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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 (A β) (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 μ m (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-1 β , IL-6, TNF- α , and interferon γ (INF- γ) (Lue et al. 2001a); chemokines such as macrophage inflammatory protein 1 α (MIP1 α), MIP1 β , 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- κ B, PPAR γ , 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 A β 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 A β spots dried down to the well floor, and to internalize portions of the A β (Lue et al. 2001b; Walker and Lue 2005). Similarly, microglia cultured on sections of AD cortex accumulate on A β deposits and appear to remove them (Bard et al. 2000). Additional studies have suggested, however, that microglia may not be able to degrade the A β 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 A β by showing that microglial processes sample and react to A β 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 A β deposits (Bolmont et al. 2008; Koenigsnecht-Talboo et al. 2008; Yan et al. 2009). Internalization and lysosome colocalization of A β 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 A β 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 A β 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 A β . In addition, A β 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 A β have also been fruitful. In vitro, A β 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 A β either as a direct or indirect ligand. For example, direct RAGE/A β binding helps guide microglia to A β deposits, an effect that is inhibited by treatment with anti-RAGE antibodies (Walker and Lue 2005; Chen et al. 2007b). Complement opsonization of A β (Rogers et al. 1992) and/or binding to anti-A β 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 A β 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 A β 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 A β 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 A β plaques, is chemotactic for adult astrocytes, and astrocytes express receptors that bind A β , 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 A β deposition (Wyss-Coray et al. 2003). Several studies suggest that plaque-localized, reactive astrocytes take up and degrade A β (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 A β degradation. Astrocyte expression of IDE is increased after A β exposure and is pronounced within glial fibrillary acidic protein (GFAP) immunoreactive astrocytes surrounding A β deposits (Leal et al. 2006). Extracellular clearance of A β may also occur via astrocyte secretion of matrix metalloproteinases (Yin et al. 2006). Exposure to A β , 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, S100 β , a neurotrophin that induces neurite proliferation, is overexpressed in AD brain and its levels are correlated with numbers of dystrophic neurites within A β deposits (Mrak et al. 1996). A similar correlation is found in APPV717F transgenic mouse brain, wherein astrocyte S100 β overexpression increases with age to a point just prior to A β deposition (Sheng et al. 2000). In S100 β overexpressing transgenic mice, inflammatory responses to intracerebroventricularly-infused A β are significantly augmented compared to wild-type and S100 β 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 A β significantly increases IL-1 β , TNF- α , iNOS, and NO production, with differential temporal effects depending on whether the A β 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-1 β , IL-6, and TNF- α are regulated by NF- κ B and C/EBP transcription factor mechanisms. Astrocyte CEBP δ is dramatically up-regulated in AD cortex (Li et al. 2004), and astrocyte NF- κ B is activated on exposure to A β , leading to increased expression of IL-1 β and IL-6 (Bales et al. 1998). NF- κ B 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 A β 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 neurologic 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 A β 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 A β into the corpus callosum induces microglial proliferation, with attendant damage to myelin and losses of oligodendrocytes (Jantaratnotai et al. 2003). In vitro, oligodendrocyte toxicity has been reported for A β 25-35 (Xu et al. 2001), A β 40 (Xu et al. 2001; Lee et al. 2004), and A β 42 (Roth et al. 2005). Perhaps because of their low glutathione and high iron content, oligodendroglia are also extremely vulnerable to oxidative stress (Juurink 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 A β 42-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 cytotoxicity 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).

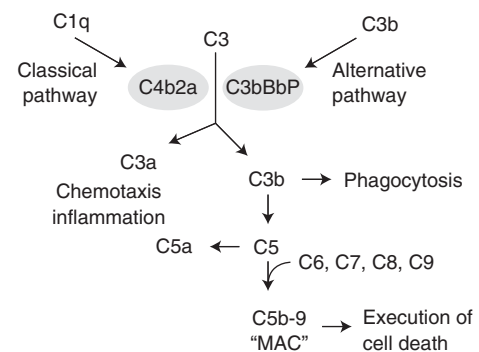


Figure 1. Brief schematic of the complement system (see text for details).

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 A β 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 A β 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 A β 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 A β 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 A β . 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 A β to A β autoantibodies, may also apply to C3-opsonized A β 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 A β . Here, C3-dependent binding of A β 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 A β 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)- β 1, which is increased in human AD brains at the transcript and protein level, whereas TGF receptor expression is decreased (Wyss-Coray et al. 1997; Teseur et al. 2006). TGF- β 1 promotes cerebrovascular amyloidosis but delays parenchymal A β 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 (Teseur 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 A β 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 A β accumulation, which may be due to a prominent increase in mouse ApoE (Yamamoto et al. 2005), a factor known to independently enhance A β 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-1 β 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-1 β in

adult APP mice resulted in strong activation of glial cells, induction of various inflammatory factors, and reduced amyloid pathology (Shafteel 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- κ B 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 A β , 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- κ B or p38 MAP kinase signaling or phagocytosis in response to fibrillar A β (Reed-Geaghan et al. 2009). Perhaps as a result, levels of TNF- α and MIP-1 β 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 A β . 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 A β deposition (Tahara et al. 2006; Richard et al. 2008). Likewise, acute administration of the TLR4 ligand LPS can promote A β 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 A β , 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 A β 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- κ B signaling, is up-regulated in AD brains, and functions as a receptor for A β (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 A β dependent neuronal perturbation that appears to involve NF- κ B 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 A β deposits in 6-month-old mice (Vodopivec et al. 2009). Thus, although RAGE seems to be sufficient to mediate detrimental effects of A β , 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 non-steroidal 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 post-synaptic 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 A β 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 pharmacy 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 A β 42 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 (≥ 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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