

The role of the JAK-STAT pathway in neural stem cells, neural progenitor cells and reactive astrocytes after spinal cord injury (Review)

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Received September 24, 2014; Accepted October 16, 2014

DOI: 10.3892/br.2014.401

Abstract. Patients with spinal cord injuries can develop severe neurological damage and dysfunction, which is not only induced by primary but also by secondary injuries. As an evolutionarily conserved pathway of eukaryotes, the JAK-STAT pathway is associated with cell growth, survival, development and differentiation; activation of the JAK-STAT pathway has been previously reported in central nervous system injury. The JAK-STAT pathway is directly associated with neurogenesis and glia scar formation in the injury region. Following injury of the axon, the overexpression and activation of STAT3 is exhibited specifically in protecting neurons. To investigate the role of the JAK-STAT pathway in neuroprotection, we summarized the effect of JAK-STAT pathway in the following three sections: Firstly, the modulation of JAK-STAT pathway in proliferation and differentiation of neural stem cells and neural progenitor cells is discussed; secondly, the time-dependent effect of JAK-STAT pathway in reactive astrocytes to reveal their capability of neuroprotection is revealed and lastly, we focus on how the astrocyte-secretory polypeptides (astrocyte-derived cytokines and trophic factors) accomplish neuroprotection via the JAK-STAT pathway.

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1. Introduction

Every year >10,000 people in China are victims of spinal cord injury (SCI) due to traffic accidents, sports injuries and a number of other accidents (1). Patients with SCI may develop severe neurological damage and dysfunction (1,2). Primary injury (mechanical injury) is the characteristic pathophysiology of acute SCI, which is followed by a phase of 'secondary injury' involving ischemia, calcium- and sodium-mediated cellular injury, cell death, inflammation and apoptosis (3,4). As an evolutionarily conserved pathway of eukaryotes, the JAK-STAT pathway is associated with cell growth, survival, development and differentiation (5).

JAK-STAT is an intracellular signaling pathway that involves the activation of two families of proteins: The Janus kinases (JAK) and the signal transducer and activator of transcription (STAT). JAK is a class of four cytoplasmic protein tyrosine kinases that includes JAK1, JAK2, JAK3 and TYK2 (6). The STAT family contains seven transcription factors: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6 (7). The JAK-STAT pathway is a highly regulated and efficient system which predominantly regulates gene expression (5). This pathway includes the activation of cell membrane receptors by polypeptides, such as growth factors, hormones, or cytokines, which induce the activation of JAK in cell membranes (8-11).

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Key words: JAK-STAT pathway, astrocyte-secretory polypeptides, neural stem cells, neural progenitor cells, spinal cord injury, reactive astrocyte

Protein tyrosine phosphorylation is a significant biochemical mechanism, by which growth factors or cytokines regulate cellular processes. Initially, JAKs undergo tyrosine phosphorylation with cell membrane receptor binding (12,13). Subsequently, phosphorylated JAKs activate STATs in the cytoplasm through tyrosine phosphorylation, leading to the dimerization of STATs (9,12,14,15). The STAT dimers translocate to the nucleus, where they bind to specific cis-elements, followed by the transcription of various target genes (9,16).

The activation of JAK and STAT has been observed in the motoneurons of rats (17,18). Activation of the JAK-STAT pathway has been previously reported in central nervous system (CNS) injury (19-22). The JAK-STAT pathway is directly associated with neurogenesis and glia scar formation of the injury region. Following an injury of the axon, the overexpression and activation of STAT3 are induced specifically in protecting neurons (17). Other studies have reported activation of STAT3 in reactive astrocytes of damage regions (19,23). In the intact spinal cord, STAT3 is localized predominantly in motoneurons and dendrite-like structures in the anterior horn (24).

This report reviews the following: i) Modulation of the JAK-STAT pathway in proliferation and differentiation of neural stem cells (NSCs) and neural progenitor cells (NPCs); ii) the time-dependent effect of JAK-STAT pathway in reactive astrocytes; and iii) astrocyte-secretory polypeptides promoting neuroprotection via the activation of the JAK-STAT pathway.

