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BIOMOLECULAR CONDENSATES

The Secret Life of the Protein VASP

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Biomolecular condensates compartmentalize and concentrate cellular components without the delimitation of a lipid membrane. The protein VASP is now shown to condense, resulting in the reorganization of actin, a key component of the cell cytoskeleton.

Membraneless biomolecular condensates form in cells via liquid-liquid phase separation. They are key to carrying out diverse cellular functions ¹, and the roster of proteins and molecules reported to form condensates is growing rapidly. Now writing in *Nature Physics* Kristin Graham and coworkers add the actin-binding protein VASP to the list ². They showed that VASP formed liquid-like droplets above a certain concentration in the presence of a crowding agent that mimicked conditions in the cell cytoplasm. VASP condensates polymerized and bundled actin, and the interplay between polymerization, bundling and droplet deformation produced different actin structures. Such mechanisms are presumably operational in the cell and may be relevant to its biology.

Actin filaments are part of the cell cytoskeleton and contribute to condensate dynamics — either keeping condensates from fusing ³ or enhancing fusion ⁴. Furthermore, although actin does not condense on its own, it is known to partition spontaneously into certain types of condensates in a non-specific manner based on charged or hydrophobic interactions ^{5,6}. In the work by Graham and colleagues, on the other hand, actin was recruited specifically to the condensate by the condensing molecule itself — the VASP protein — and this created interesting actin dynamics in the droplet interior.

VASP has been extensively characterized, in particular the molecular mechanisms of its interaction with actin and how that affects actin assembly and structure. It comes therefore somewhat as a surprise that this stolid actin-binding protein should turn out to be leading a double life as a biomolecular condensate. In retrospect it is remarkable that this was not discovered sooner since VASP is a multimeric protein with disordered domains rich in the amino acid proline — features that are known to promote protein-protein associations and therefore liquid-liquid phase separation.

Graham and coworkers found that VASP droplets recruited actin monomers to the droplet interior, where filaments formed. As the filaments lengthened, they localized to the border of the droplet to minimize their curvature. The filaments zippered together — presumably because of VASP's actin-bundling activity — transforming homogenous 3D shells into 2D rings. The rings thickened until their rigidity overcame the surface tension of the droplet and they deformed into discs and then finally collapsed into bundled linear actin structures. To

summarize, VASP droplets acted as actin bundle generators via an interplay between filament bundle rigidity, finite surface energy of the droplet and the liquid droplet interior.

The observations made by Graham and coworkers raise the question as to whether other actin-binding proteins form condensates. Many actin-binding proteins contain domains rich in proline, an amino acid that is highly predictive of disordered domains ⁷, which are a feature of biomolecular condensates. Indeed, one example of a proline-rich, actin-binding protein undergoing liquid-liquid phase separation is plant formin, the condensates of which are important for actin assembly during gamete fusion in yeast ⁸. The cell cortex actin-binding protein abLIM also condenses to ensure its function of increasing the mechanical resistance of the cell cortex ⁹. Although not forming condensates on their own, other actin-binding proteins, such as the scaffolding protein IRSp53 and the nucleation promoting factor N-WASP, have been reported to form condensates in association with effector molecules ^{10,11}.

Overall, the study by Graham and coworkers shows that sources of biomolecular condensates can be hiding in plain sight. Actin remodeling produced by the interplay of actin filament flexibility and condensate fluid forces may be relevant to other condensates formed by actin-binding proteins.

The author declares no competing interests.

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Caption: Actin monomers (red circles) are recruited to VASP condensates (green droplets, darker green circles indicate individual VASP molecules, but these molecules are the same as what makes up the green droplet). Actin filaments form (red rods) and VASP interacts with filament ends and sides. Filaments segregate to the droplet border to reduce curvature once they are longer than the droplet diameter. Filaments coalesce via VASP bundling activity to form rings, and further growth and thickening of rings ultimately results in VASP droplet deformation by actin bundles.