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Principles and roles of mRNA localization in animal development

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Summary

Intracellular targeting of mRNAs has long been recognized as a means to produce proteins locally, but has only recently emerged as a prevalent mechanism used by a wide variety of polarized cell types. Localization of mRNA molecules within the cytoplasm provides a basis for cell polarization, thus underlying developmental processes such as asymmetric cell division, cell migration, neuronal maturation and embryonic patterning. In this review, we describe and discuss recent advances in our understanding of both the regulation and functions of RNA localization during animal development.

Key words: RNA localization, RNA transport, Local translation, Cell polarity, Post-transcriptional gene regulation

Introduction

Establishment of cell polarity is crucial for the execution of developmental programmes governing key processes, including specification of cell fates, individual or collective cell movements and specialization of somatic cell types. Cell polarization depends on the asymmetric segregation of organelles and various molecules within the cell. Polarized accumulation of RNA molecules was first visualized nearly 30 years ago, when β-actin mRNA was found to be asymmetrically localized within ascidian eggs and embryos (Jeffery et al., 1983). Following this, the discovery of the first localized maternal mRNAs in *Xenopus* (Rebagliati et al., 1985) and *Drosophila* oocytes (Frigerio et al., 1986; Berleth et al., 1988) provided evidence for the earlier proposal that localized RNA determinants could be responsible for early embryonic patterning (Kandler-Singer and Kalthoff, 1976). mRNAs were soon found to be asymmetrically distributed within differentiated somatic cells, such as fibroblasts (Lawrence and Singer, 1986), oligodendrocytes (Trapp et al., 1987) and neurons (Garner et al., 1988), and to colocalize with their encoded proteins, establishing intracellular transport of mRNAs as a potential mechanism used to target the production of selected proteins to discrete sites.

Significant improvements in RNA detection methods led to the identification of a growing number of localized mRNAs. Still, in the early 2000s, the set of described targeted mRNAs was limited to ~100 (reviewed by Bashirullah et al., 1998; Palacios and St Johnston, 2001) and the process of mRNA localization was thought to be restricted to specific cell types. However, recent genome-wide analyses (see Table 1) have changed this view dramatically, and strongly suggest that subcellular targeting of mRNAs is a prevalent mechanism used by polarized cells to establish functionally distinct compartments (Fig. 1). Particularly striking was the discovery that >70% of the 2314 expressed transcripts analysed in a high-resolution in situ hybridization screen were subcellularly localized in *Drosophila* embryos (Lécuyer et al., 2007). Moreover, hundreds to thousands of mRNAs have been detected in cellular compartments as diverse as the mitotic apparatus (Blower et al., 2007; Sharp et al., 2011), pseudopodia (Mili et al., 2008), dendrites (Moccia et al., 2003; Poon et al., 2006; Zhong et al., 2006; Suzuki et al., 2007; Cajigas et al., 2012) or axons (Andreassi et al., 2010; Zivraj et al., 2010; Gumy et al., 2011). The prevalence of intracellular mRNA targeting is illustrated further by the identification of localized mRNAs in a wide range of organisms outside of the animal kingdom, including bacteria (Keiler, 2011), fungi (Zarnack and Feldbrügge, 2010; Heym and Niessing, 2011) and plants (Crofts et al., 2005).

In this Review, we briefly describe the cellular mechanisms underlying mRNA localization (for more comprehensive reviews, see Martin and Ephrussi, 2009; Bullock, 2011), and focus largely on the developmental processes in which mRNA targeting has been shown to play key roles. This includes early embryonic patterning, asymmetric cell divisions, polarization of epithelia and cell migration, as well as axonal and dendrite morphogenesis and plasticity.

Why localize mRNAs rather than proteins?

Transporting mRNAs rather than proteins presents several significant advantages for a cell. First, transport costs are reduced, as several protein molecules can be translated from a single RNA molecule. Second, transporting mRNAs can prevent proteins from acting ectopically before they reach the appropriate site, which is particularly important in the case of maternal determinants, as spatially inappropriate expression disrupts embryonic patterning. Third, localized translation can facilitate incorporation of proteins into macromolecular complexes by generating high local protein concentrations and allowing co-translation of different subunits (Mingle et al., 2005). Fourth, nascent proteins may have properties distinct from pre-existing copies, by virtue of post-translational modifications or through chaperone-aided folding pathways (Lin and Holt, 2007). Lastly, a major advantage of mRNA targeting is that it allows fine-tuning of gene expression in both space and time. Examples of this include targeting of different splice variants to distinct cellular compartments (Baj et al., 2011) and activation of localized mRNA translation specifically at their destination, in response to signals such as guidance cues, neurotransmitter release or fertilization (Besse and Ephrussi, 2008).

Proposed mechanisms for asymmetric mRNA localization

Three distinct mechanisms have been proposed to account for the asymmetric distribution of mRNAs within cells: localized protection from degradation, diffusion-coupled local entrapment, and directed transport along a polarized cytoskeleton (Fig. 2).

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Table 1. Examples of recent genome-wide screens for localized mRNAs

Cell type	Compartment	Method used	Reference
Drosophila embryos	Various	Fluorescence in situ hybridization	(Lécuyer et al., 2007)
Xenopus eggs	Vegetal cortex	Mechanical dissection followed by microarray analysis	(Cuykendall and Houston, 2010)
Xenopus eggs/human metaphasic HeLa cells	Mitotic spindle	Biochemical purification followed by microarray analysis	(Blower et al., 2007)
Xenopus eggs	Mitotic spindle	Biochemical purification followed by RNA-seq	(Sharp et al., 2011)
NIH/3T3 mouse migrating fibroblasts	Protrusions	Mechanical isolation of pseudopodia followed by microarray analysis	(Mili et al., 2008)
Rat sympathetic neurons	Axons	Mechanical isolation followed by serial analysis of gene expression (SAGE)	(Andreassi et al., 2010)
Xenopus retinal ganglion cells/E16 mouse retinal ganglion cells	Axons	Laser capture microdissection followed by microarray analysis	(Zivraj et al., 2010)
Embryonic and adult rat dorsal root ganglion neurons	Axons	Mechanical isolation followed by microarray analysis	(Gumy et al., 2011)
Aplysia sensory neurons	Dendrites	Mechanical isolation followed by cDNA library sequencing	(Moccia et al., 2003)
Rat hippocampal neurons	Neuronal processes	Mechanical isolation followed by microarray analysis	(Poon et al., 2006)
Rat CA1 hippocampal neurons	Stratum radiatum (dendritic lamina)	Dissection followed by microarray analysis	(Zhong et al., 2006)
Rat forebrain	Postsynaptic dendritic fraction	Dissection followed by microarray analysis	(Suzuki et al., 2007)
Rat CA1 hippocampal neurons	Stratum radiatum and lacunosum moleculare	Dissection followed by deep sequencing	(Cajigas et al., 2012)

Experimentally, distinguishing these mechanisms often requires combining analyses of RNA regulatory sequences with live imaging (Box 1).

Generalized RNA degradation coupled to local protection has been described in *Drosophila*, where *Hsp83* mRNA is uniformly distributed in early fertilized eggs, but restricted to the posteriorly localized germ plasm at later stages (Ding et al., 1993). In the absence of the RNA degradation machinery, this selective accumulation is lost and *Hsp83* transcripts are stabilized throughout the embryo (Semotok et al., 2005). How the posterior pool of *Hsp83* transcripts is protected from decay in wild-type conditions is, however, still unclear.

Localization through diffusion/entrapment has been illustrated for *Drosophila nanos* mRNA, accumulation of which at the posterior pole of late-stage oocytes does not depend on a polarized cytoskeleton, but rather on cortical actin-dependent entrapment and anchoring (Forrest and Gavis, 2003). In early *Xenopus* oocytes, localization of the germ plasm RNAs *Xcat2* (*Nanos1*) and *Xdazl* has also been proposed to rely on entrapment and association of freely diffusing RNA molecules with a densely packed endoplasmic reticulum (ER) concentrated in the vegetally localized mitochondrial cloud (Chang et al., 2004).

