Review Article

Stem cell therapies for injured spinal cord

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Although it was long thought that the damaged adult central nervous system (CNS) cannot regenerate, spinal cord injury (SCI) is now an important target in regenerative medicine. A series of studies on stem cell-based therapies for SCI has led us to believe that neural stem/progenitor cells (NSPCs) are a promising source for neural tissue replacement therapy after SCI, when applied appropriately. In this review, we summarize our previous findings on stem cell therapies for SCI and discuss the future directions of this work.

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Regeneration of the CNS and neural stem cells

Classically," regeneration of the CNS "referred to the *re-growth* of damaged neuronal axons. However, it was later realized that the *replenishment* of lost neural cells, and furthermore, the *recovery* of lost neural function could be included in the concept of CNS regeneration. In fact, the *recapitulation* of normal neural development has become a vital strategy for CNS regeneration[1]. Stem cells or stem-like cells appear at the earliest stage of normal CNS development. There is increasing interest in using these CNS stem cells (neural stem cells, NSCs) as a tool to recapitulate normal CNS development and regeneration.

NSCs have multilineage potential and self-renewing capability. At least *in vitro*, a single NSC can generate a variety of CNS cells, including neurons, astrocytes, and oligodendrocytes[2]. *In vivo* and *in vitro* lineage analyses have shown that the multilineage potential of NSCs is at least partly mediated by the generation of cell lineage-restricted intermediate progenitor cells: neuronal progenitor cells, which produce only neurons, and glial progenitor cells, which produce only astroglial or oligodendroglial cells[3,4]. Thus, the cellular diversity of the CNS is likely to be generated in a stepwise fashion through the production of various intermediate progenitors. Since there are currently no available definitive molecular markers for NSCs, it is experimentally difficult to distinguish NSCs from neural progenitor cells. Therefore, these cells are often inclusively referred to as neural stem/progenitor cells (NSPCs).

Experimental evidence for NSCs with multilineage potential and self-renewing capability benefited from a major breakthrough in CNS stem cell biology: the clonogenic expansion of NSCs by neurosphere formation in serum-free medium con-

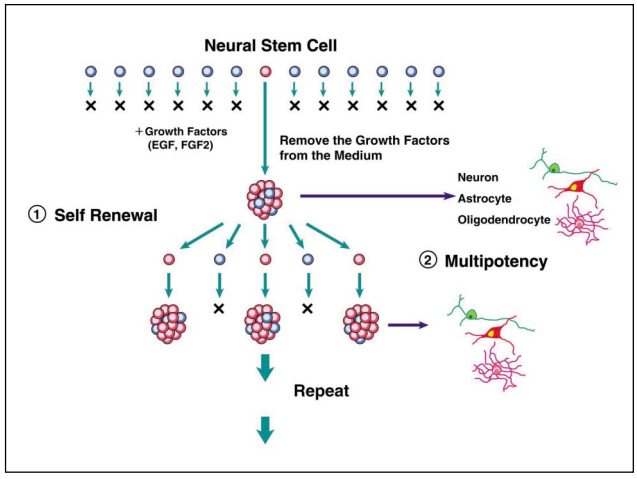

Fig.1 Expansion of NSPCs *in vitro* by the neurosphere method[9,54].

NSPCs can be expanded in floating culture by the neurosphere method in the presence of EGF and/or FGF-2[5].

taining EGF and/or FGF-2[5] (**Fig.1**). In this culture system, NSCs or NSPCs can proliferate in an undifferentiated state *in vitro*. Because of the ease of harvesting NSPCs as neurospheres after their expansion *in vitro* (or by similar methods), there have been numerous attempts to transplant *in vitro*-expanded human NSPCs into animals to treat the damaged brain or spinal cord[2,6-11].

Rationale for regenerating injured spinal cord and a summary of historical "regenerative" treatments

Traumatic spinal cord injury (SCI) affects many people, including young people, and can result in severe damage, leading to the loss of motor and sensory function at the level of the injury, through the severing of descending and ascending fiber tracts. The disruption of fibers that control the autonomic nervous system can lead to impairments of the vascular system, exocrine and endocrine glands, and bowel, bladder, and sexual function. Currently, the standard clinical treatments for SCI include surgical stabilization of the ventral column to prevent its posttraumatic instability and high doses of steroids to decrease the amount of tissue damage. However, the effects of these treatments are modest at best, and there remains a great need for novel "regenerative" treatment strategies that could significantly protect and/or restore functions following SCI[12].

The lack of self-regenerative properties in the adult mammalian spinal cord is attributable to a combination of factors, including the inhibitory effects of CNS myelin and injury-induced glial scars, the apparent inability of endogenous adult NSCs in the spinal cord to induce *de novo* neurogenesis upon injury[13], and the lack of sufficient trophic support[10,11,14].

However, in the 1980s, researchers began investigating the transplantation of peripheral nerves[15] and fetal spinal cord[16] as treatments for SCI. These studies indicated that the introduction of an appropriate environment into the injured site can cause injured axons to regenerate. In addition, there are reports describing spinal cord regeneration, including the promotion of the regeneration of injured axons by neurotrophic factors[17], and the identification of axonal growth inhibitors[18]. In one set of studies, immature and adult rats in which the thoracic spinal cord had been partially transected were treated with the transplantation of fetal spinal cord, which does not yet express CNS myelin. The rats receiving the transplant showed elongation of the injured axons with functional recovery, and this result was more pronounced in immature rats[19]. Such transplants survive and integrate with the host tissue, and may be associated with functional improvement. These studies indicated that regeneration of the injured spinal cord might really be possible.

Although researchers first focused on fetal spinal cord transplantation for spinal cord injuries, a donor shortage and ethical problems precluded the practical clinical application of this approach. The ability to expand neural progenitor cells *in vitro*[5] provided a new potential source for graft material for the regeneration of injured spinal cord that may, at least in part, overcome the practical and ethical problems associated with fetal tissue transplantation.

Microenvironments of the injured spinal cord: insight into the therapeutic time window for NSPC transplantation

One of the most important issues regarding NSPC transplantation into injured spinal cord is that the adult spinal cord appears to be a non-neurogenic site; i.e., upon injury *in situ*, endogenous NSCs in the adult rat spinal cord proliferate and differentiate exclusively into astrocytes and not into neurons or oligodendrocytes[11], leading to neuronal deficits and demyelination. However, adult spinal cord-derived NSPCs can produce neurons *in vitro* and when transplanted into neurogenic sites where neurons are newly generated even in adulthood, such as the hippocampal dentate gyrus[20], indicating that the microenvironments within CNS subdomains can greatly affect the differentiation of NSCs and their progenies.

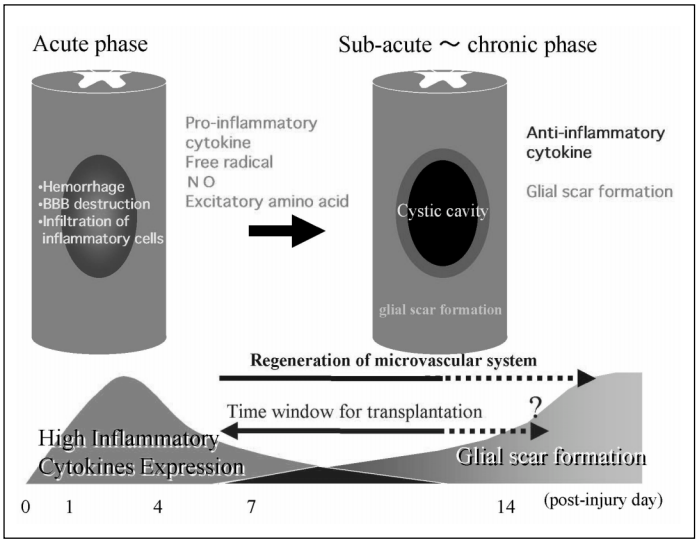

Fig. 2 Changes in microenvironment within the injured spinal cord and optimal timing for the transplantation of NSPCs[11].

