is indispensable for exploring the correlation between the theories, and for investigating what happens on the atomic level at the onset of melting. To exploit this capability, Jin *et al.*[3] define a 'Lindemann atom' as one for which the fractional root-mean-square displacement exceeds the critical value $\delta_L \approx 0.22$. The number and location of these Lindemann atoms was examined as a function of temperature, and they were found to increase rapidly in number near the melting temperature (Fig. 1a) and to form clusters of increasing size as the crystal heated up (Fig. 1b).

The authors then calculated the Born elastic moduli for the Lindemann atoms, and found that the average value of the elastic shear modulus is much closer to zero for the totality of these particles than for the crystal as a whole. To quote the carefully worded conclusion of the paper: "These results demonstrate a strong correlation between the Lindemann criterion and the Born criterion: melting is initiated by local lattice instabilities governed by both." As they see it, the simultaneous violation of both the Lindemann and Born criteria "sets the stage for the emergence of local regions that play the role of surfaces in initiating the equilibrium melting". The temperature at which these processes take place represents the maximum feasible temperature for superheating.

Perhaps the most surprising conclusion of this paper is that, at the superheating limit T_M, the clusters have properties similar to the surface atoms at the much lower equilibrium melting temperature, T_E. This is a major discovery that may well finally settle the long-standing uncertainty about the correct criterion for melting. It is also an example of what computer simulation can achieve when all of its capabilities are properly exploited. ■

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Gene expression

The odd coupling

R. Andrew Keys and Michael R. Green

Gene expression requires several complex biochemical reactions to be carried out precisely. These reactions must also be coordinated, and molecular biologists now have a better handle on how that happens.

In organisms whose cells have a nucleus, the expression of a protein-encoding gene involves several steps: transcription of the gene; extensive processing of the initial product, the 'precursor' messenger RNA; and export of the correctly processed 'mature' mRNA from the nucleus to the body of the cell. A great deal has been learned about the mechanisms and factors involved through biochemical and genetic studies of each reaction. The challenge now is to understand how these steps fit together correctly. Writing on pages 644 and 648 of this issue, Luo and colleagues[1] and Sträβer and Hurt[2] provide insight into how two reactions — the 'splicing' of precursor mRNAs and the export of processed mRNAs — may be coupled.

When a nuclear gene is transcribed, the precursor mRNA (pre-mRNA) product consists of protein-encoding portions (exons) that are interspersed with non-coding sequences (introns). During splicing, the introns are excised and the exons joined together. It has long been suspected that splicing and export must in some way be connected, to ensure that only the final mRNA product — and not unspliced pre-mRNA, splicing intermediates or excised introns — leaves the nucleus. Consistent with this suspicion, mRNAs are known to be retained in the nucleus as a result of being assembled into the spliceosome, the complex that carries out splicing. After splicing, the mature mRNA is released from its spliceosomal bondage and is free to be exported.

Studies of multicellular organisms have shown that splicing actually enhances the export of mRNA. The increased efficiency of export results from assembly of the mRNA into a special RNA–protein complex, which differs from that assembled on an otherwise equivalent RNA that has not undergone splicing[3]. This complex contains a protein known as Aly[4,5] (also called REF[6] and BEF[7]), the yeast counterpart of which, Yra1, is known to be required for mRNA export[8]. According to the current model, Aly/Yra1 mediates mRNA export through interaction with another protein, called TAP in mammals and Mex67 in yeast. TAP/Mex67 in turn interacts with the nuclear pore complex[6,8], the structure through which molecules move into and out of the nucleus. Related studies have shown that splicing results in deposition of at least five proteins on mature mRNA near the junction between exons. The resulting 'exon-junction complex' contains both Aly and TAP, as well as proteins that are thought to be involved in other mRNA-related functions[9].

The specific issue addressed in the new papers[1,2] is the mechanism by which Aly/Yra1 is recruited to spliced mRNA. Luo *et al.*[1] carried out a series of experiments involving injecting specific proteins into frog eggs, and found that Aly and UAP56, an essential human splicing factor[10], interact both physically and functionally. In particular, injection of excess UAP56 blocked the export of mature mRNA by sequestering Aly, preventing it from binding to mRNA.

