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The role of the immune system in neurodegenerative disorders: adaptive or maladaptive?

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Abstract

Neurodegenerative diseases share common features, including catastrophic neuronal loss that leads to cognitive or motor dysfunction. Neuronal injury occurs in an inflammatory milieu that is populated by resident and sometimes, infiltrating, immune cells-all of which participate in a complex interplay between secreted inflammatory modulators and activated immune cell surface receptors. The importance of these immunomodulators is highlighted by the number of immune factors that have been associated with increased risk of neurodegeneration in recent genome-wide association studies. One of the more difficult tasks for designing therapeutic strategies for immune modulation against neurodegenerative diseases is teasing apart beneficial from harmful signals. In this regard, learning more about the immune components of these diseases has yielded common themes. These unifying concepts should eventually enable immune-based therapeutics for treatment of Alzheimer's and Parkinson's diseases and amyotrophic lateral sclerosis. Targeted immune modulation should be possible to temper maladaptive factors, enabling beneficial immune responses in the context of neurodegenerative diseases.

Keywords

Central Nervous System; Neuroimmunology; Neuroinflammation; Alzheimer's Disease; Parkinson's Disease; Amyotrophic Lateral Sclerosis

1. Introduction

1.1 The immune system in neurodegenerative disorders

Neurodegenerative disorders are associated with age-dependent deposition of aggregated and misfolded proteins, cognitive disturbance, locomotive dysfunction, and neuronal loss (Forman et al., 2004). Importantly, evolution of these diseases occurs against a dysregulated

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neuroinflammatory backdrop (Glass et al., 2010). It has become clear in genetically modified animal models and from longitudinal patient studies that neuroinflammation and immune activation in the CNS develop early on in the course of disease, likely prior to large-scale neuronal loss. Activated microglia, the CNS-resident macrophage population, are present in nearly all neurodegenerative disorders (Long-Smith et al., 2009; Prokop et al., 2013; Sargsyan et al., 2005). In addition to microglia, activated astrocytes and peripheral monocytes or lymphocytes can be detected in the diseased CNS under certain conditions. Studies linking immune activation to poor prognosis in patients are raising a major question: are all neuroinflammatory pathways detrimental to CNS health?

A broad view would argue that inflammation in the CNS creates a neurotoxic environment, and must be sanctioned in order to prevent disease and to support recovery. In contrast to this ‘inflammation is strictly damaging’ view of neurodegeneration, several studies in animal models have revealed that inhibition of anti-inflammatory factors or expression of pro-inflammatory molecules can improve disease-relevant outcomes. This dichotomy supports the notion that broad-based manipulation of the immune system should likely be switched in favor of targeted immunomodulation on key effectors. This review will focus on current models of immune modulators, cytokines, chemokines, and receptors that are thought to drive immune responses within the CNS. It is becoming clear that all neurodegenerative diseases have a dominant inflammatory phenotype, and we will pay particular attention to advances in understanding immune-based mechanisms of Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). It is particularly striking that recent mechanistic studies into these debilitating diseases have provided common nodes of innate immune cell dysfunction, yielding important insight into immune modulation therapeutic strategies.

1.2 Immune players and responders within the CNS

Inflammation plays such a central role in health, that even subtle dysregulation of this highly ordered response can lead to myriad pathologies. Restricting expression of secreted inflammatory molecules and receptor/signaling cascades to certain cell types is a key physiological regulatory strategy. Resident immune cells in the CNS include microglia and astrocytes; but microglia are the only CNS cells of hematopoietic origin. Early in embryonic development, myeloid progenitors differentiate into primitive macrophage progenitors in the yolk sac (Ginhoux et al., 2010). Later, these cells engraft into the CNS, where they differentiate into mature microglia that are capable of local expansion and maintenance of a population of phagocytic monocytes for the life of the animal (Ajami et al., 2007; Elmore et al., 2014). Under physiologic conditions, microglia largely exhibit a ramified morphology with highly mobile processes optimized for sampling the local environment (Nimmerjahn et al., 2005). In this surveillance state, microglia monitor neuronal firing and synaptic function (Wake et al., 2009), drive programed cell death of neurons during development (Cunningham et al., 2013), and are responsible for synaptic pruning (Schafer et al., 2012; Stevens et al., 2007). The numerous roles microglia play in development and homeostasis have been thoroughly reviewed elsewhere (Salter and Beggs, 2014; Schwartz et al., 2013). Upon detection of molecular pathogens or danger signals, microglia switch from a ramified to a classically activated state with accompanying changes in morphology, function, and

transcriptional repertoire (Hanisch and Kettenmann, 2007). A second glial cell population that is central to neuroprotection and brain homeostasis is the astrocyte. Astrocytes are multifunctional cells, which are derived from the neuroectoderm and play essential roles in neural circuit development, synaptic pruning (Chung et al., 2013), and metabolism (reviewed in; Bouzier-Sore and Pellerin, 2013; Clarke and Barres, 2013; Sofroniew and Vinters, 2010). When activated by stimuli such as innate immune modulators, cytokines, neurotransmitters, hypoxia, and others, astrocytes release cytokines and other immune signaling molecules. In concert with microglia, these immune molecules mediate inflammatory responses that can be beneficial or deleterious in neurodegenerative diseases (Colangelo et al., 2014).

The general dogma for ‘CNS immune privilege’, that peripheral immune cells do not cross the blood brain barrier (BBB) and penetrate the CNS, has been revised in recent years. Under steady-state conditions in the healthy individual, the BBB surrounding the microvasculature and the epithelial blood-cerebrospinal fluid barrier (BCSFB) within the choroid plexus prevents passage of peripheral immune cells into the CNS parenchyma (Engelhardt and Ransohoff, 2012; Ransohoff and Cardona, 2010). However, monocyte-derived macrophages are present in the perivascular space and are able to survey the CNS and respond to stimuli (Hawkes and McLaurin, 2009; Lampron et al., 2013; Michaud et al., 2013a). This complex physiological structure has been thoroughly reviewed elsewhere (Ransohoff and Engelhardt, 2012). In response to acute injury or neurodegenerative diseases, these peripheral macrophages can infiltrate the CNS, pass through the BCSFB, and support healing (Shechter et al., 2009; Simard et al., 2006; Town et al., 2008; reviewed in Ransohoff and Engelhardt, 2012; Schwartz et al., 2013). Furthermore, lymphocytes are a major component of the CSF that can traverse the BCSFB, but do not actively penetrate the CNS parenchyma under steady-state, healthy conditions (Liblau et al., 2013; Ransohoff and Engelhardt, 2012; Schwartz et al., 2013). The majority of these lymphocytes are $CD4^+$ T cells, with characteristics of central and effector memory T cells and very few naïve cells (Ransohoff and Engelhardt, 2012). These cells play roles in homeostasis by regulating neurogenesis (Ziv et al., 2006) and brain plasticity (Kipnis et al., 2004), and can infiltrate the CNS parenchyma during inflammatory processes driven by tissue injury and disease (Ransohoff and Brown, 2012; Schwartz et al., 2013; Town et al., 2005).

1.3 Inflammatory signaling

Much of what is known regarding immune cell signaling has been established through mechanistic studies of innate immune responses to microbial pathogens. Under healthy conditions, inflammatory molecules are transcriptionally inhibited, but stand at the ready to be induced once the inflammatory process is initiated. Typically, the inflammatory response is triggered by detection of highly conserved pathogen associated molecular patterns (PAMPs) by germ-line encoded pattern recognition receptors (PRRs)(Takeuchi and Akira, 2010). One class of PRRs are the Toll-like receptors (TLRs), which has members that specialize in detecting a broad range of PAMPs that are not found in the host organism (thoroughly reviewed in (Kawai and Akira, 2010; Uematsu and Akira, 2008)). These receptors are expressed on cells that play central roles in the inflammatory response, including macrophages and microglia. In addition to non-self epitopes, PRRs can respond to

host derived molecules, referred to as danger associated molecular patterns (DAMPs) (Newton and Dixit, 2012). DAMPs can be released by necrotic cells or as a result of a pathogenic condition, and likely play roles in age-related diseases (Shimada et al., 2012). In addition to PRRs, microglia and astrocytes express a number of purinergic receptors that are capable of responding to extracellular nucleotides (i.e., ATP or UTP) and nucleosides (i.e., adenosine) released from cells after injury or death (Di Virgilio et al., 2009).

