Mechanistic studies of anti-tau antibodies effects on tau biochemistry

https://neurodegenerationresearch.eu/survey/mechanistic-studies-of-anti-tau-antibodies-effects-on-tau-biochemistry/

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Country

USA

Title of project or programme

Mechanistic studies of anti-tau antibodies effects on tau biochemistry

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397644.9541

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2

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tau Proteins, Biochemistry, Tauopathies, Microtubules, tau aggregation

Research Abstract

? DESCRIPTION (provided by applicant): Project Summary Tauopathies are a class of neurodegenerative disorders which involve tau protein. Tau stabilizes microtubules in neurons, maintains cell integrity and facilitates nutritional uptake. Once hyperphosphorylated by protein kinases, tau detaches from microtubules, aggregates leading to neuronal cell death and cell-to-cell toxicity. Currently, tauopathies remain without a cure. Immunotherapies against tau have shown promise in animal models by reducing tau aggregation, tau phosphorylation and tau

aggregate cell toxicity. Despite the advances made in immunotherapies for tau, no mechanistic work has been published that explores all three aspects of tau biochemistry (aggregation, phosphorylation, microtubule stability) in a systematic manner. This provides an opportunity to identify the mechanism of antibody-based inhibition by targeting specific tau epitopes towards improved immunotherapies for tauopathies. The long-term goals of the proposed projects are to improve our understanding of tauopathies and their treatment. Our recent studies have demonstrated that targeting R1 and R4 epitopes of tau protein by anti-tau antibodies modulates aggregation and promotes disaggregation. We also reported on inhibition of phosphorylation at Ser199 of tau by anti-phospho antibodies to pThr231. Based on this evidence, we hypothesize that by targeting specific tau epitopes, the aggregation, phosphorylation, and microtubule stability will be modulated. To test our hypothesis, we aim to (1) Determine the inhibitory effects of anti-tau antibodies to R1-R4 repeats on aggregation of 6 isoforms of tau, (2) Evaluate the inhibitory effects of anti-tau and anti- phosphotau antibodies on phosphorylation of tau441 and its aggregation, (3) Evaluate stability of microtubules as a function of phosphotau and anti-tau antibodies. The research design involves systematically determining which tau epitope when targeted by anti-tau antibodies modulates tau aggregation, phosphorylation, and microtubule stability. The biochemical and biophysical techniques that will be used to accomplish the research goals include transmission electron microscopy, fluorescence, infra-red, and circular dichroism spectroscopies, ELISA, SPR, SDS-PAGE, Western blotting and mass spectrometry. At the conclusion of these studies, the tau epitopes for effective inhibition will be identified. Or results will provide mechanistic details of how anti-tau antibodies mediate aggregation, phosphorylation, and microtubule stability. This information is critical for future development of therapeutic targets for tauopathies among other neurodegenerative disorders. Additional benefits include research opportunities for undergraduate and graduate students in biochemistry of neurodegenerative disorders, described in this grant, which will promote their interests in health-related careers.

Further information available at:

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