

RNA localization

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Messenger RNA (mRNA) molecules are transcribed in the nucleus and then undergo export into the cytoplasm, where they are translated to produce proteins. Some mRNA transcripts do not immediately undergo translation but, instead, are directed to specific areas for local translation or distribution. This produces an asymmetric distribution of cytoplasmic proteins, providing

localized activities in polarized cells or developing embryos. Studies of the localization process in various eukaryotic systems have unearthed numerous nuclear RNA-binding proteins (RBPs) involved. We present here some representative examples from different organisms.

General features of mRNA localization systems

mRNA transcripts are coated by a variety of RBPs. Some of these are essential for mRNA localization and can be detected even when the mRNA is still nuclear. In many cases, specific sequence elements, 'zipcodes', in the untranslated region (UTR) form a secondary structure that serves as a docking site for the RBPs and thus promotes the localization process.

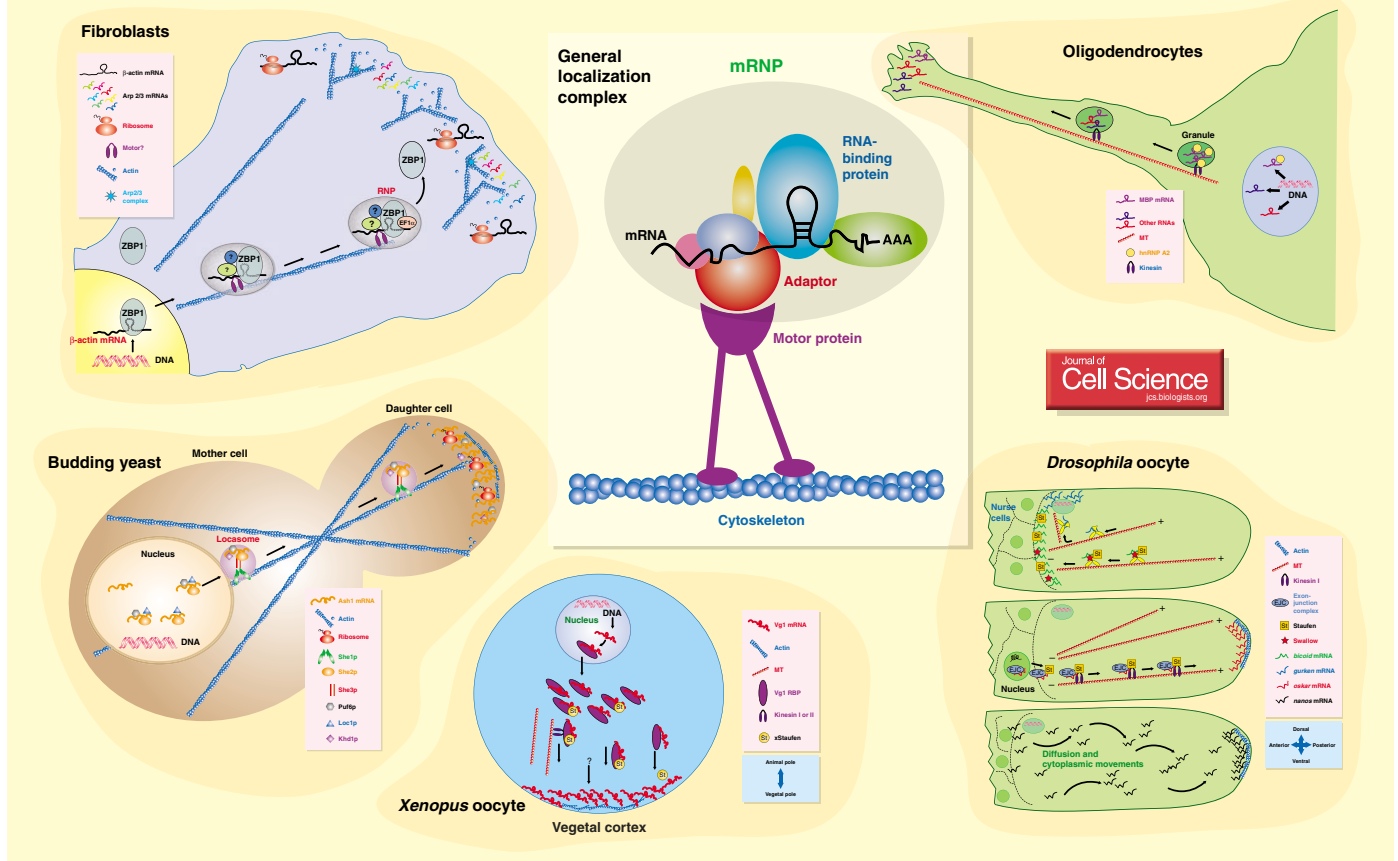
Localizing mRNAs are shuttled to specific areas of the cell or the organism along cytoskeletal elements such as microtubules or actin filaments. They seem to be actively translocated by motor proteins of the myosin, kinesin and dynein families. Although our knowledge of the components of the mRNP complexes is growing, the list we give here is by no means comprehensive and merely a general impression of the multitude of interactions necessary for the localization process.