Activation of PRRs via PAMP recognition initiates several signal transduction pathways that control diverse transcriptional processes resulting in a highly regulated inflammatory response. As one example, TLR4 activation recruits Toll-interleukin 1 receptor (TIR) domain-containing adaptor protein (TIRAP) and myeloid differentiation primary response 88 (MyD88) initiating 'MyD88-dependent' early and late-phase activation of nuclear factor-kappaB (NF-κB) and mitogen-activated protein (MAP) kinases. Additionally, TLR4 activates interferon regulatory factor 3 (IRF3) via a TRIF-dependent' signaling pathway (Kawai and Akira, 2011). These are just a few examples of the complex network of signaling initiated by innate immune cells specialized in surveying the local environment. The inflammatory response is often characterized by activation of a number a transcription factor families including NF-κB, activator protein-1 (AP-1), c-AMP response element-binding protein (CREB), CCAAT/enhancer binding protein (c/EBP), and IRF. Combinatorial activation of transcriptional pathways results in expression of specific gene subsets. However, mechanisms of gene specificity are not well established, and more work is needed to decipher the molecular steps in transcriptional activation of key inflammatory mediators. Expression of specific cytokine and chemokine networks may resolve or drive pathology, and specific effectors for each disease scenario will be discussed below.

Activation of microglial innate immune signaling leads to secretion of inflammatory molecules, and also drives expression of numerous immune receptors that can further modulate their phenotype. This autocrine phenomenon seems to be particularly important for microglial cells, and modulates phagocytosis responses. Phagocytosis by microglia occurs throughout CNS development, and is necessary for brain health by removing dead neurons and protein aggregates (Zabel and Kirsch, 2013). Activation of the complement cascade, purinergic receptors, and the TREM2/TYROBP receptor complex have the ability to regulate microglial phagocytosis of neurons during development, homeostasis, and disease (Schafer et al., 2012; Schwartz et al., 2013; Stevens et al., 2007).

Lastly, but inextricably tied to inflammatory responses within in the CNS, are factors that temper and resolve neuroinflammation. Many negative feedback mechanisms have been identified within the CNS that function to attenuate inflammation. Secreted anti-inflammatory molecules, such as transforming growth factor beta (TGF-β) and interleukin 10 (IL-10), are expressed along with pro-inflammatory cytokines and chemokines. Inhibitors of inflammatory signal transduction pathways, including suppressor of cytokine signaling (SOCS), and transcriptional modulators such as activating transcription factor 3 (ATF3) and nuclear factor erythroid 2 related factor 2 (NRF2), can also be induced during neuroimmune responses (Glass et al., 2010). The complexity of these regulatory cascades can be reduced to several nodes of interaction, many of which are likely deficient as a result of genetics,

aging, and disease stage. Herein lies the challenge that understanding neuroinflammation and neurodegenerative diseases poses.

2. Alzheimer's disease

2.1 Neuroinflammatory genetic risk factors

Alzheimer's disease (AD) is the most common form of dementia, and is pathologically characterized by extracellular deposition of amyloid-β (Aβ) peptides into β-amyloid plaques, formation of neurofibrillary tangles composed largely of hyperphosphorylated tau protein, neuroinflammation, and large-scale neuronal injury and loss. The amyloid cascade hypothesis holds that the primary etiopathological event in AD is Aβ aggregation and deposition followed by downstream neurotoxicity (Hardy and Allsop, 1991). Aβ found in senile plaques is generated from sequential endoproteolytic cleavage of the type I transmembrane glycoprotein, β-amyloid precursor protein β-APP), by β- and γ-secretases (Hardy and Selkoe, 2002). Familial (also known as early-onset) AD has been linked to rare mutations in APP and the presenilin (PSEN) components of γ-secretase (PSEN1 and PSEN2). However, the vast majority of sporadic AD cases are thought to have a complex etiology impacted by lifestyle and environmental factors. Importantly though, strong genetic susceptibility factors have been reported for sporadic or late-onset AD (LOAD); however, these polymorphisms generally act in non-Mendelian fashion as AD risk factors.

The strongest genetic risk factor for AD is generally considered to be a double polymorphism within the apolipoprotein E (*ApoE*) gene. In humans, there are three *ApoE* allelic variants: ε2, ε3, and ε4. While the most common allele is ε3, the ε4 allele is associated with increased AD risk, while the ε2 allele is protective (Kim et al., 2009). Major focus has been directed toward the role of *ApoE* ε4 in Aβ metabolism and amyloid formation; yet, numerous studies support a complex function of *ApoE* in the context of AD pathogenesis. As a modulator of Aβ-driven neuroinflammation, *ApoE* is induced as part of the innate immune response. In this regard, the *ApoE* ε4 isoform has been reported to be pro-inflammatory, inducing more activated microglia and higher levels of the cytokine interleukin-1beta (IL-1β; Guo et al., 2004). While more work is needed in this important area, it remains possible that *ApoE* ε4 confers risk for AD at least partially by exacerbating Aβ-driven neuroinflammation.

Just recently, a rare allele has been identified and reported to confer as much AD risk as the more common *ApoE* ε4 allele. Strikingly, this polymorphism lies within a key innate immune gene known as triggering receptor expressed on myeloid cells 2 (*TREM2*) (Guerreiro et al., 2013; Jonsson et al., 2013). As a receptor on microglia, TREM2, along with its core molecular complex partner TYRO protein tyrosine kinase-binding protein (TYROBP/DAP12), regulates phagocytosis. Expression of both of these genes is up-regulated in microglia surrounding amyloid plaques in transgenic mouse models of cerebral amyloidosis (Jiang et al., 2013). In humans, the risk-incurring *TREM2* allele is thought to result in TREM2 loss-of-function, possibly reducing microglial capacity to phagocytose and clear β-amyloid. Additionally, signaling through the TREM2/TYROBP complex modulates the anti-inflammatory response through inhibition of TLR signaling, which is also likely dysfunctional in individuals bearing the AD risk allele. In a separate study utilizing whole-

genome expression and genotype data sets from hundreds of LOAD individuals, network-based gene-module approaches identified TYROBP as the highest-ranking causal gene (Zhang et al., 2013). These genetic findings place innate immune responses at the epicenter of LOAD risk.

2.2 Cytokines and chemokines

If two of the greatest known risk factors for LOAD can act as neuroinflammatory mediators, this would strongly suggest that pro-inflammatory responses endorse AD progression. Indeed, pro-inflammatory cytokines are up-regulated in AD patient brains, and it is widely thought that these inflammatory signals are pathological in nature, resulting in neuronal dysfunction and death. This model is supported by over 25 retrospective epidemiologic studies to date, where broad-spectrum inhibition of pro-inflammatory mediators via non-steroidal anti-inflammatory drugs reduces AD risk by up to 50% (in t' Veld et al., 2001; Szekely and Zandi, 2010).

Interestingly, polymorphisms within the pro-inflammatory *Il1b* cytokine gene are associated with greater AD risk (Rothwell, 2000). Induction of IL-1β by microglia can be the result of 1) amyloid recognition through one of several hypothesized Aβ receptors, 2) detection of extracellular ATP as the result of tissue injury and signaling through purinergic receptors, or 3) TLR or inflammasome activation by β-amyloid (Heneka et al., 2012) or DAMPs. IL-1β signaling initiates activation of NF-κB family members and other transcription factors, which drive pro-inflammatory gene expression. One target of IL-1β signaling is inducible nitric oxide synthase (iNOS), which is responsible for production of nitric oxide (NO) and reactive oxygen species (ROS). Under physiological conditions, ROS have a potent anti-microbial innate immune role; however, these factors can also promote bystander neuronal death (Khandelwal et al., 2011). IL-1β signaling in astrocytes results in activation and secretion of a number of pro-inflammatory molecules, including the cytokine-like molecule S100B. In Tg2567 mice harboring the 'Swedish' APP mutation, overexpression of S100B accelerates AD-like pathology by increasing amyloidogenic APP cleavage, astrocytosis, microgliosis, and pro-inflammatory cytokine expression (Mori et al., 2010). IL-1β, like IL-18, is produced as a biologically inactive pro-form and matures after inflammasome activation. In mouse models of AD, genetic depletion of the IL-1β promoting NLRP3 inflammasome reduces amyloid burden and rescues special memory defects (Halle et al., 2008; Heneka et al., 2012). Additionally, the endogenous inhibitor of IL-1β, IL-1Rα, is protective and can attenuate neuronal cell death (Rothwell, 2000). For this reason, it has been hypothesized that IL-1Rα therapy (currently being used for rheumatoid arthritis) could benefit AD patients (Lucas et al., 2006; Rothwell, 2000). In sum, expression of IL-1β is thought to perpetuate inflammatory conditions in the CNS, increasing damaging ROS and supporting the chronic inflammatory environment present in the AD brain (Figure 1).