Endogenous NSPCs in the adult rat spinal cord are believed to proliferate and differentiate exclusively into astrocytes, not neurons, upon injury. However, we showed that transplanted NSPCs differentiated into neurons *in vivo* [21]. This apparent difference could be explained as follows. First, enough autocrine and/or paracrine factors may have been supplied by the donor cells to facilitate their own survival and neuronal differentiation, since we transplanted a large number of immature neural progenitor cells. Second, the microenvironment around the injury site may no longer have been in the acute phase, indicated with (A) in this figure, since we transplanted the NSPCs 9 days after the injury. The proliferation of endogenous NSPCs after injury is actively induced in this acute inflammation phase. Their differentiation into astrocytes may be due to the microenvironment in this phase favoring the generation of astrocytes to prevent the extension of inflammation into the surrounding area. By 9 days after injury, the microenvironment around the injured site may have changed to be suitable for grafted cells to survive and differentiate into neurons and oligodendrocytes. However, delaying transplantation until the chronic phase is also unlikely to lead to functional recovery, due to the enlarged cystic cavity at the injury site and glial scar formation. In fact, when we transplanted NSPCs into injured spinal cord at the chronic phase, neither their neuronal differentiation nor functional recovery was obtained[27].

On the other hand, by studying microenvironments of the injured spinal cord, we found that the adult spinal cord is not absolutely non-neurogenic for transplanted exogenous NSPCs and that a narrow therapeutic time window can allow successful transplantation[21]. The existence of this brief window of opportunity is probably due to the fact that the microenvironment in the host spinal cord changes rapidly after injury. Recent reports have shown that severe inflammation occurs transiently around the injured site during the acute phase, which immediately follows the injury. During this phase, the levels of many inflammatory cytokines that have neurotoxic or astrocyte-inducing effects, such as IL-1, IL-6, and TNF increase, and then decline sharply within 24 hr[22], indicating that the microenvironment of the acute phase would not be suitable for the survival of grafted cells. Taken together, because the immediately post-traumatic microenvironment of the spinal cord is in an acute inflammatory stage, it is adverse for the survival and differentiation of NSPC transplants. On the other hand, in the chronic stage after injury, glial scars that form in the injured site would inhibit the migration of graft-derived cells and the regeneration of neuronal axons. Thus, it is likely that the optimal timing of transplantation is between these two phases, 1-2 weeks after injury, [2,9-11,21] (**Fig.2**).

On the basis of the above-mentioned changes in microenvironments within the injured spinal cord and the proposed "optimal timing" for NSPC transplantation, we transplanted *in vitro*-expanded rat fetal spinal cord-derived NSPCs into an adult rat spinal-cord-contusion injury model at the C4 and C5 level, 9 days after the injury. We then examined whether the transplanted NSPCs generated neurons *in vivo* and improved motor function[21]. The neurosphere cells were prepared from rat embryonic day 14.5 (E14.5) spinal cord, expanded, and prelabeled with bromodeoxyuridine (BrdU) in culture. Using the 9-day transplantation time, the transplanted neurosphere cells were able to introduce neurons, astrocytes, and oligodendrocytes into the injured adult rat spinal cord. Furthermore, the transplantation resulted in the mitotic production of new neurons *in vivo*, and these neurons extended their processes into the host tissue, where they formed synaptic structures. In addition, we observed behavioral improvement in the rats with transplanted neurosphere cells compared with control rats, in terms of skilled forelimb movements assayed by a pellet retrieval test[23].

There are several possible explanations for this functional improvement: i) Synapse formation by graft-derived neurons.

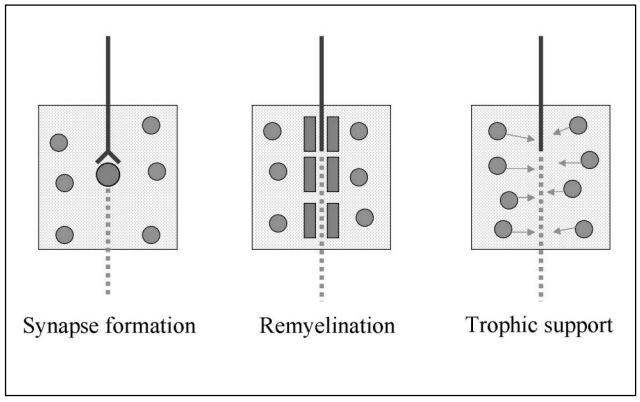

Fig. 3 Possible mechanisms for the functional recovery after NSPC transplantation into injured spinal cord[11].
See the text for details.

