Co-Localization of β-Amyloid Deposits and Metal Accumulation in Alzheimer's Disease

Beamline:
NSLS: U10B, X26A, X27A
APS: 13ID, 18ID

Technique:
Infrared Microspectroscopy
X-ray Fluorescence Microprobe

Researchers:
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Motivation: Alzheimer's disease (AD) is characterized by the misfolding and plaque-like accumulation of a naturally occurring protein, amyloid beta (Aβ) in the brain. This misfolding process has been associated with the binding of metal ions such as Fe, Cu, and Zn *in vitro*. The secondary structure of the amyloid plaques is imaged *in situ* using Fourier transform infrared microspectroscopy (FTIRM). The metal ion accumulation in the identical brain tissue is detected by synchrotron x-ray fluorescence (XRF) microprobe synchrotron. The aim is to spatially correlate the *in situ* metal distribution with the characteristic protein structure changes of amyloid plaques.

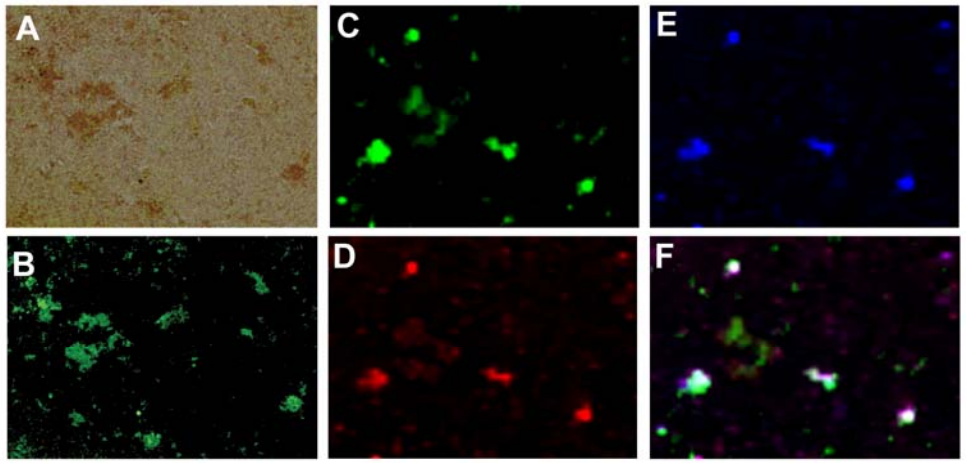

Figure 1. (A) Bright field and (B) Epifluorescence image of human AD tissue stained with Thioflavin S. (C) Single channel color FTIR correlation image of -sheet protein (green). (D) Single channel color SXRF microprobe image of Zn (red). (E) Single channel color SXRF microprobe image of Cu (blue). (F) The RGB correlation image.

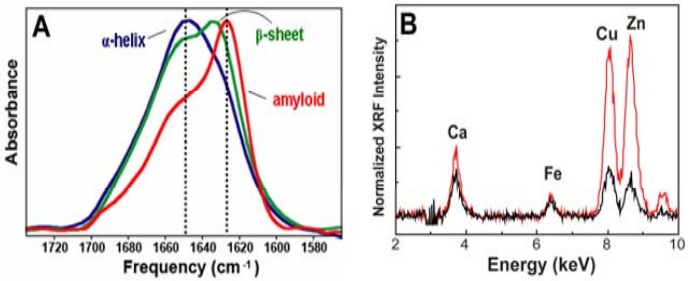

Figure 2 (A) Infrared spectra of Thioflavin-positive area (red) and Thioflavin-negative area (black) of AD tissue; FTIR spectrum of purified Aβ peptide in vitro is shown (green). (B) SXRF microprobe spectra from Thioflavin-positive area (red) and Thioflavin-negative area (black).

Results: Elevated β-sheet content was revealed by FTIRM in amyloid plaques of human AD brain tissue, as demonstrated by a strong Amide I absorbance at 1625 cm^{-1} (Fig 2A, red) in infrared spectrum and the regions of elevated β-sheet content in the AD tissue corresponded well with amyloid deposits as identified by Thioflavin staining. On the other hand, "hot spots" with elevated Ca, Fe, Cu, and Zn ions were observed in the identical tissue by SXRF imaging., which is also evident in representative XRF spectra (Fig 2B red) . A strong spatial correlation (r^2 = 0.97) was found between the locations of the Cu and Zn ions. A RGB correlation image (Fig 1F) showed that the "hot spots" of accumulated Zn and Cu ions were co-localized with the elevated regions of β-sheet protein and amyloid deposition. In contrast, Neither plaques nor accumulated metal hot spots were observed in control brain tissue. In summary, we showed for the first time a direct strong spatial correlation between AD plaques and metal ions in the brain, emphasizing the role of metal ions in AD etiology. In the future, exploring earlier stages of disease and *in-situ* probing metal-protein binding will be of interest for understanding the disease pathogenesis and mechanism.