Amara Martin
Benjamin Fogelgren, Ph.D., John A. Burns School of Medicine
Coordinating Center: University of Hawai'i at Manoa

ABSTRACT
While there is much debate about the cause and pathogenesis of Alzheimer's disease, one of the leading hypotheses is the amyloid cascade. This phenomenon is an imbalance between production and clearance of β-amyloid proteins (Aβ), resulting in the buildup of neurotoxic amyloid plaques in the brain. Aβ is generated from proteolytic processing of the amyloid precursor protein (APP), which is determined in large part by the intraceullular trafficking of APP in neurons. We hypothesize that the exocyst, an 8-protein trafficking complex, is a key regulator of the intracellular trafficking of APP and Aβ generation. Additionally, the exocyst is known to be an effector for insulin signaling in muscle and adipocytes, leading us to further hypothesize that the exocyst could be a direct connection between insulin signaling in neurons and Aβ production. We used two neuronal cell models in this research, primary mouse hippocampal neurons and the human SH-SY5Y cell line, which can be differentiated into neurons with a retinoic acid protocol. We were able to successfully generate novel SH-SY5Y cell lines expressing fluorescent fusion APP and exocyst proteins for future live-cell particle tracking experiments. We also designed and optimized glucose-uptake measurements to test for the first time if the exocyst regulates insulin-responsive glucose uptake in neurons. Finally, we isolated and cultured primary hippocampal neurons from transgenic mice to perform rigorous loss-of-function studies of the exocyst in primary neurons. This work will contribute to a greater understanding of how the exocyst regulates Aβ generation in neurons, which may lead to new approaches for Alzheimer's therapeutics.

KEY WORDS: β-amyloid proteins, Amyloid precursor protein, Exocyst, Neurons

ACKNOWLEDGEMENTS: The STEP-UP High School program is supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, Grant Number: R25DK78386-17