Published in final edited form as:

J Neural Transm. 2010 August ; 117(8): 949–960. doi:10.1007/s00702-010-0433-4.

The role of microglia in amyloid clearance from the AD brain

C. Y. Daniel Lee and Gary E. Landreth

School of Medicine, Case Western Reserve University, SOM E649, 10900 Euclid Avenue, Cleveland, OH 44106-4928, USA

C. Y. Daniel Lee: cydlee@case.edu; Gary E. Landreth: gel2@case.edu

Abstract

Alzheimer's disease (AD), the most prominent cause of senile dementia, is clinically characterized by the extracellular deposition of β -amyloid ($A\beta$) and the intra-cellular neurofibrillary tangles. It has been well accepted that AD pathogenesis arises from perturbation in the homeostasis of $A\beta$ in the brain. $A\beta$ is normally produced at high levels in the brain and cleared in an equivalent rate. Thus, even a moderate decrease in the clearance leads to the accumulation of $A\beta$ and subsequent amyloid deposition. Microglia are the tissue macrophages in the central nervous system (CNS) and have been shown to play major roles in internalization and degradation of $A\beta$. $A\beta$ exists in the brain both in soluble and in fibrillar forms. Microglia interact with these two forms of $A\beta$ in different ways. They take up soluble forms of $A\beta$ through macropinocytosis and LDL receptor-related proteins (LRPs) mediated pathway. Fibrillar forms of $A\beta$ interact with the cell surface innate immune receptor complex, initiating intracellular signaling cascades that stimulate phagocytosis. Inflammatory responses influence the activation status of microglia and subsequently regulate their ability to take up and degrade $A\beta$. ApoE and its receptors have been shown to play critical roles in these processes. In this review, we will explore the mechanisms that microglia utilize to clear $A\beta$ and the effectors that modulate the processes.

Keywords

Microglia; Abeta; Abeta receptor complex; Inflammation; Apolipoprotein E

Introduction

It has now been 100 years since the first description of a patient with Alzheimer's disease (AD). It is remarkable that we know much about the disease, yet understand comparatively less about its etiology and risk factors for the disease. Extracellular deposits of fibrillar β -amyloid ($A\beta$) and the intracellular neurofibrillary tangles composed of hyperphosphorylated tau are the distinctive hallmarks of AD. It is the most common form of senile dementia and is characterized by progressive cognitive impairment and profound neuronal loss. The senile plaques arise from the aggregation of $A\beta$ peptides which are generated through sequential proteolytic processing of the amyloid precursor protein (APP) (Hardy and Selkoe 2002). The accumulation of deposited amyloid within the brain is correlated with cognitive decline and neuronal loss (Nathalie and Jean-Noel 2008; Small et al. 2001). Thus, $A\beta$ homeostasis, with the efficient clearance of $A\beta$ from the brain, is essential to maintain the health of the brain. This review addresses the role of microglia and inflammation in disease pathogenesis and progression. Microglia are the professional phagocytes in the central nervous system (CNS). These cells play critical roles in the uptake and proteolytic clearance of both soluble and

fibrillary forms of A β . These cells also mediate a local inflammatory response in the AD brain, centered on the amyloid deposits, and the proinflammatory environment of the brain acts to regulate the capacity of these cells to perform normal A β homeostatic functions.

A β production, polymerization and the amyloid hypothesis

A β is generated through sequential proteolytic cleavage of the amyloid precursor protein (APP) by β - and γ -secretases (Hardy and Selkoe 2002). The predominant forms of A β in AD are 40 and 42 amino acid peptides, which polymerize into a variety of multimeric A β species and subsequently fibrillize, aggregate and are deposited within the parenchyma of the brain. Because of the two extra C-terminal amino acid residues, A β 42 is more hydrophobic than A β 40 and has a greater propensity to polymerize and form fibrils (Kirkitadze et al. 2001; Walsh et al. 1997). The amyloid hypothesis posits that the deposition of A β is the causative agent of AD pathogenesis, and that the neurofibrillary tangles, neuronal loss and eventually dementia follow as a direct result of this deposition (Hardy and Higgins 1992). Several lines of evidence from genetic studies of familial forms of AD support the pivotal role of A β in the pathogenesis of AD: (i) Trisomy 21 (Down's syndrome), which has an extra copy of the *App* gene located in chromosome 21, leads invariably to neuropathology of AD (Olson and Shaw 1969); (ii) mutations at or near the cleavage sites of β - and γ -secretase on the *App* gene (Goate et al. 1991; Hardy 1992; Hendriks et al. 1992; Mullan et al. 1992; Wisniewski et al. 1991b) or (iii) the mutations of γ -secretase constituents, *Psen1* and *Psen2*, result in increased production of A β 42 and consequently lead to early onset of AD (Cai et al. 1993; Citron et al. 1992; Suzuki et al. 1994). Although the familial forms of AD account for less than 5% of total AD patients, genetic analysis of heritable cases provided important insights into the pathogenesis of this disease. Transgenic mouse models of AD that develop A β plaques as they age have provided a valuable tool to test the hypothesis. Introducing human disease-related transgenes into mice recapitulates the amyloid pathology of AD as well as the cognitive impairment, but not neuronal loss (Dodart et al. 2002; Games et al. 1995). Administration of pharmacological inhibitors of β - or γ -secretase in these mice reduces amyloid deposition and ameliorates cognitive dysfunction (Comery et al. 2005; Dovey et al. 2001; Sinha et al. 1999). A β is secreted from neurons as a consequence of normal synaptic transmission (Cirrito et al. 2005; Kamenetz et al. 2003). Since A β peptides are normally generated at high levels in the brain (approximately 8% per hour) and are cleared at an equivalent rate both in humans and in mice (Bateman et al. 2006), even moderately increased production or decreased clearance of A β eventually leads to an overall elevation of its steady state levels and ultimately the enhanced deposition in the brain promoting AD pathogenesis.

Microglia

Microglia are the brain's tissue macrophages, and account for approximately 5% of the total cell population in the cerebral cortex of mice, but the abundance differs significantly between brain areas (Block et al. 2007; Lawson et al. 1990). They are the primary immune effector cells in the CNS. They originate from peripherally derived myeloid lineage progenitors and invade the CNS during embryogenesis, before the maturation of blood-brain barrier (BBB). In the mature brain microglia undergo self renewal by proliferation in situ (Ajami et al. 2007). However, whether peripheral myeloid cells can infiltrate the diseased brain remains controversial and will be discussed in the next section (Hess et al. 2004; Nakajima and Kohsaka 2001; Priller et al. 2001; Ransohoff and Perry 2009). Microglia are uniformly distributed in the brain at a density of about 6/mm³ (Nimmerjahn et al. 2005) and constantly survey their immediate environment for pathogens, foreign materials and apoptotic cells (Streit et al. 2004). It has been estimated that the resting microglia are able to completely screen the whole brain parenchyma once every few hours

by consistently extending and retracting their processes (Nimmerjahn et al. 2005). Upon injury, microglia rapidly extend processes to the site of injury, then migrate to the lesion sites, recognize the pathogen, ramify, and mount an immune response in response to the stimulus (Ransohoff and Perry 2009). In the brains of both AD patients and mouse disease models, microglia are found closely associated with the amyloid plaques and exhibit an 'activated' proinflammatory phenotype (Frautschy et al. 1998; Perlmutter et al. 1990). Microglia were initially postulated to play a role in the formation of amyloid deposition in the brain (Wisniewski and Frangione 1992), and subsequently shown not to do so. However, examination by electron microscopy of amyloid plaques showed that microglia are able to engulf A β with their processes and A β is observed in endosome-like cellular compartments (Frackowiak et al. 1992). Later in vitro studies using radioisotope or fluorescent labeled A β (Paresce et al. 1996) in combination with direct injection of fibrillar A β into rat brains (Pluta et al. 1999) further demonstrated the capability of microglia to internalize A β . The number and size of microglia increase in proportion to the size of plaques (Wegiel et al. 2001, 2003, 2004) to regulate plaque dynamics (Bolmont et al. 2008; Meyer-Luehmann et al. 2008; Perlmutter et al. 1990; Wisniewski and Frangione 1992; Yan et al. 2009). Recently, using in vivo imaging techniques, local resident microglia were visualized to rapidly extend their processes and migrate toward new plaques within 1–2 days of their appearance (Bolmont et al. 2008; Meyer-Luehmann et al. 2008). Internalization of systemically injected amyloid-binding dye at the vicinity of plaques provided direct evidence of the uptake of A β by microglia (Bolmont et al. 2008).

