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USING IMMUNOPRECIPITATION-TANDEM MASS SPECTROMETRY TO DETERMINE THE PROTEOFORMS OF APOE IN DENSE CORE NEURITIC PLAQUES

Vishal Krishnan

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Alzheimer's disease (AD) is known as the leading cause of dementia in the elderly. This disease is characterized by a severe neuronal loss and the development of extracellular amyloid plaques and intracellular neurofibrillary tangles. In our project, we will be focusing on amyloid plaques which are comprised partly of the Apolipoprotein E protein (APOE). APOE is recognized as a major genetic risk factor for the late onset of AD.

The Holtzman Lab recently developed an anti-APOE antibody that binds to the dense cores of amyloid plaques but not soluble APOE. However, the specific proteoform of APOE that the APOE antibody binds to is still unknown. The project will be divided into two main parts. This part of the project involves immunoprecipitation (IP) method development. Specifically, I worked on optimizing the Solid Phase Extraction protocol. We used a fixed Equimolar mix of ApoE3 and ApoE4 with 13C/15N-Arg as a standard. We then spiked in increasing amounts of purified native ELISA protein standard APOE. After analysis using mass spectrometry, we plotted the peak ratio which results in a linearly increasing graph. There were three potential protocols: the amyloid beta protocol, APOE protocol, and the alpha synuclein (aSyn) protocol. I was to test which of these protocols were optimal. Based on the results, it was found that the APOE protocol was optimal, although the aSyn protocol also worked well.

This project has many future potential implications. The method can allow us to discover which proteoforms of APOE are bound by the antibody, which can lend further clarity to many of the current APOE focused projects being conducted. An understanding of this would also help offer insight into APOE's role in AD pathology and ultimately provide an assessment of the potential for anti-APOE immunotherapy as a therapeutic approach for the treatment of AD.