Signed, sealed, and delivered: RNA localization and translation at centrosomes

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ABSTRACT Protein localization is intrinsic to cellular function and specialized activities, such as migration or proliferation. Many localized proteins enrich at defined organelles, forming subdomains of functional activity further specified by interacting protein assemblies. One well-studied organelle showing dynamic, functional changes in protein composition is the centrosome. Centrosomes are microtubule-organizing centers with diverse cellular functions largely defined by the composition of the pericentriolar material, an ordered matrix of proteins organized around a central pair of centrioles. Also localizing to the pericentriolar material are mRNAs. Although RNA was identified at centrosomes decades ago, the characterization of specific RNA transcripts and their functional contributions to centrosome biology remained largely unstudied. While the identification of RNA localized to centrosomes accelerated with the development of high-throughput screening methods, this discovery still outpaces functional characterization. Recent work indicates RNA localized to centrosomes is biologically significant and further implicates centrosomes as sites for local protein synthesis. Distinct RNA localization and translational activities likely contribute to the diversity of centrosome functions within cells.

CODING AND DECODING THE MESSAGE

The central dogma is a study in cryptography. First, the DNA code must be transcribed in the nucleus into a premessenger RNA (pre-mRNA) subject to mRNA processing before nuclear export. Once in the cytoplasm, the messages encoded by mature mRNAs are translated by ribosomes to generate protein products. When and where proteins are generated matters. For many cellular responses, such as cell migration or proliferation, rapid adaptation to the cellular environment requires the rapid redistribution of proteins. Conversely, errant synthesis or localization of certain protein products, such as those that define cell fates or contribute to specialized cellular functions, may have deleterious consequences for individual cells or developing tissues. Numerous proteins are translated locally at their site of function, effectively generating subcellular enrichments on demand, and protecting distal sites from ectopic exposure.

Often, local protein synthesis is coupled with RNA localization, whereby mRNAs are enriched at defined subcellular locales. RNA localization is a posttranscriptional paradigm of gene regulation conserved from single-celled bacteria and fungi through complex, multicellular organisms, including humans. Many excellent reviews address mRNA localization and local translation and its importance in diverse cellular responses (Gavis et al., 2007; Martin and Ephrussi, 2009; Meignin and Davis, 2010; Jung et al., 2014; Buxbaum et al., 2015; Ryder and Lerit, 2018; Das et al., 2021). In this Perspective, I provide a primer to RNA localization, then focus on RNA localization and translation at centrosomes and spindle poles, a topic of recently renewed interest.

AN INTRODUCTION TO RNA LOCALIZATION

While many proteins are targeted to defined subcellular compartments, others are synthesized in situ following mRNA localization. Spatial enrichments of RNAs are generated by a variety of mechanisms, including active transport (Long et al., 1997; Takizawa et al., 1997), diffusion and entrapment (Forrest and Gavis, 2003), and local

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Abbreviations used: AHA, azidohomoalanine; Asl, asterless; Asp, abnormal spindle; ASPM, abnormal spindle-like microcephaly-associated; Bcd, bicoid; BICD2, BICD cargo adaptor 2; BONCAT, bioorthogonal noncanonical amino acid tagging; CCDC88C, Coiled-coil domain-containing 88C; Cen, centrocortin; Cep350, centrosome protein 350; Cnn, centrosomin; CPEB, cytoplasmic polyadenylation element binding; Cyc B, Cyclin B; FMRP, Fragile-X mental retardation protein; γTub, γ-Tubulin; HMMR, hyaluronan-mediated motility receptor; Mud, mushroom body defective; NUMA1, nuclear mitotic apparatus protein 1; PCNT, pericentrin; PLK4, Polo-like kinase 4; PLP, pericentrin-like protein; Puro-PLA, Puromycylation-proximity ligation; RNA, Ribonucleic acid; 3'-UTR, 3'-untranslated region.

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Lehmann, 1994). Other mRNAs, including several localizing to binding proteins (Kislauskis and Singer, 1992). Many RNAs are main-
tion of sequence or structural motifs within target mRNAs by RNA-
critical functions in diverse cellular settings (Ryder and Lerit, 2018).

