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News & views

Molecular biology

Complex condensations get cells organized

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Liquid-like organelles in cells form when key constituents reach a certain concentration and then condense. Evidence now indicates that the concentration at which condensation occurs can vary, contrary to previous assumptions.

Water transitions from a liquid to a gas phase as it reaches its boiling point. Similarly, proteins in cells can transition from freely mixing in the cytoplasm or its nuclear equivalent, the nucleoplasm, to condensing into a concentrated liquid-drop phase once they reach a threshold concentration[1]. This saturation concentration has been assumed to be an invariant quantity, but, writing in *Nature*, Riback *et al.*[2] demonstrate that this assumption is invalid. Much as the boiling point of water varies depending on pressure, the saturation concentration depends on the concentrations of the proteins involved.

Condensation of molecules into a liquid-like droplet – a process called phase separation – is a well-studied physical phenomenon, which can be caused by mutual attractions between proteins or other molecules. But many biological studies of phase separation so far have used simple model systems, rather than complex living cells. Riback and colleagues reasoned that the idea of a single fixed saturation concentration might have arisen because of the use of simple systems.

In cells, phase separation produces liquid-like organelles called biomolecular condensates[3]. One such condensate is the nucleolus, in which the ribosome machinery involved in protein synthesis is made. Riback *et al.* set out to examine saturation concentration in cells by studying the protein nucleophosmin 1 (NPM1), which is a key driver of nucleolus formation[4,5]. The group found that increasing the overall concentration of NPM1 in cells increased the corresponding saturation concentration at which the nucleolus forms in the nucleoplasm. Likewise, increasing the concentration of key proteins altered the saturation concentration of stress granules – another type of liquid-like organelle.

Next, the authors showed that the variability of saturation concentration is caused by distinct interactions between a condensate's components. Rather than molecules of the same protein interacting during condensation, which might produce a fixed saturation concentration (NPM1 binding to other molecules of NPM1, for instance), the group found that phase separation depends on heterotypic interactions between different proteins in the condensate. As the concentrations of different proteins alter, the free energy of the nucleoplasmic mixture – the thermodynamic quantity that dictates how the components in the cell system are partitioned by phase separation – can change in a complicated manner, leading to changes in saturation concentration.

"The reputation of the nucleolus as the ribosome factory might be even more pertinent than people thought."

Biomolecular condensates are often intricately linked to cell functions[6]. Riback and colleagues went on to show how heterotypic interactions are exploited by nucleoli to facilitate the processing of ribosomal RNA, which makes up part of the ribosome. They found that phase-separating proteins such as NPM1 and another protein, SURF6, interact freely with immature forms of ribosomal RNA, but not as well as with more mature forms of the molecule. This leads to the mature RNA being expelled from the liquid-like nucleolus (Fig. 1). This finding highlights that nucleoli might not only act to concentrate key molecules and facilitate biochemical reactions, but also possess an underlying conveyor-belt mechanism to ensure a continuous and smooth production process. Hence, the reputation of the nucleolus as the ribosome factory might be even more pertinent than people thought[7].

Riback and colleagues complemented each of their experimental findings theoretically, using methodology borrowed from equilibrium physics – the premise that there is no flow of energy into or out of a system. However, the environment of the cell interior, with its many processes driven by energy-carrying ATP

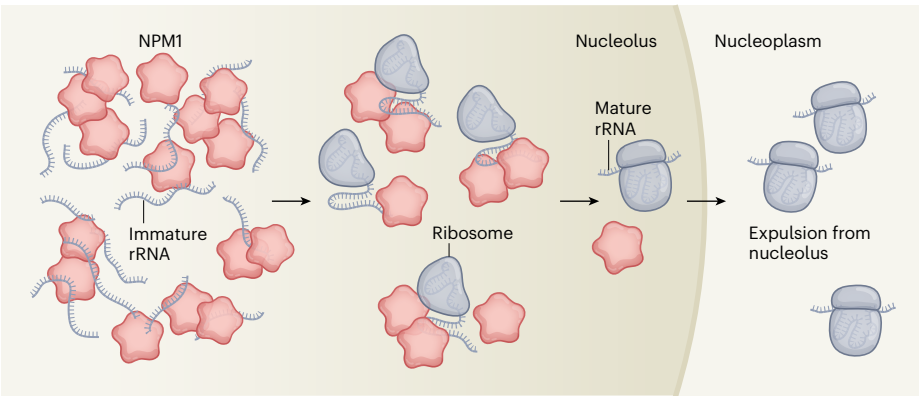

Figure 1 | Protein–RNA interactions control biological processes in the nucleolus. Riback *et al.*[2] report that complex interactions between different molecules govern the formation of liquid-like organelles such as the nucleolus, and can also regulate organelle function. The ribosome is a protein-synthesizing machine that is assembled from protein and RNA subunits in the nucleolus. The authors demonstrate that the proteins nucleophosmin 1 (NPM1) and SURF6 (not shown), which are key for formation of the nucleolus, interact freely with immature ribosomal RNA (rRNA). But as the rRNA becomes properly folded and incorporated into the ribosome, these interactions cease, and so the mature ribosomal RNA is expelled from the organelle into the surrounding nucleoplasm.

molecules, is far from existing in equilibrium. As such, it is remarkable that the authors' close-to-equilibrium theory matches their real-world observations. I think that, although the picture laid out by Riback and colleagues is a valuable starting point, the reality will inevitably be more complex. Establishing a quantitative connection between experiments and theory will require further development of our theoretical understanding of non-equilibrium phase separation, which is still in its infancy[8,9]. The fact that physicists do not know much about phase separation in non-equilibrium regimes should not be viewed as a drawback in the study of biomolecular condensates, however. Instead, it signposts a golden opportunity for life scientists, bioengineers and physicists to work closely together to expand our understanding of this complex phenomenon.

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