Bone Marrow Stromal Cell - Mediated Neuroprotection for Spinal Cord Repair

Gaby Jane Ritfeld

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Promotor
Prof. dr. R.A.C. Roos

Co-promotor
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Overige leden
Prof. dr. J. Verhaagen (Vrije Universteit Amsterdam)
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Voor mijn ouders

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PREFACE AND THESIS OUTLINE

Traumatic spinal cord injury affects an estimated 500.000 people in the United States and Europe alone and between fifteen per million (Europe) and forty per million (North America) new cases are reported each year. Mechanical force at the time of injury results in immediate neural cell death, severing of axons, rupturing of blood vessels, and overall loss of tissue integrity. Injury-induced events including inflammatory responses and release of cytotoxic substances result in progressive neuronal and oligodendrocyte death, demyelination, and axonal damage. Secondary injury contributes significantly to the pathology of spinal cord injury. The formation of scar tissue and, ultimately, a fluid-filled cyst, and the presence of axonal growth-inhibitory factors, create a chronically hostile environment for repair at and around the injury epicenter. As a result, spontaneous repair of anatomical damage and functional improvement after spinal cord injury is poor. Therapeutic interventions so far have had limited success resulting in a steadily growing group of people with paralysis due to spinal cord injury. The lifetime costs for care for a spinal cord injured person vary between one and three million dollars, making it one of the most expensive conditions to treat. The personal and societal consequences drive the research for treatments for spinal cord injury.

Current research on spinal cord repair-promoting approaches uses animal models and focuses on neuroprotection, to limit secondary tissue loss; axonal regeneration, to promote growth and synaptogenesis of damaged axons; and plasticity, to recruit newly grown and/or spared axons into axonal circuitries involved in motor and sensory function. Over the last decades, the potential of cell transplantation as a reparative approach for the injured spinal cord has become evident in animal models. Transplanted cells may secrete trophic factors that exert paracrine effects that limit secondary injury, promote axonal regeneration and/or plasticity, or serve as a substrate for regenerating axons. Alternatively, cell transplants may be a source for replacement of lost and damaged neural cells. The mesenchymal stem cell-like bone marrow stromal cell (BMSC) is among the cell types that have been explored for spinal cord repair. BMSCs were shown to elicit anatomical repair accompanied by improved, but still partial, recovery of function. At

present, our understanding of the extent of the repair potential of intraspinal BMSC transplants and their underlying mechanisms is incomplete. This thesis has two main goals: (1) to expand our knowledge of BMSC therapy for spinal cord repair, and (2) to investigate approaches to enhance the therapeutic efficacy of intraspinal BMSC transplants. In the studies an adult rat model of spinal cord contusion was employed because a contusion is the most prevalent mechanism of spinal cord injury in humans.

A comprehensive overview of the repair potential of stem cells for central nervous system repair and of BMSCs for spinal cord repair is provided in **Chapter 1**. In part A of chapter 1, stem cell terminology and experimental and clinical studies on stem cells for central nervous system repair will be discussed. In part B of Chapter 1, the advantages and disadvantages of using BMSCs as cell therapy for spinal cord repair are discussed. In addition, the spinal cord contusion model will be described in detail. To expand our knowledge of BMSC therapy for spinal cord repair, we focused on functional recovery and anatomical correlates thereof (**Chapter 2)** and the role of brain-derived neurotrophic factor (BDNF) in BMSC-mediated anatomical repair (**Chapter 3**). Comprehensive behavioral analyses were used to measure the effects of BMSC transplants on motor, sensorimotor, and sensory function recovery after BMSC transplantation into the adult rat contused spinal cord. Gene therapy was used to manipulate BDNF production in transplanted BMSCs to determine its involvement in BMSC-mediated repair. To enhance the therapeutic efficacy of BMSC transplants, we focused on BMSC survival in the injured spinal cord. The effect of reduced macrophage presence at the injury (transplant) site on BMSC survival was investigated by using clinically relevant anti-inflammatory drugs (**Chapter 4**). Whether increased survival enhances the effect of BMSC transplants on repair of the contused spinal cord is described in **Chapter 5**. A reverse thermal gel, poly(ethylene glycol)poly(serinol hexamethylene urethane) or ESHU with anti-oxidant properties was used to increase BMSC transplant survival and so prolong their presence in the injured spinal cord. In **chapter 6** the findings of our studies and future directions will be discussed. **Chapter 7** and **8** provide a summary of this thesis in English and Dutch, respectively.