This was completely unexpected — there was no reason to suspect that Aly and UAP56 would pair up. UAP56 is a member of a family of proteins known as DExD/H-box proteins, which mediate the ATP-dependent events that drive splicing. Several of these proteins can unwind RNA, an activity that is

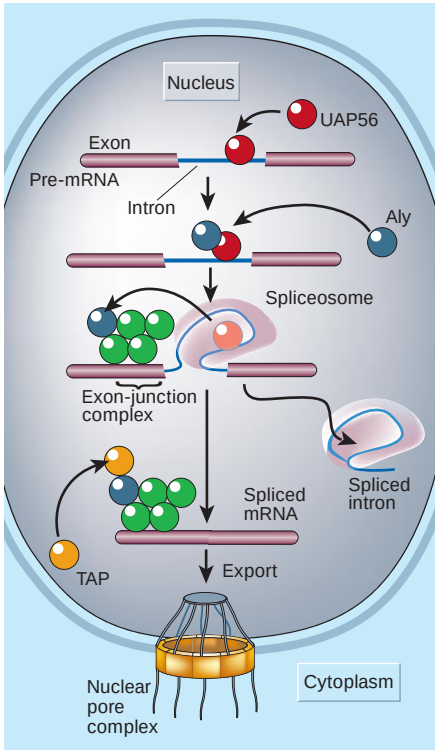

Figure 1 **A model to explain coupling between the splicing of precursor messenger RNAs (pre-mRNAs) and the export of the mature mRNA product from the nucleus. Luo *et al.*[1] and Sträβer and Hurt[2] have found that the mammalian protein Aly (or its yeast counterpart, Yra1; not shown) interacts with the splicing factor UAP56 (Sub2 in yeast). These and previous results suggest a model in which first UAP56 and then Aly is recruited to pre-mRNA (top). Next, the spliceosome — a large RNA–protein complex — is assembled on the pre-mRNA and carries out splicing (removal of the intron and joining together of the two exons). At some point during this process, Aly is moved to the exon-junction protein complex. The mRNA-export factor TAP then binds to Aly and, in so doing, targets the mature mRNA to the nuclear pore complex and transports it out of the nucleus.**

thought to promote the structural changes in the spliceosome that are required for splicing to occur[11]. Human UAP56 is needed for the first ATP-dependent step in splicing — the interaction between one of the spliceosomal RNAs and the 'branch-point' sequence in the intron[10].

Sträβer and Hurt[2], meanwhile, carried out a genetic screen in yeast to identify proteins that interact with Yra1. The screen revealed that Sub2 (also called yUAP), the yeast counterpart of human UAP56 (refs 12–14), genetically interacts with Yra1. Having fingered Sub2 as a potential export factor, the authors showed that mutation or overexpression of this protein results in a general defect in mRNA export. Finally, they found that Sub2 binds to Yra1, and that the binding of Sub2 and Mex67 to Yra1 are mutually exclusive. Together with previous studies, the new results[1,2] suggest a model in which Aly/Yra1 is first recruited to pre-mRNA through interaction with the splicing factor UAP56/Sub2. This factor is then displaced by TAP/Mex67, which targets the spliced mRNA to the nuclear pore complex (Fig. 1).

Not surprisingly, these results raise new questions. Perhaps most unexpected is Sträβer and Hurt's finding[2] that Sub2, a bona fide splicing factor[12–14], is required for the export of both spliced mRNAs and RNAs that never contained introns. The involvement of a splicing factor in the export of an intronless RNA is not without precedent[15]. Nonetheless, one is prompted to ask how Sub2 is directed to RNAs that lack splicing signals. And are the ATP-hydrolysing and RNA-helicase capabilities of Sub2 needed in processing such RNAs?

A second question is whether there are other proteins with functions similar to that of UAP56/Sub2. Although Sub2 is normally essential for viability, it is dispensable in certain mutant yeast strains[12]. But Sträβer and Hurt[2] found that nuclear export is at most only modestly compromised under these circumstances. This observation is most readily explained by the existence of a protein, yet to be identified, that can substitute for Sub2 in export.

