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Research report

Evaluation of direct and cell-mediated triple-gene therapy in spinal cord injury in rats

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ABSTRACT

Current treatment options for spinal cord injury (SCI) are scarce. One of the most promising innovative approaches include gene-therapy, however no single gene has so far been shown to be of clinical relevance. This study investigates the efficacy of various combinations of vascular endothelial growth factor (VEGF), glial cell-derived neurotrophic factor (GDNF), angiogenin (ANG) and neuronal cell adhesion molecule (NCAM) in rats. Multiple therapeutic genes were administered intrathecally either via adenoviral vectors or by using genetically modified human umbilical cord blood mononuclear cells (hUCBMCs). Following the induction of SCI, serial assessment of cord regeneration was performed, including morphometric analysis of gray and white matters, electrophysiology and behavioral test. The therapeutic gene combinations VEGF + GDNF + NCAM and VEGF + ANG + NCAM had positive outcomes on spinal cord regeneration, with enhanced recovery seen by the cell-based approach when compared to direct gene therapy. The efficacy of the genes and the delivery methods are discussed in this paper, recommending their potential use in SCI.

1. Introduction

Limited regeneration in the CNS is one of main obstacles for potential treatment of neurological disorders. Delivery of recombinant genes encoding therapeutic molecules to CNS after neurotrauma, stroke or neurodegenerative diseases is a promising strategy to suppress degeneration by increasing of the affected neuronal cells survivability and stimulate neuroregeneration by reconstructing glial environment, promoting sprouting of axons and restoring interneuronal communications. The list of therapeutic genes is quite big and diverse and includes genes that encode growth, neurotrophic, angiogenic, anti-apoptotic, and anti-inflammatory factors, different types of enzymes, and cell adhesion molecules. With new technologies, the possibility to use simultaneously a number of different genes increases the success of the therapy by finding effective tandem of genes for specific CNS disorder. Previously we have shown that intraspinal injection of recombinant adenoviral vectors with genes of glial derived neurotrophic factor (GDNF) (Mukhamedshina et al., 2016), or tandem of genes for vascular endothelial growth factor (VEGF) and angiogenin (ANG) (Povysheva et al., 2017) can stimulate functional recovery in rat after traumatic spinal cord injury (SCI). GDNF is considered as an important survival factor for motorneurons and may have clinical application for the treatment of SCI. As it was shown, the level of GDNF mRNA increases rapidly in the nervous tissue after an injury (Höke et al., 2000) and direct GDNF gene therapy can protect cortical and spinal neuron (Barati et al., 2006; Tang et al., 2004), promoted corticospinal tract regeneration and motor function improvement (Lu et al., 2002). VEGF was initially described as a vascular permeability factor with specific mitogenic activity for endothelial cells (Ferrara et al., 1992). Besides angiogenic action, VEGF acts as a typical neurotrophic factor and increases survivability of sensory (Sondell et al., 1999) and motor (Islamov et al., 2004) neurons, promotes

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