JAK-STAT Lodges in Multiple Sclerosis: Pathophysiology and Therapeutic Approach Overview

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Abstract

Multiple sclerosis (MS) is a complex inflammatory and demyelinating disease of central nervous system (CNS). The disease pathogenesis is not fully understood and no actual cure for the disease yet. The disease has genetic and environmental cause as fundamental factors which are identified for the disease pathogenesis so far. One of the characteristic features of the disease is inflammation cause due to activation of pro-inflammatory cells. Interference in signalling pathways such as JAK/STAT could result in physiological or pathological outcome in MS. Dysregulation of JAK/STAT signalling pathway is associated with chronic inflammatory process and immune disorders. In this review, considering the important role of JAK/STAT pathway in signal transduction of inflammatory process and immune responses in CNS, we describe the involvement of this signal transduction pathway in MS. Moreover, we consider the physiological and pathological involvement of JAK/STAT rout in neurogenesis/gliogenesis, cytokines production and as therapeutics target for managing MS.

Subject Areas

Immunology, Neurology, Neuroscience

Keywords

Cytokines, Janus Kinases, Multiple Sclerosis, Neurogenesis, Signal Transduction, Transcription Factors

1. Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating, and neurodegenera-
tive disease of the central nervous system [1]. MS attacks the myelinated axons in the central nervous system (CNS), destroying the myelin and axons to various degrees [2]. The pathologically distinguishing features of the disease are demyelination, axonal loss and inflammation [3]. The disease affects around 2.5 million people worldwide [4] and is commonly found in young adults, and it is more common in women [5]. Clinically, the major signs and symptoms of MS are cognitive disabilities [6], abnormal sensation, weakness, paralysis, incoordination, and ocular symptoms associated with relapses and remissions [7]. Although the etiology of MS is still unknown and its pathogenetic pathways are not fully understood [8], there is evidence of the interplay between genetic susceptibility and environmental factors [9] [10]. Existing knowledge in MS pathology indicates that the pathological process is initiated by the role of autoreactive myelin specific CD4+ T helper (Th) cells type 1 and Th17 cells and to some extent by other cell types like, CD8+ T cells, B cells, macrophages and natural killer (NK) cells [11]. Moreover, transmigration of inflammatory lymphocytes into the CNS induces an inflammatory response, which results into destruction of nearby tissue, demyelination and neurological damage [1] [12].

The Janus kinase (JAK)-signal transducer comprises of four cytoplasmic tyrosine kinases (JAK1, JAK2, JAK3 and TYK2), and the signal transducer and activator of transcription (STAT) identified in human cells are STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6 [13] [14]. These intracellular signaling pathways are essential pleiotropic cascades used to transduce a multitude of signals for numerous physiologic and pathologic processes in animals and humans [15]. The JAK and STAT expression is low in CNS when compared with other systems and it is associated with gene regulation and inflammation [13]. Moreover, signal transduction through the pathway mediates inflammatory and immune responses in the CNS [16]. Although the evidence for the role of JAK in neuroinflammation is obscure, JAK/STAT signaling pathways play both detrimental and beneficial roles by promoting nerve damaging and CNS regeneration after the resulting inflammation has declined [17].

Dysregulation of STATs can be associated with deleterious biological processes such as chronic inflammation [18] [19] [20], cancer [21] and immune disorders [13], thus having the advantage of being therapeutic targets. The activation of JAK/STAT pathway in MS is possibly due to excessive production of cytokines, loss of expression of negative regulators such as Suppressor of cytokine signaling (SOCS) proteins, and significant enrichment of genes encoding components of the JAK/STAT pathway, including STAT3 [22]. This review describes the involvement of JAK/STAT signalling pathways in MS. We describe the role of the pathway in regulation of neurogenesis/gliogenesis, immune cells proliferation and differentiation, regulation of cytokines activation and therapeutic target potential of the pathway in MS.

2. JAK/STAT System

JAK-STAT signaling pathway is evolutionarily conserved in eukaryotes [13],
which participate in important biological processes such as cell growth, differentiation, proliferation, survival, apoptosis and immune responses [23] thus are crucial in many cell types. The discovery of this pathway, especially in the field of cell biology, gives an explanation to the mechanism of gene regulation that significantly add more information on the action of hormones, interferons, colony-stimulating factors, and interleukins [24] together with its involvement in neurogenesis [25], glial differentiation [26] and CNS diseases [27] [28].

**Structural overview:** Structurally, each molecule of JAK contains seven JAK homology domains (JH1-7). The carboxyl JH1 domain is responsible for catalytic activity, whereas N-terminal JH7 domain contains the receptor binding site (Figure 1). In contrast, JH1 and JH2 domains have significant homology but JH2 lacks enzymatic activity thus regarded as pseudo-kinase domain [14]. These kinases bind to the juxtamembrane region of cytokine receptors [29]. The seven

![Figure 1. Model structure and signaling of JAK/STAT pathway. The pathway can be activated by cytokines. Binding of cytokine phosphorylate adjacent receptors, thus JAKs cross-phosphorylate each other on tyrosine. The activated JAKs phosphorylate receptors on tyrosine. This action leads to the enrollment of STAT protein to the receptor/kinase complex via SH2 domain of the STAT. The STAT is then tyrosine phosphorylated (Y) at a single residue in its C-terminus. The STAT can also be serine phosphorylated (S) in their TAD. The tyrosine phosphorylation of the STAT results in STAT dimerization via tyrosine (Y) and SH2 domain interaction. The STATs migrate into nucleus and bind to DNA and other gene regulatory proteins via their DNA-binding domain (DBD), this action leads to gene transcription in the nucleus. JAK homology (JH), amino terminal domain (ATD), coiled-coiled domain (CCD), DNA binding domain (DBD), linker domain (LD), transactivation domain (TAD).](image-url)
structurally and functionally mammalian STAT family have size range from 750 to 850 amino acids [30] and share conserved domains. This includes the amino-terminal domain (NH2), the coiled-coiled domain (CCD), the DNA binding domain (DBD), the linker domain and the SH2/tyrosine activation domain (Figure 1). In contrast, the carboxy-terminal transcriptional activation domain (TAD) differs and contributes to STAT specificity [31]. Moreover, SH2 as the most highly conserved STAT domain have the capacity to bind to specific phosphotyrosine motifs thus serve a significant role in signaling [31].

**Activation:** JAK/STAT pathway receptor is activated by cytokines, hormones or growth factors resulting in dimerization of the receptor and subsequent activation of JAK and phosphorylation of tyrosine residues [13] [32]. The activated JAK recruits and phosphorylates STAT on its conserved tyrosine residue [33]. The STAT then becomes dimerize and subsequently translocate into the nucleus where it will bind with DNA and regulate genes expression [23] (Figure 1). In contrast to other STATs, STAT5A/B are specifically activated in response to a variety of cytokines as well as tyrosine kinase receptors and were plausibly assumed that they have a basic role in cell growth regulation [35] [36]. Of note the STAT activation by non-cytokine receptor can be JAK-dependent or JAK-independent however, it varies depends on receptors [23].