While not all mRNAs localize to defined subcellular regions, a large number do. A genome-wide RNA localization screen in early Drosophila embryos revealed >70% mRNAs are enriched at defined subcellular compartments (Lecuyer et al., 2007). Spatial transcriptomics in mammalian cells similarly highlights the high prevalence of subcellular RNA localization (Fazal et al., 2019). Taken together, RNA localization is widespread, conserved, and functionally important, as its dysregulation impacts development and disease (reviewed in Holt and Bullock, 2009; Wang et al., 2016).

MESSAGES AT THE CENTROSOME
Centrosomes as microtubule-organizing centers
Among the subcellular depots for RNA localization are specific organelles, including centrosomes. Centrosomes function in microtubule nucleation and organization (Karsenti et al., 1984; Mitchison and Kirschner, 1984) and are key for the fidelity of mitosis. Upon mitotic entry, the duplicated centrosomes organize the bipolar mitotic spindle to ensure faithful segregation of the chromosomes to the two daughter cells (Pihan, 2013). During interphase, centrosomes build a network of polarized microtubules, serving as a highway for intracellular trafficking and cell polarization. Additionally, in quiescent cells, centrosomes convert into the basal bodies required for ciliogenesis (Kobayashi and Dynlacht, 2011). Indicative of its functional importance, centrosome dysfunction is associated with human developmental disorders and disease, including microcephaly, ciliopathy, and cancer (Nigg and Raff, 2009).

The microtubule-nucleating activity of the centrosome is enabled by the pericentriolar material (PCM; Figure 1A), the levels of which dramatically increase upon mitotic entry (Gould and Borisy, 1977; Khodjakov and Rieder, 1999). The advent of superresolution microscopy uncovered the conserved subconcentric organization of centrosomal proteins within PCM (Figure 1, B and C; Fu and Glover, 2012; Lawo et al., 2012; Mennella et al., 2012; Sonnen et al., 2012). Centriolar components reside near the center, while PCM proteins reside within different or partially overlapping layers radiating out (Figure 1D). The composition and organization of PCM oscillates with the cell cycle, augmenting the microtubule-organizing activity of the centrosome to direct formation of the bipolar mitotic spindle (Figure 1E).

Early evidence for RNA at centrosomes
Initial observations for RNA at centrosomes date back to the 1960s (reviewed in Marshall and Rosenbaum, 2000). Pioneering work indicated purified ciliary basal bodies from the protist Tetrahymena...
Compelling evidence indicates local RNA supports protein synthesis at centrosomes. Isolated basal bodies from Tetrahymena are capable of protein synthesis (Seaman, 1962). Moreover, ribosomes reside in close proximity to centrosomes and basal bodies, as revealed by electron microscopy from intact cells (Figure 2, A and B; Sorokin, 1962). Isolated mitotic spindles from sea urchin, Xenopus, and cultured human cells also contain RNA and ribosomes, highlighting the conservation of these associations (Goldman and Rebhun, 1969; Blower et al., 2007). Immunofluorescence likewise shows ribosomal components near centrosomes (Blower et al., 2007; Sepulveda et al., 2018). These data highlight the intimate association of centrosomes, microtubules, and the translational machinery.

More recently, nascent peptide synthesis was directly visualized at centrosomes in Drosophila embryos and cultured mammalian cells. Puromycylation-proximity ligation assay (puro-PLA) detects nascent translation based on the physical proximity (~40 nm) of puro-labeled ribosomes and a user-specified protein (tom Dieck et al., 2015). Puro-PLA indicates Centrocortin (Cen) mRNA is translated near centrosomes in Drosophila embryos (Bergalet et al., 2020). Another common tool to detect local protein synthesis is through the incorporation of azidohomoalanine (AHA), also known as biorthogonal noncanonical amino acid tagging (BONCAT; Dieterich et al., 2006). Recent work shows AHA-labeled proteins are enriched at centrosomes and along the spindle, consistent with local protein synthesis (Pascual et al., 2020). RNA localization and local protein synthesis is also noted at the base of, and even within cilia (Hao et al., 2021; Kwon et al., 2021). Additional work is required to determine differences in RNA composition and translation state during the basal body-to-centrosome conversion.

