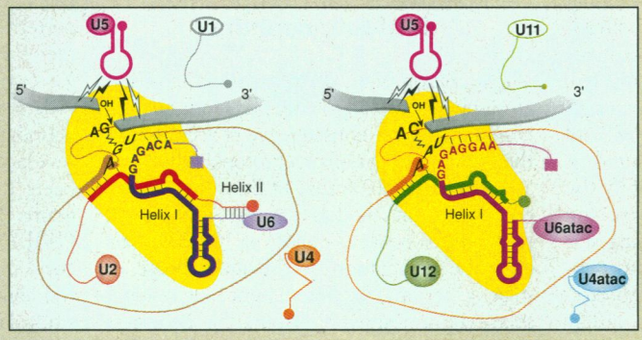
UPDATE

A Parallel Spliceosome

Timothy W. Nilsen

AT-AC introns—a recently described, rare class of introns—are spliced out of precursor mRNA (pre-mRNA) in the nucleus like their more common brethren, the GU-AG introns (*1–3*). A paper in this issue (*4*) marks a remarkable new chapter in the rapidly evolving story of this unique species, completing the identification of the RNA components of the special spliceosome that acts on these introns.

AT-AC introns (so called because of their diagnostic 5′ and 3′ termini) are processed through a two-step pathway of sequential transesterification reactions that appears to be directly analogous to the pathway by which canonical (GU-AG) introns are spliced (*3*). AT-AC intron excision occurs in a large ribonucleoprotein complex resembling the extensively studied GU-AG spliceosome (*3*). Surprisingly, the AT-AC spliceosome does not contain U1, U2, U4, or U6 small nuclear RNAs (snRNAs), all of which are highly conserved, required cofactors for the splicing of GU-AG introns; both types of spliceosome require U5 snRNA (*3*). As discussed in a recent Perspective (*1*), U11 and U12 snRNAs fulfill for AT-AC splicing the respective roles of U1 and U2 snRNAs; however, previous experiments did not offer an explanation for the lack of U4 and U6 snRNAs. The absence of U6 snRNA from the AT-AC spliceosome was particularly unsettling because several lines of evidence (albeit circumstantial) have suggested a direct catalytic role for U6 in splicing (*5*). Now, to the relief of those who found the notion of a U6-less spliceosome inconceivable, Tarn and Steitz (*4*) have identified two novel human snRNAs that resemble U4 and U6.



Two types of spliceosome. RNA-RNA interactions in the GU-AG (**left**) and AT-AC (**right**) spliceosomes after the first catalytic step of splicing. Interactions between U6atac and the 5′ splice site and U5 snRNA with exons in the AT-AC spliceosome remain to be proven. Noncanonical base-pairing interactions between the terminal bases of each type of intron (*1*) are indicated by wavy lines.

These snRNAs, designated U4atac and U6atac, are present in the AT-AC spliceosome and are unambiguously required for splicing of this class of introns. Their discovery indicates that four of five snRNAs that participate in AT-AC intron removal are distinct from their counterparts in the GU-AG spliceosome. The presence of such a radically different spliceosome would be significant if it were identified in an uninvestigated organism. The fact that such a spliceosome has remained undetected in HeLa cells is truly startling. U4atac and U6atac were not identified before because they are of low abundance and are only distantly related to their GU-AG spliceosomal cousins; for example, U6atac is significantly less similar to human U6 snRNA than yeast U6 is to its human counterpart.

How does the existence of a new spliceosome influence our understanding of how snRNAs participate in pre-mRNA processing? Remarkably, the only elements of U6atac that are conserved from other U6 snRNAs lie within regions of U6 that were previously established as essential for its presumptive catalytic function [see (*4*), figure 6]. The striking conservation of limited primary sequence elements and overall secondary structure provides strong phylogenetic support for the importance of these features of U6.

Of equal significance are the interactions of U6atac with other snRNAs in the AT-AC spliceosome. Splicing of GU-AG introns depends on an intricate network of snRNA-snRNA as well as snRNA–pre-mRNA interactions [see figure and (*5*, *6*)]. Particularly significant among these is the intermolecular helix (helix 1) formed between U2 and U6 snRNAs. The helix 1 interaction, in conjunction with two additional base-pairing interactions (U6 with the 5′ splice site and U2 with the branch point), serves to physically juxtapose the two participants in the first catalytic step of splicing, the branch point adenosine and the 5′ cleavage junction. Strikingly, this constellation of critical RNA-RNA interactions is directly recapitulated in the AT-AC spliceosome (see figure): First, base pairing occurs between U12 and an AT-AC intron branch point sequence (*3*, *7*); second, covariation between U6atac and the AT-AC intron 5′ splice site (see figure) leaves little doubt that this interaction occurs as well; and third, Tarn and Steitz (*4*) provide direct evidence for a U6atac-U12 helix 1–like pairing interaction. The congruence of RNA-RNA interactions between AT-AC and GU-AG spliceosomes is amazing, given the overall lack of similarity among the RNAs. Although the evolutionary origin of AT-AC introns and the RNAs that participate in their excision remains enigmatic, the parallels between GU-AG and AT-AC splicing provide an independent (and quite unexpected) validation of current models for the architecture of RNA components at the core of the spliceosome.

The author is at the Center for RNA Molecular Biology, Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, OH, 44106–4960, USA. E-mail: amk3@po.cwru.edu

References and Notes

1. S. M. Mount, *Science* **271**, 1690 (1996).
2. J.-P. Kreivi and A. I. Lamond, *Curr. Biol.* **6**, 802 (1996).
3. W.-Y. Tarn and J. A. Steitz, *Cell* **84**, 801 (1996).
4. ———, *Science* **273**, 1824 (1996).
5. H. D. Madhani and C. Guthrie, *Annu. Rev. Genet.* **28**, 1 (1994).
6. T. W. Nilsen, *Cell* **78**, 1 (1994).
7. S. L. Hall and R. A. Padgett, *Science* **271**, 1716 (1996).
8. I thank D. McPheeters and J. Shambaugh for help with the figure and J. Wise, P. Maroney, J. Bruzik, and J. Steitz for comments on the manuscript.