Quality control

Is there quality control of localized mRNAs?

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In eukaryotic cells many mRNAs are localized to specific regions of the cytosol, thereby allowing the local production of proteins. The process of mRNA localization can be coordinated with mRNA turnover, which can also be spatially controlled to increase the degree of mRNA localization. The coordination of mRNA localization, translation repression during transport, and mRNA degradation suggests the hypothesis that an additional layer of mRNA quality control exists in cells to degrade mRNAs that fail to be appropriately localized.

Introduction

The biogenesis and function of eukaryotic mRNAs involves a diversity of biochemical reactions. These include capping, splicing, and polyadenylation in the nucleus, as well as transport to the cytosol, where the mRNA is engaged in translation before ultimately being degraded. In each case, the biochemical reaction and its specificity are modulated by a variety of mRNA-binding factors including proteins, microRNAs, and potentially other long noncoding RNAs.

Eukaryotic cells contain a wide variety of quality control systems that lead to the degradation of RNAs defective in any of the basic steps of biosynthesis and function (Doma and Parker, 2007; Houseley and Tollervey, 2009). Quality control acts on three general populations of mRNAs. First, mRNAs with a mutation causing an inherent defect in normal function, such as a mutation inhibiting pre-mRNA splicing, or an early nonsense codon, will be subject to quality control with the vast majority of the mutant mRNAs being degraded. In addition, quality control will also act on specific mRNAs whose RNA-processing reactions have yielded an mRNA lacking normal features. For example, when alternative splicing produces an mRNA with an early translation stop codon, such mRNAs are rapidly degraded by a pathway called nonsense-mediated decay (Lamba et al., 2003; Mendell et al., 2004). Finally, due to the competition between normal function and quality control systems, a fraction of mRNAs from any given gene that fail to efficiently complete a functional step will also be degraded by quality control. For example, in yeast a low but measurable percentage of various wild-type pre-mRNAs are degraded by quality control systems (Hilleren and Parker, 2003; Harigaya and Parker, 2012).

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In general, quality control circuits can be understood as a competition between the normal function of an mRNA and a competing RNA degradation pathway (Doma and Parker, 2007). The enhanced degradation of nonfunctional RNAs by such quality control pathways is then specified by either features of functional mRNAs that promote their rapid bypassing of the competing RNA degradation step, or features of aberrant mRNAs that enhance the rate of the competing degradation pathway on such nonfunctional mRNAs.

Many mRNAs are localized to distinct regions of the cytoplasm in eukaryotic cells. Localized mRNAs were first observed in specialized biological contexts such as neurons, oocytes, and embryos (Martin and Ephrussi, 2009). However, it is now clear that many, if not the majority of mRNAs, are localized in eukaryotic cells and that mRNA localization is not limited to specialized cells. For example, a comprehensive screen of mRNA localization in *Drosophila* embryos revealed that over 70% of mRNA showed a specific pattern (Lécuyer et al., 2007). Moreover, in somatic cells, specific mRNAs are localized to the surface of mitochondria, the ER, or even with peroxisomal membranes (Weis et al., 2013). An increasing number of these types of examples argue that mRNA localization is a widespread and common feature of eukaryotic cells.

By localizing mRNAs, the production of protein can be constrained to a specific region of the cell. This can allow for more efficient assembly of proteins into larger complexes, or transport of polypeptides across membranes as in the case of localizing mRNAs to the ER or mitochondria to enhance cotranslational import. Localized translation of mRNAs can also allow for different cell fates from dividing cells as each progeny cell gets different polypeptides. A well-studied example of this phenomenon is the localization of the Ash1 mRNA to the bud tip of yeast cells to specify cell type switching only in the daughter cell (Heym and Niessing, 2012). Asymmetric localization of mRNAs also plays important roles in numerous cell fate determinations in development and presumably also in stem cell lineages (Martin and Ephrussi, 2009). Localization of mRNAs can also allow for local control of translation to allow for different cellular responses in different parts of the cell. For example, in neurons mRNAs localized to dendrites can be locally stimulated to enter into

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translation by synaptic activity (Holt and Schuman, 2013). Finally, the localization of mRNAs to specific regions can also limit the toxic effects of broadly producing specific proteins.

