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Perspective

A Comprehensive Study on Dehydration in Cell Environments

Vundano Fliti*

Department of Biochemistry, University of Tuebingen, Tuebingen, Germany

DESCRIPTION

Intrinsically disordered proteins rich in cationic amino acid groups can undergo Liquid-Liquid Phase Separation (LLPS) in the presence of charge-balancing anionic counterparts. The two most prevalent cationic amino acids found in LLPS proteins are arginine and lysine. Proteins rich in arginine undergo LLPS more quickly than proteins rich in lysine; this difference is often ascribed to arginine's capacity to create stronger cation connections with aromatic groups. They demonstrate that the promotion of LLPS by arginine is not dependent on the presence of aromatic partners and that argininerich peptides, but not lysine-rich peptides, display re-entrant phase behavior at high salt concentrations. Additionally, they demonstrate that the tunable viscoelastic characteristics and reentrant phase behavior of the dense LLPS phase are determined by the hydrophobicity of arginine.

Bioengineering stress-triggered biological phenomena and drug delivery systems becomes possible when temperature and salt concentration are used to control the behavior of arginine-induced reentrant LLPS. One of the main organizing principles of bimolecular condensates, which separate certain metabolites in the absence of a biological barrier, is liquid-liquid phase separation. In this phenomena, macromolecules separate into two immiscible liquid phases: The supernatant phase, which is diluted and depleted of macromolecules, and the coacervate phase, which is dense and rich in macromolecules. The most fundamental type of LLPS is simple or complicated coacervation powered by electrostatic interactions. This LLPS is readily realized in polyampholyte and polyelectrolyte systems.

LLPS is triggered by a variety of other alluring interactions, including cation interactions, hydrophobic interactions, hydrogen bonding, and van der Waals interactions, in addition to electrostatic cation/anion interactions, which are found in naturally occurring proteins, which have more complex sequences. While both globular and Intrinsically Disordered Proteins (IDPs) have the ability to form LLPS, most biological LLPS are attributed to IDPs. Charged, aromatic, and polar amino acids are commonly found in higher concentrations in IDPs, and the possibility of multivalent interactions is heightened by their structural flexibility. The physical characteristics of the dense coacervate phase, including diffusivity, interfacial tension, density, viscoelasticity, and exchange dynamics, are influenced by the amino acid content of IDPs.

For bioengineering uses like mRNA vaccines and protein-based medication delivery agents, these LLPS characteristics are essential. Understanding the way the content of amino acids affects the pertinent physical features of the coacervate phase is therefore potential. Arginine-rich peptides, or proteins, are an important family of biomolecules with applications ranging from gene carriers to medicine and even adhesive molecules because of their cationic nature, nucleic acid binding capacity, cell-penetrating capabilities, and biocompatibility. These proteins are among the most intriguing candidates for delivery platform development because they may undergo LLPS and the resultant protein droplets have regulated cargo recruitment and release capabilities in response to external signals.

Compared to other cationic amino acids with the same charge, such lysine, arginine is a far more potent inducer of LLPS, suggesting that electrostatic interactions may not entirely explain the LLPS proclivity of cationic polymers. Poly-lysine and protamine, an arginine-rich, clinically relevant, highly biocompatible, injectable biomolecule used in heart surgery to offset the anticoagulant effects of heparin, were the two cationic-rich systems that they investigated that might be treated to LLPS. Protamine and polylysine both conduct LLPS at low salt concentrations, but only protamine displays temperature and salt-dependent reentrant phase behavior. Additionally, they show that the protamine and poly-lysine coacervate phases have different viscoelastic physical properties.

Dehydration conditions similar to those represented in this study can be simulated by high concentrations of multi-charged metabolites observed under cellular settings or molecular chowders. Given the abundance of multi-charged metabolites and the fact that their levels are altered by cellular conditions, such as stress and cell division, the high concentration of salt and the reentrant phase behavior observed in this study are expected to account for cellular protein phase separation under cellular conditions with enhanced hydrophobic interactions.

Correspondence to: Vundano Fliti, Department of Biochemistry, University of Tuebingen, Tuebingen, Germany, E-mail: vundanofliti@tue.de

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