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"Spatial-Temporal Gene Expression Analysis of a Transgenic Model of Tauopathy in Alzheimer's Disease"

Alzheimer's disease (AD) is a neurodegenerative disorder that leads to the progressive decline of memory, speech, visuospatial processing, and general cognitive capacity. Despite an estimated 50 million people worldwide suffering from the disease, a number expected to triple by 2050, there is currently no cure or preventive treatment for AD. AD is classically identified by amyloid-β plaque deposition in the hippocampal and cortical regions of the brain, with amyloid-β aggregation produced from the cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase. A second pathological hallmark of AD is the aggregation of intracellular p-tau (tau), which leads to the formation of neurofibrillary tangles. The hyperphosphorylation of tau, a critical protein in microtubule assembly and maintenance, disrupts axonal transport, impeding synaptic functioning, and eventually causing neuronal death. Cuello's laboratory has previously developed a transgenic rat lineage of tauopathy, coded McGill-R955-hTau, which models the pathophysiological and behavioral features of AD. Utilizing this transgenic line, this project aimed to investigate genetic expression within the AD-affected brain in a spatial-temporal manner to elucidate the differing genetic states of early versus late AD. Coronal cryosections of young (10-months-old tau model and wild type) and aged (20-months-old tau model and wild type) rat brains were stained with H&E. Sections at bregma level -3.6 mm were selected for analysis using the 10x Genomics Visium spatial transcriptomics platform, which allows for the precise mapping and visualization of gene expression across tissue regions. The resulting data was then analyzed using the R package Seurat. Using this package, a UMAP plot was generated to visualize cell-specific clustering based on key neuronal and glial marker genes. The individual cell types identified were then mapped onto the cryosection images, allowing for the distinction of various brain regions. In the dentate gyrus of both early and late AD, *TRIL*, a protein linked to the progression of neurofibrillary tangles, was significantly up-regulated. Additionally, pathway analysis in the early AD model revealed significant changes in gene expression related to synaptic function, particularly in GTPase activity and ion-channel function. In contrast, the late-stage model exhibited significant changes in gene expression associated with mRNA binding and dynein transport. These results indicate that spatial-temporal variations in gene expression at different stages of AD may include distinct molecular pathways and regional protein expression reflective of disease development, thereby underscoring a promising new direction for investigating therapeutic targets for AD.