Clearance of cerebral Aβ in Alzheimer’s disease: reassessing the role of microglia and monocytes

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Abstract  Deficiency in cerebral amyloid β-protein (Aβ) clearance is implicated in the pathogenesis of the common late-onset forms of Alzheimer’s disease (AD). Accumulation of misfolded Aβ in the brain is believed to be a net result of imbalance between its production and removal. This in turn may trigger neuroinflammation, progressive synaptic loss, and ultimately cognitive decline. Clearance of cerebral Aβ is a complex process mediated by various systems and cell types, including vascular transport across the blood–brain barrier, glymphatic drainage, and engulfment and degradation by resident microglia and infiltrating innate immune cells. Recent studies have highlighted a new, unexpected role for peripheral monocytes and macrophages in restricting cerebral Aβ fibrils, and possibly soluble oligomers. In AD transgenic (ADtg) mice, monocyte ablation or inhibition of their migration into the brain exacerbated Aβ pathology, while blood enrichment with monocytes and their increased recruitment to plaque lesion sites greatly diminished Aβ burden. Profound neuroprotective effects in ADtg mice were further achieved through increased cerebral recruitment of myelomonocytes overexpressing Aβ-degrading enzymes. This review summarizes the literature on cellular and molecular mechanisms of cerebral Aβ clearance with an emphasis on the role of peripheral monocytes and macrophages in Aβ removal.

Keywords Neurodegenerative diseases · Amyloid-β protein · Aβ-degrading enzymes · Innate immune cells · Myelomonocytes · Phagocytosis

Abbreviations
AD Alzheimer’s disease
ADtg AD transgenic models
Aβ Amyloid-β protein
AICD Amyloid intracellular domain
APP Amyloid precursor protein
ACE Angiotensin-converting enzyme
ApoE Apolipoprotein E
ApoER2 ApoE receptor 2 A
AQP4 Aquaporin 4
ABC ATP-binding cassette
AV Autophagic vacuole
BACE1 β-secretase 1
BBB Blood–brain barrier
CCR2 c-c chemokine receptor type 2
CNS Central nervous system
CAA Cerebral amyloid angioapathy
CSF Cerebrospinal fluid
CMA Chaperone-mediated autophagy
ECE-1 Endothelin-converting enzyme 1
FAD Familial Alzheimer’s disease
GWAS Genome-wide association study
GA Glatiramer acetate
GFP Green fluorescent protein

This paper is dedicated to the memory of Dr. Salomon Moni Hamaoui and Lillian Jones Black, both of whom died from Alzheimer’s disease.

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Introduction

Alzheimer’s disease (AD) is a severe neurodegenerative disorder and the most common form of senile dementia, affecting over 5 million in the United States and 45 million worldwide [1, 2]. AD manifests as a progressive decline in cognitive function and behavior, invariably leading to death [3]. The epidemic of AD is especially damaging to the growing elderly population and the economy that supports them. This immense psychosocial and public health burden calls for a clearer understanding of disease pathophysiology to facilitate the development and implementation of more effective treatment strategies.

Over the past century, our understanding of the molecular mechanisms underlying the development of AD has greatly expanded. Though still pathological hallmarks, extracellular plaques and intracellular neurofibrillary tangles (NFTs) within the brain [4], comprised, respectively, of amyloid-β protein (Aβ) and hyperphosphorylated tau (pTau), no longer describe all pathogenic forms of these proteins. Beyond intracellular threads and tangles, misfolded tau may form extracellular assemblies that propagate through and disrupt synapticly dense regions [5, 6]. Meanwhile, extracellular and intracellular oligomers of Aβ were also found to be highly synaptotoxic and exist in a highly dynamic equilibrium between the small, soluble forms and the larger, insoluble intermediates and fibrils [7, 8]. Recent exploration of this disease outside the brain, in another central nervous system tissue, has further revealed Aβ pathology in the retina of AD patients, including those at early stages [9–13]. Converging data from genetic, physiologic, biochemical, and clinical studies demonstrate a strong association between Aβ accumulation and neuroinflammation, synaptic loss, impaired neuronal function, and ultimately, debilitating cognitive decline [3, 14]. Progressive accumulation and aggregation of Aβ peptides in the brain are thought to be a net result of imbalance between their production and clearance [15]. Moreover, the dramatic increase in cerebral Aβ far precedes the clinical impairment, beginning as early as 20 years prior to symptom manifestation [16]. Therefore, a common view is that any strategy that reduces Aβ levels in the brain, either by inhibiting its production/aggregation or by increasing its clearance, will be advantageous in preventing the development of AD.

Aβ denotes a group of endogenous peptides, typically of 36–43 amino acids. It derives from a larger transmembrane protein, the amyloid precursor protein (APP), in a complex proteolytic process, described extensively elsewhere [17]. The disease-associated (amyloidogenic) aggregation-prone Aβ1-40 (Aβ40) and Aβ1-42 (Aβ 42) alloforms are generated through a sequential cleavage of APP by a β-secretase (BACE1) and a γ-secretase transmembrane complex. Mutations within the gene encoding APP and its Aβ coding sequence were found to cause early-onset, autosomal-dominant inherited forms of familial AD (FAD) [18]. Similarly, patients with Down syndrome (trisomy 21) who carry three copies of the APP gene develop AD-like Aβ and tau neuropathology, leading to cognitive decline [19]. In addition, inheritance of mutations within the genes encoding for presenelin-1 and -2 (PS1 and PS2), two components of the γ-secretase complex, invariably lead to FAD [20–22] (Table 1). These rare mutations and haplotypes result in either overproduction or increased aggregation of Aβ, and
### Table 1: Genes associated with Alzheimer’s disease

| Gene   | Type   | FREQ | Risk Locus | Variants                        | ↑ Aβ prod. | ↓ Aβ clear. | Effects on Aβ | References                  |
|--------|--------|------|------------|---------------------------------|------------|------------|---------------|----------------------------|
| **APP** | FAD<sup>c</sup> | Rare | 21q21.3    | Mutations Trisomy 21            | ✓          | –          | ↑ Aβ<sub>42/40</sub> ratio; ↑ Aβ<sub>42</sub> aggregation | [4, 18, 21, 26–28] |
| **PSEN1** | FAD<sup>c</sup> | Rare | 14q24.3    | Mutations                      | ✓          | –          | ↑ Aβ<sub>42/40</sub> ratio | [20, 21, 23, 26–28] |
| **PSEN2** | FAD<sup>c</sup> | Rare | 1q42.13    | Mutations                      | ✓          | –          | ↑ Aβ<sub>42/40</sub> ratio | [21–23, 26, 28, 31] |
| **ABCA7** | LOAD 16% |       | rs3764650  | Understudied; ↑ Aβ secretion; ↓ MΦ/MG Aβ phagocytosis | ✓          | ✓          |                           | [21, 32–39] |
| **ADAM10** | LOAD | Rare | 15q21.3    | Q170H R181G                     | ✓          | –          | ↑ Aβ production; ↓ α-secretase activity | [40–43] |
| **ACE** | LOAD | 33–48% | 17q23.3    | Indel: rs4219                   | –          | ✓          | Controversial; ↓ Aβ degradation; ↑ Aβ levels | [43–50] |
| **APOE<sup>d</sup>** | LOAD | 3%<sup>e</sup> | 19q13.2    | e4 Allele<sup>e</sup> e2 Allele<sup>e</sup> | –          | ✓          | ↓ Chaperone-mediated Aβ processing, clearance | [51–56] |
| **BIN1** | LOAD | 45% | 2q14       | rs744373 rs7561528              | ✓          | ✓          | ↑ Aβ production; May ↓ MΦ Aβ phagocytosis | [33, 34, 57–61] |
| **CD2AP** | LOAD | 3% | 6p12       | rs9296559 rs9349407            | –          | ✓          | ↑ Aβ plaque burden; ↓ Endosome/lysosome clearance | [33, 37, 57, 62, 63] |
| **CD33** | LOAD | 30% | 19q13.3    | rs3865444<sup>f</sup> rs3826656 | –          | ✓          | ↓ Mo/MG Aβ phagocytosis | [33, 34, 64–67] |
| **CLU** | LOAD | 38% | 8p21-p12   | rs9331896                      | –          | ✓          | ↓ Chaperone-mediated Aβ clearance | [32, 68–75] |
| **CR1** | LOAD | 20% | 1q32       | rs3818361 rs6656401 rs6701713   | –          | ✓          | ↓ Immune-mediated Aβ clearance; ↑ Aβ<sub>42</sub> levels | [33, 34, 76–79] |
| **EPHA1** | LOAD | 34% | 7q34       | rs11771145<sup>f</sup> rs11767557<sup>f</sup> | –          | ✓          | Understudied; ↓ Immune-mediated Aβ clearance | [32–34, 80–82] |
| **PICALM** | LOAD | 36% | 11q14      | rs3851179<sup>f</sup> rs541458<sup>f</sup> | ✓          | ✓          | ↓ Trafficking of Aβ across BBB; ↑ Aβ production | [83–89] |
| **SIRT1** | LOAD | –   | 10q21.3    | –                              | ✓          | ✓          | ↑ MG-dependent Aβ toxicity; ↓ α-secretase activity | [32, 90–95] |
| **SORL1** | LOAD | 4% | 11q23.2-q24.2 | rs12285364 rs2070045 rs2282649 | ✓          | ✓          | ↑ Aβ production; ↓ APP trafficking to endosomes | [94, 96–101] |
importantly, in favored generation of the more pathogenic Aβ_{42} alloforms [4, 23]. These findings strongly tie Aβ to the etiology of AD. Further support for this notion came recently from the identification of a protective APP mutation in non-demented Icelanders [24]. The A673T mutation in APP (alternatively called A2T mutation in Aβ) was shown to reduce amyloidogenic Aβ production and aggregation in non-demented Icelanders [24]. The A673T mutation in APP recently from the identification of a protective allele [24].

While FAD represents approximately 5% of all AD cases, the remaining majority of AD cases manifest later in life (typically over 65 years of age), and are termed sporadic or late-onset AD (LOAD). The etiology of LOAD is multifactorial: multiple genetic and environmental factors likely contribute to the development of disease. Strong support for the role of Aβ accumulation in both AD forms came from several clinical studies. While in FAD cases cerebral Aβ increase was explained by Aβ_{42} overproduction [109], deficient Aβ_{42} clearance was shown in the brains of LOAD patients [110]. Despite differences in etiology, FAD and LOAD are neuropathologically indistinguishable and present with similar clinical phenotypes [4].

Growing evidence indicates that Aβ exerts its neurotoxic effects in both an alloform- and conformation-dependent manner [7]. Small, soluble oligomeric forms of Aβ_{12} were shown to be especially neurotoxic [111–113] and more strongly predict cognitive decline than Aβ plaque load [114, 115]. Specifically, Aβ oligomers were shown to impact long-term potentiation, synaptic signaling and plasticity, dendritic morphology, and cognition in rodent models [113, 116–119]. Additionally, Aβ was shown to impair neuronal glucose transport [120] and accumulate within mitochondria [121], disrupting vital enzymatic activity and increasing free radical production [122]. Aβ fibrils can also induce inflammatory processes by binding to and activating microglia [123, 124] and peripheral monocytes [125–127]. This toxic microenvironment was further associated with impaired calcium regulation and energy metabolism throughout CNS tissues [128]. Beyond amyloid pathology in brain parenchyma, AD patients frequently exhibit cerebral amyloid angiopathy (CAA) along with reduced cerebral blood flow that can further compromise cognitive capacity [129]. This phenomenon was also found in retina microvasculature [13, 130]. In murine models of AD, it was recently found that vascular amyloid deposits hardened blood vessel walls and reduced blood flow [131].

Although the existence of Aβ plaques and NFTs establishes the definitive diagnosis of AD, many researches have challenged the predominant belief that Aβ is central to the development of disease. For example, studies have demonstrated that NFT pathology correlates more strongly than amyloid plaque load with brain atrophy and cognitive decline [132, 133]. In addition, clinical trials targeting cerebral Aβ plaque removal in symptomatic patients have largely failed to provide a clinical benefit and have consequently raised concerns regarding the role of Aβ in the etiology and treatment of AD [134]. Alternative theories of AD pathogenesis have also been postulated. For instance, different groups consider AD to be a combination of multiple disorders of diverse etiology [135], a by-product of normal aging [136, 137], or initiated by faulty immune activation [138]. Others have described AD as a metabolic disorder similar to diabetes, and even coined the term Type 3 Diabetes to highlight their shared molecular and cellular
disturbances, such as insulin resistance, oxidative stress, and glycogen synthase kinase 3β activation [139]. These data are essential as the field continues to both expand and refine our understanding of AD pathogenesis and explore potential therapeutic avenues. However, this evidence does not preclude Aβ from playing a principal role in disease. Indeed, several studies have demonstrated that the presence of misfolded Aβ is sufficient to induce pTau and NFTs in vitro and in vivo [140–143]. Furthermore, overwhelming data from preclinical animal models have shown that targeting the production, aggregation, or immune-based removal of Aβ, and especially soluble Aβ42, preserved synapses and neuronal function as well as prevented cognitive decline [10, 144–146]. Importantly, a recent promising phase Ib human clinical trial, using a monoclonal antibody (aducanumab) to target the removal of both soluble oligomeric and fibrillar Aβ, has reinvigorated the field of Aβ-centered AD therapeutics. After 1 year of monthly aducanumab infusions, patients with prodromal or mild AD displayed a reduced cerebral Aβ plaque load and, by preliminary analyses, exhibited slowing of cognitive decline [147]. Taken together, it is no surprise that Aβ, in its various forms, remains the focus of AD research and a target for AD prevention and therapy.

In this review, we summarize various cellular and molecular, physiologic mechanisms of Aβ removal from the brain. Specifically, we cover Aβ transport across the blood–brain barrier (BBB), glymphatic clearance, cellular uptake, and enzymatic degradation. Large-scale genetic studies have further cemented the connection between Aβ accumulation, clearance by innate immune cells, and disease risk, and will be the topic of the following section. Finally, we place a particular emphasis on the growing evidence supporting a key role for microglia, and moreover, monocyte-derived macrophages in the physiological clearance of cerebral Aβ (see Fig. 1), and we examine their potential as targets for disease-modifying therapies.

**Genes related to Aβ homeostasis and Alzheimer’s disease**

Historically, the study of AD-related genes pertained to the rare, inheritable and early onset forms of the disease (termed FAD) [4, 22]. These early genetic studies identified FAD as a monogenic disorder resulting from mutations in APP, PS1, or PS2 leading to the amyloidogenic processing of APP and overproduction of synaptotoxic Aβ42 (Table 1) [4, 23]. In contrast, the far more common, late-onset AD (LOAD) is a multifactorial disease, with complex and heterogenous interactions between genetic and environmental factors underlying its development [149, 150]. Importantly, insufficient cerebral Aβ clearance is thought to drive LOAD pathogenesis [110]. The strongest known susceptibility locus for LOAD encodes apolipoprotein E (ApoE) [51, 151]. Carriers of a single, and moreover, carriers of double APOE4 alleles have a significantly increased risk of developing AD [51, 151]. Apoe4 has been implicated in Aβ trafficking and neurovascular function, with possible additional effects on myeloid cell phenotype and ability to phagocytose Aβ (discussed further below) [52, 152–154]. Recent genome-wide association studies (GWAS), case-control and family-based studies, whole exome sequencing studies, and meta-analyses of large LOAD patient datasets

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**Fig. 1** Cerebral Aβ clearance by peripheral monocyte-derived macrophages. a ADtg mice were immunized with dendritic cells (DCs) pulsed with an altered myelin-derived peptide (MOG45D). Brain-resident microglia (MG, Iba1+/CD45int-low), and moreover, blood-borne infiltrating Iba1+/CD45high macrophages (MΦ, red), are involved in the uptake of cerebral Aβ (4G8+; bright white areas), as shown in the hippocampal region from an immunized ADtg mouse. Image adopted from Koronyo-Hamaoui et al., J Neurochemistry [148]. b Phagocytosis of fibrillar Aβ42 (6E10) and co-localization within CD163+CD36high bone marrow-derived macrophages in cultures treated with glatiramer acetate (GA). c A GA-immunized ADtg mouse brain exhibiting increased expression of Aβ-degrading enzyme (MMP-9) by recruited blood-borne MΦ surrounding Aβ plaques. Microscopic images from Koronyo et al., Brain, [144]
have further identified over 20 novel risk factors with varying effect sizes and frequencies in the population (Table 1) [32–34, 76, 83, 96, 155]. Remarkably, a vast majority of these risk genes are associated with Aβ processing or trafficking as well as with a wide range of immunological responses, especially those related to myeloid cell-mediated Aβ clearance [156]. More specifically, LOAD risk genes have been demonstrated to impact inflammation (APOE, INPP5D, CR1, TREM2, MS4A), complement activation (CLU, CR1), the HLA gene complex (HLA-DRB1, HLA-DRB5), and myeloid-cell-mediated Aβ proteolysis (ACE, CD2AP) and phagocytosis (APOE, BIN1, INPP5D, CR1, ABCA7, TREM2) [21, 156]. In particular, polymorphisms in the genes CD33 (sialic acid-binding immunoglobulin-like lectin 3) and TREM2 (triggering receptor on myeloid cells 2) directly link impaired microglial and macrophage phagocytosis of Aβ to increased susceptibility to AD. The reported effect size of TREM2 variants on AD risk has varied in the literature [96, 155]: some investigations estimate an odds ratio of 3–4 (similar to the risk of carrying a single Apoε4 allele), while others show only a small to moderate effect [96, 151, 155, 157]. Nonetheless, TREM2 has remained in the spotlight for its effects on myelomonocytic cell phenotype and Aβ phagocytosis, which will be discussed in later sections. It has long been questioned whether AD-associated inflammation and myeloid cell dysfunction drive disease pathogenesis or instead represent a subsequent reaction to the associated neuropathology [123, 158]. Yet, these recent large-scale genetic studies, compiling data from thousands of AD subjects, illustrate unequivocally the principal role of immunological processes in development of AD, and for the first time, provide genetic evidence supporting the significance of the peripheral immune system.

Mechanisms of Aβ clearance

The key mechanisms of Aβ clearance were shown to involve either Aβ removal to the peripheral blood and lymphatic systems or degradation within the CNS tissues. Aβ reaches the peripheral circulation via chaperone-mediated transport across the blood brain barrier (BBB) [159], perivascular drainage [160], or through the lymphatic system [161, 162]. In the parenchyma, myelomonocytic cells were shown to phagocytose fibrillar Aβ, and perhaps their soluble oligomeric forms as well. These professional phagocytes, together with astrocytes and neurons, are jointly responsible for degradation and removal of amyloidogenic Aβ alloforms [123, 163]. Though each system likely contributes to Aβ clearance to varying extents, their summed effects are essential for Aβ homeostasis. This implies that perturbations of any singular process may underlie or predispose to pathologic Aβ accumulation, and consequently development of AD.

Extracellular enzymatic degradation of Aβ

Secreted peptidases are critical for the catabolism of Aβ peptides. These enzymes were reported to have an affinity for specific domains within the Aβ amino acid sequence and an ability to cleave and convert these peptides to shorter, more benign forms [164–167]. Table 2 describes major Aβ-degrading enzymes, their substrates, their cellular location and the cell types known to express and secrete them. The following paragraphs describe several Aβ-degrading enzymes that have been central in AD research.

Angiotensin-converting enzyme (ACE)

ACE is a zinc-dependent peptidase with significant expression by endothelium throughout the body as well as by cortical neurons in the brain [205]. Most well known for transforming angiotensin-I to angiotensin-II and for its role in regulating hemodynamic stability and salt balance, ACE was also shown to degrade Aβ, and importantly, cleave Aβ42 into the less toxic Aβ40 alloform [164]. In post-mortem analyses, cortical and perivascular ACE expression was upregulated in the brains of AD patients and correlated with parenchymal plaque load and extent of perivascular amyloid deposition, respectively [206, 207]. Furthermore, lower levels of ACE protein and its activity were associated with lower CSF Aβ, indicating more prominent amyloid pathology in the parenchyma [44]. It was thus hypothesized that increased ACE activity in CNS tissues is a protective response to increasing amyloid pathology. While this claim is partially supported by both genetic studies in humans and physiologic studies in ADtg mice, there are inconsistencies within the literature. Both case-control studies and several large meta-analyses have identified an insertion within intron 16 of the gene ACE1 that reduces plasma ACE levels and increases risk for AD [45–47]. However, these findings were not always replicated [208]. Interestingly, AD patients homozygous for the insertion polymorphism had a greater risk of cognitive deterioration and clinical progression than other ACE genotypes [48], suggesting ACE activity may critically modulate the pathophysiology underlying neurodegeneration. Indeed, one long-term study of the ACE-inhibitor (ACE-I) captopril in ADtg mice supports the role of ACE in Aβ clearance, as both Aβ plaque load and Aβ42 levels were elevated after 11 months of treatment [209]. It is important to note, however, that studies of shorter duration did not report a measurable effect of other ACE-Is on Aβ pathology [205]. In ADtg mice, ACE overexpression by
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Microglia and monocytes/macrophages lead to a dramatic reduction in cerebral Aβ levels and cognitive decline [145, 191], demonstrating great therapeutic potential discussed further below. Taken together, there is substantial, although inconsistent, evidence implicating ACE in the physiological clearance of Aβ that merits further investigation.

