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Review

Translational regulation of the cell cycle: when, where, how and why?

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Translational regulation contributes to the control of archetypal and specialized cell cycles, such as the meiotic and early embryonic cycles. Late meiosis and early embryogenesis unfold in the absence of transcription, so they particularly rely on translational repression and activation of stored maternal mRNAs. Here, we present examples of cell cycle regulators that are translationally controlled during different cell cycle and developmental transitions in model organisms ranging from yeast to mouse. Our focus also is on the RNA-binding proteins that affect cell cycle progression by recognizing special features in untranslated regions of mRNAs. Recent research highlights the significance of the cytoplasmic polyadenylation element-binding protein (CPEB). CPEB determines polyadenylation status, and consequently translational efficiency, of its target mRNAs in both transcriptionally active somatic cells as well as in transcriptionally silent mature *Xenopus* oocytes and early embryos. We discuss the role of CPEB in mediating the translational timing and in some cases spindle-localized translation of critical regulators of *Xenopus* oogenesis and early embryogenesis. We conclude by outlining potential directions and approaches that may provide further insights into the translational control of the cell cycle.

Keywords: cyclin–CDK; mitotic spindle; meiosis; oocyte; polyadenylation; cytoplasmic polyadenylation element-binding protein

1. INTRODUCTION

During S phase of the archetypal cell cycle (defined as G1–S–G2–M cell cycles), DNA is replicated, and during M phase the replicated sister chromatids are distributed into two daughter cells. The periods of DNA replication and segregation are separated by the G1 and G2 gap phases, when the cell grows and evaluates its internal and external environment [1]. Variant cell cycles are used to achieve developmental strategies [2–4]. Chromosome number is reduced by meiosis, a modified cell cycle in which two rounds of chromosome segregation follow a single round of DNA replication. In organisms with rapid embryogenesis, such as amphibians, insects and marine invertebrates, maternal stockpiles permit omission of gap phases, so division is driven by oscillations between S and M phases.

Cyclin-dependent kinases (Cdks) and their activators, Cyclins, drive progression through the cell cycle. Although levels of Cdks remain constant throughout the cell cycle, their activities oscillate, mostly owing to complex cell cycle-dependent phosphorylation events and changes in the abundance of Cyclins [5]. Transcriptional activation contributes to accumulation of Cyclins when they are needed to orchestrate entry into a new cell cycle phase [6,7]. Ubiquitin-mediated proteolytic destruction of Cyclins is required for proper cycling [8].

Translational control also plays an important role in regulating progression through the archetypal and variant cell cycles. Below, we discuss in detail known examples and mechanisms of translational regulation during cell cycle progression, as well as the biological context dictating a requirement for translational regulation. Here, we briefly introduce the rationale for translational regulation.

In the archetypal cycle, control at the translational level may allow faster accumulation of necessary cell cycle players compared with transcriptional regulation of gene expression [9]. Translational regulation additionally coordinates cell cycle progression with growth. Because progression through the cell cycle is linked to the attainment of certain size, translational regulation of gene expression couples cell growth and cell cycle progression with the supply of nutrients in the cell's environment [10]. Important signal-transduction pathways linking regulation of protein synthesis to nutrient sensing are mitogen-activated protein kinase and target of rapamycin signalling cascades. However, as the connection of these signalling pathways to translational regulation and cell growth has been extensively reviewed, they will not be further discussed here (for more information see reviews [11–14]).

Proper execution of specialized cell cycles in various developmental contexts also relies on translational regulation. Progression through meiosis and early embryogenesis is driven by highly ordered, sequential

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translational activation of previously repressed maternal transcripts [15]. Meiotic progression through prophase I may depend on translational regulation, because the chromosomes are engaged in homologous recombination, leading to their remodelling and consequent transcriptional shutdown.

Translational control is crucial for proper embryonic development owing to several reasons. First, early embryonic divisions are transcriptionally silent; one division in the mouse and 13 divisions in *Drosophila* occur in the absence of zygotic transcription. It has been hypothesized that the absence of transcription during early embryogenesis serves to give embryos time to switch from the maternal gene-expression programme to the markedly different programme of the zygote [16,17]. In addition, transcriptional repression of the early embryo may be required to preserve totipotency until the onset of differentiation. Second, in many organisms, translational control of maternally loaded mRNAs drives the rapid S–M cycles [3]. Third, early embryonic development in *Drosophila* and *Caenorhabditis elegans* requires establishment of body axes, a process largely dependent on spatially controlled translation of maternal morphogens [18,19]. Spatially restricting protein synthesis is an efficient way to localize a protein to a certain subcellular domain, as transcription can occur only in the nucleus [20]. Importantly, interfering with the spindle-localized translation of several cell cycle regulators blocks progression through *Xenopus* oogenesis and early embryogenesis [21,22].

In this review, we illustrate known examples of cell cycle players whose translation is regulated temporally and sometimes spatially during either archetypal or specialized cell cycles (summarized in table 1). In addition, in our concluding remarks, we will address some ideas and potential approaches for future research on the interplay between cell cycle control and translational regulation.

2. BACKGROUND

We begin with an outline of the basic translational initiation machinery used in archetypal and specialized cell cycles (figure 1). Translation, the process in which a ribosome 'converts' the sequence of an mRNA into a polypeptide, occurs through the phases of initiation, elongation and termination. Translational initiation is the rate-limiting and the most regulated step of translation [9]. During translational initiation, an 80S ribosome assembles on the start codon of mRNA. Translation during interphase and gap phases is cap-dependent, meaning that prior to loading, the pre-initiation complex must recognize a modification at the mRNA's 5′ end known as the 7-methylguanosine cap structure [9,45] (figure 1*a*). During mitosis, cap-dependent translation is inhibited, so the ribosome accesses mRNAs independently of the cap-binding protein eIF4E. It is believed that under conditions of repressed cap-dependent translation, including mitosis, a *cis*-regulatory element known as the internal ribosome entry site (IRES) recruits the ribosome to the mRNA through the IRES-*trans*-acting factors (ITAFs) [45,46]. Although IRES-mediated ribosomal recruitment is independent of eIF4E, it still requires other initiation factors [47,48] (figure 1*b*).

The first step in cap-dependent translation is the binding of the 5′ cap structure to the eIF4F complex composed of the cap-binding protein eIF4E, an RNA helicase eIF4A and the scaffolding protein eIF4G [49] (figure 1*a*). eIF4G may support mRNA circularization by interacting both with eIF4E that binds to the cap and with the poly(A)-binding protein (PABP), which coats the 3′ poly(A) tail of an mRNA [50,51]. This closed-loop model of translation proposes that mRNA circularization promotes translation [52]. The RNA helicase eIF4A, supported by its accessory proteins eIF4B and eIF4H, unfolds secondary structures in the mRNA's 5′ untranslated region (UTR) [49]. Unwinding of the 5′ UTR facilitates the interaction between mRNA and the 43S pre-initiation complex, a complex of the 40S small ribosomal subunit and specific associating factors. The 43S pre-initiation complex scans the mRNA until it reaches the start codon, where it is joined by the 60S large ribosomal subunit to form the 80S ribosome. Subsequent attachment of a methionyl-tRNA to the mRNA's start codon marks the completion of initiation and leads to the onset of the elongation phase.

