Friend, Foe or Both? Immune Activity in Alzheimer’s Disease

Georgia R. Frost1,†, Lauren A. Jonas1,2† and Yue-Ming Li1,2

1 Chemical Biology Program, Memorial Sloan Kettering Cancer Center, Manhattan, NY, United States, 2 Pharmacology Program, Weill Cornell Graduate School of Medical Sciences, Cornell University, Ithaca, NY, United States

Alzheimer’s disease (AD) is marked by the presence of amyloid beta (Aβ) plaques, neurofibrillary tangles (NFT), neuronal death and synaptic loss, and inflammation in the brain. AD research has, in large part, been dedicated to the understanding of Aβ and NFT deposition as well as to the pharmacological reduction of these hallmarks. However, recent GWAS data indicates neuroinflammation plays a critical role in AD development, thereby redirecting research efforts toward unveiling the complexities of AD-associated neuroinflammation. It is clear that the innate immune system is intimately associated with AD progression, however, the specific roles of glia and neuroinflammation in AD pathology remain to be described. Moreover, inflammatory processes have largely been painted as detrimental to AD pathology, when in fact, many immune mechanisms such as phagocytosis aid in the reduction of AD pathologies. In this review, we aim to outline the delicate balance between the beneficial and detrimental aspects of immune activation in AD as a more thorough understanding of these processes is critical to development of effective therapeutics for AD.

Keywords: neuroinflammation and neurodegeneration, glia, cytokine, amyloid, tau

ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is the most common neurodegenerative disorder and the 6th leading cause of death in the United States, next to heart disease and cancer (James et al., 2014; Alzheimer’s Association, 2015). Currently, no treatment for AD exists, making the development of therapeutics essential to public health (Katsurabayashi et al., 2016). There are two well-established hallmarks of AD: amyloid beta (Aβ) plaques and neurofibrillar tangles (NFT) (Lue et al., 1996; DeTure and Dickson, 2019). In large part, therapeutic efforts have focused on targeting and reducing the accumulation of Aβ and NFT (Panza et al., 2009). However, recent genome-wide association studies (GWAS) indicate that a large percentage of AD risk genes are associated with innate immunity and inflammation, suggesting that the immune system plays a critical, and previously unappreciated, role in AD pathology (Bis et al., 2018; Pimenova et al., 2018)

Clinical observations and bioinformatics have demonstrated that inflammatory cytokines, chemokines and other mediators are upregulated in AD patients, which further emphasizes the involvement of the immune system and neuroinflammation in AD (Tarkowski et al., 2003; Cribbs et al., 2012; Zhang et al., 2013; Broserson et al., 2014). Neuroinflammation is a broad term used to describe the innate immune response to CNS tissue damage. Neuroinflammation occurs when injury, infection, or disease (in the case of AD, misfolded proteins, namely Aβ and NFT) stimulates resident cells to produce inflammatory mediators such as cytokines and chemokines, but also, prostaglandins, free radicals, complement factors, and adhesion molecules which recruit
and activate additional immune cells (Calsolaro and Edison, 2016; Schain and Kreisl, 2017; Shabab et al., 2017). Neuroinflammation also involves the proliferation and activation of glial cells, astrocytes and microglia, as well as the presence of the aforementioned inflammatory mediators in the brain (Shabab et al., 2017). Many different cells within the CNS, including microglia and astrocytes, but also, neurons and endothelial cells, are capable of initiating an inflammatory response (Schwartz et al., 2013).

The CNS innate immune response is poorly understood and research suggests there are many differences in comparison to the peripheral immune system (although, alterations in the peripheral immune system have also been implicated in AD progression) (Cao and Zheng, 2018). Notably, immune associated clearance and repair pathways face greater challenges within the CNS environment, such as the presence of the blood brain barrier and ineffective clearance, as well as the abundance of post-mitotic cells (i.e., neurons) and the inability for growth and repair (Herrup and Yang, 2007; Muldoon et al., 2013). Therefore, it is critical to develop a better understanding of the brain's immune response in neurodegenerative disease and in AD.

While there is consensus that the immune system is intimately involved in AD, there is considerable debate over which aspects of inflammation are harmful and contribute to degeneration, and which are protective and may prevent cognitive decline. Furthermore, it has yet to be established which components of the immune system actively play a role in pathology and which are just a consequence of disease. As mentioned, gliosis, or increased numbers of activated astrocytes and microglia are a hallmark feature of neuroinflammation. However, past descriptions of this phenomenon, namely just “reactive” or “increased gliosis” are vastly oversimplified (Sofroniew and Vinters, 2010). Recent evidence highlights altered glia-specific pathways in post-mortem AD tissue and in mouse models of AD, suggesting that glial responses are much more heterogeneous and complex than previously thought (Thome et al., 2018). Overall, the broad spectrum of glial changes and functional consequences of gliosis in AD are not yet understood.

While neuroinflammation can promote efficient clearance of Aβ and neuronal debris it can also accelerate disease by causing neuronal and glial cell death (Qin et al., 2002; Block et al., 2007). This inflammatory balance is highly orchestrated and understanding how to regulate these responses is key to developing effective therapeutics for AD. The initiation of an immunological reaction can be beneficial and critical, allowing for a burst of glial activity to protect and repair the site of damage, and to clear toxic species or dysfunctional synapses (Wang M. M. et al., 2018). For example, in response to adverse conditions, microglia will undergo morphological changes, accompanied by the release of a storm of molecular mediators that increases clearances of Aβ (Sole-Domenech et al., 2016; Zhao et al., 2017). Furthermore, various types of non-neuronal cells are recruited to the site to assist in repairing the damage and consolidating excessive inflammation (Sofroniew, 2015). These reparative processes are beneficial, yet may also have harmful consequences such as sustained cytokine release which can become toxic to neuronal cells (Heneka et al., 2015). Therefore, understanding the specific cellular roles and inflammatory reactions in AD is of vital importance.

While studying familial Alzheimer’s disease (FAD) mutations has provided insight into disease etiology, FAD accounts for only a small proportion of all AD cases (St George-Hyslop et al., 1989). Sporadic Alzheimer's disease (SAD) is a late onset, multi-factorial disease for which the biggest risk factor is age (Dorszewska et al., 2016). However, genetic predisposition still plays a considerable role in risk of developing SAD with a heritability estimate of 60–80% (Gatz et al., 2006). Linkage studies have highlighted genes involved in AD pathogenesis beyond those directly involved in Aβ production identified in FAD studies (Bertram et al., 2008). FAD mutations are associated with Mendelian patterns of inheritance and age-dependent penetrance. These genes cause AD but are extremely rare in the general population (Tanzi, 2012). In contrast, genes identified in SAD linkage studies have higher prevalence in the general population but confer a much smaller risk of developing AD (Figure 1; Pimenova et al., 2018; Naj et al., 2011). Understanding the role that these AD associated genes play will give further insight into AD pathology and possibly result in the identification or novel targets for therapeutic development.

The identification of SAD associated genes has already provided novel insight into pathways involved in AD pathology. AD associated genes can be loosely grouped into those involved in Aβ accumulation, NFT formation and spread, cholesterol homeostasis, innate immunity and inflammation, endocytosis, the cytoskeleton, and epigenetics (Karch and Goate, 2015; Van Acker et al., 2019). Interestingly, many AD associated genes are involved in neuroinflammation and immune activation (Figure 1). Currently, AD associated inflammatory genes such as Trem2 and CD33 are perhaps the most widely discussed aspects of AD pathology. While the specific mechanisms as to how variants in these genes contribute to AD is still up for debate, an established feature of all three is activation of immune function. Notably, AD risk variants in triggering receptor expressed on myeloid cells 2 (TREM2) (Guerreiro et al., 2013; Jonsson et al., 2013) and myeloid cell surface antigen CD33 (Bradshaw et al., 2013) particularly highlight the importance of immune activation in clearing Aβ from the brain (Effthymiou and Goate, 2017).

**INNATE IMMUNITY IN AD**

The original amyloid cascade hypothesis notes that immune system activation occurs after Aβ deposition. However, clinical studies suggest that inflammatory changes occur much earlier in disease than originally thought (Tarkowski et al., 2003; Brosseron et al., 2014). In fact, systemic immune challenge in mice with Polyriboinosinic-polyribocytidylic acid (polyI:C), a dsRNA analog, resulted in an AD phenotype including Aβ plaques, NFT and gliosis, suggesting immune challenge can trigger an AD phenotype (Krstic et al., 2012). Furthermore, a plethora of studies have demonstrated that modulating immune system specific proteins impacts the development of AD pathology in various experimental systems, suggesting that the immune system directly impacts pathology. Both systemic inflammatory
conditions, such as obesity and diabetes, and activation of the immune system in the CNS, for example, traumatic brain injury, have been associated with the development of AD (Whitmer et al., 2008; Sivanandam and Thakur, 2012; Qizilbash et al., 2015).

The innate immune system is activated when cells expressing specialized pattern recognition receptors (PRRs) recognize pathogen-associated molecular patterns (PAMPs) on invading pathogens (Akira et al., 2006; Suressh and Mosser, 2013). Host derived PRR ligands, known as danger-associated molecular patterns (DAMPs) will also trigger an immune response. In the case of AD, misfolded or aggregated protein, such as Aβ plaques or NFT are DAMPs that trigger neuroinflammation. Activation of PRR and DAMPs provide the cell with differential signaling outcomes, most likely due to the need to differentiate between pathogen-induced toll-like receptor (TLR) activation, which requires immune participation, and tissue damage-induced TLR activation, which requires a balance between immune intervention and tissue damage repair (Miyake, 2007). PRRs such as TLRs, Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing (NLRP)s, CD36 and RAGE mediate cellular activation by DAMP’s (Cribbs et al., 2012). This activation leads to transcriptional transduction of genes promoting NFkB dependent proinflammatory gene transcription and NLRP3 inflammasome assembly, ultimately leading to the release of proinflammatory cytokines (Latz et al., 2013; Liu et al., 2017).
AD ASSOCIATED PROINFLAMMATORY CYTOKINES

Cytokines are a heterogeneous group of multifunctional proteins that can be synthesized and secreted by almost all cells (Feghali and Wright, 1997). They generally act locally in either a paracrine or autocrine manner (Zhang and An, 2007). Many cytokines are classified as interleukins (ILs) as they are secreted by, and act on, leukocytes. Other types of cytokines are tumor necrosis factors (TNFs), transforming growth factors (TGFs), interferons (IFNs), and chemokines (Feghali and Wright, 1997).

Cytokine signaling is involved in a variety of cellular processes including: cell proliferation, gliogenesis and neurogenesis, cell migration, apoptosis, and neurotransmitter release (Boulanger, 2009; Borsini et al., 2015). Chemokines, while considered cytokines, function differently than ILs, TNFs, TGFs, and IFNs, by attracting both adaptive and innate immune cells to the site of insult.

Cytokines are often categorized as either pro-inflammatory or anti-inflammatory. The balance between pro- and anti-inflammatory cytokines acts to successfully eliminate a pathogen, while also protecting surrounding tissue from excessive damage (Szelényi, 2001). Imbalance between pro- and anti-inflammatory cytokines could contribute to the development of AD. Cytokine function by binding to their receptors expressed on the surface of a variety of cell types. Expression of these receptors is tightly regulated, both spatially and temporally, as a means of controlling an inflammatory reaction (Szelényi, 2001). Research into the prevalence and function of cytokines in the AD is inconsistent, however, at least 23 cytokine polymorphisms in 13 different cytokines have been associated with risk of developing AD (Zheng C. et al., 2016; Table 1). Of these, studies have demonstrated that IL-1β, IL-6, IL-10, IL-18, IFN-γ, and TNF-α have altered expression in AD (Griffin et al., 1989; van der Wal et al., 1993; Hull et al., 1996). Furthermore, polymorphisms in IL-4, IL-12, and IL-23 and have been associated with AD but there is no consensus on whether their expression is changed with disease. Even though IL-10, IL-1ra and TGF-β are not genetically linked with AD, they have been found at higher levels in AD patients (Zheng C. et al., 2016).

INTERFERONS (IFNS) IN AD

Termed for their ability to interfere with viral replication, IFNs are a family of pleiotropic cytokines with broad immunomodulatory functions (Lindenmann, 1982; de Weerd et al., 2013). IFNs are classified based on their cognate receptor: type-I IFN; 14 subtypes, notably IFNα and IFNβ, type-II IFN; IFN-γ, and type-III IFNs; contains three IFNα subtypes (de Weerd et al., 2013). The three subtypes share pro-inflammatory properties and activate multiple signaling pathways. The most critical of these pathways is the janus-associated kinase (JAK) and signal transducer and activator of transcription (STAT) pathway (JAK-STAT) (Platanias, 2005).

