Docket #: S19-543

PopTag: A modular platform for engineering function of natural and synthetic biomolecular condensates

Researchers at Stanford have developed a protein, PopTag, that drives phase separation when it is part of a chimeric fusion protein.

Biomolecular condensation is a powerful mechanism underlying cellular organization and regulation in cell physiology and disease. Biomolecular condensates can adopt a broad spectrum of material properties, from highly dynamic liquids to semi-fluid gels and solid amyloid aggregates. Perturbing protein condensation and other pathological phase transitions have been implicated in human disease, indicating that the material properties of a biomolecular condensate may be important for its function.

Stage of Research
The inventors have created PopTag, a modular and functionalizable platform for designer condensates with tunable material properties. PopTag, a C-terminal protein tag of only 76 amino acids, is derived from the intrinsically disordered protein PopZ, which forms membraneless condensates in the bacterium Caulobacter crescentus. The inventors generated rationally designed PopZ mutants to codify a robust set of design principles used to repurpose PopZ as a modular platform for generating synthetic condensates of tunable function in prokaryotic and eukaryotic cells. Moreover, they developed EGFP-NanoPop, an N-terminal fusion with an EGFP-targeting nanobody to efficiently sequester EGFP-tagged proteins into cytoplasmic condensates. Together, PopTag provides a flexible platform for the design and manipulation of condensate properties and function.

Applications

- Generation of synthetic phase separated protein droplets in prokaryotic and eukaryotic cells and organisms
- Recombinant protein purification as phase-separated bodies
- Selective protein sequestration for therapeutic benefit or to perturb cellular pathways
- Compartmentalization of biochemical reactions (e.g., TurboID fusions) to optimize yield, specificity, and off-target reactions

Advantages

- Modular and versatile design of chimeric fusions to facilitate various cellular localizations, inducible expression and/or degradation, and biochemical functionalities
- NanoPop, nanobody PopTag fusions, efficiently sequester proteins into cytoplasmic condensates

Publications

- Lasker K, Boeynaems S, Lam V, Stainton E, Jacquemyn M, Daelemans D, Villa E, Holehouse AS, Gilter AD, Shapiro L. A modular platform for engineering function of natural and synthetic biomolecular condensates. bioRxiv. 2021.

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