Directed transport of transcripts along a polarized cytoskeletal network is a predominant mechanism to direct mRNA localization (Bullock, 2011) that has been observed in a variety of cell types, including *Drosophila* oocytes and embryos, *Xenopus* oocytes, migrating mammalian cells and vertebrate neurons (Gagnon and Mowry, 2011). A surprising finding from live-imaging analyses (Box 1) was that active motion is not restricted to localizing mRNAs, as uniformly distributed transcripts also undergo cytoskeleton-dependent movements (Fusco et al., 2003; Bullock et al., 2006). Rather, the unique feature of localized mRNA movement is that it is non-random, exhibiting a net bias explained by increased frequency and duration of directed transport events. How is this net transport achieved? As described below, key features appear to involve specific recognition by trans-acting factors, assembly of localization-competent ribonucleoprotein (RNP) complexes, recruitment of molecular motors and transport along the cytoskeleton, as well as anchoring of the mRNA at the final destination. Finally, tight coupling with translational regulation is required to achieve spatially restricted protein synthesis.

Cellular mechanisms underlying intracellular mRNA transport

Assembly of transport-competent RNPs

As revealed by proteomic analyses, mRNAs to be transported are packaged within complexes containing a large number of associated proteins (Kanai et al., 2004). Some of these proteins bind to the mRNA upon transcription or splicing, rendering it competent for the future recruitment of the cytoplasmic transport machinery (Marchand et al., 2012). Consistent with a key influence of mRNA nuclear history, nuclear processing events such as splicing, transit through the nucleolus, deposition of key nuclear factors or translocation through specific nucleopore structures have been shown to be required for cytoplasmic targeting of localized mRNAs (Giorgi and Moore, 2007; Marchand et al., 2012). Following export to the cytoplasm, RNP complexes are remodelled, and cytoplasmic factors ensuring translational repression and specific coupling with molecular motors are recruited (Lewis and Mowry, 2007; Besse and Ephrussi, 2008).

The number of mRNA molecules present in a single RNP is still an unresolved question. In favour of a co-packaging of multiple mRNA molecules, *oskar* mRNA has been shown to multimerize in *Drosophila* oocytes (Hachet and Ephrussi, 2004; Jambor et al., 2011), and differentially tagged *ASH1* and *IST2* mRNAs are co-transported in yeast (Lange et al., 2008). By contrast, RNP complexes found in *Drosophila* embryos or the dendrites of mammalian neurons seem to contain a very limited number of

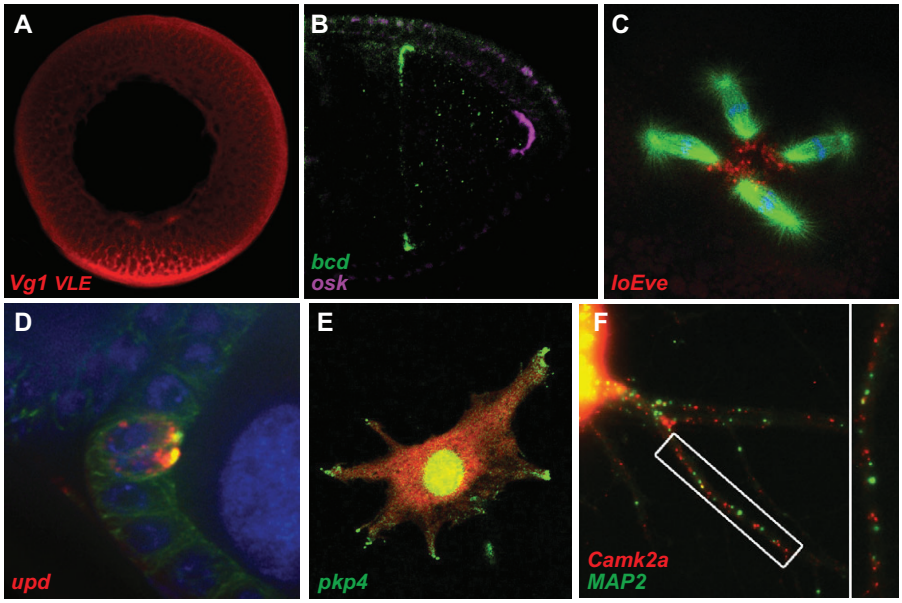


Fig. 1. Examples of asymmetrically localized mRNAs. (**A**) Injected fluorescent RNA transcribed from the *Vg1* vegetal localization element is localized to the vegetal cortex (bottom) of a stage III *Xenopus* oocyte. Image from J. Gagnon and K.M. (**B**) *bicoid* (green) and *oskar* (magenta) mRNAs accumulate, respectively, at the anterior and posterior poles of a *Drosophila* oocyte. Reproduced with permission from Bullock (Bullock, 2007). (**C**) *IoEve* mRNA accumulates at the centrosomes of a 4-cell-stage *Ilyanassa* embryo. RNA is shown in red, microtubules in green, DNA in blue. Reproduced with permission from Lambert and Nagy (Lambert and Nagy, 2002). (**D**) Apical accumulation of *unpaired* (*upd*) mRNA is shown in the *Drosophila* follicular epithelium. RNA is shown in red, microtubules in green, DNA in blue. Reproduced with permission from Van de Bor et al. (Van de Bor et al., 2011). (**E**) MS2-tagged *pkp4* 3′UTR reporter mRNAs are localized to pseudopodial protrusions of a cultured mammalian fibroblast. RNA is shown in green, cell morphology in red. Reproduced with permission from Mili et al. (Mili et al., 2008). (**F**) *Camk2a* (encoding CaMKIIα; red) and *MAP2* (*Mtap2*; green) mRNAs are localized in dendrites of cultured mammalian hippocampal neurons. Boxed area is shown at higher magnification on the right. Reproduced with permission from Mikl et al. (Mikl et al., 2011).

RNA molecules, suggesting that mRNAs are transported independently of each other in these systems (Mikl et al., 2011; Amrute-Nayak and Bullock, 2012; Batish et al., 2012).

Cis-regulatory elements and trans-acting factors

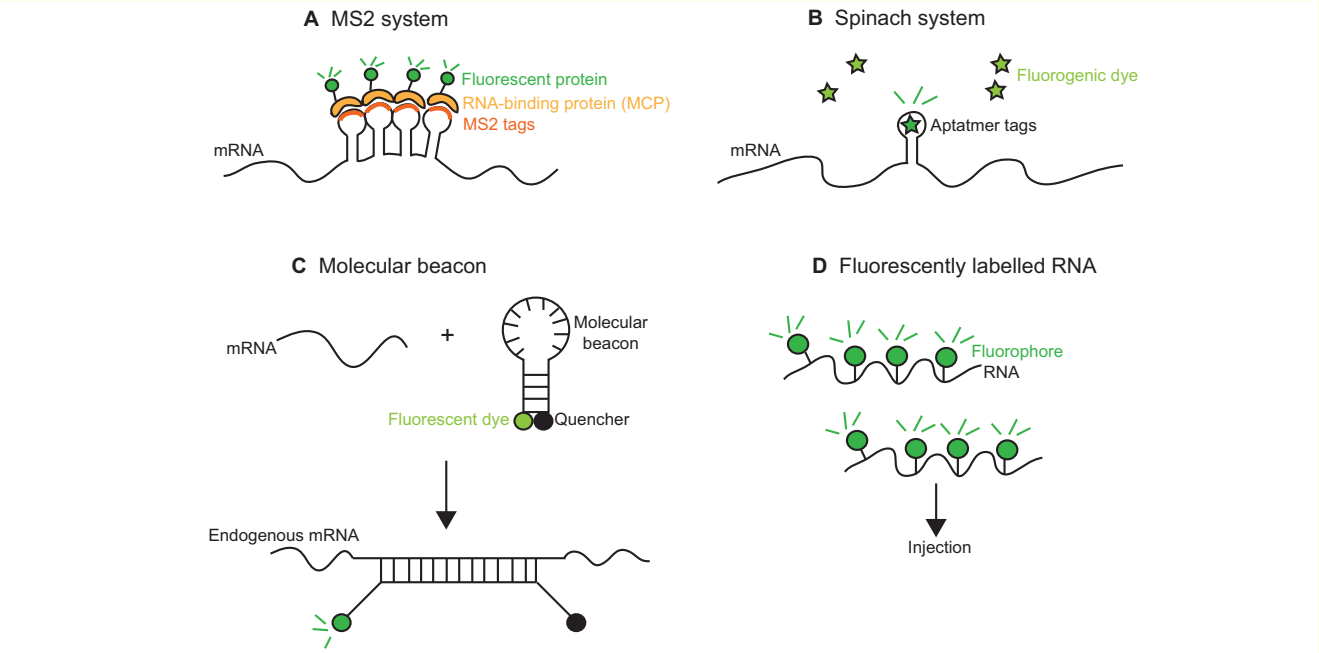
Formation of transport-competent RNPs is initiated via the recognition of cis-regulatory elements present in RNA molecules by specific RNA-binding proteins. These elements, also termed localization elements or zipcodes, are usually (but not exclusively) found in 3′UTR sequences and are necessary and sufficient for efficient mRNA targeting and recruitment of trans-acting factors. Although the molecular mechanisms underlying specific recognition of zipcodes by RNA-binding proteins have long been elusive, recent structural studies have revealed requirements for highly specific motifs and/or structures. For example, a 54-nt sequence required for the targeting of β-actin mRNA in fibroblasts has been shown to contain a bipartite element comprising two RNA motifs recognized by the RNA-binding protein Zbp1 (Chao et al., 2010; Patel et al., 2012). The RNA binding protein Egalitarian, by contrast, does not recognize a specific sequence, but rather the atypical A′-form helices formed by the 44-nt localization element of *Drosophila fs(1)K10* transcripts (Bullock et al., 2010). Notably, Egalitarian shows only a modest binding preference for its targets. However, association with BicD protein and formation of a ternary complex significantly enhances its affinity for localizing targets (Dienstbier et al., 2009). A similar synergistic binding has been observed in yeast for the She2p-She3p-*ASH1* mRNA complex (Müller et al., 2011), highlighting a role for intermolecular cooperativity in ensuring selective recognition of localizing mRNAs in vivo.