3. JAK/STAT Pathways Involvement in Neurogenesis/Gliogenesis

During proliferation and differentiation of brain cells, neural stem cells (NSC) or neural progenitor cells (NPC) mostly differentiate into neurons, astrocytes or oligodendrocytes in sub ventricular zone (SVZ) of olfactory bulbs and dentate gyrus (DG) of the hippocampus of adult brain [37]. JAK/STAT pathway is associated with regulation of NSC proliferation. Adult NSC of the SVZ expresses IL-15 which plays role in activation of STAT1, 3 and 5, and NSCs proliferation which could be blocked by JAK inhibitors [38] [39]. JAK1 is probably involved in astrocytic differentiation [40], whereas, JAK2 seems more important for NSC proliferation [41] while JAK3 is reported to induce neuronal and oligodendroglial differentiation in NSCs [42]. Both in vitro and in vivo studies showed that activation of STAT3 and Akt by leptin results in regulation of neuroproliferation in the DG of adult mice [41]. Moreover in adult’s DG, neurogenesis is reported to rely on STAT3 activation [43]. Interferon β, typically used in treatment of MS, can activate STATs [13] thus implicated in controversial role in proliferation and differentiation of NPC in murine [44], because it can either inhibit [45], have no effect [44] or enhance the proliferation of the NPC [46]. Previous study on the role of JAK-STAT in glial differentiation showed that activation of ciliary neurotrophic factor (CNTF) receptor is associated with activation of JAK1, STAT1 and STAT3 and stimulating the differentiation of embryonic cortical precursor cells into astrocytes [13]. Similarly JAK2, STAT1 and STAT3 activation is partly associated with proliferation and differentiation of astrocytes [47]. Moreover, a study showed that STAT3 knock-down mice enhanced neurogene-
sis while blocking astrogliogenesis [25]. Inhibitory proteins of JAK-STAT pathway such as SOCS 2, 3 and 6 negatively regulate neuronal differentiation and neurite outgrowth after induction of insulin-like growth factor-1 (IGF-1) and growth hormone [48]. Previous study on SOCS2 knock out mice reported that overexpression of SOCS2 can blocks GH-signalling and impairs neurogenesis, whereas neuronal differentiation was increased [42].

STAT activation could lead to apoptosis [13], for example IFN-γ activation of STAT1 affects NPCs by reducing its proliferation and inducing apoptosis via upregulation of p21 and caspase-3 signaling [49]. Rather IL-9 signaling protects neonatal neurons from apoptosis by activation of the JAK-STAT pathway [50]. Moreover, a study showed that in vitro treatment of IL-9 and AG490 activate STAT1 and STAT3, however this anti-apoptotic effect could be obstructed by possible inhibitor of JAK-STAT pathway in vivo [50]. Furthermore, STAT3 and STAT 5 are more anti-apoptotic than STAT1 [30]. However, the proportion of STAT1 activation over that of STAT3 and STAT5 seems to play a role in apoptosis [30]. JAK-STAT pathway plays a role in neuronal regeneration and glia scar formation around the lesion after injury to CNS [13] (Figure 2). In this regard

![THERAPEUTIC TARGET: Inhibition of JAK/STAT1 Pathway](image)

Figure 2. JAK/STAT involvement in MS. Activation of JAK/STAT pathway results in physiological or pathological process. Physiologically the pathway was involved in neurogenesis/gliogenesis; this process has a positive impact on MS/EAE as it supports processes such as axonal regeneration that will ameliorate MS condition. Cytokines involvement due to activation of this pathway result in pro- or anti-inflammatory processes. The differentiation of proinflammatory cells has negative consequences on MS/EAE as it exacerbate the condition, whereas the differentiation of anti-inflammatory cells and its cytokines favors amelioration of MS/EAE conditions thus have positive effect. JAK/STAT pathway serves as therapeutic target for amelioration of MS/EAE conditions. The pathway, proinflammatory cytokines and differentiation of Th1 and Th17 could be block by inhibitory compound and leads to inhibition of proinflammatory processes.
STAT3 was found to be overexpressed and activated in regenerating neurons following injury to axon [51]. Previous study on adult mouse reported axon regeneration occurs after deletion of SOCS3 [52] and SOCS3 is a potent inhibitor of the pathways. After CNS injury astrogliosis rely on STAT3 activation [28]. Inhibition of STAT3 activation via JAK2 inhibition using AG490 on the proximal nerve stump can reduce neurite outgrowth [53].

4. JAK/STAT Pathway and Cytokines in MS

Cytokines are important in activation and regulation of immune mechanisms and inflammatory responses [24]. Cytokine networks exert their pro- and anti-inflammatory effects through multiple downstream signaling pathways [54]. In this regard, the JAK-STAT signaling pathways are involved in the signaling of several of pro- and anti-inflammatory cytokines (Table 1). In pathological condition members of JAK/STAT with complementary or antagonistic effects are often activated simultaneously [34]. Moreover, a study showed that STATs activation was significantly increased in brain and spinal cord of experimental autoimmune encephalitis (EAE) mice than in healthy control mice [55]. EAE is the animal model of MS.

