Mini-Review

RNA on the Move: The mRNA Localization Pathway

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BIOLOGISTS have long been fascinated by how cells target proteins to specific intracellular compartments and maintain their localized distributions. The problem of how proteins are sorted to particular membrane-bound organelles has been the focus of considerable effort in the last decade. As a result, a good deal is known about protein sorting signals (48, 54), the protein machinery needed for budding and docking vesicles in the secretory pathway (48, 54), and the mechanisms for transporting vesicles along microtubules and actin filaments within the cytoplasm (55).

In contrast to the relative wealth of information concerning the sorting of membrane proteins, very little is understood about how cytosolic proteins are partitioned within the cytoplasm. However, it has become increasingly clear that the transport of mRNAs, and not the translated proteins themselves, constitutes an important means of localizing cytosolic proteins (Table I). The first evidence for cytoplasmic RNA localization came from the finding that actin transcripts are unevenly distributed in the ascidian embryo (29). Shortly thereafter, several maternal mRNAs were identified in *Xenopus* (53) and *Drosophila* (17) that are localized during oogenesis. More recently, localized mRNAs have been discovered in somatic cells (Table I), making it clear that mRNA localization serves as a general mechanism for creating asymmetric distributions of proteins in the cytoplasm (discussed in several recent reviews; 42, 58, 62).

While mRNA localization has been well documented in many systems, the mechanism that generates restricted RNA distributions is less well understood. mRNA could become locally trapped after diffusing randomly through the cytoplasm, or it could be actively transported along cytoskeletal elements to its target. These two possibilities can be best distinguished by directly visualizing the movements of mRNA within cells. By injecting fluorescently labeled mRNA encoding myelin basic protein into oligodendrocytes, Ainger et al. (1) report in this issue of the *Journal of Cell Biology* that mRNA forms "particles" that undergo unidirectional transport, similar to that described for motor-driven movements of membranous organelles (2, 69). These observations, as well as related work by other investigators, suggest that there is an ordered pathway (see Fig. 1) for mRNA localization consisting of: (*a*) formation of a RNP particle; (*b*) translocation of the particle to its destination; (*c*) anchoring of the particle to the cytoskeleton; and (*d*) translation of the localized mRNA. In this review, we will discuss what types of mRNAs are localized as well as the evidence supporting such a stepwise localization pathway.

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Why Sort mRNAs?

mRNA localization has been most extensively studied in *Drosophila* embryogenesis, where its role is to establish protein gradients that give rise to the embryonic body plan (for review see reference 61). Two of the best studied examples are *bicoid* and *nanos*, two mRNAs that are transferred from the nurse cells to the oocyte and are then localized to the anterior and posterior poles, respectively. The *bicoid* gene encodes a homeodomain protein that initiates the series of transcriptional events that are responsible for the formation of the anterior body segment (13, 14). *Nanos*, on the other hand, encodes a RNA binding protein that promotes the formation of the posterior body plan by blocking the translation of *hunchback*, a transcription factor induced by the *bicoid* cascade (20, 65, 73). Thus, the differential localization of these antagonistic factors plays an important role in establishing the anterior–posterior axis in *Drosophila*. Several mRNAs have also been isolated from *Xenopus* oocytes which are selectively distributed to the animal or vegetal poles and then partitioned to a subset of cells during the early embryonic cleavages. One of these is Vg1, a TGF-β homologue that can induce mesoderm formation (67, 72). Examples of localized RNAs have also been discovered in zebrafish oocytes and early embryos (Conway, G., and W. Gilbert, personal communication). Thus, mRNA localization appears to be a widely used mechanism for establishing gradients of proteins that determine cell fate during early development.

mRNA localization also serves as a means of spatially controlling macromolecular assembly reactions. Several types of cytoskeletal proteins, such as vimentin (27) and muscle myosin (28), self-assemble rapidly after translation, which necessitates restricting their synthesis to regions where filaments are required. In the case of vimentin, the coincident changes in mRNA localization and filament distribution that occur during muscle development (9) support the idea that mRNA localization determines the distribution of these polymers. Actin mRNA is also concentrated in the lamellaepodia of motile cells (38) and the apical domain of epithelial cells (7). Localized synthesis of actin in these regions may help to drive filament formation.

