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Human umbilical cord blood cells transfected with VEGF and L_1CAM do not differentiate into neurons but transform into vascular endothelial cells and secrete neuro-trophic factors to support neuro-genesis—a novel approach in stem cell therapy

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ABSTRACT

Genetically modified mono-nuclear cell fraction from human umbilical cord blood (HUCB) expressing human vascular endothelial growth factor (VEGF) and mouse neural L_1 cell adhesion molecule (L_1CAM) were used for gene-stem cell therapy of transgenic $^{G}93^{A}$ mice adopted as an animal amyotrophic lateral sclerosis (ALS) model. We generated non-viral plasmid constructs, expressing human $VEGF_{165}$ (pcDNA-VEGF) and mouse neural L_1 cell adhesion molecule (pcDNA-mL_1CAM). Mono-nuclear fraction of HUCB cells were transiently transfected by electro-poration with a mixture of expression plasmids (pcDNA-VEGF + pcDNA-mL_1CAM). Sixteen transgenic female and male mice were randomly assigned to three groups: (1) transplantation of genetically modified HUCB cells expressing L_1 and VEGF ($n = 6$), (2) transplantation of un-transfected HUCB cells ($n = 5$), and (3) control group ($n = 5$). In first two experimental groups 1×10^6 cells were injected retro-orbitally in pre-symptomatic 22–25-week-old $^{G}93^{A}$ mice. Our results demonstrate that HUCB cells successfully grafted into nervous tissue of ALS mice and survived for over 3 months. Therefore, genetically modified HUCB cells migrate in the spinal cord parenchyma, proliferate, but instead of transforming into nerve cells, they differentiate into endothelial cells forming new blood vessels. We propose that: (A) expression of mouse neural L_1CAM is responsible for increased homing and subsequent proliferation of transplanted cells at the site of neuro-degeneration, (B) expression of human VEGF directs HUCB cell differentiation into endothelial cells, and (C) neuro-protective effect may stem from the delivery of various neuro-trophic factors from newly formed blood vessels.

1. Introduction

Neuro-trauma, stroke, and neuro-degenerative diseases are accompanied by loss of nerve cells, axon degeneration, and disrupted communication in neural networks. Developing new therapies for treating neuro-degenerative diseases is an important challenge (Okano et al., 2007). Current treatments options are inadequate and do not provide sufficient quality of life. One of the promising cell therapy approaches to prevent secondary degeneration and support neuronal growth is neuro-transplantation of embryonic stem cells pre-differentiated into neural progenitor cells, and neural stem cells which are proposed as a source of new glial and neural cells, and as a mean for delivering to the damaged neural tissue of neuro-trophic factors supporting neuron survival, axon growth and establishment of new inter-cellular contacts (neuron–neuron, neuron–glia) (Liew et al., 2007; Lepore and

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