Mol Neurobiol (2017) 54:4756–4763
DOI 10.1007/s12035-016-0017-x

Tandem Delivery of Multiple Therapeutic Genes Using Umbilical Cord Blood Cells Improves Symptomatic Outcomes in ALS

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Received: 11 June 2016 / Accepted: 28 July 2016 / Published online: 6 August 2016

Abstract Current treatment options of chronic, progressive degenerative neuropsychiatric conditions offer only marginal efficacy, and there is no therapy which arrests or even reverses these diseases. Interest in genetic engineering and cell-based approaches have constantly been increasing, although most of them so far proved to be fruitless or at best provided very slight clinical benefit. In the light of the highly complex patho-mechanisms of these maladies, the failure of drugs aimed at targeting single molecules is not surprising. In order to improve their effectiveness, the role of a unique triple-combination gene therapy was investigated in this study. Intravenous injection of human umbilical cord blood mononuclear cell (hUCBMC) cotransduced with adenoviral vectors expressing vascular endothelial growth factor (VEGF), glial cell-derived neurotrophic factor (GDNF), and neural cell adhesion molecule (NCAM) resulted in prominent increase of life span and performance in behavioral tests in amyotrophic lateral sclerosis (ALS). Expression of the recombinant genes in hUCBMCs was confirmed as soon as 5 days after transduction by RT-PCR, and cells were detectable for as long as 1 month after grafting in lumbar spinal cord by immunofluorescent staining. Xenotransplantation of cells into mice blood without any immunosuppression demonstrated a high level of hUCBMCs homing and survivability in the central nervous system (CNS), most conspicuously in the spinal cord, but not in the spleen or liver. This study confirms an increased addressed homing and notable survivability of triple-transfected cells in lumbar spinal cord, yielding a remarkably enhanced therapeutic potential of hUCBMCs overexpressing neurotrophic factors.

Keywords Cell-mediated gene therapy · Adenoviral vector · Amyotrophic lateral sclerosis (ALS) · Human umbilical cord blood mononuclear cell (hUCBMC) · Vascular endothelial growth factor (VEGF) · Glial cell-derived neurotrophic factor (GDNF) · Neural cell adhesion molecule (NCAM)

Introduction

At present, there is no efficient approach to slow down or even stop the death of brain cells that is a characteristic feature of most degenerative neuropsychiatric disorders. Gene- and cell-based therapies are gaining much interest but with little clinical benefit. The use of modified cells expressing genes of several growth factors with neurotrophic functions such as insulin-like growth factor-1 (IGF_1), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), fibroblast growth factor-2 (FGF_2), angiogenin (ANG), and many others have showed some effect [1]. Viral vectors carrying these therapeutic genes may be directly injected intrathecally, intravenously, or intramuscularly (direct gene therapy), but these may be transferred by stem cells or specific mature cells or by mixed population thereof (cell-mediated gene therapy).

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