Published in final edited form as:

Traffic. 2020 June ; 21(6): 404–418. doi:10.1111/tra.12730.

Mechanisms and consequences of subcellular RNA localization across diverse cell types

Krysta L. Engel[1,3], **Ankita Arora**[1], **Raeann Goering**[1], **Hei-Yong G. Lo**[1], **J. Matthew Taliaferro**[1,2,3]

[1]Department of Biochemistry and Molecular Genetics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[2]RNA Bioscience Initiative, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Abstract

Essentially all cells contain a variety of spatially restricted regions that are important for carrying out specialized functions. Often, these regions contain specialized transcriptomes that facilitate these functions by providing transcripts for localized translation. These transcripts play a functional role in maintaining cell physiology by enabling quick response to changes in cellular environment. Here, we review how RNA molecules are trafficked within cells, with a focus on the subcellular locations to which they are trafficked, mechanisms that regulate their transport, and clinical disorders associated with misregulation of the process.

Keywords

RNA binding protein; zipcode; RNA localization; RNA cis-element; RNA transport

Introduction

Gene expression is regulated through a complex coordination of events that occur at distinct steps during the lifetime of a mRNA. Whereas control of RNA synthesis by RNA polymerases, transcription factors, and chromatin states is widely studied, less well-characterized post-transcriptional mechanisms are also essential in defining gene expression landscapes in individual cell types. These cell-type specific gene expression profiles define the protein composition of cells and ultimately cell-type specific functions. One poorly understood aspect of post-transcriptional regulation is RNA localization.

Much of the work on RNA localization has been performed in neuronal systems because early studies recognized the importance of RNA localization in these polarized cell types, and they are amenable to study due to their size and morphology. Neurons are highly polarized, with long distances between the soma, where RNAs are synthesized in the nucleus, and projections (axons/dendrites/neurites), where cells must quickly respond to stimuli (Figure 1A). These cell types have therefore been a critical model system to

[3]To whom correspondence should be addressed: krysta.engel@cuanschutz.edu, matthew.taliaferro@cuanschutz.edu.

understand how RNA localization controls gene expression using imaging-based approaches as reviewed previously[1–5]. A number of neurological diseases, including amyotrophic lateral sclerosis (ALS) and fragile X syndrome (FXS), have been associated with misregulated RNA localization in neurons. Recent advances in high-throughput sequencing and microscopy techniques have also revealed that RNAs are localized to subcellular compartments (e.g. endoplasmic reticulum and mitochondria) in many nonpolarized cell types[6–9]. This observation has led to some key questions. Do neurons and other cell types use a common set of mechanisms to achieve RNA localization? In other words, does an 'RNA localization code' exist that transcends cell types? What are the biological roles of creating localized transcriptomes that are different across subcellular compartments and cell types? What are the consequences of misregulated RNA localization? Despite the realization that local transcriptomes contribute to cell function across diverse cell types, many gaps in our understanding of how these processes are regulated still exist.

How does RNA get there?

Several RNA localization mechanisms have been observed in various cell types. Active transport of RNA as components of ribonucleoprotein (RNP) granules along cytoskeleton scaffolds is the most widely observed mechanism[10]. Long-range localization of RNA is often accomplished via active transport in neurons (Figure 1B), but cytoskeletal-associated RNA localization has also been observed in spherical cells such as yeast and *Drosophila* embryos where sometimes shorter distances are traversed[10–13]. Transcripts can also achieve localization with a combination of active transport followed by anchoring once they have arrived at a specific location. This mechanism has been characterized in multiple cell types including *Aplysia* sensory neurons[14] and yeast[11,15]. Additionally, in *Drosophila* oocytes passive diffusion followed by anchoring of *nanos* mRNA helps establish a concentration gradient across the cell[16,17] (Figure 1C). Lastly, local transcriptomes can be established by selective RNA degradation or local protection. This occurs when an RNA is unstable or susceptible to decay unless it is stabilized or protected within a specific location[18]. Even though this mechanism seems energetically wasteful, there is evidence that this process is utilized by *Drosophila* embryos[19]. These mechanisms of RNA localization are not mutually exclusive, and a single RNA transcript may be influenced by a combination of mechanisms to achieve finely tuned regulation of its localization[20]. Additionally, all of these localization mechanisms require additional protein factors to interact with the RNA. These RNA binding proteins (RBPs) are critical for understanding how RNAs are localized. Below we will discuss in detail how RNAs are localized through different mechanisms in different cell types.

Active transport of RNAs within cells

There is abundant evidence for active RNA transport along cytoskeleton scaffolds. This mechanism was characterized by inhibition of RNA transport following treatment with cytoskeletal depolymerizing drugs including nocodazole and cytochalasin[21,22]. Long range and short range cytoskeleton-mediated transport are thought to use different machinery. Long range transport is mostly mediated by dyneins and kinesins on microtubules whereas

shorter transport is mediated by myosins on actin filaments, as reviewed elsewhere[1,10] (Figure 1B).

The cytoskeleton is composed of two major structures, microtubules and microfilaments. RNA transport mechanisms have been described using both of these structures. Microtubules are polymers of the protein tubulin. In neurons, transport of many mRNAs [e.g. beta-actin (*ActB*)[23], Activity-regulated cytoskeleton-associated protein (*Arc*)[24], and calcium/calmodulin-dependent protein kinase II (*CaMKIIα*)[25]] to axons and dendrites often occurs along microtubules[26]. Microtubules are also implicated in RNA transport within *Drosophila* embryos (*bicoid* (*bcd*) mRNA[26] and *oskar* (*osk*) mRNA[18]) as well as myelin basic protein (MBP) mRNA in oligodendrocytes[27]. Cardiomyocytes also require microtubules for transport of transcripts to sarcomeres[28].

Transport along actin microfilaments by myosin motors is responsible for the bulk of RNA transport in yeast[10], where *ASH1* mRNA is localized into dividing daughter cells and accumulates at the bud tip to regulate mating type switching[11]. *ASH1* mRNA is exclusively localized along actin filaments yet there is also evidence for local sequestration activity after reaching the bud tips[12]. In this case, transport along actin is responsible for both getting transcripts to the correct region and refining their localization at the bud tip.

Both microtubules and actin filaments are used to actively localize RNAs in many cell types. RNA movements are facilitated by larger RNP complexes which contain both protein and RNA. Interactions between these components and adapter and motor proteins associated with the cytoskeleton facilitate active transport of sometimes multiple RNAs at once[29]. For example, CaMKIIα, Neurogranin, and Arc mRNAs are targeted to dendrites within the same RNP granule[30]. The exact composition of cytoskeleton-associated RNPs can also regulate the speed and direction of transport[31,32]. However, combinatorial effects of each factor make it difficult to discern exactly how an RNA achieves its specific destination. Further research into what factors are included in RNP complexes and how they impact trafficking is necessary to understand how RNAs are actively transported along the cytoskeleton, and RNP composition and dynamics are extensively reviewed here[33].

Anchoring of RNAs creates local RNA enrichment

RNAs that arrive near their destination via either active or passive mechanisms can be anchored into position through interactions with proteins and the cytoskeleton. In addition to facilitating active transport, actin also plays a role in refining and stabilizing transcripts at a destination. Both active transport as well as anchoring to a specific region sometimes requires the cytoskeleton to achieve stable localization[17,21].

Active transport followed by specific anchoring of RNA is a common mechanism in *Drosophila* and *Xenopus*; however, both active and passive mechanisms prior to anchoring are used. For *vg1* mRNA, microtubules are responsible for transport to the vegetal hemisphere, whereas microfilaments are important for anchoring at the cortex[22]. However, *gurken* mRNA requires dynein for both transport to and retention at the anterodorsal corner, indicating that anchoring can occur via microtubules[18,34]. *Nos* mRNA does not associate with microtubules in *Drosophila* and is thought to localize solely through diffusion and

cytoplasmic streaming[16]. It is trapped by an unknown protein complex containing Rumpelstiltskin at the posterior end of the embryo[17,35]. Even in a large *Drosophila* embryo, RNA anchoring alone is sufficient for maintenance of RNA localization.

Similar mechanisms are used in budding yeast to generate local concentrations of *Ash1* mRNA to control mate type switching. Active transport of *ASH1* mRNA into the daughter cells is dependent on interaction with myosin motor protein She1. Without She1, *ASH1* mRNA does not localize correctly[11,15]. However, if She1 is available but Bni1[11] or Bud6[36] is mutated, specific localization to the bud tip is unstable. This strongly indicates that RNA is generally localized by active transport but specifically retained by anchoring factors like Bni1 and Bud6.

RNA anchoring is observed in other eukaryotes as well. Beta-actin mRNA is anchored to protrusions in chicken embryo fibroblasts as well as the leading edge of rat adenocarcinoma cells by EF1α[37]. This protein is capable of simultaneously binding mRNA and F-actin. Loss of its actin binding domain results in diffuse beta-actin mRNA that is no longer localized to the leading edge. Other anchoring factors include the adenomatous polyposis coli complex (APC) which is also important for RNA localization in fibroblast protrusions. It associates with RNP granules, and without APC expression, RNAs no longer localize to protrusions[38]. Therefore, anchoring of RNAs to the cytoskeleton is critical for defining the precise localization of transcripts in several cell types.

Local RNA transcriptomes are regulated by selective degradation

Control of local transcriptomes via selective degradation or protection in subcellular regions is less studied and has been observed in only a few cell types (Figure 1C). For example, *Drosophila* embryos localize Heat Shock Protein 83 (*Hsp83*) mRNAs to the posterior pole by protecting transcripts from degradation in that region[39,40]. These transcripts are widely expressed throughout the embryo until they are selectively degraded following fertilization of the embryo. This is largely regulated by sequence in the 3'UTR of *Hsp83* that can be deleted or exchanged for other UTRs to disrupt its spatial stability phenotype[39]. This sequence in the 3' UTR is bound by Smaug, resulting in degradation of the transcript[19].

In addition to regulation of RNA abundance through canonical RNA degradation pathways (e.g. via the TRAMP complex), non-canonical roles of nonsense-mediated decay (NMD) have also been characterized. NMD was initially described to degrade mRNAs containing premature termination codons (PTCs); however, this mechanism also regulates the abundance of non-PTC containing RNAs in dendrites[41] and axons[42], which in turn influences synaptic plasticity and growth cone formation, respectively. While the degradation strategies that control RNA localization come at an energetic cost, it is effective at creating specific localized transcriptomes in a regulated way.

An RNA has arrived. Now what?

Local RNA transcriptomes may serve a variety of roles in establishing cell type specific functions by creating temporally and spatially regulated proteomes to guide differentiation and responses to environmental stimuli. The predominant theory on how RNA localization

accomplishes this is through enhancing local protein production efficiency by having the mRNA translated where the protein ultimately exerts its effect. Transporting a single mRNA is energetically efficient since a single mRNA molecule can be used to synthesize multiple copies of proteins[43], reviewed more extensively here[2,18,44]. Similarly, colocalization of mRNAs encoding members of a protein complex could produce high concentrations of multi-subunit complex components in a specific location, thus increasing complex formation efficiency and decreasing the formation of off-target, nonfunctional complexes[45–48]. mRNAs can also be localized in a translationaly silenced form. Local signals are therefore needed before initiating protein synthesis[49]. Finally, mRNAs can be localized to prevent protein toxicity in specific subcellular compartments, as is the case for MBP in oligodendrocytes[27]. However, there could be many additional reasons for RNA localization that are not yet clear. For example, the RNAs themselves might have a function as is the case for many non-coding RNAs (e.g. miRNAs and lncRNAs) and at least one mRNA[50].

Translation of localized RNAs

In many cell types, mRNA co-localizes with its encoded protein. This has been observed in neurons[51], *Drosophila* embryos[52], and HEK293 cells[7]. This phenomenon is suggestive of local translation which has been shown across species and cell types. Due to the difficult nature of quantifying local transcriptomes and proteomes, most studies focus on a single mRNA and its encoded protein. Below we discuss multiple specific examples that support the importance of mRNA localization in producing higher local protein concentrations (Figure 1A). In these examples, local mRNA translation can be important to the function of the synthesized protein and overall cell function.

In yeast, *ASH1* mRNA is locally translated in the daughter bud to control mate type switching. Normally, *ASH1* mRNA is not translated until it arrives in the bud tip[53]. Depletion of Puf6p, a translational repressor of *ASH1* mRNA, causes *ASH1* mRNA translation before it arrives at the bud tip, resulting in both cells having the same mating type[53]. Thus, *ASH1* mRNA must be properly localized, and only translated in this location to function correctly.