Insulin-degrading enzyme (IDE)

IDE is a zinc metalloprotease that is capable of degrading soluble Aβ40 and Aβ42 into non-toxic fragments [165, 174]. Although primarily localized in the cytosol, a small fraction of IDE is secreted by glial cells [175, 176, 185] or expressed on the cell surface of neurons [177], where it serves as a critical enzyme for extracellular Aβ degradation [165, 210]. Investigations in human and AD rodent models have yielded varying evidence regarding IDE mRNA expression, protein levels, and activity in the AD brain, most likely because the behavior of IDE is highly dependent on age [211–213], brain region [211–213], disease severity [212, 213], and APOE status [214]. In general, it seems IDE levels and activities are upregulated in response to Aβ exposure, with the exception of Apoe4/4 carriers, who exhibit reduced IDE expression.

Matrix metalloproteinase-9 (MMP-9)

MMP-9 is a secreted enzyme and member of the zinc metalloprotease (MMP) family. In general, MMPs are responsible for the degradation and maintenance of the extracellular matrix. MMP-9 has been shown to degrade compact plaques [186, 187] as well as soluble Aβ40,42 and Aβ40 [167]. In the CNS, MMP-9 is expressed by neurons [188], microglia [189], astrocytes [190], and infiltrating Iba+/CD45hi monocytes (Fig. 1C) [144, 148]. MMP-9 has also been shown to act as an α-secretase, favoring non-amyloidogenic processing of APP and the production of sAPPα [215]. In addition to its efficient degradation of Aβ, MMP-9 was shown to be involved in both TNFα-mediated pro-inflammatory and anti-inflammatory signaling in activated macrophages and microglia [216, 217]. Elevated levels of MMP-9 have been correlated with BBB breakdown, demyelination, and cell death in other CNS disorders like multiple sclerosis [218] and spinal cord injury [219]. These effects should be considered when modulating MMP-9 activity in vivo.
Nephrilysin (NEP)

NEP is a type II integral membrane zinc metalloprotein with the bulk of its structure, including the active site, facing the extracellular space. NEP is expressed throughout the brain, predominantly on pre- and post-synaptic neuronal membranes [168, 169], and by microglia [170] and astrocytes [171]. NEP is considered the most potent \( \beta \)-degrading enzyme [220, 221], preferentially cleaving oligomeric \( \beta_42 \) and \( \beta_40 \) [166, 172] but not fibrillar forms. NEP expression and activity has been shown to decline with age and disease in post-mortem human AD brain tissue [222], which may contribute to \( \beta \) accumulation. Modeling this reduction by dampening NEP expression [223, 224] or activity [225] in ADtg mice resulted in elevated \( \beta \) pathology and cognitive deficits. Conversely, the beneficial effects of NEP overexpression speak to the therapeutic potential of targeting nephrilysin activity, discussed further below [146, 172].

**Enzymatic degradation by innate immune cells**

NEP, IDE, ACE and MMP-9 are \( \beta \)-degrading enzymes expressed by innate immune cells and represent a crucial pathway by which these cells may eradicate pathogenic \( \beta \) (Table 2). Expression of NEP, IDE, and MMP-9 was shown to decline in microglia of aged APP/PS1 mice, which may contribute to their functional impairment in later stages of AD [170]. This altered microglial phenotype was contingent on the presence of \( \beta \), as microglia from age-matched controls did not exhibit reduced enzyme expression. Microglial expression of NEP and IDE were also shown to be highly inducible in vitro and correlated with enhanced clearance of soluble \( \beta_{1-42} \) [226].

For proteolytic processing of \( \beta \) by monocyte-derived macrophages, the expression of MMP-9 appears to be especially important. APPSWE/PS1\(_{\Delta E9}\) mice infused with CD115\(^+\) monocytes or immunized with the altered myelin-derived antigens, such as glatiramer acetate (GA) or myelin oligodendrocyte glycoprotein-derived peptide (MOG45D) displayed increased accumulation of MMP-9-secreting macrophages surrounding \( \beta \) plaques (Fig. 1c), along with a marked reduction in \( \beta \) neuropathology and cognitive impairment [144, 148]. GA stimulation of bone marrow-derived macrophages in vitro also dramatically induced MMP-9 expression [144]. Additionally, peripheral macrophages cultured on top of plaque-bearing brain sections of PDAPP mice cleared \( \beta \), in part, by upregulated expression of MMP-9 [185]. Interestingly, macrophages expressed MMP-9 in an ApoE-dependent manner. ApoE4 significantly dampened MMP-9 expression, suggesting an additional mechanism by which ApoE4 disrupts \( \beta \) clearance [185].

Furthermore, ACE has a demonstrated ability to modulate the behavior of innate immune cells in ADtg murine models [191, 227]. In other disease models, targeted overexpression of ACE to myelomonocytic cells enhances their immune function, including their ability to clear cellular debris and promote tissue repair. Targeted ACE overexpression to myelomonocytes (ACE10/10 model) introduced to APPSWE/PS1\(_{\Delta E9}\) transgenic mice resulted in increased infiltration of monocyte-derived macrophages that were tightly associated with \( \beta \) plaques and displayed increased ability to phagocytose \( \beta \) [145]. The net result was reduced soluble and insoluble \( \beta \) levels, attenuated neuroinflammation, and improved cognitive performance. In contrast, inhibition of ACE catalytic domains in ACE10/10-ADtg mice exacerbated cerebral \( \beta \) pathology [145]. Overall, the beneficial outcomes of ACE overexpression in myelomonocytes were most likely due to the summed effects of the enhanced immune response and proteolytic capacity endowed by ACE expression.

**Intracellular degradation systems**

Another important mechanism of \( \beta \) catabolism is undertaken within cells that either absorb or engulf \( \beta \) forms. Three such critical pathways—autophagy, endosomal/lysosomal degradation, and the ubiquitin–proteasome system (UPS)—prevent intracellular protein aggregation, and are thus instrumental in protecting against the neurotoxicity of cytosolic \( \beta \) accumulation. In AD brains, however, these systems are considerably compromised [228–231]. Degradation targets for both the UPS and autophagy originate from the cytosol, although their identities differ between the two processes. Autophagy typically facilitates clearance of larger protein aggregates and damaged organelles, while the UPS degrades misfolded or damaged proteins. Furthermore, the UPS is more highly regulated than autophagy, requiring poly-ubiquitination of the target protein for its degradation. The lysosome, too, facilitates intracellular protein degradation, though the origin of these proteins may be either cytosolic or extracellular. Because the lysosome is a final common pathway for several systems, including autophagy, it is discussed separately below.

**Lysosomal degradation**

The lysosome is the final destination for both autophagic vacuoles and the endosomes formed by receptor-mediated endocytosis. The latter process occurs in neurons and glia through a distinct set of molecular chaperones, discussed in greater detail in the following sections. Each lysosome contains a cocktail of hydrolytic enzymes capable of degrading \( \beta \); however, the hydrolytic machinery is often
overwhelmed in AD [228, 232–234]. As Aβ load exceeds the degradation capacity of the lysosome, aggregates may grow larger or leak into the cytosol [228, 232–234]. Aging [235] and the presence of Apoe4 [234, 236] particularly promote lysosomal instability. Intracellular Aβ negatively impacts multiple cellular and organelle functions, including proteasome inhibition, mitochondrial abnormalities, tau hyperphosphorylation, and presumably, the seeding of amyloid plaques following cell death [121, 237, 238].

Myeloid cells in particular may suffer AD-associated deficits in endosomal-lysosomal trafficking and Aβ processing. Microglia isolated from plaque-bearing sections of human AD tissue indicated that Aβ fibrils were located in the endoplasmic reticulum and deep invaginations of the cell membrane, instead of within endosomes or lysosomes [239]. Even non-diseased microglia cultured with fibrillar Aβ42 showed incomplete intracellular degradation, with non-degraded fibrils remaining in phagosomes for up to 20 days [239, 240]. This impairment was not seen in peripheral macrophage cultures under the same conditions. In fact, after 3 days of incubation with fibrillar Aβ, less than 30% of Aβ was retained in peritoneal macrophages, indicating successful degradation, while 80% remained associated with microglia [241]. One possible explanation for deficient microglial clearance is insufficient activity of lysosomal Aβ-degrading enzymes. In support of this notion, incubating microglia with mannose-6-phosphate tagged lysosomal enzymes rescued the clearance impairment. Mannose-6-phosphate typically targets hydrolytic enzymes to the lysosome from the Golgi apparatus, and this modification has been used to deliver extracellular enzymes to the lysosome in experimental conditions [242].

While healthy peripheral macrophages appear better equipped to degrade fibrillar Aβ than resident microglia, monocytes in AD patients exhibit lysosomal dysfunction [125, 229]. Specifically, more undigested Aβ molecules exist within monocytes isolated from AD patients compared to those from healthy age-matched controls, a deficit partially attributable to reduced expression and activity of cathepsin D and other major lysosomal enzymes [229, 243]. Upregulation of miR-128 was shown to target the transcripts of these enzymes and mediate their suppression. The discrepancy in lysosomal degradation capacity between microglia and infiltrating macrophages highlights their non-redundant roles in restricting Aβ pathology and as targets for future intervention.

**Autophagy-mediated degradation**

Three types of autophagy exist: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). While both macroautophagy and CMA dysfunction are implicated in AD [244, 245], the former is considered to be the predominant process, and will be referred to simply as “autophagy” throughout [245]. The mechanism of autophagy-mediated clearance involves isolation of cytoplasmic contents by a double-membrane vesicle called an autophagosome or autophagic vacuole (AV). Subsequent lysosomal fusion facilitates degradation of the AV and its contents [246], which may include Aβ and APP [247, 248]. In both AD patients and ADtg models, autophagy is markedly impaired, evidenced by the large accumulation of unprocessed, Aβ-rich AVs in dystrophic neurites [249, 250]. Indeed, deficits in the autophagy-lysosomal pathway occur early in the disease process, perhaps even preceding Aβ accumulation [230, 251]. Reduced expression of key autophagic proteins (beclin-1 and autophagy proteins 5 and 7) likely contribute to autophagic dysfunction, Aβ accumulation, and neuronal cell death [248, 252–254]. Furthermore, perturbations in signaling through the mammalian target of rapamycin (mTOR) pathway, the key regulator of autophagic activity, may also contribute to its impairment in AD. Under nutrient-rich conditions, heightened mTOR signaling suppresses autophagy by phosphorylating proteins necessary for AV formation and elongation [255]. Other pathologic conditions, such as cellular starvation, oxidative stress, organelle damage, and protein aggregation, inactivate mTOR and promote autophagy as a protective response [256, 257]. In the brains of AD patients, however, mTOR signaling was shown to be inappropriately active given the toxic environment [258]. Inhibition of the mTOR pathway has thus emerged as an attractive target for therapeutic intervention, with a demonstrated benefit on Aβ levels and cognition in murine models of AD [259].

**Ubiquitin–proteasome system (UPS)**

The UPS is a highly regulated degradation process for cytosolic short-lived and misfolded proteins. As such, it is an important protective mechanism against neurotoxic protein aggregates. Briefly, specific proteins are polyubiquitinated by a series of ligases (E1, E2, and E3) for recognition and degradation by the 26S proteasome complex. Whether UPS dysfunction is a cause or consequence of AD-related degeneration remains unknown. In favor of the former, both ubiquitin conjugation and proteasome activity decline with age and in AD tissue [231, 260, 261]. Areas with reduced proteasome function overlap with those greatly impacted by AD: the hippocampus, nearby limbic structures, and the inferior parietal lobe [231]. Diminished activity of the 26S complex promotes Aβ deposition and perhaps its production as well through increased maturation and trafficking of APP [262, 263]. Taken together, this data could imply that declining proteasome function in aging and disease leaves the brain susceptible to Aβ aggregation. Nonetheless, multiple reports have demonstrated that Aβ accumulation, in
fact, inhibits proteasome activity, possibly by directly binding to the 20S catalytic subunit [238, 263]. Aβ accumulation may then contribute to proteasome dysfunction rather than result from it, although these interactions need not be mutually exclusive.

**Aβ clearance mediated by extracellular chaperones**

Removal of Aβ into the peripheral circulation is thought to facilitate the majority of physiologic Aβ clearance [264]. Transport across the BBB requires a specialized transport system of molecular chaperones. Specifically, members of the LDL receptor (LDLR) family, such as the low-density lipoprotein-related protein 1 (LRP-1) and ATP-binding cassette (ABC) transporters, are primary receptors for Aβ efflux [264]. LRP-1-mediated transport requires the assistance of additional adaptor proteins, and this system in total will be the focus of this section. Transporters that mediate Aβ influx into the brain parenchyma, such as the receptor for advanced glycation endproducts (RAGE), will not be discussed.

**Lipoprotein-related protein 1 (LRP-1)**

Located on the abluminal surface of brain endothelial cells, LRP-1 binds either ApoE-Aβ complexes or Aβ alone [53, 265], subsequently stimulating endocytosis of either species. Notably, once Aβ is contained within endothelial cells, the luminal transport protein ABCB1 facilitates the removal of Aβ species into the vascular lumen [266]. Blocking LRP-1 expression in healthy, non-ADtg mice led to impaired Aβ clearance across the BBB, and consequently, greater Aβ deposition and cognitive deficits [267]. This study may recapitulate some of the consequences of declining LRP-1 expression reported in ADtg mice, AD patients, and aging adults [159, 265, 268]. Additionally, LRP-1 is expressed on neurons, astrocytes, and microglia, facilitating cellular Aβ uptake and lysosomal degradation within these cells [269–271].

**Phosphatidylinositol binding clathrin assembly protein (PICALM)**

PICALM is expressed on endothelial cells, and to a lesser extent, on neurons [272]. PICALM primarily functions as an adapter protein for the transcytosis of the Aβ-LRP-1 complex across the BBB. In addition to its role in Aβ clearance, recent reports show that single nucleotide polymorphisms (SNPs) in the upstream coding region for PICALM are major risk factors for AD [83, 273]. This may indicate that appropriate PICALM function is protective. In support of this, PICALM levels in cortical microvessels of subjects with advanced AD were half the levels measured in age-matched controls. Subjects with the lowest PICALM levels displayed the greatest Aβ burden and cognitive impairment [274].

**Apolipoprotein E (ApoE)**

Under physiologic conditions, ApoE is a carrier protein that maintains cholesterol and phospholipid homeostasis [275]. Major ApoE receptors include LDLR, LRP-1, the very low-density lipoprotein receptor (VLDLR), and ApoE receptor 2 (ApoER2) [276, 277]. However, the exact role of ApoE in AD pathogenesis remains elusive despite mounting evidence from genetic, physiologic, and clinical studies that unequivocally supports the carrier protein’s importance [51, 52, 151, 278–281]. In *in vitro* studies have helped to elucidate the role of ApoE, demonstrating that it binds Aβ directly under certain conditions [282]. It is thought that the resulting ApoE-Aβ complexes bind to and are internalized by LRP-1 for delivery to the vasculature and removal from the brain [53, 68]. Supporting this amyloid-clearing role for ApoE, a recent study revealed that ApoE levels inversely correlated with cerebral Aβ load in non-demented healthy controls [283]. In contrast, however, ApoE was shown to compete with fibrillar or soluble Aβ for uptake and degradation by microglia and astrocytes, respectively [54, 284]. Taken together, the literature suggests distinct mechanisms by which ApoE enhances and hinders Aβ clearance. The effect likely depends on the specific Aβ conformation, the ApoE isoform and its lipidation state, as well as the relative ApoE receptor expression on the target cell [278].

Three isoforms of ApoE exist in humans: Apoε2, Apoε3, and Apoε4 [279]. Evidence suggests that the *APOE2* allele may be protective against AD [151]; conversely, carrying one, or to a greater extent, two *APOE4* alleles significantly increases the risk of developing AD and reduces the age of onset [51, 151, 282]. Furthermore, the *APOE4/4* genotype is associated with accelerated and more pronounced cerebral amyloid pathology and CSF abnormalities [285]. Several pathogenic mechanisms may explain this increased risk associated with Apoε4. First, the rate of vascular Aβ clearance is diminished in those expressing Apoε4 compared to other isoforms [52, 53, 152], perhaps due to its reduced affinity for Aβ [286]. Additionally, Apoε4 can redirect the ApoE-Aβ complex to a different receptor, VLDLR, which has slower internalization kinetics than other LDLRs [53]. The net result is reduced internalization of Aβ by LRP-1, and ultimately reduced Aβ clearance [280, 281, 287]. Apoε4 may also promote damage to the BBB by upregulation of pro-inflammatory signaling through cyclophilin A [153]. In non-demented murine models, Apoε4 led to reduced cerebral blood flow and microvascular...
length, while also increasing BBB permeability [153]. A compromised BBB can reduce vascular Aβ clearance and predispose to further injury through leakage of toxic blood proteins [153, 288]. These destructive outcomes were not observed in mice expressing Apoe2 or Apoe3 [153, 289].

Apoe4 may hinder other important mechanisms of Aβ clearance, namely, intracellular catabolism by neurons and innate immune cells. Specifically, Apoe4 may interfere with these processes by inducing lysosomal leakage or by impeding myeloid cell-mediated clearance [185, 234, 236]. Though ApoE normally has an anti-inflammatory effect, this trait is markedly dampened by expression of Apoe4 on innate immune cells [154]. Crossing APOE4-targeted replacement mice with the 5XFAD ADtg model greatly increased microgliosis and astroglisis surrounding Aβ plaques [290]. Similarly, in cell cultures of microglia and astrocytes isolated from these Apoe4-expressing mice, more pro-inflammatory cytokines were released from these cells in response to soluble oligomeric Aβ than from those expressing Apoe3 [154]. Furthermore, peripheral macrophages expressing Apoe4 exhibited a diminished capacity to phagocytose and clear Aβ when cultured on top of plaque-bearing brain sections of PDAPP mice [185]. It remains unclear whether Apoe4 influences AD predominantly through gain of toxic function, loss of protective function (i.e. vascular/immune cell dysfunction), or both. Further investigation is required to reveal the exact role of ApoE and its isoforms in AD, and the possible therapeutic potential of its manipulation.

**Glymphatic clearance**

The glymphatic system is a pathway of brain-wide waste clearance for small proteins and metabolites. In this pathway, CSF enters the periarterial space and, driven by arterial pulsations, enters the brain parenchyma to exchange with the interstitial fluid (ISF). Bulk flow of CSF/ISF, containing extracellular molecules such as Aβ, are then driven to perivascular spaces for recirculation in the CSF or clearance to peripheral lymphatics [161, 162]. Glymphatic activity is greatest during sleep, with Aβ clearance rates doubling those observed in periods of wakefulness [291]. The glymphatic system was named, in part, for acting as a surrogate to CNS lymphatic drainage, a system the brain traditionally lacked. However, a recent, seminal study has identified meningeal lymphatic vessels for the first time [292, 293]. This groundbreaking discovery calls for a re-evaluation of current notions of the neuroimmune connection, and raises exciting potential explanations of the pathophysiology of Aβ accumulation and defective clearance in some cases.

Water channels known as aquaporin 4 (AQP4) are the key elements in CSF-ISF exchange, and thus clearance through the glymphatic pathway. AQP4 is located on astrocytic end feet and encircles the vasculature. Mice lacking astrocytic AQP4 showed reduced CSF influx by ~70% and decreased interstitial Aβ clearance by ~55–65% [161, 162]. Advanced age also reduced glymphatic clearance rates in murine models, perhaps due to an age-dependent loss of AQP4 polarization [294]. Interstitial solutes may also be cleared directly into the CSF compartment through periarterial pathways flowing opposite to the glymphatic system. These two pathways may not be mutually exclusive; they might be two components of the same system, or their activities may vary in space and time throughout the CNS [264].

**Myeloid cell-mediated phagocytosis**

A growing body of evidence supports the emerging concept that activated inflammatory cells, mainly brain-resident microglia and infiltrating blood-borne monocyte-derived macrophages, are critical for the physiological clearance of Aβ [148, 295–298]. Microglia are tightly associated with Aβ deposits and senile plaques, and early studies have documented their involvement in cellular Aβ uptake [299, 300]. However, these investigations were lacking the capacity to distinguish activated microglia from blood-borne macrophages due to their similar immunophenotype and function. Recruited macrophages were thus inappropriately characterized as part of the microglial pool, and confusion ensued over their unique behavior [296, 301].

Today’s newer methodologies delineate subtle differences in marker expression, allowing for a more accurate categorization and attribution of function to these cell populations. For example, standard CD11b (MAC1), isoelectin B4 (IB4), F4/80, or ionized calcium binding adapter molecule 1 (Iba1) markers in the brain are indistinguishably expressed by both infiltrating monocytes and resident microglia [302, 303]. Yet, the combination of one of these myelomonocytic markers with differential expression levels of CD45 [304, 305], P2RY12 [306], or Ly6C [303] can help differentiate these cell types (Fig. 1a, c). Other approaches may involve fluorescent labeling of peripheral innate immune cells (i.e. green or red fluorescent protein-labeled, GFP or RFP, respectively) or introducing genetic modifications, such as targeted NEP- or ACE overexpression in monocyte cells [145, 146, 191].

