Abstract: mRNAs encoding signal sequences are translated on endoplasmic reticulum (ER)-bound ribosomes, whereas mRNAs encoding cytosolic proteins are translated on cytosolic ribosomes. The partitioning of mRNAs to the ER occurs by positive selection; cytosolic ribosomes engaged in the translation of signal-sequence-bearing proteins are engaged by the signal-recognition particle (SRP) pathway and subsequently trafficked to the ER. Studies have demonstrated that, in addition to the SRP pathway, mRNAs encoding cytosolic proteins can also be partitioned to the ER, suggesting that RNA partitioning in the eukaryotic cell is a complex process requiring the activity of multiple RNA-partitioning pathways. In this review, key findings on this topic are discussed, and the template-partitioning model, describing a hypothetical mechanism for RNA partitioning in the eukaryotic cell, is proposed.

Key words: mRNA, ribosome, endoplasmic reticulum, translation, protein synthesis, signal sequence, RNA localization.

Résumé : Les ARNm codant des séquences signal sont traduits dans les ribosomes associés au réticulum endoplasmique (RE), alors que les ARNm codant des protéines cytosoliques sont traduits dans les ribosomes cytosoliques. La compartimentation des ARNm au RE se produit par sélection positive; les ribosomes cytosoliques engagés dans la traduction de protéines comportant une séquence signal sont recrutés par une voie impliquant des particules de reconnaissance de signal (SRP) pour être subséquemment envoyés au RE. En plus de la voie des SRP, des études récentes mais aussi plus anciennes ont démontré que les ARNm codant des protéines cytosoliques peuvent aussi être envoyées au RE, suggérant que la compartimentation des ARN chez la cellule eucaryote est un processus complexe qui requiert l’activité de sentiers de compartimentation multiples. Dans cette revue, des découvertes clés touchant ce domaine sont discutées et le modèle hypothétique de « matrice de compartimentation » pour la compartimentation de l’ARN chez la cellule eucaryote, est proposé.

Mots clés : ARNm, ribosome, réticulum endoplasmique, traduction, protéogenèse, séquence signal, localisation de l’ARN.

[Traduit par la Rédaction]
Fig. 1. The signal-recognition particle (SRP) – ribosome cycle. A pathway for mRNA partitioning to the endoplasmic reticulum. Cytosolic ribosomes engaged in the translation of mRNAs encoding secretory or membrane proteins are targeted through the SRP pathway to the endoplasmic reticulum (ER) membrane. At the ER, the signal sequence engages the protein-conducting channel and protein translocation ensues. The termination of protein synthesis leads to the release of ribosomal subunits (L, large ribosomal subunit; S, small ribosomal subunit) from the ER membrane to the cytosol.

mRNA partitioning to the ER: Is the SRP pathway the only road for RNA traffic to the ER?

At the time of its inception, the model depicted in Fig. 1 lacked an in vivo correlate. With the discovery of yeast homologs of the SRP and the SRP receptor, fundamental questions about the mechanism of RNA partitioning in vivo could be addressed, using molecular genetic approaches. The unexpected conclusion from the first such studies, conducted in Saccharomyces cerevisiae, was that the inactivation of the SRP pathway was not lethal (Hann et al. 1989; Hann and Walter 1991; Mutka and Walter 2001). Rather, genetic ablation of SRP or SRP-receptor expression resulted in a marked suppression of cell growth followed by an adaptive transcriptional response, which led to the recovery of growth and...
cell division (Mutka and Walter 2001). Interestingly, the transcriptional response to inactivation of the yeast SRP pathway (the unfolded protein response) results in a dramatic proliferation of the ER membrane area. On the basis of these and other data, Mutka and Walter (2001) suggested that an unfolded-protein-response-mediated increase in ER surface area, and thus increased ER-bound ribosome density, is sufficient to enable increased levels of protein synthesis on the ER, which then compensates for the loss of SRP-mediated RNC trafficking. The advent of gene-silencing technologies has now allowed similar experiments to be performed in mammalian tissue-culture cells and parasites (Ren et al. 2004; Liu et al. 2002). Here, too, the results are surprising. In the transformed cell line HeLa, stable depletion of SRP, via shRNA-mediated knockdown of either the SRP 72 kDa or SRP 54kDa subunits, had a remarkably limited effect on membrane-protein synthesis and trafficking, with no overt effects on cell growth and division (Ren et al. 2004). Similarly, in trypanosomes, SRP54 depletion did not wholly disrupt protein translocation at the ER, although significant secondary growth phenotypes were present (Liu et al. 2002). Great caution must be used in extrapolating these findings to global conclusions regarding the broad biology of SRP in vivo. With this necessary caveat front and center, the results of genetic analyses in yeast, humans, and trypanosomes suggest the existence of additional, perhaps redundant, ER-directed RNA trafficking pathways that act to facilitate RNA partitioning to the ER.

Given the experimental data suggesting the existence of multiple pathways for mRNA partitioning to the ER, it is of interest to ask whether the (essential) function of the signal sequence in protein translocation reflects an equally essential function in the trafficking of RNAs to the ER. This question harkens back to the very thoughtful and critical analysis of RNA partitioning posed by George Palade (1975) in his Nobel Lecture of 1974, “Intracellular Aspects of the Process of Protein Secretion”. In his commentary, Palade remarked that:

...we need more information than we have at present on the relationship between free and attached ribosomes, on the position of polysomes at the time of initiation, and on the duration of polysome attachment to the ER membrane.

Palade’s commentary was a harbinger for recent studies on ribosome and mRNA traffic on the ER, which have focused on genomic analyses of the composition of free and ER-bound polysomes and the regulation of ribosome binding and release from the ER. Two predictions of the model depicted in Fig. 1 have recently drawn attention: (i) mRNAs display a bimodal distribution between free and ER-bound polysomes, with mRNAs encoding cytoplasmic proteins residing solely in association with free ribosomes and mRNAs encoding secretory–membrane proteins displaying a high degree of partitioning to ER-bound polysomes; (ii) the termination of protein synthesis on the ER leads to the release of ribosomes from the ER membrane and their recycling to a common cytosolic pool of ribosomal subunits.

Significant new insights into the first prediction were found, unexpectedly, in the results of recent cDNA-microarray-based screens for novel secretory and integral membrane proteins, conducted in mammalian cells, fly, and yeast (Kopczynski et al. 1998; Diehn et al. 2000). In these studies, the enrichment of individual RNAs in free and ER-bound polyribosome fractions of yeast, human T cells, and Drosophila embryos was examined using cDNA-microarray analyses (Kopczynski et al. 1998; Diehn et al. 2000). In addition to achieving the stated goal of identifying novel genes encoding secretory and membrane proteins, these studies included a puzzling observation; there was a substantial overlap of mRNAs encoding cytosolic proteins in the ER-bound fraction. Kopczynski et al. (1998), in their study in Drosophila, observed the following:

Although the ER cDNA library is 4- to 5-fold enriched for membrane and secreted proteins, this library also contains a large fraction of cDNAs encoding cytosolic and nuclear proteins.

Similarly, Diehn et al. (2000), in their studies in yeast and mammalian cells remarked:

The distribution of fluorescence ratios for these characterized genes showed two overlapping populations... Thus, many mRNAs are not simply partitioned between membrane-associated and free polysomes. There are likely to be biological explanations (for example, translational regulation or ribosome-independent association of mRNAs with the membrane fraction) for the variability of the association of mRNAs with membranes.

Interestingly, much earlier studies (circa 1980) used cDNA hybridization kinetics to analyze the population similarities between cytosol and ER-bound polysomes, and also concluded that there exists substantial overlap of mRNAs encoding cytosolic proteins in the ER-bound polyosome fraction (Mechler and Rabbitts 1981; Mueckler and Pitot 1981). Indeed, Mueckler and Pitot (1981) comment:

The finding that a complete complement of poly(A)+ RNAfree is found in tightly bound polyosome structures is difficult to reconcile with the hypothesis that signal-peptide sequences are solely responsible for the segregation of free and membrane-bound polysomes.

