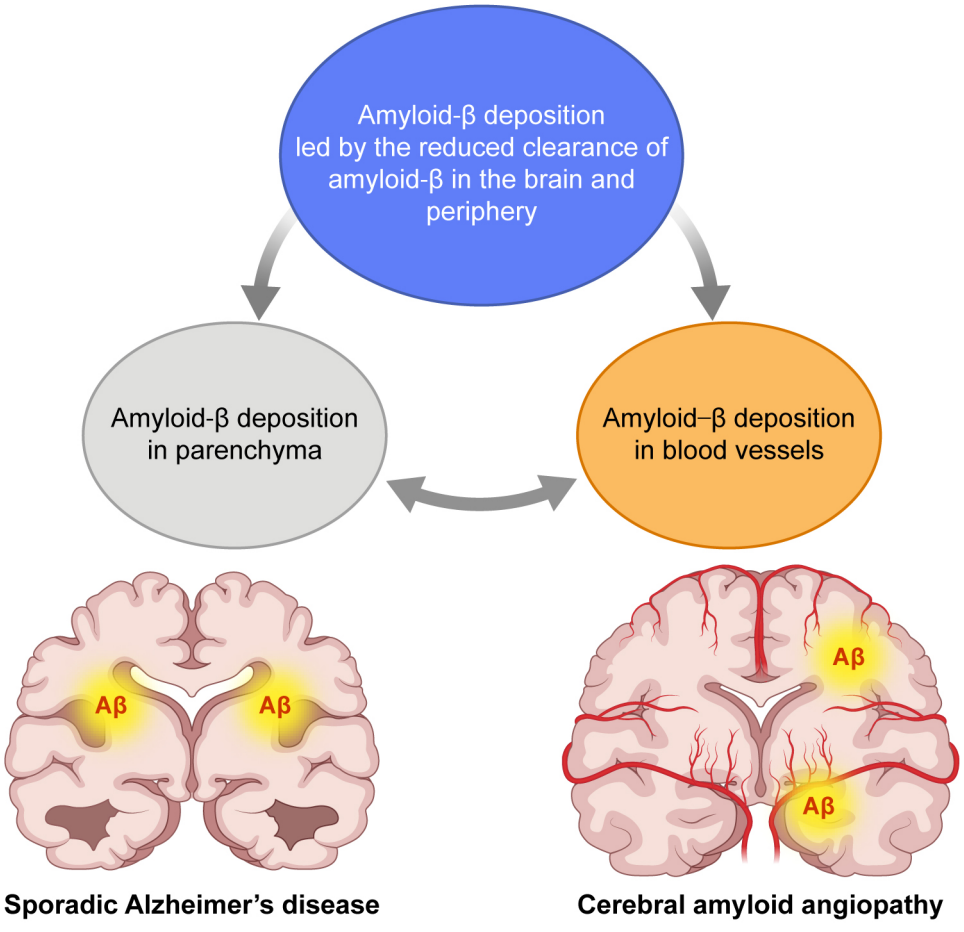

Fig. 1. Reduced clearance of amyloid-β in brain resulting in sporadic AD (amyloid-β deposition in parenchyma) and CAA (amyloid-β deposition in blood vessels).

kinetics of amyloid-β aggregation [27], which results in an early age of onset. Similarly, multiple mutations in amyloid-β sequence and other aggregation-prone proteins (ABri and Adan) are especially linked to early-onset aggressive forms of CAA and related to dementia with cerebral hemorrhage [19, 29].

Amyloid-β in CAA: risk factors and genetics

The main characteristic of CAA is the deposition of amyloid-β in the tunica media and adventitia of the arterioles and/or capillaries in the cerebral cortex and leptomeninges (Fig. 1) [30]. Amyloid-β_{1-40} is typically deposited in the vascular wall of CAA, while amyloid-β_{1-42} is primarily deposited in the senile plaques of AD. Depending on whether amyloid-β is present on cortical capillaries, sporadic CAA is divided into type 1 and type 2: CAA-type 1 is defined as the deposition of amyloid-β on cortical capillaries, but CAA-type 2 is not related with amyloid-β in the cortical capillaries [31]. Hereditary CAA is caused by Dutch, Arctic, Italian, Flemish, Iowa, Piedmont mutations in APP gene, Icelandic mutation in CST3 gene, and the British and Danish mutations in the ITM2B gene [19, 32]. CAA is recognized as a significant risk factor for "white matter hyperintensities" [33], and it occurs in 98% of AD patients, with roughly 75% of these cases categorized as severe CAA [34]. Furthermore, CAA is present in approximately 30% of non-demented elderly [34] and clinical studies have demonstrated a significant association between CAA and cognitive dysfunction [35, 36]. CAA is also closely linked to cerebral hemorrhage and weakens vascular walls as a result of amyloid deposits. Specific point mutations within the amyloid-β have been found including Iowa-type (D23N) and Dutch-type (E22Q), which cause familial forms of CAA [36].

The series of pathophysiological events that promote amyloid-β buildup in the brain and blood vessels are still not completely understood [37]. However, pathological, genetic, and functional studies suggest that the pathologies in both AD and CAA are driven by impaired amyloid-β clearance [12, 38]. Therefore, a deep understanding of amyloid-β clearance could lead to effective approaches to reduce excessive amyloid-β buildup in the brain and slow the progression of both AD and CAA [6, 39]. This review will focus on recent findings of amyloid-β clearance system in the body and try to explore potential interventional targets for future prevention and treatment of AD and CAA.

AMYLOID-β CLEARANCE IN THE BRAIN

The brain employs multiple mechanisms for amyloid-β clearance, which include both enzymatic and non-enzymatic pathways [40]. Recent studies have highlighted the potential therapeutic benefits of targeting amyloid-β-degrading enzymes (AβDEs) in reducing amyloid-β pathology. Modulating the expression or activity of AβDE has been found to effectively regulate levels of amyloid-β and improve cognitive deficits in transgenic animal models [41, 42]. In parallel to the enzymatic pathway described later, the non-enzymatic clearance pathway of amyloid-β involves the active participation of glial cells (microglia and astrocytes), the blood-brain barrier, interstitial fluid bulk flow (perivascular drainage and the glymphatic system), and cerebrospinal fluid absorption clearance [40]. Disturbances in any of these clearance pathways can significantly contribute to the accumulation of amyloid-β in the brain.In this section, we will address recent progresses in both enzymatic and non-enzymatic mechanisms of amyloid-β clearance in the brain and explore the factors that contribute to the disruption of these pathways.

The role of enzymes in clearing amyloid-β in the brain

In the brain, both intracellular and extracellular amyloid-β are primarily degraded and cleared through the proteolytic machinery [40, 43]. To date, researchers have identified multiple amyloid-β-degrading proteases (AβDPs), numbering around 20 [44, 45]. These enzymes have an affinity for certain domains of the amyloid-β amino acid sequence, enabling them to cleave and convert amyloid-β proteins into shorter, less toxic forms [46-48]. The different categories of AβDPs include zinc metalloendopeptidase, thiol-dependent metalloendopeptidase, serine/cysteine proteases and matrix metalloproteinases and others as shown below (Fig. 2).

Zinc metalloendopeptidase

The majority of AβDPs currently recognized are zinc metalloproteases possessing the zinc-binding motif, and they can be categorized into the following groups [49].

Neprilysin

Neprilysin (NEP) is a plasma membrane glycoprotein belonging to the neutral zinc metalloendopeptidase family. It is also referred to as neutral endopeptidase-24.11, enkephalinase, common acute lymphoblastic leukemia antigen, or neutrophil antigen cluster differentiation antigen 10 (CD10) [50]. NEP is a major AβDP that can cleave both monomeric and oligomeric forms of amyloid-β in the brain and periphery [41, 51]. Its expression is found in vascular smooth muscle cells and pyramidal neurons in the cerebral vasculature and neocortex of the brain [52]. Several lines of evidence suggest that NEP plays a role in the pathology of AD and CAA [53, 54], indicating an inverse relationship between NEP activity and brain amyloid-β levels [55]. NEP deficiency caused by genetic factors results in abnormal amyloid-β accumulation in the brain [56,

 https://doi.org/10.5607/en23014

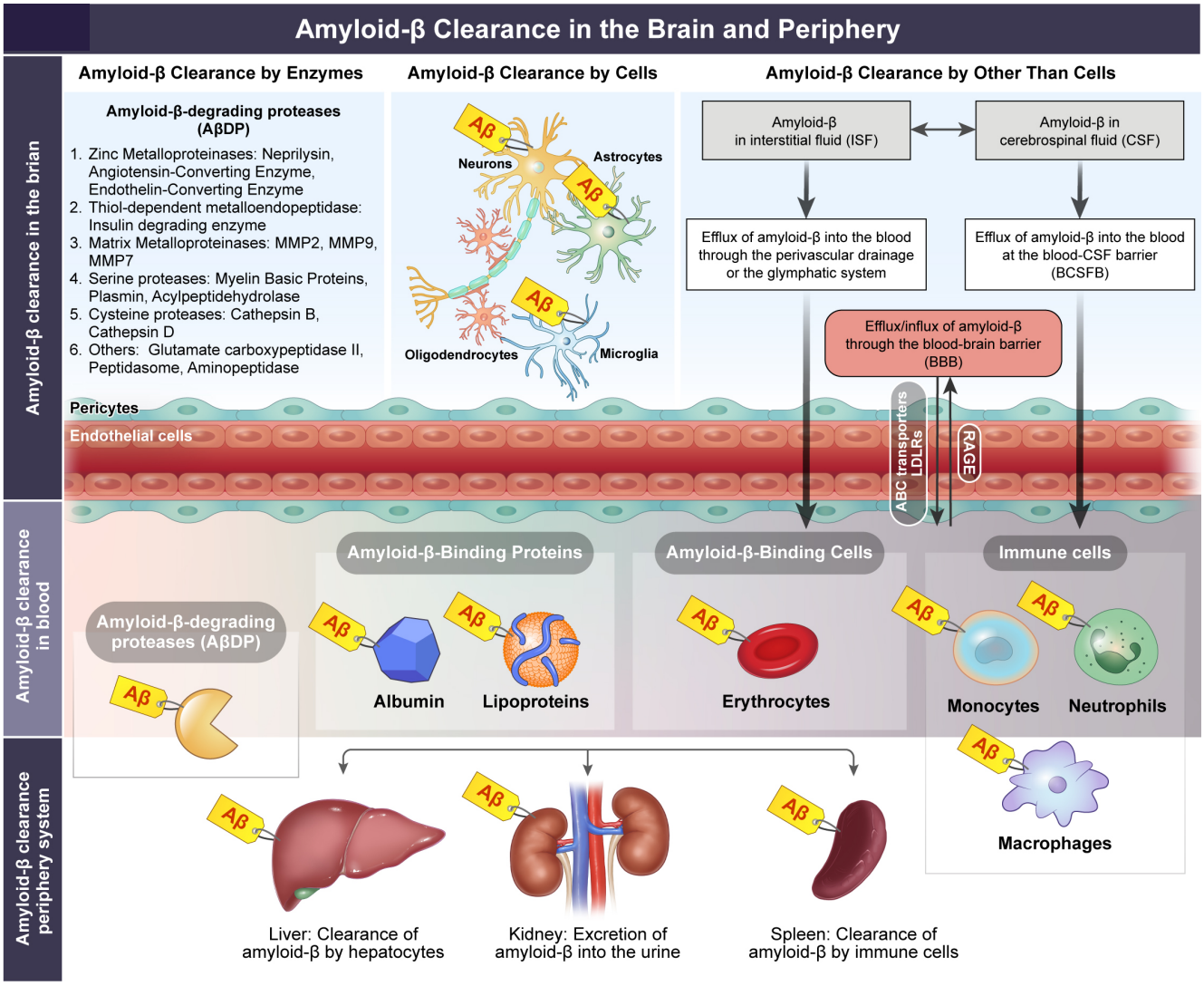

Fig. 2. Clearance mechanisms for amyloid-β in the brain and periphery. Central Clearance of amyloid-β in the brain. In the brain, amyloid-β clearance occurs through (1) enzymatic and (2) non-enzymatic pathways. Enzymatic clearance involves multiple amyloid-β-degrading enzymes (AβDPs) such as (i) zinc metalloendopeptidase, (ii) thiol-dependent metalloendopeptdiase, (iii) serine protease, (iv) cystein protease, and (v) matrix metalloproteinase. Non-enzymatic clearance mechanisms include clearance through (1) BBB, (2) cellular-mediated clearance involving (i) neurons, (ii) microglia, (iii) astrocytes, (iv) endothelial cells and (v) pericytes. (3) intestinal fluid (ISF) bulk-flow-mediated clearance through the perivascular drainage or the glymphatic pathway and (4) cerebrospinal fluid (CSF)-mediated clearance, which involves absorption into the circulatory system or the lymphatic system. Peripheral clearance of amyloid-β in blood or peripheral organs. In blood, amyloid-β is degraded or cleared by proteases, AβDPs, blood cells such as monocytes or neutrophils, or transported by carriers such as erythrocytes, albumin, and lipoproteins to peripheral organs, where itis degraded by macrophages in the spleen or hepatocytes or excreted via the liver or kidney. Abbreviations: BBB, blood-brain barrier; RAGE, advanced glycosylation end product specific receptor; CSF, cerebrospinal fluid; LRP1, Low density lipoprotein receptor-related protein 1, ISF, interstitial fluid; ABC transporters, ATP-binding cassette transporter; BCSFB, blood-CSF barrier.

57]. Conversely, increasing NEP expression and activity by direct injection [58] or overexpression in the brain or peripheral tissues [59-62] can significantly reduce amyloid-β burden and improve cognitive impairment [41, 63, 64].

Recent studies have also confirmed a correlation between NEP and amyloid-β degradation/clearance in AD and CAA [54, 65-67]. NEP has been found to metabolize not only amyloid-β_{1-40} and a partial structure of amyloid-β (amyloid-β_{1-16}) but also a peptide segment generated by the breakdown of amyloid-β_{1-40} by insulin-degrading enzyme (IDE) [68]. Additionally, loading NEP into collagen hydrogels as a vehicle and delivering intranasally has been shown to clear plaques in a transgenic mouse model [69]. Together with the latest findings, it is evident that NEP is crucial for amyloid-β clearance, and its dysfunction significantly contributes

to amyloid-β accumulation in the body.

Angiotensin-converting enzyme

Angiotensin-converting enzyme (ACE; peptidyl-dipeptidase A; EC 3.4.1.5.1) is a widely expressed zinc metalloprotease in the body, including human brains where it is found in pyramidal neurons in the cortex and cerebral vasculature [70]. Several genetic, biochemical and cell biology studies have supported the idea that ACE plays an essential role in regulating amyloid-β metabolism [71, 72]. *In vitro* studies have demonstrated that ACE can cleave amyloid-β between Asp7 and Ser8, leading to inhibition of aggregation, deposition, fibril formation, and associated cytotoxicity of amyloid-β [47, 73, 74]. However, the effects of ACE on steady-state amyloid-β concentration in animals studies remain inconclusive. Although ACE-deficient mice and mice treated with ACE inhibitors did not consistently show changes [71, 75], there is a report that the treatment of transgenic mice with captopril, another ACE inhibitor, promotes amyloid-$\beta_{1\text{-}42}$ deposition in the brain [76]. Overall, the effects of ACE on amyloid-β metabolism in animal studies are not fully understood [70].

More recently, molecular modelling and mass spectrometry studies have provided additional evidence of a strong interaction between ACE or N-domain of ACE and amyloid-β accumulation in the brain [77, 78]. Rocha et al. found a positive correlation between ACE levels and amyloid-β in AD patients, supporting the idea that ACE is linked to amyloid-β pathology [79].

The findings derived from both in vitro and in vivo studies reveal significant inconsistencies, presenting considerable challenges in scientific research. These discrepancies can be attributed, in part, to variations in the methods employed to measure ACE and the unique characteristics of the samples tested. Additionally, it is plausible that compensatory mechanisms involving other amyloid-β degrading enzymes, such as neprilysin, insulin-degrading enzyme, and endothelin-converting enzyme, may offset the observed acute reduction in ACE activity in vivo. Furthermore, insights gleaned from genetic studies may help elucidate the disparities surrounding ACE activity/levels in amyloid pathology. Notably, a comprehensive meta-analysis has demonstrated a robust correlation between the presence of an insertion (I) polymorphism within intron 16 of ACE and an increased risk of AD, while the deletion (D) variant appears to provide protection [76, 79-81].

Given the current inconsistencies and recent research findings, it is crucial to acknowledge the controversial role of ACE in amyloid-β clearance in the brain. It is strongly recommended to promote future research to address these existing disparities and to gain a clearer understanding of the specific function of ACE in clearing amyloid-β. Such insights could potentially prove valuable in preventing the buildup of amyloid-β in the brain, which is a characteristic feature of conditions like AD [82] and CAA [83].

Endothelin-converting enzyme

The endothelin-converting enzymes (ECEs) are membrane-bound proteases that belong to M13 zinc metallopeptidases family. They are named after their ability to convert the inactive precursor big endothelin into the potent vasoactive peptide endothelin-1 [84]. Two types of ECE have been identified so far: ECE-1, which is found in both vascular and nonvascular cells in all organs [85], and ECE-2, which is predominantly expressed in the brain and neural tissues, including the cerebral cortex, cerebellum, and adrenal medulla [86]. The expression level and activity of ECE are strongly correlated with amyloid-β deposition and the onset of AD [85, 86]. Importantly, evidence from cultured cells and animal models has shown that amyloid-β is a physiologically significant substrate of ECE [86, 87]. For example, *in vivo* studies of ECE deficient mice (ECE-1 and ECE-2) have shown that both genotypes have higher amyloid-β levels than wild-type mice, indicating that these ECEs are AβDPs *in vivo* [86, 88]. Conversely, overexpression of ECE reduces amyloid-β deposition [87, 88]. *In vitro* studies have also found that ECE can hydrolyze amyloid-β at several sites [89].

In conclusion, the reviewed studies offer compelling evidence supporting the crucial role of ECE as a significant amyloid-β degrading enzyme in preventing the buildup of amyloid-β in the brain. Both in vitro and in vivo investigations have demonstrated that overexpression of ECE leads to reduced amyloid-β levels, while inhibiting ECE activity results in increased amyloid-β accumulation. These findings underscore the therapeutic potential of targeting ECE to modulate amyloid-β levels and potentially attenuate the progression of disease pathology. Further exploration of ECE and its enzymatic mechanisms holds promise in providing valuable insights into preventing the amyloid-β buildup observed in AD and CAA. By unraveling the intricate workings of ECE, we may unlock new avenues for intervention and contribute to the development of novel treatments aimed at mitigating the impact of amyloid-β pathology.

Thiol-dependent metalloendopeptidase

Thiol-dependent metallo-endopeptidase, also known as Pz-peptidase, endooligopeptidase A, collagenase-like peptidase, soluble metallo-endopeptidase and endopeptidase [90], is expressed in the brain [91] and play a crucial role in the degradation of small peptides, including glucagon, insulin, and atrial natriuretic peptide and amyloid-β [92, 93]. The highly conserved thiol metalloprotease insulin-degrading enzyme (IDE), which is one of the enzymes responsible for removing amyloid-β from the brain, is now con-

 https://doi.org/10.5607/en23014

sidered a key component in the amyloid-β clearance process [91], as discussed below.

Insulin degrading enzyme (IDE, EC 3.4.24.56), also known as insulinase or insulysin, is a neutral thiol metalloprotease [94] found in several tissues, including skeletal muscle, skin, tongue, and testes [94, 95] and the brain [91, 96]. IDE is evolutionally conserved and developmentally regulated. Its physiological role encompasses several cellular functions as reviewed in Authier et al. [97]. IDE has been particularly well-known for degrading several peptides, including amylin, glucagon, calcitonin and atrial natriuretic peptide, as well as monomeric amyloid-β, which has been demonstrated by both *in vitro* and *in vivo* models [91, 98-101]. Notably, IDE expression levels and activity have been found to exhibit an inverse correlation with amyloid-β burdens in the brain [102, 103]. This finding is significant because hypofunction of IDE has been associated with defective neuronal and microglial regulation of amyloid-β, as well as deficits in memory in AD [104] and CAA [105] patients. Furthermore, genetic deletions of IDE in mouse brains have led to a significant increase in amyloidogenic amyloid-β [102]. Conversely, transgenic overexpression of IDE has been shown to significantly reduce levels of amyloid-β and amyloid plaque formation by over >50% in the brain [96, 106].

Several recent studies have extensively documented the significant role of insulin in amyloid-β clearance in the brain [42, 107, 108]. For instance, a recent study has focused on the catalytic role of IDE mutants (specifically, cysteine-free mutant cf-E111Q-IDE) in amyloid-β proteolysis/degradation, revealing that this mutant is exceptionally effective at breaking down amyloid-β peptides [106]. Additionally, Fu et al. found that microglia secrete IDE to partially degrade amyloid-β, which is inhibited by using a highly selective IDE inhibitor *in vitro* and *in vivo* [109, 110]. Moreover, Yamamoto et al. suggested that increased levels of IDE in the extracellular spaces of astrocytes aid in the degradation of soluble oligomeric and monomeric amyloid-β in the brain [111]. Taken together, these findings provide strong evidence that IDE plays a crucial role in amyloid-β clearance, and that its dysfunction significantly contributes to the accumulation of amyloid-β in the brain.

Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a family of nine highly homologous Zn^{2+}-dependent endopeptidases that are capable of cleaving a wide range of extracellular matrix (ECM) proteins under health and disease conditions [112]. Almost 28 mammalian MMPs have been identified, sub-grouped into soluble matrix MMPs and membrane type MMPs (MT-MMPs) [113, 114]. Multiple MMPs including MMP2 and MMP9 [115, 116], have been reported in the degradation of both monomeric and fibrillar forms of amyloid-β [115, 117]. Study have shown a significant increase in amyloid-β levels in the brains of both MMP2 and MMP9 knockout mice, highlighting the role of MMPs in amyloid-β catabolism [118, 119]. Previous studies have also discussed some special properties of MMPs and their impact on amyloid-β clearance [117]. Firstly, MMPs typically exist in an inactive form known as latent pro-enzymes, which can be activated through proteolytic processing [120]. Interestingly, a protease called extracellular matrix metalloproteinase inducer (EMMPRIN; CD147) has been identified as one of the enzymes responsible for activating MMPs through this mechanism. In cultured cells, EMMPRIN induction has been shown to decrease amyloid-β levels by activating multiple MMPs [121]. Secondly, the basal expression of MMPs is generally low, but it can be enhanced in response to pathological insults, including amyloid-β itself [122]. Supporting this observation, in transgenic mice expressing the amyloid precursor protein (APP), MMPs were found to be up-regulated in astrocytes located near amyloid deposits [119]. Furthermore, when a broad-spectrum MMP inhibitor called GM6001 was infused into the mice's brain ventricles (i.c.v.), it led to significant increases (approximately 50%) in both the steady-state levels and the half-life of interstitial fluid (ISF) amyloid-β [119].

Recent studies have shown a strong association between MMPs and AD [123] or CAA [124]. For example, Taniguchi et al. found that MMP7 is capable of degrading amyloid-β, inhibiting its aggregation and reversing amyloid-β pathology [125]. Additionally, a recent *in vitro* study has demonstrated that inhibiting MMP9 secretion from astroglia reduces the proteolytic clearance/degradation of amyloid-β [126].

In summary, the accumulating body of recent research provides compelling evidence supporting the critical involvement of MMPs in the degradation and clearance of amyloid-β. The activation and up-regulation of MMPs play key roles in amyloid-β metabolism. Notably, inhibiting MMPs leads to elevated amyloid-β levels, underscoring their significance in amyloid-β degradation. Consequently, targeting MMPs emerges as a promising therapeutic strategy for diseases characterized by amyloid-β accumulation, particularly AD and CAA.

Serine proteases

Serine proteinases represent the largest and most abundant class of mammalian proteinases, named as such because their active sites contain a serine residue essential for catalysis. These enzymes play significant roles in extracellular proteolysis, with optimal activity observed under neutral pH conditions [127].

Notable examples of this proteinase class include myelin basic protein (MBP), plasmin, and acylpeptide hydrolase, which will be

further discussed below [40].

Myelin basic proteins

Myelin basic proteins (MBP), comprising roughly 30% of all myelin protein, are crucial structural components of axonal myelin sheaths. MBP is recognized as a "membrane adhesion molecule", tightly sealing the cytoplasmic components of the cell membrane bilayer in the densely packed myelin sheath [128, 129]. Additionally, similar to other naturally occurring "amyloid-β chaperone molecules (such as ApoE, apolipoprotein J, apolipoprotein A-1, α1-anti-chymotrypsin, haptoglobin, transthyretin and gangliosides) in the CNS", MBP also functions as a "novel chaperone", capable of binding to both wild-type and Dutch/Iowa-type CAA mutant forms of amyloid-β, and therefore, inhibiting amyloid-β fibrillogenesis (with amyloid-β_{1-42} being more fibrillogenic than amyloid-β_{1-40}) in the brain [130, 131]. Detailed ultrastructural analysis revealed that MBP allows the assembly of oligomeric species but prevents their further assembly into fibrillar structures (protofibrils and amyloid fibrils) [130]. Furthermore, further analysis discovered that the N-terminal region of MBP contained the required amyloid-β binding domain, thereby inhibiting its assembly into fibrillar amyloid [132, 133]. Consistent with these findings, recent research indicates that purified MBP exhibits autocleavage activity, generating distinct peptide fragments [134]. Mei-Chen Liao and colleagues have reported that both purified human brain MBP and recombinant human MBP can effectively degrade amyloid-β_{1-40} and amyloid-β_{1-42} peptides. Moreover, MBP expressed in Cos-1 cells has demonstrated the ability to degrade exogenous amyloid-β_{1-40} and amyloid-β_{1-42} peptides. Additionally, purified MBP has been observed to degrade assembled fibrillar amyloid-β in vitro. Impressively, in situ experiments have shown that purified MBP can efficiently degrade parenchymal amyloid plaques and cerebral vascular amyloid in brain tissue obtained from amyloid-β precursor protein transgenic mice [128].

In conclusion, MBP serves as a unique chaperone, exerting inhibitory effects on amyloid-β fibrillogenesis and actively degrading amyloid-β peptides. Despite these compelling findings, our current knowledge regarding the role of MBP in amyloid-β clearance in the brain remains limited. Hence, we strongly encourage future research efforts aimed at unraveling the precise mechanisms underlying MBP-mediated amyloid-β clearance and developing strategies to enhance this process. Such investigations hold the potential to provide a valuable method for preventing the accumulation of amyloid-β in the brain, a phenomenon reported in conditions like AD and CAA. Through continued exploration in this area, we may unlock new insights into potential therapeutic targets and contribute to advancing the understanding and management of amyloid-β pathology.

Plasmin

Three functionally related serine proteases, including plasmin, urokinase-type plasminogen activator and tissue-type plasminogen activators, have been implicated in amyloid-β degradation [135]. Plasmin is the only one of these proteases that has been shown to directly degrade amyloid-β. Plasmin cleaves and degrades amyloid-β at multiple sites, preventing its aggregation into β-pleated sheets [135-137], which is critical for amyloid-β toxicity [138]. Notably, plasmin can degrade both aggregated and non-aggregated amyloid-β [139]. Several studies have highlighted the role of the plasmin in mediating amyloid-β degradation and preventing/blocking its neurotoxicity [135, 139, 140]. For example, purified plasmin has been shown to significantly decrease neurotoxicity induced by aggregated amyloid-β in neuronal cultured cells [136, 138]. Activation of plasmin has also consistently been shown to degrade amyloid-β, and the level of plasmin is reduced in aged brains [141]. Additionally, a significant correlation has been demonstrated between the proteolytic activity of plasmin and amyloid-β levels, suggesting that enhancing amyloid-β degradation/clearance by an increasing plasmin's proteolytic activity may be a viable therapeutic approach for lowering amyloid-β levels in the brain [135, 142].

Acylpeptidehydrolase

Acylpeptidehydrolase (APH) is a homomeric tetramer, which is a peptidase of approximately 75~80 kDa and belongs to the "prolyl oligopeptidase family". It is expressed in numerous cells and organs, including the brain, liver, kidney, erythrocytes, and plasma [143, 144]. APH is thought to play a vital role in the catabolism of acetylated proteins and the subsequent removal of acetyl group [145]. Previous studies have suggested that APH is involved in the degradation of amyloid-β in SKNMC-neuroblastoma cells, indicating its importance in this process [143, 144]. *In vitro* studies also demonstrated that APH preferentially degrades monomeric and oligomeric forms of amyloid-β [144]. Interestingly, APH levels have been found to be significantly lower in aged brains compared to controls.

As far as we are aware, there is currently limited available data on the role of acylpeptidehydrolase in amyloid-β clearance within the brain. Consequently, we strongly advocate for future research efforts aimed at unraveling the precise mechanisms by which acylpeptidehydrolase mediates amyloid-β clearance. Such investigations hold the potential to pave the way for the development of strategies to enhance this clearance mechanism. By gaining a deeper understanding of acylpeptidehydrolase-mediated amyloid-β

 https://doi.org/10.5607/en23014

clearance, we may discover valuable insights that could lead to the identification of novel therapeutic targets. This, in turn, may offer a promising avenue to prevent the accumulation of amyloid-β in the brain, a phenomenon frequently associated with conditions like AD and CAA. Through continued research in this area, we may eventually find innovative approaches to combat amyloid-β pathology and potentially ameliorate the progression of neurodegenerative diseases.

Cysteine proteases

Cathepsin B is a well-known member of cysteine proteases family and can function as either an exopeptidase or an endopeptidase. It is present in lysosomes of all cell types, participating in the degradation of proteins. Studies by Sun et al. [146] demonstrated that cathepsin B is involved in amyloid-β degradation in mice brain. Lysosomal cathepsin B is critical for the clearance of oligomeric amyloid-β peptide in microglia [147] and its upregulation enhances amyloid-β degradation in monocytes [148]. Using molecular modeling, Dhanavade et al. [149] found that cathepsin B is capable of cleaving amyloid-β peptide from the carboxylic end of Glu11. Cathepsin D, another aspartyl protease, is present in the majority of mammalian cells and functions to degrade internalized and endocytosed proteins, including amyloid-β peptide [150]. Monocytes from AD patients have been observed to show downregulation of cathepsin D [151, 152]. Recently, Suire et al. found that genetic deletion of cathepsin D in mice leads to a significant accumulation of amyloid-β in lysosomes, indicating that extracellular amyloid-β is trafficked to lysosomes and its degradation is dependent on lysosomal AβDPs, such as cathepsin B and D [153-155].

Other miscellaneous enzymes

Glutamate carboxypeptidase II (GCPII) plays a crucial role in the degradation of several amyloid-β species (monomers, oligomers, and fibrils) in the brain. *In vitro* studies have shown that GCPII cleaves both amyloid-$\beta_{1\text{-}40}$ and amyloid-$\beta_{1\text{-}42}$ monomers. Moreover, GCPII not only inhibits the formation/synthesis of amyloid-β oligomers but also cleaves existing amyloid-β oligomers. GCPII is also known to degrade fibrils *in vitro* and reduce the plaque size in brain sections of transgenic mice [156]. Additionally, a mitochondrial amyloid-β-degrading protease called "peptidasome" has been identified and characterized in brain mitochondria, which has been reported to completely degrade amyloid-β [157-159]. Aminopeptidase, a family of enzymes that removes amino acid residues at the N-termini of proteins, has also been shown to contribute to N-terminal truncation of amyloid-β [160]. It efficiently degrades amyloid-β peptides (monomers, oligomers, and fibrils) to prevent amyloid-β deposition in mammalian brains [161, 162].

The role of non-enzymes in clearing amyloid-β in the brain

Amyloid-β clearance by glial cells

The term "glia" was first coined by Virchow, referring to their ability to form "glue" in brain cells. Different types of glial cells have been recognized for their role in amyloid-β clearance, including astrocyte, microglia and oligodendrocyte [163]. In the human brain, glial cells make up about 50% of all cells [164]. Glial cells such as microglia and astrocytes can uptake amyloid-β and represent an additional functional pathway for amyloid-β degradation in the brain [165, 166].

On the other hand, strong evidence derived from fundamental molecular biology studies has also revealed that aberrant activation of glial cells can play a role in mediating neuroinflammation. This activation leads to the release of inflammatory mediators, such as inflammatory cytokines, complement components, chemokines, and free radicals. These factors collectively contribute to the production and buildup of amyloid-β, ultimately leading to the development of neurodegenerative conditions [167, 168].

The clearance of amyloid-β peptides by glial cells involves different mechanisms as described below.

Amyloid-β clearance by microglia

Microglia, a type of glial cells that make up 10~20% of glia cells in the brain and the spinal cord [169]. They serve as resident macrophages, equipped with numerous pattern recognition receptors that enable them to detect exogenous pathogen-associated molecular patterns (PAMPs) or endogenous danger-associated molecular patterns [109]. Microglia play vital roles in internalization and clearance of amyloid-β in the brain (Fig. 2). They interact with both soluble and fibrillar forms of amyloid-β in different ways. Soluble forms are taken up through macropinocytosis and LDLR (low density lipoprotein receptor)-related proteins mediated pathway, while fibrillar forms of amyloid-β interact with innate immune receptors of microglia, initiating intracellular signaling cascades and stimulating phagocytosis [170]. A wide range of innate immune receptors are involved in microglia-mediated amyloid-β clearance, including scavenger receptors, Toll-like receptors, purinergic G protein-coupled receptors, complement components and their associated receptors, and triggering receptor expressed on myeloid cells [46, 109]. The surface signaling receptor TREM2, found in microglia, can enhance the microglial phagocytosis of amyloid-β when increased expression is triggered by the presence of amyloid-β. However, the R47H mutation present in AD can impede TREM2's ability to recognize lipid ligands effectively,

resulting in failure to activate microglia and ultimately leading to amyloid-β deposition [171-173]. In addition, ATP-binding cassette transporter A7, mainly expressed in human microglial cells, regulates microglial phagocytic function to reduce amyloid-β deposition in the brain [171, 174]. In contrast to receptor-mediated amyloid-β phagocytosis, both receptor-mediated endocytosis (a biochemical and a mechanical process) and receptor-independent fluid-phase pinocytosis is also involved in the uptake and degradation of amyloid-β by microglia [109, 175-177]. Once internalized within cells, microglia rapidly traffic amyloid-β into intracellular degradation systems including autophagy, endosomal/lysosomal degradation, and ubiquitin–proteasome system, which prevent intracellular amyloid-β aggregation and accumulation, thus protecting against amyloid-β-associated neuropathology [46]. Additionally, microglia contribute to amyloid-β clearance by secreting AβDPs that degrade amyloid-β in the extracellular space, reducing its buildup in the brain [178, 179].

Amyloid-β clearance by astrocytes

In addition to microglia, stellate-shaped astrocytes also play a significant role in the metabolic functions of amyloid-β clearance [163, 180] (Fig. 2). Astrogliosis and astrocyte activation, similar to microgliosis, are closely related to amyloid-β pathogenesis [179, 181]. Notably, research has revealed that astrocytes are more proficient than microglia in removing amyloid-β, especially during the initial stages of AD [182, 183]. Mechanistically, both *in vivo* and *in vitro* studies have shown that astrocytes can release proteases, such as NEP, ACE, ECE-2 and MMP9, which aid in amyloid-β clearance in the brain [184, 185]. Additionally, astrocytes secrete kallikrein-related peptidase 7 (KLK7) and MMP membrane type-1 (MT1) [116, 186]. KLK7 protein can cleave amyloid-β within the central hydrophobic core, attenuating fibril formation and promoting the degradation of pre-formed fibrils [187]. The deletion of KLK7 in mouse brains resulted in an increased brain amyloid-β economy, supporting the notion that "KLK7-dependent amyloid-β degradation" activity is physiologically relevant in the catabolism of amyloid-β in brain [186]. Similarly, MT1 expressed in "reactive astrocytes" near amyloid deposits degrades exogenous amyloid-β and fibrillar amyloid-β *in vitro* [116].

Additionally, the endocytic and signaling receptor LRP1, along with its ligand ApoE, is widely recognized for its crucial involvement in the regulation of amyloid-β catabolism and APP processing [188, 189]. Chia-Chen Liu's study provides compelling evidence for the significant involvement of astrocytic LRP1 in amyloid-β metabolism, as demonstrated in both in vitro and in vivo models. Deficiency of astrocytic LRP1 leads to impaired clearance of amyloid-β in the interstitial fluid (ISF) and worsened amyloid-β deposition in the brains of APP/PS1 mice [190].

Astrocytes, among the various cell types in the brain, are also the primary contributors to the production of ApoE, generating the highest amounts of this protein [191]. Specifically, ApoE recycling plays a crucial role in regulating the expression of various cell surface proteins, particularly ABCA1 [192, 193]. The impaired recycling of ApoE4 results in the entrapment of ABCA1 within endosomes, preventing its localization to the cell surface [194]. This disruption in ABCA1 function is associated with decreased ABCA1-mediated cholesterol efflux activity and compromised amyloid-β degradation capacity. Remarkably, the enhancement of ABCA1 activity effectively restores amyloid-β degradation in cells treated with ApoE4 and concurrently reduces the aggregation of both ApoE and ABCA1 in mice's brains [192, 194]. Furthermore, it is essential to recognize the critical role of the autophagy pathway in cellular homeostasis, facilitating the turnover of cell organelles and promoting the degradation of aggregated proteins in response to cellular stress [195]. A defective clearance of amyloid-β-generating autophagic vacuoles can create conditions favorable for amyloid-β accumulation in the brain, as evidenced by data indicating that increasing autophagy through rapamycin reduces amyloid burden in vivo [196]. Additionally, autophagy appears to play a role in the breakdown of amyloid-β by microglia [197], and astrocytes from transgenic AD models have shown strong expression of microtubule-associated protein light chain 3, suggesting the involvement of autophagy in amyloid-β internalization by these cells, providing a link between autophagy and phagocytosis [175, 198].

Consistent with these findings, the process of amyloid-β aggregation and fibrillogenesis initiates a deleterious cascade of events in astrocytes, impacting neuronal viability and functionality [199]. For instance, in an AD mouse model, reactive astrocytes exhibit metabolic and functional changes, resulting in the abnormal production of the neurotransmitter γ-aminobutyric acid (GABA) through the activity of monoamine oxidase B (MAO-B) in the putrescine-degradation pathway [200, 201], thereby contributing to memory impairment [200, 202]. Moreover, MAO-B generates toxic byproducts such as ammonia and H_2O_2 along this pathway, ultimately leading to neurodegeneration [201, 203].

Amyloid-β clearance via the blood-brain barrier

Amyloid-β can cross the blood–brain barrier (BBB) in both directions: from brain to blood (efflux) and from blood to brain (influx) (Fig. 2). The BBB is responsible for catabolizing the majority of amyloid-β (~75%) compared to interstitial fluid (ISF) bulk flow does (~10%, as explained below) [6]. Furthermore, the BBB has the ability to uptake and catabolize not only amyloid-β in the blood

 https://doi.org/10.5607/en23014

but also amyloid-β that originates from the brain [204].

Receptor-mediated efflux of amyloid-β

Amyloid-β can travel from the brain to blood by (i) ATP-binding cassette transporters (ABC transporters) and (ii) LDLR family members, such as LRP1 [6].

The ABC transporter is one of the most common transmembrane proteins, which can be classified into subfamilies (A to G) based on sequence homology and functional similarity. These ABC transporters use energy generated through ATP hydrolysis to transport substrates across cell membranes and play an essential role in various physiological activities. Recent studies have suggested that ABC transporters are involved in amyloid-β clearance [152]. Among them, two ABC transporters, ABC transporter subfamily B member 1 (ABCB1, an efflux pump for xenobiotic molecules) and ABC transporter subfamily A member 1 (ABCA1 or Cholesterol Efflux Regulatory Protein (CERP), an efflux pump for cholesterol/phospholipids from cell membranes), have received considerable attention for their roles in amyloid-β clearance [205]. ABCB1 is directly involved in the export of amyloid-β into the bloodstream, while ABCA1 is indirectly facilitates amyloid-β efflux transfer from the brain to blood via ApoE-dependent mechanisms [206]. It has been suggested that ABCA1 controls protein levels of ApoE and its lipidation state. A highly lipidated ApoE binds to amyloid-β (ApoE-amyloid-β interaction) more efficiently, diminishing its capacity to aggregate and making amyloid-β more accessible for transport at the neurovascular unit [205].

The LDLR family is a highly conserved family of receptors that bind to a wide range of ligands, including amyloid-β [207]. LRP1 is localized to neurons, glial cells, endothelial cells in the BBB, and epithelial cells in the blood-CSF barrier (BCSFB). Studies have shown that LRP1 binds to both amyloid-$\beta_{1\text{-}40}$ and amyloid-$\beta_{1\text{-}42}$, either alone or in conjugated form with carrier proteins. Once bound, LRP1 can target amyloid-β for cellular degradation or facilitate its transcytosis [208], helping to transport amyloid-β out of the brain [209]. Furthermore, α2-macroglobulin [210] and LDLR-related protein 2 (LRP2), also known as megalin, in combination with clusterin (ApoJ) can form a complex to regulate amyloid-β clearance across the BBB [6].

Receptor-mediated influx of amyloid-β

RAGE, the receptor for advanced glycation end products, is believed to be involved in the influx of amyloid-β into the CNS [211] (Fig. 2). Fang et al. reported that the RAGE-dependent signaling pathway regulates the cleavage of APP by β- and γ-secretases to generate amyloid-β, at least in part, through the activation of two specific enzymes, GSK3β and p38 MAP kinase [212]. RAGE is a multi-ligand receptor that interacts with a variety of ligands, including ^{125}I labeled amyloid-β (monomers, oligomers, and fibrils) [213]. Using an *in vitro* BBB model, Mackic et al. [214] demonstrated that RAGE interacts with amyloid-β followed by its subsequent cellular processing (endocytosis and transcytosis) in the circulation. In addition, recent studies reported that inhibition of RAGE or its interaction with amyloid-β suppresses amyloid-β accumulation in brain parenchyma in mice [215-217]. Ma et al. [218] also showed that upregulation of RAGE in the hippocampus or prefrontal lobe significantly contributed to the amyloid-β accumulation in animal brains [152]. However, more recently, numerous amyloid-β sequestering agents in the periphery (anti-amyloid-β IgG, serum amyloid P component, and soluble forms of both RAGE (sRAGE) and LRP1 (sLRP1)) are reported to inhibit its interaction with RAGE and therefore inhibit amyloid-β from entering the brain [6, 210, 219, 220].

Amyloid-β clearance via the interstitial fluid bulk flow

The brain and spinal cord contain two extracellular fluids, cerebrospinal fluid (CSF) and interstitial fluid (ISF) [70]. Previous studies have shown that CSF enters the interstitial space in the brain and exchanges or mixes with ISF. This suggests that proteins in ISF may also be transferred or cleared directly into the CSF via ISF bulk flow [221]. In fact, ISF bulk flow can remove proteins, such as amyloid-β from the interstitium via two possible pathways: (i) into the perivascular space or (ii) into the glymphatic system, as discussed below [70, 222].

Perivascular drainage

Previous animal studies have shown that perivascular routes are crucial for the clearance of amyloid-β from the brain (Fig. 2). A failure of this drainage pathway can cause amyloid-β to become trapped in the cerebral cortex and the walls of blood vessels [223], leading to the development of AD [70, 224] and CAA [70]. The lymphatic system serves as a secondary circulation system and closely resembles the blood-vascular system [222]. ISF bulk flow provides an effective clearance route for ISF-containing amyloid-β in the brain and cerebral vessels [70, 225], mostly consisting of perivascular drainage and glymphatic clearance. In perivascular drainage pathway, amyloid-β is eliminated from extracellular spaces by first entering into the capillary spaces before it drains along the walls of arteries in human brain [223]. Notably, if the direct entry of amyloid-β into the blood is either prevented or fails, this perivascular drainage becomes apparent [70] or when the level of NEP enzyme is reduced [52]. However, this route has been shown to be six times slower than amyloid-β absorption into the blood across the BBB [70, 226]. Several factors can influence the

perivascular drainage of amyloid-β, including ApoE*ε4, arterial age, deposition of immune complexes, and arterial pulsation.

Glymphatic system

Recently, a novel pathway known as the "glymphatic pathway" has been discovered to contribute to the clearance waste, such as interstitial solutes, metabolites, amyloid-β, from the brain [6, 227]. The glymphatic system is a glial-dependent perivascular network that functions similar to a pseudo-lymphatic system in the brain [228]. The term "glymphatic" was coined based on two-photon imaging research [6, 222, 229], which emphasized the reliance on glial cells and functional similarity with the peripheral lymphatic system that helps to clear waste materials from the interstitial spaces between cells [222, 227]. According to this theory, CSF enters the paravascular spaces surrounding the brain's penetrating arteries, combines with ISF and interstitial solutes in the parenchyma, and then leaves along the paravascular spaces of the brain's draining veins. The glymphatic system contributes significantly to clearing amyloid-β from the brain, in addition to other wastes, more than was previously believed [227]. Supporting the idea, an increasing body of research has suggested a link between glymphatic dysfunction and decreased amyloid-β clearance in the brain [6, 227]. This relationship is influenced by several factors, including molecular size, arterial pulsation, aquaporin-4 (AQP4) expression and localization, and sleep [6].

The role of csf in clearing amyloid-β in the brain

The brain needs to eliminate proteins after their transport from the ISF into the CSF [6]. In particular, CSF, which is rich in amyloid-β, can be absorbed into the blood/circulation either through arachnoid villi [230] and the blood-CSF barrier (BCSFB), in the presence of amyloid-β transporters [209], or through the perivascular drainage pathways/perineural spaces and possibly meningeal lymphatics vessels, which empty into the lymphatic system [70, 222, 231]. However, the efficacy of either system to clear amyloid-β largely depends on several factors, including CSF production, BCSFB integrity and transporters, arachnoid villi resistance, and lymphatic absorption of the CSF [6].

TRANSPORT MECHANISMS OF AMYLOID-β BETWEEN THE BRAIN AND THE PERIPHERY

Brain-derived amyloid-β can be transported into the periphery for clearance through various routes, such as BBB [232, 233], BCSFB [214].

Similarly, the brain has evolved a distinct paravascular pathway that enables fluid exchange between the brain's interstitial fluid (ISF) and cerebrospinal fluid (CSF) without traversing the tightly regulated endothelial cell layer [222]. Numerous studies have demonstrated that a significant portion of cerebral amyloid-β is cleared through the transvascular route [234]. Additionally, emerging evidence suggests that the glymphatic system, which plays a crucial role in cerebral waste clearance, may also be vital for clearing amyloid-β [222]. Following the glymphatic system, the majority of CSF is believed to drain into the venous circulation through arachnoid granulations [235, 236].

On the other hand, how does amyloid-β originating in the periphery gain access to the brain's regions? Several compelling lines of evidence support the notion that amyloid-β generated in the periphery can be transported into the brain, contributing to the development of amyloid pathology. For instance, a study demonstrated that the administration of peripherally applied amyloid-β-containing inoculates resulted in the deposition of cerebral amyloid-β, indicating that amyloid-β generated in the periphery can infiltrate the brain and contribute to amyloid pathology [237, 238]. Furthermore, the receptor for advanced glycation end products (RAGE) has been proposed as a primary transporter of amyloid-β from the systemic circulation into the brain through the blood-brain barrier (BBB). The upregulation of RAGE expression in both human and animal studies provides further support for this mechanism [215, 239]. Additionally, recent research findings suggest that platelets play a role in transporting amyloid-β from the systemic circulation into the brain [240]. These findings align with several recent reports demonstrating the contribution of circulating amyloid-β to cerebral amyloidosis. Collectively, these studies corroborate the notion that amyloid-β generated outside the brain can be transported from the periphery into the brain, leading to the development of central amyloid pathology [241-243].

This close relationship between the brain and the periphery concerning amyloid-β metabolism provides additional insight into the pathophysiology of diseases and may lead to new approaches for diagnosis and treatment of AD and CAA.

AMYLOID-β CLEARANCE IN THE PERIPHERY

Although the mechanisms of amyloid-β degradation/clearance in the periphery are not fully understood, available studies suggest that approximately 60% of brain-derived amyloid-β is cleared through transportation across the BBB to the periphery [244, 245]. In addition, a recent study demonstrated that brain-derived amyloid-β can be cleared in the periphery through a single peripheral system, resulting in an approximately 80% decrease in brain amyloid-β accumulation during parabiosis in humans and mice

 https://doi.org/10.5607/en23014

[232]. This finding highlights the significant role of the periphery clearance system in clearing brain-derived amyloid-β and suggests that effective peripheral amyloid-β clearance could have a major impact on preventing amyloid-β accumulation in the brain. Multiple processes are likely involved in amyloid-β catabolism in the periphery, as explained below.

The role of peripheral enzymes in amyloid-β clearance

Several studies have reported that the expression and function of AβDPs in the brain to lower amyloid-β levels [246, 247]. Similarly, the expression and catabolic activity of these enzymes in the periphery have shown promising results [248]. Enzymes such as NEP, ECE, IDE and ACE have been found in the periphery and explored for their ability to degrade amyloid-β [249, 250]. These AβDPs have been found to bind to erythrocytes and degrade amyloid-β in plasma [248], human serum [251], skeletal muscle [232, 252, 253], and within the liver [254]. Furthermore, ECE–1 has been reported to degrade amyloid-β in the blood. The presence of ACE in blood and IDE in human CSF has been identified but their functional role in the amyloid-β metabolism remains unknown and requires future investigation [251].

The role of blood components in amyloid-β clearance

Amyloid-β from the brain can enter the bloodstream through various mechanisms [255-257]. Once is the blood, multiple components work together to clear circulating amyloid-β [103], including a wide range of amyloid-β-binding proteins such as lipoproteins and albumin, as well as amyloid-β-binding cells such as erythrocytes and immune cells [258].

Amyloid-β-binding proteins

An amyloid-β-equilibrium between blood and brain is maintained through a range of amyloid-β carrier proteins and receptors that facilitate transport and clearance of amyloid-β across the BBB [239, 248].

Human serum albumin, a most abundant protein in the blood, has been found to bind to amyloid-β (90% of amyloid-$\beta_{1\text{-}40}$ and amyloid-$\beta_{1\text{-}42}$) [259, 260], including both amyloid-β monomers [261] and oligomers [262] (Fig. 2). Numerous studies have shown that human serum albumin targets both species [259] and inhibits amyloid-β fibrillization both *in vitro* [263] and *in vivo* [259, 264], supporting the peripheral sink hypothesis. This strategy is based on the idea that amyloid-β in the brain and peripheral are in equilibrium and that reducing amyloid-β in the periphery can lead to a reduction of amyloid-β in the brain through passive diffusion down a concentration gradient [265, 266].

Amyloid-β-binding cells-erythrocytes

Amyloid-β-binding cells, such as erythrocytes, have been found to play a significant role in the transport and clearance of amyloid-β in peripheral organs [258] (Fig. 2). For example, erythrocytes facilitate the clearance of amyloid-β by relying on complement C3b-dependent adherence to complement receptor 1 on erythrocytes [171, 267]. Any alterations in the number and function of erythrocytes, or the decreased adherence to erythrocytes, may prevent amyloid-β from being transported and cleared in peripheral organs, eventually leading to amyloid-β accumulation in the brain. Recent studies also have found a significant association between amyloid-β and erythrocytes [268, 269]. For instance, Taylor et al. showed a new strategy in which immune complexes simultaneously capture amyloid-β and adhere it to erythrocytes via complement receptor 1 (CR1; CD35), promoting the rapid clearance of amyloid-β from the circulation and the brain [270].

Immune cells

Monocytes, lymphocytes, neutrophils, and macrophages are additional cell types that have been implicated in the clearance of amyloid-β peptides [258, 267, 271-273]. Just like glial cells and neurons in the brain clear amyloid-β by phagocytosis or endocytosis, amyloid-β in the periphery can also be phagocytosed in the blood by monocytes and neutrophils, as well as in tissues by macrophages [239, 274]. Monocytes in the blood are considered peripheral counterparts of microglia, and it has been shown that they are more effective at clearing amyloid-β clearance than microglia [257]. A recent study indicated that the receptors related with amyloid-β internalization (CD33, TLR2, TREM2, etc.) on blood monocytes are reduced in AD patients, implying that the capacity of monocytes to uptake and degrade amyloid-β is compromised, which contributes to an increase in amyloid-β level [50, 257].

Additionally, lymphocytes (including T cells, B cells, and natural killer cells) have been linked to amyloid-β clearance through immunoglobulin-mediated adaptive phagocytosis [239, 273, 275]. Multiple studies also have demonstrated that various types of cells derived from the peripheral system, including monocyte-derived microglia-like cells [276, 277], peripheral blood-derived microglia-like cells [278], CD11b-positive cells (predominantly monocytes) [279] and CD115-positive cells, can migrate from the bloodstream [280] into the brain to phagocytose amyloid-β peptides, potentially aiding in the prevention of amyloid-β accumulation [281].

BBB is a critical regulator of the entry of peripheral immune cells into the brain and their clearance of amyloid-β. Although the volume of blood is much larger than that of cerebrospinal fluid (CSF), the BBB limits the access of peripheral immune cells to the brain, which can affect their ability to clear amyloid-β. However, recent

research has highlighted the significant role of peripheral immune cells, particularly monocytes and macrophages, in amyloid-β clearance, particularly in the early stages of AD. Therefore, it is likely that peripheral clearance mechanisms play a crucial role in clearing soluble forms of amyloid-β that can traverse the BBB.

The role of peripheral organs in amyloid-β clearance

In the periphery, several tissues and organs are involved in amyloid-β peptide clearance, including the liver, kidney, and spleen etc. as discuss below [204, 232, 282, 283].

The role of the liver in clearing amyloid-β

The liver is a crucial metabolic organ that is responsible for synthesizing proteins, regulating metabolism, and detoxifying the body from harmful substances. Circulating amyloid-β is mainly cleared by either degradation in hepatocytes, which accounts for more than 60% of clearance, or excretion/catabolism in the bile (Fig. 2). A recent study indicated that people with liver cirrhosis have reduced liver-mediated amyloid-β clearance [284], and another study showed a significant association between hepatic function and plasma amyloid-β levels [285]. Although the molecular mechanisms governing hepatic amyloid-β uptake are not yet fully understood [286], multiple studies have revealed that transport proteins such as albumin, ApoJ, ApoE, transthyretin, and alpha-2-macroglobulin, which facilitate the degradation of amyloid-β in peripheral organs, particularly the liver, bind to amyloid-β after it is effluxed from the brain [103, 260, 287, 288]. To better comprehend the receptor-mediated amyloid-β uptake in the liver, it has been proposed that LRP1 is the major receptor involved in amyloid-β internalization [286, 289], followed by its degradation by several proteases found in the liver [254]. Although various receptors, such as SR-A and RAGE, are expressed in the liver [286], LRP1 has been identified as the primary receptor responsible for amyloid-β uptake in the liver [254]. Modulating LRP1 function in the liver, either pharmacologically or non-pharmacologically, has been shown to the reduce amyloid-β buildup in the mouse brain [254, 290]. Similarly, insulin has been hypothesized to enhance liver-mediated amyloid-β clearance by inducing intracellular translocation of LRP1 to the plasma membrane in hepatocytes [285, 291].

The role of kidney in clearing amyloid-β

The kidneys are the body's primary excretory organs, responsible for regulating blood minerals to control metabolite levels [103]. Previous research has shown that protein uptake in the renal tubule is mediated primarily by two receptors, megalin and cubilin, expressed in renal tubular epithelial cells [292]. Megalin, also known as LRP2, has been suggested to transport amyloid-β from the brain to blood across the BBB [293]. Recent studies have found that megalin-positive renal tubular epithelial cells in both humans and AD mice accumulate amyloid-β, suggesting that megalin may absorb amyloid-β from the urine [282]. Amyloid-β has also been detected in human urine samples [294], and animal experiments have shown that the kidney filtration removes amyloid-β from the blood into the urine [232, 295]. Renal failure can result in poor peripheral clearance of amyloid-β, as evidenced by an inverse relationship between serum amyloid-β levels and estimated glomerular filtration rate (eGFR) of renal function in chronic kidney disease patients [296, 297]. Human kidney donors have also shown reduced eGFR and the increased plasma levels of amyloid-β [298], demonstrating that the decreased renal function reduces amyloid-β clearance in the periphery. While the effect of renal dysfunction on amyloid-β burden in the brain is unknown, renal dysfunction has been associated with an increased risk of dementia [299]. Kidney transplantation can reduce amyloid-β deposition in the plasma [298], and hemodialysis may ameliorate amyloid-β deposition in the brains of CKD patients [300, 301].

Recent studies have provided further evidence for a strong association between kidney function and amyloid-β clearance [302]. For instance, Gronewold et al. have reported that reduced kidney function is linked to increased plasma amyloid-β level, which could contribute to cerebral amyloid-β accumulation [303]. Additionally, Tian et al. have found that amyloid-β levels in the blood of the renal artery were higher than in the blood of the renal vein [282], indicating that the kidney may participate in amyloid-β clearance by filtering it from the blood into the urine [239].

The role of spleen in clearing amyloid-β

The spleen is an organ that serves as a blood filter and performs important immunological functions, resembling a large lymph node. It stores blood and removes old erythrocytes and is composed of various immune cells, including monocytes/macrophages, which play a crucial role in the innate immune system [304]. Similar to other monocytes/macrophages in the body, the spleen is known to clear amyloid-β in the periphery [283, 305]. Recent research by Yu et al. has demonstrated that the spleen significantly contributes to the peripheral clearance of amyloid-β, with splenic monocytes and macrophages playing a significant role in this process. Conversely, splenectomy has been shown to increase amyloid-β accumulation and may accelerate the onset of AD [283, 306].

The role of other peripheral organs in clearing amyloid-β

Several studies have reported that the detection of amyloid-β deposits in non-neural tissues, such as skin, subcutaneous tissue, and

 https://doi.org/10.5607/en23014

intestine in humans, and the gastrointestinal tract in animals such as dogs [307, 308]. The presence of circulating amyloid-β in the blood is thought to be the cause of these deposits, suggesting that these organs may participate in peripheral amyloid-β metabolism, as observed in many studies [309-311].

The skin, for example, is an immune organ [312], and it develops from the same ectodermal layer as the brain during embryonic development [312, 313]. Certain genes and molecular pathways linked to the mechanisms of neurodegenerative diseases modify their expression with progressing skin aging, possibly due to the shared ectodermal origin of the skin and nervous system [313]. BACE1 (β-secretase 1), an enzyme that degrades amyloid-β_{1-40} and amyloid-β_{1-42}, generates a shorter amyloid-β_{1-34} peptide [314], which has been identified in human skin and could serve as a possible marker of amyloid-β degradation [315]. Additionally, a study showed that the majority of the ^{125}I-labeled amyloid-β_{1-40} was detected in the skin with only a minor amount in the brain, demonstrating that amyloid-β produced in the brain can be cleared in the periphery [232]. Although basal keratinocytes have been shown to express high levels of amyloid-β precursor protein [316, 317], it is still unknown whether the amyloid-β deposits are caused by local skin cells or the circulating blood [103]. Sweat secretion is another potential mechanism for excreting amyloid-β, but it is unclear whether the skin contributes to the amyloid-β clearance. More research is needed to answer this question.

Similarly, the digestive system, which is a lymphatic organ, contains a substantial number of macrophages and other immune cells, suggesting that the gut may be capable of clearing amyloid-β. Many studies imply that the brain-gut-microbiota axis is implicated in the etiology of dementia-related disorders [318]. Therefore, exploring the possibility of the gastrointestinal system influencing peripheral amyloid-β metabolism is critical.

THERAPEUTIC STRATEGIES FOR CLEARING AMYLOID-β IN THE BRAIN AND THE PERIPHERY

At present, effective preventative or therapeutic medicines for AD and CAA are lacking. Over the years, various treatment approaches targeting amyloid-β in the brain, such as anti-amyloid-β therapy (including amyloid-β immunotherapy, secretase inhibitors, and amyloid-β aggregation inhibitors), have been developed and remain in use [319, 320]. However, most of these strategies have failed in clinical trials due to high costs, drug-drug interactions, food-drug interactions, and significant side effects, which impose a significant financial and social burden on society. To achieve the desired therapeutic outcomes of these complex and multifaceted diseases, we must consider different strategies targeting amyloid-β in both the brain and periphery based on solid sources of information.

