Network of protein-RNA interaction guides phase separation

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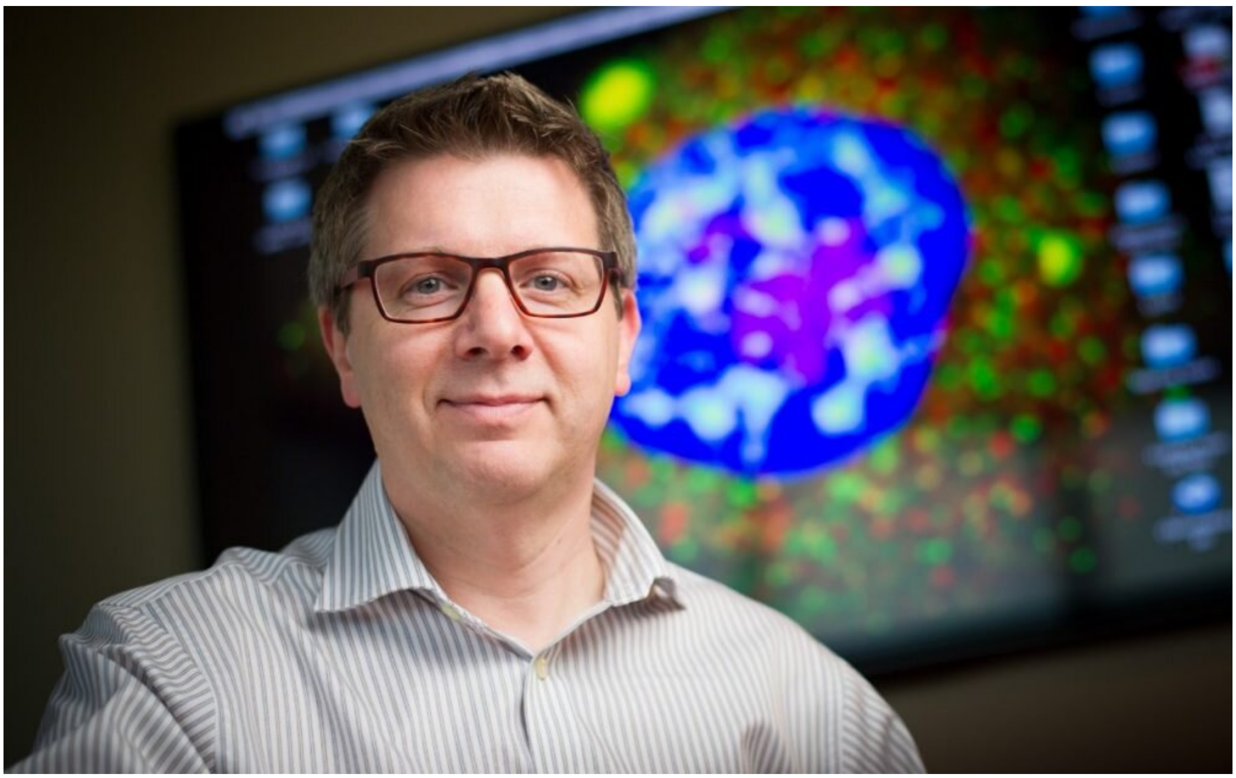

Senior author J. Paul Taylor, M.D., Ph.D., chair of the Department of Cell and Molecular Biology at St. Jude, discovered how central nodes in a network of protein-RNA interactions drive phase separation for RNA granules. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital investigators are studying the details of how phase separation leads to the formation of RNA granules, assemblies of protein and RNA that are not bound by a membrane. Their findings show that central nodes in a network of protein-RNA interactions drive phase separation for RNA granules, or condensates, called stress granules. The work appears today in *Cell*.

Like a droplet of oil in water, phase separation brings together proteins and RNA in the cytoplasm of a cell. This process is highly regulated and specific, thus allowing condensates to carry out certain essential functions. Stress granules studied in the laboratory are comparable to RNA granules in human neurons that are impaired in neurodegenerative diseases such as amyotrophic lateral sclerosis, also called Lou Gehrig's disease.

"We found that all of the constituent components of the RNA granule contribute to condensation, but they don't contribute equally," said senior author J. Paul Taylor, M.D., Ph.D., St. Jude Department of Cell and Molecular Biology chair and Howard Hughes Medical Institute Investigator. "Within the network of interactions most proteins matter very little, a few are important, and one is essential. That one essential protein undergoes phase separation with RNA, which is key to establishing and maintaining the identity of a specific class of RNA granule."

A fundamental biological process

By studying the interactions among protein nodes in the stress granule network, the researchers determined how each protein contributes. Their findings show that the most important nodes in the network drive phase separation. In the absence of the central node, the condensate doesn't form at all. For stress granules, the central node is a protein called G3BP1.

"Each kind of condensate seems to have core scaffolding elements that are essential to phase separation," said co-first author Peiguo Yang, Ph.D., of the St. Jude Department of Cell and Molecular Biology. "The core central nodes are the ones that define when and where condensation is going to take place."

Fine-tuned control

That biomolecular condensation is driven by a network of interactions, with a small number of vital nodes, is likely a general principle that underlies biomolecular condensation. In turn, the vital nodes provide a way for the cell to exert external control over biomolecular condensation. These targets can be exploited for therapeutic intervention. For stress granules, this control is exerted through the protein G3BP1.

Intrinsically disordered segments within G3BP1 provide fine control over biomolecular condensation. Intrinsically disordered proteins are notable for their lack of structure. The interplay between three distinct intrinsically disordered regions in the G3BP1 protein is critical to its ability to phase separate. In stress granules, phase separation is thus driven by G3BP1 and fine-tuned by complex interplay between the intrinsically disordered regions.

"The relationship between G3BP1 and its RNA binding partners is like the knob on a radio tuning to the right station," said co-first author Cecile Mathieu, Ph.D., of the St. Jude Department of Cell and Molecular Biology. "The process is tightly controlled to enable phase separation in the right way, at the right time."

Other authors of the paper include Regina Kolaitis, Peipei Zhang, James Messing, Ugur Yurtsever, Zemin Yang, Jinjun Wu, Qingfei Pan, Jiyang Yu, Erik Martin, Tanja Mittag and Hong Joo Kim, all of St. Jude.

This work is part of the St. Jude Research Collaborative on Membraneless Organelles. Through the collaborative, investigators from separate laboratories work together to conduct research that requires the expertise of different teams, streamlining and speeding up progress in this field.

More information: Peiguo Yang et al. G3BP1 Is a Tunable Switch that Triggers Phase Separation to Assemble Stress Granules, *Cell* (2020). [DOI: 10.1016/j.cell.2020.03.046](https://doi.org/10.1016/j.cell.2020.03.046)

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