# Evolution of the Molecules Coupling mRNA Transport with Translational Control in Metazoans

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## 1 Introduction

Eukaryotes arose from ancestral prokaryotes as a result of profound evolutionary changes at the molecular, metabolic, and morphological levels. These changes resulted in the emergence of novel and more sophisticated levels of cellular architecture. An essential structure of eukaryotes is the cytoskeleton, whose evolution from prokaryotic cytoskeleton proteins allowed novel and fundamental processes such as mitosis, meiosis, inheritance of genetic material, and cellular motility to evolve [1–7]. The emergence of the cytoskeleton also led to the evolution of motors driving intracellular transport to discrete regions of a cell, and these motors are capable of transporting an amazing variety of different cargos, ranging from vesicles and organelles to a plethora of proteins and RNAs required for most cellular processes [1, 2, 7–10]. mRNA transport coupled with translation emerged as a key process of gene expression that targets protein synthesis to specific compartments of cells. In this process, motors act in concert with the cytoskeleton to assemble, stabilize, and transport mRNAs, and this process is also coupled with the control of translation. During their journey translation of mRNAs is repressed, and it is only activated once the mRNAs reach their final destination [11–15].

In this chapter, we will review recent findings that shed new light on the evolution of the molecules involved in translational control of transported mRNAs. To date, regulation of gene expression involving this phenomenon is known for diverse transcripts, and the transport motors as well as diverse proteins involved in this

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process have been characterized to a good extent. While progress has been made across eukaryotes, we will put special emphasis on the processes described in metazoans.

## 2 mRNA Localization Is Coupled with Local Protein Synthesis in Metazoans

Translational control of asymmetrically localized mRNAs allows cells to determine the precise time and place when a protein is synthesized. Upon translational activation, the proteins can be synthesized rapidly because transcription is not required anymore. This posttranscriptional gene expression control underlies many biological processes in metazoans, such as germline development, embryonic axis specification, and embryonic patterning. Additionally, it contributes to various cell differentiation processes, including neurogenesis and synaptic transmission. Some of the first examples of gene expression regulation involving translational control of localized mRNAs were described while studying the embryonic development of *Drosophila* and *Xenopus* [11–17]. The *Drosophila* processes take place during oogenesis and embryogenesis and include *bicoid* (*bcd*), *oskar* (*osk*), and *nanos* (*nos*) mRNAs, which encode the maternal polarity determinants that localize to the anterior and to the posterior cortex of the oocyte, respectively. Their correct localization and translation are crucial for the antero-posterior axis specification of the embryo. Similarly, localization of *gurken* (*grk*) mRNA to the dorso-anterior corner of the oocyte is essential for egg chamber and embryo dorso-ventral axis specification [11–13, 16–18]. Likewise, the early examples from *Xenopus* described that mRNAs encoding the T-box transcription factor VegT and transforming growth factor-beta (TGF-ß) family member, Vg1, localize to the vegetal pole cortex of oocytes and play critical roles in endodermal and mesodermal specification during early embryogenesis [19].

Localization of mRNAs appears to be a generalized phenomenon in metazoans, since a growing number of mRNAs have also been reported to localize in oocytes, eggs, and cleaving embryos of diverse species of vertebrates, cnidarians, and arthropods [13, 20–23]. Indeed, two high-throughput in situ screens in *Drosophila* ovaries and embryos covering 1/4 − 1/3 of the transcriptome revealed that ∼35 and ∼70 % of mRNAs exhibit a differential localization pattern in the developing ovary and embryo, respectively [20, 22, 24]. An extensive correlation between mRNA localization and protein distribution was also observed in embryos, indicating that translation control is tightly regulated during mRNA transport. The high abundance of mRNA localization strongly suggests that most cellular processes are somehow impacted by mRNA localization coupled to translational control [20, 24]. The evolutionary widespread occurrence of transport and translational control of many different mRNAs also illustrates the crucial role of this process in metazoans. For example, in mammalian mesenchymal-like cells, the establishment of front-back

polarity at the proteome level is maintained by localized translation of mRNAs [25]. Surprisingly, although many mRNAs are asymmetrically localized between the cell body and the protrusions, in this study no correlation was detected between the distribution of mRNAs and the corresponding proteins, suggesting that mRNA localization alone is not a significant predictor of protein localization. Differential distribution of mRNAs in polarized cells may be a mean to store repressed mRNAs in order to rapidly activate translation on site upon specific stimuli [25].