3. TRANSLATIONAL REGULATION OF CELL CYCLE TRANSITIONS IN MITOTIC CELLS

Timely expression and activation of central regulators are required for cell cycle progression [53]. In recent years, it has been also recognized that translational regulation, exerted mainly at initiation, contributes to controlling the levels of key cell cycle players (table 1) [45,53,54]. Accumulation of most translationally controlled cell cycle regulators is assured through particular *cis*-regulatory elements. These elements are usually located in the 5′ UTRs and serve to increase translational initiation efficiency by selectively binding specialized *trans*-acting factors [55]. As will be discussed below, various specialized initiation factors have evolved in organisms ranging from yeast to humans to support the accurate translational initiation of proteins important for regulating major cell cycle events, such as the G1–S and G2–M transitions, as well as mitotic progression.

(a) *G1–S transition*

In *Saccharomyces cerevisiae*, translational control contributes to the G1–S progression, as mutants of initiation factors Cdc33 (eIF4E homologue) and Prt1 (eIF3η, a 43S pre-initiation complex component homologue) arrest in G1 [23,56–58]. Cdc33 is required in G1 to stimulate the synthesis of Cln3, a very unstable protein with a low translation rate [59]. Cln3, a G1 Cyclin that couples growth to cell cycle progression, is limiting for the G1–S transition [60]. During slow growth, a repressive element identified as an upstream open reading frame (uORF) in the long 5′ UTR of Cln3 reduces the number of pre-initiation complexes that can reach the start codon. In rich medium, however, an increase in the number of pre-initiation complexes allows bypass of the uORF and activation of Cln3 translation. This activation results in a more efficient accumulation of Cln3 and faster entry into S phase [23].

Table 1. Translationally controlled cell cycle regulators. *Trans*-acting factors mediating translational activation are shown in bold.

cell cycle event	cell cycle regulator	repression (rep.)/ **activation (act.)**	organism	*cis*-element	identified *trans*-factors	reference
mitotic cell cycle; G1–S transition	Cln3	**Act.**	*S. cerevisiae*	uORF	**Cdc33**	[23]
	Cyclin E	**Act.**	HeLa cells	complex 5′ UTR	**DDX3**	[24]
	Cig2	**Act.**	*S. pombe*	long 5′ UTR	**Ded1**	[25]
mitotic cell cycle; G2–M transition	Cdc13	**Act.**	*S. pombe*	long 5′ UTR	**Ded1**	[25]
	Cdc25	**Act.**	*S. pombe*	uORFs; complex 5′ UTR	**eIF4A**	[26]
	Cdk11	**Act.**	mammalian cell culture	IRES	**Upstream of N-Ras**	[27]
mitosis-to-meiosis transition	Cyclin E	Rep.	*C. elegans*	3′ UTR	GLD-1	[28]
maintenance of meiosis	Cyclin A	Rep.	*Drosophila*	3′ UTR (BRE)	Bruno	[29]
pachytene progression	SCP1	**Act.**	mouse	3′ UTR (**CPE, HEX**)	**CPEB**	[30]
	SCP3	**Act.**	mouse	3′ UTR (**CPE, HEX**)	**CPEB**	[30]
oocyte maturation	Ringo	Rep./**Act.**	*Xenopus*	3′ UTR (PBE)	Pum2, DAZL, ePAB	[31]
	Mos	Rep./**Act.**	*Xenopus*	3′ UTR (**CPE, HEX**)	**CPEB**	[32]
	Cyclin B	Rep./**Act.**	*Xenopus*	3′ UTR (PBE, **CPE, HEX**)	Pum2, **CPEB**	[33]
	CPEB4	Rep./**Act.**	*Xenopus*	3′ UTR (ARE, **CPE, HEX**)	**CPEB1**	[34]
	C3H-4	Rep./**Act.**	*Xenopus*	3′ UTR (**CPE, HEX**)	**CPEB**	[35]
	Cyclin B1	Rep./**Act.**	zebrafish	3′ UTR (**CPE**)	unknown	[36]
spermatocyte G2–M transition	Cyclin B	**Act.**	*Drosophila*	not tested	**eIF4G2**	[37]
	Cdc25 phosphatase (Twine)	**Act.**	*Drosophila*	most likely 3′ UTR	**eIF4G2**, **Boule**	[38]
	HSPA2	**Act.**	mouse	not tested	**eIF4g3**	[39]
meiosis II	Clb3	Rep. in meiosis I/ **Act. in meiosis II**	*S. cerevisiae*	5′ UTR	unknown	[40]
egg activation	Cyclin A	**Act.**	*Drosophila*	3′ UTR	**GLD-2, PNG kinase**	[41,42]
	Cyclin B	**Act.**	*Drosophila*	3′ UTR	**GLD-2, PNG kinase**	[42,43]
early embryo	Cyclin B	**Act.**	*Xenopus*	3′ UTR (**CPE, HEX**)	**CPEB**	[3]
	Cyclin B	Rep./**Act.**	*Drosophila*	3′ UTR (NRE-like)	PUM, **PNG kinase**	[43]
maternal–zygotic transition	Cyclin B	Rep.	*Drosophila*	3′ UTR	dFMRP, Caprin, eIF4G	[44]

The G1–S transition in HeLa cells is facilitated by a member of the DEAD (named after conserved residues Asp (D)–Glu (E)–Ala (A)–Asp (D))-box family of RNA helicases, DDX3 [24]. The *cyclin E1* mRNA may be the main translational target of DDX3, because the G1 arrest caused by DDX3 knockdown can be rescued by Cyclin E1 expression [24]. Notably, the *cyclin E1* 5′ UTR has a high guanine–cytosine content and could form a stable secondary structure. This observation provides an explanation for why this mRNA needs a specialized helicase to unwind its 5′ UTR, allowing for more efficient ribosomal scanning during initiation [24,61].

Another DEAD-box family RNA helicase, Ded1, regulates both the G1–S and the G2–M transition in *Schizosaccharomyces pombe* [25]. Loss-of-function *ded1* mutants phenocopy B-type Cyclin mutants. Importantly, in *ded1* mutants, levels of the G1–S B-type Cyclin, Cig2, and G2–M B-type Cyclin, Cdc13, are reduced independently of

