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Regulating the Ribosome: A Spotlight on RNA Dark Matter

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Abstract

In this issue Pircher *et al.*(2014) show that an abundant ribosome-associated 18-nt noncoding RNA (ncRNA),derived from the open reading frame of an mRNA,acts directly on the ribosome and regulates global translation levels in response to hypertonic shock.

All stages of gene expression, from transcription to the turnover of gene products, whether protein or RNA, involve complex molecular machinesthat not only transmit genetic informationbut also act as regulatory hubs.At the level of protein synthesis, it has become clear that translational efficiency exerts significant control over cellular protein levels (Schwanhausser et al., 2011).Like histones, RNA polymerases and spliceosomes, the ribosome isalso emerging as a key target for regulating levels of protein synthesis. Gathering evidence indicates that ribosome heterogeneity occurs with respect to composition and post-translational modification of ribosomal proteins, incorporation of different ribosomal protein paralogs, modification of the rRNA, and association of specific translation factors,all pointing tofunctional differencesin ribosomes or their specialization(Byrgazov et al., 2013; Xue and Barna, 2012). For example, the presence or absence of specific ribosomal proteins in the ribosome is now known to control the translation of specific subsets of mRNA transcripts. RpL38 is necessary for translation of a specific Hox mRNAs in developing mouse embryos and its loss results in specific skeletal malformations which are recapitulated by deficiencies in the Hox proteins (Kondrashov et al., 2011). RpL40 isnecessary for translation initiation on vesicular stomatitis virus and related *Rhabdoviridaeviral* mRNAs, as well as on a select subset of cellular mRNAs(Lee et al., 2013).In addition, changes in rRNA methylation in cancer cells resulting from p53 loss-of-function and the dysregulation of the rRNAmethyltransferaseFibrillarin generates ribosomes with an increased tendency for cap-independent initiation, stop codon read-through and

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amino acid misincorporation(Marcel et al., 2013).Even bacterial ribosomes, streamlined in size relative to their eukaryotic counterparts, are dynamically modified to overcome rapid changes in environmental conditions (Byrgazov et al., 2013).

In most eukaryotes, small noncoding RNAs including miRNAs and siRNAs are important modulators of translation. However, these generallybind mRNAs to repress translation or trigger mRNA degradation(Huntzinger and Izaurralde, 2011). Recently, a group of novel small noncoding RNAsthat associate directly with the ribosome have been identified in yeast, although their biological function, if any, was unclear(Zywicki et al., 2012). In this issue of *Molecular Cell*,Pircher *et al. (2014)* show that the most abundant of these ncRNAs is derived from an mRNA, is constitutively bound to the ribosome itself,and modulates global translation levels in response to acute hypertonic stress (Pircher et al. 2014).

Pircher *et al.*(2014) identifieda stable 18-nt ncRNAderived from the exon on the *TRM10* mRNA that predominantly associates with ribosomes in all growth conditions. In favorable osmotic conditions the 18-mer ncRNA associates with nontranslating 60S ribosomal subunitsand 80S ribosomes,but only a very small portion associates with translating ribosomes, i.e. withpolysomes. Hypertonic conditions induce this 18-mer to rapidly and almost completely redistribute to the polysomes, where it remains bound to the 60S ribosomal subunit as opposed to mRNA or other factors. The redistribution of this ncRNA to polysomes is specific to hypertonic shock and is associated with a temporary global slowdown in translation. Notably, in a series of elegant genetic experiments, Pircher *et al.* show that it is the 18-mer itself, and not the Trm10 protein, that leads to these effects. Mutations that delete the 18-mer or disrupt its ability to associate with ribosomes abolish the hypertonic-shock induced translational slowdown and cause a marked decrease in tolerance to hypertonic shock. To further demonstrate that the 18-mer acts directly on translation, Pircher *et al.*show that artificial introduction of synthetic 18-mer into eitherspheroplasts or cell-free translation systems inhibits global translation.

Because the 18-mer ncRNA appears to transmit its signal through its redistribution from nontranslating to translating ribosomes instead of new ncRNA synthesis, and because it acts directly on the ribosome, it allows the cell to adapt to changes in conditions at extraordinarily fast timescales. Global translation slowdown occurs less than five minutes into hypertonic shock. There are several possibilities as to how an immediate global translation slowdown allows yeast to survive hypertonic shock. As protein synthesis is one of the major consumers of cellular ATP, a temporary shutdown of protein synthesis would increase the ATP available for adaptation. Another likely explanation is that the global protein synthesis shutdown gives time for other regulatory pathways to adjust gene expression and generate new transcripts appropriate for survival and growth in the new conditions while avoiding a waste of cellular resources on synthesis or proteins that are no longer needed.