As discussed by many workers in the field, then and now, the results of all such studies must be tempered by concerns of cross-contamination. In addition, a number of studies emphasized the role of the cytoskeleton in the selection of sites for RNA localization (Fey et al. 1986; Heskeleth 1996). However, extensive control experiments evaluating the occurrence of mRNA and ribosome cross-contamination as a consequence of cell fractionation argue the contrary (Mechler and Vassalli 1975; Mueckler and Pitot 1981; Lerner et al. 2003). When evaluated from the standpoint of cDNA-microarray-based investigations into RNA partitioning, the view that cross-contamination provides an adequate explanation for these findings becomes seemingly untenable not only for reasons of statistical analysis, but also because the cDNA-microarray data provide insight into partitioning at the level of individual mRNAs. Here, individual mRNAs display distinct and overlapping enrichments in the free or bound polyosome fraction, rather than the variable stochastic distributions that would occur as a consequence of simple cross-contamination. A more tenable and simpler interpretation would be that current models (Fig. 1), though remarkably accurate in their depiction of the mechanism of protein
translocation, do not fully explain the observed mRNA partitioning between the cytosol and ER compartments of the cell.

In all studies to date on the distribution of mRNAs between free and bound polysomes, the 2 mRNA pools were obtained with subcellular-fractionation protocols that required homogenization of tissue or tissue-culture cells and multiple centrifugation steps. Despite efforts to resolve potential issues of cross-contamination, persistent questions regarding these observations have remained. To address these concerns, a recent study analyzed mRNA partitioning using multiple cell-fractionation protocols, including a detergent-based procedure that did not require cell homogenization and a companion single-cell in situ hybridization study (Lerner et al. 2003). Regardless of the method used to analyze mRNA partitioning, it was concluded that ER-bound ribosomes can engage in the translation of mRNAs encoding cytosolic proteins and, significantly, that mRNAs encoding cytosolic proteins can be highly partitioned to the ER (Lerner et al. 2003). These findings, viewed in the context of past studies, strongly support the existence of additional or alternative pathways for ER-directed mRNA partitioning in the cell. In fact, such pathways have been established in plant cell systems. In a series of pioneering studies, the Okita laboratory reported that mRNAs encoding rice-seed prolamines and glutelins are targeted to specific subdomains of the ER, with prolamine mRNAs targeted to the protein-binding ER fraction and glutelin mRNAs targeted to the cisternal ER fraction (Choi et al. 2000; Okita and Choi 2002; Hamada et al. 2003a, 2003b; Crofts et al. 2004). As will be later discussed, the prolamine mRNA localization pathway has been shown to use cis-targeting elements present in the translated and untranslated regions of the prolamine cDNA, and represents a compelling example of an ER-directed mRNA sorting pathway (Hamada et al. 2003b).

As depicted in Fig. 1, mRNA partitioning to the ER is thought to occur as a consequence of the translation-dependent cycle of ribosome binding and release, as directed by the SRP pathway. It is important to note that this model does not suggest that the mRNA itself undergoes continuous rounds of ER-directed targeting and release. Indeed, once RNA is targeted to the ER, the ongoing cycle of translational termination and reinitiation, occurring in context of the ER-bound polysome, would be expected to contribute to the phenomenon of ER RNA localization. Although in vitro evidence for a cytosol-to-ER RNC trafficking pathway is very well established, the existence of the complementary process — termination-coupled ribosome release — has not been established. To test this prediction, in vitro and in vivo experimental systems were developed to examine the compartmental fate of membrane-bound ribosomes following termination. In one set of experiments, pharmacological inhibitors were used to block different stages of the translation reaction. After the addition of pactamycin (initiation inhibitor) or puromycin (premature chain termination), polyribosome breakdown was observed. The pharmacological induction of polyribosome breakdown was not, however, accompanied by ribosome release from the ER membrane (Potter and Nicchitta 2000, 2002; Seiser and Nicchitta 2000).

