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Biognosys AG
Wagistrasse 21
8952 Schlieren (Zurich)
Switzerland

t: +41 (0) 44 738 20 40
f: +41 (0) 44 738 20 49
info@biognosys.com
www.biognosyscom

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

M. Tognetti[1], Y. Feng[1], R. Bruderer[1], D. Kamber[1], J. Darrow[2], A. Lewis[2], A. Moghekar[2], L. Reiter[1]

1) Biognosys, Zurich-Schlieren, Switzerland

2) Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Introduction

While aging remains the most significant risk factor for Alzheimer's disease (AD), the biological pathways that are altered in healthy aging vs. pathologic aging leading to neurodegeneration remain to be elucidated. Biomarkers in CSF and plasma can support the efforts to gain 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 obtained from individuals at the same visit. 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%. Gene ontology enrichment was performed using GOrilla.

Preliminary Data

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. 2,683 proteins were shared between CSF and plasma and stemmed from the immunoglobulins, glycoproteins and secreted proteins. 3,044 proteins unique to CSF belonged to the synapse, phosphorylation and acetylation pathways, and disease related proteins (Alzheimer's, Huntigton's and Parkionson's). In plasma, 361 were unique and belonged to platelet activation, transferases and kinases. Unsupervised clustering analysis revealed partial clustering of the conditions.

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First, we compared young vs old. The overlap of candidates between CSF and plasma was 37 proteins of totally 285 in CSF and 208 in plasma. 73% of the shared candidates had the same directionality, amongst them were Leptin, a regulator of energy balance and Transgelin, involved in senescence and CSPG4, which may regulate axon regeneration. Next, we compared old vs MCI. The overlap between CSF and plasma was eleven proteins of totally 96 in CSF and 183 in plasma. 55% of the shared candidates showed the same directionality. E.g. Neurogranin was higher abundant in the old in plasma in contrast to being lower abundant in CSF. Investigating AD in CSF, we found AD biomarkers e.g. BDNF and PARP-1. Proteins belonging to the memory function were down regulated (BDNF, NGF, SYT11, NETO1, CCK), 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.

Finally, we found peptides of APP and PCSK2 being predictive for Alzheimer's disease, while the overall protein abundance was not, this thanks to the peptides mapping to specific protein regions mapping to regions affected by known cleavage events.

Novel aspect

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