Other key developmental and functional differences between microglia and macrophages help distinguish these unique cell types. Microglia originate from hematopoietic stem cells of the yolk sac [307], while infiltrating monocyte-derived macrophages originate from bone marrow...
hematopoietic myelomonocytes [308]. In early post-natal life, microglia participate in synaptic pruning [309]. Later on, they are critical for maintaining CNS homeostasis, regulating immune surveillance, and responding to pathologic changes such as Aβ aggregation [310]. Less is known about CNS monocyte interactions under physiological conditions [311]. A comprehensive comparison of these two cell types is beyond the scope of this manuscript; however, detailed reviews on their unique embryology, development, and immune responses can be found elsewhere [303, 307, 308].

Heterogeneous populations of these immune cells exist in the brain, especially in the diseased state. Their demonstrated clearance capacity varies given the experimental paradigm and the phase of disease studied. Table 3 provides a summary of research on monocytes/macrophages in human AD subjects, while Table 4 briefly describes similar data in rodent models. The discussion that follows describes the phagocytic process mediated by microglia and monocyte-derived macrophages and the conditions in which they differ. When evaluating this data, it is important to keep in mind the difficulties involved in assessing peripheral monocytes and microglia as distinct cell types. Therefore, we cannot rule out the possibility that some investigations illustrating a role for microglia may also include effects of infiltrating monocytes.

### Microglia-mediated phagocytosis

Microglia aid in the normal development, function, and repair of the CNS. In response to injury or other pathological conditions, microglial processes and cell bodies migrate to lesion sites and initiate an immune response to contain and resolve particular insults [123, 124, 299]. Activated microglia are closely associated with senile plaques in both human and ADtg models. While microglia are capable of clearing Aβ in vitro [241, 300, 332–334], their in vivo clearance capacity has been questioned [335–337]. Successful Aβ internalization by microglia has been documented in some cases [338, 339], while others report incomplete processing [239, 240, 335–337]. In support of

**Table 3**  Alzheimer’s disease-related impairments in human myeloid cells

| Study type | Study design | Altered protein/gene | Mo phenotype and Aβ clearance | References |
|------------|--------------|----------------------|-------------------------------|------------|
| HC Mo and MG | Pulse-chase analysis of cytokine impact on Aβ degradation | ↑ IFN-γ, TNF-α, IL-4, IL-10, and TGF-β1 | ↓ Aβ degradation with pro-inflammatory cytokines; ↓ IDE | [312] |
| AD Mo | rt-PCR and flow cytometry analysis of CD33 expression | ↓ CD33 mRNA | ↓ CD33+ Mo in AD Patients; Positive correlation between number of CD33+ Mo and MMSE scores | [313] |
| Inflammatory profile; Mo analysis | | | | |
| Compared Mo from AD patients to HC | ↑ HLA-DR and CD16, MCP-1 plasma levels | ↓ Aβ degradation with anti-inflammatory and regulatory cytokines | | |
| | ↑ CCR2 expression | ↓ Cerebral recruitment of Mo;↑ Granularity by SSC | | |
| AD vs. MCI Mo | Histone acetylation; cytokine release; susceptibility to cell damage | ↑ Inflammatory profile expressing CCR2, IL-6, IL-23, TLRs, MGAT3 and TLR, Cathepsin B, D, S, Activity of β-Galactosidase, α-Mannosidase, β-Hexosaminidase | ↑ Apoptosis; ↑ Aβ phagocytosis by Mo; Impaired phenotype | [125, 127, 229, 243, 315] |
| AD peripheral blood | Microarray assessment of gene expression in blood; blood count | Multiple early changes in gene expression >700 altered in blood from MCI, AD vs. HC | ↑ Mo number in AD vs. HC; ↑ genes encoding cell adhesion molecules and other immune-related genes | [317] |

CCR2 C-C chemokine receptor type 2. CD33 Sialic acid-binding immunoglobulin-like lectin 3. H4K12 histone H4 at lysine 12. HC healthy control. HLA-DR human Leukocyte Antigen–antigen D Related (MHC class II surface receptor). IDE insulin degrading enzyme, IFN-γ interferon-γ, IL-4 interleukin-4, IL-6 interleukin-6, IL-10 interleukin-10, IL-23 interleukin-23. MCI mild cognitive impairment, MCP-1 monocyte chemotactant protein-1. MG microglia. MGAT3 beta-1,4-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase. MIP2 macrophage inflammatory protein 2. MMSE mini-mental state examination (Folstein test)—questionnaire used extensively in clinical and research settings to measure cognitive impairment. Mo/MΦ monocytes/macrophages, rt-PCR reverse transcription polymerase chain reaction, SSC side light-scatter characteristics (flow cytometry—measure of granularity and differentiation), TGF-β1 transforming growth factor-β1, TLRs toll-like receptors, TNF-α tumor necrosis factor-α.
Clearance of cerebral Aβ in Alzheimer’s disease: reassessing the role of microglia and monocytes

the latter, depletion of microglia in three different ADtg mouse models had no effect on fibrillar or soluble Aβ accumulation, indicating that microglia are not chiefly responsible for Aβ clearance in these models [335, 336]. Moreover, aging and toxic conditions in the AD brain render microglia chronically activated. This further reduces their phagocytic capacity and causes a prolonged neuroinflammatory response, including production of reactive oxygen species (ROS), cytokines [e.g. IL-1β, IL-6, TNFα, and transforming growth factor β (TGF-β)] and chemokines [e.g. macrophage inflammatory proteins (MIPs), monocyte chemotactic protein 1 (MCP-1), and C-C chemokine receptor types 3 and 5 (CCL3 and CCL5)] [340–342]. Elevated levels of these mediators have potent neurotoxic effects [343, 344] and correlate with increased Aβ pathology in certain brain regions of human AD patients and transgenic murine (APP/PS1) models [345]. Additionally, recent reports showed that microglia continue to participate in synaptic remodeling in aged mice [346], and can exacerbate synaptic dysfunction by modifying dendritic spine

| Study Type                  | Study design                                                                 | Mo infiltration<sup>a</sup> | Aβ phagocytosis by Mo | Aβ levels | Neuroinflammation | Cognition | References                  |
|-----------------------------|------------------------------------------------------------------------------|-------------------------------|-----------------------|-----------|-------------------|-----------|----------------------------|
| BM Transplantation          | GFP-labeled BM cells in ADtg                                                   | ✓                             | ✓                     | ↓         | –                 | –         | [144, 146, 295, 318, 319]   |
| Blood Enrichment of BM-derived Mo | Treated ADtg mice with M-CSF or infusion of CD115<sup>+</sup> GFP-labeled Mo | ✓                             | ✓                     | ↓         | ↓                 | ↑         | [144, 146, 320, 321]      |
| Immune Modulation           | MOG45D-DC or GA immunization of ADtg                                           | ✓                             | ✓                     | ↓         | ↓                 | ↑         | [144, 148, 297]           |
| Genetic Manipulation in Mo/MG | Infusion of GFP-labeled CD11b<sup>+</sup> WT- or NEP-overexpressing Mo from healthy murine BM donors in ADtg | ✓                             | –                     | ↓         | –                 | –         | [146]                      |
|                             | Targeted ACE overexpression of CD115<sup>+</sup> Mo/MG in ADtg                | ✓                             | ✓                     | ↓         | ↓                 | ↑         | [145, 191, 227]           |
|                             | Targeted blockade of TGF-β and Smad2/3 signaling in innate immune cells of ADtg | ✓                             | ✓                     | ↓         | ↓                 | –         | [322]                      |
|                             | Upregulation of TREM2 in ADtg                                                  | –                             | ✓                     | ↓         | ↓                 | ↑         | [323]                      |
|                             | TREM2 knockout in ADtg and stroke models                                       | X (CD45<sup>+</sup>Ly6C<sup>+</sup>) | ✓                     | ↓         | ↓                 | –         | [324, 325]                |
|                             | SCARA1 upregulation                                                           | –                             | ✓                     | ↓         | –                 | –         | [326]                      |
|                             | Cultured WT macrophages on plaque-bearing sections of murine models           | –                             | ✓                     | ↓         | –                 | –         | [185]                      |
|                             | CCL2 (MCP-1) and APP expression effects on Aβ clearance in primary BM-derived macrophages | –                             | ✓                     | ↓         | –                 | –         | [327]                      |
| Ablation                    | Depletion of CD11c<sup>+</sup> BM-derived myeloid cell or perivascular MΦ in ADtg | X                             | X                     | ↑         | –                 | –         | [296, 297, 328, 329]      |
| Inhibited Mo Infiltration   | CCR2-deficient Mo in ADtg                                                     | X                             | X                     | ↑         | –                 | –         | [298, 330, 331]           |

*Aβ* amyloid-beta protein, *ACE* angiotensin-converting enzyme, *ADtg* transgenic murine models of Alzheimer’s disease, *APOE* apolipoprotein E, *APP* amyloid-precursor protein, *BM* bone marrow, *CCL2 C-C* chemokine ligand 2, alternatively named monocyte chemotactic protein 1 (MCP-1), *CCR2 C-C* chemokine receptor type 2, *GA* glatiramer acetate, *GFP* green fluorescent protein, *M-CSF* macrophage colony-stimulating factor, *MΦ* macrophages, *MG* microglia, *Mo* monocytes, *MOG45D-DC* dendritic cells loaded with altered myelin oligodendrocyte glycoprotein-derived peptide (MOG45D; a weak agonist and a non-encephalitogenic variant of MOG<sub>35-55</sub> peptide), *NEP* neprilysin, *SCARA1* class A1 scavenger receptor, *TGF-β* transforming growth factor-β, *WT* wild type

<sup>a</sup>Increased Mo infiltration per Aβ plaques

<sup>b</sup>APoE-dependent effect
density and inappropriately engulfing endangered neurons [310, 347]. The aberrant microglial-mediated engulfment of dysfunctional synapses in ADtg models was mediated by components of the complement cascade (i.e. C1q, C3, CR3). Considering the recent genetic data linking certain SNPs in CR1 to the development of AD (Table 1), this work provides further support for the role of the immune system in AD.

Although this indicates a detrimental role for microglia in the AD brain, plaque-associated microglia have been shown to degrade scar tissue proteins with secreted proteases, clear cellular debris, and recruit the adaptive arm of the immune system to stimulate or regulate effective local immune responses [148, 348]. A recent investigation using in vivo two photon imaging also demonstrated that early on, microglia form a protective barrier around developing plaques, preventing accumulation of Aβ42 protofibrils and associated local neuritic damage [349]. Remarkably, a recent study demonstrated that stimulating hippocampal interneurons at frequencies consistent with gamma oscillations alters microglial phenotype and behavior in the 5XFAD model [350]. A 1-hour delivery of 40 Hz stimulation lowered global Aβ levels and modified microglial gene expression so that they more efficiently engulfed Aβ. Based on the available evidence, microglia cannot be labeled as either neuroprotective or neurotoxic. Instead, microglia co-exist in a range of functional states: ramified-resting under physiological conditions, classically and alternatively activated in response to injury, or dystrophic and neurotoxic in aging and chronic inflammation. These phenotypes are highly sensitive to the changes in CNS composition that accompany senescence and the neurodegeneration seen in AD [351]. Current research posits that in early stages of disease, healthy microglia comprise the first line of defense in restricting Aβ pathology, effectively clearing fibrillar and soluble Aβ through phagocytosis and proteolytic processing [123]. However, aged and diseased microglia in the AD brain have a markedly reduced capacity to do so [335, 337, 339, 349]. Taken together, it is not surprising that microglia have become candidates for potential disease-modifying therapies.

Monocyte/macrophage-mediated Aβ phagocytosis

Like microglia, monocyte-derived macrophages are professional phagocytes that support normal tissue function. However, microglial senescence in AD suggests that monocytes may have unique, complementary functions in the disease state, although this conclusion is highly controversial [303, 352–355]. Supporting evidence from genetic and physiological studies of human peripheral blood monocytes (PBMCs) highlights the importance of healthy, functional monocytes in mitigating disease (see summary of studies in Table 3). PBMCs isolated from AD patients exhibit poor differentiation, impaired phagocytosis, and increased pro-inflammatory cytokine production in response to soluble Aβ [125, 127, 229, 243, 315, 356] (Table 3). Further, rare variants of CD33 and TREM2, two genes negatively impacting the phagocytic and Aβ clearance capacity of monocytes, confer a greater risk of developing AD (Table 1) [33, 34, 64, 96, 155]. It remains to be elucidated whether the altered monocyte phenotype is a cause or consequence of disease.

Receptor-mediated Aβ phagocytosis: molecular machinery

Despite key differences highlighted previously, microglia and monocyte-derived macrophages do overlap in terms of phagocytic receptor expression and behavior [296, 301]. An extensive body of work describes under which conditions and by which mechanisms these cells are capable of engulfing distinct Aβ species. For example, microglia have been shown to phagocytose fibrillar Aβ42 and Aβ40 under in vitro [239, 299, 300, 334, 357], in vivo [358, 359], and ex vivo experimental conditions [357, 360]. However, the mechanism underlying soluble Aβ uptake is less clear. Some argue that microglia phagocytose soluble Aβ42 as they do fibrillar forms [332, 361], while others suggest uptake occurs through fluid-phase macropinocytosis [333]. These two processes may not be mutually exclusive; more precise methods of isolating distinct soluble oligomeric forms may reveal assembly dependent interactions with microglia. Similarly, studies using PBMCs isolated from healthy patients have demonstrated the ability of monocytes to effectively bind [356] and engulf soluble and fibrillar Aβ42 [125, 185, 315]. The following sections describe the major phagocytic receptors engaged in myeloid cell-mediated physiologic clearance of Aβ. Whenever possible, the discussion delineates between uptake of soluble oligomeric Aβ42, fibrillar Aβ42, and other conformations or alloforms. This distinction is particularly relevant given the varying toxicities of different Aβ species.

Toll-like receptors (TLRs)

TLRs are a family of pattern recognition receptors with distinct functions in the innate immune response. TLR2 and TLR4, in particular, were shown to be indirectly involved in Aβ phagocytosis through the formation of a receptor complex with CD14 and the subsequent activation of microglia and monocytes. Inhibiting or deleting any component of the CD14-TLR receptor complex in human monocytes or murine microglia diminished the production
of pro-inflammatory cytokines and phagocytosis of fibrillar Aβ42 [362, 363].

Macrophage scavenger receptor 1 (SCARA1)

SCARA1 (alternatively named MSR-1, CD204, type-A1 scavenger receptor, and SR-A) is one of the principal receptors involved in Aβ uptake by immune cells. It is expressed on human and rodent macrophages [364], microglia [299, 332], and human monocytes [365]. SCARA1 can bind both soluble and fibrillar Aβ42 in vitro [326, 332, 365] and facilitate its subsequent uptake. Lack of functional SCARA1 in murine microglia and monocytes reduced Aβ42 uptake by a range of 50%-65% in several experimental preparations [326, 366]. Glatiramer acetate (GA), an altered myelin-derived antigen with demonstrated immunomodulatory benefits in ADtg mice [9, 144, 148, 348, 367], was shown to upregulate surface expression of SCARA1 on monocyte-derived macrophages and to increase Aβ uptake by this cell population [144]. Immunization with the FDA approved drug, GA, is an intriguing therapeutic strategy and will be discussed further below.

The importance of SCARA1 function in Aβ clearance has also been established in vivo. SCARA1-deficient APPsw/PS1ΔE9 transgenic mice exhibited increased mortality and a significant elevation in surface area fraction stained for Aβ compared to control ADtg mice [326]. Increased microglial expression of SCARA1 around Aβ plaques has been demonstrated in multiple ADtg models [368, 369] as well as in human AD brains [370]. SCARA1 expression on CNS phagocytes appears to have a neuroprotective role in restricting toxic forms of Aβ and mitigating disease progression.

CD36

CD36 is a type B scavenger receptor expressed on the cell surface of monocytes, macrophages, astrocytes, and neurons [371]. CD36 has been shown to mediate phagocytosis of fibrillar Aβ42 through interactions with two distinct receptor complexes acting as a functional unit [334, 368, 371]. CD36-deficiency prevents microglial accumulation in response to stereotaxic intracerebral injections of fibrillar Aβ [372], and antagonists of CD36 effectively block phagocytosis of fibrillar Aβ42 in microglia cell lines [334]. Like SCARA1, expression of CD36 is substantially increased in monocyte-derived macrophages in response to GA stimulation, which may contribute to their superior Aβ clearance ability compared to untreated macrophages [144] (Fig. 1b; Table 4). CD36 was also shown to bind soluble Aβ42 directly [361, 373], although it may play a redundant role in soluble Aβ42 clearance [326]. Specific knockdown or inhibition of CD36 demonstrated a sustained ability of microglia to phagocytose soluble Aβ42 with continued expression of other scavenger receptors [332, 361].

CD36 adequately demonstrates the dichotomous role of microglia in AD pathogenesis. While CD36 confers neuroprotection through induction of Aβ removal, it also activates the NLRP3 inflammasome in microglia and stimulates pro-inflammatory cytokine release (i.e. interleukin IL-1β and ROS). Thus, microglia may contribute to the toxic environment that induces their own impairment [334, 361, 373, 374]. Moreover, a recent study has demonstrated that the soluble Aβ42-induced inflammatory milieu directly inhibits microglial phagocytosis of Aβ42 fibrils and down-regulates CD36 expression in vitro [374]. In sum, it seems the ability of CD36 to initiate Aβ uptake is differentially regulated by multiple toxic species that accumulate in AD brains.

TREM2

The triggering receptor expressed on myeloid cells 2 protein is a single-pass type 1 transmembrane protein that is part of the immunoglobulin superfamily. Ligands of this receptor include anionic carbohydrates, phospholipids, and apolipoproteins such as ApoE [375–377]. TREM2, along with the protein DAP12, forms a signaling complex that is responsible for the activation of immune responses in myeloid cells including microglia, macrophages, and monocytes [378]. In AD, however, the predominant TREM2-expressing cell type has been contested [324, 376].

GWASs have recently implicated the R47H variant of TREM2 as an AD risk factor in multiple populations [96, 155]. In a post-mortem analysis of AD and control brains with and without the R47H variant, the mutation was associated with greater levels of pro-inflammatory markers and increased amyloid load in all brain areas examined [102]. Other TREM2 risk alleles have also been identified, including R62H and D87N [96, 155]. Remarkably, these mutations and others occur exclusively in the ligand-binding domain of the protein and diminish affinity of the mutant TREM2 to its ligands [377]. It was further demonstrated that myeloid cells can clear Aβ directly through TREM2-mediated uptake of lipoprotein-Aβ complexes, modeling the ApoE-Aβ interactions observed in vivo [377]. Moreover, monocytes isolated from AD patients with the R62H variant were unable to clear lipoprotein-Aβ complexes as efficiently as healthy controls. These findings imply that microglia and monocytes require a functional TREM2 protein to appropriately phagocytose Aβ.

Studies utilizing ADtg mouse models, however, point to a much more complex role for TREM2 than previously
thought [323, 324, 376]. In one study, TREM2 knockout in APP/PS1 mice greatly ameliorated disease progression [324], while two other investigations successfully demonstrated TREM2-expressing immune cells containing AD pathology [323, 376]. The evidence appears contradictory; however, TREM2-modulated neuroinflammation and Aβ clearance may be highly context-dependent, influenced by the immune cell type and the inflammatory milieu in which it is expressed. In light of this, a recent study has shown that TREM2-deficient microglia and monocyte-derived macrophages phagocytose less fibrillar Aβ42 compared to wildtype cells, an impairment partially rescued by therapeutic anti-Aβ antibodies. Antibody-coated Aβ greatly enhanced phagocytosis by both TREM2 knockouts and wildtype cells, although clearance by mutant cells lagged behind controls under all conditions [325]. This finding has important implications for the efficacy of Aβ-targeted immunotherapies in patients with TREM2 mutations, yet further research is needed to fully elucidate these relationships.

### CD33

CD33 is a member of the sialic acid-binding immunoglobulin-like lectins (SIGLEC) family, expressed on myeloid cells [65, 379]. In general, it is thought to dampen the immune response perhaps by inhibitory signaling through immunoreceptor tyrosine-based inhibition motifs (ITIM) [380]. In the brains of AD patients, CD33-positive microglia are enriched relative to age-matched controls and correlate with greater Aβ42 levels and plaque burden [65]. The diminished capacity of CD33-expressing microglia to phagocytose Aβ42 is thought to explain this relationship. In support of this, possession of the newly discovered rs3865444C risk allele [33, 34] results in a sevenfold increase in CD33 expression on monocytes with a significant reduction in ability to phagocytose Aβ42. Monocytes isolated from young individuals with the rs3865444C risk allele also displayed an Aβ42 phagocytic deficit [64]. Enriched monocytic CD33 expression actually mediated the relationship between this risk allele and higher amyloid plaque burden in AD brains [64]. Conversely, the protective rs3865444A allele dampens CD33 expression and increases the proportion of CD33 molecules that lack a SIGLEC-specific region responsible for phagocytosis inhibition [379]. These findings provide proof of impaired monocyte-mediated interactions with Aβ and enhanced disease risk. AD-related immune deficits are thus not solely driven by senescence or the disease process itself. Rather, monocyte phagocytic impairment may far precede Aβ deposition, as seen in these cases, and arguably predisposes to greater amyloid accumulation and lifetime risk.

