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The role of inflammatory processes in Alzheimer's disease

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Abstract It has become increasingly clear that inflammatory processes play a significant role in the pathophysiology of Alzheimer's disease (AD). Neuroinflammation is characterized by the activation of astrocytes and microglia and the release of proinflammatory cytokines and chemokines. Vascular inflammation, mediated largely by the products of endothelial activation, is accompanied by the production and the release of a host of inflammatory factors which contribute to vascular, immune, and neuronal dysfunction. The complex interaction of these processes is still only imperfectly understood, yet as the mechanisms continue to be elucidated, targets for intervention are revealed. Although many of the studies to date on therapeutic or preventative strategies for AD have been narrowly focused on single target therapies, there is accumulating evidence to suggest that the most successful treatment strategy will likely incorporate a sequential, multifactorial approach, addressing direct neuronal support, general cardiovascular health, and interruption of deleterious inflammatory pathways.

Keywords Alzheimer's disease · Inflammation · Neuron · Neuronal · Astrocyte · Microglia · Cardiovascular · Microvessels · Vascular · Endothelial · Cytokine · Chemokine · Immune · Neurodegenerative · Aβ · Amyloid · β-amyloid · Pathogenesis · Pathology · Reactive oxygen species · Reactive nitrogen species · Interleukin · Blood–brain barrier · Cyclooxygenase · Inflammatory mediators · Activated endothelium

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Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase inhibitors
AGE	Advanced glycation end product
AD	Alzheimer's disease
APP	Amyloid precursor protein
AICD	Amyloid precursor protein intracellular domain
BACE-1	β-Site APP cleaving enzyme 1
Aβ	β-Amyloid
BBB	Blood–brain barrier
CNS	Central nervous system
CD14	Cluster of differentiation 14
COX	Cyclooxygenase
eNOS	Endothelial nitric oxide synthase
ET-1	Endothelin-1
GLUT-1	Glucose tansporter-1
GLT-1	Glutamate transporter-1
GSK	Glycogen synthase kinase
HPC	Hippocampal progenitor cell
Hcy	Homocysteine
4-HNE	4-Hydroxynonenal
HIF-1α	Hypoxia-inducible factor-1α
iNOS	Inducible nitric oxide synthase
IFNγ	Interferon-γ
IP-10	Interferon-γ induced protein-10
IL	Interleukin
JNK	c-Jun N-terminal kinase
KO	Knockout
LRP-1	LDL-receptor related protein-1
LTP	Long-term potentiation
LDL	Low density lipoprotein
MCSF	Macrophage colony stimulating factor
MMP	Matrix metalloproteinase

MAP	Microtubule-associated protein
MCI	Mild cognitive impairment
MLK-3	Mitogen-activated protein kinase kinase kinase 11
MCP-1	Monocyte chemotactic protein-1
NFT	Neurofibrillary tangle
NMDA	*N*-methyl-D-aspartic acid
NALP3	NACHT/LRR/PYD domains-containing protein 3
NGF	Nerve growth factor
nNOS	Neuronal nitric oxide synthase
NADPH	Nicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
NOS	Nitric oxide synthase
NSAID	Non-steroidal anti-inflammatory drug
NF-κB	Nuclear factor-κB
P-gp	P-glycoprotein
PPARγ	Peroxisome proliferator activated receptor-γ
PS-1	Presenilin-1
PGE2	Prostaglandin E2
PKC	Protein kinase C
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
RAGE	Receptor for advanced glycation end product
STAT	Signal transducer and activator of transcription
TSP	Thrombospondin
TIMP-1	Tissue inhibitor of MMP
TLR	Toll-like receptor
TNFα	Tumor necrosis factor-α
VCAM-1	Vascular cell-adhesion molecule
VEGF	Vascular endothelial growth factor
WT	Wild type

Introduction

Despite the best efforts of clinicians and researchers, Alzheimer's disease (AD) remains the most common form of senile dementia (Wirths et al. 2004). Clinically, the disease presents as a severe impairment in memory, as well as other cognitive functions, which invariably cause a decline in an individual's ability to function in society. Often, it is preceded by a prodromal state commonly referred to as mild cognitive impairment (MCI) characterized by milder cognitive deficits. With an aging population in developed countries, including the United States, it becomes increasingly imperative that pharmacological agents capable of modifying the course of the disease be developed. This is especially evident in light of the fact that there are currently over 5.3 million Americans afflicted with this disease, which has also become the seventh leading cause of death in this country (Galluzzi et al. 2010).

The major pathological hallmarks of AD include the presence of abnormal proteinaceous deposits known as senile plaques and neurofibrillary tangles (NFTs), along with extensive neuronal loss in specific cortical and subcortical regions such as the nucleus basalis of Meynert and the hippocampus (Tang 2009). Senile plaques are composed primarily of the protein fragment β-amyloid (Aβ), and are generally thought to be formed extracellularly (Plant et al. 2003), although there is also evidence from murine models which suggests that the process of oligomerization and subsequent deposition begins in intracellular compartments (Takahashi et al. 2002). NFTs are composed of the microtubule-associated protein (MAP) called tau. Tau becomes hyperphosphorylated during the disease process of AD, which results in its own aggregation as well as the disruption of various other cellular processes, including, for example, the function of other MAPs, which aid in the maintenance of the structure of axons and dendrites (Ballatore et al. 2007).

Additionally, cholinergic abnormalities such as the loss of presynaptic cholinergic markers have been described in the postmortem histological analyses of AD brains. This occurs along with the loss of acetylcholine (ACh) receptors in the putamen and the nucleus basalis of Meynert (Kihara and Shimohama 2004). Importantly, most of the pharmacological agents that have been approved to date for the treatment of AD do so by inhibiting the function of acetylcholinesterase (AChE) (Sabbagh and Cummings 2011).

Although amyloid plaques and neurofibrillary tangles are considered the major clinical pathological markers in AD (Hermann et al. 1991; Tang 2009), Alois Alzheimer himself was the first to describe the involvement of glial cells (perivascular gliosis) in AD in 1899 (Alzheimer 1991). Since then, much research has been devoted to elucidating the mechanisms whereby this progressive and highly prevalent (Lindesay et al. 2010) neurodegenerative disease wreaks destruction upon our brains, resulting in severe morbidity and mortality. Although we do not yet fully understand the disease process, and have few approved therapies—none of which is anything near curative—we are continuing to accumulate observations about the myriad biological processes that are associated with AD pathogenesis.