Resident versus infiltrating microglia

Historically, microglia were thought to enter the brain only during embryogenesis and then undergo modest self renewal, and in response to injury or pathogens they were stimulated to proliferate (Streit and Xue 2009). A number of studies have demonstrated that microglia are unable to eliminate β -amyloid deposits by phagocytosis (Wegiel et al. 2001, 2003, 2004). These findings support the view that plaque accumulation in the brain is due to the inability of microglia to effectively clear either soluble or fibrillar forms of A β . Specifically, it has been argued that phagocytic functions of microglia are impaired and this has been postulated to be a result of the proinflammatory environment of the AD brain (Bamberger et al. 2003; Koenigsnecht-Talboo and Landreth 2005). In 1989, Wisniewski et al., reported that following stroke in individuals with existing plaque pathology, the plaques were cleared owing to the action of peripheral macrophages that invaded the ischemic brain, suggesting that these plaques could be removed by phagocytosis and that endogenous microglia were distinct from macrophages in their ability to perform this function (Wisniewski et al. 1989, 1991a). However, the hematopoietic origin of microglia makes it difficult to discern the infiltrated and resident microglia. Despite tremendous efforts in the past years, monocyte-derived and resident CNS parenchymal microglia remain virtually indistinguishable on the basis of known immunophenotypic markers, although they might be functionally heterogeneous (Guillemin and Brew 2004). The advent of new techniques to selectively express fluorescent reporters in circulating myeloid cells allowed the demonstration that these cells could infiltrate the brain in a number of CNS disease models in which lethally irradiated hosts received adoptively transplanted fluorescent bone marrow cells (Kennedy and Abkowitz 1997; Malm et al. 2005; Simard and Rivest 2004; Simard et al. 2006). These studies showed that a considerable percentage (up to 30%, one year after transplantation) of microglia is derived from donor bone marrow under homeostatic conditions (Kennedy and Abkowitz 1997; Simard and Rivest 2004). Recently, several studies took advantage of the genetic models with GFP expressed in myeloid progenitors engrafted into irradiated AD mice. In these bone marrow chimeric animals, fluorescent donor bone marrow-derived monocytes were found to invade brain parenchyma, acquire microglial morphology and associate with A β deposits. Specifically, the infiltrated microglia were found to associate

with ~20% of the amyloid plaques and were able to internalize A β deposits (Bolmont et al. 2008; Malm et al. 2005; Simard et al. 2006). Simard et al., further demonstrated that bone marrow-derived monocytes/macrophages could infiltrate the AD brain and this was associated with plaque clearance. These authors then went on to show that microglia normally clear plaques by eliminating host microglia which carried CD11b-driven thymidine kinase (TK) by chronic intracerebroventricular ganciclovir delivery and showing these animals exhibited greater plaque burdens (Simard et al. 2006). However, the idea that monocytes can traffic into the brain has been challenged by experiments using parabiosis or limiting the irradiation to periphery without the exposure of CNS. The authors found no evidence of microglia progenitor recruitment from the circulation both in experiment models of denervation and in neurodegenerative disease, facial nerve axotomy and ALS, respectively (Ajami et al. 2007). Mildner et al., further demonstrated that demyelinating and neurodegenerative CNS disease models without BBB disruption were not sufficient to induce substantial microglia engraftment during adulthood. The authors concluded that additional endogenous host factors, such as irradiation damage-induced gene expression, were required to condition the adult brain for microglia engraftment (Mildner et al. 2007). Thus, their data suggested that observation of the influx of peripheral monocytes into the CNS in the previous studies using bone marrow transplant may be an artifact. Whole-body irradiation at the dosages commonly used for myeloablation might lead to the temporary disruption of the BBB, allowing the entry of circulating monocytes into the CNS that would normally not cross an intact BBB. In addition, donor cells are routinely harvested by mechanically flushing whole bone marrow from bones followed by intravascular injection into recipients. Thus, it is possible that these progenitor cells would not enter the bloodstream and consequently infiltrate CNS under physiological conditions (Ajami et al. 2007). However, it is noteworthy that in the later stage of AD, BBB break down has been reported in human patients and mouse models (Kalaria 1997; Skoog et al. 1998; Wisniewski et al. 1997). Thus as disease progress, it is possible that bone marrow-derived monocytes can cross the BBB and migrate to the plaques.

The idea that endogenous microglia might not be the principle cells to remove amyloid plaques has been further reinforced by a recent study from Grathwohl et al. (2009), in which they selectively ablate endogenous microglia using a CD11b-driven TK coupled with intracerebroventricular ganciclovir administration to the brain of mouse models of AD. The loss of microglia had no effect on amyloid plaque number or size over a 2–4 week period. The authors concluded that the CNS resident microglia play a very limited role in restricting the formation and growth of amyloid plaques. However, one major confound in these experiments is that the infiltrated monocyte-derived microglia, which are also CD11b⁺, might also be eliminated by ganciclovir ever since they infiltrated the CNS. Another rather important observation was that there was a 3 to 4-fold increase in soluble A β ₄₀ and A β ₄₂ fractions after ablation of microglia, which strongly suggested the role of microglia in clearance of soluble A β , although there is still a poor understanding of the dynamics linking soluble A β levels and plaque formation. The morbidity and mortality that accompany ganciclovir treatment, the loss of other cell populations besides microglia, most notably pericytes, the loss of the integrity of the vasculature and perturbation of normal homeostatic mechanisms in the brain also need to be considered in the interpretation of the results (Grathwohl et al. 2009). However, a primary conclusion from this study is that it has reinforced the view that endogenous microglia in the AD brain are inefficient in remodeling or removing amyloid plaque from the brain.

Recently, several studies have demonstrated that CCL2, also known as monocyte chemotactic protein-1 (MCP-1), expression is induced following various CNS insults and its receptor, CCR2, is involved in the attraction and infiltration of mononuclear phagocyte into the brain (Babcock et al. 2003; Calvo et al. 1996; Glabinski et al. 1996). Deletion of *Ccr2* in

an AD mouse model resulted in a substantial reduction of microglial accumulation around the plaque and an increase of A β deposition (El Khoury et al. 2007). These data suggest that bone marrow-derived monocytes are capable of infiltrating the CNS and may play an important role in AD pathogenesis. Thus, the role and to what extent infiltrating microglia play in the clearance of A β still need to be further investigated.

A β clearance mechanisms

There are two principal mechanisms for removal of A β from the brain: efflux of intact soluble A β (sA β) to the peripheral circulation, and proteolytic degradation of both soluble and fibrillar forms of A β (fA β). The efflux of sA β can occur through a number of different routes, including efflux across the blood–brain barrier (BBB) into the circulation mediated by LRP1 (low-density lipoprotein receptor-related protein 1), the bulk flow of interstitial fluid (ISF)/cerebrospinal fluid (CSF) into the lymphatic system, and transport via the P-glycoprotein (PgP) efflux pump across the BBB. The efflux of A β through these mechanisms has been postulated to be facilitated or inhibited by its binding to chaperone proteins, such as ApoE, ApoJ, α 2-macroglobulin, transthyretin and albumin (Bell et al. 2007; Deane and Zlokovic 2007; Narita et al. 1997; Zlokovic et al. 1996). The efflux mechanisms have recently been thoroughly discussed by Deane et al. (2009) and the reader is directed to this excellent review.

Fibrillar A β clearance

A growing body of studies has demonstrated that A β interacts with immune cells through both innate and antibody-mediated adaptive immune responses. As the resident immune cells in the brain, microglia are professional phagocytes and can internalize fA β through this mechanism. Engulfment of fA β by microglia through receptor-mediated phagocytosis and its targeting to the endosome–lysosomal pathway has been investigated in detail (D'Andrea et al. 2004; Frautschy et al. 1998; Koenigsknecht and Landreth 2004; Paresce et al. 1996). Microglia are able to engulf and phagocytose fA β readily; the question of whether fA β can be degraded intracellularly remains controversial. Early studies showed that primary mouse microglia release fA β after they have internalized it (Chung et al. 1999). Paresce et al., found that microglia retain fA β for a period of weeks without degrading the peptides (Paresce et al. 1997). A subsequent study conducted by Majumdar et al., suggested that microglia have to be activated to enhance their ability to degrade fA β . Microglia in a nonactivated state were unable to degrade fA β . However, stimulating microglia with macrophage colony-stimulating factor (M-CSF) enabled them to degrade fA β efficiently through acidification of lysosomes (Majumdar et al. 2007).

Microglial A β receptor complex—Microglia directly interact with and ingest fA β via an ensemble of cell surface receptors, including pattern recognition receptors (PRRs). PRRs, and most prominently the Toll like receptors (TLRs), are commonly used by the innate immune system to identify pathogen-associated molecular patterns (PAMPs) of bacteria and viruses. The cell surface receptor complex of fA β is composite of class A scavenger receptor (SR-A), the class B scavenger receptors CD36, α 6 β 1 integrin, CD14, CD47 and TLR2, TLR4, TLR6 and TLR9 (Bamberger et al. 2003; Paresce et al. 1996; Reed-Geaghan et al. 2009; Stewart et al. 2010). Upon binding of fA β , the receptor ensemble initiates the activation of intracellular signaling cascades leading to the induction of phagocytic activity by microglia. SRs were the first receptors reported to be involved in fA β uptake. Paresce et al., demonstrated that microglial uptake of fA β microaggregates was reduced by competitive ligands for SRs, such as acetylated low-density lipoprotein (Ac-LDL), maleylated bovine serum albumin (M-BSA) or fucoidan (Paresce et al. 1996). Recently, a study by Hickman et al. reported that the microglial mRNA levels of SR-A, CD36 and RAGE were progressively