2. Modulation of JAK-STAT pathway in proliferation and differentiation of NSCs and NPCs

Following a SCI, endogenous NSCs and NPCs proliferate and migrate to the lesion region, where they differentiate exclusively into astrocytes (25,26). Previous studies have confirmed the existence of NSCs and NPCs in the spinal cord, which has increased the possibility of the spinal cord having the capability to self-repair in response to injury or disease through the application of endogenous NSCs and NPCs (27,28). Furthermore, recent studies have demonstrated that transplanted NSCs can replace the lost neurons and glia following SCI, as well as forming functional relays to reconnect the spinal cord through the lesion (29,30). Additionally, the modulation of the JAK-STAT pathway has been revealed in the proliferation and differentiation of NSCs and NPCs (31,32).

JAK-STAT pathway promotes astroglialogenesis. Bonni *et al* (33) were the first to report the role of the JAK-STAT pathway in glial differentiation. The authors validated, in cortical precursor embryo cells, that activation of the ciliary neurotrophic factor (CNTF) receptor subsequently activates JAK1, STAT1 and STAT3 and induces the differentiation of NSCs and NPCs into astrocytes. Several additional studies have also confirmed the role of STAT3 in glial differentiation (34,35). Furthermore, glycoprotein 130 (gp130)-mediated signaling has been demonstrated to induce the astrocytic differentiation of NSCs and NPCs through the JAK-STAT pathway (33,36). Sriram *et al* (37) also revealed that the gp130-mediated activation of STAT3 is vital in the induction of astroglialogenesis. Gp130 is a type of multichain receptor complex on the cell membrane. This complex includes the ligand binding receptor and non-ligand binding membrane glycoprotein, gp130, which have been shown to be significant

in signal transduction of cytokines, such as the interleukin (IL)-6 family (38). These cytokines bind to multichain receptor complexes and induce the dimerization of gp130, followed by activation of JAK in cell membranes. This subsequently phosphorylates STAT3 at Tyr705, resulting in translocation to the nucleus. A number of articles have reported that prolactin (PRL) also allows proliferation and differentiation of astrocytes, partially via the phosphorylation of JAK2, STAT1 and STAT3 (39-45). DeVito *et al* (46-50) demonstrated that PRL can stimulate astrocyte growth and the expression of several cytokines in their early studies. Furthermore, the authors found that PRL stimulates the growth of astrocytes through increasing the phosphorylation of tyrosines in the inactivation loop of JAK2 and the subsequent phosphorylation of STAT1a, STAT5a and STAT5b (51). Another study showed that in conditional knockout mice, STAT3 knock-down inhibited astroglialogenesis (52).

Modulation of the JAK-STAT pathway can induce neuronal and oligodendrocytic differentiation. Cytokines such as interleukin (IL)-15 that are expressed by the adult NSC of CNS, activate STAT1, STAT3 and STAT5 via phosphorylation of JAK, and this activation can be blocked by JAK inhibitors (53,54). A number of studies have demonstrated that inhibitory proteins of the JAK-STAT pathway are strongly associated with neuronal differentiation and neurite outgrowth. These inhibitory proteins, including suppressor of cytokine signaling (SOCS)2, SOCS3 and SOCS6 can negatively regulate the JAK-STAT pathway induced by factors including insulin-like growth factor-1 and growth hormone (GH) (55,56). The overexpression of SOCS2 in NSC suppresses GH-signaling and promotes neuronal differentiation, while neurogenesis is inhibited (56). Following SCI, in adult mice, the absence of SOCS3 promotes gp130-mediated CNTF signaling via the JAK-STAT pathway, which subsequently promotes axon regeneration (57). This finding is consistent with the report by Sun *et al* (58). With regard to the different isoforms of JAK, it appears that JAK1 is predominantly associated with astrocytic differentiation (33) while JAK2 is considered to be essential for NSC proliferation (59,60). Other studies have indicated that the deletion of JAK2 inhibits the activation of c-myc and c-fos promoters and cell proliferation (61); additionally, the absence of STAT5 suppresses the induction of c-fos and blocks cell cycle progression (62), confirming that JAK2 and STAT5 may be indispensable in cell proliferation. The silencing of JAK3 induces to the differentiation of NPC into neurons and oligodendrocytes (60). Furthermore, the suppression of STAT3 *in vitro* (63) or its conditional ablation *in vivo* (52) has been validated to promote neurogenesis.