The picture that is emerging is very complex. Rather than a simple set of local phenomena directly injurious to the neurons whose demise is the most obvious symptom of the disease, the development and progression of AD involves physiological aberrations and reactions which are numerous, simultaneous, widespread, and interdependent. Part of this progression clearly involves a chronic inflammatory process involving neurons, astrocytes, and microglia as the former are the primary producers of Aβ, while the latter two constitute the immunocompetent cells

of the central nervous system (CNS) and show a robust inflammatory response to Aβ (Agostinho et al. 2010). But as will be described below, inflammatory chemokines and cytokines, reactive oxygen species (ROS), and inflammatory enzymes produced by cells in the CNS as well as components of the cardiovascular, endocrine, and complement systems all have a role to play in the inflammatory pathways that coincide with the pathogenesis of AD (Heneka and O'Banion 2007; Lee et al. 2009; Carlsson 2010; McGeer and McGeer 2003).

Neurons and Aβ-induced inflammation

Far from being passive spectators of the inflammatory process that is initiated in the course of AD pathology, neurons are active participants. Despite the fact that glial cells such as astrocytes and microglia have traditionally been thought of as the primary mediators of immunity and thus inflammation in the CNS, neurons are capable of both producing and responding to molecules involved in the pathways of inflammation. In addition, many of these pathways have downstream impacts on the regulation of normal cellular processes in neurons.

Inflammation and Aβ

Aβ, derived from the membrane spanning amyloid precursor protein (APP), is one of the most studied molecules involved in the pathogenesis of AD. Functional Aβ 1–40 (Plant et al. 2003) or pathological Aβ 1–42 (Abramov et al. 2004) fragments are produced by intramembrane cleavage of APP by a gamma secretase encoded by the presenilin gene (Mundy 1994), as well as cleavage at an extracellular site by a beta secretase, β-site APP cleaving enzyme 1 (BACE-1) (Selkoe 2001). Alternatively, cleavage by an alpha secretase such as disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) does not result in the production of Aβ (Galimberti and Scarpini 2011). The primary (although by no means only) producers of Aβ in the CNS are neuronal cells. In general, the mechanisms by which toxic Aβ interacts with the progression of AD are not clearly understood. However, there is well-established evidence that it exerts numerous effects on inflammatory processes associated with AD.

It has been reported in many studies that inflammatory markers co-localize with the pathological hallmarks of AD, including, but not necessarily limited to, Aβ plaques (Rogers and Shen 2000) which form extracellularly from accumulations of Aβ 1–42 fragments along with other amyloid species. Many of these inflammatory markers, when expressed in the periphery have been shown to be highly cytotoxic, and it has also been shown that non-specific systemic inflammation can quicken the onset of the clinical manifestations of AD, possibly by further activation of already primed microglia (Perry et al. 2003). Aβ plaques, which are fibrillar in nature, exhibit dense populations of microglia at their core, as well as activated astrocytes at their periphery (Akiyama et al. 2000). This is in fact true not only for human patients with firm clinical indicators of the disease prior to postmortem histological examination of brain tissue, but also for those considered to be in a less mature disease state (i.e., MCI) (Lue et al. 1996; Eikelenboom and van Gool 2004). In addition, it has been shown in in vivo models of AD that Aβ-induced inflammation occurs early in the pathology of the disease, and can be blocked by the application of an inhibitor of glial activity (Craft et al. 2006).

In several studies, it has been shown that Aβ is capable of activating many different inflammatory and apoptotic pathways. For instance, in vitro studies have shown that fibrillar forms of Aβ are capable of activating the NACHT/LRR/PYD domains-containing protein 3 (NALP3) inflammasome via a caspase-1 dependent mechanism. This leads to the production of IL-1β and IL-18, which in turn stimulate microglia to produce further inflammatory cytokines (Halle et al. 2008). In another in vitro study, primary murine microglial cultures showed increased IL-6 and tumor necrosis factor-α (TNFα) production in response to exposure to aggregated Aβ (Walter et al. 2007). Further, it has been shown in positron emission tomography studies of AD patients that there is an increased activation of microglia in the region of senile plaques (Lue et al. 1996; Edison et al. 2008).

Channel hypothesis

Another possible pathway by which Aβ may induce inflammation has been suggested by the proponents of the "channel hypothesis". Simply stated, it has been suggested that Aβ oligomers are capable of forming membrane spanning ion-permeable channels that exhibit poor specificity (Wirths et al. 2004; Kawahara et al. 2011). Studies have suggested that these channels are capable of inducing aberrant Ca^{2+} currents across the membranes of both neurons and glial cells (Kawahara et al. 2011; Abramov et al. 2004). It has also been shown that in hippocampal astrocytes co-cultured with neurons incubated with Aβ, these currents elicited the activation of a transient acidification of the extracellular media concurrent with the production of ROS (Abramov et al. 2004). As it has been suggested that acidosis may increase amyloidogenic processing of APP (Brewer 1997) and immunoreactivity of Aβ (Bell and Zlokovic 2009), the formation of Aβ channels may create a self-sustaining cycle that could potentially drive further inflammation.

Intracellular domain of amyloid precursor protein

Besides the extracellular cleavage products of APP, recent evidence also suggests that the intracellular domain of the protein (APP intracellular domain, AICD) may play an important role in AD as well. Specifically, a cleavage product of AICD, C31, has been implicated in the mediation of several deleterious processes by acting upon gene regulation in the cells in which it is released (Park et al. 2009). AICD has also been shown to impact the proliferation of hippocampal progenitor cells (HPCs) (Ghosal et al. 2010), a cell population that is associated with the processes of learning and memory (van Praag et al. 2002; Shors et al. 2001; Snyder et al. 2005; Wang et al. 2010; Klempin and Kempermann 2007). Specifically, it was observed that a mouse model induced to overproduce AICD exhibited a lower rate of production of daughter cells from the HPC population concurrent with an upregulation of several pro-inflammatory cytokines. When this model was treated with ibuprofen, the rate of cell proliferation in the HPC population fell more in line with that observed in wild-type (WT) controls (Park et al. 2009).