Type-I IFNs signal through their cognate receptor: IFNα/β receptor (IFNAR) which is composed of two subunits, IFNAR1 and IFNAR2 (de Weerd et al., 2013). Upon binding the two subunits recruit JAKs (Tyk-2 for IFNAR1 and Jak1 for IFNAR2) which act as docking sites for the phosphorylation of STATs. Upon phosphorylation, STATs translocate to the nucleus and induce transcription of interferon-regulated genes (IRGs) (Platanias, 2005). Additionally, IFN-regulated factors (IRFs) may bind to STATs prior to nuclear translocation and further modify the IFN response (Honda et al., 2005).

Table 1: Summary of the involvement of cytokines that play well established roles in AD pathology.

| Cytokine | Involvement in AD pathology |
|----------|-----------------------------|
| TNF-α    | TNF-α is involved in inducing acute phase inflammation and is elevated in AD serum, cerebrospinal fluid (CSF) and cortex (Tkaczykowski et al., 1999, 2003). Anti-TNF-α treatment reduces Aβ deposition, behavioral impairments, and inflammation in AD animal models suggesting TNF-α is detrimental factor in AD (Russo et al., 2012; Tweedie et al., 2012; Detrait et al., 2014; Gabrita et al., 2015). However, one study suggests that TNF-α expression in APP transgenic mice at early stage induces glial uptake of Aβ (Chakrabarty et al., 2011). Additionally, neuronal TNF-α expression in 3xTg AD mice promotes neuronal death (Janelins et al., 2008). |
| IL-1β    | IL-1β is rapidly secreted in response to injury and is an important mediator of inflammatory response as well as cell proliferation, differentiation and apoptosis. IL-1β has been found at high levels near the sites of Aβ plaques (Griffin et al., 1989; Das and Potter, 1995; Licastro et al., 2000). Overexpression of IL-1β in APP/PS1 mice activates a phagocytic population of microglia and reduces Aβ plaques (Ghosh et al., 2013; Cherry et al., 2015). Furthermore, mice deficient in the receptor for IL-1β have lower recruitment of microglia to Aβ plaques, supporting the idea that IL-1β can mediate microglial chemotaxis (Kamphuis et al., 2012). |
| IL-6     | IL-6 may be both proinflammatory and anti-inflammatory and is elevated in the plasma, CSF, and brain of AD patients (Ehrler and Keiler, 2000; Licastro et al., 2000, 2003; Shibata et al., 2002; Baranowska-Bik et al., 2008; Galmerti et al., 2008). |
| IL-10    | IL-10, also known as cytokine synthesis inhibitory factor (CSIF), is an anti-inflammatory cytokine upregulated in AD patients (Guillot-Sestier et al., 2015). Overexpression of IL-10 in AD animal models reduces microglial phagocytosis of Aβ leading to cognitive impairment (Chakrabarty et al., 2015; Guillot-Sestier et al., 2015). |
| TGF-β    | TGF-β is an immunosuppressive cytokine that promotes neurons against damage. A genetic polymorphism in TGF-β1 is associated with the risk of developing AD (Luedeking et al., 2003). Post mortem AD brains contain increased levels, specifically in Aβ plaques (van der Wal et al., 1993; Chao et al., 1994). Long-term overexpression of TGF-β by astrocytes can increase Aβ clearance by microglia and improve cognitive impairment (Wyss-Coray et al., 2001; Chen et al., 2013). Conversely, TGF-β induces astrocyte aggregation and Aβ deposition near brain microvessels (Jeuberm et al., 2009). |
| IFN-γ    | IFN-γ is a proinflammatory regulatory cytokine that activates microglia. It is primarily produced by T cells and natural killer cells but can also be secreted by microglia and astrocytes (Fultz et al., 1993). IFN-γ is upregulated in the AD brain (Huberman et al., 1994) and a polymorphism is associated with fast progressing AD, suggesting it could play a detrimental role in the course of AD (Asselineau et al., 2015). |
The functional consequence of IFN signaling within the CNS is particularly diverse and is important for processes such as cell survival and immunomodulation (Gough et al., 2012). IFNα and IFNβ are used therapeutically in multiple sclerosis to suppress autoimmune attacks on myelination (Wingerchuk and Carter, 2014). Furthermore, IFNβ is a driver of microglial phagocytosis of myelin in a murine autoimmune encephalitis model (Kocur et al., 2015). However, an epidemiological study suggests IFNβ treated MS patients develop Parkinson’s disease (PD)-like symptoms, such as impaired motor function and cognitive deficits, with long term type-I IFN therapy (Manouchehrinia and Constantinescu, 2012). While IFN signaling may be beneficial, particularly in the periphery, within the CNS, IFNs may also be detrimental and contribute to the development of many neurodegenerative disorders. To highlight this contradiction, IFNβ-/- mice develop Lewy body and PD like symptoms (Ejlerskov et al., 2015), yet, genetic and pharmacological inhibition of type-I IFN signaling is neuroprotective in the MPTP model of PD (Main et al., 2017). The outcome of IFN signaling within the CNS is highly specific to environmental context and requires further study. Interestingly, there is a body of evidence suggesting that IFN signaling contributes to cognitive impairments in a variety of disease states such as human immunodeficiency virus (HIV) encephalopathy (Rho et al., 1995), West Nile virus (Cunningham et al., 2007), neonatal Aicardi–Goutières syndrome (Crow et al., 2006a,b), and even normal aging (Baruch et al., 2014; Zheng et al., 2014).

The staggering diversity of cytokines and chemokines implicated in the progression of AD pathology serves to highlight the complexity of immune activation in disease. Due to the influence of so many different proinflammatory and anti-inflammatory (or both) mediators in AD, it seems unlikely that targeting any specific cytokine, without fully understanding the downstream effect on the immune system as a whole, will be an effective treatment for AD. Furthermore, cytokines may elicit different effects depending on the cell type and cellular context so the relationship between different cell types in AD needs to be explored.

GLIA

There are many different glial cell types: microglia, astrocytes, oligodendrocytes, ependymal and satellite cells. Until recently, glia were categorized as support cells for neuronal activity, however, accumulating evidence suggests glia have roles that expand far beyond neuronal support. Microglia, the most abundant mononuclear phagocyte in the CNS, are most studied for their role in immune surveillance, phagocytosis, neurodevelopment and synaptic plasticity, while astrocytes provide protection, support, and nutrients to neurons and to the vasculature (Allen and Eroglu, 2017; Li and Barres, 2018). Oligodendrocytes form myelin that coat nerve cell axons, aiding in the propagation of action potentials, while Schwann cells in the PNS act analogously (Lassmann, 1998). Ependymal cells line CNS ventricles and the central canal of the spinal cord and are responsible for the regulation of CSF (Johanson et al., 2008). It is well-established that neurons, astrocytes and microglia all play vital roles in the tripartite synapse and therefore are all necessary for synaptic transmission, learning and memory (Araque et al., 1999). A plethora of evidence highlights the roles of glia in immune activity in AD including phagocytosis of cellular debris and cytokine release (Leyns and Holtzman, 2017).

MICROGLIA

The CNS contains microglia, resident immune cells which migrate to the brain during embryonic days 8–9 (Hanisch and Kettenmann, 2007; Quan and Banks, 2007; Ginhoux and Prinz, 2015; Louveau et al., 2015; Matcovitch-Natan et al., 2016). Microglia are found throughout the CNS and their immune activity within the brain is well defined (Lawson et al., 1990; Hanisch and Kettenmann, 2007; Ransohoff and Cardona, 2010; Kierdorf and Prinz, 2013; Jay et al., 2015; Lauro et al., 2015; Matcovitch-Natan et al., 2016). Microglia play a central role in the immune system and have receptors for neurotransmitters and hormones, cytokines and chemokines, and PRRs and therefore respond to a variety of inflammatory mediators that are implicated in AD, including Aβ (Liu et al., 2005; Smith et al., 2012; Dewapriya et al., 2013; Rangaraju et al., 2018a,b). Microglial activation is associated with AD progression: however, whether this is harmful, protective, or both, remains to be established. Microglia may prevent AD pathology by reducing Aβ accumulation – Aβ can be directly removed from central nervous system circulation by activated microglia (Michaud et al., 2013). Microglia have been shown to recognize and phagocyte dysfunctional synapses (Wake et al., 2009; Tremblay et al., 2010) and stimulate synapse formation by secreting brain-derived neurotrophic factor (BDNF) (Parkhurst et al., 2013). On the other hand, microglial cytokine production has also been associated with neurotoxic effects that contribute to cognitive decline (Kettenmann et al., 2011; Heneka et al., 2015; Heppner et al., 2015; Calsolaro and Edison, 2016).

Microglia have a spectrum of phenotypes ranging from ameboid to ramified (Stence et al., 2001; Fontainhas et al., 2011) which are influenced by environmental factors such as the presence of cytokines and chemokines (Ginhoux et al., 2013). On one side of the spectrum, ramified microglia have many processes that facilitate the interaction with nearby neurons, astrocytes and blood vessels. These surveying interactions are necessary for CNS tissue maintenance and neuronal function (Wake et al., 2009; Paolicelli et al., 2012; Schafer et al., 2012; Parkhurst et al., 2013). On the other hand, ameboid microglia have retracted processes and therefore, the highest level of motility and greatest capacity for phagocytosis (Karperien et al., 2013).

The importance of microglial phagocytosis in neuroprotection and maintaining homeostasis is well appreciated, however, the contribution of dysregulated phagocytosis to disease state has only recently emerged. In fact, impaired microglial clearance of Aβ is thought to play a more significant role in the development of SAD than aberrant Aβ production (Mawuenyega et al., 2010).
A decrease in Aβ clearance has been demonstrated in AD patients compared to age-matched controls suggesting impaired microglia or astrocyte clearance may be a causative factor in AD (Mawuenyega et al., 2010). Phagocytic activity can differ with disease and environmental context, resulting in a wide spectrum of phagocytic responses. The phagocytotic pathway can be described in three steps: 1. find-me, 2. eat-me, and 3. digest-me (Sierra et al., 2013; Wolf et al., 2017). The first step is initiated when specific molecules bind to target-recognizing receptors on the microglia. These receptors can be specific toward signaling molecules on the surface of items to be phagocytosed, such as pathogens, dystrophic neurites or protein aggregates. In fact, different receptors trigger different signaling pathways that stimulate phagosome formation (Arcuri et al., 2017). In the case of AD, targets such as Aβ or NFTs are recognized by TLRs resulting in a proinflammatory cytokine storm associated with release of TNF, IL-1 and NO, while recognition of cell debris or dystrophic neurites by microglial TREM2 receptors is associated with a phagocytic response along with an increase in TGFβ and IL10 signaling (Neumann and Takahashi, 2007; Takahashi et al., 2007; Neumann et al., 2009). During the second step, eat-me, the plasma membrane extends and encloses around the target forming a vesicular phagosome. This nascent phagosome subsequently fuses with lysosomes forming a phagolysosome. The third and final step, digest-me, occurs within the phagolysosome as the target is degraded. Following this, byproducts must be either stored or recycled by the phagocytic cell (Flannagan et al., 2012).

Specifically, Aβ triggers an inflammatory response which stimulates microglia to clear it from the brain and this prevents the formation of plaques (Colton et al., 2006; Jekabson et al., 2006; Morgan, 2006; Zhao et al., 2017). After Aβ is engulfed it is targeted to the autophagic pathway for eventual degradation by the fusion of the autophagosome with a lysosome. Alternatively, reactive astrocytes can uptake Aβ and degrade it via the autophagic/lysosomal pathway. Additionally, Aβ may be cleared from the brain by proteolytic degradation. Aβ can be cleaved by the metalloprotease neprilysin (Takaki et al., 2000), therefore, mice treated with neprilysin inhibitors have increased Aβ release and improved cognitive performance in APPPS1 mice (Heneka et al., 2013). Additionally, complement binding may stimulate microglia to engulf synaptic contents in the presence of Aβ (Hong et al., 2016). Therefore, microglial phagocytosis of Aβ may be both beneficial and harmful.