In addition to IL-1β, myriad other cytokines and chemokines have been detected in cerebrospinal fluid (CSF), surrounding plaques, or in plaque-associated microglia in AD patients, including: tumor necrosis factor-alpha (TNF-α), IL-6, IL-8, IL-12, IL-23, CCL2, CCL3, CCL4, CXCL2, and cyclo-oxygenase (COX)-1/2, amongst others (Akiyama, 2000; Glass et al., 2010; Vom Berg et al., 2012). The role of many of these inflammatory

molecules in AD pathogenesis is not yet clear. TNF-α is a pluripotent cytokine that is an early responder of the innate immune system and stimulates expression of other pro-inflammatory cytokines. In the healthy brain, TNF-α expression is low, but it is elevated in multiple disease states, such as AD. Promoter polymorphisms that influence TNF-α expression are present in some populations and have been reported to be associated with AD (Culpan et al., 2003; Ma et al., 2004; Ramos et al., 2006). In mouse models, TNF-α has been shown to be both protective and pathogenic. Specifically, when TNF-α expression is induced by a viral system in the hippocampus of APP transgenic TgCRND8 animals that overexpress APP KM670/671NL (Swedish) and APP V717F (Indiana) mutations, plaque deposition is reduced, supporting a pro-phagocytic response from TNF-α expression (Chakrabarty et al., 2011). However, in another study, removal of TNF-α receptors also reduces plaque load (He et al., 2007), and supraphysiologic levels of this cytokine can be directly neurotoxic (Tan et al., 1999). Therefore, the actions of TNF-α are complex, and are likely dependent on concentration, target cell(s), TNF-α receptor type, and disease stage.

This degree of complexity has been observed with numerous other pro-inflammatory cytokines and chemokines. For example, a similar dichotomy has been reported for IL-6. IL-6, originally thought to be strictly a pro-inflammatory cytokine, has more recently been shown to have anti-inflammatory and neurotrophic properties as well (Spooren et al., 2011). In the CNS, IL-6 is produced by microglia, astrocytes, and even neurons, and influences microgliosis, astrogliosis, and BBB integrity. By participating in physiological and healthy actions in the brain, IL-6 is a neurotophic factor and is required for neurogenesis, astrogliogenesis, oligodendrogenesis, and proliferation, differentiation, and regeneration of neurons (Spooren et al., 2011). In AD, IL-6 is induced surrounding plaques and in the CSF, and higher concentrations of this cytokine are associated with terminal disease stage. A polymorphism in the *Il6* promoter region has been shown to increase gene expression both in plasma and in promoter reporter assays (Fishman et al., 1998). This polymorphism has been investigated in several sporadic LOAD studies, and there has been disagreement as to whether it represents a significant AD risk factor (Flex et al., 2013; Spooren et al., 2011). Although it is possible that the IL-6 polymorphism is AD risk-incurring, this would most likely occur in the context of other risk-associated genetic loci.

Several studies have attempted to establish a mechanism for IL-6 risk for AD. *In vitro* studies have mainly supported a pathological role, as IL-6 drives gliosis in response to Aβ, increases APP expression in neurons, and promotes tau hyperphosporylation (Erta et al., 2012; Spooren et al., 2011). However, *in vivo* studies have revealed a role for IL-6 in resolution of disease. Specifically, overexpression of IL-6 in the brains of TgCRND8 and Tg2576 animals with established disease results in increased gliosis, decreased Aβ deposition, and increased phagocytosis (Chakrabarty et al., 2010). This could be due to modification of the inflammatory microenvironment near plaques and/or modulation of microglial phenotype, resulting in acidified lysosomes and, therefore, more efficient Aβ degradation (Majumdar et al., 2007). In the context of human AD, it remains unclear if the pro-inflammatory and pro-phagocytic actions of IL-6 are protective or act to drive the chronic neuroinflammatory environment.

In addition to the cytokines already mentioned, expression of several chemokines is increased in AD patients, such as: CCL2, CCL3, CCL4, IL-8, and CXCL2. Additionally, microglia express chemokine receptors, including CCR3, CCR5, and CX3CR1, and CXCR2 and CXCR3 expression is elevated around β-amyloid plaques (Xia and Hyman, 1999; Guillot-Sestier and Town, 2013). While only a few of these factors have been mechanistically studied in the context of AD, their inducible expression in AD brains likely points to 'primed' cerebral innate immunity. One group of early studies reported that CCL2 is highly expressed around amyloid plaques and induces chemotaxis of microglia in a transgenic mouse model of cerebral amyloid deposition (El Khoury et al., 2003). Further, Tg2576 animals deficient in CCR2, the cognate receptor for CCL2, have less recruitment to sites of Aβ plaque deposition, earlier plaque formation, and premature death (El Khoury et al., 2007). However, one report suggested that CCR2 is not expressed by microglia (Mizutani et al., 2012). Therefore, it has been hypothesized that defective amyloid clearance in CCR2 deficient transgenic mice is due to reduced recruitment of bone marrow-derived circulating mononuclear phagocytes (Naert and Rivest, 2011), which can directly clear cerebral amyloid (reviewed in Naert and Rivest, 2013). In one interpretation, these data support a model where recruitment of mononuclear phagocytes is required for beneficial amyloid clearance; however, a corollary of this hypothesis is that blood-borne monocytes must be dysfunctional in the context of cerebral amyloidosis, thereby endorsing cerebral amyloid accumulation and allowing disease progression.

As mentioned at the beginning of this section, NSAID users have up to 50% reduced risk of AD (Akiyama, 2000). NSAIDs are well-established COX-1/2 inhibitors. In peripheral tissues, COX-1 is constitutively expressed and COX-2 is induced as part of the inflammatory response; however, in the brain, there is evidence of the converse (McGeer and McGeer, 2007). COX-1/2 is induced as part of the plaque-associated inflammatory response in AD patients, and one of its major roles is to metabolize prostaglandins, which can be neurotoxic at supraphysiologic levels (Lucas et al., 2006). In mouse models of cerebral amyloidosis, both selective and non-selective COX inhibitors are able to reduce amyloid burden and neuroinflammation (McGeer and McGeer, 2007). However, NSAID/AD clinical trials have not yet produced definitive results (Breitner et al., 2011; ADAPT, 2013; Szekely and Zandi, 2010), and future studies on the roles of the COX enzymes and prostaglandins in AD are warranted. It is clear that a deeper understanding of specific neuroinflammatory factors is vital to developing new therapeutic strategies that target cerebral innate immunity.

2.3 Anti-inflammatory factors

Genetic and pharmacological modulation of key pro-inflammatory molecules in mouse models of AD has illustrated a complex interplay that is both target cell and disease stage dependent. In this regard, immunomodulation of cardinal anti-inflammatory molecules has also been attempted. TGF-β is a central anti-inflammatory regulator that provides control of homeostasis and tissue repair mechanisms. Interestingly, release of this cytokine significantly increases in response to CNS injury, and astrocytes, microglia and oligodendroglia seem to be the major sources of TGF-β1 in the damaged brain (Constam et al., 1992; Finch et al., 1993). In AD patient brains, TGF-β1 is detected in amyloid plaques

(van der Wal et al., 1993) and increased levels have been detected in cerebrospinal fluid and serum of AD patients (Chao et al., 1994a, 1994b). In addition, TGF-β1 receptor immunoreactivity is higher in reactive glia in AD cases than in nondemented controls (Lippa et al., 1998) suggesting a pathogenic role for this cytokine (Wyss-Coray et al., 1997). Yet, *in vivo* studies in transgenic mouse models have yielded conflicting roles of TGF-β1, with over-expression promoting microgliosis and accelerated Aβ deposition (Wyss-Coray et al., 2000, 1997), or resolution of neuroinflammation and increased Aβ phagocytosis in other reports (Frautschy et al., 1992; Wyss-Coray et al., 2001). Another study designed to examine neuron-specific signaling revealed increased Aβ accumulation, dendritic loss, and age-dependent neurodegeneration (Tesseur et al., 2006). *In vitro* work suggests that TGF-β1 amplifies Aβ-mediated neurodegeneration via a Smad7/β-catenin-dependent mechanism (Salins et al., 2008).

