Distal brain-derived neurotrophic factor delivery to promote axonal regeneration through Schwann cell-seeded alginate hydrogels after spinal cord injury

Shengwen Liu
Doktorvater: Prof. Dr. med. Norbert Weidner

Background Spinal cord injury (SCI) leads to loss of neuronal connectivity and cavity formation, which results in sensory and locomotor dysfunction. Transplantation of cell-seeded alginate hydrogels with anisotropic capillaries after spinal cord injury was able to bridge the lesion cavity and physically direct the regenerating axons to grow in a linear pattern to reach the lesion border. Schwann cells (SCs) are considered to be a promising treatment option as a candidate graft for clinical trials in SCI, which could also facilitate the graft/host interface to be permissive for axonal growth.

Objectives In the present study, I used a combinatorial strategy combining alginate hydrogels seeded with syngeneic SCs and a distal tetracycline-regulated gradient of brain-derived neurotrophic factor (BDNF) to explore whether long-descending spinal cord axons could be induced to grow through the alginate hydrogel and then re-enter the host spinal cord.

Methods Adult female Fischer 344 rats underwent a lateral cervical 5 (C5) hemisection immediately followed by implantation of an alginate scaffold pre-seeded with SCs into the lesion site, and injection of adeno-associated virus expressing either tetracycline-regulated (tet-on) BDNF or green fluorescent protein as a control into the caudal spinal cord ipsilateral to the lesion. Biotinylated dextran amine (BDA) tracing was performed between C1 and C2 one week before sacrificing. Animals were perfused for enzyme-linked immunosorbent assay (ELISA) or histological analysis 4 weeks after lesion.

Results After 4 weeks, ELISAs from spinal cords demonstrated that BDNF expression could be tightly regulated by doxycycline administration and delivery of the vector established a BDNF gradient caudal to the lesion. Grafted SCs survived well in the scaffolds and improved the continuity between the implant and host, as well as maintained axonal growth along the capillaries without attenuation.

Serotonergic axons were able to grow into the channels and descending axons traced by BDA extended through the scaffolds. The number of regenerating axons significantly increased when the caudal BDNF expression was active.

Conclusions SC-seeded alginate hydrogels are able to direct supraspinal and propriospinal axonal growth across the lesion, which can be amplified by caudally delivered BDNF.