Development of MALDI Mass Spectrometry Imaging Methods for Probing Spatial Lipid Biochemistry of Amyloid Plaques in Alzheimer's Disease

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i KB 10:an, Kemivägen 10, Chalmers Tekniska Högskola, måndagen den 8 juni 2020, klockan 13:00

av Ibrahim Kaya

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Avhandlingen baseras på följande delarbeten

I. **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 Immunofluorescent Staining.* Analytical Chemistry 2017; 89: 4685-4694.

II. **Kaya, I.**; Brinet, D.; Michno, W.; Başkurt, M.; Zetterberg, H.; Blennow, K.; Hanrieder, J. *Novel Trimodal MALDI Imaging Mass Spectrometry (IMS3) at 10 μm Reveals Spatial Lipid and Peptide Correlates Implicated in Aβ Plaque Pathology in Alzheimer's Disease.* ACS Chemical Neuroscience 2017; 8: 2778-2790.

III. **Kaya, I.**; Zetterberg, H.; Blennow, K.; Hanrieder, J. *Shedding Light on the Molecular Pathology of Amyloid Plaques in Transgenic Alzheimer's Disease Mice Using Multimodal MALDI Imaging Mass Spectrometry.* ACS Chemical Neuroscience 2018; 9: 1802-1817.

IV. **Kaya, I.**, Jennische, E., Dunevall, J., Lange, S., Ewing, A. G., Malmberg, P., Baykal, A. T., and Fletcher, J. S. *Spatial Lipidomics Reveals Region and Long Chain Base Specific Accumulations of Monosialogangliosides in Amyloid Plaques in Familial Alzheimer's Disease Mice (5xFAD) Brain.* ACS Chemical Neuroscience 2019; 11: 14-24.

V. **Kaya, I.**, Jennische, E., Lange, S., Baykal, A. T., Malmberg, P., and Fletcher, J. S. *Brain Region-Specific Amyloid Plaque-Associated Myelin Lipid Loss, APOE Deposition and Disruption of the Myelin Sheath in Familial Alzheimer's Disease Mice.* Journal of Neurochemistry 2020.

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Abstract

Alzheimer's disease (AD) is the most prevalent cause of neurodegenerative dementia. Aggregation of amyloid β (Aβ) peptides into extracellular Aβ plaques is one of the major neuropathological features of AD. However, Aloysius Alzheimer reported remarkable lipid granule accumulations in multiple glial cell types and intense lipid granules in the plaque core in AD brain along with the proteopathic features of AD in his initial reports. While the role of lipids in AD has until recently not received as much attention, a body of molecular, immune, genetical, biochemical evidence closely links aberrant lipid metabolism to several stages of AD pathogenesis. Therefore, plaque-associated lipid molecular information in specific brain regions would be a strong asset to dissect spatial lipid biochemistry of amyloid plaques which would also provide a basis for further investigation of cell signaling and metabolic pathways that are disrupted in AD. This thesis represents the development of matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging (MSI) methods for single-plaque resolution spatial lipidomics across the brain tissue sections of transgenic AD mouse models. The developed methods include "static" MALDI for high-spatial resolution (at 10 μm) lipid imaging using low-energy laser pulses which can be followed by immunofluorescence imaging of the same brain tissue section, dual polarity MALDI-MSI on the same pixel points for spatial correlation of lipid species ionized in both negative and positive polarities and "trimodal" MALDI-MSI which allows spatial correlation of lipid species in dual polarity with peptide/protein species within the same brain tissue sections at 10 μm spatial resolution. These MALDI-MSI methods in combination with immunohistochemistry revealed plaque-associated alterations of several phospholipids, lysophospholipids, and sphingolipids along with the Aβ peptide truncations and leveraged the understanding of molecular, structural and immune signatures of Aβ pathology. For instance, we observed amyloid plaque-associated myelin lipid architecture loss, apolipoprotein E (APOE) mediated sulfatide depletion, region-specific and long chain base specific accumulations of monosialogangliosides, and accumulations of several lysophospholipids in amyloid plaques in transgenic AD mouse brain.

In summary, lipids are important components of amyloid plaques and above mentioned novel MALDI-MSI methods in combination with other modalities have great potential for probing spatial lipid molecular pathology of amyloid plaques which can provide novel insights into AD pathogenesis.

Keywords: Alzheimer's disease, amyloid plaques, APP, lipids, APOE, myelin, sulfatides, gangliosides, immunopathology, neurodegeneration, MALDI, imaging mass spectrometry, trimodal MALDI, static MALDI, dual polarity MALDI-MSI on the same pixel points, 5xFAD, tgArcSwe, tgSwe, sphingolipids, phospholipids