Mini Review

The role of cytokine signaling in pathophysiology for spinal cord injury

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Although many cytokines are involved in the pathophysiology of spinal cord injury (SCI), the role of each cytokine remains elusive. Many lines of evidence have indicated that the excess inflammation elicited by pro-inflammatory cytokines exhibit neuronal and glial toxicity and that administration of several anti-inflammatory drugs can prevent this extensive secondary injury. Besides targeting secondary injury, modulating cytokine signaling is also an attractive therapeutic strategy as differentiational regulator for neural stem/progenitor cells. Here, we review the role of cytokine signaling which are both deleterious and beneficial in the pathophysiology for spinal cord injury, with an emphasis on the role of IL-6 signaling.

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Introduction

Spinal cord injury (SCI) causes severe motor/sensory dysfunction. Mechanical trauma rapidly leads to blood-spinal cord barrier disruption, neuronal cell death, edema, axonal damage and demyelination, followed by a cascade of secondary injury that expands the additional inflammatory reaction at the lesion area[1,2)]. Although primary mechanical injury is considered irreversible, secondary extensive injury may be amenable to therapy. Currently, the only available treatment for SCI patients is the high dose of methylprednisolone sodium succinate (MPSS) and this therapy is also widely used with the purpose to minimize secondary injury (even though its clinical effect is controversial[3)]). Recruitment of inflammatory leukocytes to the injured spinal cord is a physiological response in host defense and wound repair. However, cytokines, free radicals, proteases and eicosanoids released from these infiltrated neutrophils/macrophages have been demonstrated to be toxic and deleterious in various model of SCI. Although the extent to which secondary injury is associ-

Table 1 Cytokine expression after SCI

Time	Cytokines	Events
Hours-Days	IL-1β, IL-6, TNFα LIF, IL-2α, CNTF	hemorrhage, edema, ischemic necrosis, failure of ionic conduction, inflammation
Days-Weeks	NGF, TGF β,GDNF, IL-6 BMPs, PDGF, BDNF	inflammation, apoptotic cell death, spread of lesion and demyelination
Weeks-Months	VEGF, BDNF	glial scarring, clearance of debris, upregulation of axonal inhibitor

ated with clinical paralysis remains elusive, many reports have shown remarkable protection and functional recovery using anti-inflammatory or anti-apoptotic reagents in rodent SCI models, and the strategy for minimize this auto-destructive injury is the main pillar in the field of SCI research[4-8].

Pro-inflammatory cytokines and therapeutic strategy

Owing to methodological advances in genomics, the concurrent analysis of hundreds or thousands of gene expression changes after SCI is available and mRNA profiles of cytokines also have been characterized[9] (Table 1). In the hyper acute phase, the drastic changes of gene expressions in pro-inflammatory cytokines including IL-1β, IL-6 and TNFα are observed from 30 minutes to 6 hours after injury. The increased expression is also seen in cytokine receptors such as IL-6R, IL-4R and IL-2Rα in acute phase. Anti-inflammatory cytokines such as IL-10, IL-4 and IL-13 develop several days later. Although up-regulation of nerve growth factors such as NGF, BDNF, PDGF and EGF also occurs in the acute phase, it is likely that their concentration is too weak, because the exogenous delivery of these factors have been demonstrated to provide both neuroprotective effects and improved functional recovery[10,11].