For many transcripts, RNA localization to centrosomes requires intact ribosomes. The localization of abnormal spindle-like microcephaly-associated (ASPM/asp), BICD cargo adaptor 2 (BICD2), coiled-coil domain-containing 88C (CCDC88C), Cen, centrosomal protein 350 (CEP350), hyaluronan-mediated motility receptor (HMMR), nuclear mitotic apparatus protein 1 (NUMA1)/mushroom-body defective (mud), and PCNT/plp mRNAs to Drosophila and cultured human cell centrosomes is puromycin sensitive, supporting a model for cotranslational transport (Sepulveda et al., 2018; Bergalet et al., 2020; Chouaib et al., 2020; Safieddine et al., 2021). Cotranslational transport may expedite the rapid influx of PCM components required for mitotic spindle assembly, for example. Alternatively, cotranslational transport may limit interactions among certain proteins until they reach the centrosome to safeguard microtubule organization.

Identification of mRNAs at the centrosome
Classically, subcellular RNA localization is visualized through in situ hybridization (Jeffery et al., 1983). Thus, cyclin B (cyc B) mRNA was first localized to centrosomes within early Drosophila embryos (Raff et al., 1990). Later, studies in Xenopus suggested local cyc B mRNA is important for mitotic progression (Groisman et al., 2000). A genome-wide RNA localization screen similarly detected cyc B and other defined mRNAs at Drosophila centrosomes (Lecuyer et al., 2007). Recent RNA localization screens employing higher resolution and more quantitative single molecule fluorescence in situ hybridization (smFISH; Femino et al., 1998) identified additional mRNAs localizing to centrosomes (Chouaib et al., 2020; Kwon et al., 2021; Safieddine et al., 2021), consistent with work from our own group (Ryder and Lerit, 2020; Ryder et al., 2020). Transcripтомic methods further enumerate the list of RNAs associated with mitotic spindles (Sharp et al., 2011; Hassine et al., 2020). Similarly, high-throughput analyses reveal several human microtubule-associated and centrosome-localized proteins, including Pericentrin (PCNT) and CDK5RAP2, reside in complex with RNA (Doxsey et al., 1994; Fong et al., 2008; Mallam et al., 2019). These data showcase the prevalence of RNA localized to centrosomes and spindle poles. Moreover, many of the RNAs localizing to centrosomes are conserved across divergent species, arguing for evolutionary significance (recently reviewed in Zein-Sabatto et al., 2020). Notably, most mRNAs identified in these screens encode proteins known to localize to and regulate centrosomes, hinting RNA localization to centrosomes and translation are coupled.

TRANSLATION AT THE CENTROSOME
Compelling evidence indicates local RNA supports protein synthesis at centrosomes. Isolated basal bodies from Tetrahymena are contained approximately 2% of total cellular RNA (Seaman, 1960; Argetsinger, 1965; Hoffman, 1965; Hartman et al., 1974). While it was debated whether RNA represented a contaminant following cell fractionation, there was also speculation nucleic acids supported centriole duplication (Seaman, 1968; Sagan, 1967). Thus far, there is no evidence supporting a role for RNA in centriole duplication, a process largely regulated by the conserved Polo-like kinase 4 (PLK4; Bettencourt-Dias et al., 2005; Hagedanck et al., 2005). As we will discuss below, the function of RNA localized to centrosomes remains relatively unexplored.