Neurons derived from the grafted cells might have "relayed" signals from the disrupted fibers in the host, including ascending fibers in the dorsal column. Alternatively, graft-derived inhibitory neurons might have suppressed spasticity and/or excitotoxicity by forming synapses with host neurons. ii) Remyelination. Oligodendrocytes derived from the grafted cells might have remyelinated fibers that had been demyelinated as a result of injury and restored the saltatory conduction along the axons of long-projection neurons. iii) Trophic effects. Functional improvement might not have been dependent on the transplanted human NSPCs becoming functional neurons and making the right connections, but rather on the secretion of trophic factors from the transplanted cells. Such factors might have promoted the survival and differentiation of host cells in the injured spinal cord, leading to functional recovery[11,24](**Fig.3**) .

Interestingly, a recent report indicates that prospectively isolated, human NSPCs grown as neurospheres (hCNS-SCns) survive, migrate, and express differentiation markers for neurons and oligodendrocytes after long-term engraftment in spinal cord-injured NOD-scid mice[25]. hCNS-SCns engraftment was associated with locomotor recovery, an effect that was abolished by selective ablation of the engrafted cells by diphtheria toxin. Remyelination by hCNS-SCns was found in a NOD-scid spinal cord injury model. These results indicate that remyelination might contribute to the functional recovery seen after the transplantation of NSPCs into SCI model animals and that the functional recovery obtained by NSPC transplantation cannot be explained solely by the contribution of trophic effects.

Comparison between fetal spinal-cord- and forebrain-derived neural stem/progenitor cells as a transplantation source for spinal cord injury

As mentioned above, transplanted spinal-cord-derived NSPCs can contribute to the repair of injured spinal cord in adult rats, which may correspond to a behavioral recovery[21]. To apply these results to clinical practice, a system for supplying human NSPCs on a large scale must be established. However, human spinal-cord-derived NSPCs are known to have a low proliferation rate compared with forebrain-derived NSPCs. This low proliferative potency limits the feasibility of large-scale use of spinal cord-derived NSPCs. Therefore, we examined forebrain-derived NSPCs as an alternative to spinal-cord-derived NSPCs for treating spinal cord injuries. We compared spinal-cord- and forebrain-derived NSPCs transplanted into injured spinal cords with respect to their fates *in vivo* as well as the animals' functional recovery[26]. Both spinal-cord- and forebrain-derived NSPCs promoted functional recovery in rats with spinal cord injuries. Interestingly, however, while both spinal-cord- and forebrain-derived NSPCs survived, migrated, and differentiated into neurons, astrocytes, and oligodendrocytes in response to the microenvironment in the injured spinal cord after transplantation, forebrain-derived NSPCs differentiated into more neurons and fewer oligodendrocytes, compared with spinal-cord-derived NSPCs. The neurons that differentiated from the transplanted forebrain-derived NSPCs were positive for neurotransmitters like GABA, glutamate, and glycine, even though authentic glycinergic neurons are not normally present within the forebrain. Thus, at least a subpopulation of the transplanted forebrain-derived NSPCs appeared to differentiate into spinal-cord-like neurons, at least in their neurotransmitter phenotype[26]. These findings indicated that forebrain-derived NSPCs could be used as an alternative to spinal-cord-derived NSPCs as a potential therapeutic agent for spinal cord injuries, which would have the advantage at least of supplying a large amount of cells for transplantation.

