A Mysterious Cellular Tango

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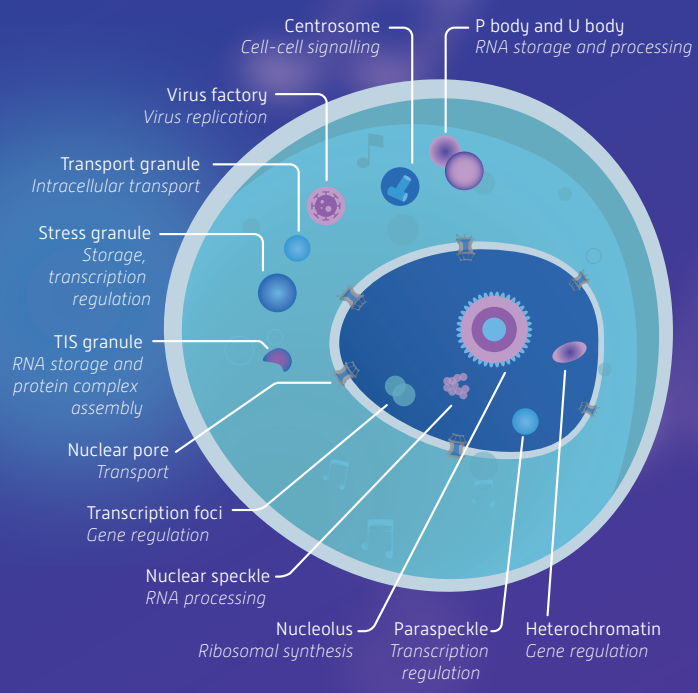
Illustrated by Anthony Lewis

Our understanding of how the cell functions is based on the presumption that most cellular processes occur due to the collective efforts of membrane-bound organelles. Teachers often explain cell regulation by comparing it to a mail delivery system. DNA is the address and name on the envelope. The mail then moves through the "mail carrier," or ribosome. Proteins are like mail, which gets packaged and shipped as it moves through the post office or the endoplasmic reticulum. Packaged proteins can undergo further processing in the Golgi apparatus or move into the cytoplasm to do their job. The rest was considered a defiant, anti-bureaucratic dance performed by floating proteins accidentally waltzing with the correct partner as they glided through the cytoplasm.

Researchers no longer think that proteins blindly swim through the cytoplasm hoping to bump into one another. Instead, they intentionally aggregate with other biomolecules, forming membrane-free, transient organelles called condensates. Scientists don't know how cells regulate this process yet, but condensates appear to be involved in almost every cellular process(1). Now, researchers are considering how therapeutics may interact with condensates to develop effective drugs.