A current limitation to our understanding of localized RNA recognition is the small number of well-characterized localization elements. Although genome-wide analyses have provided large datasets for the discovery of new zipcodes, it has proven difficult to identify common signatures shared by RNA molecules targeted to the same cellular sites. This probably stems from the difficulty of predicting tertiary structures in silico, as well as from the fact that localized mRNAs can contain multiple localizing elements with redundant or complementary functions (Gautreau et al., 1997; Deshler et al., 1998; Macdonald and Kerr, 1998).

Recruitment of molecular motors and directed transport

The nature and number of active molecular motors recruited to a target mRNA dictate the cytoskeletal tracks (actin filaments or microtubules) used for mRNA transport, the type of movement (uni- or bidirectional), and the properties (e.g. speed, processivity) of mRNA motion (Bullock, 2011; Gagnon and Mowry, 2011; Marchand et al., 2012). For example, the recruitment of several molecules of the myosin motor Myo4p by multiple localization elements increases the efficiency of *ASH1* mRNA transport on actin filaments in yeast (Chung and Takizawa, 2010). Furthermore, dendritically transported RNPs exhibit microtubule-dependent bidirectional movement, suggesting the recruitment and the activity of opposite polarity motors (Doyle and Kiebler, 2011). Consistent with this view, the RNA-binding protein Fmrp has been shown to associate with dendritically localized transcripts, and to bind to KLC (a component of the plus-end motor Kinesin-1) as well as to the dynein-interacting BicD protein (Dictenberg et al., 2008; Bianco et al., 2010). A general trend emerging from live-imaging analyses is that bidirectional transport is commonly used in higher

Box 1. Live-imaging methods for visualizing mRNA localization



Over the last decade, methods relying on RNA tagging and high-resolution microscopy have been developed to improve mRNA detection in living cells and organisms (Armitage, 2011). A tethering approach, in which RNA recognition sequences bound by a specific RNA-binding protein are inserted into the transcript of interest, allows dynamic distribution of mRNA in living tissues to be monitored by co-expression of exogenous RNA-binding protein (e.g. MS2, λN or U1A) fused to a fluorescent protein (FP) (A) (Bertrand et al., 1998). Drawbacks of this technique include background fluorescence produced by unbound chimeric FPs, and the high number of RNA tags necessary for a strong signal, potentially altering mRNA behaviour. A recently developed technique uses RNA motifs (aptamers) that bind fluorogenic dyes. This RNA-fluorophore complex, termed Spinach, emits a green fluorescence comparable in brightness to enhanced GFP (B) (Paige et al., 2011). Spinach has been used for live imaging of abundant RNAs in cultured cells, but utility for in vivo mRNA imaging must yet be demonstrated. Fluorescence imaging techniques have also been developed to follow endogenous mRNAs in live samples. These methods use molecular beacons, which are non-membrane-permeable hairpin-shaped molecules with an internally quenched fluorophore, fluorescence of which is restored upon binding to target RNAs (C) (Bratu et al., 2003). Potential disadvantages include target accessibility and impairment of mRNA function upon binding of multiple beacons. Finally, injection of fluorescently labelled in vitro synthesized RNAs has been used to monitor RNA localization in vivo (D) (Ainger et al., 1993). Potential caveats here are that injected RNAs are not processed by endogenous machineries, and fluorophores might alter the function of labelled RNAs.

eukaryotes for mRNA targeting. This might allow RNPs to navigate around obstacles and ensure a constant reassessment and fine-tuning of directional transport.

mRNA anchoring

Once transported, mRNAs must be retained at their destinations. In cells with no static pre-localized anchor, this can be achieved via continuous rounds of short-range active transport, as shown for maintenance of *bicoid* mRNA localization at the anterior pole of late-stage *Drosophila* oocytes (Weil et al., 2006). In various cell types, including *Drosophila* oocytes, *Xenopus* oocytes and dividing yeast cells, static anchoring of mRNAs relies on cortical actin and actin-binding proteins (King et al., 2005; Becalska and Gavis, 2009; Heym and Niessing, 2011). Interestingly, alternative actin-independent mechanisms have been discovered: one in mammalian migrating cells, in which accumulation of transcripts in protrusions depends on the tumour-suppressor APC (Mili et al., 2008); one in *Drosophila* blastoderm embryos, in which apical anchoring of pair-rule transcripts requires a motor activity-independent function of dynein (Delanoue and Davis, 2005); and another in ascidian eggs, in which transcripts are associated with a sub-domain of the cortical ER (Paix et al., 2011).

Translational regulation

Local protein production requires translational repression of localized mRNAs during transport and subsequent activation at the final destination. Translational repressors have been shown to associate with transport RNPs by directly binding RNA regulatory sequences and blocking translation, largely at the initiation stage (Besse and Ephrussi, 2008). Although the mechanisms regulating local activation of translation are much less clear, a theme emerging from studies in multiple systems is that phosphorylation of repressors at the destination (either directly upon arrival or in response to external signals) can decrease affinity for their target mRNAs, thereby relieving translational blockage. Thus, the RNA-binding protein Zbp1 has been shown to repress the translation of its target mRNA (β-actin) and to exhibit a reduced binding efficiency upon phosphorylation (Hüttelmaier et al., 2005). Furthermore, expression of a non-phosphorylatable form of Zbp1 reduces β-actin protein accumulation at the site of mRNA localization, the cell periphery. Similarly, altering the phosphorylation status of the RNA-binding protein Fmrp (Fmr1 – Mouse Genome Informatics) appears to trigger a translational switch: whereas Fmrp phosphorylation promotes the formation of a RNA-induced silencing complex (RISC)-microRNA (miRNA) inhibitory complex on the dendritically localized *PSD-95* (*Dlg4* –

