Characterization of Amyloid Beta 1-42 Aggregation using Conformational-Sensitive Fast Photochemical Oxidation of Proteins (FPOP) and Mass Spectrometry: Implications for Drug Development in Alzheimer's Disease

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Alzheimer's disease is associated with the aggregation of amyloid beta 1-42 ($A\beta_{1-42}$) to give oligomers, protofibrils and fibrils. Here we describe footprinting of oligomerizing soluble $A\beta_{1-42}$ by fast photochemical oxidation of proteins (FPOP) and mass spectrometry (MS) to monitor the time-dependent aggregation at the whole protein, peptide, and some residue-specific resolution of $A\beta_{1-42}$ in its native, unmodified state. The time-dependent self-association support five steps some of which were previously seen in fluorescence and hydrogen exchange studies. We unambiguously resolved these five stages that report on the transitions of monomers → paranuclei → protofibrils → fibrillar aggregates. The N-terminus of $A\beta_{1-42}$ retains most of its solvent-accessibility whereas the middle domain plays a major role in aggregation, and the hydrophobic C-terminus is intermediately involved. This platform is suitable for collaborations in drug development for Alzheimer's disease and in basic protein biophysics to understand the mechanism of amyloid formation.