Intersection of alpha synuclein and tau contributions to neurotoxicity

https://neurodegenerationresearch.eu/survey/intersection-of-alpha-synuclein-and-tau-contributions-to-neurotoxicity/

Principal Investigators

KAYED, RAKEZ

Institution

UNIVERSITY OF TEXAS MEDICAL BR GALVESTON

Contact information of lead PI
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USA

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Intersection of alpha synuclein and tau contributions to neurotoxicity

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Alzheimer's disease & other dementias|Parkinson's disease & PD-related disorders

Keywords

alpha synuclein, tau Proteins, neurotoxicity, synucleinopathy, tau aggregation

Research Abstract

Parkinson’s disease and related synucleinopathies afflict 10% of those older than age 65. Since there are currently no effective treatments, it is essential that we find a way to prevent or treat these devastating neurodegenerative diseases. The pathological hallmark of synucleinopathies

such as Parkinson’s disease is the deposition of insoluble aggregates of misfolded ?-synuclein; however, mounting evidence suggests that soluble aggregates of ?-synuclein (e.g., oligomers) are a key causal agent in synucleinopathies. An emerging concept in neurodegenerative disease research and diagnosis is that disease pathology overlaps or even forms a continuum of pathologies. For example, concomitance of ?-synuclein and tau pathology in Parkinson’s disease and dementia with Lewy bodies is not rare; in fact, several studies report co-localization of ?-synuclein and tau. Thus, it has been put forth that soluble aggregates of ?-synuclein and tau contribute to secondary symptoms and clinical heterogeneity in these dementing disorders and that ?-synuclein and tau interaction is essential for the full development of pathology and neurotoxicity. Despite the outstanding efforts of many investigators, the relationship between ?-synuclein and tau aggregation in synucleinopathies remains unresolved. Moreover, the role and mechanisms of neurotoxicity remain largely unknown. Finally, the ability to detect ?-synuclein and tau oligomers in early stage disease and exploit them as therapeutic targets for synucleinopathies remains largely unexplored. In this MPI, R01 proposal, we will test the exciting hypothesis that tau and ?-synuclein oligomers synergize to promote neurotoxicity. This project utilizes a diversity of state-of-the-art conceptual and technical approaches from a multidisciplinary and highly collaborative team to address the important problem of identifying mechanisms specific to ?-synuclein toxicity, the role of tau oligomerization and targeting these entities through immunotherapy. Aim 1 will test whether ?-synuclein and tau oligomers synergize to induce motor, learning, and memory deficits in vivo. Aim 2 will test whether ?-synuclein and tau synergize to promote neurotoxicity as well as investigate specific mechanisms. Aim 3 will determine the contribution of ?-synuclein posttranslational modifications to ?-synuclein and tau oligomer neurotoxicity. These aims integrate highly specialized transgenic animals, protein biochemistry, mass spectrometry-based proteomics, and Drosophila genetics. Our proposal, if successful, will provide much needed novel molecular insight into the mechanisms of neurotoxicity in synucleinopathies that may prove crucial in moving forward to a disease modifying therapy.

Lay Summary
Parkinson’s disease and related disorders afflict 10% of those older than age 65. Since there are currently no effective treatments, it is essential that we find a way to prevent or treat these devastating neurodegenerative diseases.

Further information available at:

Types:
Investments > €500k

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United States of America

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