Toll-like receptors

One important mediator of Aβ-induced inflammation is the family of Toll-like receptors (TLRs), a class of pattern recognition receptors recently identified as having important roles in the innate immune system (Landreth and Reed-Geaghan 2009). Many TLRs, including TLR1, 2, 4, 5, 6, and 7 show increased expression as a function of age in mouse models (Liu et al. 2005; Walter et al. 2007), as one would expect of a receptor type capable of interacting with the pathogenic mediators of AD.

The primary subtypes of TLRs implicated in AD-associated inflammation include TLR2 and TLR4. Both subtypes have been implicated not only in mediating inflammation induced by Aβ, but also with aiding in the clearance of Aβ from the extracellular space. Specifically, blockage of TLR2 in vivo was shown to reduce the inflammatory response to Aβ, and when a TLR2−/− murine model was crossed with an APP/PS1 (presenilin-1) mutant, Aβ deposition was increased coinciding with a concomitant decrease in cognitive function. This effect was reversed by bone marrow gene therapy for TLR2 in this model (Triantafilou et al. 2004). Further, another study found that primary cultures of microglia from TLR2 knockout (KO) mice were incapable of increasing the expression of TNFα, IL-1β, IL-6, and inducible nitric oxide synthase (iNOS) following exposure to fibrillar forms of Aβ 1–42 (Udan et al. 2008).

Aβ has also been found to activate microglia and astrocytes via TLR4 as well as its co-receptor, cluster of differentiation 14 (CD14). The effects of Aβ on this receptor complex is similar to its effect on TLR2, in that KO models of TLR4 or CD14 exhibited decreased inflammatory markers in response to Aβ, and the ability of microglia in such models to clear Aβ is significantly impaired (Reed-Geaghan et al. 2009; Walter et al. 2007; Tahara et al. 2006). Additionally, cultured microglia with intact TLR4 and CD14 genotypes produce neurotoxic factors in response to incubation with Aβ 1–42 and also directly kill neurons which had sustained damage from Aβ in a CD14, contact dependent manner (Combs et al. 2001; Bate et al. 2004, 2006). Further, TLR4 was shown to be upregulated in in vitro neuronal populations in response to Aβ and 4-hydroxynonenal (4-HNE), a lipid peroxidation product. Within this population, a c-Jun N-terminal kinase (JNK) dependent, caspase-3 mediated apoptosis was observed, presumably in response to Aβ challenge. In the same study, TLR4 KO cell cultures were shown to be spared from this fate despite Aβ exposure. While it has been shown that TLR4 can be upregulated in neuronal populations exposed to Aβ both in vivo and in vitro, cortical neurons of end-stage AD patients exhibit reduced TLR4 expression. This may be a result of increased cell death in neurons that upregulate TLR4 earlier in the disease process (Tang et al. 2007, 2008). Finally, human carriers of the asp299gly allele, associated with decreased activity of TLR4 (Arbour et al. 2000) exhibit significant protection from the late onset AD (Minoretti et al. 2006).

Advanced glycation end products and their receptors

Another receptor/ligand axis that has been shown to have interactions with the production of Aβ as well as inflammatory response in AD is that of advanced glycation end products (AGEs) and their receptors (RAGEs) (Yan et al. 1996). RAGE expression is increased in neuronal and astroglial cell populations in AD patients, which correlates with increased levels of production of ROS by these cells. Further, Aβ is capable of binding to RAGE, and as such is a possible mediator of this effect (Yan et al. 1996). Aβ also activates RAGEs at the surface of microglia, which in turn stimulates these cells to produce proinflammatory cytokines and chemotactic factors, an effect that is abrogated by blocking the interaction between Aβ and RAGE (Yan et al. 1996, 2009). Another intriguing experimental observation is that activation of RAGEs by in vivo treatment with AGEs in mouse models caused a nuclear factor-κB (NF-κB) dependent upregulation of BACE-1 (Guglielmotto et al. 2010). This finding makes sense in light of evidence suggesting that there are NF-κB binding sites in the promoter regions of BACE-1, as well as presenilin and APP. The genetic sequence coding for RAGE also contains a binding site for NF-κB (Li and Schmidt 1997).

Taken together, these findings suggest a NF-κB mediated positive feedback mechanism in which Aβ and RAGE each stimulate further production of the other.

Other intracellular signaling pathways

Aβ has also been shown to interact extensively with many intracellular signaling pathways within neurons. For instance, glycogen synthase kinase 3 (GSK3), and specifically its beta isoform (GSK3β), has been shown to increase amyloidogenic processing of APP (Phiel et al. 2003). At the same time, Aβ has been reported to be capable of activating GSK3β by as yet unidentified mechanisms (Takashima et al. 1993), establishing another means by which Aβ could possibly upregulate its own production. In addition to this effect, GSK3 has been shown to be capable of indirectly increasing NF-κB, signal transducer and activator of transcription (STAT)3/5, and mitogen-activated protein kinase kinase kinase 11 (MLK3), all of which can increase the production of inflammation mediating cytokines, such as IL-6, TNFα, and monocyte chemotactic protein-1 (MCP-1) (Beurel et al. 2010; Schmitz et al. 2004). Murine models induced to overexpress GSK3β exhibited increased microglial and astrocyte activation as well as neuronal structural abnormalities concomitant with deficits in spatial memory. This effect was rescued in a conditional KO model when the overexpression of GSK3β ceased (Lucas et al. 2001; Hernandez et al. 2002; Engel et al. 2006; Mines et al. 2011).

Additionally, an inflammatory milieu has been shown to be conducive to the hyperphosphorylation of the microtubule-associated protein, tau. This leads to the formation of intracellular insoluble plaques known as NFTs, a hallmark of AD pathology (Ballatore et al. 2007). The hyper-phosphorylation of tau is mediated by the activation of its kinases, and an inflammatory microenvironment is thought to promote the activation of these molecules (Ballatore et al. 2007; Iqbal et al. 2005). Further, GSK3 is one of the primary mediators of phosphorylation of the tau protein (Avila et al. 2010). Thus, GSK3 and its isoforms are capable of generating both the inflammatory effects observed in AD, as well as several pathological hallmarks of the disease.