The observation that ribosomes reside in stable association with the protein translocation apparatus after termination raises a number of important issues, foremost being physiological significance. In the studies noted above, pharmacological methods were used to inhibit the initiation reaction of protein synthesis or to elicit premature chain termination, thereby eliciting polysome breakdown. It will be important to establish whether similar phenomena occur under physiological scenarios in which the initiation reaction of protein synthesis is inhibited. Such scenarios would include activation of the unfolded-protein response, which activates the eIF2α-directed kinase PERK and infection of cells with viruses encoding translation products known to proteolytically inactivate the eIF4F complex, thereby inhibiting cap-dependent translation (i.e., picornaviruses). Assuming that the results observed with pharmacological inhibitors are of physiological relevance, 2 further questions can be posed: Can post-termination membrane-bound ribosomes initiate mRNA translation de novo? And, if so, are they selective for mRNAs encoding secretory or membrane proteins? In initial experiments designed to address these questions, rough microsomal membranes were incubated in the presence of a ribosome-free reticulocyte lysate fraction, and their capacity to synthesize secretory and cytosolic proteins was examined (Potter and Nicchitta 2000). It was observed that membrane-bound post-termination ribosomes could engage in the de novo synthesis of cytosolic proteins and, under these circumstances, could be released from the membrane as RNCs (Potter and Nicchitta 2000; Potter et al. 2001). These observations provided unexpected possible answers to the above questions: ribosome release from the ER membrane can occur in response to the synthesis of a protein lacking a signal sequence; and de novo protein synthesis can be initiated on ER-bound ribosomes (Potter and Nicchitta 2000). It has been suggested that this process, which has been called elongation-coupled ribosome release (E-CRR), participates in the cellular partitioning of mRNAs. In this process, E-CRR directs mRNAs that partition to the cytosol at steady state and for which translation is initiated on ER-bound ribosomes to their proper compartment. As schematically illustrated in Fig. 2, E-CRR can be viewed as the complement to the SRP pathway.

Although the E-CRR model provides an explanation for the way mRNAs encoding cytosolic proteins, the translation of which is initiated on ER-bound ribosomes, can be partitioned to the cytosol, it does not explain how an mRNA encoding a cytosolic protein (mRNA<sub>cyt</sub>) is selectively partitioned to the ER. In essence, E-CRR describes a process of negative selection, whereas the SRP pathway describes a process of positive selection. Combined, the 2 models provide an explanation for a bimodal and nonoverlapping distribution of mRNAs between the cytosol and ER compartments, and may well describe how mRNAs that are uniquely distributed in either compartment achieve such a distribution. However, the more common observation is that mRNA<sub>SER</sub> are generally present, albeit at low enrichment, in the ER-bound fraction and (or), as noted, a given mRNA<sub>cyt</sub> can be highly enriched in this fraction (Mueckler and Pitot 1981; Diehn et al. 2000). It appears, then, that additional mechanisms—processes are needed to explain the more commonly observed overlapping distribution of mRNA<sub>cyt</sub> between the ER and cytosol compartments. To this end, it is useful to summarize...
some common features of known RNA localization processes.

**RNA localization: cellular pathways for compartmentalizing protein synthesis**

Although the current model for the mechanism of RNA partitioning to the ER, summarized in Fig. 1, is well accepted, a growing body of experimental data suggests that additional processes contribute to RNA partitioning, which leads to overlapping patterns of RNA distribution between the cytosol and ER compartments of the cell. This conclusion stems from 3 recently established observations: first, analyses of the cellular consequences of inactivating the SRP pathway (through gene deletion or gene silencing) reveal the presence of complementary pathways for maintaining RNA partitioning when SRP function is compromised (Hann et al. 1989; Hann and Walter 1991; Mutka and Walter 2001; Ren et al. 2004); second, RNAs encoding cytosolic proteins can be highly partitioned to ER-bound ribosomes (Mechler and Rabbitts 1981; Mueckler and Pitot 1981; Kopczynski et al. 1998; Diehn et al. 2000); and third, after the induction of termination, ribosomes remain in continued stable association with the Sec61 ribosome receptor of the ER (Potter and Nicchitta 2000; Potter et al. 2001). To reconcile these differences, we propose the following amendment to the current model: RNA partitioning to the ER is influenced by, and in some cases wholly dependent upon, RNA encoded cis-acting ER-localization signals. This proposal is consistent with the broad biology of RNA localization. To quote from a recent review on mRNA localization in higher eukaryotes (Palacios and Johnston 2001):

> The intracellular localization of mRNA, a common mechanism for targeting proteins to specific regions of the cell, occurs in most if not all cell types and provides an important mechanism for targeting proteins to the cellular regions where they are required.