Mammalian cells

mRNA localization in fibroblasts
β-actin mRNA localization has been identified in several mammalian systems (Lawrence and Singer, 1986). In migrating fibroblasts, β-actin mRNA is

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localized to the leading edge of the cells (Lawrence and Singer, 1986). This correlates with the elevated levels of β -actin protein required in lamellipodia, which depend on the rapid polymerization of actin for cell movement (Condeelis and Singer, 2005). Zipcode sequences (Kislauskis and Singer, 1992) immediately downstream of the stop codon (Kislauskis et al., 1993) recruit the zipcode-binding protein ZBP1 by interacting with its KH domains (Ross et al., 1997; Farina et al., 2003). ZBP1 and β -actin mRNA associate in the nucleus (Oleynikov and Singer, 2003) and travel in cytoplasmic granules to the leading edge. ZBP2, a predominantly nuclear protein, also binds the zipcode and affects localization (Gu et al., 2002). Translation is thought to be inhibited, perhaps by ZBP1, until the mRNA reaches the lamellipodia. β -actin-containing granules are transported on actin filaments (Sundell and Singer, 1991) and might anchor at specific sites through interactions with EF1 α (Liu et al., 2002). The responsible motor is unidentified, although inhibition of myosin activity does disrupt the process (Latham et al., 2001).

The formation of the branched actin cytoskeleton at the protruding edge of migrating fibroblasts requires the Arp2/3 complex (Machesky et al., 1994). This seven-subunit complex (Machesky et al., 1997; Mullins et al., 1997; Welch et al., 1997), caps the slow-growing ends of actin filaments, while stabilizing the fast-growing polymerizing ends. The seven mRNAs that encode Arp2/3 subunits are all localized to the leading edge of fibroblasts, which supports the idea that localized translation of functionally-related mRNAs is coupled to the assembly of complexes (Mingle et al., 2005).

mRNA localization in the neuronal system

mRNA localization mechanisms also allow local translation in the extremities (dendrites and axons) of cells from the neuronal system (Job and Eberwine, 2001). The mRNAs typically travel from the cell body in granules that contain several copies of the mRNA or several types of mRNA. Myelin basic

protein (MBP) mRNAs, for example, are targeted to the myelin membranes of oligodendrocyte cell processes (Ainger et al., 1993). They probably associate with microtubules through a kinesin motor (Carson et al., 1997) and are bound by the RNA-binding protein hnRNP A2 (Hoek et al., 1998). Other examples are localization of CamKII α mRNA by kinesin in hippocampal dendrites (Kanai et al., 2004; Rook et al., 2000) and translocation of tau mRNA on microtubules in axons, in which a relative of ZBP1, IMP-1, is involved (Atlas et al., 2004). β -actin mRNA is localized to neuronal growth cones and hippocampal dendrites through similar association with ZBP1 (Bassell et al., 1998; Eom et al., 2003). Long-distance translocation occurs along microtubules (Zhang et al., 2001), using an unidentified motor protein, probably kinesin (our unpublished data). Since the distance between dendrites or axons and the cell nucleus can be extremely large, this localization mechanism allows rapid translational responses that are independent of the ongoing transcription in the nucleus.

