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Cerebrospinal fluid peptidomics: discovery of endogenous peptides as biomarkers of Alzheimer's disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula, Sahlgrenska Universitetssjukhuset, Vita Stråket 12, den 19e oktober, klockan 09:00

av Karl Hansson

Fakultetsopponent:
Jonas Bergquist, Professor
Uppsala Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. **Hansson K**, Skillbäck T, Pernevik E, Kern S, Portelius E, Höglund K, Brinkmalm G, Holmén-Larsson J, Blennow K, Zetterberg H and Gobom J. *Expanding the cerebrospinal fluid endopeptidome.* Proteomics 2017, 17:5.

II. **Hansson K**, Zetterberg H, Blennow K, and Gobom J. *Turbulent flow chromatography for rapid cerebrospinal fluid sample preparation for clinical peptidomics in Alzheimer's disease*. Manuscript.

III. Skillbäck T, Mattsson N, **Hansson K**, Mirgorodskaya E, Dahlén R, van der Flier W, Scheltens P, Duits F, Hansson O, Teunissen C, Blennow K, Zetterberg H and Gobom J. *A novel quantification-driven proteomic strategy identifies an endogenous peptide of pleiotrophin as a new biomarker of Alzheimer's disease*. Scientific Reports 2017, 7:1.

IV. **Hansson K**, Dahlén R, Hansson O, Pernevik E, Paterson R W, Schott J M, Magdalinou N, Zetterberg H, Blennow,K and Gobom J. *The protein-to-peptide ratio improves the performance of tau in CSF as a biomarker of Alzheimer's disease*. Manuscript submitted.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Abstract

Neurodegenerative diseases (NDs), the most prominent example of which is Alzheimer's disease (AD), has turned out to be among the greatest challenges for modern medicine. Not only have NDs proven complicated to diagnose, study and treat but have also over time increased in incidence as a consequence of improved global life expectancy, not least due to progress in other areas of medicine.

Analysis of cerebrospinal fluid (CSF) is valuable to the study of NDs. Produced as an ultra-filtrate of blood in the ventricles and around the blood vessels of the central nervous system (CNS). Previous studies have revealed that CSF, besides proteins, contains many endogenous peptides. Being the products of a variety of processes, such as enzymatic protein processing, secretion, and aggregation, these peptides may convey valuable biomarker information.

The initial aim of this thesis was to develop and optimise methods for isolation, separation, detection and identification of endogenous CSF peptides through with a special focus on low-abundant species. Further, strategies for improved data utilisation and quantitative analysis were also evaluated and subsequently implemented with the goal of identifying endogenous CSF peptide biomarker candidates from clinical cohorts.

Our studies have shown both that the endopeptidome of human CSF is substantially larger than previously indicated and containing a large number of peptides originating from proteins of noted interest in the study of NDs. Further, by means of extensive sample preparation and improved data analysis-techniques we were able to identify a multitude of potential biomarker prospects and, most importantly, three novel biomarker candidates for AD of validated diagnostic value.

More studies are required to further investigate the biomarker candidates and even more to evaluate the identified biomarker prospects for diagnostic value and to determine what their respective presence in CSF may tell about pathological processes in the CNS. However, the studies included in this thesis have shown that the CSF endopeptidome is a source of information into neurodegeneration with great potential.

Keywords: Alzheimer's disease, endogenous peptides, cerebrospinal fluid, liquid chromatography, mass spectrometry

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