Inference of Cell-Cell Communication to Understand the Molecular Mechanisms of Alzheimer's Disease

Samanta, Adrita (School: Greater Commonwealth Virtual School)

Alzheimer’s disease (AD) is the seventh leading cause of death in the U.S. and remains incurable. Most existing therapeutics target beta-amyloid plaques, but plaque removal has shown no evidence of preventing cognitive decline. The goal of this study is to use an unbiased approach to understand the root causes of AD, leveraging single-nucleus RNA-sequencing data from 2.3 million nuclei in the prefrontal cortex of 427 donors. Specifically, I developed computational methods to study the factors contributing to AD beyond amyloid accumulation, including immune system dysfunction, vascular instability, and sex-based differences that influence disease onset and progression. I studied cell-cell communication between glial, immune, vascular, and neuronal cells to identify dysregulated interactions that may contribute to disease progression, understand sex differences associated with these communication differences, and guide more effective therapeutics. I also validated my findings using spatial transcriptomic data to assess whether these genes interact given the positioning of their cells. I found that disruptions in cell communication during earlier AD stages affect insulin and calcium signaling, while changes during later stages contribute to blood-brain barrier dysfunction and beta-amyloid accumulation. These results suggest that amyloid-targeting therapeutics might be ineffective against cognitive decline, as amyloid accumulation is only a late-stage feature of the disease, and propose additional therapeutic targets for early intervention. My results also revealed sex-specific variations in AD like differences in neuronal and vascular signaling, emphasizing the need for personalized therapeutic strategies and offering future directions for drug development in AD.

Awards Won: