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Role of the JAK/STAT signaling pathway in regulation of innate immunity in neuroinflammatory diseases

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Abstract

The Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway is utilized by numerous cytokines and interferons, and is essential for the development and function of both innate and adaptive immunity. Aberrant activation of the JAK/STAT pathway is evident in neuroinflammatory diseases such as Multiple Sclerosis and Parkinson's Disease. Innate immunity is the front line defender of the immune system and is composed of various cell types, including microglia, macrophages and neutrophils. Innate immune responses have both pathogenic and protective roles in neuroinflammation, depending on disease context and the microenvironment in the central nervous system. In this review, we discuss the role of innate immunity in the pathogenesis of neuroinflammatory diseases, how the JAK/STAT signaling pathway regulates the innate immune response, and finally, the potential for ameliorating neuroinflammation by utilization of JAK/STAT inhibitors.

Keywords

JAK/STAT pathway; Innate immunity; Multiple sclerosis; Parkinson's disease

1. Introduction

The Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling pathway was elucidated in the 1980s as the pathway mediating interferon signaling [1]. It is now recognized as one of the most important pathways for the development and function of cells that mediate innate and adaptive immunity, given that over seventy different cytokines and interferons use this pathway [2]. Although the central nervous system (CNS) was once considered immune-privileged, we now know that innate immunity is the first line of defense in the CNS, and there is constant surveillance of the CNS by T cells [3,4]. Inflammation in the CNS is associated with diseases such as Multiple Sclerosis (MS) and Parkinson's Disease (PD), and activation of the JAK/STAT pathway contributes to

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pathogenic inflammation. This review will focus on the function of JAK/STAT signaling in innate immunity in the context of neuroinflammatory diseases, and will also discuss the potential for use of therapeutics targeting this pathway.

1.1. The role of innate immunity in the CNS

The immune system in the CNS differs from the peripheral immune system in many ways. In contrast to the wide variety of peripheral immune cells that patrol the blood and secondary lymphoid organs, such as B cells, T cells, granulocytes, macrophages and dendritic cells (DCs), only a few types of immune cells exist in the undisturbed CNS [3]; (Fig. 1A). As first-line defenders, microglia survey the CNS via highly motile processes that undergo repeated extension and retraction, although their cell bodies are immotile [5]. When tissue injury is sensed by microglia, they become activated and help clear damaged cells, in part, by the process of phagocytosis [6]. Microglia are also equipped with a pattern recognition system that allows them to respond to foreign antigens and inflammation in the CNS. Upon activation, microglia proliferate and migrate to affected sites where they produce a variety of cytokines and chemoattractants that recruit and activate immune cells from the periphery to initiate secondary responses [7].

Astrocytes have critical functions in the normal CNS in regulating ion homeostasis, clearance of neurotransmitters, synapse formation, and regulation of neurovascular coupling [8]. Under disease states, astrocytes work in conjunction with microglia in the CNS to influence inflammatory responses. In response to damage at a site not surveyed by microglia, astrocytes can recruit microglial processes to form a continuous network composed of processes from individual microglia [7]. In addition, upon inflammation, astrocytes produce a variety of cytokines and chemokines, including CCL2, CXCL1, CXCL2, CXCL10, GM-CSF, and IL-6, which activate microglia and recruit peripheral immune cells to the CNS [9–11].

Oligodendrocytes, the myelin producing cells within the CNS, have essential functions in the intact CNS with respect to myelin maintenance and axonal conduction. Myelin and oligodendrocytes are susceptible to injury or disease which causes myelin damage [12]. This damage leads to axonal dysfunction, pathology and pronounced neurologic impairment. The promotion of remyelination by oligodendrocyte progenitor cells (OPCs) and/or oligodendrocytes has been difficult to achieve, and remains a major obstacle in MS [13]. The influence of neuroinflammation on oligodendrocytes and OPCs is complex, with both detrimental and beneficial properties [12]. Oligodendrocytes are particularly sensitive to the effects of IFN-γ, which can inhibit remyelination through modulation of ER stress [14,15]. In contrast, the immune receptor TLR4 supports OPC growth and replacement, promotes myelin debris clearance, and enhances functional recovery in spinal cord injury models [16]. Astrocytes and pro-inflammatory microglia, via secreted products, can inhibit OPC differentiation [17]. Importantly, oligodendrocytes themselves can modulate the immune response in the CNS. Oligodendrocyte death triggers an adaptive autoimmune response against myelin, indicating that oligodendrocytes may contribute to autoimmune responses in MS [18].

Under normal conditions, only a small number of immune cells from the periphery, mainly T cells, are present in the CNS. The CNS is isolated from the peripheral immune system by the blood-brain barrier (BBB), comprised of endothelial cells, astrocyte end-feet and pericytes, and the blood-cerebrospinal fluid (CSF) barrier, comprised of choroid plexus epithelial cells [19]. Recently, functional lymphatic vessels were discovered in the dural sinuses, which connect with deep cervical lymph nodes in the periphery [20]. Mice lacking a dural lymphatic vascular system show impaired CNS macromolecule clearance and compromised CSF uptake into the deep cervical lymph nodes, without affecting interstitial fluid pressure and water content [21]. These findings indicate that peripheral immune cells are connected with the CSF through lymphatic vessels, and during infection or inflammatory conditions, innate immune cells (DCs, neutrophils, monocytes, and natural killer cells) and adaptive immune cells (activated B cells and CD4+ and CD8+ T cells) from the periphery are recruited by chemoattractants to cross the BBB and blood-CSF barrier, infiltrate the CNS, and mount an immune response (Fig. 1B).

The presence of innate immune cells in the CNS can directly and indirectly cause neuroinflammation by production of pro-inflammatory cytokines/chemokines and generation of oxidative stress (Fig. 1B). Activated endogenous microglia and infiltrating macrophages secrete pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IFN-γ, IL-23), which promote inflammatory functions of CD4+ T cells [22]. They also produce reactive oxygen species (ROS) and nitric oxide (NO), which directly induce neuronal death [23,24]. Furthermore, activated microglia are capable of upregulating CD11c [25], MHC Class 1 [26], and MHC Class II [27] to act as antigen-presenting cells in some murine models. Consistent with this role, HLA-DR$^+$ microglia have been found in brain tissue from PD and MS patients [28,29]. In addition to microglia and macrophages, DCs are also potent antigen-presenting cells, and the population of these cells in the CNS has been shown to be increased after infection with *Toxoplasma gondii* [30] and during MS and experimental autoimmune encephalomyelitis (EAE), a mouse model of MS [31]. Neutrophils also play multiple pathogenic roles after infiltration into the CNS. First, neutrophils secrete a wide variety of cytokines and chemokines that recruit and activate numerous immune cells [32]. For example, production of CCL2 and CCL20 by neutrophils is critical for the recruitment of Th17 cells [33]. IL-1β produced by neutrophils is required for CNS endothelial cell (EC) activation and EC-driven neuroinflammation [34]. Neutrophils also directly cause neuronal damage by secreting ROS, TNF-α and iNOS [24,35]. Furthermore, neutrophils assist with the maturation of DCs [36]. In contrast, the function of NK cells in neuroinflammation has been less studied, and there are conflicting results demonstrating both neuroprotective and neurotoxic functions in EAE models [37–39].

12. JAK/STAT signaling

The JAK/STAT signaling pathway is widely utilized in signal transduction activated by numerous cytokines and interferons. Signaling through the JAK/STAT pathway plays critical roles in initiation and regulation of innate immune responses and adaptive immunity. The JAK/STAT pathway promotes cytokine-mediated cell activation in a simple but efficient manner. When a cytokine binds to its specific receptor on the cell membrane, the kinase activity of cytoplasmic, receptor-associated JAKs is activated. The activated JAKs

phosphorylate a tyrosine residue in the cytoplasmic domain of the cytokine receptor to provide a docking site for STATs. STATs bind the cytokine receptor via their SH2 domains and are phosphorylated on tyrosine residues by JAKs, leading to the formation of homo- or hetero-dimers via SH2-phosphate interactions. Dimerized STATs then translocate from the cytoplasm into the nucleus, where they modulate expression of cytokine-responsive genes by binding to specific DNA elements [40] (Fig. 2). In mammals, four JAKs (JAK1, JAK2, JAK3, TYK2) and seven STATs (STAT1, 2, 3, 4, 5a, 5b, 6) have been identified, and each cytokine utilizes a specific combination of JAK and STAT members to transduce a unique signal. Changes in gene expression in response to a specific cytokine vary amongst different cell types, although the same JAK/STAT components are used [41]. This may reflect different composition of other transcription factors recruited to promoters [42].

JAK/STAT signaling is negatively regulated by Suppressors Of Cytokine Signaling (SOCS) proteins. Eight members of the SOCS protein family (SOCS1–7, CIS) have been identified. In a negative feedback mechanism, expression of SOCS proteins is induced by activated STATs, resulting in inhibition of JAK/STAT signaling (Fig. 2). SOCS proteins contain an SH2 domain, which allows them to dock at the cytokine receptor and inhibit JAK kinase activity by promoting proteasome-mediated degradation of the entire signaling complex. Two members of the SOCS family, SOCS1 and SOCS3, also contain an additional kinase-inhibitory region (KIR), which inhibits the catalytic activity of JAKs [43–45].

2. Role of JAK/STAT signaling in innate immunity in neuro-inflammatory diseases

2.1. Multiple sclerosis/EAE

MS is a demyelinating disease of the CNS that causes chronic inflammation and neuronal degeneration in the brain, spinal cord, and optic nerves [46]. The etiology of MS is still a mystery, although it is well established that auto-reactive lymphocytes, especially $CD4^+$ T cells targeting CNS components, trigger disease initiation [47]. However, other immune cell types such as $CD8^+$ T cells, B cells and myeloid cells directly or indirectly promote lesion formation and neuronal damage [34,48–50]. Numerous proteins may serve as auto-antigens in MS, including myelin basic protein (MBP), proteolipid protein (PLP), myelin oligodendrocyte glycoprotein (MOG), myelin-associated glycoprotein (MAG), glial fibrillary acidic protein (GFAP), and heat shock proteins [51]. Among these antigens, MBP, PLP, and MOG have been demonstrated to cause clinical symptoms in experimental animals and are used to induce EAE in mice. Currently, MOG-induced EAE is the model most commonly used to study the pathogenesis of MS due to its strong autoimmune response and clinical relevance [51].

