NEUROSCIENCE

Special Topic: Stem Cell Research in China

Functional biomaterial-based regenerative microenvironment for spinal cord injury repair

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Spinal cord injury (SCI) often leads to the serious loss of motor and sensory functions below the level of the lesion. The etiology of SCI is mainly traumatic, caused by events such as car accidents and falls. It remains a worldwide clinical challenge to improve neural regeneration after SCI. The main reason for the difficulty of regeneration is that SCI usually initiates a cascade of biochemical reactions to produce a regeneration inhibiting microenvironment around the injury site. Composed mainly of scar tissue and myelin proteins, the microenvironment hinders SCI recovery by inhibiting the axonal regeneration and neuronal differentiation of neural stem cells (NSCs). Myelin proteins in the adverse microenvironment inhibit the axonal regeneration through the RhoA-ROCK pathway [1]. They are also involved in the process of NSCs differentiation, by promoting the differentiation of NSCs into the glial lineage and inhibiting their differentiation into neuronal lineage via the mTOR-STAT3 pathway [2]. Thus, overcoming these obstacles to establish a regenerative microenvironment at the injury site is essential for promoting SCI repair and recovery.

Biomaterial scaffolds play a vital role for construction of regenerative microenvironment within the injured cord. In addition to providing physical support for cell and tissue growth, they also allow the attachment of cells or signal factors to form a regenerative microenvironment, therefore regulating cell behavior and inducing tissue regeneration. A collagen scaffold was developed to guide the growth of neural axons [3]. Biologically active molecules (neurotrophic factor or antagonists to myelin-associated inhibitors) as well as stem cells were specifically bound to a collagen scaffold to construct a nerve regenerative microenvironment. Two novel biomaterial modification techniques were developed with this goal. (i) The specific binding between biomaterials and active molecules or antagonists was established by the

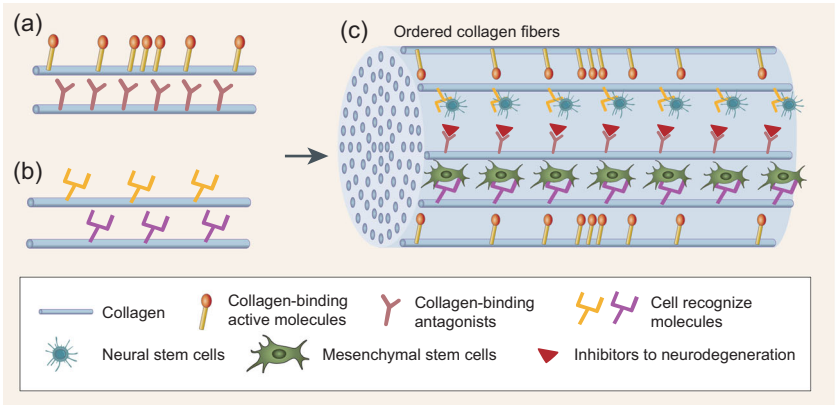

Figure 1. Neuroregenerative microenvironment constructed with functional biomaterials. (a) Collagen-binding biologically active molecules or antagonists were produced, which could be retained at the lesion site in a predetermined spatial arrangement. (b) Collagen-binding cell-recognition molecules can be incorporated in biomaterials to capture target cells. (c) A reconstructed neuroregenerative microenvironment produced by multi-functional biomaterials.

genetic recombination of matrix-binding peptides with these factors. It avoided the rapid diffusion of these molecules from biomaterials and achieved the desired spatial arrangement of them on scaffolds [4,5]. (ii) Cell surface recognition proteins have also been linked to biomaterials through genetic engineering or chemical cross-linking, enabling targeted and therapeutic cells to be captured and retained at the injury site. Thus, a regenerative microenvironment could be developed using the functional biomaterials (Fig. 1).

The therapeutic efficacy for SCI repair of several functional biomaterials has been tested in rats and canines with complete SCI models. When collagen-binding biologically active molecules such as collagen-binding domain-fused(CBD)-BDNF, CBD-NT3 and CBD-SDF1α were added to the collagen scaffolds and transplanted into animal SCI models, the bioactive molecules could be retained at the lesion site or form a spatial arrangement. The functional scaffold could guide the growth of neural fibers, decrease scar formation and induce functional recovery [5,6]. When the collagen-binding antagonists to myelin-associated inhibitors such as CBD-EGFR antibody, CBD-EphA4-LBD and CBD-PlexinB1-LBD were added to the collagen scaffolds, the resultant reconstructed microenvironments were shown to promote axon growth and NSCs differentiation [7,8]. Meanwhile, EGFR was the surface protein of NSCs. When EGFR antibody was added to the collagen scaffolds, the functional biomaterial could capture and retain NSCs at the injury sites, promote neuronal differentiation and, ultimately, improve the motor function of SCI animals.

