ADPriOMICS

Prioritization of pathways linking aging and Alzheimer's disease to cognitive decline and dementia

Aging is a major risk factor for cognitive decline and increases the vulnerability of the brain to neurodegenerative diseases, such as Alzheimer's disease (AD) that, in turn, dramatically accelerates cognitive deterioration and increases the risk for dementia. The biological pathways linking aging and AD are still poorly understood, partly due to the multitude of alterations induced by both processes. Identifying biological processes operating at the intersection of aging and AD that convey downstream effects on cognitive decline could enhance our understanding of the aging brain. Furthermore, these processes could provide efficient drug targets since their modulation would simultaneously affect two major determinants of dementia.

In this context, ADPriOMICs hypothesize that aging and AD act via distinct but not mutually exclusive conceptual pathways. The processes at the intersection of aging and AD are fascinating concerning identifying novel drug targets and biomarkers. Leveraging a novel framework to identify and prioritize processes shared between aging and AD ("priOMICs"), ADpriOMICs will identify, rank, sort, and validate new genes and proteins. Using an unbiased approach, ADPriOMICs will combine extensive genome-wide genotype and gene expression data, sequencing information, proteomics, and deep phenotyping in longitudinal cognitive data to identify these processes and the underlying molecular culprit. Using this approach, ADpriOMICs expect to find an enrichment of inflammatory pathways in the shared pathways group. However, we also place a focus on pathways involved in the maintenance of the neurovascular unit (NVU), a physiological and functional unit composed of endothelial cells, pericytes, smooth muscle cells, astrocytes, microglia, and neurons. The NVU interacts with other cell types to create the blood-brain barrier (BBB), regulating cerebral blood flow.

The consortium will examine the strongest and most consistent targets from the "shared" and "unique" classes with cell-biological AD models and in pharmacoepidemiological data. In sum, ADPriOMICs will provide new perspectives on the biology of aging and dementia and have great potential to provide biologically prioritized, druggable entry points to address the dementia burden in aging populations.

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