Third, UAP56/Sub2 is thought to function at the branch-point sequence in introns[10,12–14], so this is where one would expect Aly/Yra1 to be recruited. But on spliced mRNA, Aly/Yra1 is found in the exon-junction complex[9], raising the question of how Aly/Yra1 moves from intron to exon.

Finally, Aly was originally identified as a protein that is involved in transcription[5,7]. Apparently, then, it participates in several steps in gene expression. How can one protein be involved in reactions as seemingly diverse as transcription and mRNA export? A clue may be that Aly has properties that are characteristic of molecular chaperones[9], a class of proteins that help other proteins to fold into the correct shape. A parsimonious (and testable) theory is that Aly functions as a chaperone in several nuclear events that have in common the assembly, remodelling or disassembly of multiprotein complexes on nucleic-acid scaffolds. Transcription and splicing factors could function as 'adaptor' proteins that recruit a single factor, such as Aly, to different substrates to participate in seemingly unrelated events. If this proves to be the case, the integration of nuclear processes may be much more extensive than was originally imagined. ■

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Nanotechnology

Molecules join the assembly line

Paul S. Weiss

Making patterns from molecular building blocks sounds like child's play, but has been surprisingly difficult to do. A new approach to assembling molecules into patterns may ultimately lead to molecule-based devices.

Synthetic molecules can be designed to form assemblies with predictable structures, rather like the complex molecular assemblies found in nature. Such artificial assemblies are seen as a means of bridging the gap between the small molecules created by synthetic chemistry and the larger structures made using nanolithography that can be linked to the outside world. Chemists can already tailor molecules that have specific functions with atomic-scale precision; the objective now is to develop technologies that exploit them. But one of the biggest challenges is bridging the gap between molecular features 1 nanometre across and device features on the order of 100 nanometres. Ultimately, the two will have to meet in the middle.

On page 619 of this issue, Yokoyama *et al.*[1] describe a step from the bottom up — they have designed molecules with prescribed attachments that fit together in specific ways, much like a molecular tinker toy set. They use the exquisite control provided by molecular synthesis to govern the formation of molecular assemblies over scales as large as 100 nm.

Nature is replete with examples of how to join molecules together to obtain structures on many length scales. Most protein structures are formed from strongly bound repeating units called polypeptide chains, which assemble into structures governed by weaker hydrogen bonds and van der Waals interactions. These include regular structures such as sheets, helices and what appear to be walls made of miniature bricks. Chemists and others have borrowed molecules from biology, most notably DNA, to make structures of their own. For example, Seeman and his group[2] have constructed three-dimensional

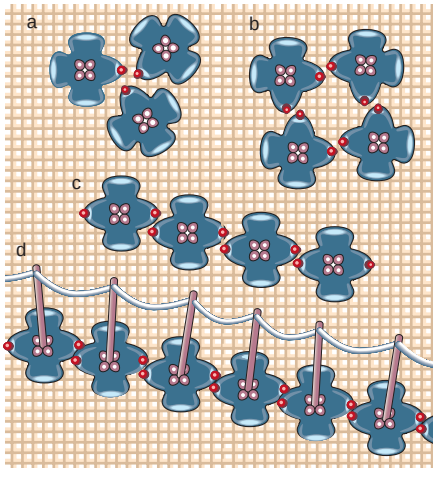

Figure 1 **Patterns with porphyrins. Yokoyama *et al.*[1] show that, by selecting the number of linkages (red) between porphyrin molecules and the orientation of these linkages with respect to one another, both localized and extended structures can be formed.** a, **With only one linkage per molecule, localized assemblies of three molecules form.** b, **With two linkages per molecule and these linkages at 90° relative to one another, localized assemblies of four molecules form.** c, **With two linkages per molecule at 180° relative to one another, extended linear structures form.** d, **By taking advantage of the chemistry of the centre of the molecule, these extended structures could be used to guide the formation of superstructures.**