Recent work has suggested that mRNA localization is also used to segregate actin isotypes. Two studies have shown that the β-actin message accumulates at the periphery of cultured

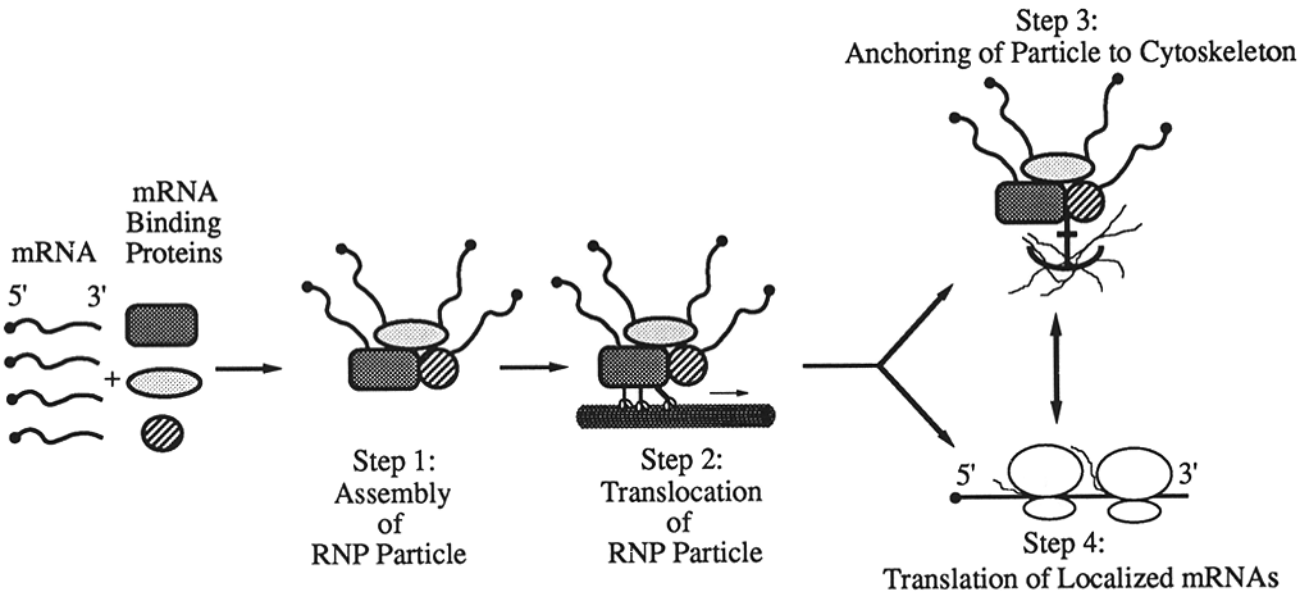

Figure 1. A model of the mRNA transport pathway (see text for details).

myoblasts, while the messages for α- and γ-actin are restricted to the perinuclear region (24, 32). Although the functional differences between these actin isotypes remain unknown, one reason for segregating their mRNAs may be to incorporate different actin isotypes into distinct filament arrays. Consistent with this idea, β-actin protein is not incorporated into stress fibers in migrating pericytes, but is only found at the leading edge where its mRNA is localized (25). An alternative explanation for the differential localization of actin isotypes is that some messages are localized to increase regional actin concentration, whereas other actin mRNAs adopt a perinuclear distribution to maintain steady-state actin levels throughout the cell (24).

While the purpose of segregating actin isotype mRNAs remains uncertain, localization of mRNAs encoding microtubule-associated proteins (MAPs)[1] plays a clear role in establishing the distinct packing arrangements of microtubules observed in axonal and dendritic processes (6). MAP2 mRNA, for example, is localized to dendritic processes and cell bodies, but not to axons (4, 19, 33). On the other hand, the mRNA encoding tau, an axonally localized MAP, is concentrated in the proximal axon and axon hillock (40), where the newly translated protein presumably can bind to microtubules destined for transport down the axon (30). The distribution of these mRNAs stands in marked contrast to most other neuronal mRNAs which are restricted to the cell body and are unable to enter neuronal processes.

Given the need for partitioning cytosolic proteins, why is mRNA transport used when other forms of protein targeting, such as nuclear, mitochondrial, or chloroplast import, rely upon protein-based signals? One reason for exploiting mRNA transport is that a single mRNA can be translated many times, making it an efficient mechanism for producing high local protein concentrations. Translation can also be made dependent on proper mRNA localization (to be discussed later), thereby ensuring correct protein positioning and preventing deleterious protein–protein interactions from occurring elsewhere in the cell. Furthermore, a variety of spatial patterns of proteins can be achieved by modulating the distribution of RNA as well as the diffusion of the translated protein from its site of synthesis. In the case of proteins such as vimentin that assemble rapidly after translation, the distribution of protein can be very precisely defined by the localization of its mRNA (9). Bicoid protein, on the other hand, diffuses from its site of synthesis, thereby establishing a gradient across the *Drosophila* oocyte (13). Thus, mRNA transport affords a number of advantages over posttranslational sorting for regulating protein distribution.

Assembly of an RNA Transport Particle

Most biological sorting events, such as membrane trafficking (54), nuclear import (57), and protein translocation across the ER (52), are mediated by large macromolecular assemblies. mRNA transport and sorting will most likely prove to be no exception. The first hint that RNA may be transported as a large RNP particle (Fig. 1, *Step 1*) came from work on the BC1 message, a 152-bp polymerase III transcript that is localized to dendrites of mammalian neurons (68). When extracted from neuronal tissue, the BC1 RNA was discovered to be part of a 10S RNP complex (35), whose function and components remain to be elucidated. Since BC1 is not translated and hence different from other localized RNAs, it was uncertain whether RNP formation is a universal requirement of the RNA localization pathway. However, Ainger et al. (1), as well as other investigators (9, 64), have shown by high resolution in situ hybridization that localized mRNAs display a granular pattern in the cytoplasm. Although such observations might be discounted as fixation artifacts, fluorescently labeled mRNA encoding myelin basic protein (MBP) also forms similar-sized particles within a few minutes after being microinjected into oligodendrocytes. RNP formation, however, is not uniquely associated with localized mRNAs, since globin mRNA also forms particles after microinjection

1. *Abbreviations used in this paper*: MAP, microtubule-associated protein; MBP, myelin basic protein; UTR, untranslated region.

Table I. Localized RNAs

Cell type and transcript	Activity	mRNA distribution	Reference
Neurons			
MAP2	Microtubule associated protein	Dendrites and cell body	4, 19, 33
Tau	Microtubule associated protein	Proximal axon and cell body	40
α-CAM kinase II	Kinase	Dendrites and cell body	5
BC1	Unknown	Dendrites and cell body	68
Oxytocin‖	Hormone	Axon and cell body	45
Vasopresin‖	Hormone	Axon and cell body	45
Oligodendrocytes			
Myelin basic protein	Myelin formation	Cell body and processes	1
Xenopus oocytes			
Vg1*	TGF-β homologue; induces mesoderm	Vegetal pole	44
TGF-β5	TGF-β isoform	Vegetal pole	49
XCAT-2	Nanos-like zinc finger	Vegetal pole	46
An1	Ubiquitin-like protein	Animal pole	39
An2	α-subunit of mitochondrial ATPase	Animal pole	71
An3	Homology to RNA dependent ATPases	Animal pole	23
Drosophila oocytes‡			
Bicoid*	Homeobox gene; establishes anterior embryonic pattern	Anterior pole	13, 14, 17
Oskar	Required for abdomen and germ cell formation	Posterior pole	16, 31
Nanos*	Zn finger RNA binding protein; represses hunchback translation	Posterior pole	20
Cyclin B*	Cell cycle regulator	Posterior pole	10
fs (1)K10*	Required to establish dorsoventral axis	Anterior pole	8
Adducin-like	Possible cytoskeletal associated protein	Anterior pole	12
Muscle cells			
Vimentin	Intermediate filament	Costameres	9
α-actin*	Actin isoform	Perinuclear	32
β-actin*§	Actin isoform	Peripheral and perinuclear	24, 32
γ-actin	Actin isoform	Perinuclear	24

