emission frequency is determined by the energy drop at each step, which can be adjusted by changing the layer thickness.

Liang and co-workers' quantum cascade random laser raises hopes of new imaging applications. Many biochemical molecules have spectral 'fingerprints' in the mid-infrared range, a property that can be used for sensing and imaging applications — for example, in trace-gas sensing for pollution control and environmental monitoring; combustion diagnostics; and medical diagnostics (such as breath analysis). A crucial characteristic of random lasers is that the spatial coherence of their laser emission can be easily tuned[8]. Spatial coherence describes the correlation between waves at different points in space: sunlight shining through a cloud has low spatial coherence, whereas stars in the night sky have high spatial coherence. Low spatial coherence is desirable for parallel imaging, because light illuminating different spatial positions is uncorrelated, and so coherence artefacts such as crosstalk and speckle (random granular patterns) are avoided[9].

To produce emission that has low spatial coherence, a random laser must have many modes (oscillating waves) lasing simultaneously[8]. Liang and colleagues' laser supports only a limited number of random-lasing modes, so its spatial coherence could still be high, although this has not been measured. A further increase in the laser's scattering strength would probably cause more modes to lase, thereby reducing the spatial coherence of the emission. However, because random-laser emission is non-directional, in this case a clever scheme would need to be developed for the efficient collection of total emission.

Looking to the future, this method of making mid-infrared random lasers could be extended to terahertz (10^{12} Hz) frequencies. In fact, lasers known as quasi-periodic, distributed-feedback quantum cascade lasers operating in the terahertz regime were constructed only three years ago[10]. Common packaging materials such as cardboard and plastics are transparent to terahertz radiation, making it useful for package inspection, quality control and non-destructive testing[7]. A combination of low spatial coherence and high radiance would also make a terahertz random laser suitable for applications such as high-speed parallel inspection. ■

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1. Maiman, T. H. *Nature* **187,** 493–494 (1960).
2. Liang, H. K. *et al. Adv. Mater.* http://dx.doi.org/10.1002/adma.201303122 (2013).
3. Cao, H. *Prog. Opt.* **45,** 317–370 (2003).
4. Wiersma, D. S. *Nature Phys.* **4,** 359–367 (2008).
5. Ambartsumyan, R. V., Basov, N. G., Kryukov, P. G. & Letokhov, V. S. *IEEE J. Quantum Electron.* **2,** 442–446 (1966).
6. Letokhov, V. S. *Sov. Phys. JETP* **26,** 1246–1251 (1968).
7. Gmachl, C., Capasso, F., Sivco, D. L. & Cho, A. Y. *Rep. Prog. Phys.* **64,** 1533–1601 (2001).
8. Redding, B., Choma, M. A. & Cao, H. *Opt. Lett.* **36,** 3404–3406 (2011).
9. Redding, B., Choma, M. A. & Cao, H. *Nature Photon.* **6,** 355–359 (2012).
10. Mahler, L. *et al. Nature Photon.* **4,** 165–169 (2010).

BIOCHEMISTRY

Metal ghosts in the splicing machine

Chemical analysis of the spliceosome's active site reveals that it is the RNA components of this enzyme complex that coordinate the catalytic metal ions responsible for production of a spliced messenger RNA. SEE ARTICLE P.229

SCOTT A. STROBEL

Genes are transcribed as pre-messenger RNA molecules in which the coding exon segments are typically interrupted with non-coding sequences, or introns. To create a functional mRNA, the introns must be removed and the exons joined together in a process known as pre-mRNA splicing. The two phosphoryl-transfer reactions of splicing are catalysed by the spliceosome, a metalloenzyme complex comprising five small nuclear RNAs (snRNAs) and dozens of core proteins[1]. The spliceosome uses magnesium ions at its active site as catalytic cofactors, and researchers have long been captivated by the question of whether the ligands for these metal ions are provided by the snRNAs or by the proteins, as this speaks to the evolutionary roots of the splicing process. On page 229 of this issue, Fica *et al.*[2] report that a specific constellation of phosphate oxygens in the U6 snRNA supplies the ligands that coordinate the catalytic metal cofactors in the active site. This finding establishes the concept that pre-mRNA splicing is fundamentally an RNA-catalysed reaction.