Activated microglia can secrete toxic proinflammatory cytokines (Colonna and Butovsky, 2017; Kinney et al., 2018) and also release mediators that induce astrocytes to secrete a neurotoxic substance (Liddelow et al., 2017) contributing to neurodegeneration. On the other hand, many of the previously discussed cytokines released by microglia, also have physiological roles in synaptic plasticity and neurogenesis (Albensi and Mattson, 2000; Bernardino et al., 2008; Morris et al., 2013). For example, IL-1β, TNF, IL-6, and complement cascade proteins are all involved in memory consolidation (Goshen et al., 2007; Boulanger, 2009; Yirmiya and Goshen, 2011). In conclusion, microglial activity and cytokine release are vital to normal cognitive processes, however, in other contexts these processes can be neurotoxic.

**ASTROCYTES**

Astrocytes are another major glial cell type within the CNS. Unlike microglia, which are known to be highly motile, astrocytes operate within territorial domains, either supporting the vasculature or enveloping neuronal synapses, through processes terminating in the endfoot (Oberheim et al., 2006). This enables astrocytes to exert control over various CNS functions including blood brain barrier regulation, nutrient delivery, ion and metabolite balance, and innate immune regulation (Attwell et al., 2010; Bazargani and Attwell, 2016). Astrocytic end-foot express Ca2+ ion channels and glutamate receptors, allowing for the propagation of calcium currents and the release of gliotransmitters. A pertinent member of the tripartite synapse, astrocytes enable communication with and between neurons (Lind et al., 2018). Specifically, astrocytes can uptake and release neurotransmitters such as glutamate, GABA and ATP, neuromodulators; d-serine and kynurenic acid, as well as growth factors and inflammatory mediators (Malarkey and Parpura, 2008; Choi et al., 2014; Martineau et al., 2014). Further, astrocytes offer protection against CNS injury and are critical for repair of nervous tissue. After injury, astrocytes propagate and become reactive, a process known as astrogliosis. Astrogliosis is an evolutionarily conserved and neuroprotective process that contributes to the isolation of damaged tissue through formation of a glial scars and consolidation.

Astrocytes are key regulators of the brains inflammatory response and are capable of releasing, and responding to, a spectrum of immune mediators (Farina et al., 2007). Astrocytes secrete many of the cytokines known to be upregulated in human AD brain samples and in transgenic mouse models of AD (Benzing et al., 1999; Apelt and Schliebs, 2001; Abbas et al., 2002; Tan et al., 2002), notably: IFNγ, IL-1β, TNFα, IL-6, and TGFβ...
A defining feature of senile plaques is the presence of surrounding astrocytes and microglia (Itagaki et al., 1989), in fact, the presence of reactive astrocytes follows amyloid deposition throughout the course of AD (Vehmas et al., 2003). Glial barriers surrounding plaques are neuroprotective in two ways: (1) glia, particularly microglia, can break down and phagocytose amyloid plaques, and (2) astrocytes can prevent the spread of toxic material and therefore, limit collateral damage (Faulkner et al., 2004) and can respond to immune activity in the brain. In fact, complement reactive oligodendrocytes in association with activated microglia can be found in the white matter of aged brains (Duce et al., 2006). Furthermore, microglia have diverse phenotypes depending on the region of the brain and may be more activated in white matter (Olah et al., 2011).

GLIA BARRIERS

Damage to the CNS, in the form of injury or disease, results in a multifaceted immune response. The formation of glial barriers, also known as glial scars, is one type of response to injury and is formed by both glial and non-glial cells that surround the site of damage (Adams and Gallo, 2018). This phenomenon is most widely studied in the context of traumatic brain injury. Glial scarring has also been found after incidence of ischemic stroke and in neurodegenerative diseases such as multiple sclerosis (Woodcock and Morganti-Kossmann, 2013).

While many have reported the heterogeneity of glial scar formation across brain region and disease-type, the development of the glial barrier often begins with the proliferation of reactive astrocytes near the damaged tissue, and the subsequent orchestration of astrocytes, oligodendrocyte precursor cells and microglia to build a rigid wall surrounding damage (Sofroniew, 2009; Wanner et al., 2013). Ultimately a barrier is formed, culminating in the existence of two distinct regions: the lesion core, consisting of oligodendrocyte precursor, fibroblasts and macrophages, and the penumbra, containing reactive astrocytes and microglia (Anderson et al., 2014). The induction of glial scar formation is specific and is stimulated by a range of signaling molecules including IL-1, IL-6, TGF-B1, EGF, BMPs and LIF, from damaged tissue (Wang H. et al., 2018). These signaling molecules aid in the activation of transcription factors that regulate the astrocytic response to tissue damage. Specifically, signaling for the activation of transcription factors STAT3, SP1, OLG2, Smad3, and NFKB pathways initiate glial scarring mechanisms including astrocytic hypertrophy, migration, proliferation, gliogenesis, and inflammation (Justicia et al., 2000; Hamby et al., 2012).

A defining feature of senile plaques is the presence of surrounding astrocytes and microglia (Itagaki et al., 1989), in fact, the presence of reactive astrocytes follows amyloid deposition throughout the course of AD (Vehmas et al., 2003). Glial barriers surrounding plaques are neuroprotective in two ways: (1) glia, particularly microglia, can break down and phagocytose amyloid plaques, and (2) astrocytes can prevent the spread of toxic material and therefore, limit collateral damage (Faulkner et al., 2004) (Anderson et al., 2016). Studies have shown that a deficiency in the ability to form glial barriers worsens AD pathology. When GFAP was knocked out in a mouse model of AD there was a

OLIGODENDROCYTES

Alzheimer’s disease research has often been restricted to gray matter, however, it’s important to note that abnormalities in white matter have been identified in AD patients. In fact, white matter hyperintensities volume is found to be elevated in FAD patients 20 years prior to the onset of symptoms and can be used to predict incidence of AD and rate of cognitive decline in SAD cases as well (Lee et al., 2018; Nasrabad et al., 2018).
marked increase in plaque-associated dystrophic neurites (Kraft et al., 2013). Further, research shows that glial barriers can aid in axonal regrowth and repair in brain regions where barrier stiffness impacts neuronal growth are more widely affected (Yu and Bellamkonda, 2001; Bollmann et al., 2015).

Glia barriers surrounding amyloid plaques and NFT-associated damage may initially aid in the breakdown and consolidation of toxic debris from the CNS yet subsequently limit the brain’s ability to reform neuronal connections. Moreover, neurons are post mitotic and are unable to divide, making recovery from glial scarring even more difficult (Herrup and Yang, 2007). Thus, immune therapies aimed at regulating the formation of glial scars in AD could help to promote the beneficial regrowth of neuronal connections in the CNS.

**AD ASSOCIATED GENES**

The discovery of immune related AD associated genes from AD linkage studies has provided substantial insight into the involvement of immunity in AD pathology. Numerous variants in immune related genes have been identified in whole-genome sequencing and GWAS analyses, including APOE, BIN1, CD33, CLU, CR1, INPP5D, PICALM, PIGC2, MS4A6D, and TREM2, these genes are involved in a wide range of immune related functions (Table 2, Figure 1; Efthymiou and Goate, 2017; Long and Holtzman, 2019; McQuade and Burton-Jones, 2019; van der Lee et al., 2019). While most of the identified loci confer only a small contribution to AD development, they serve to highlight the involvement of various immune functions in the development of AD. A notable example is the Apolipoprotein E (APOE) gene. APOE has three alleles (ε2, ε3, ε4) accounting for proteins that differ by only one or two amino acids (Ward et al., 2012; Najm et al., 2019). A single copy of APOE4 increases risk of developing AD by 4-fold, and individuals homozygous for APOE4 have an approximately 12-fold increased risk of AD (Bu, 2009). The APOE4 allele is more common than FAD mutations and also has a substantial effect on risk of developing AD (Corder et al., 1993). Conversely, the ε2 allele may protect against developing AD (Berlau et al., 2009). Post mortem analysis revealed that both AD patients and healthy controls with the APOEe2e3 genotype have reduced amyloid load (Lippa et al., 1997). A possible mechanism behind this phenomenon is that APOE allele can affect the efficiency of Aβ clearance (Kim et al., 2009) and also impact the formation of and morphology of NFT (Shi et al., 2017). The C→A substitution at position 158 allows for differential lipidation and higher APOE2 stability and resistance to thermal and chemical denaturation (Morrow et al., 2000; Ma et al., 2018). Thus, differential physical interactions and binding between APOE and soluble Aβ may be the cause for this change in clearance efficiency. Since presence of the ε4 allele is thought to reduce Aβ clearance, this underscores the importance of immune clearance of toxic proteins from the brain in preventing AD symptoms. In fact, APOE alleles have been found to impact the efficacy of passive anti-Aβ immunization suggesting that the different alleles effect microglia’s phagocytic ability for Aβ (Pankiewicz et al., 2017).

### Table 2 | Alzheimer’s disease risk loci with proposed immune functions.

| SNP ID   | Proposed gene | Immune function                          |
|----------|---------------|------------------------------------------|
| rs2305421 | ADAM10        | Cleaves TNFα (Mezyk-Kopec et al., 2009)  |
| rs679615  | CR1           | Complement receptor, Aβ clearance (Fogers et al., 2008) |
| rs3818361 | B300D (BCL3)  | Regulator of NF-κB (immune cell survival and inflammatory response) (Poveda et al., 2017) |
| rs2965101 | CLU           | Inhibition of complement system, lipid transport, cell survival (Foster et al., 2019) |
| rs11136000| MARK4         | Limits inflammasome (Li et al., 2017)    |
| rs4420638 | APOC1         | Inhibits pro-inflammatory cytokine secretion from astrocytes and microglia (Cudaback et al., 2012) |
| rs117612135| MEF2C         | B cell proliferation and antigen presentation (Sao et al., 2018) |

---

Frost et al.  Neuroinflammation in Alzheimer’s Disease
Many other SAD associated genes have also been shown to play vital roles in immune reactivity in the brain.

Rare variants in TREM2, which are thought to be loss of function, and increase the risk of developing AD by approximately 2- to 4-fold, were identified by whole-genome sequencing (Sierra et al., 2013; Jonsson et al., 2013). TREM2 binds to the aforementioned AD associated gene APOE and other apolipoproteins, including APOA1, APOB, and APOJ (Yeh et al., 2016). TREM2 associates with DAP12, upon ligand binding, DAP12 is phosphorylated which leads to the recruitment of spleen tyrosine kinase (Syk). Subsequently, Syk signals through activation of phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinases (MAPKs) and the elevation of intracellular Ca\(^{2+}\) through release of IP3-gated Ca\(^{2+}\) stores (Colonna and Wang, 2016). A number of cellular functions have been attributed to this signaling, including: inhibition of inflammatory signaling, phagocytosis and cell survival (Colonna, 2003). Furthermore, A\(\beta\) has been demonstrated as a TREM2 ligand capable of triggering TREM2 signaling (Zhao et al., 2018; Zhong et al., 2018).

TREM2 mediated phagocytosis is critical for A\(\beta\) and neuronal debris clearance in AD (Kleinberger et al., 2014; Xiang et al., 2016; Yeh et al., 2016). Specifically, TREM2 expression is important for microglia to physically associate with A\(\beta\) plaques (Ulrich et al., 2014; Wang et al., 2016; Yuan et al., 2016; Jay et al., 2015, 2017a,b). In fact, high-resolution confocal microscopy revealed that microglial processes that are in contact with A\(\beta\) have enhanced expression of TREM2 and DAP12, possibly suggesting an enrichment of activated DAP12 signaling. These findings suggest that TREM2 is necessary for sustaining or initiating microgliosis in AD (Yuan et al., 2016). Presence of the Trem2 R47H allele in an AD mouse model results in reduced TREM2 expression around plaques, a decrease in microglia associated with plaques and an increase in neuritic dystrophy near plaques (Cheng-Hathaway et al., 2018). Additionally, TREM2 is important for microglia survival as TREM2 knockout mice have increased apoptosis in plaque-associated microglia (Wang et al., 2016). Furthermore, soluble TREM2 (sTREM2) levels in the CSF are correlated with AD progression (Suarez-Calvet et al., 2019).

Taken together, the critical role of TREM2 in AD underscores the involvement of the immune system, particularly the aspect of microglial activation and phagocytosis, in pathology. Features of immune activation are thus beneficial, as microglia play a critical role in the surveillance and recognition of toxic species, in the initiation of an immune response and in the final clearance and degradation of pathogens.