and significantly reduced as mice aged (Hickman et al. 2008). It suggests that the advance of AD pathogenesis may result from the decreased ability of microglia to clear A β . Activating TLRs and their coactivator CD14 were shown to stimulate the phagocytosis of fA β (Liu et al. 2005; Tahara et al. 2006). Activation of TLRs (TLR2, TLR4 or TLR9) with their specific ligands significantly enhanced the uptake of fA β by clonal BV-2 microglial and primary microglia. However, microglia carrying defective TLR4 were less efficient than wild-type microglia in their ability to take up fA β after being stimulated by lipopolysaccharide (LPS). The results suggest that TLR signaling stimulates microglial phagocytosis of fA β . Interestingly, fA β itself activates microglia and induces their phagocytic activity through TLR signaling (Bamberger et al. 2003; Koenigsknecht-Talboo and Landreth 2005; Koenigsknecht and Landreth 2004; Reed-Geaghan et al. 2009). Blocking TLRs signaling by interfering with receptor–ligand interaction or their downstream effectors also reduced fA β -induced phagocytosis and signaling (Bamberger et al. 2003; Koenigsknecht and Landreth 2004). Microglia deficient in TLR2, TLR4 or their coreceptor CD14 failed to induce phagocytosis in response to fA β stimulation (Reed-Geaghan et al. 2009). These results highlight the key function of these PRRs in fA β uptake and their stimulation of phagocytosis. The roles of TLRs in AD pathogenesis have been evaluated in various animal models of AD, and the effect of genetically inactivating the TLRs is confusing. APP^{swe}/PSEN1dE9 mice with inactive TLR4 exhibited increased cortical and hippocampal A β burden when compared with mice with an intact TLR4 gene at 14–16 months of age. These authors argued that the change in A β load was due to a change in microglial-mediated A β clearance that was reliant upon TLR4 function (Tahara et al. 2006). In contrast, TLR2-null mice with APP^{swe}/PSEN1dE9 transgene showed delayed A β deposition through 6 months of age. Interestingly, these animals had comparable deposition to their wild-type littermates at 9 months of age (Richard et al. 2008). It is noteworthy that although TLR2-null transgenic mice had decreased plaque load, their cognition was dramatically impaired compared to the TLR2-bearing littermate controls. Total A β ₄₂ levels were significantly increased in TLR2-knockout mice. Thus, the role of TLRs in AD pathogenesis remains unclear. The controversy of the outcomes may reflect the different ages of analysis.

Role of inflammation in fibrillar A β clearance—The consequences of activating TLR signaling on A β plaque burden in animal models of AD has also been controversial. Acute single intrahippocampal injection of the CD14/TLR4 ligand LPS into Tg2576, an animal model of AD, resulted in clearance of diffuse, but not compact, A β plaques that required microglial activation (DiCarlo et al. 2001; Herber et al. 2007). On the other hand, chronic administration of LPS by daily infusion of LPS into the lateral ventricles for 2 weeks in APP^{V717F} mice or weekly injection of LPS intraperitoneally in APP^{swe} mice resulted in enhanced A β deposition (Qiao et al. 2001; Sheng et al. 2003). The effects of chronic LPS exposure was ameliorated by blocking TNF signaling cascade with a dominant negative TNF inhibitor in vivo, and prevented the acceleration of AD pathology (McAlpine et al. 2009). These data clearly demonstrate that TLR activation can have quite different effects depending on the length of exposure to LPS.

We have shown that proinflammatory cytokines, like LPS, inhibit microglial phagocytosis induced by fA β in vitro (Koenigsknecht-Talboo and Landreth 2005). Exposure of microglia to fA β activates microglia and induces their phagocytic activity through TLR signaling (Bamberger et al. 2003; Koenigsknecht and Landreth 2004; Koenigsknecht-Talboo and Landreth 2005; Reed-Geaghan et al. 2009). Blocking TLR signaling or other elements of the fA β receptor complex by interfering with receptor–ligand interaction or their downstream effectors also reduced fA β -induced phagocytosis (Bamberger et al. 2003; Koenigsknecht and Landreth 2004). Microglia lacking TLR2, TLR4, or their coreceptor CD14, failed to induce phagocytosis in response to fA β stimulation (Reed-Geaghan et al. 2009). These results combined highlight the key function of these PRRs in fA β uptake and its stimulated

phagocytosis. Interestingly, the $\text{fA}\beta$ -induced phagocytosis was inhibited when microglia were co-incubated with proinflammatory cytokines, including $\text{IL-1}\beta$, $\text{TNF}\alpha$, $\text{IFN}\gamma$, MCP-1, and CD40L (Koenigsknecht-Talboo and Landreth 2005). The results were consistent with the effect observed in LPS-treated cells. Importantly, co-incubation of cells with anti-inflammatory cytokines, including IL-4 and IL-10, or cyclooxygenase (COX) inhibitors, blocked the ability of proinflammatory cytokines to suppress $\text{fA}\beta$ -elicited phagocytosis through the inhibition of prostaglandin E2 (PGE2) production or its signaling pathways (Koenigsknecht-Talboo and Landreth 2005). Proinflammatory cytokines have also been shown to inhibit microglial degradation of $\text{fA}\beta$, whereas anti-inflammatory cytokines promote degradation in vivo. The inhibition of $\text{A}\beta$ degradation was possibly a consequence of the down-regulation of proteosomal enzymes (Yamamoto et al. 2008). Consistent with their findings, knocking out the PGE2 EP2 receptor in a mouse model of AD was reported to significantly reduce total $\text{A}\beta$ levels and amyloid plaque burden (Liang et al. 2005). Treating AD mice with anti-inflammatory agents, such as LXR agonist, PPAR γ agonists and non-steroidal anti-inflammatory drugs (NSAIDs), resulted in enhanced phagocytosis in response to $\text{fA}\beta$ and ameliorated AD pathology (Heneka et al. 2005; Lim et al. 2000; Zelcer et al. 2007). These findings support the importance of inflammatory status in regulating microglial-mediated $\text{A}\beta$ clearance and suggesting the use of anti-inflammatory therapies in the treatment of AD.

Antibody- and complement-mediated clearance of fibrillar $\text{A}\beta$ —Schenk et al., reported that active immunization to $\text{A}\beta$ in a mouse model of AD prevented plaque formation in younger animals and reduced the plaque burden and associated neuropathy in animals with established plaque pathology. Decoration of the plaques with IgG was observed in immunized animals, demonstrating that anti- $\text{A}\beta$ antibodies could pass the BBB, albeit at low levels, and mediate the removal of plaques from the brain (Schenk et al. 1999). Introduction of anti- $\text{A}\beta$ antibodies directly into the brain or peripherally resulted in a robust phagocytic response of microglia and consequently the dissolution of $\text{A}\beta$ deposition in the brain (Bard et al. 2000; Wilcock et al. 2003). These data argue that the uptake and degradation of $\text{A}\beta$ by microglia were a result of the $\text{A}\beta$ -antibody complex interacting with Fc receptors (FcR) which stimulated the phagocytic uptake of $\text{A}\beta$. These findings are consistent with previous reports of enhanced phagocytosis of $\text{A}\beta$ -IgG conjugates in vitro (Brazil et al. 2000; Paresce et al. 1996). Interestingly, the presence of $\text{A}\beta$ -specific antibodies in the blood and cerebrospinal fluid (CSF) of healthy humans and AD patients are reported (Du et al. 2001; Hyman et al. 2001; Moir et al. 2005). The increase of auto-immune anti- $\text{A}\beta$ antibodies has been viewed as a consequence of aging. However, the role of endogenous anti- $\text{A}\beta$ antibodies in AD pathogenesis remains unclear. Indeed, the relative levels of anti- $\text{A}\beta$ antibodies in AD patients and healthy individuals are highly variable. It is important to note that FcR-mediated phagocytosis was not inhibited by the presence of proinflammatory cytokines and this may underlie the efficacy of $\text{A}\beta$ vaccination therapy in AD (Koenigsknecht-Talboo and Landreth 2005).

The complement system has also been reported to be involved $\text{A}\beta$ clearance (Rogers et al. 1992, 2002). Fibrillar $\text{A}\beta$ is a strong stimulator of the complement system and can activate the classical (antibody-dependent) pathway by binding C1q and the alternative (antibody-independent) pathway by binding C3b (Bradt et al. 1998; Chen et al. 1996; Jiang et al. 1994; Rogers et al. 1992; Webster et al. 1997). Upon opsonization of $\text{A}\beta$ by complement, microglia elicited more aggressive phagocytosis via complement receptors (~1.5-fold increase over $\text{fA}\beta$ alone) (Brazil et al. 2000; Rogers et al. 2002; Webster et al. 2001). Interestingly, the association of the complement component C1q with $\text{A}\beta$ inhibited microglial phagocytosis (Webster et al. 2000). Thus, C1q may have opposing effects on ingestion of $\text{A}\beta$ via the SR- and FcR-mediated pathways, inhibiting naked $\text{A}\beta$ uptake and enhancing the $\text{A}\beta$ immune complex uptake. A recent study conducted by Maier et al.

demonstrated that complement C3 deficiency in APP mice resulted in elevated cerebral A β levels and amyloid plaque burden. The authors also noticed that the activation status of microglia was switched from the classical activation M1 state to the alternative activation M2 state, suggesting the important role of complement system in A β clearance and microglia activation (Maier et al. 2008).

Soluble A β clearance

A variety of cell types has been reported to take up sA β . One of the most well-described pathways is LDL receptor-related protein 1 (LRP1)-mediated transcytosis, through which brain capillary endothelial cells export sA β across the BBB to the peripheral circulation without significant degradation during transport (Deane et al. 2004). LRP1 is a well-described ApoE receptor and is highly expressed in the CNS (Zerbinatti and Bu 2005). It binds A β in complex with ApoE at nanomolar concentrations (Jordan et al. 1998; Urmoneit et al. 1997). Injecting antibodies against LRP-1 or its inhibitor, receptor-associated protein (RAP) into brain parenchyma substantially reduces the export of A β to the periphery (Shibata et al. 2000). Compared to wild-type mice, A β efflux is also significantly reduced in *ApoE* knockout mice, indicating that the association of A β with ApoE might be required for LRP1-mediated transcytosis of A β (Shibata et al. 2000). Although microglia also express LRP1, the LRP1-mediated endocytosis is not the major pathway for sA β uptake by microglia since antagonizing LDLR-related protein 1 (LRP1) by receptor-associated protein (RAP) had no effect on internalization of sA β (Mandrekar et al. 2009; Marzolo et al. 2000). We have demonstrated that inhibition of the fA β receptor components, including scavenger receptor class A, class B, CD36 and CD47 did not impair the internalization of sA β (Mandrekar et al. 2009) and receptor-mediated endocytosis was not the major pathway which microglia utilize to take up sA β (Chung et al. 1999; Mandrekar et al. 2009). Further studies demonstrated that microglia internalize sA β through constitutive, nonsaturable, fluid phase macropinocytosis, which requires both actin and microtubules. Internalized sA β is rapidly delivered to the lysosomes via the late endolytic pathway (Mandrekar et al. 2009).

The role of ApoE in soluble A β clearance—The polymorphism of ApoE was identified as the most important risk factor for late onset AD. However, how ApoE contributes to disease pathogenesis remains unclear (Corder et al. 1993; Schmechel et al. 1993). ApoE is the predominant apolipoprotein of the high-density lipoprotein (HDL) involved in the redistribution of cholesterol and phospholipids within the brain. It is mainly produced by astrocytes (and to a lesser extent by microglia) and lipidated by the ATP-binding cassette transporter A1 (ABCA1) to form HDL particles (Grehan et al. 2001; Wahrle et al. 2004). Three common variants of ApoE (ApoE ϵ 2, ϵ 3 and ϵ 4) in humans differ in amino acids at positions 112 and 158 conferring differences in cholesterol efflux efficiency, lipidation status and receptor-binding affinity (Mahley et al. 2006a, b). The ApoE3 is the most common allele in the population. Inheriting ApoE4 allele leads to higher risk, faster disease progression and poorer clinical outcome of AD. The ApoE2 allele is associated with lower disease risk (Roses 1996). It has only recently been appreciated that ApoE plays a critical role in the normal proteolytic clearance of sA β from the brain (Jiang et al. 2008). In the presence of ApoE, both intracellular degradation by microglia and extracellular degradation by microglial conditioned media of sA β were induced. The efficiency of the ability of ApoE to facilitate clearance is dependent upon the lipidation status of ApoE since primary microglia with deficient ABCA1 were inefficient to degrade sA β . The lipidation status of ApoE is an important functional parameter, governing its conformation (Fisher and Ryan 1999), intrinsic stability (Hirsch-Reinshagen et al. 2004; Wahrle et al. 2004), interactions with membrane receptors (Dergunov et al. 2000; LaDu et al. 2006) and most importantly, its binding affinity to A β (Tokuda et al. 2000). Knocking out *Abca1* resulted in significantly higher amyloid burden in four different mouse models of

AD (Hirsch-Reinshagen et al. 2005; Koldamova et al. 2005; Wahrle et al. 2005). In these mice, soluble ApoE levels were diminished by 75–85%. On the other hand, overexpression of ABCA1 in the brain of PDAPP mouse model of AD reduced amyloid deposition (Wahrle et al. 2008). Although the soluble ApoE levels were also decreased in the transgenic mice, the insoluble ApoE levels doubled, accompanied with overall higher lipidation status. These results thus suggest that the gene dosage of *Abca1* appears to influence A β clearance through its effects on ApoE lipidation, although an effect on amyloidogenesis by ApoE could not be completely ruled out. The degree of ApoE lipidation is not only governed by the expression level of ABCA1, but also depends on the allele of ApoE. ApoE2 and E3 are more highly lipidated than the E4 isoform, and E4 is much less efficient in promoting sA β proteolysis both within microglia and in the extracellular milieu (Jiang et al. 2008). Examination of PDAPP mice carrying target-replaced human *ApoE* genes both young (3 months old) and old (18 months old) mice showed ApoE isoform-dependent accumulation of soluble and insoluble A β levels and plaque burden (E4 >> E3 > E2), supporting the conclusion that the lipidation status of ApoE is critical for the clearance of A β (Bales et al. 2009; Hirsch-Reinshagen et al. 2005; Jiang et al. 2008; Wahrle et al. 2004, 2005).

Proteolysis of soluble A β —Although fA β is largely resistant to proteolytic degradation, sA β has been shown to be sensitive to many proteases, including neprilysin (NEP), insulin degrading enzyme (IDE), endothelin converting enzyme 1 (ECE1), angiotensin converting enzyme (ACE), plasmin, matrix metalloprotease 9 (MMP9) and presequence peptidase (PreP) (Falkevall et al. 2006; Mukherjee and Hersh 2002; Soto and Castano 1996). Among these proteases, NEP and IDE are the principle intracellular and extracellular enzymes for A β degradation by microglia and other cell types, respectively (Iwata et al. 2000; Jiang et al. 2008; Kurochkin and Goto 1994; Mukherjee and Hersh 2002). NEP is a type II transmembrane protein with catalytic domain facing the lumen/extracellular spaces (Malito et al. 2008). It was first identified as the major A β degrading enzyme using biochemical methods (Iwata et al. 2000). Deletion of the *Nep* gene or inhibition of NEP activity with the metalloprotease inhibitor phosphoramidon were shown to increase A β levels in mouse models of AD (Eckman et al. 2006; Farris et al. 2007; Iwata et al. 2001). Conversely, transgenic mice with NEP overexpression (Leissring et al. 2003) or ex vivo delivery of *Nep* gene by injecting transgenic fibroblast cells into the ventricles (Hemming et al. 2007) resulted in reduced soluble A β levels and plaque burden. In addition, the decrease of NEP levels upon aging in mice and humans implicates a role of NEP in A β catabolism and suggests that regulation of NEP levels or activity might be a potential therapeutic approach (Iwata et al. 2002; Russo et al. 2005).

Insulin degrading enzyme (IDE) is a zinc metalloprotease and can be secreted or associated with the cell surface depending on the cell type. Microglia are found to secrete IDE, yet hippocampal neurons only possess membrane-associated IDE (Malito et al. 2008). IDE binds insulin with high affinity (~100 nM) and degrades insulin into fragments which links it to the type 2 diabetes (Sladek et al. 2007). In addition to insulin, sA β has been reported to be the canonical substrate of IDE (Iwata et al. 2000). It is interesting to note that patients with type 2 diabetes have an increased risk of Alzheimers disease (Qiu and Folstein 2006). Elevation of insulin levels led to the increase of A β in the cerebrospinal fluid since IDE has higher affinity to insulin than A β (Taubes 2003). However, the link between these two substrates of IDE needs further investigation. IDE has been reported to participate in A β metabolism in vivo as genetically inactivation of the *Ide* gene in mice resulted in elevated levels of A β in the brain and this effect was dependent on the gene dosage of *Ide* (Farris et al. 2003; Miller et al. 2003). In mice heterozygous for the *Ide* gene, IDE activity was decreased to ~50%, whereas sA β levels in brain homogenates were increased to intermediate levels between wild-type mice and homozygous *Ide* knockout mice. A recent study conducted by Hickman et al. reported that the levels of IDE, NEP and MMP9 were

dramatically reduced in older mice with the concomitant upregulation of proinflammatory cytokines (Hickman et al. 2008). Thus, it is possible that inflammation in the CNS during normal aging leads to the reduction of A β degrading enzymes and consequently results in increased A β levels and amyloid pathogenesis.

Clearance of A β by other glial cells

Astrocytes have been reported to be able to internalize and degrade A β . In vivo, intracellular A β has been detected in the lysosomal granules of subpial astrocytes indicating phagocytic and lysosomal activity (Funato et al. 1998; Nagele et al. 2003). Ultrastructural analysis showed that astrocytes separated fibrillar amyloid from neurons by extending hypertrophic processes and internalizing the amyloid into endosomes/lysosomes, suggesting their role in degradation of A β (Funato et al. 1998; Wegiel et al. 2000, 2001). Our laboratory demonstrated that astrocytes were able to take up fluorescently labeled sA β , though were less efficient than microglia (Mandrekar et al. 2009). Furthermore, adult mouse astrocytes have also been shown to effectively degrade A β deposits in brain sections obtained from a mouse model of AD (Koistinaho et al. 2004; Wyss-Coray et al. 2003). It is noteworthy that astrocytes prepared from adult *ApoE*^{-/-} mice were unable to degrade A β deposits present in PDAPP mouse brain sections. It suggests that ApoE is essential for astrocytes to bind, internalize and degrade A β deposits in brain sections in vitro (Koistinaho et al. 2004).

Conclusion

The amyloid hypothesis predicts that a decrease of A β levels in the brain will lead to reduction of plaque formation and ameliorate AD pathology. Thus, modulation on either production or clearance of A β could be a potential target for AD therapy. In this review, we have explored the role of microglia in the clearance of A β and the factors that are involved in the processes. Inflammatory responses of microglia and the levels and lipidation status of ApoE are of importance. However, the underlying mechanisms remain largely unclear. Understanding the mechanisms will be challenging, but will provide a potential therapeutic angle to treat AD. Therapeutic approaches which enhance microglial clearance may be of utility in treating AD.