Although it is known that JAK/STAT signaling plays an important role in the pathogenesis of MS/EAE, the underlying mechanisms are complex, as multiple cellular components are involved in the initiation and progression of this multifaceted disease. Auto-reactive $CD4^+$ Th1 and Th17 cells are the primary effector cells in MS/EAE [47]. In fact, adoptive transfer of auto-reactive Th1 or Th17 cells alone can cause EAE [47,52]. However, we appreciate that $CD4^+$ T cells alone do not mediate disease initiation and progression. Rather, it is the

complex interaction of cells of the innate immune system with T cells that lead to ultimate pathophysiology.

2.1.1. Microglia and infiltrating macrophages—Microglia and infiltrating macrophages are the major population of immune cells isolated from the CNS during EAE. Microglia and infiltrating macrophages can be distinguished by morphology and surface markers. Microglia have multiple primary processes and are CD45-^{int}CD11b^{+}, whereas infiltrating macrophages lack processes and are CD45^{hi}CD11b^{+} [53–55]. Microglia and infiltrating macrophages also express different chemokine receptors; microglia express the fractalkine receptor CX3CR1, whereas infiltrating macrophage express CCR2 [34]. Upon activation by different stimuli, many of which utilize JAK/STAT signaling, microglia and infiltrating macrophages can be polarized into a spectrum of phenotypes, which at extremes represent either pro-inflammatory or anti-inflammatory phenotypes [56,57]. Due to the variety of stimuli existing in the CNS during inflammation, microglia and infiltrating macrophages have complex functions ranging from detrimental to beneficial [58–63].

In EAE, autoreactive Th1 cells produce IFN-γ via STAT4, which promotes activation of pro-inflammatory macrophages via STAT1. Similarly, Th17 cells produce GM-CSF in the CNS, which favors pro-inflammatory polarization of macrophages via JAK2/STAT5 [64]. Other transcription factors besides STATs, such as Tbet and RORγt, play critical roles in T cell activation. They are not discussed in this article, as there are abundant reviews on this topic [65–68]. These pro-inflammatory macrophages play a detrimental role in development and progression of EAE. Mice with a targeted GM-CSF receptor deficiency in CCR2^{+} monocytes are completely resistant to induction of EAE [69], demonstrating the importance of this JAK/STAT-mediated signaling pathway in EAE. Similar to EAE mice, pro-inflammatory macrophages are also found in CNS lesions associated with human MS [70]. MS patients with protein tyrosine phosphatase SHP-1 deficiency have elevated levels of STAT1 and STAT6 activation along with a pro-inflammatory phenotype of macrophages [71]. Additionally, pro-inflammatory macrophages are involved in the polarization of pathogenic T cells. In EAE, by producing IL-12, pro-inflammatory microglia/macrophages facilitate Th1 polarization via JAK2/TYK2 and STAT4 [72–74]. In addition, by producing IL-23 and IL-6, pro-inflammatory microglia/macrophages facilitate Th17 polarization via JAK1/2 and STAT3 [75,76]. Pro-inflammatory myeloid cells also produce a number of factors which promote neuronal degeneration [77].

On the other hand, macrophages that are polarized into the anti-inflammatory phenotype tend to be beneficial in the context of neuroinflammatory diseases. Polarization of anti-inflammatory macrophages and microglia can be driven by IL-4 and IL-13 via JAK1/3 and STAT6 [78], by IL-10 via JAK1 and STAT3, or by M-CSF through other pathways [64]. Macrophages polarized in those conditions elicit a strong anti-inflammatory response by increasing production of IL-10 and decreasing production of IL-23 and IL-6 [73]. Macrophages secreting IL-10 have been shown to attenuate EAE by strongly suppressing Th1 and Th17 phenotypes via STAT3 [79] and promoting Th2 and Treg differentiation [80]. Thus, anti-inflammatory macrophages play a crucial role in diminishing the clinical symptoms of EAE. Consistent with this role, mice lacking STAT6 exhibit an earlier onset of

EAE and attain a higher disease grade, which could be attributed to decreased induction of Th2 cells and Th2-induced anti-inflammatory microglia/macrophages [81].

2.1.2. Neutrophils—Neutrophils are the most abundant immune cell type in human peripheral blood and are the major pathogen-fighting cells [82]. However, the contribution of neutrophils to MS/EAE has long been overlooked because they are rarely observed in MS or EAE lesions [83]. Recently, new evidence has suggested that these cells do, in fact, have important functions in the progression of MS/EAE. Infiltrating neutrophils contribute to brain inflammation in EAE and are critical for the occurrence of the atypical phenotype of EAE [35,84]. Administration of recombinant G-CSF, a cytokine critical for neutrophil activation, was found to exacerbate progression of MS [83,85]. In EAE, autoreactive Th17 cells, via STAT3 activation, produce IL-17A, which strongly stimulates astrocytes to produce the neutrophil recruiting factors G-CSF and CXCL1 [86].Similarly, in mice with EAE induced by adoptive transfer of Th17 cells, levels of G-CSF and the neutrophil-recruiting chemokines CXCL1 and CXCL2 are elevated in the CNS, leading to increases in the number of lesion-associated neutrophils, as well as G-CSF [87]. G-CSF promotes neutrophil differentiation and activation via JAK1/2 and STAT3 [88]. G-CSF also promotes neutrophil migration through STAT3-mediated activation of CXCR2, a chemokine receptor for the neutrophil recruitment ligand CXCL1/2 [89]. G-CSF signaling is crucial for development of MS/EAE, as mice deficient in the G-CSF receptor are resistant to MOG-induced EAE [83]. In MS patients, levels of the systemic neutrophil-recruiting chemokines CXCL1 and CXCL5 correlate with measures of MS lesion burden and clinical disability [83]. Dimethyl fumarate, a drug that has been shown to improve functional outcomes for patients with MS, appears to exert its protective effect in EAE by affecting neutrophil adhesion and chemotaxis [90]. Activated neutrophils disrupt the integrity of the BBB, thereby promoting MS/EAE development [91, 92]. Infiltrating neutrophils also secrete various cytokines such as IL-6, IL-12, and IFN-γ that promote activation of pro-inflammatory macrophages and Th1/17 differentiation via distinct JAK/STAT signaling mechanisms in EAE [36], resulting in neuronal death in response to secretion of TNF-α and iNOS [35].

2.1.3. Astrocytes—Astrocytes continuously sense the microenvironment and their responses may play a dual function in MS/EAE. During EAE, JAK/STAT signaling activates astrocytes to release a variety of soluble mediators that activate and recruit immune cells into the CNS [9–11]. We have shown that astrocytes, in respond to IFN-β and activation of STAT1, secrete various chemokines to recruit monocytes (CCL2, CCL3, CCL5) and $CD4^+$ T cells (CXCL10) [93]. Astrocytes can also be activated in response to endoplasmic reticulum (ER) stress, which has been shown to be associated with MS [94]. We found that astrocyte activation in response to ER stress occurs via JAK1/STAT3 signaling and that activation of STAT3 is dependent on PERK, a central sensor of ER stress. ER stress-activated astrocytes secrete pro-inflammatory cytokines such as IL-6 and oncostatin M (OSM) [95], and IL-6 produced by astrocytes has been shown to be critical for the induction of EAE [96,97]. IFN-γ signaling in astrocytes is involved in EAE, and the severity of EAE was reduced by depletion of IFN-γ receptors in these cells [98]. Astrocytes also produce GM-CSF during the EAE disease process, which polarizes microglia and infiltrating monocytes into the pro-

inflammatory phenotype via JAK2/STAT5 [11]. It is important to note that in addition to these pro-inflammatory functions, astrocytes have also been reported to have beneficial effects in CNS neuroinflammatory responses [99–101].

2.1.4. Regulation of JAK/STAT signaling in EAE and demyelinating disorders—

As described in Section 1.2, SOCS proteins are negative regulators of JAK/STAT signaling. We previously demonstrated that mice with a conditional deletion of SOCS3 in myeloid cells (LysMCre-SOCS3$^{fl/fl}$) develop a severe, non-resolving, atypical form of EAE after MOG immunization. We observed enhanced STAT3 activation and increased levels of proinflammatory cytokines/chemokines in the CNS of these mice, as well as prolonged JAK/STAT activation and enhancement of the pro-inflammatory macrophage phenotype [77]. The hyperactivated macrophages produced higher levels of pro-inflammatory cytokines, including IL-1β, IL-6, IL-12, and IL-23, and also more strongly induced Th1 and Th17 cell responses, consistent with a pathogenic role in EAE [102]. Enhanced neutrophil infiltration in the CNS was also observed in LysMCre-SOCS3$^{fl/fl}$ mice with MOG-induced EAE. We reported that the preferential recruitment of neutrophils to the cerebellum and brainstem is critical for the atypical EAE phenotype. Infiltrating SOCS3-deficient neutrophils in the cerebellum and brainstem exhibited increased production of proinflammatory cytokines and chemokines, including CXCL2, NO and TNF-α, and their numbers correlated with disease phenotype and severity. Neutrophil depletion in LysMCre-SOCS3$^{fl/fl}$ mice converted the phenotype from atypical to classical or mixed classical/atypical EAE [35]. These findings strongly suggest a role for neutrophils in the pathogenesis of EAE, and an important role of the JAK/STAT pathway in regulating neutrophil function.

Regulation of JAK/STAT signaling also appears to modulate chemical-induced demyelination. Cuprizone is a copper chelator that induces oligodendrocyte apoptosis and demyelination in the CNS. It has recently been reported that CXCR2-positive neutrophils are essential for cuprizone-induced demyelination, as mice deficient in CXCR2 are relatively resistance to cuprizone-induced demyelination [103]. CX3CR1^{+} microglia are critical for remyelination in this model. In CX3CR1 deficient mice the clearance of myelin debris is abrogated, leading to improper remyelination [104]. A recent study demonstrated that myelin-reactive Th17 cells impair the endogenous remyelination process, possibly due to recruitment of pro-inflammatory peripheral monocytes [105]. Our unpublished data reveal that SOCS3 deficiency in myeloid cells results in a more severe and accelerated demyelination in response to cuprizone. Five weeks after feeding with cuprizone chow, mice with myeloid SOCS3 deficiency exhibited extensive demyelination, compared to SOCS3$^{fl/fl}$ mice, which exhibited myelin loss at eight weeks (Fig. 3). This suggests a role for innate immunity and JAK/STAT signaling in promoting oligodendrocyte apoptosis and demyelination.

2.2. Parkinson’s disease

Parkinson’s Disease (PD) is a chronic neurodegenerative disorder characterized by decreased motor activity, which is caused by the loss of dopaminergic (DA) neurons in the substantia nigra pars compacta in the midbrain [106,107]. The pathology of PD brain is characterized by inclusions of aggregated α-synuclein (α-SYN) in the cytoplasmic region of

DA neurons, named Lewy bodies (LB) and Lewy neurites (LN) [108]. Ample evidence indicates that the JAK/STAT pathway is involved in PD pathogenesis. IFN-γ and IL-6 are two of the most potent activators of the JAK/STAT pathway, and are elevated in PD [109–111]. Regarding IL-6, higher levels were associated with a greater risk of PD [109,110]. IFN-γ contributes to degeneration of DA neurons through a mechanism involving microglia, and IFN-γ deficient mice are protected against MPTP-induced neurotoxicity [111].

