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Multimodal Chemical Imaging of Amyloid Plaque Pathology in Alzheimer's Disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, fredagen den 20 september 2019, klockan 13:00

av Wojciech Michno

Fakultetsopponent:

Ron Heeren, Professor

Maastricht University, Netherlands

Avhandlingen baseras på följande delarbeten

I. Carlred L*, **Michno W***, Kaya I, Sjövall P, Syvänen S, Hanrieder J. *Probing amyloid-β pathology in transgenic Alzheimer's disease (tgArcSwe) mice using MALDI imaging mass spectrometry.* J Neurochem 2016; 138(3):469-78. *contributed equally

II. **Michno W**, Wehrli PM, Zetterberg H, Blennow K, Hanrieder J. *GM1 locates to mature amyloid structures implicating a prominent role for glycolipid-protein interactions in Alzheimer pathology.* Biochim Biophys Acta Proteins Proteom 2019; 1867(5):458-467.

III. Kaya I, **Michno W**, Brinet D, Iacone Y, Zanni G, Blennow K, Zetterberg H, Hanrieder J. *Histology-compatible MALDI mass spectrometry based imaging of neuronal lipids for subsequent immuno-fluorescent staining.* Anal Chem 2017; 18;89(8):4685-4694.

IV. **Michno W**, Kaya I, Nyström S, Guerard L, Nilsson KPR, Hammarström P, Blennow K, Zetterberg H, Hanrieder J. *Multimodal chemical imaging of amyloid plaque polymorphism reveals Aβ aggregation dependent anionic lipid accumulations and metabolism.* Anal Chem 2018; 3;90(13):8130-8138.

V. **Michno W**, Nyström S, Wehrli P, Lashley T, Brinkmalm G, Guerard L, Syvänen S, Sehlin D, Kaya I, Brinet D, Nilsson KPR, Hammarström P, Blennow K, Zetterberg H, Hanrieder J. *Pyroglutamation of amyloid-βx-42 (Aβx-42) followed by Aβ1-40 deposition underlies plaque polymorphism in progressing Alzheimer's disease pathology.* J Biol Chem 2019; 26;294(17):6719-6732.

VI. **Michno W**, Wehrli P, Sehlin D, Syvänen S, Zetterberg H, Blennow K, Hanrieder J. *Chemical imaging of evolving amyloid plaque pathology and associated Aβ peptide aggregation in transgenic AD Mice.* Manuscript

VII. **Michno W**, Stringer K, Escrig S, Enzlein T, Passarelli M, Hopf C, Blennow K, Zetterberg H, Meibon A, Edwards FA, Hanrieder J. *Imaging spatial Aβ plaque aggregation dynamics in evolving AD pathology using iSILK.* Manuscript

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Multimodal Chemical Imaging of Amyloid Plaque Pathology in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common form of dementia. AD has been linked to the aggregation of amyloid beta (Aβ) peptides into extracellular deposits, Aβ plaques. These are also found in cognitively unimpaired amyloid-positive (CU-AP) individuals, but these Aβ plaques are primarily diffuse in structure. In AD brains, Aβ plaques often have a dense core and a more diffuse periphery. Aβ exists in various lengths, where the 42 amino acid-long Aβ form (Aβ1-42) is considered most neurotoxic. Aβ1-42 is currently used as an AD biomarker when measured in cerebrospinal fluid or plasma. Measurements of the relative amount of different biomolecules within Aβ plaques are generally performed using antibodies. Usually, up to three molecules, can be visualized using this technique. Recently it has been shown that Aβ aggregates can have distinct 3D structures. These differences in structures can be the result of which particular Aβ peptides the aggregates are made of. Aβ aggregates may also differ between AD patients, which makes it difficult to visualize and compare Aβ plaque pathology, and poses challenges in the development of new drugs targeting Aβ aggregates. It is likely that the composition of different Aβ plaques, making them more or less diffuse, could vary depending on different Aβ peptides.

This thesis presents the development of methods to study chemical factors underlying the variation between different types of Aβ plaques. These are mainly based on three advanced technologies. The first is imaging mass spectrometry, which enables the accurate separation and visualization of molecules based on their mass in brain tissue. The second is hyperspectral light microscopy, which utilizes different light wavelengths to characterize the structural properties of Aβ aggregates in different plaque types. The third is high resolution electron microscopy, which enables the visualization of individual aggregates. Furthermore, stable-isotope labelling is used to study the dynamics of Aβ plaque formation. These methods were applied to characterize the biomolecules (different Aβ peptides and lipids) between diffuse and dense structures within and between Aβ plaques in mice, AD patients and CU-AP individuals. It was demonstrated that the shorter Aβ1-40 peptide localized to the dense core, and, at least in mice, this localization appeared to be a result of Aβ plaque maturation. CU-AP-associated diffuse plaques were not the same as the AD-associated diffuse or cored plaques, when it came to the aggregation state. The chemical modification of the N-terminal part could be responsible for such structural heterogeneity, and possibly for the neurotoxicity associated with AD. Further, an altered lipid composition was identified between diffuse and dense Aβ aggregate structures. Finally, with the help of stable-isotope labelling, it was verified that Aβ plaque spread starts in the cortex and continues towards the hippocampus. This was initiated through the deposition of Aβ1-42. Shorter C-terminally truncated peptides were deposited only at a later stage. These peptides were newly produced, and did not stem from already accumulated Aβ1-42.

In summary, Aβ plaque pathology is much more complex than what it is currently considered during ordinary post-mortem neuropathological assessments. It needs to be researched with the help of advanced methods, to provide us with important information about how, where and why Aβ and other biomolecular factors contribute to the development of AD.

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