CD33, a myeloid cell transmembrane receptor, is another top ranked AD associated gene identified by GWAS studies; two main variants, rs3865444 and rs12459419, confer risk of developing AD, and higher expression in the brain has been associated with advanced cognitive decline and AD (Carrasquillo et al., 2011; Hollingworth et al., 2011; Naj et al., 2011; Lambert et al., 2013; Malik et al., 2013; Li et al., 2015; Dos Santos et al., 2017). The rs9865444 variant is associated with increased CD33 expression and microglial activation with reduced AB42 internalization and increased brain amyloid load, while the rs12459419 variant has been identified as protective. CD33, a sialic-binding immunoglobulin-like lectin (Siglec-3), is most studied for its role in immunoreceptor tyrosine-based inhibitor motif (ITIM) signaling. CD33 signaling works counter to TREM2 signaling; Upon ligand binding to (i.e., sialylated glycolipids or amyloid plaques), CD33 signals for the phosphorylation of ITIM by SHP1/2, resulting in the inhibition of a variety of receptors containing the immunoreceptor-tyrosine-based activation motifs (ITAM). Inhibition of ITAM results in reduced cellular activity and suppression of proinflammatory cytokine release, oxidative burst and phagocytosis (Lajaunias et al., 2005; Jiang et al., 2014). The rs12459419 variant results in altered splicing of the CD33 mRNA and a loss of the sialic acid binding domain, thereby inhibiting ITIM inhibition and preserving the cell’s ability to phagocytose (Malik et al., 2013).

CD33 is elevated in the AD brain in microglia and infiltrating macrophages and is thought to modulate microglial activation and A\(\beta\) clearance (Griciuc et al., 2013; Walker et al., 2015). In fact, knock-out of CD33 in AD mouse models results in reduced A\(\beta\) plaque burden (Griciuc et al., 2013). Additionally, CD33 inhibits microglial cytokine release and immune cell proliferation (Tateno et al., 2007; Crocker et al., 2012) further supporting the involvement of inflammation and innate immunity in AD etiology. Further, the hypothesis that CD33 inhibition could increase phagocytosis of A\(\beta\) has fueled efforts to design immunotherapy agents and small molecule inhibitors for therapeutic use. However, strides to find specific pharmacological inhibitors of CD33 in the brain have been difficult due to the lack of an atomic resolution structure of the sialic binding domain.

**CURRENT IMMUNE RELATED THERAPIES**

Currently available treatments for AD are limited to cholinesterase inhibitors and memantine, both of which work by modifying transmission of the neurotransmitters: acetylcholine and glutamate, respectively. (Thomas and Grossberg, 2009; Ferreira-Vieira et al., 2016) While these drugs have proven effective for the slowing of symptoms in mild to moderate AD, no current therapies are effective in significantly slowing of AD progression (Burns et al., 1999; Reisberg et al., 2006). Epidemiological evidence has suggested non-steroidal anti-inflammatory drugs (NSAIDS) are beneficial in the slowing of AD progression – individuals taking NSAIDS for chronic inflammatory conditions have a lower incidence of AD (de Craen et al., 2005). These studies led to a series of clinical trials testing the effects of naproxen or celecoxib on AD progression. Naproxen’s mechanism of action is through reversible inhibition of both COX-1 and COX-2 enzymes, resulting in the reduction of prostaglandin synthesis. Prostaglandins act as inflammatory inducers, and thus naproxen works as a non-selective inhibitor of an inflammatory response (Robinson, 1983). NSAIDS and naproxen, were originally thought to plateau AD pathology by targeting the immune system. However, results from the INTREPAD study indicate that naproxen had no clinical
benefits as adults that took naproxen for 2 years did not show slowed cognitive impairment or a decrease in AD-CSF markers (Pellicano, 2014).

It is possible that failure of these clinical trials was due to poor study design rather than a lack of efficacy. The majority of these trials took place early in disease progression, a time when inflammation is critical to initial clearance and consolidation. Therefore, while these studies deem NSAIDS not effective in preventing AD development, targeting inflammation remains a feasible goal. Many studies illustrate the ability to slow cognitive decline with a more selective reduction of detrimental inflammation in AD, while maintaining repair mechanisms. Thus, while studies for the use of NSAIDS in AD proved less than favorable, accumulated research supports the testing of immune modifying therapies.

Immunotherapy has emerged as one of the most promising strategies to tackle AD as it would enable specific clearance of the accumulated toxic proteins of Aβ and NFT without effective other functions in the brain (Valera and Masliah, 2013). Specifically, the development of active and passive antibodies against Aβ, has been utilized as a therapeutic approach (Folch et al., 2016). Active immunotherapy exploits the body's own immune system and therefore is longer lasting, however, has a high risk of triggering an autoimmune reaction. Furthermore, active immunotherapy can be limited by epitope availability and specificity (Bard et al., 2003; Winblad et al., 2014). Alternatively, passive immunotherapy can be far more specific but has a short effect and therefore requires continuous antibody treatment (Ward M. et al., 2012).

One of the earliest Aβ immunotherapy trials utilized AN1792, a synthetic Aβ peptide, that induces the generation of antibodies against Aβ by active immunotherapy. Unfortunately, 6% of patients during phase 2 of clinical trials developed meningoencephalitis (Gilman et al., 2005; Cao et al., 2018). Furthermore, treatment did not provide a protective cognitive effect despite significantly reducing Aβ pathology. However, a follow-up study performed 4 years after immunization found improvements in cognition in 68% of patients. reduction in Aβ plaque load locally in the brain. Interestingly, a follow-up study, done 3.6–4.6 years after immunization with AN1792, found significant improvements in brain volume and cognitive decline in immunized vs. placebo group. Although, these improvements were only observed in 68% of antibody responders which was less than 20% of the total patients immunized (Vellas et al., 2009). Another active immunotherapy CAD106 has been found to be safe and well tolerated in clinical trials and is still in development (Farlow et al., 2015).

Two notable passive immunotherapeutic agents have entered clinical trials: bapineuzumab and solanezumab. Bapineuzumab that targets the N-terminus of Aβ and failed clinical trials due to a poor safety profile in mild to moderate AD patients (though some of these were APOE4 carriers) (Doody et al., 2014; Liu et al., 2015; Vandenbergh et al., 2016). Solanezumab is a humanized IgG1 monoclonal antibody targeting soluble monomeric Aβ that has passed Phases 1 and 2 of clinical trials with a favorable safety profile. Unfortunately, solanezumab did not show efficacy in phase 3 and was abandoned until it reentered clinical trials for FAD patients (Doody et al., 2014; Siemers et al., 2016).

Aducanumab is also a monoclonal antibody. In August 2016, very promising phase I results were published showing that Aducanumab decreased soluble and fibrillar forms of Aβ and slowed down cognitive decline 54 weeks after treatment in a dose-dependent manner (Sevigny et al., 2016). However, phase 3 trials for Aducanumab were canceled in March of 2019 after an independent data monitoring committee concluded that the trial would not meet its primary end points. Despite this, in October 2019, Biogen Inc., announced that they would resume clinical trials following further analysis of the phase 3 data (Biogen, 2019).

INFECTION HYPOTHESIS

The antimicrobial peptide (AMP) hypothesis of AD suggests that Aβ is initially generated as a defense mechanism against a real or perceived infection signifying a direct link between AD and innate immunity (Moir et al., 2018). AMPs are evolutionarily conserved proteins that participate in the innate immune system’s first line of defense, with roles in microbial killing and immune regulation (Haney et al., 2017). AMPs require oligomerization for normal functioning, and soluble oligomers form fibrils that target viruses, fungi, bacteria, and some forms of cancerous host cells (Arnusch et al., 2007; Wiesner and Vilinskas, 2010). Aβ has structural similarities to a family of host-encoded AMPs and possesses antimicrobial activity. In vitro studies show Aβ as having a greater potency compared to the archetypal human AMP LL-37 against microbes (Soscia et al., 2010). Further, in vivo and in vitro studies demonstrate how AMPs promote amyloid fibrilization for use in disruption of microbial cell membranes, neutralization of bacterial endotoxins and pathogen entrapment (Sood et al., 2008; Wang et al., 2014; Chai et al., 2017). Additionally, Aβ42-overexpressing cells are resistant to killing by yeast and bacteria (Eimer et al., 2018). The Aβ-yeast interaction caused Aβ fibril nucleation allowing for the entrapment of yeast, a mechanism that is comparable to the antimicrobial activity of many AMPs (Eimer et al., 2018). Moreover, a mouse model overexpressing Aβ42 displayed higher resistance to certain yeast and bacterial infections (Soscia et al., 2010). Further, recent reports have indicated higher levels of AMPs and pathogen derived epitopes in post mortem AD brain tissue (Williams et al., 2013; Alonso et al., 2014). Pathogen signatures (i.e., Chlamydia Pneumoniae, HSV-1 DNA) specifically colocalize with AD pathology (Balin et al., 1998; Wozniak et al., 2009). Further, HSV infection is significantly associated with development of AD and HSV-1 is shown to increase Aβ generation (Letenneur et al., 2008).

Amyloid beta was previously deemed physiologically irrelevant, however, the presence of antimicrobial activity supports a role in the innate immune response and thus could be an important finding for AD research. Knowledge of Aβ’s AMP capabilities may help put into perspective Aβ and the immune system’s causative role in Alzheimer's disease. If the physiological role of APP is in pathogen/virus defense, then an overproduction
of Aβ could be the result of an innate immune reaction. Indeed, the AMP hypothesis helps to shed a new light on aspects of immune involvement in AD pathogenesis. Understanding the initial benefits provided by amyloid's AMP properties could prove beneficial to disease treatment.

OTHER NEURODEGENERATIVE DISEASES

Recent genetic evidence has indicated a critical role for inflammation in many neurodegenerative diseases including Multiple Sclerosis (MS), Huntington's disease (HD), Parkinson's disease (PD), Ischemia, traumatic brain injury (TBI), and Parkinson's disease (PD) (Dzamko et al., 2015; Baranzini and Oksenberg, 2017). A common link between these disorders is chronic activation of the innate immune system through specific activation of resident glial cells, release of inflammatory mediators, and the potential for recruitment of peripheral immune cells. While the specifics of immune activation vary between disorders, due to the pathogenic environment, it is clear that inflammation can play both a beneficial and harmful role in these other neurodegenerative diseases as well. Based on the initial trigger (i.e., alpha-synuclein in PD, ROS in Ischemia) chronic immune signaling can lead to neurotoxicity, increased oxidative stress and synaptic and neuronal death (Stephenson et al., 2018; Hassanzadeh and Rahimmi, 2019). However, immune activation can also be beneficial, resulting in the clearance of cell debris and aggregated/misfolded proteins, in the consolidation of inflammation, and in the mediation of cellular repair.

For example, MS is an autoimmune demyelinating disease of the CNS. While chronic immune activity is responsible for neurodegeneration in MS, evidence has also illustrated that inflammation is necessary for clearance of blood-borne inflammatory cells via emigration or in situ apoptosis. Proinflammatory cytokines, such as IFNγ and TNFα, promote in situ apoptosis of infiltrating T cells, as well as remyelination. Further, macrophages are critical in phagocytosing myelin debris in situ highlighting the beneficial immune activities in MS (Furlan et al., 2001).

Following brain injury, such as TBI and ischemic stroke, microglia actively promote injury-induced neurogenesis via production of insulin—like growth factor—1, which suppresses apoptosis and increases proliferation and differentiation of neural stem cells (Thored et al., 2009). Further, microglial activation aids in the consolidation of injured tissue and resultant inflammation, thereby limiting the spread of damage (Kitamura et al., 2009; Thored et al., 2009; Cunha et al., 2018). During PD, alpha-synuclein activates microglia, resulting in excessive release of pro-inflammatory mediators and an overactivation of the phagocytic pruning pathway on dopamine neurons (De Virgilio et al., 2016). Simultaneously, anti-inflammatory microglia are responsible for cytokine cleanup and phagocytosis of extracellular alpha-synuclein (Ferreira and Romero-Ramos, 2018). While it is clear the neuroinflammation can lead to disease progression, the beneficial aspects of inflammation remain critical to the underlying repair and clearance pathways in disorders of the CNS.

CONCLUSION

The genetic, cellular, and molecular changes associated with AD provide strong support for an innate immune contribution to disease pathology (Kim et al., 2018). However, which aspects of this contribution are positive or negative is still up for debate. In this review, we propose that there is a delicate balance involved in the innate immune response to AD, which can provide beneficial or detrimental effects. We suggest that some aspects of inflammation in AD are necessary and beneficial and are capable of restricting or preventing AD pathology. By harnessing the benefits provided by the AD immune reaction, we can work to find successful treatments for AD. For too long researchers have fixated on the negative consequences of microgliosis and astrogliosis, broadly categorizing glial cells as...
“reactive” or “activated.” However, recent genetic and cellular data has highlighted the extreme heterogeneity of glial cells, and the spectrum on which they function. Furthermore, while we have focused on the involvement of the innate immune system, substantial evidence suggests that the adaptive immune system also plays a role in pathology which is an area requiring further study (Sommer et al., 2017).