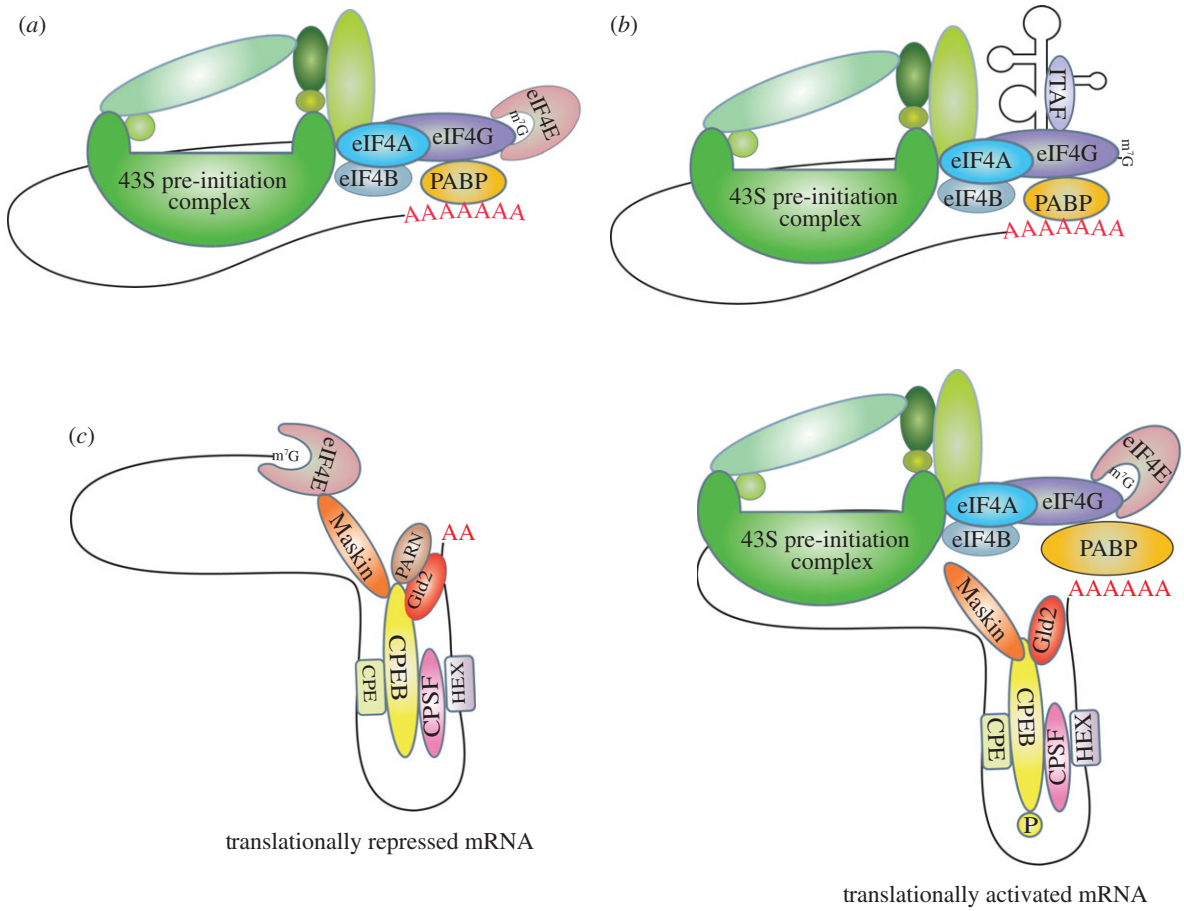


Figure 1. Translational initiation during progression through the archetypal and specialized cell cycle. (*a*) During archetypal cell cycles, with the exception of M phase, translation is cap-dependent and is initiated by a cap-binding protein, eIF4E, binding to the 7-methylguanosine cap structure at the 5′ end of mRNA. Subsequently, eIF4E recruits eIF4G, which further associates with eIF4A. The RNA helicase activity of eIF4A is supported by its accessory proteins, eIF4B (or eIF4H, not shown). The eIF4A can only bind one of its auxiliary proteins at a time, because these interactions are mutually exclusive. Upon binding of eIF4G to the poly(A) binding protein (PABP), mRNA circularizes. This closed-loop mRNA structure may facilitate recruitment of the multi-subunit 43S pre-initiation complex (40S small ribosomal subunit and at least five additional factors; subunits are shown in different shades of green) to the mRNA. The interaction between eIF4G and one of the subunits of the 43S pre-initiation complex ultimately brings the pre-initiation complex to the mRNA. (*b*) During mitosis, translational initiation is cap-independent. The 5′ UTRs (and occasionally ORFs) of mRNAs translated during mitosis are thought to carry an internal ribosome entry site (IRES). It is proposed that the IRESs often assume a complex secondary structure and recruit 43S pre-initiation machinery with the help of IRES-*trans*-acting factors (ITAFs). (*c*) Schematic of translational regulation during *Xenopus* oocyte maturation. The left panel shows translationally repressed mRNAs in immature *Xenopus* oocytes. In immature oocytes, mRNAs that contain cytoplasmic polyadenylation element (CPE) in their 3′ UTRs interact with CPE-binding protein (CPEB), which associates with an eIF4E-binding protein, Maskin. Maskin inhibits interaction between eIF4E and eIF4G, thereby blocking recruitment of the 43S pre-initiation complex to mRNA. Simultaneously, CPEB binds to the poly(A) polymerase Gld2 and more active poly(A) ribonuclease (PARN), resulting in short poly(A) tails and consequently repressed translation. To regulate the polyadenylation status of an mRNA, CPEB relies on cleavage and polyadenylation specificity factor (CPSF) that binds to the hexanucleotide AAUAAA sequence (HEX). As shown in the right panel, upon progesterone stimulation during oocyte maturation, CPEB becomes phosphorylated, which causes its dissociation from PARN deadenylase. Consequently, Gld2 polyadenylation activity prevails, leading to the binding of PABP to the elongated poly(A) tail. Then, PABP interacts with eIF4G, and the mRNA assumes a closed-loop structure. Because this mRNA circularization is accompanied by disassembly of at least a portion of the Maskin–eIF4E complex, translation can be initiated.

anaphase-promoting complex/cyclosome (APC/C) activity [25]. Translational initiation of the *cig2* transcript may need extra helicase activity owing to its very long UTRs. Both the 5′ UTR and 3′ UTR of *cig2* mRNA are approximately 1 kb long, whereas the median length of the 5′ UTR in the *S. pombe* genome is approximately 152 nucleotides [62]. Indeed, Cig2 is more efficiently translated once its UTRs are deleted [25]. Interestingly, mRNAs that encode factors involved both in G1–S and G2–M cell cycle transitions in *S. cerevisiae* have longer than average 5′ UTRs, suggesting that these transcripts also may require some specialized helicase activities during translational initiation [63].

(b) *G2–M transition and mitotic progression*

As previously mentioned, the DEAD-box family of RNA helicases regulate not only the G1–S but also the G2–M progression. For example, in *S. pombe*, the DEAD-box family member eIF4A influences

polysomal association and protein levels of the Cdc2-activating phosphatase, Cdc25, as well as the B-type Cyclin, Cdc13 [26]. The *eIF4A* mutants, as well as a strain overexpressing a dominant negative construct of eIF4A, show a phenotype similar to *cdc2* mutants: elongated cells arrested in G2 [64]. This G2 arrest is alleviated by Cdc25 overexpression. The 5′ UTR of Cdc25 contains several uORFs and stem-loop structures, resulting in inefficient Cdc25 synthesis in the absence of eIF4A. Owing to the complex 5′ UTR of *cdc25*, Cdc25 accumulation, which is needed for cells to enter mitosis, may require regulation at the level of translational initiation [26].

During the archetypal cell cycle, cap-dependent translation peaks in G1 phase and decreases by 60–80% in mitosis, when cellular energy is mostly invested into ensuring accurate cell division [45,46,65]. Genome-wide polysome profiling showed that approximately 3 per cent of HeLa cell mRNAs, encoding mostly nuclear RNA-binding proteins, efficiently associate with actively translating polysomes in mitosis [66]. Some of these nuclear RNA-binding proteins are known as ITAFs. ITAFs are thought to recognize IRES and could contribute to translation of IRES-containing mRNAs [66–68]. Although the role of IRES in mitosis is controversial, it has been proposed that IRESs, through ITAFs, allow recruitment of translational machinery independently of eIF4E, which is largely inhibited in mitosis [45,46,69–72]. IRESs are present in the 5′ UTRs or ORFs of certain mitotic regulators whose translation is essential for mitotic progression. Examples of mRNAs that are translated in mitosis and have IRES include: ornithine decarboxylase (involved in synthesis of polyamines, a component of the mitotic spindle), c-myc and Cdk11/p58^{PITSLRE} [45,46].

