Regulation of the oligodendroglial accumulation of alpha-synuclein in Multiple System Atrophy

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Principal Investigators

DESPLATS, PAULA ALEJANDRA

Institution

UNIVERSITY OF CALIFORNIA SAN DIEGO

Contact information of lead PI
Country

USA

Title of project or programme

Regulation of the oligodendroglial accumulation of alpha-synuclein in Multiple System Atrophy

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,590,536.70

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01/04/2016

Total duration of award in years

5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Multiple System Atrophy, alpha synuclein, MicroRNAs, Endocytic Vesicle, Autophagocytosis

Research Abstract

? DESCRIPTION (provided by applicant): Synucleonopathies are a group of neurodegenerative disorders that affect over 1.5 million people in the US. Multiple system atrophy (MSA) is a fatal, rapidly progressive synucleonopathy characterized by parkinsonism and oligodendroglial accumulation of ?-synuclein (?-syn). While considerable effort has been devoted at understanding the pathogenesis of Parkinson's Disease, less is known about MSA and the mechanisms through which ?-syn accumulates in oligodendroglial cells, resulting in neurodegenerative pathology, is not completely clear. One possibility is that autophagy failure could lead to ?-syn propagation from neurons to oligodendroglial cells. We recently found that in MSA microRNA (miR-101, miR-30a, miR183, miR-96) that regulate autophagy are affected. The HYPOTHESIS is that miRNA dysregulation in MSA might down-regulate autophagy, which in turn results in defective ?-syn clearance with the consequent propagation from neurons to glia. The OBJECTIVES will be to better understand the mechanisms through which alterations in autophagy- related miRNAs are involved in the pathogenesis of MSA and to evaluate the potential value of modulating miRNA's as a novel therapeutical approach for MSA. For this purpose we will utilize a combined strategy including studies in unique mixed cell cultures in chambers, transgenic mouse models of MSA and brain tissues from MSA patients from multiple sites. The AIMS are: ONE. To investigate in mixed neuron- oligodendroglial cell cultures the mechanisms through which alterations in miRNAs might lead to ?-syn propagation into glial cells. TWO. To determine in transgenic models of MSA if modulating miRNAs that regulate autophagy ameliorate the ?-syn pathology and spreading. THREE. To analyze the regional relationship between alterations in specific miRNAs and autophagy targets in MSA. These goals are in agreement with the NINDS 2014 PD ""Basic Research"" recommendations. Finding a link between miRNA dysregulation, autophagy deficits, and ?-syn spreading will shed light on pathogenesis of MSA, and will open the door for the study of these interactions in other neurodegenerative disorders. These studies could also lead to the development of novel therapeutical strategies for MSA.

Lay Summary

PUBLIC HEALTH RELEVANCE: Synucleonopathies such as multiple system atrophy (MSA) affect over 1 million in the US. For this proposal we will investigate how alterations in autophagy-related miRNAs are involved in the pathogenesis of ?-synuclein propagation in MSA and evaluate the value of modulating miRNAs as a novel therapeutic approach for MSA.

Further information available at:

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Investments > €500k

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Parkinson's disease & PD-related disorders

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