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Intravenous Transplantation of Human Umbilical Cord Blood Mononuclear Cells Overexpressing Nerve Growth Factor Improves Spatial Memory in APP/PS1 Transgenic Mice with a Model of Alzheimer's Disease

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Abstract
Alzheimer's disease is a progressive incurable neurodegenerative disease manifested by dementia and other cognitive disorders. Gene-cell therapy is one of the most promising trends in the development of treatment for Alzheimer's disease. The study was aimed to evaluate the therapeutic potential of intravenous transplantation of human umbilical cord blood mononuclear cells (UCBMCs) transduced with adenoviral vectors overexpressing nerve growth factor (NGF) for the treatment of Alzheimer's disease in an APP/PS1 transgenic mice model. The transplantation of NGF-expressing UCBMCs was found to improve spatial memory and decrease anxiety in APP/PS1 mice. Grafted cells and their expression of NGF were detected in the cortex and hippocampus of transgenic mice in the period up to 90 days after transplantation. Thus, gene-cell therapy based on the use of NGF-overexpressing UCBMCs is a promising approach for the development of Alzheimer's disease treatments.

Keywords Alzheimer's disease · Nerve growth factor · Stem cells · Gene-cell therapy · APP/PS1 transgenic mice · Umbilical cord blood mononuclear cells

1 Introduction

Alzheimer's disease is a progressive incurable neurodegenerative disease manifested by dementia and other cognitive disorders. Excessive production and accumulation of neurotoxic β-amyloid peptide in nervous and other tissues is thought by most of researchers to be a key factor in Alzheimer's disease pathogenesis [1–3]. To date, the considerable experience in the search and use of various drugs for treatment of Alzheimer's disease is obtained; however, there is still no effective cure available. Thus, the development of novel therapeutic approaches to treat Alzheimer's disease is one of the most important goals for medical science.

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The use of umbilical cord blood mononuclear cells (UCBMCs) to deliver various neurotrophic factors into the sites of neurodegeneration is a promising approach in the development of therapy for neurodegenerative diseases [4–8]. A nerve growth factor (NGF), a protein of the family of neurotrophins which is involved in the maintenance of survival, stimulation of growth, and activity of neurons, has a significant therapeutic potential in this regard [9, 10]. NGF was shown to prevent neuronal death in a number of models of neurodegenerative disorders [11–14]. NGF has a positive effect on neuronal survival, synaptic function, and memory in models of Alzheimer's disease [7]. A recombinant NGF gene can be delivered into sites of neurodegeneration using gene-cell constructs.

This study is aimed to transplant UCBMCs transduced with adenoviral vectors expressing NGF to transgenic mice with a model of Alzheimer's disease (APP/PS1 line) with subsequent evaluation of mice behavior and the ability of grafted cells for homing, survival, and expression of a therapeutic gene in the brain.