The chemical biology of macromolecule self-assembly —from wood cellulose microfibrils to tau protein aggregates.

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The self-assembly of biomacromolecules underlies many critical physiological processes, but it may also contribute to severe pathological states. The biosynthesis of cellulose microfibrils (CMFs) in wood cell walls, the most abundant organic material on earth, is a two-stage self-assembly process. After decades of investigations, there is still a vigorous debate about the number of glucan chains in wood CMFs. By developing new methodologies in small-angle X-ray scattering (SAXS) and solid-state NMR, we observed that wood CMFs contain 24 glucan chains that exhibit a core-shell configuration. By advanced synchrotron SAXS measurements, we successfully visualized a single molecular layer of shell glucans and single hemicellulose chains. Our data do not support standard textbook models with 36 chains or recent consensus models with 18 chains. Elucidating CMF chain numbers is crucial for modeling cell-wall properties and biomass applications.

On the other hand, the self-assembly of prion-like proteins is the common propagation mechanism of many neurodegenerative disorders. In particular, the aggregates of misfolded tau proteins are found in over 30 neurodegenerative disorders, including Alzheimer's disease (AD), but there is no FDA-approved anti-tau therapy. We have uncovered new mechanisms that promote tau self-assembly into fibrils without cofactors, overturning the decades-old belief that tau does not self-aggregate. Moreover, we identified prion-like tau oligomers in the brain synapses of AD patients and developed a novel immunotherapy (APNmAb005) to neutralize their toxicity. APNmAb005 is a conformation-specific monoclonal antibody against soluble tau aggregates (oligomers and protofibrils), which recently entered phase 1 clinical trial in the US. In AD brain extracts, APNmAb005 selectively captures granular oligomers (>40 subunits) enriched in beta-sheet structures. In tauopathy mice, long-term treatments with APNmAb005 rescue neuronal and synaptic losses.