### Role of monocytes in AD: evidence and controversy

Despite the surging data favoring a critical role of monocytes in AD pathophysiology, it is important to acknowledge the contradictory evidence in the field surrounding monocyte-mediated Aβ clearance in chronic neurodegenerative diseases. Major questions remain. (1) Under what conditions do monocytes infiltrate the CNS? (2) Do monocytes and macrophages behave differently from microglia once in the CNS parenchyma, especially in their ability to resist misfolded Aβ forms? (3) Is the neuroprotection exhibited by monocytes a predominantly peripheral blood or a local effect? And (4) Is the effect cell-mediated, molecular or plasma-mediated, or both? The following sections address these controversies given the available literature and identify methodological discrepancies that may have generated some confusion.

### Cerebral infiltration of monocytes in murine models of Alzheimer's disease

Monocyte infiltration in AD was first documented by seminal studies transplanting GFP-labeled bone marrow cells into irradiated ADtg mice [295–297, 318]. Monocytes were shown to preferentially home to Aβ targets and participate in the clearance [295–297, 318]. The applicability of these studies to normal physiology was later questioned due to the use of whole body irradiation (including brain) and bone marrow transplantation; the former in particular may artificially enhance monocyte infiltration into the brain parenchyma [355, 381]. Specifically, irradiation is known to induce transient BBB leakage, permitting greater passage of cells and blood contents. In addition, whole marrow transplantation increases the number of progenitor cells in the circulation.

To further elucidate the effects of irradiation, the GFP-transplantation paradigm was repeated, this time shielding the heads of recipient mice to conserve BBB integrity. This procedure reduced monocyte infiltration into the CNS, and called into question the conditions necessary for monocyte recruitment [330]. However, several investigations have successfully demonstrated spontaneous monocyte infiltration in the absence of irradiation, genetic manipulation, or chemotherapy (Table 4) [144, 146]. These experiments enriched the peripheral circulation with either CD11b+ or CD115+ monocytes from the bone marrow of young adult wildtype mice, rather than whole blood marrow, eliminating the additional confounder of increased progenitor cell numbers seen in earlier studies. Importantly, blood enrichment with GFP monocytes in age-matched wildtype (non-ADtg) animals did not cause recruitment of monocytes to the CNS [144, 146], implicating that a diseased-brain is a...
precondition for their cerebral recruitment. Taken together, brain irradiation is neither necessary nor sufficient for monocyte recruitment. Rather, several other conditions are consistently required, at least in ADtg models—namely, the presence of amyloid pathology, especially soluble oligomeric or fibrillar Aβ42 forms [382, 383], and binding of the monocytic surface receptor CCR2 to its ligand, MCP-1 [126, 298, 384, 385].

The mechanism by which cerebral amyloid accumulation induces monocyte infiltration is multifactorial. Vascular Aβ deposition can directly damage the vessel wall [386] and allow greater passage of monocytes into the parenchyma. Indeed, the presence of a leaky BBB was confirmed in 40–60% of AD patients [387, 388]. Furthermore, the Aβ-induced immune response alters the expression and production of inflammatory cytokines, chemokines, and their receptors [123, 311, 340–342]. The expression of MCP-1, a critical signaling factor for monocyte recruitment, is upregulated near Aβ plaques, on microglia, and on microvessels in the brains of AD patients and ADtg mice [127, 384, 385]. It is therefore postulated that the AD brain, and specifically chronically activated and overwhelmed microglia, solicit additional assistance from peripheral monocytes through MCP-1 signaling [126, 144, 148, 191, 297, 311, 389]. Other signaling cascades remain poorly understood.

Depletion or enrichment of myeloid cells: impact on cerebral Aβ burden

Modulation of monocyte recruitment to the CNS clearly demonstrates the significant contribution of monocyte-derived macrophages to Aβ clearance. Blocking CCR2 signaling [298, 330, 331] or selectively ablating these cells in the blood [296, 297, 328] greatly accelerates Aβ accumulation in ADtg models. Conversely, inducing monocyte recruitment by lipopolysaccharide (LPS) stimulation, immunization, or monocyte engraftment significantly reduces parenchymal and vascular amyloid pathology in transgenic mice [144–146, 148]. These investigations coupled with compelling in vitro data [144, 241] led to the conclusion that monocyte-derived macrophages, compared to their resident counterparts, possess a superior ability to clear fibrillar Aβ in AD (Fig. 1), resolving inflammation in spite of the toxic environment [240, 241, 296, 297, 300, 390].

Other studies utilizing microglial ablation techniques challenge this assumption. Crossing ADtg mice with the CD11b-HSVTK model, in which the thymidine kinase of the herpes simplex virus is expressed under the CD11b promoter, allows for elimination of local, proliferating myeloid cells upon intracerebroventricular administration of ganciclovir. Peripheral GFP-labeled macrophages can then repopulate the CNS, introduced by either transplantation [354] or parabiosis with an actin-enhanced GFP partner [353]. In both cases, repopulation did not augment plaque burden, insoluble Aβ, or soluble forms. Importantly, macrophages were diffusely spread across the parenchyma, in stark contrast to the plaque-associated microglia of control mice and the demonstrated plaque-homing abilities of monocytes in other models [353, 354]. Given the inability of re-populating monocytes to clear Aβ, these studies concluded that monocytes do not play a significant role in restricting amyloid pathology. However, it is possible that microglial depletion critically alters the delicate milieu required to induce monocyte phagocytic and anti-inflammatory properties. Indeed, the interplay between microglia, astrocytes, monocytes, and molecular mediators such as scar tissue proteins [i.e. chondroitin sulfate proteoglycans (CSPGs)], has been shown to attract these cells to the lesion sites and induce phenotypic shifts needed for protection in various disease states [144, 145, 148, 191, 297, 348, 367, 391]. Specifically, senescent, plaque-associated microglia are known to release MCP-1 required for monocyte recruitment [126, 298, 384, 385, 389, 392]. In addition, the impact of ganciclovir-induced neurotoxicity is poorly understood. From these repopulation studies, it is apparent that elimination of microglia impacts monocyte phenotype and function, and as such, these findings may not be representative of monocyte behavior in the natural progression of disease.

It is undeniable though that certain conditions do in fact enhance the migratory and Aβ clearing capacity of infiltrating monocytes over their resident counterparts. In particular, ADtg mice immunized with the myelin-derived peptides MOG45D or GA exhibited reduced Aβ levels and neuroinflammation, attributable to the increased recruitment of anti-inflammatory monocytes that directly engulfed Aβ [144, 148]. Other immunomodulatory approaches involving targeted overexpression of Aβ-degrading enzymes to [145, 146, 191] or genetic manipulation of [322] peripheral monocytes have demonstrated similar monocyte-mediated abrogation of Aβ deposition [Table 4]. These interventions may form the basis of promising, disease-modifying therapies that will be discussed further below.

Peripheral effects of monocytes on Aβ clearance

Recognition of the heterogeneity of different monocyte subtypes has emerged from recent studies that identified new functional biomarkers for myelomonocytic cells. An immunohistochemical and activity-based distinction has been proposed between murine monocyte subsets: an inflammatory (Ly6C<sup>hi</sup>CX3CR1<sup>low</sup>CCR2<sup>±</sup>) type pertaining to CNS recruitment and parenchymal Aβ clearance, and a patrolling (Ly6C<sup>lo</sup>CX3CR1<sup>hi</sup>CCR2<sup>±</sup>) type that remains
associated with the vasculature [303, 308]. The discussion thus far has exclusively focused on the local effects of the inflammatory subset and their ability to reduce cerebral Aβ load in the parenchyma through cellular uptake and enzymatic degradation. However, mounting evidence suggests an additional role for patrolling monocytes and perivascular macrophages in the regulation of cerebral amyloid angiopathy (CAA), a disease process in which amyloid plaques accumulate within the walls of small cerebral blood vessels [129, 160]. CAA is seen in over 80% of AD patients and is frequently associated with microhemorrhages and cognitive deficits. Real-time in vivo imaging of APP/PS1 mice has elegantly demonstrated that patrolling monocytes are in fact attracted to and crawl along Aβ-positive veins, where they engulf Aβ and subsequently recirculate into the bloodstream [329]. To further confirm their role in perivascular Aβ clearance, depletion of patrolling monocytes substantially increased Aβ levels in the vasculature as well as in the cortex and hippocampus [329]. A proposed equilibrium of Aβ clearance exists between the different CNS-associated compartments, including the brain parenchyma, perivascular spaces, CSF, and peripheral blood [328, 393, 394]. Thus, the recirculation of Aβ-containing monocytes to the periphery may effectively pull other Aβ species out of the parenchyma—a process termed the peripheral sink effect.

In addition to monocytes and macrophages in the perivascular space, recent data suggest that the activity of these cells in the peripheral blood may be pivotal for the regulation of neuroinflammation associated with AD and for inducing neuronal regeneration [144, 148, 163, 348, 367, 395–397]. Murine parabiosis studies, in which the vasculatures of two mice are joined, have effectively illustrated the impact of peripheral immune cells and, moreover, blood-soluble immune mediators on brain health. Joining the vasculatures of wildtype and ADtg mice, either before or after the onset of Aβ deposition, reduced Aβ plaque burden in the cortex and hippocampus of the ADtg parabiont, while also attenuating neuroinflammation, hyperphosphorylated tau, and neuronal apoptosis [397]. This was achieved in the absence of monocyte infiltration or CNS manipulation of known Aβ clearance pathways. It is therefore inferred that effective Aβ removal in murine models can be achieved by several mechanisms: either by blood enrichment of wildtype peripheral monocytes to boost infiltration and clearance of Aβ from brain parenchyma or by replacement and repair of the blood-soluble milieu to induce beneficial phenotypic changes in brain parenchymal cells that promote Aβ clearance. In support of the latter, earlier studies of parabiosis between young and old wildtype mice demonstrated increased synaptic plasticity, neurogenesis, and cognitive capacity in the older parabionts when sharing blood with young mice [395, 396]. This effect was attributed to the specific milieu in the blood of the younger mice rather than infiltration of peripheral immune cells [395]. Indeed, monocytes release small, soluble mediators, such as cytokines and chemokines, which can traverse the BBB and enter the brain parenchyma. Monocytes were also shown to promote anti-inflammatory behavior of surrounding microglia and astrocytes in several other disease models [144, 145, 148, 191, 297, 348, 367, 391]. Further investigation is greatly needed to understand the signaling that takes place in these models.

### Therapeutic effects of peripheral monocytes and macrophages

Given the believed function of monocytes in AD etiology and the ease of access to the peripheral blood, modulation of monocyte phenotype and behavior represents a promising therapeutic target. Though not yet translated into clinical practice, recent investigations in murine models highlight the potential benefit of enhancing monocyte recruitment to the AD brain.

Stimulation with two distinct exogenous compounds has been successful in promoting Aβ clearance. Dietary curcumin, a major component of the spice turmeric, directly interacts with oligomeric and fibrillar Aβ [398] and may enhance Aβ phagocytosis by human PBMCs [315, 399]. Additionally, injections of the macrophage colony-stimulating factor (M-CSF) into APPswe/PS1 mice prior to signs of cognitive impairment had a number of positive effects. These included increased circulating levels of CD45+/CD11b+/CD115+ monocytes and phagocytic activity of Aβ by Iba-1+ immune cells in brain parenchyma [320], leading to decreased size and density of Aβ plaques, and prevention of learning and memory deficits [321].

As mentioned above, peripheral immunization with DCs loaded with MOG45D (MOG45D-DC) or with GA also had profound effects on the function of innate immune cells, which consequently reduced various pathological features of AD. In ADtg mice, MOG45D-DC immunization increased CNS recruitment of anti-inflammatory macrophages, demonstrated by reduced TNF-α and increased IL-10 and TGF-β expression, that efficiently phagocytosed Aβ [148]. As a result, these mice showed restricted vascular and parenchymal Aβ deposits and reduced soluble Aβ1-42 levels, as well as increased expression of the Aβ-degrading enzyme MMP-9. GA immunization of ADtg mice yielded the same beneficial immunomodulatory and plaque-clearing effects [144, 297, 348], while also promoting neurogenesis and preservation of synapses and cognitive function [144]. In agreement with these findings, several other studies have shown that suppression of regulatory T-cells, either via peripheral blockade of the programmed cell

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death protein-1 (PD-1) [400] or of TGF-β signaling in monocyte-derived macrophages [322], enhanced monocyte recruitment to the brain in ADtg mice, and resulted in Aβ removal and improved cognitive performance [322, 400].

Other methods of immune modulation include adoptive transfer of healthy monocytes and bone marrow transplantation. Infusion of wildtype CD115+ monocytes to the peripheral blood of ADtg mice stimulated their spontaneous migration to amyloid lesions in the absence of irradiation, genetic manipulation, or chemotherapy. Treated mice exhibited reduced cerebral Aβ protein levels and astrogliosis, preserved pre-synaptic integrity, and ameliorated cognitive deficits [144]. Likewise, bone marrow transplants from wildtype donors increased monocyte recruitment to the CNS at sites of amyloid accumulation, while also reducing plaque burden [295, 297, 318].

Because peripheral monocytes were shown to cross the BBB and home to sites of Aβ accumulation, they can function as a delivery system of therapeutic agents. Targeted overexpression of either NEP or ACE has proven beneficial in abrogating AD progression in murine models. Injecting 9-month-old ADtg mice with NEP-expressing monocytes completely prevented further Aβ deposition when compared to untreated ADtg mice or those infused with monocytes containing inactive NEP [146]. Similarly, targeted overexpression of ACE to monocytic cells in the bigenic APP/PS1 mouse model of AD markedly reduced both soluble and insoluble levels of Aβ12, limited plaques and astrogliosis, and preserved cognitive function [145, 191].

Conclusion

Aβ clearance is a complex, multifactorial process, requiring the collaboration of various systems and cell types. Aβ can be removed to the peripheral circulatory or lymphatic systems by transport across the BBB or by absorption from the CSF and ISF. While innate immune cells are known to phagocytose and degrade fibrillar Aβ, these cells were only recently shown to engulf and clear soluble Aβ species as well. It is still unclear whether Aβ accumulation is a cause or consequence of disease. However, mounting evidence has shown that increased cerebral Aβ burden is the earliest pathognomonic event in AD. Moreover, soluble, oligomeric Aβ was shown to directly incite nerve and synaptic damage, leading to impaired neuronal function. In the late-onset, common cases of AD, Aβ buildup is attributed to defective clearance, rather than to its overproduction. The observed deficiency could result from impairments in any one of the removal processes or, more likely, a combination of minor clearance deficits and compounding risk factors that varies from patient to patient. Modulation of clearance mechanisms may be an important early strategy for curtailing Aβ accumulation and disease progression.

As our knowledge of AD continues to expand, so does a body of evidence that supports a key role for innate immune cells, especially monocyte-derived macrophages, in Aβ removal, local immune regulation, and repair. Bone marrow-derived monocytes can cross the BBB and clear Aβ through cellular uptake and enzymatic degradation, perhaps even more efficiently than resident microglia. The clearance process is, again, complex. Phagocytosis requires the coordination of many surface receptors (e.g. TLRs, integrins, scavenger receptors) for recognition and uptake, followed by intracellular trafficking, ultimately to lysosomes, for degradation. Monocytes, macrophages, and microglia also mediate extracellular Aβ degradation through surface expression or release of various proteases, such as ACE, IDE, NEP, and MMP-9. These functions were reported to be markedly impaired in peripheral monocytes isolated from AD patients. It is possible that the observed deficiency is a consequence of immune senescence and AD-related degeneration, or perhaps their dysfunction is a direct contributor to disease development. In support of the latter, possession of a rare variant of the AD-associated CD33 gene impacts the phagocytic capacity of monocytes isolated from young adult patients, indicating that this particular functional deficit is present throughout life. Other GWAS data have linked multiple immune-related risk factors to AD. Known relationships between the major risk gene TREM2 and monocyte/microglia phagocytic function offer a compelling demonstration of the immune system’s impact in AD.

Aggregates of misfolded Aβ are known to trigger a prolonged neuroinflammatory response that is tightly associated with synaptic dysfunction and cognitive decline. Enhancing cerebral recruitment of monocytes through either peripheral infusion or immunization with altered myelin-derived antigens was shown to temper these degenerative changes in murine models. Specifically, monocytes were able to efficiently clear Aβ and resolve the resulting astrogliosis and neuroinflammation, thereby preserving synaptic integrity and cognitive function. Immunomodulation approaches that enhance cerebral recruitment of neuroprotective monocytes hold great promise as disease-modifying therapeutic interventions and represent a valuable target for further application and translation.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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References