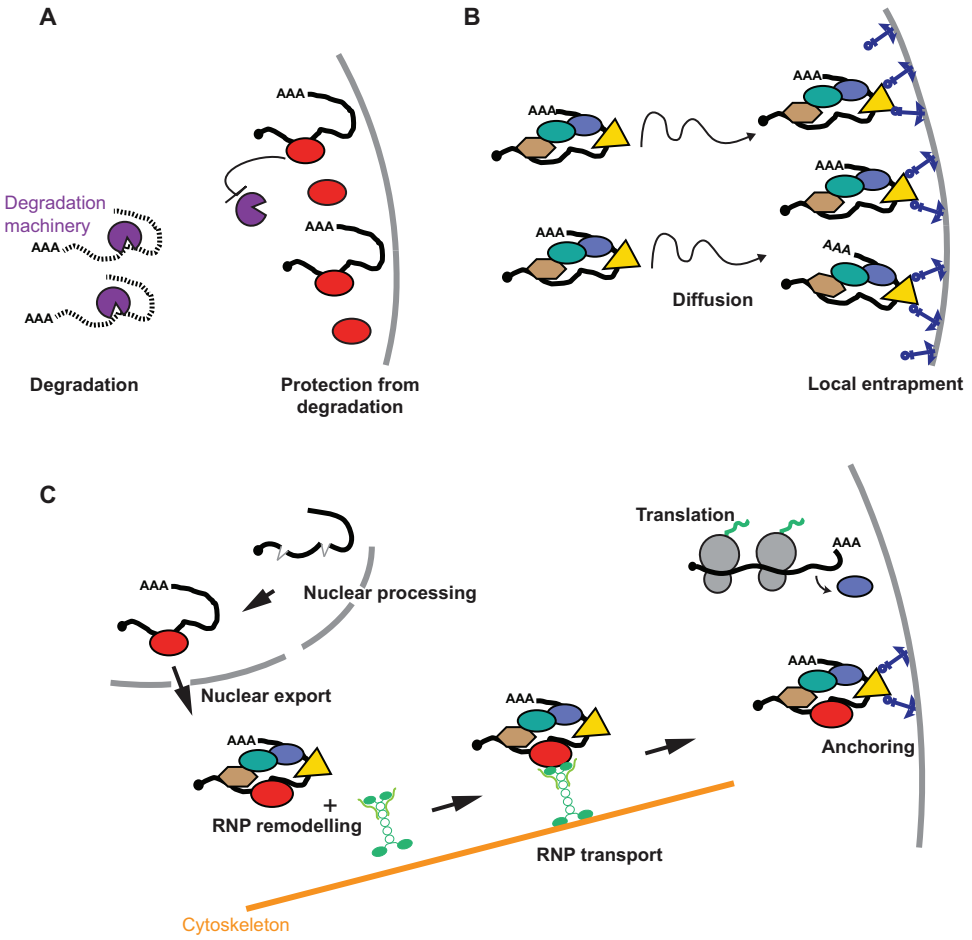


Fig. 2. Three distinct mechanisms underlying mRNA localization. (**A-C**) Three distinct mechanisms account for the asymmetric distribution of mRNAs within cells: localized protection from degradation (A), diffusion-coupled local entrapment (B) and directed transport along a polarized cytoskeleton (C). (A) Non-localized mRNAs are targeted by the degradation machinery, whereas localized mRNAs are protected by as yet unknown mechanisms. (B) mRNAs freely diffuse in the cytoplasm and are locally entrapped, at the cell cortex for example. (C) mRNAs destined for directional transport are recognized by specific trans-acting factors in the nucleus, where RNPs undergo different maturation steps. Upon export to the cytoplasm, RNP complexes are remodelled, and cytoplasmic factors ensuring coupling with molecular motors and transport along a polarized cytoskeleton are recruited. Once at the final destination, mRNAs are anchored and their translation is activated.

Mouse Genome Informatics) mRNA, dephosphorylation of Fmrp upon stimulation induces release of RISC from the mRNA and translation activation (Muddashetty et al., 2011).

Together, these mechanisms ensure tight localization of mRNAs, and subsequent protein production, to particular subcellular compartments. In the next sections, we will discuss the functional significance of such localization.

Establishment of embryonic polarity by localized maternal RNA determinants

In many vertebrate and invertebrate organisms, localization of mRNA molecules in oocytes and eggs establishes a spatially restricted pattern of gene expression that acts to specify embryonic axes and cell fates (reviewed by Kumano, 2011).

Axis specification and positional identity during *Drosophila* oogenesis

Roles for asymmetric RNA localization in embryonic patterning are perhaps best studied in *Drosophila*, in which localized mRNAs underlie patterning along both the anteroposterior and dorsoventral axes (Fig. 3A). The anteroposterior axis is first established by localization of *gurken* mRNA to the posterior pole during early oogenesis (González-Reyes et al., 1995; Roth et al., 1995). *gurken* mRNA, which encodes a TGFα signalling molecule, is also necessary for dorsoventral axis specification by subsequent localization to the anterodorsal corner of the growing oocyte (Neuman-Silberberg and Schüpbach, 1993). Localization of *bicoid* mRNA to the anterior of the developing oocyte establishes a gradient of transcription factor activity that specifies anterior cell fates (Berleth et al., 1988; Driever and Nüsslein-Volhard, 1988), whereas posterior and germ cell fates are established through localization of *oskar* mRNA and subsequent posterior accumulation of *nanos* mRNA (Ephrussi et al., 1991; Kim-Ha et al., 1991; Bergsten and Gavis, 1999).

Germ layer patterning and axis specification in vertebrate oocytes

In *Xenopus* oocytes, maternal mRNAs localized to the vegetal cortex (Fig. 3B) act in both germ layer patterning and germ cell specification (reviewed by King et al., 2005). Early in oogenesis, mRNAs encoding RNA-binding proteins with roles in germ cell determination, such as *Xdazl* and *Nanos1* (Houston and King, 2000; Lai et al., 2011), are deposited at the vegetal cortex after initial accumulation in the Balbiani body or mitochondrial cloud (Chang et al., 2004). Later in oogenesis, *Vg1* and *VegT* mRNAs are transported to the vegetal cortex and are inherited during cleavage by the vegetal blastomeres (Melton, 1987; Zhang and King, 1996). Vegetally restricted expression of *Vg1* and *VegT*, which encode a TGFβ signalling molecule and a T-box transcription factor, respectively, is crucial for endoderm and mesoderm specification during embryogenesis (Zhang et al., 1998; Birsoy et al., 2006). During oogenesis in zebrafish, many maternal mRNAs are differentially localized along the animal-vegetal axis (Fig. 3C) (Abrams and Mullins, 2009). Whereas several mRNAs, including *dazl*, are localized to the vegetal pole, *pou2* (*pou5f1* – Zebrafish Information Network) mRNA, which encodes a transcription factor

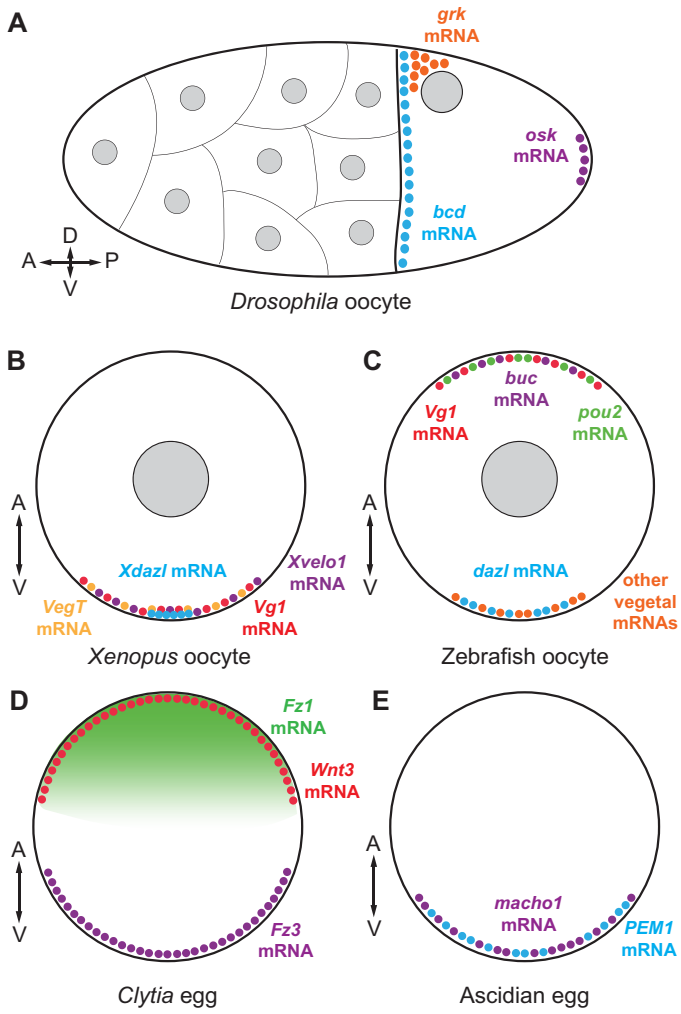


Fig. 3. Localized maternal mRNAs in eggs and oocytes. (**A**) A stage 9 *Drosophila* oocyte is depicted, with accessory nurse cells shown on the left. *bicoid* mRNA (*bcd*, blue) is localized to the anterior margin of the oocyte and *oskar* mRNA (*osk*, purple) is localized to the posterior pole. *gurken* mRNA (*grk*, orange) is localized to the anterodorsal corner of the oocyte, adjacent to the oocyte nucleus. The anteroposterior and dorsoventral axes are indicated on the left. (**B**) A *Xenopus* stage IV oocyte is depicted, with *Xdazl* mRNA (blue) indicated at the vegetal pole and *Vg1* (red), *VegT* (yellow) and *Xvelo1* (purple) mRNAs shown at the vegetal cortex. (**C**) A zebrafish stage III oocyte is shown, with *pou2* (green), *bucky ball* (*buc*, purple) and *Vg1* (red) mRNAs localized to the animal hemisphere. Shown in the vegetal hemisphere are *dazl* (blue) and other vegetally localized mRNAs (orange). (**D**) A *Clytia* egg is depicted, with *Wnt3* (red) and *Frizzled1* (*Fz1*, green) mRNAs localized to the animal hemisphere, and *Frizzled3* mRNA (*Fz3*, purple) localized to the vegetal hemisphere. (**E**) A fertilized Ascidian egg is depicted, with *macho1* (purple) and *PEM1* (blue) mRNAs localized to the vegetal cortex. (B-E) The animal-vegetal axis is indicated on the left.

that functions in endoderm specification, is localized to the animal pole (Howley and Ho, 2000; Lunde et al., 2004). *bucky ball* (*buc*) mRNA is localized first to the vegetal Balbiani body, and relocalizes later in oogenesis to the animal pole, along with *Vg1* (*dvr1* – Zebrafish Information Network) mRNA (Marlow and Mullins, 2008). *buc* mRNA encodes a protein of unknown function that is homologous to *Xenopus* Xvelo1 (Fig. 3B) and is necessary for animal-vegetal polarity (Bontems et al., 2009).

Axis specification by maternal mRNA localization in marine invertebrates

In eggs of the jellyfish *Clytia*, mRNAs encoding the Wnt receptor Frizzled1 and its ligand Wnt3 are localized to the animal hemisphere (Fig. 3D), whereas mRNA encoding the negatively acting receptor Frizzled3 is localized to the vegetal hemisphere (Momose and Houliston, 2007; Momose et al., 2008). The Wnt signalling pathway activated by these localized maternal mRNAs acts to establish the oral-aboral axis during embryogenesis (Momose et al., 2008). In ascidians (including *Ciona* and *Halocynthia*), a group of maternal mRNAs termed PEM RNAs (reviewed by Sardet et al., 2005), are localized to the vegetal cortex immediately after fertilization (Fig. 3E). This diverse group of mRNAs includes *PEM1*, which encodes a protein of unknown function that plays a role in anterodorsal patterning (Yoshida et al., 1996), and the muscle determinant *macho1*, a zinc-finger transcription factor (Nishida and Sawada, 2001). During cleavage, the PEM RNAs are segregated to the posterior blastomeres and act to specify cell fates and axial polarity during embryogenesis (Sardet et al., 2003).

Evolutionary considerations

As exemplified above, localization of maternal RNA determinants is a widely used strategy for establishing axial polarity during animal development. Although commonalities exist among the localization mechanisms, the molecular identities of localized mRNAs can, in some cases, be rapidly evolving. Studies in the wasp *Nasonia* showed that anterior patterning is specified by anterior localization of *orthodenticle* mRNA (Lynch et al., 2006; Olesnicky and Desplan, 2007), rather than *bicoid* mRNA, as in *Drosophila* (Berleth et al., 1988). Nonetheless, functional conservation is apparent, as the DNA-binding specificity of the homeodomain transcription factor encoded by *orthodenticle* is the same as that of *bicoid* (Wilson et al., 1996). A contrasting view emerges, however, from overlap in molecular identities of localized mRNAs such as *dazl*, *buc/Xvelo1* and *Vg1* in *Xenopus* and zebrafish (Fig. 3), suggesting an evolutionarily ancient origin for some patterning circuits directed by mRNA localization.

Specification of cell fate by asymmetric segregation of RNA determinants in dividing cells

Asymmetric cell divisions produce daughter cells with distinct fates, and rely on the asymmetric segregation of key determinants, including localized mRNAs.

Asymmetric RNA inheritance in cleavage-stage embryos

Specific populations of mRNAs are localized for the first time in cleavage-stage embryos, where they are partitioned into only one daughter cell upon cell division. During the early cleavage cycles of the *Ilyanassa* mollusc embryo, for example, a large fraction of mRNAs are localized to one of the two centrosomes and asymmetrically inherited (Fig. 4A) (Lambert and Nagy, 2002). As most of these mRNAs encode developmental patterning genes known for their regulatory functions in other organisms, it is likely that their differential segregation controls cell fate specification (Kingsley et al., 2007).

In mesendoderm cells of the 16-cell stage *Halocynthia* ascidian embryo, *Not* mRNA is delivered to the cytoplasm of the future mesoderm-forming pole after nuclear migration, and is asymmetrically partitioned into the mesoderm daughter cell through cytokinesis (Fig. 4B). *Not* mRNA encodes a transcription

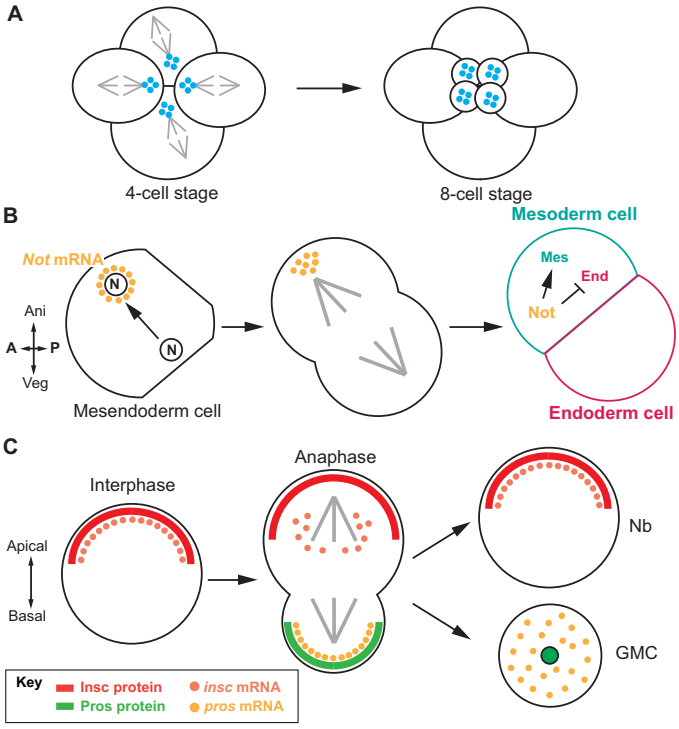


Fig. 4. Asymmetrically segregating mRNAs in dividing cells. (**A**) In *Ilyanassa* embryos, specific mRNAs (blue) localize to one of the two centrosomes of metaphasic cells at the 4-cell stage (left). Upon division, these mRNAs are differentially inherited by daughter cells (right). (**B**) *Not* mRNA (yellow) is delivered to one side of a *Halocynthia* embryo mesendoderm cell by nuclear migration. *Not* mRNA is inherited by the mesoderm daughter cell, but not the endoderm daughter cell. Adapted from Takatori et al. (Takatori et al., 2010). (**C**) *Drosophila* embryo neuroblasts (Nb) divide asymmetrically to regenerate a Nb and produce a smaller cell, the ganglion mother cell (GMC). Whereas *inscuteable* (*insc*) mRNA (orange) and Insc protein (red) localize at the apical side of interphasic Nb, *prospero* (*pros*) mRNA (yellow) and Pros protein (green) localize basally at anaphase, thus ensuring a differential inheritance of the two components. A, anterior; Ani, animal; P, posterior; Veg, vegetal.

factor that promotes mesoderm fate and suppresses endoderm fate, suggesting that this asymmetric partitioning is responsible for the segregation of germ layer fates (Takatori et al., 2010).

The role of mRNA localization in lineage diversification has recently been extended to mammalian early embryogenesis. During early mouse development, the first cell fate decision is between the pluripotent inner cell mass and the external trophectoderm (Jedrusik et al., 2008). In this context, the trophectoderm determinant-encoding *cdx2* mRNA has been shown to concentrate at the apical side of 8- to 16-cell blastomeres, and to be inherited exclusively by outside daughter cells upon division (Jedrusik et al., 2008). Although additional functional studies are required, these results suggest that unequal mRNA distribution might contribute to symmetry breaking between inside and outside cells.

Asymmetric RNA inheritance in stem cell divisions

Asymmetric segregation of mRNAs encoding cell fate determinants has also been observed in the context of stem cell divisions. In *Drosophila* embryos, neural precursors (neuroblasts) divide unequally to generate a neuroblast and a smaller ganglion mother cell (GMC). *prospero* mRNA, which encodes a transcription factor that activates GMC-specific gene expression, is localized to the basal pole of neuroblasts during mitosis and is exclusively inherited by the GMC (Li et al., 1997; Broadus et al., 1998). In the absence of mRNA localization, Prospero protein still localizes basally, suggesting that *prospero* mRNA and protein are targeted independently. Functionally, these two processes appear to act redundantly to establish GMC-specific patterns of gene expression (Broadus et al., 1998). Asymmetric mRNA inheritance requires segregation to be coupled with precise orientation of cell division. In *Drosophila* neuroblasts, coupling is mediated by the adapter protein Inscuteable, and *inscuteable* mRNA is targeted apically in interphase neuroblasts (Fig. 4C). Interestingly, mislocalization of *inscuteable* mRNA significantly reduces Inscuteable protein apical accumulation, and is associated with mitotic spindle misorientation (Hughes et al., 2004).

Asymmetric segregation of the glial determinant-encoding *glide*/*gcm* (*gcm* – FlyBase) mRNA has also been observed in early *Drosophila* embryos during neuroglioblast division. Surprisingly, the preferential inheritance of *glide* mRNA by the glioblast does not result in asymmetric inheritance of the Glide protein, but seems to contribute to a glioblast-specific positive autoregulatory loop (Bernardoni et al., 1999).

Control of epithelial cell polarization by precise mRNA targeting

Specific localization along the apicobasal axis has been observed for a large number of transcripts (up to 10-15% of the expressed mRNAs in maturing *Drosophila* epithelia) (Lécuyer et al., 2007). Studies on specific transcripts suggest that this process is essential for epithelial cell polarization and functions.

Apically distributed mRNA encoding cell junction components and cytoskeletal regulators

Establishment and maintenance of epithelial cell polarity rely on the asymmetric distribution of evolutionarily conserved protein complexes, such as the Crumbs complex. This complex is composed of the transmembrane protein Crumbs (Crb), the scaffolding protein Stardust/MPP5 (Sdt), and the PALS-1 Associated Tight Junction protein (dPatj). *crb*, *sdt* and *Patj* mRNAs have been shown to localize to discrete subapical domains within *Drosophila* embryonic and follicular epithelial cells (Lécuyer et al., 2007; Horne-Badovinac and Bilder, 2008; Li et al., 2008). Remarkably, apical localization of *sdt* mRNA is developmentally regulated through an alternative splicing event and appears to contribute exclusively to the early phase of Sdt and Crb apical accumulation (Fig. 5A) (Horne-Badovinac and Bilder, 2008); at later time points, the mRNA is no longer localized, whereas the protein still is. mRNA targeting coupled to local translation might thus be particularly important in immature epithelia, when polarity is still labile. mRNA localization is also important for epithelial cell polarity in mammals. Most recently, apical localization of the mRNA encoding the zonal occludens-1 (ZO-1; also known as Tjp1) protein has been shown to control tight junction assembly and cell polarity in mammary epithelial cells (Fig. 5B) (Nagaoka et al., 2012).

Apical mRNA localization might also play crucial roles in the nucleation and positioning of cytoskeletal networks. Indeed, *short stop* mRNA encoding the *Drosophila* actin-microtubule cross-linker Spectraplakin is apically distributed within the embryonic epithelium (Lécuyer et al., 2007). *diaphanous*

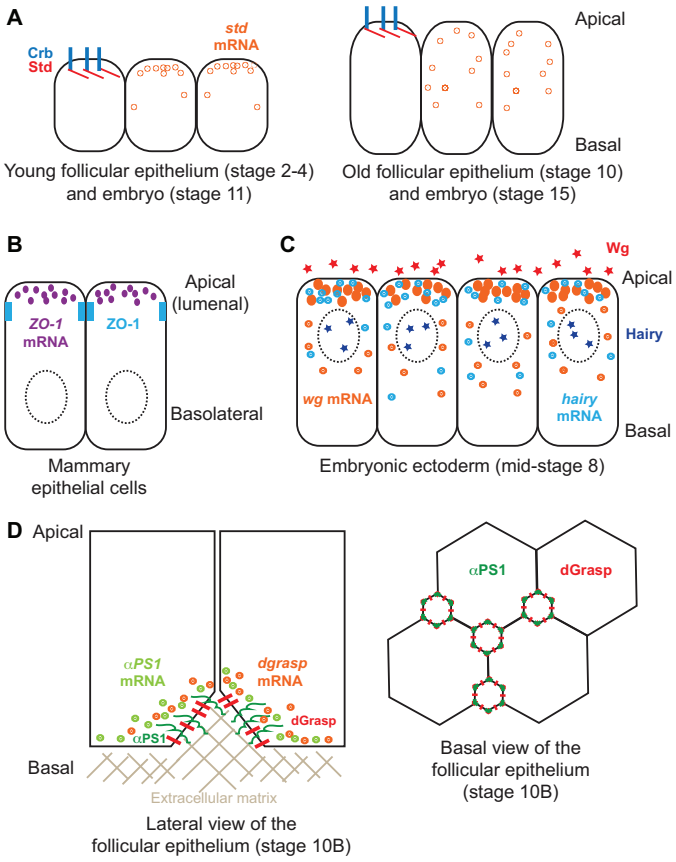


Fig. 5. Apicobasal mRNA targeting in epithelial cells. (**A**) In *Drosophila* follicular cells and embryonic epithelia, apical targeting of *stardust* (*sdt*, orange) mRNA is necessary to localize Crumbs (Crb, blue) and Sdt (red) proteins in young epithelial cells. At later stages, *sdt* mRNA is no longer apically distributed. (**B**) mRNA encoding zonal occludens-1 (*ZO-1*, purple) is targeted apically in mammalian mammary epithelial cells, which is necessary for the localization of its protein product (blue) to apical tight junctions. (**C**) *wingless* mRNA (*wg*, orange) accumulates at the apical pole of *Drosophila* embryonic epithelial cells, thereby promoting the secretion of Wg protein (red stars). *hairy* mRNA (light blue) is also localized at the apical side of epithelial cells, which would favour nuclear uptake of Hairy protein (dark blue stars). (**D**) *dgrasp* mRNA (orange) accumulates together with its product dGrasp (red) at the basal side of *Drosophila* follicular cells, in the zone of contact (ZOC) where it controls the basal targeting of integrin αPS1 mRNA (light green) and protein (dark green). The left panel represents a lateral view of the follicular epithelium, and the right panel a basal view. Adapted from Schotman et al. (Schotman et al., 2008).

mRNA, coding for the *Drosophila* actin-nucleating factor Formin, is also accumulated at the apical side of epithelial tubular structures (Massarwa et al., 2009). Whether targeting of these mRNAs is functionally relevant however remains to be studied.

Functional signalling pathways and transcript localization along the apicobasal axis

One means of optimizing secretion of signalling molecules in epithelia is to accumulate their transcripts near the site of secretion prior to translation. Transcripts encoding Wingless (Wg), a *Drosophila* member of the Wnt family, are apically localized within epithelial cells of the embryonic ectoderm (Fig. 5C) and salivary glands (Simmonds et al., 2001). Importantly, apical targeting of *wg* mRNA is crucial for autoregulation of Wg protein levels and apical secretion, thus ensuring robustness of the signalling activity. Similarly, *unpaired* (*upd*) mRNA, encoding a cytokine ligand for the JAK/STAT pathway, accumulates at the apical side of polar cells in the *Drosophila* follicular epithelium (Van de Bor et al., 2011). Apical targeting of *upd* mRNA is essential for efficient Upd secretion and signalling to adjacent epithelial cells, triggering their differentiation into migrating cells. Transcripts such as *hairy*, *runt* and *even skipped*, which encode pair-rule transcription factors responsible for *Drosophila* embryonic patterning, are also targeted apically in blastoderm embryos (Fig. 5C). This process is conserved through dipteran evolution and is essential for efficient transcription of patterning genes (Bullock et al., 2004). By targeting translation near apically localized nuclei, mRNA transport could favour the nuclear uptake of encoded transcription factors.

mRNA targeting to basolateral domains of epithelial cells also plays important roles in the maintenance of epithelium integrity. For instance, the *Drosophila* peripheral Golgi protein dGrasp (Grasp65 – FlyBase) is preferentially found in the ZOC (zone of contact), a subcellular domain close to the basal surface of follicular cells, where it is required for αPS1 integrin (Mew – FlyBase) deposition (Fig. 5D). Basal deposition of αPS1 is essential for the formation of focal adhesion sites and the maintenance of epithelial structures, and has been shown to fully depend on the basal targeting of both *dgrasp* and *αPS1* mRNAs to the ZOC (Schotman et al., 2008).

Regulation of cell migration and guidance by mRNA targeting

Cellular protrusions in migrating cells and growing neuronal processes accumulate proteins involved in sensing external cues, and regulating cell motility and directionality. mRNA localization has been shown to underlie local translation of some of these proteins in response to environmental signals (Lin and Holt, 2007; Mili and Macara, 2009).

mRNA targeting to migrating cell protrusions

As revealed by a recent global analysis, ~50 mRNAs encoding proteins involved in various functions, including membrane trafficking, signalling and cytoskeleton organization are enriched in cell protrusions of migrating mammalian fibroblasts (Mili et al., 2008). Complementary to this finding, mRNAs encoding β-actin and the seven subunits of the actin-polymerization nucleating Arp2/3 complex have been shown to accumulate together with their corresponding products in protrusions of cultured chicken embryonic fibroblasts (Fig. 6A) (Lawrence and Singer, 1986; Mingle et al., 2005). Asymmetric targeting of these mRNAs is crucial for directional cell migration (Condeelis and Singer, 2005; Liao et al., 2011), and probably promotes the formation of actin nucleation centres at the cell front. Supporting a role for mRNA localization during in vivo cell migration, the conserved RNA-binding protein Zbp1/Vg1RBP, known for its role in mRNA localization in multiple systems, accumulates in the processes of *Xenopus* migratory neural crest cells and is required for their migration (Yaniv et al., 2003). However, mRNA targets for Zbp1/Vg1RBP have not been identified so far.

mRNA localization has also been suggested to influence the invasiveness of tumour cells by regulating the cell orientation necessary for proper chemotaxis (Lapidus et al., 2007), or the targeting of pro-migratory adhesive molecules (Adereth et al.,

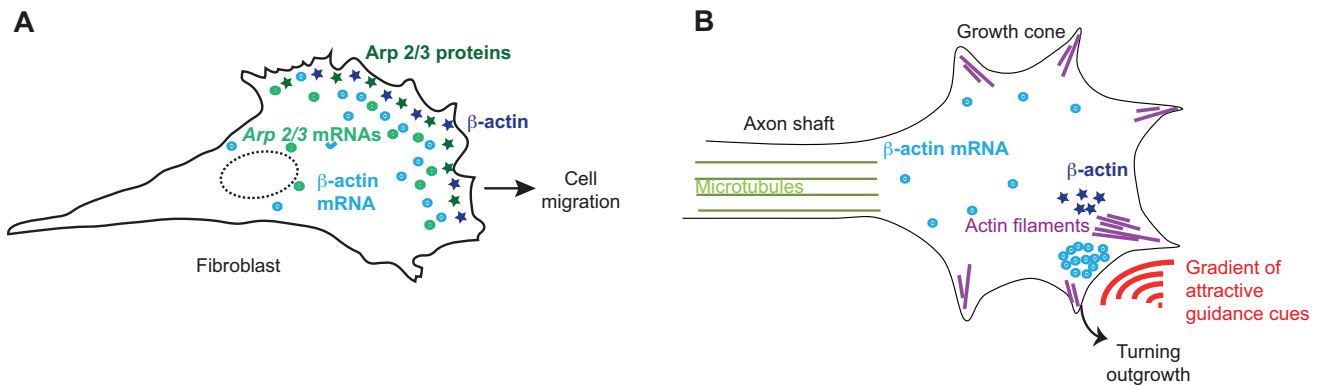


Fig. 6. Targeted mRNAs in migrating cells. (**A**) β-actin mRNA (light blue) or mRNAs encoding subunits of the Arp2/3 complex (light green) are targeted to the leading edge of migrating fibroblasts. Local synthesis of their corresponding proteins (dark blue and dark green stars, respectively) contributes to directional migration. (**B**) β-actin mRNA (light blue) is transported to the side of the axonal growth cone exposed to an attractive guidance cue (red). Locally translated β-actin protein (dark blue stars) accumulates at the same location, promoting the nucleation of actin filaments (purple) and triggering growth cone turning.

2005; Gu et al., 2012). Consistent with this, the tumour suppressor APC plays a crucial role in anchoring mRNAs specifically targeted to the protrusions of migrating fibroblasts (Mili et al., 2008).

Axonal mRNA localization

As revealed by studies performed on cultured *Xenopus* retinal neurons, axonal growth cone steering decisions require local translation of mRNAs targeted to growing axon tips (Campbell and Holt, 2001). Strikingly, two recent microarray analyses have shown that hundreds of mRNAs (6-10% of the transcriptome) are present in the axons of cultured vertebrate sensory neurons, suggesting that a large panoply of proteins might be locally translated (Zivraj et al., 2010; Gumy et al., 2011). Consistent with this, axonal translation of proteins as diverse as polarity proteins involved in axon outgrowth (Hengst et al., 2009), actin cytoskeleton regulators involved in axon guidance (Wu et al., 2005; Piper et al., 2006), lamins promoting mitochondrial function (Yoon et al., 2012), and transcription factors signalling back to the nucleus (Cox et al., 2008; Ben-Yaakov et al., 2012) has been demonstrated to be important for polarized axon growth, maintenance or regeneration.

A strong link between axonal mRNA localization, local translation, and axon steering has been provided through studies performed in growing *Xenopus* and murine axons. Asymmetric gradients of attractive cues trigger an asymmetric recruitment of β-actin mRNA and a polarized increase in β-actin translation on the near side of the axon growth cone, both being essential for the turning response (Fig. 6B) (Leung et al., 2006; Yao et al., 2006; Welshhans and Bassell, 2011). Interestingly, the nature of locally translated proteins depends on the type of applied stimuli (Lin and Holt, 2007), and the repertoire of axonally localized mRNAs is regulated in response to external signals (Willis et al., 2007) and developmental cues (Zivraj et al., 2010; Gumy et al., 2011). In rat sensory neurons, for instance, mRNAs encoding cytoskeletal regulators and transport-related proteins are found in embryonic, but not adult axons (Gumy et al., 2011).

In addition to the ex vivo results described above, in vivo studies have shown that mRNA translation in axons is regulated during nervous system development. For example, translation of EphA2 guidance receptor mRNA reporter constructs is activated in chick spinal cord axons only once commissural growth cones have crossed the midline (Brittis et al., 2002). Also consistent with developmental regulation of axonal protein synthesis in vivo, local translation of mouse odorant receptor mRNAs is higher in immature than in adult olfactory bulbs (Dubacq et al., 2009).

Control of dendritic maturation by localized mRNAs

Maturation of neuronal circuits involves remodelling of dendritic trees and refinement of synapse number and strength, two processes controlled by local translation of dendritically targeted mRNAs (Sutton and Schuman, 2006; Doyle and Kiebler, 2011).

Dendritogenesis

The complexity of dendritic trees is a key parameter underlying neuronal activity and connectivity. Strikingly, recent studies have revealed that the transport of specific mRNAs to dendrites is crucial for dendritic branching during development. Targeting of *nanos* mRNA to dendrites, for example, is required for proper branching of peripheral sensory neurons in *Drosophila* larvae (Brechbiel and Gavis, 2008). In young mouse hippocampal neurons, inactivation of the RNA-binding protein Staufen1 impairs the transport of β-actin mRNA to dendrites and reduces dendritic length and branching (Vessey et al., 2008). Similarly, hippocampal neurons lacking the RNA-binding protein Zbp1/Vg1RBP exhibit reduced accumulation of β-actin mRNA and protein in distal dendrites, with a concomitant decrease in dendritic branching (Perycz et al., 2011). Interestingly, the function of Zbp1/Vg1RBP is developmentally regulated, as it is required for intensive dendritogenesis in young neurons, but not for dendrite maintenance in mature neurons (Perycz et al., 2011).

In rat hippocampal neurons, differential localization of *Bdnf* splice variants along dendrites has been shown to lead to spatially restricted effects on dendritic architecture. Whereas *Bdnf* transcripts restricted to the cell soma and proximal dendrites selectively affect proximal dendritic branching, transcripts with a distal dendritic localization affect peripheral dendrite complexity (Baj et al., 2011). These results have led to a ‘spatial code hypothesis’ (Baj et al., 2011), in which selective targeting of BDNF to distinct dendritic regions through differential mRNA localization allows both a precise shaping of dendritic compartments during development, and spatially restricted control of dendritic plasticity in mature neurons.