References

- Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nat Neurosci.* 2007; 10:1538–1543. [PubMed: 18026097]
- Babcock AA, Kuziel WA, Rivest S, Owens T. Chemokine expression by glial cells directs leukocytes to sites of axonal injury in the CNS. *J Neurosci.* 2003; 23:7922–7930. [PubMed: 12944523]
- Bales KR, Liu F, Wu S, Lin S, Koger D, DeLong C, Hansen JC, Sullivan PM, Paul SM. Human APOE isoform-dependent effects on brain beta-amyloid levels in PDAPP transgenic mice. *J Neurosci.* 2009; 29:6771–6779. [PubMed: 19474305]
- Bamberger ME, Harris ME, McDonald DR, Husemann J, Landreth GE. A cell surface receptor complex for fibrillar beta-amyloid mediates microglial activation. *J Neurosci.* 2003; 23:2665–2674. [PubMed: 12684452]
- Bard F, Cannon C, Barbour R, Burke RL, Games D, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, et al. Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med.* 2000; 6:916–919. [PubMed: 10932230]
- Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. *Nat Med.* 2006; 12:856–861. [PubMed: 16799555]

- Bell RD, Sagare AP, Friedman AE, Bedi GS, Holtzman DM, Deane R, Zlokovic BV. 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.* 2007; 27:909–918. [PubMed: 17077814]
- Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci.* 2007; 8:57–69. [PubMed: 17180163]
- Bolmont T, Haiss F, Eicke D, Radde R, Mathis CA, Klunk WE, Kohsaka S, Jucker M, Calhoun ME. Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. *J Neurosci.* 2008; 28:4283–4292. [PubMed: 18417708]
- Bradt BM, Kolb WP, Cooper NR. Complement-dependent proinflammatory properties of the Alzheimer's disease beta-peptide. *J Exp Med.* 1998; 188:431–438. [PubMed: 9687521]
- Brazil MI, Chung H, Maxfield FR. Effects of incorporation of immunoglobulin G and complement component C1q on uptake and degradation of Alzheimer's disease amyloid fibrils by microglia. *J Biol Chem.* 2000; 275:16941–16947. [PubMed: 10747968]
- Cai XD, Golde TE, Younkin SG. Release of excess amyloid beta protein from a mutant amyloid beta protein precursor. *Science.* 1993; 259:514–516. [PubMed: 8424174]
- Calvo CF, Yoshimura T, Gelman M, Mallat M. Production of monocyte chemotactic protein-1 by rat brain macrophages. *Eur J Neurosci.* 1996; 8:1725–1734. [PubMed: 8921263]
- Chen S, Frederickson RC, Brunden KR. Neuroglial-mediated immunoinflammatory responses in Alzheimer's disease: complement activation and therapeutic approaches. *Neurobiol Aging.* 1996; 17:781–787. [PubMed: 8892352]
- Chung H, Brazil MI, Soe TT, Maxfield FR. Uptake, degradation, and release of fibrillar and soluble forms of Alzheimer's amyloid beta-peptide by microglial cells. *J Biol Chem.* 1999; 274:32301–32308. [PubMed: 10542270]
- Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S, Holtzman DM. Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron.* 2005; 48:913–922. [PubMed: 16364896]
- Citron M, Oltersdorf T, Haass C, McConlogue L, Hung AY, Seubert P, Vigo-Pelfrey C, Lieberburg I, Selkoe DJ. Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production. *Nature.* 1992; 360:672–674. [PubMed: 1465129]
- Comery TA, Martone RL, Aschmies S, Atchison KP, Diamantidis G, Gong X, Zhou H, Kreft AF, Pangalos MN, Sonnenberg-Reines J, et al. Acute gamma-secretase inhibition improves contextual fear conditioning in the Tg2576 mouse model of Alzheimer's disease. *J Neurosci.* 2005; 25:8898–8902. [PubMed: 16192379]
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science.* 1993; 261:921–923. [PubMed: 8346443]
- D'Andrea MR, Cole GM, Ard MD. The microglial phagocytic role with specific plaque types in the Alzheimer disease brain. *Neurobiol Aging.* 2004; 25:675–683. [PubMed: 15172747]
- Deane R, Zlokovic BV. Role of the blood-brain barrier in the pathogenesis of Alzheimer's disease. *Curr Alzheimer Res.* 2007; 4:191–197. [PubMed: 17430246]
- Deane R, Wu Z, Sagare A, Davis J, Du Yan S, Hamm K, Xu F, Parisi M, LaRue B, Hu HW, et al. LRP/amyloid beta-peptide interaction mediates differential brain efflux of Aβ isoforms. *Neuron.* 2004; 43:333–344. [PubMed: 15294142]
- Deane R, Bell RD, Sagare A, Zlokovic BV. Clearance of amyloid-beta peptide across the blood-brain barrier: implication for therapies in Alzheimer's disease. *CNS Neurol Disord Drug Targets.* 2009; 8:16–30. [PubMed: 19275634]
- Dergunov AD, Smirnova EA, Merched A, Visvikis S, Siest G, Yakushkin VV, Tsibulsky V. Conformation of apolipoprotein E both in free and in lipid-bound form may determine the avidity of triglyceride-rich lipoproteins to the LDL receptor: structural and kinetic study. *Biochim Biophys Acta.* 2000; 1484:14–28. [PubMed: 10685027]
- DiCarlo G, Wilcock D, Henderson D, Gordon M, Morgan D. Intrahippocampal LPS injections reduce Aβ load in APP + PS1 transgenic mice. *Neurobiol Aging.* 2001; 22:1007–1012. [PubMed: 11755009]

- Dodart JC, Mathis C, Bales KR, Paul SM. Does my mouse have Alzheimer's disease? *Genes Brain Behav.* 2002; 1:142–155. [PubMed: 12884970]
- Dovey HF, John V, Anderson JP, Chen LZ, de Saint Andrieu P, Fang LY, Freedman SB, Folmer B, Goldbach E, Holsztynska EJ, et al. Functional gamma-secretase inhibitors reduce beta-amyloid peptide levels in brain. *J Neurochem.* 2001; 76:173–181. [PubMed: 11145990]
- Du Y, Dodel R, Hampel H, Buerger K, Lin S, Eastwood B, Bales K, Gao F, Moeller HJ, Oertel W, et al. Reduced levels of amyloid beta-peptide antibody in Alzheimer disease. *Neurology.* 2001; 57:801–805. [PubMed: 11552007]
- Eckman EA, Adams SK, Troendle FJ, Stodola BA, Kahn MA, Fauq AH, Xiao HD, Bernstein KE, Eckman CB. Regulation of steady-state beta-amyloid levels in the brain by neprilysin and endothelin-converting enzyme but not angiotensin-converting enzyme. *J Biol Chem.* 2006; 281:30471–30478. [PubMed: 16912050]
- El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, Luster AD. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nat Med.* 2007; 13:432–438. [PubMed: 17351623]
- Falkevall A, Alikhani N, Bhushan S, Pavlov PF, Busch K, Johnson KA, Eneqvist T, Tjernberg L, Ankarcrona M, Glaser E. Degradation of the amyloid beta-protein by the novel mitochondrial peptidosome, PreP. *J Biol Chem.* 2006; 281:29096–29104. [PubMed: 16849325]
- Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ, Guenette S. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intra-cellular domain in vivo. *Proc Natl Acad Sci USA.* 2003; 100:4162–4167. [PubMed: 12634421]
- Farris W, Schutz SG, Cirrito JR, Shankar GM, Sun X, George A, Leissring MA, Walsh DM, Qiu WQ, Holtzman DM, Selkoe DJ. Loss of neprilysin function promotes amyloid plaque formation and causes cerebral amyloid angiopathy. *Am J Pathol.* 2007; 171:241–251. [PubMed: 17591969]
- Fisher CA, Ryan RO. Lipid binding-induced conformational changes in the N-terminal domain of human apolipoprotein E. *J Lipid Res.* 1999; 40:93–99. [PubMed: 9869654]
- Frackowiak J, Wisniewski HM, Wegiel J, Merz GS, Iqbal K, Wang KC. Ultrastructure of the microglia that phagocytose amyloid and the microglia that produce beta-amyloid fibrils. *Acta Neuropathol.* 1992; 84:225–233. [PubMed: 1414275]
- Frautschy SA, Yang F, Irizarry M, Hyman B, Saido TC, Hsiao K, Cole GM. Microglial response to amyloid plaques in APPsw transgenic mice. *Am J Pathol.* 1998; 152:307–317. [PubMed: 9422548]
- Funato H, Yoshimura M, Yamazaki T, Saido TC, Ito Y, Yokofujita J, Okeda R, Ihara Y. Astrocytes containing amyloid beta-protein (A β)-positive granules are associated with A β 40-positive diffuse plaques in the aged human brain. *Am J Pathol.* 1998; 152:983–992. [PubMed: 9546359]
- Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, Clemens J, Donaldson T, Gillespie F, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature.* 1995; 373:523–527. [PubMed: 7845465]
- Glabinski AR, Balasingam V, Tani M, Kunkel SL, Strieter RM, Yong VW, Ransohoff RM. Chemokine monocyte chemoattractant protein-1 is expressed by astrocytes after mechanical injury to the brain. *J Immunol.* 1996; 156:4363–4368. [PubMed: 8666808]
- Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature.* 1991; 349:704–706. [PubMed: 1671712]
- Grathwohl SA, Kalin RE, Bolmont T, Prokop S, Winkelmann G, Kaeser SA, Odenthal J, Radde R, Eldh T, Gandy S, et al. Formation and maintenance of Alzheimer's disease beta-amyloid plaques in the absence of microglia. *Nat Neurosci.* 2009; 12:1361–1363. [PubMed: 19838177]
- Grehan S, Tse E, Taylor JM. Two distal downstream enhancers direct expression of the human apolipoprotein E gene to astrocytes in the brain. *J Neurosci.* 2001; 21:812–822. [PubMed: 11157067]
- Guillemin GJ, Brew BJ. Microglia, macrophages, perivascular macrophages, and pericytes: a review of function and identification. *J Leukoc Biol.* 2004; 75:388–397. [PubMed: 14612429]
- Hardy J. Framing beta-amyloid. *Nat Genet.* 1992; 1:233–234. [PubMed: 1363811]

- Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992; 256:184–185. [PubMed: 1566067]
- Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002; 297:353–356. [PubMed: 12130773]
- Hemming ML, Patterson M, Reske-Nielsen C, Lin L, Isacson O, Selkoe DJ. Reducing amyloid plaque burden via ex vivo gene delivery of an Abeta-degrading protease: a novel therapeutic approach to Alzheimer disease. *PLoS Med*. 2007; 4:e262. [PubMed: 17760499]
- Hendriks L, van Duijn CM, Cras P, Cruts M, Van Hul W, van Harskamp F, Warren A, McInnis MG, Antonarakis SE, Martin JJ, et al. Presenile dementia and cerebral haemorrhage linked to a mutation at codon 692 of the beta-amyloid precursor protein gene. *Nat Genet*. 1992; 1:218–221. [PubMed: 1303239]
- Heneka MT, Sastre M, Dumitrescu-Ozimek L, Hanke A, Dewachter I, Kuiperi C, O'Banion K, Klockgether T, Van Leuven F, Landreth GE. Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta1–42 levels in APPV717I transgenic mice. *Brain*. 2005; 128:1442–1453. [PubMed: 15817521]
- Herber DL, Mercer M, Roth LM, Symmonds K, Maloney J, Wilson N, Freeman MJ, Morgan D, Gordon MN. Microglial activation is required for Abeta clearance after intracranial injection of lipopolysaccharide in APP transgenic mice. *J Neuroimmune Pharmacol*. 2007; 2:222–231. [PubMed: 18040847]
- Hess DC, Abe T, Hill WD, Studdard AM, Carothers J, Masuya M, Fleming PA, Drake CJ, Ogawa M. Hematopoietic origin of microglial and perivascular cells in brain. *Exp Neurol*. 2004; 186:134–144. [PubMed: 15026252]
- Hickman SE, Allison EK, El Khoury J. Microglial dysfunction and defective beta-amyloid clearance pathways in aging Alzheimer's disease mice. *J Neurosci*. 2008; 28:8354–8360. [PubMed: 18701698]
- Hirsch-Reinshagen V, Zhou S, Burgess BL, Bernier L, McIsaac SA, Chan JY, Tansley GH, Cohn JS, Hayden MR, Wellington CL. Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain. *J Biol Chem*. 2004; 279:41197–41207. [PubMed: 15269218]
- Hirsch-Reinshagen V, Maia LF, Burgess BL, Blain JF, Naus KE, McIsaac SA, Parkinson PF, Chan JY, Tansley GH, Hayden MR, et al. The absence of ABCA1 decreases soluble ApoE levels but does not diminish amyloid deposition in two murine models of Alzheimer disease. *J Biol Chem*. 2005; 280:43243–43256. [PubMed: 16207707]
- Hyman BT, Smith C, Buldyrev I, Whelan C, Brown H, Tang MX, Mayeux R. Autoantibodies to amyloid-beta and Alzheimer's disease. *Ann Neurol*. 2001; 49:808–810. [PubMed: 11409436]
- Iwata N, Tsubuki S, Takaki Y, Watanabe K, Sekiguchi M, Hosoki E, Kawashima-Morishima M, Lee HJ, Hama E, Sekine-Aizawa Y, Saido TC. Identification of the major Abeta1–42-degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. *Nat Med*. 2000; 6:143–150. [PubMed: 10655101]
- Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, Gerard C, Hama E, Lee HJ, Saido TC. Metabolic regulation of brain Abeta by neprilysin. *Science*. 2001; 292:1550–1552. [PubMed: 11375493]
- Iwata N, Takaki Y, Fukami S, Tsubuki S, Saido TC. Region-specific reduction of A beta-degrading endopeptidase, neprilysin, in mouse hippocampus upon aging. *J Neurosci Res*. 2002; 70:493–500. [PubMed: 12391610]
- Jiang H, Burdick D, Glabe CG, Cotman CW, Tenner AJ. beta-Amyloid activates complement by binding to a specific region of the collagen-like domain of the C1q A chain. *J Immunol*. 1994; 152:5050–5059. [PubMed: 8176223]
- Jiang Q, Lee CY, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Willson TM, Collins JL, et al. ApoE promotes the proteolytic degradation of Abeta. *Neuron*. 2008; 58:681–693. [PubMed: 18549781]
- Jordan J, Galindo MF, Miller RJ, Reardon CA, Getz GS, LaDu MJ. Isoform-specific effect of apolipoprotein E on cell survival and beta-amyloid-induced toxicity in rat hippocampal pyramidal neuronal cultures. *J Neurosci*. 1998; 18:195–204. [PubMed: 9412500]

- Kalaria RN. Cerebrovascular degeneration is related to amyloid-beta protein deposition in Alzheimer's disease. *Ann N Y Acad Sci.* 1997; 826:263–271. [PubMed: 9329698]
- Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, Malinow R. APP processing and synaptic function. *Neuron.* 2003; 37:925–937. [PubMed: 12670422]
- Kennedy DW, Abkowitz JL. Kinetics of central nervous system microglial and macrophage engraftment: analysis using a transgenic bone marrow transplantation model. *Blood.* 1997; 90:986–993. [PubMed: 9242527]
- Kirkitadze MD, Condrón MM, Teplow DB. Identification and characterization of key kinetic intermediates in amyloid beta-protein fibrillogenesis. *J Mol Biol.* 2001; 312:1103–1119. [PubMed: 11580253]
- Koenigsknecht J, Landreth G. Microglial phagocytosis of fibrillar beta-amyloid through a beta1 integrin-dependent mechanism. *J Neurosci.* 2004; 24:9838–9846. [PubMed: 15525768]
- Koenigsknecht-Talboo J, Landreth GE. Microglial phagocytosis induced by fibrillar beta-amyloid and IgGs are differentially regulated by proinflammatory cytokines. *J Neurosci.* 2005; 25:8240–8249. [PubMed: 16148231]
- Koistinaho M, Lin S, Wu X, Esterman M, Koger D, Hanson J, Higgs R, Liu F, Malkani S, Bales KR, Paul SM. Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-beta peptides. *Nat Med.* 2004; 10:719–726. [PubMed: 15195085]
- Koldamova R, Staufenbiel M, Lefterov I. Lack of ABCA1 considerably decreases brain ApoE level and increases amyloid deposition in APP23 mice. *J Biol Chem.* 2005; 280:43224–43235. [PubMed: 16207713]
- Kurochkin IV, Goto S. Alzheimer's beta-amyloid peptide specifically interacts with and is degraded by insulin degrading enzyme. *FEBS Lett.* 1994; 345:33–37. [PubMed: 8194595]
- LaDu MJ, Stine WB Jr, Narita M, Getz GS, Reardon CA, Bu G. Self-assembly of HEK cell-secreted ApoE particles resembles ApoE enrichment of lipoproteins as a ligand for the LDL receptor-related protein. *Biochemistry.* 2006; 45:381–390. [PubMed: 16401069]
- Lawson LJ, Perry VH, Dri P, Gordon S. Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience.* 1990; 39:151–170. [PubMed: 2089275]
- Leissring MA, Farris W, Chang AY, Walsh DM, Wu X, Sun X, Frosch MP, Selkoe DJ. Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. *Neuron.* 2003; 40:1087–1093. [PubMed: 14687544]
- Liang X, Wang Q, Hand T, Wu L, Breyer RM, Montine TJ, Andreasson K. Deletion of the prostaglandin E2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. *J Neurosci.* 2005; 25:10180–10187. [PubMed: 16267225]
- Lim GP, Yang F, Chu T, Chen P, Beech W, Teter B, Tran T, Ubeda O, Ashe KH, Frautschy SA, Cole GM. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *J Neurosci.* 2000; 20:5709–5714. [PubMed: 10908610]
- Liu Y, Walter S, Stagi M, Cherny D, Letiembre M, Schulz-Schaeffer W, Heine H, Penke B, Neumann H, Fassbender K. LPS receptor (CD14): a receptor for phagocytosis of Alzheimer's amyloid peptide. *Brain.* 2005; 128:1778–1789. [PubMed: 15857927]
- Mahley RW, Huang Y, Weisgraber KH. Putting cholesterol in its place: apoE and reverse cholesterol transport. *J Clin Invest.* 2006a; 116:1226–1229. [PubMed: 16670767]
- Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. *Proc Natl Acad Sci USA.* 2006b; 103:5644–5651. [PubMed: 16567625]
- Maier M, Peng Y, Jiang L, Seabrook TJ, Carroll MC, Lemere CA. Complement C3 deficiency leads to accelerated amyloid beta plaque deposition and neurodegeneration and modulation of the microglia/macrophage phenotype in amyloid precursor protein transgenic mice. *J Neurosci.* 2008; 28:6333–6341. [PubMed: 18562603]
- Majumdar A, Cruz D, Asamoah N, Buxbaum A, Sohar I, Lobel P, Maxfield FR. Activation of microglia acidifies lysosomes and leads to degradation of Alzheimer amyloid fibrils. *Mol Biol Cell.* 2007; 18:1490–1496. [PubMed: 17314396]