Many of the factors involved in coupling transport with translation of homologous mRNAs are conserved in different species. For example, a 54-nucleotide cytoplasmic localization element of the 3′-UTR of *β-actin* mRNA (termed a zipcode) is recognized by zipcode-binding protein 1 (ZBP1), a step that is required for carrying and translating mRNA to lamellipodia of chicken fibroblasts. This event produces an enrichment of actin at the leading edge of cells, which is required for cell motility [26]. Similar phenomena of localized *β-actin* mRNA have been observed for different cell lines from several vertebrates, including developing neurons of rat hippocampus and the *Xenopus* retinal axons where its translation might also be regulated by ZBP1 [14, 27–30]. Moreover, it has been found that ZBP1 inhibits mRNA translation by preventing 80S ribosomal complex formation [31]. In *Drosophila*, Fragile X Mental Retardation Protein (FMR1) also exerts translational control on localized mRNAs. FMR1 forms a complex with Argonaute 2 (AGO2), an essential component of the RNA-induced silencing complex (RISC) [32], and with the ribosome to directly block translation by inhibiting tRNA association [33]. FMR1 is also able to function as a translational activator [34]. dFMR1 not only regulates translation but also controls the efficacy of mRNA transport in neurons [35] In mammalian neurons, FMRP colocalizes and coimmunoprecipitates with subsets of dendritically localized mRNAs [36]. FMRP knockdown enhances protein synthesis of some localized mRNAs in mice and interferes with DHPG trafficking of specific mRNAs in neurons, indicating that FMRP promotes transport and regulation of local translation of mRNAs at the synapses [35, 36].

## 3 Origin of Cytoskeleton and Molecular Motors

The highly sophisticated organization of eukaryotic cells was made possible by the evolutionary emergence of protein motors that facilitate trafficking between different cellular compartments. Molecular motors carry a plethora of cargoes such as RNAs, proteins, organelles, and diverse macromolecular complexes to a variety of destinations within the cytoplasm. To do so, motors travel directionally along the tracks of a dynamic and extremely elaborate system of intracellular polymers termed a cytoskeleton, which is also responsible for maintaining the shape and the mechanical dynamics of the cell [37].

In all extant eukaryotes, cytoskeletal elements involved in the transport of cargo consist of two major types of structural components: tubulins form microtubules

(MT) [37, 38], whereas actins form actin filaments (AF) [37, 39]. Unlike MT and AF, a third class of cytoskeletal elements, the intermediate filaments (IFs), lack structural directionality and cytomotiliy, and no motor proteins have been found associated with them [37, 40].

MT and AF evolved from prokaryotic homolog filaments. Indeed, both bacteria and archaea are endowed with cytomotive cytoskeletons that can function as motors because of the kinetics of polymerization/depolymerization itself [41]. Bacteria and archaea possess genes encoding clear homologs of tubulin and actin, namely FtsZ, TubZ, and RepX for tubulin (being FtsZ the nearest extant relative), and MreB and FtsA families for actin, the latter playing critical roles in prokaryotic plasmid segregation and cell shape and septation [1–4, 6, 7, 42, 43]. Regarding the origin of cytoskeleton proteins, on one hand highly conserved orthologs of tubulins have only been found in the genomes of archaeal species of the *phylum* Thaumarchaeota [1, 5, 7, 44, 45]. On the other hand, actin and its prokaryotic homologs MreB and FtsA belong to a large superfamily of ATPases present in all three domains of life. Recently, phylogenomic analyses have discovered proteins with high similarity to eukaryotic actins in archaeal species of the *phylum* Crenarchaeota. Accordingly, they are dubbed "crenactins." Altogether, these findings support the emerging view that the two major components of the eukaryotic cytoskeleton have archaeal origins [5, 43] and that the *l*ast *c*ommon *e*ukaryotic *a*ncestor (LECA) possessed an established, complex cytoskeleton composed of multiple paralogs of the tubulin (FtsZ/TubZ) and actin (MreB/crenactin) families of proteins [1–7, 42, 43].

