Regulation of cellular release of proteins in Parkinson neurodegeneration

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Country

USA

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Regulation of cellular release of proteins in Parkinson neurodegeneration

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3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

cell growth regulation, prion-like, paracrine, Parkinson Disease, Nerve Degeneration

Research Abstract

DESCRIPTION (provided by applicant): The personal and societal costs of Parkinson’s disease (PD) are expected to increase significantly in the next two decades. The mechanisms of

neurodegeneration are not well understood, and no treatment clearly slows the neurodegenerative process in PD. Alpha-synuclein (?syn) is a protein that is central to PD pathogenesis, and recent studies show that the transmission of ?syn between different cell populations is key to its ability to cause toxicity. Release of ?syn is the first critical componen of transmission, and occurs through exosomal and non-exosomal mediated pathways. A second key feature of prion-like spread of ?syn is the uptake in target neurons, leading to consequent misfolding of endogenous ?syn. What mechanisms regulate the release and spread of ?syn pathology are not known. The 14-3-3 proteins are chaperone-like proteins that can reduce protein aggregation, regulate protein secretion, and promote cell survival. We have previously shown that 14-3-3s are protective in several models of PD and can regulate the exosomal release of LRRK2, a key protein implicated in PD. In this proposal, we present preliminary data that overexpression of the 14-3-3? isoform in ?syn-producing cells reduces the toxicity of released ?syn. Our central hypothesis is that 14-3-3 proteins can protect against ?syn toxicity by reducing the transmission of toxic ?syn species. In Aims 1 and 2, we will investigate whether 14-3-3s can regulate ?syn release through exosomes or alternative non-exosomal pathways and assess how any changes in release impacts paracrine ?syn toxicity. For these studies, we will use a paracrine inducible ?syn culture system in which released ?syn induced cell death in separately culture primary neurons. In Aim 1, we will use biochemical and imaging approaches to determine if 14-3-3s alter the amount and conformation of ?syn in exosomes. We will also assess how alterations in exosomal ?syn impact paracrine ?syn toxicity. In Aim 2, we will use similar techniques to test if 14-3-3s reduce ?syn release and toxicity through inhibition of the recycling endosomal pathway. In Aim 3, we will focus on the effects of 14-3-3s in target cells exposed to extracellular ?syn. Specifically, we will use in vitro and in vivo ?syn fibril models to test whether 14-3-3s can reduce ?syn uptake, aggregation, and toxicity in these models. If we can establish that 14-3-3s regulate the pathological transmission of ?syn, this would justify exploration of potential PD therapies targeting the 14-3-3s.

Lay Summary
PUBLIC HEALTH RELEVANCE: Parkinson’s disease (PD) is the second most common neurodegenerative disorder with no current therapies that slow disease progression. In this proposal, we will investigate the role of 14-3-3 proteins in the regulation of alpha-synuclein transmission, a key protein linked to PD with prion-like properties. Our long-term goal is to establish whether 14-3-3s may be a therapeutic target for this disabling disorder.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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