- Malito E, Hulse RE, Tang WJ. Amyloid beta-degrading cryptidases: insulin degrading enzyme, presequence peptidase, and neprilysin. *Cell Mol Life Sci.* 2008; 65:2574–2585. [PubMed: 18470479]
- Malm TM, Koistinaho M, Parepalo M, Vatanen T, Ooka A, Karlsson S, Koistinaho J. Bone-marrow-derived cells contribute to the recruitment of microglial cells in response to beta-amyloid deposition in APP/PS1 double transgenic Alzheimer mice. *Neurobiol Dis.* 2005; 18:134–142. [PubMed: 15649704]
- Mandrekar S, Jiang Q, Lee CY, Koenigsnecht-Talboo J, Holtzman DM, Landreth GE. Microglia mediate the clearance of soluble A β through fluid phase macropinocytosis. *J Neurosci.* 2009; 29:4252–4262. [PubMed: 19339619]
- Marzolo MP, von Bernhardi R, Bu G, Inestrosa NC. Expression of alpha(2)-macroglobulin receptor/low density lipoprotein receptor-related protein (LRP) in rat microglial cells. *J Neurosci Res.* 2000; 60:401–411. [PubMed: 10797543]
- McAlpine FE, Lee JK, Harms AS, Ruhn KA, Blurton-Jones M, Hong J, Das P, Golde TE, LaFerla FM, Oddo S, et al. Inhibition of soluble TNF signaling in a mouse model of Alzheimer's disease prevents pre-plaque amyloid-associated neuropathology. *Neurobiol Dis.* 2009; 34:163–177. [PubMed: 19320056]
- Meyer-Luehmann M, Spires-Jones TL, Prada C, Garcia-Alloza M, de Calignon A, Rozkalne A, Koenigsnecht-Talboo J, Holtzman DM, Bacskai BJ, Hyman BT. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. *Nature.* 2008; 451:720–724. [PubMed: 18256671]
- Mildner A, Schmidt H, Nitsche M, Merkler D, Hanisch UK, Mack M, Heikenwalder M, Bruck W, Priller J, Prinz M. Microglia in the adult brain arise from Ly-6ChiCCR2+ monocytes only under defined host conditions. *Nat Neurosci.* 2007; 10:1544–1553. [PubMed: 18026096]
- Miller BC, Eckman EA, Sambamurti K, Dobbs N, Chow KM, Eckman CB, Hersh LB, Thiele DL. Amyloid-beta peptide levels in brain are inversely correlated with insulysin activity levels in vivo. *Proc Natl Acad Sci USA.* 2003; 100:6221–6226. [PubMed: 12732730]
- Moir RD, Tseitin KA, Soscia S, Hyman BT, Irizarry MC, Tanzi RE. Autoantibodies to redox-modified oligomeric A β are attenuated in the plasma of Alzheimer's disease patients. *J Biol Chem.* 2005; 280:17458–17463. [PubMed: 15728175]
- Mukherjee A, Hersh LB. Regulation of amyloid beta-peptide levels by enzymatic degradation. *J Alzheimers Dis.* 2002; 4:341–348. [PubMed: 12446966]
- Mullan M, Crawford F, Axelman K, Houlden H, Lilius L, Winblad B, Lannfelt L. A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid. *Nat Genet.* 1992; 1:345–347. [PubMed: 1302033]
- Nagele RG, D'Andrea MR, Lee H, Venkataraman V, Wang HY. Astrocytes accumulate A β 42 and give rise to astrocytic amyloid plaques in Alzheimer disease brains. *Brain Res.* 2003; 971:197–209. [PubMed: 12706236]
- Nakajima K, Kohsaka S. Microglia: activation and their significance in the central nervous system. *J Biochem.* 2001; 130:169–175. [PubMed: 11481032]
- Nathalie P, Jean-Noel O. Processing of amyloid precursor protein and amyloid peptide neurotoxicity. *Curr Alzheimer Res.* 2008; 5:92–99. [PubMed: 18393795]
- Narita M, Holtzman DM, Schwartz AL, Bu G. Alpha2-macroglobulin complexes with and mediates the endocytosis of beta-amyloid peptide via cell surface low-density lipoprotein receptor-related protein. *J Neurochem.* 1997; 69:1904–1911. [PubMed: 9349534]
- Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science.* 2005; 308:1314–1318. [PubMed: 15831717]
- Olson MI, Shaw CM. Presenile dementia and Alzheimer's disease in mongolism. *Brain.* 1969; 92:147–156. [PubMed: 4237656]
- Paresce DM, Ghosh RN, Maxfield FR. Microglial cells internalize aggregates of the Alzheimer's disease amyloid beta-protein via a scavenger receptor. *Neuron.* 1996; 17:553–565. [PubMed: 8816718]

- Paresce DM, Chung H, Maxfield FR. Slow degradation of aggregates of the Alzheimer's disease amyloid beta-protein by microglial cells. *J Biol Chem.* 1997; 272:29390–29397. [PubMed: 9361021]
- Perlmutter LS, Barron E, Chui HC. Morphologic association between microglia and senile plaque amyloid in Alzheimer's disease. *Neurosci Lett.* 1990; 119:32–36. [PubMed: 2097581]
- Pluta R, Barcikowska M, Misicka A, Lipkowski AW, Spisacka S, Januszewski S. Ischemic rats as a model in the study of the neurobiological role of human beta-amyloid peptide. Time-dependent disappearing diffuse amyloid plaques in brain. *Neuroreport.* 1999; 10:3615–3619. [PubMed: 10619654]
- Priller J, Flugel A, Wehner T, Boentert M, Haas CA, Prinz M, Fernandez-Klett F, Prass K, Bechmann I, de Boer BA, et al. Targeting gene-modified hematopoietic cells to the central nervous system: use of green fluorescent protein uncovers microglial engraftment. *Nat Med.* 2001; 7:1356–1361. [PubMed: 11726978]
- Qiao X, Cummins DJ, Paul SM. Neuroinflammation-induced acceleration of amyloid deposition in the APPV717F transgenic mouse. *Eur J Neurosci.* 2001; 14:474–482. [PubMed: 11553297]
- Qiu WQ, Folstein MF. Insulin, insulin-degrading enzyme and amyloid-beta peptide in Alzheimer's disease: review and hypothesis. *Neurobiol Aging.* 2006; 27:190–198. [PubMed: 16399206]
- Ransohoff RM, Perry VH. Microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol.* 2009; 27:119–145. [PubMed: 19302036]
- Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE. CD14 and toll-like receptors 2 and 4 are required for fibrillar A β -stimulated microglial activation. *J Neurosci.* 2009; 29:11982–11992. [PubMed: 19776284]
- Richard KL, Filali M, Prefontaine P, Rivest S. Toll-like receptor 2 acts as a natural innate immune receptor to clear amyloid beta 1–42 and delay the cognitive decline in a mouse model of Alzheimer's disease. *J Neurosci.* 2008; 28:5784–5793. [PubMed: 18509040]
- Rogers J, Cooper NR, Webster S, Schultz J, McGeer PL, Styren SD, Civin WH, Brachova L, Bradt B, Ward P, et al. Complement activation by beta-amyloid in Alzheimer disease. *Proc Natl Acad Sci USA.* 1992; 89:10016–10020. [PubMed: 1438191]
- Rogers J, Strohmeier R, Kovelowski CJ, Li R. Microglia and inflammatory mechanisms in the clearance of amyloid beta peptide. *Glia.* 2002; 40:260–269. [PubMed: 12379913]
- Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. *Annu Rev Med.* 1996; 47:387–400. [PubMed: 8712790]
- Russo R, Borghi R, Markesbery W, Tabaton M, Piccini A. NPY decreases uniformly in Alzheimer's disease and in normal aging. *FEBS Lett.* 2005; 579:6027–6030. [PubMed: 16226260]
- Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature.* 1999; 400:173–177. [PubMed: 10408445]
- Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D, Roses AD. 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.* 1993; 90:9649–9653. [PubMed: 8415756]
- Sheng JG, Bora SH, Xu G, Borchelt DR, Price DL, Koliatsos VE. Lipopolysaccharide-induced-neuroinflammation increases intracellular accumulation of amyloid precursor protein and amyloid beta peptide in APP^{swe} transgenic mice. *Neurobiol Dis.* 2003; 14:133–145. [PubMed: 13678674]
- Shibata M, Yamada S, Kumar SR, Calero M, Bading J, Frangione B, Holtzman DM, Miller CA, Strickland DK, Ghiso J, Zlokovic BV. 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.* 2000; 106:1489–1499. [PubMed: 11120756]
- Simard AR, Rivest S. Bone marrow stem cells have the ability to populate the entire central nervous system into fully differentiated parenchymal microglia. *FASEB J.* 2004; 18:998–1000. [PubMed: 15084516]

