Structural Polymorphism in Evolving Amyloid Pathology is Associated with Distinct Amyloid-Beta (Aβ) Truncation Profiles

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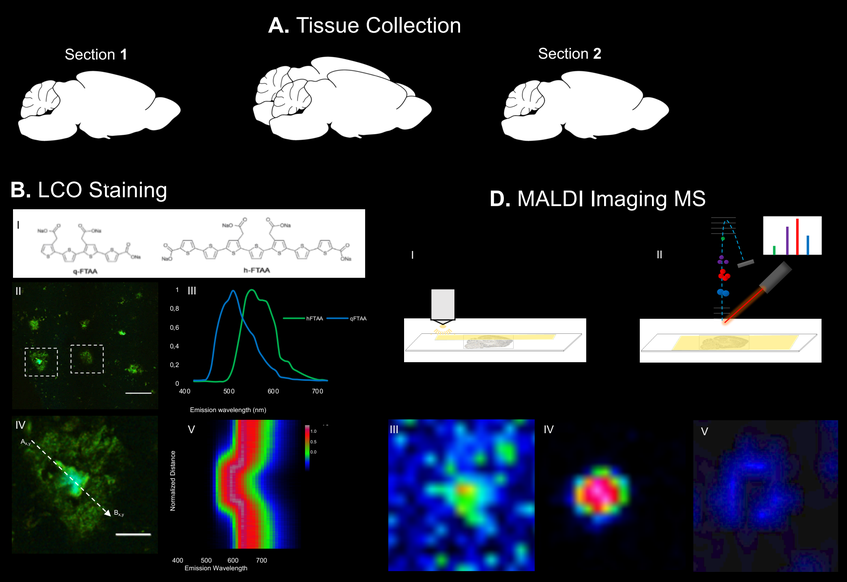
Background

Amyloidogenic aggregation of beta-amyloid peptides into senile deposits is the major pathological hallmark of Alzheimer's disease (AD) [1,2]. While the exact mechanisms of AD pathogenesis are not fully understood, plaque pathology has been identified as critical, driving AD pathogenesis. Still, the correlation of plaque burden and AD progression has been questioned. For instance, amyloid plaques have been found in cognitively normal patients that exhibit amyloid pathology – cognitively unaffected-amyloid positive (CU-AP) patients [1]. However, Aβ plaques present in CU-AP brains are mostly diffuse in nature, while plaques in AD brain tissue are mostly mature/compact. Diffuse plaques can be a consequence of an alternative, neuroprotective aggregation mechanism. Alternatively, diffuse plaques can represent an immature non-toxic state of mature compact amyloid plaques. The factors that promote neurotoxic plaque formation are still unknown. Changes in amyloid peptide truncation have been implicated with proteopathic mechanisms in AD [2]. Therefore, a chemical imaging that allows the efficient discrimination of structural and molecular plaque architecture is of essential interest to resolve Aβ plaque pathology in AD. Such plaque pathology delineation calls for novel, multimodal chemical imaging tools such as imaging mass spectrometry [3] in combination with fluorescent probes and immunohistochemistry [5].

