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Title:	Spatiotemporal modulations in heterotypic condensates of prion and α -synuclein control phase transitions and amyloid conversion
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Keywords:	Spatiotemporal modulations heterotypic condensates of prion and α -synuclein control amyloid conversion
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Abstract:	Biomolecular condensation via liquid-liquid phase separation of proteins and nucleic acids is associated with a range of critical cellular functions and neurodegenerative diseases. Here, we demonstrate that complex coacervation of the prion protein and α -synuclein within narrow stoichiometry results in the formation of highly dynamic, reversible, thermo-responsive liquid droplets via domain-specific electrostatic interactions between the positively-charged intrinsically disordered N-terminal segment of prion and the acidic C-terminal tail of α -synuclein. The addition of RNA to these coacervates yields multiphasic, vesicle-like, hollow condensates. Picosecond time-resolved measurements revealed the presence of transient electrostatic nanoclusters that are stable on the nanosecond timescale and can undergo breaking-and-making of interactions on slower timescales giving rise to a liquid-like behavior in the mesoscopic regime. The liquid-to-solid transition drives a rapid conversion of complex coacervates into heterotypic amyloids. Our results suggest that synergistic prion- α -synuclein interactions within condensates provide mechanistic underpinnings of their physiological role and overlapping neuropathological features
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