Physiological role of Aβ

Strong evidence has been presented that Aβ is involved in the inflammatory and various other pathological mechanisms of AD. However, much research has been done in recent years suggesting a physiological role for Aβ in memory formation and retention (Morley et al. 2010; Puzzo et al. 2011; Barbagallo et al. 2010). Several studies have demonstrated that when otherwise healthy animal models were induced to produce Aβ at abnormally low levels, significant deficits in long-term potentiation (LTP), spatial memory, and synaptic plasticity were observed (Morley et al. 2010; Puzzo et al. 2011). Furthermore, ectopically introduced Aβ 1–42 was found to be sufficient to rescue the deficits in LTP only when it was allowed to oligomerize prior to application (Morley et al. 2010). Thus, Aβ clearly has a complex interaction with the cells of the CNS, and more work is required to characterize precisely what impact different forms and concentrations of this molecule have on cognitive function.

Role of microglia and astrocytes

Astrocytes and microglia are each a subset of the larger classification of glial cells which serve many supporting functions in the CNS. Astrocytes in a non-reactive state are involved in ion homeostasis, regulation of metabolic function and synaptic levels of glutamate, production of anti-oxidant species, maintenance of the blood-brain barrier (BBB), and other functions (Wang and Bordey 2008; Benarroch 2005; Shih et al. 2006; Attwell and Laughlin 2001; Abbott et al. 1992). Microglia are the resident immunocompetent cells of the CNS. When not actively engaged in an inflammatory response, they play the role of quiescent sentinels, constantly extending and contracting processes that probe the surrounding extracellular space as well as cellular neighbors for signs of both exogenously and endogenously derived danger signals (Banati et al. 1993).

In terms of neuroinflammation in AD, microglia and astrocytes play a critical role. In situations which call for inflammatory response (i.e., pathogenic infiltration) astrocytes and microglia take on an activated phenotype and begin proliferating (Akiyama et al. 2000; McGeer and McGeer 2003). Neuroinflammation is mediated, at least in part, by arrays of cytokines which are released by reactive astrocytes and activated microglia (Tan et al. 1999; Heneka and O'Banion 2007). For example, levels of the potent pro-inflammatory cytokines interleukin (IL)-1β and IL-6 are elevated in the cerebrospinal fluid of AD patients (Griffin et al. 1989; Blum-Degen et al. 1995; Huell et al. 1995), while the ratio of IL-10, a cytokine with anti-inflammatory properties, to the pro-inflammatory IL-1β is decreased (Remarque et al. 2001).

During the progression of the AD disease process, it has been observed that there is a steady increase in the number of morphologically identifiable reactive astrocytes (Sastre et al. 2008). These are recruited by activated microglia and enhance the inflammatory response to extracellular Aβ deposits which colocalize with activated microglia. Local acute phase neuroinflammatory response mechanisms

mediated by enzymes such as COX-2 and nitric oxide synthase (NOS) have been demonstrated to be major contributors to neuronal dysfunction and cell death (McAdam et al. 1999; Montine et al. 1999; Brown and Bal-Price 2003; Edison et al. 2008).

Microglia

The activation of microglia can occur in response to the formation of amyloid plaques. At the same time, APP and amyloid peptides can act as potent glial activators (Barger and Harmon 1997; Schubert et al. 2000). Increased microglial activation is an event that colocalizes with the areas of heavy Aβ concentration in the CNS of AD patients (Edison et al. 2008). Microglial activation is an early event in AD pathology (Craft et al. 2006; Vehmas et al. 2003) and progresses in line with the increase of Aβ deposition in the brains of AD afflicted individuals (Vehmas et al. 2003).

Despite the clear connection that microglial distribution in the CNS exhibits with the pathological markers of AD, there has been no small amount of disagreement over the role that these cells actually play at their sites of activation. For example, depletion of microglia in animal models can cause an increase in Aβ load (Majumdar et al. 2007), suggesting that they play a role in the clearance of Aβ by phagocytosis. At the same time, as the primary resident immune cells of the CNS, they are also capable of producing many pro-inflammatory factors that can potentially be neurotoxic in nature (Kreutzberg 1996).

Macrophages are thought to be one of the primary mediators of Aβ removal from the extracellular space in the brain as they have been shown capable in in vitro assays of internalizing Aβ via various receptor-mediated mechanisms (Berthiaume et al. 1995). The deposition of Aβ may reflect an overabundance of amyloidogenic processing of APP, overwhelming the ability of microglia to effectively clear this substance (Paresce et al. 1997). Microglial activation by pro-inflammatory cytokines such as macrophage colony stimulating factor (MCSF) and IL-6 can increase their ability to degrade Aβ (Majumdar et al. 2007). Alternatively, it has been suggested that CNS resident microglia may be capable of phagocytosing Aβ, but that their ability to degrade the peptide may be lacking due to a relatively high lysosomal pH. As such, the purported role of CNS-derived microglia as recruiters of peripheral macrophages to the sites of Aβ accumulation may be their primary mechanism of Aβ clearance (Majumdar et al. 2007; Simard and Rivest 2004).

Besides their role as clearers of Aβ, microglia are also capable of performing various other functions with potentially neuroprotective effects. For instance, a study has shown that microglia are capable of acting as sinks for glutamate during circumstances that might otherwise lead to *N*-methyl-D-aspartic acid (NMDA) receptor-linked Ca^{2+}-mediated neurotoxicity (Persson et al. 2005). Additionally, microglia also release factors such as brain derived neurotrophic factor and thrombospondins (TSPs) capable of stimulating neurogenesis and synaptogenesis in the mature CNS (Kettenmann et al. 2011). Further, it has been suggested that microglia themselves may serve as potential precursors for other CNS cells, including neurons (Yokoyama et al. 2004). Microglia are also thought to function as effective removers of synapses of damaged neurons (Cullheim and Thams 2007).

While Aβ clearance by microglia can play a beneficial role in the pathogenesis of AD, this is not the only effect exerted by microglia in this process. As immune-associated cells, microglia are also important producers of pro-inflammatory factors including cytokines, chemokines, and reactive oxygen/nitrogen species (ROS/RNS) (Nathan et al. 2005; Block et al. 2007; Ard et al. 1996). One such pro-inflammatory cytokine, TNFα, has been shown to decrease the phagocytic function of CNS immune cells in vivo (Koenigsknecht-Talboo and Landreth 2005). This demonstrates one means by which inflammation limits the efficacy of microglia in curtailing the production of AD markers.