In vivo imaging of engrafted neural stem cells: application for evaluating the optimal timing of transplantation for spinal cord injury

As mentioned above, NSPCs hold promise as a source for neural tissue replacement therapy after SCI. However, understanding the survival time of grafted NSPCs and determining

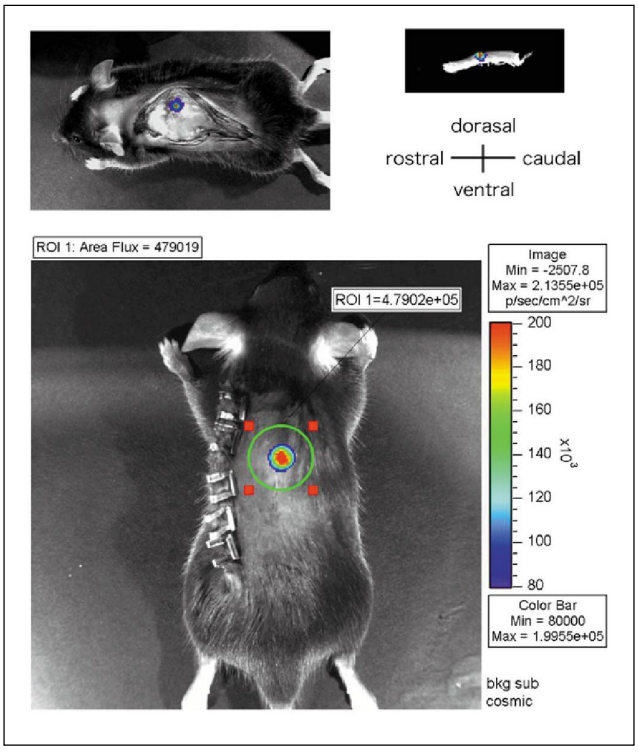

Fig. 4 Monitoring the viable transplanted cells by the BLI system.

The viability of Luciferase-expressing cells, which had been transplanted into injured spinal cord, can be visualized quantitatively by the BLI system[27,28]. The figure shows the B6 mice SCI model which had received the transplantation of luciferase-expressing NSPCs.

the extent of their migration away from transplantation sites are essential for optimizing treatment regimens. To address these issues, we used *in vivo* bioluminescence imaging (BLI) to non-invasively assess the survival and residence time of transplanted NSPCs at the injury sites in living animals[27]. BLI is a useful tool for tumor, immune, and hematopoietic cell-tracking studies[28]. In this method, transplanted cells stably expressing luciferase can be detected *in vivo* through the tissue of live animals using ultrasensitive cooled charged-coupled device (CCD) cameras after the administration of luciferin, the luciferase substrate. Since this reaction depends on adenosine triphosphate (ATP) and oxygen, it is a metabolic indicator only where living cells release photons. However, the long-term tracking of primary cultured cells including NSPCs has been limited by the relative difficulty of obtaining a high level of sustained reporter gene expression, including luciferase. To address this limitation, we used third-generation lentiviral vectors[29], which enabled the efficient transduction and stable expression of both luciferase and a variant of green fluorescent protein into primary cultured NSPCs. Signals from these cells were detectable for 10 months or more after transplantation into the injured spinal cords of C57BL/6J mice (**Fig.4**). Histological and functional data supported the imaging data and suggested that the timing of NSPC transplantation is a key determinant of the fates and function of the integrated cells, since cell survival and migration depended on the time of transplantation relative to injury, consistent with our earlier studies[21]. The optimization of cell therapies can be greatly accelerated and refined by imaging, and the methods in the present study can be widely applied to various research fields of regenerative medicine, including transplantation studies.

Microenvironments of the injured spinal cord: the blockade of IL-6 signaling as a new therapy for SCI at the acute phase

Our studies on the optimal timing for transplanting NSPCs gave us some insights for therapeutic interventions at the acute phase[30]. It has been reported that after SCI, the intrinsic NSPCs do not differentiate into neurons but into astrocytes[13], resulting in the formation of glial scars, which could prevent axonal regeneration at the lesioned site. It has also been shown that the expression of IL-6[22] and the IL-6 receptor[30] is sharply increased in the acute stages after SCI, and that IL-6 may strongly induce the selective differentiation of NSPCs into astrocytes through the JAK/STAT pathway. IL-6 has also been demonstrated to play a critical role as a proinflammatory cytokine and to be associated with secondary tissue damage in SCI. We therefore assessed the efficacy of a rat anti-mouse IL-6 receptor monoclonal antibody (MR16-1) for the treatment of acute SCI in mice[30].