3. Time-dependent effects of the JAK-STAT pathway in reactive astrocytes

Kernie *et al* (64) reported that a significant amount of the formation of astroglial scars after CNS trauma may be attributed to newly generated astrocytes, but not to the activation or migration of resident astrocytes. The traditional view is that reactive astrocytes can inhibit axonal regrowth due to the microenvironmental factors that significantly alter immediately following SCI. The major causes include production of chondroitin sulfate proteoglycans (65), a type

of inhibitory extracellular matrix molecule, and the release of pro-inflammatory cytokines, including IL-1 β , IL-6 and tumor necrosis factor- α (TNF- α) (66-69). These pro-inflammatory cytokines are immunoreactive for phosphorylated STAT3 following SCI; this indicates a role for the phosphorylation of STAT3 in the activation of astrocytes (70-72), particularly in chronic phases, within injury of the spinal cords. Okada *et al* (73) confirmed that suppression of the IL-6 receptor not only inhibited the astrocytic differentiation promoted by IL-6 signaling via the JAK-STAT pathway, but also prevented the development of astrogliosis, which reduces the axonal regeneration in the chronic phases after SCI (73,74). In a relative sense, a time-dependent analysis of the reactive astrocytes is critical for the identification of its effects in the injured spinal cord. At the acute and subacute phases after SCI, the reactive astrocytes serve to separate the healthy tissue from the lesion area by restoring the blood-spinal cord barrier (75). This prevents the potential overwhelming inflammatory response (76), massive cellular degeneration and death (77), and tissue damage during the secondary injury (78). Therefore, a number of scholars believe that astrogliosis after CNS injury is dependent on STAT3 activation, an indispensable step for the formation of glia scar and limitation of the spread of inflammation (70). Additional studies reported that the deletion of STAT3 following SCI leads to the limited migration of reactive astrocytes, which was associated with widespread infiltration of inflammatory cells, demyelination and severe loss of motor function (79,80). Furthermore, this finding was also validated by a study by Leung *et al* (81), where conditional ablation of SOCS3 was observed to prolong expression of STAT3 in reactive astrocytes and significantly improve wound healing and motor function.

4. Astrocyte-secretory polypeptides promote neuroprotection via activating the JAK-STAT pathway

The neuroprotective effect of reactive astrocytes is multifaceted and includes astrocyte-secretory polypeptides, which contribute to endogenous neuroprotection and repair. Reactive astrocytes can secrete and respond to a number of vital cytokines, which affects the cellular state of the surrounding cells (microglia and neurons) and of astrocytes themselves (82). Reactive astrocytes can preserve neurons and oligodendrocytes, and protect motor functions after SCI (72,76,78), potentially due to the astrocyte-secretory polypeptides (astrocyte-derived cytokines and trophic factors), which alter the microenvironment (83-85). These cytokines include IL-1 β , TNF- α , IL-6, IL-11 and transforming growth factor- β 1 (86-92) and the trophic factors include brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, nerve growth factor (NGF), CNTF, basic fibroblast growth factor and leukemia inhibiting factor (LIF) (93-97). Recently, increasing evidence has indicated that cytokines and trophic factors secreted by reactive astrocytes may protect the injured tissues and cells through the JAK-STAT pathway (82,98).

Specifically, IL-6 and its family members, such as IL-11, LIF and CNTF may be activators of JAK-STAT signalling in neurons following SCI (99-103). Yamauchi *et al* (104) demonstrated the peak expression of IL-6 to be consistent with the maximum activation of JAK1 and STAT3 in neurons, with translocation of phosphorylated STAT3 to the nucleus. It has

previously been validated that the co-administration of IL-6 and soluble IL-6 receptor can improve neurological manifestations and protect motor neurons of the spinal cord from degeneration (105). Additional research also indicated that, compared with wild-type mice after injury, IL-6 gene knockout mice exhibited more severe damage and death of the spinal cord neurons (106). Further studies have provided evidence that IL-6 is significant in the regulation of sensory functions *in vivo* (107). The study by Yamauchi *et al* (104) revealed that pretreatment with the JAK2 inhibitor, AG-490 (108) reduced the functional recovery of hindlimbs after SCI, which indicated that activation of the JAK-STAT pathway induced by IL-6 in neurons may contribute to neuroprotection after SCI. As an effective trophic factor and pro-inflammatory factor, the LIF concentration increased within 24 h following SCI, indicating its vital role in regulating inflammatory reactions and preservation of oligodendrocyte following SCI (80,109). Although NGF and CNTF have diverse effects on the CNS, including differentiation and proliferation, they are able to enhance the survival of oligodendrocyte progenitors in CNS (110-117). Oyesiku *et al* (118) have previously indicated an upregulation of CNTF-receptors in the motoneurons of ventral horn and increase of CNTF in white matter, within 24 h after SCI. The expression of CNTF in reactive astrocytes was triggered by the SCI (119). Dell'Albani *et al* (120) reported that CNTF induces a rapid tyrosine phosphorylation of JAK1, JAK2, STAT1a/b and STAT3. The authors also considered JAK-STATs to be crucial in enhancing cell survival in CNS.