* mRNAs whose localization signals have been mapped. In all cases the localization signal has mapped to the 3′UTR.
‡ This is only a partial list of the mRNAs that are localized during *Drosophila* oogenesis.
§ β-actin is also localized to lamellaepodia in fibroblasts.
‖ Only the magnocellular neurons express these transcripts.

(1). Although not demonstrated directly by coinjection experiments, these results further suggest that localized and nonlocalized mRNAs are segregated into different particles.

The recognition system that distinguishes localized mRNAs from the majority of other RNAs in the cell is just beginning to be deciphered. The *cis*-acting localization signals have been identified for a number of mRNAs, and all, without exception, lie within the 3′ untranslated region (3′UTR) (see Table I). The minimum region within the 3′UTR required for localization has been mapped by deletion analysis for Vg1 (47) and *bicoid* (43), and in both instances, it was found to be relatively large (340 bp for Vg1 and 625 bp for *bicoid*). Although there has been one report of a 9-bp sequence motif that is common to the 3′UTRs of several localized transcripts (22), most analyses have found very little conservation of the primary sequence amongst localized mRNAs. For example, the 3′UTRs of *bicoid* mRNAs from different *Drosophila* species localize properly in *D. melanogaster*, even though they have diverged considerably in sequence. Interestingly, these *bicoid* 3′UTRs are all predicted to form a similar secondary structure (41), which suggests that trans-acting factors may recognize the RNA's conformation rather than its sequence.

While progress has been made in identifying the *cis*-acting localization signals, identification of the protein components that recognize these elements has proven more difficult. Genetic studies in *Drosophila*, however, have identified a number of possible candidates (for review see reference 42). One of the best-characterized candidates is *staufen*, a gene that is required for the proper localization of several mRNAs in oocytes (60). The staufen protein has been shown to bind double-stranded RNA in vitro, suggesting that it may play a role in the formation of a mRNA transport particle (61). Consistent with this idea, *bicoid* 3′UTRs aggregate into particles when microinjected into *Drosophila* embryos, but this is not observed in *staufen* mutants (Ferrandon, D., and C. Nusslein-Volhard, personal communication). *Staufen* may not be essential for the transport of all mRNAs, however, since mutations in *staufen* abolish the localization of posteriorly targeted mRNAs (16, 31), but only have mild effects on anteriorly localized messages (12, 14). A number of other genes have been identified that also play a role in mRNA localization in *Drosophila*, but again, none of these appears to be essential for the localization of all transcripts in the oocyte. This implies that either independent localization pathways exist or that the proteins required for both anterior and posterior localization have yet to be identified.

Biochemical approaches have recently begun to complement genetic studies in isolating components of the transport complex. The most tantalizing finding so far is the discovery of a 69-kD protein that specifically binds to the portion of the Vg1 3′UTR that is required for localization (56). Binding is competitively inhibited by another transcript that is localized to the vegetal pole, TGF-β5, but not by a mRNA that is localized to the animal pole, An2. Thus, this 69-kD protein may represent a component of the transport complex that specifically recognizes vegetal pole localization signals.