In order to determine the effect of blocking the TGF-β1 signaling pathway in peripheral mononuclear phagocytes, our group developed a transgenic mouse model with blockade of TGF-β receptor and downstream Smad2/3 signaling in peripheral macrophages (designated CD11c–DNR mice). When crossed with Tg2576 mice, bi-transgenic animals had reduced Aβ deposits in brain parenchyma, accompanied by increased infiltration of peripheral macrophages in and around β-amyloid plaques (Town et al., 2008). *In vitro*, CD11c–DNR-derived peripheral macrophages exhibit blockade of the classical TGF-β-activated Smad2/3 pathway accompanied by hyperactivation of the alternative Smad1/5/8 signaling cascade and markedly increased Aβ phagocytosis. At least in this context then, blockade of a key anti-inflammatory signaling pathway activates innate immunity, promoting clearance and resolution of cerebral amyloidosis.

2.4 The role of innate immune receptors

The signaling cascades responsible for activation of innate immunity and release of inflammatory mediators initiate at receptors. A prototypical example is the TLR family. In this regard, TLR4 and TLR2 have been the major focus in AD. In studies of LOAD in both Italian and Han Chinese populations, two polymorphisms have been identified that occur at higher frequencies in AD verses healthy controls. Interestingly, both polymorphisms reduce the activity of TLR4 (Minoretti et al., 2006; Wang et al., 2011). A beneficial role of TLR4 is further supported by a recent study in which detoxified monophosphoryl lipid A (MPL), a TLR4 ligand, significantly improved AD-like pathology in APP/PS1 mice (Michaud et al., 2013b). These studies compliment other reports that TLR4 and TLR2 participate in Aβ phagocytosis (Reed-Geaghan et al., 2009). In contrast, another study showed that loss of IRAK4, a common TLR downstream mediator, results in increased amyloid clearance, reduced microgliosis, and reduced astrogliosis in aged mice (Cameron et al., 2012). These contradictory studies in mice and observations in patients highlight the challenge of attempting to modulate TLR signaling as an AD therapeutic modality. Further, these and other results underscore the notion that broad-based inhibition of cerebral innate immunity is not likely to be beneficial, because some aspects are adaptive and necessary for normal brain function and homeostasis.

In addition to the TLR family of receptors, there are other major innate immune receptors that have been identified as risk factors in AD. Reduction in TREM2 activity, as highlighted in section 2.1, is likely to attenuate phagocytic capacity of microglia in individuals carrying the mutant allele. In addition to TREM2, genome-wide association studies (GWAS) have identified several other innate immune receptors that confer risk, such as the complement component (3b/4b) receptor 1 (*CR1*) and *CD33. CR1* inhibits complement activation and the risk allele is expressed at lower levels, resulting in increased complement activation and modulation of a possible route for Aβ clearance (Hazrati et al., 2012). CD33 is a sialic acid binding immunoglobulin-like lectin that regulates innate immunity, is increased in AD patients relative to age-matched controls, and inhibits Aβ uptake and clearance (Griciuc et al., 2013). A common observation that links these innate immune gene risk alleles is modulation of microglial phagocytosis. In principle then, rescue of these defective alleles would require compensatory activation of the pro-phagocytic microglial phenotype and therefore, the specific molecular mechanisms of this pathway need to be delineated. The myriad types of cerebral innate immunity in the context of AD are summarized in Figure 1.

3. Parkinson's Disease

3.1 Multiple immune players

Parkinson's disease (PD) is the second-most common neurodegenerative disorder after AD. It is one of the three main types of α-synucleopathies, along with dementia with Lewy bodies and multiple system atrophy, characterized by abnormal accumulation of α-synuclein aggregates in neurons, nerve fibers or glial cells (for review see McCann et al., 2014). The histopathological hallmarks of PD are 1) age-related neurodegeneration of extrapyramidal motor neurons: in particular, loss of dopaminergic neurons of the basal ganglia from the substantia nigra pars compacta (SNpc) to the striatum (caudate and putamen), 2) Lewy bodies formed of intracellular proteinaceous inclusions containing α-synuclein (AS), and 3) chronic neuroinflammation. The third feature is characterized by the presence of activated microglia in the putamen, hippocampus, transentorhinal cortex, cingulate cortex, and temporal cortices of patients associated with mild astrogliosis and increased numbers of infiltrating lymphocytes (Brochard et al., 2009; Hirsch and Hunot, 2009; Imamura et al., 2003; McGeer et al., 1988; J Miklossy et al., 2006; Mirza et al., 2000; Orr et al., 2005). The density of microglia in the SNpc is higher than in other brain regions, and microglia are found predominantly in the vicinity of degenerated dopaminergic neurons in PD brains (Banati et al., 1998; Lawson et al., 1990). Furthermore, microglia are activated by substances produced by damaged neurons, such as α-synuclein aggregates (Zhang et al., 2005), ATP (Davalos et al., 2005), MMP-3 (Kim et al., 2007) and neuromelanin (Wilms et al., 2003). In return, activated microglia produce excessive quantities of various pro-inflammatory and neurotoxic factors including cytokines and free radicals (discussed below in sections 3.4 and 3.5); triggering a vicious cycle of inflammation that likely exacerbates neurotoxicity in PD. Importantly, activated microglia may also contribute to the non-motor symptoms of the disease (*e.g.*, dementia) (Emre, 2003). This self-amplifiying cycle of neuronal injury and microglial activation may be one of the key processes driving progressive neurodegeneration. In experimental PD models, anti-inflammatory neuroprotective agents have proved to reduce microglial activation in association with

reduced neuronal loss (Liu, 2006). Less is known about the exact role of astrocytes in PD pathogenesis. Animal studies suggest that astrocytes recruit microglia during the early phases of the disease via expression of pro-inflammatory molecules (Halliday and Stevens, 2011; Lee et al., 2010), but a potential neuroprotective role has also been proposed (Chen et al., 2006; Ishida et al., 2006; Lin et al., 1993).

3.2 Genetic risk factors for both familial and sporadic cases

PD is a multifactorial neurodegenerative disease considered to involve genetic defects and environmental factors that act together to promote disease progression. Unlike AD, where less than 1% of cases are due to mutations in *APP* or *PSEN1/2*, roughly 10% of PD cases are linked to a purely genetic cause. Interestingly, discrepancies exist between genetic and sporadic forms of the disease; however, similar disease features tend to indicate a common pathological mechanism for both forms of PD. The most common autosomal-dominant causes of PD are mutations in α-synuclein (*SNCA*) and leucine-rich repeat kinase 2 (*LRRK2*), whereas parkin (*PARK2*), PTEN-induced putative kinase 1 (*PINK1*), and DJ-1 (Parkinson protein 7; *PARK7*) are known to be responsible for autosomal-recessive cases (Trinh and Farrer, 2013). Remarkably, mutations in *PARK2*, *SNCA*, and *LRRK2* have also been reported in sporadic PD, suggesting that these genes influence the development of the disease with age (Moore et al., 2005). Importantly, *SNCA* (Austin et al., 2006; Gu et al., 2010; Klegeris et al., 2008), *LRRK2* (Gardet et al., 2010; Gillardon et al., 2012; Judith Miklossy et al., 2006; Moehle et al., 2012), *PARK2* (Frank-Cannon et al., 2008; Ledesma et al., 2002; Watson et al., 2012), *PINK1* (Akundi et al., 2011), and *DJ-1* (Bandopadhyay et al., 2004; Mullett et al., 2009; Waak et al., 2009) have all been shown to regulate adaptive and innate immune responses; notably, activation of T and B cells, microglia and astrocytes, and regulation of cytokine production. Thus, it remains possible that these genetic risk factors contribute to disease by inducing immune cell dysfunction.

More recently, several genetic studies have identified polymorphisms in immune-related genes associated with risk for PD. For example, GWAS has identified genetic variation of the HLA region (Hamza et al., 2010), the T cell receptor signaling pathway (Holmans et al., 2013; Srinivasan et al., 2009), and polymorphisms within inflammatory cytokines including TNF-α, IL-1β, IL-6, IL-18, IL-10, and the TLR4 co-receptor, CD14 (Deleidi and Gasser, 2013; Wahner et al., 2007) as risk factors for late-onset PD. In addition, TLRs have been implicated as genetic factors for sporadic and familial forms of PD, with proposed roles in dopaminergic neuronal degeneration and α-synucleinopathy. Indeed, transcription of *PARK2* is regulated by TLR4-MyD88-NF-κB and TNF-β-NF-κB-dependent pathways in microglia and macrophages (Tran et al., 2011), suggesting that activation of TLR-dependent pathways could play a role in dysregulation of neuroinflammation during PD progression (Noelker et al., 2013; Panaro et al., 2008).

3.3 Toll-like receptor dependent neuroinflammation

As mentioned above, activation of TLR-dependent pathways could play a role in Neuroinflammation and endorse PD progression. Studies have found increased abundance of TLRs in α-synucleinopathies, and TLR4 has been shown to be elevated in brains of patients suffering from α-synucleinopathy and in a transgenic mouse model of the disease

(Letiembre et al., 2009; Stefanova et al., 2011). Interestingly, DJ-$1^{-/-}$astrocytes selectively induce TLR4-dependent increased NO production, which likely contributes to neuronal death (Waak et al., 2009). In microglial cultures, blockade or knockdown of TLR4 suppresses phagocytosis of α-synuclein. Furthermore, genetic ablation of TLR4 in mice reduces phagocytosis by microglia, leading to α-synuclein accumulation, loss of dopaminergic neurons, and motor disability (Cookson, 2009; Fellner et al., 2013; Stefanova et al., 2011; Zhang et al., 2005). These results suggest that α-synuclein-dependent activation of microglia, their phagocytic capacity, and liberation of cytokines and ROS are modulated by TLR4. One important implication is that TLR4 may have a neuroprotective role via α-synuclein clearance (Stefanova et al., 2011). Interestingly, misfolded α-synuclein itself seems to be responsible for microglial activation by up-regulation of cytokines, increased expression of antioxidant response enzymes, and altered TLR gene expression (Béraud et al., 2011).

TLR2 may also be involved in the microglial response in PD. Indeed, TLR2 expression is increased in the transgenic mouse model expressing the α-synuclein mutation A30P (Martin et al., 2011), and extracellular α-synuclein released from neuronal cells activates inflammatory responses in microglia via association with TLR2 (Kim et al., 2013).

3.4 Molecular mediators of neuroinflammation

Although the pathomechanisms of PD are still unclear, neuroinflammation and microglial activation are now thought to play central roles in the disease. Numerous markers of microglial activation in PD-relevant brain regions have been reported in patients, including: human leukocyte antigen-DR (HLA-DR; McGeer et al., 1988), complement receptor (CR)3/43, the activated macrophage/microglial marker CD68 (Banati et al., 1998), intracellular adhesion molecule-1 (ICAM-1), lymphocyte function-associated antigen-1 (LFA-1), and major histocompatibility (MHC) class II (Imamura et al., 2003). On one hand, a plethora of studies indicate that pro-inflammatory cytokine and chemokine abundance is altered in PD compared to control brains. Elevated levels of IL-1β, IL-2, IL-4, CCL5, and TGF-α have all been reported in the CSF of PD patients (Blum-Degen et al., 1995; Mogi et al., 1996; Tufekci et al., 2011). Furthermore, IFN-γ, NF-κB, IL-1β, TGF-α (Mogi et al., 2007, 1994a), COX-1and COX-2 (Knott et al., 2000; Teismann et al., 2003) are up-regulated in the SN and in the striatum, and TNF-α and IL-6 are increased in CSF as well as in PD-relevant brain regions (Blum-Degen et al., 1995; Boka et al., 1994; Dobbs et al., 1999; Imamura et al., 2003; Mogi et al., 1996, 1994b). In addition, the hippocampus, cerebellum, and mesencephalon of PD patients present with increased abundance of IL-2, IFN-γ, and NF-κB (Hunot et al., 1997; Mogi et al., 2007, 1996). On the other hand, anti-inflammatory cytokines (such as TGF-β1) have also been detected in the CSF and in brain parenchyma of patients suffering from PD (Mogi et al., 1995; Nagatsu et al., 2000). These data reflect the complexity of the neuroinflammatory milieu present in PD patients' brains.

3.5 The role of oxidative stress

Oxidative stress (OS) is also thought to contribute to neuronal degeneration and microglial activation in PD. The dopaminergic neurons present in the SNpc exhibit high oxygen consumption and low levels of the antioxidant enzymes superoxide dismutase (SOD),

glutathione (GSH), and catalase, making them particularly susceptible to oxidative damage (Floyd, 1999). Several lines of evidence strongly suggest that oxidative stress is involved in microglial activation during PD evolution. Markers of oxidative stress, such as NOS and inducible NOS (iNOS), are increased in PD patients' brains (Hirsch et al., 2012; Hunot et al., 1996; Knott et al., 2000; Varçin et al., 2012). Reactive oxygen species (ROS) are downstream products of the free radical superoxide, and are generated by NADPH oxidase (NOX)-dependent transfer of electrons from NADPH to molecular oxygen. Interestingly, NOX isoforms are widely expressed in the CNS; in particular, by neurons, astrocytes and microglia. NOX-dependent generation of ROS relies on the highly expressed voltage–gated proton channel HV1 that regulates intracellular pH (Wu, 2014). The NOX family and its regulator HV1 are an important source of CNS oxidative stress, and NOX-derived ROS participate in various microglia-mediated events such as microglial proliferation, neuronal apoptosis, glutamate neurotransmitter release and astrocyte signaling (for a review see Gao et al., 2012). Further, dopamine can undergo auto-oxidation to produce cytotoxic ROS, and *in vitro* studies suggest that dopaminergic neuron cell death could be induced by L-DOPA-dependent generation of ROS (Coyle and Puttfarcken, 1993; Lipski et al., 2011). ROS can also perpetrate excitotoxicity via over-activation of N-methyl-D-aspartate (NMDA) receptors (implicated in control of synaptic plasticity and memory function), leading to a hyper-production of NO (Barnham et al., 2004). Additionally, increased levels of neuromelanin (that pigments neurons of the substantia nigra and acts as a chelating agent and neuroprotector) released from dying cells can activate microglia, increasing the sensitivity of dopaminergic neurons to oxidative stress-induced cell death (Halliday et al., 2005; Kastner et al., 1992; Zhang et al., 2011). Finally, dopaminergic neurons are more vulnerable to pro-inflammatory cytokines such as TNF-α, and this phenomenon has been linked to elevated oxidative stress (McGuire et al., 2001).

Astrocytes may play a protective role vis-à-vis oxidative stress in PD. The dopaminergic neurons in the SNpc of PD patients exhibit high levels of nuclear factor erythroid 2-related factor 2 (NFR2), which has the ability to activate endogenous antioxidant responses to oxidative stress (Kumar et al., 2012). In fact, NRF2 is a transcription factor present in astrocytes that plays a major role in protection against ROS injury by triggering cytoprotective products (Tanji et al., 2013). Interestingly, NRF2 deficiency diminishes striatal dopamine and increases neurotoxicity in the MPTP mouse model of PD (Chen et al., 2009; Innamorato et al., 2010). In dopaminergic neurons *in vitro*, stimulation of NRF2-induced anti-oxidant and neuroprotective effects oppose neurotoxicity induced by MPTP or 6-OHDA (a dopamine analog) treatment (Jakel et al., 2007; Yamamoto et al., 2007). *In vivo*, mice receiving transplantation of NRF2-overexpressing astrocytes in the striatum are more resistant to 6-OHDA, and dopaminergic neuronal loss in the SNpc is rescued (Chen et al., 2009; Jakel et al., 2007). Additionally, greater loss of dopamine transporter levels in striatum of NRF2 knockout mice post-MPTP has also been reported (Burton et al., 2006). Therefore, NRF2 represents an important anti-oxidant factor that is neuroprotective in the context of PD.

