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Title:	Characterization of Salt-Induced Oligomerization of Human β2-Microglobulin at Low pH
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Abstract:	Misfolding and amyloid aggregation of human β2-microglobulin (β2m) have been linked to dialysis-related amyloidosis. Previous studies have shown that in the presence of different salt concentrations and at pH 2.5, β2m assembles into aggregates with distinct morphologies. However, the structural and mechanistic details of the aggregation of β2m, giving rise to different morphologies, are poorly understood. In this work, we have extensively characterized the salt-induced oligomers of the acid-unfolded state of β2m using an array of biophysical tools including steady-state and time-resolved fluorescence, circular dichroism, dynamic light scattering, and atomic force microscopy imaging. Fluorescence studies using the oligomer-sensitive molecular rotor, 4-(dicyanovinyl)-julolidine, in conjunction with the light scattering and cross-linking assay indicated that at low salt (NaCl) concentrations β2m exists as a disordered monomer, capable of transforming into ordered amyloid. In the presence of higher concentrations of salt, β2m aggregates into a larger oligomeric species that does not appear to transform into amyloid fibrils. Site-specific fluorescence experiments using single Trp variants of β2m revealed that the middle region of the protein is incorporated into these oligomers, whereas the C-terminal segment is highly exposed to bulk water. Additionally, stopped-flow kinetic experiments indicated that the formation of hydrophobic core and oligomerization occur concomitantly. Our results revealed the distinct pathways by which β2m assembles into oligomers and fibrils.
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