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Inflammation in Alzheimer Disease—A Brief Review of the Basic Science and Clinical Literature

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Biochemical and neuropathological studies of brains from individuals with Alzheimer disease (AD) provide clear evidence for an activation of inflammatory pathways, and long-term use of anti-inflammatory drugs is linked with reduced risk to develop the disease. As cause and effect relationships between inflammation and AD are being worked out, there is a realization that some components of this complex molecular and cellular machinery are most likely promoting pathological processes leading to AD, whereas other components serve to do the opposite. The challenge will be to find ways of fine tuning inflammation to delay, prevent, or treat AD.

A recent PubMed search using the key word "Alzheimer's," the Boolean connector "AND," and several key words related to inflammation (e.g., cytokine, chemokine, complement) returned some 6114 different citations. Although that is less than a third of the 20,452 citations for "Alzheimer's AND amyloid," it is 423 citations more than the 5691 for "Alzheimer's AND tau." Clearly, inflammatory mechanisms in Alzheimer disease (AD) are a mainstream area of research.

Whether they are also an important area of research is a different question. As with virtually all the other mechanisms under investigation in AD, it still cannot be definitively stated whether inflammation is a cause, contributor, or secondary phenomenon in the disorder. Treatment trials have been a major disappointment, as they have been for virtually all other therapeutics that have attempted to address the underlying pathogenesis of AD rather than ameliorate its symptoms.

Much has been learned, nonetheless, at both basic science and clinical levels. Here, we review this literature and attempt to address, in as balanced and objective a manner as we can, some of the major controversies in the field. If nothing else, the burgeoning number of papers on inflammation and AD that are summarized in this review make plain the remarkable

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complexity of inflammatory mechanisms in AD and the many challenges that such complexity imposes with respect to selecting or developing appropriate therapeutics.

CELLULAR MEDIATORS

Microglia

In the mid-1980s it was discovered that microglia in the AD cortex could be labeled with antibodies to major histocompatibility complex type II cell surface glycoprotein (MHCII), a classic marker for activated immune cells (Luber-Narod and Rogers 1988; McGeer et al. 1988; Rogers et al. 1988). This not only created a much more convenient way to identify microglia compared to previous silver methods, but also opened the possibility that the brain might not be quite so immunologically privileged as previously supposed. Today, microglia are generally recognized as the brain's resident macrophages, and are considered to be pivotal players in innate immune/inflammatory responses in multiple neurologic disorders, including Parkinson's disease (Rogers et al. 2007), HIV dementia (Garden 2002), multiple sclerosis (Muzio et al. 2007), amyotrophic lateral sclerosis (Dewil et al. 2007), AD (Mandrekar-Colucci and Landreth 2010), and others. There is also general consensus on mechanisms of microglial actions in both the normal and diseased CNS, from the remarkable ability of these cells to survey vast extents of the brain (Davalos et al. 2005; Nimmerjahn et al. 2005; Wake et al. 2009) to their expression of classic pro- and anti-inflammatory mediators and receptors (Lue et al. 2001a,b; Wyss-Coray 2006; Cameron and Landreth 2010). Important advances beyond this basic body of knowledge, however, continue to be made, particularly with regard to intermediate states of microglial activation (reviewed in Colton and Willcock 2010) and microglial interactions with amyloid β peptide (Aβ) (reviewed in Combs 2009; Lee and Landreth 2010). For other recent and thorough reviews of microglia, the reader is referred to the excellent summaries by Colton (2009), Mandrekar-Colucci and Landreth (2010), and El Khoury and Luster (2008).

Microglia in the developing brain ultimately derive from the mesenchyme, in which myeloid progenitors give rise to cells that migrate to the CNS and proliferate as microglia (Rezaie and Male 2002). Migration of blood-derived macrophages into the CNS has also been suggested to occur later in fetal development (reviewed in Chan et al. 2007). Throughout development, microglia may play an important role in remodeling of the brain by removing presumably redundant, apoptotic neurons (Bessis et al. 2007; Caldero et al. 2009). In vivo activity of microglia has recently been visualized using two photon microscopy techniques (Davalos et al. 2005; Nimmerjahn et al. 2005; Wake et al. 2009). The extraordinary, dynamic images from these studies reveal that microglia constantly sample their immediate environment, including neighboring glia, blood vessels, and neurons, by extending and retracting their processes for distances up to some 80 μm (Nimmerjahn et al. 2005). In this manner, it has been estimated that the microglial population may survey the entire brain every few hours. Loss of synapses encountered by microglial processes has been reported using in vivo microscopy (Wake et al. 2009), supporting the potential role of microglia in normal synaptic remodeling. Microglia also contribute to a healthy CNS by attacking and removing potential pathogens and detritus, and by secreting tissue rebuilding factors (Wyss-Coray 2006). These essential, supportive mechanisms have been emphasized by Streit and Xue (2009), who have contended that "the only 'bad' microglial cell is a dead microglial cell."

Alternatively, several hundred reports of microglial attack mechanisms in neurologic disease suggest a more complex view. For example, in vitro, these cells secrete a wide range of inflammatory factors, many of which have the potential to automodulate microglial phenotype (see below) and to impact bystander neurons and their processes. These include reactive oxygen species (Coraci et al. 2002); Th1 cytokines such as IL-1β, IL-6, TNF-α, and interferon γ (INF-γ) (Lue et al. 2001a); chemokines such as macrophage inflammatory protein 1α (MIP1α), MIP1β, CXCL8, RANTES,

and monocyte chemotactic protein 1 (MCP1) (El Khoury et al. 2003, 2007 2008); growth factors such as macrophage colony stimulating factor (Lue et al. 2001a); and complement components such as C1q, C3, C4, and C9 (Walker et al. 1995, 2001). They also express receptors associated with inflammatory activation, attack, and phagocytosis, including cytokine receptors (reviewed in Akiyama et al. 2000; John et al. 2003), chemokine receptors (Cartier et al. 2005; El Khoury et al. 2008), complement receptor 3 (Sedgwick et al. 1991), the receptor for advanced glycation endproducts (RAGE) (Walker and Lue 2005), Fc receptors (Okun et al. 2010), CD40 (Tan et al. 1999), formyl peptide (FP) receptors (Chen et al. 2007a; Brandenburg et al. 2008), various scavenger receptors (El Khoury et al. 1998; El Khoury and Luster 2008), and toll-like receptors (TLRs) (Landreth and Reed-Geaghan 2009). Elevation of these factors in culture and animal models typically results in neurodegeneration, and all have been reported to be elevated in pathologically-vulnerable regions of the AD brain (reviewed in Akiyama et al. 2000; Rogers et al. 2007; Landreth and Reed-Geaghan 2009). Similarly, signal transduction and transcription factor (e.g., NF-κB, PPARγ, Sp1) alterations associated with inflammation have been observed in microglial cultures and AD brain (Citron et al. 2008; Jiang et al. 2008; Granic et al. 2009; Mandrekar-Colucci and Landreth 2010). Not surprisingly, microglia are also capable of secreting anti-inflammatory mediators and growth factors such as IL-4, IL-10, IL-13, and TGF-β (reviewed in Wyss-Coray 2006; Colton 2009), just as peripheral monocytes do in the tissue-rebuilding phase that follows inflammatory attack.

Although there are likely to be multiple stimuli for the inflammatory responses of microglia in the AD brain, including simple detritus from other pathogenic reactions, aggregated Aβ deposits appear to be especially potent, as indicated by the dense accumulations of microglia expressing MHCII and other markers of activation within and around such deposits (Luber-Narod and Rogers 1988; McGeer et al. 1988; Rogers et al. 1988). Consistent with these histologic findings in situ, human elderly microglia in culture have been shown to migrate to aggregated Aβ spots dried down to the well floor, and to internalize portions of the Aβ (Lue et al. 2001b; Walker and Lue 2005). Similarly, microglia cultured on sections of AD cortex accumulate on Aβ deposits and appear to remove them (Bard et al. 2000). Additional studies have suggested, however, that microglia may not be able to degrade the Aβ they have taken up (Paresce et al. 1997; Walker and Lue 2005; Majumdar et al. 2007, 2008), potentially leading to a state of "frustrated phagocytosis" and to phenotypic and functional changes in the microglia.

Two-photon microscopy has clarified the anatomic relationships of microglia to Aβ by showing that microglial processes sample and react to Aβ deposits in transgenic mouse models. Recruitment of microglia to newly-formed plaques occurred within a few days in one study (Meyer-Luehmann et al. 2008), and was followed, in several studies, by establishment of a dynamic interface between microglial processes and Aβ deposits (Bolmont et al. 2008; Koenigsknecht-Talboo et al. 2008; Yan et al. 2009). Internalization and lysosome colocalization of Aβ was observed by Bolmont and colleagues (2008), and damage to neighboring neurons, coincident with the arrival of microglia, has also been reported (Meyer-Luehmann et al. 2008). Alternatively, Meyer-Luehmann and coworkers (2008) did not observe resolution of plaques over "days to weeks," and it remains to be shown whether or not the neurodegeneration following microglial recruitment to plaques is directly caused by the microglia. Positron emission tomography (PET) using benzodiazepine ligands for activated microglia has shown increasing signal for these cells in living AD versus control subjects (Cagnin et al. 2001; Edison et al. 2008), and an inverse correlation between benzodiazepine-positive microglial load and cognitive status scores (Edison et al. 2008). Notably, however, microglial load did not correlate with Aβ burden in the same subjects (Edison et al. 2008), and Wiley et al. (2009) were unable to confirm elevated microglial signal in AD subjects. Given repeated histologic findings of dense accumulations of

microglia labeled with other activation markers (e.g., MHCII, IL-1) at sites of Aβ deposition, it may be that benzodiazepine binding, which also marks at least some astrocytes (Ji et al. 2008), may be labeling a microglial phenotype that is less engaged in interactions with Aβ. In addition, Aβ is unlikely to be the only stimulus for microglial activation in the AD brain. New studies with potentially more specific microglial ligands may help resolve these issues.

Mechanistic studies of the inflammatory factors and receptors mediating microglial localization and responses to Aβ have also been fruitful. In vitro, Aβ has been shown to stimulate expression of nearly all the proinflammatory mediators discussed earlier (c.f., Lue et al. 2001a; Walker et al. 2001), and many of the previously mentioned innate immune response receptors found on microglia have Aβ either as a direct or indirect ligand. For example, direct RAGE/Aβ binding helps guide microglia to Aβ deposits, an effect that is inhibited by treatment with anti-RAGE antibodies (Walker and Lue 2005; Chen et al. 2007b). Complement opsonization of Aβ (Rogers et al. 1992) and/or binding to anti-Aβ antibodies (Bard et al. 2000) may also permit indirect interactions via microglial expression of complement receptor 3 (Sedgwick et al. 1991) and Fc receptors (Okun et al. 2010).

Over the last two decades, controversies have arisen as to whether microglia should be regarded as friend or foe to the nervous system (reviewed in Wyss-Coray 2006). This is perhaps natural given a cell type that is neuroprotective primarily by virtue of its capacity for attack. Microglia do not prevent apoptosis, neurodegenerative debris, bacterial invasion, or Aβ deposits; they attempt to remove such pathologies before further damage is performed. They also secrete anti-inflammatory mediators and growth factors. For these and other reasons, microglia are certainly vital to promoting a healthy CNS. Alternatively, many studies have shown that microglia are capable of killing or damaging neurons and, indeed, multiple mechanisms and mediators in brain appear to be devoted to keeping such toxicity in check, including CD22 (Mott et al. 2004), CD200 (Walker et al. 2009), fractalkine (Ransohoff 2007), TREM2 (Hsieh et al. 2009), and the complement defense protein CD59 (Singhrao et al. 1999; Yang et al. 2000).

A more balanced and sophisticated view of these issues is emerging from new research showing a continuum of microglial activation states that parallel similar phenotypic changes in peripheral macrophages (reviewed in Gordon and Taylor 2005; Colton 2009). Mediated primarily by the Th2 cytokines, IL-4, IL-10, IL-13, and TGF-β, deactivating alterations to macrophage and microglial morphology, antigenicity, and function appear to occur as coordinated, restorative sequelae after initial proinflammatory responses to pathogens and injury, and may be invoked in a long term fashion under conditions in which small amounts of the offending agent persist after an inflammatory attack (Bogdan 2008). Frustrated phagocytosis of Aβ may qualify as such an event. Several activation state nomenclatures have been suggested. Some are based on peripheral macrophage responses (M1, M2a, M2b, M2c) and reflect macrophage populations that are induced by specific Th2 cytokines and other factors (e.g., immune complexes, apoptotic cells) (Gordon and Taylor 2005). Colton (2009), has summarized an activation nomenclature that embraces many of the findings that have been reported for macrophages but works particularly well for microglia. Here, three activation states are proposed: 1) classical activation, which is stimulated by IFN-γ and characterized functionally by attack mechanisms; 2) alternative activation, which is stimulated by IL-4 and IL-13 and characterized functionally by tissue restorative, anti-inflammatory mechanisms; and 3) acquired deactivation, which is stimulated by TGF-β, IL-10, and apoptotic cells and characterized functionally by immunosuppression (but with a retained ability to phagocytose apoptotic cells). A mixture of classical activation, acquired deactivation, and increasing alternative activation is observed in AD (Colton 2009), and may ultimately further our understanding of the complex roles that microglia may play in neurodegenerative diseases, as well as how to manipulate them therapeutically.

For example, agents that drive microglia to a phenotype that favors attack on potential pathogens rather than bystander neurons should be an appealing target.