Local translation has been demonstrated to occur at neuronal dendritic spines, which are substantial distances from the cell nucleus. It has long been suggested that ribosomes locally translate mRNAs, but we now know that ribosomes are localized to dendritic spines along with many translation factors[54] and engage in active translation in many neuronal cell types (reviewed here[3]). One of the best examples is beta-actin mRNA, which is localized to dendritic spines in neurons[55]. Reducing beta-actin mRNA translation with morpholinos provided evidence that local translation of this transcript in retinal neurons is required for axonal branching and stabilization[56].

The majority of protrusion-enriched transcripts in fibroblasts are locally translated to produce localized proteins[57]. This is especially true for actin-associated proteins which help structure the protrusions. Furthermore, mRNAs encoding ribosome subunits have been shown to localize to protrusions of migrating cells in a LARP6 dependent manner. Local translation of ribosomal proteins at these protrusions enhances ribosome biogenesis and

local protein production[58]. In each of these cases, the localized mRNA helps determine localization of the resulting proteins which aid critical cell functions.

Assembly of multi-subunit protein complexes

Formation of multi-subunit complexes can depend on chaperones, subunit stoichiometry, and local concentrations of each subunit. Local translation of the protein subunits can increase their local concentrations, thereby facilitating complex assembly by reducing the physical distance between components[59]. Additionally, spatially isolating complex members could help reduce unwanted protein interactions that might result in non-canonical complexes or other unfavorable interactions.

Local transcriptome mapping using proximity labeling has revealed that RNAs encoding complex members co-localize to the ER and mitochondria in yeast[8]. These results support previous observations that mRNAs encoding several mitochondrial associated complex members are found near the mitochondria (reviewed here[60]). Presumably, the mRNAs that encode ER and mitochondrial protein complexes localize to the organelle to facilitate local translation and assembly.

This phenomenon also occurs in less defined subcellular locations. mRNAs encoding the seven subunits of the Actin stabilizing complex Arp2/3 localize to fibroblast protrusions where they are required for stable growth[46]. Localization of these seven separate transcripts to protrusions aid in Arp2/3 assembly through local translation and assembly. In some cases, local translation of protein complex members can result in co-translational assembly as observed for heteromeric ion channels[47] and histone acetyltransferase[48].

RNA localization in response to environmental stimuli

mRNAs can also be localized in response to a specific signal, such as following glutamate stimulation in neurons, as reviewed here[49]. It is suggested that mRNAs are localized to produce local proteins that help remodel or stabilize activated synapses.

Intestinal absorptive enterocytes also localize RNAs across their apicobasal axis in response to refeeding to initiate recovery after starvation[61]. This reorganization changes the translational status of many mRNAs and may contribute to the cellular response to the refeeding stimulus, although exactly how this happens is unknown.

Control of cell size and projection length might also use active mRNA transport followed by local protein translation[62]. This model suggests that localization of mRNA to projections, local translation to produce protein, followed by retrograde protein diffusion back to the nucleus allows the cell to sense projection length. This mechanism has been suggested to regulate cilia, flagella[63,64], and neurite length[65,66]. However, it could be broadly applicable to other subcellular components such as organelle size.

Role of cis and trans factors in RNA localization

The RNA localization mechanisms discussed above rely on multiple components, specifically RNA and their protein binding partners. First, *cis*-elements within the RNAs

themselves, often referred to as zipcodes, ‘mark’ the RNA for a destination. Information can be stored in the RNA in the form of linear sequences or in RNA structure. These RNA features facilitate interactions between the RNA and specific trans-acting RBPs, which typically associate with RNAs through an RNA binding domain (RBD)[31,67]. Further interactions between RBPs and other proteins, such as those associated with the cytoskeleton[68], create a network of interactions that regulate subcellular localization patterns of RNA. RNP granules can vary in their composition. This produces a heterogenous pool of RNPs inside of cells, further complicating study of their protein and RNA components. For example, *Arc* and *CaMKIIα* mRNAs associate selectively with Barentsz (Btz)- and Staufen 2 (Stau2)- containing RNPs, respectively whereas RNAs such as Lysophospholipase 1 (*Lypla1*) and Cap-Binding Protein (CBP80) are found in both of them[69]. A handful of RBPs and their cognate zipcodes are known (Table 1). However, these complex multivalent interactions have been difficult to dissect. For example, a single RNA can interact with multiple RBPs at once, and likewise a single RBP can have the capacity to recognize different zipcodes and therefore multiple RNAs. Below, we will focus on the role and identification of these *cis*- and *trans*-acting factors.

Cis-elements or zipcodes

Zipcode elements serve as the signal to target an RNA for delivery to a specific subcellular location. They can vary from a few bases to a kilobase in their length. Although hundreds to thousands of RNAs are known to be trafficked to a variety of subcellular locations, the sequence elements within those transcripts that regulate transport have been identified for only a few dozen. Most of the known localization regulatory elements are located in 3′ untranslated regions (UTRs) of mRNA, although some localization elements have been identified in 5′ UTRs[14,70], coding regions[11,12,71–73], and intronic sequences[74]. Additionally, localization elements are often repetitive and redundant. This repetition might allow many low affinity sequences to act in union to achieve specificity. Most of the zipcodes identified are thought to function independently and be modular in nature. Mutation and truncation experiments using reporter transcripts have led to the discovery of a small number of necessary and sufficient zipcode sequences. Combined with additional biochemical methods, these approaches have uncovered zipcodes that depend on primary sequence and/or RNA structures for their function and have been reviewed here[75,76] (Table 1).

An RNA zipcode alone is not always enough to facilitate localization. Some elements are necessary but not sufficient, suggesting that neighboring RNA sequences can be an important context for the zipcode. For example, *xcat2* mRNA in *Xenopus* oocytes localizes to the vegetal pole using six repeats of a short motif, UGCAC, present within the 3′ UTR of *xcat2*. However, insertion of this motif into the 3′ UTR of another mRNA, *vg1*, did not result in its localization to the vegetal pole[77]. Additionally, nuclear processing also plays an important role in mRNA localization. For example, *oskar* localization at the posterior pole of the *Drosophila* oocyte requires both spliced *oskar* localization element (SOLE, which comprises nucleotides of both exon 1 and exon 2) and the exon junction complex (EJC) deposited during splicing for efficient transport along the microtubules by kinesin[71,78].

Many bacterial RNAs are also differentially distributed at locations such as in the cytoplasm in a helical like pattern, at membranes, and at polar or septal sites[79,80]. In *E. coli*, the *bglG–bglF* operon, which codes for proteins necessary for aryl-β-glucoside metabolism, localize to the cell membrane. The *bglG–bglF* zipcode is located within the sequence encoding the first two transmembrane helices of bglF and is uracil-rich, a common feature observed in transmembrane proteins across species[81,82].

Another example of an element that hints at conservation across species and cell types is the cytoplasmic polyadenylation element (CPE). CPE is a nucleotide sequence (UUUUUAU) within the 3′ UTR of most mRNAs which binds to the CPE-binding protein (CPEB). Although this interaction has been most studied for its effects on translation upon synaptic activation[83] studies have shown that CPEB can also act as a transport protein for dendritic mRNAs such as MAP2 and intestinal apical RNA such as ZO-1 responsible for maintaining tight junction assembly and cell polarity[84,85].

Lastly, many zipcode elements depend on RNA secondary and/or tertiary structures, e.g. stem loops, for recognition by trans-factors[31,86]. For example, bicoid mRNA 3'UTR stem loops[87,88] are recognized by the RBP Staufen (STAU)[89,90]. The complex roles RNA structure plays in defining zipcodes contributes to the difficulty of finding them since structural elements are much more difficult to define and identify computationally than linear sequence motifs.

Cis-elements in non-coding RNAs

Non-coding RNA such as miRNAs and lncRNAs also use sequence elements to direct localization patterns (Table 2). For example, miR-29b contains a hexanucleotide 3′motif (AGUGUU) responsible for nuclear localization[91]. This is in contrast to the cytoplasmic enrichment observed commonly for miRNAs. Additionally, the lncRNA MALAT1 uses sequences present at both the 5′ and 3′ ends to target its localization to paraspeckles within the nucleus[92]. Recent studies using massively parallel reporter assays (MPRAs) have also discovered C-rich motifs present in several lncRNAs that lead to their nuclear enrichment[93,94]. lncRNA BC1 and it's human analog BC200 are enriched in dendrites and synapses, where it represses translation locally in nerve cells by inhibiting eIF4a-mediated unwinding of RNA duplexes[95–97]. The lack of evidence for the role of lncRNAs is primarily due to the fact that techniques developed to study complex RNA-RNA interactions are still in their infancy. Further, there has been some evidence that RNA modifications might also play a role in localization. For example, mitochondrial localization of $tRNA^{Glu}$ in the RNA virus *Leishmania* is driven by a specific modification of the tRNA[98].

Identification of potential *cis*-ating elements using computational methods (e.g. MEME[99], HOMER[100], SeAMotE[101], and others dependent on structure[102–105] have had limited success. Despite our increasing understanding of principles governing *cis*-localization elements using specific examples, we still lack a systematic charaterization of general rules. One of the challenges to overcome is the implementation of strategies that combine sequence motifs and structural features while keeping in mind the redundancy observed in many known zipcode examples. In the future, focusing on transcriptome-wide studies

coupled with high-throughput functional assays along with advanced *in silico* analyses will further efforts to uncover novel zipcodes.

Trans-factors that regulate localization

RBPs regulate all aspects of RNA metabolism, including transcription, splicing, translation, and decay. RNA localization is also subject to regulation by RBPs, which bind and recognize RNA elements to form RNP complexes. RBPs generally contain a variety of RBDs that impart specificity. Some of the common RBDs are the RNA recognition motif (RRM), K homology (KH) domain, DEAD-box motif, and zinc finger domains[106]. These domains allow for sequence specific binding to short single stranded RNA (ssRNA) motifs. For example, RBPs including heterogeneous nuclear ribonucleoproteins (hnRNPs) recognize specific elements such as a 21-nt sequence known as hnRNP A2 response element (A2RE) present in many dendritic mRNAs[107]. Additionally, some RBPs recognize RNA secondary structure, sequence elements present within structural elements, or a combination of the two. Many RBPs also contain intrinsically disordered regions (IDRs) that could regulate the assembly and dynamics of RNP complexes[108]. Most of the RBPs involved in localization have been identified through genetic screens and/or affinity purification of proteins that bind the localized transcript. Using these approaches, conserved roles in localization have been identified for a few RBPs across various species[67] (Table 1).

The complex combinatorial regulation of RNA localization by multiple RBPs was demonstrated in a recent study[109]. The use of genetic manipulations and high-resolution imaging showed that TDP-43 binds to Rac1 mRNA. Additional interactions occur between the mRNA and either FMRP or Staufen. These interactions further regulate Rac1 mRNA transport to mouse dendrites by facilitating anterograde or retrograde movement, respectively. This illustrates that a number of different RBPs in cooperation with each other might dictate the appropriate location of the target mRNA.[109]

Protein capture using oligo-dT to purify polyA mRNA followed by mass spectrometry has found that over 1500 proteins directly bind polyA containing RNA[110]. Further experiments then identified the sequence binding preferences of many of these RBPs. Two techniques, RNAcompete[111] and RNA Bind-n-Seq (RBNS)[112], were developed to provide an inventory of RBP motif preferences and their specificity. To complement these *in vitro* approaches and identify RNA sequences bound by RBPs *in vivo*, a number of techniques involving crosslinking combined with RBP immunoprecipitation such as RIP-seq[113], CLIP-seq[114], HITS-CLIP[115], eCLIP[116], and PAR-CLIP[117] were developed. These methods, in conjunction with further variations (reviewed in[118]), have enabled high resolution profiling of transcriptome wide RBP-RNA binding interactions. It still remains to be seen if these techniques and databases can be routinely successfully applied to the study of RNA localization on a transcriptomic scale to derive regulatory principles that govern the process. However, given their utility in the study of other RNA-based processes, the possibility is intriguing.

Methods that allow the detection of RNA-RNA interactions may also provide insight into RNA localization mechanisms. These include techniques which combine the use of cross-linking agents, proximity ligation, and RNA-seq to profile RNA interactomes (CLASH,

SPLASH, PARIS, LIGR-seq and MARIO)[119]. Combining these techniques with RBP-based approaches may have the potential to yield rich datasets that detail the RBP-RNA and RNA-RNA interactions that regulate RNA localization.

Clinical Relevance

RNA localization is critical for proper development from yeast to humans[11,120–122]. These initial observations, coupled with recent technological advances, have linked RNA localization to clinical disease (Figure 2). To date, RNA localization defects contribute to neuromuscular/skeletal diseases, neuronal disorders such as Alzheimer's, depression, embryonal disorders, and cancer initiation[123]. But which RNAs are mislocalized, what binding partners regulate their localization, and what causes their mislocalization remain unknown. Furthermore, the lack of functional studies have stalled our understanding of the direct significance of RNA mislocalization during the establishment of disease phenotypes.

