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Spinal cord molecular and cellular changes induced by adenoviral vector- and cell-mediated triple gene therapy after severe contusion

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Abstract

© 2017 Izmailov, Povysheva, Bashirov, Sokolov, Fadeev, Garifulin, Naroditsky, Logunov, Salafutdinov, Chelyshev, Islamov and Lavrov. The gene therapy has been successful in treatment of spinal cord injury (SCI) in several animal models, although it still remains unavailable for clinical practice. Surprisingly, regardless the fact that multiple reports showed motor recovery with gene therapy, little is known about molecular and cellular changes in the post-traumatic spinal cord following viral vector- or cell-mediated gene therapy. In this study we evaluated the therapeutic efficacy and changes in spinal cord after treatment with the genes encoding vascular endothelial growth factor (VEGF), glial cell-derived neurotrophic factor (GDNF), angiogenin (ANG), and neuronal cell adhesion molecule (NCAM) applied using both approaches. Therapeutic genes were used for viral vector- and cell-mediated gene therapy in two combinations: (1) VEGF+GDNF+NCAM and (2) VEGF+ANG+NCAM. For direct gene therapy adenoviral vectors based on serotype 5 (Ad5) were injected intrathecally and for cell-mediated gene delivery human umbilical cord blood mononuclear cells (UCB-MC) were simultaneously transduced with three Ad5 vectors and injected intrathecally 4 h after the SCI. The efficacy of both treatments was confirmed by improvement in behavioral (BBB) test. Molecular and cellular changes following post-traumatic recovery were evaluated with immunofluorescent staining using antibodies against the functional markers of motorneurons (Hsp27, synaptophysin, PSD95), astrocytes (GFAP, vimentin), oligodendrocytes (Olig2, NG2, Cx47) and microglial cells (Iba1). Our results suggest that both approaches with intrathecal delivery of therapeutic genes may support functional recovery of post-traumatic spinal cord via lowering the stress (down regulation of Hsp25) and enhancing the synaptic plasticity (up regulation of PSD95 and synaptophysin), supporting oligodendrocyte proliferation (up regulation of NG2) and myelination (up regulation of Olig2 and Cx47), modulating astrogliosis by reducing number of astrocytes (down regulation of GFAP and vimetin) and microglial cells (down regulation of Iba1).

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Keywords

Angiogenin, Gene therapy, Glial cell-derived neurotrophic factor, Glial cells, Human umbilical cord blood mononuclear cell, Neural cell adhesion molecule, Spinal cord injury, Vascular endothelial growth factor

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