Title:	pH-Responsive Mechanistic Switch Regulates the Formation of Dendritic and Fibrillar Nanostructures of a Functional Amyloid
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Abstract:	In contrast to pathological amyloids, functional amyloids are involved in crucial physiological functions. For instance, the melanosomal protein comprising a highly amyloidogenic polypeptide repeat domain assembles into amyloid fibrils that act as templates for melanin biosynthesis within acidic melanosomes. However, the mechanism–morphology–function relationship of functional amyloids is poorly understood. Here, we demonstrate that the repeat domain of the melanosomal protein exhibits two distinct types of aggregation pathways that display nanoscale polymorphism in acidic pH. In the pH range of 4.5–6, aggregation proceeds via a typical nucleation-dependent mechanism, resulting in the formation of highly ordered β-rich curvy thread-like fibrils. On the contrary, at pH < 4.5, aggregation occurs through a rapid nucleation-independent isodesmic polymerization process that yields dendritic aggregates having lower degree of internal packing. These dendritic nanostructures can be converted into more stable fibrils by switching the pH. The nanoscale polymorphism associated with the mechanistic switch is likely to be mediated by the altered conformational propensities and intermolecular interactions due to the protonation/deprotonation of critical glutamate residues. We propose that this striking shift in the mechanism that dictates the nanoscale morphology regulates the melanosomal maturation.
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