The activation of STAT not only rapidly activates caspase-9, -7, -6 and -3 (121) but also induces the transcription of non-apoptotic proteins. It appears that the ratio of STAT1 and STAT3 or STAT5 activation is significant in cell survival and apoptosis, with STAT1 being more apoptotic and STAT3 and STAT5 exhibiting anti-apoptotic properties (122). Several studies have demonstrated that STAT3 phosphorylation is involved in neuroprotection. Cheng *et al* (22) reported that the activation of STAT3 may be associated with the reduction of neuronal apoptosis following cerebral injury. Suzuki *et al* (123) revealed that the rapid enhancement of phosphorylated STAT3 was detected after the application of high-dose recombinant LIF. The phosphorylation of STAT3 correlated with a down-regulation of damage to the CNS, including a decrease in the number of TUNEL-positive cells in the damage area (123,124). Another study was also consistent with this finding; inhibition of STAT3 phosphorylation following damage to the CNS was associated with an increased seriousness of the secondary injury, and potential enlargement of the lesion, and exacerbation of neurological deficits (125). Neuroprotection requires the active suppression of apoptosis, which is accomplished either through suppressing caspases or by inhibiting their activation. The function of STAT3 in neuroprotection appears to be associated with the transcriptional modulation of antiapoptotic regulatory proteins, including the Bcl-2 family (126). Ahn *et al* (127) reported that survival factors cause the activation of STAT3, which was upregulated at 6 h following SCI; this prevents the release of cytochrome *c* and subsequent activation of caspase through the induction of Bcl-2 and Bcl-xL. All of these factors indicate that the increased expression of the transcription factors of the JAK and STAT family have antiapoptotic effects, which promote neuronal protection.

5. Conclusions

The JAK-STAT pathway is a critical pathway in proliferation and differentiation of NSCs and NPCs after SCI; it has been validated that the JAK-STAT pathway is significant in astrocytic differentiation, which is closely associated with glial scar formation and neuroprotection following SCI. Contrary to the conventional view that reactive astrocytes may inhibit axonal regrowth, the present view is that time-dependent effects of the JAK-STAT pathway in reactive astrocytes must be considered. In particular, that these effects are positive and protective in acute and subacute phases, while negative and inhibitory effects are observed in chronic phases. Reactive astrocytes may promote neuronal and oligodendrocytic protection and also protect motor functions following SCI. This is due to cytokines and trophic factors, including IL-6, IL-11, LIF and CNTF, secreted by reactive astrocytes. This indicates the neuronal protection and prevention of demyelination, partially through the JAK-STAT pathway. However, the mechanisms and the association between the JAK-STAT pathway, NSCs and NPCs, reactive astrocytes and astrocyte-secretory polypeptides remain unclear. Further studies are required to elucidate these mechanisms and associations to improve understanding of SCI and its treatment further detail. Elucidation of the mechanisms of JAK-STAT pathway may improve treatment with stem cell transplantation and aid in the identification of a new therapeutic tool that induces neuroprotection by controlling the function of reactive astrocytes.

Acknowledgements

This study was supported by the Medical Science and Technology Youth Cultivation Project of the Chinese People's Liberation Army (grant no. 13QNP017), the Key Program of National Natural Science Foundation of China (grant no. 81330042), the General Program of National Natural Science Foundation of China (grant nos. 81371957 and 81171714), the Special Project between Ministry of Science and Technology of China and Russia (grant no. 2014DFR31210) and the Cooperation Project between Tianjin Municipal Science and Technology Commission and Australia (grant no. 13RCGFSY19000).

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