- Simard AR, Soulet D, Gowing G, Julien JP, Rivest S. Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. *Neuron*. 2006; 49:489–502. [PubMed: 16476660]
- Sinha S, Anderson JP, Barbour R, Basi GS, Caccavello R, Davis D, Doan M, Dovey HF, Frigon N, Hong J, et al. Purification and cloning of amyloid precursor protein beta-secretase from human brain. *Nature*. 1999; 402:537–540. [PubMed: 10591214]
- Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, Boutin P, Vincent D, Belisle A, Hadjadj S, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature*. 2007; 445:881–885. [PubMed: 17293876]
- Small DH, Mok SS, Bornstein JC. Alzheimer's disease and Abeta toxicity: from top to bottom. *Nat Rev Neurosci*. 2001; 2:595–598. [PubMed: 11484003]
- Skoog I, Wallin A, Fredman P, Hesse C, Aevansson O, Karlsson I, Gottfries CG, Blennow K. A population study on blood-brain barrier function in 85-year-olds: relation to Alzheimer's disease and vascular dementia. *Neurology*. 1998; 50:966–971. [PubMed: 9566380]
- Soto C, Castano EM. The conformation of Alzheimer's beta peptide determines the rate of amyloid formation and its resistance to proteolysis. *Biochem J*. 1996; 314(Pt 2):701–707. [PubMed: 8670088]
- Stewart CR, Stuart LM, Wilkinson K, van Gils JM, Deng J, Halle A, Rayner KJ, Boyer L, Zhong R, Frazier WA, et al. CD36 ligands promote sterile inflammation through assembly of a Toll-like receptor 4 and 6 heterodimer. *Nat Immunol*. 2010; 11:155–161. [PubMed: 20037584]
- Streit WJ, Xue QS. Life and death of microglia. *J Neuroimmune Pharmacol*. 2009; 4:371–379. [PubMed: 19680817]
- Streit WJ, Mrak RE, Griffin WS. Microglia and neuroinflammation: a pathological perspective. *J Neuroinflammation*. 2004; 1:14. [PubMed: 15285801]
- Suzuki N, Cheung TT, Cai XD, Odaka A, Otvos L Jr, Eckman C, Golde TE, Younkin SG. An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants. *Science*. 1994; 264:1336–1340. [PubMed: 8191290]
- Tahara K, Kim HD, Jin JJ, Maxwell JA, Li L, Fukuchi K. Role of toll-like receptor signalling in Abeta uptake and clearance. *Brain*. 2006; 129:3006–3019. [PubMed: 16984903]
- Taubes G. Neuroscience. Insulin insults may spur Alzheimer's disease. *Science*. 2003; 301:40–41. [PubMed: 12843374]
- Tokuda T, Calero M, Matsubara E, Vidal R, Kumar A, Permanne B, Zlokovic B, Smith JD, Ladu MJ, Rostagno A, et al. Lipidation of apolipoprotein E influences its isoform-specific interaction with Alzheimer's amyloid beta peptides. *Biochem J*. 2000; 348(Pt 2):359–365. [PubMed: 10816430]
- Urmoneit B, Prikulis I, Wihl G, D'Urso D, Frank R, Heeren J, Beisiegel U, Prior R. Cerebrovascular smooth muscle cells internalize Alzheimer amyloid beta protein via a lipoprotein pathway: implications for cerebral amyloid angiopathy. *Lab Invest*. 1997; 77:157–166. [PubMed: 9274858]
- Wahrle SE, Jiang H, Parsadanian M, Legleiter J, Han X, Fryer JD, Kowalewski T, Holtzman DM. ABCA1 is required for normal central nervous system ApoE levels and for lipidation of astrocyte-secreted apoE. *J Biol Chem*. 2004; 279:40987–40993. [PubMed: 15269217]
- Wahrle SE, Jiang H, Parsadanian M, Hartman RE, Bales KR, Paul SM, Holtzman DM. Deletion of Abca1 increases Abeta deposition in the PDAPP transgenic mouse model of Alzheimer disease. *J Biol Chem*. 2005; 280:43236–43242. [PubMed: 16207708]
- Wahrle SE, Jiang H, Parsadanian M, Kim J, Li A, Knoten A, Jain S, Hirsch-Reinshagen V, Wellington CL, Bales KR, et al. Overexpression of ABCA1 reduces amyloid deposition in the PDAPP mouse model of Alzheimer disease. *J Clin Invest*. 2008; 118:671–682. [PubMed: 18202749]
- Walsh DM, Lomakin A, Benedek GB, Condron MM, Teplow DB. Amyloid beta-protein fibrillogenesis. Detection of a protofibrillar intermediate. *J Biol Chem*. 1997; 272:22364–22372. [PubMed: 9268388]
- Webster S, Bradt B, Rogers J, Cooper N. Aggregation state-dependent activation of the classical complement pathway by the amyloid beta peptide. *J Neurochem*. 1997; 69:388–398. [PubMed: 9202333]

- Webster SD, Yang AJ, Margol L, Garzon-Rodriguez W, Glabe CG, Tenner AJ. Complement component C1q modulates the phagocytosis of Abeta by microglia. *Exp Neurol*. 2000; 161:127–138. [PubMed: 10683279]
- Webster SD, Galvan MD, Ferran E, Garzon-Rodriguez W, Glabe CG, Tenner AJ. Antibody-mediated phagocytosis of the amyloid beta-peptide in microglia is differentially modulated by C1q. *J Immunol*. 2001; 166:7496–7503. [PubMed: 11390503]
- Wegiel J, Wang KC, Tarnawski M, Lach B. Microglia cells are the driving force in fibrillar plaque formation, whereas astrocytes are a leading factor in plaque degradation. *Acta Neuropathol*. 2000; 100:356–364. [PubMed: 10985692]
- Wegiel J, Wang KC, Imaki H, Rubenstein R, Wronska A, Osuchowski M, Lipinski WJ, Walker LC, LeVine H. The role of microglial cells and astrocytes in fibrillar plaque evolution in transgenic APP(SW) mice. *Neurobiol Aging*. 2001; 22:49–61. [PubMed: 11164276]
- Wegiel J, Imaki H, Wang KC, Wronska A, Osuchowski M, Rubenstein R. Origin and turnover of microglial cells in fibrillar plaques of APPsw transgenic mice. *Acta Neuropathol*. 2003; 105:393–402. [PubMed: 12624793]
- Wegiel J, Imaki H, Wang KC, Rubenstein R. Cells of monocyte/microglial lineage are involved in both microvessel amyloidosis and fibrillar plaque formation in APPsw tg mice. *Brain Res*. 2004; 1022:19–29. [PubMed: 15353209]
- Wilcock DM, DiCarlo G, Henderson D, Jackson J, Clarke K, Ugen KE, Gordon MN, Morgan D. Intracranially administered anti-Abeta antibodies reduce beta-amyloid deposition by mechanisms both independent of and associated with microglial activation. *J Neurosci*. 2003; 23:3745–3751. [PubMed: 12736345]
- Wisniewski T, Frangione B. Apolipoprotein E: a pathological chaperone protein in patients with cerebral and systemic amyloid. *Neurosci Lett*. 1992; 135:235–238. [PubMed: 1625800]
- Wisniewski HM, Wegiel J, Wang KC, Kujawa M, Lach B. Ultrastructural studies of the cells forming amyloid fibers in classical plaques. *Can J Neurol Sci*. 1989; 16:535–542. [PubMed: 2553231]
- Wisniewski HM, Barcikowska M, Kida E. Phagocytosis of beta/A4 amyloid fibrils of the neuritic neocortical plaques. *Acta Neuropathol*. 1991a; 81:588–590. [PubMed: 1858487]
- Wisniewski T, Ghiso J, Frangione B. Peptides homologous to the amyloid protein of Alzheimer's disease containing a glutamine for glutamic acid substitution have accelerated amyloid fibril formation. *Biochem Biophys Res Commun*. 1991b; 180:1528. [PubMed: 1953795]
- Wisniewski HM, Vorbrodt AW, Wegiel J. Amyloid angiopathy and blood-brain barrier changes in Alzheimer's disease. *Ann N Y Acad Sci*. 1997; 826:161–172. [PubMed: 9329688]
- Wyss-Coray T, Loike JD, Brionne TC, Lu E, Anankov R, Yan F, Silverstein SC, Husemann J. Adult mouse astrocytes degrade amyloid-beta in vitro and in situ. *Nat Med*. 2003; 9:453–457. [PubMed: 12612547]
- Yamamoto M, Kiyota T, Walsh SM, Liu J, Kipnis J, Ikezu T. Cytokine-mediated inhibition of fibrillar amyloid-beta peptide degradation by human mononuclear phagocytes. *J Immunol*. 2008; 181:3877–3886. [PubMed: 18768842]
- Yan P, Bero AW, Cirrito JR, Xiao Q, Hu X, Wang Y, Gonzales E, Holtzman DM, Lee JM. Characterizing the appearance and growth of amyloid plaques in APP/PS1 mice. *J Neurosci*. 2009; 29:10706–10714. [PubMed: 19710322]
- Zelcer N, Khanlou N, Clare R, Jiang Q, Reed-Geaghan EG, Landreth GE, Vinters HV, Tontonoz P. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. *Proc Natl Acad Sci USA*. 2007; 104:10601–10606. [PubMed: 17563384]
- Zerbinatti CV, Bu G. LRP and Alzheimer's disease. *Rev Neurosci*. 2005; 16:123–135. [PubMed: 15959937]
- Zlokovic BV, Martel CL, Matsubara E, McComb JG, Zheng G, McCluskey RT, Frangione B, Ghiso J. Glycoprotein 330/megalin: probable role in receptor-mediated transport of apolipoprotein J alone and in a complex with Alzheimer disease amyloid beta at the blood-brain and blood-cerebrospinal fluid barriers. *Proc Natl Acad Sci U S A*. 1996; 93:4229–4234. [PubMed: 8633046]