In this review, we discuss emerging lines of evidence suggesting that the processes of mRNA localization and mRNA turnover can be interrelated. For example, there are a growing number of examples where mRNA degradation is regulated in a spatially restricted manner. Second, there are several RNA-binding proteins that regulate both localization and mRNA degradation. Finally, fundamental and general relationships between mRNA localization, translation, and degradation dictate that mRNA localization and degradation will be intertwined. Moreover, these relationships lead us to hypothesize that quality control systems will exist such that mislocalized mRNAs will be preferentially degraded.

mRNA turnover can be spatially controlled

Several observations have established that the degradation of mRNA can be controlled in a spatially restricted manner, which can then have an impact on the subcellular distribution of mRNAs within the cell. In principle, this could be achieved either by cis-mRNA sequences in mRNAs that promote degradation only in a specific region of the cell, or by regulated localization of the mRNA decay enzymes. Examples where cis-RNA elements determine mRNA fate include *Drosophila* embryos, where the enhanced concentration of the Nanos and Hsp83 mRNAs at the posterior pole is partially dictated by increased degradation of these mRNAs elsewhere in the embryo (Bashirullah et al., 2001). Similarly, the Arc mRNA is only degraded in the dendrites of neurons after synaptic activity, which promotes its entry into translation (Giorgi et al., 2007).

Directing specific mRNA decay programs to distinct subcellular locations can also spatially control mRNA decay. Ire1-mediated decay is localized to the ER, where it alters mRNA stability during stress (Gaddam et al., 2013). Alternatively, the concentration of general decay enzymes such as Dcp2 and Xrn1 into cytoplasmic P-bodies could either accelerate decay of P-body–localized transcripts or protect nonresident transcripts from decay (Decker and Parker 2012). Given improved technological advancements in subcellular mRNA resolution, one anticipates that more examples of the local control of mRNA degradation will be identified in the future.

Inherent coupling of localization, translation, and mRNA degradation

Two aspects of the inherent and fundamental relationships between mRNA localization, translation, and mRNA degradation impact how cells intertwine localization and mRNA turnover. First, during mRNA localization, mRNAs are generally kept in a translationally repressed state (Martin and Ephrussi, 2009). This is to facilitate transport because localizing an mRNP is potentially simpler than localizing a polysome. Moreover, by repressing translation of mRNAs until they are localized, where translation repression is relieved, it ensures that proteins are only produced in the proper location. Translation repression of mRNAs during transport is often achieved by the formation of mRNP complexes that sequester the 5′ cap structure away from the translation machinery (Sonenberg and Hinnebusch, 2009). Once mRNAs are appropriately localized, modification of mRNA-binding proteins can lead to mRNP remodeling and relief of translation repression (Hüttelmaier et al., 2005, Paquin et al., 2007).

The second key principle is that translation initiation and mRNA degradation are generally inversely related (Coller and Parker 2004; Roy and Jacobson, 2013). This relationship can be understood as the dual role of the poly(A) tail and cap structures as both promoting translation initiation through the binding of the poly(A)-binding protein (Pab1) and the cap-binding protein eIF4E, respectively, as well as being the targets of the deadenylases and decapping enzymes that catalyze the major pathway of mRNA turnover.

Given the repression of translation during localization, and the typical stimulation of mRNA degradation by repression of translation initiation, it creates an optimal functional mRNP for efficient and accurate mRNA localization. In this view, an mRNP for transport should be translationally repressed until localized, and also protected from mRNA degradation for a window of time to allow for localization before degradation. However, the transport mRNP should only be stable for a sufficient time to allow for efficient transport, and would ideally be subject to degradation if not localized within a biologically appropriate time period. Possible mechanisms to achieve this balance are discussed below.

Dual use proteins: Coupling localization and decay

Another line of evidence for the coupling of mRNA localization and degradation comes from the observation that several RNA-binding proteins are now known to control both mRNA localization and degradation. The specifics of how these proteins function suggest possible manners by which the cell couples localization and mRNA degradation.

In some cases, proteins play bi-functional roles in promoting both localization and mRNA degradation, and by doing so could increase the decay rate of unlocalized mRNAs. One example of this phenomenon is the yeast Puf3 protein, which is a member of the pumilio family of RNA-binding proteins (Wickens et al., 2002). The Puf3 protein binds to ∼200 yeast mRNAs that encode proteins involved in mitochondrial function and affect their metabolism in two manners (Gerber et al., 2004). First, Puf3 can target bound mRNAs to the surface of mitochondria, presumably to increase the efficiency of cotranslational import (Saint-Georges et al., 2008; Eliyahu et al., 2010; Gadir et al., 2011). Second, Puf3 is known to promote the deadenylation and decapping of its bound mRNAs (Olivas and Parker, 2000). Strikingly, the ability of Puf3 to promote decay is modulated by carbon source and Puf3 stimulates decay when cells are grown in glucose (and mitochondrial function is decreased) but not when cells are grown in glycerol or ethanol (where mitochondria function is increased; Foat et al., 2005; Miller et al., 2013).