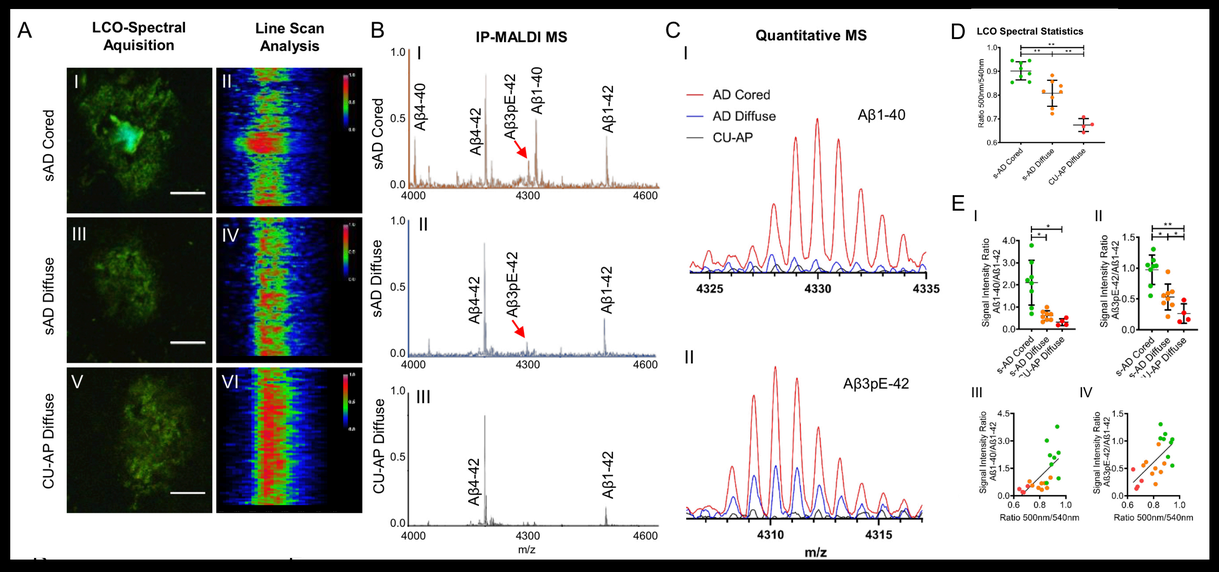
Experimental

- Fresh frozen cryosections: human sAD, CU-AP and mice $tgAPP_{SWE}$
- Electrooptic fluorescent probes (LCO)
- Hyperspectral LSM 710 NLO (Zeiss)
- IP-MALDI MS towards total Aβ
- 2,5-DHA matrix appplied with an TM Sprayer (HTX)
- MALDI IMS was performed using ultrafleXtreme (Bruker), 25um