4. Amyotrophic lateral sclerosis

4.1 Brain inflammation

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that is characterized by selective loss of motor neurons in the brainstem, spinal cord, and motor cortex. Individuals suffering from ALS experience fasciculation, muscle wasting, and hyper-reflexia, making this neurodegenerative disease both debilitating and fatal. The vast majority of ALS cases are sporadic in nature, likely resulting from a complex interplay between polygenetic variants and environment, and it is currently estimated that only ~10% of ALS is familial (Renton et al., 2014). The first mutation reported for familial ALS was in the Cu/Zn-superoxide dismutase gene (*SOD1*; Rosen et al., 1993). Since the introduction of next-generation high-throughput sequencing, the pace of identifying causal genes has greatly increased. In European populations, it is estimated that the genetic etiology of about two-thirds of familial ALS and 11% of sporadic ALS has been accounted for (Renton et al., 2014). In addition to *SOD1*, the most common mutations in ALS are found in *C9orf72* (DeJesus-Hernandez et al., 2011; Renton et al., 2011), RNA-binding gene fused in sarcoma (*FUS*) (Kwiatkowski et al., 2009; Vance et al., 2009), TDP-43 (*TARDBP*) (Kabashi et al., 2008; Sreedharan et al., 2008; Van Deerlin et al., 2008), and sequestosome-1 (*SQSTM1*) (Shimizu et al., 2013; Teyssou et al., 2013). A common pathological hallmark in ALS is the presence of ubiquitin-positive cytoplasmic inclusions containing TDP-43 in pathologic neurons (McGeer and McGeer, 2002). The genetic and mechanistic linkage of the RNA-binding proteins TDP-43 and FUS, as well as the intronic expansion of *C9orf72*, suggests that defective RNA metablolism, ribonucleoprotein binding, and splicing support ALS proteinopathy (Renton et al., 2014). In general, genetic abnormalities associated with ALS support the hypothesis of neurotoxicity due to abnormal protein aggregation, ineffective ubiquitin-mediated protein clearance, and faulty RNA processing.

Similar to AD and PD, neuroinflammation in ALS is routinely documented in pathologically affected brain areas, and is characterized by gliosis, activated microglia and astrocytes, and elevated production of pro-inflammatory cytokines (McGeer and McGeer, 2002). Additionally, infiltrating lymphocytes and macrophages are also observed in ALS-associated brain areas. Two general approaches to modeling ALS in rodents have been taken. The first has been to express mutant human *SOD1* and, more recently, to express or deplete TDP-43. The most well-established mouse model of ALS expresses human $SOD1^{G93A}$ and recapitulates both motor neuron loss and neuroinflammation observed in human ALS (Gurney et al., 1994). More recently, $SOD1^{G93A}$, $SOD1^{G37R}$, or $SOD1^{G37R}$ expression in neurons vs. glia was explored and it was shown that onset and progression represent distinct disease phases. Specifically, mSOD1 expression in motor neurons could establish an early disease phase; however, microglial expression is required to perpetrate late stage neuronal pathology and loss (Boillée et al., 2006; Clement et al., 2003). Rodent models of ALS that express wild-type TDP-43 (Wils et al., 2010; Xu et al., 2010) or ALS-linked mutant $TDP\text{-}43^{A315T}$ (Wegorzewska et al., 2009) or $TDP\text{-}43^{M337V}$ (Huang et al., 2012; Xu et al., 2011) have a neurodegeneration phenotype (reviewed in Tsao et al., 2012). Interestingly, a recent study utilizing an RNAi transgene targeting *TARDBP* reported neurodegeneration with only partial TDP-43 depletion (Yang et al., 2014). Similar to the

human *mSOD1* overexpression model, this phenotype is dependent on another glial cell population, astrocytes, in addition to neurons, and highlights the key role of glial cells in ALS pathogenesis.

4.2 Neuroinflammation is linked to motor neuron loss

Similar to AD, activated microglia and reactive astrocytes can be found in spinal cords of ALS patients and in transgenic mouse models of the disease (McGeer and McGeer, 2002). Reactive glial cells have been reported to mediate both neuroprotective and neurotoxic signals; therefore, the relative contribution of each to disease pathogenesis remains unclear (Bowerman et al., 2013). Cytokines and chemokines detected in ALS spinal cords are similar to AD and PD, and include: IL-1β, TNF-α, CCL2, and IL-6, amongst others. For IL-1β, much of the evidence supports increased abundance in conjunction with the pro-inflammatory cascade of factors that drive chronic inflammation in ALS. Mutant human SOD1 can form aggregates that activate the inflammasome, (including caspase-1 and IL-1β release; Ilieva et al., 2009; Meissner et al., 2010). When this signaling cascade is interrupted in $SOD1^{G93A}$ mice by removing caspase-1, IL-1β, or overexpressing the IL-1β inhibitory receptor (IL-1Rα), $SOD1^{G93A}$ transgenic mice live longer and have less neuroinflammation (Meissner et al., 2010). Interestingly, while TNF-α is up-regulated in this ALS mouse model, genetic ablation of TNF-α does not impact lifespan or motor neuron loss in these animals (Gowing et al., 2006). This somewhat puzzling result may be specific to this model, or it could represent a compensatory mechanism due to elevated IL-1β and TLR2 expression (Gowing et al., 2006).

Increased abundance of chemokines, including CCL2, has been reported in patients and in animal models of ALS in early stages of disease, and these changes track well with development of pathology (Henkel et al., 2006; Kuhle et al., 2009). It is not clear if this expression pattern is injurious or protective, although recruitment of monocytes could play an important role in disease progression. Much akin to other neurodegenerative disorders, it has been demonstrated that microglia can have neuroprotective or neurotoxic phenotypes in ALS (reviewed in Appel et al., 2011). Specifically, reconstitution of PU.1 null mice that are unable to develop myeloid and lymphoid cells with wild-type or mSOD1 bone marrow revealed that wild-type microglia are protective while mSOD1 microglia are toxic (Beers et al., 2006). Additionally, *ex vivo* microglia from early-stage mSOD1 mice were shown to be alternatively activated (M2 phenotype) and neuroprotective, whereas late-stage microglia were more classically activated (M1) and neurotoxic to motor neurons in co-culture (Liao et al., 2012). Nonetheless, the role of most cytokines and chemokines in ALS pathogenesis remains enigmatic. Establishing which secreted factors are neuroprotective, neurotoxic, serve to recruit immune cells, or to activate these cells toward a particular phenotype, is needed to determine the best candidates for therapeutic intervention.

As previously addressed, cytokine and chemokine expression are often induced by activation of innate immune receptors, such as TLRs. Elevated expression of TLR2, TLR4, and CD14 have been observed in animal models of ALS; however, something similar was not observed in patients (Casula et al., 2011; Letiembre et al., 2009). *In vitro* studies have demonstrated that extracellular *mSOD1* can induce microglial secretion of pro-inflammatory

IL-1β and TNF-α, and this effect is TLR2/4 and CD14 dependent (Liu et al., 2009; Zhao et al., 2010). While increased abundance of TLRs could potentiate microglial activation, ALS patient data suggests that this phenomenon is associated with general neuroinflammatory events as opposed to disease-specific pathogenesis. For example, large-scale motor neuron degeneration releases ATP that signals through P2×7 receptors on microglia and astrocytes resulting in the expression of inflammatory molecules, including IL-1β, TNF-α, COX-1/2, and ROS (Apolloni et al., 2013; Bowerman et al., 2013; Gandelman et al., 2010). This neurotoxic response can be attenuated by inhibition of P2×7 signaling (Apolloni et al., 2013; Gandelman et al., 2010). The intracellular nature of ALS inclusions suggests that closer investigation into potential immune responses and associated transcriptional changes is required.