These dual roles of Puf3 suggest a model whereby the cell regulates its ability to control mRNA localization and degradation in a manner dependent on carbon source (Fig. 1) with mRNAs that fail to get localized being subject to Puf3 mediated degradation, while mRNAs that get localized are protected from the stimulation of degradation by Puf3. An untested prediction of this

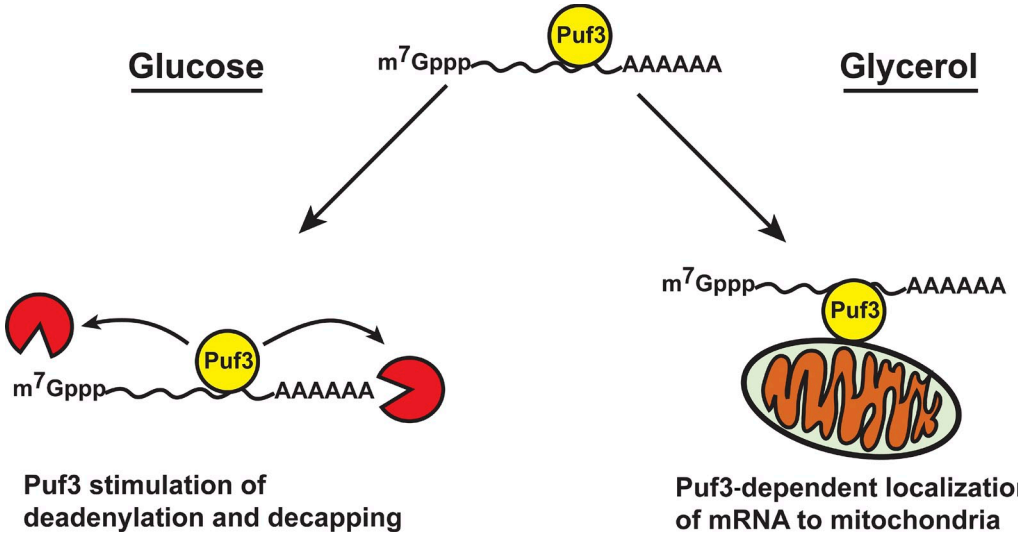

Figure 1. **Dual functions of Puf3.** Under normal growth conditions (i.e., glucose), Puf3 in yeast enhances decapping and deadenylation (left). When grown in the presence of glycerol or ethanol—where mitochondria function is increased—Puf3 trafficks mRNAs to the surface of the mitochondria (right). The red "pacman" elements represent 5′- and 3′-directed mRNases.

model is that interactions of Puf3 with the mitochondrial surface receptors are anticipated to block its ability to promote deadenylation and decapping.

Puf6 is a second protein that may also have dual roles in mRNA localization and degradation. Puf6 binds to Ash1 mRNA and is required for its localization to the bud tip (Gu et al., 2004), and affects the localization of other mRNAs to the bud tip (Aronov et al., 2007). Puf6 also inhibits translation initiation in a manner proposed to be through interaction with eIF5B (Deng et al., 2008). Because Puf6 represses translation initiation, one would predict that it would also promote mRNA degradation given the inverse relationship between translation initiation and mRNA degradation, although no direct examination of how Puf6 affects mRNA degradation has been performed. Interestingly, in puf6Δ strains it appears that Ash1 mRNA might be somewhat elevated (see Fig. 6 in Gu et al., 2004), raising the possibility that Puf6 can also promote mRNA degradation, perhaps preferentially of unlocalized mRNAs.

A third example of the direct coupling of localization and mRNA degradation is the Staufen protein. In metazoans, Staufen proteins affect both mRNA transport and stability. Staufen is a dsRNA-binding protein and interacts with and can affect the localization or degradation of mRNAs that form extensive dsRNA regions in their 3′ UTR. A role for Staufen in mRNA transport was first observed during embryogenesis in *Drosophila* (St Johnston et al., 1991; Ferrandon et al., 1994). Staufen family members also play important roles in the transport of mRNAs in neurons and in the localization of specific mRNAs to dendritic spines (Lebeau et al., 2011; Heraud-Farlow et al., 2013). For example, knockdown of Staufen2 causes mislocalization of Rgs4 mRNA from neuronal dendritic spines (Heraud-Farlow et al., 2013). Moreover, neuronal transport of reporters bearing either multiple Staufen1- or Staufen2-binding sites was impaired upon corresponding Staufen knockdowns (Lebeau et al., 2011).

Staufen also affects mRNA degradation by triggering a pathway referred to as Staufen-mediated decay. In this pathway, Staufen bound to the 3′ UTR of an mRNA can recruit Upf1 (Park and Maquat, 2013). Upf1 is an RNA helicase involved in nonsense-mediated decay at premature stop codons and can also serve a second role in promoting mRNA decay when recruited to an mRNA by Staufen. An unresolved issue is how the processes of Staufen-mediated decay and its role in mRNA localization are related. One possibility is that they are independent effects on different mRNAs in different cells or organisms. For example, Staufen's role in mRNA decay has primarily been studied in human tissue culture cells, whereas its role in mRNA localization is best documented in neurons or oocytes. Alternatively, it remains possible that these two functions can overlap and mRNAs bound by Staufen may recruit Upf1 to allow for the activation of a distinct mRNA decay pathway if the mRNAs are not localized properly in a reasonable time frame.

mRNA localization and turnover should also be coupled by proteins that function to limit degradation of the mRNA during the transport process. In this case, defects in these proteins would be expected to cause accelerated decay and loss of localization. Moreover, because a common way of keeping the mRNA stable is to sequester the 5′ cap structure, which also blocks translation, such mRNP factors would also be expected to be translational repressors. One example of this type of relationship is the yeast Khd1 protein. Khd1 is known to affect the localization of the Ash1 and other mRNAs to the bud tip (Irie et al., 2002; Paquin et al., 2007). In addition, Khd1 can affect the stability of at least some localized mRNAs. For example, Khd1 binds to and plays a role in localizing the Mtl1 mRNA to the yeast bud tip (Hasegawa et al., 2008), but also stabilizes the Mtl1 mRNA from decapping (Hasegawa et al., 2008; Mauchi et al., 2010). One possibility in this case is that Khd1 stabilizes the Mtl1 mRNA by forming a translationally repressed complex on the 5′ cap structure consisting of Khd1, eIF4E, and eIF4G, which has been shown to be bound by Khd1 in a manner that blocks translation (Paquin et al., 2007; Rajyaguru and Parker, 2012). This would be an example wherein an mRNA that was

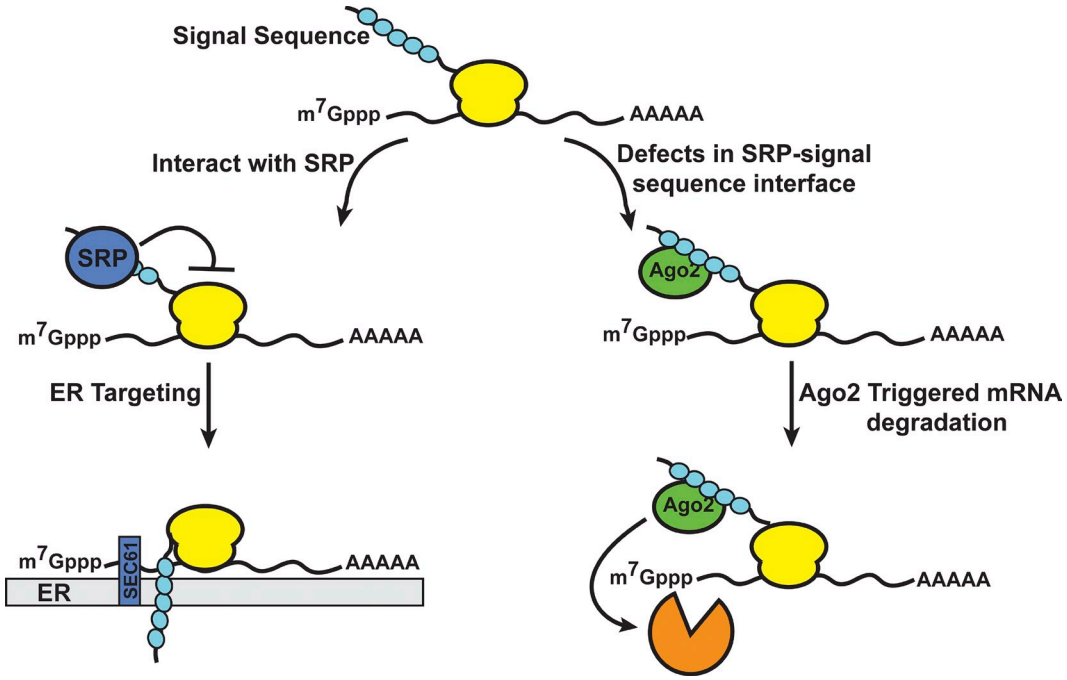

Figure 2. **Coupling of SRP-dependent localization and mRNA decay.** Proteins bound for the ER contain a signal sequence, a short peptide recognized by the SRP, which inhibits translation and targets these nascent polypeptides to the ER for cotranslational insertion through interactions with the Sec61 receptor (gray bar). mRNAs that encode a variant signal sequence that affects SRP binding are preferentially degraded. With SRP (blue) no longer able to bind, Ago2 (green) associates with these mRNPs undergoing translation. These mRNAs then undergo accelerated decay (illustrated by orange "pacman").

not properly translationally repressed would be degraded (and thus not localized).

Quality control of mRNAs targeted to the ER

A new example for mRNAs encoding proteins that are imported into the ER highlights how mRNA degradation can be used to preferentially degrade misfunctional and/or mislocalized mRNAs. Normally, the nascent signal sequence on mRNAs destined for the ER is bound by SRP, which both limits translation and facilitates the interaction of the nascent chain with the Sec61 receptor in the ER, thereby allowing translation to resume and cotranslational import of the polypeptide. Strikingly, defects in the signal sequence, or SRP itself, allow the nascent signal sequence to bind Ago2 in human cells, and this then triggers accelerated mRNA decay (Karamyshev et al., 2014). This suggests a model where there is competition between Ago2 and SRP for the emerging signal sequence, and failure of SRP to bind the signal sequence and localize the mRNA allows for Ago2 to bind the signal peptide and trigger mRNA degradation (Fig. 2).

Coupling of mRNA localization and turnover to allow quality control of localized mRNAs: A potential model

The inherent coupling of localization, translation, and decay, along with the mRNP remodeling that occurs when mRNAs are properly localized and enter translation suggests a model whereby the degradation of localized and unlocalized mRNAs will be different. This intersection of localization and degradation then plays roles in increasing the degree of mRNA localization, and also provides a possible quality control system to preferentially degrade mRNAs that fail to be properly localized.

In one model (Fig. 3), nascent mRNPs targeted for localization would enter the cytosol in a translationally repressed state. Such mRNAs would be initially protected from mRNA decay both by mRNP features that sequester the 5′ cap, and by the presence of a long poly(A) tail, which can both inhibit decapping (Muhlrad et al., 1994; Caponigro and Parker, 1995) and protect mRNAs from an alternative 3′-to-5′ degradation mechanism catalyzed by the cytoplasmic exosome (Anderson and Parker, 1998). Once in the cytosol, these mRNPs would become substrates for mRNA localization, as well as beginning the deadenylation process. If mRNAs are localized efficiently they enter translation and serve their normal function. Alternatively, if deadenylation is sufficiently advanced before proper subcellular localization then such mislocalized mRNAs would then be subject to an increased rate of degradation, potentially both by decapping and 3′-to-5′ degradation by the exosome. Note that for such a system to be effective in quality control, in the nontargeted region of the cell the rate of mRNA degradation simply must be faster than the rate of inappropriate entry into translation before localization.

The preeminence of the poly(A) tail in this model is due to two basic tenets: (1) the overwhelming number of examples where transported, translationally repressed mRNPs are cap protected; and (2) deadenylation is a two-step process, whereby loss of significant poly(A) tract residues is tolerated to a point where decapping, and/or 3′-to-5′ degradation can then occur. Moreover, at least in some cases, localized and translationally repressed mRNAs have short poly(A) tails once present at their destination. For example, in neurons several mRNAs delivered to the synapse