Neuronal and Neuromuscular Diseases

A handful of neurological disorders have been attributed to defects in RNA localization, and have previously been reviewed extensively here[123–126]. Below we highlight a handful of these key findings for amyotrophic lateral sclerosis (ALS), spinal muscular atrophy (SMA), fragile X syndrome (FXS), and myotonic dystrophy (DM). RNA localization has also been implicated in other neurological disorders such as depression and Alzheimer's, though many more studies are needed to find a definite link[127,128]. Taken together, these associations suggest that small perturbations in RNA localization can manifest in a variety of neuronal diseases, though few have been thoroughly explored.

ALS is a neurodegenerative disease characterized by the loss of motor neurons[129]. Mutations in a number of genes found in ALS patients have been implicated to cause defects in RNA metabolism, including alternative splicing, stabilization, and localization. These include *SOD1, TARDBP* (TDP-43), *FUS, and C9orf72*, all of them covered extensively in other reviews[130]. Mutations in the RBP TDP-43 are strongly linked to ALS[131]. TDP-43 has also been shown to regulate RNA localization[132], but how the potential mislocalization of RNA in ALS neurons relates to disease phenotype is still unknown.

SMA is another neurodegenerative disease associated with a loss of motor neurons[133]. SMA results from insufficient levels of the protein SMN. SMN, like TDP-43, facilitates RNA localization to neurites[133]. Reduced levels of SMN results in mislocalization of various transcripts, such as *ActB*, growth-associated protein 43 (*GAP43*), and *neuritin/cpg15*[123,134]. Overexpression of RNP granule assembly and transport regulating RBPs, HuD and IMP1/ZBP1, can restore localization of transcripts and partially rescue the phenotype. These findings also implicate SMN as a regulator of RNA transport[135,136]. However, as with ALS, it is unknown whether and how RNA mislocalization in SMA neurons contributes to phenotypes.

FXS is a neurological disorder that results from the loss of FMRP expression[137]. Loss of FMRP results in dysregulated RNA localization in neurons, resulting in slower RNA granule localization as well as mislocalized mRNAs, such as *Kif26a* in dendrites[138,139]. The role of

FMRP in regulating neuronal RNA localization is well established and covered in other reviews[139–141]. Again, whether mislocalization of RNAs within FXS neurons is related to disease phenotypes is unknown.

Misregulated sequestration of RNA can have dramatic impacts on cellular function. In DM, mutant *Dmpk* mRNA contains expanded CUG repeats that trap transcripts in the nucleus. The retention of these transcripts in the nucleus is sufficient to generate a DM phenotype in mice[142]. This example illustrates the importance of exploring mechanisms behind transcript localization and mislocalization to better understand its impact on human disease.

Stem Cells and Development

Development relies on strict temporal and spatial control of gene expression[17,39,143,144]. Control of RNA localization is one method cells use to regulate cell fate and function. For example, spermatid maturation and non-genomic inheritance of traits is influenced by localization of specific RNA transcripts (mainly small RNAs) as the sperm develops to various compartments, such as the head, mid-piece, or tail. It is becoming increasingly clear that RNAs are transferred to sperm as they mature. Irregularities in the amount of RNA in spermatid have been associated with sperm maturation, affecting human male infertility, and others have implicated these RNAs in seeding non-genetic inheritance in zygotes[145,146]. While future studies are needed to investigate the implication of mislocalized transcripts, it is clear local RNAs play a key role during sperm maturation and inheritance[147–149].

Similarly, defined RNA localization patterns also govern temporal control of translation in oocytes and cell polarity in *Drosophila* embryos[120]. These observations suggest that RNA localization might be a conserved phenomenon necessary for cell differentiation during development. Indeed, localization of RNA is important in the developing mammalian embryo as well. Discovered more than 100 years ago, the balbiano body is an organelle consisting of endoplasmic reticulum, golgi, proteins, and RNA[150]. It is known to be asymmetrically positioned across species and is involved in fate determination through RNA sequestration, though its importance in mammals remains unknown.

Localization of individual RNA transcripts affects mammalian cell differentiation. For example, NEAT2/MALAT1 displays differential localization patterns during development. Regulation of its localization is important for RNA shuttling, splicing, and differential gene expression[92,151]. NEAT2/MALAT1 is localized to the nucleus in the oocyte, but becomes cytoplasmic in the developing embryo, only to return to its nuclear localization in differentiated cell states[152]. *CDX2* mRNA localization is also polarized in blastomeres to establish cell polarity in early mammalian embryonic development[144]. The consequence of mislocalizing these RNAs has yet to be reported.

RNA localization patterns are also particularly important during asymmetric cell division. Certain cell types, e.g. B and T cells, hematopoietic cells, and ganglions in the nervous system[153–155], utilize asymmetric cell division for fate determination. For example, localization of *CYCLIN D2* mRNA in neural progenitor cells of the developing neocortex allows them to maintain their pluripotency whereas the daughter cell differentiates[156,157].

These observations suggest that RNA localization might be a conserved phenomenon that regulates cell differentiation during development.

Developmental disorders attributed to disruption of RNA localization patterns are continuing to be discovered. Loss of the RBP Gle1 disrupts centrosomal RNA localization and centrosome function in human cells, leading to lethal motor neuron disease and fetal hydrops[158–160]. Dyskeratosis Congenita is a stem cell disorder caused by mislocalization of *TERT* transcripts from Cajal bodies to nucleoli, resulting in telomerase shortening in patient stem cells[161] and predisposing affected individuals to aplastic anemia.

Mature cell function also relies on proper RNA localization. As discussed above, intestinal epithelial cell RNA localization helps regulate local protein production along the apicobasal axis[61] (Figure 2C). Consequences of disrupting RNA localization in these cell types may underlie disease states such as inflammatory bowel disease, maldigestion, or local immune responses[162,163].

Cancer

Asymmetric RNA localization to daughter cells may contribute to cancer initiation and progression[164,165] (Figure 2D). Recently, hundreds of RBPs involved in post-transcriptional RNA modifications, alternative splicing, and localization have been implicated in numerous cancers[166,167]. These studies have led to speculations that RNA mislocalization may play a role in cancer progression. Whether these observations are a cause, consequence, or correlation is unclear. In Melanoma, cytoplasmic and mitochondrial localization of long noncoding RNA *SAMMSON* has been shown to increase clonogenic potential, and knock-down of *SAMMSON* decreases melanoma viability[168]. Additionally, the noncoding RNA *GINIR* associates with centrosomal proteins, with over-expression resulting in disruption of Brca1 protein activity and more aggressive tumors[169].

A link between RNA localization and epithelial mesenchymal transition (EMT) is also emerging (Figure 2B), supported by the observation that altered localization of certain transcripts promotes cell adhesion and migration[170]. The long noncoding RNA *LINC00460* promotes EMT in head and neck squamous cell carcinoma by localizing to the nucleus[171]. *SAM68* transcripts are normally nuclear, but become cytoplasmic during cell adhesion processes, a key factor in promoting cancer metastasis[172,173]. Local protein translation at the tips of filopodia also increases Rho and Rho Kinase (ROCK) activation in the pseudopodia of tumor cells[86,170]. The local transcriptome found there includes mRNAs encoding for proteins such as M-Ras, whose overexpression is known to be sufficient for EMT transition[174].

The observations described above implicate misregulation of RNA localization during disease establishment, but very few cases have established a direct link. This is due to the technical challenges associated with functional studies of RNA and RBP localization, particularly in disease contexts. These challenges are reflected by the paucity of data we have describing direct links between individual RNAs, their RBP regulators, mechanisms that drive localization, and ultimately the dependence of cellular functions on establishment of local transcriptomes. Fundamental insights have been gained from manipulatable model

systems, but the relevance of mechanisms observed in these systems to disease phenotypes is unclear. Further studies utilizing advanced cell culture models such as iPSCs and organoids, advancing RNA visualization tools, and developing more sophisticated approaches to analyze large data sets may help to address these challenges.

Discussion

Many transcriptome-scale sequencing[51,57,175–177] and imaging[178] experiments have illuminated how pervasive the phenomenon of RNA localization is. However, we are still left without a mechanistic understanding of *how* the vast majority of these RNAs end up at their destination and *why* their transport is regulated. Specific examples of mislocalized RNAs leading to specific phenotypes are rare, even though there are many connections between RNA localization and cellular function or human diseases. For thousands of localized RNAs, further work is needed to understand the *cis*-elements and *trans*-factors that regulate their transport as well as the effect that their localization has on cell function and physiology. These studies are required before we can begin to formulate a more thorough understanding of general mechanisms that govern RNA localization, some of which might transcend cell types and species.

In addition to the RNA localization mechanisms described above, it is likely that additional RNA localization patterns exist, possibly even some that are trans-cellular. Recent studies have shown transport of *Arc* mRNA across synapses between motor neurons and muscle cells[179,180]. This process is mediated through interactions between the retroviral-like Arc1 protein and retrotransposon-like sequences within the 3′ UTR of its own mRNA. Disruption of trans-synaptic *Arc1* mRNA transfer leads to defective synaptic plasticity. Furthermore, genetic mutations in the human *Arc* protein are linked to autism[181] and schizophrenia[182]. These findings are intriguing, and suggest that we have much yet to learn about modes of RNA localization, cell types that use them, and consequences of its disruption.

Acknowledgements

This work was supported by funding from the RNA Bioscience Initiative at the University of Colorado Anschutz Medical Campus.

References:

1. Das S, Singer RH, Yoon YJ. The travels of mRNAs in neurons: do they know where they are going? Curr Opin Neurobiol. 2019;57:110–116. [PubMed: 30784978]
2. Ryder PV, Lerit DA. RNA localization regulates diverse and dynamic cellular processes. Traffic. 2018;19(7):496–502. [PubMed: 29653028]
3. Holt CE, Martin KC, Schuman EM. Local translation in neurons: visualization and function. Nat Struct Mol Biol. 2019;26(7):557–566. [PubMed: 31270476]
4. Lee BH, Bae S-W, Shim JJ, Park SY, Park HY. Imaging Single-mRNA Localization and Translation in Live Neurons. Mol Cells. 2016;39(12):841–846. [PubMed: 28030897]
5. Taliaferro JM. Classical and emerging techniques to identify and quantify localized RNAs. Wiley Interdiscip Rev RNA. 2019;10(5):e1542. [PubMed: 31044542]
6. Xia C, Babcock HP, Moffitt JR, Zhuang X. Multiplexed detection of RNA using MERFISH and branched DNA amplification. Sci Rep. 2019;9(1):7721. [PubMed: 31118500]

7. Fazal FM, Han S, Parker KR, et al. Atlas of Subcellular RNA Localization Revealed by APEX-Seq. Cell. 2019;178(2):473–490.e26. [PubMed: 31230715]
8. Wang P, Tang W, Li Z, et al. Mapping spatial transcriptome with light-activated proximity-dependent RNA labeling. Nat Chem Biol. 10 2019. doi:10.1038/s41589-019-0368-5
9. Nicchitta CV. A platform for compartmentalized protein synthesis: protein translation and translocation in the ER. Curr Opin Cell Biol. 2002;14(4):412–416. [PubMed: 12383790]
10. López de Heredia M, Jansen R-P. mRNA localization and the cytoskeleton. Curr Opin Cell Biol. 2004;16(1):80–85. [PubMed: 15037309]
11. Long RM, Singer RH, Meng X, Gonzalez I, Nasmyth K, Jansen RP. Mating type switching in yeast controlled by asymmetric localization of ASH1 mRNA. Science. 1997;277(5324):383–387. [PubMed: 9219698]
12. Bertrand E, Chartrand P, Schaefer M, Shenoy SM, Singer RH, Long RM. Localization of ASH1 mRNA particles in living yeast. Mol Cell. 1998;2(4):437–445. [PubMed: 9809065]
13. Lantz VA, Clemens SE, Miller KG. The actin cytoskeleton is required for maintenance of posterior pole plasm components in the Drosophila embryo. Mech Dev. 1999;85(1–2):111–122. [PubMed: 10415352]
14. Meer EJ, Wang DO, Kim S, Barr I, Guo F, Martin KC. Identification of a cis-acting element that localizes mRNA to synapses. Proc Natl Acad Sci U S A. 2012;109(12):4639–4644. [PubMed: 22383561]
15. Münchow S, Sauter C, Jansen RP. Association of the class V myosin Myo4p with a localised messenger RNA in budding yeast depends on She proteins. J Cell Sci. 1999;112 (Pt 10):1511–1518. [PubMed: 10212145]
16. Forrest KM, Gavis ER. Live imaging of endogenous RNA reveals a diffusion and entrapment mechanism for nanos mRNA localization in Drosophila. Curr Biol. 2003;13(14):1159–1168. [PubMed: 12867026]
17. Kugler J-M, Lasko P. Localization, anchoring and translational control of oskar, gurken, bicoid and nanos mRNA during Drosophila oogenesis. Fly . 2009;3(1):15–28. [PubMed: 19182536]
18. Lipshitz HD, Smibert CA. Mechanisms of RNA localization and translational regulation. Curr Opin Genet Dev. 2000;10(5):476–488. [PubMed: 10980424]
19. Semotok JL, Luo H, Cooperstock RL, et al. Drosophila maternal Hsp83 mRNA destabilization is directed by multiple SMAUG recognition elements in the open reading frame. Mol Cell Biol. 2008;28(22):6757–6772. [PubMed: 18794360]
20. Farris S, Lewandowski G, Cox CD, Steward O. Selective localization of arc mRNA in dendrites involves activity- and translation-dependent mRNA degradation. J Neurosci. 2014;34(13):4481–4493. [PubMed: 24671994]
21. Bloom K, Beach DL. mRNA localization: motile RNA, asymmetric anchors. Curr Opin Microbiol. 1999;2(6):604–609. [PubMed: 10607633]
22. Yisraeli JK, Sokol S, Melton DA. A two-step model for the localization of maternal mRNA in Xenopus oocytes: involvement of microtubules and microfilaments in the translocation and anchoring of Vg1 mRNA. Development. 1990;108(2):289–298. [PubMed: 2351071]
23. Tiruchinapalli DM, Oleynikov Y, Kelic S, et al. Activity-dependent trafficking and dynamic localization of zipcode binding protein 1 and beta-actin mRNA in dendrites and spines of hippocampal neurons. J Neurosci. 2003;23(8):3251–3261. [PubMed: 12716932]
24. Lyford GL, Yamagata K, Kaufmann WE, et al. Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. Neuron. 1995;14(2):433–445. [PubMed: 7857651]
25. Mikl M, Vendra G, Kiebler MA. Independent localization of MAP2, CaMKIIα and β-actin RNAs in low copy numbers. EMBO Rep. 2011;12(10):1077–1084. [PubMed: 21869818]
26. Eliscovich C, Buxbaum AR, Katz ZB, Singer RH. mRNA on the move: the road to its biological destiny. J Biol Chem. 2013;288(28):20361–20368. [PubMed: 23720759]
27. Barbarese E, Barry C, Chou CH, et al. Expression and localization of myelin basic protein in oligodendrocytes and transfected fibroblasts. J Neurochem. 1988;51(6):1737–1745. [PubMed: 2460587]