The accumulation of amyloid-β in the brain is largely caused by a reduction in AβDPs activity. Thus, increasing the expression levels of AβDPs would dramatically reduce amyloid-β buildup and associated pathologies. Strategies to translate AβDPs into therapeutic applications include enhancing AβDPs activity through the administration of compounds, gene therapy using genes encoding AβDPs, and cell therapies based on stem cell transplantation [40]. Additionally, non-enzymatic pathways (such as targeting microglial phagocytosis, photo-oxygenation [321, 322], BBB transporters, perivascular drainage etc.) should be improved to reduce the level of amyloid-β in the brain [171].

Besides mechanisms underlying the clearance of amyloid-β in the brain, peripheral intervention has also received much attention, with positive outcomes in reducing amyloid-β in the brain and the incidence of dementia. These peripheral approaches include managing cardiovascular risk factor [323], treating sleep-disordered breathing with sustained positive airway pressure [324, 325], lowering peripheral blood cholesterol levels by using statins [326, 327], plasma exchange programs [328], dialysis (peritoneal dialysis and hemodialysis) [329], improving the phagocytic ability/function of peripheral blood monocytes through proteolytic degradation [272, 305], targeting enzymes (NEP/ACE) processes [252, 253, 330], developing nanozymes [331], and various therapeutic agents targeting peripheral clearance of amyloid-β (such as inorganic nanoparticles, polymer nanoparticles and liposomes) [332-336]. In recent years, researchers have been investigating immunotherapy as a "gold standard strategy" to promote amyloid-β clearance, leading to an increased focus on development of anti-Aβ therapies [337-339]. However, amyloid-related imaging abnormalities (ARIA) are the major severe side effect associated with amyloid-β immunotherapy [340]. Despite the clinical therapeutic effects of anti-amyloid-β immunotherapies for Alzheimer's disease (AD), aducanumab and solanezumab have been shown to improve cognitive function, while aducanumab and bapineuzumab may also increase the risks of ARIA [341].

In addition to immunotherapy, non-immune approaches, such as peripheral amyloid-β-binding agents (e.g., gelsolin, GM1, sRAGE, sLRP fragments) [215, 335], blood cells, and protein [248, 265], have also made significant progress in disease prevention.

These findings suggest that both "central therapeutic strategies" in the brain and "systemic therapeutic strategies" may be helpful in reducing the amyloid-β burden in the brain and attenuating disease pathology. Therefore, a combination of both central and systemic therapeutic approaches may be necessary to effectively treat AD and CAA.

CONCLUSION

AD and CAA are often associated with each other, sharing the common factor of amyloid-β. The impaired clearance of amyloid-β peptide in the body is believed to contribute to the accumulation of central amyloid-β, leading to the pathogenesis of sporadic AD in the brain parenchyma and CAA in blood vessels. This review has highlighted the importance of clearing amyloid-β in the brain, which can be achieved through enzymatic or non-enzymatic pathways. Likewise, multiple mechanisms are involved in amyloid-β clearance in peripheral organs, such as immunomodulation, immune cells, enzymes, amyloid-β-binding proteins, and amyloid-β-binding cells. Therefore, it is recommended to investigate central therapeutic strategies targeting amyloid-β clearance in the brain and systemic therapeutic strategies targeting clearance mechanisms in peripheral organs to eliminate excess amyloid-β deposits. This approach will not only enhance our understanding of molecular mechanisms underlying both diseases but also provide new targets for inhibiting amyloid-β deposition in the pathogenesis of sporadic AD and CAA.

ACKNOWLEDGEMENTS

This review was supported by National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT) (2022R1C1C1005741 and RS-2023-00217595 to E.J.L.) and the new faculty research fund of Ajou University School of Medicine (to E.J.L).

REFERENCES

1. Bero AW, Yan P, Roh JH, Cirrito JR, Stewart FR, Raichle ME, Lee JM, Holtzman DM (2011) Neuronal activity regulates the regional vulnerability to amyloid-β deposition. Nat Neurosci 14:750-756.
2. Neve RL, McPhie DL (2007) Dysfunction of amyloid precursor protein signaling in neurons leads to DNA synthesis and apoptosis. Biochim Biophys Acta 1772:430-437.
3. Chow VW, Mattson MP, Wong PC, Gleichmann M (2010) An overview of APP processing enzymes and products. Neuromolecular Med 12:1-12.
4. Blennow K, de Leon MJ, Zetterberg H (2006) Alzheimer's disease. Lancet 368:387-403.
5. Zheng L, Cedazo-Minguez A, Hallbeck M, Jerhammar F, Marcusson J, Terman A (2012) Intracellular distribution of amyloid beta peptide and its relationship to the lysosomal system. Transl Neurodegener 1:19.
6. Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, Frangione B, Blennow K, Ménard J, Zetterberg H, Wisniewski T, de Leon MJ (2015) Clearance systems in the brain-implications for Alzheimer disease. Nat Rev Neurol 11:457-470.
7. Morris AW, Carare RO, Schreiber S, Hawkes CA (2014) The cerebrovascular basement membrane: role in the clearance of β-amyloid and cerebral amyloid angiopathy. Front Aging Neurosci 6:251.
8. Mueller-Steiner S, Zhou Y, Arai H, Roberson ED, Sun B, Chen J, Wang X, Yu G, Esposito L, Mucke L, Gan L (2006) Antiamyloidogenic and neuroprotective functions of cathepsin B: implications for Alzheimer's disease. Neuron 51:703-714.
9. Moro ML, Giaccone G, Lombardi R, Indaco A, Uggetti A, Morbin M, Saccucci S, Di Fede G, Catania M, Walsh DM, Demarchi A, Rozemuller A, Bogdanovic N, Bugiani O, Ghetti B, Tagliavini F (2012) APP mutations in the Aβ coding region are associated with abundant cerebral deposition of Aβ38. Acta Neuropathol 124:809-821.
10. Glabe C (2001) Intracellular mechanisms of amyloid accumulation and pathogenesis in Alzheimer's disease. J Mol Neurosci 17:137-145.
11. Dawkins E, Small DH (2014) Insights into the physiological function of the β-amyloid precursor protein: beyond Alzheimer's disease. J Neurochem 129:756-769.
12. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ (2020) Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. Nat Rev Neurol 16:30-42.
13. Thal DR, Ghebremedhin E, Orantes M, Wiestler OD (2003) Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. J Neuropathol Exp Neurol 62:1287-1301.
14. Park JS, Kam TI, Lee S, Park H, Oh Y, Kwon SH, Song JJ, Kim D, Kim H, Jhaldiyal A, Na DH, Lee KC, Park EJ, Pomper MG, Pletnikova O, Troncoso JC, Ko HS, Dawson VL, Dawson TM, Lee S (2021) Blocking microglial activation of reactive astrocytes is neuroprotective in models of Alzheimer's disease. Acta Neuropathol Commun 9:78.
15. Wan YW, Al-Ouran R, Mangleburg CG, Perumal TM, Lee TV, Allison K, Swarup V, Funk CC, Gaiteri C, Allen M, Wang M, Neuner SM, Kaczorowski CC, Philip VM, Howell GR, Martini-Stoica H, Zheng H, Mei H, Zhong X, Kim JW, Dawson VL, Dawson TM, Pao PC, Tsai LH, Haure-Mirande JV, Ehrlich ME, Chakrabarty P, Levites Y, Wang X, Dammer EB,

Srivastava G, Mukherjee S, Sieberts SK, Omberg L, Dang KD, Eddy JA, Snyder P, Chae Y, Amberkar S, Wei W, Hide W, Preuss C, Ergun A, Ebert PJ, Airey DC, Mostafavi S, Yu L, Klein HU; Accelerating Medicines Partnership-Alzheimer's Disease Consortium; Carter GW, Collier DA, Golde TE, Levey AI, Bennett DA, Estrada K, Townsend TM, Zhang B, Schadt E, De Jager PL, Price ND, Ertekin-Taner N, Liu Z, Shulman JM, Mangravite LM, Logsdon BA (2020) Meta-analysis of the Alzheimer's disease human brain transcriptome and functional dissection in mouse models. Cell Rep 32:107908.

16. Chua JJE (2023) HEBP1 - an early trigger for neuronal cell death and circuit dysfunction in Alzheimer's disease. Semin Cell Dev Biol 139:102-110.
17. Leng F, Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 17:157-172.
18. Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 82:239-259.
19. Parodi-Rullán R, Sone JY, Fossati S (2019) Endothelial mitochondrial dysfunction in cerebral amyloid angiopathy and Alzheimer's disease. J Alzheimers Dis 72:1019-1039.
20. Charidimou A, Boulouis G, Gurol ME, Ayata C, Bacskai BJ, Frosch MP, Viswanathan A, Greenberg SM (2017) Emerging concepts in sporadic cerebral amyloid angiopathy. Brain 140:1829-1850.
21. Hickman RA, Faustin A, Wisniewski T (2016) Alzheimer disease and its growing epidemic: risk factors, biomarkers, and the urgent need for therapeutics. Neurol Clin 34:941-953.
22. Verghese PB, Castellano JM, Holtzman DM (2011) Apolipoprotein E in Alzheimer's disease and other neurological disorders. Lancet Neurol 10:241-252.
23. Guerreiro RJ, Gustafson DR, Hardy J (2012) The genetic architecture of Alzheimer's disease: beyond APP, PSENs and APOE. Neurobiol Aging 33:437-456.
24. Bellenguez C, Küçükali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, Naj AC, Campos-Martin R, Grenier-Boley B, Andrade V, Holmans PA, Boland A, Damotte V, van der Lee SJ, Costa MR, Kuulasmaa T, Yang Q, de Rojas I, Bis JC, Yaqub A, Prokic I, Chapuis J, Ahmad S, Giedraitis V, Aarsland D, Garcia-Gonzalez P, Abdelnour C, Alarcón-Martín E, Alcolea D, Alegret M, Alvarez I, Álvarez V, Armstrong NJ, Tsolaki A, Antúnez C, Appollonio I, Arcaro M, Archetti S, Pastor AA, Arosio B, Athanasiu L, Bailly H, Banaj N, Baquero M, Barral S, Beiser A, Pastor AB, Below JE, Benchek P, Benussi L, Berr C, Besse C, Bessi V, Binetti G, Bizarro A, Blesa R, Boada M, Boerwinkle E, Borroni B, Boschi S, Bossù P, Bråthen G, Bressler J, Bresner C, Brodaty H, Brookes KJ, Brusco LI, Buiza-Rueda D, Bûrger K, Burholt V, Bush WS, Calero M, Cantwell LB, Chene G, Chung J, Cuccaro ML, Carracedo Á, Cecchetti R, Cervera-Carles L, Charbonnier C, Chen HH, Chillotti C, Ciccone S, Claassen JAHR, Clark C, Conti E, Corma-Gómez A, Costantini E, Custodero C, Daian D, Dalmasso MC, Daniele A, Dardiotis E, Dartigues JF, de Deyn PP, de Paiva Lopes K, de Witte LD, Debette S, Deckert J, Del Ser T, Denning N, DeStefano A, Dichgans M, Diehl-Schmid J, Diez-Fairen M, Rossi PD, Djurovic S, Duron E, Düzel E, Dufouil C, Eiriksdottir G, Engelborghs S, Escott-Price V, Espinosa A, Ewers M, Faber KM, Fabrizio T, Nielsen SF, Fardo DW, Farotti L, Fenoglio C, Fernández-Fuertes M, Ferrari R, Ferreira CB, Ferri E, Fin B, Fischer P, Fladby T, Fließbach K, Fongang B, Fornage M, Fortea J, Foroud TM, Fostinelli S, Fox NC, Franco-Macías E, Bullido MJ, Frank-García A, Froelich L, Fulton-Howard B, Galimberti D, García-Alberca JM, García-González P, Garcia-Madrona S, Garcia-Ribas G, Ghidoni R, Giegling I, Giorgio G, Goate AM, Goldhardt O, Gomez-Fonseca D, González-Pérez A, Graff C, Grande G, Green E, Grimmer T, Grünblatt E, Grunin M, Gudnason V, Guetta-Baranes T, Haapasalo A, Hadjigeorgiou G, Haines JL, Hamilton-Nelson KL, Hampel H, Hanon O, Hardy J, Hartmann AM, Hausner L, Harwood J, Heilmann-Heimbach S, Helisalmi S, Heneka MT, Hernández I, Herrmann MJ, Hoffmann P, Holmes C, Holstege H, Vilas RH, Hulsman M, Humphrey J, Biessels GJ, Jian X, Johansson C, Jun GR, Kastumata Y, Kauwe J, Kehoe PG, Kilander L, Ståhlbom AK, Kivipelto M, Koivisto A, Kornhuber J, Kosmidis MH, Kukull WA, Kuksa PP, Kunkle BW, Kuzma AB, Lage C, Laukka EJ, Launer L, Lauria A, Lee CY, Lehtisalo J, Lerch O, Lleó A, Longstreth W Jr, Lopez O, de Munain AL, Love S, Löwemark M, Luckcuck L, Lunetta KL, Ma Y, Macías J, MacLeod CA, Maier W, Mangialasche F, Spallazzi M, Marquié M, Marshall R, Martin ER, Montes AM, Rodríguez CM, Masullo C, Mayeux R, Mead S, Mecocci P, Medina M, Meggy A, Mehrabian S, Mendoza S, Menéndez-González M, Mir P, Moebus S, Mol M, Molina-Porcel L, Montrreal L, Morelli L, Moreno F, Morgan K, Mosley T, Nöthen MM, Muchnik C, Mukherjee S, Nacmias B, Ngandu T, Nicolas G, Nordestgaard BG, Olaso R, Orellana A, Orsini M, Ortega G, Padovani A, Paolo C, Papenberg G, Parnetti L, Pasquier F, Pastor P, Peloso G, Pérez-Cordón A, Pérez-Tur J, Pericard P, Peters O, Pijnenburg YAL, Pineda JA, Piñol-Ripoll G, Pisanu C, Polak T, Popp J, Posthuma D, Priller J, Puerta R, Quenez O, Quintela I, Thomassen JQ, Rábano A, Rainero I, Rajabli F, Ramakers I, Real LM, Reinders MJT, Reitz C, Reyes-Dumeyer D, Ridge P, Riedel-Heller S, Riederer P, Roberto N, Rodriguez-Rodriguez E, Rongve A, Allende IR, Rosende-Roca M, Royo JL, Rubino E, Rujescu D,

Sáez ME, Sakka P, Saltvedt I, Sanabria Á, Sánchez-Arjona MB, Sanchez-Garcia F, Juan PS, Sánchez-Valle R, Sando SB, Sarnowski C, Satizabal CL, Scamosci M, Scarmeas N, Scarpini E, Scheltens P, Scherbaum N, Scherer M, Schmid M, Schneider A, Schott JM, Selbæk G, Seripa D, Serrano M, Sha J, Shadrin AA, Skrobot O, Slifer S, Snijders GJL, Soininen H, Solfrizzi V, Solomon A, Song Y, Sorbi S, Sotolongo-Grau O, Spalletta G, Spottke A, Squassina A, Stordal E, Tartan JP, Tárraga L, Tesí N, Thalamuthu A, Thomas T, Tosto G, Traykov L, Tremolizzo L, Tybjærg-Hansen A, Uitterlinden A, Ullgren A, Ulstein I, Valero S, Valladares O, Broeckhoven CV, Vance J, Vardarajan BN, van der Lugt A, Dongen JV, van Rooij J, van Swieten J, Vandenberghe R, Verhey F, Vidal JS, Vogelgsang J, Vyhnalek M, Wagner M, Wallon D, Wang LS, Wang R, Weinhold L, Wiltfang J, Windle G, Woods B, Yannakoulia M, Zare H, Zhao Y, Zhang X, Zhu C, Zulaica M; EADB; GR@ACE; DEGESCO; EADI; GERAD; Demgene; FinnGen; ADGC; CHARGE; Farrer LA, Psaty BM, Ghanbari M, Raj T, Sachdev P, Mather K, Jessen F, Ikram MA, de Mendonça A, Hort J, Tsolaki M, Pericak-Vance MA, Amouyel P, Williams J, Frikke-Schmidt R, Clarimon J, Deleuze JF, Rossi G, Seshadri S, Andreassen OA, Ingelsson M, Hiltunen M, Sleegers K, Schellenberg GD, van Duijn CM, Sims R, van der Flier WM, Ruiz A, Ramirez A, Lambert JC (2022) New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet 54:412-436.

25. Lanoiselée HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, Richard AC, Pasquier F, Rollin-Sillaire A, Martinaud O, Quillard-Muraine M, de la Sayette V, Boutoleau-Bretonniere C, Etcharry-Bouyx F, Chauviré V, Sarazin M, le Ber I, Epelbaum S, Jonveaux T, Rouaud O, Ceccaldi M, Félician O, Godefroy O, Formaglio M, Croisile B, Auriacombe S, Chamard L, Vincent JL, Sauvée M, Marelli-Tosi C, Gabelle A, Ozsancak C, Pariente J, Paquet C, Hannequin D, Campion D; collaborators of the CNR-MAJ project (2017) APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: a genetic screening study of familial and sporadic cases. PLoS Med 14:e1002270.
26. Bernardi L, Geracitano S, Colao R, Puccio G, Gallo M, Anfossi M, Frangipane F, Curcio SA, Mirabelli M, Tomaino C, Vasso F, Smirne N, Maletta R, Bruni AC (2009) AbetaPP A713T mutation in late onset Alzheimer's disease with cerebrovascular lesions. J Alzheimers Dis 17:383-389.
27. Hatami A, Monjazeb S, Milton S, Glabe CG (2017) Familial Alzheimer's disease mutations within the amyloid precursor protein alter the aggregation and conformation of the amyloid-β peptide. J Biol Chem 292:3172-3185.
28. Murrell JR, Hake AM, Quaid KA, Farlow MR, Ghetti B (2000) Early-onset Alzheimer disease caused by a new mutation (V717L) in the amyloid precursor protein gene. Arch Neurol 57:885-887.
29. Revesz T, Holton JL, Lashley T, Plant G, Frangione B, Rostagno A, Ghiso J (2009) Genetics and molecular pathogenesis of sporadic and hereditary cerebral amyloid angiopathies. Acta Neuropathol 118:115-130.
30. Yamada M (2015) Cerebral amyloid angiopathy: emerging concepts. J Stroke 17:17-30.
31. Qi XM, Ma JF (2017) The role of amyloid beta clearance in cerebral amyloid angiopathy: more potential therapeutic targets. Transl Neurodegener 6:22.
32. Rostagno A, Holton JL, Lashley T, Revesz T, Ghiso J (2010) Cerebral amyloidosis: amyloid subunits, mutants and phenotypes. Cell Mol Life Sci 67:581-600.
33. Viswanathan A, Greenberg SM (2011) Cerebral amyloid angiopathy in the elderly. Ann Neurol 70:871-880.
34. Jellinger KA (2010) Prevalence and impact of cerebrovascular lesions in Alzheimer and lewy body diseases. Neurodegener Dis 7:112-115.
35. Attems J, Quass M, Jellinger KA, Lintner F (2007) Topographical distribution of cerebral amyloid angiopathy and its effect on cognitive decline are influenced by Alzheimer disease pathology. J Neurol Sci 257:49-55.
36. Yang J, Ji Y, Mehta P, Bates KA, Sun Y, Wisniewski T (2011) Blocking the apolipoprotein E/amyloid-β interaction reduces fibrillar vascular amyloid deposition and cerebral microhemorrhages in TgSwDI mice. J Alzheimers Dis 24:269-285.
37. Auriel E, Greenberg SM (2012) The pathophysiology and clinical presentation of cerebral amyloid angiopathy. Curr Atheroscler Rep 14:343-350.
38. Zhong L, Xu Y, Zhuo R, Wang T, Wang K, Huang R, Wang D, Gao Y, Zhu Y, Sheng X, Chen K, Wang N, Zhu L, Can D, Marten Y, Shinohara M, Liu CC, Du D, Sun H, Wen L, Xu H, Bu G, Chen XF (2019) Soluble TREM2 ameliorates pathological phenotypes by modulating microglial functions in an Alzheimer's disease model. Nat Commun 10:1365.
39. Tanaka M, Saito S, Inoue T, Satoh-Asahara N, Ihara M (2020) Potential therapeutic approaches for cerebral amyloid angiopathy and Alzheimer's disease. Int J Mol Sci 21:1992.
40. Yoon SS, Jo SA (2012) Mechanisms of amyloid-β peptide clearance: potential therapeutic targets for Alzheimer's disease. Biomol Ther (Seoul) 20:245-255.
41. Qian C, Yang C, Lu M, Bao J, Shen H, Deng B, Li S, Li W, Zhang M, Cao C (2021) Activating AhR alleviates cognitive deficits of Alzheimer's disease model mice by upregulating