Previous studies have suggested that inflammatory responses spread the damage to surrounding tissue, induce apoptotic cell death, and impair spontaneous regeneration and functional recovery, and that the number of inflammatory cells is significantly correlated with the amount of tissue damage[6,12]. In order to protect the injured spinal cord from secondary pathological processes, several approaches allowing manipulation of inflammatory responses have been assessed and been demonstrated to be effective: i.e. blockage or neutralizing the specific cytokine signaling using monoclonal antibody, delivery of anti-inflammatory drugs, and use of genetically modified animals. Among the SCI experiments using monoclonal antibody, α-TNFα antibody[13], α-IL-6 antibody[14], α-IL-6R antibody[15], IL-1R antagonist[16], α-ICAM-1 andtibody[17] and α-P-selectin anti-body[18] were reported to be effective to protect from secondary injury through anti-inflammatory effect. Similarly, Methylprednisolone[19], cyclosporine[20], Tacrolimus[21], minocycline[22], IL-10[23] and erythropoietin[24] were also reported to have anti-inflammatory and anti-apoptotic effects and to be effective by improving cell survival and tissue sparing after SCI. Mutant mouse models also contributed significantly to our understanding of the role of cytokines. In LIF KO mouse, the number of infiltrated CD-11b positive macrophage/microglia is decreased after SCI[26]. On the contrary, over expression of LIF result in the increase of CD-11b positive cells and development of severe motor dysfunction[26]. MMP-9-null mice exhibited significantly less disruption of the blood-spinal cord barrier, attenuation of neutrophil infiltration, and significantly enhanced locomotor recovery compared with wild-type mice[25]. Regards to TNFα, there was no difference in functional recovery after SCI between TNFα knockout mouse and wild-type mouse[27], but worse functional recovery was observed in TNF receptor 1 knockout mouse[28]. From only these results, however it is difficult to determine whether the role of each cytokine signaling is simply neuroprotective or neurodestructive for the reason that it varies depending on the dose and phase of injury and that each effect can be interferential or synergistic due to the crosstalk mechanisms with another cytokines.

Cytokine signaling as differentiation regulator for neural stem/progenitor cells

Recent studies have shown the existence of neural stem/progenitor cells (NSPCs) in adult mammalian spinal cord and have raised the possibility that the spinal cord has latent capacity for self-repair in response to injury or disease through the use of NSPCs[29,30]. After a spinal cord injury (SCI), however, these cells proliferate and migrate to the lesion site, where they differenti-

ate exclusively into astrocytes, never into neurons, and are eventually associated with glial scar formation[31]. In addition, the majority of engrafted NSPCs also differentiated into astrocytes when implanted into non-neurogenic region including adult injured spinal cord[32]. The major causes of this inhibitory mechanism of neuronal differentiation include the microenvironmental factors that dramatically change immediately following SCI[33]. IL-6 family cytokines including IL-6, LIF and CNTF are known to induce NSPCs to differentiate into astrocytes by activating the gp130/Janus kinase 2 (JAK2)/signal transducers and activators of transcription 3 (STAT3) pathway[34] (Fig.1). This inducible effect of IL-6 family cytokines is markedly enhanced with bone morphogenetic protein 2 (BMP2), which synergistically act to induce NSPCs to become astrocytes by forming a complex of the respective downstream transcription factors, Smads and STAT3, bridged by p300[35]. The expression level of IL-6, LIF, CNTF and BMPs dramatically elevate in injured spinal cord at acute phase, suggest that these cytokines are feasible involved factors for the inhibitory differentiation. Actually, Ogawa et al. demonstrated that the transplantation of *in vitro* expanded NSPCs results in mitogenic neurogenesis when the transplantation into the injured adult rat spinal cord is carried out 9 days after injury, but not when the transplantation is done within an acute phase of the injury[36]. Setoguchi et al. demonstrated that gene modification to inhibit BMP signaling by noggin expression promoted differentiation of NSPCs into neurons and oligodendrocytes and that better functional recovery was observed when noggin-expressing NSPCs were transplanted into SCI mice compared to control NSPCs[37]. Although we don't yet fully understand what types of cells are most effective for SCI treatment, these strategies are significant to enhance the effect of cell therapy.

The role of IL-6 in the injured spinal cord

IL-6 is one of the principal proinflammatory cytokines; it plays roles in regulating various steps in inflammatory reactions, i.e., activation and infiltration by neutrophils, monocytes, macrophages, and lymphocytes[38]. Previous studies reported that administration of IL-6 cytokines at lesion sites 1 day after an injury increases the recruitment and activation of macrophages, neutrophils, and microglial cells[39] and that delivery of IL-6/sIL-6R fusion protein to injury sites induces a six-fold increase in neutrophils, a twofold increase of macrophages and microglial cells and expand the damaged area[40]. So, we speculated that blockage of IL-6 signaling would suppress the inflammatory response and minimize the secondary injury after SCI.

In addition, we focused on the IL-6 signaling as differentiational regulator for neural stem/progenitor cells (NSPCs) as mentioned above. We speculated that activation of IL-6 signaling could be one of the major contributions of the selective astrocytic differentiation after SCI. Consistent with this idea, Klein et al. observed a massive reduction in the number of activated GFAP positive astrocytes when the facial nerve of IL-6-deficient mice was transected[41], and Brunello et al. demonstrated massive reactive gliosis with numerous GFAP-immunoreactive astrocytes in all parts of the CNS in uninjured IL-6/sIL-6R double-transgenic mice[42]. Therefore, we hypothesized that the astrogliosis could be suppressed by blocking IL-6 signaling after SCI *in vivo*. Based on these studies, we tested our hypothesis using a rat anti-mouseIL-6 receptor monoclonal antibody (MR16-1) in the treatment of acute SCI in mice[15]. Immediately after inducing a contusion injury at the level of Th9 in mice, we administered MR16-1 by intraperitoneal injection (100 mg/g body weight). In this model, MR16-1-treatment decreased the number of Mac-1-positive cells infiltrated both gray and white matter and the lesion volume of epicenter was significantly smaller in the MR16-1 group than in the control group. We also found that the number of GFAP-BrdU double-positive astrocytes was decreased by MR16-1 treatment, indicating that proliferation of astrocytes and/or mitotic production of astrocytes was inhibited by this treatment. In addition, significantly enhanced functional recovery was observed in mice treated with MR16-1 compared with control mice. This modulation of the inflammatory response after injury by administration of MR16-1 probably attenuated the tissue damage and secondary neural destruction and caused the functional recovery.

However, the precise mechanism regulating astrogliosis remains to be elucidated and we were not able to determine the extent to which endogenous multipotential progenitors or resident astrocytes contributed to the GFAP/BrdU double positive cells in this study. In addition, it is possible that the reduction of astrogliosis (the number of GFAP/BrdU double positive cells) by MR16-1 resulted from the significant reduction of lesion volume brought about by the anti-inflammatory effect of MR16-1 rather than the inhibition of astrocytic differentiation of NSPCs.

Experiments using STAT3 conditional knockout mouse and novel role for reactive astrocytes

So, in order to have selectively reduced astrogliosis due to the inhibition of astrocytic differentiation of NSPCs through the STAT3 pathway, we performed experiments by using mice with a selective deletion of STAT3 under the control of Nestin gene

promoter/enhancer ($STAT3^{N-/-}$). We initially expected selective disruption of stat3 in NSPCs and reduced reactive gliosis as well as increased functional recovery in this mouse. However, the result showed that Cre-mediated recombination was highly observed in reactive astrocytes rather in NSPCs, and contrary to our expectation, widespread tissue damage and significant functional impairment were observed in this conditional STAT3 knockout mouse although the reactive gliosis appeared normal at 6 weeks after injury[43]. To further examine the workings behind this unexpected result, we performed elaborate experiments using another genetically altered mice, and through these studies we ascertained the novel role of reactive astrocytes in SCI[43].

In this experiment, we firstly examined the progressive state of neural cells in serial histological sections of contused spinal cords in wild-type mice so as to assess how the deteriorated pathophysiology developed in $STAT3^{N-/-}$ mouse after injury. The histological examinations revealed that the area of neural cell loss gradually enlarged in a rostral-caudal direction within a few days after SCI (acute phase) and a portion of neurons were positive for cleaved caspase-3, indicating that the secondary injury process lasted for several days in this model during which limited functional recovery was observed. Meanwhile, astrocytes surrounding the lesion underwent a typical change of morphology with hypertrophy, process extension and increased expression of intermediate filaments such as GFAP and Nestin at subacute phase of injury, characteristic of "reactive astrocytes". These reactive astrocytes gradually formed a physical barrier, commonly referred to as a glial scar (Fig.2,3). The glial scar contains extracellular matrix molecules that chemically inhibit axonal regeneration as well as physically and definitely plays a crucial part in CNS regeneration failure[44]. Surprisingly, we observed that reactive astrocytes exerted a positive role during the subacute phase (around from 1w to 2w after SCI in this model), prior to the completion of the glial scar. Interestingly, during the first two weeks after injury reactive astrocytes migrated towards the lesion epicenter and gradually compacted the inflammatory cells and contracted the lesion area (Fig.3). It is noteworthy that gradual functional improvement was observed only during this phase and functional improvement reached a plateau after completion of glial scar formation. These results strongly suggest that the emergence and migration of reactive astrocytes play a prominent beneficial role in the repair of injured tissue and the restoration of motor function, contrary to previous thoughts that reactive astrocytes were only detrimental for regeneration after SCI. In addition, the widespread tissue damage in $STAT3^{N-/-}$ mice after several weeks was very comparable to the phenotype of injured spinal cord at 1 week after SCI, suggesting that migration ability of reactive astrocytes was compromised in $STAT3^{N-/-}$. To further investigate the relationship between STAT3 signaling and function of reactive astrocytes, analysis of SCI in $SOCS3^{N-/-}$ mice was conducted. SOCS3 is the negative feedback molecule of STAT3 and the "bipolar" relationship between STAT3 and SOCS3 has been noted in several selective deletion experiments. In the injured spinal cord in $SOCS3^{N-/-}$ mice, rapid migration of reactive astrocytes to seclude inflammatory cells, enhanced contraction of lesion area and dramatic improvement in functional recovery were observed. These results strengthens the idea that STAT3 signaling is associated with the migration of reactive astrocytes and thereby is a key regulator in the healing process after SCI.

The context-dependent pleiotropic actions of IL-6 family cytokines and STAT3-signaling in the injured spinal cord

As mentioned above, we previously demonstrated that blockage of IL-6 signaling using MR16-1 ameliorated functional recovery in experimental SCI[15]. However, Penkowa et al. showed the neuroprotective role of IL-6 using transgenic mice that overexpress IL-6 in the CNS under the control of the GFAP gene promoter[45]. This GFAP-IL-6 transgenic mouse showed faster tissue repair and decreased oxidative stress and apoptosis compared with WT mice after brain injury. In addition, Swartz reported that IL-6 deficient mice were found to have a comparatively slower rate of recovery and healing after brain injury[46]. Although these results initially seem inconsistent, we believe that this is a consequence of the context-dependent pleiotropic actions of IL-6 family cytokines and STAT3-signaling in the injured CNS. During the acute phase of SCI, IL-6 family cytokines act primarily as inflammatory inducers and cause the secondary injury. Overexpression of IL-6 or LIF in the acute phase causes a significant increase in inflammatory cells and results in a widespread area of damage[26,40]. However, after subacute phase of injury, IL-6 and STAT3 signaling may provide an enhancement of repair process associated with the migration of reactive astrocytes as mentioned above[43]. In experiments using MR16-1, the one-shot administration of MR16-1 had little influence on the migration of reactive astrocytes due to the short half-life of this agent and the presence of other gp130 related cytokines that can activate STAT3 signaling[15]. So, it is comprehensible that astrocyte-targeted IL-6 expressing transgenic mice showed prompt migration of reactive astrocytes and significant tissue repair similar to $SOCS3^{N-/-}$ mice[45], though hyperactivation