Cdk11/p58^{PITSLRE} is a shorter isoform of p110^{PITSLRE} that during the G2–M transition may be expressed from an IRES located within the ORF of *p110^{PITSLRE}* mRNA [73]. Cdk11/p58^{PITSLRE} is a Cdc2-related kinase required for centrosome maturation, spindle assembly and cytokinesis [74–76]. Mitotic translation of Cdk11/p58^{PITSLRE} is regulated at multiple levels. For example, unfolding of the *p110^{PITSLRE}* IRES requires a putative RNA chaperone, Upstream of N-Ras (Unr), whose translation was suggested to also peak in mitosis in an IRES-dependent manner [27,77]. In addition, two independent groups recently discovered that a failure to decrease cap-dependent translation during mitosis leads to impaired translation of cap-independent mRNAs and aberrant cytokinesis. These cytokinesis defects can be attributed to the reduced translation of Cdk11/p58^{PITSLRE} [75,76]. Thus, tightly controlled translation of an IRES-containing *Cdk11/p58^{PITSLRE}* mRNA is crucial for proper execution of the mitotic programme.

In addition to being regulated by 5′ UTR elements, the G1–S and G2–M transitions depend on elements within 3′ UTRs that mediate polyadenylation. A recent analysis performed using HeLa cells demonstrated that 349 mRNAs are more polyadenylated in S phase than in G2–M, whereas 222 mRNAs have longer poly(A) tails in G2–M than in S phase [78]. These differentially polyadenylated mRNAs encode proteins involved in cell cycle regulation, cell death, as well as cell growth and proliferation. It remains to be determined whether the hundreds of mRNAs that display cell cycle-dependent differential polyadenylation regulate progression through the cell cycle phases in which their polyadenylation, and presumably protein levels, peak. Some of the polyadenylation events in mitosis are dependent on cytoplasmic polyadenylation element-binding protein 1 (CPEB1) and CPEB4, proteins that bind to the cytoplasmic polyadenylation element (CPE) in the 3′ UTRs of target mRNAs and induce elongation of their poly(A) tails through recruitment of poly(A) polymerase [34,78,79]. CPEB1 and CPEB4 are especially important in regulating polyadenylation of mRNAs coding for cell cycle regulators at the G2–M transition [78].

4. DEVELOPMENTAL CONTROL OF THE CELL CYCLE VIA TRANSLATIONAL REGULATION

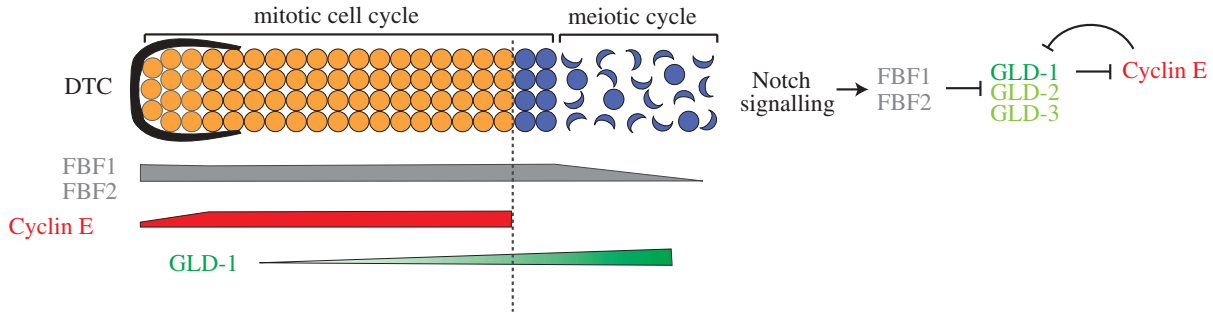
During development, cell proliferation must be coordinated with developmental cues, often necessitating modification of the cell cycle. These specialized cell cycles commonly occur in cells that are not undergoing transcription. Thus, translational regulation of the cell cycle has been found to be crucial in these contexts (table 1). The best-known and most understood example is the triggering of oocyte maturation, release of the prophase I arrest and progression in meiotic divisions, by cytoplasmic polyadenylation and translation of cell cycle regulators. This developmental event has been shown to be controlled by positive and negative feedback loops. Here we also review other examples of developmental control of the cell cycle through translation.

(a) *Exit from mitosis and the onset of meiosis*

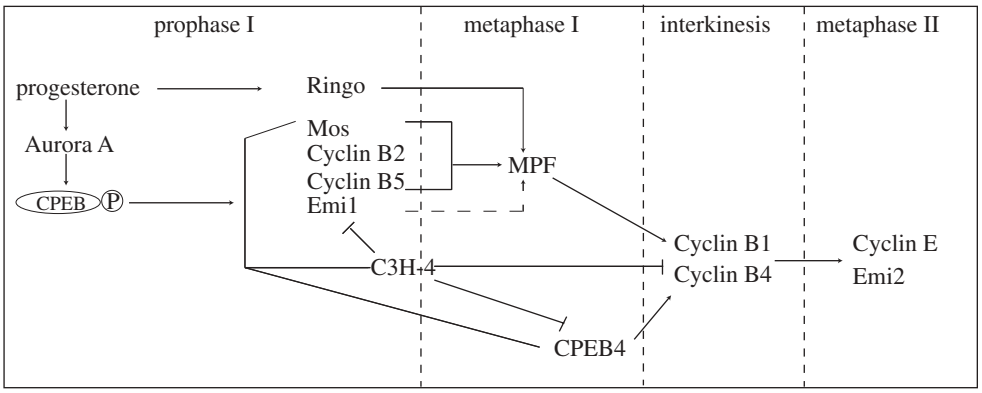
In metazoans, the regulatory network responsible for the transition of germline cells from mitosis to meiosis is poorly understood. The developmental signals and regulators responsible for this transition have been defined most fully in *C. elegans*, with the striking finding that each step in the commitment to and onset of meiosis involves translational regulation.

In the *C. elegans* gonad, the somatic distal tip cell (DTC) via Notch signalling maintains mitotic divisions in the germline cells at the adjacent end of the gonad (figure 2*a*) [81]. This control is mediated by two members of the PUF (Pumilio and FBF) family of translational repressors: FBF (*fem-3* mRNA-binding factor)1 and FBF2. In response to Notch signalling from the DTC, FBF1 and FBF2 block the translation of GLD (germ-line development)-1, GLD-2 and GLD-3, themselves proteins that control translation. GLD-1 is a translational repressor, whereas GLD-2, via its poly(A) polymerase activity, and GLD-3 positively affect translation (figure 2*a*). GLD-1 inhibits self-renewal and the mitotic cell cycle in the germline cells, and GLD-2 and GLD-3 promote the onset of meiosis. Recent studies have demonstrated that direct repression of Cyclin E translation is at least part of the mechanism by which GLD-1 inhibits mitosis [28]. In turn, Cyclin E–Cdk2 directly phosphorylates GLD-1, which leads to a reduction in GLD-1 levels [80].

