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Nucleotides modulate RNA-driven phase separation of CIRBP

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Background: Intrinsically disordered regions (IDRs) promote formation of protein condensates via liquid-liquid phase separation (LLPS). It could further develop into aggregations under pathological conditions. Within a cell, proteins with IDRs are exposed to high concentration of metabolites, which could be up to millimolar range and form an environment diverged from buffer used in biochemical studies. This rendered difficult to predict the behavior of IDRs in cell from purified proteins.

Aims: We used cold inducible RNA binding protein (CIRBP), containing an arginine glycine/arginine glycine glycine (RG/RGG)-rich region, as a paradigm to investigate in detail of the interaction between condensate-forming IDRs and cellular metabolites. In the meanwhile, we aimed to characterize the dynamics of interactions within a protein condensate.

Method: We used solution nuclear magnetic resonance (NMR) spectroscopy to characterize titrations of purified CIRBP in its full length or individual regions by various metabolites. In addition, we performed molecular dynamic (MD) simulations to study the condensate driven by RG/RGG regions.

Results: We found that CIRBP forms direct interactions with nucleotides and dinucleotides, including ATP, ADP, and AMP as well as NAD+, NADH, NADP+, and NADPH. These interactions are through the RNA recognition motif (RRM) and the disordered RG/RGG region, with the latter modulates RNA-driven CIRBP phase separation. From MD simulation, we observed that aromatic cycles can effectively prolong the time of peptide intra- and interchain contact formed between amino acid side chains.

Conclusion: Given that proteins harboring RG/RGG regions are highly abundant in the human proteome, their phase separation in the cellular environment could be commonly modulated by (di)nucleotides. This could be an important factor regulating the development of cancers or neurodegenerative diseases.