Understanding the mechanism of SPI1 dependent Alzheimer disease risk

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USA

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1

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Research Abstract

Alzheimer’s disease (AD) is the only disease among the top ten killers in the U.S. without a disease modifying therapy. As a result it is also the only one that is increasing in prevalence. Human genetic studies provide a powerful means to identify genes and pathways that are causally linked to the etiology of disease, and to generate new therapeutic hypotheses for drug discovery. Technological advances in the last few years have enabled large-scale genome-wide association studies (GWAS) to identify common variants that modulate AD risk, and whole genome/whole exome sequencing to identify rare mutations associated with AD. This work has led to the discovery of more than 20 loci (in addition to APOE) that are causally linked to AD. Our systems- level analysis of genetic variants associated with AD in GWAS and sequencing studies implicate defective phagocytic clearance of cellular debris by myeloid cells (efferocytosis), as an important component of the etiology of AD as have analyses of gene regulatory networks in healthy and AD human brains by other investigators. Fine mapping of one of these GWAS loci led us to identify a common variant (rs1057233) in SPI1, which reduces SPI1 expression and risk for AD. Like ABCA7 and TREM2, two other established AD risk factors that play key roles in efferocytosis, SPI1 is expressed in immune cells of the myeloid lineage (e.g., monocytes, macrophages and microglia). SPI1 is a transcription factor (PU.1) that is critical for microglial development and regulates expression of many of the AD-associated genes implicated in efferocytosis. We hypothesize that modulation of SPI1 expression influences AD risk through global changes in gene expression within microglia that lead to altered efferocytosis. We will integrate computational and experimental approaches to define the mechanism(s) by which functional variation in SPI1 reduces SPI1 expression and risk for AD. To investigate this protective effect, we will first seek to replicate it in vitro using microglial cells derived from isogenic human iPSC cell lines with different rs1057233 genotypes (Aim 1). We will also genetically decrease/increase SPI1 expression in microglial cells of the mouse brain and measure the effect of these interventions on molecular, cellular and AD-related phenotypes in vivo (Aim 2 and 3 respectively). To enable these studies, we have recently developed a novel mouse model that can be used to profile the ribosome-bound transcriptome of microglial cells in the brain while also conditionally and specifically down- or up-regulating the expression of a gene of interest like SPI1 in microglia. Using the same model crossed with an AD mouse model, we will investigate AD-related outcomes like micro-gliosis and ß-amyloid deposition in the context of reduced or increased SPI1 expression in microglia.

Lay Summary

Alzheimer’s disease (AD) is the most common form of dementia but has no effective prevention or treatment. Genetic and genomic studies have implicated dysregulation in microglial function as a risk factor for AD. We have recently identified a common variant in the transcription factor, SPI1/PU.1, a master regulator of myeloid microglial development and homeostasis that reduces risk for and delays onset of AD. The goal of this study is to use cell and animal models to understand how variation in SPI1/PU.1 expression and/or function influence risk for AD, with the ultimate goal of harnessing this information to design therapeutics that reduce risk for or prevent onset of AD.

Further information available at:

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