(*a*) the mitosis-to-meiosis transition in the *C. elegans* gonad



(*b*) *Xenopus* oocyte maturation



(*c*) *Drosophila* late oogenesis and early embryogenesis

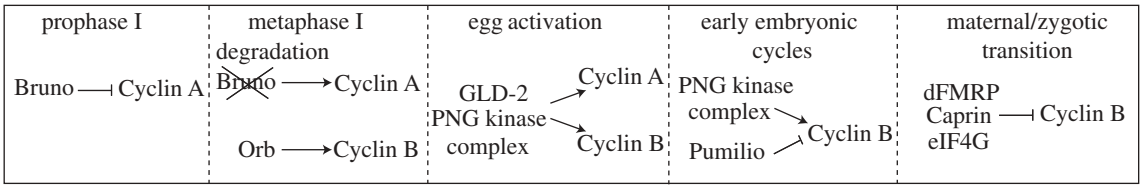


Figure 2. Translational regulation of specialized cell cycles in different developmental contexts. (*a*) The upper panel of this figure illustrates an arm of the *C. elegans* gonad. The self-renewing germ cells undergoing mitosis (orange circles) are shown on the left, whereas cells that are in meiotic S phase (blue circles) and crescent-shaped nuclei of cells that are in meiotic prophase are depicted on the right. The dashed line demarcates the border between the mitotic and meiotic cells. Notch signalling from the distal tip cell (DTC, shown in black) promotes mitosis in the germ cells through two members of the PUF family of translational repressors, FBF-1 and FBF-2. FBF-1 and FBF-2 (levels are shown in grey) inhibit translation of a translational repressor GLD-1 and of a heterodimeric translational activator, GLD-2–GLD-3. GLD-1 (levels are shown in green) represses translation of Cyclin E, which promotes germ cell proliferation. Cyclin E levels (levels are shown in red) are high in mitotic germ cells that express the GLD-1 repressors, FBF-1 and FBF-2. Cyclin E–Cdk2 complex phosphorylates GLD-1, causing a further reduction in GLD-1 levels in mitotic germ cells. The levels of FBF-1 and FBF-2 decrease at a certain distance from DTC, so GLD-1 levels increase. Cells in which GLD-1 accumulates show a drop in Cyclin E levels, and they can enter meiosis. Adapted from fig. 1 by Jeong *et al.* [80]. (*b*) This panel depicts a sequence in which proteins that drive progression through *Xenopus* oogenesis are translated. Upon progesterone stimulation in prophase I, one of the first translated proteins is Ringo. Simultaneously, phosphorylation of CPEB allows the conversion of CPEB from a translational repressor into an activator that induces polyadenylation and translation of *mos*, *cyclin B2*, *cyclin B5* and *emi1* mRNA. These proteins activate and stabilize maturation-promoting factor (MPF) that is essential for transition into metaphase I. As the contribution of Emi1 to MPF stabilization in meiosis I is still controversial, it is represented by a dashed line. Another protein translated in prophase I in a CPEB-dependent manner is C3H-4, a translational repressor that recruits deadenylase to the ARE-containing mRNAs. Although *CPEB4* is also polyadenylated upon progesterone stimulation, C3H-4 counteracts CPEB1-dependent polyadenylation of *CPEB4*, postponing CPEB4 accumulation until late metaphase I. At metaphase I, the CPEB1 is degraded, and polyadenylation events in late oogenesis are driven by CPEB4. For example, Cyclin B1 and Cyclin B4 that are required to support MPF through interkinesis are translated in a CPEB4-dependent manner. The transition into metaphase II and subsequent metaphase II arrest is mediated by accumulation of Emi2 and Cyclin E. As the polyadenylation of *emi2* is determined by the balance of opposing activities of CPEB4 and C3H-4, its polyadenylation and translation peak only in metaphase II, leading to an accumulation of this factor late in oogenesis. Adapted from fig. 7 by Igea *et al.* [34]. (*c*) Outline of translational regulation of Cyclin A and Cyclin B at various developmental transitions during *Drosophila* oogenesis and early embryogenesis.

(b) *Maintenance of meiosis*

In both *C. elegans* and *Drosophila*, translational regulation of Cyclins is essential for the oocyte to remain in meiosis. In *C. elegans*, GLD-1-mediated repression of Cyclin E translation remains crucial even after the onset of meiosis. Indeed, when GLD-1 is mutated, oocytes revert to mitosis, resulting in germline tumours [28]. This is associated with elevated levels of Cyclin E protein, and the phenotype can be suppressed by reducing *cyclin E* gene dosage.

In *Drosophila*, translational repression of Cyclin A is needed to maintain the oocyte arrested in meiosis [29]. Cyclin A accumulation in the oocyte is prevented by the translational repressor Bruno (figure 2*c*). The *Drosophila* oocyte is connected by cytoplasmic bridges to sister nurse cells, which become polyploid because they enter the endo cycle, a specialized cell cycle in which successive rounds of DNA replication occur in the absence of mitosis. When Bruno is mutated, the elevated levels of Cyclin A lead oocytes to exit meiosis, and nurse cells to leave the endo cycle, and transit into a 'mitosis-like' state. The decrease in Bruno levels at the exit from prophase I allows for Cyclin A translation and meiotic progression [41].

In *S. cerevisiae*, translation of one of four mitotic Cyclins, Clb3, needs to be repressed until meiosis II, otherwise its premature translation causes defective meiosis I chromosome segregation [40].

(c) *Transition from G2 into the first meiotic division*

(i) *Oocyte maturation*

Nearly all metazoans arrest the meiotic cell cycle to permit oocyte differentiation and patterning as well as deposition of maternal components [82]. The primary arrest is in prophase I, after recombination and homologue pairing, and this arrest can last for years in *Xenopus* and as long as decades in humans. Release of the prophase I arrest in oocytes and progression into the meiotic divisions is termed oocyte maturation. During maturation, oocytes progress to a secondary arrest point, metaphase I in insects and metaphase II in most vertebrates. The secondary arrest facilitates coordination of the completion of meiosis with fertilization.

Activation of translation at oocyte maturation was one of the first identified examples of developmental control of the cell cycle by translation. The maternal mRNAs in the oocyte are prevented from being translated until the correct developmental stage by being masked [15,83]. A molecular basis for this masking was found to be a short poly(A) tail on these maternal mRNAs, preventing them from being recruited to polysomes and translated. At maturation, in response to progesterone in vertebrates and unknown signals in insects, cytoplasmic polyadenylation permits translation.

Key cell cycle regulators that become translated at *Xenopus* oocyte maturation are Ringo, Mos, Emi1 and several forms of Cyclin B (figure 2*b*) [32,33,84–86]. Active Cyclin B–Cdk1, synonymous with maturation promotion factor (MPF), is the catalytic function necessary for the onset of the meiotic divisions [86]. MPF activation is initiated by Ringo and it is supported by Mos and possibly Emi1 [31,86–89]. In addition to promoting maturation by activating MPF, Mos is also necessary for the secondary arrest at metaphase II [90], whereas the role of Emi1 in controlling meiotic progression is still under debate [86,91–93].

An important issue raised by the hierarchy of MPF activation at maturation is the temporal control of translation. Indeed, although the mRNAs for all of these proteins undergo polyadenylation at maturation, this polyadenylation is sequential (figure 2*b*). The order of polyadenylation and translation is as follows: Ringo is first, prior to exit from prophase I, followed by Mos, Cyclin B2, Cyclin B5 and Emi1 prior to the completion of meiosis I and even later followed by Cyclin B1 and Cyclin B4 [34,35,94,95]. Polyadenylation and regulated translation of Cyclin B have also been shown to accompany oocyte maturation in zebrafish [36,96].