It appears that the ability of cargo-carrying molecules was strongly augmented in eukaryotes by the mergence in early eukaryotic evolution of molecular motors that function in coordination with the cytoskeleton [1, 3, 7, 8, 46]. However, it is intriguing that prokaryotes possess only cytoskeletal cytomotive polymers while no good candidate motor protein has been found yet. Eukaryotes evolved three major superfamilies of motors that drive transport of mRNA cargoes. These are kinesins and dyneins, which work along MTs, and myosins that work along AFs. Thus, numerous kinesins, myosins, and dyneins have evolved to cope with the much more sophisticated needs that have arisen during eukaryotic evolution. Even though we do not know the origin of motors, kinesins and myosins share a common ancestor. Dyneins belong to the large AAA+ superfamily of proteins and most likely evolved from multiple duplication events of a single AAA+ domain before LECA. Some evidence suggests that the closest relative prokaryotic protein is MoxR, but it does not possess any motor activity. The ubiquitous distribution of different paralogous proteins of all three motors across eukaryotes supports the notion that LECA already possessed several families of all three motor types working along with an established cytoskeleton. However, multiple losses of paralogs of the three families of motors happened during eukaryotic diversification. After eukaryotes emerged, the ancient "toolbox" of motors expanded into a wide battery of motors coupled with different and additional cargo-bound "receptor" proteins, each designed to carry distinct and specific cargoes [1–4, 7, 9, 10].

## 4 The *Drosophila* BicD/Egl/Dynein Machinery Paradigm

The *Drosophila* BicD/Egl/Dyn complex is arguably one of the best-studied mRNA transport machineries. It plays a key role in oogenesis and embryogenesis by localizing a plethora of mRNAs required for cell determination, differentiation, and formation of the anterior-posterior and dorsal-ventral axes. This machinery is composed of BicD and Egalitarian (Egl) proteins, which interact with the motor dynein (Dyn)/dynactin to transport mRNA cargoes along the microtubule cytoskeleton to specific cellular compartments. To form the complex, Egl interacts directly with both BicD and Dyn, as well as with transported mRNAs [11, 13, 47–50]. BicD/Egl/dynein complex may work in conjunction with additional proteins that confer specificity and, at the same time, translational control.

Genetic and biochemical studies have provided evidence of the *Drosophila* BicD/Egl function in mRNA transport. During oogenesis, a single germline cell produces a cluster of 16 interconnected cells of which one differentiates into an oocyte. In parallel, the remaining 15 germline cells differentiate into nurse cells that provide the oocyte with all the material required for growth and differentiation. This process includes the transport into the oocyte of a subset of mRNAs produced in the nurse cells. *BicD* loss-of-function mutant females produce a germline that is composed only of cells with nurse cell appearance, indicating that *BicD* is essential for oocyte differentiation. *BicD* mutant egg chambers also fail to accumulate oocyte-specific mRNAs [such as *osk*, *orb, BicD* and *fs(1)K10*] in the oocyte. Thus, it is suggested that the loss of oocyte differentiation may be due to a failure in the transport of oocyte-specific proteins and mRNAs from the nurse cells into the oocyte [51, 52]. Ovaries mutant for *egl* as well as wild-type ovaries treated with microtubule disrupting drugs show the same 16-nurse-cell phenotype as *BicD* mutants [53, 54]. Studies using fluorescently labeled *grk* and *bcd* mRNAs injected into the nurse cells have shown that BicD and Egl are recruited to these mRNAs and that these genes are required for *grk* transport into the oocyte [55]. This study also revealed that transport along MTs requires Dyn for efficient localization of *grk*, *bcd*, and *osk* mRNAs from the nurse cells into the oocyte [55]. Moreover, the BicD/Egl/Dyn machinery is not only active in the germline, but is also used for the apical localization of *inscuteable* mRNA in neurons [56] and for apical localization of mRNAs from several segmentation genes in blastoderm embryos [57].