Fica and colleagues used an approach known as a metal-specificity switch to establish how the catalytic metal ions are bound within the spliceosome. They systematically introduced single atoms of sulphur in place of phosphate oxygens in the U6 snRNA of the spliceosome. Of the 20 positions tested, they found five substitutions that impaired splicing in the presence of magnesium ions (Mg^{2+}), a metal that binds efficiently to oxygen but not to sulphur. The splicing activity of these impaired spliceosomes could be rescued by the addition of manganese (Mn^{2+}) or cadmium (Cd^{2+})

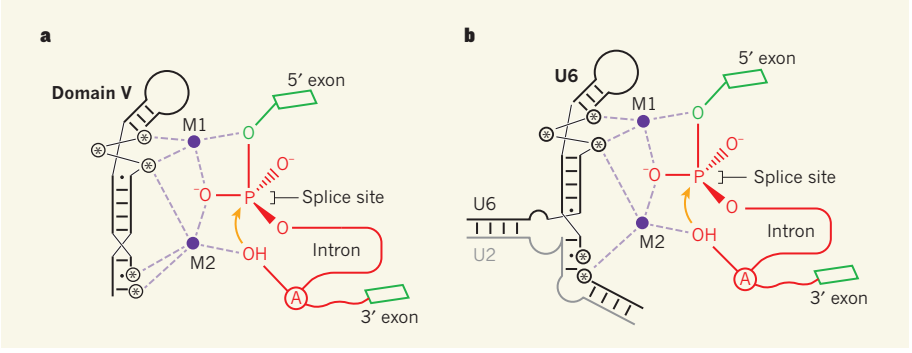

Figure 1 | Active sites of group II introns and the spliceosome. **a**, Group II introns are RNA elements that self-catalyse splicing — the removal of introns (red) and the joining of adjacent exon regions (green). They contain a hairpin structure called domain V; the phosphoryl-transfer reactions of splicing (the first of which is shown with an orange arrow) are catalysed by two divalent metal ions (M1 and M2) that are coordinated (dashed purple lines) to phosphate-group oxygen atoms of nucleotides (asterisks) in this region[5], to a non-bridging oxygen at the splice site and to an OH group from an adenosine nucleotide (A) in the intron. **b**, Fica *et al.*[2] now show that RNA also catalyses these reactions during pre-mRNA splicing by the spliceosome — a metalloenzyme complex composed of small nuclear RNAs (snRNAs) and proteins. They show that the U6 snRNA of the spliceosome (which forms a hairpin structure similar to that of domain V) provides the phosphate oxygens that bind to two catalytic metal ions at the enzyme's active site, in a similar manner to the metal-ion coordination of group II introns. The adjoining U2 snRNA of the spliceosome is also shown.

ions — metals that bind more efficiently to sulphur than does magnesium. Such changes in metal specificity constitute a chemical signature that has been used to establish metal-ion binding to specific oxygens within other RNA active sites[3].

Efforts to map metal-ion binding sites in the U6 snRNA have been made before using this approach, albeit on a less comprehensive scale (for example, see ref. 4). What sets Fica and colleagues' work apart is the triangulation of binding sites in U6 to the reactive groups in the pre-mRNA substrate. The authors establish that at least four of the five phosphate oxygens are coordinated to the catalytic Mg^{2+} ions during the two phosphoryl-transfer reactions of splicing. They demonstrated this by preparing complexes with double and even triple sulphur-substituted spliceosomes and substrates. As the number of substitutions increased, they observed a requirement for greater thiophilicity (sulphur-binding preference) of the rescuing metal: Cd^{2+} provided rescue but Mn^{2+} did not.

Titration of the Cd^{2+} concentration needed to achieve rescue suggests that there are two different catalytic metal ions within the active site (one coordinated to the nucleophilic hydroxyl and one coordinated to the leaving group), and that these metals interact with distinct phosphate oxygens in U6. Interestingly, no specificity switch was detected upon sulphur substitution in the RNaseH domain of Prp8, a protein at the core of the spliceosome that had been speculated to have a catalytic role[5].

The inorganic architecture of the spliceosome active site that emerges from these studies is strikingly similar to that seen in the self-splicing group II introns[6] (Fig. 1). This subclass of introns are able to splice themselves out of the pre-mRNA without the need for the spliceosome, yet group II splicing and spliceosomal splicing involve the same two phosphoryl-transfer reactions and generate the same reaction intermediates and products. The crystal structure of a group II intron[6] revealed an active site with two catalytic metal ions coordinated to phosphate groups in the domain V helix of the RNA that are spatially and functionally equivalent to the phosphates that Fica *et al.* show are coordinated between the U6 snRNA and the pre-mRNA. The parallels between these molecules even extend to the stereochemistry of the oxygen atoms that serve as ligands for the two metal ions. Although it has long been known that the hairpin-loop structures of U6 and domain V are functionally similar, this work demonstrates the chemical equivalence between these two systems in their metal-ion coordination.

