Muscle stem cells: New ALS growth factor therapy and disease model

https://neurodegenerationresearch.eu/survey/muscle-stem-cells-new-als-growth-factor-therapy-and-disease-model/

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Country

USA

Title of project or programme

Muscle stem cells: New ALS growth factor therapy and disease model

Source of funding information

NIH (NINDS)

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01/04/2015

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Muscle satellite cell, Amyotrophic Lateral Sclerosis, Skeletal Muscle, Disease model, progenitor

Research Abstract

? DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) is a progressive disease causing motor neuron degeneration, muscular atrophy and, ultimately, death by respiratory failure. Our major goal in this project is to determine if newly established human

skeletal muscle progenitor/stem cells (hSMPCs) derived from induced pluripotent stem cells (iPSCs) can be used for ex vivo cell therapy (stem cell-based growth factor delivery), and as an in vitro model to study ALS. The fundamental hypothesis guiding this proposal is that iPSC-derived hSMPCs efficiently differentiate into new skeletal muscle cells and contribute to muscle regeneration. This capacity confers the capacity for iPSC-derived hSMPCs to deliver ex vivo growth factors, and to model aspects of ALS in vitro. Our hypothesis is based on our published works and new preliminary data demonstrating the feasibility of producing hSMPCs from iPSCs. We will prepare genetically modified hSMPCs to deliver key growth factors known to be neuroprotective in ALS rodent models, including glial cell line-derived neurotrophic factor (GDNF) and vascular endothelial growth factor (VEGF). After establishing the cells, we will transplant them into the limb muscles to deliver growth factors in ALS rats (Aim 1). We expect integrated progenitors to effectively deliver growth factors to target muscles (including their neuromuscular junctions), thereby preserving motor neuron/muscle attachments, motor neuron survival and limb function. Since the most common cause of death in ALS is respiratory failure, we will further test the hypothesis that diaphragm hSMPC-based growth factor delivery prolongs motor neuron survival, thereby preserving respiratory motor function in ALS rats (Aim 2). Finally, we will create new hSMPC lines from iPSCs derived from familial ALS patient donors. By analyzing their cellular characteristics and co-culturing these cells with motor neurons, we will extend the utility of hSMPCs by simulating ALS in vitro, furthering our understanding of the roles played by muscle derived trophic factors (Aim 3). These aims will provide highly novel insights concerning the potential of ex vivo cell and growth factor-based treatments, and will establish a new disease model to advance our understanding of the relative contributions from muscles and neuromuscular connections in this fatal neurodegenerative disease. iPSC- derived hSMPCs can be used to develop patient-specific, cell-based ALS treatments, and provide novel in vitro models of human disease. The results of this project are expected to accelerate progress towards pre-clinical studies in ALS patients. Given the devastating outcome in ALS, the lack of effective treatments, and the burden on society, it is imperative that the questions posed here be answered in a timely manner.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS) is an incurable disease characterized by rapid loss of muscle control and eventual paralysis. The proposed research directly addresses the major goal of the NIH: i.e. essential knowledge will be gain about a specific incurable disease that will have an impact on the health of patients. The approaches developed here have direct relevance to treatment strategies, as transplantation of stem cell transplantation is a real future possibility for this devastating disorder.

Further information available at:

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Investments > €500k

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United States of America

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Motor neurone diseases

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