Immune Regulation of Neuronal Injury and Repair

https://neurodegenerationresearch.eu/survey/immune-regulation-of-neuronal-injury-and-repair/

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Contact information of lead PI
Country

USA

Title of project or programme

Immune Regulation of Neuronal Injury and Repair

Source of funding information

NIH (NINDS)

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Start date of award

01/04/2001

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2

The project/programme is most relevant to:

Motor neurone diseases

Keywords

superoxide dismutase 1, Axotomy, injury and repair, Neuronal Injury, Facial nerve structure

Research Abstract

DESCRIPTION (provided by applicant): We have established a physiologically relevant mechanism of CD4+ T cell-mediated neuroprotection involving axotomized wildtype (WT) mouse facial motoneurons (FMN) that may have significance in the treatment of amyotrophic

lateral sclerosis (ALS), a fatal motoneuron disease. Superimposition of facial nerve axotomy (FNA) on the transgenic mouse model of ALS (SOD1G93A) during pre-symptomatic stages indicates that SOD1 mice behave like immunodeficient (ID) mice in terms of increased FMN loss and decreased functional recovery, through a mechanism that, paradoxically, is not inherent within the motoneuron itself, but, instead, involves a defect in peripheral immune: CNS glial cell interactions. The long-term goal of this project is to utilize our WT mouse model of immune-mediated neuroprotection after FNA as a template to elucidate how a malfunctioning peripheral immune system contributes to motoneuron cell loss in the SOD1 mouse model of ALS. Our central hypothesis is that CD4+ effector T cells provide neuroprotection to motoneurons through regulation of the central microglial and astrocytic response to peripheral nerve damage. There are 4 specific aims designed to: 1) elucidate the functional role of IL-10 in the WT facial nucleus following FNA, 2) determine if CD4+ T cells rescue FMN from FNA-induced cell death in RAG-2 KO mice through activation of the IL-10 cascade within the facial nucleus, 3) determine the mechanism that prevents CD4+T cell-mediated neuroprotection following FNA in the pre-symptomatic SOD1 mouse, and 4) test the ability of in vitro-generated, neuroprotective SOD1 CD4+ T cells to alter disease onset and/or progression in SOD1 mice. IL-10 reporter and conditional IL-10 knockout mice, along with adoptive transfer experiments with WT, ID and SOD1 mice, and laser capture microdissection will be used. Based on new data generated for this revision suggesting that SOD1 T cells are normal, but antigen-presenting cells (APC) are defective, SOD1 T cells and APC will be examined phenotypically and functionally both in vitro using relevant and irrelevant antigens and in vivo using adoptive transfer. Finally, adoptive immunotherapy with either neuroprotective FNA-specific T cells or APC into SOD1 mice will be done prior to disease onset, and the effects on disease onset, progression, and lifespan assessed. With respect to expected outcomes, the work is expected to identify key mechanistic elements in CD4+ T-mediated neuroprotection following FNA, reveal peripheral immune system defects following FNA in the SOD1 mouse model of ALS that prevent effective CD4+ T cell activation/differentiation and determine the therapeutic potential of adoptive immunotherapy with neuroprotective SOD1 T cells generated in vitro by FNA antigens. ALS strikes 30,000 Americans each year (15 cases a day), often at peak productive points in their lives and with enormous cost to affected individuals, their families, and the health care system. Identification of defects in neural:immune interactions will have an important positive impact because they can then be the target of therapeutic intervention in ALS treatment.

Lay Summary

PUBLIC HEALTH RELEVANCE: This project focuses on interactions between the nervous and immune systems that occur normally, and/or in response to trauma or diseases involving the brain and spinal cord. If not regulated correctly, innate immunity and T cell interactions in the brain can be destructive and contribute significantly to the development and progression of neurodegenerative diseases, including amyotrophic lateral sclerosis, or Lou Gehring’s disease. Given that ALS strikes many Americans during the prime of their lives, and is usually fatal within 3-5 years of diagnosis, understanding defects in the immune system of ALS patients is very important and may provide targets for development of therapeutics in the treatment of ALS and other neurodegenerative disorders.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
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