Saccharomyces cerevisiae was chosen as model organism for these studies as it lacks miRNA pathways and the abundant miRNA would mask the signal from similar ribosome-associated ncRNA in other species (Zywicki et al., 2012). The question arises as to whether analogous processes exist in other organisms. Interestingly Pircher *et al.*(2014) show that the

yeast-derived 18-mer is able to inhibit translation in wheat germ, rabbit reticulocyte and even *E. coli* based cell-free translation systems suggesting that direct regulation of the ribosome by ncRNAcould be a widespread phenomenon.

Taken together, Pircher *et al.*(2014) have demonstrated a remarkable example of direct regulation of the ribosome by a small ncRNA, allowing the cells to make near immediate adjustments and survive sudden changes in their environment. Determination ofhow hypertonic stress signals are transduced to the ribosome pool and the mechanism by which the 18-mer redistributes from non-translating 60S ribosomal subunits to enter polysomes is an important question for future research. Other outstanding questions include the location of the 18-mer binding site on the 60S subunit, the mode of binding and the mechanism by which the 18-mer inhibits translation. The work of Pircher *et al.* presented in this issue adds ribosome-associated ncRNA to the growing list of the ways that the ribosome can be specializedto modify its activity and allow the cell to adapt to changing conditions. It also highlights that important regulatory RNAs can be repurposed from many different sources. The major challenge will be to identify the needle in the haystack of conditions in which each of these possible ncRNAs plays its crucial role.

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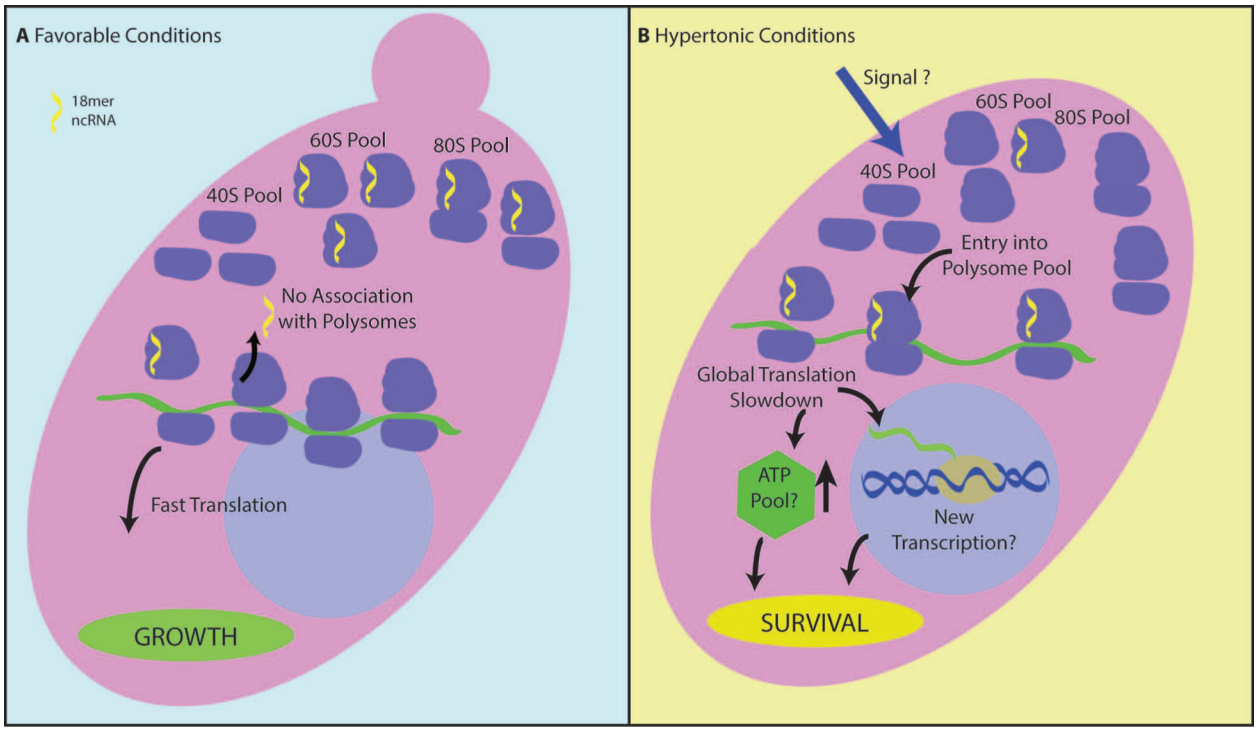

Figure 1. The *TRM10*mRNA-derived ncRNA directly modulates ribosome activity to allow yeast to survive hypertonic shock

(A) Under favorable osmotic conditions the 18-nt. ncRNA associates with 60S ribosomal subunits and 80S ribosomes but does not enter polysomes. (B) Under hypertonic conditions the 18-nt. ncRNA rapidly redistributes to the polysomes and causes a global slowdown of translation, which promotes cell survival.Possible explanations for the increase in viability include providing the cell time to synthesize new transcripts and undergo longer term adaptations, and providing a temporary boost in ATP levels to aid other cellular processes, such as stress responses.