dissipative Kerr solitons is that they have unfavourable power-conversion efficiencies[8]. In the case of Marin-Palomo and colleagues' system, less than 1% of the laser pump's power is transferred to the newly generated frequencies. There are alternative microresonator combs that have much higher power-conversion efficiencies[9], but they have not yet been investigated in the context of optical-fibre communications. Increasing the efficiency of microresonator combs will be essential for future optical-fibre communication systems, which will use a special type of fibre containing multiple spatial channels to achieve unprecedented transmission speeds[6].

Marin-Palomo *et al.* have clearly demonstrated that dissipative Kerr solitons can be used for wavelength-division multiplexing. Using a light source that has phase-locked frequencies represents a fundamental difference from an array of individual lasers because the frequency spacing between channels is fixed. This aspect might be the key to mitigating transmission impairments[10] or drastically simplifying the way signals are received. In this respect, the use of laser frequency combs (be it in the form of dissipative Kerr solitons or something else) constitutes a pivotal change in the design of optical-fibre communication systems. Exploiting their unique properties will require a collaborative effort between the disciplines of photonic integration, fibre optics, ultrafast optics, computer engineering, information theory and signal processing. ■

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NEURODEGENERATIVE DISEASE

RNA repeats put a freeze on cells

Droplet-like assemblies of RNA in cell nuclei are associated with certain neurodegenerative diseases. Experiments reveal that these assemblies become 'frozen' gels in cells, potentially explaining their toxicity. SEE ARTICLE P.243

DAVID W. SANDERS
& CLIFFORD P. BRANGWYNNE

Many inherited neurodegenerative diseases are associated with nucleotide-repeat expansions, in which a normal tract of DNA that has a repetitive nucleotide sequence expands to many times its original size. When this occurs in non-coding regions (introns), it results in the formation of repetitive RNA sequences that are not translated to make proteins. An explanation for the toxicity of these RNA expansions has remained elusive, but a potential clue lies in the observation that such RNAs form spherical clusters called RNA foci in cell nuclei[1]. Jain and Vale[2] report on page 243 that RNA repeats can undergo a phase transition to form either a condensed liquid or a gel-like state. Such 'frozen' RNA foci might contribute to neuronal dysfunction.

RNA and proteins can condense into dynamic organelles, in much the same way that water vapour condenses to form droplets at the dew point. This behaviour is known as liquid–liquid phase separation (LLPS) and forms the basis of an emerging hypothesis of intracellular organization[3,4]. Unlike most organelles, the cellular compartments formed by RNA and proteins lack a phospholipid bilayer, and arise from repetitive, weak interactions between their resident molecules. Many proteins associated with the neurodegenerative disease amyotrophic lateral sclerosis (ALS) are prone to undergo LLPS *in vitro*, and disease-associated mutations in these proteins may trigger further conversion of the resulting dynamic liquid to a gel[5], a process similar to the setting of a gelatin dessert.

Jain and Vale wanted to test whether such phase transitions might also take place with RNA alone. They first performed *in vitro* experiments with purified RNA, focusing on poly-CUG (an RNA consisting of repeats of the CUG nucleotide sequence, which are associated with the disease myotonic dystrophy), poly-CAG (which is associated with Huntington's disease) and poly-G4C2 (which consists of GGGGCC repeats and is implicated in a form of ALS known as C9ORF72-associated ALS). The authors observed that each of these RNAs undergoes LLPS at nanomolar concentrations, resulting in spherical assemblies

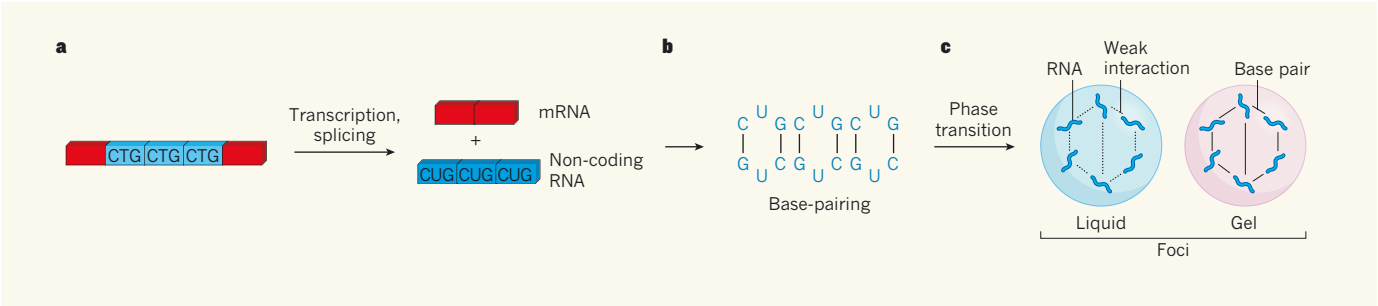

Figure 1 | Foci formation. **a**, Nucleotide-repeat expansions occur when a section of DNA that has a repetitive nucleotide sequence (here, repeats of CTG) expands to many times its original size. When expansions occur in the non-coding regions (blue) of genes, transcription and processing (splicing) of the nascent transcript generates non-coding RNAs that have repetitive sequences (here, CUG), in addition to messenger RNAs. Coding regions of the gene are shown in red. **b**, **c**, Jain and Vale[2] present evidence suggesting that complementary pairing of bases between non-coding RNA molecules (**b**) might trigger RNA assembly processes, driving an RNA phase transition (**c**) from a diffuse form to a dynamic liquid state, or to a gel in which molecules are 'frozen' into position. These results provide a biophysical foundation for the formation of RNA foci — spherical clusters of RNA molecules in cell nuclei that are characteristic of diseases associated with certain nucleotide-repeat expansions.

