Text by Ruth Williams
ruth.williams@rockefeller.edu

Blood, stress, and tiRNAs

Two studies identify the pathways to tRNA destruction under stress.

Many of us experience destructive urges when stressed. Cells actually act on them, by chopping tRNA molecules to pieces. Two studies, one in yeast and one in human cells, identify the tRNA molecular scissors.

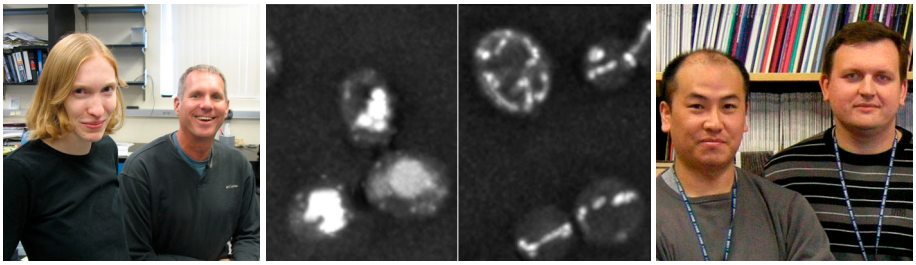
Stressed cells reduce their levels of protein production to conserve energy and resources (1). One way they do this is to switch off a protein production factor called eIF2α. In cells that contain a permanently 'on' version of eIF2α, however, protein production can still be dialed down by stress. Yamasaki et al. thought that stress-induced tRNA destruction, as reported in bacteria, fungi, and mammals, might be a backup mechanism for stalling protein synthesis (destroy the tRNAs, destroy the amino acid source).

The Harvard-based team identified a somewhat unexpected stress-induced tRNA-hacking factor in human cells (2). They found that angiogenin—a secreted protein better known for its blood vessel building properties—directly cleaved tRNAs, and that the resulting fragments (tiRNAs) halted protein synthesis. These tiRNAs only suppressed synthesis if they contained a certain part of the original tRNA molecules (the 5′ end). Exactly why is unclear, but the authors suggest that the 5′ end fragments possess a modification that makes them resistant to degradation.

What's also unclear is how angiogenin's blood vessel building activity is linked to its part in the stress response. Senior author Paul Anderson speculates that although tiRNAs reduce general levels of protein synthesis, some proteins might be preferentially produced during stress. "[Angiogenin] might actually turn on the translation of certain other angiogenic factors."

It is plausible that mammalian tissues might need new blood vessels after heat shock or UV irradiation (two of the stress conditions used). And, as Anderson points out, angiogenin requires its RNA cleavage function to promote blood vessel growth, so "using Occam's razor, it's likely that there's a link between the two."

Focal Point



(L-R) Debrah Thompson and Roy Parker find that a ribonuclease called Rny1p is mainly localized to the vacuole in yeast cells (left), but stress (right) sends it to the cytoplasm, where it chops up tRNAs and can promote cell suicide. In human cells angiogenin does the tRNA chopping, show Satoshi Yamasaki and Pavel Ivanov, lead authors on Anderson's study.

Yeast don't have a blood supply, of course, but they do chop up tRNAs when stressed. In a second study, Thompson and Parker identify the enzyme responsible as Rny1p. This enzyme, they show, is released from the yeast cell vacuole into the cytoplasm during stress (3).

Thompson and Parker speculate that Rny1p-produced tRNA fragments reduce protein production just like their human cell equivalents, though this was not the subject of their investigation. Instead the two researchers from Arizona uncovered a secondary stress-induced function of Rny1p—promoting cell death.

Overexpression in yeast of Rny1p or its human orthologue RNASET2 led to reduced viability. Following this hint, the authors went on to confirm Rny1p's death-promoting ability by showing that suicide-prone yeast could be rescued by deleting Rny1p.

Surprisingly, Rny1p's death-promoting function is independent of its tRNA cleavage activity. Release of Rny1p from the vacuole might be analogous to the release of cytochrome *c* from mitochondria, which triggers apoptosis, surmise the authors. The increasing cytoplasmic Rny1p would be a stress signal to the cell. A small increase, and tRNA destruction might be sufficient stress relief. A big increase, and suicide might be the only answer.

> "But maybe in mammalian cells it's more complicated… it's always more complicated."

Working out how the cell senses Rny1p, and decides upon its fate is the subject of Thompson and Parker's next experiments. Determining whether RNASET2 plays a similar role in mammalian cells will be of interest too, especially since RNASET2 has a cleavage-independent tumor-suppressing activity. Mammalian cells don't have vacuoles, but they do have lysosomes, where RNASET2 can be found. And certain drugs that increase lysosome membrane permeability induce apoptosis (4).

Interestingly, even though RNASET2 is capable of cleaving tRNAs, and can functionally replace Rny1p in yeast cells, it does not appear to be involved in tiRNA production in humans—the role instead going to angiogenin. "In yeast there's one nuclease and it does both these things," says Parker. "But maybe in mammalian cells it's more complicated… it's always more complicated."

1. Yamasaki, S., and P. Anderson. 2008. *Curr. Opin. Cell Biol.* 20:222–226
2. Yamasaki, S. et al. 2009. *J. Cell Biol.* 185: 35–42.
3. Thompson, D. M., and R. Parker. 2009. *J. Cell Biol.* 185:43–50.
4. De Milito, A., et al. 2007. *Cancer Res.* 67:5408–5417.