Propagation of tauopathy: role of degeneration and impact of immunotherapy

https://neurodegenerationresearch.eu/survey/propagation-of-tauopathy-role-of-degeneration-and-impact-of-immunotherapy/

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USA

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Propagation of tauopathy: role of degeneration and impact of immunotherapy

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2

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Alzheimer's disease & other dementias

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Tauopathies, tau Proteins, entorhinal cortex, Immunotherapy, conformer

Research Abstract

DESCRIPTION (provided by applicant): In AD, neurofibrillary pathology (NFTs) starts in the trans/entorhinal cortex (EC) area and spreads to neuroanatomically connected areas of the

brain. The ”Braak”” stages of tau pathology go from stages I to VI (Braak, H. and Braak, E. (1991). Stages I and II correlate with preclinical AD and alterations that are largely confined to the upper layers of the transentorhinal cortex (transentorhinal stages). Stages III and IV correlate with mild cognitive impairment and are characterized by robust involvement of the transentorhinal and entorhinal regions, with a less severe involvement of the hippocampus and several subcortical nuclei (limbic stages). Stages V-VI are characterized by extensive neurofibrillary pathology in neocortical association areas (isocortical stages) and a further increase in pathology in the brain regions affected during stages I-IV. As tangle pathology correlates well with cognitive impairment, targeting tau may be a good therapeutic strategy. To explore why tauopathy maps the way it does in the brain we created a mouse model of the earliest Braak stages of AD (Liu et. al. 2012). Our new transgenic mouse model (line EC-tau) has predominant EC expression of pathological tau, and it replicates the spatio-temporal aspects of tauopathy in the AD brain. Of significant interest was the observation that human tau could cross a synapse into monosynaptically connected cells (“”downstream”” or “”secondary”” circuits), which explains how pathology may propagate through the brain, and why it follows a trans-synaptic route. To begin to understand how tauopathy propagates, we need to understand new aspects of cellular biology with respect to tau. We propose that as tauopathy worsens, tau is released into the extracellular space from whence it could be taken up by adjacent cells. Once inside, templating to endogenous tau is likely to occur allowing the process to perpetuate. In aim 1 we will perform a careful timecourse quantifying pre and post synaptic markers with pathological tau distribution to assess the order of events in primary and secondary circuits. In aim 2, to understand the functional consequences of worsening tauopathy, especially on secondary circuits, we will monitor the “”cellular behavior”” readout molecule, Arc, and synaptic function, assessed by electrophysiology. In aim 3 we will develop a polarized cell culture model to study how the accumulation of tau conformers impacts pathology propagation from the somatodendritic compartments (transneuronal propagation) or the axonal compartment (trans-synaptic propagation). In aim 4.1 we will test whether a therapeutic approach, immunotherapy using the anti-tau antibody MC1 can prevent cell to cell propagation of tauopathy in the EC-tau mouse line, and in aim 4.2, we will assess whether attenuation of tauopathy correlates with improved structural and functional outcomes.

Lay Summary

PUBLIC HEALTH RELEVANCE: In the earliest stages of AD, neurofibrillary tangle pathology is limited to the hippocampal formation but as the disease progresses, pathology is seen in cortical areas and these later stages correlate with the onset of overt dementia. To model the initial stages of AD, and to map the spread of pathology through the brain, we have created a novel line of mice with regionally restricted expression of pathological, human tau. We now intend to investigate how the spread of pathology is related to brain degeneration, what the effects of worsening pathology are on brain function and whether the spread of pathology can be prevented or slowed using a therapeutic approach (immunotherapy).

Further information available at:

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Investments > €500k

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United States of America

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