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REVIEW

Oligomeric Intermediates in Amyloid Formation: Structure Determination and Mechanisms of Toxicity

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Oligomeric intermediates are non-fibrillar polypeptide assemblies that occur during amyloid fibril formation and that are thought to underlie the aetiology of amyloid diseases, such as Alzheimer's disease, Parkinson's disease and Huntington's disease. Focusing primarily on the oligomeric states formed from Alzheimer's disease β-amyloid (Aβ) peptide, this review will make references to other polypeptide systems, highlighting common principles or sequence-specific differences. The covered topics include the structural properties and polymorphism of oligomers, the biophysical mechanism of peptide self-assembly and its role for pathogenicity in amyloid disease. Oligomer-dependent toxicity mechanisms will be explained along with recently emerging possibilities of interference.

Intermediates in Amyloid Fibril Formation

The formation of amyloid fibrils is a molecular self-assembly reaction that involves the transient stabilization of a range of differently structured intermediates.[1] Interest in these states was strongly fuelled by data demonstrating their role as pathogenic agents in several neurodegenerative disorders.[2] Different classes of amyloid intermediates have been identified, including oligomers, protofibrils and annular aggregates.[2–4] Each class probably represents a group of states and comprises multiple subspecies. A plethora of additional terms have been coined to account for this diversity. For instance, Aβ peptide forms structures including paranuclei, globulomers, Aβ*56 and Aβ-derived diffusible ligands.[5] This peptide also represents one of the most intensively examined amyloidogenic systems. Therefore, a significant proportion of this overview will be dedicated to this peptide and its structural intermediates, but comparisons will be made with other polypeptide systems to highlight important analogies or differences. Initially, this review will outline the structural specifics of the different classes of intermediates and mature fibrils, before closing up with their biological properties and currently pursued strategies of interference.

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Abbreviations used: AD, Alzheimer's disease; PD, Parkinson's disease; CR, Congo red; ThT, thioflavin T; EM, electron microscopy; FCS, fluorescence correlation spectroscopy; ANS, 1-anilino-8-naphthalene sulfonate; MD, molecular dynamics; ROS, reactive oxygen species; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; LTP, long-term potentiation; NMDA, *N*-methyl D-aspartate.

Structure of Mature Amyloid Fibrils

Mature amyloid fibrils are the terminal stage of the fibrillogenic pathway.[1,4] They possess a long,

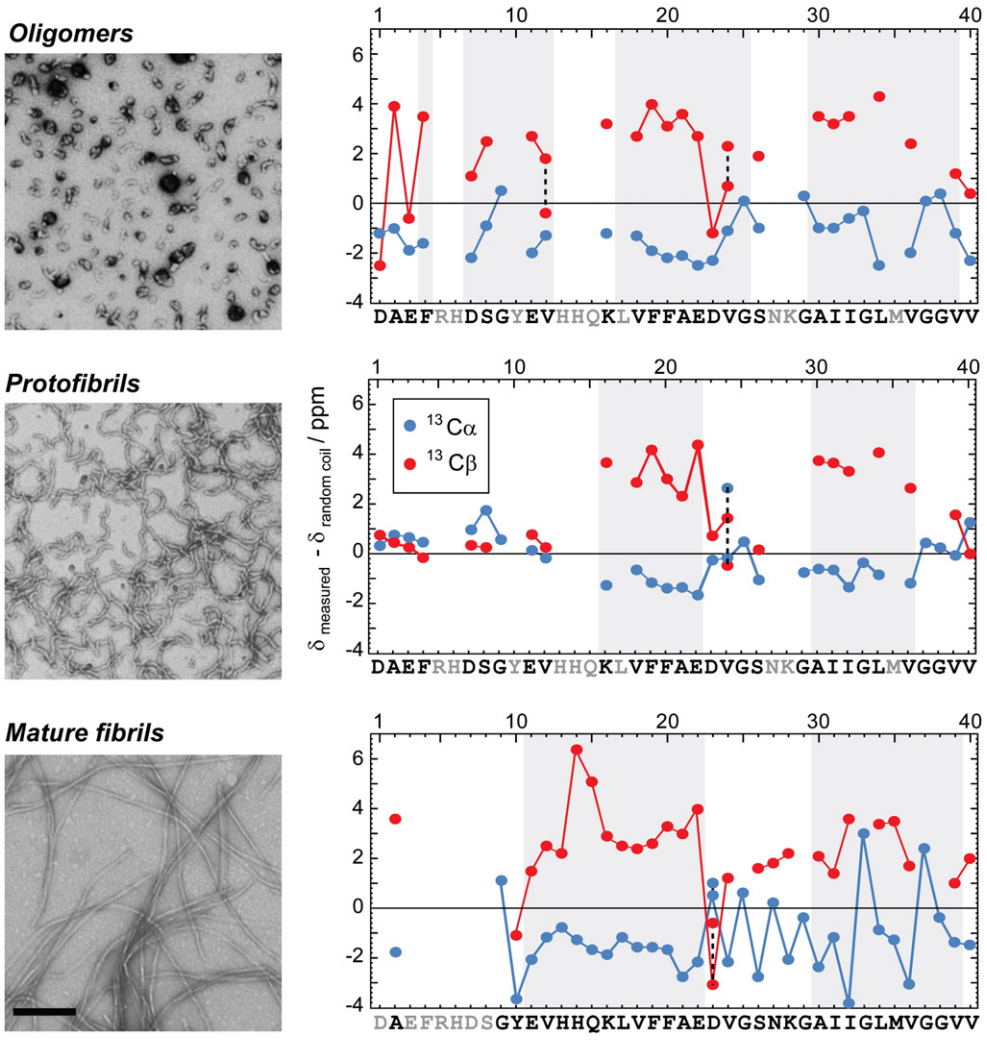

Fig. 1. Structure of mature Aβ(1-40) amyloid fibrils, protofibrils and oligomers. Left: negative stain EM images (scale bar represents 200 nm). Right: solid-state NMR spectroscopy $^{13}C^{\alpha}$ (blue) and $^{13}C^{\beta}$ (red) chemical shifts measured with the three different conformers and plotted as deviation from random-coil values.[6] Gray boxes indicate segments assigned by previous studies as β-strand conformation.[7–9] Residues measured in the respective studies are labeled black within the sequence. Broken line: two chemical shift values reported for the same nucleus.

straight and highly regular morphology (Fig. 1) that is visible by transmission electron microscopy (EM) and other detailed microscopic techniques.[10] These fibrils are constructed from a cross-β-sheet structure that has been demonstrated by X-ray diffraction to characteristically produce spacings at 4.7 and ~10 Å.[11,12] This structure is generic for different amyloid fibrils, irrespective of the sequence of the component polypeptide chains, and all amyloid fibrils comprise, despite some modifications, this basic structural motif. Mature amyloid fibrils can extend several micrometers in length, while the fibril width is 10–20 nm.[13,14] This value is highly conserved along the axis of a single fibril, but different fibril polymorphs can present significantly different values.[14] Amyloid fibrils are often twisted, leading to apparent fibril constrictions at regular distances, termed crossovers.[15] The helical sense of fibril superhelices is usually left-handed,[10] but rare exceptions have been documented.[16] Mature amyloid fibrils are usually characterized by a high affinity for certain dyes, such as Congo red (CR) and thioflavin T (ThT).[17] In the case of Aβ peptide, detailed structural data are now available, including residue-specific assignments of the secondary structural elements of different fibril polymorphs[7,15] and electron density maps obtained with electron cryomicroscopy at subnanometer resolutions.[18,19] These data have revealed the global fibril topology and features of the peptide assembly, such as the probably dimeric subunit constructing the investigated Aβ fibrils.[20] For other amyloid fibrils, even atomic resolution structures of the molecular subunits have been obtained.[21,22]