Spatial and single-nucleus transcriptomic analysis of genetic and sporadic forms of Alzheimer's disease

Miyoshi, E., Morabito, S., Henningfield, C.M. et al.Nat Genet 56, 2704–2717 (2024).

Presenter: Chun-Chen Chen **Date/Time:** 2025/03/20, 16:20 -17:10

Commentator: Dr. Chun-Hsien Chu **Location:** Room 601, Med College Building

Background:

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive cognitive decline influenced by a combination of genetic and environmental factors. Despite significant advancements in understanding its pathogenesis, the molecular mechanisms underlying AD remain poorly defined, such as identifying disease-associated cell populations and their functional transcriptomic alterations. Individuals with Down syndrome (DS) have a markedly increased risk of developing AD, with a lifetime risk of dementia exceeding 90%. This high prevalence offers a unique opportunity to explore transcriptomic alterations associated with AD in a genetically predisposed population. However, comparative analyses of single-cell or spatial transcriptomic changes between sporadic AD (sAD) and AD in Down syndrome (DSAD) remain limited, constraining our understanding of their shared and distinct molecular features. Therefore, elucidating these differences is crucial for identifying potential biomarkers further to expand our knowledge of transcriptome changes across AD subtypes.

Objective/Hypothesis: To elucidate the transcriptomic alterations associated with sAD and DSAD by employing spatial transcriptomic (ST) and single-nucleus transcriptomic analyses.

Results:

The study conducted a thorough analysis of transcriptomic changes related to early-stage and late-stage AD and DSAD using ST and snRNA-seq. Differential expression analyses between human clinical samples and the 5xFAD mouse model revealed consistent amyloid-associated transcriptomic changes across both groups, suggesting conserved gene expression alterations in response to amyloid pathology. Additionally, spatial co-expression network analyses demonstrated elevated amyloid-β and phospho-tau levels in neurons affected by AD, with DSAD neurons exhibiting even higher phospho-tau levels, indicating a distinct tau pathology in this population. Moreover, cell–cell communication (CCC) analysis identified significant disruptions in signaling networks across the upper cortical layers in AD and DSAD, with pathways such as NECTIN, ANGPTL, and CD99 altered in disease states, highlighting complex molecular interactions underlying pathology. Furthermore, key hub genes within the amyloid-associated gene module (SM6) were identified in the 5xFAD ST dataset, showing expression patterns consistent with previously characterized plaque-induced genes. Collectively, these findings provide deeper insights into the molecular landscape of AD and DSAD, emphasizing the dynamic shifts in gene expression and the roles of various cell types in disease progression.

Conclusion:

This study identifies specific cell types associated with AD and further connects transcriptomic changes to AD genetic risk and amyloid pathology accumulation, highlighting the dynamic shifts in neuronal and glial components involved in AD progression.