1. Hebert LE, Weuve J, Scherr PA, Evans DA (2013) Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. Neurology 80(19):1778–1783. doi:10.1212/WNL.0b013e31828726f5
2. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M (2015) World Alzheimer Report 2015: the global impact of dementia. Alzheimer’s Disease International, London
3. Selkoe DJ (2002) Alzheimer’s disease is a synaptic failure. Science 298(5594):789–791. doi:10.1126/science.1074069
4. Selkoe DJ (2001) Alzheimer’s disease: genes, proteins, and therapy. Physiol Rev 81(2):741–766
5. Holmes BB, Diamond MI (2014) Prion-like properties of Tau protein: the importance of extracellular Tau as a therapeutic target. J Biol Chem 289(29):19855–19861. doi:10.1074/jbc.R114.549295
6. Jucker M, Walker LC (2013) Self-propagation of pathogenic protein aggregates in neurodegenerative diseases. Nature 501(7465):45–51. doi:10.1038/nature12481
7. Selkoe DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer’s disease at 25 years. EMBO Mol Med 8(6):595–608. doi:10.15252/emmm.2016066210
8. Meli G, Lecci A, Manca A, Krako N, Prina M (2015) Alzheimer’s disease is a synaptic failure. Science 349(6248):1664–1668. doi:10.1126/science.aaa0568
9. Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL, Schwartz M, Farkas DL (2011) Identification of amyloid plaques in retinas from Alzheimer’s patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. NeuroImage 54 Suppl 1:S204–217. doi:10.1016/j.neuroimage.2010.06.020
10. Koronyo Y, Salumbides BC, Black KL, Koronyo-Hamaoui M (2012) Alzheimer’s disease in the retina: imaging retinal abeta plaques for early diagnosis and therapy assessment. Neurodegener Dis 10(1–4):285–293. doi:10.1159/000335154
11. La Morgia C, Ross-Cisneros FN, Koronyo Y, Hannibal J, Gallassi R, Cantalupo G, Sambati L, Pan BX, Tozer KR, Barboni P, Provini F, Avanzini P, Carbonelli M, Pelosi A, Chui H, Ligugui R, Baruzzi A, Koronyo-Hamaoui M, Sadun AA, Carelli V (2016) Melanopsin retinal ganglion cell loss in Alzheimer disease. Ann Neurol 79(1):90–109. doi:10.1002/ana.24548
12. Tsai Y, Lu B, Ljubimov AV, Girman S, Ross-Cisneros FN, Sadun AA, Svendsen CN, Cohen RM, Wang S (2014) Ocular changes in TgF344-AD rat model of Alzheimer’s disease. Invest Ophthalmol Vis Sci 55(1):523–534. doi:10.1167/iovs.13-12888
13. Hart NJ, Koronyo Y, Black KL, Koronyo-Hamaoui M (2016) Ocular indicators of Alzheimer’s: exploring disease in the retina. Acta Neuropathol (Berl) 132(6):767–787. doi:10.1007/s00401-016-1613-6
14. Querfurth HW, LaFerla FM (2010) Alzheimer’s disease. N Engl J Med 362(4):329–344. doi:10.1056/NEJMra0909142
15. Hardy J, Selkoe DJ (2002) The amyloid hypothesis of Alzheimer’s disease: progress and problems on the road to therapeutics. Science 297(5580):353–356. doi:10.1126/science.1072994
16. Spirling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH (2011) Toward defining the preclinical stages of Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. Alzheimer’s Dement J Alzheimer’s Assoc 7(3):280–292. doi:10.1016/j.jalz.2011.03.003
17. Haass C, Caether C, Thnarakaran G, Sisodia S (2012) Trafficking and proteolytic processing of APP. Cold Spring Harb Perspect Med 2(5):a006270. doi:10.1101/cshperspect.a006270
18. Haass C, Hung AY, Selkoe DJ, Teplow DB (1994) Mutations associated with a locus for familial Alzheimer’s disease result in alternative processing of amyloid beta-protein precursor. J Biol Chem 269(26):17741–17748
19. Zigman WB, Devenny DA, Krinsky-McHale SJ, Jenkins EC. Urv TK, Wegiel J, Schupt N, Silverman W (2008) Alzheimer’s disease in adults with down syndrome. Int Rev Res Ment Retard 36:103–145. doi:10.1016/j.ierr.2008.004-9
20. Borchelt DR, Thinakaran G, Eckman CB, Lee MK, Davenport F, Ratovitsky T, Prada CM, Kim G, Seeckins S, Yager D, Slunt HH, Wang R, Seeger M, Levey AI, Gandy SE, Copeland NG, Jenkins NA, Price DL, Younkin SG, Sisodia SS (1996) Familial Alzheimer’s disease-linked presenilin 1 variants elevate Abeta1-42/1-40 ratio in vitro and in vivo. Neuron 17(5):1005–1013
21. Karch CM, Goate AM (2015) Alzheimer’s disease risk genes and mechanisms of disease pathogenesis. Biol Psychiatry 77(1):43–51. doi:10.1016/j.biopsych.2014.05.006
22. Nicolas G, Wallon D, Charbonnier C, Quenez O, Rousseau S, Richard AC, Roelet-Lecrub A, Couant S, Le Guennec K, Baqc D, Garnier JG, Olaro R, Boland A, Meyer V, Deleuze JF, Munter HM, Bourque G, Auld D, Montpetit A, Lathrop M, Guyant-Marechal L, Martinaud O, Pariente J, Rollin-Saille A, Pasquier F, Le Ber I, Sarazin M, Croisile B, Boutoule-Brenoniere C, Thomas-Anterion C, Paquet C, Sauvee M, Moreaud O, Gabelle A, Sellal F, Ceccaldi M, Chamard L, Blane F, Frebrou T, Campion D, Hannenquin D (2016) Screening of dementia genes by whole-exome sequencing in early-onset Alzheimer disease: input and lessons. Eur J Hum Genet 24(5):710–716. doi:10.1038/ejhg.2015.173
23. Scheuner D, Eckman C, Jensen M, Song X, Citron M, Suzuki N, Bird TD, Hardy J, Hutton M, Kukull W, Larson E, Levy-Lahad E, Viitanen M, Peskind E, Poorkaj P, Schellenberg G, Tanzi R, Wasco W, Lannfelt L, Selkoe D, Younkin S (1996) Secreted amyloid beta-protein similar to that in the senile plaques of Alzheimer’s disease: input and lessons. Eur J Hum Genet 2(5):a006270. doi:10.1101/cshperspect.a006270
24. Jonsson T, Atwal JK, Steinberg S, Snaedal J, Hoyte K, Gustafson A, Liu Y, Lu Y, Bhangale T, Graham RR, Johnson CS, Burne TM, Palotie A, Behrens TW, Magnusson OT, Kong A, Thorsteinsson U, Watts RJ, Stefansson K (2012) A mutation in APP
proteins against Alzheimer’s disease and age-related cognitive decline. Nature 488(7409):96–99. doi:10.1038/nature11283
25. Benilova I, Gallardo R, Ungureanu AA, Castillo Cano V, Snelinx A, Ramakers M, Bartic C, Rousseau F, Schymkowitz J, De Strooper B (2014) The Alzheimer disease protective mutation A2T modulates kinetic and thermodynamic properties of amyloid-beta (Abeta) aggregation. J Biol Chem 289(45):30977–30989. doi:10.1074/jbc.M114.590027
26. Cruchaga C, Haller G, Chakraverty S, Mayo K, Vallania FL, Mitra RD, Faber K, Williamson J, Bird T, Diaz-Arrastia R, Foroud TM, Boeve BF, Graff-Radford NR, St Jean P, Lawson M, Elhm MG, Mayeux R, Goate AM (2012) Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer’s disease families. PLoS one 7(2):e31039. doi:10.1371/journal.pone.0031039
27. Sleeegers K, Brouwers N, Gijselinklinck I, Theuns J, Goossens D, Wauters J, Del-Favero J, Cruts M, van Duijn CM, Van Broeckhoven C (2006) APP duplication is sufficient to cause early onset Alzheimer’s dementia with cerebral amyloid angiopathy. Brain J Neurol 129(Pt 11):2977–2983. doi:10.1093/brain/awi203
28. Guerreiro RJ, Gustafson DR, Hardy J (2012) The genetic architecture of Alzheimer’s disease: beyond APP, PSEns and APOE. Neurobiol Aging 33(3):437–456. doi:10.1016/j.neurobiolaging.2010.03.025
29. Hutton M, Busfield F, Wragg M, Crook R, Perez-Tur J, Clark RF, Prihar G, Talbot C, Phillips H, Wright K, Baker M, Lendon C, Duff K, Martinez A, Houlden H, Nichols A, Karran E, Roberts G, Roques P, Rossor M, Venter JC, Adams MD, Cline RT, Phillips CA, Goate A et al (1996) Complete analysis of the presenilin 1 gene in early onset Alzheimer’s disease. Neuroreport 7(3):801–805
30. Barton AJ, Crook BW, Karran EH, Brown F, Dewar D, Mann DM, Pearson RC, Graham DI, Hardy J, Hutton M, Duff K, Goate AM, Clark RF, Roberts GW (1996) Alteration in brain presenilin 1 mRNA expression in early onset familial Alzheimer’s disease. Neurodegeneration 5(3):213–218
31. Chouraki V, Seshadri S (2014) Genomics of Alzheimer’s disease. Adv Genet 87:245–294. doi:10.1016/}
32. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStefano AL, Bis JC, Beecham GW, Greiner-Boley B, Russo G, Thorton-Wellis TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Sorbi S, van Duijn CM, Breteler MM, Ikram MA, DeStefano AL, Fitzpatrick AL, De Jager PL, Morgan K, Younkin SG, Morgan L, DeCarli C, DeKosky ST, Diaz-Arrastia R, Dickson DW, Graff-Radford NR, Petersen RC, van Duijn CM, Bihoreau MT, Choi SH, Reitz C, Pahwa JS, Mayeux R, Hulténen M, Lannefelt L, Hakonarson H, Wauters J, Del-Favero J, Cruts M, van Duijn CM, van Broeckhoven C, Moskvin V, Seshadri S, Williams J, Schellenberg GD, Amouyel P (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer’s disease. Nature genetics 45(12):1452–1458. doi:10.1038/ng.2802
33. Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrausillo MM, Abrahm, Arland, Mah, Pahwa JS, Moskvin V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Beaumont H, Warden D, Wilcock G, Love S, Kehoe P, Hooper NM, Vardy ER, Hardy J, Mead S, Fox NC, Rossor M, Collinge J, Maier W, Jessen R, Ehrlich S, Schurrman B, Heun R, Kolsch V, van den Bussen H, Heuser I, Kornhuber J, Wiltfang J, Dichtgans M, Frollich L, Hampel H, Gallacher J, Hull M, Rujescu D, Giegling I, Goate AM, Kauwe JS, Cruchaga C, Novotny P, Morris JC, Mayo K, Sleeegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McLquin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsoalki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Kopp N, Wichmann HE, Pankratz VS, Sando SB, Aasly JO, Barcikowska M, Wszolek ZK, Dickson DW, Graff-Radford NR, Petersen RC, van Duijn CM, Bihoreau MT, Ikram MA, DeStefano AL, Fitzpatrick AL, Lopez O, Launer LJ, Seshadri S, Cerr J, Campion D, Epelbaum J, Martigues JF, Tzourio C, Alperovich A, Lathrop M, Feulner TM, Friedrich P, Kiel H, Krawczyk A, Schreiber S, Mayhaus N, Nicolaius S, Wagenpfel S, Steinberg S, Stefanosn H, Stefanosn K, Snaadl J, Bjor汉字son S, Jonsson PV, Chouraki V, Genier-Boley B, Hultenen M, Soininen H, Combarros O, Zeila K, Delempine M, Buillido MJ, Pashquier F, Mateo I, Frank Garcia A, Porcelli E, Hanon O, Coto E, Alvarez C, Bosro P, Siciliano G, Mancuso M, Panser F, Soffizrtiz V, Nacimian B, Sorbi S, Rossor N, Bossu P, Piccardi P, Arosio B, Annungi G, Seripa D, Piotato A, Scarpini E, Galmimerti B, Driche A, Hannequin D, Lencastro F, Jones L, Olomans PA, Jonsson T, Riemenschneider M, Morgan K, Yonkun SG, Owens MJ, O’Donovan M, Amouyel P, Williams J (2011) Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer’s disease. Nat Genet 43(5):429–435. doi:10.1038/ng.803
43. Kim M, Suh J, Romano D, Truong MH, Mullin K, Hooli B, Parisi JE, Perl DP, Peskind E, Petersen RC, Poon WW, Quinn JF, Rajbhandary RA, Raskind M, Reisberg B, Ringman JM, Roberson ED, Rosenberg RN, Sano M, Schneider LS, Seeley W, Shelanski ML, Slifer MA, Smith CD, Sonnen JA, Spina S, Stern RA, Tanzi RE, Trojanowski JQ, Troncoso JC, Van Deerlin VM, Vinters HV, Vonsattel JP, Weintraub S, Welsh-Bohmer KA, Williamson J, Woljter RL, Cantwell LB, Dombroski BA, Beechy D, Lunetta KL, Martin ER, Kamboh MI, Saykin AJ, Reiman EM, Bennett DA, Morris JC, Montine TJ, Goate AM, Blacker D, Tsuang DW, Hakonarson H, Kukull WA, Foroud TM, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD (2011) Common variants at MS4A4/Ms4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer’s disease. Nat Genet 43(5):436–441. doi:10.1038/ng.801

35. Chan SL, Kim WS, Kwok JB, Hill AF, Cappai R, Rye KA, Garner B (2008) ATP-binding cassette transporter A7 regulates processing of amyloid precursor protein in vitro. J Neurochem 106(2):793–804. doi:10.1111/j.1471-4159.2008.05433.x

36. Kim WS, Li H, Ruberu K, Chan S, Elliott DA, Low JK, Cheng D, Karl T, Garner B (2013) Deletion of Abca7 increases cerebral amyloid-beta accumulation in the J20 mouse model of Alzheimer’s disease. The Journal of neuroscience : the official journal of the Society for Neuroscience 33(10):4387–4394. doi:10.1523/jneurosci.4165-12.2013

37. Shulman JM, Chen K, Keenan BT, Hoyt KL, Staley LA, Harari O, Cruchaga C, Ainscough BJ, Bales K, Pickering EH, Bertelsen S, Fagan AM, Holtzman DM, Morris JC, Goate AM (2014) Genome-wide association study of CSF levels of 59 Alzheimer’s disease candidate proteins: significant associations with proteins involved in amyloid processing and inflammation. PLoS Genet 10(10):e1004758. doi:10.1371/journal.pgen.1004758

38. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1993) Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer’s disease in late onset families. Science 261(5123):921–923.

39. Castellano JM, Kim J, Stewart FR, Jiang H, DeMattos RB, Patterson BW, Fagan AM, Morris JC, Mawuenya EG, Cruchaga C, Goate AM, Bales KR, Paul SM, Bateman RJ, Holtzman DM (2011) Human apoE isoforms differentially regulate brain amyloid-beta peptide clearance. Sci Transl Med 3(89):89ra57. doi:10.1126/scitranslmed.3002156

40. Deane R, Sagare A, Hammad K, Parisi M, Lane S, Finn MB, Holtzman DM, Zlokovic BV (2008) ApoE isoform-specific disruption of amyloid beta peptide clearance from mouse brain. J Clin Invest 118(12):4002–4013. doi:10.1172/jci36663

41. Vergheze PB, Castellano JM, Garai K, Wang Y, Jiang H, Shah A, Bu G, Frieden C, Holtzman DM (2013) ApoE influences amyloid-beta (Abeta) clearance despite minimal apoE/Abeta association in physiological conditions. Proc Natl Acad Sci USA 110(19):E1807–E1816. doi:10.1073/pnas.1220484110

42. M115.655076

43. Conejero-Goldberg C, Gomar JJ, Bobes-Bascaran T, Hyde TM, Kleinman JE, Herman MM, Chen S, Davies P, Goldberg TE (2014) APOE2 enhances neuroprotection against Alzheimer’s disease.
disease through multiple molecular mechanisms. Mol Psychiatry 19(11):1243–1250. doi:10.1038/mp.2013.194

57. Beecham GW, Hamilton K, Naj AC, Martin ER, Huentelman M, Myers AJ, Corneveaux JJ, Hardy J, Vonsattel JP, Younkin SG, Bennett DA, De Jager PL, Larson EB, Crane PK, Kambh MI, Kohler JK, Mash DC, Duque L, Gilbert JR, Gwirtsman H, Buxbaum JD, Kramer P, Dickson DW, Farrer LA, Frosch MP, Gbessa B, Haines JL, Hyman BT, Kukull WA, Mayeux RP, Perez-Vance MA, Schneider JA, Trojanowksi JQ, Reiman EM, Schellenberg GD, Montine TJ (2014) Genome-wide association meta-analysis of neuropathologic features of Alzheimer’s disease and related dementias. PLoS Genet 10(9):e1004606. doi:10.1371/journal.pgen.1004606

58. Rezaeadeh M, Khorrami A, Yeghaneh T, Talebi M, Kiani SJ, Hashmati Y, Gharexsouran J (2016) Genetic factors affecting late-onset Alzheimer’s disease susceptibility. Neuromol Med 18(1):37–49. doi:10.1007/s10017-015-8376-4

59. Miyawaka T, Ebinuma I, Morohashi H, Yori H, Young Chang M, Hattori H, Maehara T, Yokoshiba S, Fukuyma T, Tsuji S, Iwatsubo T, Prendergast GC, Tomita T (2016) BIN1 regulates BACE1 intracellular trafficking and amyloid-beta production. Hum Mol Genet. doi:10.1093/hmg/ddw146

60. Chapuis J, Hansmannel F, Gistelinck M, Mounier A, Van Cauwenberge C, Khorrami A, Yeghaneh T, Talebi M, Kiani SJ, Hashmati Y, Gharexsouran J (2016) Genetic factors affecting late-onset Alzheimer’s disease susceptibility. Neuromol Med 18(1):37–49. doi:10.1007/s10017-015-8376-4

61. Liao F, Jiang H, Srivatsan S, Xiao Q, Lefton KB, Yamada K, Cribari-Vance MA, Mcgraw TE, Le Marchand-Brustel Y (2003) CD2AP/CMS form, function, and Alzheimer's disease. Trends Mol Med 9(10):594–603. doi:10.1016/j.molmed.2013.06.004

62. Cormont M, Meton I, Mari M, Monzo P, Keslair F, Gaskin C, Dermaut B, Lambert JC (2013) Increased expression of BIN1 mediates Alzheimer genetic risk by modulating tau pathology. Mol Psychiatry 18(11):1225–1234. doi:10.1038/mp.2013.11

63. Tan MS, Yu JT, Tan L (2013) Bridging integrator 1 (BIN1): form, function, and Alzheimer’s disease. Trends Mol Med 19(10):594–603. doi:10.1016/j.molmed.2013.06.004

64. Cormont M, Meton I, Mari M, Monzo P, Keslair F, Gaskin C, McGraw TE, Le Marchand-Brustel Y (2003) CD2AP/CMS regulates endosome morphology and traffic to the degradative pathway through its interaction with Rab4 and c-Cbl. Traffic 4(2):97–112. doi:10.1046/j.1600-0854.2003.00414.x

65. Liao F, Jiang H, Srivatsan S, Xiao Q, Lefton KB, Yamada K, Cribari-Vance MA, Mcgraw TE, Le Marchand-Brustel Y (2003) CD2AP/CMS form, function, and Alzheimer's disease. Trends Mol Med 9(10):594–603. doi:10.1016/j.molmed.2013.06.004

66. Rezazadeh M, Khorrami A, Yeghaneh T, Talebi M, Kiani SJ, Hashmati Y, Gharexsouran J (2016) Genetic factors affecting late-onset Alzheimer’s disease susceptibility. Neuromol Med 18(1):37–49. doi:10.1007/s10017-015-8376-4

67. Rao M, Murphy A, Wagner SL, Blacker D, Becker KD, Tanzi RE (2008) Genome-wide association analysis reveals putative Alzheimer’s disease susceptibility loci in addition to APOE. Am J Hum Genet 83(5):623–632. doi:10.1016/j.ahg.2008.10.008

68. Bell RD, Sagare AP, Friedman AE, Berti 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(5):909–918. doi:10.1038/jcbfm.9600419

69. Oda T, Wais P, Osterburg HR, Johnson SA, Passinetti GM, Morgan TE, Rozovsky I, Stine WB, Snyder SW, Holtzman TF et al. (1995) Clusterin (apol) alters the aggregation of amyloid beta-peptide (A beta 1–42) and forms slowly sedimenting A beta complexes that cause oxidative stress. Exp Neurol 136(1):22–31

70. Matsubara E, Frangione B, Ghiso J (1995) Characterization of apolipoprotein J-Alzheimer's J alpha beta interaction. J Biol Chem 270(13):7563–7567

71. Matsubara E, Soto C, Governale S, Frangione B, Ghiso J (1996) Apolipoprotein J and Alzheimer's amyloid beta solubility. Biochem J 316( Pt 2):671–679

72. Yerbury JJ, Poon S, Meehan S, Thompson B, Kumita JR, Dobson CM, Wilson MR (2007) The extracellular chaperone clusterin influences amyloid formation and toxicity by interacting with prefibrillar structures. FASEB J Off Publ Feder Am Soc Exp Biol 21(10):2312–2322. doi:10.1096/fj.06-7986com

73. Niuhten T, Hsuuskonen J, Suuronen T, Ojala J, Miettinen R, Salminen A (2007) Amyloid-beta 1–42 induced endocytosis and clusterin/apoJ protein accumulation in cultured human astrocytes. Neurochem Int 50(3):540–547. doi:10.1016/j.neuint.2006.11.002

74. Niuhten T, Suuronen T, Kauppinen A, Salminen A (2009) Clusterin: a forgotten player in Alzheimer’s disease. Brain Res Rev 61(2):89–104. doi:10.1016/j.brainresrev.2009.05.007

75. DeMattos RB, Cirrito JR, Pasadarian M, May PC, O’Dell MA, Taylor JW, Harmony JA, Aronow BJ, Bales KR, Paul SM, Holtzman DM (2004) ApoE and clusterin cooperatively suppress Abeta levels and deposition: evidence that ApoE regulates extracellular Abeta metabolism in vivo. Neuron 41(2):193–202

76. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltnen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fievet N, Barberger-Gateau P, Engelborghs S, De Deyn PP, Mateo I, Franch A, Helisalmi S, Porcellini E, Honan O, de Pancorbo MM, Lenon D, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licalisto F, Soininen H, Ritchie K, Blanche H, Darguetes JF, Tzourio C, Gut I, Van Broeckhoven C, Alperovitch A, Lathrop M, Amouyel P (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer’s disease. Nat Genet 41(10):1094–1099. doi:10.1038/ng.439

77. Karch CM, Jung AT, Nowotny P, Cady J, Cruchaga C, Goate AM (2012) Expression of novel Alzheimer’s disease risk genes in control and Alzheimer’s disease brains. PloS one 7(11):e50976. doi:10.1371/journal.pone.0050976

78. Crehan H, Hardy J, Pocock J (2013) Blockage of CR1 prevents Abeta accumulation in cultured astrocytes. Neurochem Int 50(3):540–547. doi:10.1016/j.neuint.2006.11.002

79. Karch CM, Jung AT, Nowotny P, Cady J, Cruchaga C, Goate AM (2012) Expression of novel Alzheimer’s disease risk genes in control and Alzheimer’s disease brains. PloS one 7(11):e50976. doi:10.1371/journal.pone.0050976

80. Schellenberg GD, Montine TJ (2012) The genetics and neuropathology of Alzheimer’s disease. Acta Neuropathol (Berl) 124(3):305–323. doi:10.1007/s00401-012-0996-2

81. Sakamoto A, Sugamoto Y, Tokunaga Y, Yoshimura T, Hayashi K, Konno T, Kawashiri M, Takeda Y, Yamagishi M (2011)
Expression profiling of the ephrin (EFN) and Eph receptor (EPH) family of genes in atherosclerosis-related human cells. J Int Med Res 39(2):522–527.

82. Lai KO, Ip NY (2009) Synapse development and plasticity: roles of ephrin/Eph receptor signaling. Curr Opin Neurobiol 19(3):275–283. doi:10.1016/j.conb.2009.04.009

83. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Lai KO, Ip NY (2009) Synapse development and plasticity: the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. J Biol Chem 281(31):21745–21754.

84. Miller SE, Sahlender DA, Graham SC, Honing S, Robinson MS, Peden AA, Owen DJ (2011) The molecular basis for the endocytosis of small R-SNAREs by the clathrin adaptor CALM. Mol Biol Cell 23(14):2645–2657. doi:10.1091/mbc.E11-02-0014

85. Xiao Q, Gil SC, Yan P, Wang Y, Han S, Gonzales E, Perez R, Schmidt V, Sporbert A, Rohe M, Reimer T, Rehm A, Andersen OM (2012) Retromer binds the FANSHY sorting motif in SorLA to regulate amyloid precursor protein sorting and processing. J Neurosci Off J Soc Neurosci 32(4):1467–1480. doi:10.1523/jneurosci.2272-11.2012

86. Schmidt V, Baum K, Lao A, Rateitschak K, Schmitz Y, Teichmann A, Fjorback AW, Seaman M, Gustafsen C, Mehmedbasic A, Sokolowski T, Madsen P, Nyengaard JR, Willnow TE (2012) Quantitative modelling of amyloidogenic processing and its influence by SORLA in Alzheimer’s disease. Embo j 31(1):187–200. doi:10.1038/emboj.2011.352

87. Herskowitz JH, Oliffe K, Deshpande A, Kahn RA, Levey AI, Lah JJ (2012) GGA1-mediated endocytic traffic of LR11/SorLA alters APP intracellular distribution and amyloid-beta production. Mol Biol Cell 23(14):2645–2657. doi:10.1091/mbc.E11-02-0014

88. Jesko H, Wencel P, Strosznajder RP, Strosznajder JB (2016) Sirtuins and their roles in brain aging and neurodegenerative disorders. Neurochem Res. doi:10.1007/s11064-016-2110-y

89. Corpas R, Revilla S, Ureutel S, Castro-Freire M, Kaliman P, Petegnieur V, Gimenez-Llort L, Sarkis C, Pallas M, Sanfelici C (2016) SIRT1 overexpression in mouse hippocampus induces cognitive enhancement through proteostatic and neurotrophic mechanisms. Mol Neurobiol. doi:10.1007/s12035-016-0087-9

90. Wang Z, Lei H, Zheng M, Li Y, Cui Y, Hao F (2016) Meta-analysis of the association between Alzheimer disease and variants in GAB2, PICALM, and SORL1. Mol Neurobiol 53(9):601–6510. doi:10.1007/s12035-015-9546-y

91. Qin W, Yang T, Ho L, Zhao Z, Wang J, Chen L, Zhou W, Thyagarajan M, MacGrogan D, Rodgers JT, Puigserver P, Sadoshima J, Deng H, Pedrini  S, Gandy S, Sauve AA, Pasinetti GM (2006) Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. J Biol Chem 281(31):21745–21754. doi:10.1074/jbc.M509329200

92. Takehara K, Prinz M, Stagi M, Checchenna O, Neumann H (2007) TREM2-transduced myeloid precursors mediate nerveous tissue debris clearance and facilitate recovery in an animal model of multiple sclerosis. PLoS Med 4(4):e124. doi:10.1371/journal.pmed.0040124

93. Takehara K, Rochford CD, Neumann H (2005) Clearance of apoptotic neurons without inflammation by microglial triggering receptor expressed on myeloid cells-2. J Exp Med 201(4):647–657. doi:10.1084/jem.20041611
105. Hsieh CL, Koike M, Spusta SC, Niemi EC, Yenari M, Nakamura MC, Seamann WE (2009) A role for TREM2 ligands in the phagocytosis of apoptotic neuronal cells by microglia. J Neurochem 109(4):1144–1156. doi:10.1111/j.1471-4159.2009.06042.x

106. Hamerman JA, Jarjoura JR, Humphrey MB, Nakamura MC, Seamann WE, Lanier LL (2006) Cutting edge: inhibition of TLR and FcR responses in macrophages by triggering receptor expressed on myeloid cells (TREM)-2 and DAP12. Journal of immunology (Baltimore, Md : 1950) 177 (4):2051–2055

107. Turnbull IR, Gillillan S, Cella M, Aoshi T, Miller M, Piccio L, Hernandez M, Colonna M (2006) Cutting edge: TREM-2 attenuates macrophage activation. Journal of immunology (Baltimore, Md : 1950) 177 (6):3520–3524

108. Pottier C, Wallon D, Rousseau S, Rovelet-Lecruix A, Richard AC, Rollin-Sillaire A, Frebourg T, Campion D, Hannequin D (2013) TREM2 R47H variant as a risk factor for early-onset Alzheimer’s disease. Journal of Alzheimer’s disease : JAD 35(1):45–49. doi:10.3233/jad-122311

109. Potter R, Patterson BW, Elbert DL, Ovod V, Kasten T, Sigurdsson W, Mauwuenyega K, Blazey T, Goate A, Chott R, Yarasheski KE, Holtzman DM, Morris JC, Benzinger TL, Bateman RJ (2013) Increased in vivo amyloid-beta42 production, exchange, and loss in presenilin mutation carriers. Sci Transl Med 5(189):189ra177. doi:10.1126/scitranslmed.3005615

110. Mawuenyega KG, Sigurdsson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ (2010) Decreased clearance of CNS beta-amyloid in Alzheimer’s disease. Science 330(6012):1774. doi:10.1126/science.1197623

111. Kayed R, Head E, Thompson JL, McIntire TM, Milton SC, Cotman CW, Glabe CG (2003) Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science 300(5618):486–489. doi:10.1126/science.1079469

112. Haass C, Selkoe DJ (2007) Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer’s amyloid beta-peptide. Nature reviews Molecular cell biology 8 (2):101–112. doi:10.1038/nrm2101

113. Lesnê S, Koh MT, Kotlín L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH (2006) A specific amyloid-beta peptide assembly in the brain impairs memory. Nature 440(7082):352–357. doi:10.1038/nature04533

114. McLean CA, Cherry RA, Fraser FW, Fuller SJ, Smith MJ, Beyreuther K, Bush AI, Masters CL (1999) Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer’s disease. Ann Neurol 46(6):860–866

115. Mc Donald JM, Savva GM, Brayne C, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ (2008) Amyloid-beta protein dimers isolated directly from Alzheimer’s brains impair synaptic plasticity and memory. Nat Med 14(8):837–842. doi:10.1038/nm1782

116. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ (2002) Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 416(6880):535–539. doi:10.1038/416535a

117. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, Ashe KH (2005) Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. Nat Neurosci 8(1):79–84. doi:10.1038/nn1372

118. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, Regan CM, Walsh DM, Sabatini BL, Selkoe DJ (2008) Amyloid-beta protein dimers isolated directly from Alzheimer’s brains impair synaptic plasticity and memory. Nat Med 14(8):837–842. doi:10.1038/nm1782

119. Viola KL, Klein WL (2015) Amyloid beta oligomers in Alzheimer’s disease pathogenesis, treatment, and diagnosis. Acta Neuropathol (Berl) 129(2):183–206. doi:10.1007/s00401-015-1386-3

120. Mark RJ, Pang Z, Geddes JW, Uchida K, Mattson MP (1997) Amyloid beta-peptide impairs glucose transport in hippocampal and cortical neurons: involvement of membrane lipid peroxidation. The Journal of neurochemistry : the official journal of the Society for Neuroscience 17(3):1046–1054

121. Caspersen C, Wang N, Yao J, Susonov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G, Yan SD (2005) Mitochondrial Aβeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer’s disease. FASEB J 19 (14):2040–2041. doi:10.1096/f05-7375je

122. Manczak M, Anekonda TS, Hanson E, Park BS, Quinn J, Reddy PH (2006) Microtubulae are a direct site of alpha beta accumulation in Alzheimer’s disease neurons: implications for free radical generation and oxidative damage in disease progression. Hum Mol Genet 15(9):1437–1449. doi:10.1093/hmg/ddi066

123. Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brose nson F, Feinstein DL, Jacobs AH, Wyss-Coray T, Vitorica J, Ransohoff RM, Herrup K, Frautschy SA, Finsen B, Brown GC, Vercrhratsky A, Yamanaka K, Koistinaho J, Lutz E, Halle A, Petzdold GC, Town T, Morgan D, Shinohara ML, Perry VH, Holmes C, Bazan NG, Brooks DJ, Hunot S, Joseph B, Deigenesch N, Garaschuk O, Boddeke E, Dinarello CA, Breitner JC, Cole GM, Golenbock DT, Kummer MP (2015) Neuraminification in Alzheimer’s disease. Lancet Neurol 14(4):388–405. doi:10.1016/S1474-4422(15)70016-5

124. Mosher KL, Wyss-Coray T (2014) Microglial dysfunction in brain aging and Alzheimer’s disease. Biochem Pharmacol 88(4):594–604. doi:10.1016/j.bcp.2014.01.008

125. Fiala M, Lin J, Ringman J, Kermami-Arab V, Tsoa G, Patel A, Lossinsky AS, Graves MC, Gustavson A, Sayre J, Sofroni E, Suarez T, Chiappelli F, Bernard G (2005) Ineffective phagocytosis of amyloid-beta by macrophages of Alzheimer’s disease patients. Journal of Alzheimer’s disease : JAD 7(3):221–232 discussion 255–262

126. Fiala M, Zhang L, Gan X, Sherry B, Taub D, Graves MC, Hama S, Way D, Weinand M, Witte M, Lorton D, Kuo YM, Roher AE (1998) Amyloid-beta induces chemokine secretion and monocyte migration across a human blood–brain barrier model. Mol Med 4(7):480–489

127. Saresella M, Marventano I, Calabrese E, Piancone F, Rainone V, Gatti A, Alberoni M, Nemni R, Clerici M (2014) A complex proinflammatory role for peripheral monocytes in Alzheimer’s disease. JAD 38(2):403–413. doi:10.3233/jad-131160

128. Smith MA, Perry G, Richey PL, Sayre LM, Anderson VE, Beal MF, Kowall N (1996) Oxidative damage in Alzheimer’s. Nature 382(6587):120–121. doi:10.1038/382120b0

129. Bell RD, Zlokovic BV (2009) Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer’s disease. Acta Neuropathol (Berl) 118(1):103–113. doi:10.1007/s00401-009-0522-3

130. Frost S, Guymer R, Aung KZ, Macaulay SL, Sohrabi HR, Bourgeat P, Salvador O, Rowe CC, Ames D, Masters CL, Martin RN, Kanagasingam Y, Group AT (2016) Alzheimer’s disease and the early signs of age-related macular degeneration. Curr Alzheimer Res 13(11):1259–1266. doi:10.2174/15672052138066160603003800

131. Kimbrough IF, Robel S, Roberson ED, Sontheimer H (2015) Vascular amyloidosis impairs the gliovascular unit in a mouse model of Alzheimer’s disease. Brain J Neurol 138(Pt 12):3716–3733. doi:10.1093/brain/awv327
132. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE (2004) Neurofibrillary tangles mediate the association of amyloid load with clinical Alzheimer disease and level of cognitive function. Arch Neurol 61(3):378–384. doi:10.1001/archneur.61.3.378

133. Murray ME, Lowe VJ, Graff-Radford NR, Liesinger AM, Cannon A, Przybelski SA, Rawal B, Parisi JE, Petersen RC, Kantarci K, Ross OA, Duara R, Knopman DS, Jack CR, Dickson DW (2015) Clinicopathologic and 11 C-Pittsburgh compound B implications of Thal amyloid phase across the Alzheimer’s disease spectrum. Brain J Neurol 138(Pt 5):1370–1381. doi:10.1093/brain/awv050

134. Karran E, Hardy J (2014) A critique of the drug discovery and phase 3 clinical programs targeting the amyloid hypothesis for Alzheimer disease. Ann Neurol 76(2):185–205. doi:10.1002/ana.24188

135. Morris GP, Clark IA, Vissel B (2014) Inconsistencies and controversies surrounding the amyloid hypothesis of Alzheimer’s disease. Acta Neuropathol Commun 2:135. doi:10.1186/s40478-014-0135-5

136. Chen M, Maleski JJ, Sawmill DR (2011) Scientific truth or false hope? Understanding Alzheimer’s disease from an aging perspective. JAD 24(1):3–10. doi:10.3233/jad-2010-101638

137. Herrup K (2010) Reimagining Alzheimer’s disease—an age-based hypothesis. J Neurosci 30(50):16755–16762. doi:10.1523/jneurosci.4521-10.2010

138. Morris GP, Clark IA, Zinn R, Vissel B (2013) Microglia: a new frontier for synaptic plasticity, learning and memory, and neurodegenerative disease research. Neurobiol Learn Mem 105:40–53. doi:10.1016/j.nlm.2013.07.002

139. Kandimalla R, Thirumala V, Reddy PH (2016) Is Alzheimer’s disease a Type 3 diabetes? A critical appraisal. Biochim Biophys Acta. doi:10.1016/j.bbadi.2016.08.018

140. Götz J, Chen F, van Dorpe J, Nitsch RM (2001) Formation of neurofibrillary tangles in P301T tau transgenic mice induced by Abeta 42 fibrils. Science 293(5534):1491–1495. doi:10.1126/science.1062097

141. Lewis J, Dickson DW, Lin WL, Chisholm L, Corral A, Jones G, Yen SH, Sahara N, Skipper L, Yager D, Eckman C, Hardy J, Hutton M, McGowan E (2001) Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP. Science 293(5534):1487–1491. doi:10.1126/science.1058189

142. Jin M, Shepardson N, Yang T, Chen G, Walsh D, Selkoe DJ (2011) Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration. Proc Natl Acad Sci USA 108(14):5819–5824. doi:10.1073/pnas.1017033108

143. Choi SH, Kim YH, Hebisch M, Sliwinski C, Lee S, D’Avanzo L, Kim EY, Shin J, Yoo JS, Bhanji R, Black KL, Shen XZ, Fuchs S, Koronyo-Hamaoui M (2014) Angiotensin-converting enzyme overexpression in myelomonocytes prevents Alzheimer’s-like cognitive decline. J Clin Invest 124(3):1000–1012. doi:10.1172/JCI66541

144. Sevigny J, Chiao P, Bussiere T, Weinreb PH, Williams L, Maier M, Dunstan R, Solloway S, Chen T, Ling Y, O’Gorman J, Qiao D, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannev RN, Arnold HM, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A (2016) The antibody aducanumab reduces Abeta plaques in Alzheimer’s disease. Nature 537(7618):50–56. doi:10.1038/nature19323

145. Lebson L, Nash K, Kamath S, Herber D, Carty N, Lee DC, Li Q, Szeckers 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(29):9651–9658. doi:10.1523/jneurosci.0329-10.2010

146. Wyss-Conray T (2006) Inflammation in Alzheimer disease: a new frontier for synaptic plasticity, learning and memory, and phase 3 clinical programs targeting the amyloid hypothesis for Alzheimer disease. Acta Neuropathol Commun 2:135. doi:10.1186/1742-2094-2-135

147.ACCEPTED MANUSCRIPT

148. Grant WB, Campbell A, Izhaki RF, Savory J (2002) The significance of environmental factors in the etiology of Alzheimer’s disease. JAD 4(3):179–189

149. Butler LA, Cupples L, Haines JL et al (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein e genotype and Alzheimer disease: a meta-analysis. JAMA 278(16):1349–1356. doi:10.1001/jama.1997.03551060090401

150. Majounie E, Cruchaga C, Zhang Y, LaDu MJ, Xu H, Bu G (2012) Differential regulation of amyloid-beta endocytotic trafficking and lysosomal degradation by apolipoprotein E isoforms. J Biol Chem 287(53):44593–44601. doi:10.1074/jbc.M112.420224

151. Bell RD, Winkler EA, Singh I, Sagare AP, Deane R, Wu Z, Holtzman DM, Betsholtz C, Arutz I, Zlokovic BV (2012) Apolipoprotein E controls cerebrovas- cular integrity through cytolphilin A. Nature 485(7399):512–516. doi:10.1038/nature11087

152. Lombardo F, Ghura S, Koster KP, Liakaite V, Maienschein-Cline M, Kanabar P, Collins N, Ben-Aissa M, Lee AZ, Bahroos N, Green SJ, Hendrickson B, Van Eldik LJ, LaDu MJ (2015) APOE-modulated Abeta-induced neuroinflammation in Alzheimer’s disease: current landscape, novel data, and future perspective. J Neurochem 133(4):465–488. doi:10.1111/jnc.13072

153. Deane R, Zlokovic BV (2012) Apolipoprotein E controls cerebrovas- cular integrity through cytolphilin A. Nature 485(7399):512–516. doi:10.1038/nature11087

154. Lombardo F, Ghura S, Koster KP, Liakaite V, Maienschein-Cline M, Kanabar P, Collins N, Ben-Aissa M, Lee AZ, Bahroos N, Green SJ, Hendrickson B, Van Eldik LJ, LaDu MJ (2015) APOE-modulated Abeta-induced neuroinflammation in Alzheimer’s disease: current landscape, novel data, and future perspective. J Neurochem 133(4):465–488. doi:10.1111/jnc.13072

155. Guerreiro R, Wijmenga R, Pajk W, Bessaqui M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Haz- rati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J (2013) TREM2 variants in Alzheimer’s disease: current landscape, novel data, and future perspective. J Neurochem 133(4):465–488. doi:10.1111/jnc.13072

156. Malik M, Parikh I, Vasquez JB, Smith C, Tai L, Bu G, LaDu MJ, Fardo DW, Rebeck GW, Estus S (2015) Genetics ignite new frontier for synaptic plasticity, learning and memory, and phase 3 clinical programs targeting the amyloid hypoth- esis for Alzheimer disease. Acta Neuropathol Commun 2:135. doi:10.1186/s13024-015-0048-1

157. Guerreiro R, Wijmenga R, Pajk W, Bessaqui M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Haz- rati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J (2013) TREM2 variants in Alzheimer’s disease. N Engl J Med 368(2):117–127. doi:10.1056/NEJMoa1211851

158. Wyss-Conray T (2006) Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med 12(9):1005–1015. doi:10.1038/nm1484
Clearance of cerebral Aβ in Alzheimer’s disease: reassessing the role of microglia and monocytes

159. Shibata M, Yamada S, Kumar SR, Calero M, Bading J, Franzone B, Holtzman DM, Miller CA, Strickland DK, Ghiso J, Zlokovic BV (2000) Clearance of Alzheimer’s amyloid-ss(1–40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier. J Clin Invest 106(12):1489–1499. doi:10.1172/jci10498

160. 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(2):253–266. doi:10.1111/j.1750-3693.2008.00133.x

161. Iliff JJ, Nedergaard M (2013) Is there a cerebral lymphatic system? Stroke 44(6 Suppl 1):S93–95. doi:10.1161/strokea.112.768698

162. 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 beta. Sci Transl Med 4(147):147ra111. doi:10.1126/scitranslmed.3003748

163. Malm T, Koistinaho M, Muona A, Magga J, Koistinaho J (2010) The role and therapeutic potential of monocytes in Alzheimer’s disease. Glia 58(8):889–900. doi:10.1002/glia.20973

164. 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(45):37644–37650. doi:10.1074/jbc.M504602000

165. Mukherjee A, Song E, Kihiko-Ehmann M, Goodman JP Jr, Hemming ML, Selkoe DJ (2005) Amyloid beta-degrading endopeptidase, neprilysin, in mouse human hippocampus and is capable of degrading amyloid beta peptide not only in the mononuclear form but also the pathological oligomeric form. Neurosci Lett 350(2):113–116

166. 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(43):10939–10948. doi:10.1523/jneurosci.2085-06.2006

167. Ito S, Kimura K, Haneda M, Ishida Y, Sawada M, Isobe K (2007) Induction of matrix metalloproteinases (MMP3, MMP12 and MMP13) expression in the microglia by amyloid-beta-stimulation via the PI3K/Akt pathway. Exp Gerontol 42(6):532–537. doi:10.1016/j.exger.2006.11.012

168. Zhao L, Lin S, Bales KR, Gelfanova V, Koger D, Delong C, Hale J, Liu F, Hunter JM, Paul SM (2009) Macrophage-mediated degradation of beta-amyloid via apolipoprotein E isoform-dependent mechanism. J Neurosci 29(11):461–469. doi:10.1523/jneurosci.0081-09.2009

169. Kurochkin IV, Goto S (1994) Alzheimer’s beta-amyloid peptide specifically interacts with and is degraded by insulin degrading enzyme. FEBS Lett 345(1):33–37

170. Qi 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(49):32730–32738

171. Backstrom JR, Lim GP, Cullen MJ, Tokes ZA (1996) Matrix metalloproteinase-9 (MMP-9) is synthesized in neurons of the human hippocampus and is capable of degrading the amyloid-beta peptide (1–40). J Neurosci 16(24):7910–7919
Higaki J, Catalano R, Guzzetta AW, Quon D, Nave JF, Tar- 

 sistemas in Alzheimer’s disease—friend or foe? Trends Neurosci 32(12):619–628. 

doi:10.1016/j.tins.2009.07.006 

Miners JS, Ashby E, Van Helmond Z, Chalmers KA, Palmer 

reduced by the cysteine protease inhibitor E64d, representing 

Miller BC, Eckman EA, Sambamurti K, Dobbs N, Chow KM, 

Eckman EA, Reed DK, Eckman CB (2001) Degradation of the 

Carty NC, Nash K, Lee D, Mercer M, Gottschall PE, Meyers 

Russell FD, Skepper JN, Davenport AP (1998) Human endothe-

etendin-converting enzyme. Circ Res 83(3):314–321 

Toneff T, Kindy M, Hook V (2014) Brain pyro-

Muir EM, Adcock KH, Morgenstern DA, Clayton R, von Still- 

Fragkouli A, Tsilibary EC, Tzinia AK (2014) Neuroprotective 

Miller, Miners, Baig, Tayler, Speedy E, Prince JA, Love S, Kehoe PG (2009) Angiotensin-converting 

mines expressing human wild-type amyloid precursor 

Miller BC, Eckman EA, Sambamurti K, Dobbs N, Chow KM, 

Miller, Miners, Baig, Tayler, Speedy E, Prince JA, Love S, Kehoe PG (2009) Angiotensin-converting 

Hook V, Hook G, Kindy M (2010) Pharmacogenetic features of cathepsin B inhibitors that improve memory deficit and 

Mueller-Steiner S, Zhou Y, Arai H, Roberson ED, Sun B, Chen 

Mueller-Steiner S, Zhou Y, Arai H, Roberson ED, Sun B, Chen 

 Mueller-Steiner S, Ashby E, Van Helmond Z, 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(2):181–193. 

doi:10.1111/j.1650-312X.2014.05906.x 

Miners JS, Ashby E, Baig S, Harrison R, Taylor H, Speedy E, 

Zou K, Yamaguchi H, Akatsu H, Sakamoto T, Ko M, Mizoguchi 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(32):8628–8635. doi:10.1523/jneurosci.1549-07.2007 

Wang XB, Cui NH, Yang J, Qiu XP, Gao JJ, Yang N, Zheng F (2014) Angiotensin-converting enzyme insertion/deletion polymorphism is not a major determining factor in the development of sporadic Alzheimer disease: evidence from an updated meta-analysis. PloS One 9(10):e111406. doi:10.1371/journal.pone.0111406 

Zou K, Maeda T, Watanabe A, Liu J, Liu S, Oba R, Satoh Y, Komano H, Michikawa M (2009) Abeta42-to-Abeta40- and angiotensin-converting activities in different domains of angiotensin-converting enzyme. J Biol Chem 284(46):31914–31920. doi:10.1074/jbc.M109.011437 

Russell FD, Skepper JN, Davenport AP (1998) Human endothelial cell storage granules: a novel intracellular site for isofoms of the endothelin-converting enzyme. Circ Res 83(3):314–321 

Carty NC, Nash K, Lee D, Mercer M, Gottschall PE, Meyers 

Caccamo A, Oddo S, Sugarman MC, Akbari Y, LaFerla FM (2005) Age- and region-dependent alterations in Abeta-degrading enzymes: implications for Abeta-induced disorders. Neurobiol Aging 26(5):645–654. doi:10.1016/j. 