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FIGURE 2: The intimate association of the translational machinery with microtubules and centrosomes. (A) Reproduction of “Biosites: Cytoplasm, 2005” illustrated by David S. Goodsell; available online (doi: 10.2210/rcsb_pdb/ goodsell-gallery-006). Illustration shows a microtubule filament (light blue, left) juxtaposed to ribosomes (dark blue) synthesizing proteins (pink). (B) Electron micrograph of a rat lymphocyte showing abundant polyribosomes (PR) clustered near the duplicated centrioles from Murray et al. (1965) originally published in Journal of Cell Biology and reprinted with permission from Rockefeller University Press.
Additional evidence for local translation was beautifully demonstrated through live imaging. Translated SunTag sequences are rapidly bound by fluorescent nanobodies, permitting in vivo imaging of active translation when inserted upstream of a protein of interest (Yan et al., 2016). Similarly, SunTag technology permitted detection of cotranslational transport and on-site translation of ASPM and NUMA1 mRNAs at centrosomes (Chouaib et al., 2020; Safieddine et al., 2021). Taken together, these data strongly implicated centrosomes as sites for local translation.

**FUNCTIONAL ROLES OF RNAs LOCALIZED TO CENTROSOMES**

Early attempts to ascribe function to RNA at centrosomes yielded conflicting results. Basal bodies isolated from Chlamydomonas or Tetrahymena and injected into unfertilized Xenopus eggs organized microtubule asters that were RNase sensitive, suggesting RNA promoted the microtubule-organizing activity of centrosomes (Heidemann et al., 1977). Consistent with these findings, microtubule growth and the abundance of PCM from isolated centrosomes proved to be RNase sensitive in other systems, too (Zackroff et al., 1976; Pepper and Brinkley, 1980). Subsequent work contradicted some of these findings, however (Klotz et al., 1990). Consequently, functional roles for RNA localized to centrosomes remained unclear.

Evidence of a likely role for local RNA influencing centrosome function later arose from the Richter laboratory. Groisman and co-workers mutated sites within the cyclin B mRNA 3′-untranslated region (3′-UTR) required for RNA localization to spindle poles. Altering these sites or depleting the activity of the cognate RNA-binding protein, cytoplasmic polyadenylation element binding (CPEB), in Xenopus oocytes led to diminished cyclin B mRNA and protein localization to the spindle pole, spindle defects, and mitotic delays (Groisman et al., 2000). This work suggests local cyclin B mRNA is required for spindle morphogenesis and mitotic progression, perhaps supporting local synthesis of Cyc B protein.

More recently, our group similarly manipulated the RNA-binding protein fragile-X mental retardation protein (FMRP) to investigate consequences for RNA localization and downstream phenotypic responses. Cen mRNA localizes to Drosophila centrosomes, and this localization requires intact polysomes, consistent with a cotranslational localization mechanism (Lecuyer et al., 2007; Bergalet et al., 2020). We identified FMRP, an RNA-binding protein that functions in translational repression (Darnell et al., 2011), in a biochemical complex with Cen mRNA (Ryder et al., 2020). Moreover, loss of Fmr1, the gene encoding FMRP, led to increased Cen mRNA localization to centrosomes and increased Cen protein translation, suggesting Cen mRNA localization and translation are regulated by FMRP (Ryder et al., 2020). Consistently, reducing Cen dosage in Fmr1 mutants partially rescued spindle defects and centrosome separation errors, indicating the titration of local Cen mRNA and/or protein dosage at centrosomes is functionally significant.

To directly test the role of local RNA, we mistargeted Cen mRNA to the anterior cortex of developing Drosophila embryos by fusing the Cen coding sequence with the bicoid (bcd) 3′-UTR (Cen-bcd-3′-UTR embryos), sufficient for RNA localization to the anterior cortex (Macdonald and Struhl, 1988). Mistargeting Cen mRNA to the anterior pole blocked localization of Cen mRNA or protein to distal centrosomes, resulting in phenotypes consistent with Cen loss, including centrosome separation errors and spindle defects (Kao and Megraw, 2009; Ryder et al., 2020). This work shows local Cen mRNA is required at centrosomes for Cen protein localization and function. Ectopic Cen mRNA at the anterior pole also disrupted local microtubule organization and centrosome position, leading to DNA damage, and demonstrating the deleterious effects of excess local Cen activity (Figure 3, A and B). Based on the Cen-bcd-3′-UTR studies, we conclude local dosage of Cen mRNA is finely tuned to ensure normal centrosome function. Going forward, it will be of significant interest to determine whether the local translation of other centrosome-localized mRNAs is likewise required for normal centrosome function.

