Simple physical mechanism for assembly and disassembly of structures inside cells

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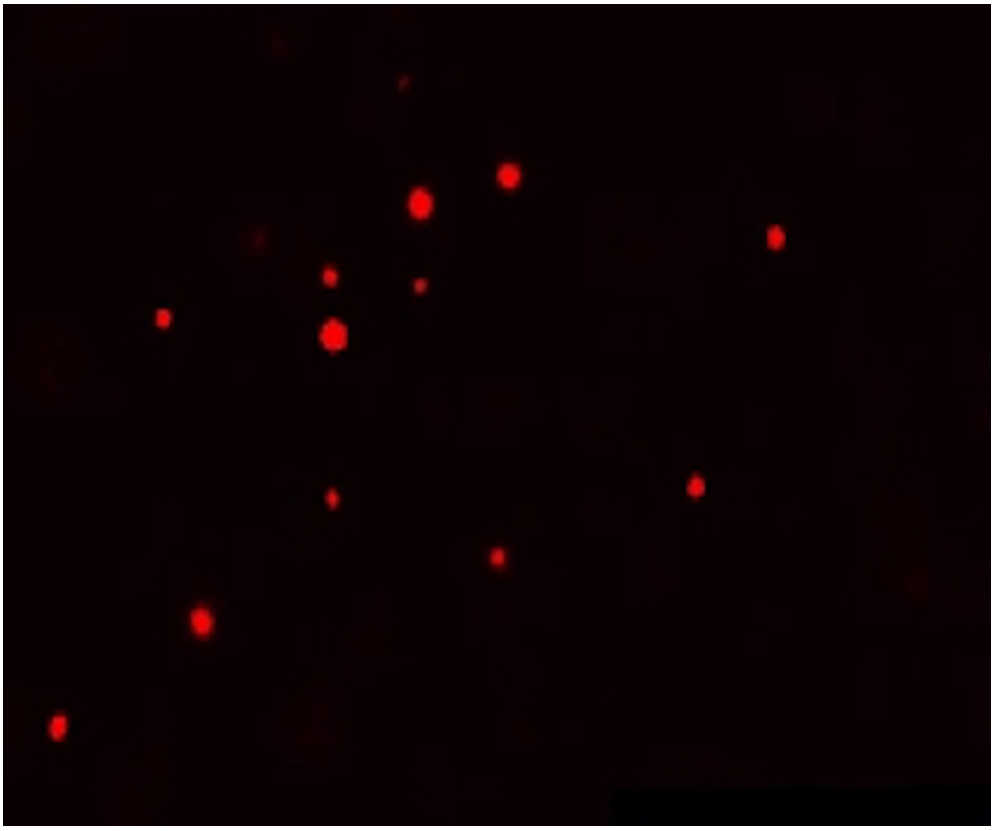

Synthetic "liquid organelles." Fluorescently labeled, positively-charged peptides (red) are attracted to negatively-charged RNAs (invisible in this image) forming droplets that simulate cellular structures called liquid organelles. Credit: Penn State University

For the first time, scientists have demonstrated a simple charge-based mechanism for regulating the formation and dissolution of liquid-like

structures that lack outer membranes inside cells. The research provides a first step in deciphering how these poorly-understood structures function in the cell and how they may have evolved. The research, conducted by Penn State University scientists, will appear December 14, 2015, as an advance online publication of the journal, *Nature Chemistry*.

"Cells contain many of these liquid-like structures that are in some ways conceptually similar to droplets of oil in water," said Christine Keating, professor of chemistry at Penn State University. "The structures, which we call liquid organelles, often appear and disappear inside cells. We were able to replicate this process in a biologically-reasonable way in the lab by controlling the electrostatic charge of the molecules that form our synthetic liquid organelles. We used tools that the cell itself might use, giving us the first clues about how the process may occur in nature."

"The assumption is that these liquid organelles compartmentalize molecules like RNAs and proteins in order to speed up reactions inside cells," said William Aumiller, a graduate student at Penn State at the time the research was conducted. "This field is very new and there are likely many different mechanisms by which liquid organelles form in cells, so exploring fundamental questions like 'what are the minimum requirements to make these structures come and go as they do in the cell' is very important."

The researchers created synthetic liquid organelles by combining, in a solution, negatively-charged RNA molecules with positively-charged short peptides—chains of amino acids similar to, but smaller than, proteins. Because the two molecules have opposite charges, the RNAs and peptides are attracted to one another and self-assemble into droplets that simulate liquid organelles.

The researchers then adjusted the charge of the peptide molecules in the synthetic liquid organelles by using common enzymes—proteins that

catalyze specific reactions in a cell. They used one type of enzyme, called a kinase, to add phosphate groups—negatively-charged chemical components—to the peptides to neutralize their positive charge. Neutralizing the peptides in this manner caused the synthetic liquid organelles to break apart. The scientists then reversed this process and the synthetic liquid organelles reformed by adding another type of enzyme, called a phosphatase, which removed the phosphate group from the peptides, reestablishing their positive charge.

"All sorts of reactions in cells are controlled by modifying proteins with kinases and phosphatases," said Keating. "As chemists, we were thinking about the most basic mechanisms that could be involved in the formation of these liquid organelles, and it's reasonable to think that this is one mechanism that cells might use. Now, we can use our new system to study these liquid-like structures and how they may have evolved."

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