Cook DG, Leverenz JB, McMillan PJ, Kuldstad JJ, Ericksen S, Roth RA, Schellenberg GD, Jin LW, Kovacina KS, Craft S (2003) Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer’s disease is associated with the apolipoprotein E-epsilon4 allele. Am J Pathol 162(1):313–319 

Frargkouli A, Tsilibrary EC, Tzinia AK (2014) Neuroprotective role of MMP-9 overexpression in the brain of Alzheimer’s 5xFAD mice. Neurobiol Dis 70:179–189. doi:10.1016/j. 

Chong YH, Sung JH, Shin SA, Chung JH, Suh YH (2001) Effects of the beta-amyloid and carboxyl-terminal fragment of Alzheimer’s amyloid precursor protein on the production of the tumor necrosis factor-alpha and matrix metalloproteinase-9 by human monocytic THP-1. J Biol Chem 276(26):23511–23517. doi:10.1074/jbc.M009466200 

Lee EJ, Moon PG, Baek MC, Kim HS (2014) Comparison of the effects of matrix metalloproteinase inhibitors on
TNF-alpha release from activated microglia and TNF-alpha converting enzyme activity. Biomol Ther (Seoul) 22 (5):414–419. doi:10.4062/biomolther.2014.099

218. Yong VW, Power C, Forsyth P, Edwards DR (2001) Metalloproteinases in biology and pathology of the nervous system. Nat Rev Neurosci 2(7):502–511. doi:10.1038/35081571

219. de Castro JC Jr, Burns CL, McDaid DJ, Romanic AM (2000) Metalloproteinase increases in the injured rat spinal cord. Neuroreport 11(16):3551–3554

220. Shiriotani K, Tsubuki S, Iwata N, Takaki Y, Harigaya W, Maruyama K, Kiyuro-Seo S, Kiyma H, Iwata H, Tomita T, Iwatsubo T, Saida TC (2001) Neprilysin degrades both amyloid beta peptides 1–40 and 1–42 most rapidly and efficiently among thiorphan- and phosphoramidon-sensitive endopeptidas. J Biol Chem 276(24):21895–21901. doi:10.1074/jbc.M008511200

221. Iwata N, Tsubuki S, Takaki Y, Watanabe K, Sekiguchi M, Hosoki E, Kawashima-Morishima M, Lee HJ, Hama E, Sekine-Aizawa Y, Saida TC (2000) Identification of the major Abeta 1–42-degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. Nat Med 6(2):143–150. doi:10.1016/S1074-7223(00)00054-2

222. Russo R, Borghi R, Markebsey W, Tabaton M, Piccini A (2005) Neprilysin decreases uniformly in Alzheimer’s disease and in normal aging. FEBS Lett 579 (27):6027–6030. doi:10.1016/j.febslet.2005.09.054

223. Iwata N, Tsubuki S, Takaki Y, Shiriotani K, Lu B, Gerard NP, Gerard C, Hama E, Lee HJ, Saida TC (2001) Metabolic regulation of brain Abeta by neprilysin. Science 292(5515):1550–1552. doi:10.1126/science.1059946

224. Huttonrauch M, Baches S, Gerth J, Bayer TA, Weggen S, Wirths O (2015) Neprilysin deficiency alters the neuropathological and behavioral phenotype in the 5XFAD mouse model of Alzheimer’s disease. JAD 44(4):1291–1302. doi:10.1016/j.jad.2014.12.026

225. Mouri A, Zou LB, Iwata N, Saida TC, Wang D, Wang MW, Noda Y, Nabeshima T (2006) Inhibition of neprilysin by thiorphan (i.c.v.) causes an accumulation of amyloid beta and impairment of learning and memory. Behav Brain Res 168(1):83–91. doi:10.1016/j.bbr.2005.10.014

226. Shimizu E, Kawahara K, Kajizono M, Sawada M, Nakayama H (2008) HI-4-induced selective clearance of oligomeric beta-amyloid peptide by rat primary type 2 microglia. J Immunol (Baltimore, Md: 1950) 181(9):6503–6513

227. Bernstein KE, Gonzalez-Villalobos RA, Giani JF, Shah K, Iwatsubo T, Tsubuki S, Takaki Y, Shirotani K, Tsubuki S, Iwata N, Takaki Y, Harigaya W, de Castro RC Jr, Burns CL, McAdoo DJ, Romanic AM (2000) Impaired proteasome function in Alzheimer’s disease. J Neurochem 75(1):436–439

228. Yang AJ, Chandswangbhuvana D, Margol L, Glabe CG (1998) Loss of endosomal/lysosomal membrane impermeability is an early event in amyloid Abeta–42 pathogenesis. J Neurosci Res 52(6):691–698

229. Umeda T, Tomiyama T, Sakama N, Tanaka S, Lambert MP, Klein WL, Mori H (2011) Intraneuronal amyloid beta oligomers cause cell death via endoplasmic reticulum stress, endosomal/lysosomal leakage, and mitochondrial dysfunction in vivo. J Neurosci Res 89(7):1031–1042. doi:10.1002/jnr.22640

230. Ji ZS, Mullendore R, Cheng H, Miranda RD, Huang Y, Mahley RW (2006) Reactivity of apolipoprotein E4 and amyloid beta peptide: lysosomal stability and neurodegeneration. J Biol Chem 281(5):2683–2692. doi:10.1074/jbc.M506646200

231. Brunk U, Brun A (1972) The effect of aging on lysosomal permeability in nerve cells of the central nervous system. An enzyme histochemical study in rat. Histochemistry 30(4):315–324

232. Ji ZS, Miranda RD, Newhouse YM, Weisgraber KH, Huang Y, Mahley RW (2002) Apolipoprotein E4 potentiates amyloid beta peptide-induced lysosomal leakage and apoptosis in neuronal cells. J Biol Chem 277(24):21821–21828. doi:10.1074/jbc.M1112109200

233. Echeverria V, Ducatenzeiler A, Dowd E, Janne J, Grant SM, Szfy M, Wandosell F, Avila J, Grimm H, Dunnett SB, Hartmann T, Alfonen L, Cuello AC (2004) Altered mitogen-activated protein kinase signaling, tau hyperphosphorylation and mild spatial learning dysfunction in transgenic rats expressing the beta-amyloid peptide intracellularly in hippocampal and cortical neurons. Neuroscience 129(3):583–592. doi:10.1016/j.neuroscience.2004.07.036

234. Oh S, Hong HS, Hwang E, Sim HJ, Lee W, Shin SJ, Mook-Jung I (2005) Amyloid peptide attenuates the proteasome activity in neuronal cells. Mech Ageing Dev 126(12):1292–1299. doi:10.1016/j.mad.2005.07.006

235. Frackowiak J, Wisniewski HM, Wegiel J, Merz GS, Iqbal K, Wang KC (1992) Ultrastructure of the microglia that phagocytose amyloid and the microglia that produce beta-amyloid fibrils. Acta Neuropathol (Berl) 84(3):225–233

236. Paresce DM, Chung H, Maxfield FR (1997) Slow degradation of aggregates of the Alzheimer’s disease amyloid beta protein by microglial cells. J Biol Chem 272(46):29390–29397

237. Majumdar A, Chung H, Dolios G, Wang R, Asamoah N, Lobel F, Maxfield FR (2008) Degradation of fibrillar forms of Alzheimer’s amyloid beta-peptide by macrophages. Neurobiol Aging 29(5):707–715. doi:10.1016/j.neurobiolaging.2006.12.001

238. Dahms NM, Lobel P, Kornfeld S (1989) Mannose 6-phosphate receptors and lysosomal enzyme targeting. J Biol Chem 264(21):12115–12118

239. Shimizu E, Kawahara K, Kajizono M, Sawada M, Nakayama H (2008) HI-4-induced selective clearance of oligomeric beta-amyloid peptide by rat primary type 2 microglia. J Immunol (Baltimore, Md: 1950) 181(9):6503–6513

240. Bernstein KE, Gonzalez-Villalobos RA, Giani JF, Shah K, Bernstein E, Janjulia T, Koronyo Y, Shirotani K, Tsubuki S, Iwata N, Takaki Y, Harigaya W, de Castro RC Jr, Burns CL, McAdoo DJ, Romanic AM (2000) Impaired proteasome function in Alzheimer’s disease. J Neurochem 75(1):436–439

241. Majumdar A, Chung H, Dolios G, Wang R, Asamoah N, Lobel F, Maxfield FR (2008) Degradation of fibrillar forms of Alzheimer’s amyloid beta-peptide by macrophages. Neurobiol Aging 29(5):707–715. doi:10.1016/j.neurobiolaging.2006.12.001

242. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

243. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

244. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

245. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

246. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

247. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

248. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

249. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

250. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200

251. Tiribuzi R, Crispoltoni L, Porcellati S, Di Lullo M, Florenzano M,008511200
248. Tian Y, Chang JC, Greengard P, Flajolet M (2014) The convergence of endosomal and autophagosomal pathways: implications for APP-CTF degradation. Autophagy 10(4):694–696. doi:10.4161/auto.27802

249. Boland B, Kumar A, Lee S, Platt FM, Wegiel J, Yu WH, Nixon RA (2008) Autophagy induction and autophagic clearance in neurons: relationship to autophagic pathology in Alzheimer’s disease. J Neurosci 28(27):6926–6937. doi:10.1523/jneurosci.0808-08.2008

250. Nixon RA (2007) Autophagy, amyloidogenesis and Alzheimer disease. J Cell Sci 120(Pt 23):4081–4091. doi:10.1242/jcs.019265

251. Correia SC, Resende R, Moreira PI, Pereira CM (2015) Alzheimer’s disease-related misfolded proteins and dysfunctional organelles on autophagy menu. DNA Cell Biol 34 (4):261–273. doi:10.1089/dna.2014.2757

252. Lipinski MM, Zheng B, Lu T, Yan Z, Py BF, Ng A, Xavier RJ, Li C, Yankner BA, Scherzer CR, Yuan J (2010) Genome-wide analysis reveals mechanisms modulating autophagy in normal brain aging and in Alzheimer’s disease. Proc Natl Acad Sci USA 107(32):14164–14169. doi:10.1073/pnas.1009485107

253. Nilsson P, Loganathan K, Sekiguchi M, Matsuba Y, Hui K, Tsukuki S, Tanaka M, Iwata N, Saito T, Saito TC (2013) Abeta secretion and plaque formation depend on autophagy. Cell Rep 5(1):61–69. doi:10.1016/j.celrep.2013.08.042

254. Pickford F, Masliah E, Britschgi M, Lucin K, Narasimhan R, Correia T, Bredesen D, Richardson A, Strong R, Galvan V (2010) Inhibition of mTOR by rapamycin abolishes cognitive deficits in normal aging. J Neurosci Res 62(2):302–310. doi:10.1002/jnr.21515

255. Jung CH, Ro SH, Cao J, Otto NM, Kim DH (2010) mTOR regulation of autophagy. FEBS Lett 584 (7):1287–1295. doi:10.1016/j.febslet.2010.01.017

256. Kuma A, Hatanou M, Matsu M, Yamamoto A, Nakaya H, Yoshimori T, Osunteers Y, Kuchisaka T, Mizushima N (2004) The role of autophagy during the early neonatal starvation period. Nature 432(2004):1032–1036. doi:10.1038/nature03029

257. Scherz-Shouval R, Elazar Z (2007) ROS, mitochondria and aging. Ageing Res Rev 1(2):279–293. doi:10.1016/j.ager.2006.12.003

258. Li X, Alafuzoff I, Soininen H, Winblad B, Pei JJ (2005) Apolipoprotein E: cholesterol transport, barrier transcytosis and clearance. Nat Neurosci 8(7):1071–1077. doi:10.1038/nn1402

259. Li X, Alafuzoff I, Soininen H, Winblad B, Pei JJ (2005) Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides. Nat Med 11(10):1071–1077. doi:10.1097/NEN.0b013e3181f3a7b1

260. Li X, Alafuzoff I, Soininen H, Winblad B, Pei JJ (2005) Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides. Nat Med 11(10):1071–1077. doi:10.1097/NEN.0b013e3181f3a7b1

261. Liang WS, Fu WC, Younkin SG (2010) Replication of the late-onset Alzheimer’s disease CN gene association in a China population. Neurobiol Aging 31(9):1395–1403. doi:10.1016/j.neurobiolaging.2008.02.003

262. Tseng BP, Green KN, Chan JL, Blument-Jones M, LaFerla FM (2008) Abeta inhibits the proteasome and enhances amyloid and tau accumulation. Neurobiol Aging 29(11):1607–1618. doi:10.1016/j.neurobiolaging.2007.04.014

263. Tarassoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, Frangione B, Blennow K, Manend J, Zetterberg H, Wisniewski T, de Leon MJ (2015) Clearance systems in the brain-implications for Alzheimer disease. Nat Rev Neurol 11(8):457–470. doi:10.1038/nrneurol.2015.119

264. Deane R, Wu Z, Sagare A, Davis J, Du Yan S, Hamm K, Xu F, Parisi M, LaRue B, Hu HW, Spijkers P, Guo H, Song X, Lenting PJ, Van Nostrand WE, Zlokovic BV (2004) LRPs/amyloid beta-peptide interaction mediates differential brain efflux of Abeta isoforms. Neuron 43(3):333–344. doi:10.1016/j.neuron.2004.07.017

265. Elali A, Rives S (2013) The role of ABCB1 and ABCA1 in beta-amyloid clearance at the neurovascular unit in Alzheimer’s disease. Front Physiol 4:45. doi:10.3389/fphys.2013.00045

266. Jaeger LB, Rohu S, Hwang R, McCra SA, Murphy MP, Fleegel-DeMotta MA, Lynch JL, Robinson SM, Niehoff ML, Johnson SN, Kumar VB, Banks WA (2009) Testing the neurovascular hypothesis of Alzheimer’s disease: LRPI-antismone reduces blood-brain barrier clearance, increases brain levels of amyloid-beta protein, and improves cognition. JAD 17(3):553–570. doi:10.3331/jad.2009-1074

267. Silverberg GD, Messier AA, Miller MC, Machan JT, Majmundar SS, Stopa EG, Donahue JE, Johnson CE (2010) Amyloid efflux transporter expression at the blood-brain barrier declines in normal aging. J Neuropathol Exp Neurol 69(10):1034–1043. doi:10.1097/NEN.0b013e3181f46e25

268. Koistinaho M, Lin S, Wu X, Esterman M, Kogler 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(7):719–726. doi:10.1038/nm1058

269. Laporte V, Lombard Y, Levy-Benezra R, Tranchant C, Poirson P, Warter JM (2004) Uptake of Abeta 1-40 and Abeta 1-42 coated yeast by microglial cells: a role for LRPJ. Neurobiol Aging 25(10):1177–1184. doi:10.1016/j.neurobiolaging.2004.03.017

270. Elali A, Rives S (2013) The role of ABCB1 and ABCA1 in beta-amyloid clearance at the neurovascular unit in Alzheimer’s disease. Front Physiol 4:45. doi:10.3389/fphys.2013.00045

271. Kanekiyo T, Cirrito JR, Liu CC, Shihara M, Li J, Schuler DR, Shihara M, Holtzman DM, Bu G (2013) Neuronal clearance of amyloid-beta by endocytic receptor LRPI. J Neurosci 33(49):19276–19283. doi:10.1523/jneurosci.3487-13.2013

272. Baig S, Joseph SA, Taylor H, Abraham R, Owen MJ, Williams J, Kehoe PG, Love S (2010) Distribution and expression of picalm in Alzheimer disease. J Neuropathol Exp Neurol 69(10):1071–1077. doi:10.1097/NEN.0b013e3181f52e01

273. Carrasquillo MM, Bellin O, Hunter TA, Ma L, Bisceglio GD, Zou F, Crook JE, Pankratz VS, Dickson DW, Schneider JA, Ahuja A, Zhu D, Miller CA, Schneider JA, Zou F, Crook JE, Pankratz VS, Dickson DW, Schro-Raford NR, Petersen RC, Morgan K, Younkin SG (2010) Replication of CLU, CR1, and PICALM associations with alzheimer disease. Arch Neurol 67(8):961–964. doi:10.1001/archneurol.2010.147

274. Zhao Z, Sagare AP, Ma Q, Halliday MR, Kong P, Kiser L, Winkler EA, Ramamathan 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-beta blood-brain barrier transcytosis and clearance. J Neurosci 35(7):2882–2891. doi:10.1523/jneurosci.5305-14.2015

275. Mahley RW (1988) Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science 240(4852):622–630

276. Beisiegel U, Weber W, Ihle G, Her R, Stanley KK (1989) The LDL-receptor-related protein, LRP, is an
apolipoprotein E-binding protein. Nature 341(6238):162–164. doi:10.1038/341162a0

277. Kim DH, Iijima H, Goto K, Sakai J, Ishii H, Kim HJ, Suzuki H, Kondo H, SaeKI S, Yamamoto T (1996) Human apolipoprotein E receptor 2. A novel lipoprotein receptor of the low density lipoprotein receptor family predominantly expressed in brain. J Biol Chem 271(41):8373–8380

278. Kanekiyo T, Xu H, Bu G (2014) ApoE and Abeta in Alzheimer’s disease: accidental encounters or partners? Neuron 81(4):740–754. doi:10.1016/nejm.2014.01.045

279. Raber J, Huang Y, Ashford JW (2004) ApoE genotype accounts for the vast majority of AD risk and AD pathology. Neurobiol Aging 25(5):641–650. doi:10.1016/j.neurobiolaging.2003.12.023

280. Holtzman DM, Bales KR, Tenkova T, Fagan AM, Parsadahan M, Sartorius LJ, Mackey B, Olney J, McKeel D, Wozniak D, Paul SM (2000) Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer’s disease. Proc Natl Acad Sci USA 97(6):2892–2897. doi:10.1073/pnas.050004797

281. Schmechel DE, Saunders AM, Strittmatter WJ, Pericak-Vance MA, Goldgaber D, Roses AD (1993) Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proc Natl Acad Sci USA 90(20):9649–9653

282. Strittmatter WJ, Saunders AM, Schmechel DE, Pericak-Vance MA, Englund J, Salvesen GS, Roses AD (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 90(5):1977–1981

283. Shinohara M, Petersen RC, Dickson DW, Bu G (2013) Brain regional correlation of amyloid-beta with synapses and apolipoprotein E in non-demented individuals: potential mechanisms underlying regional vulnerability to amyloid-beta accumulation. Acta Neuropathol (Berl) 125(4):535–547. doi:10.1007/s00401-013-1086-9

284. Mulder SD, Nielsen HM, Blankenstein MA, Eikelenboom P, Veerhuis R (2014) Apolipoproteins E and J interfere with amyloid-beta uptake by primary human astrocytes and microglia in vitro. Glia 62(4):493–503. doi:10.1002/glia.22619

