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Bioengineering with synthetic biomolecular condensates

Leveraging the underlying mechanism of phase-separating biomolecular condensates could prove a great asset for developing designer condensates in bioengineering applications.

Biomolecular condensates are membraneless compartments that form through phase separation of specific biomolecules. This concept has provided a new framework for understanding intracellular organization and function, as well as a new mode of biomolecular interaction different from the 'lock-and-key' model. Since the first demonstration that P granules undergo liquid–liquid phase separation in *Caenorhabditis elegans*[1], biomolecular condensates have been found to play a role in various cellular functions, including in cell division and adhesion, mRNA processing and transport, transcription and translation regulation, protein degradation, gene silencing, chromatin compaction and genome organization[2]. Importantly, dysregulation of biomolecular condensates (also named 'condensatopathy') has been linked to diseases, such as cancer, viral infections (including SARS-CoV-2), cardiomyopathy and neurodegeneration[2]. Therefore, despite being a young field, synthetic biomolecular condensates are gaining philanthropic interest (2023 Breakthrough Prize in Life Sciences).

Unlike most 'lock-and-key' interactions, biomolecular condensates enable reversible spatiotemporal control of cellular processes by sequestering or excluding molecular components into distinct compartments. Building on this mechanism, synthetic condensates (that is, genetically encoded polymers of short peptide repeats) can be designed to enhance reaction selectivity by partitioning specific biomolecules, accelerate reaction kinetics by enriching biomolecules and/or inhibit functional pathways by exclusion of selected biomolecules, as discussed by Ashutosh Chilkoti and colleagues in this issue. Such designs could prove particularly useful for targeting 'undruggable' molecules, for which no specific or selective ligand has yet been discovered[2].

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Owing to their simplicity and versatility, the sequence, composition and chain length of synthetic condensates can be rationally tuned to achieve specific topologies, chemical selectivity, interfacial properties and selected phase behaviours, more easily than for natural condensates. The ability to spatiotemporally modulate the localization of intracellular molecules could be a great asset for synthetic biologists, as well as for drug delivery, protein purification and soft robotics applications. However, only few studies have reported in vivo applications of synthetic condensates so far.

Interestingly, several approved and established drugs (such as Cisplatin, Tamoxifen and Leptomycin B) have been identified to not only partition into transcriptional condensates themselves, but also function, at least in part, by influencing intracellular biomolecular condensates phase behaviour[2]. Thus, so-called 'condensate-modifying therapeutics' are being increasingly explored, with pharma investing in condensate-focused companies (Bayer invested US $100 million in Dewpoint Therapeutics[3]).

Nonetheless, the dynamic nature of biomolecular condensates greatly complicates their characterization; most structural biology methods and in vitro reconstitution assays are not informative enough, unless accompanied by quantitative biophysical techniques. Therefore, more sophisticated tools are needed to label and modulate condensates non-invasively (such as optogenetic-based techniques), to visualize them in real-time at high resolution and high throughput (using advanced super resolution microscopy), and to probe their materials and partitioning properties in situ. Predictive computational models will prove essential for streamlining and optimizing these efforts. Such advances will hopefully provide the highly sought causation proof of the role of condensates dysfunction in certain diseases, which remains elusive thus far.

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