Recent investigation into the developmental control of translation timing at maturation highlights the role of binding of translational regulators to the mRNAs combined with both positive feed-forward and negative feedback loops. The CPEB protein is central to the regulation of polyadenylation in the oocyte (for more details, see figures 1*c* and 2*b*). In addition to the interacting proteins summarized in figure 1*c*, CPEB is in a large complex with other additional proteins that also may regulate its function [97,98].

An important translational repressor at maturation is Pumilio 2 (Pum2), a PUF family member. Pum2 represses translation of Ringo and Cyclin B1 until maturation by binding to PBE (Pumilio-binding element) sequences in the 3′ UTR of *ringo* and *cyclin B1* mRNAs. Pum2 exerts its effects at least in part by affecting the interaction between the RNA-binding protein DAZL (deleted in azoospermia-like) and the embryonic PABP, but it also may affect polyadenylation [31]. Another translational regulator, Musashi, is implicated in promoting the translation of Mos and Cyclin B5 by binding to the MBE (Musashi-binding element) and acting together with CPE to influence polyadenylation [94,99,100].

In addition to the activation of translation at maturation, active control of translation ensures progression through the meiotic divisions. Two distinct CPEB proteins control translation as the oocyte progresses through meiosis (figure 2*b*). CPEB1 is responsible for translation at oocyte maturation, and it is partially degraded during the first meiotic division. In a feed-forward loop, CPEB1 activates the translation of CPEB4, which then drives the metaphase I through metaphase II transitions [34].

Maturation also triggers the translation of a translational repressor, C3H-4, generating a negative feedback loop (figure 2*b*) [35]. C3H-4 blocks the translation of mRNAs containing an ARE ((A+U)-rich element) sequence in their 3′ UTR (such as *emi1*, *CPEB4* and *emi2*), because it binds and recruits a deadenylase. C3H-4 appears to oppose Cyclin B–Cdk1 activity, and knockdown experiments show that its function is required for the exit from metaphase I. C3H-4 thus could limit the activity of newly translated cell cycle regulators by promoting deadenylation of their mRNAs.

Translational control of cell cycle regulators at maturation is not restricted to vertebrates. Both Cyclin A and Cyclin B are translated at maturation, correlated

with the loss of the Bruno repressor protein. Translation of Cyclin B also is promoted by *Drosophila* CPEB, called ORB (figure 2*c*). In addition, a GLD-2 homologue is required at maturation for polyadenylation and translation of many proteins, including the *Drosophila* orthologue of Mos and a meiosis-specific activator of the APC/C called Cortex [42,101,102].

(ii) *Spermatocytes*

Meiotic progression in spermatocytes relies on translational regulation of the cell cycle as well. The RNA-binding protein DAZL is now known to play a key role in the translation of Ringo [31], but its function in the meiotic cell cycle was first recognized by mutation of the *Drosophila* homologue, Boule, which causes a failure of spermatocytes to translate the Cdc25 phosphatase Twine and enter the meiotic divisions [38].

Developmental specificity of the translation machinery also contributes to regulation of the meiotic cell cycle in spermatocytes. In *Drosophila*, eIF4G2, a member of the eIF4G protein family, is essential in spermatogenesis [37,103]. Although spermatocytes in which eIF4G2 is mutated fail to progress beyond early prophase I and skip both meiotic divisions, they still initiate spermatid differentiation. eIF4G2 affects the cell cycle by promoting translation of Cyclin B and possibly the Cdc25 phosphatase Twine.

In mouse spermatocytes, another eIF4G family member, eIF4g3, is necessary for the meiotic cell cycle [39]. Spermatocytes of eIF4g3 mutants progress through prophase I, because they go through recombination as well as synaptonemal complex assembly and disassembly, but they do not undergo the meiotic divisions. eIF4g3 seems to be needed for adequate activation of Cyclin B–Cdk1, although it does not appear to control the translation of Cyclin B. Rather, it controls the translation of HSPA2—Cdk1′s chaperone protein. In mouse, CPEB1 is required both in spermatocytes and oocytes for translation of structural components of the synaptonemal complex and consequently for synaptonemal complex assembly [30].

(d) *Egg activation and the completion of meiosis*

In *Drosophila*, another burst of translation accompanies egg activation and the release of the secondary meiotic arrest. *Drosophila* egg activation induces renewed translation of cell cycle regulators, such as Cyclin A and Cyclin B [41,43]. The GLD-2 poly(A) polymerase promotes further lengthening of the poly(A) tail of these and other mRNAs at activation [101]. In addition, translation of the *cyclin* mRNAs is promoted by a protein kinase complex composed of the Pan Gu (PNG) kinase and two regulatory subunits (figure 2*c*) [41,43,104]. When PNG kinase is nonfunctional, meiosis is completed but mitosis does not occur in the embryo. Although the precise mechanism by which PNG promotes translation remains to be determined, both poly(A)-dependent and poly(A)-independent control are involved [18,43]. To date, it has not been determined whether in vertebrates and *C. elegans* translational control is crucial for egg activation, but this could be an important goal for future research.

(e) *Early embryonic divisions*

In organisms with a reproductive strategy of external embryonic development, rapid embryogenesis permits the progeny to become motile. In insects, amphibians and fish this is accomplished by a rapid embryonic cell cycle characterized by the absence of growth and transcription, in which S–M oscillations run off maternal stockpiles. This developmental strategy may explain the need for translational regulation of the cell cycle. In *Xenopus*, CPEB-mediated translation of Cyclin B1 is critical for embryonic divisions [3]. In *Drosophila*, the PNG kinase regulates translation at this window of development, the transition from the oocyte to the embryo (figure 2*c*). In early embryogenesis, Cyclin B is the critical PNG target for promoting mitosis [105]. PNG appears to counteract repression of Cyclin B translation by Pumilio (PUM), a member of the evolutionarily conserved PUF family of translational repressors [43]. It is not known how PNG kinase offsets PUM during the mitotic divisions of early *Drosophila* embryos, and it is also unclear whether PNG–PUM antagonism regulates Cyclin B levels already at egg activation. Moreover, PUM may have an even stronger impact on cell cycle regulation than previously thought. For example, PUM interacts with 714 mRNAs in adult ovaries and with 165 mRNAs in early embryos. Because many of these mRNAs encode cell cycle regulators, much remains to be discovered about PUM's role in controlling meiotic progression and early embryonic divisions [106].

(f) *Repression of translation of maternal transcripts at the maternal–zygotic transition*

In organisms with maternally driven early embryonic cell cycles, a key developmental step is the hand-off of regulation from maternal mRNAs and proteins to zygotically expressed transcripts. One aspect of this switch involves blocking translation of maternal mRNAs and degradation of these transcripts. In zebrafish and *Xenopus*, microRNAs are important for this process, and their targets include mRNAs for cell cycle regulators [107–109]. In *Drosophila*, PNG promotes the translation of Smaug, which recruits the deadenylase machinery to some maternal transcripts to block their translation and destabilize the mRNAs [110].