While it is clear that inflammation contributes to AD pathogenesis, it is too broad a word to describe the amalgam of innate immune mechanisms that arise during disease. Microgliosis involves phagocytosis of amyloid plaques and dysfunctional synapses, as well as the increased expression of complement proteins for neuronal pruning, and the release of trophic factors for cell plasticity and growth. Conversely, microgliosis increases quantities of cytokine and chemokines which can become toxic and harmful to neuronal cells. Astroglial reaction can also be beneficial, resulting in propagation of calcium currents for enhanced signal transduction and enhanced repair and protection. On the other hand, excessive astrogliosis may result in the increase of toxic species. It is very clear that neuroinflammation is heavily involved in AD pathogenesis, but a more precise understanding of the AD-specific immune reaction is critical to our developing effective therapeutics for AD (Figure 2).

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by NIH grant R01NS096275 (Y-ML), RFIAG057593 (Y-ML), the JPB Foundation (Y-ML), the MetLife Foundation (Y-ML), Cure Alzheimer’s Fund (Y-ML), The Edward and Della L. Thome Memorial Foundation (Y-ML), and Coins for the Alzheimer’s Research Trust (Y-ML). The Authors acknowledge the MSK Cancer Center Support Grant/Core Grant (Grant P30 CA008748), Mr. William H. Goodwin and Mrs. Alice Goodwin and the Commonwealth Foundation for Cancer Research, the Experimental Therapeutics Center of MSKCC, and the William Randolph Hearst Fund in Experimental Therapeutics.

REFERENCES

Abbas, N., Bednar, I., Mix, E., Marie, S., Paterson, D., Ljungberg, A., et al. (2002). Up-regulation of the inflammatory cytokines IFN-gamma and IL-12 and down-regulation of IL-4 in cerebral cortex regions of APP(SWE) transgenic mice. J. Neuroimmunol. 126, 50–57.

Adams, K. L., and Gallo, V. (2018). The diversity and disparity of the glial scar. Nat. Neurosci. 21, 9–15. doi: 10.1038/s41593-017-0033-9

Aikawa, T., Holm, M. L, and Kanekiyo, T. (2018). ABCA7 and pathogenic pathways of Alzheimer’s disease. Brain Sci. 8:E27. doi: 10.3390/brainsci8020027

Akira, S., Uematsumo, S., and Takeuchi, O. (2006). Pathogen recognition and innate immunity. Cell 124, 783–801. doi: 10.1016/j.cell.2006.02.015

Albeni, B. C., and Mattson, M. P. (2000). Evidence for the involvement of TNF and NF-kB in hippocampal synaptic plasticity. Synapse 35, 151–159.

Allen, N. J., and Eroglu, C. (2017). Cell biology of Astrocyte-synapse interactions. Neuron 96, 697–708. doi: 10.1016/j.neuron.2017.09.056

Alonso, R., Pisa, D., Marina, A. I., Morato, E., Rabano, A., and Carrasco, L. (2014). Fungal infection in patients with Alzheimer's disease. J. Alzheimer Dis. 41, 301–311. doi: 10.3233/JAD-132681

Alzheimer’s Association, (2015). 2015 Alzheimer’s disease facts and figures. Alzheimers Dement. 11, 332–384. doi: 10.1016/j.jalz.2015.02.003

Anderson, M. A., Ao, Y., and Sofroniew, M. V. (2014). Heterogeneity of reactive astrocytes. Neurosci. Lett. 565, 23–29. doi: 10.1016/j.neulet.2013.12.030

Anderson, M. A., Burda, J. E., Ren, Y., Ao, Y., O’Shea, T. M., Kawaguchi, R., et al. (2014). Astrocyte scar formation aids central nervous system axon regeneration. Science 346, 195–200. doi: 10.1038/nature17623

Apelt, J., and Schliebs, R. (2001). Beta-amyloid-induced gial expression of both pro- and anti-inflammatory cytokines in cerebral cortex of aged transgenic Tg2576 mice with Alzheimer plaque pathology. Brain Res. 894, 21–30.

Araque, A., Parpura, V., Sanzgiri, R. P., and Haydon, P. G. (1999). Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci. 22, 208–215. doi: 10.1016/S0166-2236(98)01349-6

Arcuri, C., Mecca, C., Bianchi, R., Giambanco, I., and Donato, R. (2017). The pathophysiological role of microglia in dynamic surveillance, phagocytosis and structural remodeling of the developing CNS. Front. Mol. Neurosci. 10:191. doi: 10.3389/fnmol.2017.00191

Arnusch, C. J., Branderhorst, H., de Kruijff, B., Liskamp, R. M., Breukink, E., and Pieters, R. J. (2007). Enhanced membrane pore formation by multimeric/oligomeric antimicrobial peptides. Biochemistry 46, 13437–13442. doi: 10.1021/bi7015553

Asselineau, D., Benihassen, K., Arosio, B., Mari, D., Ferri, E., Casati, M., et al. (2015). Interleukin-10 Production in response to amyloid-β differs between slow and fast decliners in patients with Alzheimer’s disease. J. Alzheimer Dis. 46, 837–842. doi: 10.3233/JAD-142832

Attwell Buchan, A. M., Charpak, S., Lauritzen, M., Macvicar, B. A., and Newman, E. A. (2010). Glial and neuronal control of brain blood flow. Nature 468, 232–243. doi: 10.1038/nature09613

Balin, B. J., Gerard, H. C., Arking, E. J., Appelt, D. M., Brangan, P. J., Abrams, J. T., et al. (1998). Identification and localization of Chlamydia pneumoniae in the Alzheimer’s brain. Med. Microbiol. Immunol. 187, 23–42.

Baranowska-Bik, A., Bik, W., Wolinska-Witort, E., Martyńska, L., Chimliowska, M., and Barciokwska, M. (2008). Plasma beta amyloid and cytokine profile in women with Alzheimer’s disease. Neuro. Endocrinol. Lett. 29, 75–79.

Baranizini, E., and Oksenberg, J. R. (2017). The genetics of multiple sclerosis: from pathogenesis to therapy. Trends Gene. 33, 960–970. doi: 10.1016/j.tig.2017.09.004

Bard, F., Barbour, F., Cannon, C., Barretto, R., Fox, M., Games, D., et al. (2003). Epitope and isotype specificities of antibodies to beta-amyloid peptide for protection against Alzheimer’s disease-like neuropathology. Proc. Natl. Acad. Sci. U.S.A. 100, 2023–2028. doi: 10.1073/pnas.0436286100

Baruch, K., Deczkowska, A., David, E., Castellano, J. M., Miller, O., Kertser, A., et al. (2014). Aging-induced type I interferon response at the choroid plexus negatively affects brain function. Science 346, 89–93. doi: 10.1126/science.1259245

Bazargani, N., and Attwell, D. (2016). Astrocyte calcium signaling: the third wave. Nat. Neurosci. 19, 182–189. doi: 10.1038/nn.4201

Ben Haim, L., and Rowitch, D. H. (2017). Functional diversity of astrocytes in neural circuit regulation. Nat. Rev. Neurosci. 18, 31–41. doi: 10.1038/nrn.2016.159

Benzing, W. C., Wujek, J. R., Ward, E. K., Shaffer, D., Ashe, K. H., Younkin, S. G., et al. (1999). Evidence for glial-mediated inflammation in aged APP(SW) transgenic mice. J. Alzheimer Dis. 21, 93ñ15. doi: 10.1038/s41593-017-0033-9

Berlau, D. J., Corrada, M. M., Head, E., and Kawas, C. H. (2009). APOE 2 is a contribution to the work, and approved it for publication.
differentiation in neonatal subventricular zone cell cultures. Stem Cells 26, 2361–2371. doi: 10.1038/ stemcells.2007-0014
Bertram, L., Lange, C., Mullin, K., Parkinson, M., Hsiao, M., Hogan, M. F., et al. (2008). Genome-wide association analysis reveals putative Alzheimer's disease susceptibility loci in addition to APOE. Am. J. Hum. Genet. 83, 623–632. doi: 10.1016/j.ajhg.2008.03.008
Biogen (2019). Biogen: Aducanumab Update. Cambridge, MA: Biogen.
Bis, J. C., Jian, X., Kunkle, B. W., Chen, Y., Hamilton-Nelson, K. L., Bush, W. S., et al. (2018). Whole exome sequencing study identifies novel rare and common Alzheimer’s-Associated variants involved in immune response and transcriptional regulation. Mol. Psychiatry 1–17. doi: 10.1038/s41380-018-0112-7
Block, M. L., Zecca, L., and Hong, J. S. (2007). Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat. Rev. Neurosci. 8, 57–69. doi: 10.1038/nn2038
Bollmann, L., Koser, D. E., Shahapure, R., Gautier, H. O., Holzapfel, G. A., Scarcelli, M., et al. (2007). Microglia-mediated neurotoxicity: transforming growth factor beta in Alzheimer’s disease. Clin. NEURON.2014.11.020
Boulanger, L. M. (2009). Immune proteins in brain development and synaptic plasticity. Neuron 64, 93–109. doi: 10.1016/J.NEURON.2009.09.001
Bradshaw, E. M., Chibnuk, L. B., Keenan, B. T., Ottoboni, L., Raj, T., Tang, A., et al. (2013). CD33 Alzheimer’s disease locus: altered monocyte function and amyloid biology. Nat. Neurosci. 16, 848–850. doi: 10.1038/nn.3435
Brosser, F., Krauthausen, M., Kummer, M., and Heneka, M. T. (2014). Body fluid cytokine levels in mild cognitive impairment and Alzheimer’s disease: a comparative overview. Mol. Neurobiol. 50, 534–544. doi: 10.1007/s12035-014-8657-1
Bu, G. (2009). Apolipoprotein E and its receptors in Alzheimer’s disease: pathways, pathogenesis and therapy. Nat. Rev. Neurosci. 10, 333–344. doi: 10.1038/nn2620
Burns, A., Rosser, M., Hecker, J., Gauthier, S., Petit, H., Möller, H. J., et al. (1999). The effects of donepezil in Alzheimer’s disease - results from a multinational trial. Dement. Geriatr. Cogn. Disord. 10, 237–244. doi: 10.1159/000017126
Calsonaro, L., and Edison, P. (2016). Neuroinflammation in Alzheimer’s disease: current evidence and future directions. Alzheimers Dement. 12, 719–732. doi: 10.1016/j.jalz.2016.02.010
Cao, J., Hou, J., Peng, J., and Cai, D. (2018). Advances in developing novel therapeutic strategies for Alzheimer’s disease. Mol. Neurodegener. 13, 64. doi: 10.1186/s13024-018-0299-8
Cao, W., and Zheng, H. (2018). Peripheral immune system in aging and Alzheimer’s disease. Mol. Neurodegener. 13:51. doi: 10.1186/s13024-018-0284-2
Carassuollo, M. M., Belbin, O., Hunter, T. A., Ma, L., Bisceglio, G. D., Zou, F., et al. (2011). Replication of EPHA1 and CD33 associations with late-onset Alzheimer’s disease: a multi-centre case-control study. Mol. Neurodegener. 6:54. doi: 10.1186/1750-1266-6-54
Ceyzeriat, K., Abjej, L., de Sauvage, M. A., Ben Haim, L., and Escartin, C. (2016). The complex STATs of astrocyte reactivity: how are they controlled and common Alzheimer's-Associated variants involved in immune response and transcriptional regulation. Mol. Psychiatry 1–17. doi: 10.1038/s41380-018-0112-7.
de Craen, J., Gussenkoo, J., Vrijssen, B., and Westendorp, R. G. (2005). Meta-analysis of nonsteroidal antiinflammatory drug use and risk of dementia. *Am. J. Epidemiol.*, 161, 114–120. doi: 10.1093/aje/kwi029

De Virgilio, A., Greco, A., Fabbrini, G., Inghilleri, M., Rizzo, M. I., Gallo, A., et al. (2016). Parkinson’s disease: Autoimmunity and neuroinflammation. *Autoimmun. Rev.*, 15, 1005–1011. doi: 10.1016/j.autrev.2016.07.022

de Weer, N. A., Vivian, J. P., Nguyen, T. K., Mangan, N. E., Gould, J. A., Braniff, S. J., et al. (2013). Structural basis of a unique interferon-β signaling axis mediated via the receptor IFNAR1. *Nat. Immunol.*, 14, 901–907. doi: 10.1038/ni.2667

Deming, Y., Filippello, F., Cignarella, F., Cantoni, C., Hsu, S., Mikessell, R., et al. (2019). The MS4A gene cluster is a key modulator of soluble TREM2 and Alzheimer’s disease risk. *Sci. Transl. Med.*. 11:eaaau2291

Dietr, E. R., Danis, B., Lamberty, V., and Foerch, P. (2014). Peripheral administration of an anti-TNF-α receptor fusion protein counteracts the amyloid induced elevation of hippocampal TNF-α levels and memory deficits in mice. *Neurochem. Int.* 72, 10–13. doi: 10.1016/J.NEUNI.2014.04.001

DeTure, M. A., and Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer’s disease. *Mol. Neurodegener.* 14,32. doi: 10.1186/s13024-019-0133-5

Dewapriya, P., Li, Y. X., Himaya, S. W. A., Pangusteti, R., and Kim, S. K. (2013). Neurocholinin A suppresses amyloid-β-oligomer-induced microglia activation and thereby protects PC-12 cells from inflammation-mediated toxicity. *Neuro. Toxicol.* 35, 30–40. doi: 10.1016/j.neuro.2012.12.004

Do, R. S., Thomas, R. G., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S., et al. (2014). Phase 3 trials of solanezumab for mild-to-moderate Alzheimer’s disease. *Doody, R. S., Thomas, R. G., Farlow, M., Iwatsubo, T., Vellas, B., Joffe, S., et al.* (2016). *Alzheimer’s disease: targeting the cholinergic system. *Curr. Neuropharmacol.* 14, 101–115.