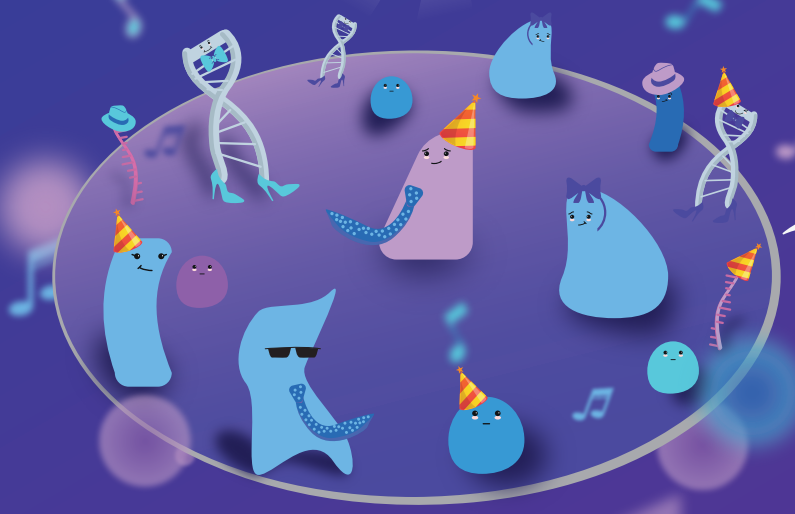
Types of condensates



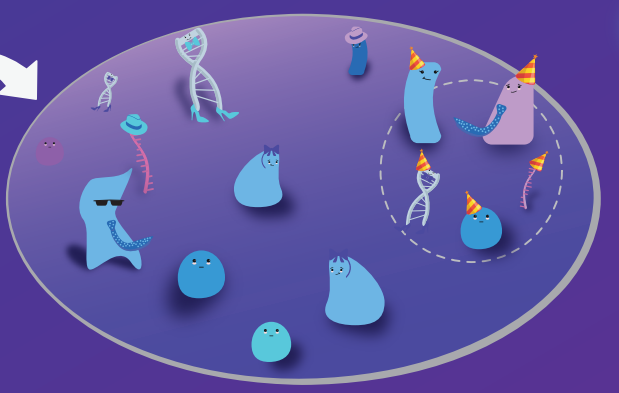
FINDING A DANCE PARTNER

All cellular molecules — RNA, DNA, proteins — seem to form transient, membrane-free condensates. Biomolecular condensates are simply local concentrations of molecules that perform similar jobs. Condensing together allows spatiotemporal control of protein-mediated cellular processes (2).

Biomolecular condensates often form via a process called biological phase separation. The gooey mix of proteins and nucleic acids separate into two phases: dense and dilute. In the dense phase, molecules with a similar job — transcription, translation, or protein turnover — condense, forming the dense phase, while leaving a diluted cytoplasm and unrelated molecules in their wake.

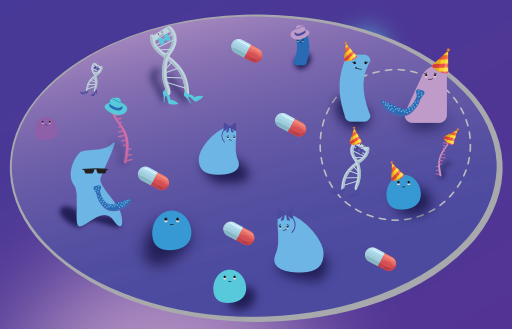


Condensates are transient because biomolecules connect to each other in these structures through Van der Waals interactions where weak, electrical forces attract molecules to one another.

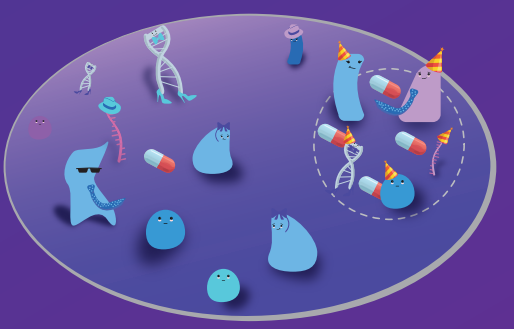


TURN OFF THE MUSIC

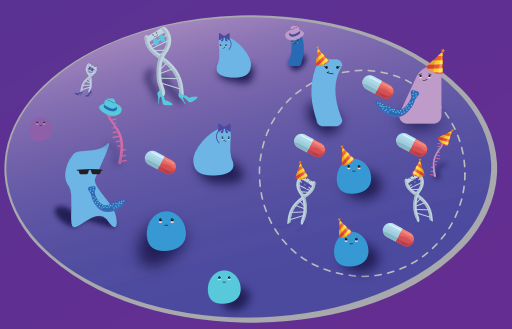
Researchers are trying to figure out how to concentrate drugs into condensates to ensure that the drugs effectively target the intended biological interaction or process. Our understanding of how these strange organelles are regulated is limited, however, so modifying drugs to penetrate condensates is challenging.



Many researchers at new biotech companies focused on understanding and therapeutically targeting proteins in condensates are working to modify new or existing therapeutics for cancer and Alzheimer's disease where condensate function seems to be prevalent (3-4).



Some researchers hypothesize that cancer cells overexpress condensate-promoting proteins, allowing them to produce larger condensates. The drug is more diluted in the condensate, rendering it less effective. Increasing the amount of drug that makes it into these larger condensates could help treat drug-resistant cancers (4).



References
1. Alberti, S. & Hyman, A. Biomolecular condensates at the nexus of cellular stress, protein aggregation disease and ageing. *Nat Rev Mol Cell Biol* **22**, 196-213 (2021).
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