The maternal/zygotic transition (also called the mid-blastula transition, MBT) additionally requires a slowing of the cell cycle, which is accomplished by the addition of gap phases. The *Drosophila* MBT is known to be controlled by lengthening S phase through activation of the DNA replication checkpoint and regulated degradation of maternal proteins [111–113]. Recently, it has been established that translational repression of maternal pools of the *cyclin B* mRNA also plays a role in controlling *Drosophila* MBT (figure 2*c*) [44]. The fragile X mental retardation protein (dFMRP) complexes both with the translational regulator Caprin and the initiator protein eIF4G to limit translation of Cyclin B, thus presumably contributing to slowing of the cell cycle and the corresponding addition of a G2 phase.

5. SPINDLE-LOCALIZED TRANSLATION DURING OOGENESIS AND EARLY EMBRYOGENESIS

The 3′ UTR-binding protein, CPEB, not only ensures the precise timing of translation of maternally loaded

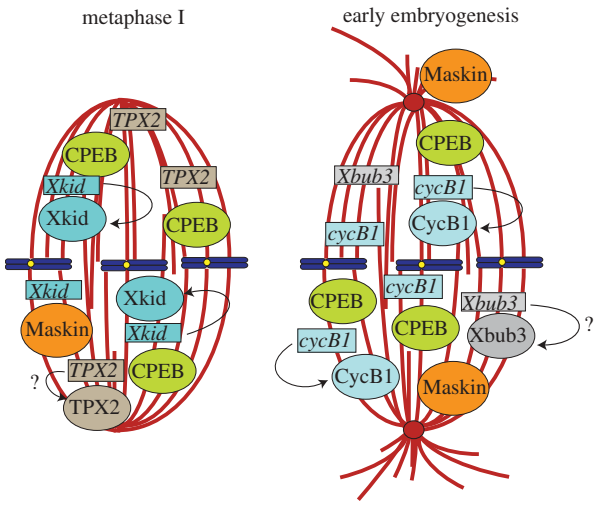


Figure 3. Spindle-localized translation during *Xenopus* oogenesis and early embryogenesis. CPEB and Maskin, proteins that regulate polyadenylation and translation, localize to the spindles of mature oocytes and early embryos. *TPX2* and *Xkid* mRNAs also localize to the spindles in mature *Xenopus* oocytes, and *cyclin B1* as well as *Xbub3* mRNAs are spindle-associated in early *Xenopus* embryos. *Xkid* and *cyclin B1* are translated in a CPEB-dependent manner on the spindles of *Xenopus* oocytes and early embryos, respectively. The spindle-localized translation of *Xkid* is required for the transition from the first to the second meiotic division during *Xenopus* oogenesis. Moreover, *cyclin B1* needs to be translated on the spindles of early embryos to allow for proper spindle assembly and execution of embryonic cleavages. The spindle-localized translation of *TPX2* and *Xbub3* awaits investigation. The mRNAs are designated by rectangles and the proteins by ovals; arrows show proposed translational regulation.

mRNAs during *Xenopus* oogenesis and early embryogenesis, but it also regulates spindle-localized translation of certain mRNAs encoding key proteins implicated in cell division (figure 3). Both CPEB and its interactor Maskin are present on the spindles of *Xenopus* mature oocytes, fertilized eggs and early embryos [22]. *Xbub3* and *cyclin B* are two spindle-associated CPE-containing mRNAs that colocalize with CPEB and Maskin on spindles and centrosomes of early *Xenopus* embryos [22]. If CPEB is displaced from the spindles, then spindle-localized translation of Cyclin B decreases. Cleavages are in turn inhibited, suggesting that the spindle-localized synthesis of Cyclin B is essential for proper execution of cell division in early *Xenopus* embryos [22,114,115].

CPEB-mediated spindle-localized translation also controls the meiosis I-to-meiosis II transition during *Xenopus* oogenesis [21]. Bioinformatic analysis identified several CPE-containing mRNAs as potential CPEB translational targets. Interestingly, these mRNAs, conserved among vertebrates, have known roles in spindle assembly as well as chromosome segregation. They encode spindle assembly checkpoint proteins (Bub1, Bub3, Mad1, Mad2, BubR1), mitotic kinases and their activators (Nek 2B, Aurora A, Aurora B and TPX2) and chromatin/kinetochore-associated motors (CENP-E and Xkid) [21]. One of these mRNAs, *Xkid*, was shown to colocalize with CPEB on the spindles and chromosomes of *Xenopus* metaphase I oocytes and in metaphase II-arrested *Xenopus* egg extracts [21]. Knockdown of Xkid leads to misaligned chromosomes and to the absence of the polar body extrusion during the first meiotic division. This phenotype can only be rescued by expression of *Xkid* mRNA whose 3′ UTR mediates spindle localization and not by a variant of *Xkid* mRNA whose 3′ UTR abolishes targeting to the spindle. Moreover, excess competitor CPE-containing mRNAs, which delocalize CPE-containing mRNAs from the spindle, cause a phenotype that is more severe than that of Xkid depletion and that is not rescued by Xkid overexpression [21]. Therefore, CPEB-mediated spindle-localized translation not only of *Xkid* mRNA but also of other CPE-containing mRNAs is required for proper chromosome alignment and transition into the second meiotic division. Future work should reveal whether some of the candidate CPE-containing mRNAs encoding cell cycle regulators mentioned above contribute to meiosis I-to-meiosis II progression.

In addition to performing translation-dependent functions during the transition from the first to the second meiosis, spindle-localized mRNAs play an essential but translation-independent role in spindle assembly in metaphase II-arrested *Xenopus* egg extracts [116]. Namely, RNAse treatment of metaphase II-arrested *Xenopus* egg extracts severely disrupts spindle assembly, whereas addition of puromycin or cycloheximide to block protein translation has no obvious effect on spindle organization. A recent genome-wide analysis discovered that as many as approximately 5 per cent of *Xenopus* mRNAs are enriched on mitotic microtubules when compared with total mitotic extracts [117]. Some of these mRNAs associate with actively translating ribosomes and their protein products become incorporated into the spindle [117]. Therefore, localized spindle translation contributes to, although it is not essential for, spindle assembly in metaphase II-arrested *Xenopus* egg extracts. It is unclear why metaphase II-arrested *Xenopus* egg extracts would not require spindle-localized translation of cell division regulators when it is required in *Xenopus* oocytes during the transition from the first to second meiotic division as well as in early embryos. Perhaps metaphase II-arrested *Xenopus* egg extracts have lost spatial information present in intact oocytes, and their ample supply of maternal protein eliminates the need for spindle-localized translation. It is also plausible, however, that the proteins translated from the spindle-localized mRNAs are indeed not required during metaphase II. Alternatively, the proteins synthesized on the spindles during metaphase II may be needed during the transition to anaphase II.

Because of their large size, *Xenopus* oocytes and eggs probably rely on spindle-localized translation to ensure efficient assembly of protein complexes required for spindle formation and chromosome segregation. Indeed, mathematical modelling has shown that in large cells with a radius greater than 50 μm, such as *Xenopus* and *Drosophila* oocytes, diffusion-mediated assembly of complexes may take too long for certain cellular functions to be accomplished, especially if the components are short-lived and synthesized at different subcellular locations [118]. In early *Drosophila* embryos,

approximately 70 per cent of expressed mRNAs (approx. 1650 mRNAs) show distinct patterns of subcellular localization, with 33 mRNAs associating with the spindle poles and microtubules [119]. Proteins encoded by these mRNAs also localize to the cell division apparatus, suggesting that they may be locally translated [119]. The physiological significance of this putative spindle-localized translation in early *Drosophila* embryos has yet to be determined.

