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Genetically modified human umbilical cord blood cells expressing vascular endothelial growth factor and fibroblast growth factor 2 differentiate into glial cells after transplantation into amyotrophic lateral sclerosis transgenic mice

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Abstract

Current therapy of a number of neuropsychiatric maladies has only symptomatic modality. Effective treatment of these neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), may benefit from combined gene/stem-cell approaches. In this report, mononuclear fraction of human umbilical cord blood cells (hUCBCs) were transfected by electroporation with dual plasmid constructs, simultaneously expressing vascular endothelial growth factor 165 (VEGF165) and human fibroblast growth factor 2 (FGF2) (pBud-VEGF-FGF2). These genetically modified hUCBCs were injected retro-orbitally into presymptomatic ALS transgenic animal models (G93A mice). Lumbar spinal cords of rodents were processed for immunofluoresent staining with antibodies against human nuclear antigen (HNA), oligodendrocyte-specific protein, S100, iba1, neuronal β3-tubulin and CD34. Co-localization of HNA and S100 was found in the spinal cord of mice after transplantation of genetically modified hUCBCs over-expressing VEGF-FGF2. Double staining in control animals treated with unmodified hUCBCs, however, revealed HNA+ cells expressing iba1 and CD34. Neuron-specific β3-tubulin or oligodendrocyte-specific protein were not expressed in hUCBCs in either control or experimental mice. These results demonstrate that genetically naïve hUCBCs may differentiate into endothelial (CD34+) and microglial (iba1+) cells; however when over-expressing VEGF-FGF2, hUCBCs transform into astrocytes (S100+). Autocrine regulation of VEGF and FGF2 on hUCBCs, signal molecules from dying motor neurons in spinal cord, as well as self-differentiating potential may provide a unique microenvironment for the transformation of hUCBCs into astrocytes that eventually serve as a source of growth factors to enhance the survive potential of surrounding cells in the diseased regions.

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Keywords

Amyotrophic lateral sclerosis (ALS), Gene therapy, Human umbilical cord blood (hUCB), Stem cell