Astrocytes

Recent studies have demonstrated the prominence of astrogliosis—an increase in the number of astrocytes in response to neuronal distress—in AD brains. This is observed mainly in the regions surrounding amyloid plaques with processes of activated astrocytes participating in the formation of neuritic plaques (Nagele et al. 2003; Rodriguez et al. 2009). However, there is evidence suggesting that this activation is more widespread (Vehmas et al. 2003). A recent hypothesis posits that progression of astrocytosis per se may play a role in the observed cognitive deficits of aging populations beyond that which is attributed to those pathways that are more traditionally associated with the pathology of AD. It has been demonstrated that reactive glia are major contributors to ongoing neurodegeneration. Recent studies also suggest that neuroinflammation plays an important role in the early stage of AD pathology (Maccioni et al. 2009; Simpson et al. 2010).

There are several mechanisms by which astroglia are thought to interact with inflammation in AD. One idea that has recently received attention is that astroglia can exert neurotoxic effects simply by taking part in an inflammatory response. During this period, the normal role of astroglia in their support function is likely compromised (Fuller et al. 2010). Several studies have suggested that compromised glucose metabolism in neurons may be a contributing

factor in AD, and that this effect is observable early in the disease process in both human and animal models (Freemantle et al. 2006; Drzezga et al. 2003; Mielke et al. 1998; Alexander et al. 2002; Small et al. 2000). As the ratio of astroglia to neurons in the CNS is quite high, it has been suggested that this deficit in glucose metabolism must be due at least in part to the loss of astroglial glucose uptake (Alexander et al. 2002). Additionally, a dearth of both glutamate transporter (GLT)-1, which functions in astrocytes to regulate synaptic glutamate concentration, and glutathione, which is an antioxidant produced by astrocytes, is a characteristic of AD (Li et al. 1997; Calabrese et al. 2006). In aggregate, this evidence suggests that one of the most deleterious effects of astroglial inflammatory activation is the neglect of their typical role as supporters of neuronal function.

It has been suggested that microglial activation precedes astroglial activation in AD (Zhang et al. 2009). At the same time, it has also been suggested that the precipitating event in astrocytic activation is the formation of fibrillar Aβ (Paris et al. 2002b; Hensley et al. 1998). A large body of literature has implicated various other possible mechanisms that may cause astrogliosis, including ischemia (Wakasa et al. 2009), infiltration by infectious agents (Okamoto et al. 2005), and other chemical exposure (El-Fawal and O'Callaghan 2008). Regardless of the causative event, the effects of astrocytic activation on neuroinflammation in AD have been well documented. Generally speaking, these fall into two categories: production of cytokines and chemokines and the production of free radical species.

With regard to the first of these, as activated astroglia are immunocompetent cells, it is not surprising that they are capable of producing cytokines and chemokines. Specifically, it has been reported that in co-cultures of neurons with astroglia, there is an increased production of IL-1β, IL-6, TNFα, and interferon-γ (IFNγ) which coincides with the introduction of Aβ 1–42 to the cells' growth media (Jana and Pahan 2010). A more recent study has shown that IL-13, IL-17, and IFNγ induced protein-10 (IP-10) production were increased in a similar disease model (Garwood et al. 2011). This pattern of cytokine and chemokine production suggests a mechanism for reciprocal activation as, for example, IL-17 has been shown capable of inducing further IL-6 production in astrocytes (Anisman 2009). Additionally, IL-6 production is increased during the early stages of the appearance of major deposits of Aβ, suggesting a connection between IL-6 and Aβ (Huell et al. 1995).

As to the production of free radicals, astrocytes have been shown to be capable of producing both RNS and ROS (Hashioka et al. 2009), production of which results in oxidative stress in the physiological processes of cells, with downstream effects such as damage to lipids, proteins, and DNA. This may in turn result in necrosis or apoptosis (Simonian and Coyle 1996). Nitric oxide (NO), produced by activation of iNOS in particular, is a signaling molecule in this pathway with multiple effects. For example, it has been suggested that astroglial-derived NO can exert such varied effects as neuronal energy depletion (Bolanos et al. 1997), deleterious interactions with protein thiol groups and iron–protein complexes (Chen et al. 2001), and upregulation of inducible as well as constitutive cyclooxygenases (COX-2 and COX-1, respectively) (Calabrese et al. 2007). Oxidative stress induced by the production of ROS has been implicated in the early stages of the development of AD (Mondragon-Rodriguez et al. 2010). Therefore, the inhibition of the production of these radical species has received considerable attention in recent years as a potential avenue for intervention in the progression of the disease.

Under normal conditions in the brain, COX-2 is not produced by astroglia (Yermakova and O'Banion 2001). On the other hand, COX-2 activity is increased in astrocytes associated with the fibrillar Aβ deposits in a double transgenic murine model of AD (Matsuoka et al. 2001). COX production is particularly insidious with regard to its ability to mediate inflammation as its enzymatic activity produces both prostaglandins from arachidonic acid as well as oxidative species (Smith et al. 1996). The production of each of these molecules has been implicated in the enhanced production of inflammatory cytokines such as IL-6 in CNS cells (Fiebich et al. 2001). Furthermore, COX-2 production in astrocytes can be induced by IL-1β (O'Banion et al. 1996). In another link to AD pathology, it has been shown that APP production is induced in microglia and astrocytes by the activation of prostaglandin E2 (PGE2) receptors (Lee et al. 1999; Pooler et al. 2004). Despite these findings, it has also been reported that while COX-2 production is increased in the initial phases of AD, its expression is actually downregulated as the pathological hallmarks of the disease develop (Hoozemans et al. 2008; Krause and Muller 2010).

Cardiovascular inflammatory processes

Neurovascular interactions in AD

Recently, it has become clear that vascular dysfunction likely plays an important role in the pathogenesis of AD. Vascular dementia is a form of dementia which has a clinical presentation similar to that of AD, but which has a pathogenesis involving specific insult to the cerebrovasculature. It is well known that vascular dementia and AD share risk factors, and one-third of patients with a clinical

and pathological diagnosis of AD have some degree of vascular pathology (Gearing et al. 1995; Ince et al. 2000) and vice versa (Sadowski et al. 2004). Furthermore, cardiovascular disease risk factors such as diabetes and hypertension have been well established as risk factors for AD. Among AD patients with similar amounts of plaques and tangles, only those with both AD and cardiovascular disease had significant dementia (Snowdon et al. 1997).

