ICT1 comes to the rescue of mitochondrial ribosomes

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In the current issue, Richter *et al* (2010) show that mammalian mitochondrial ribosomes contain a ribosomal protein (ICT1) that acts as a ribosome-dependent, codon-independent peptidyl-tRNA hydrolase. This ribosomal protein can rescue ribosomes stalled on mRNAs lacking a termination codon.

Every translational system runs into trouble when it encounters mRNAs that have lost the translation termination codon (Akimitsu, 2008). Different translational systems have responded to the challenge of non-stop mRNAs with different strategies. Bacteria use a trans-translation mechanism in which tmRNA enters the A-site of a ribosome stalled at the 3' end of mRNA. One region of this RNA donates Ala to the stalled polypeptide chain (Figure 1A). The other portion acts as mRNA, displacing the non-stop RNA and providing information for a short peptide tail and a conventional stop codon. In the eukaryotic cytoplasm, a ribosome stalled at the poly(A) tail of the non-stop mRNA is recognized by a protein such as yeast Ski7p (Figure 1B). The mRNA is then degraded.

The stalled ribosome:non-stop mRNA complexes are also translationally repressed.

Animal cells have a distinct protein biosynthetic system in the mitochondria, which is responsible for the synthesis of essential polypeptides that are subunits of the respiratory chain complexes. In a fascinating analysis described in this issue (Richter *et al*, 2010), mammalian mitochondrial ribosomes are shown to handle the problem of non-stop mRNAs by a unique mechanism (Figure 1C). These ribosomes have a novel protein, ICT1, which acts as a ribosome-dependent codon-independent peptidyl-tRNA hydrolase. When mitochondrial ribosomes stall at the 3' end of a non-stop mRNA, ICT1 cleaves the peptidyl-tRNA, releasing the nascent chain and freeing the ribosomes for proper recycling.

ICT1 is one of four members of the release factor family found in mitochondria. It has a number of homologues in bacteria and may be of prokaryotic origin. Richter *et al* show that immunoprecipitation of ICT1 pulls down many

Figure 1 Model of non-stop RNA surveillance systems. (A) Bacteria use trans-translation to free ribosomes trapped on a non-stop mRNA. (B) Eukaryotic cytoplasmic ribosomes stalled on non-stop mRNAs recruit proteins that trigger mRNA degradation and repress translation. (C) Mammalian mitochondrial ribosomes on non-stop mRNAs hydrolyse peptidyl-tRNA through the action of ICT1.

mitochondrial ribosomal proteins, indicating a strong association of ICT1 with the ribosome. ICT1 co-sediments with the large subunit of the ribosome and is essential for its assembly, indicating that it is an integral part of the ribosome.

At present, it is not possible to test ICT1 directly, owing to the lack of an active *in vitro* mitochondrial translational system. To circumvent this limitation, ICT1 was expressed in *Escherichia coli* and tested for its ability to promote the hydrolysis of peptidyl-tRNAs on bacterial ribosomes. Quite surprisingly, hydrolysis of the peptidyl-tRNA bond was observed regardless of the presence or absence of a codon in the A-site. What is also surprising is that ICT1, which functions as a ribosomal protein in mitochondria, interacts with bacterial ribosomes to carry out its biological

function. Mammalian mitochondrial ribosomes have much shorter rRNAs and are very protein rich compared with bacterial ribosomes. About half of the proteins present in these ribosomes do not have homologues in bacteria (Koc *et al*, 2001; Suzuki *et al*, 2001). It will be of great interest to determine where ICT1 binds to bacterial ribosomes and where it is located on the mitochondrial ribosome. This work opens a new chapter in our understanding of the specialized translational system in mammalian mitochondria.

Conflict of interest

The authors declare that they have no conflict of interest.

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