After SCI, endogenous NSCs proliferate rapidly and migrate to the injury site, rarely differentiating into neurons owing to the adverse microenvironment (Fig. 2a). The implantation of functional biomaterials re-established the regenerative microenvironment and induced the neuronal differentiation of endogenous or transplanted NSCs [7,8]. The neurons could achieve neuronal relay formation throughout the lesion area. They may further rebuild the synaptic connections with each other or the host spinal neurons to transmit the neural signals and improve functional recovery in transected SCI animals (Fig. 2b), suggesting that the neuronal relays formed by newborn neurons from NSCs (endogenous or exogenous) could be a major mechanism for biomaterial-based SCI repair.

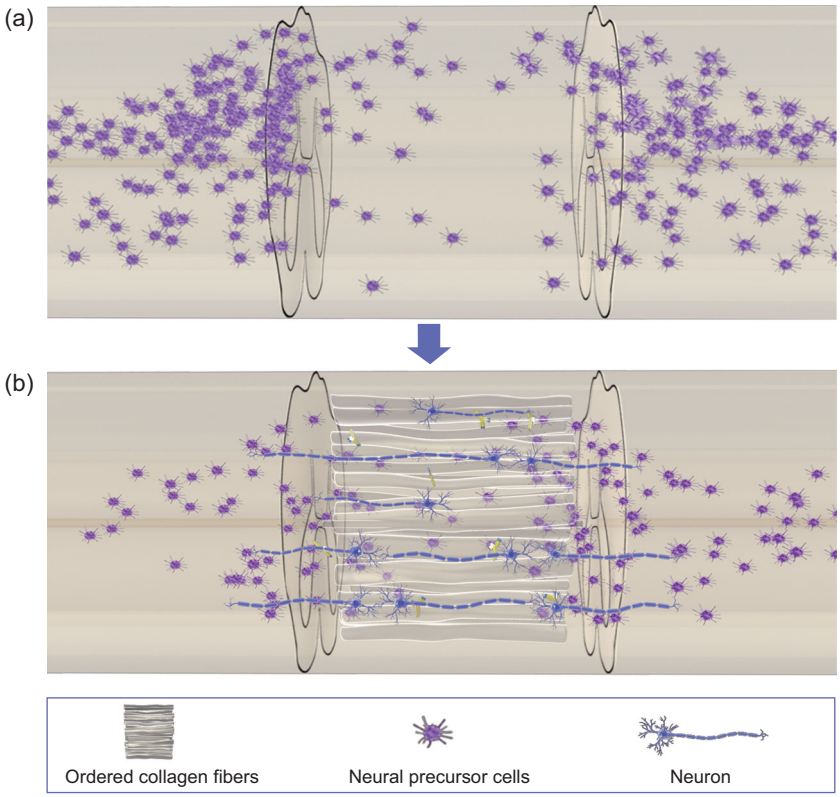

Figure 2. Potential mechanism of SCI repair. (a) Endogenous NSCs proliferating rapidly after injury and migrating to the injury site. (b) The functional biomaterials induced the neuronal differentiation of NSCs. The newborn neurons achieve neuronal relay formation throughout the lesion area. They may rebuild the synaptic connections with the host spinal neurons to transmit the neural signals and improve functional recovery in the transected injured spinal cord.

A clinical study of the collagen scaffold, named the NeuroRegen scaffold, in patients with complete SCI was initiated in January 2015. The safety and feasibility of the study were evaluated in chronic complete SCI patients. The scar tissue was surgically resected using an electrophysiology method to distinguish the scar tissue from the normal neural tissue. NeuroRegen scaffold with autologous bone marrow mononuclear cells or human umbilical mesenchymal stem cells was transplanted into the spinal cord gap following scar tissue resection. No obvious adverse effects related to scar resection or NeuroRegen scaffold transplantation were observed immediately after surgery or during the 12 months of follow-up and neural function was partially recovered [9,10]. The acute complete SCI patients were also enrolled in the clinical study and treated with the NeuroRegen scaffold functionalized by mesenchymal stem cells. A strict criterion was established to judge the patients as the complete injury, including the ASIA Impairment Scale, magnetic resonance imaging and nerve electrophysiology. The voluntary movements of the lower limbs and urine sensation were regained, accompanied by the recovery of interrupted neural conduction in the patients three to four months after NeuroRegen scaffold implantation. These results have provided the first evidence that functional biomaterial implantation represents a promising clinical approach to establish a regenerative microenvironment for SCI patients.

In summary, growing evidence in SCI animal models and patients indicates that construction of a functional biomaterial-based regenerative microenvironment is a promising strategy for SCI repair. Additional work is needed to provide a more in-depth understanding of the spinal cord microenvironment. That would allow us to optimize the regenerative microenvironment to improve overall neural regeneration and motor function in SCI patients.

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