Tau-binding B Cells in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/tau-binding-b-cells-in-alzheimers-disease/

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Country

USA

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Tau-binding B Cells in Alzheimers Disease

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2

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Research Abstract

? DESCRIPTION (provided by applicant): This project concerns human B cells that produce antibodies binding specifically to phosphorylated tau, a molecule found in the pathogenic neurofibrillary tangles that characterize Alzheimer’s Disease. The background for this work lies in the observation that in normal, healthy individuals, antibody is produced against pathogenic microorganisms and autologous antigens in the absence of infection or immunization, termed natural antibodies. Targets for natural antibodies include molecules implicated in

neurodegenerative diseases as well as bacterial surface antigens. In mice natural antibodies are produced primarily by the small B1 cell population, and the nature of these B cells and the antibodies they produce change with advancing age. In keeping with this, treatment of mice with Alzheimer's-like disease by passive transfer of exogenous anti-tau antibodies depletes abnormal tau and improves behavioral measures. These findings suggest that natural anti-tau antibodies in healthy individuals could play a role in resisting AD. In preliminary studies we have identified human B cells that bind different phosphorylated tau peptides. Here we will test the hypothesis that certain human B cells that specifically recognize phosphorylated tau are lost with advancing age thereby producing enhanced susceptibility to tau-generated pathology and in turn providing a rationale for therapy with exogenous anti-tau Ab. We will determine the population(s) of B cells that bind phospho-tau, identify the changes in ptau-binding B cells that occur with age and disease, and elucidate the nature of antibodies that tau-binding B cells produce. We will examine samples obtained from healthy young controls, AD patients, and healthy old controls that are age/gender-matched to AD patients. We will focus on 3 aims: 1) We will determine the B cell population that binds key peptides containing phosphorylated residues found in pathological PHF tau, and we will determine which phosphopeptides are bound; 2) We will elucidate changes that occur in phospho-tau-binding B cells with age and with disease, to identify losses that may be related to AD pathology; and, 3) We will examine the nature of antibodies produced by phospho-tau-binding B cells using single cell sorting and immunoglobulin amplification followed by sequence analysis, and expression cloning followed by repertoire assessment. The results of this work will reveal the nature of B cells that produce ptau-binding Ab in normal individuals and most importantly, will determine whether these B cells are lost with advancing age. This work is likely to provide important information regarding the interface between the immune system and AD, to provide a conceptual basis for treatment of patients with anti-phospho-tau antibody, and to indicate which antibodies directed against which phosphorylated residues are missing in aged or diseased individuals for which corresponding exogenous Abs may be helpful.

Further information available at:

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