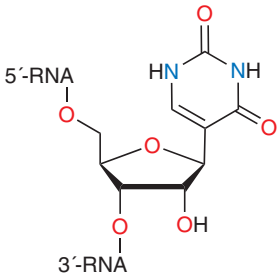
Lending pri-mRNA a helping heme

MicroRNAs (miRNAs), which interfere with gene expression by silencing mRNA targets, are involved in regulating biological pathways including development and tumorigenesis. miRNAs are produced from larger transcripts (pri-miRNAs) that are trimmed to smaller precursor miRNAs (pre-miRNAs) through the action of the nuclease Drosha in concert with a second protein, DGCR8. DGCR8 is believed to aid Drosha-mediated cleavage by binding pri-mRNAs, but its precise role has remained undetermined. A recent study now suggests that heme, an iron-containing cofactor, may be essential for the assembly of active pri-miRNA processing complexes. Faller *et al.* discovered that heme copurifies with a truncated form of DGCR8 (NC1) and promotes dimerization of NC1. $(NC1)_2$–heme complexes bind to pri-mRNA as a trimer of dimers, and RNA cleavage by Drosha is enhanced by this heme-induced oligomerization. The authors propose that heme binding to a conserved cysteine residue in DGCR8 organizes a hexameric complex of DGCR8, which positions its double-stranded RNA binding domains as effectors for pri-miRNA processing. Although the mechanism is still under investigation, the current study suggests a surprising role for a small molecule in miRNA processing and raises interesting questions about why heme was selected for this purpose. (*Nat. Struct. Mol. Biol.*, published online 10 December 2006, doi:10.1038/nsmb1182) *TLS*

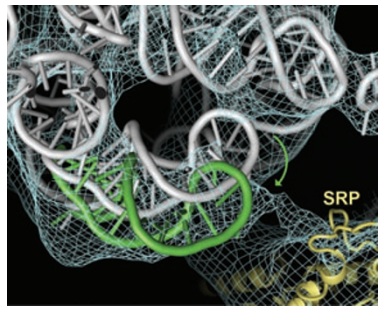
Pseudo-recognition



Pseudouridine (ψ) synthases catalyze the isomerization of uridine to ψ, an important step in the maturation of several types of RNA. Although the sites of this modification are conserved, the global structure of RNA substrates can vary. For example, RluA, one of five types of ψ synthases, is capable of acting on both rRNA and tRNA substrates. The only known structure of a ψ synthase–RNA complex shows sequence-specific contacts that allow the enzyme, TruB, to directly identify the proper nucleotide for modification. In contrast, the new structure by Hoang *et al.* demonstrates that RluA, though closely related to TruB, does not make any direct contacts to nucleotides in the consensus sequence. Instead, the protein initiates reactivity by enforcing a specific secondary structure involving substantial rearrangements of several bases. Biochemical assays confirmed that the formation of a reverse-Hoogsteen base pair between U33 and A36 is critical for orienting the substrate nucleotide, U32, properly within the enzyme. The intercalation of an arginine residue between A31 and U33 then forces U32 into the active site. Several water-mediated hydrogen bonds are made to other residues in the consensus sequence, but there are no interactions that allow RluA to directly determine the substrate sequence. A comparison of the distinct mechanisms used by these two enzymes highlights the versatility of the synthase fold. (*Mol. Cell* **24**, 535–545, 2006) *CG*

Research Highlights written by Mirella Bucci, Catherine Goodman, Joanne Kotz and Terry L. Sheppard

The path to recognition



As a newly formed nascent protein chain is leaving the ribosome, it is scanned by the signal recognition particle (SRP), a ribonucleoprotein complex. SRP binds to the signal sequence, which dictates whether the protein will be inserted into or through a cellular membrane, and targets the protein to the protein translocation machinery in the membrane. To follow more precisely how SRP manages recognition and targeting, Schaffitzel *et al.* and Halic *et al.* monitored the structure of a ribosome-bound nascent chain with SRP from both eukaryotic and prokaryotic systems. Comparing the structures from *Escherichia coli* with those of empty ribosomes, Schaffitzel *et al.* found that the ribosome exit tunnel of the polypeptide is not fully covered by SRP. Also, there were no hints of ribosome stalling as is seen in eukaryotic ribosomes. They also found that SRP becomes tenuously bound to the empty ribosome via one binding site, which, followed by the recognition of a nascent chain, permits the binding of SRP to three additional sites of the ribosome–nascent chain complex to stabilize the interaction. An SRP "opening" was seen by Halic *et al.*, who showed that specific ribosomal proteins bind to the protein component of *E. coli* SRP to open a hydrophobic groove within SRP for signal sequence binding. These authors also propose further differences between the prokaryotic and eukaryotic systems, including the presence of a "parking position" just outside the tunnel exit in which signal sequences could be retained for recognition by SRP. (*Nature* **444**, 503–506, 2006; *Nature* **444**, 507–511, 2006) *MB*

Poison by ammonium

Although free ammonium is toxic to both plants and mammals, ammonium has been considered the preferred nitrogen source for bacteria and yeast. Using a chemostat, which ensures constant growth conditions, Hess *et al.* stumbled upon the first evidence of ammonium toxicity in yeast. Initially interested in studying the physiology of potassium in yeast, the authors found that yeast growth is impaired at physiologically relevant concentrations of potassium ions, but not at the higher potassium concentrations typically found in growth media. Gene expression analysis revealed that most of the genes regulated by potassium limitation are involved in nitrogen metabolism. Based on this result, the authors found that high ammonium concentrations are toxic to yeast, but only when potassium concentrations are low. The known ability of potassium transporters to transport ammonium provides a likely explanation for the connection between the effects of these ions. Overexpression of ammonium transporters induces a similar growth defect, which demonstrates that increased ammonium flux by itself is toxic to yeast. In contrast to mammals, which use the urea cycle, yeast were found to detoxify ammonium by upregulating amino acid transporters and excreting amino acids. This study reveals a new aspect of yeast nitrogen metabolism and highlights the potential of systems biology approaches for investigating physiology. (*PLoS Biol.* **4**, 2012–2023, 2006) *JK*