28. Lewis YE, Moskovitz A, Mutlak M, Heineke J, Caspi LH, Kehat I. Localization of transcripts, translation, and degradation for spatiotemporal sarcomere maintenance. J Mol Cell Cardiol. 2018;116:16–28. [PubMed: 29371135]
29. Wilhelm JE, Vale RD. RNA on the move: the mRNA localization pathway. J Cell Biol. 1993;123(2):269–274. [PubMed: 8408211]
30. Gao Y, Tatavarty V, Korza G, Levin MK, Carson JH. Multiplexed dendritic targeting of alpha calcium calmodulin-dependent protein kinase II, neurogranin, and activity-regulated cytoskeleton-associated protein RNAs by the A2 pathway. Mol Biol Cell. 2008;19(5):2311–2327. [PubMed: 18305102]
31. Buxbaum AR, Haimovich G, Singer RH. In the right place at the right time: visualizing and understanding mRNA localization. Nat Rev Mol Cell Biol. 2015;16(2):95–109. [PubMed: 25549890]
32. Mitsumori K, Takei Y, Hirokawa N. Components of RNA granules affect their localization and dynamics in neuronal dendrites. Mol Biol Cell. 2017;28(11):1412–1417. [PubMed: 28404748]
33. Kiebler MA, Bassell GJ. Neuronal RNA granules: movers and makers. Neuron. 2006;51(6):685–690. [PubMed: 16982415]
34. Delanoue R, Herpers B, Soetaert J, Davis I, Rabouille C. Drosophila Squid/hnRNP helps Dynein switch from a gurken mRNA transport motor to an ultrastructural static anchor in sponge bodies. Dev Cell. 2007;13(4):523–538. [PubMed: 17925228]
35. Jain RA, Gavis ER. The Drosophila hnRNP M homolog Rumpelstiltskin regulates nanos mRNA localization. Development. 2008;135(5):973–982. [PubMed: 18234721]
36. Beach DL, Salmon ED, Bloom K. Localization and anchoring of mRNA in budding yeast. Curr Biol. 1999;9(11):569–578. [PubMed: 10359695]
37. Liu G, Grant WM, Persky D, Latham VM Jr, Singer RH, Condeelis J. Interactions of elongation factor 1alpha with F-actin and beta-actin mRNA: implications for anchoring mRNA in cell protrusions. Mol Biol Cell. 2002;13(2):579–592. [PubMed: 11854414]
38. Mili S, Moissoglu K, Macara IG. Genome-wide screen reveals APC-associated RNAs enriched in cell protrusions. Nature. 2008;453(7191):115–119. [PubMed: 18451862]
39. Bashirullah A, Cooperstock RL, Lipshitz HD. Spatial and temporal control of RNA stability. Proc Natl Acad Sci U S A. 2001;98(13):7025–7028. [PubMed: 11416182]
40. Bashirullah A, Halsell SR, Cooperstock RL, et al. Joint action of two RNA degradation pathways controls the timing of maternal transcript elimination at the midblastula transition in Drosophila melanogaster. EMBO J. 1999;18(9):2610–2620. [PubMed: 10228172]
41. Notaras M, Allen M, Longo F, et al. UPF2 leads to degradation of dendritically targeted mRNAs to regulate synaptic plasticity and cognitive function. Mol Psychiatry. 10 2019. doi:10.1038/s41380-019-0547-5
42. Colak D, Ji S-J, Porse BT, Jaffrey SR. Regulation of axon guidance by compartmentalized nonsense-mediated mRNA decay. Cell. 2013;153(6):1252–1265. [PubMed: 23746841]
43. Wang C, Han B, Zhou R, Zhuang X. Real-Time Imaging of Translation on Single mRNA Transcripts in Live Cells. Cell. 2016;165(4):990–1001. [PubMed: 27153499]
44. Cody NAL, Iampietro C, Lécuyer E. The many functions of mRNA localization during normal development and disease: from pillar to post: mRNA localization in development and disease. WIREs Dev Biol. 2013;2(6):781–796.
45. Williams NK, Dichtl B. Co-translational control of protein complex formation: a fundamental pathway of cellular organization? Biochem Soc Trans. 2018;46(1):197–206. [PubMed: 29432142]
46. Mingle LA, Okuhama NN, Shi J, Singer RH, Condeelis J, Liu G. Localization of all seven messenger RNAs for the actin-polymerization nucleator Arp2/3 complex in the protrusions of fibroblasts. J Cell Sci. 2005;118(Pt 11):2425–2433. [PubMed: 15923655]
47. Liu F, Jones DK, de Lange WJ, Robertson GA. Cotranslational association of mRNA encoding subunits of heteromeric ion channels. Proc Natl Acad Sci U S A. 2016;113(17):4859–4864. [PubMed: 27078096]
48. Kassem S, Villanyi Z, Collart MA. Not5-dependent co-translational assembly of Ada2 and Spt20 is essential for functional integrity of SAGA. Nucleic Acids Res. 2017;45(12):7539. [PubMed: 28874010]

49. Formicola N, Vijayakumar J, Besse F. Neuronal ribonucleoprotein granules: Dynamic sensors of localized signals. Traffic. 2019;20(9):639–649. [PubMed: 31206920]
50. Crerar H, Scott-Solomon E, Bodkin-Clarke C, et al. Regulation of NGF Signaling by an Axonal Untranslated mRNA. Neuron. 2019;102(3):553–563.e8. [PubMed: 30853298]
51. Zappulo A, van den Bruck D, Ciolli Mattioli C, et al. RNA localization is a key determinant of neurite-enriched proteome. Nat Commun. 2017;8(1):583. [PubMed: 28928394]
52. Lécuyer E, Yoshida H, Parthasarathy N, et al. Global analysis of mRNA localization reveals a prominent role in organizing cellular architecture and function. Cell. 2007;131(1):174–187. [PubMed: 17923096]
53. Gu W, Deng Y, Zenklusen D, Singer RH. A new yeast PUF family protein, Puf6p, represses ASH1 mRNA translation and is required for its localization. Genes Dev. 2004;18(12):1452–1465. [PubMed: 15198983]
54. Ostroff LE, Fiala JC, Allwardt B, Harris KM. Polyribosomes redistribute from dendritic shafts into spines with enlarged synapses during LTP in developing rat hippocampal slices. Neuron. 2002;35(3):535–545. [PubMed: 12165474]
55. Paquin N, Chartrand P. Local regulation of mRNA translation: new insights from the bud. Trends Cell Biol. 2008;18(3):105–111. [PubMed: 18262421]
56. Wong HH-W, Lin JQ, Ströhl F, et al. RNA Docking and Local Translation Regulate Site-Specific Axon Remodeling In Vivo. Neuron. 2017;95(4):852–868.e8. [PubMed: 28781168]
57. Mardakheh FK, Paul A, Kümper S, et al. Global Analysis of mRNA, Translation, and Protein Localization: Local Translation Is a Key Regulator of Cell Protrusions. Dev Cell. 2015;35(3):344–357. [PubMed: 26555054]
58. Dermit M, Dodel M, Lee FCY, et al. Subcellular mRNA localization regulates ribosome biogenesis in migrating cells. doi:10.1101/829739
59. Batada NN, Shepp LA, Siegmund DO. Stochastic model of protein-protein interaction: why signaling proteins need to be colocalized. Proc Natl Acad Sci U S A. 2004;101(17):6445–6449. [PubMed: 15096590]
60. Margeot A, Garcia M, Wang W, Tetaud E, di Rago JP, Jacq C. Why are many mRNAs translated to the vicinity of mitochondria: a role in protein complex assembly? Gene. 2005;354:64–71. [PubMed: 15979254]
61. Moor AE, Golan M, Massasa EE, et al. Global mRNA polarization regulates translation efficiency in the intestinal epithelium. Science. 2017;357(6357):1299–1303. [PubMed: 28798045]
62. Rishal I, Fainzilber M. Cell size sensing-a one-dimensional solution for a three-dimensional problem? BMC Biol. 2019;17(1):36. [PubMed: 31035993]
63. Lechtreck KF, Van De Weghe JC, Harris JA, Liu P. Protein transport in growing and steady-state cilia. Traffic. 2017;18(5):277–286. [PubMed: 28248449]
64. Hendel NL, Thomson M, Marshall WF. Diffusion as a Ruler: Modeling Kinesin Diffusion as a Length Sensor for Intraflagellar Transport. Biophys J. 2018;114(3):663–674. [PubMed: 29414712]
65. Toriyama M, Sakumura Y, Shimada T, Ishii S, Inagaki N. A diffusion-based neurite length-sensing mechanism involved in neuronal symmetry breaking. Mol Syst Biol. 2010;6(1). https://www.embopress.org/doi/abs/10.1038/msb.2010.51.
66. Perry RB-T, Rishal I, Doron-Mandel E, et al. Nucleolin-Mediated RNA Localization Regulates Neuron Growth and Cycling Cell Size. Cell Rep. 2016;16(6):1664–1676. [PubMed: 27477284]
67. Besse F, Ephrussi A. Translational control of localized mRNAs: restricting protein synthesis in space and time. Nat Rev Mol Cell Biol. 2008;9(12):971–980. [PubMed: 19023284]
68. Gagnon JA, Mowry KL. Molecular motors: directing traffic during RNA localization. Crit Rev Biochem Mol Biol. 2011;46(3):229–239. [PubMed: 21476929]
69. Fritzsche R, Karra D, Bennett KL, et al. Interactome of two diverse RNA granules links mRNA localization to translational repression in neurons. Cell Rep. 2013;5(6):1749–1762. [PubMed: 24360960]
70. Bi J, Tsai N-P, Lin Y-P, Loh HH, Wei L-N. Axonal mRNA transport and localized translational regulation of kappa-opioid receptor in primary neurons of dorsal root ganglia. Proc Natl Acad Sci U S A. 2006;103(52):19919–19924. [PubMed: 17167054]

71. Ghosh S, Marchand V, Gáspár I, Ephrussi A. Control of RNP motility and localization by a splicing-dependent structure in oskar mRNA. Nat Struct Mol Biol. 2012;19(4):441–449. [PubMed: 22426546]
72. Serano J, Rubin GM. The Drosophila synaptotagmin-like protein bitesize is required for growth and has mRNA localization sequences within its open reading frame. Proc Natl Acad Sci U S A. 2003;100(23):13368–13373. [PubMed: 14581614]
73. Van De Bor V, Hartswood E, Jones C, Finnegan D, Davis I. gurken and the I factor retrotransposon RNAs share common localization signals and machinery. Dev Cell. 2005;9(1):51–62. [PubMed: 15992540]
74. Buckley PT, Lee MT, Sul J-Y, et al. Cytoplasmic intron sequence-retaining transcripts can be dendritically targeted via ID element retrotransposons. Neuron. 2011;69(5):877–884. [PubMed: 21382548]
75. Jambhekar A, Derisi JL. Cis-acting determinants of asymmetric, cytoplasmic RNA transport. RNA. 2007;13(5):625–642. [PubMed: 17449729]
76. Bovaird S, Patel D, Padilla J-CA, Lécuyer E. Biological functions, regulatory mechanisms, and disease relevance of RNA localization pathways. FEBS Lett. 2018;592(17):2948–2972. [PubMed: 30132838]
77. Chang P, Torres J, Lewis RA, Mowry KL, Houliston E, King ML. Localization of RNAs to the mitochondrial cloud in Xenopus oocytes through entrapment and association with endoplasmic reticulum. Mol Biol Cell. 2004;15(10):4669–4681. [PubMed: 15292452]
78. Hachet O, Ephrussi A. Splicing of oskar RNA in the nucleus is coupled to its cytoplasmic localization. Nature. 2004;428(6986):959–963. [PubMed: 15118729]
79. Russell JH, Keiler KC. Subcellular localization of a bacterial regulatory RNA. Proc Natl Acad Sci U S A. 2009;106(38):16405–16409. [PubMed: 19805312]
80. Fei J, Sharma CM. RNA Localization in Bacteria. Microbiol Spectr. 2018;6(5). doi:10.1128/microbiolspec.RWR-0024-2018
81. Nevo-Dinur K, Nussbaum-Shochat A, Ben-Yehuda S, Amster-Choder O. Translation-independent localization of mRNA in E. coli. Science. 2011;331(6020):1081–1084. [PubMed: 21350180]
82. Prilusky J, Bibi E. Studying membrane proteins through the eyes of the genetic code revealed a strong uracil bias in their coding mRNAs. Proc Natl Acad Sci U S A. 2009;106(16):6662–6666. [PubMed: 19366666]
83. Wu L, Wells D, Tay J, et al. CPEB-mediated cytoplasmic polyadenylation and the regulation of experience-dependent translation of alpha-CaMKII mRNA at synapses. Neuron. 1998;21(5):1129–1139. [PubMed: 9856468]
84. Huang Y-S, Carson JH, Barbarese E, Richter JD. Facilitation of dendritic mRNA transport by CPEB. Genes Dev. 2003;17(5):638–653. [PubMed: 12629046]
85. Nagaoka K, Udagawa T, Richter JD. CPEB-mediated ZO-1 mRNA localization is required for epithelial tight-junction assembly and cell polarity. Nat Commun. 2012;3:675. [PubMed: 22334078]
86. St Johnston D Moving messages: the intracellular localization of mRNAs. Nat Rev Mol Cell Biol. 2005;6(5):363–375. [PubMed: 15852043]
87. Macdonald PM, Kerr K. Redundant RNA recognition events in bicoid mRNA localization. RNA. 1997;3(12):1413–1420. [PubMed: 9404892]
88. Weil TT, Forrest KM, Gavis ER. Localization of bicoid mRNA in late oocytes is maintained by continual active transport. Dev Cell. 2006;11(2):251–262. [PubMed: 16890164]
89. Ferrandon D, Elphick L, Nüsslein-Volhard C, St Johnston D. Staufen protein associates with the 3'UTR of bicoid mRNA to form particles that move in a microtubule-dependent manner. Cell. 1994;79(7):1221–1232. [PubMed: 8001156]
90. Ferrandon D, Koch I, Westhof E, Nüsslein-Volhard C. RNA-RNA interaction is required for the formation of specific bicoid mRNA 3' UTR-STAUFEN ribonucleoprotein particles. EMBO J. 1997;16(7):1751–1758. [PubMed: 9130719]
91. Hwang H-W, Wentzel EA, Mendell JT. A hexanucleotide element directs microRNA nuclear import. Science. 2007;315(5808):97–100. [PubMed: 17204650]

92. Miyagawa R, Tano K, Mizuno R, et al. Identification of cis- and trans-acting factors involved in the localization of MALAT-1 noncoding RNA to nuclear speckles. RNA. 2012;18(4):738–751. [PubMed: 22355166]

93. Shukla CJ, McCorkindale AL, Gerhardinger C, et al. High-throughput identification of RNA nuclear enrichment sequences. EMBO J. 2018;37(6). doi:10.15252/embj.201798452

94. Lubelsky Y, Ulitsky I. Sequences enriched in Alu repeats drive nuclear localization of long RNAs in human cells. Nature. 2018;555(7694):107–111. [PubMed: 29466324]

95. Muslimov IA, Santi E, Homel P, Perini S, Higgins D, Tiedge H. RNA transport in dendrites: a cis-acting targeting element is contained within neuronal BC1 RNA. J Neurosci. 1997;17(12):4722–4733. [PubMed: 9169532]

96. Lin D, Pestova TV, Hellen CUT, Tiedge H. Translational control by a small RNA: dendritic BC1 RNA targets the eukaryotic initiation factor 4A helicase mechanism. Mol Cell Biol. 2008;28(9):3008–3019. [PubMed: 18316401]

97. Tiedge H, Chen W, Brosius J. Primary structure, neural-specific expression, and dendritic location of human BC200 RNA. J Neurosci. 1993;13(6):2382–2390. [PubMed: 7684772]

98. Kaneko T, Suzuki T, Kapushoc ST, et al. Wobble modification differences and subcellular localization of tRNAs in Leishmania tarentolae: implication for tRNA sorting mechanism. EMBO J. 2003;22(3):657–667. [PubMed: 12554666]

99. Bailey TL, Johnson J, Grant CE, Noble WS. The MEME Suite. Nucleic Acids Res. 2015;43(W1):W39–W49. [PubMed: 25953851]

100. Duttke SH, Chang MW, Heinz S, Benner C. Identification and dynamic quantification of regulatory elements using total RNA. Genome Res. 2019;29(11):1836–1846. [PubMed: 31649059]

101. Agostini F, Cirillo D, Ponti RD, Tartaglia GG. SeAMotE: a method for high-throughput motif discovery in nucleic acid sequences. BMC Genomics. 2014;15:925. [PubMed: 25341390]

102. Zhang Y, Ponty Y, Blanchette M, Lecuyer E, Waldispühl J. SPARCS: a web server to analyze (un) structured regions in coding RNA sequences. Nucleic Acids Res. 2013;41(W1):W480–W485. [PubMed: 23748952]

103. Lorenz R, Bernhart SH, Höner Zu Siederdissen C, et al. ViennaRNA Package 2.0. Algorithms Mol Biol. 2011;6:26. [PubMed: 22115189]

104. Yao J, Reinharz V, Major F, Waldispühl J. RNA-MoIP: prediction of RNA secondary structure and local 3D motifs from sequence data. Nucleic Acids Res. 2017;45(W1):W440–W444. [PubMed: 28525607]

105. Kazan H, Ray D, Chan ET, Hughes TR, Morris Q. RNAcontext: a new method for learning the sequence and structure binding preferences of RNA-binding proteins. PLoS Comput Biol. 2010;6:e1000832. [PubMed: 20617199]

106. Cléry A, Allain FH-T. FROM STRUCTURE TO FUNCTION OF RNA BINDING DOMAINS. Landes Bioscience; 2013.

107. Shan J, Munro TP, Barbarese E, Carson JH, Smith R. A molecular mechanism for mRNA trafficking in neuronal dendrites. J Neurosci. 2003;23(26):8859–8866. [PubMed: 14523087]

108. Davey NE. The functional importance of structure in unstructured protein regions. Curr Opin Struct Biol. 2019;56:155–163. [PubMed: 31003202]

109. Chu J-F, Majumder P, Chatterjee B, Huang S-L, Shen C-KJ. TDP-43 Regulates Coupled Dendritic mRNA Transport-Translation Processes in Co-operation with FMRP and Staufen1. Cell Rep. 2019;29(10):3118–3133.e6. [PubMed: 31801077]

110. Castello A, Fischer B, Eichelbaum K, et al. Insights into RNA Biology from an Atlas of Mammalian mRNA-Binding Proteins. Cell. 2012;149(6):1393–1406. [PubMed: 22658674]

111. Ray D, Kazan H, Chan ET, et al. Rapid and systematic analysis of the RNA recognition specificities of RNA-binding proteins. Nat Biotechnol. 2009;27(7):667–670. [PubMed: 19561594]

112. Lambert N, Robertson A, Jangi M, McGeary S, Sharp PA, Burge CB. RNA Bind-n-Seq: quantitative assessment of the sequence and structural binding specificity of RNA binding proteins. Mol Cell. 2014;54(5):887–900. [PubMed: 24837674]

113. Wheeler EC, Van Nostrand EL, Yeo GW. Advances and challenges in the detection of transcriptome-wide protein-RNA interactions: Advances and challenges in detection of transcriptome-wide protein-RNA interactions. WIREs RNA. 2018;9(1):e1436.
114. Ule J, Jensen KB, Ruggiu M, Mele A, Ule A, Darnell RB. CLIP identifies Nova-regulated RNA networks in the brain. Science. 2003;302(5648):1212–1215. [PubMed: 14615540]
115. Licatalosi DD, Mele A, Fak JJ, et al. HITS-CLIP yields genome-wide insights into brain alternative RNA processing. Nature. 2008;456(7221):464–469. [PubMed: 18978773]
116. Van Nostrand EL, Pratt GA, Shishkin AA, et al. Robust transcriptome-wide discovery of RNA-binding protein binding sites with enhanced CLIP (eCLIP). Nat Methods. 2016;13(6):508–514. [PubMed: 27018577]
117. Hafner M, Landthaler M, Burger L, et al. Transcriptome-wide identification of RNA-binding protein and microRNA target sites by PAR-CLIP. Cell. 2010;141(1):129–141. [PubMed: 20371350]
118. Lin C, Miles WO. Beyond CLIP: advances and opportunities to measure RBP-RNA and RNA-RNA interactions. Nucleic Acids Res. 2019;47(11):5490–5501. [PubMed: 31076772]
119. Gong J, Ju Y, Shao D, Zhang QC. Advances and challenges towards the study of RNA-RNA interactions in a transcriptome-wide scale. Quantitative Biology. 2018;6(3):239–252.
120. St Johnston D, Driever W, Berleth T, Richstein S, Nüsslein-Volhard C. Multiple steps in the localization of bicoid RNA to the anterior pole of the Drosophila oocyte. Development. 1989;107 Suppl:13–19. [PubMed: 2483989]
121. Condeelis J, Singer RH. How and why does beta-actin mRNA target? Biol Cell. 2005;97(1):97–110. [PubMed: 15601261]
122. Arn EA, Cha BJ, Theurkauf WE, Macdonald PM. Recognition of a bicoid mRNA localization signal by a protein complex containing Swallow, Nod, and RNA binding proteins. Dev Cell. 2003;4(1):41–51. [PubMed: 12530962]
123. Wang ET, Taliaferro JM, Lee J-A, et al. Dysregulation of mRNA Localization and Translation in Genetic Disease. J Neurosci. 2016;36(45):11418–11426. [PubMed: 27911744]
124. Dahm R, Macchi P. Human pathologies associated with defective RNA transport and localization in the nervous system. Biol Cell. 2007;99(11):649–661. [PubMed: 17939777]
125. Chin A, Lécuyer E. RNA localization: Making its way to the center stage. Biochim Biophys Acta Gen Subj. 2017;1861(11 Pt B):2956–2970.
126. Wang W, van Niekerk E, Willis DE, Twiss JL. RNA transport and localized protein synthesis in neurological disorders and neural repair. Dev Neurobiol. 2007;67(9):1166–1182. [PubMed: 17514714]
127. Baj G, D'Alessandro V, Musazzi L, et al. Physical exercise and antidepressants enhance BDNF targeting in hippocampal CA3 dendrites: further evidence of a spatial code for BDNF splice variants. Neuropsychopharmacology. 2012;37(7):1600–1611. [PubMed: 22318196]
128. Baleriola J, Walker CA, Jean YY, et al. Axonally synthesized ATF4 transmits a neurodegenerative signal across brain regions. Cell. 2014;158(5):1159–1172. [PubMed: 25171414]
129. Zarei S, Carr K, Reiley L, et al. A comprehensive review of amyotrophic lateral sclerosis. Surg Neurol Int. 2015;6:171. [PubMed: 26629397]
130. Fiesel FC, Kahle PJ. TDP-43 and FUS/TLS: cellular functions and implications for neurodegeneration. FEBS J. 2011;278(19):3550–3568. [PubMed: 21777389]
131. Lagier-Tourenne C, Polymenidou M, Cleveland DW. TDP-43 and FUS/TLS: emerging roles in RNA processing and neurodegeneration. Hum Mol Genet. 2010;19(R1):R46–R64. [PubMed: 20400460]
132. Alami NH, Smith RB, Carrasco MA, et al. Axonal transport of TDP-43 mRNA granules is impaired by ALS-causing mutations. Neuron. 2014;81(3):536–543. [PubMed: 24507191]
133. Fallini C, Bassell GJ, Rossoll W. Spinal muscular atrophy: the role of SMN in axonal mRNA regulation. Brain Res. 2012;1462:81–92. [PubMed: 22330725]
134. Donlin-Asp PG, Bassell GJ, Rossoll W. A role for the survival of motor neuron protein in mRNP assembly and transport. Curr Opin Neurobiol. 2016;39:53–61. [PubMed: 27131421]