2.2.1. Microglial involvement in PD—A genome-wide association study (GWAS) has revealed a close relationship between immune activation and susceptibility to PD [112]. Chronic inflammation in the CNS has long been noted in PD and has been proposed to play important roles in the pathogenesis of disease [113]. Aggregation of α-SYN, a protein encoded by *SNCA1* gene whose function is not well understood, is considered to be pathogenic due to chronic activation of the innate immune system [114,115]. Microglia are the front-line defenders and exhibit pro-inflammatory phenotype in PD [116]. Activated microglia and infiltrating macrophages have been observed post-mortem in the substantia nigra of human PD patients, and the degree of MHC Class II expression correlates with the level of α-SYN [28,117]. This observation suggests that α-SYN drives the activation of microglia and infiltrating macrophages, which is supported by experiments in vitro and in vivo. Stimulation of mouse microglial cell lines or primary microglia with aggregated α-SYN results in MHC Class II expression and production of NO, TNF-α, and IL-1β [23, 114,118,119]. This response was abrogated by the inclusion of the JAK1/ 2 inhibitor, AZD1480, by preventing activation of the JAK/STAT pathway [119]. Overexpression of α-SYN in the substantia nigra using adeno-associated virus (AAV), a model for PD, leads to microgliosis and upreg-ulation of MHC Class II in microglia as early as four weeks post-injection [119]. Increases in pro-inflammatory cytokines including IL-1β, IFN-γ, and TNF-α were detected in the striatum, and α-SYN-induced chronic inflammation resulted in subsequent neuronal death [117,119,120].

Just as enhanced activation of microglia contributes to progression of PD, inhibition of microglia activation appears to be beneficial. Blockade of the CD200-CD200R interaction, an inhibitory mechanism that represses microglial activation, exacerbates microglial activation and DA neurodegeneration in a rat model of PD [121]. Similarly, treatment with minocycline, an FDA-approved tetracycline derivative that inhibits microglial activation, prevented nigrostriatal DA neurodegeneration in the MPTP model of PD [122,123]. Mice with a deficiency in IFN-γ, which promotes polarization of pro-inflammatory macrophages through activation of the JAK/STAT pathway, displayed attenuated MPTP-induced substantia nigra pars compacta DA neuron loss [111].

Genetic models also suggest a role for microglia in the pathogenesis of PD. Leucine-rich repeat kinase 2 (LRRK2) is the most commonly mutated gene in idiopathic and familial PD [124,125]. LRRK2 expression is enriched in immune cells, especially in B cells, monocytes and DCs [126]. LRRK2 is an IFN-γ induced gene, and is involved in ROS production during host defense [126]. Although LRRK2 mutations have been shown to correlate with PD, its function, especially in immune cells during neuroinflammation, is not well understood. The G2019S mutation in LRRK2 was shown to exacerbate α-SYN induced neuroinflammation and DA neurodegeneration, and this detrimental effect was mitigated by

LRRK2 inhibition [127]. A recent study showed that the G2019S mutation of LRRK2 attenuates microglial motility by inhibiting focal adhesion kinase activity and, as a result, suppresses the microglial response to stab-wound and laser-induced brain injury [128].

GWAS analysis has also revealed a correlation between PD susceptibility and HLA-DR, the gene that encodes MHC Class II in humans [129]. Additional evidence further supports a role for MHC Class II in PD pathogenesis. In a mouse model of PD, overexpression of α-SYN led to striking upregulation of MHC Class II in microglia. Moreover, MHC Class II deletion prevented activation of microglia, $CD4^+$ T cell proliferation, and DA neurodegeneration [27].

2.2.2. Involvement of other immune cells in PD—In addition to microglia, other cell types are involved in the pathogenesis of PD. In PD, susceptibility alleles are enriched in monocyte-specific genes, suggesting a critical role for myeloid cells in the prodromal phase of disease [130]. LRRK2-deficient rats exhibit abrogated α-SYN-mediated DA neurodegeneration. This attenuation is correlated with reduced numbers of activated myeloid cells in the substantia nigra [131]. Another study found that astrocyte-mediated production of pro-inflammatory cytokines also contributes to neuronal loss in an LPS-induced PD model [132]. The aforementioned role of MHC Class II upregulation in microglia/macrophages in PD pathogenesis also suggests the involvement of $CD4^+$ T cells in the pathogenesis of PD, since they are activated by antigen presenting cells expressing MHC Class II [27]. There is evidence for T cell involvement in PD, particularly that of $CD4^+$ T cells [133–135].

3. Therapeutic value of inhibitors of JAK/STAT signaling in neuroinflammatory disease models

Although JAK/STAT signaling plays important roles in both pro- and anti-inflammatory responses, the acute phase of MS/EAE and the chronic inflammation observed in PD are primarily consequences of pro-inflammatory responses. The involvement of JAK/STAT signaling in the pathogenesis of neuroinflammatory diseases suggests that inhibition of JAK/STAT signaling could provide therapeutic benefit. In support of this hypothesis, pre-clinical studies have demonstrated efficacy of JAK/STAT inhibition in neuroinflammatory diseases.

3.1. Inhibition of JAK/STAT signaling is beneficial in EAE models

Numerous small molecules have been designed to target JAKs, termed Jakinibs (JAK inhibitors) [136]. Many of these agents have been tested in various cancers, autoimmune diseases and inflammatory disorders. Because the pathogenesis of MS/EAE encompasses dysregulation of both innate and adaptive immunity, the efficacy and mechanism of disease attenuation by Jakinibs has been analyzed in EAE models. For example, the JAK2 inhibitor Tyrophostin B42 (AG490) has been shown to improve EAE scores through inhibition of JAK2/STAT1 signaling and disruption ofTh1 cell differentiation [137]. CEP-701, a JAK2 inhibitor, was demonstrated to suppress STAT1/3/5 signaling and reduce secretion of TNF-α, IL-6, and IL-23 in DCs, resulting in attenuation of EAE [138]. Recently, we found that AZD1480, an inhibitor of JAK1 and JAK2, is anti-inflammatory and confers protection in

multiple EAE models [139]. Treatment with AZD1480 inhibited activation of STAT1/ 3/4 and blocked differentiation of both Th1 and Th17 cells. Similarly, in antigen-presenting cells (APCs), AZD1480 disrupted IFN-γ-, IL-6-, and GM-CSF-induced activation of STAT1, STAT3, and STAT5, respectively. Pro-inflammatory phenotypic markers such as MHC Class II, iNOS, and CD40 were also inhibited by AZD1480 treatment. Together, these observations indicate that AZD1480 attenuates EAE by preventing CNS infiltration of immune cells, suppressing differentiation of Th1 and Th17 cells, and deactivating innate immune cells.

Many herbal compounds from plants have long been recognized as having anti-inflammatory or immune-suppressive effects. Recent studies have demonstrated that some of these natural compounds inhibit JAK/STAT signaling and have beneficial effects in neuroinflammatory diseases. For example, berbamine (BM), an herbal compound commonly used in traditional Chinese medicine derived from *Berberis vulgaris* L, has been shown to attenuate EAE symptoms by promoting STAT4 degradation. BM treatment reduced the stimulatory functions of APCs and inhibited IFN-γ production by T cells [140]. Berberine (BBR), an isoquinoline alkaloid derived from plants, also ameliorated EAE symptoms through a mechanism involving inhibition of JAK/STAT signaling in Th1 and Th17 cells, as well as reduced production of IL-6 by innate immune cells [141]. Similar studies have demonstrated the efficacy of other natural compounds, such as Tripchlorolide [142], Quercetin [143], and vitamin D3 [144], in ameliorating EAE through inhibition of JAK/ STAT signaling and Th1 and Th17 differentiation.

Some pharmacologic compounds, although not designed to be JAK/ STAT inhibitors, have been shown to have therapeutic benefit in MS/ EAE due to inhibition of JAK/STAT signaling. Glatiramer acetate (GA), a FDA-approved treatment for MS, was shown to promote activation of anti-inflammatory monocytes by reducing STAT1 signaling. Antiinflammatory monocytes produced lower levels of pro-inflammatory cytokines and increased production of IL-10 and TGF-β in the CNS, leading to attenuation of EAE [80]. Fumarates have been reported to improve MS by promoting development of type II DCs that produce IL-10, instead of IL-12 and IL-23, via inhibition of STAT1. The increase in type II DCs promoted Th2 cell differentiation and protected mice from EAE [145]. Statins are utilized primarily for treatment of hypercholesterolemia [146,147], but recent studies have demonstrated that simvastatin has therapeutic benefit in some MS patients [148,149]. Simvastatin treatment suppresses STAT1/3 activation by inducing SOCS3/7, inhibits IL-6 and IL-23 production, and induces IFN-γ, IL-4, and IL-27 production in monocytes. These phenotypic changes in monocytes inhibited the differentiation of Th17 cells in MS patients [150]. Furthermore, we demonstrated that simvastatin-mediated inhibition of STAT1 signaling resulted in abrogation of IFN-γ-induced expression of CD40 in macrophages and microglia [151].

3.2. Therapeutic potential for treatment of PD with JAK/STAT inhibitors

Since there is evidence that the disease of PD has a strong neuro-inflammatory component, the concept of treating PD with immunomodulatory agents is promising. In a rat model of PD, where α-SYN was overexpressed in the substantia nigra by AAV, AZD1480 treatment

decreased microgliosis and macrophage infiltration, reduced expression of MHC Class II and decreased pro-inflammatory cytokines produced by microglia/macrophages at 4 weeks after transfection. Furthermore, STAT3 activation in the substantia nigra was reduced by AZD1480 treatment [119]. RNA-seq analysis demonstrated that numerous genes involved in cell-cell signaling, nervous system development and function, inflammatory diseases and processes, and neurological diseases were enhanced in the substantia nigra of rats with α-SYN overexpression, and were inhibited upon treatment with AZD1480. AZD1480 treatment also reduced $CD4^+$ T cell infiltration into CNS and prevented degeneration of DA neurons in the substantia nigra 12 weeks after infection. Together, these results indicate that JAK/STAT signaling promotes activation of both innate and adaptive immune responses in a PD model.