Budding yeast

Actin-based translocation of localized mRNAs also occurs in yeast (Darzacq et al., 2003; Gonsalvez et al., 2005). In budding yeast, many RNAs translocate from the mother cell into the budding daughter cell and concentrate at the bud tip (Shepard et al., 2003). One of the best studied examples is *ASH1* mRNA (Long et al., 1997; Takizawa et al., 1997). Ash1p is a nuclear DNA-binding protein required for control of mating-type switching, and its asymmetric distribution causes the repression of *HO* endonuclease expression only in the daughter cell (Bobola et al., 1996; Sil and Herskowitz, 1996). *ASH1* RNA is moved along actin filaments by a type V myosin, She1p/Myo4p, as part of an RNP complex termed the locosome (Beach et al., 1999; Bertrand et al., 1998). She2p is an RBP that binds to the *ASH1* mRNA zipcode sequences in the nucleus, accompanies the mRNA in the cytoplasm (Bohl et al., 2000; Long et al., 2000; Niessing et al., 2004) and bridges the connection to the motor via She3p (Takizawa and Vale, 2000). Once at the

bud tip, *ASH1* mRNA might be anchored to cortical actin. The Puf6p protein interacts directly with the *ASH1* mRNA and represses its translation during translocation to the daughter cell (Gu et al., 2004). Because Puf6p is nuclear, it might associate with *ASH1* mRNA in the nucleus. Khd1p is a component of the locosome and localizes with *ASH1* mRNA at the bud tip and also inhibits translation (Irie et al., 2002). Loc1p is another nuclear protein that associates with *ASH1* mRNA and might be important for mRNP assembly (Long et al., 2001).

Xenopus

Several mRNAs are localized to the different poles of *Xenopus* oocytes (Kloc and Etkin, 2005). The unequal distribution of specific mRNAs results in the development of unique daughter cells, providing a means by which germ cell lineages are defined and the primary axis for development is established. Vg1 protein is a member of the transforming growth factor β (TGF β) superfamily and has roles in mesoderm and endoderm development. Vg1 mRNA is localized to a tight region in the vegetal cortex of frog oocytes during oogenesis (Melton, 1987). It harbors a zipcode (Mowry and Melton, 1992) that interacts with the protein Vg1-RBP/Vera (Deshler et al., 1998; Havin et al., 1998; Schwartz et al., 1992) through its KH domains (Git and Standart, 2002) and mediates association with microtubules (Elisha et al., 1995). *Xenopus* Vg1-RBP/Vera is highly related to mammalian ZBP1, and both are part of a family of closely related RBPs involved in RNA regulation (Yisraeli, 2005). Movement of Vg1 mRNA along microtubules (Yisraeli et al., 1990) could involve kinesin motors and the Staufen RBP (see below) (Allison et al., 2004; Betley et al., 2004; Yoon and Mowry, 2004). Interestingly, during these stages of *Xenopus* development most of the microtubules have their plus ends pointed towards the nucleus (Pfeiffer and Gard, 1999), and therefore it remains unclear how mRNAs localize in the opposite direction (Kloc and Etkin, 2005). Other transport mechanisms might exist – for instance, the association of Vg1 mRNA with ER-membrane vesicles (Deshler et al., 1997).

Several other proteins have also been implicated as being part of the zipcode-binding localization complex: VgRBP60/PTB/hnRNP I (Cote et al., 1999); Prp (Zhao et al., 2001); xStau (Yoon and Mowry, 2004); VgRBP71 (Kroll et al., 2002); 40LoVe (Czaplinski et al., 2005). Some of these, like ZBP2, are predominantly nuclear, which suggests a nuclear connection for cytoplasmic localization (Farina and Singer, 2002; Kress et al., 2004).

Drosophila

Localization of *nanos*, *oskar*, *bicoid* and *gurken* mRNAs during oogenesis

Localized translation is controlled spatially and temporally in specified areas in *Drosophila* oocytes and embryos. In the oocyte, *nanos* mRNA is localized to the posterior during development, and Nanos protein is required for the formation of the anterior-posterior body axis (Gavis and Lehmann, 1992; Tautz, 1988). Most *nanos* mRNA does not localize and is translationally repressed (Bergsten and Gavis, 1999) or degraded (Bashirullah et al., 1999). Posterior-localized *nanos* mRNA, however, is stable and translated. The localization of *nanos* mRNA occurs late in oogenesis when the nurse cells release their cytoplasmic contents and the mRNA moves into the oocyte. In contrast to other systems, *nanos* mRNA seems to move by diffusion, enhanced by microtubule-dependent cytoplasmic streaming, to the posterior region, where it is anchored to the actin cytoskeleton (Forrest and Gavis, 2003). *nanos* mRNA contains several regions in its 3' UTR that are required for its localization (Dahanukar and Wharton, 1996; Gavis et al., 1996). One stem-loop element is bound by the Smaug protein (Smg), which acts in translational repression of Nanos (Crucis et al., 2000; Dahanukar et al., 1999; Smibert et al., 1996).

