



**Karolinska
Institutet**

Institutionen för klinisk neurovetenskap

A REGENERATION STRATEGY FOR SPINAL CORD INJURY

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i Leksellsalen, Eugeniahemmet,
2 tr. (byggnad T3), Karolinska Universitetssjukhuset, Solna

Fredagen den 8 juni 2012, kl. 09.00

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Stockholm 2012

ABSTRACT

A severe traumatic spinal cord injury (SCI) frequently leads to a devastating and permanent disability. Due to glial scarring and an inhibitory local environment, regrowth of disrupted axons in the injured spinal cord beyond a lesion is obstructed, thus preventing reconnection with neurons at the other side. Many experimental strategies have been presented to limit the damage and improve outcome after SCI, but few options are available for the patient.

Neurons in the central nervous system may regenerate using a growth permissive medium, such as peripheral nerve grafts. This capacity has been used to bridge a spinal cord gap by facilitating regeneration of long tracts in the spinal cord through transplanted peripheral nerve grafts, aimed at redirecting the regenerating axons into growth permissive grey matter on the other side of the injury. This principle was demonstrated in 1996, when surgical transplantations combined with adjuvant acidic fibroblastic growth factor (FGF1) led to partial recovery of hind limb function.

The aim of this thesis was to develop a reproducible microsurgical method for precise placement of peripheral nerve grafts (PNGs), construct a biodegradable graft holder, assess the effect of controlled delivery of FGF1, evaluate potential regeneration of corticospinal tracts after spinal cord repair and investigate if it is possible to determine the cranial and caudal injury borders in patients with chronic and complete spinal cord injury.

Our experiments in the adult rat demonstrate that replacing a section of thoracic spinal cord with a graft holder filled with peripheral nerves induced a spinal cord regeneration of various axonal types, including corticospinal axons. Further, we provide evidence of axonal ingrowth into the caudal spinal cord by anterograde neural pathway tracing and electrophysiological studies. This regeneration induced a functional improvement and robust electrophysiological response in the hind limbs, paced-up by the addition of graded doses of FGF1. The thesis also demonstrates that the cranial and caudal injury borders of patients with thoracic chronic and complete SCI can be diagnosed with high accuracy, which may be important for future diagnosis in spinal cord injury.

In conclusion, we present a regeneration strategy for the transected spinal cord, primarily through the use of a biodegradable graft holder filled with individually directed peripheral nerve grafts in combination with FGF1.