4.3 Messenger RNA splicing may impact inflammatory gene expression

The frequent presence of TDP-43/FUS in ALS intracellular inclusions, regardless of pathogenic allelic variant, is likely to have broad implications for transcriptional regulation (Ling et al., 2013). Aggregation of splicing factors in the cytoplasm leads to depletion in the nucleus and dysregulation of thousands of target mRNAs (Ling et al., 2013). It is unclear if this phenomenon plays a dominant role in production of neurotoxic vs. neuroprotective mediators. Increased NF-κB has been reported in TDP-43 aggregates, and work in the mSOD1 model suggests that activation of the NF-κB and AP-1 families are key transcriptional inducers in ALS (Glass et al., 2010; Swarup et al., 2011). One factor that is down-regulated by NF-κB activation, but is thought to be neuroprotective, is NRF2. Insufficient activation of NRF2, as observed in aging and in neurodegenerative disease, has been linked to reduced ability to activate cytoprotective genes, such as those required for protection from oxidative stress (Sandberg et al., 2014). Glial transcriptional dysregulation, disrupting the balance of pro-inflammatory and cytoprotective transcription factors as illustrated by NRF2, has been reported in both PD and in ALS, and may be linked to neuronal survival.

4.4 CNS infiltrating immune cells

In contrast to AD, copious blood-derived immune cells are associated with pathological ALS tissue. In patients suffering from ALS, the BBB and the blood-spinal cord barrier are damaged (Winkler et al., 2013). These pathologies are associated with reduced numbers of pericytes, vascular dysfunction, and infiltration of immune cells. Peripheral macrophages, mast cells, and lymphocytes are all found in close association with brain and spinal cord lesions in ALS patients (Graves et al., 2004; Lewis et al., 2012). Yet, lymphocyte populations have been hypothesized to have diametric roles in disease progression. For example, when *mSOD1* transgenic mice were bred with mice lacking functional T cells, motor neuron disease was accelerated (Beers et al., 2008).

Additionally, T regulatory cell numbers were found to inversely correlate with disease, and this population of $CD4^+$ T cells is believed to be responsible for neuroprotection (Beers et al., 2011; Bowerman et al., 2013; Henkel et al., 2013). Alternatively, CD8 cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells are increased in number surrounding ALS lesions (Rentzos et al., 2012). CTLs express Fas ligand and could induce Fas-mediated cell

death in motor neurons, which are more susceptible to injury when expressing human mSOD1 (Raoul et al., 2006, 2002). The role of NK cells in ALS progression is unknown; yet, increased expression of IFN-γ or other NK-associated cytokines could potentiate CTL/T helper type I-mediated motor neuron death (Bowerman et al., 2013).

5. Therapeutic implications and conclusions

Progress toward understanding of the role of inflammation in neurodegenerative diseases is driving innovative work that will be central to the development of immune-based therapies for these disorders. While there are certainly maladaptive components of neuroinflammatory events that serve to perpetuate a neurotoxic environment and to drive neuropathogenic lesions, there is also the opportunity to use newly-deciphered immune pathways to steer beneficial neuroimmune responses (Figure 2). One therapeutic target, common amongst these disorders, includes altering capacity of phagocytic monocytes to clear protein aggregates (i.e., Aβ, α-synuclein). Secondly, proper expression and regulation of ROS by astrocytes through the cytoprotective role of NRF2 target genes would be predicted to ameliorate neurotoxicty. Finally, proper recruitment of beneficial immune cells from within the CNS and from the periphery needs to be explored as a potential strategy to promote healthy CNS immune responses.

Whereas the death and dysfunction of neurons is the main phenomenon leading to neurological syndromes, it is becoming increasingly evident that neuroinflammation and oxidative stress are substantial players in the pathoethiology of neurodegenerative disorders. Genetic variants may modulate immune and inflammatory pathways both in familial and in sporadic forms of these diseases, and modify disease onset and progression. Neuroinflammatory mediators (i.e., cytokines, receptors and transcription factors) are driving forces in neurodegenerative diseases that have a profound impact on progression of inflammation and neuronal injury. Thus, regulating the production or action of these mediators may prove to be an effective approach to mitigate CNS inflammatory processes and neurodegeneration.

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Abbreviations

AD	Alzheimer's Disease
ALS	Amyotrophic Lateral Sclerosis
ApoE	Apolipoprotein E
AP-1	Activator Protein-1
β-APP	β-amyloid precursor protein

ATF	Activating Transcription Factor
ATP	Adenosine Triphosphate
BBB	Blood Brain Barrier
BCSFB	Blood-cerebrospinal fluid barrier
BSCB	Blood-spinal cord barrier
c/EBP	CCAAT/enhancer binding protein
CCL	Chemokine ligand
CCR	C-C Chemokine Receptor
CNS	Central Nervous System
COX	Cyclo-OXygenase
CR	Complement Receptor
CREB	C-AMP Response Element-Binding protein
CSF	Cerebrospinal Fluid
CTLs	Cytotoxic T Lymphocytes
CX3CR	CX3C Chemokine Receptor
CXCL	Chemokine (C-X-C motif) ligand
DAMPs	Danger Associated Molecular Patterns
GSH	glutathione
HLA-DR	human leukocyte antigen-DR
ICAM-1	intracellular adhesion molecule-1
IL	interleukin
iNOS	inducible nitric oxide synthase
IRAK	Interleukin-1 Receptor-Associated Kinase
IRF	interferon regulatory factor
LFA-1	lymphocyte function-associated antigen-1
LOAD	Late-Onset AD
LRRK	Leucine-Rich Repeat Kinase
MAPK	mitogen-activated protein kinases
MHC	major histocompatibility
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MyD88	myeloid differentiation primary response 88
NF-κB	nuclear factor-kappaB

NFR	nuclear factor erythroid 2-related factor
NK	Natural Killer
NLRP3	NOD-like receptor family, pyrin domain containing 3
NMDA	N-methyl-D-aspartate
NO	nitric oxide
NRF	Nuclear factor erythroid 2 Related Factor
NSAID	Non-steroidal anti-inflammatory drugs
OS	Oxidative Stress
PAMPs	Pathogen Associated Molecular Patterns
PD	Parkinson's Disease
PRRs	Pattern Recognition Receptors
PS	presenilin
ROS	Reactive Oxygen Species
SNpc	Substantia Nigra Pars Compacta
SOCS	Suppressor Of Cytokine Signaling
SOD	superoxide dismutase
TIR	Toll-Interleukin Receptor
TIRAP	Toll-Interleukin Receptor domain-containing Adaptor Protein
TGF-β	Transforming Growth Factor beta
TLRs	Toll-Like Receptors
TNF-α	tumor necrosis factor-alpha
TREM	Triggering Receptor Expressed on Myeloid cells
TRIF	TIR-domain-containing adapter-inducing interferon- β
TYROBP	TYRO protein tyrosine kinase-binding protein
UTP	Uridine Triphosphate

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Highlights

- Teasing apart immune modulation signals is key for neurodegenerative diseases.
- Determining specific phenotypes of microglia and astrocytes is critical.
- Engaging beneficial immune responses is important to promote CNS health.
- One therapeutic target to clear misfolded proteins is phagocytic monocytes.
- These unifying themes should enable immunotherapeutics against neurodegeneration.