It has even been postulated that AD is primarily a vascular disorder with neurodegenerative consequences, with the initial pathogenic insult arising from cerebral hypoperfusion, and with impairment of NO bioactivity contributing to the progression of the disease (Hollenberg 2006). Indeed, reduced cerebral blood flow (Iadecola et al. 1999) and a reduction in vasoreactivity (Vicenzini et al. 2007) have been found in AD patients. Chronic hypoperfusion can result in oxidative stress, leading in turn to vascular endothelial permeability (Aliyev et al. 2004) and neuronal death associated with mitochondrial failure (Aliev et al. 2003). Hypoperfusion also results in decreased pH, which contributes to inflammatory processes in AD by increasing Aβ immunoreactivity (Bell and Zlokovic 2009).

Blood–neuron barriers in AD

Changes in the BBB make up a pronounced element of AD pathology, and the functional integrity of the BBB in AD has been called into question. It has been found that serum amyloid P component, a protein synthesized in the periphery which can serve to stabilize amyloid plaques, is associated with senile plaques and neurofibrillary tangles in postmortem AD brains even though it is not synthesized in the brain. This observation has lead to the suggestion that the BBB may be compromised in AD (Kalaria and Grahovac 1990). Indeed, both Aβ and extracellular tau have been posited to influence inflammatory responses in AD by contributing to vascular leakiness (Kovac et al. 2009).

In a healthy state, the BBB comprises endothelial cells joined by tight junctions, the basal lamina, and surrounding pericytes and astrocytic foot processes. Movement across this barrier of substances which cannot freely pass through the phospholipid cell membrane is tightly regulated by endothelial and astrocytic transport mechanisms. This protects the brain from harmful substances and oxidative damage. Importantly, the BBB regulates the entry of soluble Aβ, which is also produced in the periphery, into the CNS, via RAGEs, and the clearance of Aβ out of the CNS into the bloodstream, mediated by LDL-receptor related protein-1 (LRP-1) (Deane et al. 2003, 2004; Bell et al. 2007; Ji et al. 2001; Shibata et al. 2000; Zlokovic et al. 2000; Bading et al. 2002; Mackic et al. 1998; Tanzi et al. 2004). LRP-1 is downregulated in AD patients, with regional downregulation patterns consistent with the patterns of increased Aβ deposit density (Shibata et al. 2000). ATP binding cassette transport protein P-glycoprotein (P-gp) is also involved in Aβ export from the brain. P-gp is found to be downregulated in the vessel walls where there is accumulated Aβ. Unaffected capillaries have high P-gp expression, and it has been suggested that Aβ itself plays a role in downregulating expression of P-gp in the neurovasculature, thus exacerbating its effects (Brenn et al. 2011).

In addition to the BBB, the blood–cerebrospinal fluid barrier is another means by which neurons are protected from circulating factors. There is some evidence that this barrier undergoes damage early in the disease process, preceding Aβ and tau pathologies, although the functional significance of this with regard to passage of inflammatory factors is not yet fully known (Chalbot et al. 2011).

Vascular/endothelial involvement in AD

Diffusible mediators of inflammation

Endothelial cells are capable of producing a host of inflammatory, neurotoxic, and neuroprotective chemicals that interact with the progression AD. For example, while being more widely recognized for its role in the coagulation cascade, thrombin can also act as an inflammatory and neurotoxic protein that is produced by endothelial cells (Luo and Grammas 2010). Thrombin can induce expression of the protein endothelin-1 (ET-1), which has neuroprotective as well as vasoactive properties. On the other hand, ET-1 may play a deleterious role, as it can also interact synergistically with Aβ to cause increased vasoconstriction via activation of an inflammatory pathway (Paris et al. 2002a). Thrombin also induces the transcription factor hypoxia-inducible factor-1α (HIF-1α) which is involved in the regulation of pro-inflammatory gene expression. Thrombin, ET-1, and HIF-1α are all elevated in AD (Luo and Grammas 2010; Grammas et al. 2006).

Matrix metalloproteinases (MMPs) are endoproteases which cleave proteins in the extracellular matrix and participate in the regulation of growth factors, adhesion molecules, and receptors. One means by which MMPs may affect the progression of AD is through their ability to regulate the activity of nerve growth factor (NGF). Specifically, MMP-9 has been shown to be involved in the conversion of the mature form of NGF (mNGF) to a prefunctional form (proNGF). NGF-dependent cholinergic neurons in the nucleus basalis are differentially lost during the progression of AD. Further, MMP-9 activity is increased in the frontal and parietal cortical tissue harvested from humans afflicted with both AD and MCI relative to controls. The degree of MMP-9 upregulation

correlated with the degree of mental impairment observed in the test subjects, which in turn supports the theory that it is a dysregulation of trophic factors that leads to the demise of cholinergic neurons in the nucleus basalis (Bruno et al. 2009). On the other hand, it has also been shown that MMP-2 and MMP-9 are released from AD-derived microvessels, but their activity may be suppressed as increased levels of thrombin associated with AD induce elevated levels of tissue inhibitor of matrix metalloproteinases-1 (TIMP-1) (Thirumangalakudi et al. 2006). Ultimately, while correlational evidence suggests an interaction, the effects that MMPs may have on the progression of AD, as well as the time course with which they occur, have not been fully elucidated.

In addition, microvessels in AD patients also express the angiogenic substances angiopoietin-2 and vascular endothelial growth factor (VEGF) (Thirumangalakudi et al. 2006), and the integrin $\alpha V\beta 3$, a marker of angiogenesis, is also elevated in many brain regions in AD (Desai et al. 2009), which might account for the increased levels of capillary density observed in AD patients (Fioravanzo et al. 2010). Brain capillary endothelial cells have also been shown to proliferate in response to NGF, express NGF receptors, and secrete NGF after inflammation (Moser et al. 2004).

Nitric oxide

Nitric oxide plays a key role in maintaining normal vascular function and structure. Originally discovered by Robert Furchgott and named endothelial-derived relaxation factor, it is known to mediate the relaxation of vascular smooth muscle both in the brain and throughout the body, ensuring proper perfusion of tissues (Furchgott 1999). NO is produced enzymatically by NOS which is produced by cell types in many different systems. These employ different isoforms of the enzyme depending on the local function for which it is required. Neuronal NOS (nNOS) is the isoform expressed in the brain, and is believed to be used for neurotransmission. Inducible NOS (iNOS) is produced by astroglial cells and neurons in response to inflammatory conditions. Endothelial NOS (eNOS) influences vasodilation, and thus the state of cerebral perfusion (Hollenberg 2006).