Dolmanger, R. S., Jaumouille, V., and Grinstein, S. (2012). The cell biology of phagocytosis. *Annu. Rev. Pathol.* 7, 61–98. doi: 10.1146/annurev-pathol-011811-132445

Folch, J., Petrov, D., Etcheto, M., Abad, S., Sanchez-Lopez, E., Garcia, M. L., et al. (2016). Current research therapeutic strategies for Alzheimer’s disease treatment. *Neural. Plast.* 2016:8501693. doi: 10.1155/2016/8501693

Fontainhas, M., Wang, M., Liang, K. J., Chen, S., Mettu, P., Damani, M., et al. (2011). Microglial morphology and dynamic behavior is regulated by ionotropic glutamatergic and GABAergic neurotransmission. *PLoS One* 6:e19573. doi: 10.1371/journal.pone.0019573

Foster, E. M., Dangla-Valls, A., Lovestone, S., Ribe, E. M., and Buckley, N. J. (2019). Clustering in Alzheimer’s disease: mechanisms, genetics, and lessons from other pathologies. *Front. Neurosci.* 13:164. doi: 10.3389/fnins.2019.00116

Frost, R., and Li, Y. M. (2017). The role of astrocytes in amyloid production and Alzheimer’s disease. *Open Biol.* 7:170228. doi: 10.1098/rsob.170228

Fultz, M. J., Barber, S. A., Diefenbach, C. W., and Vogel, S. N. (1993). Induction of IFN-gamma in macrophages by lipopolysaccharide. *Int. Immunol.* 5, 1383–1392. doi: 10.1093/intimm/5.11.1383

Furlan, R., Brambilla, E., Ruffini, F., Poliani, P. L., Bergami, A., Marconi, P. C., et al. (2001). Intrathecal delivery of IFN-gamma protects C57BL/6 mice from chronic-progressive experimental autoimmune encephalomyelitis by increasing apoposis of central nervous system-infiltrating lymphocytes. *J. Immunol.* 167, 1821–1829. doi: 10.4049/jimmunol.167.3.1821

Gabbita, S. P., Johnson, M. F., Kobritz, N., Eslami, P., Poteshkina, A., Varadarajan, S., et al. (2015). Oral TNFα modulation alters neutrophil infiltration, improves cognition and diminishes tau and amyloid pathology in the 3xTgAD mouse model. *PLoS One*10:e0137305. doi: 10.1371/journal.pone.0137305

Galimberti, D., Venturelli, E., Fsnogli, C., Guidi, I., Villa, C., Bergamaschi, L., et al. (2008). Intrathecal levels of IL-6, IL-11 and LIF in Alzheimer’s disease and frontotemporal lobar degeneration. *J. Neurool.* 255, 539–544. doi: 10.1007/s00415-008-0737-6

Gatz, M., Reynolds, C. A., Fratiglioni, L., Johansson, B., Mortimer, J. A., Berg, S., et al. (2006). Role of genes and environments for explaining Alzheimer disease. *Arch. Gen Psychiatry* 63, 168–174. doi: 10.1001/archpsyc.63.2.168

Ghosh, S., Wu, M. D., Shafel, S. S., Kyrkanides, S., LaFerla, F. M., Osloucha, J. A., et al. (2013). Sustained interleukin-1β overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer’s mouse model. *J. Neurosci.* 33, 5053–5064. doi: 10.1523/JNEUROSCI.4361-12.2013

Gilman, S., Koller, M., Black, R. S., Jenkins, L., Griffith, S. G., Fox, N. C., et al. (2005). Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. *Neurology* 64, 1553–1562. doi: 10.1223/01.WNL.0000194694.31086.c2

Ginko, R., and Prinz, M. (2015). Origin of microglia: current concepts and past controversies. *Cold Spring Harb. Perspect. Biol.* 7:e020537. doi: 10.1101/cshperspect.a020537

Ginko, R., Lim, S., Hoefel, G., Low, D., and Huber, T. (2013). Origin and differentiation of microglia. *Front. Cell. Neurosci.* 7:45. doi: 10.3389/fncel.2013.00045

Goshen, L., Kreisel, T., Ounallah-Saad, H., Renbaum, P., Zalzstein, Y., Ben-Hur, T., et al. (2007). A dual role for interleukin-1 in hippocampal-dependent memory processes. *Psychoneuroendocrinology* 32, 1106–1115. doi: 10.1016/j.psyneuen.2007.09.004

Gough, D. J., Messina, N. L., Clarke, C. J., Johnstone, R. W., and Levy, D. E. (2012). Constitutive Type 1 interferon modulates homeostatic balance through tonic signaling. *Immunity* 36, 166–174. doi: 10.1016/j.immuni.2012.01.011

Gratuze, M., Leyns, C. E. G., and Holtzman, D. M. (2018). New insights into the role of TREM2 in Alzheimer’s disease. *Mol. Neurodegener.* 13:66. doi: 10.1186/s13024-018-0298-9

Griciuc, A., Serrano-Pozo, A., Parrado, A. R., Lesinski, A. A., Asselin, C. N., et al. (2013). Alzheimer’s disease risk gene CD33 inhibits microglial uptake of amyloid beta. *Neuron* 78, 631–643. doi: 10.1016/j.neuron.2013.04.014

Griffin, W. S., Stanley, L. C., Ling, C., White, L., MacLeod, V., Perrot, I. L., et al. (1989). Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer disease. *Proc. Natl. Acad. Sci. U.S.A.* 86, 7611–7615. doi: 10.1073/PNAS.86.19.7611
Guerreiro, R., Wojtas, A., Bras, J., Carraquillo, M., Rogaeva, E., Majounie, E., et al. (2013). TREM2 variants in Alzheimer’s disease. *Neurol. J. Med.* 368, 117–127. doi: 10.1056/NEJMoa1211851

Guillot-Sestier, M. V., Doty, K. R., Gate, D., Gregorius, J. J., Leung, B. P., and Bauer, J. (1996). Occurrence of interleukin-6 in cortical plaques of Alzheimer’s disease patients may precede transformation of diffuse into Neuritic Plaques. *Ann. N. Y. Acad. Sci.* 777, 205–212. doi: 10.1111/j.1749-6632.1996.tb4420.x

Itagaki, S., McGeer, P. L., Akiyama, H., Zhu, S., and Selkoe, D. (1989). Relationship of microglia and astrocytes to amyloid deposits of Alzheimer’s disease. *J. Neuroimmunol.* 24, 173–182
Kitamura, Y., Yanagisawa, D., Takata, K., and Taniguchi, T. (2009). Neuroprotective function in brain microglia. *Curr. Anaeth. Crit. Care* 20, 142–147.

Kleinberger, G., Yamanishi, Y., Suárez-Calvet, M., Czirr, E., Lohmann, E., Cuver, E., and et al. (2014). TREM2 mutations implicated in neurodegeneration impair cell surface transport and phagocytosis. *Sci. Transl. Med.* 6:243ra86. doi: 10.1126/scitranslmed.3009093

Kocur, M., Schneider, R., Pultm, A. K., Bauer, J., Kroppe, S., Gliem, M., et al. (2015). IFNβ secreted by microglia mediates clearance of myelin debris in CNS autoimmunity. *Acta Neuropathol. Commun.* 3:20. doi: 10.1186/s40478-015-0192-4

Kraft, W., Hu, X., Yoon, H., Yan, P., Xiao, Q., Wang, Y., et al. (2013). Attenuating astrocyte activation accelerates plaque pathology in APP/PS1 mice. *FASEB J.* 27, 187–198. doi: 10.1096/fj.0.12-208660

Krstic, D., Madhusudan, A., Dohner, J., Vogel, P., Notter, T., Imhof, C., et al. (2012). Systemic immune challenges trigger and drive Alzheimer-like neuropathology in mice. *J. Neuroinflamm.* 9:151. doi: 10.1186/1744-8013-9-151

Lajaunias, F., Dayer, J. M., and Chizzolini, C. (2005). Constitutive repressor activity of CD33 on human monocytes requires sialic acid recognition and phosphoinositide 3-kinase-mediated intracellular signaling. *Eur. J. Immunol.* 35, 243–251. doi: 10.1002/eji.200425273

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., et al. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer’s disease. *Nat. Genet.* 45, 1452–1458. doi: 10.1038/ng.2902

Lassmann, H. (1998). Neuropathology in multiple sclerosis: new concepts. *Mult. Scler.* 4, 93–98.

Latz, E., Xiao, T. S., and Stutz, A. (2013).Activation and regulation of the inflammasomes. *Nat. Rev. Immunol.* 13, 397–411. doi: 10.1038/nri3452

Lauro, C., Catalano, M., Trettel, F., and Limatola, C. (2015). Fractalkine in the nervous system: neuroprotective or neurotoxic molecule? *Ann. N. Y. Acad. Sci.* 1351, 141–148. doi: 10.1111/nyas.12805

Lawson, J. F., Fisher, V. H., Dri, P., and Gordon, S. (1990). Heterogeneity in the distribution and morphology of microglia in the normal adult mouse brain. *Neuroscience* 39, 151–170. doi: 10.1016/0306-4522(90)90229-W

Lee, S., Zimmerman, M. E., Narkhede, A., Nasrabady, S. E., Tosto, G., Meier, I. B., et al. (2018). White matter hyperintensities and the mediating role of cerebral amyloid angiopathy in dominantly-inherited Alzheimer’s disease. *PLoS One* 13:e0195838. doi: 10.1371/journal.pone.0195838

Letteneur, L., Peres, K., Fleury, H., Garrigue, I., Barberger-Gateau, P., Helmer, A., et al. (2017). IFNβ and Exon 2 splicing.

Liu, T., Zhang, L., Joo, D., and Sun, S. C. (2017). NF-kB signaling in inflammation. *Signal Trans. Target. Ther.* 2:17023. doi: 10.1038/sigtrans.2017.23

Liu, Y., Walter, S., Stagi, M., Cheny, D., Letiembre, M., Schulz-Schaeffer, W., et al. (2005). LPS receptor (CD14): a receptor for phagocytosis of Alzheimer’s amyloid peptide. *Brain* 128, 1778–1789. doi: 10.1093/brain/awh531

Long, J. M., and Holtzman, D. M. (2019). Alzheimer disease: an update on pathobiology and treatment strategies. *Cell* 179, 312–339. doi: 10.1016/j.cell.2019.09.001

Louveau, A., Harris, T. H., and Kipnis, J. (2015). Revisiting the mechanisms of CNS immune privilege. *Trends Immunol.* 36, 569–577. doi: 10.1016/J.TI.2015.08.006

Lue, L. F., Brachova, L., Cisin, W. H., and Rogers, J. (1996). Inflammation, A beta deposition, and neurofibrillary tangle formation as correlates of Alzheimer's disease neurodegeneration. *J. Neuroexp. Exp. Neurol.* 55, 1083–1088.

Ludecking, E. K., DeKosky, S. T., Mehdi, H., Ganguli, M., and Kambhoi, M. I. (2000). Analysis of genetic polymorphisms in the transforming growth factor-beta1 gene and the risk of Alzheimer’s disease. *Hum. Genet.* 106, 565–569.