285. Morris JC, Roe CM, Xiong C, Fagan AM, Holtzman DM, Mintun MA (2010) APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol 67(1):122–131. doi:10.1002/ana.21843

286. LaDu MJ, Falduto MT, Manelli AM, Reardon CA, Getz GS, Frail DE (1994) Isoform-specific binding of apolipoprotein E to beta-amyloid. J Biol Chem 269(38):23403–23406

287. Wildsmith KR, Holley M, Savage JC, Skerrett R, Landreth GE (2013) Evidence for impaired amyloid beta clearance in Alzheimer’s disease. Alzheimer’s Res Ther 5(4):33. doi:10.1186/alztr1187

288. Donahue JE, Johanson CE (2008) Apolipoprotein E, amyloid-beta, and blood-brain barrier permeability in Alzheimer disease. J Neuruphath Exp Neurol 67(4):261–270. doi:10.1097/NEN.0b013e31816adec8

289. Nishitsuji K, Hosono T, Nakamura T, Bu G, Michikawa M (2011) Apolipoprotein E regulates the integrity of tight junctions in an isoform-dependent manner in an in vitro blood-brain barrier model. J Biol Chem 286(20):17536–17542. doi:10.1074/jbc.M111.225532

290. Rodriguez GA, Tai LM, LaDu MJ, Rebeck GW (2014) Human APOE4 increases microglia reactivity at Abeta plaques in a mouse model of Abeta deposition. J Neuroinflmm 11:111. doi:10.1186/1742-2094-11-111

291. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O’Donnell J, Christensen DJ, Nicholson C, Iliff JJ, Takano T, Deane R, Nedergaard M (2013) Sleep drives metabolite clearance from the adult brain. Science 342(6156):373–377. doi:10.1126/science.1241124

292. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecke NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J (2015) Structural and functional features of central nervous system lymphatic vessels. Nature 523(7560):337–341. doi:10.1038/nature14432

293. Aspeltun A, Antila S, Proulx ST, Karlens TV, Karaman S, Det-ter Meulen V (1991) Isolation and direct characterization of normal adult ramified microglia separated from other central nervous system macrophages by flow cytometric sorting. Phe-notypic differences defined and direct ex vivo antigen presentation to myelin basic protein-reactive CD4+ T cells compared. J Immunol (Baltimore, Md: 1950) 154(9):4309–4321
305. Juedes AE, Ruddle NH (2001) Resident and infiltrating central nervous system APCs regulate the emergence and resolution of experimental autoimmune encephalomyelitis. J Immunol (Baltimore, Md: 1950) 165(6):5168–5175

306. Butovsky O, Jedrychowski MP, Moore CS, Cialric R, Lanser AJ, Gabriely G, Koeiglsperger T, Dake B, Wu PM, Doykan CE, Fanek Z, Liu L, Chen Z, Rothstein JD, Ransohoff RM, Gygi SP, Antel JP, Weiner HL (2014) Identification of a unique TGF-beta-dependent molecular and functional signature in microglia. Nat Neurosci 17(1):131–143. doi:10.1038/nn.3599

307. Prinz M, Priller J (2014) Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. Nat Rev Neurosci 15(5):300–312. doi:10.1038/nrn3722

308. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K (2010) Development of monocytes, macrophages, and dendritic cells. Science 327(5966):656–661. doi:10.1126/science.1178331

309. Paolicelli RC, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, Ragozzino D, Gross CT (2011) Sustained pruning by microglia is necessary for normal brain development. Science 333(6048):1456–1458. doi:10.1126/science.120259

310. Chung WS, Welsh CA, Barres BA, Stevens B (2015) Do glia drive synaptic and cognitive impairment in disease? Nat Neurosci 18(11):1539–1545. doi:10.1038/nn.4142

311. Naert G, Rivest S (2012) Age-related changes in synaptic markers and monocyte subsets link the cognitive decline of APP(Swe)PS1 mice. Front Cell Neurosci 6:51. doi:10.3389/fncel.2012.00051

312. Boissonnault V, Filali M, Lessard M, Relton J, Wong G, Rivest S (2009) Powerful beneficial effects of macrophage colony-stimulating factor on beta-amyloid deposition and cognitive impairment in Alzheimer’s disease. Brain 132(Pt 4):1078–1092. doi:10.1093/brain/awn331

313. Town T, Lauaro Y, Pittenger C, Mori T, Szekely CA, Tan J, Duman RS, Flavell RA (2008) Blocking TGF-beta-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. Nat Med 14(6):681–687. doi:10.1038/nm1781

314. 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 neurodegeneration and rescues spatial cognitive impairment in a transgenic mouse model of Alzheimer’s disease. Neuropsychopharmacology 39(13):2949–2962. doi:10.1038/npp.2014.164

315. Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, Xu G, Margevicius D, Karlo JC, Sousa GL, Cotleur AC, Butovsky O, Bekris L, Staugaitis SM, Leverenz JB, Pimplikar SW, Landreth GE, Howell GR, Ransohoff RM, Lamb BT (2015) TREM2 deficiency eliminates TREM2 + inflammatory macrophages and ameliorates pathology in Alzheimer’s disease mouse models. J Exp Med 212(3):287–295. doi:10.1084/jem.20142322

316. Xiang X, Werner G, Bohrmann B, Liesz A, Mazarperi F, Capell A, Feederle R, Knesel I, Kleinberger G, Haass C (2016) TREM2 deficiency reduces the efficacy of immunotherapeutic amyloid clearance. EMBO Mol Med. doi:10.15222/emmm.201606370

317. Frenkel D, Wilkinson K, Zhao L, Hickman SE, Means TK, Puckett L, Farfara D, Kingery ND, Weiner HL, El Khoury J (2013) Scarel deficiency impairs clearance of soluble amyloid-beta mononuclear phagocytes and accelerates Alzheimer-like disease progression. Nature Commun 4:2030. doi:10.1038/ncomms3030

318. Yamamoto M, Kiyota T, Walsh SM, Liu J, Kipnis J, Izeeu T (2008) Cytokine-mediated inhibition of fibrillary amyloid-beta peptide degradation by human mononuclear phagocytes. J Immunol (Baltimore, Md: 1950) 181(6):3877–3886

319. Hu N, Tan MS, Sun L, Jiang T, Wang YL, Tan L, Zhang W, Yu JT, Tan L (2014) Decreased expression of CD33 in peripheral mononuclear cells of Alzheimer’s disease patients. Neurosci Lett 565:51–54. doi:10.1016/j.neulet.2014.01.004

320. Zhang R, Miller RG, Madison C, Jin X, Honrada R, Har - yama M, Kiyota T, Walsh SM, Ikezu T, Naert G, Rivest S (2012) Age-related changes in synaptic markers and monocyte subsets link the cognitive decline of APP(Swe)PS1 mice. Front Cell Neurosci 6:51. doi:10.3389/fncel.2012.00051

321. Butovsky O, Jedrychowski MP, Moore CS, Cialric R, Lanser AJ, Gabriely G, Koeiglsperger T, Dake B, Wu PM, Doykan CE, Fanek Z, Liu L, Chen Z, Rothstein JD, Ransohoff RM, Gygi SP, Antel JP, Weiner HL (2014) Identification of a unique TGF-beta-dependent molecular and functional signature in microglia. Nat Neurosci 17(1):131–143. doi:10.1038/nn.3599

322. Boissonnault V, Filali M, Lessard M, Relton J, Wong G, Rivest S (2009) Powerful beneficial effects of macrophage colony-stimulating factor on beta-amyloid deposition and cognitive impairment in Alzheimer’s disease. Brain 132(Pt 4):1078–1092. doi:10.1093/brain/awn331

323. Town T, Lauaro Y, Pittenger C, Mori T, Szekely CA, Tan J, Duman RS, Flavell RA (2008) Blocking TGF-beta-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. Nat Med 14(6):681–687. doi:10.1038/nm1781

324. 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 neurodegeneration and rescues spatial cognitive impairment in a transgenic mouse model of Alzheimer’s disease. Neuropsychopharmacology 39(13):2949–2962. doi:10.1038/npp.2014.164

325. Jay TR, Miller CM, Cheng PJ, Graham LC, Bemiller S, Broihier ML, Xu G, Margevicius D, Karlo JC, Sousa GL, Cotleur AC, Butovsky O, Bekris L, Staugaitis SM, Leverenz JB, Pimplikar SW, Landreth GE, Howell GR, Ransohoff RM, Lamb BT (2015) TREM2 deficiency eliminates TREM2 + inflammatory macrophages and ameliorates pathology in Alzheimer’s disease mouse models. J Exp Med 212(3):287–295. doi:10.1084/jem.20142322

326. Xiang X, Werner G, Bohrmann B, Liesz A, Mazarperi F, Capell A, Feederle R, Knesel I, Kleinberger G, Haass C (2016) TREM2 deficiency reduces the efficacy of immunotherapeutic amyloid clearance. EMBO Mol Med. doi:10.15222/emmm.201606370

327. Frenkel D, Wilkinson K, Zhao L, Hickman SE, Means TK, Puckett L, Farfara D, Kingery ND, Weiner HL, El Khoury J (2013) Scarel deficiency impairs clearance of soluble amyloid-beta mononuclear phagocytes and accelerates Alzheimer-like disease progression. Nature Commun 4:2030. doi:10.1038/ncomms3030

328. Yamamoto M, Kiyota T, Walsh SM, Ikezu T (2007) Kinetic analysis of aggregated amyloid-beta peptide clearance in adult bone-marrow-derived macrophages from APP and CCL2 transgenic mice. J Neuroimmune Pharmacol 2(2):213–221. doi:10.1007/s11481-006-9049-8

329. Hawkes CA, McLaurin J (2009) Selective targeting of perivascular macrophages for clearance of beta-amyloid in cerebral amyloid angiopathy. Proc Natl Acad Sci USA 106(4):1261–1266. doi:10.1073/pnas.0805453106

330. Michaud JP, Bellavance MA, Prefontaine P, Rivest S (2013) Real-time in vivo imaging reveals the ability of monocytes to clear vascular amyloid beta. Cell Rep 5(3):646–653. doi:10.1016/j.celrep.2013.10.010

331. Milh transformers, Bachovchin BA, Kierdorff K, Bottcher C, Erny D, Kummer MP, Quinn M, Bruck W, Bechmann I, Heneka MT, Priller J, Prinz M (2011) Distinct and non-redundant roles of microglia and myeloid subsets in mouse models of Alzheimer’s disease. J Neurosci 31(11):11159–11171. doi:10.1523/jneurosci.6209-10.2011

332. Naert G, Rivest S (2011) CC chemokine receptor 2 deficiency aggravates cognitive impairments and amyloid pathology in a transgenic mouse model of Alzheimer’s disease. J Neurosci 31(16):6208–6220. doi:10.1523/jneurosci.0299-11.2011
Otin M, Pamplona R, Pujol A, Ferrer I (2015) Neuroinflammatory disease—a double-edged sword. Neuron 35(3):419–432. doi:10.1016/j.neuron.2004.04.004

Krabbe G, Halle A, Matyash V, Rinnenthal JL, Eom GD, Koenigsknecht J, Landreth GE (2004) Microglial phagocytosis of fibrillar beta-amyloid through a betal integrin-dependent mechanism. J Neurosci 24(44):9838–9846. doi:10.1523/jneurosci.2557-04.2004

Kolb WE, Kohlsaka S, Jucker M, Calhoun ME (2008) Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. J Neurosci 28(16):4283–4292. doi:10.1523/jneurosci.4814-07.2008

Hellwig S, Masuch A, Nestel S, Katzmarski N, Meyer-Luehmann M, Biber K (2015) Forebrain microglia from wild-type but not adult 5xFAD mice prevent amyloid-beta plaque formation in organotypic hippocampal slice cultures. Sci Rep 5:14624. doi:10.1038/srep14624

Wyss-Coray T, Rogers SD, Ghilardi JR, Finke MP, Cleary JP, O'Hare E, Esler WP, Maggio JE, Mantyh PW (1998) Fibrillar Alzheimer beta-amyloid. Am J Pathol 140(6):1389–1399

Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, CSHperspect.a006346

Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, Mathys H, Seo J, Kritskiy O, Abdurrob F, Adailkan C, Cantner RG, Rueda B, Brown EN, Boyd ES, Tsai LH (2016) Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 540(7632):230–235. doi:10.1038/nature20587

Michell-Robinson MA, Toull H, Healy LM, Owen DR, Duranteau BA, Bar-Or A, Antel JP, Moore CS (2015) Roles of microglia in brain development, tissue maintenance and repair. Brain J Neur 138(Pt 5):1138–1159. doi:10.1093/brain/awv066

Mildner A, Schmidt H, Nitsche M, Merkler D, Hanisch UK, Mack M, Heikenwalder M, Bruck W, Priller J, Prinz M (2007) Microglia in the adult brain arise from Ly-6ChiCCR2 + monocytes only under defined host conditions. Nat Neurosci 10(12):1544–1553. doi:10.1038/nn2015

Prokop S, Miller KR, Drost N, Hendrick S, Mathur V, Luo J, Wegner A, Wyss-Coray T, Heppner FL (2015) Impact of peripheral myeloid cells on amyloid-beta pathology in Alzheimer’s disease-like mice. J Exp Med 212(11):1811–1818. doi:10.1084/jem.20150479

Jung ME, Grafton SA, Deghardin G, Resch C, Bosch A, Jucker M, Neher JJ (2015) Replacement of brain-resident peripheral myeloid cells on amyloid-beta deposition in mouse models of Alzheimer’s disease. J Exp Med 212(11):1803–1809. doi:10.1084/jem.20150478

Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM (2007) Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. Nat Neurosci 10(12):1538–1543. doi:10.1038/nn2014

Zaghi J, Goldenson B, Inayathullah M, Lossinsky AS, Masoumi A, Avagyan H, Mahanian M, Bernas M, Weinand M, Rosenthal MJ, Espinosa-Jeffrey A, de Vellis J, Teplow DB, Fiala M (2009) Alzheimer disease macrophages shuttle amyloid-beta from neurons to vessels, contributing to amyloid angiopathy. Acta Neuropathol (Berl) 117(2):111–124. doi:10.1007/s00401-008-0481-0

Ard MD, Cole GM, Wei J, Mehrle AP, Fratkin JD (1996) Scavenging of Alzheimer’s amyloid beta-protein by microglia in culture. J Neurosci Res 43(2):190–202. doi:10.1002/jnr.4980430200

Frautschy SA, Cole GM, Baird A (1992) Phagocytosis and deposition of vascular beta-amyloid in rat brains injected with Alzheimer beta-amyloid. Am J Pathol 140(6):1389–1399

Weldon DT, Rogers SD, Gihlardi JR, Finke MP, Cleary JP, O’Hare E, Esler WP, Maggio JE, Manthey PW (1998) Fibrillar...
beta-amyloid induces microglial phagocytosis, expression of inducible nitric oxide synthase, and loss of a select population of neurons in the rat CNS in vivo. J Neurosci 18(6):2161–2173

Akiyama H, Schwab C, Kondo H, Mori H, Kametani F, Ikeda K, McGeer PL (1996) Granules in glial cells of patients with Alzheimer’s disease are immunopositive for C-terminal sequences of beta-amyloid protein. Neurosci Lett 206(2–3):169–172

Wilkinson K, Boyd JD, Glicksman M, Moore KJ, El Khoury J (2011) A high content drug screen identifies uroside acid as an inhibitor of amyloid beta-protein interactions with its receptor CD36. J Biol Chem 286(40):34914–34922. doi:10.1074/jbc.M111.232116

Udan ML, Ajit D, Crouse NR, Nichols MR (2008) Toll-like receptors 2 and 4 mediate Abeta(1–42) activation of the innate immune response in a human monocytic cell line. J Neurochem 104(2):524–533. doi:10.1111/j.1471-4159.2007.05001.x

Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE (2009) Uptake of fibrillar beta-amyloid by microglia isolated from MSR-A (type I and type II) knockout mice. Neuroreport 20(7):669–672. doi:10.1097/WNR.0b013e32831f5a3d

Chung H, Brail M, Irizarry MC, Hyman BT, Maxfield FR (2001) Uptake of fibrillar beta-amyloid by microglia isolated from MSR-A (type I and type II) knockout mice. Neuroreport 12(6):1151–1154

Bakalash S, Pham M, Koronyo Y, Salumbides BC, Kramerov A, Seidenberg H, Berel D, Black KL, Koronyo-Hamaoui M (2011) Egr1 expression is induced following glatiramer acetate immunotherapy in rodent models of glaucoma and Alzheimer’s disease. Invest Ophthalmol Vis Sci 52(12):9033–9046. doi:10.1167/iovs.11-7498

Wilkinson K, El Khoury J (2012) Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer’s disease. Int J Alzheimers Dis 2012:849456. doi:10.1155/2012/849456

Bornemann KD, Wiederhold KH, Paulli C, Ermini F, Stalder M, Schnell L, Sommer B, Jucker M, Staufenbiel M (2001) Abeta-induced inflammatory processes in microglia cells of APP23 transgenic mice. Am J Pathol 158(1):63–73

Christie RH, Freeman M, Hyman BT (1996) Expression of the macrophage scavenger receptor, a multifunctional lipoprotein receptor, in microglia associated with senile plaques in Alzheimer’s disease. Am J Pathol 148(2):399–403

Yu Y, Ye RD (2015) Microglial Abeta receptors in Alzheimer’s disease. Cell Mol Neurobiol 35(1):71–83. doi:10.1007/s10571-014-0101-6

El Khoury JB, Moore KJ, Means TK, Leung J, Terada K, Toft J, Freeman MW, Luster AD (2003) CD36 mediates the innate host response to beta-amyloid. J Exp Med 197(12):1657–1666. doi:10.1084/jem.20021546

Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhelawon B, Carpenter SB, Becker CE, Edirweera HN, Mullick AE, Golenbock DT, Stewart CA, Latz E, Fitzgerald KA, Moore KJ (2013) CD36 coordinates NLRP3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. Nat Immunol 14(8):812–820. doi:10.1038/ni.2639
and microglial cells. J Immunol (Baltimore, Md: 1950) 157 (3):1213–1218
390. London A, Cohen M, Schwartz M (2013) Microglia and monocyte-derived macrophages: functionally distinct populations that act in concert in CNS plasticity and repair. Front Cell Neurosci 7:34. doi:10.3389/fncel.2013.00034
391. Shechter R, Raposo C, London A, Sagi I, Schwartz M (2011) The glial scar-macrophage interplay: a pivotal resolution phase in spinal cord repair. PloS One 6(12):e27969. doi:10.1371/journal.pone.0027969
392. Huang D, Wujek J, Kidd G, He TT, Cardona A, Sasse ME, Stein EJ, Kish J, Tani M, Charo IF, Proudfoot AE, Rollins BJ, Hanel T, Ransohoff RM (2005) Chronic expression of monocyte chemotactic protein-1 in the central nervous system causes delayed encephalopathy and impaired microglial function in mice. FASEB J 19(7):761–772. doi:10.1096/fj.04-3104com
393. Deane R, Bell RD, Sagare A, Zlokovic BV (2009) Clearance of amyloid-beta peptide across the blood-brain barrier: implication for therapies in Alzheimer’s disease. CNS Neurol Disord Drug Targ 8(1):16–30
394. 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 USA 109(9):3510–3515. doi:10.1073/pnas.1112209109
395. Villeda SA, Luo J, Mosher KL, Zou B, Britschgi M, Bieri G, Stan TM, Fainberg N, Ding Z, Eggel A, Lucin KM, Czirr E, Park JS, Couillard-Despres S, Aigner L, Li G, Peskind ER, Kaye JA, Quinn JF, Galasko DR, Xie XS, Rando TA, Wyss-Coray T (2011) The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature 477(7362):90–94. doi:10.1038/nature10357
396. Villeda SA, Plambeck KE, Middeldorp J, Castellano JM, Mosher KL, Luo J, Smith LK, Bieri G, Lin K, Berndik D, Wabl R, Udeochu J, Wheatley EG, Zou B, Simmons DA, Xie XS, Longo FM, Wyss-Coray T (2014) Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med 20(6):659–663. doi:10.1038/nm.3569
397. 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 (Berl) 130(4):487–499. doi:10.1007/s00401-015-1477-1
398. Yang F, Lim GP, Begum AN, Ubeda OJ, Simmons MR, Ambegaokar SS, Chen PP, Kayed R, Glabe CG, Frautschy SA, Cole GM (2005) Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques, and reduces amyloid in vivo. J Biol Chem 280(7):5892–5901. doi:10.1074/jbc.M404751200
399. Zhang L, Fiala M, Cashman J, Sayre J, Espinosa A, Mahanian M, Zaghi J, Badmaev V, Graves MC, Bernard G, Rosenthal M (2006) Curcuminoids enhance amyloid-beta uptake by macrophages of Alzheimer’s disease patients. JAD 10(1):1–7
400. Baruch K, Deczkowska A, Rosenzweig N, Tsitsou-Kampeli A, Sharir AM, Matcovitch-Natan O, Kertser A, David E, Amit I, Schwartz M (2016) PD-1 immune checkpoint blockade reduces pathology and improves memory in mouse models of Alzheimer’s disease. Nat Med 22(2):135–137. doi:10.1038/nm.4022