endogenous Aβ catabolic enzyme Neprilysin. Theranostics 11:8797-8812.
42. Abramov-Harpaz K, Miller Y (2022) Insights into non-proteolytic inhibitory mechanisms of polymorphic early-stage amyloid β oligomers by insulin degrading enzyme. Biomolecules 12:1886.
43. Turner AJ, Nalivaeva NN (2007) New insights into the roles of metalloproteinases in neurodegeneration and neuroprotection. Int Rev Neurobiol 82:113-135.
44. Nalivaeva NN, Belyaev ND, Zhuravin IA, Turner AJ (2012) The Alzheimer's amyloid-degrading peptidase, neprilysin: can we control it? Int J Alzheimers Dis 2012:383796.
45. Miners JS, Palmer JC, Tayler H, Palmer LE, Ashby E, Kehoe PG, Love S (2014) Aβ degradation or cerebral perfusion? Divergent effects of multifunctional enzymes. Front Aging Neurosci 6:238.
46. Zuroff L, Daley D, Black KL, Koronyo-Hamaoui M (2017) Clearance of cerebral Aβ in Alzheimer's disease: reassessing the role of microglia and monocytes. Cell Mol Life Sci 74:2167-2201.
47. Hemming ML, Selkoe DJ (2005) Amyloid beta-protein is degraded by cellular angiotensin-converting enzyme (ACE) and elevated by an ACE inhibitor. J Biol Chem 280:37644-37650.
48. Mukherjee A, Song E, Kihiko-Ehmann M, Goodman JP Jr, Pyrek JS, Estus S, Hersh LB (2000) Insulysin hydrolyzes amyloid beta peptides to products that are neither neurotoxic nor deposit on amyloid plaques. J Neurosci 20:8745-8749.
49. Leissring MA (2008) The AbetaCs of Abeta-cleaving proteases. J Biol Chem 283:29645-29649.
50. Boche D, Nicoll JA (2008) The role of the immune system in clearance of Abeta from the brain. Brain Pathol 18:267-278.
51. Lim CS, Han JS (2018) The antioxidant xanthorrhizol prevents amyloid-β-induced oxidative modification and inactivation of neprilysin. Biosci Rep 38:BSR20171611.
52. Miners JS, Van Helmond Z, Chalmers K, Wilcock G, Love S, Kehoe PG (2006) Decreased expression and activity of neprilysin in Alzheimer disease are associated with cerebral amyloid angiopathy. J Neuropathol Exp Neurol 65:1012-1021.
53. Miners S, van Helmond Z, Barker R, Passmore PA, Johnston JA, Todd S, McGuinness BM, Panza F, Seripa D, Solfrizzi V, Love S, Prince JA, Kehoe PG (2012) Genetic variation in MME in relation to neprilysin protein and enzyme activity, Aβ levels, and Alzheimer's disease risk. Int J Mol Epidemiol Genet 3:30-38.
54. Miners JS, Kehoe P, Love S (2011) Neprilysin protects against cerebral amyloid angiopathy and Aβ-induced degeneration of cerebrovascular smooth muscle cells. Brain Pathol 21:594-605.
55. Bossak-Ahmad K, Mital M, Płonka D, Drew SC, Bal W (2019) Oligopeptides generated by neprilysin degradation of β-amyloid have the highest Cu(II) affinity in the whole Aβ family. Inorg Chem 58:932-943.
56. Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, Gerard C, Hama E, Lee HJ, Saido TC (2001) Metabolic regulation of brain Abeta by neprilysin. Science 292:1550-1552.
57. Madani R, Poirier R, Wolfer DP, Welzl H, Groscurth P, Lipp HP, Lu B, El Mouedden M, Mercken M, Nitsch RM, Mohajeri MH (2006) Lack of neprilysin suffices to generate murine amyloid-like deposits in the brain and behavioral deficit in vivo. J Neurosci Res 84:1871-1878.
58. Park MH, Lee JK, Choi S, Ahn J, Jin HK, Park JS, Bae JS (2013) Recombinant soluble neprilysin reduces amyloid-beta accumulation and improves memory impairment in Alzheimer's disease mice. Brain Res 1529:113-124.
59. El-Amouri SS, Zhu H, Yu J, Marr R, Verma IM, Kindy MS (2008) Neprilysin: an enzyme candidate to slow the progression of Alzheimer's disease. Am J Pathol 172:1342-1354.
60. Hemming ML, Patterson M, Reske-Nielsen C, Lin L, Isacson O, Selkoe DJ (2007) Reducing amyloid plaque burden via ex vivo gene delivery of an Abeta-degrading protease: a novel therapeutic approach to Alzheimer disease. PLoS Med 4:e262.
61. Blurton-Jones M, Spencer B, Michael S, Castello NA, Agazaryan AA, Davis JL, Müller FJ, Loring JF, Masliah E, LaFerla FM (2014) Neural stem cells genetically-modified to express neprilysin reduce pathology in Alzheimer transgenic models. Stem Cell Res Ther 5:46.
62. Chen PT, Chen CL, Lin LT, Lo CH, Hu CJ, Chen RP, Wang SS (2016) Design of peptide substrate for sensitively and specifically detecting two Aβ-degrading enzymes: neprilysin and angiotensin-converting enzyme. PLoS One 11:e0153360.
63. Turrel O, Goguel V, Preat T (2017) *Drosophila* neprilysin 1 rescues memory deficits caused by amyloid-β peptide. J Neurosci 37:10334-10345.
64. Klein C, Roussel G, Brun S, Rusu C, Patte-Mensah C, Maitre M, Mensah-Nyagan AG (2018) 5-HIAA induces neprilysin to ameliorate pathophysiology and symptoms in a mouse model for Alzheimer's disease. Acta Neuropathol Commun 6:136.
65. Wang N, Jia Y, Zhang B, Li Y, Murtaza G, Huang S, Liu X (2020) Kai-Xin-San, a Chinese herbal decoction, accelerates the degradation of β-amyloid by enhancing the expression of neprilysin in rats. Evid Based Complement Alternat Med 2020:3862342.
66. Leite JP, Lete MG, Fowler SB, Gimeno A, Rocha JF, Sousa SF, Webster CI, Jiménez-Bar Bero JJ, Gales L (2021) $A\beta_{31-35}$ de-

creases neprilysin-mediated Alzheimer's amyloid-β peptide degradation. ACS Chem Neurosci 12:3708-3718.
67. Becker M, Moore A, Naughton M, Boland B, Siems WE, Walther T (2018) Neprilysin degrades murine Amyloid-β (Aβ) more efficiently than human Aβ: further implication for species-specific amyloid accumulation. Neurosci Lett 686:74-79.
68. Kato D, Takahashi Y, Iwata H, Hatakawa Y, Lee SH, Oe T (2022) Comparative studies for amyloid beta degradation: "neprilysin vs insulysin", "monomeric vs aggregate", and "whole $A\beta_{40}$ vs its peptide fragments". Biochem Biophys Rep 30:101268.
69. Humpel C (2021) Intranasal delivery of collagen-loaded neprilysin clears beta-amyloid plaques in a transgenic Alzheimer mouse model. Front Aging Neurosci 13:649646.
70. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO (2008) Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol 18:253-266.
71. Hemming ML, Selkoe DJ, Farris W (2007) Effects of prolonged angiotensin-converting enzyme inhibitor treatment on amyloid beta-protein metabolism in mouse models of Alzheimer disease. Neurobiol Dis 26:273-281.
72. Ouk M, Wu CY, Rabin JS, Edwards JD, Ramirez J, Masellis M, Swartz RH, Herrmann N, Lanctôt KL, Black SE, Swardfager W (2021) Associations between brain amyloid accumulation and the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. Neurobiol Aging 100:22-31.
73. Hu J, Igarashi A, Kamata M, Nakagawa H (2001) Angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide (A beta); retards A beta aggregation, deposition, fibril formation; and inhibits cytotoxicity. J Biol Chem 276:47863-47868.
74. Oba R, Igarashi A, Kamata M, Nagata K, Takano S, Nakagawa H (2005) The N-terminal active centre of human angiotensin-converting enzyme degrades Alzheimer amyloid beta-peptide. Eur J Neurosci 21:733-740.
75. Eckman EA, Adams SK, Troendle FJ, Stodola BA, Kahn MA, Fauq AH, Xiao HD, Bernstein KE, Eckman CB (2006) Regulation of steady-state beta-amyloid levels in the brain by neprilysin and endothelin-converting enzyme but not angiotensin-converting enzyme. J Biol Chem 281:30471-30478.
76. Zou K, Yamaguchi H, Akatsu H, Sakamoto T, Ko M, Mizoguchi K, Gong JS, Yu W, Yamamoto T, Kosaka K, Yanagisawa K, Michikawa M (2007) Angiotensin-converting enzyme converts amyloid beta-protein 1-42 (Abeta(1-42)) to Abeta(1-40), and its inhibition enhances brain Abeta deposition. J Neurosci 27:8628-8635.
77. Ouk M, Wu CY, Rabin JS, Edwards JD, Ramirez J, Masellis M, Swartz RH, Herrmann N, Lanctôt KL, Black SE, Swardfager W; Alzheimer's Disease Neuroimaging Initiative (2021) Associations between brain amyloid accumulation and the use of angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers. Neurobiol Aging 100:22-31.
78. Kugaevskaya EV, Veselovsky AV, Indeykina MI, Solovyeva NI, Zharkova MS, Popov IA, Nikolaev EN, Mantsyzov AB, Makarov AA, Kozin SA (2018) N-domain of angiotensin-converting enzyme hydrolyzes human and rat amyloid-β(1-16) peptides as arginine specific endopeptidase potentially enhancing risk of Alzheimer's disease. Sci Rep 8:298.
79. Rocha NP, Toledo A, Corgosinho LTS, de Souza LC, Guimarães HC, Resende EPF, Braz NFT, Gomes KB, Simoes E Silva AC, Caramelli P, Teixeira AL (2018) Cerebrospinal fluid levels of angiotensin-converting enzyme are associated with amyloid-β42 burden in Alzheimer's disease. J Alzheimers Dis 64:1085-1090.
80. Miners JS, Baig S, Palmer J, Palmer LE, Kehoe PG, Love S (2008) SYMPOSIUM: clearance of Aβ from the brain in Alzheimer's disease: Aβ-degrading enzymes in Alzheimer's disease. Brain Pathol 18:240-252.
81. Elkins JS, Douglas VC, Johnston SC (2004) Alzheimer disease risk and genetic variation in ACE: a meta-analysis. Neurology 62:363-368.
82. Xu C, Garcia D, Lu Y, Ozuna K, Adjeroh DA, Wang K, On Behalf of the Alzheimer's Disease Neuroimaging Initiative (2021) Levels of angiotensin-converting enzyme and apolipoproteins are associated with Alzheimer's disease and cardiovascular diseases. Cells 11:29.
83. Miners JS, Ashby E, Van Helmond Z, Chalmers KA, Palmer LE, Love S, Kehoe PG (2008) Angiotensin-converting enzyme (ACE) levels and activity in Alzheimer's disease, and relationship of perivascular ACE-1 to cerebral amyloid angiopathy. Neuropathol Appl Neurobiol 34:181-193.
84. Palmer JC, Baig S, Kehoe PG, Love S (2009) Endothelin-converting enzyme-2 is increased in Alzheimer's disease and up-regulated by Abeta. Am J Pathol 175:262-270.
85. Carty NC, Nash K, Lee D, Mercer M, Gottschall PE, Meyers C, Muzyczka N, Gordon MN, Morgan D (2008) Adeno-associated viral (AAV) serotype 5 vector mediated gene delivery of endothelin-converting enzyme reduces Aβ deposits in APP + PS1 transgenic mice. Mol Ther 16:1580-1586.
86. Eckman EA, Watson M, Marlow L, Sambamurti K, Eckman CB (2003) Alzheimer's disease beta-amyloid peptide is increased in mice deficient in endothelin-converting enzyme. J

Biol Chem 278:2081-2084.
87. Wang R, Wang S, Malter JS, Wang DS (2009) Effects of 4-hydroxy-nonenal and Amyloid-beta on expression and activity of endothelin converting enzyme and insulin degrading enzyme in SH-SY5Y cells. J Alzheimers Dis 17:489-501.
88. Choi DS, Wang D, Yu GQ, Zhu G, Kharazia VN, Paredes JP, Chang WS, Deitchman JK, Mucke L, Messing RO (2006) PKCepsilon increases endothelin converting enzyme activity and reduces amyloid plaque pathology in transgenic mice. Proc Natl Acad Sci U S A 103:8215-8220.
89. Eckman EA, Reed DK, Eckman CB (2001) Degradation of the Alzheimer's amyloid beta peptide by endothelin-converting enzyme. J Biol Chem 276:24540-24548.
90. Tisljar U (1993) Thimet oligopeptidase--a review of a thiol dependent metallo-endopeptidase also known as Pz-peptidase endopeptidase 24.15 and endo-oligopeptidase. Biol Chem Hoppe Seyler 374:91-100.
91. Morelli L, Llovera R, Gonzalez SA, Affranchino JL, Prelli F, Frangione B, Ghiso J, Castano EM (2003) Differential degradation of amyloid beta genetic variants associated with hereditary dementia or stroke by insulin-degrading enzyme. J Biol Chem 278:23221-23226.
92. Qiu WQ, Walsh DM, Ye Z, Vekrellis K, Zhang J, Podlisny MB, Rosner MR, Safavi A, Hersh LB, Selkoe DJ (1998) Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation. J Biol Chem 273:32730-32738.
93. Miners JS, Barua N, Kehoe PG, Gill S, Love S (2011) Aβ-degrading enzymes: potential for treatment of Alzheimer disease. J Neuropathol Exp Neurol 70:944-959.
94. Pérez A, Morelli L, Cresto JC, Castaño EM (2000) Degradation of soluble amyloid beta-peptides 1-40, 1-42, and the Dutch variant 1-40Q by insulin degrading enzyme from Alzheimer disease and control brains. Neurochem Res 25:247-255.
95. Kuo WL, Montag AG, Rosner MR (1993) Insulin-degrading enzyme is differentially expressed and developmentally regulated in various rat tissues. Endocrinology 132:604-611.
96. Behl M, Zhang Y, Zheng W (2009) Involvement of insulin-degrading enzyme in the clearance of beta-amyloid at the blood-CSF barrier: consequences of lead exposure. Cerebrospinal Fluid Res 6:11.
97. Authier F, Cameron PH, Taupin V (1996) Association of insulin-degrading enzyme with a 70 kDa cytosolic protein in hepatoma cells. Biochem J 319(Pt 1):149-158.
98. Zhao Z, Xiang Z, Haroutunian V, Buxbaum JD, Stetka B, Pasinetti GM (2007) Insulin degrading enzyme activity selectively decreases in the hippocampal formation of cases at high risk to develop Alzheimer's disease. Neurobiol Aging 28:824-830.
99. Kurochkin IV, Goto S (1994) Alzheimer's beta-amyloid peptide specifically interacts with and is degraded by insulin degrading enzyme. FEBS Lett 345:33-37.
100. Bennett RG, Duckworth WC, Hamel FG (2000) Degradation of amylin by insulin-degrading enzyme. J Biol Chem 275:36621-36625.
101. Kurochkin IV (2001) Insulin-degrading enzyme: embarking on amyloid destruction. Trends Biochem Sci 26:421-425.
102. Miller BC, Eckman EA, Sambamurti K, Dobbs N, Chow KM, Eckman CB, Hersh LB, Thiele DL (2003) Amyloid-beta peptide levels in brain are inversely correlated with insulysin activity levels in vivo. Proc Natl Acad Sci U S A 100:6221-6226.
103. Cheng Y, Tian DY, Wang YJ (2020) Peripheral clearance of brain-derived Aβ in Alzheimer's disease: pathophysiology and therapeutic perspectives. Transl Neurodegener 9:16.
104. Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ, Guenette S (2003) Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. Proc Natl Acad Sci U S A 100:4162-4167.
105. Morelli L, Llovera RE, Mathov I, Lue LF, Frangione B, Ghiso J, Castaño EM (2004) Insulin-degrading enzyme in brain microvessels: proteolysis of amyloid {beta} vasculotropic variants and reduced activity in cerebral amyloid angiopathy. J Biol Chem 279:56004-56013.
106. Sahoo BR, Panda PK, Liang W, Tang WJ, Ahuja R, Ramamoorthy A (2021) Degradation of Alzheimer's amyloid-β by a catalytically inactive insulin-degrading enzyme. J Mol Biol 433:166993.
107. Gali CC, Fanaee-Danesh E, Zandl-Lang M, Albrecher NM, Tam-Amersdorfer C, Stracke A, Sachdev V, Reichmann F, Sun Y, Avdili A, Reiter M, Kratky D, Holzer P, Lass A, Kandimalla KK, Panzenboeck U (2019) Amyloid-beta impairs insulin signaling by accelerating autophagy-lysosomal degradation of LRP-1 and IR-β in blood-brain barrier endothelial cells in vitro and in 3XTg-AD mice. Mol Cell Neurosci 99:103390.
108. Rezaei M, Kalhor HR (2022) Amyloid fibril reduction through covalently modified lysine in HEWL and insulin. Arch Biochem Biophys 727:109350.
109. Fu H, Liu B, Li L, Lemere CA (2020) Microglia do not take up soluble amyloid-beta peptides, but partially degrade them by secreting insulin-degrading enzyme. Neuroscience 443:30-43.
110. Sideris DI, Danial JSH, Emin D, Ruggeri FS, Xia Z, Zhang YP, Lobanova E, Dakin H, De S, Miller A, Sang JC, Knowles TPJ,

Vendruscolo M, Fraser G, Crowther D, Klenerman D (2021) Soluble amyloid beta-containing aggregates are present throughout the brain at early stages of Alzheimer's disease. Brain Commun 3:fcab147.