(Fig. 1), but only at lengths above a specific threshold — which might explain why nucleotide-repeat expansions cause disease only when they reach or exceed a critical length.

Crucially, Jain and Vale found that versions of the RNAs in which the nucleotide sequence had been scrambled did not undergo LLPS, but remained in a diffuse state. Furthermore, when the authors added molecules to their *in vitro* systems to disrupt the formation of complementary interactions between RNA bases (base-pair formation), this abolished RNA-cluster formation — highlighting the role of such interactions in the process. And although the spherical clusters resembled liquid droplets, they were actually solid-like, which suggests that a rapid liquid-to-solid phase transition (gelation) may occur.

The authors next examined whether the *in vitro* findings could be reproduced in cells. They observed that RNAs at sub-threshold lengths exist mainly as diffuse populations in the cytosol. However, at lengths approaching those observed in disease, the RNAs reside in nuclear speckles — membrane-less organelles that are essential for the processing of messenger RNA. The researchers found that the formation of RNA foci is abolished when base-pairing is blocked, consistent with their *in vitro* experiments showing that RNA–RNA interactions mediate foci assembly, but that speckle integrity is not disrupted.

Jain and Vale also report that, in cells, poly-G4C2 foci exhibit gel-like properties similar to all of the assemblies formed *in vitro*, whereas the poly-CAG foci display liquid-like characteristics. These differences might be explained by the strength of base-pairing for the two types of RNA. However, the origin of these biophysical properties and the mechanism by which expanded RNAs are confined in speckles remain unclear.

This work has clear implications for human disease, although it should be noted that the cells in which RNA foci were induced did not die or exhibit noticeable dysfunction. Moreover, a major caveat of the findings is that the RNA levels studied *in vitro* and in cells were much greater than those produced in the neurons of people who have neurodegenerative diseases. For example, a recent study[6] suggests that, in neurons from people with C9ORF72-associated ALS, individual foci contain a single RNA molecule, and only a few foci exist in an average cell nucleus. Furthermore, although the localization of poly-CAG and poly-CUG RNAs in nuclear speckles has been described[7] in people with Huntington's disease and myotonic dystrophy, respectively, poly-G4C2 RNAs are not localized in such speckles in people with C9ORF72-associated ALS[8]. Finally, studies in model organisms[5] suggest that proteins known as dipeptide repeats, which are produced by an unconventional form of translation called repeat-associated non-AUG (RAN) translation, might be the primary driver of disease, rather than RNA alone. The contribution of RNA gelation to these diseases therefore remains to be determined, particularly for ALS.

Nevertheless, Jain and Vale's study is important and inspires many questions. For example, how do expanded repeats affect the dynamics of nuclear speckles? Could repeat RNAs drive the gelation of non-expanded RNAs and proteins, thus disrupting information transfer from DNA to protein? And if RNA gelation indeed occurs in C9ORF72-associated ALS, how might this initiate the downstream formation of RNA-binding protein (RBP) aggregates, which are the best predictor of neuronal loss in all forms of ALS[9]? Despite a flurry of studies[5], the relative contributions of protein loss of function, RNA foci and RAN translation to the onset of C9ORF72-associated ALS are unclear, especially with respect to the formation of RBP aggregates.

Another key question concerns conditions such as Huntington's disease, in which nucleotide-repeat expansions occur in the coding regions (exons) of DNA, so that repetitive RNA molecules and proteins are both produced. What are the relative roles of phase transitions for proteins and for RNA, and might both act synergistically to cause disease? Most recent research has been dedicated to examining toxic protein aggregates in these diseases[10], but Jain and Vale's findings are likely to renew interest in the contributions of expanded RNAs.

The new findings probably also have implications for fundamental cellular biology. For example, the described RNA phase transitions might have a role in the formation of certain membrane-less organelles, such as paraspeckles, which depend on the presence of long non-coding RNAs (lncRNAs; see ref. 11, for example). Indeed, interactions in repetitive sequences of some lncRNAs could provide the structural basis for the formation of such cellular compartments[12]. Further exciting results in this area are likely to be forthcoming as researchers from both basic science and translational laboratories continue to coalesce around the field of intracellular phase transitions. ■

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CONDENSED-MATTER PHYSICS

Magnetism in flatland

A pair of two-dimensional materials have been shown to exhibit ferromagnetism — the familiar type of magnetism found in iron bar magnets. Such materials could have applications from sensing to data storage. SEE LETTERS P.265 & P.270

NITIN SAMARTH

Ferromagnetism is perhaps the oldest known phenomenon of purely quantum-mechanical origin. It refers to the alignment of magnetic moments (spins) in certain materials that results in uniform, permanent magnetization, such as that seen in iron. An approach to studying truly two-dimensional ferromagnets has been lacking, but on pages 265 and 270, respectively, Gong *et al.*[1] and Huang *et al.*[2] report an advance in this direction. Using a high-sensitivity microscopy technique, the authors remarkably observe ferromagnetic behaviour in atomically thin layers of two magnetic materials: chromium germanium telluride ($Cr_2Ge_2Te_6$) and chromium triiodide (CrI_3).

The study of low-dimensional ferromagnets, comprised of spins arranged on 1D or 2D lattices, was motivated in the 1970s by a broad interest in understanding how the number of spatial dimensions affects phase transitions and associated phenomena[3,4]. Experimentalists initially used 3D crystalline magnetic materials to approximate 2D spin lattices. In these crystals, the interactions between the spins in a given plane of the crystal lattice are much stronger than those between spins on different planes[5]. Later, epitaxial synthesis