There is some controversy regarding the role of NO in AD, and it likely plays both protective and detrimental roles. For example, NO is known to be involved in normal neurotransmission and is believed to play an important role in memory function as a retrograde transmitter in LTP (Kuiper et al. 2000). On the other hand, NO is a free radical which can cause both nitrosative and oxidative stress, lipid peroxidation, DNA damage, and impairment of mitochondrial function (Contestabile et al. 2006) and may play a role in the initiation of apoptosis (Warner et al. 2004), neuroinflammation, and neurodegeneration (Calabrese et al. 2000). Both chronic cerebral hypoperfusion and oxidative stress have been implicated in the pathogenesis of AD (Calabrese et al. 2000). As such, regulation of the expression and activation of the NOS isoforms presents itself as an attractive potential avenue of pharmacological modification.

Vascular amyloid deposits

In addition to its role in neuronal function and pathology, Aβ is also a physiological component of plasma (Altman and Rutledge 2010). It is transported across the blood–brain barrier into the plasma, and in vitro studies have shown that Aβ can be produced and released by activated platelets exposed to collagen, arachidonic acid, or thrombin in a process involving protein kinase C (PKC) and, under some conditions, COX (Skovronsky et al. 2001). Plasma Aβ 1–42 is elevated in AD patients prior to the development of symptoms (Mayeux et al. 1999, 2003). In addition, in AD, Aβ is also produced by cerebrovascular endothelial cells, which exhibit α-, β-, and γ-secretase like activity, and which may contribute to amyloidogenic deposits which have been found associated with the cerebral vasculature of AD patients (Davies et al. 1998). Indeed, more than 80 % of autopsied AD patients show some amount of cerebral amyloid angiopathy (Ellis et al. 1996), which is associated with an increased frequency of hemorrhage or ischemic lesions. These deposits contain predominantly the Aβ 1–42 isoform (Roher et al. 1993) and can have deleterious effects, compounding pathogenesis in AD as the distortion and occlusion of the capillaries leads to reduction in cerebral blood flow, further hindering the clearance of Aβ from the brain (Iadecola 2004).

Homocysteine

Elevated plasma levels of the amino acid homocysteine (Hcy) have been associated with an increased risk of both AD and vascular dementia (Seshadri 2006; Gallucci et al. 2004), and elevated Hcy levels in the brain can result from deficiencies in vitamins B_6 and B_{12} (Weir and Molloy 2000). Hcy interferes with the activity of eNOS, induces iNOS, and produces ROS via a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase dependent pathway, and can upregulate NF-κB and TNFα in endothelial cells (Faraci 2003). By increasing the expression of vascular cell-adhesion molecule-1 (VCAM-1) while simultaneously decreasing expression of glucose transporter-1 (GLUT-1) and eNOS, Hcy has been shown to induce endothelial dysfunction in rat brain (Lee et al. 2004). Neurotoxicity, abnormalities in brain chemistry, and

cerebrovascular dysfunction were all observed in a murine model produced by dietary addition of Hcy, and these effects could be abolished by pharmacological modification (Troen 2005). However, the neurotoxic mechanisms may be more direct as well, as Hcy has been shown to kill cerebrocortical neurons via an NMDA dependent mechanism (Lipton et al. 1997).

Drug targets

Drugs currently in use

There are only five drugs which are currently approved for use in the treatment of AD. Of these, donepezil (Aricept®), galantamine (Reminyl®), rivastigmine (Exelon®), and tacrine (Cognex®) all belong to the class of drugs called acetylcholinesterase inhibitors (AchEI). The fifth drug, memantine (Namenda®), is a non-competitive antagonist at the NMDA glutamate receptor.

The AChEI have been proven to be effective in slowing the progression of dementia in AD (Sabbagh and Cummings 2011). All four drugs in this class are primarily prescribed for the treatment of mild to moderate stages of the disease, although donepezil has also been approved for use in severe AD as well. Although efficacy appears to be similar for drugs in this class, they differ in their mechanism of inhibition, selectivity, and pharmacokinetics (Schneider 2000), and differences in side effects may influence the choice of drug (Qaseem et al. 2008). Notably, tacrine, which was the first drug approved for clinical use, is now only rarely used due to a relatively high risk of hepatotoxicity (Watkins et al. 1994).

AD patients have reduced ACh synthesis and impaired cortical cholinergic function (Whitehouse et al. 1982). This is consistent with animal studies showing that Aβ reduces ACh production and release (Kar et al. 2004; Bales et al. 2006). The AChEI act by inhibiting the enzyme AChE which is anchored in the synaptic cleft at cholinergic synapses. AChE cleaves ACh into choline and acetate, thus limiting the ability of this neurotransmitter to bind to and activate receptors (Schneider 2000). By inhibiting this enzyme, the AChEI prolong the activity of the remaining endogenously released ACh, compensating at least partially for the cholinergic deficit.

Although it is not clearly understood how a cholinergic deficit contributes to AD pathophysiology, multiple mechanisms are likely involved. For example, activation of M1 muscarinic ACh receptors stimulates α-secretase cleavage of APP, reducing the production of toxic Aβ fragments (Nitsch et al. 1992), so a reduction in ACh would be expected to increase Aβ production. Furthermore, by the activation of α4 and α7 nicotinic ACh receptors, both donepezil and galantamine, but not tacrine have been shown to be protective against glutamate-induced neurotoxicity, via a mechanism involving the phosphatidylinositol 3-kinase-Akt/protein kinase B pathway (Takatori 2006). In addition to their effect at cholinergic synapses, the clinical efficacy of the AChEI likely results from other pharmacologic mechanisms as well, which may include effects on inflammatory processes both through α7 nicotinic ACh receptors peripherally (Wang et al. 2003), and directly, as donepezil has been shown to suppress iNOS gene expression, inhibit the production of NO, TNFα, and IL-1β, and inhibit inflammatory NF-κB signaling in microglial cell cultures (Hwang et al. 2010) as well as suppressing IL-1β and COX 2 production, and reducing neuroinflammation in vivo in a tau mutant mouse model of AD (Yoshiyama et al. 2010).