Astrocytes

Astrocytes are an essential neurosupportive cell type in brain. Their well-known interactions with neurons include secretion and recycling of transmitters, ion homeostasis, regulation of energy metabolism, synaptic remodeling, and modulation of oxidative stress. Tiling the entire brain in contiguous, orderly fashion, each single gray matter astrocyte has been estimated to envelope as many as 100,000 synapses (Halassa et al. 2007). As such, perturbation of the many neurosupportive astrocyte functions can have extremely deleterious consequences for the CNS (reviewed in Belanger and Magistretti 2009). Moreover, like microglia, astrocytes respond quickly to pathology with changes in their morphology, antigenicity, and function, and, like microglia, these reactive states have been increasingly recognized as a continuum with potentially beneficial and destructive consequences (reviewed in Sofroniew and Vinters 2010).

In brain of AD patients (Sofroniew and Vinters 2010) and AD transgenic mouse models (Rodriguez et al. 2009), reactive astrocytes occupy peri-plaque positions, encircling Aβ deposits in a manner reminiscent of glial scarring, a mechanism by which the cells may provide a barrier between healthy tissue and areas of injury or infection (Sofroniew and Vinters 2010). MCP1, which is highly concentrated in Aβ plaques, is chemotactic for adult astrocytes, and astrocytes express receptors that bind Aβ, including RAGE, low density lipoprotein receptor-like protein, membrane-associated proteoglycans, and scavenger receptor-like receptors. Collectively, these mechanisms may therefore account for the dense accumulation of reactive astrocytes at sites of aggregated Aβ deposition (Wyss-Coray et al. 2003). Several studies suggest that plaque-localized, reactive astrocytes take up and degrade Aβ (Nagele et al. 2003; Wyss-Coray et al. 2003; Koistinaho et al. 2004). In Tg2576 transgenic mice such effects may be linked to insulin degrading enzyme (IDE), which appears to play a key role in Aβ degradation. Astrocyte expression of IDE is increased after Aβ exposure and is pronounced within glial fibrillary acidic protein (GFAP) immunoreactive astrocytes surrounding Aβ deposits (Leal et al. 2006). Extracellular clearance of Aβ may also occur via astrocyte secretion of matrix metalloproteinases (Yin et al. 2006). Exposure to Aβ, in turn, appears to disrupt astrocyte calcium homeostasis (Abramov et al. 2004; Chow et al. 2010), with subsequent increases in GFAP (Chow et al. 2010), a typical marker of astrocyte reactivity, as well as degeneration of neurons in astrocyte-neuron cocultures (Abramov et al. 2004).

Reactive astrocytes may provoke neuropathology through expression or overexpression of a number of inflammation-related factors. For example, S100β, a neurotropin that induces neurite proliferation, is overexpressed in AD brain and its levels are correlated with numbers of dystrophic neurites within Aβ deposits (Mrak et al. 1996). A similar correlation is found In APPV717F transgenic mouse brain, wherein astrocyte S100β overexpression increases with age to a point just prior to Aβ deposition (Sheng et al. 2000). In S100β overexpressing transgenic mice, inflammatory responses to intracerebroventricularly-infused Aβ are significantly augmented compared to wild-type and S100β knockout mice (Craft et al. 2005). After intracerebroventricular administration of lipopolysaccharide (LPS) or brain injury, both of which induce brain inflammation, astrocytes become more reactive and begin to show immunoreactivity for the γ-secretase components presenilin-1 and nicastrin (Nadler et al. 2008). Presenilin-2 expression also appears in AD but not nondemented control (ND) astrocytes (Takami et al. 1997). Exposure of cultured astrocytes to Aβ significantly increases IL-1β, TNF-α, iNOS, and NO production, with differential temporal effects depending on whether the Aβ is in fibrillar or oligomeric, nonfibrillar form (White et al. 2005). Transcripts for INF-γ and IL-12 are also increased in Tg2576 transgenic mouse astrocytes (and

microglia) in an age-dependent manner (Abbas et al. 2002).

Many of these effects may trace back to alterations in astrocyte transcription factors. For example, the proinflammatory cytokines IL-1β, IL-6, and TNF-α are regulated by NF-κB and C/EBP transcription factor mechanisms. Astrocyte CEBPδ is dramatically upregulated in AD cortex (Li et al. 2004), and astrocyte NF-κB is activated on exposure to Aβ, leading to increased expression of IL-1β and IL-6 (Bales et al. 1998). NF-κB mechanisms in astrocytes also control secretion of chemokines and adhesion molecules that might permit invasion by peripheral leukocytes, further fueling the inflammatory response (Moynagh 2005). Calcineurin, a calcium-dependent phosphatase that helps mediate a wide range of inflammatory and calcium-dysregulatory responses, is increased in reactive AD astrocytes. In culture, adenoviral transfer of activated calcineurin results in astrocyte morphologic and gene expression profiles that closely parallel those observed in AD and AD transgenic mouse models (Norris et al. 2005). In turn, calcineurin actions induce activation and translocation of the transcription factor nuclear factor of activated T-cells (NFAT). Exposure of cultured astrocytes to Aβ activates NFAT, leading to decreases in excitatory amino acid transporter 2, increases in glutamate, and death of cocultured neurons (Abdul et al. 2009).

Oligodendrocytes

Oligodendrocytes and the myelin sheath they produce envelope axons and are critical for neurotransmission. Oligodendrocytes and myelin are also well known targets of immune reactions in other neurolgic disorders, particularly multiple sclerosis. Although AD research lags far behind in this area, histologic, molecular, electrophysiologic, and imaging data have revealed lesions and myelin abnormalities in AD white matter (reviewed in Roth et al. 2005), and focal demyelination of axons associated with Aβ deposits in gray matter has been convincingly shown in familial and sporadic AD, as well as in transgenic mouse models of AD (Mitew et al. 2010). Stereotaxic injection of nM quantities of Aβ into the corpus callosum induces microglial proliferation, with attendent damage to myelin and losses of oligodendrocytes (Jantaratnotai et al. 2003). In vitro, oligodendrocyte toxicity has been reported for Aβ25-35 (Xu et al. 2001), Aβ40 (Xu et al. 2001; Lee et al. 2004), and Aβ42 (Roth et al. 2005). Perhaps because of their low glutathione and high iron content, oligodendroglia are also extremely vulnerable to oxidative stress (Juurlink 1997), one of the main weapons of inflammatory attack. Finally, oligodendrocytes have been reported to express mRNAs and to be immunoreactive for complement components C1q, C1s, C2, C3, C4, C5, C6, C7, C8, and C9, leading to the suggestion that they may be primary sources for the significantly increased levels of complement in pathologically-vulnerable regions of the AD brain (Hosokawa et al. 2003). Complement activation occurs on oligodendrocytes via C1q binding to myelin oligodendrocyte protein (Johns and Bernard 1997), and is likely to be enhanced by the low levels of C1 inhibitor and membrane cofactor protein expressed by the cells (Hosokawa et al. 2004). Given these conditions, it is not surprising that complement-activated oligodendroglia are observed in many neurodegenerative conditions in which inflammation has been identified, particularly AD (Yamada et al. 1990).

As with all the other cell types in this review, inflammation may play dual roles with respect to the oligodendrocyte. For example, several multiple sclerosis studies have suggested that an active, acute inflammatory response may be necessary for remyelination of demyelinated axons (Arnett et al. 2003; Foote and Blakemore 2005; Setzu et al. 2006). Likewise, Roth et al. (2005) have reported that Aβ42-mediated oligodendrocyte toxicity is actually reduced by prior exposure to LPS or INF-γ.

Neurons

As previously noted, neurons express a wide range of molecules that are designed to protect against inflammatory attack. These include CD22 (Mott et al. 2004), CD200 (Walker et al.

2009), fractalkine (Ransohoff 2007), TREM2 (Hsieh 2009), and the complement defense protein CD59 (Singhrao et al. 1999). Some of these protective mechanisms have been found to be deficient in AD. For example, neuronal expression of CD59 (Yang et al. 2000), and CD200 (Walker et al. 2009) is selectively decreased in pathologically-vulnerable regions of the AD brain. Fractalkine is also decreased in APP transgenic mouse cortex and hippocampus at ages in which these animals begin to show AD pathology (Duan et al. 2008). In fact, neither AD nor ND neurons express the complement regulators decay accelerating factor and complement receptor 1, and only weakly express membrane cofactor protein, suggesting that neurons should be particularly vulnerable to complement reactions (Singhrao et al. 1999).

MOLECULAR MEDIATORS

The Complement System

The complement system represents a key inflammatory pathway for the activation and execution of immune responses (Holers 1996). Because complement appears to be activated in neurodegenerative diseases and complement proteins are associated with plaques and tangles in AD, this pathway may hold clues to AD inflammation in general.

The complement system is capable of recognizing molecular patterns on pathogens or molecular patterns associated with injured tissues and dying cells. Recognition may be through C1q or mannose binding proteins, which contain collagen-like receptor binding domains (Tenner 1999), or through interactions with the multifunctional protein C3 (Sahu and Lambris 2001). Once activated, a diverse array of almost 30 proteins in the complement pathway can attract and activate immune cells, amplify antigen-specific immune responses, promote phagocytosis, facilitate complement-mediated cytolysis by the membrane attack complex (MAC), and regulate cell proliferation and differentiation (Fig. 1) (Holers 1996). Antigen-antibody complexes or antibodies bound to solid surfaces activate the classical pathway of complement by binding C1q and then activating C1r and C1s, followed by C4, C2, and C3. Bacteria and various molecular patterns present, for example, on DNA or certain sugars can activate the alternative pathway by binding C3b and Factor B. Finally, mannose moieties on bacteria are recognized by mannan binding lectin in the lectin pathway (not shown in figure). All pathways result in the formation of multiprotein catalytic activities, the C3 convertases, generating two proteolytic C3 fragments: C3a, which is released in the fluid phase and involved in the chemotaxis of phagocytes, and C3b, which can bind covalently to acceptor molecules in solution or on cellular surfaces (Carroll 1998). C3b binding may activate the lytic pathway involving C5, C6, C7, C8, and C9, which culminates in the formation of the MAC, C5b-9, and may lead to cytotoxicity. This pathway also leads to the formation of C5a, another small proinflammatory peptide. Alternatively, C3b binding to targeted molecules, in a process called opsonization, mediates phagocytosis by a number of cells through their surface expression of complement receptors (Carroll 1998). In addition, bound C3b can be cleaved into smaller fragments, including iC3b, C3dg, and C3d, that can mediate binding of opsonized fragments to distinct complement receptors (CRs) (Holers 1996; Sahu and Lambris 2001). The CRs include C3aR, CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18), and CR4 (CD11c/CD18).

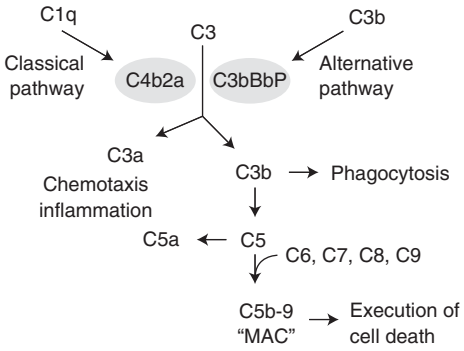

Figure 1. Brief schematic of the complement system (see text for details).

Complement proteins are produced mostly in the liver and are present at high levels in serum. However, glial cells and neurons in the CNS can synthesize these proteins as well, and their production is increased in brain injury and neurodegeneration (D'Ambrosio et al. 2001; Gasque 2004), including AD (Rogers et al. 1996; McGeer and McGeer 1999; Akiyama et al. 2000; Emmerling et al. 2000; Gasque et al. 2000). C1q and the MAC colocalize with amyloid plaques and tangle-bearing neurons (Eikelenboom and Stam 1982; Eikelenboom et al. 1989; Itagaki et al. 1994; Webster et al. 1997; Shen et al. 2001; Fonseca et al. 2004a). More recent support for activation of complement in AD comes from a number of transcriptome studies showing that complement gene expression is increased in the disease (Blalock et al. 2004; Katsel et al. 2009).

Assuming an absence of microbial pathogens, what might be the cause for activation of complement? Aggregated Aβ activates the complement system in vitro through the classical pathway by binding C1q and through the alternative pathway by binding C3b (Rogers et al. 1992; Jiang et al. 1994). Isolated tangles or tau aggregates can also activate the classical pathway by binding C1q (Shen et al. 2001). The accumulation of Aβ and tau may therefore promote the activation of complement and possibly neuroinflammation. Others have hypothesized that CNS antigen-specific autoantibodies can reach the CNS and, similar to glutamate receptor specific antibodies in Rasmussen's encephalitis, bind to neurons and other cells and activate the classical pathway of complement (D'Andrea 2003).

As mentioned earlier, complement can recognize degenerating or dying cells and fulfills an important role in the clearance of dead or degenerating cells in various tissues (Botto et al. 1998; Taylor et al. 2000). Although there is no direct support for this mechanism in AD, C1q has been shown to tag apoptotic neurons or neuronal blebs and promote their uptake by microglia in cell culture (Fraser et al. 2010). Moreover, C1q and C3 have recently been shown to mediate synaptic pruning during development and in a model of glaucoma, opening the possibility that complement factors may contribute to elimination of synapses in neurodegenerative diseases (Stevens et al. 2007).

Although none of the above observations can answer whether complement activation is beneficial or detrimental in AD, a number of studies have begun to address this question. APP mouse models in which C3 activation is inhibited by the overexpression of soluble complement receptor-related protein y (sCrry) show an increase in Aβ deposition and an accumulation of degenerating neurons (Wyss-Coray et al. 2002). Consistent with these findings, APP mice with a complete knockout of C3 also show increased Aβ and neuronal degeneration, accompanied by changes in microglial activation (Maier et al. 2008). These data suggest that C3 may work with microglia to help clear Aβ. Other studies have additionally shown that APP mice lacking complement C1q have less neuronal damage and glial cell activation than complement-sufficient mice, suggesting a role for C1q in neuronal integrity (Fonseca et al. 2004b). Alternatively, the "peripheral sink" hypothesis of DeMattos and colleagues (2001), involving binding of circulating Aβ to Aβ autoantibodies, may also apply to C3-opsonized Aβ in the peripheral circulation. In particular, a well-established mechanism for clearance of circulating pathogens, immune adherence (reviewed in Atkinson et al. 1994; Birmingham and Hebert 2001), appears to be operative with respect to circulating Aβ. Here, C3-dependent binding of Aβ to human erythrocyte CR1 has been shown, and is reported to be significantly deficient in the vast majority of AD patients, as well as many mild cognitive impairment (MCI) subjects (Rogers et al. 2006). Notably, subprimates do not express erythrocyte CR1, so that this pathway would not be evident in AD transgenic mouse models. Because previous transgenic mouse manipulations of the complement system (Wyss-Coray et al. 2002; Maier et al. 2008) were systemic and not restricted to brain, it is also possible that the effects observed on Aβ loads and neurodegeneration might have been mediated by alterations in peripheral complement mechanisms, alterations in brain complement mechanisms, or both.

In summary, complement is activated in AD, where it may exert regulatory functions and aid in the clearance of degenerating cells and protein aggregates. However, it is likely also to promote unwanted inflammation. Genetic susceptibility studies have recently linked single nucleotide polymorphisms in clusterin (ApoJ), a potent regulator of complement activation, and CR1 as relatively strong susceptibility genes for AD (Harold et al. 2009; Lambert et al. 2009). How these polymorphisms affect complement activity is unknown.

Cytokines and Other Soluble Signaling Proteins

Cytokines, chemokines, and related immune proteins are part of a soluble network of communication factors between cells. Although many of these proteins were discovered as potent regulators of inflammation and immune function, it is well accepted now that they have pleiotropic effects in many tissues, including the CNS, and regulate diverse cellular processes such as proliferation, survival, and differentiation. Numerous cytokines and chemokines have also been linked to CNS development. It is therefore not surprising that many of these proteins have altered levels in AD (Akiyama et al. 2000). Cytokine or chemokine changes in the brain parenchyma are frequently accompanied by parallel changes in protein levels in the CSF, and some of these proteins appear to be dysregulated in the periphery as well (Ray et al. 2007; Zhang et al. 2008; Soares et al. 2009; Hu et al. 2010b). The consequences of cytokine or chemokine changes on brain function and neurodegeneration relevant to AD are unknown, but a growing number of genetic studies in mice show that these immune proteins have potent effects on amyloidosis, neurodegeneration, and cognition (Wyss-Coray and Mucke 2002; Wyss-Coray 2006). Tumor necrosis factor (TNF)-α is one such factor that has received much attention because of its ability to promote Parkinson's disease (PD) progression (McCoy et al. 2006), whereas TNF receptor 1 knockout protects against AD- and PD-like disease in mice (Sriram et al. 2002; He et al. 2007). Similarly potent effects are exerted by transforming growth factor (TGF)-β1, which is increased in human AD brains at the transcript and protein level, whereas TGF receptor expression is decreased (Wyss-Coray et al. 1997; Tesseur et al. 2006). TGF-β1 promotes cerebrovascular amyloidosis but delays parenchymal Aβ accumulation in APP mice that also overproduce this cytokine from astrocytes (Wyss-Coray et al. 2001). Interestingly, although APP mice with deficient TGF-β signaling in neurons show more neurodegeneration and amyloid accumulation (Tesseur et al. 2006), other APP mice expressing the same receptor in myeloid cells have reduced disease (Town et al. 2008). These studies on TGF-β provide a good example of the complexity of cytokine biology and how targeting such pathways in disease may be very challenging. Likewise, the chemokine CCL2 and its receptor CCR2, which play a key role in regulating the infiltration of peripheral monocytes into the brain (Charo and Ransohoff 2006), show a complex role in AD. Lack of CCR2 in mice results in reduced accumulation of microglia/monocytes in the brain and accelerates disease progression and Aβ deposition in a mouse model of AD (El Khoury et al. 2007). Because microglia from CCR2 knockout mice do not show aberrant proliferation (El Khoury et al. 2007), it has been postulated that changes in microglia accumulation are a consequence of monocyte infiltration. Conversely, overexpressing CCL2 in the brain results in increased microglial accumulation (Yamamoto et al. 2005). However, overexpressing CCL2 also results in increased Aβ accumulation, which may be due to a prominent increase in mouse ApoE (Yamamoto et al. 2005), a factor known to independently enhance Aβ deposition (Bales et al. 1999).

Several other cytokine mRNAs or proteins are expressed at increased or decreased levels in AD brain or periphery (Wyss-Coray 2006). A number of these have also been studied in AD mouse models, including IL-1β and IL-6, which surprisingly both appear to have beneficial effects on amyloidosis. Thus, using an inducible expression cassette, O'Banion's group showed that short-term expression of IL-1β in

adult APP mice resulted in strong activation of glial cells, induction of various inflammatory factors, and reduced amyloid pathology (Shaftel et al. 2007). Similarly, viral overexpression of IL-6 in the hippocampus led to massive gliosis and neuroinflammation, reduced amyloidosis, and amelioration of cognitive deficits in APP mice (Chakrabarty et al. 2010). Interestingly, lifelong stable overexpression of IL-1 receptor antagonist or IL-6 had no effect on pathogenesis in another APP mouse model consistent with the concept that acute but not chronic activation of certain types of immune responses in the brain may be beneficial (Wyss-Coray 2006). Treatment of APP mice with macrophage-colony stimulating factor (M-CSF) (Boissonneault et al. 2009) or granulocyte-colony stimulating factor (G-CSF) (Sanchez-Ramos et al. 2009) in the periphery also had ameliorating effects on cognition and disease progression in these mice.

In summary, many cytokines and chemokines are clearly expressed at abnormal levels in AD. Although these proteins can strongly activate glial cells and induce neuroinflammation, they have surprisingly beneficial effects in mouse models of AD. Whether therapies based on these findings may be efficient in humans is unknown.

Toll-Like and Other Pattern Recognition Receptors

The immune system uses a large number of highly conserved pattern recognition receptors to detect either exogenous molecules associated with pathogens or endogenous molecules generated in response to cell and tissue injury (Janeway and Medzhitov 2002; Seong and Matzinger 2004). In addition to the complement recognition proteins discussed earlier, toll-like receptors (TLRs) have received particular attention with respect to their role in the injured CNS and possibly in AD (Landreth and Reed-Geaghan 2009). Stimulation of TLRs, of which there are at least 13 distinct members to date (Iwasaki and Medzhitov 2004), induces activation of NF-κB and subsequent transcriptional activation of numerous proinflammatory genes (Nguyen et al. 2002). In the CNS, TLRs are expressed prominently on microglia, but other cells express certain TLRs as well (Aravalli et al. 2007). CNS microinjections of the TLR 2 or 4 ligands zymosan and lipopolysaccharide (LPS), respectively, cause robust glial activation and elicit substantial neurodegeneration (Popovich et al. 2002; Lehnardt et al. 2003). Consistent with these findings, TLR4-deficient mice have smaller infarct volumes and better functional outcomes than control mice in a sterile model of experimental stroke (Caso et al. 2007). One well-known TLR activator is Aβ, which binds the TLR4 coreceptor CD14 (Fassbender et al. 2004; Liu et al. 2005) and can trigger microglia to secrete nitric oxide, IL-6, and other neurotoxic factors (Walter et al. 2007). Microglia lacking CD14, TLR2, or TLR4 appear to be unable to activate NF-κB or p38 MAP kinase signaling or phagocytosis in response to fibrillar Aβ (Reed-Geaghan et al. 2009). Perhaps as a result, levels of TNF-α and MIP-1β are significantly higher in the brains of AD mice with wild-type TLR4 than their mutant TLR4 AD mouse counterparts (Jin et al. 2008). On the other hand, TLR-mediated activation of microglia may also aid in the clearance of Aβ. Studies in AD mouse models with mutant TLR2 or TLR4 suggest that deficiencies in TLR signaling may cause cognitive impairments with a concomitant increase in Aβ deposition (Tahara et al. 2006; Richard et al. 2008). Likewise, acute administration of the TLR4 ligand LPS can promote Aβ clearance (DiCarlo et al. 2001). Whether these receptors normally exacerbate neurodegeneration or guide the clearance of protein aggregates is still largely unknown. In addition, it may be noteworthy that many studies, particularly with Aβ, have not considered the aggregation state of the peptide. The TLRs, however, are likely to be differentially engaged by monomers, oligomers, or fibrillar assemblies of Aβ and other amyloidogenic peptides, eliciting different types of responses in microglia (and other cells).

The receptor for advanced glycation end-products (RAGE) is yet another pattern recognition receptor that has been linked to AD and has a critical role in inflammation. RAGE

ligand binding results in the activation of Jak/Stat and NF-κB signaling, is up-regulated in AD brains, and functions as a receptor for Aβ (Schmidt et al. 2009). Using double transgenic PDAPP-J20 mice overproducing either wild-type RAGE (APP/RAGE) or a mutant RAGE protein that inhibits the endogenous receptor function (i.e., a dominant negative RAGE receptor, APP/dnRAGE), Arancio and colleagues showed a detrimental role for RAGE signaling in Aβ dependent neuronal perturbation that appears to involve NF-κB and MAPK signaling and results in increased synaptic transmission deficits, as well as cognitive impairment (Arancio et al. 2004). In a more aggressive mouse model of amyloidosis, expressing APP with an arctic mutation deletion of the RAGE gene did not have an effect on amyloid deposition or cognition in 12-month-old mice, although it dramatically reduced fibrillar Aβ deposits in 6-month-old mice (Vodopivec et al. 2009). Thus, although RAGE seems to be sufficient to mediate detrimental effects of Aβ, it may not be necessary.

Cyclooxygenases and Arachidonic Acid Metabolites

Cyclooxygenases (COX) convert arachidonic acid to prostaglandinH2 (PGH2), the first step in the synthesis of numerous prostanoids with different functions. Although COX-1 is constitutively expressed in many cell types and tissues and may be involved in the physiological production of prostanoids, COX-2 is increased during inflammation, resulting in proinflammatory prostanoid synthesis (Warner and Mitchell 2004). As one of the key targets of nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenases were first strongly implicated in AD by a meta-analysis of 17 epidemiologic studies of long term NSAID use, wherein such long term use reduced AD risk by half (McGeer et al. 1996). These findings have been confirmed in a number of subsequent reports, but have not led to successful treatment trials thus far (see Clinical Studies below).

One possible reason for this failure may be that, like many other inflammatory mediators, prostaglandins are janus-faced, exerting beneficial or toxic functions depending on the setting. For example, COX-2, which is localized to postsynaptic sites, is involved in modulating physiological synaptic transmission, but excessive activation in pathological conditions or genetic overexpression in neurons in transgenic mice induces neuronal apoptosis and cognitive deficits (Andreasson et al. 2001; Liang et al. 2007). Transgenic overexpression of COX-2 in neurons has also been shown to lead to a two-fold increase in Aβ plaque formation in one APP mouse model (Xiang et al. 2002) and cognitive deficits in another model (Melnikova et al. 2006), supporting a detrimental role for COX-2 and its downstream products in neurodegeneration and AD. To characterize the function of the various prostanoids in CNS function and in AD, the Andreasson laboratory has studied mouse models with deficiencies in specific prostanoid receptors. Mice lacking PGE2 receptor EP2 have electrophysiological defects in the hippocampus and are cognitively impaired (Savonenko et al. 2009), but deletion of this receptor in APP mice results in less amyloidosis. Compared to APP mice without EP2 deletion, APP/EP2 knockout mice also show half the levels of F2-isoprostanes and F4-neuroprostanes, both of which are indicators of lipid peroxidation (Liang et al. 2005). On the other hand, EP4, another PGE2 receptor, seems to strongly inhibit inflammatory activation of microglia in vivo based on selective deletion experiments using the cre-lox system in mice (Shi et al. 2010). Together, these studies show that EP2 is necessary for normal physiological function in the CNS, but has detrimental effects in the inflammatory setting present in APP mouse brains, whereas EP4 functions as an inhibitor of inflammation. New therapeutic strategies targeting specific prostanoid receptors may therefore provide better tools to regulate inflammation in AD than conventional NSAIDs.

MOLECULAR GENETICS

Technologies to interrogate ever-larger numbers of biological molecules from complex fluids or tissues have become more generally available

to researchers, and many studies have taken advantage of these tools to characterize vast numbers of genetic polymorphisms in the human genome, the complete transcriptome, or subsets of the proteome in AD. Perhaps not surprisingly, many of the "hits" or final lists of factors from these studies include molecules involved in immune and inflammatory responses. Future studies will nonetheless be necessary to determine whether any of them do indeed have a role in AD or could be used as biomarkers.

For example, two genome-wide association studies that interrogated several hundred thousand polymorphisms in the human genome in thousands of patients and controls have recently identified clusterin and CR1 as genetically linked to sporadic AD (Harold et al. 2009; Lambert et al. 2009). A similarly-scaled study from the Mayo Clinic confirmed these findings with a surprising congruency in effect size and probability (Jun et al. 2010), although odds ratios for both genes were rather small. The biological significance or functional involvement of clusterin and CR1 in AD are unknown, but it is intriguing that both genes point to the complement system (see above). In addition, significant genetic linkages of single nucleotide polymorphisms or haplotypes in case-control or population-based studies have been described for cytokines, chemokines, and acute phase proteins. These genes show typically very modest effects on AD risk and their biological significance is unknown. A ranking of polymorphisms based on meta-analyses of multiple association studies is available at AlzGene.org (http://www.alzgene.org) (Bertram et al. 2007).