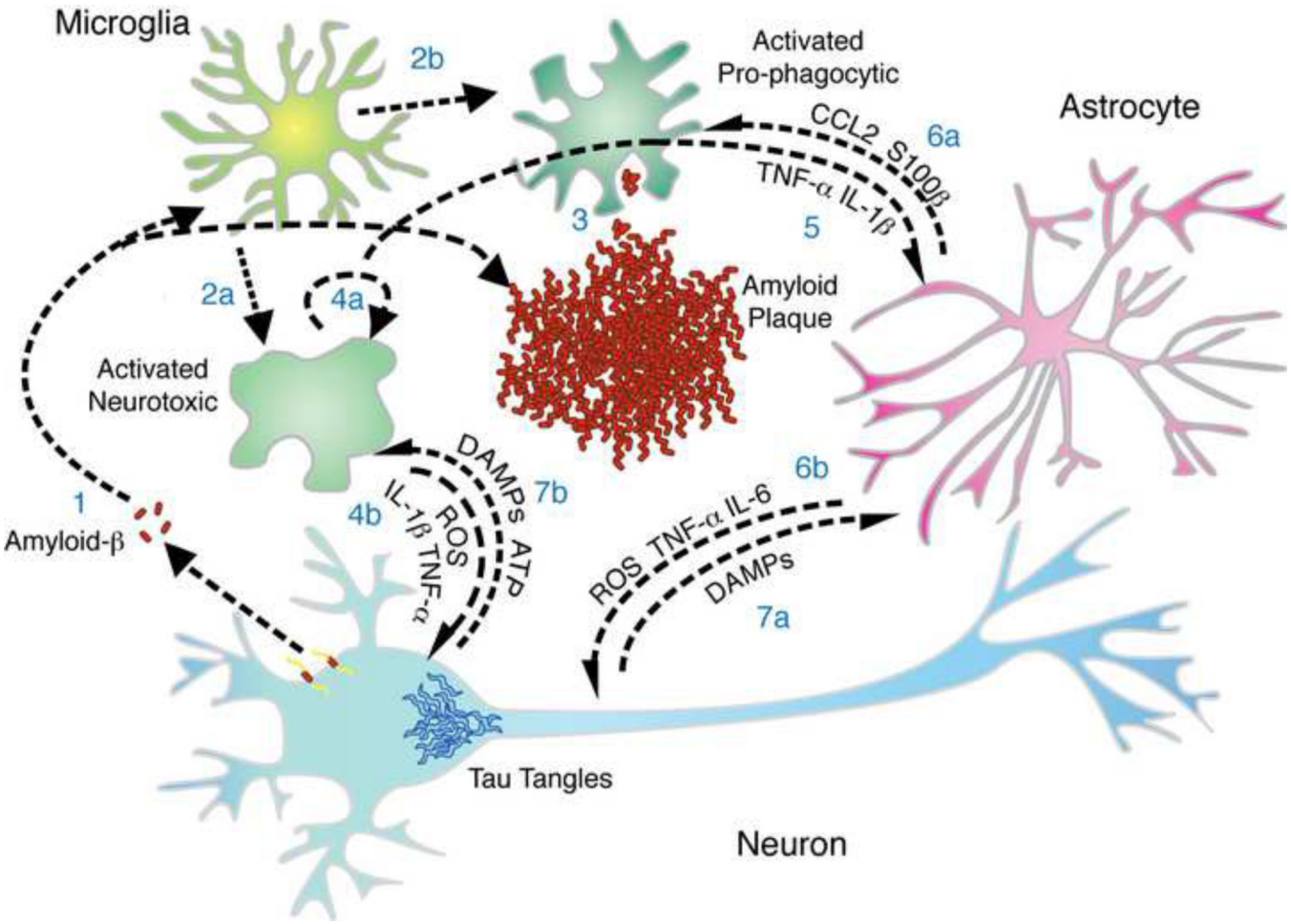

Figure 1. Inflammation in Alzheimer's Disease

There is a complex interplay between mediators of inflammation at sites of amyloid deposition in Alzheimer's disease (AD). (1) Amyloid-β peptide forms aggregates and activates microglia. Microglia transition from ramified to activated, which can be (2a) neurotoxic, producing ROS, IL-1β, and TNF-α, or (2b) pro-phagocytic. (3) Phagocytic microglia will clear amyloid while neurotoxic microglia (4a) will secrete factors that act in an autocrine manner to reinforce/maintain the inflammatory phenotype and (4b) factors that directly damage neurons. (5) Factors secreted by microglia stimulate a response by astrocytes that can (6a) feedback onto microglia, driving recruitment and neuroinflammatory modulation, or (6b) act on neurons, which can be either neurotoxic or neurotrophic. Neurons, as a response to intracellular injury by tau tangles or neurotoxic ROS and cytokines, may die and release DAMPs and ATP that influence the inflammatory phenotype of (7a) astrocytes and (7b) microglia.

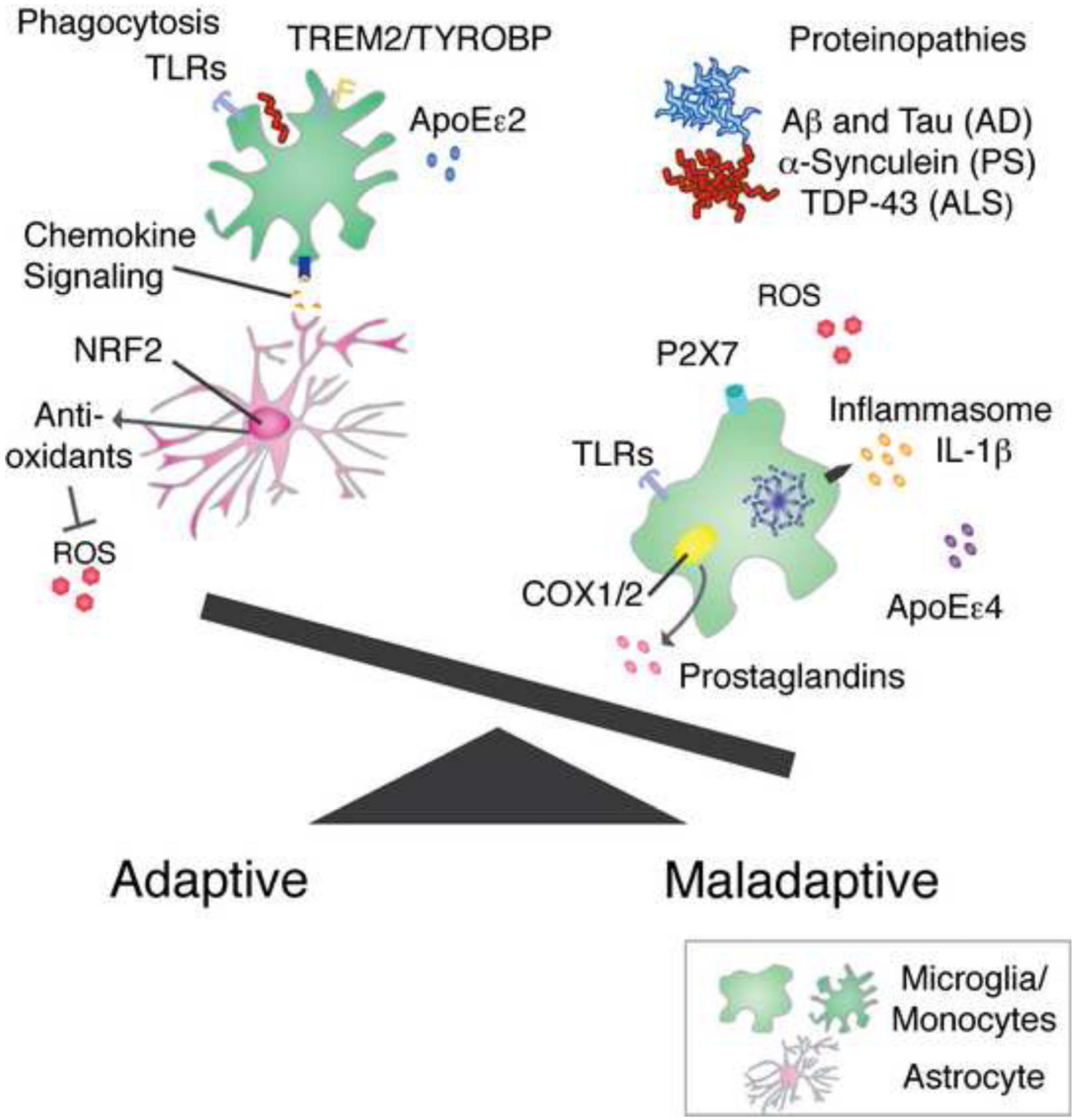

Figure 2. Microglial phenotype is a major determinant of adaptive vs. maladaptive inflammation in neurodegenerative disorders

Once neurodegenerative disease has been diagnosed, the scale has already been tipped towards maladaptive immunity for a significant amount of time. Specifically, protein aggregates have become established and a pro-inflammatory/pro-neurotoxic microglial phenotype predominates. This phenotype is characterized by ROS production, inflammasome activation and secretion of IL-1β, COX1/2 mediated prostaglandins, activation of P2×7 and TLRs by DAMPs, and immune modulation by *ApoEε4* in carriers. Adaptive and beneficial microglial/monocyte phenotypes are pro-phagocytic and are

accompanied by signaling by astrocytes (i.e. CXCR2/IL-8 or other chemokines in microglia or CCR2/CCL2 in peripheral monocytes), activation of TREM2/TYROBP and TLRs in a pro-phagocytic manner, reduction of ROS by NRF2 target genes, and immune modulation by the protective *ApoEε2* allele in carriers.