Ma, J., Yu, J. T., and Tan, L. (2015). MS4A4 cluster in Alzheimer’s disease. *Mol. Neurobiol.* 51, 1240–1248. doi: 10.1007/s12052-014-8800-z

Ma, Q., Zhao, Z., Sagare, A. P., Wu, Y., Wang, M., Owens, N. C., et al. (2018). Blood-brain barrier-associated pericytes internalize and clear aggregated amyloid-beta42 by LRPI-dependent apolipoprotein E isospecific mechanism. *Mol. Neurodegener.* 13:57. doi: 10.1186/s13024-018-0286-0

Main, B. S., Zhang, M., Brody, K. M., Kirby, F. J., Crack, P. J., and Taylor, J. M. (2017). Type-I interferons mediate the neuroinflammatory response and neurotoxicity induced by rodent. *J. Neurochem.* 141, 75–85. doi: 10.1111/jnc.13940

Malarkey, E. B., and Parpura, V. (2008). Mechanisms of glutamate release from astrocytes. *Neurochem. Int.* 52, 142–154. doi: 10.1016/j.neuint.2007.06.005

Malik, M., Simpson, J. F., Parikh, I., Wilfred, B. R., Fardo, D. W., Nelson, P. T., et al. (2013). CD33 Alzheimer’s disease risk-altering polymorphism, CD33 expression, and Exon 2 splicing. *J. Neurosci.* 33, 13320–13325. doi: 10.1523/JNEUROSCI.1224-13.2013

Manouchehrinia, A., and Constantinescu, C. S. (2012). Cost-effectiveness of disease-modifying therapies in multiple sclerosis. *Curr. Neurol. Neurosci. Rep.* 12, 592–600. doi: 10.1007/s11910-012-0291-6

Marr, R. A., Rockenstein, E., Mukherjee, A., Kindy, M. S., Hersh, L. B., Gage, F. H., et al. (2003). Neprilysin gene transfer reduces human amyloid pathology in transgenic mice. *J. Neurosci.* 23, 1992–1996.

Martineau, M., Parpura, V., and Moteth, J. P. (2014). Cell-type specific mechanisms of D-serine uptake and release in the brain. *Front. Syn. Neurosci.* 6:12. doi: 10.3389/fnsyn.2014.00012

Matovcich-Natan, O., Matcovitch, N., Galis, A., Zargar, D. M., et al. (2015). Neprilysin gene transfer reduces human amyloid pathology in transgenic mice. J. Neurosci. 23, 1992–1996.

McComb, C., Pardi, M., Parpura, V., and Mothet, J. P. (2014). Cell-type specific mechanisms of D-serine uptake and release in the brain. *Front. Syn. Neurosci.* 6:12. doi: 10.3389/fnsyn.2014.00012

McGeer, L., and McGeer, E. G. (1995). The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res. Rev.* 21, 195–218.
Frost et al.  

Neuroinflammation in Alzheimer’s Disease

McQuade, A., and Blutront-Jones, M. (2019). Microglia in Alzheimer’s disease: exploring how genetics and phenotype influence risk. *J. Mol. Biol.*, 431, 1805–1817. doi: 10.1016/j.jmb.2019.01.045

Mezyk-Kopec, R., Bzowska, M., Stalinska, K., Chelmicki, T., Podkalicki, M., Jcha, J., et al. (2009). Identification of ADAM10 as a major TNF sheddase in ADAM17-deficient fibroblasts. *Cytokine*, 46, 309–315. doi: 10.1016/j.cytok.2009.03.002

Michaud, J. P., Halle, M., Lampron, A., Theriault, P., Prefontaine, P., Filali, M., et al. (2013). Toll-like receptor 4 stimulation with the detoxified ligand monophosphoryl lipid A improves Alzheimer’s disease-related pathology. *Proc. Natl. Acad. Sci. U.S.A.* 110, 1940–1946. doi: 10.1073/pnas.1215165110

Miyake, K. (2007). Innate immune sensing of pathogens and danger signals by cell surface Toll-like receptors. *Semin. Immunol.*, 19, 3–10. doi: 10.1016/j.smim.2006.12.002

Moir, R. D., Lathe, R., and Tanzi, R. E. (2018). The antimicrobial protection of microglia: an essential link between degeneration and regeneration. *Acta Neuropathol.* 136, 1–17. doi: 10.1007/s00401-018-1861-8

Mrak, R. E. (2012). Microglia in Alzheimer Brain: a neuropathological perspective. *Nat. Rev. Neurosci.*, 13:24. doi: 10.1186/s13024-018-0266-4

Ng, C. T., Mendoza, J. L., Garcia, K. C., and Oldstone, M. B. (2016). Alpha and beta isoforms determined by the amino-terminal domain. *Biochemistry*, 55, 13666–13672. doi: 10.1021/bi000099m

Najm, R., Jones, E. A., and Huang, Y. (2019). Apolipoprotein E4, inhibitory network dysfunction, and Alzheimer’s disease. *Mol. Neurodegener.* 14:24. doi: 10.1186/s13234-019-0324-6

Narahasky, S. E., Rizvi, B., Goldman, J. E., and Brickman, A. M. (2018). White matter changes in Alzheimer’s disease: a focus on myelin and oligodendrocytes. *Acta Neurochir. (Wien)* 264, 1161–1171. doi: 10.1007/s00701-018-3625-4

Rangaraju, S., Dammer, E. B., Raza, S. A., Gao, T., Xiao, H., Betarbet, R., et al. (2018a). Quantitative proteomics of acutely-isolated mouse microglia identifies novel immune-Alzheimer’s disease-related proteins. *Mol. Neurodegener.* 13:34. doi: 10.1186/s13234-018-0266-4

Rangaraju, S., Dammer, E. B., Raza, S. A., Rathakrishnan, P., Xiao, H., Gao, T., et al. (2018b). Identification and therapeutic modulation of a pro-inflammatory subset of disease-associated-microglia in Alzheimer’s disease. *Mol. Neurodegener.* 13:24. doi: 10.1186/s13234-018-0254-8

Ransohoff, R. M., and Cardona, A. E. (2010). The myeloid cells of the central nervous system parenchyma. *Nature*, 468, 253–262. doi: 10.1038/nature09615

Reisberg, B., Doody, R., Stoffler, A., Schmitt, F., Ferris, S., and Mohs, H. J. (2006). A 24-week open-label extension study of memantine in moderate to severe Alzheimer disease. *Arch. Neurol.*, 63, 49–54. doi: 10.1001/archneur.63.1.49

Riedel, B. C., Thompson, P. M., and Brinton, R. D. (2016). Age, APOE and sex: a comprehensive analysis of the relationship between BMI and risk of dementia in two million people over two decades: a retrospective cohort study. *Lancet Diabetes Endocrinol.*, 4, 431–436. doi: 10.1016/s2213-8587(15)00039-9

Robel, S., Sori, T., Zoubaa, S., Schlegel, J., Sirko, S., Faissner, A., et al. (2009). Conditional deletion of beta1-integrin in astroglia causes partial reactive gliosis. *GLIA*, 57, 1630–1647. doi: 10.1002/glia.20876

Rozenszajn, M. (2003). Pyk2 regulates multiple signaling events crucial for macrophage morphology and migration. *Proc. Natl. Acad. Sci. U.S.A.* 100, 10740–10745. doi: 10.1073/pnas.183438100

Rozenszajn, M. (2003). Pyk2 regulates multiple signaling events crucial for macrophage morphology and migration. *Proc. Natl. Acad. Sci. U.S.A.* 100, 10740–10745. doi: 10.1073/pnas.183438100

Robinson, D. R. (1983). Prostaglandins and the mechanism of action of anti-inflammatory drugs. *Am. J. Med.*, 75, 136–147. doi: 10.1016/0002-9343(83)90325-x

Rodriguez, J. J., Yeh, C. Y., Terzieva, S., Olabarria, M., Kulijewicz-Nawrot, M., and Verkhratsky, A. (2014). Complex and region-specific changes in...
astroglial markers in the aging brain. Neurobiol Aging. 35, 15–23. doi: 10.1016/j.neurobiolaging.2013.07.002

Rogers, J., Li, R., Mastroeni, D., Grover, A., Leonard, B., Ahern, G., et al. (2006). Peripheral clearance of amyloid beta peptide by complement C3-dependent adherence to erythrocytes. Neurobiol Aging. 27, 1733–1739. doi: 10.1016/j.neurobiolaging.2005.09.043

Russo, L., Caracciolo, L., Tweedie, D., Choi, S. H., Greig, N. H., Barlati, S., et al. (2012). 3,6′-Dithiothalidomide, a new TNF-α synthesis inhibitor, attenuates the effect of Aβ1-42 intracerebroventricular injection on hippocampal neurogenesis and memory deficit. J. Neurochem. 122, 1181–1192. doi: 10.1111/j.1471-4159.2012.07846.x

Sahleender, D. A., Sartchouk, I., and Volterra, A. (2014). What do we know about gliotransmitter release from astrocytes? Philos. Trans. R. Soc. B Biol Sci. 369:20130592. doi: 10.1098/rstb.2013.0592

Sao, T., Yoshino, Y., Yamazaki, K., Oraki, Y., Mori, Y., Ochi, S., et al. (2018). MEFS2 mRNA expression and cognitive function in Japanese patients with Alzheimer’s disease. Psychiatr. Clin. Neurosci. 72, 160–167. doi: 10.1111/pcn.12618

Satoh, J. I., Kino, Y., Yanaihu, M., Tosa, Y., Sakai, K., Ishida, T., et al. (2017). Microglia express AB13 in the brains of Alzheimer’s disease and Nasu-Hakola disease. Intractable Rare Dis. Res. 6, 262–268. doi: 10.1523/irdr.2017.010773

Schafer, D. P., Lehrman, E. K., Kautzman, A. G., Koyama, R., Mardinly, A. R., Schreiber, G., and Piehler, J. (2015). The molecular basis for functional plasticity and support and shape the brain in health, disease, and aging? J. Neurochem. 36, 139–149. doi: 10.1016/j.jnci.2015.01.002

Schwab, M. E. (1990). Myelin-associated inhibitors of neurite growth and regeneration in the CNS. Trends Neurosci. 13, 452–456. doi: 10.1016/0166-2236(90)90098-u

Schwartz, M., Kipnis, J., Rivest, S., and Prat, A. (2013). How do immune cells support and shape the brain in health, disease, and aging? J. Neurosci. 33, 17587–17596. doi: 10.1523/nersci.2013.12010

Sevigny, J., Chiao, P., Bussiere, T., Weinreb, P. H., Williams, L., Maier, M., et al. (2016). The antibody aducanumab reduces ABeta plaques in Alzheimer’s disease. Nature 537, 50–56. doi: 10.1038/nature19323

Shabab, T., Khababali, R., Moghadamtousi, S. Z., Kadir, H. A., and Mohan, G. (2017). Neuroinflammation pathways: a general review. Int. J. Neurosci. 127, 624–633. doi: 10.1080/00207454.2016.1212854

Shi, Y., and Holtzman, D. M. (2018). Interplay between innate immunity and neurodegeneration: a review. Curr. Neurol. Neurosci. Rep. 17:25. doi: 10.1007/s11910-017-0733-2

Schreiber, G., and Pfehrer, J. (2015). The molecular basis for functional plasticity in type I interferon signaling. Trends Immunol. 36, 139–149. doi: 10.1016/j.it.2015.01.002

Sofroniew, M. V. (2015). Astrocyte barriers to neurotoxic inflammation. Nat. Rev. Neurosci. 16, 249–263. doi: 10.1038/nrn3989

Sofroniew, M. V., and Vinters, H. V. (2010). Astrocytes: biology and pathology. Acta Neuropathol. 119, 7–35. doi: 10.1007/s00401-009-0619-8

St George-Hyslop, P. H., Myers, R. H., Haines, J. L., Farrer, L. A., Tanzi, R. E., Abé, K., et al. (1989). Familial Alzheimer’s disease: progress and problems. Neurobiol Aging. 10, 417–425.