4. Conclusions

Innate immunity is critical for host defense and homeostasis of the immune system, however, dysregulation leads to severe consequences, such as neuroinflammatory diseases. Aberrant activation of innate immune cells causes demyelination and/or neuronal degeneration by production of pro-inflammatory cytokines, chemokines, ROS and NO, or by activation of effector T cells. Many of these processes involve utilization of JAK/STAT signaling. Hence, this suggests the feasibility of targeting the JAK/STAT pathway as a protective therapy for neuroinflammatory and neurodegenerative diseases. Currently, more than 25 Jakinibs are in Phase I, II and III clinical trials for a variety of diseases, including psoriasis, transplant rejection, diabetic nephropathy, Crohn's diseases, lupus, lymphoma, and solid tumors [136]. Our pre-clinical studies in animal models of MS and PD suggest that suppression of the JAK/STAT pathway disrupts both neuroinflammatory and neurodegenerative processes. As such, Jakinibs may be a viable therapeutic option for MS and PD patients, especially since they are orally available and well tolerated.

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References

1. O'Shea JJ, Gadina M, Kanno Y. Cytokine signaling: birth of a pathway. J Immunol. 2011; 187:5475–5478. [PubMed: 22102730]
2. O'Shea JJ, Plenge R. JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. Immunity. 2012; 36:542–550. [PubMed: 22520847]
3. Ransohoff RM, Brown MA. Innate immunity in the central nervous system. J Clin Invest. 2012; 122:1164–1171. [PubMed: 22466658]
4. Louveau A, Harris TH, Kipnis J. Revisiting the mechanisms of CNS immune privilege. Trends Immunol. 2015; 36:569–577. [PubMed: 26431936]
5. Nimmerjahn A, Kirchhoff F, Helmchen F. Resting microglial cells are highly dynamic surveillants of brain parenchyma. in vivo, Science. 2005; 308:1314–1318. [PubMed: 15831717]

6. Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB. ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci. 2005; 8:752–758. [PubMed: 15895084]
7. Nayak D, Roth TL, McGavern DB. Microglia development and function. Annu Rev Immunol. 2014; 32:367–402. [PubMed: 24471431]
8. Khakh BS, Sofroniew MV. Diversity of astrocyte functions and phenotypes in neural circuits. Nat Neurosci. 2015; 18:942–952. [PubMed: 26108722]
9. Tanuma N, Sakuma H, Sasaki A, Matsumoto Y. Chemokine expression by astrocytes plays a role in microglia/macrophage activation and subsequent neurodegeneration in secondary progressive multiple sclerosis. Acta Neuropathol. 2006; 112:195–204. [PubMed: 16733654]
10. Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. Trends Immunol. 2007; 28:138–145. [PubMed: 17276138]
11. Mayo L, Trauger SA, Blain M, Nadeau M, Patel B, Alvarez JI, Mascanfroni ID, Yeste A, Kivisakk P, Kallas K, Ellezam B, Bakshi R, Prat A, Antel JP, Weiner HL, Quintana FJ. Regulation of astrocyte activation by glycolipids drives chronic CNS inflammation. Nat Med. 2014; 20:1147–1156. [PubMed: 25216636]
12. Goldstein EZ, Church JS, Hesp ZC, Popovich PG, McTigue DM. A silver lining of neuroinflammation: beneficial effects on myelination. Exp Neurol. 2016; 283:550–559. [PubMed: 27151600]
13. Gaesser JM, Fyffe-Maricich SL. Intracellular signaling pathway regulation of myelination and remyelination in the CNS. Exp Neurol. 2016; 283:501–511. [PubMed: 26957369]
14. Lin W, Kemper A, Dupree JL, Harding HP, Ron D, Popko B. Interferon-γ inhibits central nervous system remyelination through a process modulated by endoplasmic reticulum stress. Brain. 2006; 129:1306–1318. [PubMed: 16504972]
15. Hussien Y, Podojil JR, Robinson AP, Lee AS, Miller SD, Popko B. ER chaperone BiP/ GRP78 is required for myelinating cell survival and provides protection during experimental autoimmune encephalomyelitis. J Neurosci. 2015; 35:15921–15933. [PubMed: 26631473]
16. Church JS, Kigerl KA, Lerch JK, Popovich PG, McTigue DM. TLR4 deficiency impairs oligodendrocyte formation in the injured spinal cord. J Neurosci. 2016; 36:6352–6364. [PubMed: 27277810]
17. Moore CS, Cui QL, Warsi NM, Durafourt BA, Zorko N, Owen DR, Antel JP, Bar-Or A. Direct and indirect effects of immune and central nervous system-resident cells on human oligodendrocyte progenitor cell differentiation. J Immunol. 2015; 194:761–772. [PubMed: 25505283]
18. Traka M, Podojil JR, McCarthy DP, Miller SD, Popko B. Oligodendrocyte death results in immune-mediated CNS demyelination. Nat Neurosci. 2016; 19:65–74. [PubMed: 26656646]
19. Ousman SS, Kubes P. Immune surveillance in the central nervous system. Nat Neurosci. 2012; 15:1096–1101. [PubMed: 22837040]
20. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J. Structural and functional features of central nervous system lymphatic vessels. Nature. 2015; 523:337–341. [PubMed: 26030524]
21. Aspelund A, Antila S, Proulx ST, Karlsen TV, Karaman S, Detmar M, Wiig H, Alitalo K. A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. J Exp Med. 2015; 212:991–999. [PubMed: 26077718]
22. Li J, Gran B, Zhang GX, Ventura ES, Siglienti I, Rostami A, Kamoun M. Differential expression and regulation of IL-23 and IL-12 subunits and receptors in adult mouse microglia. J Neurol Sci. 2003; 215:95–103. [PubMed: 14568135]
23. Lee EJ, Woo MS, Moon PG, Baek MC, Choi IY, Kim WK, Junn E, Kim HS. Alpha-synuclein activates microglia by inducing the expressions of matrix metal-loproteinases and the subsequent activation of protease-activated receptor-1. J Immunol. 2010; 185:615–623. [PubMed: 20511551]
24. Noubade R, Wong K, Ota N, Rutz S, Eidenschenk C, Valdez PA, Ding J, Peng I, Sebrell A, Caplazi P, DeVoss J, Soriano RH, Sai T, Lu R, Modrusan Z, Hackney J, Ouyang W. NRROS negatively regulates reactive oxygen species during host defence and autoimmunity. Nature. 2014; 509:235–239. [PubMed: 24739962]

25. Herz J, Johnson KR, McGavern DB. Therapeutic antiviral T cells noncytopathically clear persistently infected microglia after conversion into antigen-presenting cells. J Exp Med. 2015; 212:1153–1169. [PubMed: 26122661]
26. Mack CL, Vanderlugt-Castaneda CL, Neville KL, Miller SD. Microglia are activated to become competent antigen presenting and effector cells in the inflammatory environment of the Theiler's virus model of multiple sclerosis. J Neuroimmunol. 2003; 144:68–79. [PubMed: 14597100]
27. Harms AS, Cao S, Rowse AL, Thome AD, Li X, Mangieri LR, Cron RQ, Shacka JJ, Raman C, Standaert DG. MHCII is required for α-synuclein-induced activation of microglia, CD4 T cell proliferation, and dopaminergic neurodegeneration. J Neurosci. 2013; 33:9592–9600. [PubMed: 23739956]
28. McGeer PL, Itagaki S, Boyes BE, McGeer EG. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. Neurology. 1988; 38:1285–1291. [PubMed: 3399080]
29. Gobin SJP, Montagne L, Van Zutphen M, Van Der Valk P, Van Den Elsen PJ, De Groot CJA. Upregulation oftranscription factors controlling MHC expression in multiple sclerosis lesions. Glia. 2001; 36:68–77. [PubMed: 11571785]
30. Fischer HG, Bonifas U, Reichmann G. Phenotype and functions of brain dendritic cells emerging during chronic infection of mice with *Toxoplasma gondii*. J Immunol. 2000; 164:4826–4834. [PubMed: 10779791]
31. McMahon EJ, Bailey SL, Castenada CV, Waldner H, Miller SD. Epitope spreading initiates in the CNS in two mouse models of multiple sclerosis. Nat Med. 2005; 11:335–339. [PubMed: 15735651]
32. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol. 2011; 11:519–531. [PubMed: 21785456]
33. Pelletier M, Maggi L, Micheletti A, Lazzeri E, Tamassia N, Costantini C, Cosmi L, Lunardi C, Annunziato F, Romagnani S, Cassatella MA. Evidence for a cross-talk between human neutrophils and Th17 cells. Blood. 2010; 115:335–343. [PubMed: 19890092]
34. Yamasaki R, Lu H, Butovsky O, Ohno N, Rietsch AM, Cialic R, Wu PM, Doykan CE, Lin J, Cotleur AC, Kidd G, Zorlu MM, Sun N, Hu W, Liu L, Lee JC, Taylor SE, Uehlein L, Dixon D, Gu J, Floruta CM, Zhu M, Charo IF, Weiner HL, Ransohoff RM. Differential roles of microglia and monocytes in the inflamed central nervous system. J Exp Med. 2014; 211:1533–1549. [PubMed: 25002752]
35. Liu Y, Holdbrooks AT, Meares GP, Buckley JA, Benveniste EN, Qin H. Preferential recruitment of neutrophils into the cerebellum and brainstem contributes to the atypical experimental autoimmune encephalomyelitis phenotype. J Immunol. 2015; 195:841–852. [PubMed: 26085687]
36. Steinbach K, Piedavent M, Bauer S, Neumann JT, Friese MA. Neutrophils amplify autoimmune central nervous system infiltrates by maturing local APCs. J Immunol. 2013; 191:4531–4539. [PubMed: 24062488]
37. Hao J, Liu R, Piao W, Zhou Q, Vollmer TL, Campagnolo DI, Xiang R, La Cava A, Van Kaer L, Shi FD. Central nervous system (CNS)-resident natural killer cells suppress Th17 responses and CNS autoimmune pathology. J Exp Med. 2010; 207:1907–1921. [PubMed: 20696699]
38. Winkler-Pickett R, Young HA, Cherry JM, Diehl J, Wine J, Back T, Bere WE, Mason AT, Ortaldo JR. In vivo regulation of experimental autoimmune encephalomyelitis by NK cells: alteration of primary adaptive responses. J Immunol. 2008; 180:4495–4506. [PubMed: 18354171]
39. Poli A, Kmiecik J, Domingues O, Hentges F, Blery M, Chekenya M, Boucraut J, Zimmer J. NK cells in central nervous system disorders. J Immunol. 2013; 190:5355–5362. [PubMed: 23687193]
40. Benveniste EN, Liu Y, McFarland BC, Qin H. Involvement of the Janus kinase/signal transducer and activator of transcription signaling pathway in multiple sclerosis and the animal model of experimental autoimmune encephalomyelitis. J Interf Cytokine Res. 2014; 34:577–588.
41. Murray PJ. The JAK-STAT signaling pathway: input and output integration. J Immunol. 2007; 178:2623–2629. [PubMed: 17312100]
42. van Boxel-Dezaire AH, Rani MR, Stark GR. Complex modulation of cell type-specific signaling in response to type I interferons. Immunity. 2006; 25:361–372. [PubMed: 16979568]