STAT1 induces the activation of Th1 and IFN-γ cytokines which have an essential role in inflammatory disease in the CNS [56]. STAT1 is required for development of Th1 cells, which are associated with proinflammatory processes [57]. Furthermore, STAT5A/B increases Th1 responses by regulating T-box transcription factor (TBX21) and interleukin-12 receptor subunit beta-2 (IL12Rβ2) [58]. Interestingly, STAT3 takes part in Th2 differentiation and binds to Th2-associated gene loci [59].

In MS IFN-γ and IL-6 were detected in higher levels in target tissues and they exert their effects via the activation of STAT1 and STAT3, respectively [34]. Moreover, IL-6 promotes Th17 and B cell differentiation [60], whereas, IFN-γ induced JAK1/2-STAT1 signaling effect which was observed in classically-activated macrophages [61] [62]. IFN-γ also involved in the acute pro-inflammatory response by inducing pro-inflammatory cytokines such as TNF-α, IL-12, 23, 6 and chemotactic factors [62] [63], thus exacerbate disease condition in MS (Figure 2).

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Signalling pathway</th>
<th>Effect</th>
<th>Cytokines secreted</th>
<th>Reference</th>
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<tbody>
<tr>
<td>IFN-γ</td>
<td>JAK1/STAT-1</td>
<td>Macrophage</td>
<td>TNF-α, IL-12, IL-23, IL-6, chemotactic factors</td>
<td>[64]</td>
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<td>IL-12</td>
<td>JAK2/STAT-4</td>
<td>T cell differentiation to Th1</td>
<td>IFN-α, TNF-α, IL-6</td>
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<td>IL-23</td>
<td>JAK2/STAT-3</td>
<td>Th17</td>
<td>TNF-α, IL-6, IL-17, IL-22</td>
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<td>IL-27</td>
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<td>Treg</td>
<td>IL-10, TGFRβ1</td>
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JAK/STAT4 and NF-κB play an important role in the pathways involved in pro-inflammatory processes [54]. Activation of the NF-κB transcription factor results in the production of pro-inflammatory cytokines, nitric oxide (NO) and secretion of chemokines by macrophages, whereas on Dendritic cells there is an increase expression of CD83, CD86, and CD40, as well as MHC class II [64] which could be important in MS pathogenesis. A study by Jiang and co-workers reported significant upregulation of JAK/STAT4 and NF-κB signaling pathways in EAE [65]. However, STAT4 knockout mice failed to develop EAE [66], this suggests STAT4 pathway could be irrelevant in EAE. However, CD4/STAT3 knockout mice are resistant to EAE, this shows the important role of STAT3 pathway in MS inflammatory diseases [57].

Th17 cells produce a wide range of effector cytokines such as IL-17A, IL-17F, IL-6, IL-9, IL-21, IL-22, IL-23, IL-26, and TNFa [67] [68]. In a brain, these cytokines induce inflammation which is characterized by infiltration of neutrophils into CNS and myelin loss [69]. High levels of IL-17 in MS lesion are associated with a strong inflammatory response that could lead to exacerbations of the disease [70]. The IL-17-producing T cells (CD4+ or CD8+) have been detected in both acute and chronic MS [71]. Therefore, various studies linked this cytokine with autoimmune and chronic inflammatory conditions [72]. For instance, a study on IL-17 knockout mice shows a significant reduction in severity of EAE; this denotes the important role of this cytokine in EAE pathogenesis [72]. Moreover, the upregulation of IL-10 by immunoregulatory cytokines IL-27, suppresses IL-17, this action ultimately suppresses EAE [73]. Both Th1 and Th17 cells responses are required for EAE development [74]. IL-6/STAT3 pathway was identified as regulators of Th17 cells differentiation and function by increasing the expression and activation of the IL-6 itself, IL-17 and STAT3 [75]. IL-2/STAT5A/B signalling pathway regulates Th17 differentiation [76] by competing with STAT3 in binding to the IL17A/F locus [77]. STAT3 directly binds to IL17A/F, RAR-related orphan receptor C (RORC) and interleukin-23 receptor (IL23R) and some genes involved in Th17 differentiation to influence the regulation of the differentiation [78]. However, STAT3 upregulates anti-inflammatory cytokines such as IL-10 and TGF-β1 to inhibit pro-inflammatory proteins IFN-γ, IFN-β, TNF-α, IL-12, chemokines, MHC II, CD80, CD86 [79]. Of interest, STAT3 physically associates with Foxp3 [34].

