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The role of microglia in amyloid clearance from the AD brain

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Abstract

Alzheimer's disease (AD), the most prominent cause of senile dementia, is clinically characterized by the extracellular deposition of β-amyloid (Aβ) and the intra-cellular neurofibrillary tangles. It has been well accepted that AD pathogenesis arises from perturbation in the homeostasis of Aβ in the brain. Aβ 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 Aβ 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 Aβ. Aβ exists in the brain both in soluble and in fibrillar forms. Microglia interact with these two forms of Aβ in different ways. They take up soluble forms of Aβ through macropinocytosis and LDL receptor-related proteins (LRPs) mediated pathway. Fibrillar forms of Aβ 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 Aβ. 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 Aβ 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 (Aβ) 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 Aβ 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, Aβ homeostasis, with the efficient clearance of Aβ 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

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fibrillary forms of Aβ. 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 Aβ homeostatic functions.

Aβ production, polymerization and the amyloid hypothesis

Aβ 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 Aβ in AD are 40 and 42 amino acid peptides, which polymerize into a variety of multimeric Aβ species and subsequently fibrillize, aggregate and are deposited within the parenchyma of the brain. Because of the two extra C-terminal amino acid residues, Aβ42 is more hydrophobic than Aβ40 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 Aβ 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 Aβ 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 Aβ42 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 Aβ 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). Aβ is secreted from neurons as a consequence of normal synaptic transmission (Cirrito et al. 2005; Kamenetz et al. 2003). Since Aβ 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 Aβ 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/mm^3 (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 Aβ with their processes and Aβ is observed in endosome-like cellular compartments (Frackowiak et al. 1992). Later in vitro studies using radioisotope or fluorescent labeled Aβ (Paresce et al. 1996) in combination with direct injection of fibrillar Aβ into rat brains (Pluta et al. 1999) further demonstrated the capability of microglia to internalize Aβ. 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 Aβ 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 Aβ. 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; Koenigsknecht-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 Aβ deposits. Specifically, the infiltrated microglia were found to associate

with ~20% of the amyloid plaques and were able to internalize Aβ 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 Aβ40 and Aβ42 fractions after ablation of microglia, which strongly suggested the role of microglia in clearance of soluble Aβ, although there is still a poor understanding of the dynamics linking soluble Aβ 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 Aβ 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 Aβ still need to be further investigated.

Aβ clearance mechanisms

There are two principal mechanisms for removal of Aβ from the brain: efflux of intact soluble Aβ (sAβ) to the peripheral circulation, and proteolytic degradation of both soluble and fibrillar forms of Aβ (fAβ). The efflux of sAβ 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 Aβ through these mechanisms has been postulated to be facilitated or inhibited by its binding to chaperone proteins, such as ApoE, ApoJ, α2-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 Aβ clearance

A growing body of studies has demonstrated that Aβ 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 fAβ through this mechanism. Engulfment of fAβ 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 fAβ readily; the question of whether fAβ can be degraded intracellularly remains controversial. Early studies showed that primary mouse microglia release fAβ after they have internalized it (Chung et al. 1999). Paresce et al., found that microglia retain fAβ 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 fAβ. Microglia in a nonactivated state were unable to degrade fAβ. However, stimulating microglia with macrophage colony-stimulating factor (M-CSF) enabled them to degrade fAβ efficiently through acidification of lysosomes (Majumdar et al. 2007).

Microglial Aβ receptor complex—Microglia directly interact with and ingest fAβ 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 fAβ is composite of class A scavenger receptor (SR-A), the class B scavenger receptors CD36, α6β1 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 fAβ, 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 fAβ uptake. Paresce et al., demonstrated that microglial uptake of fAβ 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 Aβ. Activating TLRs and their coactivator CD14 were shown to stimulate the phagocytosis of fAβ (Liu et al. 2005; Tahara et al. 2006). Activation of TLRs (TLR2, TLR4 or TLR9) with their specific ligands significantly enhanced the uptake of fAβ 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 fAβ after being stimulated by lipopolysaccharide (LPS). The results suggest that TLR signaling stimulates microglial phagocytosis of fAβ. Interestingly, fAβ 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 fAβ-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 fAβ stimulation (Reed-Geaghan et al. 2009). These results highlight the key function of these PRRs in fAβ 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. APPswe/PSEN1dE9 mice with inactive TLR4 exhibited increased cortical and hippocampal Aβ burden when compared with mice with an intact TLR4 gene at 14–16 months of age. These authors argued that the change in Aβ load was due to a change in microglial-mediated Aβ clearance that was reliant upon TLR4 function (Tahara et al. 2006). In contrast, TLR2-null mice with APPswe/PSEN1dE9 transgene showed delayed Aβ 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 Aβ42 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 Aβ clearance—The consequences of activating TLR signaling on Aβ 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, Aβ 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 Aβ 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 fAβ in vitro (Koenigsknecht-Talboo and Landreth 2005). Exposure of microglia to fAβ 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 fAβ receptor complex by interfering with receptor–ligand interaction or their downstream effectors also reduced fAβ-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 fAβ stimulation (Reed-Geaghan et al. 2009). These results combined highlight the key function of these PRRs in fAβ uptake and its stimulated

phagocytosis. Interestingly, the fAβ-induced phagocytosis was inhibited when microglia were co-incubated with proinflammatory cytokines, including IL-1β, TNFα, IFNγ, 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 fAβ-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 fAβ, whereas anti-inflammatory cytokines promote degradation in vivo. The inhibition of Aβ 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 Aβ levels and amyloid plaque burden (Liang et al. 2005). Treating AD mice with anti-inflammatory agents, such as LXR agonist, PPARγ agonists and non-steroidal anti-inflammatory drugs (NSAIDs), resulted in enhanced phagocytosis in response to fAβ 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 Aβ clearance and suggesting the use of anti-inflammatory therapies in the treatment of AD.

Antibody- and complement-mediated clearance of fibrillar Aβ—Schenk et al., reported that active immunization to Aβ 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-Aβ 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-Aβ antibodies directly into the brain or peripherally resulted in a robust phagocytic response of microglia and consequently the dissolution of Aβ deposition in the brain (Bard et al. 2000; Wilcock et al. 2003). These data argue that the uptake and degradation of Aβ by microglia were a result of the Aβ-antibody complex interacting with Fc receptors (FcR) which stimulated the phagocytic uptake of Aβ. These findings are consistent with previous reports of enhanced phagocytosis of Aβ-IgG conjugates in vitro (Brazil et al. 2000; Paresce et al. 1996). Interestingly, the presence of Aβ-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-Aβ antibodies has been viewed as a consequence of aging. However, the role of endogenous anti-Aβ antibodies in AD pathogenesis remains unclear. Indeed, the relative levels of anti-Aβ 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 Aβ vaccination therapy in AD (Koenigsknecht-Talboo and Landreth 2005).

The complement system has also been reported to be involved Aβ clearance (Rogers et al. 1992, 2002). Fibrillar Aβ is a strong stimulator of the complement system and can activate the classical (antibody-dependent) pathway by binding Clq 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 Aβ by complement, microglia elicited more aggressive phagocytosis via complement receptors (~1.5-fold increase over fAβ alone) (Brazil et al. 2000; Rogers et al. 2002; Webster et al. 2001). Interestingly, the association of the complement component C1q with Aβ inhibited microglial phagocytosis (Webster et al. 2000). Thus, C1q may have opposing effects on ingestion of Aβ via the SR- and FcR-mediated pathways, inhibiting naked Aβ uptake and enhancing the Aβ immune complex uptake. A recent study conducted by Maier et al.

demonstrated that complement C3 deficiency in APP mice resulted in elevated cerebral Aβ 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 Aβ clearance and microglia activation (Maier et al. 2008).

Soluble Aβ clearance

A variety of cell types has been reported to take up sAβ. One of the most well-described pathways is LDL receptor-related protein 1 (LRP1)-mediated transcytosis, through which brain capillary endothelial cells export sAβ 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 Aβ 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 Aβ to the periphery (Shibata et al. 2000). Compared to wild-type mice, Aβ efflux is also significantly reduced in *Apoe* knockout mice, indicating that the association of Aβ with ApoE might be required for LRP1-mediated transcytosis of Aβ (Shibata et al. 2000). Although microglia also express LRP1, the LRP1-mediated endocytosis is not the major pathway for sAβ uptake by microglia since antagonizing LDLR-related protein 1 (LRP1) by receptor-associated protein (RAP) had no effect on internalization of sAβ (Mandrekar et al. 2009; Marzolo et al. 2000). We have demonstrated that inhibition of the fAβ receptor components, including scavenger receptor class A, class B, CD36 and CD47 did not impair the internalization of sAβ (Mandrekar et al. 2009) and receptor-mediated endocytosis was not the major pathway which microglia utilize to take up sAβ (Chung et al. 1999; Mandrekar et al. 2009). Further studies demonstrated that microglia internalize sAβ through constitutive, nonsaturable, fluid phase macropinocytosis, which requires both actin and microtubules. Internalized sAβ is rapidly delivered to the lysosomes via the late endolytic pathway (Mandrekar et al. 2009).

The role of Apoe in soluble Aβ 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 ε2, ε3 and ε4) 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 sAβ 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 sAβ 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 sAβ. 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 Aβ (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 Aβ 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 sAβ proteolysis both within microglia and in the extracellular mileau (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 Aβ levels and plaque burden (E4 $\gg$ E3 > E2), supporting the conclusion that the lipidation status of ApoE is critical for the clearance of Aβ (Bales et al. 2009; Hirsch-Reinshagen et al. 2005; Jiang et al. 2008; Wahrle et al. 2004, 2005).

Proteolysis of soluble Aβ—Although fAβ is largely resistant to proteolytic degradation, sAβ 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 Aβ 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 Aβ 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 Aβ 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 Aβ levels and plaque burden. In addition, the decrease of NEP levels upon aging in mice and humans implicates a role of NEP in Aβ 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, sAβ 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 Aβ in the cerebrospinal fluid since IDE has higher affinity to insulin than Aβ (Taubes 2003). However, the link between these two substrates of IDE needs further investigation. IDE has been reported to participate in Aβ metabolism in vivo as genetically inactivation of the *Ide* gene in mice resulted in elevated levels of Aβ 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 sAβ 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 Aβ degrading enzymes and consequently results in increased Aβ levels and amyloid pathogenesis.

Clearance of Aβ by other glial cells

Astrocytes have been reported to be able to internalize and degrade Aβ. In vivo, intracellular Aβ 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 Aβ (Funato et al. 1998; Wegiel et al. 2000, 2001). Our laboratory demonstrated that astrocytes were able to take up fluorescently labeled sAβ, though were less efficient than microglia (Mandrekar et al. 2009). Furthermore, adult mouse astrocytes have also been shown to effectively degrade Aβ 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 Aβ deposits present in PDAPP mouse brain sections. It suggests that ApoE is essential for astrocytes to bind, internalize and degrade Aβ deposits in brain sections in vitro (Koistinaho et al. 2004).

Conclusion

The amyloid hypothesis predicts that a decrease of Aβ levels in the brain will lead to reduction of plaque formation and ameliorate AD pathology. Thus, modulation on either production or clearance of Aβ could be a potential target for AD therapy. In this review, we have explored the role of microglia in the clearance of Aβ 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.

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