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18S rRNA: A Tale of the Tail

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More than 40 years ago, the Nomura group seduced the ribosome community with the breath-takingly simple reconstitution of the 30S ribosomal subunit from its component RNA and proteins (1). However, as with many seductions, the morning-after reality is sobering. In actual fact, the complexity of ribosome synthesis and assembly is staggering, especially in eukaryotes, where some 200 proteins and 100 small RNA molecules are required to covalently modify the rRNA transcript, cleave it, trim it, fold it, and assemble it with the ribosomal proteins (reviewed in (2,3)).

The details of this complex process have slowly leaked out in many dozens of papers over the past decade. However, in this issue of *J. Mol. Biol.* (4) Lamanna & Karbstein have made a giant leap forward by deducing the series of events that lead to the formation of the 3' end of 18S rRNA as well as to the proper folding of an adjacent helix, H44. The latter is critical in providing a framework for the specific interactions of mRNA codon with tRNA anticodon. Previous work had shown that cleavage at site A2 (See Figure), often co-transcriptional (5,6), precedes cleavage at site D, that occurs only when the molecule reaches the cytoplasm (7). Yet there were puzzling observations: cleavage at site A3, only 71 nt downstream, induced by a variety of mutations, leads to a 23S molecule which is never cleaved at site D. Another was that Nob1, apparently the nuclease that cleaves site D, binds to the pre-18S rRNA at an early stage, perhaps during transcription, long before it acts (8).

In a series of thorough and ingenious experiments Lamanna & Karbstein have made sense of these observations. In brief, using RNA probing chemistry supplemented with genetic analysis *in vivo*, they show that within the original transcript a portion of H44 sequences forms a base-paired structure with sequences between the A2 and the A3 cleavage sites (Fig. Double-headed arrow). This prevents H44 from forming, and also prevents attack by Nob1. Cleavage at A2 severs these sequences, thus permitting a rearrangement that leads to formation of the mature H44 and alters the location or orientation of Nob1 so as to permit its cleavage of site D. Since cleavage at site A3 does not sever the sequences that interact with H44, such rearrangements cannot take place and the D site is never available; thus cleavage at A3 leads to a dead end! The authors suggest that the conformational switch is not spontaneous but is chaperoned, perhaps by Prp43, and is likely to be coupled with the export of the pre-40S ribosomal subunit from the nucleus to the cytoplasm. The authors have pursued this concept of conformational rearrangement *in silico* and find evidence for widespread use among yeast species, and likely in mammals as well. (There is much more; read the paper!)

This model suggests a number of intriguing biological implications. One is that preventing the formation of H44 until the 40S subunit is almost mature ensures that it will not interact

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with tRNA prematurely. A second, as pointed out by the authors, is that the many reactions of ribosome assembly must occur in parallel pathways. This conformational rearrangement is a bottleneck reaction that provides an ideal opportunity for quality control.

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Figure.

Above: The ~6650 nt 35S primary pre-rRNA transcript with the locations of the mature species indicated. *Below:* The region near the 3' end of 18S is exploded to show the locations of Helix 44 and the cleavage sites A2, A3, and D (X). The sites of interaction in the original conformation, prior to A2 cleavage, are indicated by the double-headed arrow.