Life Sciences Seminar

A multimodal Atlas of Alzheimer's Disease to Arrange Molecular and Cellular Changes Along Disease Progression

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Histopathology studies of Alzheimer’s disease (AD) have long noted progressive, and stereotyped changes across numerous brain regions, but the underlying molecular and cellular mechanisms that cause AD and facilitate its progression remain unknown or are only coarsely understood, hampering efforts to treat or cure the disease. To uncover these mechanisms, we characterized the transcriptomic and epigenetic landscapes of AD from the middle temporal gyrus, and prefrontal cortex by applying single nucleus RNA and ATAC sequencing to ~8 million nuclei isolated in 84 aged donors that span the histopathological and cognitive disease spectrums as part of the broader Seattle AD Brain Cell Atlas (SEA-AD) effort. We leveraged machine learning approaches to hierarchically define ~130 highly resolved transcriptional cell types borrowing from the BRAIN initiatives’ neurotypical reference. We utilized Bayesian statistical models to define a continuous scale of pathological progression using multiple measures of pathological proteins, and cellular populations. We aligned donors according to disease severity, akin to the pseudotime score commonly used to align cells in neurodevelopment.These tools enabled characterization of cell type abundance, gene expression, and chromatin accessibility differences associated with AD. Our comprehensive molecular atlas identified specific neuronal and non-neuronal subsets, having altered abundances, gene expression, and/or chromatin accessibility, and suggesting they may be selectively vulnerable to disease processes. Their differentially expressed genes and accessible chromatin regions provided new clues to the molecular pathways that underpin AD. We integrated with SEA-AD 10 external datasets that had applied snRNA-seq to 4.3 million cells from the DLPFC of 780 donors. We used this as replication cohorts and identified cellular changes consistently associated with AD. Finally, we created mapping algorithms to map published single cell data sets to our taxonomical reference. These mapping tools create a resource for the research community to align newly profiled cells to a common reference frame. All data sets and mapping algorithms are available sea-ad.org.

Friday, May 10, 2024 11:00am - 12:00pm
Moonstone Seminar room C

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