The localization of *nanos* mRNA requires the Oskar protein (Ephrussi et al., 1991). *oskar* mRNA is also localized to the posterior of the embryo and is one of the first molecules to be recruited – probably by a kinesin-I-based mechanism (Brendza et al., 2000). Although *oskar* mRNA has a 3' UTR

that is required for its localization (Kim-Ha et al., 1993), protein components of the exon-junction-complex (EJC) accompany the mRNA from the nucleus to its destination (Hachet and Ephrussi, 2001; Mohr et al., 2001), and the splicing reaction itself may be necessary for *oskar* mRNA localization (Hachet and Ephrussi, 2004). Several other trans-acting factors required have been identified. Staufen, for example, is an RBP that colocalizes with *oskar* mRNA at the posterior pole and is required for its localization and translation (Micklem et al., 2000; Rongo et al., 1995; St Johnston et al., 1991).

Staufen is necessary for the localization of another *Drosophila* mRNA, *bicoid*, to the anterior pole during late stages of oogenesis (St Johnston et al., 1991), interacting with stem-loop structures in the 3' UTR of this mRNA (Ferrandon et al., 1994). Bicoid is a transcription factor that diffuses from the anterior pole to form a gradient throughout the embryo. During earlier stages of oogenesis, *bicoid* localization depends on the Exuperantia protein (St Johnston et al., 1989) and then on Swallow protein for anterior anchoring (Stephenson et al., 1988). *bicoid* mRNA is transcribed in the oocyte nurse cells and then translocates into the oocyte, where it moves along microtubules (Cha et al., 2001), connecting through Swallow to a dynein motor (Duncan and Warrior, 2002; Januschke et al., 2002; Schnorrer et al., 2000).

Dynein also moves *gurken* mRNA along microtubules to the anterior; there it changes direction moving towards the oocyte nucleus, where it localizes (MacDougall et al., 2003). The localization of Gurken, the *Drosophila* homologue of transforming growth factor α (TGF α), is important for the establishment of both the antero-posterior and the dorso-ventral axes.

Localization in the embryo

Later stages of *Drosophila* development also require RNA localization events, which occur after the setting of anterior-posterior protein gradients in the oocyte. In the blastoderm embryo, gap genes are located in broad segments along the anterior-posterior axis, yielding local

mRNA expression and protein translation. The differences in concentrations of gap gene products such as Krüppel, Hunchback and Giant give rise to embryo segmentation in conjunction with localized expression of pair-rule genes. The pair-rule genes *ftz*, *hairy* and *runt* are expressed in a segmental seven-stripe pattern in the syncytial embryo (Davis and Ish-Horowicz, 1991). When transcribed, these transcripts diffuse into the cytoplasm in all directions and later localize to their correct positions in RNA particles, moving on microtubules by dynein motors (Wilkie and Davis, 2001). Two other proteins, Bicaudal-D (BicD) and Egalitarian (Egl), are important for dynein-mediated transport of localized mRNAs both in the oocyte and the embryo (Bullock and Ish-Horowicz, 2001). Egl binds to dynein light chain and to BicD and might bridge the connection between the motor and RNA cargo (Mach and Lehmann, 1997; Navarro et al., 2004).

Outlook

The list of mRNAs known to be localized now stands at well over 100. In neurons alone, the number is probably even higher. Many questions remain: what are the complex motor systems that transport mRNAs and how do they 'choose' their respective cargos and cytoskeletal tracks, do mRNAs commit to localization in the nucleus, which proteins cooperate in the assembly of localization granules, which mRNAs are co-transported in the same granules and how is the translation of these mRNAs regulated? The combination of molecular and protein strategies in conjunction with live-cell imaging techniques should bring us closer to understanding the different mechanisms of mRNA localization and how they evolved in various species. For instance, following single, localizing mRNAs indicates that events involving RNA diffusion, assembly of motor complexes and interaction with cytoskeletal filaments are all probabilistic. Having a zipcode increases the probability of each of those events that lead to localization (Fusco et al., 2003). Further analysis of these factors at the molecular level will be an important next step in decoding the localization process.

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