Atomic Resolution Map of the Soluble Amyloid Beta Assembly Toxic Surfaces

Soluble amyloid beta assemblies (Aβₙ) are neurotoxic and play a central role in the early phases of the pathogenesis cascade leading to Alzheimer’s disease. However, the current knowledge about the molecular determinants of Aβₙ toxicity is at best scant. Here, we comparatively analyze Aβₙ prepared in the absence or presence of a catechin library that modulates cellular toxicity. By combining solution NMR with dynamic light scattering, fluorescence spectroscopy, electron microscopy, wide-angle X-ray diffraction and cell viability assays, we identify a cluster of unique molecular signatures that distinguish toxic vs. nontoxic Aβ assemblies. These include the exposure of a hydrophobic surface spanning residues 17-28 and the concurrent shielding of a highly charged N-terminus. We show that the combination of these two dichotomous structural transitions promotes the colocalization and insertion of β-sheet rich Aβₙ into the membrane, compromising membrane integrity. These previously elusive toxic surfaces mapped here provide an unprecedented foundation to establish structure-toxicity relationships of Aβ assemblies.

References: