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Spatial regulation of translation through RNA localization

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Abstract

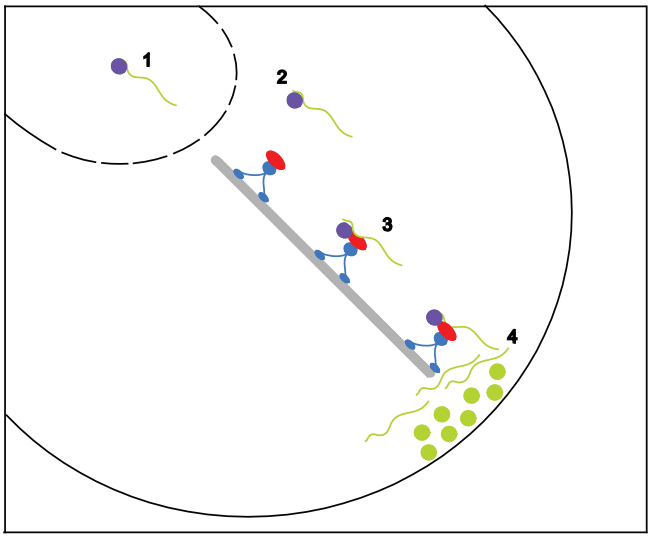
RNA localization is a mechanism to post-transcriptionally regulate gene expression. Eukaryotic organisms ranging from fungi to mammals localize mRNAs to spatially restrict synthesis of specific proteins to distinct regions of the cytoplasm. In this review, we provide a general summary of RNA localization pathways in *Saccharomyces cerevisiae*, *Xenopus*, *Drosophila* and mammalian neurons.

Introduction

Eukaryotic cells need to temporally and spatially regulate gene expression in response to a variety of cues. While temporal regulation of gene expression can be achieved through transcriptional regulation, the ability of a cell to spatially restrict synthesis of a specific protein within the cytoplasm requires post-transcriptional control. Consequently, eukaryotic cells have developed a variety of mechanisms to spatially sort specific proteins to distinct intracellular locations. Proteins destined for organelles, such as mitochondria and the ER (endoplasmic reticulum), contain signal peptides that direct the protein to the proper location within the cell. Another mechanism to spatially sort proteins is RNA localization. In this process the mRNA encoding the protein is localized to the site where the protein functions. Once the mRNA reaches the proper destination, the mRNA is translated, resulting in the spatial restriction of the corresponding protein. In addition to sorting proteins to distinct regions within the cytoplasm, RNA localization has a role in sorting proteins to the ER and mitochondria [1,2].

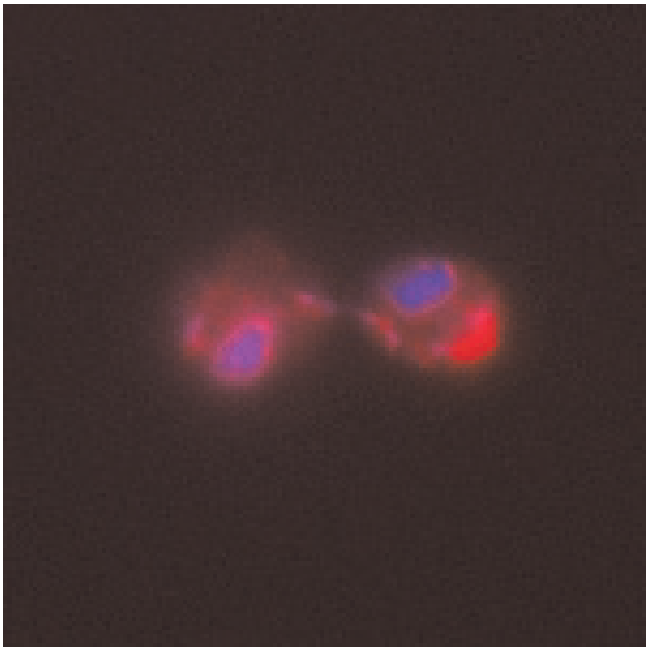
There are at least three mechanisms by which an mRNA can be localized: (1) local protection from degradation, (2) diffusion and entrapment by a localized anchor and (3) direct transport by motor proteins on cytoskeletal filaments [3,4]. In *Drosophila*, *Hsp83* mRNA localizes to the posterior pole plasma of the egg using the protection from degradation pathway [5]. In this RNA localization pathway, the RNAs are protected from degradation at the site of localization and are highly susceptible to degradation in other areas of the cell. In contrast, the *Xcat-2* mRNA in *Xenopus* utilizes the diffusion and entrapment mechanism [6]. RNA localization substrates that utilize this pathway randomly diffuse throughout the cytoplasm, and, when the RNA reaches the site of localization, it is captured and retained. In this article, we will focus on direct transport (Figure 1). In this mechanism, the RNA contains a *cis*-acting localization element, also referred to as a "zip code". The *cis*-acting element directs the RNA to the proper intracellular location. RNA-binding proteins recognize a nucleotide sequence and/or structure in the *cis*-acting localization element. Some RNA-binding proteins identify the RNA localization substrate in the nucleus and escort the RNA to the cytoplasm. Subsequently, the RNA-protein complex interfaces with a molecular motor (myosin, kinesin or dynein), which directly transports the RNA on cytoskeletal components. During transport of the RNA to the site of localization, translation of the RNA is repressed. Once the RNA arrives at its destination, it is hypothesized that the RNA is anchored at the site of localization, and translational repression of the RNA is relieved.

Figure 1. A general pathway for cytoplasmic RNA localization can be broken into distinct steps



Step 1 – RNA localization substrates (green line) can be identified in the nucleus by RNA-binding proteins (purple ball). Step 2 – the RNA-protein complex is exported from the nucleus to the cytoplasm through the nuclear pore complex. Step 3 – once in the cytoplasm, the RNA can associate with additional proteins (red) that interface the RNA with motor proteins (blue) that transport the RNA along cytoskeletal filaments (gray) to the site of localization. Step 4 – upon reaching the correct destination, translational repression is relieved and the corresponding protein (green ball) is synthesized at the site of action.

Figure 2. *ASH1* mRNA localization in *S. cerevisiae*



The distribution of *ASH1* mRNA is shown in red, and the positions of the nuclei are shown in blue.

ASH1 mRNA localization in *S. cerevisiae*

In the yeast *S. cerevisiae*, there are at least 30 mRNAs that are directly transported and localized to the bud tip [7-11], and of these *ASH1* mRNA is the most extensively studied. Localization of *ASH1* mRNA to the distal tip of the daughter cell (Figure 2) results in the asymmetric sorting of Ash1 to the daughter cell nucleus [12-14]. Ash1 is a transcriptional repressor, and asymmetric sorting of Ash1 results in differential gene expression between mother and daughter cells [15-19].

Localization of *ASH1* mRNA requires four *cis*-acting localization elements: E1, E2A, E2B and E3 [20,21]. Each of the elements is mechanistically redundant, since each is dependent on the same set of *trans*-acting factors for mRNA localization to the bud tip [22]. She2 is a unique RNA-binding protein that directly associates with each of the *cis*-acting localization elements [22-24]. The *ASH1* mRNA localization pathway originates in the nucleus where She2 co-transcriptionally identifies RNA localization substrates [25-27]. After exiting the nucleus, She2 forms a transport particle with She3 and the Myo4 motor protein, and the transport particle directly delivers *ASH1* mRNA to the bud tip on the actin cytoskeleton [13,14,16,28-32]. Initially, the function for She3 in *ASH1* mRNA localization was limited to its ability to simultaneously associate with She2 and Myo4 [32]. However, more recent studies indicate that She3 has additional roles in *ASH1* mRNA localization [33,34]. One of these studies provides compelling evidence that She3 directly contacts the *cis*-acting localization elements [34]. In addition, She2 increases the specificity of She3 for *cis*-acting localization elements, and She3p increases the specificity of She2 for *cis*-acting localization elements [34]. Myo4 is a type V non-processive myosin motor protein that directly transports *ASH1* mRNA to the bud tip through its association with She3 and the actin cytoskeleton [13,14, 28-31,35,36]. Processive motors are characterized by a single motor molecule possessing the ability to promote continuous transport of a cargo over long distances, while non-processive motors require multiple motor molecules to promote continuous transport over long distances. Given that Myo4 is a non-processive motor, the mechanism by which Myo4 continuously transports *ASH1* mRNA is an active area of interest [36]. Recently, a mechanism has been described that results in continuous transport of *ASH1* mRNA. In this mechanism, a tetramer of She2 binds to a *cis*-acting localization element, subsequently recruiting multiple molecules of Myo4, which increases processivity of the transport complex [37-39].

During the transport of *ASH1* mRNA from the mother cell to the daughter cell, translation of Ash1 is repressed. The E1, E2A and E2B *cis*-acting localization elements are located in the ORF (open reading frame), and the position of these *cis*-acting localization elements participate in reducing translation of Ash1 [12]. Furthermore, Khd1 and Puf6 participate in translational repression of *ASH1* mRNA [40,41]. Khd1 is an RNA-binding protein that associates with the E1 element and with the C terminus of the translational initiation factor eIF4G1 [41]. However, the mechanism by which these interactions repress translation of *ASH1* mRNA remains elusive. Translational repression of *ASH1* mRNA by Khd1 is relieved at the bud tip through the action of Yck1, a protein kinase located in the plasma membrane [41]. Puf6, a member of the PUF family of RNA-binding proteins, represses translation of *ASH1* mRNA in a manner similar to Khd1. The E3 *cis*-acting localization element contains a binding site for Puf6 [40]. Translational repression of *ASH1* mRNA by Puf6 occurs through an interaction with the translational initiation factor Fun12, also known as eIF5B [42]. Through an unknown mechanism the interaction between Puf6 and Fun12 prevents conversion of the 43S pre-initiation complex to the 80S initiation complex [42]. Analogous to the mechanism employed by Khd1, translational repression by Puf6 is relieved by phosphorylation at the bud tip through the action of casein kinase II [42].

Xenopus

Vg1 mRNA is localized to the vegetal hemisphere of developing *Xenopus* oocytes [43]. Spatial restriction of Vg1 protein is necessary for proper specification of endoderm and mesoderm fates during embryogenesis [44-47]. As with *ASH1* mRNA, Vg1 mRNA appears to be marked for its unique fate while still in the nucleus. Two proteins, hnRNP (heterogeneous nuclear ribonucleoprotein) I and Vg1RBP/vera, are thought to identify Vg1 mRNA in the nucleus and to accompany the transcript into the cytoplasm during nuclear export [48]. These proteins bind to localization elements present within the 3'UTR (3'untranslated region) of Vg1 mRNA. The hnRNP I protein binds to a localization element termed VM1 (YYUCU) (Vg1 motif 1), whereas Vg1RBP/vera binds to a localization element termed E2 (A/U,YCAC) [49-53]. Both localization elements are present in multiple copies within the 3'UTR of Vg1 mRNA [50, 54-56]. The specific sequence of these elements, rather than secondary structure, is the determining factor for binding by hnRNP I and Vg1RBA/vera [49-52]. Once in the cytoplasm, additional factors, such as Prrp and XStau, are thought to assemble on the mRNP (messenger ribonucleoprotein) [48]. Importantly, XStau is the *Xenopus* homolog of Staufen, a protein that has been shown to participate in mRNA localization in numerous systems [57-60].

Vg1 mRNA is transported to the vegetal cortex in a microtubule-dependent manner [61]. Recent evidence has implicated two different microtubule plus end-directed motor proteins in the transport step: Kinesin-1 and Kinesin-2 [62,63]. Initial studies described a role for Kinesin-2 in the transport of Vg1 mRNA [62]. Kinesin-2 is a heterotrimeric protein containing two distinct motor subunits and a non-motor accessory protein [64]. Consistent with a role for this motor in the transport of Vg1 mRNA, Kinesin-2 co-localizes with the message at the vegetal cortex of developing oocytes [62]. Furthermore, injecting oocytes with function-blocking antibodies directed against Kinesin-2 disrupts the localization of Vg1 mRNA [62].

Interestingly, XStau was shown to co-immunoprecipitate with Kinesin-1 [65]. Kinesin-1 is also known as conventional Kinesin, and is composed of two identical heavy chains containing the motor domain and two identical light chains [66]. This finding raised an important question: does Kinesin-1 also function in Vg1 mRNA transport? A recent report demonstrated that it does [63]. The two motors do not appear to function in a redundant manner, as blocking the activity of either motor causes defects in the localization of Vg1 mRNA [63]. It is unclear why Vg1 mRNA requires two motors for efficient transport to the vegetal cortex. One possibility is that the motors perform mechanistically distinct roles in the transport of Vg1 mRNA. Another possibility is that the endogenous level of either motor is insufficient for efficient transport. The latter possibility is supported by the finding that over-expression of either Kinesin motor is able to compensate for a deficit in the other [63].

The finding of this requirement for plus end motor proteins in the transport of Vg1 mRNA was somewhat surprising given that the prevailing view at the time held that the cortex of the oocyte was enriched in microtubule minus ends [67]. However, it was observed that a sub-set of plus ends are indeed enriched at the vegetal cortex [63]. Thus, Vg1 mRNA appears to be transported by Kinesin-1 and Kinesin-2 on a specialized population of microtubules. The mechanism by which the motor complexes are able to identify this unique population of microtubules remains elusive.

As with most localized fate determinants, it is important that Vg1 mRNA not be translated until the message is delivered to the correct site within the cell. Consistent with this notion, a region, named the VTE (Vg1

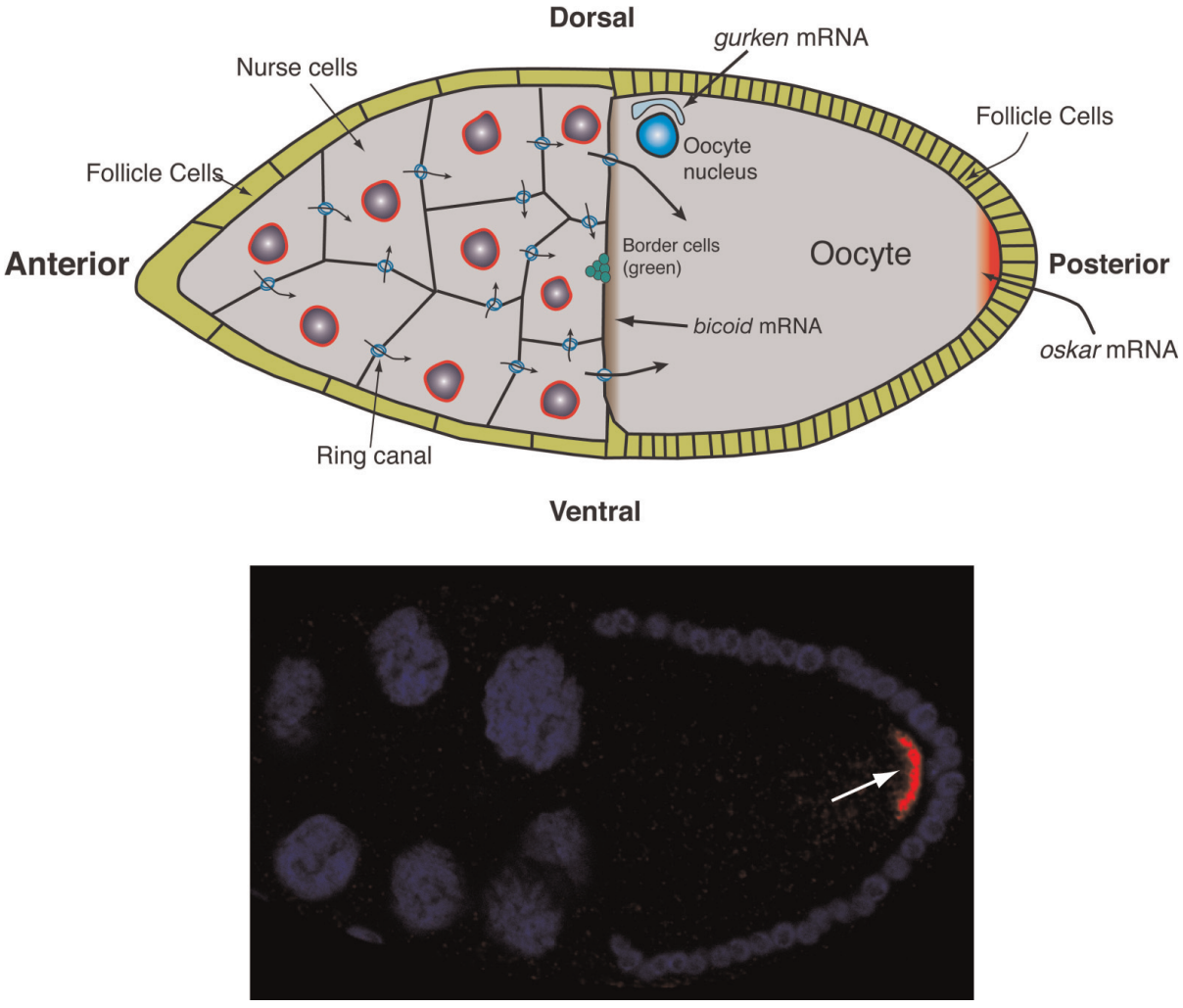
transitional element), in the 3'-untranslated region (UTR) of Vg1 mRNA, has been identified that functions to maintain the mRNA in a translationally repressed state [68,69]. An intriguing feature of the VTE is that it is very AU rich. Recent work demonstrated that the AU-rich binding proteins ElrA and ElrB bind to the VTE and function to repress the translation of Vg1 mRNA [70], but further work is needed to define the mechanism.

Drosophila

In a somewhat Herculean effort, Lécuyer and colleagues performed *in situ* hybridization against 3300 mRNAs expressed in *Drosophila* embryos [71]. Surprisingly, approximately 70% of these mRNAs are localized [71], showing that mRNA localization is widely used during *Drosophila* development for spatial sorting of proteins. Although the mechanism by which these thousands of mRNAs are localized has not been characterized, the localization of *bicoid*, *gurken* and *oskar* mRNA in *Drosophila* oocytes has been extensively studied [72-75]. In addition, apically localizing mRNAs, such as *even skipped*, *wingless* and *hairy* has also been studied in *Drosophila* embryos [76-79]. In this review, we will focus our discussion on the mechanism of *oskar* mRNA localization.

oskar mRNA is localized to the posterior of the oocyte in a microtubule-dependent manner [4,73,74] (Figure 3). The specific localization of *oskar* mRNA, as well as precise translational regulation of the message, results in restriction of Oskar protein to the posterior of the oocyte

Figure 3. mRNA localization in *Drosophila* oocytes



A schematic representation of the *Drosophila* egg chamber (top panel) *oskar* mRNA is transcribed in the nurse cells, transported into the oocyte and localized at the posterior pole (red). The bottom panel shows *oskar* mRNA (red) localization as detected by *in situ* hybridization. DAPI stained DNA is shown in blue.

[73,80,81], which is essential for establishing the anterior-posterior polarity of the egg [81,82]. The importance of this is illustrated by the demonstration that mis-localization of *oskar* mRNA results in an oocyte that lacks polarity and an embryo that dies during development [73,81,82].

Like many localized mRNAs, *oskar* is identified as a target for localization while still in the nucleus. Splicing at the first intron position of *oskar* mRNA appears to be required for its localization [83]. The position of this intron, but not the nucleotide sequence, is the critical factor for localization [83]. The mechanism by which splicing at this position regulates mRNA localization is unclear, but the Exon Junction Complex (EJC) proteins have all been shown to be involved in *oskar* mRNA localization [84-89]. Although EJC proteins are deposited on all spliced mRNAs, it is possible that they recruit an unknown factor important for *oskar* mRNA localization when they are present at the position of the first intron. In addition to the presence of this first intron, the 3'UTR of *oskar* mRNA is also required for localization [90]. Various regions in the 3'UTR of *oskar* mRNA are thought to mediate distinct steps in its transport from the nurse cells to the posterior of the oocyte [90]. However, the identity of specific proteins that bind to these elements is unknown.

The motor responsible for transporting *oskar* mRNA to the oocyte posterior appears to be Kinesin-1 [91]. Typically, cargoes that are transported by Kinesin-1 are directly bound by the Kinesin light chain (Klc) adaptor protein [66], and this complex then directly interacts with the motor subunit of the complex, Kinesin heavy chain (Khc) [66]. However, the transport of *oskar* mRNA does not fit this paradigm. While null mutants in *khc* result in *oskar* mRNA delocalization around the oocyte cortex [91,92], null mutants in *klc* do not have a significant effect on *oskar* mRNA localization [92]. Thus, *oskar* mRNA is transported to the oocyte posterior by a Kinesin complex that lacks the canonical light chain adaptor. Consistent with this picture, another study found that the number of *oskar* mRNP particles displaying fast, directed movement was reduced by five-fold in *khc* null oocytes [93]. However, a significant number of fast-moving *oskar* mRNP particles could still be detected in *khc* null mutant [93]. These results suggest that another, as yet unidentified, motor participates in *oskar* mRNP transport.

Collectively, these findings raise two very important questions. The first is "How does Khc recognize *oskar* mRNA as a target for localization?". One possibility is that an unknown protein links Khc to *oskar* mRNA. If so, identifying this factor will be a critical next step. The expectation would be that this protein co-localizes with Khc at the posterior of the oocyte, and that mutations in this gene resemble *khc* null mutants. Another possibility is that a known component of the *oskar* mRNP directly binds to Khc and serves as the bridge between the motor and the transcript. This scenario does not seem likely because mutants in known components of the *oskar* mRNP result in mRNA that is either diffusely distributed throughout the oocyte, or in mRNA that is trapped at the anterior of the oocyte. This is in contrast to the *khc* null phenotype, in which *oskar* mRNA is found around the oocyte cortex [91,92]. A final possibility is that Khc directly binds to *oskar* mRNA. At present there are no data to support a direct interaction between Khc and *oskar* mRNA. Thus, although there is ample evidence implicating Khc in *oskar* mRNA transport, the mechanism by which this motor binds *oskar* mRNA is still an open question. The second intriguing question suggested by the live imaging of *oskar* mRNPs is whether a motor other than Khc also participates in *oskar* transport.

In addition to transporting *oskar* mRNA to the posterior pole, spatial restriction of Oskar protein is achieved by numerous mechanisms of translational repression [80,94]. Only once the mRNA is delivered to the posterior is the repression relieved. Additionally, specific mechanisms operate at the posterior of the oocyte to activate translation of *oskar* [80,94]. A detailed discussion of this topic is beyond the scope of this review. However, some recent findings have shed light on the mechanism by which the translation of *oskar* mRNA is regulated.

The first factor identified with a role in translational repression of *oskar* mRNA was Bruno [95]. Bruno was shown to bind to specific BRE (Bruno response element) sequences in the 3'UTR of *oskar* mRNA [95]. Initially, these elements were thought to function solely in translational repression. However, a recent report from the MacDonald lab demonstrated that one of these BREs also functions in activating the translation of *oskar* mRNA [96]. The precise mechanism by which Bruno regulates translation is not known. However, Bruno has been shown to associate with the protein Cup [97]. Cup in turn forms a complex with the transition initiation factor eIF4E and prevents it from binding eIF4G [97,98], an interaction which is required for translation initiation. Thus, Bruno and Cup may function together to prevent translation initiation of *oskar* mRNA. Interestingly, Bruno also appears to package *oskar* mRNPs into large aggregates called silencing particles, rendering them inaccessible to the translation machinery [99]. Finally, the *Drosophila* ortholog of hnRNP I/PTB has also been shown to bind *oskar* mRNA and to package the message into higher-order particles that are translationally silent [100].

RNA localization in neurons

Mature neurons are highly polarized and generally consist of a cell body, a single long axon and several shorter branching dendrites. In developing neurons, the axonal growth cone receives extracellular signals and directs the axon to the proper destination. For a neuron to locate its final destination and properly function, distinct proteins need to be sorted to these various regions of the cell. RNA localization is one mechanism by which proteins are sorted to dendrites, axons and axonal growth cones [101]. Specifically, beta-actin mRNA localizes to the growth cone where its localized translation is required for axon turning in response to guidance cues [102,103].