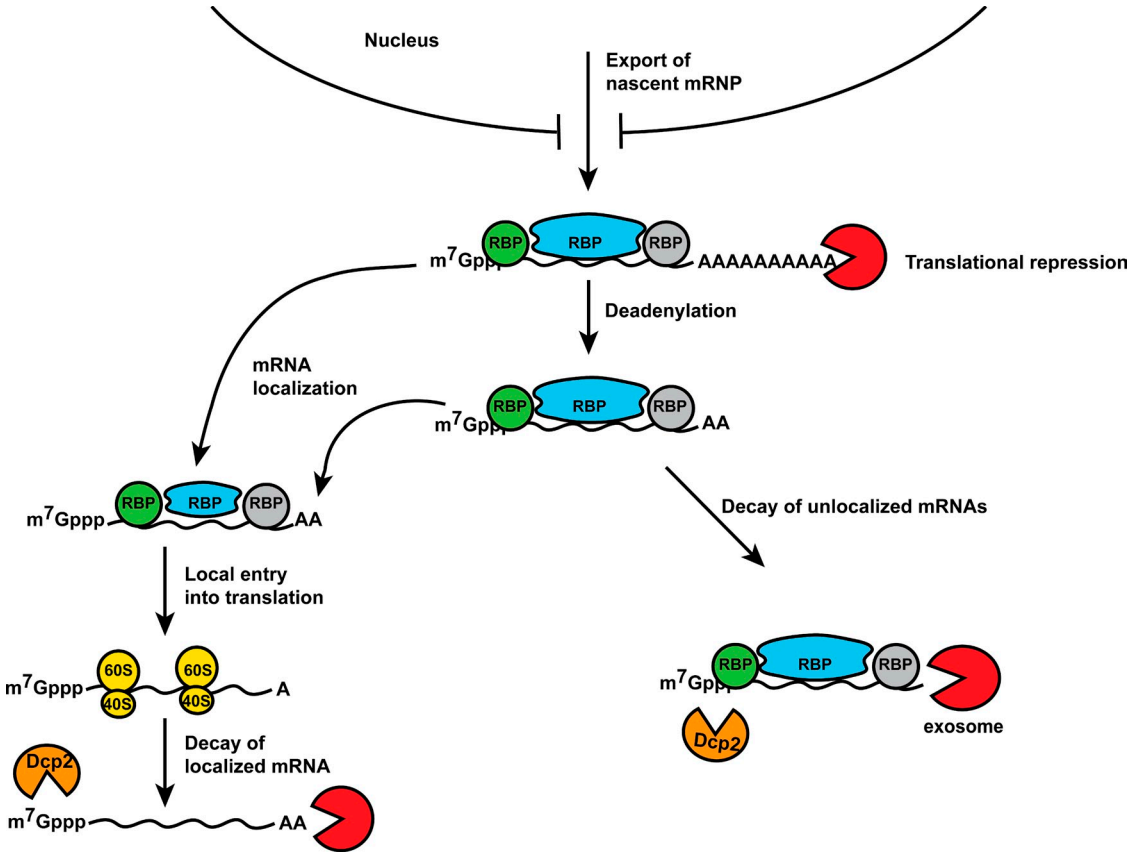

Figure 3. **Putative model of the decay of mislocalized mRNAs.** Once entering the cytoplasm, mRNAs that are bound for a specific subcellular location are initially translationally repressed and are subject to deadenylation. If localization proceeds faster than decay (left), the mRNA will be properly localized and enter into translation. Canonical decay processes will then degrade the mRNA. However, if there is a localization defect, which manifests in accelerated decay of the mRNA (right), the mRNA will be degraded before reaching its final destination. Gray, blue, and green features represent RNA-binding proteins (RBPs) bound to mRNAs before localization. Cellular nucleases are shown as red "pacman" figures.

are thought to have short poly(A) tails, which are then elongated upon translation activation by the recruitment of cytoplasmic adenylases in an mRNA-specific manner (Richter, 2010). Similarly, many maternal mRNAs are stored in a deadenylated state before readenylation and translational activation during development (McGrew et al., 1989).

This general model makes several predictions. First, before mRNA localization, mRNAs should be subject to deadenylation. Second, mRNAs that fail to get localized should be degraded at a faster rate. Third, some kinetic defects in localization could be rescued by slowing the deadenylation and/or decay rate of the mRNA in the nonlocalized compartment. Finally, cells will have taken advantage of this coupling to create "mRNA localization" mechanisms that really are selective mRNA translation and stabilization in specific regions of the cytosol. One anticipates that mRNA localization will involve an overlapping set of mechanisms where the spatial localization of each mRNA is dictated by differential effects of localization mechanisms and mRNA decay contributions.

Perspective

It is becoming increasingly clear that mRNA localization and turnover will be coupled in interesting and biologically relevant manners. Given the importance of mRNA localization, one anticipates that quality control mechanisms will exist to degrade mislocalized mRNAs. Such quality control mechanisms could take advantage of bi-functional proteins that affect both localization and mRNA turnover, or in some cases may be simply achieved by manipulation of the inherent coupling of translation, localization, and mRNA degradation mechanisms.

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