ERAD substrates are tagged and recognized as defective and how they are extracted into the cytosol for proteasomal degradation[19]. However, a large gap remains in our understanding of how the ERAD substrates are targeted to a membrane channel for retranslocation. Further studies will be required to determine if EDEM itself helps with the initial retranslocation process by targeting ERAD substrates to the translocon.

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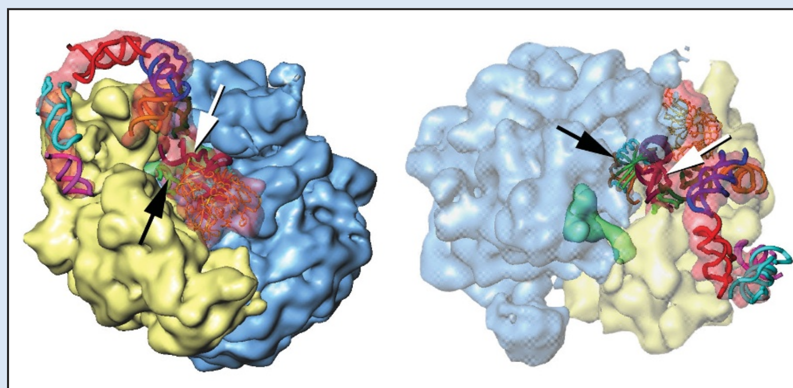
tmRNA to the rescue

When a bacterial ribosome encounters a defective mRNA during the course of protein synthesis, the ribosome may 'stall', thereby blocking further protein synthesis at that ribosome. Such a stalled ribosome is rescued by tmRNA, a molecule that possesses the functions of both tRNA and mRNA.

tmRNA contains an alanyl-tRNA–like domain (TLD) and an open reading frame (ORF) encoding a peptide degradation tag. During the rescue process, alanyl-tmRNA binds in the ribosome A site and allows its alanine to be added to the nascent polypeptide chain. Then, in the not-so-well understood process referred to as trans-translation, the ribosome shifts from the defective mRNA to the ORF of tmRNA and resumes normal translation. The stalled ribosome is thereby rescued and the defective protein is tagged for degradation.

In a report in the April 4 issue of *Science* (**300**, 127–130; 2003), Valle *et al.* used cryo-EM to examine the ribosome rescue complex. They prepared a 70S ribosome complex stalled at the end of a short mRNA and reacted it with alanyl-tmRNA, SmpB (a small protein required for tmRNA-mediated rescue), elongation factor Tu (EF-Tu) and GTP in the presence of the antibiotic kirromycin. Kirromycin allows GTP hydrolysis by EF-Tu but prevents the dissociation of EF-Tu–GDP from the ribosome, halting the rescue process at an early stage.



The cryo-EM map of the resulting complex (pictured in two different orientations) revealed the tmRNA TLD (burgundy ribbon within red surface, indicated by white arrow) engaged with EF-Tu (thin orange ribbon in red surface) at the ribosome A site in a similar manner to that observed for normal tRNA. SmpB (black arrow) bridges between the tmRNA TLD and the ribosome, approximating the D loop of tRNA.

A large part of the tmRNA molecule (red surface with multicolored ribbon) is loosely wrapped around a portion of the 30S subunit (yellow), positioning the ORF near the mRNA entrance to the A site. This arrangement is suggestive of events that may occur following EF-Tu release and TLD translocation to the ribosome P site (tRNA occupying the P site is shown as a green surface). Translocation would guide the ORF into the A site where it serves as the template for the degradation tag that is attached to the defective protein.

Of course, the details surrounding other events in bacterial ribosome rescue — how tmRNA is recruited to the stalled ribosome and how trans-translocation is achieved — remain unclear. Nonetheless, the study by Valle *et al.* offers a first look into the mechanism of action of tmRNA and sets the stage for future studies of ribosome rescue.

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