



**Karolinska
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Department of NEUROSCIENCE

Experimental spinal cord injury

**Methodological and neuroimmunological
contributions with some historical background**

AKADEMISK AVHANDLING

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ABSTRACT

Spinal cord injury (SCI) is an incurable neurotraumatic catastrophe that afflicts mostly young individuals with resultant functional impairment of varying degrees of severity. The single pharmacologic treatment option at present is systemic methylprednisolone administration within 8 hours postinjury oftentimes accompanied by neurosurgical interventions. As a rule, SCI becomes a chronic condition with significant handicap for the patient and socioeconomic repercussions for the affected families and health care system. Important discoveries in the field of central nervous system regeneration since the early 80's have led to diverse potential therapeutic approaches for neuroprotection and repair. Unfortunately, most envisioned treatment approaches would only be applicable at the acute and subacute stages of SCI, thereby excluding the large patient base with chronic SCI. In the first part of this thesis work the methodological aspects of a neurosurgical treatment protocol in a rat model of acute and chronic SCI were explored. In complete spinal cord transection experiments in rat, the acute and chronic spinal cord lesions were characterized with high-resolution magnetic resonance technology. A microneurosurgical 'repair' protocol was employed in both acute and chronic (at 2, 4 or 8 months postinjury) SCI. Behavioral evaluation of the operated animals with standard locomotor behavior tests and two novel behavioral tests, developed by the author, the Bipedal test and the Head-scratch test, demonstrated a statistically significant recovery for those animals that were subjected to the microsurgical reconstruction protocol. Partial functional recovery and histologically verifiable axonal regeneration was achieved in rats with both acute and chronic SCI. In the second part of this thesis work the neuroinflammatory and neuroimmunological correlates of peripheral and central nervous system injury were studied in mice. In one set of KO mice (TNF α , STAT4, STAT6) and their corresponding wild type controls, behavioral recovery and axonal regeneration were evaluated after spinal cord overhemisection. In another set of KO mice (STAT4, STAT6, IFN γ , IFN γ R and IRF1) and their corresponding wild type controls inflammatory and glial cell reactions were assessed after unilateral facial nerve transection lesions. The results suggest a positive role for the T_H2 subset of the adaptive immune response in anatomic recovery after SCI. Finally, in this thesis work the historical origins of the 'inhibitory white matter hypothesis' were researched shedding light on the pioneering work of Lugaro. Future treatments will have to address the complexity of SCI with a multipronged approach in order to effect the appropriate type and degree of immunomodulation, achieve neuroprotection, and promote collateral sprouting and axonal regeneration ultimately resulting in tissue repair and functional recovery. This thesis suggests: 1) that even complete, long-standing SCI can be amenable to therapy by demonstrating that the functional incapacity of experimental chronic paraplegia in rat is partially reversible, and 2) that judicious modulation of the immune response after SCI may have a role to play in axonal regeneration after SCI.