A recent NMR study on the *K10* mRNA localization signal showed that it folds in a special A'-form RNA conformation that is also found in the stem loops responsible for localization of other BicD/Egl targets, namely, *ftz, h, grk, wg, bcd, I-factor,* and *osk* mRNAs, suggesting that they are all recognized directly by Egl [58, 59]. However, whether Egl is a general link for all mRNAs transported by the BicD/Egl/Dyn machinery or whether other proteins are required for cargo specificity is not known.

## 5 The Importance of Being *Oskar*

*Drosophila osk* gene expression has been one of the most studied models of translation control during mRNA transport, becoming a paradigm for this phenomenon. Localization of *osk* mRNA to the posterior of the oocyte proceeds by the action of the BicD/Egl/Dyn transport motor that imports the mRNA from nurse cells into the oocyte [55, 57, 60–64]. Then, *osk* mRNA switches to a kinesin-based motor that transports it towards the posterior cortex. Kinesin heavy chain (KHC) and the kinesin light chain (KLC)-like protein PAT1 are required for this process. While kinesin is involved in the long-range MT-based transport of *osk* mRNA throughout the oocyte, there is evidence that *osk* mRNA localization is followed by a myosin-V-dependent short-range actomyosin translocation of *osk* mRNA at the posterior cortex [65].

During its journey, the translation of *osk* mRNA is repressed until it reaches its final destination at the oocyte posterior cortex after stage 8 of oogenesis. Mutants in *armitage* (*armi*), *aubergine* (*aub*), *spindle-E* (*spn-E*), *maelstrom* (*mael*) [66], *zucchini* (*zuc*), *squah* (*squ*) [67], and *krimper* (*krimp*) [68] show premature translation of *osk* mRNA in the oocyte during early oogenesis. It is therefore possible that translational silencing of *osk* mRNA during these stages is driven by piRNA-Piwi-Argonaute complexes interacting with *osk* mRNA. Alternatively, the reduced activity of any of these proteins coupled with the higher expression of mobile genetic elements might titrate the repressors of *osk* mRNA translation. Other proteins are also involved in exerting *osk* mRNA translational repression. As opposed to wild types, egg chambers mutant for the *Maternal expression at 31B* (*Me31B*) gene show ectopic Osk protein accumulation in the nurse cells rather than in the oocyte during early oogenesis, indicating that Me31Bs normally repress *osk* translation during its transport through the nurse cell into the oocyte [69].

During oogenesis, polypyrimidine tract-binding protein (PTB) mediates assembly of high-order complexes containing multiple *osk* RNAs, and this causes translational silencing [70]. A complex made up by Bruno (Bru) and Cup represses cap-dependent translation of *osk* mRNA from stage 5-6 onwards [71]. Bru binds simultaneously to Bru-response elements (BRE) in *osk* 3′-UTR and to Cup, which in turn binds eIF4E, thereby inhibiting recruitment of the small ribosomal subunit to *osk* mRNA [71]. Accordingly, egg chambers expressing mutant Cup unable to bind eIF4E show precocious expression of *osk* mRNA in stages 6–9 as well as increased expression in stage 9 oocytes. Another mechanism is independent of the Cup-eIF4E interaction, but still depends on Bru. This one causes translation repression during mid oogenesis, and it also involves the formation of Bru-dependent *osk* mRNA oligomers, which, bound to Bru, form large silencing complexes that cannot be accessed by ribosomes [72]. Finally, the *Drosophila* hnRNPA/B homolog (hrp48) binds sequences in the *osk* 5′- and 3′-UTRs, being involved in localization and translational repression of *osk* mRNA after stage 9 of oogenesis [73].

