Title:	Liquid–liquid phase separation of tau: From molecular biophysics to physiology and disease
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Abstract:	Biomolecular condensation via liquid–liquid phase separation (LLPS) of intrinsically disordered proteins/regions (IDPs/IDRs), with and without nucleic acids, has drawn widespread interest due to the rapidly unfolding role of phase-separated condensates in a diverse range of cellular functions and human diseases. Biomolecular condensates form via transient and multivalent intermolecular forces that sequester proteins and nucleic acids into liquid-like membrane-less compartments. However, aberrant phase transitions into gel-like or solid-like aggregates might play an important role in neurodegenerative and other diseases. Tau, a microtubule-associated neuronal IDP, is involved in microtubule stabilization, regulates axonal outgrowth and transport in neurons. A growing body of evidence indicates that tau can accomplish some of its cellular activities via LLPS. However, liquid-to-solid transition resulting in the abnormal aggregation of tau is associated with neurodegenerative diseases. The physical chemistry of tau is crucial for governing its propensity for biomolecular condensation which is governed by various intermolecular and intramolecular interactions leading to simple one-component and complex multi-component condensates. In this review, we aim at capturing the current scientific state in unveiling the intriguing molecular mechanism of phase separation of tau. We particularly focus on the amalgamation of existing and emerging biophysical tools that offer unique spatiotemporal resolutions on a wide range of length- and time-scales. We also discuss the link between quantitative biophysical measurements and novel biological insights into biomolecular condensation of tau. We believe that this account will provide a broad and multidisciplinary view of phase separation of tau and its association with physiology and disease.
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