The Role of Cytoskeletal Motors in RNA Localization

After a RNP particle is formed, it must then reach its target (Fig. 1, *Step 2*). Localization of *bicoid* mRNA to the anterior pole of *Drosophila* oocytes was initially believed to occur by a diffusion-trapping mechanism. However, later studies showed that localization of several RNAs could be blocked by cytoskeletal inhibitors (see below), indicating that cytoskeletal filaments and motor proteins may play a role in moving RNP particles. This hypothesis has now received its strongest support from Ainger et al. (1), who have made microscopic observations of fluorescently labeled MBP mRNA inside of oligodendrocytes. Within these cells, particles containing fluorescently labeled RNA moved unidirectionally from the cell body through the long processes to the membranous sheets where the endogenous transcript is normally found. A control microinjected mRNA (globin), on the other hand, did not move into oligodendrocyte processes. This finding conclusively reveals the existence of an active transport process for localizing mRNA.

MBP mRNA particles moved at 12 μm/min, which is comparable with the speed with which membrane vesicles are transported along microtubules or actin filaments (2, 55). This rate is far faster, however, than those measured for RNA transport in *Xenopus* oocytes (0.07 μm/min) (74) and neurons (0.35 μm/min) (11). The difference in these rates is comparable to that observed for slow and fast axonal transport (3), which could indicate that different mRNAs are transported by distinct mechanisms. However, the slow net RNA transport observed in oocytes and neurons could also be explained by pausing or discontinuous movement of individual RNP particles. The observation that the majority of MBP mRNA particles are stationary at any given moment of time lends support to the latter hypothesis.

Ainger et al. also observed that mRNA particles are in close proximity to microtubules, suggesting that these polymers serve as the tracks for mRNA translocation. Microtubules have also been implicated in mRNA transport in other systems as well. Pharmacological agents that inhibit microtubule polymerization prevent the localization of both Vg1 in *Xenopus* (74) and *bicoid* in *Drosophila* (50). Furthermore, a dramatic reorganization and polarization of the microtubule array occurs in these oocytes just at the onset of RNA localization (18, 66), again implicating microtubule involvement in RNA transport.

A variety of microtubule force-generating proteins belonging to the kinesin and dynein superfamilies (15, 21, 70) have been identified that could serve as motors for mRNA transport. One clue as to what type of motor might be involved comes from ascertaining the direction of mRNA movement with respect to the polarity of the microtubules. During the time when *bicoid* and *oskar* transcripts are being localized to the anterior and posterior poles of the *Drosophila* oocyte, the microtubule network is nucleated at the anterior pole. Although the polarity of this network has not been established directly, the localization of a β-galactosidase/kinesin fusion protein to the posterior pole (Clark, I., and Y. N. Jan, personal communication) suggests that the minus ends of microtubules are clustered at the anterior end of the oocyte while the plus ends project toward the posterior pole. Thus, posterior pole mRNAs (*nanos*, *oskar*) may be moved by plus-end directed motors (e.g., kinesin), while anterior pole mRNAs (*bicoid* and K10) are likely to be translocated by minus-end directed motors (e.g., cytoplasmic dynein).

Actin and myosin may also participate in the translocation of some mRNAs. Evidence for actomyosin involvement comes from the finding that actin mRNA localization in fibroblasts is inhibited by the actin depolymerizing drug cytochalasin, but not by microtubule depolymerizing agents (63). This finding raises the possibility that mRNAs might be capable of moving along both actin and microtubule filaments. This idea is not without precedent, since neuronal vesicles have been found to translocate on both microtubules and actin filaments (36).

How motors associate with RNA remains unresolved. Motors could attach directly to RNP particles, much as mitotic motors bind the nucleic acid–protein complex of the kinetochore (26). Alternatively, the association between the motor and the RNP could be indirect, with the RNP binding to vesicles and hitching a ride on the normal organelle transport pathways. The isolation and biochemical characterization of RNA transport complexes as well as the development of in vitro assays to assess RNA motility should provide a means for determining which of these possibilities is correct.

