The role of PU.1 (*SPI1*) transcription factor in Alzheimer's disease

Byungwook Kim[1,2], Mason Douglas Tate[1,2,3,6], Hande Karahan[1,2,6], H.R. Sagara Wijeratne[1,2,4,6], Ahmad Daniel Sharify[1,2], Justin R. Kim[1,2], Md Mamun Al-Amin[1,2], Selena S. Wang[1,2], Luke Child Dabin[1,2], Dominic J. Acri[1,2], Emma Doud[4,5], Sutha K John[1,2], Amber L. Mosley[4,5], Jungsu Kim[1,2,3*]

[1]Department of Medical & Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA; [2]Stark Neuroscience Research Institute, Indiana University School of Medicine, Indianapolis, IN 46202, USA; [3]Medical Neuroscience Graduate Program, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA ; [4]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA; [5]Center for Computational Biology and Bioinformatics, Indiana University School of Medicine, Indianapolis, Indiana 46202, USA; [6]These authors contributed equally to this work and have the right to list their names second in their CV.

Recent human genetic studies have identified microglial genes, including the transcription factor PU.1 (encoded by *SPI1* gene), as critical regulators in the pathogenesis of Alzheimer's disease (AD)[1]. Although *SPI1* is a well-established AD genetic risk factor, it remained unclear whether its downregulation or upregulation would confer benefits. A recent study reported that *Spi1* knockdown exacerbated insoluble Aβ accumulation, plaque deposition, and gliosis[2]. However, the use of a whole-body knockdown model, although informative, has limitations in dissecting the cell-specific effects of *SPI1* modulation. This is particularly important given the complex interplay of different brain cell types in the brain during AD pathogenesis.Here, we demonstrate that the selective deletion of *Spi1* in microglia worsens AD-related pathologies in an amyloid mouse model. Specifically, microglial *Spi1* deficiency increases amyloid deposition, gliosis, and dystrophic neurites, while impairing the microglial response to plaques. To elucidate the underlying mechanisms, we performed integrative analysis of proteomics data and functional cell biology data. Our findings reveal that loss of *Spi1* in microglia disrupts phagocytic function, primarily through dysregulation of a few key signaling proteins. These results provide crucial *in vivo* evidence to guide future therapeutic strategies for AD.

Sponsored By: grant from NIH R01AG077829

Presenter Name and contact information:
Jungsu Kim, Ph.D.
P. Michael Conneally Professor of Medical and Molecular Genetics
Professor, Stark Neurosciences Research Institute
Department of Medical and Molecular Genetics
Indiana University School of Medicine
Indianapolis, IN, USA
Email: jk123@iu.edu