Title:	Hofmeister Ions Modulate the Autocatalytic Amyloidogenesis of an Intrinsically Disordered Functional Amyloid Domain via Unusual Biphasic Kinetics
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Abstract:	Hofmeister ions are thought to play fundamentally important roles in protein solubility, folding, stability, and function. Salt ions profoundly influence the course of protein misfolding, aggregation, and amyloid formation associated with devastating human diseases. However, the molecular origin of the salt-effect in protein aggregation remains elusive. Here, we report an unusual biphasic amyloidogenesis of a pH-responsive, intrinsically disordered, oligopeptide repeat domain of a melanosomal protein, Pmel17, that regulates the amyloid-assisted melanin synthesis in mammals via functional amyloid formation. We demonstrate that a symphony of molecular events involving charge-peptide interactions and hydration, in conjunction with secondary phenomena, critically governs the course of this biphasic amyloid assembly. We show that at mildly acidic pH, typical of melanosomes, highly amyloidogenic oligomeric units assemble into metastable, dendritic, fractal networks following the forward Hofmeister series. However, the subsequent condensation of fractal networks via conformational maturation into amyloid fibrils follows an inverse Hofmeister series due to fragmentation events coupled with secondary nucleation processes. Our results indicate that ions exert a strong influence on the aggregation kinetics as well as on the nanoscale morphology and also modulate the autocatalytic amplification processes during amyloid assembly via an intriguing dual Hofmeister effect. This unique interplay of molecular drivers will be of prime importance in delineating the aggregation pathways of a multitude of intrinsically disordered proteins involved in physiology and disease.
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