Before conducting *in vivo* experiments, we examined the effects of MR16-1 in the differentiation assay of neurosphere-derived cells and found it to inhibit the astrocytic differentiation of NSPCs *in vitro*. For the *in vivo* experiment, immediately after inducing a contusion injury at the level of Th9 in mice, we administered MR16-1 by intraperitoneal injection (100 microg/g body weight), which significantly inhibited the activation of the JAK/STAT3 pathway. The lesions were then assessed histologically, and the functional recovery was evaluated. MR16-1 not only suppressed the astrocytic differentiation-promoting effect of IL-6 signaling *in vitro* but also inhibited the development of astrogliosis after SCI *in vivo*. MR16-1 also decreased the number of invading inflammatory cells and

the severity of connective tissue scar formation. In addition, significant functional recovery was observed in the mice treated with MR16-1 compared with control mice. These findings suggest that the neutralization of IL-6 signaling in the acute phase of SCI is an attractive option in the treatment of SCI.

A humanized monoclonal antibody against human IL-6R (MRA; Atlizumab) has an excellent inhibitory effect on IL-6 signaling. Its safety and metabolic distribution, tolerance, etc., are being investigated in detail, and clinical research in its application for the treatment of inflammatory diseases, such as rheumatoid arthritis, Crohn's disease, and Castleman's disease, has progressed[31-33]. MRA is currently regarded as a potential acute-phase treatment for spinal cord injury instead of high-dose steroids, whose efficacy has been questioned, and we are establishing a system for the early clinical studies.

Chondroitinase ABC combined with neural stem/progenitor cell transplantation enhances transplanted cell migration and axonal regeneration after rat spinal cord injury

Although transplanted NSPCs can contribute to the repair of injured spinal cord in adult rats[21], in some cases most of the transplanted cells adhered to the cavity wall and failed to migrate and integrate into the host spinal cord. To address this issue, we focused on chondroitin sulfate proteoglycan (CSPG)[34], a constituent of glial scar tissue that is strongly expressed after spinal cord injury, as a putative inhibitor of NSPC migration[35-37]. Furthermore, CSPG is known to act as an inhibitor of axonal regeneration[38].

We hypothesized that the digestion of CSPG by chondroitinase ABC (C-ABC) would promote the migration of grafted NSPCs and enhance axonal regeneration after SCI. First, an *in vitro* study revealed that the migration of NSPCs was inhibited by CSPG, and this inhibitory effect was attenuated by C-ABC pretreatment. Consistently, *in vivo* experiments in which C-ABC treatment was combined with NSPC transplantation into the injured spinal cord revealed that C-ABC pretreatment promoted the migration of the grafted NSPCs, whereas in animals without the pretreatment, CSPG immunopositive scar tissue around the lesion cavity prevented their migration into the host spinal cord. Furthermore, these combined treatments significantly promoted axonal regeneration at the lesion epicenter compared with the single treatment of NSPC transplantation. These findings suggest that the application of C-ABC enhances the benefits of NSPC transplantation for spinal cord injury by overcoming the inhibitory effects of the glial scars, and that the combined treatment of NSPC transplantation and C-ABC application may be a promising strategy for the regeneration of injured spinal cord.

Development of a primate SCI model and NSPC transplantation

As mentioned above, recent studies have shown that the delayed transplantation of NSPCs into the injured spinal cord can promote functional recovery in adult rats. Direct extrapolation of the results obtained in rodents to clinical cases is difficult, however, because of neurofunctional and anatomic differences between rodents and primates. For example, the corticospinal tract (CST) fibers localize mainly to the dorsal funiculus in rodents whereas in primates, they localize mainly to the lateral funiculus[39,40]. There are also some differences between rodents and primates in descending spinal tracts other than the cortico-spinal tract. Preclinical studies using nonhuman primates, however, are necessary before NSPCs can be used in clinical trials to treat human patients with SCI.

