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Investigation of Proteomic Signatures in Healthy Aging, Mild Cognitive Impairment and Alzheimer's Disease in a Paired CSF and Plasma Study

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Introduction

While aging remains the primary risk factor for Alzheimer's disease (AD), the biological pathways that are altered in healthy aging vs. pathologic aging remain to be elucidated. Biomarkers in cerebrospinal fluid (CSF) and plasma can yield biological insights and support therapy development. Here, we seek to address this unmet need by applying a novel mass spectrometry-based discovery workflow.

Methods

Matched CSF and plasma samples were collected from young control subjects (n= 53), subjects with mild cognitive impairment (MCI) (n = 40), age-matched healthy control subjects (n = 40) and subjects with autopsy-proven Alzheimer's disease (n = 21, only CSF). The plasma and CSF samples were subsequently processed to tryptic peptides and analyzed using a Thermo Scientific Orbitrap Exploris 480 equipped with a FAIMS Pro device. Differential abundance testing was performed in Spectronaut and the candidate lists were filtered by an FDR <1%.

Results

Using our optimized discovery proteomics workflow, we analyzed 133 matched plasma and CSF pairs from young, old, MCI and AD specimen. This resulted in 5,727 proteins identified in CSF and 3,136 in plasma.

First, we compared young vs old. Proteins that were changed with the same directionality in both CSF and plasma included Leptin, a regulator of energy balance, Transgelin, involved in senescence, and CSPG4, which may regulate axon regeneration. Investigating AD in CSF, we found AD biomarkers e.g. BDNF and PARP-1. Proteins belonging to the memory function were down regulated and were not detected in plasma. Four candidates were shared between old vs MCI and old vs AD indicating that some proteins indicative for AD are already altered in MCI.

Conclusion

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Harnessing the power of the latest advancement in mass spectrometry-based technology, we generated a comprehensive and quantitative map of proteomes linked to healthy and pathological aging.