Optogenetic control of amyloid beta protective gene expression in the C. elegans gut microbiota

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Optogenetic control of amyloid beta protective gene expression in the C. elegans gut microbiota

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Research Abstract

Project Summary/Abstract Aggregation of amyloid-? (A?) into plaques is a hallmark of AD and considered a primary event in AD pathologies. Transgenic variants of the rapidly reproducing nematode C. elegans expressing human A? accumulate aggregates with age and exhibit early lethality. C. elegans feed on E. coli bacteria, 10% of which escape digestion and constitute the gut microbiota. Due to the high genetic tractability of both host and microbe, C. elegans and E. coli provide a powerful model for studying the molecular mechanisms of gut microbiota-host

interactions. In exciting preliminary work, co-investigator Wang has identified 14 E. coli genes that protect against A? induced lethality in transgenic C. elegans. We have determined that four are linked to production of the extracellular polysaccharide Colanic Acid (CA). Furthermore, we have shown that pure CA protects against A? toxicity when delivered with live bacteria. The next step is to identify the mechanism by which CA and the remaining 10 genes protect against A? toxicity. Such results would inform future studies in mammals and the engineering of therapeutic bacteria that prevent or treat AD. The major current limitation in studying the mechanisms of gut microbiota-host interactions is the lack of technologies for externally manipulating bacterial gene expression in vivo. Traditional chemical effectors of bacterial gene expression are insufficient due to complications arising from delivery, transport, and degradation. Optogenetics is a rapidly advancing technology combining light and genetically-encoded photoreceptors to control molecular biological processes in live organisms. Light can be controlled with exquisite precision in the wavelength, intensity, spatial, and temporal dimensions, affording unmatched levels of control. Previously, P.I. Tabor has transported light sensing two-component histidine kinase signal transduction systems from cyanobacteria into E. coli, and used them for unprecedented quantitative, spatial and temporal control of gene expression in vitro. The goal of this proposal is to combine P.I. Tabor’s and co-I Wang’s methodologies to characterize how gut bacterial gene expression affects A? toxicity in the C. elegans model. We will achieve this goal through two Specific Aims: Demonstrate precise optogenetic control of the expression of E. coli genes that protect against A? toxicity in the gut of live C. elegans (Aim 1), and characterize the relationships between the quantitative, spatial and temporal pattern of the expression of E. coli genes in the gut and the amelioration of A? toxicity (Aim 2). By achieving these aims, we will demonstrate the first optogenetic control of microbiota function in a live animal. This proposed research will directly improve scientific knowledge in gut microbiota-host interactions, and molecular mechanisms of AD pathologies. Optogenetics has revolutionized neuroscience, and is now enabling major breakthroughs in cell biology and systems and synthetic biology. The research proposed here will bring optogenetics to the fundamental and timely problem of the microbiome.

Further information available at:

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