Title:	Appearance of annular ring-like intermediates during amyloid fibril formation from human serum albumin
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Abstract:	The self-assembly of proteins triggered by a conformational switch into highly ordered β-sheet rich amyloid fibrils has captivated burgeoning interest in recent years due to the involvement of amyloids in a variety of human diseases and a diverse range of biological functions. Here, we have investigated the mechanism of fibrillogenesis of human serum albumin (HSA), an all-α-helical protein, using an array of biophysical tools that include steady-state as well as time-resolved fluorescence, circular dichroism and Raman spectroscopy in conjunction with atomic force microscopy (AFM). Investigations into the temporal evolution of nanoscale morphology using AFM revealed the presence of ring-like intermediates that subsequently transformed into worm-like fibrils presumably by a ring-opening mechanism. Additionally, a multitude of morphologically-diverse oligomers were observed on the pathway to amyloid formation. Kinetic analysis using multiple structural probes in-tandem indicated that HSA amyloid assembly is a concerted process encompassing a major structural change that is primarily mediated by hydrophobic interactions between thermally-induced disordered segments originating in various domains. A slower growth kinetics of aggregates suggested that the protein structural reorganization is a prerequisite for fibril formation. Moreover, time-dependent Raman spectroscopic studies of HSA aggregation provided key molecular insights into the conformational transitions occurring within the protein amide backbone and at the residue-specific level. Our data revealed the emergence of conformationally-diverse disulfides as a consequence of structural reorganization and sequestration of tyrosines into the hydrophobic amyloid core comprising antiparallel cross β-sheets
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