111. Yamamoto N, Nakazawa M, Nunono N, Yoshida N, Obuchi A, Tanida M, Suzuki K, Ikeda-Matsuo Y, Sobue K (2021) Protein kinases A and C regulate amyloid-β degradation by modulating protein levels of neprilysin and insulin-degrading enzyme in astrocytes. Neurosci Res 166:62-72.
112. Birkedal-Hansen H, Moore WG, Bodden MK, Windsor LJ, Birkedal-Hansen B, DeCarlo A, Engler JA (1993) Matrix metalloproteinases: a review. Crit Rev Oral Biol Med 4:197-250.
113. Ahmad M, Takino T, Miyamori H, Yoshizaki T, Furukawa M, Sato H (2006) Cleavage of amyloid-beta precursor protein (APP) by membrane-type matrix metalloproteinases. J Biochem 139:517-526.
114. Seiki M (1999) Membrane-type matrix metalloproteinases. APMIS 107:137-143.
115. Yan P, Hu X, Song H, Yin K, Bateman RJ, Cirrito JR, Xiao Q, Hsu FF, Turk JW, Xu J, Hsu CY, Holtzman DM, Lee JM (2006) Matrix metalloproteinase-9 degrades amyloid-beta fibrils in vitro and compact plaques in situ. J Biol Chem 281:24566-24574.
116. Liao MC, Van Nostrand WE (2010) Degradation of soluble and fibrillar amyloid beta-protein by matrix metalloproteinase (MT1-MMP) in vitro. Biochemistry 49:1127-1136.
117. Saido T, Leissring MA (2012) Proteolytic degradation of amyloid β-protein. Cold Spring Harb Perspect Med 2:a006379.
118. Gough M, Parr-Sturgess C, Parkin E (2011) Zinc metalloproteinases and amyloid Beta-Peptide metabolism: the positive side of proteolysis in Alzheimer's disease. Biochem Res Int 2011:721463.
119. Yin KJ, Cirrito JR, Yan P, Hu X, Xiao Q, Pan X, Bateman R, Song H, Hsu FF, Turk J, Xu J, Hsu CY, Mills JC, Holtzman DM, Lee JM (2006) Matrix metalloproteinases expressed by astrocytes mediate extracellular amyloid-beta peptide catabolism. J Neurosci 26:10939-10948.
120. Van Wart HE, Birkedal-Hansen H (1990) The cysteine switch: a principle of regulation of metalloproteinase activity with potential applicability to the entire matrix metalloproteinase gene family. Proc Natl Acad Sci U S A 87:5578-5582.
121. Vetrivel KS, Zhang X, Meckler X, Cheng H, Lee S, Gong P, Lopes KO, Chen Y, Iwata N, Yin KJ, Lee JM, Parent AT, Saido TC, Li YM, Sisodia SS, Thinakaran G (2008) Evidence that CD147 modulation of beta-amyloid (Abeta) levels is mediated by extracellular degradation of secreted Abeta. J Biol Chem 283:19489-19498.
122. Deb S, Gottschall PE (1996) Increased production of matrix metalloproteinases in enriched astrocyte and mixed hippocampal cultures treated with beta-amyloid peptides. J Neurochem 66:1641-1647.
123. Hoogmartens J, Hens E, Engelborghs S, De Deyn PP, van der Zee J, Van Broeckhoven C, Cacace R; BELNEU consortium (2021) Investigation of the role of matrix metalloproteinases in the genetic etiology of Alzheimer's disease. Neurobiol Aging 104:105.e1-105.e6.
124. Xia M, Su Y, Fu J, Xu J, Wang Q, Gao F, Shen Y, Dong Q, Cheng X (2021) The use of serum matrix metalloproteinases in cerebral amyloid angiopathy-related intracerebral hemorrhage and cognitive impairment. J Alzheimers Dis 82:1159-1170.
125. Taniguchi M, Matsuura K, Nakamura R, Kojima A, Konishi M, Akizawa T (2017) MMP-7 cleaves amyloid β fragment peptides and copper ion inhibits the degradation. Biometals 30:797-807.
126. Porter KN, Sarkar SN, Dakhlallah DA, Vannoy ME, Quintana DD, Simpkins JW (2020) Medroxyprogesterone acetate impairs amyloid beta degradation in a matrix metalloproteinase-9 dependent manner. Front Aging Neurosci 12:92.
127. Owen CA (2006) Serine proteinases. In: Encyclopedia of respiratory medicine (Laurent GJ, Shapiro SD, eds), pp 1-10. Elsevier, Amsterdam.
128. Liao MC, Ahmed M, Smith SO, Van Nostrand WE (2009) Degradation of amyloid beta protein by purified myelin basic protein. J Biol Chem 284:28917-28925.
129. Staugaitis SM, Colman DR, Pedraza L (1996) Membrane adhesion and other functions for the myelin basic proteins. Bioessays 18:13-18.
130. Hoos MD, Ahmed M, Smith SO, Van Nostrand WE (2007) Inhibition of familial cerebral amyloid angiopathy mutant amyloid beta-protein fibril assembly by myelin basic protein. J Biol Chem 282:9952-9961.
131. Hoos MD, Ahmed M, Smith SO, Van Nostrand WE (2009) Myelin basic protein binds to and inhibits the fibrillar assembly of Abeta42 in vitro. Biochemistry 48:4720-4727.
132. Liao MC, Hoos MD, Aucoin D, Ahmed M, Davis J, Smith SO, Van Nostrand WE (2010) N-terminal domain of myelin basic protein inhibits amyloid beta-protein fibril assembly. J Biol Chem 285:35590-35598.
133. Kotarba AE, Aucoin D, Hoos MD, Smith SO, Van Nostrand WE (2013) Fine mapping of the amyloid β-protein binding site on myelin basic protein. Biochemistry 52:2565-2573.
134. D'Souza CA, Wood DD, She YM, Moscarello MA (2005) Autocatalytic cleavage of myelin basic protein: an alternative to molecular mimicry. Biochemistry 44:12905-12913.

135. Yang D, Zhu W, Wang Y, Tan F, Ma Z, Gao J, Lin X (2020) Selection of mutant μplasmin for amyloid-β cleavage in vivo. Sci Rep 10:12117.
136. Tucker HM, Kihiko-Ehmann M, Wright S, Rydel RE, Estus S (2000) Tissue plasminogen activator requires plasminogen to modulate amyloid-beta neurotoxicity and deposition. J Neurochem 75:2172-2177.
137. Exley C, Korchazhkina OV (2001) Plasmin cleaves Abeta42 in vitro and prevents its aggregation into beta-pleated sheet structures. Neuroreport 12:2967-2970.
138. Tucker HM, Kihiko-Ehmann M, Estus S (2002) Urokinase-type plasminogen activator inhibits amyloid-beta neurotoxicity and fibrillogenesis via plasminogen. J Neurosci Res 70:249-255.
139. Van Nostrand WE, Porter M (1999) Plasmin cleavage of the amyloid beta-protein: alteration of secondary structure and stimulation of tissue plasminogen activator activity. Biochemistry 38:11570-11576.
140. Tucker HM, Kihiko M, Caldwell JN, Wright S, Kawarabayashi T, Price D, Walker D, Scheff S, McGillis JP, Rydel RE, Estus S (2000) The plasmin system is induced by and degrades amyloid-beta aggregates. J Neurosci 20:3937-3946.
141. Ledesma MD, Da Silva JS, Crassaerts K, Delacourte A, De Strooper B, Dotti CG (2000) Brain plasmin enhances APP alpha-cleavage and Abeta degradation and is reduced in Alzheimer's disease brains. EMBO Rep 1:530-535.
142. Jacobsen JS, Comery TA, Martone RL, Elokdah H, Crandall DL, Oganesian A, Aschmies S, Kirksey Y, Gonzales C, Xu J, Zhou H, Atchison K, Wagner E, Zaleska MM, Das I, Arias RL, Bard J, Riddell D, Gardell SJ, Abou-Gharbia M, Robichaud A, Magolda R, Vlasuk GP, Bjornsson T, Reinhart PH, Pangalos MN (2008) Enhanced clearance of Abeta in brain by sustaining the plasmin proteolysis cascade. Proc Natl Acad Sci U S A 105:8754-8759.
143. Yamin R, Bagchi S, Hildebrant R, Scaloni A, Widom RL, Abraham CR (2007) Acyl peptide hydrolase, a serine proteinase isolated from conditioned medium of neuroblastoma cells, degrades the amyloid-beta peptide. J Neurochem 100:458-467.
144. Yamin R, Zhao C, O'Connor PB, McKee AC, Abraham CR (2009) Acyl peptide hydrolase degrades monomeric and oligomeric amyloid-beta peptide. Mol Neurodegener 4:33.
145. Perrier J, Durand A, Giardina T, Puigserver A (2005) Catabolism of intracellular N-terminal acetylated proteins: involvement of acylpeptide hydrolase and acylase. Biochimie 87:673-685.
146. Sun B, Zhou Y, Halabisky B, Lo I, Cho SH, Mueller-Steiner S, Devidze N, Wang X, Grubb A, Gan L (2008) Cystatin C-cathepsin B axis regulates amyloid beta levels and associated neuronal deficits in an animal model of Alzheimer's disease. Neuron 60:247-257.
147. Yang CN, Shiao YJ, Shie FS, Guo BS, Chen PH, Cho CY, Chen YJ, Huang FL, Tsay HJ (2011) Mechanism mediating oligomeric Aβ clearance by naïve primary microglia. Neurobiol Dis 42:221-230.
148. Tiribuzi R, Crispoltoni L, Chiurchiù V, Casella A, Montecchiani C, Del Pino AM, Maccarrone M, Palmerini CA, Caltagirone C, Kawarai T, Orlacchio A, Orlacchio A (2017) Transcrocetin improves amyloid-β degradation in monocytes from Alzheimer's Disease patients. J Neurol Sci 372:408-412.
149. Dhanavade MJ, Parulekar RS, Kamble SA, Sonawane KD (2016) Molecular modeling approach to explore the role of cathepsin B from Hordeum vulgare in the degradation of Aβ peptides. Mol Biosyst 12:162-168.
150. Sakamoto T, Saito H, Ishii K, Takahashi H, Tanabe S, Ogasawara Y (2006) Aluminum inhibits proteolytic degradation of amyloid beta peptide by cathepsin D: a potential link between aluminum accumulation and neuritic plaque deposition. FEBS Lett 580:6543-6549.
151. Tian L, Zhang K, Tian ZY, Wang T, Shang DS, Li B, Liu DX, Fang WG, Wang ZY, Chen YH (2014) Decreased expression of cathepsin D in monocytes is related to the defective degradation of amyloid-β in Alzheimer's disease. J Alzheimers Dis 42:511-520.
152. Madadi S, Schwarzenbach H, Saidijam M, Mahjub R, Soleimani M (2019) Potential microRNA-related targets in clearance pathways of amyloid-β: novel therapeutic approach for the treatment of Alzheimer's disease. Cell Biosci 9:91.
153. Suire CN, Leissring MA (2021) Cathepsin D: a candidate link between amyloid β-protein and tauopathy in Alzheimer disease. J Exp Neurol 2:10-15.
154. Oberstein TJ, Utz J, Spitzer P, Klafki HW, Wiltfang J, Lewczuk P, Kornhuber J, Maler JM (2021) The role of cathepsin B in the degradation of Aβ and in the production of Aβ peptides starting with Ala2 in cultured astrocytes. Front Mol Neurosci 13:615740.
155. Zuo X, Hu S, Tang Y, Zhan L, Sun W, Zheng J, Han Y, Xu E (2020) Attenuation of secondary damage and Aβ deposits in the ipsilateral thalamus of dMCAO rats through reduction of cathepsin B by bis(propyl)-cognitin, a multifunctional dimer. Neuropharmacology 162:107786.
156. Kim MJ, Chae SS, Koh YH, Lee SK, Jo SA (2010) Glutamate carboxypeptidase II: an amyloid peptide-degrading enzyme with physiological function in the brain. FASEB J 24:4491-

4502.
157. Alikhani N, Guo L, Yan S, Du H, Pinho CM, Chen JX, Glaser E, Yan SS (2011) Decreased proteolytic activity of the mitochondrial amyloid-β degrading enzyme, PreP peptidasome, in Alzheimer's disease brain mitochondria. J Alzheimers Dis 27:75-87.
158. Falkevall A, Alikhani N, Bhushan S, Pavlov PF, Busch K, Johnson KA, Eneqvist T, Tjernberg L, Ankarcrona M, Glaser E (2006) Degradation of the amyloid beta-protein by the novel mitochondrial peptidasome, PreP. J Biol Chem 281:29096-29104.
159. Alikhani N, Ankarcrona M, Glaser E (2009) Mitochondria and Alzheimer's disease: amyloid-beta peptide uptake and degradation by the presequence protease, hPreP. J Bioenerg Biomembr 41:447-451.
160. Sevalle J, Amoyel A, Robert P, Fournié-Zaluski MC, Roques B, Checler F (2009) Aminopeptidase A contributes to the N-terminal truncation of amyloid beta-peptide. J Neurochem 109:248-256.
161. Yoo C, Ahn K, Park JE, Kim MJ, Jo SA (2010) An aminopeptidase from Streptomyces sp. KK565 degrades beta amyloid monomers, oligomers and fibrils. FEBS Lett 584:4157-4162.
162. Checler F, Valverde A (2022) Aminopeptidase A and dipeptidyl peptidase 4: a pathogenic duo in Alzheimer's disease? Neural Regen Res 17:2215-2217.
163. Perez-Nievas BG, Serrano-Pozo A (2018) Deciphering the astrocyte reaction in Alzheimer's disease. Front Aging Neurosci 10:114.
164. Azevedo FA, Carvalho LR, Grinberg LT, Farfel JM, Ferretti RE, Leite RE, Jacob Filho W, Lent R, Herculano-Houzel S (2009) Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. J Comp Neurol 513:532-541.
165. Kanekiyo T, Cirrito JR, Liu CC, Shinohara M, Li J, Schuler DR, Shinohara M, Holtzman DM, Bu G (2013) Neuronal clearance of amyloid-β by endocytic receptor LRP1. J Neurosci 33:19276-19283.
166. Koistinaho M, Lin S, Wu X, Esterman M, Koger D, Hanson J, Higgs R, Liu F, Malkani S, Bales KR, Paul SM (2004) Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides. Nat Med 10:719-726.
167. Singh D (2022) Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease. J Neuroinflammation 19:206.
168. Cai Z, Hussain MD, Yan LJ (2014) Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's disease. Int J Neurosci 124:307-321.
169. Fu R, Shen Q, Xu P, Luo JJ, Tang Y (2014) Phagocytosis of microglia in the central nervous system diseases. Mol Neurobiol 49:1422-1434.
170. Lee CY, Landreth GE (2010) The role of microglia in amyloid clearance from the AD brain. J Neural Transm (Vienna) 117:949-960.
171. Xin SH, Tan L, Cao X, Yu JT, Tan L (2018) Clearance of amyloid beta and tau in Alzheimer's disease: from mechanisms to therapy. Neurotox Res 34:733-748.
172. Jiang T, Tan L, Zhu XC, Zhang QQ, Cao L, Tan MS, Gu LZ, Wang HF, Ding ZZ, Zhang YD, Yu JT (2014) Upregulation of TREM2 ameliorates neuropathology and rescues spatial cognitive impairment in a transgenic mouse model of Alzheimer's disease. Neuropsychopharmacology 39:2949-2962.
173. Zhao N, Qiao W, Li F, Ren Y, Zheng J, Martens YA, Wang X, Li L, Liu CC, Chen K, Zhu Y, Ikezu TC, Li Z, Meneses AD, Jin Y, Knight JA, Chen Y, Bastea L, Linares C, Sonustun B, Job L, Smith ML, Xie M, Liu YU, Umpierre AD, Haruwaka K, Quicksall ZS, Storz P, Asmann YW, Wu LJ, Bu G (2022) Elevating microglia TREM2 reduces amyloid seeding and suppresses disease-associated microglia. J Exp Med 219:e20212479.
174. Zhao QF, Yu JT, Tan MS, Tan L (2015) ABCA7 in Alzheimer's disease. Mol Neurobiol 51:1008-1016.
175. Ries M, Sastre M (2016) Mechanisms of Aβ clearance and degradation by glial cells. Front Aging Neurosci 8:160.
176. Mandrekar S, Jiang Q, Lee CY, Koenigsknecht-Talboo J, Holtzman DM, Landreth GE (2009) Microglia mediate the clearance of soluble Abeta through fluid phase macropinocytosis. J Neurosci 29:4252-4262.
177. Li HQ, Chen C, Dou Y, Wu HJ, Liu YJ, Lou HF, Zhang JM, Li XM, Wang H, Duan S (2013) P2Y4 receptor-mediated pinocytosis contributes to amyloid beta-induced self-uptake by microglia. Mol Cell Biol 33:4282-4293.
178. Estfanous S, Daily KP, Eltobgy M, Deems NP, Anne MNK, Krause K, Badr A, Hamilton K, Carafice C, Hegazi A, Abu Khweek A, Kelani H, Nimjee S, Awad H, Zhang X, Cormet-Boyaka E, Haffez H, Soror S, Mikhail A, Nuovo G, Barrientos RM, Gavrilin MA, Amer AO (2021) Elevated expression of MiR-17 in microglia of Alzheimer's disease patients abrogates autophagy-mediated amyloid-β degradation. Front Immunol 12:705581.
179. Brown MR, Radford SE, Hewitt EW (2020) Modulation of β-amyloid fibril formation in Alzheimer's disease by microglia and infection. Front Mol Neurosci 13:609073.
180. Wyss-Coray T, Loike JD, Brionne TC, Lu E, Anankov R, Yan F, Silverstein SC, Husemann J (2003) Adult mouse astrocytes degrade amyloid-beta in vitro and in situ. Nat Med 9:453-457.

181. Nagele RG, D'Andrea MR, Lee H, Venkataraman V, Wang HY (2003) Astrocytes accumulate A beta 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. Brain Res 971:197-209.
182. Söllvander S, Nikitidou E, Brolin R, Söderberg L, Sehlin D, Lannfelt L, Erlandsson A (2016) Accumulation of amyloid-β by astrocytes result in enlarged endosomes and microvesicle-induced apoptosis of neurons. Mol Neurodegener 11:38.
183. Nielsen HM, Mulder SD, Beliën JA, Musters RJ, Eikelenboom P, Veerhuis R (2010) Astrocytic A beta 1-42 uptake is determined by A beta-aggregation state and the presence of amyloid-associated proteins. Glia 58:1235-1246.
184. Pihlaja R, Koistinaho J, Kauppinen R, Sandholm J, Tanila H, Koistinaho M (2011) Multiple cellular and molecular mechanisms are involved in human Aβ clearance by transplanted adult astrocytes. Glia 59:1643-1657.
185. Vafadari B, Salamian A, Kaczmarek L (2016) MMP-9 in translation: from molecule to brain physiology, pathology, and therapy. J Neurochem 139 Suppl 2:91-114.
186. Kidana K, Tatebe T, Ito K, Hara N, Kakita A, Saito T, Takatori S, Ouchi Y, Ikeuchi T, Makino M, Saido TC, Akishita M, Iwatsubo T, Hori Y, Tomita T (2018) Loss of kallikrein-related peptidase 7 exacerbates amyloid pathology in Alzheimer's disease model mice. EMBO Mol Med 10:e8184.
187. Shropshire TD, Reifert J, Rajagopalan S, Baker D, Feinstein SC, Daugherty PS (2014) Amyloid β peptide cleavage by kallikrein 7 attenuates fibril growth and rescues neurons from Aβ-mediated toxicity in vitro. Biol Chem 395:109-118.
188. Kim J, Basak JM, Holtzman DM (2009) The role of apolipoprotein E in Alzheimer's disease. Neuron 63:287-303.
189. Cam JA, Bu G (2006) Modulation of beta-amyloid precursor protein trafficking and processing by the low density lipoprotein receptor family. Mol Neurodegener 1:8.
190. Liu CC, Hu J, Zhao N, Wang J, Wang N, Cirrito JR, Kanekiyo T, Holtzman DM, Bu G (2017) Astrocytic LRP1 mediates brain Aβ clearance and impacts amyloid deposition. J Neurosci 37:4023-4031.
191. Mahan TE, Wang C, Bao X, Choudhury A, Ulrich JD, Holtzman DM (2022) Selective reduction of astrocyte apoE3 and apoE4 strongly reduces Aβ accumulation and plaque-related pathology in a mouse model of amyloidosis. Mol Neurodegener 17:13.
192. Rawat V, Wang S, Sima J, Bar R, Liraz O, Gundimeda U, Parekh T, Chan J, Johansson JO, Tang C, Chui HC, Harrington MG, Michaelson DM, Yassine HN (2019) ApoE4 alters ABCA1 membrane trafficking in astrocytes. J Neurosci 39:9611-9622.
193. Yassine HN, Finch CE (2020) *APOE* alleles and diet in brain aging and Alzheimer's disease. Front Aging Neurosci 12:150.
194. Husain MA, Laurent B, Plourde M (2021) APOE and Alzheimer's disease: from lipid transport to physiopathology and therapeutics. Front Neurosci 15:630502.
195. Lee JH, Yang DS, Goulbourne CN, Im E, Stavrides P, Pensalfini A, Chan H, Bouchet-Marquis C, Bleiwas C, Berg MJ, Huo C, Peddy J, Pawlik M, Levy E, Rao M, Staufenbiel M, Nixon RA (2022) Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. Nat Neurosci 25:688-701.
196. Nixon RA (2007) Autophagy, amyloidogenesis and Alzheimer disease. J Cell Sci 120(Pt 23):4081-4091.
197. Cho MH, Cho K, Kang HJ, Jeon EY, Kim HS, Kwon HJ, Kim HM, Kim DH, Yoon SY (2014) Autophagy in microglia degrades extracellular β-amyloid fibrils and regulates the NLRP3 inflammasome. Autophagy 10:1761-1775.
198. Pomilio C, Pavia P, Gorojod RM, Vinuesa A, Alaimo A, Galvan V, Kotler ML, Beauquis J, Saravia F (2016) Glial alterations from early to late stages in a model of Alzheimer's disease: evidence of autophagy involvement in Aβ internalization. Hippocampus 26:194-210.
199. Allaman I, Gavillet M, Bélanger M, Laroche T, Viertl D, Lashuel HA, Magistretti PJ (2010) Amyloid-beta aggregates cause alterations of astrocytic metabolic phenotype: impact on neuronal viability. J Neurosci 30:3326-3338.
200. Jo S, Yarishkin O, Hwang YJ, Chun YE, Park M, Woo DH, Bae JY, Kim T, Lee J, Chun H, Park HJ, Lee DY, Hong J, Kim HY, Oh SJ, Park SJ, Lee H, Yoon BE, Kim Y, Jeong Y, Shim I, Bae YC, Cho J, Kowall NW, Ryu H, Hwang E, Kim D, Lee CJ (2014) GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease. Nat Med 20:886-896.
201. Chun H, Im H, Kang YJ, Kim Y, Shin JH, Won W, Lim J, Ju Y, Park YM, Kim S, Lee SE, Lee J, Woo J, Hwang Y, Cho H, Jo S, Park JH, Kim D, Kim DY, Seo JS, Gwag BJ, Kim YS, Park KD, Kaang BK, Cho H, Ryu H, Lee CJ (2020) Severe reactive astrocytes precipitate pathological hallmarks of Alzheimer's disease via H2O2- production. Nat Neurosci 23:1555-1566.
202. Park JH, Ju YH, Choi JW, Song HJ, Jang BK, Woo J, Chun H, Kim HJ, Shin SJ, Yarishkin O, Jo S, Park M, Yeon SK, Kim S, Kim J, Nam MH, Londhe AM, Kim J, Cho SJ, Cho S, Lee C, Hwang SY, Kim SW, Oh SJ, Cho J, Pae AN, Lee CJ, Park KD (2019) Newly developed reversible MAO-B inhibitor circumvents the shortcomings of irreversible inhibitors in Alzheimer's disease. Sci Adv 5:eaav0316.
203. Ju YH, Bhalla M, Hyeon SJ, Oh JE, Yoo S, Chae U, Kwon J, Koh W, Lim J, Park YM, Lee J, Cho IJ, Lee H, Ryu H, Lee CJ (2022) Astrocytic urea cycle detoxifies Aβ-derived ammonia