**Mechanisms of RNA localization**

In recent years, it has become abundantly clear that RNA localization is a common and phylogenetically conserved process for efficiently directing gene products to discrete compartments in the cell. The biological significance of RNA localization became prominent after the developmental biology community demonstrated that RNA localization dictates cell polarity, which is essential to pattern formation and plays key roles in cell-fate determination (Palacios and Johnston 2001). Beginning with studies on the mechanism of axis generation, which identified an essential process of mRNA
localization for cellular identification of the animal and vegetal poles of the *Xenopus* oocyte, investigations into the mechanism of antero-posterior patterning in the Drosophila embryo identified *bicoid*, *oskar*, and *gurken* mRNAs, which localize to 3 distinct positions within the embryo (St Johnston 1995; Palacios and Johnston 2001). Further investigations into the mechanism of RNA localization have resulted in the discovery of a number of RNA-binding proteins that interact with compartmentalized mRNAs, and substantial inroads into the mechanism(s) of mRNA targeting have been achieved (Dreyfuss et al. 2002; Colegrove-Otero et al. 2005). An appreciation for the role of mRNA localization in the cell-polarity events critical to early development stimulated interest in potential roles of mRNA localization in the genesis of cell polarity in somatic mammalian cells, in particular highly polarized cells such as neurons. Such studies have yielded significant rewards. For example, because of early studies demonstrating that mRNAs encoding myelin basic protein were enriched in the distal processes of oligodendrocytes, it has now been established that dendritic localization of myelin basic protein mRNA is essential for proper axonal myelination (Colman et al. 1982; Trapp et al. 1987). In addition, mRNA localization is thought to play critical roles in synaptic plasticity, where mRNAs encoding calcium-calmodulin kinase II, MAP2, and the glycine receptor have been localized to terminal dendritic processes (Kleiman et al. 1990; Racca et al. 1998).

Although multiple mechanisms contribute to RNA localization in the systems studied to date, all known RNA localization processes require cis-acting elements in the RNA, which serve as signals to direct RNA localization, and trans-acting factors, which recognize such signals. In general, cis-acting mRNA localization signals have been mapped to the 3′ untranslated-region (UTR) and, to a lesser extent, the 5′ UTR elements (Garner et al. 1988; Ainger et al. 1997; Chartrand et al. 1999; Palacios and Johnston 2001). These localization sequences can function autonomously, do not display conserved primary nucleotide motifs, and often require higher-order (stem-loop) structures to function (Palacios and Johnston 2001). Progress on the identification of trans-acting factors has lagged somewhat, although recent genetic screens for gene products essential in mRNA localization are proving successful. For example, it has been demonstrated that the RNA-binding proteins VgRB60 and hnRNP2 play critical roles in the localization of Vg1 and myelin basic protein RNA, respectively, (Hoek et al. 1998; Cote et al. 1999). Intriguingly, it has also been demonstrated that this paradigm functions in the localization of prolamine- and glutelin-encoding mRNAs to subdomains of rice-seed ER, formally demonstrating that cis-element-dependent RNA partitioning to the ER may contribute to, if not define, the mechanism of ER-directed RNA partitioning in eukaryotic cells (Choi et al. 2000; Okita and Choi 2002; Hamada et al. 2003b). As with other RNA localization pathways, RNA localization to subdomains of plant ER is dependent on cis-targeting elements present in the 3′ UTRs of the prolamine and glutelin mRNAs (Choi et al. 2000; Okita and Choi 2002; Hamada et al. 2003b). As well, these signals have been shown to function autonomously and, thus, can direct the ER localization of reporter-coding regions. It will be interesting to determine whether analogous pathways operate in mammalian cells, and whether such putative pathways function to globally regulate RNA partitioning to the ER.

**The template-partitioning model**

Combined, the positive-selection (SRP pathway) and negative-selection (E-CRR pathway) models provide a means of achieving a nonoverlapping bimodal distribution of mRNAs, particularly if it is recognized that ribosomes in the cytosol and on the ER membrane can participate in de novo mRNA translation. To achieve the more commonly observed pattern of mixed RNA partitioning, we propose the tempate-partitioning model. This model has 2 basic predictions: that newly exported mRNAs are preferentially translated on membrane-bound ribosomes of the outer nuclear envelope – ER; and that individual mRNAs exist as a population ensemble, differing in RNA-binding protein composition, with the RNA-binding protein composition determining the subcellular locale of the mRNA. With this mechanism, a given mRNA can stably reside in both the cytosol and ER compartments of the cell, to varying degrees. These 2 predictions are briefly discussed below.

