2020 IMPACT CIRCLE

Investigating Synapse Decline in Alzheimer's disease

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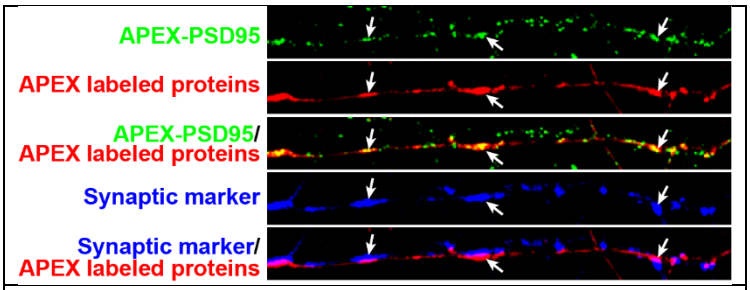
Unmet Need: People living with Alzheimer's disease or related dementias are afflicted with memory loss, often for as long as 10 years from the start of their symptoms. This loss of memory interferes with their daily lives, causes them to lose their independence, and it can be extremely difficult for their families and friends to cope with. There are only a few options for treatment of memory impairment in Alzheimer's disease that are often not very effective. We need to better understand the changes in the brain that underlie memory loss in order to develop new treatment strategies for people with dementia that will restore their quality of life.

Background: Trillions of synapses in the brain form the connections between neurons that enable cognitive processes such as memory. In fact, the dynamic modulation of synapse strength is critical for the encoding of new memories. Long-term potentiation (LTP) is the enhancement of synapse strength that occurs during memory formation and it requires the orchestration of many synaptic proteins and signaling pathways. Previous research supports that LTP is inhibited by the toxic tau protein that accumulates in the brain in Alzheimer's disease and related dementias. However, how toxic tau blocks the LTP from occurring at synapses is unknown.

Novel Hypothesis: We hypothesize that toxic tau disrupts a subset of proteins at synapses which blocks LTP and promotes memory loss in Alzheimer's disease. Furthermore, we hypothesize that by manipulating the activity of these dysregulated synaptic proteins during LTP we may be able to alleviate the toxicity caused by tau and restore memory.

Proposal: We propose to identify the synaptic proteins that are dysregulated by toxic tau during LTP. We will study the effect of toxic tau on synapses in human induced pluripotent stem cell (iPSC)-derived neuron models of Alzheimer's disease. We have developed an innovative new tool that will enable us to monitor the dynamic changes in the proteins at synapses in living human iPSC-derived neurons by mass spectrometry called APEX-PSD95. Using this approach we expect to identify which critical synaptic proteins are altered by tau and contribute to memory loss in Alzheimer's disease. These findings will enable us to establish which synaptic proteins could be targeted for restoring Alzheimer's disease associated memory loss. This collaborative project will be driven by the expertise of the Tracy laboratory in Alzheimer's disease pathogenesis and synapse biology and the expertise of the Schilling laboratory in mass spectrometry and the analysis of cellular protein dynamics in age-related disease.



Staining of APEX-PSD95 (green) at synapses (blue) in human iPSC-derived neurons. In this proposal, we will use APEX-PSD95 combined with mass spectrometry to identify the proteins in synapses (red) that are altered by toxic tau in Alzheimer's disease.

Impact: It is critical that we find new ways to ameliorate the memory loss experienced by patients starting at the earliest stages of Alzheimer's disease. Our research will improve our understanding of the synaptic mechanisms that promote memory loss in Alzheimer's disease. We can use this knowledge about the specific tau-mediated synaptic alterations we identify to design new strategies to reverse memory loss in Alzheimer's disease and related dementias.

Specialized Equipment Needs: N/A