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Sequence-specific random-phase-approximation theory for polyampholytic intrinsically disordered proteins in liquid-liquid phase separation

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Intrinsically disordered proteins (IDPs) are proteins lacking hydrophobic but are enriched in polar, charged, and aromatic amino acids. IDPs do not fold into a unique structure in isolation and often remain disordered in performing biological function. Recently, some IDPs have been discovered to undergo reversible liquid-liquid phase separation (LLPS) in aqueous solution, forming membraneless organelles of condensed IDPs or mixtures of IDPs with other proteins and/or nucleic acids in the cell. Without a membrane, these organelles can rapidly respond to environmental stimuli, thus playing critical roles in many biological functions. Charge sequence pattern has been identified as one of the most important determining factor for the propensity of an IDP to undergo LLPS. To understand this sequence-specific phenomenon, we develop a random-phase-approximation (RPA) theory for phase separation of polyampholytic IDPs. We have applied our theory to the disordered N-terminus region of RNA helicase Ddx4 proteins, an IDP enriched in charged and aromatic amino acids. Our theory predicts that Ddx4 phase behavior is significantly influenced by its charged sequence and pi-electron interactions driven by aromatic rings, consistent with experiments on wild-type, a charge-scrambled mutant, and a mutant with reduced aromaticity of Ddx4. We then investigated 30 model sequences that are different permutations of an equal number of positively and negatively charged residues. We demonstrated a strong correlation between phase separation and single-chain compactness of IDPs. We have also researched salt-free ternary aqueous solutions including two different IDP species. Depending on the similarity/dissimilarity in charge pattern between the two IDP sequences, they can either coalesce or exclude each other when forming LLPS. Such sequence-sensitive phase behavior indicates a possible "fuzzy" mechanism for molecular recognition between IDPs. Our theory can be applied to arbitrary charged biopolymers as a general framework for studying sequence-dependent biological phase separation.

Primary authors: Dr LIN, Yi-Hsuan (University of Toronto); Dr FORMAN-KAY, Julie D. (Hospital for Sick Children); Dr CHAN, Hue Sun (University of Toronto)

Presenter: Dr LIN, Yi-Hsuan (University of Toronto)

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