135. Akten B, Kye MJ, Hao LT, et al. Interaction of survival of motor neuron (SMN) and HuD proteins with mRNA cpg15 rescues motor neuron axonal deficits. Proc Natl Acad Sci U S A. 2011;108(25):10337–10342. [PubMed: 21652774]
136. Fallini C, Donlin-Asp PG, Rouanet JP, Bassell GJ, Rossoll W. Deficiency of the Survival of Motor Neuron Protein Impairs mRNA Localization and Local Translation in the Growth Cone of Motor Neurons. J Neurosci. 2016;36(13):3811–3820. [PubMed: 27030765]
137. Santoro MR, Bray SM, Warren ST. Molecular mechanisms of fragile X syndrome: a twenty-year perspective. Annu Rev Pathol. 2012;7:219–245. [PubMed: 22017584]
138. Kao D-I, Aldridge GM, Weiler IJ, Greenough WT. Altered mRNA transport, docking, and protein translation in neurons lacking fragile X mental retardation protein. Proc Natl Acad Sci U S A. 2010;107(35):15601–15606. [PubMed: 20713728]
139. Pilaz L-J, Lennox AL, Rouanet JP, Silver DL. Dynamic mRNA Transport and Local Translation in Radial Glial Progenitors of the Developing Brain. Curr Biol. 2016;26(24):3383–3392. [PubMed: 27916527]
140. Bassell GJ, Warren ST. Fragile X syndrome: loss of local mRNA regulation alters synaptic development and function. Neuron. 2008;60(2):201–214. [PubMed: 18957214]
141. Goering R, Hudish LI, Guzman BB, et al. FMRP promotes RNA localization to neuronal projections through interactions between its RGG domain and G-quadruplex RNA sequences. bioRxiv. 9 2019:784728. doi:10.1101/784728
142. Mankodi A, Logigian E, Callahan L, et al. Myotonic dystrophy in transgenic mice expressing an expanded CUG repeat. Science. 2000;289(5485):1769–1773. [PubMed: 10976074]
143. Yi H, Xue L, Guo M-X, et al. Gene expression atlas for human embryogenesis. FASEB J. 2010;24(9):3341–3350. [PubMed: 20430792]
144. Jedrusik A, Parfitt D-E, Guo G, et al. Role of Cdx2 and cell polarity in cell allocation and specification of trophectoderm and inner cell mass in the mouse embryo. Genes Dev. 2008;22(19):2692–2706. [PubMed: 18832072]
145. Platts AE, Dix DJ, Chemes HE, et al. Success and failure in human spermatogenesis as revealed by teratozoospermic RNAs. Hum Mol Genet. 2007;16(7):763–773. [PubMed: 17327269]
146. Chen Q, Yan W, Duan E. Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications. Nat Rev Genet. 2016;17(12):733–743. [PubMed: 27694809]
147. Schuster A, Tang C, Xie Y, Ortogero N, Yuan S, Yan W. SpermBase: A Database for Sperm-Borne RNA Contents. Biol Reprod. 2016;95(5):99. [PubMed: 27628216]
148. Sharma U, Sun F, Conine CC, et al. Small RNAs Are Trafficked from the Epididymis to Developing Mammalian Sperm. Dev Cell. 2018;46(4):481–494.e6. [PubMed: 30057273]
149. Peng H, Shi J, Zhang Y, et al. A novel class of tRNA-derived small RNAs extremely enriched in mature mouse sperm. Cell Res. 2012;22(11):1609–1612. [PubMed: 23044802]
150. Hadzhinesheva V, Nikolova V, Chakarova I, Delimitreva S, Markova M, Zhivkova R. Mammalian Balbiani body as a sign of ancestral oocyte asymmetry. Acta Morphol Anthropol. 2015;22:159–162.
151. Arun G, Diermeier S, Akerman M, et al. Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. Genes Dev. 2016;30(1):34–51. [PubMed: 26701265]
152. Jansova D, Tetkova A, Koncicka M, Kubelka M, Susor A. Localization of RNA and translation in the mammalian oocyte and embryo. PLoS One. 2018;13(3):e0192544. [PubMed: 29529035]
153. Yen B Asymmetric Cell Division in the Generation of Immunity and Tolerance. 2018. doi:10.7916/D8NP3GB7
154. Gómez-López S, Lerner RG, Petritsch C. Asymmetric cell division of stem and progenitor cells during homeostasis and cancer. Cell Mol Life Sci. 2014;71(4):575–597. [PubMed: 23771628]
155. Knoblich JA. Mechanisms of asymmetric stem cell division. Cell. 2008;132(4):583–597. [PubMed: 18295577]
156. Tsunekawa Y, Britto JM, Takahashi M, Polleux F, Tan S-S, Osumi N. Cyclin D2 in the basal process of neural progenitors is linked to non-equivalent cell fates. The EMBO Journal. 2012;31(8):1879–1892. doi:10.1038/emboj.2012.43 [PubMed: 22395070]

157. Tsunekawa Y, Kikkawa T, Osumi N. Asymmetric inheritance of Cyclin D2 maintains proliferative neural stem/progenitor cells: a critical event in brain development and evolution. Dev Growth Differ. 2014;56(5):349–357. [PubMed: 24835888]
158. Nousiainen HO, Kestilä M, Pakkasjärvi N, et al. Mutations in mRNA export mediator GLE1 result in a fetal motoneuron disease. Nat Genet. 2008;40(2):155–157. [PubMed: 18204449]
159. Jao L-E, Akef A, Wente SR. A role for Gle1, a regulator of DEAD-box RNA helicases, at centrosomes and basal bodies. Mol Biol Cell. 2017;28(1):120–127. [PubMed: 28035044]
160. Okamura M, Yamanaka Y, Shigemoto M, et al. Depletion of mRNA export regulator DBP5/DDX19, GLE1 or IPPK that is a key enzyme for the production of IP6, resulting in differentially altered cytoplasmic mRNA expression and specific cell defect. PLOS ONE. 2018;13(5):e0197165. doi:10.1371/journal.pone.0197165 [PubMed: 29746542]
161. Batista LFZ, Pech MF, Zhong FL, et al. Telomere shortening and loss of self-renewal in dyskeratosis congenita induced pluripotent stem cells. Nature. 2011;474(7351):399–402. [PubMed: 21602826]
162. Yarani R, Mirza AH, Kaur S, Pociot F. The emerging role of lncRNAs in inflammatory bowel disease. Exp Mol Med. 2018;50(12):161.
163. Carow B, Hauling T, Qian X, Kramnik I, Nilsson M, Rottenberg ME. Spatial and temporal localization of immune transcripts defines hallmarks and diversity in the tuberculosis granuloma. Nat Commun. 2019;10(1):1823. [PubMed: 31015452]
164. Yao Y, Dai W. Genomic Instability and Cancer. J Carcinog Mutagen. 2014;5. doi:10.4172/2157-2518.1000165
165. Zeraati M, Moye AL, Wong JWH, et al. Cancer-associated noncoding mutations affect RNA G-quadruplex-mediated regulation of gene expression. Sci Rep. 2017;7(1):708. [PubMed: 28386116]
166. Neelamraju Y, Gonzalez-Perez A, Bhat-Nakshatri P, Nakshatri H, Janga SC. Mutational landscape of RNA-binding proteins in human cancers. RNA Biol. 2018;15(1):115–129. [PubMed: 29023197]
167. Zhang B, Babu KR, Lim CY, et al. A comprehensive expression landscape of RNA-binding proteins (RBPs) across 16 human cancer types. RNA Biol. 10 2019:1–16.
168. Leucci E, Vendramin R, Spinazzi M, et al. Melanoma addiction to the long non-coding RNA SAMMSON. Nature. 2016;531(7595):518–522. doi:10.1038/nature17161 [PubMed: 27008969]
169. Panda S, Setia M, Kaur N, et al. Noncoding RNA Ginir functions as an oncogene by associating with centrosomal proteins. PLOS Biology. 2018;16(10):e2004204. doi:10.1371/journal.pbio.2004204 [PubMed: 30296263]
170. Stuart HC, Jia Z, Messenberg A, et al. Localized Rho GTPase Activation Regulates RNA Dynamics and Compartmentalization in Tumor Cell Protrusions. Journal of Biological Chemistry. 2008;283(50):34785–34795. doi:10.1074/jbc.m804014200 [PubMed: 18845542]
171. Jiang Y, Cao W, Wu K, et al. LncRNA LINC00460 promotes EMT in head and neck squamous cell carcinoma by facilitating peroxiredoxin-1 into the nucleus. Journal of Experimental & Clinical Cancer Research. 2019;38(1). doi:10.1186/s13046-019-1364-z
172. Huot M-E E, Huot M, Brown CM, Lamarche-Vane N, Richard S. An Adaptor Role for Cytoplasmic Sam68 in Modulating Src Activity during Cell Polarization. Molecular and Cellular Biology. 2009;29(7):1933–1943. doi:10.1128/mcb.01707-08 [PubMed: 19139276]
173. Bergeman J, Caillier A, Houle F, Gagné LM, Huot M-É. Localized translation regulates cell adhesion and transendothelial migration. Journal of Cell Science. 2016:jcs.191320. doi:10.1242/jcs.191320
174. Ward KR, Zhang K-X, Somasiri AM, Roskelley CD, Schrader JW. Expression of activated M-Ras in a murine mammary epithelial cell line induces epithelial-mesenchymal transition and tumorigenesis. Oncogene. 2004;23(6):1187–1196. [PubMed: 14961075]
175. Taliaferro JM, Vidaki M, Oliveira R, et al. Distal Alternative Last Exons Localize mRNAs to Neural Projections. Mol Cell. 2016;61(6):821–833. [PubMed: 26907613]
176. Cajigas IJ, Tushev G, Will TJ, tom Dieck S, Fuerst N, Schuman EM. The local transcriptome in the synaptic neuropil revealed by deep sequencing and high-resolution imaging. Neuron. 2012;74(3):453–466. [PubMed: 22578497]

177. Tushev G, Glock C, Heumüller M, Biever A, Jovanovic M, Schuman EM. Alternative 3' UTRs Modify the Localization, Regulatory Potential, Stability, and Plasticity of mRNAs in Neuronal Compartments. Neuron. 2018;98(3):495–511.e6. [PubMed: 29656876]

178. Chen KH, Boettiger AN, Moffitt JR, Wang S, Zhuang X. RNA imaging. Spatially resolved, highly multiplexed RNA profiling in single cells. Science. 2015;348(6233):aaa6090. [PubMed: 25858977]

179. Ashley J, Cordy B, Lucia D, Fradkin LG, Budnik V, Thomson T. Retrovirus-like Gag Protein Arc1 Binds RNA and Traffics across Synaptic Boutons. Cell. 2018;172(1-2):262–274.e11. [PubMed: 29328915]

180. Pastuzyn ED, Day CE, Kearns RB, et al. The Neuronal Gene Arc Encodes a Repurposed Retrotransposon Gag Protein that Mediates Intercellular RNA Transfer. Cell. 2018;173(1):275. [PubMed: 29570995]

181. Alhowikan AM. Activity-Regulated Cytoskeleton-Associated Protein Dysfunction May Contribute to Memory Disorder and Earlier Detection of Autism Spectrum Disorders. Med Princ Pract. 2016;25(4):350–354. [PubMed: 26967659]

182. Fromer M, Pocklington AJ, Kavanagh DH, et al. De novo mutations in schizophrenia implicate synaptic networks. Nature. 2014;506(7487):179–184. [PubMed: 24463507]

183. Zimyanin VL, Belaya K, Pecreaux J, et al. In vivo imaging of oskar mRNA transport reveals the mechanism of posterior localization. Cell. 2008;134(5):843–853. [PubMed: 18775316]

184. Brendza RP, Serbus LR, Duffy JB, Saxton WM. A function for kinesin I in the posterior transport of oskar mRNA and Staufen protein. Science. 2000;289(5487):2120–2122. [PubMed: 11000113]

185. Kim-Ha J, Smith JL, Macdonald PM. oskar mRNA is localized to the posterior pole of the Drosophila oocyte. Cell. 1991;66(1):23–35. [PubMed: 2070416]

186. St Johnston D, Beuchle D, Nüsslein-Volhard C. Staufen, a gene required to localize maternal RNAs in the Drosophila egg. Cell. 1991;66(1):51–63. [PubMed: 1712672]

187. Trovisco V, Belaya K, Nashchekin D, et al. bicoid mRNA localises to the Drosophila oocyte anterior by random Dynein-mediated transport and anchoring. Elife. 2016;5. doi:10.7554/eLife.17537

188. Betley JN, Heinrich B, Vernos I, Sardet C, Prodon F, Deshler JO. Kinesin II mediates Vg1 mRNA transport in Xenopus oocytes. Curr Biol. 2004;14(3):219–224. [PubMed: 14761654]

189. Yoon YJ, Mowry KL. Xenopus Staufen is a component of a ribonucleoprotein complex containing Vg1 RNA and kinesin. Development. 2004;131(13):3035–3045. [PubMed: 15163628]

190. Mori Y, Imaizumi K, Katayama T, Yoneda T, Tohyama M. Two cis-acting elements in the 3' untranslated region of alpha-CaMKII regulate its dendritic targeting. Nat Neurosci. 2000;3(11):1079–1084. [PubMed: 11036263]

191. Mallardo M, Deitinghoff A, Müller J, et al. Isolation and characterization of Staufen-containing ribonucleoprotein particles from rat brain. Proc Natl Acad Sci U S A. 2003;100(4):2100–2105. [PubMed: 12592035]

192. Kohrmann M, Luo M, Kaether C, DesGroseillers L, Dotti CG, Kiebler MA. Microtubule-dependent recruitment of Staufen-green fluorescent protein into large RNA-containing granules and subsequent dendritic transport in living hippocampal neurons. Mol Biol Cell. 1999;10(9):2945–2953. [PubMed: 10473638]

193. Yamagishi M, Ishihama Y, Shirasaki Y, Kurama H, Funatsu T. Single-molecule imaging of β-actin mRNAs in the cytoplasm of a living cell. Exp Cell Res. 2009;315(7):1142–1147. [PubMed: 19245805]

194. Lifland AW, Zurla C, Yu J, Santangelo PJ. Dynamics of Native β-actin mRNA Transport in the Cytoplasm. Traffic. 2011;12(8):1000–1011. doi:10.1111/j.1600-0854.2011.01209.x [PubMed: 21518164]

195. Zhang HL, Eom T, Oleynikov Y, et al. Neurotrophin-induced transport of a beta-actin mRNP complex increases beta-actin levels and stimulates growth cone motility. Neuron. 2001;31(2):261–275. [PubMed: 11502257]

196. Chao JA, Patskovsky Y, Patel V, Levy M, Almo SC, Singer RH. ZBP1 recognition of β-actin zipcode induces RNA looping. Genes Dev. 2010;24(2):148–158. [PubMed: 20080952]

197. Deshler JO, Highett MI, Schnapp BJ. Localization of Xenopus Vg1 mRNA by Vera protein and the endoplasmic reticulum. Science. 1997;276(5315):1128–1131. [PubMed: 9148809]

198. Deshler JO, Highett MI, Abramson T, Schnapp BJ. A highly conserved RNA-binding protein for cytoplasmic mRNA localization in vertebrates. Curr Biol. 1998;8(9):489–496. [PubMed: 9560341]

199. Havin L, Git A, Elisha Z, et al. RNA-binding protein conserved in both microtubule- and microfilament-based RNA localization. Genes & Development. 1998;12(11):1593–1598. doi:10.1101/gad.12.11.1593 [PubMed: 9620847]

200. Kwon S, Abramson T, Munro TP, John CM, Köhrmann M, Schnapp BJ. UUCAC- and Vera-Dependent Localization of VegT RNA in Xenopus Oocytes. Current Biology. 2002;12(7):558–564. doi:10.1016/s0960-9822(02)00740-6 [PubMed: 11937024]

201. Aronov S, Aranda G, Behar L, Ginzburg I. Visualization of translated tau protein in the axons of neuronal P19 cells and characterization of tau RNP granules. J Cell Sci. 2002;115(Pt 19):3817–3827. [PubMed: 12235292]

202. Litman P, Barg J, Rindzoonski L, Ginzburg I. Subcellular localization of tau mRNA in differentiating neuronal cell culture: implications for neuronal polarity. Neuron. 1993;10(4):627–638. [PubMed: 8476613]

203. Atlas R, Behar L, Elliott E, Ginzburg I. The insulin-like growth factor mRNA binding-protein IMP-1 and the Ras-regulatory protein G3BP associate with tau mRNA and HuD protein in differentiated P19 neuronal cells. J Neurochem. 2004;89(3):613–626. [PubMed: 15086518]

204. Torvund-Jensen J, Steengaard J, Reimer L, Fihl LB, Laursen LS. Transport and translation of MBP mRNA is regulated differently by distinct hnRNP proteins. J Cell Sci. 2014;127(Pt 7):1550–1564. [PubMed: 24522184]

205. Hoek KS, Kidd GJ, Carson JH, Smith R. hnRNP A2 selectively binds the cytoplasmic transport sequence of myelin basic protein mRNA. Biochemistry. 1998;37(19):7021–7029. [PubMed: 9578590]

206. Norvell A, Kelley RL, Wehr K, Schüpbach T. Specific isoforms of squid, a Drosophila hnRNP, perform distinct roles in Gurken localization during oogenesis. Genes Dev. 1999;13(7):864–876. [PubMed: 10197986]

207. Dienstbier M, Boehl F, Li X, Bullock SL. Egalitarian is a selective RNA-binding protein linking mRNA localization signals to the dynein motor. Genes Dev. 2009;23(13):1546–1558. [PubMed: 19515976]

208. Huynh J-R, Munro TP, Smith-Litière K, Lepesant J-A, St Johnston D. The Drosophila hnRNPA/B homolog, Hrp48, is specifically required for a distinct step in osk mRNA localization. Dev Cell. 2004;6(5):625–635. [PubMed: 15130488]

209. Yano T, López de Quinto S, Matsui Y, Shevchenko A, Shevchenko A, Ephrussi A. Hrp48, a Drosophila hnRNPA/B homolog, binds and regulates translation of oskar mRNA. Dev Cell. 2004;6(5):637–648. [PubMed: 15130489]

210. Groisman I, Huang Y-S, Mendez R, Cao Q, Theurkauf W, Richter JD. CPEB, Maskin, and Cyclin B1 mRNA at the Mitotic Apparatus: Implications for Local Translational Control of Cell Division. Cell. 2000;103(3):435–447. [PubMed: 11081630]

211. Olivier C, Poirier G, Gendron P, Boisgontier A, Major F, Chartrand P. Identification of a conserved RNA motif essential for She2p recognition and mRNA localization to the yeast bud. Mol Cell Biol. 2005;25(11):4752–4766. [PubMed: 15899876]

212. Long RM. She2p is a novel RNA-binding protein that recruits the Myo4p-She3p complex to ASH1 mRNA. The EMBO Journal. 2000;19(23):6592–6601. doi:10.1093/emboj/19.23.6592 [PubMed: 11101531]

213. Dynes JL, Steward O. Dynamics of bidirectional transport ofArc mRNA in neuronal dendrites. The Journal of Comparative Neurology. 2007;500(3):433–447. doi:10.1002/cne.21189 [PubMed: 17120280]

214. Steward O, Wallace CS, Lyford GL, Worley PF. Synaptic activation causes the mRNA for the IEG Arc to localize selectively near activated postsynaptic sites on dendrites. Neuron. 1998;21(4):741–751. [PubMed: 9808461]

215. Huang F, Chotiner JK, Steward O. Actin polymerization and ERK phosphorylation are required for Arc/Arg3.1 mRNA targeting to activated synaptic sites on dendrites. J Neurosci. 2007;27(34):9054–9067. [PubMed: 17715342]
216. Sylvestre J, Margeot A, Jacq C, Dujardin G, Corral-Debrinski M. The Role of the 3′ Untranslated Region in mRNA Sorting to the Vicinity of Mitochondria Is Conserved from Yeast to Human Cells. MBoC. 2003;14(9):3848–3856. [PubMed: 12972568]
217. Zabezhinsky D, Slobodin B, Rapaport D, Gerst JE. An Essential Role for COPI in mRNA Localization to Mitochondria and Mitochondrial Function. Cell Rep. 2016;15(3):540–549. [PubMed: 27068463]
218. Saint-Georges Y, Garcia M, Delaveau T, et al. Yeast mitochondrial biogenesis: a role for the PUF RNA-binding protein Puf3p in mRNA localization. PLoS One. 2008;3(6):e2293. [PubMed: 18523582]
219. García-Rodríguez LJ, Gay AC, Pon LA. Puf3p, a Pumilio family RNA binding protein, localizes to mitochondria and regulates mitochondrial biogenesis and motility in budding yeast. J Cell Biol. 2007;176(2):197–207. [PubMed: 17210948]
220. Olivas W, Parker R. The Puf3 protein is a transcript-specific regulator of mRNA degradation in yeast. EMBO J. 2000;19(23):6602–6611. [PubMed: 11101532]
221. Tian L, Chou H-L, Zhang L, Okita TW. Targeted Endoplasmic Reticulum Localization of Storage Protein mRNAs Requires the RNA-Binding Protein RBP-L. Plant Physiol. 2019;179(3):1111–1131. [PubMed: 30659066]
222. Tian L, Chou H-L, Zhang L, et al. RNA-Binding Protein RBP-P Is Required for Glutelin and Prolamine mRNA Localization in Rice Endosperm Cells. Plant Cell. 2018;30(10):2529–2552. [PubMed: 30190374]
223. Banerjee A, Ifrim MF, Valdez AN, Raj N, Bassell GJ. Aberrant RNA translation in fragile X syndrome: From FMRP mechanisms to emerging therapeutic strategies. Brain Res. 2018;1693(Pt A):24–36. [PubMed: 29653083]
224. Dictenberg JB, Swanger SA, Antar LN, Singer RH, Bassell GJ. A direct role for FMRP in activity-dependent dendritic mRNA transport links filopodial-spine morphogenesis to fragile X syndrome. Dev Cell. 2008;14(6):926–939. [PubMed: 18539120]
225. Majumder P, Chu J-F, Chatterjee B, Swamy KBS, Shen C-KJ. Co-regulation of mRNA translation by TDP-43 and Fragile X Syndrome protein FMRP. Acta Neuropathol. 2016;132(5):721–738. [PubMed: 27518042]
226. Racca C, Gardiol A, Eom T, Ule J, Triller A, Darnell RB. The Neuronal Splicing Factor Nova Co-Localizes with Target RNAs in the Dendrite. Front Neural Circuits. 2010;4:5. [PubMed: 20407637]
227. Zalfa F, Adinolfi S, Napoli I, et al. Fragile X mental retardation protein (FMRP) binds specifically to the brain cytoplasmic RNAs BC1/BC200 via a novel RNA-binding motif. J Biol Chem. 2005;280(39):33403–33410. [PubMed: 16006558]
228. Kriegel AJ, Terhune SS, Greene AS, Noon KR, Pereckas MS, Liang M. Isomer-specific effect of microRNA miR-29b on nuclear morphology. J Biol Chem. 2018;293(36):14080–14088. [PubMed: 30006350]
229. Saunders C, Cohen RS. The role of oocyte transcription, the 5′ UTR, and translation repression and derepression in Drosophila gurken mRNA and protein localization. Mol Cell. 1999;3(1):43–54. [PubMed: 10024878]
230. Groisman I, Huang Y-S, Mendez R, Cao Q, Theurkauf W, Richter JD. CPEB, Maskin, and Cyclin B1 mRNA at the Mitotic Apparatus. Cell. 2000;103(3):435–447. doi:10.1016/s0092-8674(00)00135-5 [PubMed: 11081630]
231. Olivas W The Puf3 protein is a transcript-specific regulator of mRNA degradation in yeast. The EMBO Journal. 2000;19(23):6602–6611. doi:10.1093/emboj/19.23.6602 [PubMed: 11101532]

Synopsis

Here we review what is currently known about mechanisms of RNA localization in a variety of cell types. Many reviews have previously focused on mechanisms, consequences, and diseases associated with defective RNA localization in the central nervous system. However, here we have compiled what is known about mechanisms and consequences of RNA localization across other cell types and organisms, including yeast, oocytes, epithelial cells, and in diseases such as cancer and those affecting development.

