Re-Establishing Vascular Integrity in ALS via Endothelial Cell Transplant

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USA

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Re-Establishing Vascular Integrity in ALS via Endothelial Cell Transplant

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Cell Transplants, Amyotrophic Lateral Sclerosis, motor neuron degeneration, Spinal Cord, Endothelial Cells

Research Abstract
? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a fatal disease

characterized by widespread motor neuron degeneration in the brain and spinal cord. Mechanisms of disease onset and progression remain poorly understood, but vascular pathology, including damage of the blood-brain barrier (BBB) and blood-spinal cord barrier (BSCB), has recently been recognized as a key factor identifying ALS as a neurovascular disease. Our original studies showed damage to the BBB/BSCB in a mouse model of ALS, characterized by microvessel endothelial cell degeneration in the brain and spinal cord revealed. This new discovery, leading to the innovative concept of vascular leakage in areas of motor neuron degeneration, may point to additional disease mechanisms. Importantly, barrier impairment was noted in ALS mice prior to motor neuron degeneration, suggesting that barrier damage is central to disease initiation. Recent studies, including ours, have shown some degree of barrier damage in ALS patients. Notably, pervasive microvascular barrier impairment was determined in the gray and white matter of the brain and spinal cord from sporadic ALS patients. In this application, we propose to test a new therapeutic approach that has direct relevance to the treatment of ALS. The purpose of this project is to determine whether endothelial progenitor cells from human bone marrow (BMEPCs) can serve as a novel source of transplant cells to repair BSCB integrity and retard motor neuron degeneration in an experimental model of ALS. The significant scientific advance of this project is the demonstration that BMEPC transplantation will restore BSCB competence in ALS and as a result delay motor neuron degeneration. In an effort to determine the optimal transplant regimen, we will assess the effective cell dose then embark on elucidating the reparative processes involved in the repair of BSCB. Whereas most treatment-based studies have largely focused on pre-symptomatic ALS in testing therapeutic efficacy, this proposal strengthens its translational application to the clinic by examining the benefits of BMEPC transplantation in repairing BSCB in a symptomatic mouse model of ALS, essentially equivalent to ALS patients 2-3 years after diagnosis. Specific Aim 1 will establish effect of vascular repair via BMEPC transplant on reversing behavioral deficits (Aim 1A) and motor neuron cell death (Aim 1B) in symptomatic ALS mice. Specific Aim 2 will determine structural vascular repair via BMEPC transplant by examining BMEPC engraftment into the vascular wall (Aim 2A) and microvasculature status of the cervical and lumbar spinal cord with an electron microscope in areas of motor neuron degeneration (Aim 2B). Specific Aim 3 will determine functional vascular repair via BMEPC transplant by assessing endothelial cell viability (Aim 3A), capillary leakage in areas of motor neuron degeneration (Aim 3B), and tightness between endothelial cells (Aim 3C). Our experimental design advances a mechanism-based hypothesis and a highly translational framework for development of a novel therapy for ALS. Positive outcomes from this project will not only provide evidence of a mechanistic role of vascular damage in ALS, but will also offer a preclinical basis to pursue cell therapy to repair the altered barrier. This study represents a relatively low-risk, but high-reward and innovative therapy, as the transplant cells can potentially be expanded from the patient’s own bone marrow, thereby expediting entry of this autologous transplantation approach into clinical application for ALS patients.

Lay Summary

PUBLIC HEALTH RELEVANCE: This proposal will test a mechanism-based hypothesis and will advance a highly translational framework for development of a novel therapy for amyotrophic lateral sclerosis (ALS). If vascular repair via an optimal cell dose transplantation is proven effective for delaying motor neuron degeneration, it is likely to greatly impact the treatment of ALS, as well as therapies for other neurodegenerative diseases with known vascular damage such as Alzheimer’s, Parkinson’s, multiple sclerosis, or stroke.

Further information available at:

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United States of America

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