Changes in inflammatory pathways have also been noted in several microarray studies of gene expression profiles in AD brains or peripheral blood cells compared with those from healthy controls. In a review comparing several such transcriptome studies of the aging brain with those in AD, Blalock and colleagues (2005) noted that genes associated with inflammation are increased in aging, and that this is accentuated in AD. In agreement with this conclusion, a recent study in people above or below age 86 with or without AD reported a striking increase in transcripts related to major histocompatibility complex (MHC) genes, the complement cascade, and phagocytosis in the cognitively normal oldest-old compared to the other groups (Katsel et al. 2009), supporting the concept that a gain in brain immunity may be protective and that a failure to adapt to aging underlies neurodegeneration. Gene expression studies in blood cells from AD patients have also found many changes associated with immune and inflammatory pathways when compared to age-matched controls (Kalman et al. 2005; Fiala et al. 2007; Maes et al. 2007).

Consistent with transcriptional changes in immune-related factors in brain and blood, differences in levels of soluble immune mediators and other communication factors in cerebrospinal fluid or plasma have been linked to AD in antibody-based proteomic studies (Ray et al. 2007; Soares et al. 2009; Hu et al. 2010a,b). In addition, several reports have found complement proteins as well as clusterin to be among the most significant proteins discriminating AD from healthy control plasma using two-dimensional gel electrophoresis and mass spectrometry-based unbiased approaches (Hye et al. 2006; Sheta et al. 2006; Thambisetty et al. 2010). Whether these systemic changes directly relate to the neuropathology and cognitive impairment in AD is unknown and it remains to be seen whether they have diagnostic utility.

CLINICAL STUDIES

Epidemiology

Over 30 epidemiologic studies, including nine prospective studies, have evaluated the possibility that anti-inflammatory drug use might reduce risk or delay onset of AD, with the vast majority reporting beneficial effects. Many caveats have been given, however, for both the positive and negative findings. With respect to negative results, for example, many of the earliest surveys (e.g., Heyman et al. 1984) simply included anti-inflammatory drugs as one of many potential risk or protective factors for

AD, and may therefore have had an insufficient number of drug users to detect an effect. Other early studies, both positive and negative, were somewhat indirect, examining risk for AD given the presence of other disorders such as rheumatoid arthritis (reviewed as a meta-analysis by McGeer et al. 1996) and leprosy (McGeer et al. 1992), in which chronic and substantial use of anti-inflammatory drugs would be expected. The timing and duration of drug administration might also have been a complicating factor, as suggested by two early observational reports (in 't Veld et al. 2001; Zandi et al. 2002). Here, NSAID reduction of AD risk appeared to require the completion of a 2- to 3-year period of prior NSAID use. During that period of use, however, there was no reduction of AD risk (Zandi et al. 2002) or even a nonsignificant increase in AD risk (in 't Veld et al. 2001), suggesting that there may be a critical period and minimum duration for NSAID administration. Finally, lack of detail about the amount, duration, and, especially, type of anti-inflammatory drug taken by subjects was a common problem among early observational reports.

More recent, prospective studies have circumvented many of these challenges, typically evaluating a thousand or more subjects, categorizing anti-inflammatory drug classes, and sometimes obtaining explicit data on drug amounts and durations of use from pharamacy and computer records. In general, seven of these nine studies (Stewart et al. 1997; in 't Veld et al. 2001; Lindsay et al. 2002; Zandi et al. 2002; Cornelius et al. 2004; Szekely et al. 2008; Vlad et al. 2008) found that NSAID use was associated with a significantly decreased risk for AD. Moreover, a meta-analysis of a subset of these reports in which duration of use data were available showed that longer periods of NSAID use decreased risk in a duration-dependent manner (Szekely et al. 2007), a finding confirmed in a subsequent study with >200,000 AD and control cases (Vlad et al. 2008). Of the two remaining prospective studies (Arvanitakis et al. 2008; Breitner et al. 2009), Breitner and colleagues (2009) have argued that their discrepant, negative findings may be due to the possibility that NSAID use does not simply decrease AD risk, but rather delays AD onset to later ages. If so, then one would expect a higher incidence of AD among very old NSAID users and a lower incidence among younger NSAID users. Subjects in the two discrepant studies were, in fact, markedly older than those in the seven positive studies.

Treatment Trials

Given the epidemiologic results, treatment trials with anti-inflammatory drugs have been disappointing. Again, however, many caveats can be given. A large-scale treatment trial with an enantiomer of flurbiprofen, for example, is often lumped into summaries of the negative results of anti-inflammatory drug treatment despite the fact that, by design, the enantiomer had little to no anti-inflammatory activity (Green et al. 2009). Rather, the drug was designed to modulate γ-secretase, a property shared by ibuprofen, which also failed in a recent clinical trial—albeit with only 132 subjects and a 12-month duration (Pasqualetti et al. 2009).

Cyclooxygenase-2 (COX-2) inhibitors have also been employed, without success, in AD treatment trials (Aisen et al. 2003; Reines et al. 2004), and one such study with rofecoxib in MCI patients actually reported an increased hazard ratio (Thal et al. 2005). Alternatively, COX-2 is expressed in brain primarily by neurons (Yasojima et al. 1999), and may be neuroprotective (reviewed in McGeer 2000). Moreover, COX-2 inhibition increases Aβ42 secretion in vitro (Kukar et al. 2005). It has therefore been argued that inhibition of COX-2 mechanisms would likely have null or deleterious consequences in AD treatment trials (McGeer et al. 2006). COX-1, by contrast, is highly expressed by microglia, and has been suggested to be a more appropriate target (McGeer et al. 2006). Although the lone positive NSAID treatment trial for AD did, in fact, employ a potent COX-1 inhibitor, indomethacin, it should be noted that the study only evaluated 44 total subjects and used pooled data across multiple cognitive status tests (Rogers et al. 1993).

Finally, the steroid anti-inflammatory, prednisone, has been partially investigated in one pilot trial (Rogers et al. 1993) and explored specifically in a larger, randomized, multicenter trial (Aisen et al. 2000) with no positive outcome and with some notable adverse reactions. In the pilot trial, Rogers and colleagues (1993) anecdotally reported increased agitation and wandering in several AD patients treated with prednisone. Aisen and coinvestigators (2000) also observed behavioral abnormalities in such subjects.

Prevention Trials

Aside from the MCI treatment trial with rofecoxib cited earlier (Thal et al. 2005), no large-scale clinical trial of the ability of NSAIDs to prevent or delay onset of AD has ever been completed. The ADAPT Research Group (Lyketsos et al. 2007) attempted such a study, administering the nonselective COX-1 inhibitor naproxen, the selective COX-2 inhibitor celecoxib, or placebo to nearly 3000 cognitively normal individuals who were at elevated risk for AD by virtue of their age ($\geq$70 years old) and possession of a first-degree relative with dementia. However, the study was halted early on because of newly emerging cardiovascular concerns about celecoxib (e.g., Mukherjee et al. 2001), as well as adverse reactions observed in the trial itself (ADAPT Research Group 2006). Among subjects who completed at least one cognitive assessment and were included in an interim analysis, a significant increase in AD risk ratios was observed for both celecoxib and naproxen, but only when 46 patients qualifying for a diagnosis of MCI or prodromal AD and erroneously entered into the study as cognitively normal were included. Excluding these participants, as well as seven others with AD who were also erroneously enrolled, revealed no significant change in the hazard ratio for either celecoxib ($P = 0.24$) or naproxen ($P = 0.30$). Several other caveats may obtain as well. For example, median durations of celecoxib and naproxen exposure were 1.54 and 1.53 years, respectively, whereas previous epidemiologic studies have generally observed duration-dependent effects of NSAIDs (e.g., the meta-analysis of Szekely et al. 2007), with a likely minimum duration of 2–3 years exposure before beneficial outcomes are observed (in 't Veld et al. 2001; Zandi et al. 2002). It is also worth noting that instances of conversion to AD were quite few in the trial, such that the results actually appear to rest almost wholly on nine conversions in the placebo group, 11 in the celecoxib group, and 12 in the naproxen group. Finally, anecdotal reports of presentations at international symposia by the study authors have suggested that further follow up of the study participants has shown at least a trend to a beneficial effect of treatment.

CONCLUSIONS

The genetic, cellular, and molecular changes associated with AD provide ever-stronger support for an activation of immune and inflammatory processes in the disease. Together with the epidemiological studies, which show a strong benefit of long-term use of NSAIDs, it is tempting to conclude that AD is an inflammatory disease and that inhibiting inflammation would be beneficial. However, there are several observations that indicate a more complex view, as well as the difficulties inherent in targeting inflammation in AD.

It is clear, most notably from animal models for AD, that many classical inflammatory proteins and cytokines have double-edged functions and that simply suppressing them may cause more harm than good. It is also puzzling that—at least in one study (Katsel et al. 2009), but not another (Blalock et al. 2004)—brains from the oldest-old, cognitively normal humans showed stronger expression of complement factors and other immune molecules than brains from age-matched AD patients or younger people, suggesting protective functions of molecules typically seen as deleterious. Lastly, the observation that inflammatory pathways are altered in the periphery in AD, together with evidence that increased peripheral inflammation leads to more neurodegeneration and accelerated disease progression in animal models (Nguyen et al. 2004; Cunningham et al. 2005; Frank-Cannon et al. 2008; Godoy et al. 2008;

Palin et al. 2008) and possibly in AD (Holmes et al. 2003), argue for caution in deciding where inflammation should be therapeutically targeted.

In their balanced, cogent synthesis of the clinical literature on anti-inflammatory drugs and AD, Szekely and Zandi (2010) conclude with several arguments for why AD clinical trials with anti-inflammatory drugs should not be disbanded because of the generally negative treatment trial results to date, but rather should continue to be explored. They note, for example, that some 30% of elderly adults take NSAIDs for indications other than AD. If nothing else, would it not be prudent to know what effect the drugs are having on cognition in this very large population, especially in view of reports that NSAIDs might actually increase AD risk under certain conditions (Thal et al. 2005; Breitner et al. 2009)? Moreover, even if all the positive results from the dozens of epidemiologic studies on inflammation and AD risk are spurious, these widely-obtained, statistically significant results are unlikely to have derived simply from chance. If associations of inflammation with other factors account for the data, would it not be useful to know what those other factors are? Much has also been made of the potential risks of NSAID use in the elderly, and these risks certainly exist—particularly gastrointestinal and nephrologic complications. However, at least for prevention trials, how can one make rational risk-benefit comparisons when the only data with respect to benefit derive from a handful of patients who converted to AD in a single, disbanded study (ADAPT Research Group 2006; Lyketsos et al. 2007)?

Finally, it may be worth considering that virtually no large-scale treatment trial of any drug has successfully halted, much less reversed, the pathological or cognitive decline of AD, perhaps because so much irremediable damage has been done to the brain in the already-afflicted patients employed in treatment trials. Such caveats may apply in double measure to anti-inflammatory drugs, which are typically employed not to redress existing damage, but to address additional, subsequent damage that may be caused by the inflammatory response itself. Moreover, as covered in this review, inflammation encompasses dozens of highly interactive molecular mediators and mechanisms, some potentially helpful and some potentially harmful. Likewise, the different anti-inflammatory drug classes target different sets of mediators and mechanisms. If the new data on microglial activation states (reviewed in Colton 2009; Colton and Wilcock 2010) tell us nothing else, it is that more selectively targeted NSAIDs need to be developed or explored so as to encourage beneficial phenotypes and mechanisms while discouraging harmful phenotypes and mechanisms. Given the continuing stream of basic science and epidemiologic publications on inflammation and AD, prevention trials with rationally selected anti-inflammatory drugs may continue to warrant consideration.

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REFERENCES

Abbas N, Bednar I, Mix E, Marie S, Paterson D, Ljungberg A, Morris C, Winblad B, Nordberg A, Zhu J. 2002. Up-regulation of the inflammatory cytokines IFN-γ and IL-12 and down-regulation of IL-4 in cerebral cortex regions of APP(SWE) transgenic mice. *J Neuroimmunol* **126:** 50–57.

Abdul HM, Sama MA, Furman JL, Mathis DM, Beckett TL, Weidner AM, Patel ES, Baig I, Murphy MP, LeVine H III, et al. 2009. Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling. *J Neurosci* **29:** 12957–12969.

Abramov AY, Canevari L, Duchen MR. 2004. β-amyloid peptides induce mitochondrial dysfunction and oxidative stress in astrocytes and death of neurons through activation of NADPH oxidase. *J Neurosci* **24:** 565–575.

ADAPT Research Group. 2006. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's disease anti-inflammatory prevention trial (ADAPT). *PLoS Clin Trials* **1:** e33.

Aisen PS, Davis KL, Berg JD, Schafer K, Campbell K, Thomas RG, Weiner MF, Farlow MR, Sano M, Grundman M, et al. 2000. A randomized controlled trial of prednisone in Alzheimer's disease. *Neurology* **54:** 588–593.

Aisen PS, Schafer KA, Grundman M, Pfeiffer E, Sano M, Davis KL, Farlow MR, Jin S, Thomas RG, Thal LJ. 2003. Effects of rofecoxib or naproxen vs placebo on

Alzheimer disease progression: A randomized controlled trial. *JAMA* **289:** 2819–2826.

Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, et al. 2000. Inflammation and Alzheimer's disease. Neuroinflammation Working Group. *Neurobiol Aging* **21:** 383–421.

Andersen K, Launer LJ, Ott A, Hoes AW, Breteler MM, Hofman A. 1995. Do nonsteroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study. *Neurology* **45:** 1441–1445.

Andreasson KI, Savonenko A, Vidensky S, Goellner JJ, Zhang Y, Shaffer A, Kaufmann WE, Worley PF, Isakson P, Markowska AL. 2001. Age-dependent cognitive deficits and neuronal apoptosis in cyclooxygenase-2 transgenic mice. *J Neurosci* **21:** 8198–8209.

Anthony JC, Breitner JC, Zandi PP, Meyer MR, Jurasova I, Norton MC, Stone SV. 2000. Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: The Cache County study. *Neurology* **54:** 2066–2071.

Arancio O, Zhang HP, Chen X, Lin C, Trinchese F, Puzzo D, Liu S, Hegde A, Yan SF, Stern A, et al. 2004. RAGE potentiates Aβ-induced perturbation of neuronal function in transgenic mice. *Embo J* **23:** 4096–4105.

Aravalli RN, Peterson PK, Lokensgard JR. 2007. Toll-like receptors in defense and damage of the central nervous system. *J Neuroimmune Pharmacol* **2:** 297–312.

Arnett HA, Wang Y, Matsushima GK, Suzuki K, Ting JP. 2003. Functional genomic analysis of remyelination reveals importance of inflammation in oligodendrocyte regeneration. *J Neurosci* **23:** 9824–9832.

Arvanitakis Z, Grodstein F, Bienias JL, Schneider JA, Wilson RS, Kelly JF, Evans DA, Bennett DA. 2008. Relation of NSAIDs to incident AD, change in cognitive function, and AD pathology. *Neurology* **70:** 2219–2225.

Atkinson JP, Krych M, Nickells M, Birmingham D, Subramanian VB, Clemenza L, Alvarez J, Liszewski K. 1994. Complement receptors and regulatory proteins: Immune adherence revisited and abuse by microorganisms. *Clin Exp Immunol* **97:** 1–3.

Bales KR, Du Y, Dodel RC, Yan GM, Hamilton-Byrd E, Paul SM. 1998. The NF-κB/Rel family of proteins mediates Aβ-induced neurotoxicity and glial activation. *Brain Res Mol Brain Res* **57:** 63–72.

Bales KR, Verina T, Cummins DJ, Du Y, Dodel RC, Saura J, Fishman CE, DeLong CA, Piccardo P, Petegnief V, et al. 1999. Apolipoprotein E is essential for amyloid deposition in the APP(V717F) transgenic mouse model of Alzheimer's disease. *Proc Natl Acad Sci* **96:** 15233–15238.

Bard F, Cannon C, Barbour R, Burke RL, Games D, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, et al. 2000. Peripherally administered antibodies against amyloid β-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nat Med* **6:** 916–919.

Beard CM, Kokman E, Kurland LT. 1991. Rheumatoid arthritis and susceptibility to Alzheimer's disease. *Lancet* **337**.

Beard CM, Waring SC, O'Brien PC, Kurland LT, Kokmen E. 1998. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease: A case-control study in Rochester, Minnesota, 1980 through 1984. *Mayo Clin Proc* **73:** 951–955.

Belanger M, Magistretti PJ. 2009. The role of astroglia in neuroprotection. *Dialogues Clin Neurosci* **11:** 281–295.

Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. 2007. Systematic meta-analyses of Alzheimer disease genetic association studies: The AlzGene database. *Nat Genet* **39:** 17–23.

Bessis A, Bechade C, Bernard D, Roumier A. 2007. Microglial control of neuronal death and synaptic properties. *Glia* **55:** 233–238.

Birmingham DJ, Hebert LA. 2001. CR1 and CR1-like: The primate immune adherence receptors. *Immunol Rev* **180:** 100–111.

Blalock EM, Geddes JW, Chen KC, Porter NM, Markesbery WR, Landfield PW. 2004. Incipient Alzheimer's disease: Microarray correlation analyses reveal major transcriptional and tumor suppressor responses. *Proc Natl Acad Sci* **101:** 2173–2178.

Blalock EM, Chen KC, Stromberg AJ, Norris CM, Kadish I, Kraner SD, Porter NM, Landfield PW. 2005. Harnessing the power of gene microarrays for the study of brain aging and Alzheimer's disease: Statistical reliability and functional correlation. *Ageing Res Rev* **4:** 481–512.

Bogdan C. 2008. Mechanisms and consequences of persistence of intracellular pathogens: Leishmaniasis as an example. *Cell Microbiol* **10:** 1221–1234.

Boissonneault V, Filali M, Lessard M, Relton J, Wong G, Rivest S. 2009. Powerful beneficial effects of macrophage colony-stimulating factor on β-amyloid deposition and cognitive impairment in Alzheimer's disease. *Brain* **132:** 1078–1092.

Bolmont T, Haiss F, Eicke D, Radde R, Mathis CA, Klunk WE, Kohsaka S, Jucker M, Calhoun ME. 2008. Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. *J Neurosci* **28:** 4283–4292.

Botto M, Dell'Agnola C, Bygrave AE, Thompson EM, Cook HT, Petry F, Loos M, Pandolfi PP, Walport MJ. 1998. Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. *Nat Genet* **19:** 56–59.

Brandenburg LO, Konrad M, Wruck C, Koch T, Pufe T, Lucius R. 2008. Involvement of formyl-peptide-receptor-like-1 and phospholipase D in the internalization and signal transduction of amyloid β 1–42 in glial cells. *Neuroscience* **156:** 266–276.

Breitner JC, Gau BA, Welsh KA, Plassman BL, McDonald WM, Helms MJ, Anthony JC. 1994. Inverse association of anti-inflammatory treatments and Alzheimer's disease: Initial results of a co-twin control study. *Neurology* **44:** 227–232.

Breitner JC, Welsh KA, Helms MJ, Gaskell PC, Gau BA, Roses AD, Pericak-Vance MA, Saunders AM. 1995. Delayed onset of Alzheimer's disease with nonsteroidal anti-inflammatory and histamine H2 blocking drugs. *Neurobiol Aging* **16:** 523–530.

Breitner JC, Haneuse SJ, Walker R, Dublin S, Crane PK, Gray SL, Larson EB. 2009. Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. *Neurology* **72:** 1899–1905.

Broe GA, Henderson AS, Creasey H, McCusker E, Korten AE, Jorm AF, Longley W, Anthony JC. 1990. A case-control study of Alzheimer's disease in Australia. *Neurology* **40:** 1698–1707.

Broe GA, Grayson DA, Creasey HM, Waite LM, Casey BJ, Bennett HP, Brooks WS, Halliday GM. 2000. Anti-inflammatory drugs protect against Alzheimer disease at low doses. *Arch Neurol* **57:** 1586–1591.

Cagnin A, Brooks DJ, Kennedy AM, Gunn RN, Myers R, Turkheimer FE, Jones T, Banati RB. 2001. In-vivo measurement of activated microglia in dementia. *Lancet* **358:** 461–467.

Caldero J, Brunet N, Ciutat D, Hereu M, Esquerda JE. 2009. Development of microglia in the chick embryo spinal cord: Implications in the regulation of motoneuronal survival and death. *J Neurosci Res* **87:** 2447–2466.

Cameron B, Landreth GE. 2010. Inflammation microglia, and Alzheimer's disease. *Neurobiol Dis* **37:** 503–509.

Canadian Study of Health and Aging. 1994. The Canadian Study of Health and Aging: Risk factors for Alzheimer's disease in Canada. *Neurology* **44:** 2073–2080.

Carroll MC. 1998. The role of complement and complement receptors in induction and regulation of immunity. *Annu Rev Immunol* **16:** 545–568.

Cartier L, Hartley O, Dubois-Dauphin M, Krause KH. 2005. Chemokine receptors in the central nervous system: Role in brain inflammation and neurodegenerative diseases. *Brain Res Brain Res Rev* **48:** 16–42.

Caso JR, Pradillo JM, Hurtado O, Lorenzo P, Moro MA, Lizasoain I. 2007. Toll-like receptor 4 is involved in brain damage and inflammation after experimental stroke. *Circulation* **115:** 1599–1608.

Chakrabarty P, Jansen-West K, Beccard A, Ceballos-Diaz C, Levites Y, Verbeeck C, Zubair AC, Dickson D, Golde TE, Das P. 2010. Massive gliosis induced by interleukin-6 suppresses Aβ deposition in vivo: Evidence against inflammation as a driving force for amyloid deposition. *FASEB J* **24:** 548–559.

Chan WY, Kohsaka S, Rezaie P. 2007. The origin and cell lineage of microglia: New concepts. *Brain Res Rev* **53:** 344–354.

Charo IF, Ransohoff RM. 2006. The many roles of chemokines and chemokine receptors in inflammation. *N Engl J Med* **354:** 610–621.

Chen K, Iribarren P, Huang J, Zhang L, Gong W, Cho EH, Lockett S, Dunlop NM, Wang JM. 2007a. Induction of the formyl peptide receptor 2 in microglia by IFN-γ and synergy with CD40 ligand. *J Immunol* **178:** 1759–1766.

Chen X, Walker DG, Schmidt AM, Arancio O, Lue LF, Yan SD. 2007b. RAGE: A potential target for Aβ-mediated cellular perturbation in Alzheimer's disease. *Curr Mol Med* **7:** 735–742.

Chow SK, Yu D, Macdonald CL, Buibas M, Silva GA. 2010. Amyloid β-peptide directly induces spontaneous calcium transients, delayed intercellular calcium waves and gliosis in rat cortical astrocytes. *ASN Neuro* **2:** e00026.

Citron BA, Dennis JS, Zeitlin RS, Echeverria V. 2008. Transcription factor Sp1 dysregulation in Alzheimer's disease. *J Neurosci Res* **86:** 2499–2504.

Colton CA. 2009. Heterogeneity of microglial activation in the innate immune response in the brain. *J Neuroimmune Pharmacol* **4:** 399–418.

Colton CA, Wilcock DM. 2010. Assessing activation states in microglia. *CNS Neurol Disord Drug Targets* **9:** 174–191.

Combs CK. 2009. Inflammation and microglia actions in Alzheimer's disease. *J Neuroimmune Pharmacol* **4:** 380–388.

Coraci IS, Husemann J, Berman JW, Hulette C, Dufour JH, Campanella GK, Luster AD, Silverstein SC, El-Khoury JB. 2002. CD36, a class B scavenger receptor, is expressed on microglia in Alzheimer's disease brains and can mediate production of reactive oxygen species in response to β-amyloid fibrils. *Am J Pathol* **160:** 101–112.

Cornelius C, Fastbom J, Winblad B, Viitanen M. 2004. Aspirin, NSAIDs, risk of dementia, and influence of the apolipoprotein E ε4 allele in an elderly population. *Neuroepidemiology* **23:** 135–143.

Craft JM, Watterson DM, Marks A, Van Eldik LJ. 2005. Enhanced susceptibility of S-100B transgenic mice to neuroinflammation and neuronal dysfunction induced by intracerebroventricular infusion of human β-amyloid. *Glia* **51:** 209–216.

Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. 2005. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. *J Neurosci* **25:** 9275–9284.

D'Ambrosio AL, Pinsky DJ, Connolly ES. 2001. The role of the complement cascade in ischemia/reperfusion injury: Implications for neuroprotection. *Mol Med* **7:** 367–382.

D'Andrea MR. 2003. Evidence linking neuronal cell death to autoimmunity in Alzheimer's disease. *Brain Res* **982:** 19–30.

Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB. 2005. ATP mediates rapid microglial response to local brain injury in vivo. *Nat Neurosci* **8:** 752–758.

DeMattos RB, Bales KR, Cummins DJ, Dodart J-C, Paul SM, Holtzman DM. 2001. Peripheral anti-Ab antibody alters CNS and plasma Ab clearance and decreases brain Ab burden in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci* **98:** 8850–8855.

Dewil M, Van Den Bosch L, Robberecht W. 2007. Microglia in amyotrophic lateral sclerosis. *Acta Neurol Belg* **107:** 63–70.

DiCarlo G, Wilcock D, Henderson D, Gordon M, Morgan D. 2001. Intrahippocampal LPS injections reduce Ab load in APP+PS1 transgenic mice. *Neurobiol Aging* **22:** 1007–1012.

Duan RS, Yang X, Chen ZG, Lu MO, Morris C, Winblad B, Zhu J. 2008. Decreased fractalkine and increased IP-10 expression in aged brain of APP(swe) transgenic mice. *Neurochem Res* **33:** 1085–1089.

Edison P, Archer HA, Gerhard A, Hinz R, Pavese N, Turkheimer FE, Hammers A, Tai YF, Fox N, Kennedy A, et al. 2008. Microglia, amyloid, and cognition in Alzheimer's disease: An [11C](R)PK11195-PET and [11C]PIB-PET study. *Neurobiol Dis* **32:** 412–419.

Eikelenboom P, Stam FC. 1982. Immunoglobulins and complement factors in senile plaques. An immunoperoxidase study. *Acta Neuropathol (Berl)* **57:** 239–242.

Eikelenboom P, Hack CE, Rozemuller JM, Stam FC. 1989. Complement activation in amyloid plaques in Alzheimer's dementia. *Virchows Arch B Cell Pathol* **56:** 259–262.

El Khoury J, Luster AD. 2008. Mechanisms of microglia accumulation in Alzheimer's disease: Therapeutic implications. *Trends Pharmacol Sci* **29:** 626–632.