**FIGURE 3:** Mistargeting Cen mRNA in syncytial Drosophila embryos impairs centrosome function. Schematic shows Cen mRNA and protein localization and associated centrosome-related phenotypes in (A) control and (B) Cen-bcd-3′-UTR embryos. In control embryos, Cen mRNA and protein colocalize as pericentrosomal granules asymmetrically enriched at the mother centrosome. Expression of Cen-bcd-3′UTR within otherwise Cen null embryos, however, results in the ectopic localization of Cen mRNA and protein to the anterior cortex. Mislocalized Cen mRNA and protein also form massive centrosome-enriched granules. In contrast, Cen-bcd-3′UTR embryos lack Cen mRNA or protein at more distal centrosomes near the embryo midregion or posterior. Mistargeting Cen mRNA to the anterior cortex significantly disrupts centrosome function, resulting in defects in centrosome position and centrosome–nucleus tethering. More severe phenotypes consistent with mitotic errors are apparent near the anterior, including disorganized microtubules, supernumerary centrosomes, enlarged and dysmorphic nuclei, as well as nuclear fallout, the ejection of damaged nuclei from the syncytial blastoderm cortex. Consequently, Cen-bcd-3′-UTR embryos also show elevated rates of embryonic lethality. Taken together, these observations indicate the local concentration of Cen mRNA is important for centrosome function and mitotic integrity.
CONCLUDING REMARKS AND OPEN QUESTIONS

Despite historic debate, the localization of mRNA to centrosomes is now irrefutable. Moreover, recent work from independent laboratories and divergent model systems further implicates centrosomes as sites for local protein synthesis. While local translation is predicted to facilitate the rapid increase in PCM proteins intrinsic to centrosome activation before mitotic onset (i.e., centrosome maturation), further work is required to test this model. Indeed, the discovery of RNAs localized to the centrosome far outpaces their functional characterization. To understand the full impact of RNA localized to centrosomes, several critical questions remain to be addressed. The first set of questions relates to identifying which RNAs reside at centrosomes and how they get there. Foremost, for most mRNAs, the molecular machinery required for centrosomal localization, interacting binding partners, and key cis elements required for localization are still unknown. Understanding mechanisms of RNA localization will allow researchers to perturb the process and examine consequences to centrosome function. These investigations will also clarify whether cotranslational transport is generalizable to most centrosome-localized RNAs, as currently suggested by the literature, or whether transport mechanisms are transcript specific. Related to RNA transport, do multiple RNAs cotraffic? Transport particles comprising multiple RNAs may efficiently direct multiple RNA transcripts to a common destination. Also, what regulates the cell cycle dynamics of RNA enrichment to centrosomes, and are these oscillations relevant to centrosome activity or function? How do RNA distributions differ at centrosomes versus basal bodies, or in response to external stimuli? Do changes in RNA distribution contribute to centrosome heterogeneity observed in distinct cell types? Resolving these fundamental questions will allow researchers to better understand how RNA localization influences centrosome composition and frame additional experiments to ascertain biological consequences. Many questions remain pertaining to the biological significance of RNA localized to centrosomes. Why is a specific RNA localized to the centrosome, and does it matter? While evidence supports the idea that some RNAs are subject to translational regulation at the centrosome, as demonstrated for *Drosophila Cen mRNA*, whether this is true for other centrosome-enriched RNAs requires further study. Similarly, details of what regulates translational control at the centrosome, and whether these mechanisms are linked to the cell cycle, are exciting areas of investigation. Do such mechanisms impinge on centrosome maturation, microtubule nucleation, or other processes? Conversely, do RNAs influence centrosome structure? Manipulating RNA localization is one approach to test these ideas. Continued investigation will unearth the answers.

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