while impairing memory in Alzheimer's disease. Cell Metab 34:1104-1120.e8.
204. Ghiso J, Shayo M, Calero M, Ng D, Tomidokoro Y, Gandy S, Rostagno A, Frangione B (2004) Systemic catabolism of Alzheimer's Aβ40 and Aβ42. J Biol Chem 279:45897-45908.
205. Elali A, Rivest S (2013) The role of ABCB1 and ABCA1 in beta-amyloid clearance at the neurovascular unit in Alzheimer's disease. Front Physiol 4:45.
206. Fitz NF, Cronican AA, Saleem M, Fauq AH, Chapman R, Lefterov I, Koldamova R (2012) Abca1 deficiency affects Alzheimer's disease-like phenotype in human ApoE4 but not in ApoE3-targeted replacement mice. J Neurosci 32:13125-13136.
207. Herz J, Bock HH (2002) Lipoprotein receptors in the nervous system. Annu Rev Biochem 71:405-434.
208. Jaeger S, Pietrzik CU (2008) Functional role of lipoprotein receptors in Alzheimer's disease. Curr Alzheimer Res 5:15-25.
209. Pascale CL, Miller MC, Chiu C, Boylan M, Caralopoulos IN, Gonzalez L, Johanson CE, Silverberg GD (2011) Amyloid-beta transporter expression at the blood-CSF barrier is age-dependent. Fluids Barriers CNS 8:21.
210. Zlokovic BV, Frangione B (2013) Transport-clearance hypothesis for Alzheimer's disease and potential therapeutic implications. In: Madame Curie bioscience database. Landes Bioscience, Austin, TX.
211. Candela P, Gosselet F, Saint-Pol J, Sevin E, Boucau MC, Boulanger E, Cecchelli R, Fenart L (2010) Apical-to-basolateral transport of amyloid-β peptides through blood-brain barrier cells is mediated by the receptor for advanced glycation end-products and is restricted by P-glycoprotein. J Alzheimers Dis 22:849-859.
212. Fang F, Yu Q, Arancio O, Chen D, Gore SS, Yan SS, Yan SF (2018) RAGE mediates Aβ accumulation in a mouse model of Alzheimer's disease via modulation of β- and γ-secretase activity. Hum Mol Genet 27:1002-1014.
213. Malherbe P, Richards JG, Gaillard H, Thompson A, Diener C, Schuler A, Huber G (1999) cDNA cloning of a novel secreted isoform of the human receptor for advanced glycation end products and characterization of cells co-expressing cell-surface scavenger receptors and Swedish mutant amyloid precursor protein. Brain Res Mol Brain Res 71:159-170.
214. Mackic JB, Stins M, McComb JG, Calero M, Ghiso J, Kim KS, Yan SD, Stern D, Schmidt AM, Frangione B, Zlokovic BV (1998) Human blood-brain barrier receptors for Alzheimer's amyloid-beta 1- 40. Asymmetrical binding, endocytosis, and transcytosis at the apical side of brain microvascular endothelial cell monolayer. J Clin Invest 102:734-743.
215. Deane R, Du Yan S, Submamaryan RK, LaRue B, Jovanovic S, Hogg E, Welch D, Manness L, Lin C, Yu J, Zhu H, Ghiso J, Frangione B, Stern A, Schmidt AM, Armstrong DL, Arnold B, Liliensiek B, Nawroth P, Hofman F, Kindy M, Stern D, Zlokovic B (2003) RAGE mediates amyloid-beta peptide transport across the blood-brain barrier and accumulation in brain. Nat Med 9:907-913.
216. Zhou R, Chen LL, Yang H, Li L, Liu J, Chen L, Hong WJ, Wang CG, Ma JJ, Huang J, Zhou XF, Liu D, Zhou HD (2021) Effect of high cholesterol regulation of LRP1 and RAGE on Aβ transport across the blood-brain barrier in Alzheimer's disease. Curr Alzheimer Res 18:428-442.
217. Tolstova AP, Adzhubei AA, Mitkevich VA, Petrushanko IY, Makarov AA (2022) Docking and molecular dynamics-based identification of interaction between various beta-amyloid isoforms and RAGE receptor. Int J Mol Sci 23:11816.
218. Ma LY, Fei YL, Wang XY, Wu SD, Du JH, Zhu M, Jin L, Li M, Li HL, Zhai JJ, Ji LP, Ma RR, Liu SF, Li M, Ma L, Ma XR, Qu QM, Lv YL (2017) The research on the relationship of RAGE, LRP-1, and Aβ accumulation in the hippocampus, prefrontal lobe, and amygdala of STZ-induced diabetic rats. J Mol Neurosci 62:1-10.
219. Gao L, Wang J, Jiang Y, Wei S, Shang S, Chen C, Dang L, Huo K, Deng M, Wang J, Qu Q (2020) Relationship between peripheral transport proteins and plasma amyloid-β in patients with Alzheimer's disease were different from cognitively normal controls: a propensity score matching analysis. J Alzheimers Dis 78:699-709.
220. Zlokovic BV, Deane R, Sagare AP, Bell RD, Winkler EA (2010) Low-density lipoprotein receptor-related protein-1: a serial clearance homeostatic mechanism controlling Alzheimer's amyloid β-peptide elimination from the brain. J Neurochem 115:1077-1089.
221. Abbott NJ (2004) Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology. Neurochem Int 45:545-552.
222. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M (2012) A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 4:147ra111.
223. Preston SD, Steart PV, Wilkinson A, Nicoll JA, Weller RO (2003) Capillary and arterial cerebral amyloid angiopathy in Alzheimer's disease: defining the perivascular route for the elimination of amyloid beta from the human brain. Neuropathol Appl Neurobiol 29:106-117.

224. Weller RO, Massey A, Newman TA, Hutchings M, Kuo YM, Roher AE (1998) Cerebral amyloid angiopathy: amyloid beta accumulates in putative interstitial fluid drainage pathways in Alzheimer's disease. Am J Pathol 153:725-733.
225. Hawkes CA, Härtig W, Kacza J, Schliebs R, Weller RO, Nicoll JA, Carare RO (2011) Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Acta Neuropathol 121:431-443.
226. Bell RD, Sagare AP, Friedman AE, Bedi GS, Holtzman DM, Deane R, Zlokovic BV (2007) Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse central nervous system. J Cereb Blood Flow Metab 27:909-918.
227. Bacyinski A, Xu M, Wang W, Hu J (2017) The paravascular pathway for brain waste clearance: current understanding, significance and controversy. Front Neuroanat 11:101.
228. Plog BA, Nedergaard M (2018) The glymphatic system in central nervous system health and disease: past, present, and future. Annu Rev Pathol 13:379-394.
229. Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew JA, Plog BA, Ding F, Deane R, Nedergaard M (2014) Impairment of paravascular clearance pathways in the aging brain. Ann Neurol 76:845-861.
230. Silverberg GD, Mayo M, Saul T, Rubenstein E, McGuire D (2003) Alzheimer's disease, normal-pressure hydrocephalus, and senescent changes in CSF circulatory physiology: a hypothesis. Lancet Neurol 2:506-511.
231. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J (2015) Structural and functional features of central nervous system lymphatic vessels. Nature 523:337-341.
232. Xiang Y, Bu XL, Liu YH, Zhu C, Shen LL, Jiao SS, Zhu XY, Giunta B, Tan J, Song WH, Zhou HD, Zhou XF, Wang YJ (2015) Physiological amyloid-beta clearance in the periphery and its therapeutic potential for Alzheimer's disease. Acta Neuropathol 130:487-499.
233. DeMattos RB, Bales KR, Cummins DJ, Paul SM, Holtzman DM (2002) Brain to plasma amyloid-beta efflux: a measure of brain amyloid burden in a mouse model of Alzheimer's disease. Science 295:2264-2267.
234. Zhao Z, Sagare AP, Ma Q, Halliday MR, Kong P, Kisler K, Winkler EA, Ramanathan A, Kanekiyo T, Bu G, Owens NC, Rege SV, Si G, Ahuja A, Zhu D, Miller CA, Schneider JA, Maeda M, Maeda T, Sugawara T, Ichida JK, Zlokovic BV (2015) Central role for PICALM in amyloid-β blood-brain barrier transcytosis and clearance. Nat Neurosci 18:978-987.
235. Wang J, Gu BJ, Masters CL, Wang YJ (2017) A systemic view of Alzheimer disease - insights from amyloid-β metabolism beyond the brain. Nat Rev Neurol 13:612-623.
236. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K (2015) A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med 212:991-999.
237. Eisele YS, Obermüller U, Heilbronner G, Baumann F, Kaeser SA, Wolburg H, Walker LC, Staufenbiel M, Heikenwalder M, Jucker M (2010) Peripherally applied Abeta-containing inoculates induce cerebral beta-amyloidosis. Science 330:980-982.
238. Eisele YS, Fritschi SK, Hamaguchi T, Obermüller U, Füger P, Skodras A, Schäfer C, Odenthal J, Heikenwalder M, Staufenbiel M, Jucker M (2014) Multiple factors contribute to the peripheral induction of cerebral β-amyloidosis. J Neurosci 34:10264-10273.
239. Donahue JE, Flaherty SL, Johanson CE, Duncan JA 3rd, Silverberg GD, Miller MC, Tavares R, Yang W, Wu Q, Sabo E, Hovanesian V, Stopa EG (2006) RAGE, LRP-1, and amyloid-beta protein in Alzheimer's disease. Acta Neuropathol 112:405-415.
240. Wu T, Chen L, Zhou L, Xu J, Guo K (2021) Platelets transport β-amyloid from the peripheral blood into the brain by destroying the blood-brain barrier to accelerate the process of Alzheimer's disease in mouse models. Aging (Albany NY) 13:7644-7659.
241. Bu XL, Xiang Y, Jin WS, Wang J, Shen LL, Huang ZL, Zhang K, Liu YH, Zeng F, Liu JH, Sun HL, Zhuang ZQ, Chen SH, Yao XQ, Giunta B, Shan YC, Tan J, Chen XW, Dong ZF, Zhou HD, Zhou XF, Song W, Wang YJ (2018) Blood-derived amyloid-β protein induces Alzheimer's disease pathologies. Mol Psychiatry 23:1948-1956.
242. Burwinkel M, Lutzenberger M, Heppner FL, Schulz-Schaeffer W, Baier M (2018) Intravenous injection of beta-amyloid seeds promotes cerebral amyloid angiopathy (CAA). Acta Neuropathol Commun 6:23.
243. Morales R, Bravo-Alegria J, Moreno-Gonzalez I, Duran-Aniotz C, Gamez N, Edwards Iii G, Soto C (2021) Transmission of cerebral amyloid pathology by peripheral administration of misfolded Aβ aggregates. Mol Psychiatry 26:5690-5701.
244. Qosa H, Abuasal BS, Romero IA, Weksler B, Couraud PO, Keller JN, Kaddoumi A (2014) Differences in amyloid-β clearance across mouse and human blood-brain barrier models: kinetic analysis and mechanistic modeling. Neuropharmacology 79:668-678.
245. Yuede CM, Lee H, Restivo JL, Davis TA, Hettinger JC, Wallace CE, Young KL, Hayne MR, Bu G, Li CZ, Cirrito JR (2016)

Rapid in vivo measurement of β-amyloid reveals biphasic clearance kinetics in an Alzheimer's mouse model. J Exp Med 213:677-685.
246. Hong CS, Goins WF, Goss JR, Burton EA, Glorioso JC (2006) Herpes simplex virus RNAi and neprilysin gene transfer vectors reduce accumulation of Alzheimer's disease-related amyloid-beta peptide in vivo. Gene Ther 13:1068-1079.
247. Iwata N, Mizukami H, Shirotani K, Takaki Y, Muramatsu S, Lu B, Gerard NP, Gerard C, Ozawa K, Saido TC (2004) Presynaptic localization of neprilysin contributes to efficient clearance of amyloid-beta peptide in mouse brain. J Neurosci 24:991-998.
248. Liu Y, Guan H, Beckett TL, Juliano MA, Juliano L, Song ES, Chow KM, Murphy MP, Hersh LB (2007) In vitro and in vivo degradation of Abeta peptide by peptidases coupled to erythrocytes. Peptides 28:2348-2355.
249. Nalivaeva NN, Belyaev ND, Kerridge C, Turner AJ (2014) Amyloid-clearing proteins and their epigenetic regulation as a therapeutic target in Alzheimer's disease. Front Aging Neurosci 6:235.
250. Verdile G, Fuller SJ, Martins RN (2015) The role of type 2 diabetes in neurodegeneration. Neurobiol Dis 84:22-38.
251. Liu Z, Zhu H, Fang GG, Walsh K, Mwamburi M, Wolozin B, Abdul-Hay SO, Ikezu T, Leissring MA, Qiu WQ (2012) Characterization of insulin degrading enzyme and other amyloid-β degrading proteases in human serum: a role in Alzheimer's disease? J Alzheimers Dis 29:329-340.
252. Liu Y, Studzinski C, Beckett T, Guan H, Hersh MA, Murphy MP, Klein R, Hersh LB (2009) Expression of neprilysin in skeletal muscle reduces amyloid burden in a transgenic mouse model of Alzheimer disease. Mol Ther 17:1381-1386.
253. Guan H, Liu Y, Daily A, Police S, Kim MH, Oddo S, LaFerla FM, Pauly JR, Murphy MP, Hersh LB (2009) Peripherally expressed neprilysin reduces brain amyloid burden: a novel approach for treating Alzheimer's disease. J Neurosci Res 87:1462-1473.
254. Sehgal N, Gupta A, Valli RK, Joshi SD, Mills JT, Hamel E, Khanna P, Jain SC, Thakur SS, Ravindranath V (2012) Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. Proc Natl Acad Sci U S A 109:3510-3515.
255. Roberts KF, Elbert DL, Kasten TP, Patterson BW, Sigurdson WC, Connors RE, Ovod V, Munsell LY, Mawuenyega KG, Miller-Thomas MM, Moran CJ, Cross DT 3rd, Derdeyn CP, Bateman RJ (2014) Amyloid-β efflux from the central nervous system into the plasma. Ann Neurol 76:837-844.
256. Maness LM, Banks WA, Podlisny MB, Selkoe DJ, Kastin AJ (1994) Passage of human amyloid beta-protein 1-40 across the murine blood-brain barrier. Life Sci 55:1643-1650.
257. Chen SH, Tian DY, Shen YY, Cheng Y, Fan DY, Sun HL, He CY, Sun PY, Bu XL, Zeng F, Liu J, Deng J, Xu ZQ, Chen Y, Wang YJ (2020) Amyloid-beta uptake by blood monocytes is reduced with ageing and Alzheimer's disease. Transl Psychiatry 10:423.
258. Kuo YM, Kokjohn TA, Kalback W, Luehrs D, Galasko DR, Chevallier N, Koo EH, Emmerling MR, Roher AE (2000) Amyloid-beta peptides interact with plasma proteins and erythrocytes: implications for their quantitation in plasma. Biochem Biophys Res Commun 268:750-756.
259. Guo C, Zhou HX (2019) Fatty acids compete with Aβ in binding to serum albumin by quenching its conformational flexibility. Biophys J 116:248-257.
260. Biere AL, Ostaszewski B, Stimson ER, Hyman BT, Maggio JE, Selkoe DJ (1996) Amyloid beta-peptide is transported on lipoproteins and albumin in human plasma. J Biol Chem 271:32916-32922.
261. Rózga M, Kłoniecki M, Jabłonowska A, Dadlez M, Bal W (2007) The binding constant for amyloid Abeta40 peptide interaction with human serum albumin. Biochem Biophys Res Commun 364:714-718.
262. Milojevic J, Raditsis A, Melacini G (2009) Human serum albumin inhibits Abeta fibrillization through a "monomer-competitor" mechanism. Biophys J 97:2585-2594.
263. Bohrmann B, Tjernberg L, Kuner P, Poli S, Levet-Trafit B, Näslund J, Richards G, Huber W, Döbeli H, Nordstedt C (1999) Endogenous proteins controlling amyloid beta-peptide polymerization. Possible implications for beta-amyloid formation in the central nervous system and in peripheral tissues. J Biol Chem 274:15990-15995.
264. Ezra A, Rabinovich-Nikitin I, Rabinovich-Toidman P, Solomon B (2016) Multifunctional effect of human serum albumin reduces Alzheimer's disease related pathologies in the 3xTg mouse model. J Alzheimers Dis 50:175-188.
265. Ishima Y, Mimono A, Tuan Giam Chuang V, Fukuda T, Kusumoto K, Okuhira K, Suwa Y, Watanabe H, Ishida T, Morioka H, Maruyama T, Otagiri M (2020) Albumin domain mutants with enhanced Aβ binding capacity identified by phage display analysis for application in various peripheral Aβ elimination approaches of Alzheimer's disease treatment. IUBMB Life 72:641-651.
266. Georgievska B, Gustavsson S, Lundkvist J, Neelissen J, Eketjäll S, Ramberg V, Bueters T, Agerman K, Juréus A, Svensson S, Berg S, Fälting J, Lendahl U (2015) Revisiting the peripheral sink hypothesis: inhibiting BACE1 activity in the periphery does not alter β-amyloid levels in the CNS. J Neurochem