Beta-actin mRNA contains a 54 nt *cis*-acting localization element in the 3′UTR, and the *cis*-acting localization element functions to target beta-actin mRNA to dendrites and axonal growth cones [104-107]. The RNA-binding protein Zbp1 binds the *cis*-acting localization element and, through an unknown mechanism, helps target beta-actin mRNA to the sites of localization [108-110]. Zbp1 co-transcriptionally identifies beta-actin mRNA in the nucleus of fibroblasts [111], but it is not yet known whether this also happens in neurons. Binding of Zbp1 with beta-actin mRNA in the nucleus is facilitated by another RNA-binding protein, Zbp2 [111]. It has been hypothesized that Zpb2 initially identifies beta-actin mRNA in the nucleus and transfers it to Zbp1 [111]. Subsequently, the Zbp1/beta-actin mRNA complex is exported from the nucleus to the cytoplasm. In neurons, the working hypothesis is that cytoplasmic beta-actin mRNA is interfaced with a molecular motor that directly transports the mRNA on the cytoskeleton to the site of localization. This hypothesis is supported by a number of key observations. First, RNA granules enriched from rat embryonic brains contain numerous proteins and RNAs, including Zbp1, the molecular motor dynein and beta-actin mRNA [112]. Second, in A549 lung carcinoma cells and human dermal fibroblasts, beta-actin mRNA is transported by molecular motors on microtubules [113]. Third, the RNA-binding protein FMRP participates in the transport of MAP1b and CaMKIIα mRNAs to dendrites by associating these RNAs with Kinesin [114]. Consequently, based on these observations, we anticipate that a molecular motor will be identified that functions to directly transport beta-actin mRNA to the site of localization.

Besides participating in the targeting of beta-actin mRNA to the sites of localization, Zbp1 represses its translation [115]. The presence of Zbp1 prevents the formation of the 80S ribosomal initiation complex by an unknown mechanism [115]. Translational repression by Zbp1 is relieved through Src-dependent phosphorylation of Tyr396, which negatively regulates Zbp1 RNA-binding activity [115]. The signalling pathway that leads to the localized synthesis of beta-actin in axonal growth cones has been further elucidated. Axonal growth cones turn in response to brain-derived neurotrophic factor (BDNF). Phosphorylation of Zbp1 by Src family kinases is stimulated by BDNF, and when phosphorylation of Zbp1 is prevented in the presence of BDNF, axonal growth cones are unable to turn, providing additional insight into the mechanism by which local translation of beta-actin contributes to the turning of axonal growth cones [116].

Conclusion

RNA localization was once considered a mechanism employed by eukaryotic cells for the sorting of only a few select proteins. However, it has become increasingly evident that RNA localization is a common mechanism to post-transcriptionally regulate gene expression. A genomic screen of 3370 genes in *Drosophila* revealed that 71% of the analysed mRNAs are localized to specific regions of the cytoplasm [71]. In this review, we have provided a general overview of the transit of a localization substrate from the site of transcription to the site of localization. We have focused on the *cis*- and *trans*-acting factors that have a role in the transport of *ASH1*, Vg1, *oskar* and beta-actin mRNAs. We anticipate the discovery of more details concerning how nuclear factors influence RNA localization in the cytoplasm. In addition to transport of the cargo to the site of localization, it is widely hypothesized that, once the RNA reaches the site of localization, it is anchored at that position. Compared with our knowledge of transport, there is very little information concerning the mechanistic details of anchoring, so we look forward to insights into these mechanisms. Besides mechanistic details related to mRNA localization, we expect future developments related to the physiological significance of RNA localization. The genetic advantages in studying lower eukaryotes have provided some understanding of the physiological significance of RNA localization. However, in higher eukaryotic organisms, the physiological significance for RNA localization has been harder to determine, since investigations have been limited to cell culture systems. However, a number of mouse strains have recently been developed to investigate this question [117-119]. Consequently, we can expect advances in understanding the role of RNA localization in human development and disease.

Abbreviations

BDNF, brain-derived neurotrophic factor; BRE, Bruno response element; EJC, exon junction complex; ER,

endoplasmic reticulum; hnRNP, heterogeneous nuclear ribonucleoprotein; ORF, open reading frame; mRNP, messenger ribonucleoprotein; VM1, Vg1 motif 1; VTE, Vg1 translational element; 3′UTR, 3′untransated region.

Competing interests

The authors declare that they have no competing interests.

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