The first prediction of the template-partitioning model is that newly exported mRNAs are preferentially translated on membrane-bound ribosomes of the outer nuclear envelope – ER. This prediction stems from studies demonstrating that membrane-bound ribosomes are capable of the de novo initiation of protein synthesis, as well as extensive literature on the RNA surveillance process referred to as nonsense-mediated decay (NMD). Regarding the former, past analyses of the subcellular site of translation of the 7S Balbiani ring RNA have demonstrated that ribosomes can assemble on transcripts coincident with their emergence from the nuclear pore complex (Mehlin et al. 1991). It remains to be determined whether such a cotranslational RNA export is mediated by membrane-bound and (or) free ribosomes. It is reasonable, though, to consider a role for bound ribosomes of the outer nuclear envelope – ER in cotranslational RNA export in which bound ribosomes of the outer nuclear envelope – ER participate, if only transiently, in the translation of all newly exported mRNAs. Such a phenomenon would account for the observation that mRNAs encoding cytosolic proteins are well represented, although generally not enriched, on membrane-bound ribosomes. With respect to the latter, it has been established that mRNAs encoding frameshift or nonsense mutations that generate premature termination codons are subject to a regulated process of recognition and degradation, referred to as NMD. NMD requires translation and, in general, but with exception, occurs in association with the nucleus (Wormington 2003; Maquat 2004; Wilkinson 2005). The translation-dependent scanning of mRNAs for premature-termination codons is thought to occur during the initial, or pioneer, round of translation (Ishigaki et al. 2001). Although the precise subcellular site of NMD has not been identified, it has been suggested that the translation event are coincident with the exit of the 5′ end of the mRNA from the nuclear pore complex (Maquat 2004). As noted above, we speculate that bound ribosomes of the outer nuclear envelope – ER may contribute to this translation function.
The second prediction of the template-partitioning model is that individual mRNAs can exist as a population ensemble, differing in their RNA-binding protein composition and, through this binding protein heterogeneity, displaying complex patterns of partitioning in the cell. In this proposal, schematically illustrated in Fig. 3, mRNAs encoding a particular gene product comprise different subpopulations, each of which contains a particular cohort of RNA-binding proteins that localize the mRNA to a given compartment of the cell. For the sake of simplicity, this is depicted as the cytosol and the ER compartments; more likely, such signals would also include RNA-binding proteins determining localization to other organelles of the cell, such as mitochondria and (or) chloroplasts (Lightowlers et al. 1996; Ossenbuhl et al. 2002; Sylvestre et al. 2003) or different regions of the cell, such as the apical or basolateral domains of a polarized epithelia, or structures in highly polarized cells, such as the nodes of Ranvier in central myelinated neuronal fibers. How such a population ensemble would be created is not known, although a simple model predicts that the affinities of a particular RNA-binding protein recognition sequence for different RNA-binding proteins would allow, from a population perspective, overlapping patterns of RNA-binding protein composition, as influenced by the relative affinities and the abundance of different RNA-binding proteins. Implicit in this prediction is the existence of compartment- or organelle-restricted RNA-binding protein receptors that recognize the ribonucleoprotein and constrain it to a particular locale. Such proteins have not yet been identified.

This second prediction of the template-partitioning model is highly speculative, and there exists no direct evidence for such a mechanism. Such a model could explain, however, why mRNAs reside in different compartments of the cell. Of course, the more puzzling question is why the phenomenon of multicompartmental mRNA partitioning occurs at all. In all likelihood, this question will have to be addressed in a transcript-by-transcript manner. As one example, the mRNA encoding glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a glycolytic enzyme, is enriched in the cytosol compartment, yet has been reported to have a distinct ER-associated component (Lerner et al. 2003). Interestingly, it has recently been proposed that GAPDH has a function other than its role in glycolysis; it regulates, through direct binding interactions, the calcium-release function of the ER inositol trisphosphate-regulated calcium channel (Patterson et al. 2005). Perhaps a subpopulation of GAPDH mRNA is translated on ER-bound ribosomes to facilitate this function.

Conclusions

With the advent of cDNA-microarray technology, previous observations regarding the unexpected and overlapping steady-state partitioning of mRNAs between the cytosol and ER compartments of the cell have again come under investigation. Ironically, insights into this phenomenon are likely to be accompanied by answers to fundamental questions proposed by Palade decades ago, for which we have only the barest of insights. It can be argued that current models do not satisfactorily answer how RNAs are partitioned in eukaryotic cells;
the template-partitioning model is proposed as a beginning framework for understanding this process.

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