Interestingly, Cup is also involved in translational repression of *grk* mRNA, which is also transported by the BicD/Egl complex. A model for translation

regulation of *grk* mRNA during its transport has been put forward in which both Cup and Bru also function in complex with Sqd, out, and Hrb27C/Hrp48 [74]. It was shown that that before *grk* RNA reaches its final destination at the dorsal-anterior region of the oocyte, a well-established translation factor, poly(A)-binding protein (PABP), functions with Encore (Enc) to facilitate translational activation of *grk* mRNA [74].

Our research group has reported that *Drosophila Pabp* interacts genetically and biochemically with *BicD* and that the biochemical interaction depends on RNA [75]. *Pabp* mutants show both reduced stability and mislocalization of *osk* mRNA during early oogenesis, demonstrating that PABP plays a key role in *osk* mRNA localization [75]. Although there is no evidence for PABP involvement in *osk* mRNA translational control during early oogenesis, it might be possible that PABP activates *osk* mRNA translation after it has reached its final destination during late oogenesis. All in all, Cup, Me31B, PTB, PABP, IMP, Bru, and Hrp48 are factors that can associate with the BicD/Egl/Dyn motor to regulate the fate and translation of *osk* and of other transported mRNAs as well.

## 6 Evolution of the BicD/Egl/Dyn Complex

Recent studies in the wasp *Nasonia vitripennis* have shown a conserved role of BicD in mRNA localization and organization of a polarized microtubule network during oogenesis in non-dipteran insects [76]. *Drosophila* and *Nasonia* share a similar germline development, even though they diverged over 200 million years ago. Although a role of BicD in mRNA transport in other *phyla* has not been described yet, BicD are coiled-coil protein adaptors linking the Dyn/dynactin minus-end-directed motor complex with different cargos [13, 47, 49, 77]. Because of this versatility *Drosophila* BicD does not only perform mRNA localization, but is also involved in the transport of other cargoes, such as clathrin, synaptic vesicles at the neuromuscular junction, lipid droplets, and even nuclei of photoreceptor cells and oocytes, [13, 47, 49, 77, 78].

A conserved role of BicD in neuronal development in other species is supported by several recent findings. Like *D. melanogaster BicD*, *C. elegans* BicD is also involved in nuclear migration and in neuron branching [79, 80], while the mammalian BicD1/Rab6 complex regulates COPI-independent Golgi-ER transport as well as retrograde membrane transport in human neurons [47, 49, 78]. Furthermore, *BicD2*-deficient mice show impaired radial neuronal migration [81], suggesting that *BicD2* is linked to cargo trafficking also in glial cells. In a similar way, mouse BicD1 was recently shown to modulate endosomal trafficking and signaling of ligand-activated neurotrophin receptors in motor neurons [82]. Furthermore, mutations in human *BicD2* have been shown to cause congenital autosomal-dominant spinal muscular atrophy and hereditary spastic paraplegia in humans [83–85]. These mutations cause BicD to bind more strongly to dynein/dynactin complexes and to produce Golgi fragmentation, which may result in defects in neuronal cargo

trafficking and impairment of neuron outgrowth. Altogether, these findings highlight the essential and conserved role of *BicD* in nervous system development and physiology. It appears to perform the same function across metazoans by regulating different cargo trafficking needed for polarizing nerve and glial cells.

The *BicD* gene is conserved throughout metazoans, but is not present in other eukaryotes. Like in *Drosophila*, mammalian orthologs of BicD bind directly to components of the Dyn and dynactin complexes [86]. While there is only one gene encoding BicD in insects, *C. elegans*, and some ascidians, the gene is duplicated in various vertebrates including humans. In the amphibian *Xenopus,* one *BicD1* and two *BicD2* homologs are present. Interestingly, the fishes *Danio rerio, Gasterosteus aculeatus, Oryzias latipes, Takifugu rubripes,* and *Tetraodon nigroviridis* have two homologs of the *BicD1* gene and two homologs of *Bic-D2*. In addition, in fishes there is also a third, deeply divergent gene, probably representing an ancestral version of the *BicD* gen. The sea lamprey *Petromyzon marinus* has also two *BicD* genes, one *BicD1* ortholog and one that could also be close to the ancestral *BicD* gene [13, 47, 87–89]. Two shorter BicD-related genes, BicDR1 and BicDR2, contain only two coiled coil regions and have been described in mammals and other vertebrates. These cognate genes are involved in neural development in *Zebrafish* [90]. Despite both genes being conserved in vertebrates, only BicDR1 is present in flies. Like BicD1/2, BicDR1 also binds Rab6. The highest degree of similarity to BicD is in the cargo-binding domain at the C-terminus of BicDR.

Egl is present in many arthropods and in *C. elegans*. As in *Drosophila*, studies on the giant tiger shrimp (*Penaeus monodon*) *egl* ortholog gene have suggested an involvement of Egl in ovary development as well [91]. In contrast to BicD, a clear Egl homolog has not been identified in mammals. Thus, it is possible that different, so-far unidentified adaptor proteins not related to Egl might link the BicD/Dyn localization motor to localized mRNAs in other *phyla* [13].

Several RNA-binding proteins present in *Drosophila* BicD complexes, such as PABP [75], FMRP [92], and the insulin-like growth factor II mRNA binding proteins (IMPs; Vazquez-Pianzola, Bullock and Suter, unpublished), are highly conserved across eukaryotes. Cytoplasmic PABP is a translation factor that is present in all eukaryotes and that has diversified in multiple gene families. Indeed, cytoplasmic PABP proteins are involved in different processes of RNA metabolism, including mRNA stability, transport, and translation [93–98]. To date, most functional studies have been focused on the prototype PABP1. However, the versatility and high number of genes encoding PABPs in different species point to the possibility that distinct PABPs might regulate the localization and/or translation of different localized mRNAs. Interestingly, PABPs have been found to bind not only to the poly(A) tail of mRNAs, but also to A-rich sequences in the UTRs of *osk*, *bcd*, and *Vasopressin* mRNAs, and their binding is critical for proper mRNA localization in *Drosophila* oocytes and mammalian neurons, respectively [75, 99–102]. These additional binding sites further contribute to the versatility of PABPs.

In addition to Egl, another RNA-binding protein has been reported to link mRNAs with BicD and FMR1 [92], and this function was implicated in branching

of the dendritic arbor [92]. FMRP regulates mRNA transport and also functions as a negative regulator of translation [36]. While the three vertebrate paralogs, FMR1, FXR1, and FXR2, share a conserved gene structure derived from a common ancestral gene, *Drosophila* and most invertebrates possess a single ortholog with high overall similarity to human FXR2 [103–105]. Thus, as opposed to Egl, FMRP is conserved in vertebrates and invertebrates opening the possibility that FMRP/BicD complexes regulate RNA transport and translation in higher eukaryotes.

