

The Brain Endothelial Proteome Is Involved In Early Alzheimer Disease Pathogenesis

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Comprehensive CSF proteomics reveals that brain endothelial proteins are prominently and coordinately altered in the earliest preclinical stages of AD. Endothelial biomarkers act as key drivers of functional protein networks associated with amyloid, tau, synaptic dysfunction, and cognition.

INTRODUCTION	METHODS	RESULTS
Growing evidence suggests that brain endothelial dysfunction is an early and central feature of AD, which contributes to protein aggregation, synaptic dysfunction, and cognitive decline. We here aim to investigate endothelial contributions to early AD pathogenesis using high-dimensional cerebrospinal fluid (CSF) proteomics.	We performed deep CSF proteomic profiling using Olink Explore HT1 in $n=652$ cognitively normal individuals and participants with biomarker-defined preclinical AD. Differentially abundant proteins (DAPs) were identified using ANCOVA in the OlinkAnalyze R package. Hierarchical clustering was performed using the stats R package to identify groups of proteins with similar expression patterns. Functional network organization identified protein modules associated with disease stage using the weighted gene co-expression network analysis (WGCNA) R package.	16 endothelial-related gene sets are differentially enriched between pre-clinical AD and healthy controls