El Khoury J, Hickman SE, Thomas CA, Loike JD, Silverstein SC. 1998. Microglia, scavenger receptors, and the pathogenesis of Alzheimer's disease. *Neurobiol Aging* **19:** S81–S84.

El Khoury J, Moore KJ, Means TK, Leung J, Terada K, Toft M, Freeman MW, Luster AD. 2003. CD36 mediates the innate host response to β-amyloid. *J Exp Med* **197:** 1657–1666.

El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, Luster AD. 2007. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nat Med* **13:** 432–438.

Emmerling MR, Watson MD, Raby CA, Spiegel K. 2000. The role of complement in Alzheimer's disease pathology. *Biochim Biophys Acta* **1502:** 158–171.

Fassbender K, Walter S, Kuhl S, Landmann R, Ishii K, Bertsch T, Stalder AK, Muehlhauser F, Liu Y, Ulmer AJ, et al. 2004. The LPS receptor (CD14) links innate immunity with Alzheimer's disease. *FASEB J* **18:** 203–205.

Fiala M, Liu PT, Espinosa-Jeffrey A, Rosenthal MJ, Bernard G, Ringman JM, Sayre J, Zhang L, Zaghi J, Dejbakhsh S, et al. 2007. Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. *Proc Natl Acad Sci* **104:** 12849–12854.

Fonseca MI, Kawas CH, Troncoso JC, Tenner AJ. 2004a. Neuronal localization of C1q in preclinical Alzheimer's disease. *Neurobiol Dis* **15:** 40–46.

Fonseca MI, Zhou J, Botto M, Tenner AJ. 2004b. Absence of C1q leads to less neuropathology in transgenic mouse models of Alzheimer's disease. *J Neurosci* **24:** 6457–6465.

Foote AK, Blakemore WF. 2005. Inflammation stimulates remyelination in areas of chronic demyelination. *Brain* **128:** 528–539.

Frank-Cannon TC, Tran T, Ruhn KA, Martinez TN, Hong J, Marvin M, Hartley M, Trevino I, O'Brien DE, Casey B, et al. 2008. Parkin deficiency increases vulnerability to inflammation-related nigral degeneration. *J Neurosci* **28:** 10825–10834.

Fraser DA, Pisalyaput K, Tenner AJ. 2010. C1q enhances microglial clearance of apoptotic neurons and neuronal blebs, and modulates subsequent inflammatory cytokine production. *J Neurochem* **112:** 733–743.

French LR, Schuman LM, Mortimer JA, Hutton JT, Boatman RA, Christians B. 1985. A case-control study of dementia of the Alzheimer type. *Am J Epidemiol* **121:** 414–421.

Garden GA. 2002. Microglia in human immunodeficiency virus-associated neurodegeneration. *Glia* **40:** 240–251.

Gasque P. 2004. Complement: A unique innate immune sensor for danger signals. *Mol Immunol* **41:** 1089–1098.

Gasque P, Dean YD, McGreal EP, Beek JV, Morgan BP. 2000. Complement components of the innate immune system in health and disease in the CNS. *Immunopharmacology* **49:** 171–186.

Godoy MC, Tarelli R, Ferrari CC, Sarchi MI, Pitossi FJ. 2008. Central and systemic IL-1 exacerbates neurodegeneration and motor symptoms in a model of Parkinson's disease. *Brain* **131:** 1880–1894.

Gordon S, Taylor PR. 2005. Monocyte and macrophage heterogeneity. *Nat Rev Immunol* **5:** 953–964.

Granic I, Dolga AM, Nijholt IM, van Dijk G, Eisel UL. 2009. Inflammation and NF-κB in Alzheimer's disease and diabetes. *J Alzheimers Dis* **16:** 809–821.

Graves AB, White E, Koepsell TD, Reifler BV, van Belle G, Larson EB, Raskind M. 1990. A case-control study of Alzheimer's disease. *Ann Neurol* **28:** 766–774.

Green RC, Schneider LS, Amato DA, Beelen AP, Wilcock G, Swabb EA, Zavitz KH. 2009. Effect of tarenflurbil on cognitive decline and activities of daily living in patients with mild Alzheimer disease: A randomized controlled trial. *JAMA* **302:** 2557–2564.

Halassa MM, Fellin T, Takano H, Dong JH, Haydon PG. 2007. Synaptic islands defined by the territory of a single astrocyte. *J Neurosci* **27:** 6473–6477.

Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, et al. 2009. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* **41:** 1088–1093.

He P, Zhong Z, Lindholm K, Berning L, Lee W, Lemere C, Staufenbiel M, Li R, Shen Y. 2007. Deletion of tumor necrosis factor death receptor inhibits amyloid β generation and prevents learning and memory deficits in Alzheimer's mice. *J Cell Biol* **178:** 829–841.

Heyman A, Wilkinson WE, Stafford JA, Helms MJ, Sigmon AH, Weinberg T. 1984. Alzheimer's disease: A study of epidemiological aspects. *Ann Neurol* **15:** 335–341.

Holers VM. 1996. Complement. In *Clinical immunology principles and practice* (ed. Rich RR), pp. 363–391. Mosby–Year Book, St. Louis, MO.

Holmes C, El-Okl M, Williams AL, Cunningham C, Wilcockson D, Perry VH. 2003. Systemic infection, interleukin 1β, and cognitive decline in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **74:** 788–789.

Hosokawa M, Klegeris A, Maguire J, McGeer PL. 2003. Expression of complement messenger RNAs and proteins by human oligodendroglial cells. *Glia* **42:** 417–423.

Hosokawa M, Klegeris A, McGeer PL. 2004. Human oligodendroglial cells express low levels of C1 inhibitor and membrane cofactor protein mRNAs. *J Neuroinflammation* **1**.

Hsieh CL, Koike M, Spusta SC, Niemi EC, Yenari M, Nakamura MC, Seaman WE. 2009. A role for TREM2 ligands in the phagocytosis of apoptotic neuronal cells by microglia. *J Neurochem* **109:** 1144–1156.

Hu WT, Chen-Plotkin A, Arnold SE, Grossman M, Clark CM, Shaw LM, McCluskey L, Elman L, Karlawish J, Hurtig HI, et al. 2010a. Biomarker discovery for Alzheimer's disease, frontotemporal lobar degeneration, and Parkinson's disease. *Acta Neuropathol* **120:** 385–399.

Hu WT, Chen-Plotkin A, Arnold SE, Grossman M, Clark CM, Shaw LM, Pickering E, Kuhn M, Chen Y, McCluskey L, et al. 2010b. Novel CSF biomarkers for Alzheimer's disease and mild cognitive impairment. *Acta Neuropathol* **119:** 669–678.

Hye A, Lynham S, Thambisetty M, Causevic M, Campbell J, Byers HL, Hooper C, Rijsdijk F, Tabrizi SJ, Banner S, et al.

2006. Proteome-based plasma biomarkers for Alzheimer's disease. *Brain* **129:** 3042–3050.

in 't Veld BA, Launer LJ, Hoes AW, Ott A, Hofman A, Breteler MM, Stricker BH. 1998. NSAIDs and incident Alzheimer's disease. The Rotterdam Study. *Neurobiol Aging* **19:** 607–611.

in 't Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, Breteler MM, Stricker BH. 2001. Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* **345:** 1515–1521.

Itagaki S, Akiyama H, Saito H, McGeer PL. 1994. Ultrastructural localization of complement membrane attack complex (MAC)-like immunoreactivity in brains of patients with Alzheimer's disease. *Brain Res* **645:** 78–84.

Iwasaki A, Medzhitov R. 2004. Toll-like receptor control of the adaptive immune responses. *Nat Immunol* **5:** 987–995.

Janeway CA Jr, Medzhitov R. 2002. Innate immune recognition. *Annu Rev Immunol* **20:** 197–216.

Jantaratnotai N, Ryu JK, Kim SU, McLarnon JG. 2003. Amyloid β peptide-induced corpus callosum damage and glial activation in vivo. *Neuroreport* **14:** 1429–1433.

Jenkinson ML, Bliss MR, Brain AT, Scott DL. 1989. Rheumatoid arthritis and senile dementia of the Alzheimer's type. *Br J Rheumatol* **28:** 86–88.

Ji B, Maeda J, Sawada M, Ono M, Okauchi T, Inaji M, Zhang MR, Suzuki K, Ando K, Staufenbiel M, et al. 2008. Imaging of peripheral benzodiazepine receptor expression as biomarkers of detrimental versus beneficial glial responses in mouse models of Alzheimer's and other CNS pathologies. *J Neurosci* **28:** 12255–12267.

Jiang H, Burdick D, Glabe CG, Cotman CW, Tenner AJ. 1994. b-Amyloid activates complement by binding to a specific region of the collagen-like domain of the C1q A chain. *J Immunol* **152:** 5050–5059.

Jiang Q, Heneka M, Landreth GE. 2008. The role of peroxisome proliferator-activated receptor-γ (PPARγ) in Alzheimer's disease: Therapeutic implications. *CNS Drugs* **22:** 1–14.

Jin JJ, Kim HD, Maxwell JA, Li L, Fukuchi K. 2008. Toll-like receptor 4-dependent upregulation of cytokines in a transgenic mouse model of Alzheimer's disease. *J Neuroinflammation* **5:** 23.

John GR, Lee SC, Brosnan CF. 2003. Cytokines: Powerful regulators of glial cell activation. *Neuroscientist* **9:** 10–22.

Johns TG, Bernard CC. 1997. Binding of complement component C1q to myelin oligodendrocyte glycoprotein: A novel mechanism for regulating CNS inflammation. *Mol Immunol* **34:** 33–38.

Jun G, Naj AC, Beecham GW, Wang LS, Buros J, Gallins PJ, Buxbaum JD, Ertekin-Taner N, Fallin MD, Friedland R, et al. 2010. Meta-analysis confirms CR1, CLU, and PICALM as Alzheimer disease risk loci and reveals interactions with APOE genotypes. *Arch Neurol* **67:** 1473–1484.

Juurlink BH. 1997. Response of glial cells to ischemia: Roles of reactive oxygen species and glutathione. *Neurosci Biobehav Rev* **21:** 151–166.

Kalman J, Kitajka K, Pakaski M, Zvara A, Juhasz A, Vincze G, Janka Z, Puskas LG. 2005. Gene expression profile analysis of lymphocytes from Alzheimer's patients. *Psychiatr Genet* **15:** 1–6.

Katsel P, Tan W, Haroutunian V. 2009. Gain in brain immunity in the oldest-old differentiates cognitively normal from demented individuals. *PLoS One* **4:** e7642.

Koenigsknecht-Talboo J, Meyer-Luehmann M, Parsadanian M, Garcia-Alloza M, Finn MB, Hyman BT, Bacskai BJ, Holtzman DM. 2008. Rapid microglial response around amyloid pathology after systemic anti-Aβ antibody administration in PDAPP mice. *J Neurosci* **28:** 14156–14164.

Koistinaho M, Lin S, Wu X, Esterman M, Koger D, Hanson J, Higgs R, Liu F, Malkani S, Bales KR, et al. 2004. Apolipoprotein E promotes astrocyte colocalization and degradation of deposited amyloid-β peptides. *Nat Med* **10:** 719–726.

Kukar T, Murphy MP, Eriksen JL, Sagi SA, Weggen S, Smith TE, Ladd T, Khan MA, Kache R, Beard J, et al. 2005. Diverse compounds mimic Alzheimer disease-causing mutations by augmenting Aβ42 production. *Nat Med* **11:** 545–550.

Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, et al. 2009. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* **41:** 1094–1099.

Landi F, Cesari M, Onder G, Russo A, Torre S, Bernabei R. 2003. Non-steroidal anti-inflammatory drug (NSAID) use and Alzheimer disease in community-dwelling elderly patients. *Am J Geriatr Psychiatry* **11:** 179–185.

Landreth GE, Reed-Geaghan EG. 2009. Toll-like receptors in Alzheimer's disease. *Curr Top Microbiol Immunol* **336:** 137–153.

Leal MC, Dorfman VB, Gamba AF, Frangione B, Wisniewski T, Castano EM, Sigurdsson EM, Morelli L. 2006. Plaque-associated overexpression of insulin-degrading enzyme in the cerebral cortex of aged transgenic tg2576 mice with Alzheimer pathology. *J Neuropathol Exp Neurol* **65:** 976–987.

Lee CY, Landreth GE. 2010. The role of microglia in amyloid clearance from the AD brain. *J Neural Transm* **117:** 949–960.

Lee JT, Xu J, Lee JM, Ku G, Han X, Yang DI, Chen S, Hsu CY. 2004. Amyloid-β peptide induces oligodendrocyte death by activating the neutral sphingomyelinase-ceramide pathway. *J Cell Biol* **164:** 123–131.

Lehnardt S, Massillon L, Follett P, Jensen FE, Ratan R, Rosenberg PA, Volpe JJ, Vartanian T. 2003. Activation of innate immunity in the CNS triggers neurodegeneration through a Toll-like receptor 4-dependent pathway. *Proc Natl Acad Sci* **100:** 8514–8519.

Li G, Shen YC, Li YT, Chen CH, Zhau YW, Silverman JM. 1992. A case-control study of Alzheimer's disease in China. *Neurology* **42:** 1481–1488.

Li R, Strohmeyer R, Liang Z, Lue LF, Rogers J. 2004. CCAAT/enhancer binding protein delta (C/EBPdelta) expression and elevation in Alzheimer s disease. *Neurobiol Aging* **25:** 991–999.

