Title:	Intermolecular Charge-Transfer Modulates Liquid-Liquid Phase Separation and Liquid-to-Solid Maturation of an Intrinsically Disordered pH-Responsive Domain
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Abstract:	Liquid–liquid phase separation of intrinsically disordered proteins into mesoscopic, dynamic, liquid-like supramolecular condensates is thought to govern critical cellular functions. These condensates can mature from a functional liquid-like state to a pathological gel-like or solid-like state. Here, we present a unique case to demonstrate that an unusual cascade of intermolecular charge-transfer coupled with a multitude of transient noncovalent interactions and conformational fluctuations can promote liquid phase condensation of a pH-responsive, intrinsically disordered, oligopeptide repeat domain of a melanosomal protein. At neutral cytosolic pH, the repeat domain forms highly dynamic, mesoscopic, permeable, liquid-like droplets possessing rapid internal diffusion and torsional fluctuations. These liquid condensates mature via pervasive intermolecular charge-transfer and persistent backbone interactions driving the liquid-to-solid phase transition into heterogeneous solid-like aggregates that are structurally and morphologically distinct from typical amyloids formed at mildly acidic melanosomal pH. Our findings reveal the regulatory role of the repeat domain as a specific pH-sensor that critically controls the phase transition and self-assembly processes akin to prion-like low-complexity domains modulating intracellular phase separation.
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