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Title:	Aberrant phase transitions of a pathological Stop codon mutant of the prion protein
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Keywords:	Aberrant phase transitions pathological Stop codon prion protein
Issue Date:	2022
Publisher:	Elsevier
Citation:	Biophysical Journal, 121(3), 473a.
Abstract:	Liquid-liquid phase separation (LLPS) of intrinsically disordered proteins/regions (IDPs/IDRs) into intracellular biomolecular condensates is involved in critical cellular functions. However, aberrant phase transitions are associated with debilitating neurodegenerative diseases. We show that the prion protein (PrP) can undergo LLPS via weak, multivalent, transient intermolecular interactions between the N-terminal IDR that resembles a yeast prion-like domain comprising five glycine-rich octapeptide repeats and a hydrophobic segment. An intriguing disease-associated amber stop codon mutation (Y145Stop) yields a C-terminally truncated intrinsically disordered fragment that is associated with Gerstmann-Sträussler-Scheinker syndrome and familial cerebral amyloid angiopathy. We demonstrate that Y145Stop spontaneously phase-separates into highly dynamic liquid droplets under physiological conditions. Our bioinformatic, spectroscopic, microscopic, and mutational studies coupled with single-droplet vibrational Raman spectroscopy revealed highly dynamic internal organization within condensates and illuminated the critical molecular drivers of LLPS of Y145Stop. We also show that Y145Stop exhibits a reentrant phase behavior in the presence of RNA. Upon aging, these highly dynamic liquid droplets undergo a liquid-to-solid phase transition into highly ordered, beta-rich, amyloid aggregates that exhibit a characteristic autocatalytic self-templating behavior. Therefore, LLPS-mediated amyloid formation can potentially represent a noncanonical phase transition pathway to self-replicating prions. The propensity for this aberrant phase transition is much lower for the full-length PrP indicating an evolutionarily conserved role of the folded C-terminal domain. I will also discuss our recent results on spatiotemporal modulation in complex coacervation of PrP into multicomponent, multiphasic, hollow condensates. These multicomponent condensates can act as reaction crucibles to catalyze the amyloid conversion of these functional assemblies into pathological aggregates associated with overlapping neuropathological features.
Description:	Only IISERM authors are available in the record
URI:	<a href="https://doi.org/10.1016/j.bpj.2021.11.420">https://doi.org/10.1016/j.bpj.2021.11.420</a> ( <a href="https://doi.org/10.1016/j.bpj.2021.11.420">https://doi.org/10.1016/j.bpj.2021.11.420</a> ) <a href="http://hdl.handle.net/123456789/4793">http://hdl.handle.net/123456789/4793</a> ( <a href="http://hdl.handle.net/123456789/4793">http://hdl.handle.net/123456789/4793</a> )
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