IL2/STAT5A/B signalling pathway plays an important role in differentiation of Treg cells, in that STAT5/A directly binds the Foxp3 gene and influence the expression of the gene [80]. In addition, STAT5A/B regulates the expression of interleukin-2 receptor alpha (IL2RA), which is also required by Treg cells. Treg cells play an important role in regulating the proliferation of T cells but to some extent unable to inhibit Th17 mediated pathology [34]. However, Treg cells could promote Th17 differentiation due to involvement of IL-2 [81] [82].

5. JAK/STAT Pathway as Therapeutic Target in MS

The pathway has received attention as a therapeutic target in autoimmune dis-
eases [17] [24] [83]. Many of the MS-promoting cytokines such as IL-1β, TNF-α and especially that of IL-6 and IL-12 either signal through or induce JAK/STAT signaling molecules [84]. Studies have implicated the JAK/STAT axis in regulating clinical manifestations of EAE [85]. JAK inhibitors produced promising result in some inflammatory diseases [86] [87]. JAK inhibitors interrupt cytokine signaling; consequently, break the inflammatory process, a useful process in MS and EAE [85] (Figure 2). Indeed, previous study reported tyrphostin B42, a JAK2 inhibitor; ameliorate EAE [84]. A study found that AZD1480 treatment is effective in suppressing clinical symptoms in EAE. Similarly Peroxisome proliferator activated receptor-γ (PPARγ) and Cyclooxygenase 2 (COX2) inhibitors block the activation of JAK/STAT pathway to some extent by IL-12 thus will be able to ameliorate EAE condition [88]. In a Study using AG490 to inhibit the action of JAK2 and TYK2 as treatment of EAE showed a decrease in the activity of Th1, NK and microglial cells and reduces IL-12 levels [84]. Plumbagin (PL) and berberine are herbal compounds which inhibit the activation of JAK-STAT pathway and Th1 and Th17 cell differentiation thus prevent exacerbation of EAE model [89] [90]. Similarly, in EAE, glatiramer acetate (GA) to some extent inhibits the phosphorylation of STAT4 and STAT3 in T-cells thus exerts some effect on Th1 and Th17 cell differentiation, respectively [91]. IFN-β action in treatment of MS requires the activity of JAK1 to activate phosphoinositide 3-kinase (PI3K) and protein kinase B (PKB), this result in repression of glycogen synthase kinase-3 beta (GSK3β) activity in EAE [92].

6. Conclusion

JAK/STAT signalling pathway involvement in MS could be physiological or pathological. This pathway plays a role in regulation of neurogenesis and gliogenesis via proliferation, differentiation, survival/apoptosis and regeneration of brain cells and neural cells precursors. JAK/STAT pathways are also involved in the signalling of both pro- and anti-inflammatory cytokines via regulation of proliferation and differentiation of immune cells responsible for the secretion of these cytokines and interference in cytokine signalling pathways for inflammatory process ameliorates or exacerbates MS pathogenesis. STAT1 induces the action of several cytokines and some are important in inflammatory diseases such as MS whereas STAT3 plays multiple roles in regulation of immune responses. In modern days, JAK/STAT pathways could serve as a potential therapeutic target for managing MS. Inhibitors of these pathways could interrupt signalling process leading to inflammation, a useful process in MS and EAE. Recently promising compounds were identified as potential inhibitors of the pathways. Researches related to JAK/STAT and MS need good attention and concern, considering the complex nature of the disease and its treatment.

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