There are more than 100 proteins in the spliceosome, so what role do they have if RNA is the catalyst of pre-mRNA splicing? Some proteins are retained throughout the splicing process, whereas others associate or dissociate at various steps in the reaction. Fica and colleagues' data do not exclude the possibility that some of the catalytic metal ligands are provided by protein functional groups. The authors tested one amino-acid candidate in spliceosomal factor Prp8 and obtained a negative result, but other segments of Prp8, particularly a loop close to the active site[7], remain a possibility. In addition to the two catalytic divalent metals present in domain V of group II introns, this structure also contains two monovalent potassium (K^+) ions, resulting in a cluster of four metal ions[6]. Does the inorganic architecture extend to the monovalent ions, or do proteins play the part of K^+ within the spliceosome? Whatever the answers to these questions, it seems that the main role of the proteins is not catalytic, but that they are instead involved in regulation, in determining splice-site specificity and as a scaffold to promote the proper conformation of the snRNAs.

Although the group II intron structure is invaluable, we still lack high-resolution crystal structures of the spliceosome in any of its various reaction states. Such a structure would reveal the full relationship of U6 and its associated proteins to the catalytic metals and pre-mRNA substrate. The complexity, heterogeneity and size of the spliceosome have so far precluded structural analysis at high enough resolution to extract biochemical mechanistic information, but cryo-electron microscopy images continue to improve[8]. There is also a need to confirm the mechanistic parallels between the spliceosome and the group II self-splicing system. The biochemical data available on U6 have outpaced those for domain V, so it has not been tested whether the metals observed in domain V show a metal-specificity signature consistent with a direct role in catalysis, as has now been demonstrated for the metal ions in U6.

In the early days of our understanding of self-splicing RNAs, chemist Thomas Cech posed the question: is RNA-based catalysis a general phenomenon or a rare molecular fossil[9]? For many years, the study of RNA catalysis was confined to introns in genomes outside the nucleus and in non-model organisms, including yeast mitochondria and ciliated protozoa. But the crystal structure of the ribosome[10] revealed that RNA provides the active site responsible for protein synthesis across all forms of life. The functional demonstration by Fica *et al.* that pre-mRNA splicing is catalysed within an RNA metalloenzyme active site clearly shows that RNA-based catalysis is a fundamental and ubiquitous process involved at several steps in the conversion of genetic information to functional proteins. ■

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1. Sontheimer, E. J., Sun, S. & Piccirilli, J. A. *Nature* **388,** 801–805 (1997).
2. Fica, S. M. *et al. Nature* **503,** 229–234 (2013).
3. Fredericksen, J. K. & Piccirilli, J. A. *Methods* **49,** 148–166 (2009).
4. Yean, S. L. *et al. Nature* **408,** 881–884 (2000).
5. Pena, V., Rozov, A., Fabrizio, P., Lührmann, R. & Wahl, M. C. *EMBO J.* **27,** 2929–2940 (2008).
6. Marcia, M. & Pyle, A. M. *Cell* **151,** 497–507 (2012).
7. Galej, W. P., Oubridge, C., Newman, A. J. & Nagai, K. *Nature* **493,** 638–643 (2013).
8. Golas, M. M. *et al. Mol. Cell* **40,** 927–938 (2010).
9. Cech, T. R. *Cell* **44,** 207–210 (1986).
10. Nissen, P., Hansen, J., Ban, N., Moore, P. B. & Steitz, T. A. *Science* **289,** 920–930 (2000).

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SOLAR SYSTEM

Russian skyfall

The recent entry of a 20-metre-wide celestial rock into Earth's atmosphere offered both a spectacular show and a source of invaluable data that advance our understanding of high-velocity impacts. SEE LETTERS P.235 & P.238

NATALIA ARTEMIEVA

Two papers in this issue focus on the scientific reconstruction of the asteroid-impact event that was observed on 15 February 2013 in Chelyabinsk, Russia — the largest impact event on Earth since the Tunguska blast of 1908. Borovička *et al.*[1] (page 235) extract substantial scientific information from several low-quality video recordings. Meanwhile, by analysing infrasound airwaves and the brightness of the light flash generated by the impact, as well as the damage caused to Earth's surface, Brown *et al.*[2] (page 238) estimate the total energy of the event to have been 400–600 kilotons of trinitrotoluene (1 kt of TNT is equivalent to 4.185×10^{12} joules of energy), and say that such events occur more often than previously thought.

There are three fundamental physical processes involved as meteoroids — asteroids' smaller counterparts — enter the atmosphere. First, atmospheric drag decelerates meteoroids from their initial velocity of about