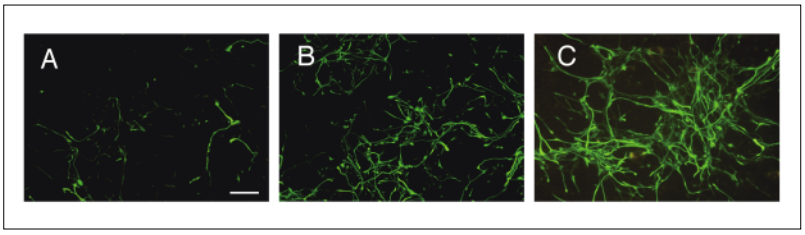

Fig.1 IL-6 signaling induces NSPCs to differentiate into GFAP-positive astrocytes

Dissociates of human neural progenitor cells were cultured for 7days with medium alone (A), IL-6 and soluble IL-6 receptor at 250ng/ml (B), and IL-6 and soluble IL-6 receptor at 500ng/ml (C) and then subjected to immunofluorescence staining for GFAP (green). Scale bar: 100 μm.

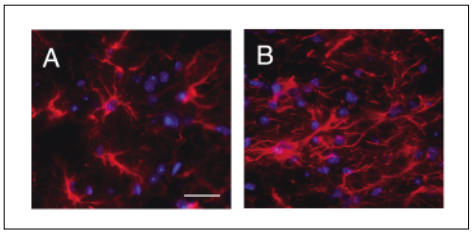

Fig.2 Typical change of astrocytes: "Reactive astrocytes"

Astrocytes surrounding the lesion underwent typical morphological changes characterized by hypertrophy and process extension, commonly referred to as reactive astrocytes (B). (A) Images of normal (residual) astrocytes. Sections of gray matter in spinal cord were counterstained with GFAP (red) and Hoechst (blue). Scale bar: 50 μm.

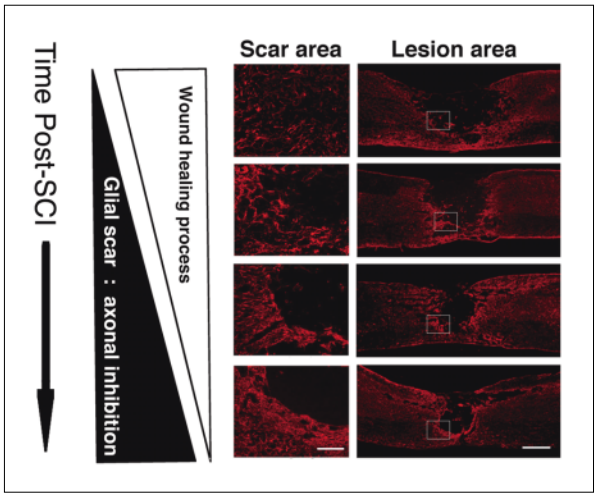

Fig.3 The dual role of reactive astrocytes in the subacute phase of SCI

Reactive astrocytes surrounding the lesion area (insets) gradually form the glial scar, during which they progressively contracted the lesion area. Once completed, glial scar, often compared to a chemical and physical barrier, does inhibit axonal regeneration. Scale bar: 100 μm (left) and 500 μm (right).

of IL-6 signaling without a specific cellular-target caused significantly larger damage due to robust inflammation after CNS injury[40].

Concluding remarks

From these results, what we consider to be most important is the appropriate treatment strategy in accordance with each phase of injury; protection from secondary injury by anti-inflammatory and/or anti-apoptotic treatment in the acute phase, enhancement of the repair process by reactive astrocytes in the subacute phase, and facilitation of axonal regeneration by attenuating axonal inhibitors in the chronic phase.

Nevertheless, before efficient and safe therapeutics based on modulation of cytokine signaling could be established, more basic research should continue to define the detailed biological role of each cytokines in SCI.

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