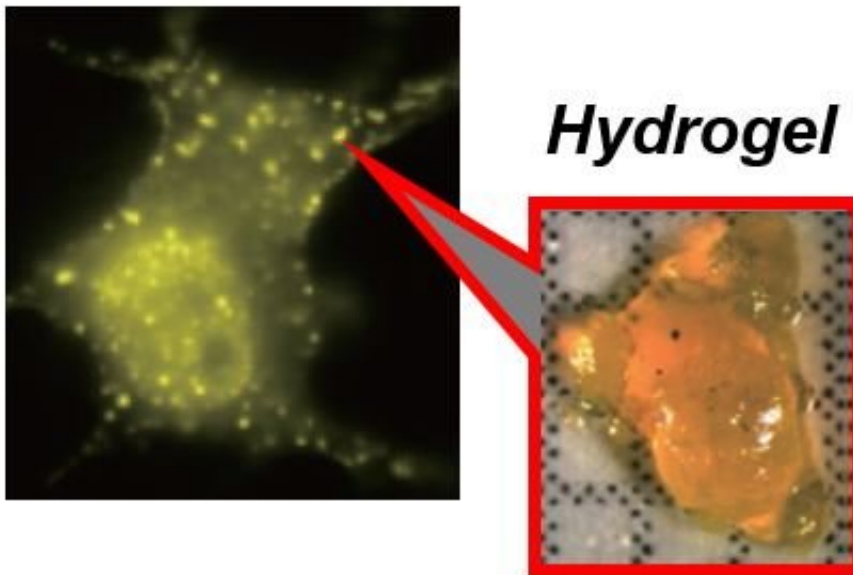


Researchers report first-ever protein hydrogels made in living cells

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Hydrogels inside a cell. Credit: Takanari Inoue, Ph.D., and Hideki Nakamura, Ph.D

Johns Hopkins cell biologists report what they believe is the first-ever creation of tiny protein-based gelatin-like clumps called hydrogels inside living cells. The ability to create hydrogels on demand, they say, should advance the long scientific struggle to study the elusive structures—which form in nature when proteins or other molecules aggregate under certain conditions—and to uncover their suspected contributions to human diseases.

"The exciting part of this work is not just that we made hydrogels, but that we're now equipped with this powerful technique that lets us ask fundamental—and very challenging—questions about them," says Takanari Inoue, Ph.D., an associate professor of cell biology at the Johns Hopkins University School of Medicine and senior author of the report on the research published online Nov. 6 in the journal *Nature Materials*.

A hydrogel is any solid gel material that holds together because of tight connections among its molecules but also absorbs lots of water. Man-made hydrogels are used in such everyday products as contact lenses, disposable diapers and hair gels, which exploit their water-loving nature.

In living cells, most floating structures are enclosed by membranes that help them retain their shape in the cells' watery cytoplasm. But when cells undergo stress—anything from heat to starvation or infection—proteins and ribonucleic acid (RNA) molecules can clump into stress granules, which are free of enclosing membranes and often form small globs akin to hair gel suspended in a tub of water.

Some researchers have hypothesized that the accumulation of these natural hydrogels may be linked to neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), and that too many or too few stress granules could impact cells' ability to function. But finding evidence has been difficult, in part because other kinds of hydrogels inside cells may be normal parts of cell physiology.

"These hydrogels lack membranes, so it's hard to isolate and purify them," says Inoue. "They're so fragile that we can't just collect them like we can with nuclei or mitochondria," he adds. Even worse, he says, when their surroundings change, stress granules switch from being hydrogels to a different type of structure, called liquid droplets, the same way hair gel might dissolve in water if you heat it up. Scientists worldwide have tried to inject chemical hydrogels into living cells to study them, but

usually the cells become sick, likely due to toxicity from the chemicals.

In a bid to overcome such barriers to study, Inoue's team designed a system they dubbed iPOLYMER, composed of two binding proteins, FKBP and FRB, and an immunosuppressive chemical and drug called rapamycin. Researchers already knew that rapamycin could be used to mediate interactions between FKBP and FRB.

Previous studies had shown that without rapamycin present, FKBP and FRB exist as separate proteins, but once rapamycin is added, it binds to both, pulling the proteins together into a firm complex. Designing the proteins so that they'd form the right physical structure for hydrogels took lots of trial and error, says Inoue.

To create iPOLYMER in living cells, the researchers engineered cells to contain two kinds of [protein](#) strings composed of tandem FKBP and FRBs, and then added rapamycin, which isn't usually found in [living cells](#). By watching these cells under a microscope as they added rapamycin, Inoue's team could see hydrogels form.

"To our knowledge, this is the first time anyone has made a hydrogel in a living cell this way," says Inoue.

The scientists are now modifying the iPOLYMER system so that the hydrogels integrate RNA molecules into their structures, making them better mimics of the stress granules seen in human [cells](#). The scientists would also like to create a system in which the proteins, FKBP and FRB, form liquid droplets so that they can compare the effects of the liquid droplet and [hydrogel](#) forms of the protein structures.

More information: Intracellular production of hydrogels and synthetic RNA granules by multivalent molecular interactions, *Nature Materials* (2017). [nature.com/articles/doi:10.1038/nmat5006](https://doi.org/10.1038/nmat5006)

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