Molecular biology

Complex condensations get cells organized

Chiu Fan Lee

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. **See p.209**

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, on page 209, 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.

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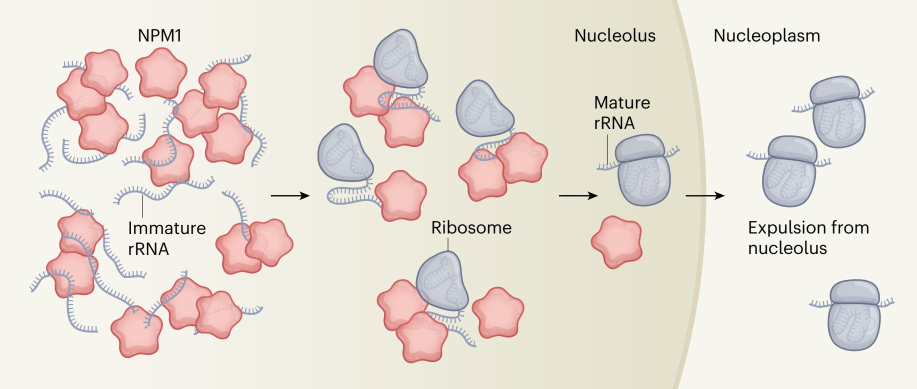

Figure 1 | Protein–RNA interactions control biological processes in the nucleolus. Riback *et al.*[2] report that complex interactions between different molecules govern the formation of liquid-like organelles such as the nucleolus, and can also regulate organelle function. The ribosome is a protein-synthesizing 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.

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.

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 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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Atmospheric science

Airborne particles might grow fast in cities

Hugh Coe

Nanoscale particles have been observed to form and grow in the atmospheres of many cities, contradicting our understanding of particle-formation processes. Experiments now reveal a possible explanation for this mystery. **See p.184**

On page 184, Wang *et al.*[1] report observations of the rapid growth of newly formed atmospheric particles through the condensation of ammonium nitrate under conditions typical of many urban environments in wintertime. The observations were made in a chamber in a laboratory, but the authors convincingly argue that similar conditions can occur transiently in megacities. The findings fill a major gap in our knowledge of particle growth rates in cities.

Particulate matter is a key factor in the air quality of many of the world's megacities because it has been directly linked to multiple non-communicable diseases (see go.nature.com/2w49q1t). It also substantially affects regional climate through its interactions with solar radiation and clouds[2]. Particle-formation processes are important in the air above large cities because they replenish the particle population, determine the total particle-number concentration and can act as 'seeds' for cloud formation. We therefore need to know how particles form and grow in order to predict the effects of particulate matter on health and regional climate.

Although our knowledge of particle formation has improved over the past few years[3,4], our understanding of the early stages of particle growth — particularly the crucial step in which an initial cluster of molecules grows large enough to become an actual particle — cannot explain why new particles form in megacity environments[5]. The persistence of newly formed clusters depends on the ratio of the condensation sink (the rate at which vapour and clusters are scavenged by pre-existing particles) to the growth rate of the clusters[3]. In the real world, both of these quantities depend on the particle-size distribution.

The condensation sink can be derived directly from the particle-size distribution. However, the growth rate is commonly determined by monitoring how clusters grow over time, typically in the size range between 1 and 10 nanometres. This method assumes that the environmental factors that affect cluster growth are uniform throughout a given region, and it has worked well in describing particle-growth behaviour in rural environments. However, it has failed to explain particle growth in cities[5].

The particle loading of air in urban environments can be greater than 500 micrograms per cubic metre (ref. 6), whereas that of rural or remote environments is usually less than $5\ \mu g\ m^{-3}$ (ref. 7). Newly formed clusters in cities must therefore rapidly scavenge vapour or combine with other clusters so that they can grow large enough for the rates at which they are themselves scavenged to be reduced (Fig. 1a), and therefore survive to become more-persistent, larger particles. Given that observed growth rates in urban areas are only a few times greater than those in remote environments, it is hard to understand how newly formed particles can reach diameters of 10 nm or more in urban areas — but such growth seems to be widespread in megacities in wintertime.

Wang *et al.* investigated this issue by carrying out a set of chamber experiments that reproduced atmospheric conditions typical of a megacity, focusing on the behaviour of ammonium nitrate. This compound is a crucial component of urban winter- and springtime particulate matter[8], but has not been thought to have a major role in particle formation.

Ammonium nitrate exists in a temperature-dependent equilibrium with gaseous ammonia and nitric acid, and this equilibrium favours the gas phase when it is warm. However, the authors observed that ammonium nitrate rapidly condenses onto newly formed clusters at temperatures below 5 °C (Fig. 1b). This is

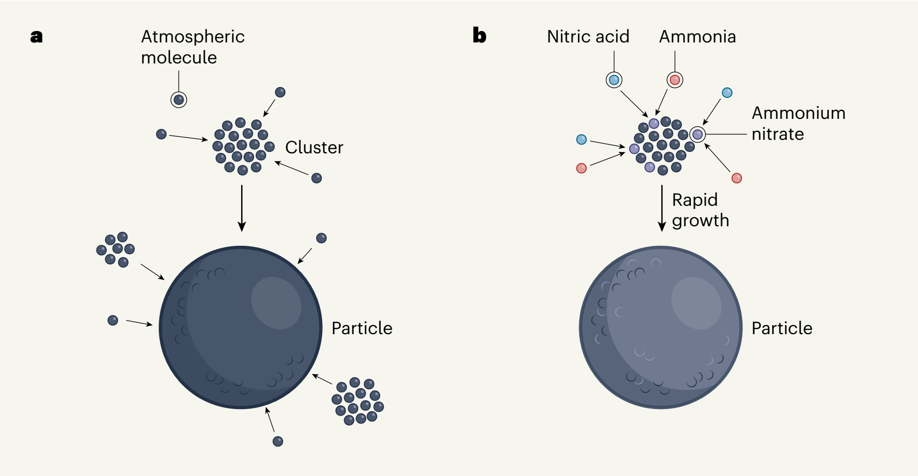

Figure 1 | The growth and formation of atmospheric particles. a, Small clusters of atmospheric molecules can gradually accumulate more molecules until they form stable particles. However, other particles in the atmosphere can scavenge the available vapour, limiting cluster growth, or even scavenge whole clusters. The concentration of particles in urban environments is high, which means that any clusters or vapour would be expected to be scavenged by existing particles before they form stable particles themselves. Yet the observed rate of new-particle formation is surprisingly high in megacities. **b**, Wang *et al.*[1] report that clusters can grow rapidly by accumulating ammonium nitrate (which forms from ammonia and nitric acid molecules) under conditions known to occur in megacities in winter. This allows the clusters to reach stable particle sizes before they are scavenged by other particles — and might explain the high particle-formation rates observed in urban areas.