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Journal club

THE MOMENT WHEN TRANSLATIONAL CONTROL HAD A THEORY OF EVERYTHING

By the beginning of the 1990s, there was considerable interest in translational control in eukaryotic cells, but its prime examples seemed unrelated. We knew that AUG recognition during translation initiation usually depended on 5′ to 3′ scanning of mRNA by the 40S ribosomal subunit and associated factors, that some stresses led to phosphorylation of the α-subunit of the translation initiation factor eIF2, and that mRNA upstream open reading frames (uORFs) could function as *cis*-acting repressors of translation. In February 1992, Dever *et al.* connected the dots on several seemingly disparate observations, and translational control instantly acquired rock star recognition as a well-integrated means to regulate gene expression. How did it happen?

Hinnebusch cloned and sequenced GCN4, the yeast gene for a transcriptional activator of amino acid biosynthesis, which accumulates during amino acid starvation. He found four uORFs in the 5′ untranslated region (5′ UTR) of the *GCN4* mRNA that seemed to control *GCN4* translation. Several years of yeast genetics studies led to a model proposing that in non-starvation conditions: ribosomes scanned the *GCN4* 5′ UTR; translation initiation, elongation and termination occurred at uORF1; and scanning then resumed, followed by another initiation–elongation–termination cycle at uORF4 that ended with the release of ribosomes from the mRNA. In this model, few if any ribosomes made it further downstream to synthesize Gcn4 if they first engaged in the translation of uORF4. The model also posited that, during starvation, Gcn4 synthesis was derepressed because reassembly of a competent initiation complex was delayed after translation of uORF1, ensuring that scanning ribosomes bypassed uORF4 and initiated translation at the Gcn4 ORF (Abastado *et al.*).

At the same time, other research groups found that viral infection of mammalian cells activated a kinase, double-stranded RNA-activated inhibitor (DAI; later known as PKR), which phosphorylated eIF2α at Ser51, trapping eIF2 in a non-productive complex with eIF2B (the guanine nucleotide exchange factor for eIF2) and inhibiting general protein synthesis (Schneider *et al.*; Reichel *et al.*; Colthurst *et al.*).

Dever *et al.* connected these findings. They showed that Gcn2 — an activator of *GCN4* expression whose activity increased during amino acid starvation — was also a kinase that phosphorylated eIF2 at Ser51. As in virus-infected mammalian cells, eIF2α phosphorylation in amino acid-starved yeast was thought to reduce cellular levels of eIF2–GTP, which is required for translation initiation, thus explaining why, on *GCN4* mRNA, reinitiation by ribosomes terminating at uORF1 was delayed until those ribosomes had bypassed uORF4.

The Dever *et al.* tour de force not only tied up several loose ends, but also reminded us to pay attention to the possibility that biological regulatory mechanisms are often conserved.

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