When Proteins Go Bad: The Intrinsic Propensity of Proteins to Polymerize and its Relation to Human Diseases

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Accumulation of long, unbranching fibrils formed by proteins or peptides is associated with an ever-increasing series of human disorders called amyloid diseases. Amyloid diseases include such serious and widespread disorders as Alzheimer's disease and type-II diabetes. Surprisingly, though, many aspects of the underlying mechanisms of protein assembly and how they are related to disease have remained elusive. Recent findings have implicated small, metastable oligomers that precede fibril formation as the dominant cause of amyloid-related pathologies. Therefore, understanding the molecular mechanisms regulating and promoting the self-assembly of distinct amyloid aggregate species *in vitro* and in *vivo* represents a critical step towards devising effective treatment strategies. Our lab is approaching amyloid formation as a problem in soft-condensed matter physics of polymeric system. We have determined a kinetic phase diagram outlining the conditions required for amyloid oligomer formation prior to fibril nucleation. In addition, we investigated how the process of oligomer formation is related to and interacts with amyloid fibril formation. These insights into the interrelation between early-stage oligomers and late-stage fibrils can inform the search for drugs manipulating the amyloid assembly process and targeting the disease-relevant amyloid species.