Liang X, Wang Q, Hand T, Wu L, Breyer RM, Montine TJ, Andreasson K. 2005. Deletion of the prostaglandin E2 EP2 receptor reduces oxidative damage and amyloid burden in a model of Alzheimer's disease. *J Neurosci* **25:** 10180–10187.

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Liang X, Wu L, Wang Q, Hand T, Bilak M, McCullough L, Andreasson K. 2007. Function of COX-2 and prostaglandins in neurological disease. *J Mol Neurosci* **33:** 94–99.

Lindsay J, Laurin D, Verreault R, Hebert R, Helliwell B, Hill GB, McDowell I. 2002. Risk factors for Alzheimer's disease: A prospective analysis from the Canadian Study of Health and Aging. *Am J Epidemiol* **156:** 445–453.

Liu Y, Walter S, Stagi M, Cherny D, Letiembre M, Schulz-Schaeffer W, Heine H, Penke B, Neumann H, Fassbender K. 2005. LPS receptor (CD14): A receptor for phagocytosis of Alzheimer's amyloid peptide. *Brain* **128:** 1778–1789.

Luber-Narod J, Rogers J. 1988. Immune system associated antigens expressed by cells of the human central nervous system. *Neurosci Lett* **94:** 17–22.

Lue LF, Rydel R, Brigham EF, Yang LB, Hampel H, Murphy GM, Brachova L, Yan SD, Walker DG, Shen Y, et al. 2001a. Inflammatory repertoire of Alzheimer's disease and nondemented elderly microglia in vitro. *Glia* **35:** 72–79.

Lue LF, Walker DG, Rogers J. 2001b. Modeling microglial activation in Alzheimer's disease with human postmortem microglial cultures. *Neurobiol Aging* **22:** 945–956.

Lyketsos CG, Breitner JC, Green RC, Martin BK, Meinert C, Piantadosi S, Sabbagh M. 2007. Naproxen and celecoxib do not prevent AD in early results from a randomized controlled trial. *Neurology* **68:** 1800–1808.

Maes OC, Xu S, Yu B, Chertkow HM, Wang E, Schipper HM. 2007. Transcriptional profiling of Alzheimer blood mononuclear cells by microarray. *Neurobiol Aging* **28:** 1795–1809.

Maier M, Peng Y, Jiang L, Seabrook TJ, Carroll MC, Lemere CA. 2008. Complement C3 deficiency leads to accelerated amyloid β plaque deposition and neurodegeneration and modulation of the microglia/macrophage phenotype in amyloid precursor protein transgenic mice. *J Neurosci* **28:** 6333–6341.

Majumdar A, Cruz D, Asamoah N, Buxbaum A, Sohar I, Lobel P, Maxfield FR. 2007. Activation of microglia acidifies lysosomes and leads to degradation of Alzheimer amyloid fibrils. *Mol Biol Cell* **18:** 1490–1496.

Majumdar A, Chung H, Dolios G, Wang R, Asamoah N, Lobel P, Maxfield FR. 2008. Degradation of fibrillar forms of Alzheimer's amyloid β-peptide by macrophages. *Neurobiol Aging* **29:** 707–715.

Mandrekar-Colucci S, Landreth GE. 2010. Microglia and inflammation in Alzheimer's disease. *CNS Neurol Disord Drug Targets* **9:** 156–167.

McCoy MK, Martinez TN, Ruhn KA, Szymkowski DE, Smith CG, Botterman BR, Tansey KE, Tansey MG. 2006. Blocking soluble tumor necrosis factor signaling with dominant-negative tumor necrosis factor inhibitor attenuates loss of dopaminergic neurons in models of Parkinson's disease. *J Neurosci* **26:** 9365–9375.

McGeer PL. 2000. Cyclo-oxygenase-2 inhibitors: Rationale and therapeutic potential for Alzheimer's disease. *Drugs Aging* **17:** 1–11.

McGeer PL, McGeer EG. 1999. Inflammation of the brain in Alzheimer's disease: Implications for therapy. *J Leukoc Biol* **65:** 409–415.

McGeer PL, Itagaki S, McGeer EG. 1988. Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. *Acta Neuropathol* **76:** 550–557.

McGeer PL, McGeer E, Rogers J, Sibley J. 1990. Anti-inflammatory drugs and Alzheimer disease. *Lancet* **335:** 1037.

McGeer PL, Harada N, Kimura H, McGeer EG, Schulzer M. 1992. Prevalence of dementia amongst elderly Japanese with leprosy: Apparent effect of chronic drug therapy. *Dementia* **3:** 146–149.

McGeer PL, Schulzer M, McGeer EG. 1996. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology* **47:** 425–432.

McGeer PL, Rogers J, McGeer EG. 2006. Inflammation, anti-inflammatory agents and Alzheimer disease: The last 12 years. *J Alzheimers Dis* **9:** 271–276.

Melnikova T, Savonenko A, Wang Q, Liang X, Hand T, Wu L, Kaufmann WE, Vehmas A, Andreasson KI. 2006. Cycloxygenase-2 activity promotes cognitive deficits but not increased amyloid burden in a model of Alzheimer's disease in a sex-dimorphic pattern. *Neuroscience* **141:** 1149–1162.

Meyer-Luehmann M, Spires-Jones TL, Prada C, Garcia-Alloza M, de Calignon A, Rozkalne A, Koenigsknecht-Talboo J, Holtzman DM, Bacskai BJ, Hyman BT. 2008. Rapid appearance and local toxicity of amyloid-β plaques in a mouse model of Alzheimer's disease. *Nature* **451:** 720–724.

Mitew S, Kirkcaldie MT, Halliday GM, Shepherd CE, Vickers JC, Dickson TC. 2010. Focal demyelination in Alzheimer's disease and transgenic mouse models. *Acta Neuropathol* **119:** 567–577.

Mott RT, Ait-Ghezala G, Town T, Mori T, Vendrame M, Zeng J, Ehrhart J, Mullan M, Tan J. 2004. Neuronal expression of CD22: Novel mechanism for inhibiting microglial proinflammatory cytokine production. *Glia* **46:** 369–379.

Moynagh PN. 2005. The interleukin-1 signalling pathway in astrocytes: A key contributor to inflammation in the brain. *J Anat* **207:** 265–269.

Mrak RE, Sheng JG, Griffin WS. 1996. Correlation of astrocytic S100 β expression with dystrophic neurites in amyloid plaques of Alzheimer's disease. *J Neuropathol Exp Neurol* **55:** 273–279.

Mukherjee D, Nissen SE, Topol EJ. 2001. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* **286:** 954–959.

Muzio L, Martino G, Furlan R. 2007. Multifaceted aspects of inflammation in multiple sclerosis: The role of microglia. *J Neuroimmunol* **191:** 39–44.

Myllykangas-Luosujarvi R, Isomaki H. 1994. Alzheimer's disease and rheumatoid arthritis. *Br J Rheumatol* **33:** 501–502.

Nadler Y, Alexandrovich A, Grigoriadis N, Hartmann T, Rao KS, Shohami E, Stein R. 2008. Increased expression of the γ-secretase components presenilin-1 and nicastrin in activated astrocytes and microglia following traumatic brain injury. *Glia* **56:** 552–567.

Nagele RG, D'Andrea MR, Lee H, Venkataraman V, Wang HY. 2003. Astrocytes accumulate A β 42 and give rise to

astrocytic amyloid plaques in Alzheimer disease brains. *Brain Res* **971:** 197–209.

Nguyen MD, Julien JP, Rivest S. 2002. Innate immunity: The missing link in neuroprotection and neurodegeneration? *Nat Rev Neurosci* **3:** 216–227.

Nguyen MD, D'Aigle T, Gowing G, Julien JP, Rivest S. 2004. Exacerbation of motor neuron disease by chronic stimulation of innate immunity in a mouse model of amyotrophic lateral sclerosis. *J Neurosci* **24:** 1340–1349.

Nilsson SE, Johansson B, Takkinen S, Berg S, Zarit S, McClearn G, Melander A. 2003. Does aspirin protect against Alzheimer's dementia? A study in a Swedish population-based sample aged > or =80 years. *Eur J Clin Pharmacol* **59:** 313–319.

Nimmerjahn A, Kirchhoff F, Helmchen F. 2005. Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. *Science* **308:** 1314–1318.

Norris CM, Kadish I, Blalock EM, Chen KC, Thibault V, Porter NM, Landfield PW, Kraner SD. 2005. Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models. *J Neurosci* **25:** 4649–4658.

Okun E, Mattson MP, Arumugam TV. 2010. Involvement of Fc receptors in disorders of the central nervous system. *Neuromolecular Med* **12:** 164–178.

Palin K, Cunningham C, Forse P, Perry VH, Platt N. 2008. Systemic inflammation switches the inflammatory cytokine profile in CNS Wallerian degeneration. *Neurobiol Dis* **30:** 19–29.

Paresce DM, Chung H, Maxfield FR. 1997. Slow degradation of aggregates of the Alzheimer's disease amyloid β-protein by microglial cells. *J Biol Chem* **272:** 29390–29397.

Pasqualetti P, Bonomini C, Dal Forno G, Paulon L, Sinforiani E, Marra C, Zanetti O, Rossini PM. 2009. A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease. *Aging Clin Exp Res* **21:** 102–110.

Popovich PG, Guan Z, McGaughy V, Fisher L, Hickey WF, Basso DM. 2002. The neuropathological and behavioral consequences of intraspinal microglial/macrophage activation. *J Neuropathol Exp Neurol* **61:** 623–633.

Ransohoff RM. 2007. The MHP36 line of murine neural stem cells expresses functional CXCR1 chemokine receptors that initiate chemotaxis in vitro. *J Neuroimmunol* **186:** 199–200.

Ray S, Britschgi M, Herbert C, Takeda-Uchimura Y, Boxer A, Blennow K, Friedman LF, Galasko DR, Jutel M, Karydas A, et al. 2007. Classification and prediction of clinical Alzheimer's diagnosis based on plasma signaling proteins. *Nat Med* **13:** 1369–1362.

Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE. 2009. CD14 and toll-like receptors 2 and 4 are required for fibrillar A{β}-stimulated microglial activation. *J Neurosci* **29:** 11982–11992.

Reines SA, Block GA, Morris JC, Liu G, Nessly ML, Lines CR, Norman BA, Baranak CC. 2004. Rofecoxib: No effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. *Neurology* **62:** 66–71.

Rezaie P, Male D. 2002. Mesoglia & microglia–a historical review of the concept of mononuclear phagocytes within the central nervous system. *J Hist Neurosci* **11:** 325–374.

Rich JB, Rasmusson DX, Folstein MF, Carson KA, Kawas C, Brandt J. 1995. Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. *Neurology* **45:** 51–55.

Richard KL, Filali M, Prefontaine P, Rivest S. 2008. Toll-like receptor 2 acts as a natural innate immune receptor to clear amyloid β 1–42 and delay the cognitive decline in a mouse model of Alzheimer's disease. *J Neurosci* **28:** 5784–5793.

Rodriguez JJ, Olabarria M, Chvatal A, Verkhratsky A. 2009. Astroglia in dementia and Alzheimer's disease. *Cell Death Differ* **16:** 378–385.

Rogers J, Luber-Narod J, Styren SD, Civin WH. 1988. Expression of immune system-associated antigens by cells of the human central nervous system: Relationship to the pathology of Alzheimer's disease. *Neurobiol Aging* **9:** 339–349.

Rogers J, Cooper NR, Webster S, Schultz J, McGeer PL, Styren SD, Civin WH, Brachova L, Bradt B, Ward P, et al. 1992. Complement activation by b-amyloid in Alzheimer disease. *Proc Natl Acad Sci* **89:** 10016–10020.

Rogers J, Kirby LC, Hempelman SR, Berry DL, McGeer PL, Kaszniak AW, Zalinski J, Cofield M, Mansukhani L, Willson P, et al. 1993. Clinical trial of indomethacin in Alzheimer's disease. *Neurology* **43:** 1609–1611.

Rogers J, Webster S, Lue LF, Brachova L, Civin WH, Emmerling M, Shivers B, Walker D, McGeer P. 1996. Inflammation and Alzheimer's disease pathogenesis. *Neurobiol Aging* **17:** 681–686.

Rogers J, Li R, Mastroeni D, Grover A, Leonard B, Ahern G, Cao P, Kolody H, Vedders L, Kolb WP, et al. 2006. Peripheral clearance of amyloid beta peptide by complement C3-dependent adherence to erythrocytes. *Neurobiol Aging* **27:** 1733–1739.

Rogers J, Mastroeni D, Leonard B, Joyce J, Grover A. 2007. Neuroinflammation in Alzheimer's disease and Parkinson's disease: Are microglia pathogenic in either disorder? *Int Rev Neurobiol* **82:** 235–246.

Roth AD, Ramirez G, Alarcon R, Von Bernhardi R. 2005. Oligodendrocytes damage in Alzheimer's disease: β amyloid toxicity and inflammation. *Biol Res* **38:** 381–387.

Sahu A, Lambris J. 2001. Structure and biology of complement protein C3, a connecting link between innate and acquired immunity. *Immunol Rev* **180:** 35–48.

Sanchez-Ramos J, Song S, Sava V, Catlow B, Lin X, Mori T, Cao C, Arendash GW. 2009. Granulocyte colony stimulating factor decreases brain amyloid burden and reverses cognitive impairment in Alzheimer's mice. *Neuroscience* **163:** 55–72.

Savonenko A, Munoz P, Melnikova T, Wang Q, Liang X, Breyer RM, Montine TJ, Kirkwood A, Andreasson K. 2009. Impaired cognition, sensorimotor gating, and hippocampal long-term depression in mice lacking the prostaglandin E2 EP2 receptor. *Exp Neurol* **217:** 63–73.

Schmidt AM, Sahagan B, Nelson RB, Selmer J, Rothlein R, Bell JM. 2009. The role of RAGE in amyloid-β peptide-mediated pathology in Alzheimer's disease. *Curr Opin Investig Drugs* **10:** 672–680.

Sedgwick JD, Schwender S, Imrich H, Dorries R, Butcher GW, ter Meulen V. 1991. Isolation and direct characterization of resident microglial cells from the normal and inflamed central nervous system. *Proc Natl Acad Sci* **88:** 7438–7442.

Seong SY, Matzinger P. 2004. Hydrophobicity: An ancient damage-associated molecular pattern that initiates innate immune responses. *Nat Rev Immunol* **4:** 469–478.

Setzu A, Lathia JD, Zhao C, Wells K, Rao MS, French-Constant C, Franklin RJ. 2006. Inflammation stimulates myelination by transplanted oligodendrocyte precursor cells. *Glia* **54:** 297–303.

Shaftel SS, Kyrkanides S, Olschowka JA, Miller JN, Johnson RE, O'Banion MK. 2007. Sustained hippocampal IL-1 β overexpression mediates chronic neuroinflammation and ameliorates Alzheimer plaque pathology. *J Clin Invest* **117:** 1595–1604.

Shen Y, Lue L-F, Yang L-B, Roher A, Kuo Y-M, Strohhmeyer R, Goux WJ, Lee V, Johnson GVW, Webster SD, et al. 2001. Complement activation by neurofibrillary tangles in Alzheimer's disease. *Neurosci Lett* **305:** 165–168.

Sheng JG, Mrak RE, Bales KR, Cordell B, Paul SM, Jones RA, Woodward S, Zhou XQ, McGinness JM, Griffin WS. 2000. Overexpression of the neuritotrophic cytokine S100 beta precedes the appearance of neuritic beta-amyloid plaques in APPV717F mice. *J Neurochem* **74:** 295–301.

Sheta EA, Appel SH, Goldknopf IL. 2006. 2D gel blood serum biomarkers reveal differential clinical proteomics of the neurodegenerative diseases. *Expert Rev Proteomics* **3:** 45–62.

Shi J, Johansson J, Woodling NS, Wang Q, Montine TJ, Andreasson K. 2010. The prostaglandin E2 E-prostanoid 4 receptor exerts anti-inflammatory effects in brain innate immunity. *J Immunol* **184:** 7207–7218.

Singhrao SK, Neal JW, Rushmere NK, Morgan BP, Gasque P. 1999. Differential expression of individual complement regulators in the brain and choroid plexus. *Lab Invest* **79:** 1247–1259.

Soares HD, Chen Y, Sabbagh M, Roher A, Schrijvers E, Breteler M. 2009. Identifying early markers of Alzheimer's disease using quantitative multiplex proteomic immunoassay panels. *Ann NY Acad Sci* **1180:** 56–67.

Sofroniew MV, Vinters HV. 2010. Astrocytes: Biology and pathology. *Acta Neuropathol* **119:** 7–35.

Sriram K, Matheson JM, Benkovic SA, Miller DB, Luster MI, O'Callaghan JP. 2002. Mice deficient in TNF receptors are protected against dopaminergic neurotoxicity: Implications for Parkinson's disease. *FASEB J* **16:** 1474–1476.

Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N, Micheva KD, Mehalow AK, Huberman AD, Stafford B, et al. 2007. The classical complement cascade mediates CNS synapse elimination. *Cell* **131:** 1164–1178.

Stewart WF, Kawas C, Corrada M, Metter EJ. 1997. Risk of Alzheimer's disease and duration of NSAID use. *Neurology* **48:** 626–632.

Streit WJ, Xue QS. 2009. Life and death of microglia. *J Neuroimmune Pharmacol* **4:** 371–379.

Szekely CA, Zandi PP. 2010. Non-steroidal anti-inflammatory drugs and Alzheimer's disease: The epidemiological evidence. *CNS Neurol Disord Drug Targets* **9:** 132–139.

Szekely CA, Town T, Zandi PP. 2007. NSAIDs for the chemoprevention of Alzheimer's disease. *Subcell Biochem* **42:** 229–248.

Szekely CA, Breitner JC, Fitzpatrick AL, Rea TD, Psaty BM, Kuller LH, Zandi PP. 2008. NSAID use and dementia risk in the Cardiovascular Health Study: Role of APOE and NSAID type. *Neurology* **70:** 17–24.

Tahara K, Kim HD, Jin JJ, Maxwell JA, Li L, Fukuchi K. 2006. Role of toll-like receptor signalling in Aβ uptake and clearance. *Brain* **129:** 3006–3019.

Takami K, Terai K, Matsuo A, Walker DG, McGeer PL. 1997. Expression of presenilin-1 and -2 mRNAs in rat and Alzheimer's disease brains. *Brain Res* **748:** 122–130.

Tan J, Town T, Paris D, Mori T, Suo Z, Crawford F, Mattson MP, Flavell RA, Mullan M. 1999. Microglial activation resulting from CD40-CD40L interaction after β-amyloid stimulation. *Science* **286:** 2352–2355.

Taylor PR, Carugati A, Fadok VA, Cook HT, Andrews M, Carroll MC, Savill JS, Henson PM, Botto M, Walport MJ. 2000. A hierarchical role for classical pathway complement proteins in the clearance of apoptotic cells *in vivo* . *J Exp Med* **192:** 359–366.

Tenner AJ. 1999. Membrane receptors for soluble defense collagens. *Curr Opin Immunol* **11:** 34–41.

Tesseur I, Zou K, Esposito L, Bard F, Berber E, Can JV, Lin AH, Crews L, Tremblay P, Mathews P, et al. 2006. Deficiency in neuronal TGF-β signaling promotes neurodegeneration and Alzheimer's pathology. *J Clin Invest* **116:** 3060–3069.

Thal LJ, Ferris SH, Kirby L, Block GA, Lines CR, Yuen E, Assaid C, Nessly ML, Norman BA, Baranak CC, et al. 2005. A randomized, double-blind, study of rofecoxib in patients with mild cognitive impairment. *Neuropsychopharmacology* **30:** 1204–1215.

Thambisetty M, Simmons A, Velayudhan L, Hye A, Campbell J, Zhang Y, Wahlund LO, Westman E, Kinsey A, Guntert A, et al. 2010. Association of plasma clusterin concentration with severity, pathology, and progression in Alzheimer disease. *Arch Gen Psychiatry* **67:** 739–748.

Town T, Laouar Y, Pittenger C, Mori T, Szekely CA, Tan J, Duman RS, Flavell RA. 2008. Blocking TGF-β-Smad2/3 innate immune signaling mitigates Alzheimer-like pathology. *Nat Med* **14:** 681–687.

Vlad SC, Miller DR, Kowall NW, Felson DT. 2008. Protective effects of NSAIDs on the development of Alzheimer disease. *Neurology* **70:** 1672–1677.

Vodopivec I, Galichet A, Knobloch M, Bierhaus A, Heizmann CW, Nitsch RM. 2009. RAGE does not affect amyloid pathology in transgenic ArcAβ mice. *Neurodegener Dis* **6:** 270–280.

Wake H, Moorhouse AJ, Jinno S, Kohsaka S, Nabekura J. 2009. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. *J Neurosci* **29:** 3974–3980.

Walker DG, Lue LF. 2005. Investigations with cultured human microglia on pathogenic mechanisms of Alzheimer's disease and other neurodegenerative diseases. *J Neurosci Res* **81:** 412–425.

Walker DG, Kim SU, McGeer PL. 1995. Complement and cytokine gene expression in cultured microglial derived from postmortem human brains. *J Neurosci Res* **40:** 478–493.

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Walker DG, Lue LF, Beach TG. 2001. Gene expression profiling of amyloid β peptide-stimulated human post-mortem brain microglia. *Neurobiol Aging* **22:** 957–966.

Walker DG, Dalsing-Hernandez JE, Campbell NA, Lue LF. 2009. Decreased expression of CD200 and CD200 receptor in Alzheimer's disease: A potential mechanism leading to chronic inflammation. *Exp Neurol* **215:** 5–19.

Walter S, Letiembre M, Liu Y, Heine H, Penke B, Hao W, Bode B, Manietta N, Walter J, Schulz-Schuffer W, et al. 2007. Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease. *Cell Physiol Biochem* **20:** 947–956.

Warner TD, Mitchell JA. 2004. Cyclooxygenases: New forms, new inhibitors, and lessons from the clinic. *FASEB J* **18:** 790–804.

Webster S, Lue L-F, Brachova L, Tenner AJ, McGeer PL, Terai K, Walker DG, Bradt B, Cooper NR, Rogers J. 1997. Molecular and cellular characterization of the membrane attack complex, C5b-9, in Alzheimer's disease. *Neurobiol Aging* **18:** 415–421.

White JA, Manelli AM, Holmberg KH, Van Eldik LJ, Ladu MJ. 2005. Differential effects of oligomeric and fibrillar amyloid-β 1–42 on astrocyte-mediated inflammation. *Neurobiol Dis* **18:** 459–465.

Wiley CA, Lopresti BJ, Venneti S, Price J, Klunk WE, DeKosky ST, Mathis CA. 2009. Carbon 11-labeled Pittsburgh Compound B and carbon 11-labeled (R)-PK11195 positron emission tomographic imaging in Alzheimer disease. *Arch Neurol* **66:** 60–67.

Wolfson C, Perrault A, Moride Y, Esdaile JM, Abenhaim L, Momoli F. 2002. A case-control analysis of nonsteroidal anti-inflammatory drugs and Alzheimer's disease: Are they protective? *Neuroepidemiology* **21:** 81–86.

Wyss-Coray T. 2006. Inflammation in Alzheimer disease: Driving force, bystander or beneficial response? *Nat Med* **12:** 1005–1015.

Wyss-Coray T, Mucke L. 2002. Inflammation in neurodegenerative disease: A double-edged sword. *Neuron* **35:** 419–432.

Wyss-Coray T, Masliah E, Mallory M, McConlogue L, Johnson-Wood K, Lin C, Mucke L. 1997. Amyloidogenic role of cytokine TGF-b1 in transgenic mice and Alzheimer's disease. *Nature* **389:** 603–606.

Wyss-Coray T, Lin C, Yan F, Yu G, Rohde M, McConlogue L, Masliah E, Mucke L. 2001. TGF-b1 promotes microglial amyloid-b clearance and reduces plaque burden in transgenic mice. *Nat Med* **7:** 612–618.

Wyss-Coray T, Yan F, Lin AH, Lambris JD, Alexander JJ, Quigg RJ, Masliah E. 2002. Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. *Proc Natl Acad Sci* **99:** 10837–10842.

Wyss-Coray T, Loike JD, Brionne TC, Lu E, Anankov R, Yan F, Silverstein SC, Husemann J. 2003. Adult mouse astrocytes degrade amyloid-β in vitro and in situ. *Nat Med* **9:** 453–457.

Xiang Z, Ho L, Yemul S, Zhao Z, Qing W, Pompl P, Kelley K, Dang A, Teplow D, Pasinetti GM. 2002. Cyclooxygenase-2 promotes amyloid plaque deposition in a mouse model of Alzheimer's disease neuropathology. *Gene Expr* **10:** 271–278.

Xu J, Chen S, Ahmed SH, Chen H, Ku G, Goldberg MP, Hsu CY. 2001. Amyloid-β peptides are cytotoxic to oligodendrocytes. *J Neurosci* **21:** RC118.

Yamada T, Akiyama H, McGeer PL. 1990. Complement-activated oligodendroglia: A new pathogenic entity identified by immunostaining with antibodies to human complement proteins C3d and C4d. *Neurosci Lett* **112:** 161–166.

Yamamoto M, Horiba M, Buescher JL, Huang D, Gendelman HE, Ransohoff RM, Ikezu T. 2005. Overexpression of monocyte chemotactic protein-1/CCL2 in β-amyloid precursor protein transgenic mice show accelerated diffuse β-amyloid deposition. *Am J Pathol* **166:** 1475–1485.

Yan P, Bero AW, Cirrito JR, Xiao Q, Hu X, Wang Y, Gonzales E, Holtzman DM, Lee JM. 2009. Characterizing the appearance and growth of amyloid plaques in APP/PS1 mice. *J Neurosci* **29:** 10706–10714.

Yang LB, Li R, Meri S, Rogers J, Shen Y. 2000. Deficiency of complement defense protein CD59 may contribute to neurodegeneration in Alzheimer's disease. *J Neurosci* **20:** 7505–7509.

Yasojima K, Schwab C, McGeer EG, McGeer PL. 1999. Distribution of cyclooxygenase-1 and cyclooxygenase-2 mRNAs and proteins in human brain and peripheral organs. *Brain Res* **830:** 226–236.

Yin KJ, Cirrito JR, Yan P, Hu X, Xiao Q, Pan X, Bateman R, Song H, Hsu FF, Turk J, et al. 2006. Matrix metalloproteinases expressed by astrocytes mediate extracellular amyloid-β peptide catabolism. *J Neurosci* **26:** 10939–10948.

Zandi PP, Anthony JC, Hayden KM, Mehta K, Mayer L, Breitner JC. 2002. Reduced incidence of AD with NSAID but not H2 receptor antagonists: The Cache County Study. *Neurology* **59:** 880–886.

Zhang J, Sokal I, Peskind ER, Quinn JF, Jankovic J, Kenney C, Chung KA, Millard SP, Nutt JG, Montine TJ. 2008. CSF multianalyte profile distinguishes Alzheimer and Parkinson diseases. *Am J Clin Pathol* **129:** 526–529.

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