Label-free characterization of Amyloid-β-plaques using hyperspectral stimulated Raman scattering microscopy

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The brains of patients with Alzheimer's Disease (AD) commonly exhibit large numbers of abnormal extracellular aggregates of Amyloid-β (Aβ) peptides ("Aβ plaques"). Several recent studies also pointed out lipid structures that colocalize in part with these pathological Aβ structures. Interactions between lipids and Aβ aggregates are considered highly relevant for neurotoxicity in AD, since lipids are known to have the potential to extract small Aβ oligomers from plaques and transport them to the intracellular space where they can become neurotoxic. However, the precise molecular and cell biological mechanisms leading to the formation of these plaque-associated lipid structures remain poorly understood, highlighting the need for novel analytical techniques to probe these structures.

Stimulated Raman Scattering (SRS) microscopy is an emerging nonlinear optical microscopy technique that images biological structures by exploiting the characteristic, vibrational contrast of the sample molecules. Here, we demonstrate that label-free, chemically specific imaging using SRS can provide novel insights into the biophysical properties and biochemical composition of pathological structures in the brain.

In brain slices of mice carrying an amyloid precursor protein and a presenilin 1 mutation that exhibit AD-like pathology, we find large numbers of Aβ plaques. Two-color SRS imaging of CH_2 stretch vibrations and a frequency-shifted Amide-I vibration, characteristic of β-sheet proteins, allows us to visualize the peptide and lipid components of plaques in a highly specific manner. We find that plaques commonly exhibit a characteristic, three-dimensional core-shell structure, in which a fibrillar core consisting of misfolded Aβ peptides is surrounded by a halo-like arrangement of lipid-rich deposits. Hyperspectral SRS microscopy allows for a detailed compositional analysis of plaque-associated lipid structures, demonstrating that these contain lower levels of cholesterol than nearby white matter structures, whereas concentrations of membrane lipids (sphingomyelin and phosphatidylcholine) are comparatively high in plaques. Overall, SRS spectra of plaque-associated lipid structures are very similar to those of nearby neurites, with the notable difference of a significantly higher degree of lipid unsaturation compared to healthy brain structures. We hypothesize that pathological lipid deposits might be a result of neuritic dystrophy associated with AD, and that the observed increased levels of unsaturation might contribute to pathology. Taken together, our results highlight the potential of stimulated Raman scattering to contribute to a deeper understanding of neurodegenerative diseases more broadly.