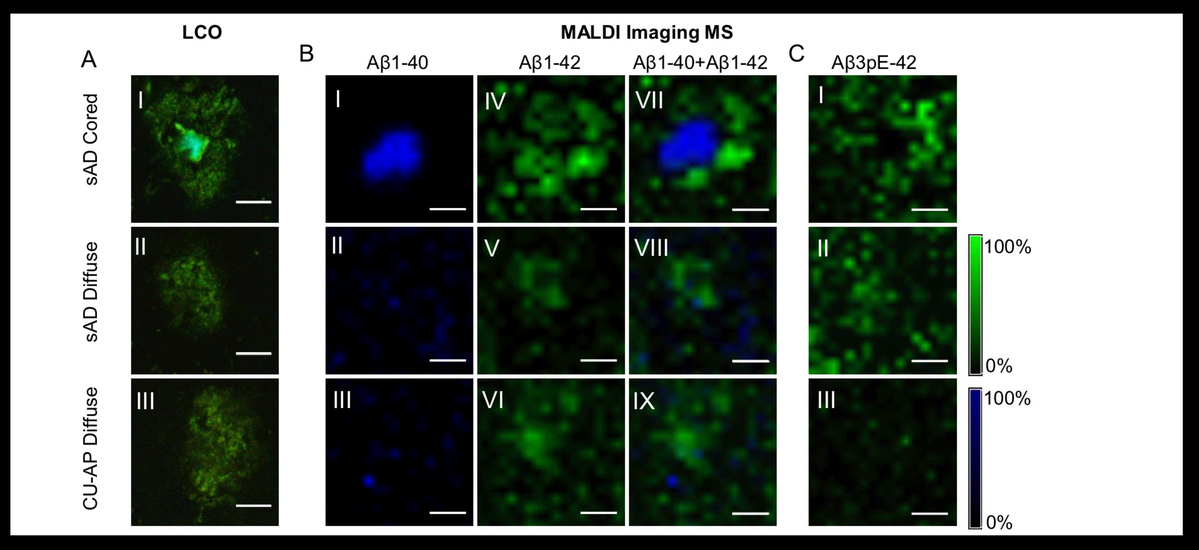


Results and Discussion

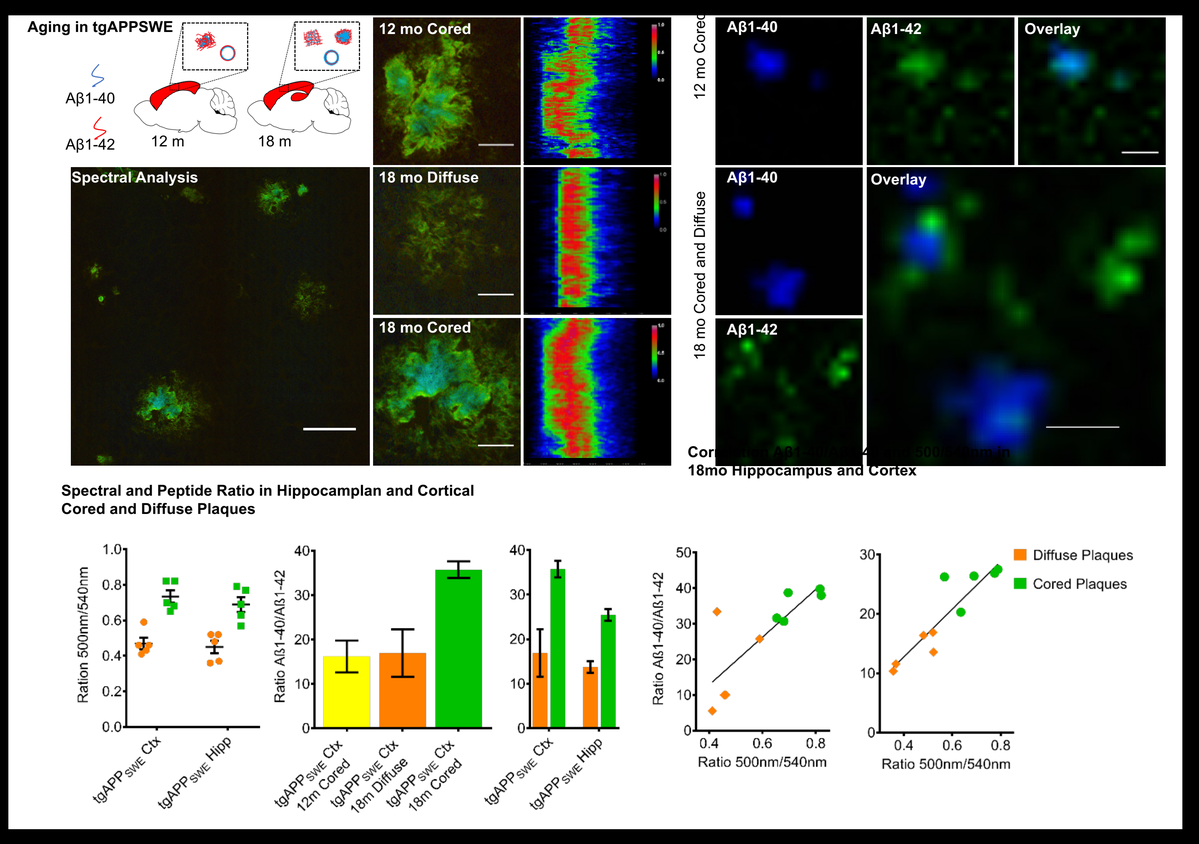
1. Hyperspectral and MS analysis identifies characteristic Aβ profiles in associated with amyloid polymorphism in sAD and CU-AP



2. Imaging MS reveals specific deposition of Aβ 1-40 at the core in senile, neurotoxic plaques



3. Imaging MS in $tgAPP_{SWE}$ mice reveals that plaque maturation is associated with Aβ 1-40 deposition



- We observed a significant increase of Aβ1-40 in senile, neurotoxic plaques solely present in AD as compared to diffuse plaques that are observed both in human AD and CU-AP
- Further, plaques in AD show increased levels of 3pE modification of Aβ1-42
- Data from $tgAPP_{SWE}$ show that this increase in Aβ1-40 was associated with plaque maturation over time, where both senile plaques and cerebrovascular deposits at 18 months contained higher Aβ1-40/1-42 levels than at 12 months.
- Higher Aβ1-42 levels appear therefore to be characteristic for pre-mature deposits suggesting diffuse plaques to be precursors of senile plaques that are associated with AD pathogenesis.
- This maturation involves hydrophobic priming of Aβ1-42 through pyroglutamation followed by Aβ1-40 deposition and core formation
- These data show for the first time what Aβ peptide species are associated with differences in plaque morphology in progressing Aβ pathology.

References

(1) Moore, B. D.; Chakrabarty, P.; Levites, Y. et al Alzheimers Res Ther 2012, 4, 18.
(2) Selkoe, D. J.and Schenk, D. Annu. Rev. Pharmacol. Toxicol. 2003, 43, 545-584.
(3) Michno W., Wehrli P, Blennow K. et al 2019 J Neurochem (in print)
(5) Kaya, I., Michno W., Brinet D. et al Anal. Chem. 2017 89(8):4685-4694.
(6) Michno W, Nyström S., Wehrli P. et al. J Biol Chem 2019 294(17):6719-6732

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