IMPs form a family of RNA-binding proteins highly conserved across the animal kingdom. In *Drosophila*, IMP is required for translational control of localized *osk* and *grk* mRNAs [106, 107]. Chicken IMP1, also known as ZBP-1, is required for *beta-actin* mRNA localization and translational repression during transport to the leading edge of motile fibroblasts and neurons. In *Xenopus*, IMP is required for localization of *Vg1* mRNAs to the oocyte vegetal pole during maturation [108, 109]. Preliminary results from our laboratory indicate that *Drosophila* IMP also forms a complex with BicD/Egl during specific developmental stages (Vazquez-Pianzola, Bullock and Suter, unpublished). Because most invertebrates, including *D. melanogaster, C. elegans*, and different ascidian species, are endowed with only one *IMP* gene, whereas most vertebrates possess more than one paralog, it appears that the vertebrate IMP family originated from repeated gene duplications shortly after the divergence of these two lineages. Most vertebrates (i.e., humans, rats, mice, birds, and reptiles) contain three IMP paralogs, namely IMP1, IMP2, and IMP3. Interestingly, *Gorilla* and the fish *D. rerio* have four orthologous *IMP* genes, the additional one being most closely related to mammalian IMP2. On the other hand, the frog *Xenopus tropicalis* contains only one *IMP* gene, an ortholog of mammalian IMP3 [87–89].

Dyneins are microtubule-based motor complexes consisting of a core of heavy chains (HCs) that contain the motor domains, associated with a variety of smaller subunits termed intermediate, light intermediate, and light chains, which can interact with diverse cargoes [2, 10, 77, 110]. In comparison to lower eukaryotes, metazoans have expanded the number of multifunctional adaptors associated to dyneins, including dynactin, nuclear distribution protein E, lissencephaly 1, Spindly, and BicD, among others. This has led metazoan dyneins to play a role in a large diversity of activities, such as mitotic spindle assembly, apoptosis, centrosomal protein transport, chromosome segregation, and the transport of diverse cargoes such as mRNAs, viruses, organelles, signaling molecules, and intermediate filaments.

Dynein HCs comprise a large eukaryotic family of proteins [2, 10, 77, 110]. Phylogenomic analyses of hundreds of genomes have established the notion that LECA was endowed with at least nine distinct types of dynein HCs [46, 111] and that further diversification of eukaryotes led to multiple duplication of the dynein repertory in most phyla but also to lineage-specific losses in some others [2, 46, 111, 112]. For example, higher plants are devoid of dynein genes and use primarily myosin motors; *Entamoeba* and red algae also have independently lost all dyneins. In contrast, the unicellular parasite *Giardia* contains many dynein and kinesin

genes, but no myosins [2, 46, 113], and ciliates encode more dynein HC genes than most eukaryotes thus far analyzed [114]. The *chlamydomonas*, sea urchin, and human genomes possess between 14 and 16 dynein HC genes.

While all sequenced species of arthropods [112], including 12 *Drosophila* species, contain only one copy for each gene encoding a dynactin subunit, they contain a highly variable repertory of dynein heavy chains, and different numbers of light chains, which allows these species to form a large variety of dynein complexes for many cargoes [112]. All *Drosophila* species have the largest number and most divergent set of light chains [112].

The high conservation of BicD proteins and the associated dynein/dynactin motors in the animal kingdom suggests that BicD orthologs have played a conserved role in the transport of diverse cargoes, including mRNAs. Other proteins that are needed for mRNA localization have been found associated with BicD, and they are conserved throughout evolution. The future will show whether the human BicD orthologs have lost their ability to transport mRNAs or whether this function and its mRNA adaptor have simply not been discovered yet.

## 7 Concluding Remarks

To cope with the high sophistication of cell architecture, eukaryotes evolved two cytoskeletons that also serve as tracks for molecular motors. These are filamentous actin and microtubules. A limited number of molecular motors, myosins, kinesins, and dyneins, associate with a wide array of adaptors to gain specificity for many different cargoes. This provides the cells with the opportunity to evolve cargo-specific regulatory controls [2]. One example is the BicD/Egl complex in *Drosophila*, which exerts mRNA localization coupled with translational control of various mRNAs and which is crucial for oogenesis and embryogenesis. However, despite their importance, only a few cargo-specific adaptors for dynein have been studied so far [77]. Moreover, studies on which proteins regulate the translation of the majority of localized mRNAs are still missing. Since dynein-based motors function in the transport of a plethora of disparate cargoes, many more dynein adaptors as well as additional proteins controlling translation may still await their discovery.

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