Representative membraneless chambers in eukaryotic cells. Present in the nucleus are mainly gems, Cajal body, PML body, nuclear speckles, PcG body, amyloid bodies, and gems. Membraneless compartments, including emergency granules, are located outside the nucleus. Credit: MedComm (2024). DOI: 10.1002/mco2.640

A recent study, led by Professor Wu (Wenzhou Institute University,
Wenzhou Medical University) and Professor Huang (Northeastern University), explores liquid–liquid phase separation (LLPS), a phenomenon closely associated with various diseases, including cancer and neurodegenerative disorders. The research is published in the journal *MedComm*.

As a frontier research area, LLPS plays a significant role in cancer through its regulation of multiple facets, including signaling pathways, gene expression, and tumor microenvironment. Dysregulation of LLPS leads to the formation of various aggregates, such as amyloid proteins, suggesting that modulating LLPS in pathogenic proteins could present a promising direction for treating neurodegenerative diseases and cancer.

LLPS refers to the spontaneous formation of highly concentrated, segregated liquid-phase regions within cells through interactions between specific biomacromolecules (e.g., proteins and RNA). A notable characteristic of this mechanism is the formation of membraneless organelles, which achieve functional compartmentalization and local concentration without membrane structures. RNA-RNA and RNA-protein interactions play critical roles in LLPS, with scaffolding proteins supporting protein-RNA interaction networks to form condensates involved in various diseases through multivalent interactions and external factors.

The authors unveil the enigmatic role of LLPS in various signaling pathways, including cGAS–STING, Wnt/β-Catenin, and RAS/MAPK, by discussing its role in immune cell maturation and activation, immune signal transduction, and immunomodulation. The paper also introduces RNA modifications, which have emerged as crucial regulatory factors for transcript expression, molecular function, and homeostasis. These modifications participate in diverse signaling pathways, with multiple proteins regulating disease progression. The article enumerates the roles and manifestations of LLPS in various modifications, including m⁶A and
m⁷G.

In conclusion, this comprehensive review provides a detailed summary of LLPS complexity in constructing signaling pathways, emphasizing its role in neurodegenerative diseases and cancer. It explores how RNA modifications influence LLPS to alter disease progression and discusses the possibility of manipulating LLPS processes to restore cellular homeostasis or develop therapeutic drugs.

By elucidating the connections between LLPS, RNA modifications, and their roles in diseases, this review aims to highlight potential therapeutic opportunities in this emerging field.


Provided by Sichuan International Medical Exchange and Promotion Association


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