The role of a Synuclein transcript variants in neuronal pathology and function

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Country

USA

Title of project or programme

The role of a Synuclein transcript variants in neuronal pathology and function

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NIH (NINDS)

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01/07/2013

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

alpha synuclein, Transcript, 3' Untranslated Regions, Pathology, Parkinson Disease

Research Abstract

DESCRIPTION (provided by applicant): Common genetic variants in the human population play a significant role in the pathogenesis of non-familial (‘sporadic’) Parkinson’s disease (PD).

Among such PD risk variants, the alpha-synuclein (aSyn) locus is of particular interest, as SNPs in this locus show the strongest and most robust impact on sporadic PD risk Furthermore, very rare mutations in aSyn as well as triplication of the aSyn gene locus lead to familial inherited forms of PD. aSyn is thus an attractive therapeutic target for PD, with most strategies aimed at reducing its level or aggregation. Our preliminary data point to a novel regulatory mechanism that we hypothesize to impact aSyn physiological and pathological functions: aSyn messenger RNA (mRNA) transcript differential 3? untranslated region (3'UTR) usage. Longer transcript isoforms (aSynL) correlate with increased protein accumulation, intraneuronal protein redistribution, and pathological functions, both in human brain and in model systems. This ultimately may provide a novel therapeutic approach by targeting specifically pathological rather than physiological functions of aSyn. aSyn 3'UTR usage is modified by dopamine exposure as well as by aSyn locus common genetic single nucleotide polymorphism (SNP) variants that increase PD risk. The 2 mechanisms appear largely separate. Whereas a small segment of the 3'UTR (sufficient to confer dopamine sensitivity) is conserved in rodent aSyn, most of the 3'UTR sequences are unique to human. Our specific hypothesis is that longer mRNA transcript isoforms of human aSyn, with extended 3'UTRs, aSynL, play important pathological roles, by impacting the accumulation of aSyn protein. The goals of this proposal are to (i) define regulatory mechanisms of the aSyn 3'UTR and (ii) relate the molecular properties of different aSyn mRNA 3'UTR isoforms to pathological aSyn functions in vivo. The impact of this proposal is potentially high, as pinpointing a specific pathogenic transcript would present a novel therapeutic target. Such regulation could be especially amenable to high-content drug screens. The deliverables of the project are (i) to provide a structure/function analysis of aSyn 3'UTR sequences with respect to aSyn regulation, and (ii) to potentially identify novel drug targets for PD and other synucleinopathies, by identifying molecular mechanisms that mediate the process.

Lay Summary
PUBLIC HEALTH RELEVANCE: There is a tremendous need for therapeutics that alter the course of Parkinson's disease. Our preliminary data point to a novel molecular target for Parkinson's disease therapeutics: a unique form of aSynuclein not previously associated with the disease.

Further information available at:

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Investments > €500k

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