A New Paradigm for Spinal Cord Regeneration and Repair

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INTRODUCTION: Spinal cord injury (SCI) is a devastating injury and currently there is no cure for this disease. A functional biomaterial consisting of a collagen scaffold and biologically active molecules (neurotrophic factors and the antagonists to myelin-associated inhibitors), and stem cells was used to rebuild a nerve regenerative microenvironment. The endogenous or implanted neural stem cells could be differentiated into neurons, which re-established the neuronal circuits under a favourable environment.

COLLAGEN SCAFFOLDS: A collagen based nerve guidance scaffold mainly consists of ordered collagen fibers. The linear ordered collagen scaffold was named LOCS. When LOCS was transplanted into hemisected or transected SCI animal models, the neural fibers grew along the direction of the LOCS. It is well known that a dense glial scar was formed at the injured site following SCI, and the glial-derived chondroitin sulfate proteoglycans (CSPGs) within the glial scar form a barrier to axonal regrowth and sprouting after SCI. When LOCS was transplanted into complete transected SCI model, it induced a significant decrease in the density of astrocytes (GFAP staining) surrounding the lesion site.

COLLAGEN BINDING GROWTH FACTORS: Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3 (NT-3) have been proved to promote neuronal survival or regeneration of neural fiber in the central nervous system. When growth factors were used in practice, it is difficult to maintain the therapeutic concentrations at the injury site because these factors rapidly diffuse away. A collagen-binding domain (CBD) was fused with them, and the fusion proteins acquired the ability to bind specifically to collagen, which could prevent the rapid diffusion of growth factors at the target site [1]. LOCS + CBD-BDNF transplantation showed a striking therapeutic effect on completely transected SCI animal models.

DIRECTING THE DIFFERENTIATION OF NEURAL STEM CELLS: When neural stem/progenitor cells (NPCs) are transplanted into the adult mammalian spinal cord, they rarely differentiate into neuronal lineage. The results have also been detected for endogenous NPCs during spinal cord injury. We have identified that myelin protein and Nogo-66 could inhibit the differentiation of NPCs into the neuronal lineage and promote its differentiation into the glial lineage. The NgR and mTOR-Stat3 pathways were involved in this process [2]. An epidermal growth factor receptor (EGFR) neutralizing antibody was used to inhibit the downstream signaling activated by myelin-associated inhibitors. When implanted into SCI animals, it induced neuronal differentiation and decreased astrocytic differentiation of NPCs and eventually promoted functional recovery [3, 4].

CONCLUSIONS: Following SCI, an inhibitory environment for neural regeneration develops at the injury site. A functional LOCS was made to decrease glial scar formation, guide neural fibers regenerating along LOCS, and induced neuronal differentiation of neural stem cells. Rebuilding neuronal relays by newborn neurons induced from endogenous or implanted neural stem cells may be a major mechanism for SCI repair [5, 6].

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ACKNOWLEDGEMENTS: Supported by grants from Chinese Academy of Sciences (XDA01030000 and ZDRW-ZS-2016-2).