Stamm, H., Klainguti, F., Grosshans, E., Muschhammer, J., Vettorazzi, E., Heuser, M., et al. (2018a). Immune checkpoints PVR and PVRL2 are prognostic markers in AML and their blockade represents a new therapeutic option. Oncogene 37, 5269–5280. doi: 10.1038/s41388-018-0288-y

Stamm, H., Wellbrock, J., and Fiedler, W. (2018b). Interaction of PVR/PVRL2 with TIGIT/DNAM-1 as a novel immune checkpoint axis and therapeutic target in cancer. Mammm. Genome 29, 694–702. doi: 10.1002/mmg2.13035-018-0301-5

Stephenson, J., Nutima, E., van der Valk, P., and Amor, S. (2018). Inflammation in CNS neurodegenerative diseases. Immunology 154, 204–219. doi: 10.1111/imm.12922

Suarez-Calvet, M., Morenas-Rodriguez, E., Kleinerger, G., Schlepckow, K., Araque Caballero, M. A., Franzemeier, N., et al. (2019). Early increase of CSF sTREM2 in Alzheimer’s disease is associated with tau-related-neurodegeneration but not with amyloid-beta pathology. Mol. Neurodegener. 14:1. doi: 10.1186/s13024-018-0301-5

Suresh, R., and Mosser, D. M. (2013). Pattern recognition receptors in innate immunity, host defense, and immunopathology. Adv. Physiol. Educ. 37, 284–291. doi: 10.1152/advan.00058.2013

Suzuki, A., Stern, S. A., Boxlagi, O., Huntley, G. W., Walker, R. H., Magistretti, P. J., et al. (2011). Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 144, 810–823. doi: 10.1016/j.cell.2011.02.018

Szelenyi, J. (2001). Cytokines and the central nervous system. Brain Res. Bull. 54, 329–338. doi: 10.1016/S0361-9230(01)00428-2

Takahashi, K., Prinz, M., Stagi, M., Checneva, O., and Neumann, H. (2007). TREM2-transduced myeloid precursors mediate nervous tissue debris clearance and facilitate recovery in an animal model of multiple sclerosis. PLoS Med. 4:e124. doi: 10.1371/journal.pmed.0040124

Tan, J., Town, T., Crawford, F., Mori, T., DelleDonne, A., Crescentini, R., et al. (2002). Role of CD40 ligand in amyloidosis in transgenic Alzheimer’s mice. Nat. Neurosci. 5, 1288–1293. doi: 10.1038/nn968

Tanzi, R. E. (2012). The genetics of Alzheimer disease. Cold Spring Harb. Perspect. Med. 2:a006296. doi: 10.1101/cshperspect.a006296

Tarkowski, E., Andreasen, N., Tarkowski, A., and Blennow, K. (2003). Intrathecal production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia. J. Clin. Immunol. 19, 223–230.
Tateno, H., Li, H., Schur, M. J., Bovin, N., Crocker, P. R., Wakarchuk, W. W., et al. (2007). Distinct endocytic mechanisms of CD22 (Siglec-2) and Siglec-F reflect roles in cell signaling and innate immunity. Mol. Cell. Biol. 27, 5699–5710. doi: 10.1128/MCB.00383-07

Thomas, J., and Grossberg, G. T. (2009). Memantine: a review of its safety and efficacy in treating Alzheimer’s disease and other dementias. Clin. Interv. Aging 4, 367–377.

Thome, D., Faridar, A., Beers, D. R., Thonhoff, J. R., Zhao, W., Wen, S., et al. (2018). Functional alterations of myeloid cells during the course of Alzheimer’s disease. Mol. Neurodegener. 13:61. doi: 10.1186/s13024-018-0293-1

Thored, P., Heldmann, U., Gomes-Leal, W., Gisler, R., Darsalia, V., Taneera, J., et al. (2017). Immunotherapy for neurodegenerative diseases: roles in cell signaling and innate immunity. Mol. Neurodegener. 14:20. doi: 10.1186/s13024-019-0323-7

Trapp, B. D., Wujek, J. R., Criste, G. A., Jalabi, W., Yin, X., Kidd, G. J., et al. (2014). Functional alterations of myeloid cells during the course of Alzheimer’s disease. Curr. Alzheimer Res. 11:6, 144ñ151. doi: 10.2174/15672050978602852

Wake, H., Moorhouse, A. J., Jinno, S., Kohsaka, S., and Nabetuka, 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. doi: 10.1523/JNEUROSCI.4363-08.2009

Walker, D. G., Ward, A. M., Serrano, G., Sue, L. I., Beach, T. G., and Lue, L. F. (2015). Association of CD33 polymorphism rs3865444 with Alzheimer’s disease pathway and CD33 expression in human cerebral cortex. Neurobiol. Aging 36, 571–582. doi: 10.1016/j.neurobiolaging.2014.09.023

Wang, H., Song, G., Chuang, H., Chiu, C., Abdelmalsoud, A., Ye, Y., et al. (2018). Portrait of glial scar in neurological diseases. Int. J. Immunopathol. Pharmacol. 31:2058783818804106. doi: 10.1177/0149207618804106

Wang, J., Li, Y., Wang, X., Chen, W., Sun, H., and Wang, J. (2014). Lipo-poly saccharide induces amyloid formation of antimicrobial peptide HAl-2. Biochem. Biophys. Acta 1838, 2910–2918. doi: 10.1016/j.bbamem.2014.07.028

Wang, M. M., Miao, D., Cao, X. P., Tan, L., and Tan, L. (2018). Inmate immune activation in Alzheimer’s disease. Ann. Transl. Med. 6, 177–177. doi: 10.21037/atm.2018.04.20

Wang, Y., Ulland, T. K., Ulrich, J. D., Song, W., Tzafiras, J. A., Hole, J. T., et al. (2016). TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. J. Exp. Med. 213, 667–675. doi: 10.1084/jem.20151948

Wanner, B., Anderson, M. A., Song, B., Levine, J., Fernandez, A., Gray-Thompson, Z., et al. (2013). Glial scar borders are formed by newly proliferated, elongated astrocytes that interact to corral inflammatory and fibrotic cells via STAT3-dependent mechanisms after spinal cord injury. J. Neurosci. 33, 12870–12886. doi: 10.1523/NEUROSCI.2112-13.2013

Ward, A., Crean, S., Mercaldi, C. J., Collins, J. M., Boyd, D., Cook, M. N., et al. (2012). Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer’s disease: a systematic review and meta-analysis. Neuroepidemiology 38, 1–17. doi: 10.1159/000330460

Ward, M., Himmelstein, D. S., Lancia, J. K., and Binder, L. I. (2012). Tau oligomers and tau toxicity in neurodegenerative disease. Biochem. Soc. Trans. 40, 667–671. doi: 10.1042/BST20120134

White, J. A., Manelli, A. M., Holmberg, K. H., Van Eldik, L. J., and LaDu, M. J. (2005). Differential effects of oligomeric and fibrillary amyloid-β42 on astrocyte-mediated inflammation. Neurobiol. Dis. 18, 459–465. doi: 10.1016/j.nbd.2004.12.013

Whitmer, R. A., Gustafson, D. R., Barrett-Conner, E., Haan, M. N., Gunderson, E. P., and Yaffe, K. (2008). Central obesity and increased risk of dementia more than three decades later. Neurology 71, 1057–1064. doi: 10.1212/0wan.0b013e31816915e5

Wiesner, J., and Vilcinskas, A. (2010). Antimicrobial peptides: the ancient arm of the human immune system. Virulence 1, 440–446. doi: 10.4161/viru.1.5.12983

Wilhelmsson, U., Bushong, E. A., Price, D. L., Smarr, B. L., Phung, V., Terada, M., et al. (2006). Redefining the concept of reactive astrocytes as cells that remain within their unique domains upon reaction to injury. Proc. Natl. Acad. Sci. U.S.A. 103, 17513–17518. doi: 10.1073/pnas.0602841103

Williams, M., Torres, S., Siedlak, S. L., Castellani, R. J., Perry, G., Smith, M. A., et al. (2013). Antimicrobial peptide beta-defensin-1 expression is upregulated within their unique domains upon reaction to injury. Proc. Natl. Acad. Sci. U.S.A. 103, 17513–17518. doi: 10.1073/pnas.0602841103

Woodcock, T., and Morganti-Kossmann, M. C. (2013). The role of markers of inflammation in traumatic brain injury. Front. Neuro. 4:18. doi: 10.3389/fneur.2013.00018

Woźniak, M. A., Mee, A. P., and Itzhaki, R. F. (2009). Herpes simplex virus type 1 DNA is located within Alzheimer’s disease amyloid plaques. J. Pathol. 217, 131–138. doi: 10.1002/path.2449

Wyse-Coray, T., Lin, C., Yan, F., Yu, G. Q., Rohde, M., McConlogue, L., et al. (2001). GliA/B promotes microglial amyloid-β clearance and reduces plaque burden in transgenic mice. Nat. Med. 7, 612–618. doi: 10.1038/87945

Xiang, X., Werner, G., Bohrmann, B., Liesz, A., Mazaheri, F., Capell, A., et al. (2016). TREM2 deficiency reduces the efficacy of immunotherapeutic amyloid clearance. EMBO Mol. Med. 8, 992–1004. doi: 10.15252/emmm.201606370

Yamada, J., Hayashi, Y., Jinnou, S., Wu, Z., Inoue, K., Kohsaka, S., et al. (2008). Reduced synaptic activity precedes synaptic stripping in vagal motoneurons after axotomy. Glia 56, 1448–1462. doi: 10.1002/glia.20711
Yamazaki, T., Masuda, J., Omori, T., Usui, R., Akiyama, H., and Maru, Y. (2009). EphA1 interacts with integrin-linked kinase and regulates cell morphology and motility. J. Cell Sci. 122(Pt 2), 243--255. doi: 10.1242/jcs.036467

Yeh, F. L., Wang, Y., Tom, I., Gonzalez, L. C., and Sheng, M. (2016). TREM2 Binds to Apolipoproteins, Including APOE and CLU/APOJ, and Thereby Facilitates Uptake of Amyloid-Beta by Microglia. Neuron 91, 328--340. doi: 10.1016/J.NEURON.2018.01.031

Yirmiya, R., and Goshen, I. (2011). Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain Behav. Immun. 25, 181--213. doi: 10.1016/j.bbi.2010.10.015

Yu, X., and Bellamkonda, R. V. (2001). Dorsal root ganglia neurite extension is inhibited by mechanical and chondroitin sulfate-rich interfaces. J. Neurosci. Res. 66, 303--310. doi: 10.1002/jnr.1225

Yuan, P., Condello, C., Keene, C. D., Wang, Y., Thomas Bird, D., Steven Paul, M., et al. (2016). TREM2 haplodeficiency in mice and humans impairs the microglia barrier function leading to decreased amyloid compaction and severe axonal dystrophy. Neuron 90, 724--739. doi: 10.1016/j.neuron.2016.05.003

Zhao, R., Hu, W., Tsai, J., Li, W., and Gan, W. B. (2017). Microglia limit the expansion of beta-amyloid plaques in a mouse model of Alzheimer's disease. Mol. Neurodegener. 12:47. doi: 10.1186/s13024-017-0188-6

Zhao, Y., Wu, X., Li, X., Jiang, L. L., Gui, X., Liu, Y., et al. (2018). TREM2 Is a receptor for beta-amyloid that mediates microglial function. Neuron 97:1023--e1031.e7. doi: 10.1016/j.neuron.2018.01.031

Zhao, Z., Sagare, A. P., Ma, Q., Halliday, M. R., Kong, P., Kistler, K., et al. (2015). Central role for PICALM in amyloid-beta blood-brain barrier transcytosis and clearance. Nat. Neurosci. 18, 978--987. doi: 10.1038/nn.4025

Zheng, C., Zhou, X. W., and Wang, J. Z. (2016). The dual roles of cytokines in Alzheimer's disease: update on interleukins, TNF-α, TGF-β and IFN-γ. Transl. Neurodegener. 5:7. doi: 10.1186/s40035-016-0054-4

Zheng, H., Liu, C. C., Atagi, Y., Chen, X. F., Jia, L., Yang, L., et al. (2016). Opposing roles of the triggering receptor expressed on myeloid cells 2 and triggering receptor expressed on myeloid cells-like transcript 2 in microglia activation. Neurobiol. Aging 42, 132--141. doi: 10.1016/j.neurobiolaging.2016.03.004

Zheng, L. S., Hitsuji, S., Kaneko, N., Takao, K., Miyakawa, T., Tanaka, Y., et al. (2014). Mechanisms for Interferon-α-induced depression and neural stem cell dysfunction. Stem Cell Rep. 3, 73--84. doi: 10.1016/j.stemcr.2014.05.015

Zhong, L., Wang, Z., Wang, D., Wang, Z., Martens, Y. A., Wu, L., et al. (2018). Amyloid-beta modulates microglial responses by binding to the triggering receptor expressed on myeloid cells 2 (TREM2). Mol. Neurodegener. 13:15. doi: 10.1186/s13024-018-0247-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2019 Frost, Jonas and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.