For the preclinical study, we used common marmosets (*Callithrix jacchus*), which can be bred in experimental colonies, are available in a stable and reliable supply, and come from breeding programs with adequate genetic and microbiological control to minimize biases[41-44]. We therefore established a graded-contusive SCI model in common marmosets that has characteristics quite similar to human SCI[40], and examined the effectiveness of human NSPC transplantation on the recovery of motor functions in tetraplegic primates after contusive SCI[8].

Cervical contusion SCIs were induced in 10 adult common marmosets using a stereotaxic device. Nine days after injury, *in vitro*-expanded human NSPCs prepared according to the modified neurosphere method[45] were transplanted into the spinal cord of five randomly selected animals, and the other animals were sham-operated controls that received culture medium alone. Motor functions were evaluated by measuring the marmosets' bar grip power and spontaneous motor activity, and temporal changes in the intramedullary signals were monitored by magnetic resonance imaging (MRI). Eight weeks after transplantation, histologic analysis revealed that the grafted human NSPCs survived and differentiated into neurons, astrocytes, and oligodendrocytes, and that the cavities were smaller than those in the sham-operated control animals.

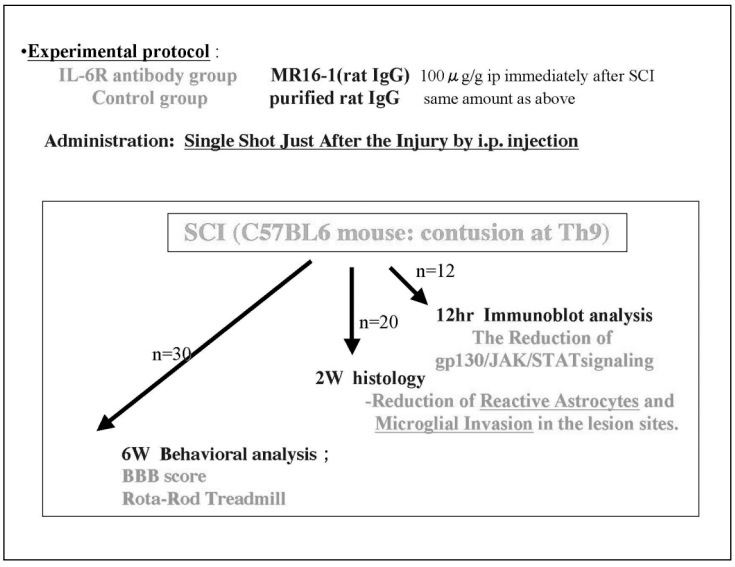

Fig. 5 Injection of anti-IL-6 receptor antibody (MR16-1) into the spinal cord of injured animals[55].

Immediately after the contusion spinal cord injury was induced at the T9 level, the mice were given an intraperitoneal injection of a single dose of MR16-1 or the same volume and concentration of purified rat IgG (control group). To quantify the IL-6-mediated signaling, the amount of phosphorylated STAT3 within the spinal cord tissue of the lesion epicenter was measured by immunoblotting 12 hrs after the injury. Two weeks after the injury, animals in both the MR16-1 group and the control group were characterized immunohistochemically. Six weeks after the injury, the recovery of motor function after the injury was assessed by three kinds of behavioral tests[30].

The bar grip power and spontaneous motor activity of the NSPC-transplanted animals were significantly higher than those of the sham-operated control animals (**Fig. 5**). These findings show that NSPC transplantation was effective for SCI in primates and suggest that human NSPC transplantation may be a feasible treatment for human SCI.

Other recently developed sources of cell therapy for injured spinal cord

In addition to NSPCs, there have been numerous other cell transplantation efforts aimed at regenerating the CNS after SCI, including genetically engineered NSPCs, Schwann cells, marrow stromal cells, olfactory ensheathing glia, activated macrophages, dendritic cells, ES cell-derived cells, and others[46]. Here, we will briefly summarize the effects of transplanting these cells, except for Schwann cells and activated macrophages, the details of which are available in the original or other review papers[47,48].