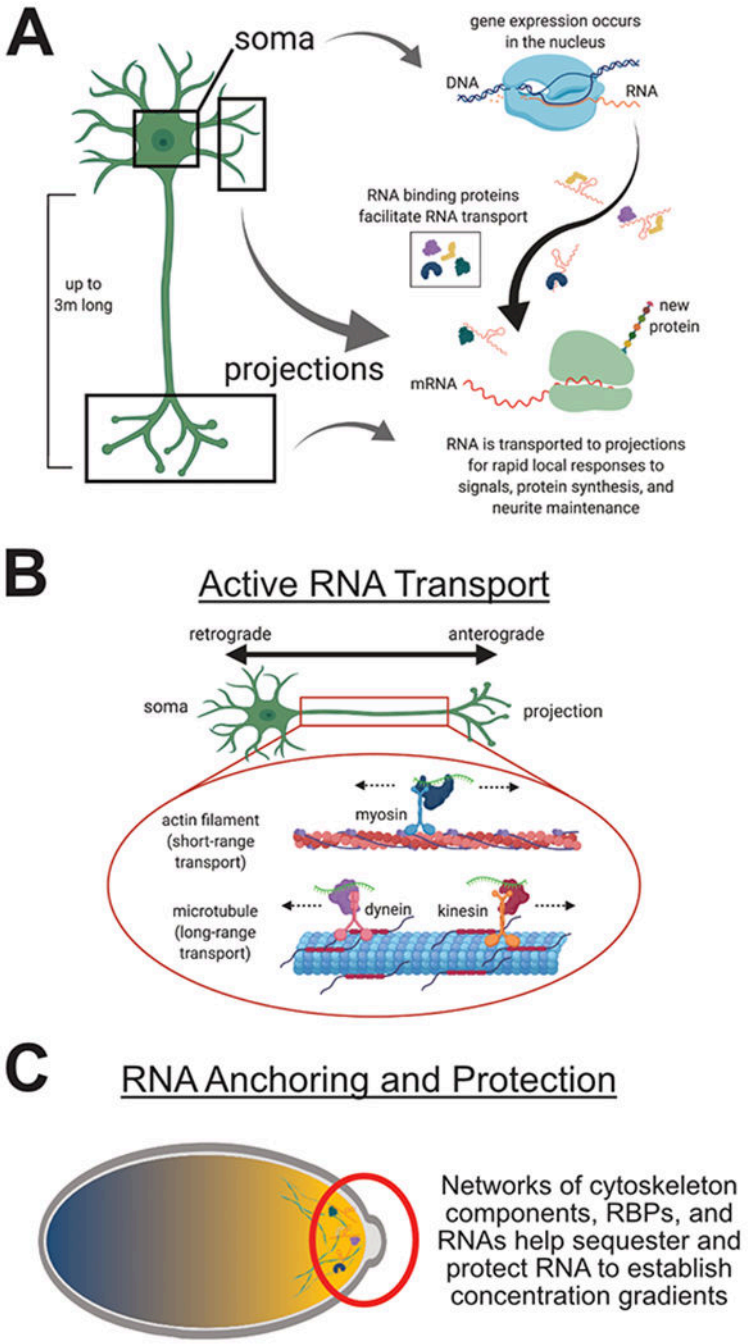

Figure 1: Mechanisms of RNA localization.

A) Local RNA transcriptomes are established in neurons to facilitate local protein production in response to stimuli. RNA binding proteins are essential for transport of these RNAs. B) RNAs are transported along cytoskeletal networks in various cell types. Short range transport is typically mediated by actin filaments and myosins, which can facilitate retrograde and anterograde movement. Long range transport is achieved with microtubules in both retrograde and anterograde movement using dynein and kinesin, respectively. C)

Concentration gradients of RNAs are established using anchors composed of proteins that sequester RNA.

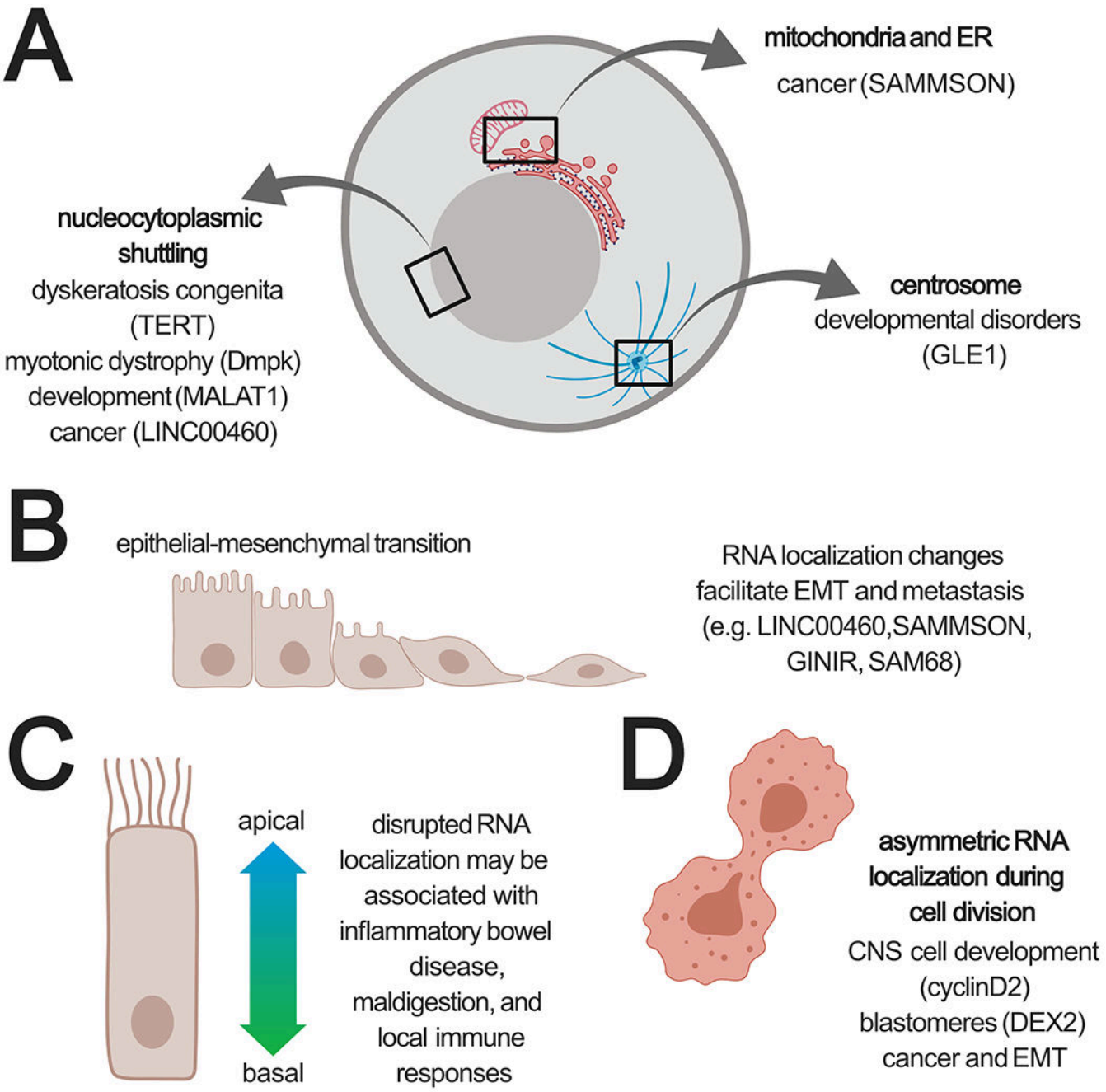

Figure 2: Misregulation of RNA localization is relevant to disease phenotypes.

A) RNA localization patterns to various subcellular compartments are disrupted in various diseases. B) Establishment of EMT is associated with RNA localization changes. C) Gradients of RNA concentrations are observed between the apical and basal axis of epithelial cells; however, it is not clear if disruption of these patterns contributes to disease phenotypes. D) Asymmetric distribution of RNAs helps establish developmental states and disruption of these patterns contributes to establishment of cancer.

Table 1:
Known RNA/RBP pairs that drive RNA localization.

Many additional RBPs and mRNAs are known to facilitate localization and be localized; however, we did not include those in this table since either the RBP component or the mRNA zipcode is unknown. abbreviations used: cytoplasmic polyadenlyation element (CPE), spliced oskar localization element (SOLE), exon junction complex (EJC), hnRNP A2 response element (A2RE), untranslated region (UTR), open reading frame (ORF), pumilio homology domain (PHD), RNA recognition motif (RRM), K homology (KH), double stranded RNA binding domain (dsRBD), arginine-glycine-glycine (RGG).

RBP; RBDs (if known)	mRNA (species)	zipcode	transport mechanism	cellular function	references
STAU; 4 conserved dsRBDs	oskar (*Drosophila*) bicoid (*Drosophila*) *vg1* (*Xenopus*) *CamKlla* (mammalian)	3′ UTR (SOLE; EJC deposition) 3′ UTR and 5′ stem loops 3′ UTR (366nt) 3′ UTR (30nt)	active transport (kinesin) with biased random walk active transport (dynein) and anchoring active transport (kinesin) and anchoring active transport	germ line differentiation embryonic patterning embryonic development memory formation; dendrites	183–186 88–90, 187 22, 188, 189 190–192
ZBP1, VERA, IMP1; 2 RRM and 4 KH	*ActB* (mammalian) *vg1* and *vegT* (*Xenopus*) *Tau* (rat)	3′ UTR, 5′-GGACU-3′ (4-8) and 5′-ACA-3′ (22-24) 3′ UTR (element X4) U-rich sequence	active transport, diffusion, and anchoring active transport (kinesin) and anchoring active transport (kinesin)	fibroblast movement and axon guidance embryonic endoderm differentiation axonal polarity maintenance	23, 193–196 77, 197–200 201–203
hnRNPA/B, Squid, Hrp48; RRM, KH, and RGG	*MBP* (mammalian) *gurken* (*Drosophila*) *oskar* (*Drosophila*)	3′ UTR (21nt A2RE) 5′ UTR 3′ UTR (SOLE; EJC deposition)	active transport active transport (dynein) and anchoring active transport (kinesin)	myelin sheath formation embryonic development germ line differentiation	204, 205 34, 206, 207 208, 209
CPEB	*MAP2* (*rat*) *ZO-1* (mouse) *cyclinB1* and *Xbub3* (*Xenopus*)	3′ UTR CPE 3′ UTR (5 conserved CPEs) 3′ UTR CPE	active transport unknown unknown	microtubule assembly epithelial tight junction assembly and polarity mitotic spindle and division	84 85 210
Rump	*nanos* (*Drosophila*)	3′ UTR (4 partly redundant regions)	diffusion, streaming, and anchoring	embryonic polarity	16, 35
ARC1	*Arc1* (mammalian)	3′ UTR	active transport and exovesicles	synaptic plasticity	179, 215–215
She2/She3	*ASH1* (yeast)	ORFs and 3′ UTR	active transport (myosin) and anchoring	mate type switching	11, 12, 211, 212
Sec27	*OXA1* (yeast)	3′ UTR and ORF	unknown	mitochondrial inner membrane biogenesis	216, 217
Puf3p; PHD	*COX17* (*yeast*)	3′ UTR (UGUR motif)	unknown	mitochondrial biogenesis and motility	218–220
RBP-L/RBP-P; 3 RRM	*glutelin* (rice) *prolamine* (rice)	ORF (repeated motifs) and 3′ UTR (U-rich) ORF (repeated motifs) and 3′ UTR (U-rich)	active transport active transport	grain development grain development	221, 222 221, 222
FMRP; KH and RGG	*MAP1b* and *CamKlla* (mammalian)	G-quadruplex	active transport	neurogenesis and memory formation	140, 141, 223, 224

RBP; RBDs (if known)	mRNA (species)	zipcode	transport mechanism	cellular function	references
SMAUG	*hsp83* (*Drosophila*)	3′ UTR	degradation and local protection	development; maternal transcript elimination	19, 40
LARP6	ribosomal protein mRNAs (mammalian)	5′ TOP	unknown	fibroblast protrusion formation	58
TDP-43; RRM and Gly-rich C-term	*NEFL* and *RAC1* (mammalian)	3′ UTR	active transport	neuronal development and plasticity	109, 225
NOVA	*girk2* (mouse)	intronic and 3′ UTR YCAY	unknown	spinal motor neuron dendrite activity	226

Table 2:
Localized noncoding RNA and their RBP partners.

abbreviations used: K homology (KH), arginine-glycine-glycine (RGG).

RBP; RBDs (if known)	ncRNA (species)	zipcode	transport mechanism	cellular function	references
FMRP; KH and RGG	BC1 (mouse) BC200 (human)	unknown unknown	unknown unknown	dendritic mRNA translation regulation dendritic mRNA translation regulation	95, 227 95, 227
ANT2	mir29-b (human)	unknown	unknown	cell division	91, 228
RNPS1, SRm160, and IBP160	NEAT2/MALAT1 (human)	region E and region M	unknown	nuclear speckle function	92