The NMDA receptor antagonist memantine is considered to be neuroprotective, and is currently approved by FDA for moderate to severe AD patients. It has been shown to produce a notable improvement in clinical deterioration in AD patients compared to placebo (Reisberg et al. 2003), and has been reported to have fewer side effects compared to AChEI (McShane et al. 2006). Furthermore, memantine can be used in combination with existing AChEIs (Tariot et al. 2004).

Glutamate is the principal excitatory amino acid neurotransmitter in cortical and hippocampal neurons, and NMDA receptors are important for many physiologically relevant processes, including learning and memory (Orrego and Villanueva 1993; Danysz and Parsons 1998). However, since part of the current passing through open NMDA receptor-mediated channels is carried by Ca^{2+}, excessive stimulation of NMDA receptors can lead to Ca^{2+}-mediated toxicity, which is detrimental in AD (Dong et al. 2009) and other neurodegenerative diseases (Dong et al. 2009; Levine et al. 1999; Klapstein and Colmers 1997; Klapstein and Levine 2005). Memantine exerts a neuroprotective effect by binding within and physically blocking the ion channel which is integral to the NMDA receptor, thereby preventing the entry of Ca^{2+}.

As with the AChEI, however, memantine also has pharmacological actions in addition to those described above, which interfere with inflammatory processes. It has been shown to reduce inflammatory microglial activation and increase the release of neurotrophic factors by astroglia (Wu et al. 2009), both of which would be beneficial in AD.

Drugs in trial

Because of the role of inflammation in the pathogenesis of AD, several drug targets with anti-inflammatory or antioxidative properties have been investigated. An extensive review of recent studies and clinical trials involving disease-modifying treatments for AD has recently been published (Galimberti and Scarpini 2011); therefore, we

shall briefly discuss some of those agents which have been postulated to be beneficial in the treatment of AD through interaction or interference with inflammatory processes.

By acting as agonists at the ligand-activated nuclear receptor peroxisome proliferator activated receptor-γ (PPARγ), non-steroidal anti-inflammatory drugs (NSAIDs), thiazolidinediones, and prostaglandin J2 all initiate neuroprotective mechanisms. Combs et al. (2000) have found that PPARγ agonists inhibit the secretion of proinflammatory products by microglia, as well as the production of IL-6 and TNFα in response to Aβ stimulation, and the differentiation of activated macrophages from monocytes. Indeed, some epidemiological studies correlate the use of NSAIDs with reduced risk of developing AD within 2–3 years if taken prior to age 65 (Hayden et al. 2007), but others show increased risk in older populations (Breitner et al. 2009). Disappointingly, there is no evidence that NSAIDs have any effect in changing disease progression, and their use may actually be detrimental (Willard et al. 2000; Moore and O'Banion 2002; Martin et al. 2008; Wolfson et al. 2002). Several compounds with anti-oxidative properties, such as vitamin E, alpha lipoic acid and resveratrol are also being investigated for effectiveness in slowing the progression of AD, but there has been no conclusive evidence of benefit (Granzotto and Zatta 2011; Isaac et al. 2008; Cho et al. 2010).

Ginkgo biloba has historically been used to improve cognition, and is known to increase cerebral blood flow, reduce blood viscosity, modify neurotransmitter systems, and scavenge free radicals. While negative side effects have not been shown, consistent beneficial evidence for the use of Ginkgo biloba in AD patients is lacking (Birks and Grimley Evans 2009).

Folic acid and vitamin B_{12} deficiency have been linked to elevated Hcy levels, which are associated with elevated AD risk, as described above. As such, it has been proposed that increasing levels of these vitamins might be of benefit in reducing risk or symptoms of AD. In fact, there is some evidence that folate and B_{12} supplementation can improve cognition in healthy older people with high levels of Hcy, but this effect has not been found in AD patients (Malouf and Grimley Evans 2008).

There is some evidence that cannabinoids may be a good target for AD drug development, as they may regulate excessive glutamate production and neuroinflammation. Although there is no current evidence of benefit to AD patients in using cannabinoids, extensive studies have not been done, and further research is warranted (Krishnan et al. 2009).

Colostrinin, a polypeptide with immunomodulatory properties derived from ovine colostrum (Blach-Olszewska and Leszek 2007), has been shown in animal models in vivo to improve cognitive performance, and in cell-based assays to reduce Aβ aggregation and neurotoxicity. Although clinical trials in AD patients were initially encouraging, showing modest improvements in mild AD (Leszek et al. 1999), this effect did not appear to be sustained with therapy continued more than 15 weeks (Bilikiewicz and Gaus 2004).

Another promising drug is Huperzine A, a chemical with AChEI activity, derived from the Chinese herb *Huperzia serrata*. Huperzine A has been shown to be protective against ischemia, hydrogen peroxide, glutamate, and Aβ-mediated toxicity. Clinical trials have shown some evidence of improvements in cognition, activities of daily living, and behavioral disturbances (Li et al. 2008), and in vitro studies have indicated that Huperzine, when added to cells exposed to Aβ, increased cell survival and activity of glutathione peroxidase and catalase, and produced decreased levels of malondialdehyde (Xiao et al. 2000).

Curcumin is a component of the spice turmeric and has been proven to contain antioxidant, anti-inflammatory, and cholesterol-lowering properties (Ringman et al. 2005). In animal studies, it was shown to reduce Aβ and amyloid levels (Yang et al. 2005). Clinical trials have not proven the direct effect of curcumin on AD progression, however, this could be due to time limitations or the experimental design (Baum et al. 2008), and further studies are warranted.

Summary

Inflammatory processes are extensively involved in the pathophysiological processes of AD. These processes provide numerous targets for intervention with therapeutic or preventative agents, but they must be approached with caution as many of the inflammatory processes are obviously involved in pathogenesis of the disease, yet others contribute to compensatory defense mechanisms and some play dual roles. Several compounds which interfere with inflammatory mechanisms have made their way to clinical trial, and many more have shown promise of therapeutic potential in preclinical studies. Of these compounds, few have shown unequivocal success, especially at later stages of the disease when neuronal death may render cerebral dysfunction irreversible. Yet hope remains. Many trials report modest but positive results. As we gather more of the pieces to the puzzle of AD, we may find that testing such drugs at different stages of the disease or in synergistic combinations may lead to significant, clinically relevant treatment strategies.

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