1) Olfactory Ensheathing Glia

Olfactory Ensheathing Glia are neuronal support cells that guide and support the axons of the olfactory receptor neurons from the olfactory mucosa to the olfactory bulb, presumably by creating an environment that is favorable for axonal growth. The transplantation of OECs into animal SCI models resulted in increased axonal growth, remyelination of demyelinated axons, and improved motor function. Human trials of OEC transplantation into SCI patients are currently being conducted[46].

2) Genetically engineered NSPCs

To increase the effects of NSPC-mediated cell therapy on various types of CNS damage, including SCI, some researchers have sought to improve the therapeutic action of NSPCs by genetic engineering (stem cell gene therapy) or by combining various therapeutic interventions (e.g. scaffolds for cell therapy) with NSPC transplantation. For example, a Neurogenin-2 (Ngn-2) gene-based stem cell gene therapy for an SCI model was recently developed by Olson's group[49]. Adult NSPCs transfected with Ngn-2, a neuronal basic Helix-Loop-Helix gene, before their transplantation into a rat thoracic spinal cord weight-drop injury model, suppressed the astrocytic differentiation of the engrafted cells and prevented graft-induced sprouting and allodynia-like hypersensitivity of the forepaws. In the same model, the transplantation of NSPCs without the Ngn-2 transgene caused the aberrant axonal sprouting associated with allodynia. Transduction with Ngn-2 also improved the positive effects of the engrafted stem cells, including increased amounts of myelin in the injured area, and the recovery of hindlimb locomotor function and hindlimb sensory responses, as determined by functional magnetic resonance imaging.

3) Marrow stromal cells

Marrow stromal cells (MSCs) have been suggested to provide support for directed axonal regeneration and have been shown to improve functional recovery following experimental spinal cord injury. However, the contribution of enhanced nerve fiber outgrowth to functional improvements is not clear. Rather, it is likely that MSCs mediate beneficial effects as "trophic effects" via the release of growth factors[50] and the ensheathment

of spared nerve fibers. There is increased interest in MSCs a cell source for autografts.

4) Dendritic cells

Dendritic cells (DCs), which act as professional antigen-presenting cells in the immune system, exhibit regenerating activities upon their administration into a rodent model of injured spinal cord[51]. When various immune cells were co-cultured with NSPCs using neurosphere methods, DCs showed the strongest activity for inducing the proliferation and survival of NSPCs *in vitro*. Furthermore, in DC-implanted adult mice, endogenous NSPCs in the injured spinal cord were activated for mitotic *de novo* neurogenesis. These DCs produced neurotrophin-3 and activated endogenous microglia in the injured spinal cord. In addition, the regeneration of long axonal tracts (CST) was demonstrated in DC-implanted animals by injecting an anterograde tracer into the primary motor cortex. Behavioral analysis revealed that the locomotor functions of the DC-implanted mice recovered significantly compared with those of control mice. These results suggest that DC implantation exerts trophic effects, including the activation of endogenous NSPCs and regeneration of long axonal tracts, leading to repair of the injured adult spinal cord.

5) Human ES cell-derived oligodendroglial progenitor cells

Demyelination contributes to the loss of function after spinal cord injury; therefore, a potential therapeutic strategy involves replacing myelin-forming cells. Recently, Keirstead et al.[52] showed that the transplantation of human embryonic stem cell (hESC)-derived oligodendrocyte progenitor cells (OPCs)[53] into an adult rat SCI model enhanced remyelination and promoted an improvement in motor function. OPCs were injected 7 d or 10 months after injury. In both cases, the transplanted cells survived, were redistributed over short distances, and differentiated into oligodendrocytes. Animals that received OPCs 7 d after injury exhibited enhanced remyelination and substantially improved locomotor ability. In contrast, when OPCs were transplanted 10 months after injury, there was no enhanced remyelination or locomotor recovery. These studies indicate the feasibility of a strategy in which predifferentiating hESCs differentiate into functional OPCs and demonstrate their therapeutic potential at early time points after SCI.

Conclusion and Perspectives

Currently, the precise mechanisms underlying the functional improvement and other benefits associated with most of the cell-based transplant studies including NSPC transplantation are not completely understood. Elucidation of the mechanisms of the benefits and shortcomings of cell-based transplantation should guide the development of improved therapeutic interventions for SCI patients[10,46].

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