Synapse formation and plasticity

Formation of new synapses is crucial during early development of the nervous system, and is a multistep process involving initial assembly, maturation and stabilization. As shown in cultured *Aplysia* neurons, recruitment of the neuropeptide-encoding *sensorin* mRNA to nascent synapses is induced upon recognition of pre- and postsynaptic partners, and is required for further synaptic development and maturation (Lyles et al., 2006). These results illustrate that synaptogenesis not only involves recruitment of proteins or organelles, such as synaptic vesicles, but also requires mRNA targeting. In more mature neurons, local translation of dendritically localized mRNAs encoding proteins such as neurotransmitter receptors, ion channels and signal transduction enzymes is essential for the regulation of synaptic activity (Sutton and Schuman, 2006; Doyle and Kiebler, 2011). Interestingly, specific populations of mRNAs are recruited to dendrites upon synaptic activity (Steward et al., 1998), and their translation can be regulated in a synapse- and stimulus-specific manner (Wang et al., 2009), providing a means of individually tagging activated synapses (Fig. 7).

Although most of the aforementioned studies have been performed ex vivo, evidence has been provided for a functional requirement for dendritically localized protein synthesis in stable forms of synaptic plasticity and memory consolidation in vivo. Key experiments performed in mice have shown that the disruption of *Camk2a* (encoding CaMKIIα) or *Bdnf* mRNA dendritic targeting impairs long-term potentiation (Miller et al., 2002; An et al., 2008) and long-term memory (Miller et al., 2002). Moreover, mutations in genes involved in dendritic mRNA targeting or translation have been linked to several human neurological disorders, including the most common cause of inherited mental retardation Fragile X syndrome, consistent with a role for dendritically localized protein synthesis in the regulation of synaptic morphogenesis and plasticity (Liu-Yesucevitz et al., 2011).

Controlling the repertoire of localized mRNAs

The examples discussed above highlight the importance of mRNA localization, as well as its complexity. Given that hundreds of mRNAs can be targeted to diverse subcellular compartments and that their localization can be dynamic, it is clearly essential that the cell can tightly regulate complementary transport machineries in space and time.

Targeting various mRNAs to different cellular locations

Polarized cells must use specific machineries to target mRNAs (or groups of mRNAs) to distinct cellular compartments. For this, combinations of RNA-binding proteins selectively recognize different target mRNAs, ensuring the recruitment of specific molecular motors. In the *Drosophila* oocyte, for example, *oskar* and *gurken* mRNAs assemble into distinct RNP complexes, and their transport to the posterior and anterodorsal poles depends on the activity of kinesin and dynein, respectively (Becalska and Gavis, 2009). How many mRNAs are transported by a given targeting machinery in a given cell type is still unclear, although individual RNA-binding proteins have the capacity to associate with hundreds of functionally related mRNAs (Hogan et al., 2008).

Localizing various mRNAs to distinct cellular locations also implies that these compartments must be provided with a functional translation machinery. Consistent with this, biochemical and electron-microscopy studies have demonstrated that ribosomes are associated with structures as diverse as the mitotic apparatus, mitochondria, neuronal processes and cell adhesion structures (Lécuyer et al., 2009). Whether components of the translation machinery are transported concomitantly with or independently of mRNAs is still unclear, although ribosomal

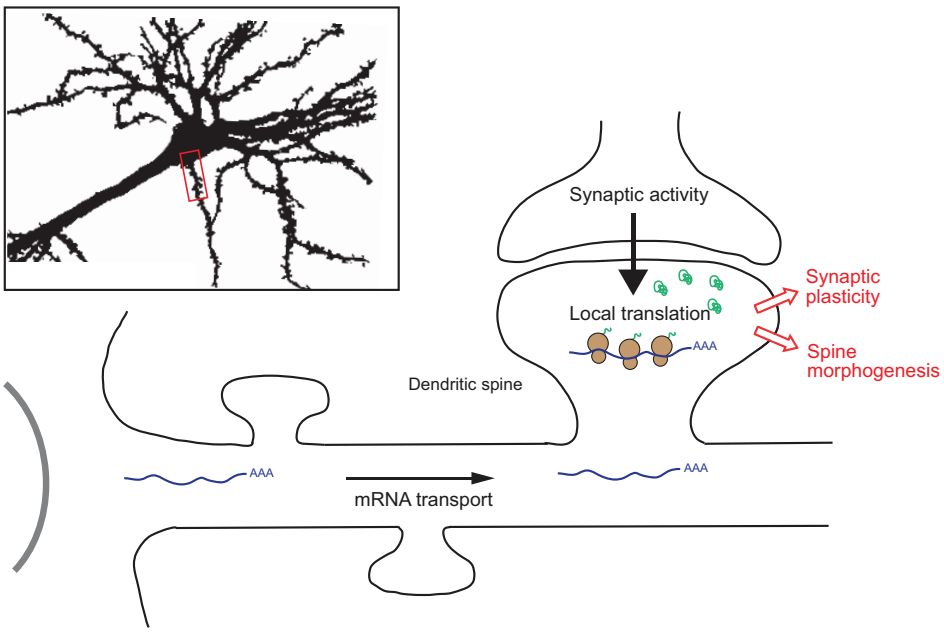


Fig. 7. Local translation of dendritic mRNAs in response to synaptic activity. Translation of dendritically targeted mRNAs is activated in response to synaptic activity and is essential for modulation of synaptic activity and dendritic spine morphogenesis. Strikingly, translation can be regulated at the synapse level, and thus represents an efficient way to individually tag activated synapses. Upper left box: representation of the somatodendritic compartment of a mammalian neuron. Lower panel: schematic of the proximal part of a dendrite that roughly corresponds to the region boxed in the upper panel (red rectangle). Proteins synthesized locally in dendritic spines are represented in green.

constituents can be found in localizing RNP complexes (Besse and Ephrussi, 2008).

Dynamically adjusting the populations of localized mRNAs

As demonstrated in a variety of cell types, both the number and the identity of localized mRNAs are regulated in response to external stimuli and/or developmental signals (Crino and Eberwine, 1996; Chicurel et al., 1998; Steward et al., 1998; Willis et al., 2007; Dictenberg et al., 2008; Horne-Badovinac and Bilder, 2008; Zivraj et al., 2010; Gumy et al., 2011). To modulate their repertoire of localized mRNAs, polarized cells must thus dynamically regulate the activity of their mRNA targeting machineries. In mouse hippocampal neurons, transport of the Fmrp cargo *Camk2a* mRNA to dendrites is increased upon stimulation of metabotropic glutamate (mGluR) receptors (Dictenberg et al., 2008). Although the underlying mechanisms are still unclear, an increased association between Fmrp and the Kif5 motor is observed after stimulation, suggesting that differential recruitment of molecular motors to RNPs could modulate mRNA trafficking in response to a stimulus. In migrating mammalian cells, two independent pathways controlled by the Zbp1 and Apc proteins can regulate the targeting of mRNAs to the leading edge (Mili and Macara, 2009); their activity has been proposed be modulated in such a way that they are not simultaneously operational.

Conclusions

Intracellular mRNA targeting is now recognized as a central mechanism used in many (if not all) polarized cells and, as detailed here, plays a key role in multiple developmental contexts in a wide range of organisms. Strikingly, although the nature of transported mRNAs can vary greatly between cell types and species, mRNA targeting machineries appear to be conserved. For example, the Egl-BicD-Dynein complex is used to target mRNAs in various *Drosophila* cell types (Bullock and Ish-Horowicz, 2001; Hughes et al., 2004; Van de Bor et al., 2011). Furthermore, the RNA-binding protein Zbp1/Vg1RBP has been shown to promote intracellular mRNA transport in chicken fibroblasts (Ross et al., 1997), mouse axons (Donnelly et al., 2011; Welshhans and Bassell, 2011) and *Xenopus* oocytes (Deshler et al., 1998; Havin et al., 1998).

Despite recent progress in the dissection of mRNA transport mechanisms and the dramatic proliferation of newly identified localized mRNAs, significant challenges remain. First, how cells dynamically regulate transport machineries to control their repertoire of localized mRNAs during development is still unclear. Second, the relative contribution of mRNA and protein targeting must be systematically explored, as they may act in parallel (either synergistically or redundantly) in different contexts. Finally, the extent to which non-coding RNAs are asymmetrically targeted is still largely unknown, although some intriguing studies have suggested that non-coding RNAs with specific distributions might have local regulatory or structural roles (Tiedge et al., 1991; Kloc et al., 2005). Interestingly, recent work has demonstrated a strong interplay between miRNA and proteins binding to localization elements (Koebernick et al., 2010). Answering these questions will require combining high-throughput biochemical and imaging approaches with functional analyses specifically addressing the role of mRNA transport in vivo.

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Competing interests statement

The authors declare no competing financial interests.

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