43. Baker BJ, Akhtar LN, Benveniste EN. SOCS1 and SOCS3 in the control of CNS immunity. Trends Immunol. 2009; 30:392–400. [PubMed: 19643666]
44. Babon JJ, Sabo JK, Zhang JG, Nicola NA, Norton RS. The SOCS box encodes a hierarchy of affinities for Cullin 5: implications for ubiquitin ligase formation and cytokine signalling suppression. J Mol Biol. 2009; 387:162–174. [PubMed: 19385048]
45. Yoshimura A, Naka T, Kubo M. SOCS proteins, cytokine signalling and immune regulation. Nat Rev Immunol. 2007; 7:454–465. [PubMed: 17525754]
46. Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. Nat Rev Immunol. 2015; 15:545–558. [PubMed: 26250739]
47. Goverman J. Autoimmune T cell responses in the central nervous system. Nat Rev Immunol. 2009; 9:393–407. [PubMed: 19444307]
48. Ortega SB, Kashi VP, Tyler AF, Cunnusamy K, Mendoza JP, Karandikar NJ. The disease-ameliorating function of autoregulatory CD8 T cells is mediated by targeting of encephalitogenic CD4 T cells in experimental autoimmune encephalomyelitis. J Immunol. 2013; 191:117–126. [PubMed: 23733879]
49. Ray A, Basu S, Williams CB, Salzman NH, Dittel BN. A novel IL-10-independent regulatory role for B cells in suppressing autoimmunity by maintenance of regulatory T cells via GITR ligand. J Immunol. 2012; 188:3188–3198. [PubMed: 22368274]
50. Ransohoff RM, Hafler DA, Lucchinetti CF. Multiple sclerosis-a quiet revolution. Nat Rev Neurol. 2015; 11:134–142. [PubMed: 25686758]
51. Robinson AP, Harp CT, Noronha A, Miller SD. The experimental autoimmune encephalomyelitis (EAE) model of MS: utility for understanding disease pathophysiology and treatment. Handb Clin Neurol. 2014; 122:173–189. [PubMed: 24507518]
52. Jager A, Dardalhon V, Sobel RA, Bettelli E, Kuchroo VK. Th1, Th17, and Th9 effector cells induce experimental autoimmune encephalomyelitis with different pathological phenotypes. J Immunol. 2009; 183:7169–7177. [PubMed: 19890056]
53. Saederup N, Cardona AE, Croft K, Mizutani M, Cotleur AC, Tsou CL, Ransohoff RM, Charo IF. Selective chemokine receptor usage by central nervous system myeloid cells in CCR2-red fluorescent protein knock-in mice. PLoS One. 2010; 5:e13693. [PubMed: 21060874]
54. Mizutani M, Pino PA, Saederup N, Charo IF, Ransohoff RM, Cardona AE. The fractalkine receptor but not CCR2 is present on microglia from embryonic development throughout adulthood. J Immunol. 2012; 188:29–36. [PubMed: 22079990]
55. Shaked I, Hanna RN, Shaked H, Chodaczek G, Nowyhed HN, Tweet G, Tacke R, Basat AB, Mikulski Z, Togher S, Miller J, Blatchley A, Salek-Ardakani S, Darvas M, Kaikkonen MU, Thomas GD, Lai-Wing-Sun S, Rezk A, Bar-Or A, Glass CK, Bandukwala H, Hedrick CC. Transcription factor Nr4a1 couples sympathetic and inflammatory cues in CNS-recruited macrophages to limit neuroinflammation. Nat Immunol. 2015; 16:1228–1234. [PubMed: 26523867]
56. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, Gordon S, Hamilton JA, Ivashkiv LB, Lawrence T, Locati M, Mantovani A, Martinez FO, Mege JL, Mosser DM, Natoli G, Saeij JP, Schultze JL, Shirey KA, Sica A, Suttles J, Udalova I, van Ginderachter JA, Vogel SN, Wynn TA. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014; 41:14–20. [PubMed: 25035950]
57. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Rep. 2014; 6:1–13. [PubMed: 24592313]
58. O'Rourke JG, Bogdanik L, Yanez A, Lall D, Wolf AJ, Muhammad AK, Ho R, Carmona S, Vit JP, Zarrow J, Kim KJ, Bell S, Harms MB, Miller TM, Dangler CA, Underhill DM, Goodridge HS, Lutz CM, Baloh RH. C9orf72 is required for proper macrophage and microglial function in mice. Science. 2016; 351:1324–1329. [PubMed: 26989253]
59. Zhu C, Herrmann US, Falsig J, Abakumova I, Nuvolone M, Schwarz P, Frauenknecht K, Rushing EJ, Aguzzi A. A neuroprotective role for microglia in prion diseases. J Exp Med. 2016; 213:1047–1059. [PubMed: 27185853]
60. Goldmann T, Zeller N, Raasch J, Kierdorf K, Frenzel K, Ketscher L, Basters A, Staszewski O, Brendecke SM, Spiess A, Tay TL, Kreutz C, Timmer J, Mancini GM, Blank T, Fritz G, Biber K,

Lang R, Malo D, Merkler D, Heikenwalder M, Knobeloch KP, Prinz M. USP18 lack in microglia causes destructive interferonopathy of the mouse brain. EMBO J. 2015; 34:1612–1629. [PubMed: 25896511]

61. Olah M, Amor S, Brouwer N, Vinet J, Eggen B, Biber K, Boddeke HW. Identification of a microglia phenotype supportive of remyelination. Glia. 2012; 60:306–321. [PubMed: 22072381]
62. Waschbisch A, Schroder S, Schraudner D, Sammet L, Weksler B, Melms A, Pfeifenbring S, Stadelmann C, Schwab S, Linker RA. Pivotal role for CD16+ monocytes in immune surveillance of the central nervous system. J Immunol. 2016; 196:1558–1567. [PubMed: 26746191]
63. Wang Y, Ulland TK, Ulrich JD, Song W, Tzaferis JA, Hole JT, Yuan P, Mahan TE, Shi Y, Gilfillan S, Cella M, Grutzendler J, DeMattos RB, Cirrito JR, Holtzman DM, Colonna M. TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. J Exp Med. 2016; 213:667–675. [PubMed: 27091843]
64. Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. Nat Rev Immunol. 2008; 8:533–544. [PubMed: 18551128]
65. Lee Y, Awasthi A, Yosef N, Quintana FJ, Xiao S, Peters A, Wu C, Kleinewietfeld M, Kunder S, Hafler DA, Sobel RA, Regev A, Kuchroo VK. Induction and molecular signature of pathogenic T(H)17 cells. Nat Immunol. 2012; 13:991–999. [PubMed: 22961052]
66. Xiao S, Yosef N, Yang J, Wang Y, Zhou L, Zhu C, Wu C, Baloglu E, Schmidt D, Ramesh R, Lobera M, Sundrud MS, Tsai PY, Xiang Z, Wang J, Xu Y, Lin X, Kretschmer K, Rahl PB, Young RA, Zhong Z, Hafler DA, Regev A, Ghosh S, Marson A, Kuchroo VK. Small-molecule RORgammat antagonists inhibit T helper 17 cell transcriptional network by divergent mechanisms. Immunity. 2014; 40:477–489. [PubMed: 24745332]
67. Basu R, Hatton RD, Weaver CT. The Th17 family: flexibility follows function. Immunol Rev. 2013; 252:89–103. [PubMed: 23405897]
68. Palmer MT, Weaver CT. Autoimmunity: increasing suspects in the CD4+ T cell lineup. Nat Immunol. 2010; 11:36–40. [PubMed: 20016508]
69. Croxford AL, Lanzinger M, Hartmann FJ, Schreiner B, Mair F, Pelczar P, Clausen BE, Jung S, Greter M, Becher B. The cytokine GM-CSF drives the inflammatory signature of CCR2+ monocytes and licenses autoimmunity. Immunity. 2015; 43:502–514. [PubMed: 26341401]
70. Vogel DY, Vereyken EJ, Glim JE, Heijnen PD, Moeton M, van der Valk P, Amor S, Teunissen CE, van Horssen J, Dijkstra CD. Macrophages in inflammatory multiple sclerosis lesions have an intermediate activation status. J Neuroinflammation. 2013; 10:35. [PubMed: 23452918]
71. Christophi GP, Panos M, Hudson CA, Christophi RL, Gruber RC, Mersich AT, Blystone SD, Jubelt B, Massa PT. Macrophages of multiple sclerosis patients display deficient SHP-1 expression and enhanced inflammatory phenotype. Lab Investig. 2009; 89:742–759. [PubMed: 19398961]
72. Krausgruber T, Blazek K, Smallie T, Alzabin S, Lockstone H, Sahgal N, Hussell T, Feldmann M, Udalova IA. IRF5 promotes inflammatory macrophage polarization and T(H)1-T(H)17 responses. Nat Immunol. 2011; 12:231–238. [PubMed: 21240265]
73. Mantovani A, Sica A, Locati M. Macrophage polarization comes of age. Immunity. 2005; 23:344–346. [PubMed: 16226499]
74. Natarajan C, Bright JJ. Curcumin inhibits experimental allergic encephalomyelitis by blocking Il-12 signaling through Janus kinase-STAT pathway in T lymphocytes. J Immunol. 2002; 168:6506–6513. [PubMed: 12055272]
75. Samoilova EB, Horton JL, Hilliard B, Liu TS, Chen Y. IL-6-deficient mice are resistant to experimental autoimmune encephalomyelitis: roles of IL-6 in the activation and differentiation of autoreactive T cells. J Immunol. 1998; 161:6480–6486. [PubMed: 9862671]
76. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymore B, Lucian L, To W, Kwan S, Churakova T, Zurawski S, Wiekowski M, Lira SA, Gorman D, Kastelein RA, Sedgwick JD. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. Nature. 2003; 421:744–748. [PubMed: 12610626]
77. Qin H, Yeh WI, De Sarno P, Holdbrooks AT, Liu Y, Muldowney MT, Reynolds SL, Yanagisawa LL, Fox THI, Park K, Harrington LE, Raman C, Benveniste EN. Signal transducer and activator of transcription-3/suppressor of cytokine signaling-3 (STAT3/SOCS3) axis in myeloid cells regulates neuroinflammation. Proc Natl Acad Sci U S A. 2012; 109:5004–5009. [PubMed: 22411837]