132:477-486.
267. Rogers J, Li R, Mastroeni D, Grover A, Leonard B, Ahern G, Cao P, Kolody H, Vedders L, Kolb WP, Sabbagh M (2006) Peripheral clearance of amyloid beta peptide by complement C3-dependent adherence to erythrocytes. Neurobiol Aging 27:1733-1739.
268. Tarbali S, Zahmatkesh M, Torkaman-Boutorabi A, Khodagholi F (2022) Assessment of lipophilic fluorescence products in β-amyloid-induced cognitive decline: a parallel track in hippocampus, CSF, plasma and erythrocytes. Exp Gerontol 157:111645.
269. Zambrano P, Suwalsky M, Jemiola-Rzeminska M, Gallardo-Nelson MJ, Strzalka K, Muñoz-Torrero D (2021) Protective role of a donepezil-huprine hybrid against the β-amyloid (1-42) effect on human erythrocytes. Int J Mol Sci 22:9563.
270. Taylor RP, Lindorfer MA, Atkinson JP (2020) Clearance of amyloid-beta with bispecific antibody constructs bound to erythrocytes. Alzheimers Dement (N Y) 6:e12067.
271. Bawa KK, Krance SH, Herrmann N, Cogo-Moreira H, Ouk M, Yu D, Wu CY, Black SE, Lanctôt KL, Swardfager W; Alzheimer's Disease Neuroimaging Initiative (2020) A peripheral neutrophil-related inflammatory factor predicts a decline in executive function in mild Alzheimer's disease. J Neuroinflammation 17:84.
272. Bradshaw EM, Chibnik LB, Keenan BT, Ottoboni L, Raj T, Tang A, Rosenkrantz LL, Imboywa S, Lee M, Von Korff A; Alzheimer Disease Neuroimaging Initiative; Morris MC, Evans DA, Johnson K, Sperling RA, Schneider JA, Bennett DA, De Jager PL (2013) CD33 Alzheimer's disease locus: altered monocyte function and amyloid biology. Nat Neurosci 16:848-850.
273. Baruch K, Rosenzweig N, Kertser A, Deczkowska A, Sharif AM, Spinrad A, Tsitsou-Kampeli A, Sarel A, Cahalon L, Schwartz M (2015) Breaking immune tolerance by targeting Foxp3(+) regulatory T cells mitigates Alzheimer's disease pathology. Nat Commun 6:7967.
274. Zenaro E, Pietronigro E, Della Bianca V, Piacentino G, Marongiu L, Budui S, Turano E, Rossi B, Angiari S, Dusi S, Montresor A, Carlucci T, Nanì S, Tosadori G, Calciano L, Catalucci D, Berton G, Bonetti B, Constantin G (2015) Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. Nat Med 21:880-886.
275. Marsh SE, Abud EM, Lakatos A, Karimzadeh A, Yeung ST, Davtyan H, Fote GM, Lau L, Weinger JG, Lane TE, Inlay MA, Poon WW, Blurton-Jones M (2016) The adaptive immune system restrains Alzheimer's disease pathogenesis by modulating microglial function. Proc Natl Acad Sci U S A 113:E1316-E1325.
276. Simard AR, Rivest S (2004) Bone marrow stem cells have the ability to populate the entire central nervous system into fully differentiated parenchymal microglia. FASEB J 18:998-1000.
277. Simard AR, Soulet D, Gowing G, Julien JP, Rivest S (2006) Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron 49:489-502.
278. Kuroda E, Takata K, Nishimura K, Oka H, Sueyoshi M, Aitani M, Kouda A, Satake S, Shima C, Toda Y, Nakata S, Kitamura Y, Ashihara E (2020) Peripheral blood-derived microglia-like cells decrease amyloid-β burden and ameliorate cognitive impairment in a mouse model of Alzheimer's disease. J Alzheimers Dis 73:413-429.
279. Lebson L, Nash K, Kamath S, Herber D, Carty N, Lee DC, Li Q, Szekeres K, Jinwal U, Koren J, Dickey CA, Gottschall PE, Morgan D, Gordon MN (2010) Trafficking CD11b-positive blood cells deliver therapeutic genes to the brain of amyloid-depositing transgenic mice. J Neurosci 30:9651-9658.
280. Koronyo Y, Salumbides BC, Sheyn J, Pelissier L, Li S, Ljubimov V, Moyseyev M, Daley D, Fuchs DT, Pham M, Black KL, Rentsendorj A, Koronyo-Hamaoui M (2015) Therapeutic effects of glatiramer acetate and grafted CD115^{+} monocytes in a mouse model of Alzheimer's disease. Brain 138(Pt 8):2399-2422.
281. Kuroda E, Nishimura K, Kawanishi S, Sueyoshi M, Ueno F, Toji Y, Abo N, Konishi T, Harada K, Satake S, Shima C, Toda Y, Kitamura Y, Shimohama S, Ashihara E, Takata K (2020) Mouse bone marrow-derived microglia-like cells secrete transforming growth factor-β1 and promote microglial Aβ phagocytosis and reduction of brain Aβ. Neuroscience 438:217-228.
282. Tian DY, Cheng Y, Zhuang ZQ, He CY, Pan QG, Tang MZ, Hu XL, Shen YY, Wang YR, Chen SH, Sun HL, Sun PY, Yu ZY, Fan DY, Bu XL, Tan CR, Zeng GH, Wang J, Zhao HW, Wang YJ (2021) Physiological clearance of amyloid-beta by the kidney and its therapeutic potential for Alzheimer's disease. Mol Psychiatry 26:6074-6082.
283. Yu ZY, Chen DW, Tan CR, Zeng GH, He CY, Wang J, Bu XL, Wang YJ (2022) Physiological clearance of Aβ by spleen and splenectomy aggravates Alzheimer-type pathogenesis. Aging Cell 21:e13533.
284. Wiest R, Weiss TS, Danielyan L, Buechler C (2021) Serum amyloid beta42 is not eliminated by the cirrhotic liver: a pilot study. J Clin Med 10:2669.
285. Wang YR, Wang QH, Zhang T, Liu YH, Yao XQ, Zeng F, Li J, Zhou FY, Wang L, Yan JC, Zhou HD, Wang YJ (2017) As-

sociations between hepatic functions and plasma amyloid-beta levels-implications for the capacity of liver in peripheral amyloid-beta clearance. Mol Neurobiol 54:2338-2344.
286. Tamaki C, Ohtsuki S, Iwatsubo T, Hashimoto T, Yamada K, Yabuki C, Terasaki T (2006) Major involvement of low-density lipoprotein receptor-related protein 1 in the clearance of plasma free amyloid beta-peptide by the liver. Pharm Res 23:1407-1416.
287. Sagare A, Deane R, Bell RD, Johnson B, Hamm K, Pendu R, Marky A, Lenting PJ, Wu Z, Zarcone T, Goate A, Mayo K, Perlmutter D, Coma M, Zhong Z, Zlokovic BV (2007) Clearance of amyloid-beta by circulating lipoprotein receptors. Nat Med 13:1029-1031.
288. Alemi M, Gaiteiro C, Ribeiro CA, Santos LM, Gomes JR, Oliveira SM, Couraud PO, Weksler B, Romero I, Saraiva MJ, Cardoso I (2016) Transthyretin participates in beta-amyloid transport from the brain to the liver--involvement of the low-density lipoprotein receptor-related protein 1? Sci Rep 6:20164.
289. Estrada LD, Ahumada P, Cabrera D, Arab JP (2019) Liver dysfunction as a novel player in Alzheimer's progression: looking outside the brain. Front Aging Neurosci 11:174.
290. Shinohara M, Tachibana M, Kanekiyo T, Bu G (2017) Role of LRP1 in the pathogenesis of Alzheimer's disease: evidence from clinical and preclinical studies. J Lipid Res 58:1267-1281.
291. Tamaki C, Ohtsuki S, Terasaki T (2007) Insulin facilitates the hepatic clearance of plasma amyloid beta-peptide (1 40) by intracellular translocation of low-density lipoprotein receptor-related protein 1 (LRP-1) to the plasma membrane in hepatocytes. Mol Pharmacol 72:850-855.
292. Nielsen R, Christensen EI, Birn H (2016) Megalin and cubilin in proximal tubule protein reabsorption: from experimental models to human disease. Kidney Int 89:58-67.
293. Dietrich M, Antequera D, Pascual C, Castro N, Bolos M, Carro E (2014) Alzheimer's disease-like impaired cognition in endothelial-specific megalin-null mice. J Alzheimers Dis 39:711-717.
294. Ghiso J, Calero M, Matsubara E, Governale S, Chuba J, Beavis R, Wisniewski T, Frangione B (1997) Alzheimer's soluble amyloid beta is a normal component of human urine. FEBS Lett 408:105-108.
295. Ghersi-Egea JF, Gorevic PD, Ghiso J, Frangione B, Patlak CS, Fenstermacher JD (1996) Fate of cerebrospinal fluid-borne amyloid beta-peptide: rapid clearance into blood and appreciable accumulation by cerebral arteries. J Neurochem 67:880-883.
296. Arvanitakis Z, Lucas JA, Younkin LH, Younkin SG, Graff-Radford NR (2002) Serum creatinine levels correlate with plasma amyloid Beta protein. Alzheimer Dis Assoc Disord 16:187-190.
297. Liu YH, Xiang Y, Wang YR, Jiao SS, Wang QH, Bu XL, Zhu C, Yao XQ, Giunta B, Tan J, Zhou HD, Wang YJ (2015) Association between serum amyloid-beta and renal functions: implications for roles of kidney in amyloid-beta clearance. Mol Neurobiol 52:115-119.
298. Gronewold J, Klafki HW, Baldelli E, Kaltwasser B, Seidel UK, Todica O, Volsek M, Haußmann U, Wiltfang J, Kribben A, Bruck H, Hermann DM (2016) Factors responsible for plasma β-amyloid accumulation in chronic kidney disease. Mol Neurobiol 53:3136-3145.
299. Deckers K, Camerino I, van Boxtel MP, Verhey FR, Irving K, Brayne C, Kivipelto M, Starr JM, Yaffe K, de Leeuw PW, Köhler S (2017) Dementia risk in renal dysfunction: a systematic review and meta-analysis of prospective studies. Neurology 88:198-208.
300. Sakai K, Senda T, Hata R, Kuroda M, Hasegawa M, Kato M, Abe M, Kawaguchi K, Nakai S, Hiki Y, Yuzawa Y, Kitaguchi N (2016) Patients that have undergone hemodialysis exhibit lower amyloid deposition in the brain: evidence supporting a therapeutic strategy for Alzheimer's disease by removal of blood amyloid. J Alzheimers Dis 51:997-1002.
301. McAdams-DeMarco MA, Daubresse M, Bae S, Gross AL, Carlson MC, Segev DL (2018) Dementia, Alzheimer's disease, and mortality after hemodialysis initiation. Clin J Am Soc Nephrol 13:1339-1347.
302. Hasegawa M, Kitaguchi N, Takechi H, Kawaguchi K, Ito K, Kato T, Kato M, Nii N, Yamada S, Ohashi A, Koide S, Hayashi H, Takahashi K, Inaguma D, Yuzawa Y, Tsuboi N (2022) First-in-human study of blood amyloid β removal from early Alzheimer's disease patients with normal kidney function. Ther Apher Dial 26:529-536.
303. Gronewold J, Todica O, Klafki HW, Seidel UK, Kaltwasser B, Wiltfang J, Kribben A, Bruck H, Hermann DM (2017) Association of plasma β-amyloid with cognitive performance and decline in chronic kidney disease. Mol Neurobiol 54:7194-7203.
304. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, Figueiredo JL, Kohler RH, Chudnovskiy A, Waterman P, Aikawa E, Mempel TR, Libby P, Weissleder R, Pittet MJ (2009) Identification of splenic reservoir monocytes and their deployment to inflammatory sites. Science 325:612-616.
305. Gu BJ, Huang X, Ou A, Rembach A, Fowler C, Avula PK,

Horton A, Doecke JD, Villemagne VL, Macaulay SL, Maruff P, Fletcher EL, Guymer R, Wiley JS, Masters CL; Australian Imaging, Biomarkers and Lifestyle (AIBL) Study (2016) Innate phagocytosis by peripheral blood monocytes is altered in Alzheimer's disease. Acta Neuropathol 132:377-389.
306. Wei Y, Wang T, Liao L, Fan X, Chang L, Hashimoto K (2022) Brain-spleen axis in health and diseases: a review and future perspective. Brain Res Bull 182:130-140.
307. Tani Y, Uchida K, Uetsuka K, Nakamura S, Nakayama H, Goto N, Doi K (1997) Amyloid deposits in the gastrointestinal tract of aging dogs. Vet Pathol 34:415-420.
308. Joachim CL, Mori H, Selkoe DJ (1989) Amyloid beta-protein deposition in tissues other than brain in Alzheimer's disease. Nature 341:226-230.
309. Leonardi L, Adam C, Beaudonnet G, Beauvais D, Cauquil C, Not A, Morassi O, Benmalek A, Trassard O, Echaniz-Laguna A, Adams D, Labeyrie C (2022) Skin amyloid deposits and nerve fiber loss as markers of neuropathy onset and progression in hereditary transthyretin amyloidosis. Eur J Neurol 29:1477-1487.
310. Hansen CT, Møller HEH, Rojek AM, Marcussen N, Beck HC, Abildgaard N (2021) Combined subcutaneous fat aspirate and skin tru-cut biopsy for amyloid screening in patients with suspected systemic amyloidosis. Molecules 26:3649.
311. March ME, Gutierrez-Uzquiza A, Snorradottir AO, Matsuoka LS, Balvis NF, Gestsson T, Nguyen K, Sleiman PMA, Kao C, Isaksson HJ, Bragason BT, Olafsson E, Palsdottir A, Hakonarson H (2021) NAC blocks Cystatin C amyloid complex aggregation in a cell system and in skin of HCCAA patients. Nat Commun 12:1827.
312. Jameson C, Boulton KA, Silove N, Nanan R, Guastella AJ (2023) Ectodermal origins of the skin-brain axis: a novel model for the developing brain, inflammation, and neurodevelopmental conditions. Mol Psychiatry 28:108-117.
313. Zouboulis CC, Makrantonaki E, Hossini AM (2021) Skin mirrors brain: a chance for Alzheimer's disease research. Adv Exp Med Biol 1339:371-380.
314. Hanbouch L, Schaack B, Kasri A, Fontaine G, Gkanatsiou E, Brinkmalm G, Camporesi E, Portelius E, Blennow K, Mourier G, Gilles N, Millan MJ, Marquer C, Zetterberg H, Boussicault L, Potier MC (2022) Specific mutations in the cholesterol-binding site of APP alter its processing and favor the production of shorter, less toxic Aβ peptides. Mol Neurobiol 59:7056-7073.
315. Akerman SC, Hossain S, Shobo A, Zhong Y, Jourdain R, Hancock MA, George K, Breton L, Multhaup G (2019) Neurodegenerative disease-related proteins within the epidermal layer of the human skin. J Alzheimers Dis 69:463-478.
316. Kummer C, Wehner S, Quast T, Werner S, Herzog V (2002) Expression and potential function of beta-amyloid precursor proteins during cutaneous wound repair. Exp Cell Res 280:222-232.
317. Hoffmann J, Twiesselmann C, Kummer MP, Romagnoli P, Herzog V (2000) A possible role for the Alzheimer amyloid precursor protein in the regulation of epidermal basal cell proliferation. Eur J Cell Biol 79:905-914.
318. Zhuang ZQ, Shen LL, Li WW, Fu X, Zeng F, Gui L, Lü Y, Cai M, Zhu C, Tan YL, Zheng P, Li HY, Zhu J, Zhou HD, Bu XL, Wang YJ (2018) Gut microbiota is altered in patients with Alzheimer's disease. J Alzheimers Dis 63:1337-1346.
319. Wang YJ (2014) Alzheimer disease: lessons from immunotherapy for Alzheimer disease. Nat Rev Neurol 10:188-189.
320. Yu TW, Lane HY, Lin CH (2021) Novel therapeutic approaches for Alzheimer's disease: an updated review. Int J Mol Sci 22:8208.
321. Tomizawa I, Nakagawa H, Sohma Y, Kanai M, Hori Y, Tomita T (2022) Photo-oxygenation as a new therapeutic strategy for neurodegenerative proteinopathies by enhancing the clearance of amyloid proteins. Front Aging Neurosci 14:945017.
322. Ozawa S, Hori Y, Shimizu Y, Taniguchi A, Suzuki T, Wang W, Chiu YW, Koike R, Yokoshima S, Fukuyama T, Takatori S, Sohma Y, Kanai M, Tomita T (2021) Photo-oxygenation by a biocompatible catalyst reduces amyloid-β levels in Alzheimer's disease mice. Brain 144:1884-1897.
323. Satizabal CL, Beiser AS, Chouraki V, Chêne G, Dufouil C, Seshadri S (2016) Incidence of dementia over three decades in the Framingham heart study. N Engl J Med 374:523-532.
324. Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natarajan L, Liu L, Ayalon L, He F, Loredo JS (2008) Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J Am Geriatr Soc 56:2076-2081.
325. Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, Wohlleber ME, Ducca EL, Koushyk V, Glodzik L, Mosconi L, Ayappa I, Rapoport DM, de Leon MJ; Alzheimer's Disease Neuroimaging Initiative (2015) Sleep-disordered breathing advances cognitive decline in the elderly. Neurology 84:1964-1971.
326. Haag MD, Hofman A, Koudstaal PJ, Stricker BH, Breteler MM (2009) Statins are associated with a reduced risk of Alzheimer disease regardless of lipophilicity. The Rotterdam study. J Neurol Neurosurg Psychiatry 80:13-17.
327. Papadopoulos P, Tong XK, Hamel E (2014) Selective benefits of simvastatin in bitransgenic APPSwe,Ind/TGF-β1 mice.

Neurobiol Aging 35:203-212.
328. Boada M, Ortiz P, Anaya F, Hernández I, Muñoz J, Núñez L, Olazarán J, Roca I, Cuberas G, Tárraga L, Buendia M, Pla RP, Ferrer I, Páez A (2009) Amyloid-targeted therapeutics in Alzheimer's disease: use of human albumin in plasma exchange as a novel approach for Abeta mobilization. Drug News Perspect 22:325-339.
329. Jin WS, Bu XL, Wang YR, Li L, Li WW, Liu YH, Zhu C, Yao XQ, Chen Y, Gao CY, Zhang T, Zhou HD, Zeng F, Wang YJ (2017) Reduced cardiovascular functions in patients with Alzheimer's disease. J Alzheimers Dis 58:919-925.
330. Koronyo-Hamaoui M, Sheyn J, Hayden EY, Li S, Fuchs DT, Regis GC, Lopes DHJ, Black KL, Bernstein KE, Teplow DB, Fuchs S, Koronyo Y, Rentsendorj A (2020) Peripherally derived angiotensin converting enzyme-enhanced macrophages alleviate Alzheimer-related disease. Brain 143:336-358.
331. Ma M, Liu Z, Gao N, Pi Z, Du X, Ren J, Qu X (2020) Self-protecting biomimetic nanozyme for selective and synergistic clearance of peripheral amyloid-β in an Alzheimer's disease model. J Am Chem Soc 142:21702-21711.
332. Brambilla D, Verpillot R, Le Droumaguet B, Nicolas J, Taverna M, Kóňa J, Lettiero B, Hashemi SH, De Kimpe L, Canovi M, Gobbi M, Nicolas V, Scheper W, Moghimi SM, Tvaroška I, Couvreur P, Andrieux K (2012) PEGylated nanoparticles bind to and alter amyloid-beta peptide conformation: toward engineering of functional nanomedicines for Alzheimer's disease. ACS Nano 6:5897-5908.
333. Carradori D, Balducci C, Re F, Brambilla D, Le Droumaguet B, Flores O, Gaudin A, Mura S, Forloni G, Ordoñez-Gutierrez L, Wandosell F, Masserini M, Couvreur P, Nicolas J, Andrieux K (2018) Antibody-functionalized polymer nanoparticle leading to memory recovery in Alzheimer's disease-like transgenic mouse model. Nanomedicine 14:609-618.
334. Kim D, Kwon HJ, Hyeon T (2019) Magnetite/ceria nanoparticle assemblies for extracorporeal cleansing of amyloid-β in Alzheimer's disease. Adv Mater 31:e1807965.
335. Matsuoka Y, Saito M, LaFrancois J, Saito M, Gaynor K, Olm V, Wang L, Casey E, Lu Y, Shiratori C, Lemere C, Duff K (2003) Novel therapeutic approach for the treatment of Alzheimer's disease by peripheral administration of agents with an affinity to beta-amyloid. J Neurosci 23:29-33.
336. Ordóñez-Gutiérrez L, Re F, Bereczki E, Ioja E, Gregori M, Andersen AJ, Antón M, Moghimi SM, Pei JJ, Masserini M, Wandosell F (2015) Repeated intraperitoneal injections of liposomes containing phosphatidic acid and cardiolipin reduce amyloid-β levels in APP/PS1 transgenic mice. Nanomedicine 11:421-430.
337. Barrera-Ocampo A, Lopera F (2016) Amyloid-beta immunotherapy: the hope for Alzheimer disease? Colomb Med (Cali) 47:203-212.
338. Song C, Shi J, Zhang P, Zhang Y, Xu J, Zhao L, Zhang R, Wang H, Chen H (2022) Immunotherapy for Alzheimer's disease: targeting β-amyloid and beyond. Transl Neurodegener 11:18.
339. Karran E, De Strooper B (2022) The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. Nat Rev Drug Discov 21:306-318.
340. DiFrancesco JC, Longoni M, Piazza F (2015) Anti-Aβ autoantibodies in amyloid related imaging abnormalities (ARIA): candidate biomarker for immunotherapy in Alzheimer's disease and cerebral amyloid angiopathy. Front Neurol 6:207.
341. Mo JJ, Li JY, Yang Z, Liu Z, Feng JS (2017) Efficacy and safety of anti-amyloid-β immunotherapy for Alzheimer's disease: a systematic review and network meta-analysis. Ann Clin Transl Neurol 4:931-942.

 https://doi.org/10.5607/en23014