The role of ATP13A2/PARK9 in secretion of exosomes and alpha synuclein

https://neurodegenerationresearch.eu/survey/the-role-of-atp13a2-park9-in-secretion-of-exosomes-and-alpha-synuclein/

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The role of ATP13A2/PARK9 in secretion of exosomes and alpha synuclein

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Neurodegenerative disorders are characterized by the accumulation of misfolded aggregated proteins in neurons. Since neurons are permanently postmitotic, efficient intracellular protein degradation systems are critically important for normal neuronal function. Recent evidence suggests that disruption of lysosomal degradation pathways directly contributes to neurodegeneration in Parkinson’s disease and related synucleinopathies. We have previously

shown that loss of function of lysosomal ATPase PARK9 (ATP13A2) leads to zinc dyshomeostasis, lysosomal dysfunction and a-syn accumulation. In addition, we and other found that PARK9 localizes to multivesicular endosomes and regulates exosome biogenesis. Here, we propose to further analyze the physiological role of PARK9 in generation and secretion of exosomes and how loss of PARK9 function contributes to neuronal dysfunction and neurodegeneration. First, we will test the hypothesis that PARK9 plays an important role in the formation of intraluminal vesicles by recruitment of zinc-dependent FYVE proteins to early endosomes. Second, we will examine if a-syn secretion via exosomes and lysosomal exocytosis contributes to PARK9-mediated neuronal dysfunction. Finally, we will test the hypothesis that PARK9 is protective in synucleinopathies by overexpressing PARK9 in mouse models that accumulate a-synuclein. We will also examine propagation of a-synuclein in PARK9 knockout and transgenic mice. These findings will also provide further mechanistic insights into PARK9 loss of function in the context of Kufor-Rakeb syndrome as well as more general forms of syncleinopathies such as Parkinson’s disease (PD), especially in terms of cell- to-cell transmission of a-syn that has been implicated in the pathogenesis of these disorders.

Lay Summary

Neurodegenerative disorders affect the lives of millions of people worldwide. Recently, enormous strides have been made in identifying disease mechanisms and with these advances, the chances of finding cures are increasing rapidly. We propose a research project that is carried out using new and creative collaborations to accelerate the pre-clinical validation lysosomal proteins as therapeutic targets for PD. If successful, this approach will have high impact for PD as well as other neurodegenerative disorders.

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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