78. Gordon S. Alternative activation of macrophages. Nat Rev Immunol. 2003; 3:23–35. [PubMed: 12511873]

79. Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol. 2001; 19:683–765. [PubMed: 11244051]

80. Weber MS, Prod'homme T, Youssef S, Dunn SE, Rundle CD, Lee L, Patarroyo JC, Stuve O, Sobel RA, Steinman L, Zamvil SS. Type II monocytes modulate T cell-mediated central nervous system autoimmune disease. Nat Med. 2007; 13:935–943. [PubMed: 17676050]

81. Chitnis T, Najafian N, Benou C, Salama AD, Grusby MJ, Sayegh MH, Khoury SJ. Effect of targeted disruption of STAT4 and STAT6 on the induction of experimental autoimmune encephalomyelitis. J Clin Invest. 2001; 108:739–747. [PubMed: 11544280]

82. Mayadas TN, Cullere X, Lowell CA. The multifaceted functions of neutrophils. Annu Rev Pathol. 2014; 9:181–218. [PubMed: 24050624]

83. Rumble JM, Huber AK, Krishnamoorthy G, Srinivasan A, Giles DA, Zhang X, Wang L, Segal BM. Neutrophil-related factors as biomarkers in EAE and MS. J Exp Med. 2015; 212:23–35. [PubMed: 25559893]

84. Simmons SB, Liggitt D, Goverman JM. Cytokine-regulated neutrophil recruitment is required for brain but not spinal cord inflammation during experimental autoimmune encephalomyelitis. J Immunol. 2014; 193:555–563. [PubMed: 24913979]

85. Burt RK, Fassas A, Snowden J, van Laar JM, Kozak T, Wulffraat NM, Nash RA, Dunbar CE, Arnold R, Prentice G, Bingham S, Marmont AM, McSweeney PA. Collection of hematopoietic stem cells from patients with autoimmune diseases. Bone Marrow Transplant. 2001; 28:1–12. [PubMed: 11498738]

86. Kang Z, Altuntas CZ, Gulen MF, Liu C, Giltiay N, Qin H, Liu L, Qian W, Ransohoff RM, Bergmann C, Stohlman S, Tuohy VK, Li X. Astrocyte-restricted ablation of interleukin-17-induced Act1-mediated signaling ameliorates autoimmune encephalomyelitis. Immunity. 2010; 32:414–425. [PubMed: 20303295]

87. Kroenke MA, Carlson TJ, Andjelkovic AV, Segal BM. IL-12- and IL-23-modulated T cells induce distinct types of EAE based on histology, CNS chemokine profile, and response to cytokine inhibition. J Exp Med. 2008; 205:1535–1541. [PubMed: 18573909]

88. Tian SS, Tapley P, Sincich C, Stein RB, Rosen J, Lamb P. Multiple signaling pathways induced by granulocyte colony-stimulating factor involving activation of JAKs, STAT5, and/or STAT3 are required for regulation of three distinct classes of immediate early genes. Blood. 1996; 88:4435–4444. [PubMed: 8977235]

89. Nguyen-Jackson H, Panopoulos AD, Zhang H, Li HS, Watowich SS. STAT3 controls the neutrophil migratory response to CXCR2 ligands by direct activation of G-CSF-induced CXCR2 expression and via modulation of CXCR2 signal transduction. Blood. 2010; 115:3354–3363. [PubMed: 20185584]

90. Chen H, Assmann JC, Krenz A, Rahman M, Grimm M, Karsten CM, Kohl J, Offermanns S, Wettschureck N, Schwaninger M. Hydroxycarboxylic acid receptor 2 mediates dimethyl fumarate's protective effect in EAE. J Clin Invest. 2014; 124:2188–2192. [PubMed: 24691444]

91. Christy AL, Walker ME, Hessner MJ, Brown MA. Mast cell activation and neutrophil recruitment promotes early and robust inflammation in the meninges in EAE. J Autoimmun. 2013; 42:50–61. [PubMed: 23267561]

92. Aube B, Levesque SA, Pare A, Chamma E, Kebir H, Gorina R, Lecuyer MA, Alvarez JI, De Koninck Y, Engelhardt B, Prat A, Cote D, Lacroix S. Neutrophils mediate blood-spinal cord barrier disruption in demyelinating neuroinflammatory diseases. J Immunol. 2014; 193:2438–2454. [PubMed: 25049355]

93. Qin H, Niyongere SA, Lee SJ, Baker BJ, Benveniste EN. Expression and functional significance of SOCS-1 and SOCS-3 in astrocytes. J Immunol. 2008; 181:31–3176.

94. Roussel BD, Kruppa AJ, Miranda E, Crowther DC, Lomas DA, Marciniak SJ. Endoplasmic reticulum dysfunction in neurological disease. Lancet Neurol. 2013; 12:105–118. [PubMed: 23237905]

95. Meares GP, Liu Y, Rajbhandari R, Qin H, Nozell SE, Mobley JA, Corbett JA, Benveniste EN. PERK dependent activation of JAK1 and STAT3 contributes to ER stress induced inflammation. Mol Cell Biol. 2014; 34:3911–3925. [PubMed: 25113558]

96. Quintana A, Muller M, Frausto RF, Ramos R, Getts DR, Sanz E, Hofer MJ, Krauthausen M, King NJ, Hidalgo J, Campbell IL. Site-specific production of IL-6 in the central nervous system retargets and enhances the inflammatory response in experimental autoimmune encephalomyelitis. J Immunol. 2009; 183:2079–2088. [PubMed: 19597000]

97. Giralt M, Ramos R, Quintana A, Ferrer B, Erta M, Castro-Freire M, Comes G, Sanz E, Unzeta M, Pifarre P, Garcia A, Campbell IL, Hidalgo J. Induction of atypical EAE mediated by transgenic production of IL-6 in astrocytes in the absence of systemic IL-6. Glia. 2013; 61:587–600. [PubMed: 23322593]

98. Ding X, Yan Y, Li X, Li K, Ciric B, Yang J, Zhang Y, Wu S, Xu H, Chen W, Lovett-Racke AE, Zhang GX, Rostami A. Silencing IFN-gamma binding/signaling in astrocytes versus microglia leads to opposite effects on central nervous system autoimmunity. J Immunol. 2015; 194:4251–264. [PubMed: 25795755]

99. Anderson MA, Ao Y, Sofroniew MV. Heterogeneity of reactive astrocytes. Neurosci Lett. 2014; 565:23–29. [PubMed: 24361547]

100. Burda JE, Sofroniew MV. Reactive gliosis and the multicellular response to CNS damage and disease. Neuron. 2014; 81:229–248. [PubMed: 24462092]

101. Sofroniew MV. Multiple roles for astrocytes as effectors of cytokines and inflammatory mediators. Neuroscientist. 2013; 20:160–172. [PubMed: 24106265]

102. Qin H, Holdbrooks AT, Liu Y, Reynolds SL, Yanagisawa LL, Benveniste EN. SOCS3 deficiency promotes M1 macrophage polarization and inflammation. J Immunol. 2012; 189:3439–3448. [PubMed: 22925925]

103. Liu L, Belkadi A, Darnall L, Hu T, Drescher C, Cotleur AC, Padovani-Claudio D, He T, Choi K, Lane TE, Miller RH, Ransohoff RM. CXCR2-positive neutrophils are essential for cuprizone-induced demyelination: relevance to multiple sclerosis. Nat Neurosci. 2010; 13:319–326. [PubMed: 20154684]

104. Lampron A, Larochelle A, Laflamme N, Prefontaine P, Plante MM, Sanchez MG, Yong VW, Stys PK, Tremblay ME, Rivest S. Inefficient clearance of myelin debris by microglia impairs remyelinating processes. J Exp Med. 2015481–495; 212

105. Baxi EG, DeBruin J, Tosi DM, Grishkan IV, Smith MD, Kirby LA, Strasburger HJ, Fairchild AN, Calabresi PA, Gocke AR. Transfer of myelin-reactive th17 cells impairs endogenous remyelination in the central nervous system of cuprizone-fed mice. J Neurosci. 2015; 35:8626–8639. [PubMed: 26041928]

106. Kannarkat GT, Boss JM, Tansey MG. The role of innate and adaptive immunity in Parkinson's disease. J Parasit Dis. 2013; 3:493–514.

107. Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet. 2004; 363:1783–1793. [PubMed: 15172778]

108. Brundin P, Li JY, Holton JL, Lindvall O, Revesz T. Research in motion: the enigma of Parkinson's disease pathology spread. Nat Rev Neurosci. 2008; 9:741–745. [PubMed: 18769444]

109. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. Am J Epidemiol. 2008; 167:90–95. [PubMed: 17890755]

110. Sherer TB. Biomarkers for Parkinson's disease. Sci Transl Med. 2011; 3:1–5.

111. Mount MP, Lira A, Grimes D, Smith PD, Faucher S, Slack R, Anisman H, Hayley S, Park DS. Involvement of interferon-gamma in microglial-mediated loss of dopaminergic neurons. J Neurosci. 2007; 27:3328–3337. [PubMed: 17376993]

112. Nalls MA, Pankratz N, Lill CM, Do CB, Hernandez DG, Saad M, DeStefano AL, Kara E, Bras J, Sharma M, Schulte C, Keller MF, Arepalli S, Letson C, Edsall C, Stefansson H, Liu X, Pliner H, Lee JH, Cheng R, International Parkinson's Disease Genomics, G.I. Parkinson's Study Group Parkinson's Research: The Organized, and Me, GenePd, C. NeuroGenetics Research, G. Hussman Institute of Human, I. Ashkenazi Jewish Dataset, H. Cohorts for, E. Aging Research in Genetic, C. North American Brain Expression, C. United Kingdom Brain Expression, C. Greek Parkinson's Disease, G. Alzheimer Genetic Analysis, M.A. Ikram JP, Ioannidis GM,

Hadjigeorgiou JC, Bis M, Martinez JS, Perlmutter A, Goate K, Marder B, Fiske M, Sutherland G, Xiromerisiou RH, Myers LN, Clark K, Stefansson JA, Hardy P, Heutink H, Chen NW, Wood H, Houlden H, Payami A, Brice WK, Scott T, Gasser L, Bertram N, Eriksson T, Foroud AB, Singleton. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat Genet. 2014; 46:989–993. [PubMed: 25064009]

113. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. Cell. 2010; 140:918–934. [PubMed: 20303880]
114. Allen Reish HE, Standaert DG. Role of alpha-synuclein in inducing innate and adaptive immunity in Parkinson disease. J Parasit Dis. 2015; 5:1–19.
115. Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, Pike B, Root H, Rubenstein J, Boyer R, Stenroos ES, Chandrasekharappa S, Athanassiadou A, Papapetropoulos T, Johnson WG, Lazzarini AM, Duvoisin RC, Di Iorio G, Golbe LI, Nussbaum RL. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science. 1997; 276:2045–2047. [PubMed: 9197268]
116. Qian L, Flood PM. Microglial cells and Parkinson's disease. Immunol Res. 2008; 41:155–164. [PubMed: 18512160]
117. Croisier E, Moran LB, Dexter DT, Pearce RK, Graeber MB. Microglial inflammation in the parkinsonian substantia nigra: relationship to alpha-synuclein deposition. J Neuroinflammation. 2005; 2:14. [PubMed: 15935098]
118. Couch Y, Alvarez-Erviti L, Sibson NR, Wood MJ, Anthony DC. The acute inflammatory response to intranigral alpha-synuclein differs significantly from intranigral lipopolysaccharide and is exacerbated by peripheral inflammation. J Neuroinflammation. 2011; 8:166. [PubMed: 22122884]
119. Qin H, Buckley JA, Li X, Liu Y, Fox TH, Meares GP, Yu H, Yan Z, Harms AS, Li Y, Standaert DG, Benveniste EN. Inhibition of the JAK/STAT pathway protects against α-synuclein-induced neuroinflammation and dopaminergic neurodegeneration. J Neurosci. 2016; 36:5144–5159. [PubMed: 27147665]
120. Martin JLS, Klucken J, Outeiro TF, Nguyen P, Keller-McGandy C, Cantuti-Castelvetri I, Grammatopoulos TN, Standaert DG, Hyman BT, McLean PJ. Dopaminergic neuron loss and up-regulation of chaperone protein mRNA induced by targeted over-expression of alpha-synuclein in mouse substantia nigra. J Neurochem. 2007; 100:1449–1457. [PubMed: 17241127]
121. Zhang S, Wang XJ, Tian LP, Pan J, Lu GQ, Zhang YJ, Ding JQ, Chen SD. CD200-CD200R dysfunction exacerbates microglial activation and dopaminergic neurodegeneration in a rat model of Parkinson's disease. J Neuroinflammation. 2011; 8:154. [PubMed: 22053982]
122. Wu DC, Jackson-Lewis V, Vila M, Tieu K, Teismann P, Vadseth C, Choi DK, Ischiropoulos H, Przedborski S. Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease. J Neurosci. 2002; 22:1763–1771. [PubMed: 11880505]
123. Du Y, Ma Z, Lin S, Dodel RC, Gao F, Bales KR, Triarhou LC, Chernet E, Perry KW, Nelson DL, Luecke S, Phebus LA, Bymaster FP, Paul SM. Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. Proc Natl Acad Sci U S A. 2001; 98:14669–14674. [PubMed: 11724929]
124. Schapansky J, Nardozzi JD, LaVoie MJ. The complex relationships between microglia, alpha-synuclein, and LRRK2 in Parkinson's disease. Neuroscience. 2015; 302:74–88. [PubMed: 25284317]
125. Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, Brice A, Aasly J, Zabetian CP, Goldwurm S, Ferreira JJ, Tolosa E, Kay DM, Klein C, Williams DR, Marras C, Lang AE, Wszolek ZK, Berciano J, Schapira AH, Lynch T, Bhatia KP, Gasser T, Lees AJ, Wood NW. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 2008; 7:583–590. [PubMed: 18539534]
126. Gardet A, Benita Y, Li C, Sands BE, Ballester I, Stevens C, Korzenik JR, Rioux JD, Daly MJ, Xavier RJ, Podolsky DK. LRRK2 is involved in the IFN-gamma response and host response to pathogens. J Immunol. 2010; 185:5577–5585. [PubMed: 20921534]

127. Daher JP, Abdelmotilib HA, Hu X, Volpicelli-Daley LA, Moehle MS, Faser KB, Needle E, Chen Y, Steyn SJ, Galatsis P, Hirst WD, West AB. LRRK2 pharmacological inhibition abates alpha-synuclein induced neurodegeneration. J Biol Chem (. 2015:19433–19444. [PubMed: 26078453]
128. Choi I, Kim B, Byun JW, Baik SH, Huh YH, Kim JH, Mook-Jung I, Song WK, Shin JH, Seo H, Suh YH, Jou I, Park SM, Kang HC, Joe EH. LRRK2 G2019S mutation attenuates microglial motility by inhibiting focal adhesion kinase. Nat Commun. 2015; 6:8255. [PubMed: 26365310]
129. Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, Kay DM, Doheny KF, Paschall J, Pugh E, Kusel VI, Collura R, Roberts J, Griffith A, Samii A, Scott WK, Nutt J, Factor SA, Payami H. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet. 2010; 42:781–785. [PubMed: 20711177]
130. Raj T, Rothamel K, Mostafavi S, Ye C, Lee MN, Replogle JM, Feng T, Lee M, Asinovski N, Frohlich I, Imboywa S, Von Korff A, Okada Y, Patsopoulos NA, Davis S, McCabe C, Paik HI, Srivastava GP, Raychaudhuri S, Hafler DA, Koller D, Regev A, Hacohen N, Mathis D, Benoist C, Stranger BE, De Jager PL. Polarization of the effects of autoimmune and neurodegenerative risk alleles in leukocytes. Science. 2014; 344:519–523. [PubMed: 24786080]
131. Daher JP, Volpicelli-Daley LA, Blackburn JP, Moehle MS, West AB. Abrogation of alpha-synuclein-mediated dopaminergic neurodegeneration in LRRK2-deficient rats. Proc Natl Acad Sci U S A. 2014; 111:9289–9294. [PubMed: 24927544]
132. Saijo K, Winner B, Carson CT, Collier JG, Boyer L, Rosenfeld MG, Gage FH, Glass CK. A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. Cell. 2009; 137:47–59. [PubMed: 19345186]
133. Brochard V, Combadiere B, Prigent A, Laouar Y, Perrin A, Beray-Berthat V, Bonduelle O, Alvarez-Fischer D, Callebert J, Launay JM, Duyckaerts C, Flavell RA, Hirsch EC, Hunot S. Infiltration of CD4 + lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. J Clin Invest. 2009; 119:182–192. [PubMed: 19104149]
134. Nolan YM, Sullivan AM, Toulouse A. Parkinson's disease in the nuclear age of neuroinflammation. Trends Mol Med. 2013; 19:187–196. [PubMed: 23318001]
135. Appel SH, Beers DR, Henkel JS. T cell-microglial dialogue in Parkinson's disease and amyotrophic lateral sclerosis: are we listening? Trends Immunol. 2010; 31:7–17. [PubMed: 19879804]
136. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The jak-stat pathway: impact on human disease and therapeutic intervention. Annu Rev Med. 2015; 66:311–328. [PubMed: 25587654]
137. Constantin G, Brocke S, Izikson A, Laudanna C, Butcher EC. Tyrphostin AG490, a tyrosine kinase inhibitor, blocks actively induced experimental autoimmune encephalomyelitis. Eur J Immunol. 1998; 28:3523–3539. [PubMed: 9842895]
138. Skarica M, Wang T, McCadden E, Kardian D, Calabresi PA, Small D, Whartenby KA. Signal transduction inhibition of APCs diminishes th17 and Th1 responses in experimental autoimmune encephalomyelitis. J Immunol. 2009; 182:4192–4199. [PubMed: 19299717]
139. Liu Y, Holdbrooks AT, De Sarno P, Rowse AL, Yanagisawa LL, McFarland BC, Harrington LE, Raman C, Sabbaj S, Benveniste EN, Qin H. Therapeutic efficacy of suppressing the JAK/STAT pathway in multiple models of experimental autoimmune encephalomyelitis. J Immunol. 2014; 192:59–72. [PubMed: 24323580]
140. Ren Y, Lu L, Guo TB, Qiu J, Yang Y, Liu A, Zhang JZ. Novel immunomodulatory properties of berbamine through selective down-regulation of STAT4 and action of ĨFN-γ in experimental autoimmune encephalomyelitis. J Immunol. 2008; 181:1491–1498. [PubMed: 18606704]
141. Qin X, Guo BT, Wan B, Fang L, Lu L, Wu L, Zang YQ, Zhang JZ. Regulation of Th1 and Th17 cell differentiation and amelioration of experimental autoimmune encephalomyelitis by natural product compound berberine. J Immunol. 2010; 185:1855–1863. [PubMed: 20622114]
142. Zhang J, Zeng YQ, Pan XD, Kang DY, Huang TW, Chen XC. Tripchlorolide ameliorates experimental autoimmune encephalomyelitis by down-regulating ERK1/2-NF-kappaB and JAK/STAT signaling pathways. J Neurochem. 2015; 133:104–112. [PubMed: 25662403]

143. Muthian G, Bright JJ. Quercetin, a flavonoid phytoestrogen, ameliorates experimental allergic encephalomyelitis by blocking IL-12 signaling through JAK-STAT pathway in T lymphocyte. J Clin Immunol. 2004; 24:542–552. [PubMed: 15359113]

144. Muthian G, Raikwar HP, Rajasingh J, Bright JJ. 1,25 dihydroxyvitamin-D3 modulates JAK-STAT pathway in IL-12/IFNgamma axis leading to Th1 response in experimental allergic encephalomyelitis. J Neurosci Res. 2006; 83:1299–1309. [PubMed: 16547967]

145. Ghoreschi K, Bruck J, Kellerer C, Deng C, Peng H, Rothfuss O, Hussain RZ, Gocke AR, Respa A, Glocova I, Valtcheva N, Alexander E, Feil S, Feil R, Schulze-Osthoff K, Rupec RA, Lovett-Racke AE, Dringen R, Racke MK, Rocken M. Fumarates improve psoriasis and multiple sclerosis by inducing type II dendritic cells. J Exp Med. 2011; 208:2291–2303. [PubMed: 21987655]

146. Weitz-Schmidt G. Statins as anti-inflammatory agents. Trends Pharmacol Sci. 2002; 23:482–486. [PubMed: 12368073]

147. Stuve O, Youssef S, Steinman L, Zamvil SS. Statins as potential therapeutic agents in neuroinflammatory disorders. Curr Opin Neurol. 2003; 16:393–401. [PubMed: 12858078]

148. Vollmer T, Key L, Durkalski V, Tyor W, Corboy J, Markovic-Plese S, Preiningerova J, Rizzo M, Singh I. Oral simvastatin treatment in relapsing-remitting multiple sclerosis. Lancet. 2004; 363:1607–1608. [PubMed: 15145635]

149. Chataway J, Schuerer N, Alsanousi A, Chan D, MacManus D, Hunter K, Anderson V, Bangham CR, Clegg S, Nielsen C, Fox NC, Wilkie D, Nicholas JM, Calder VL, Greenwood J, Frost C, Nicholas R. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet. 2014; 383:2213–2221. [PubMed: 24655729]

150. Zhang X, Jin J, Peng X, Ramgolam VS, Markovic-Plese S. Simvastatin inhibits IL-17 secretion by targeting multiple IL-17-regulatory cytokines and by inhibiting the expression of IL-17 transcription factor RORC in cd4+ lymphocytes. J Immunol. 2008; 180:6988–6996. [PubMed: 18453621]

151. Lee SJ, Qin H, Benveniste EN. Simvastatin inhibits IFN-γ-induced CD40 gene expression by suppressing STAT-1α. J Leukoc Biol. 2007; 82:436–447. [PubMed: 17507688]

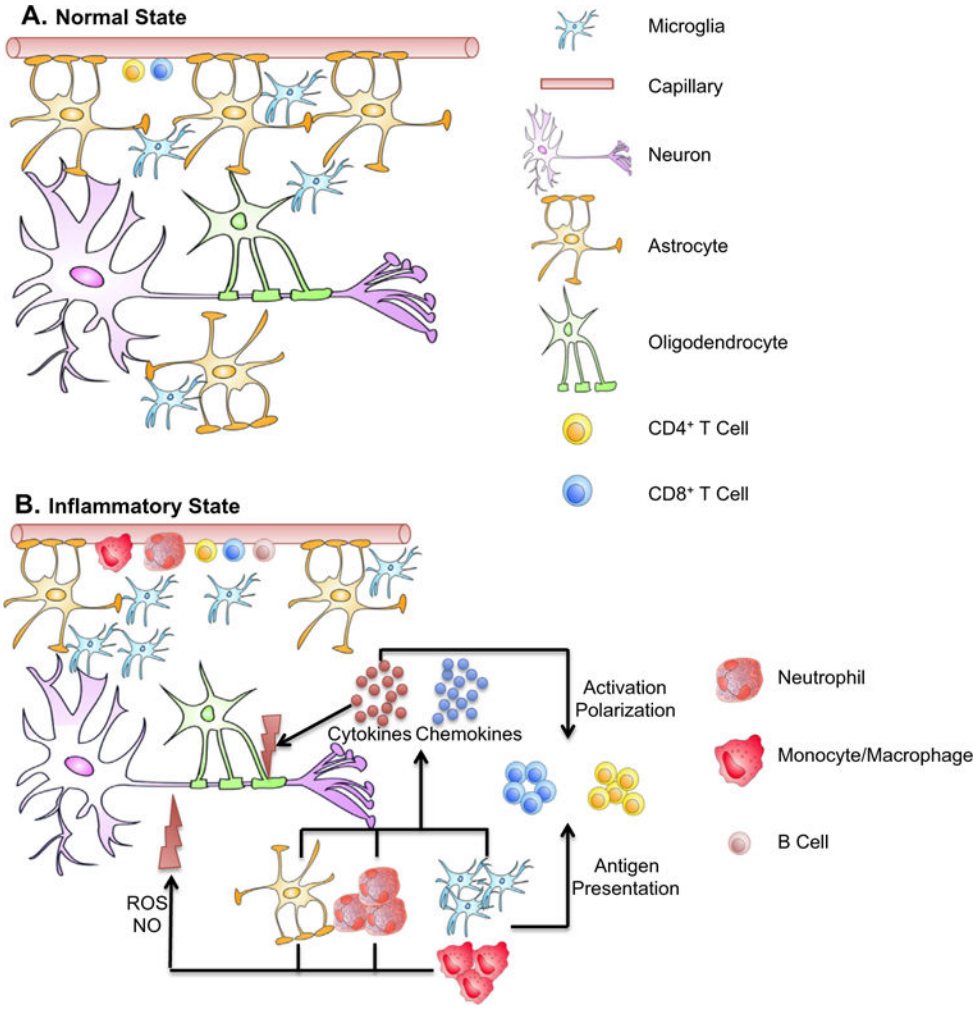

Fig. 1.

Overview of innate immune cells and their functions in the CNS. A Under normal conditions, astrocytes and other cells (not shown) form the BBB and blood-CSF barrier, microglia surveil the CNS, and oligodendrocytes form the myelin sheath around neurons. As well, T cells are present in small numbers. B. During inflammation, immune cells such as macrophages, neutrophils, B cells and T cells cross the BBB and enter the CNS. Activated astrocytes, microglia/macrophages and neutrophils secrete cytokines and chemokines to recruit, activate and polarize T cells. ROS and cytokines such as TNF-α, produced by astrocytes, microglia/macrophages and neutrophils, directly cause demyelination and neuronal damage.

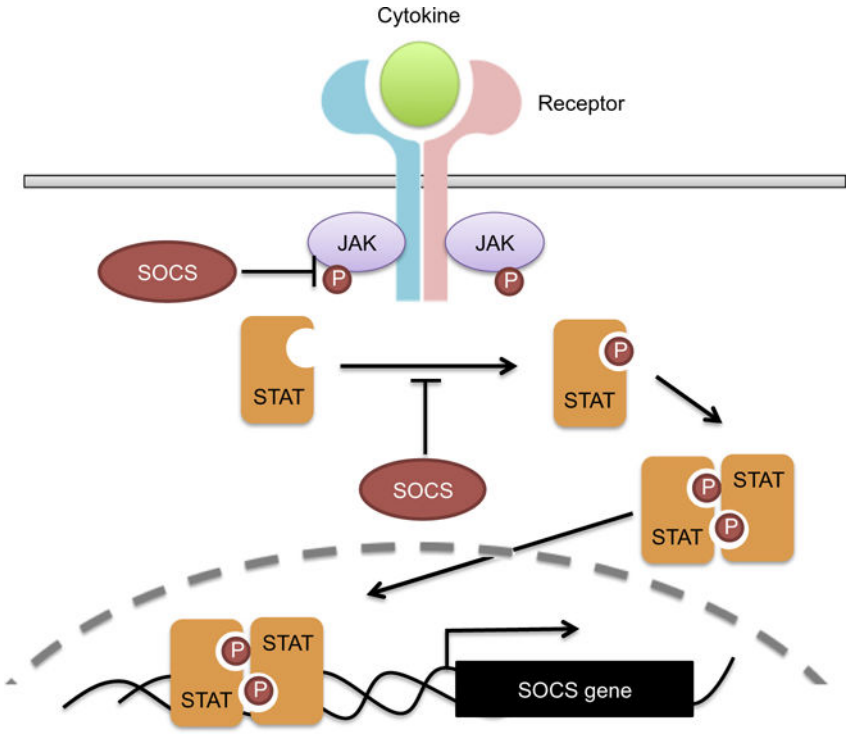

Fig. 2.

Key components of the JAK/STAT pathway. In brief, cytokines bind to their receptors, and activate JAKs. Activated JAKs then auto- and trans-phosphorylate each other, and phosphorylate tyrosine residues in the cytoplasmic domain of the receptor. STATs are then recruited to the receptor complex, phosphorylated by JAKs, form dimers, translocate into the nuclei, and then initiate transcription. SOCS genes are induced by activated STATs. SOCS proteins inactivate JAK/STAT pathway by inhibition of JAK kinase activity and/or promoting degradation of the signaling complex.

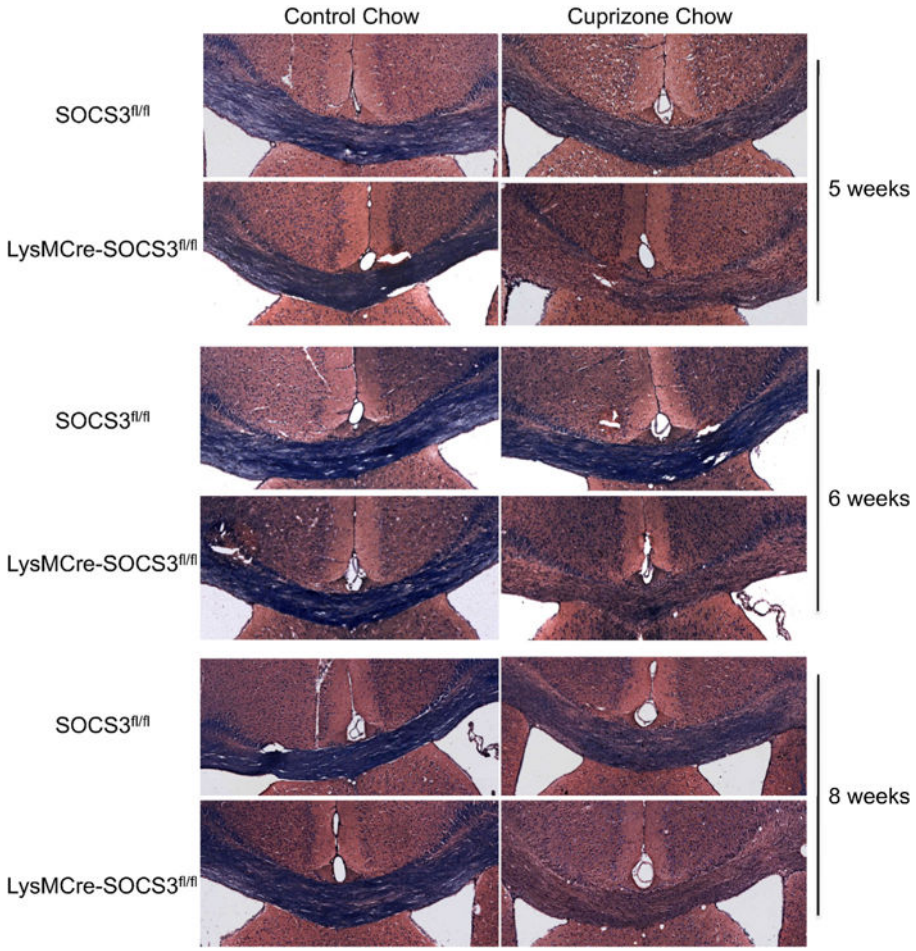

Fig. 3.

Kinetics of demyelination in cuprizone-fed SOCS3$^{fl/fl}$ and LysMCre-SOCS3$^{fl/fl}$ mice. SOCS3$^{fl/fl}$ and LysMCre-SOCS3$^{fl/fl}$ mice were fed with 0.3% cuprizone or control diet for 5,6, or 8 weeks. Hematoxylin and eosin staining followed by Luxol Fast Blue staining shows demyelination after cuprizone treatment. Data shown represent 3 individual experiments.