Anchoring of Localized mRNAs

After reaching its final destination, the mRNA must maintain its localized distribution (Fig. 1, *Step 3*). The active transport process that initially localized the mRNA could be used to collect the RNA that wanders astray by diffusion. However, microtubule inhibitors, which abolish active transport of mRNA in oocytes, fail to disperse localized Vg1 (74) or *bicoid* (50) mRNA. Furthermore, the reorganization of microtubules at stage 10 of *Drosophila* oogenesis (66) is not accompanied by a corresponding redistribution of localized messages. These results argue that mRNAs become anchored at their final target by a mechanism independent of microtubules and cytoplasmic transport.

Some element of the cytoskeleton is almost certainly involved in anchoring messages, since localized mRNAs, in contrast to other RNAs, are not solubilized by Triton X-100 (74). Actin filaments are the most likely candidates, since Vg1 becomes dispersed after cytochalasin treatment (74). Cytokeratins have also been suggested to participate in RNA retention (51), but their role is probably secondary to actin's, since fragmentation and disassembly of cytokeratins in oocytes does not release the Vg1 transcript from the detergent-insoluble matrix (34).

The anchoring of transcripts to the cytoskeleton presents another opportunity for the cell to regulate mRNA distribution. The localized Vg1 message, for instance, is found initially in the detergent-insoluble cytoskeletal fraction, but then becomes detergent soluble at the time of oocyte maturation. This change in detergent extractability occurs at the time that Vg1 message loses its tight cortical localization and becomes diffusely distributed over the vegetal hemisphere (44). In contrast, the XCAT-2 transcript remains in the detergent insoluble fraction throughout oogenesis (46). Thus, the cytoskeletal associations of different localized mRNAs can be controlled independent of one another.

Coordinating mRNA Translation with Localization

To ensure a highly restricted protein distribution, it is gener-

ally thought that mRNA translation is repressed during transport and then activated upon arrival at its destination (Fig. 1, *Step 4*). The dependence of translation on proper mRNA localization would prevent the synthesis of proteins from transcripts that are either en route to their destination or that have become mislocalized. This may be particularly important in oocytes, where translation of mislocalized mRNAs could potentially have deleterious effects on embryogenesis.

Supporting the idea that mistargeted mRNAs are translationally repressed, Gavis, E., and R. Lehmann (personal communication) have shown that unlocalized *nanos* RNA is not translated and that this repression is mediated by the 3′UTR. The 3′UTR has also been implicated in the translational repression of cyclin B, a posteriorly localized mRNA. In this case, the deletion of a 39-bp segment in the 3′UTR relieved the translational repression of microinjected cyclin B mRNA, but did not interfere with its ability to be retained at the posterior pole (10). These results suggest that separate elements within the 3′UTR may control translation and localization.

How is translational repression relieved once mRNAs reach their correct destination? A likely possibility is that the components that override repression are themselves localized factors. Consistent with this idea, a posteriorly localized protein in *Drosophila* oocytes, *vasa*, has homology to eIF-4A, a double-stranded RNA helicase required for the initiation of translation (37). A putative RNA helicase is also encoded by one of the mRNAs localized to the animal pole of *Xenopus* oocyte (23). Direct evidence linking these proteins to translational activation of localized mRNAs, however, has not yet been obtained.

Conclusion

A variety of phenomenological observations have provided insight into the types of mRNAs that are transported, the *cis*-acting signals needed for localization and translational control, and the nature of mRNA movement through the cytoplasm. The molecular details of these events, however, still remain obscure. The next stage in understanding this problem must involve identifying and characterizing the proteins that are needed for each particular step in the RNA localization pathway. If previous work on membrane protein sorting provides any precedent, studies of the RNA localization system should yield a host of novel proteins and interesting regulatory mechanisms that will keep biologists busy for years to come.

We thank the members of the Vale laboratory and G. Banker for their comments on this manuscript.

Received for publication 31 August 1993 and in revised form 6 September 1993.

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