It has not yet been investigated whether smaller, somatic cells use localized translation of spindle-enriched mRNAs in regulating spindle assembly and cell division. HeLa cells would be a good candidate for this analysis as 10 per cent of their mRNAs associate more strongly with mitotic microtubules than whole extracts, and these localized mRNAs are enriched for regulators of mitosis and DNA metabolism [117].

6. CONCLUDING REMARKS AND FUTURE PERSPECTIVES

Translational control enables faster transitions and fine-tuning of archetypal and specialized cell cycles [20]. Accumulation of translationally controlled cell cycle regulators is rapid, because time-consuming transcription and mRNA processing have already occurred. For many key cell cycle regulators, translational control represents an additional mechanism to precisely adjust their abundance, working in concert with transcriptional regulation, control of mRNA stability and ubiquitin-mediated degradation [6–8]. It remains to be discovered how all these different steps of gene-expression control are integrated to produce optimal levels of cell cycle players.

Although some progress has been made in understanding 5′ UTR-mediated translational control during archetypal cell cycle progression, the contribution of the 3′ UTR and 3′ UTR-binding proteins is largely unexplored. RNA-affinity chromatography could lead to identification of additional RNA-binding proteins interacting with 5′ UTRs or 3′ UTRs of mRNAs [120,121]. This approach may elucidate some novel translational controls required for efficient translation of mRNAs encoding cell cycle regulators, which, as discussed above, in some cases require specialized translational initiation factors owing to their long and complex UTRs. Moreover, recent genome-wide profiling experiments of poly(A) tail lengths performed in transcriptionally active mitotically dividing cells have been a step forward in delineating the role of 3′ UTRs in regulation of archetypal cell cycle progression [78,122,123]. This work suggests that polyadenylation status of mRNAs could be implicated in the regulation of archetypal cell cycle progression [78,122].

In HeLa cells, some of these polyadenylation events are promoted by the 3′ UTR-binding proteins CPEB1 and CPEB4, whereas others proceed in a CPEB-independent manner. The 3′ UTR-binding proteins that mediate CPEB-independent polyadenylation of mRNAs await identification [78]. It also remains to be discovered how CPEBs and other 3′ UTR-binding proteins are recruited to different messages in different phases of the cell cycle. Are they perhaps guided by some unknown cell cycle-specific factors? Or, are cell cycle-dependent post-translational modifications responsible for changes in their target specificity? CPEB has been recently described to recruit Gld4, a non-canonical poly(A) polymerase that lacks an RNA-binding domain, to the CPE-containing *p53* mRNA in mouse embryo fibroblasts [124].

In the future, it will be interesting to identify other polymerases, in addition to Gld2 and Gld4, involved in polyadenylation in mitotically dividing cells and to understand the mechanisms controlling their activities during the cell cycle. An important direction for future research will be to investigate the cell cycle-related functions of mRNAs that are differentially polyadenylated in a cell cycle-dependent manner. Other mechanisms of translational regulation acting on the 3′ UTR will also be an exciting field for further studies. For example, microRNAs contribute to degradation of inhibitors of cell cycle progression during the exit from quiescence, and they are required for destabilization of maternal transcripts in *Xenopus* and zebrafish embryos [106–108,125]. Therefore, it remains to be seen if microRNA-dependent post-transcriptional control of cell cycle regulators is a commonly used strategy both in archetypal and specialized cell cycles.

Recently, genome-wide approaches have led to the identification of additional cell cycle players that are translationally regulated. For example, polysome profiling combined with microarray analysis has allowed comprehensive identification of translationally regulated mRNAs, including those that encode cell cycle players, during HeLa cell mitosis, mouse male germ cell meiosis, as well as early *Drosophila* embryogenesis [66,126,127]. For a majority of these transcripts, the exact mechanisms of their cell cycle-dependent translational regulation and their roles in cell cycle progression still remain to be elucidated. Another high-throughput method, a quantitative proteomic approach, has been applied to the study of the maternal-to-zygote transition in *Drosophila* [128]. This study revealed that the levels of approximately 340 zygotic proteins were upregulated, and approximately 230 maternal proteins were downregulated, many of them involved in the regulation of mitosis. It will be interesting to apply genome-wide polysome profiling and quantitative proteomics experiments to study other cell cycle transitions during development.

Genome-wide analyses have identified spindle-localized mRNAs in *Xenopus* metaphase II-arrested egg extracts, HeLa cells and early *Drosophila* embryos [117,118]. As described earlier, so far it has only been shown that the spindle-localized translation of *Xkid* and *cyclin B* is required during *Xenopus* oogenesis and early embryogenesis [21,22]. Therefore, it will be important to determine whether other spindle-localized transcripts identified in *Xenopus* egg extracts, HeLa cells or *Drosophila* embryos are translated on the spindle and whether this is required for cell cycle progression [21,22,117,119]. Spindle-localized translation can now be visualized in live cells or extracts by ReAsH (resorufin-based arsenical hairpin binder) technology [96,129,130]. ReAsH is based on an interaction between a tetracysteine tag of a recombinant reporter protein and a membrane-permeable biarsenical dye. Immediately upon interacting with the newly

synthesized tetracysteine tag, the biarsenical dye emits fluorescence and 'lights up' the sites of translation [129].

Another exciting question that can be addressed by ReAsH technology is whether localized translation of mRNAs restricted to other subcellular locations could play a role in regulating cell cycle transitions. For example, 22 transcripts in *S. cerevisiae*, including B-type Cyclin *Clb2* mRNA, asymmetrically localize to the distal tip of the bud during mitosis [130]. Clb2 protein has also been detected at the distal tip, but it has not been tested whether *Clb2* mRNA is locally translated there and whether this putative localized translation plays a role in regulating cell cycle progression [131,132].

Similarly, centrosome-localized translation also may be important for cell cycle progression. Six mRNAs associate with centrosomes in early *Drosophila* embryos, and five mRNAs have been reported to localize to the centrosome in surf clam oocytes [119,133]. Perhaps some of these centrosome-associated mRNAs are locally translated, and their corresponding proteins may contribute to centrosomal integrity and function. It is tempting to speculate that some specialized factors may be involved in spatially restricted translation of cell cycle regulators, but this hypothesis awaits further investigation.

In addition to exploring how translational control influences cell cycle progression, future research needs to resolve certain controversies. For example, it needs to be determined rigorously whether IRES elements are present in mitotically translated mRNAs as well as whether and to what extent IRES activity contributes to translation during mitosis. Several recently published reviews raise valid concerns about weak criteria used to claim that an mRNA carries an IRES and about insufficient reliability of the assays used to identify IRES activity in cellular mRNAs [69,70,134]. Moreover, it is important to exclude the possibility that alternative protein isoforms arise from alternative splicing, as opposed to IRES-mediated translational initiation [69]. Although, in this review, we mention that in mitosis Cdk11/p58^{PITSLRE} may be translated from an IRES, it also has been reported that *Cdk11/p110*^{PITSLRE} and *Cdk11/p58*^{PITSLRE} mRNAs can be created by alternative splicing of duplicated genes [69,73,135]. Regardless of the outcome of the IRES issue, future research will need to identify the factors that allow for translation of selected mRNAs in mitosis when general translation is inhibited.

Translational regulation makes an evolutionarily conserved contribution to cell cycle control during both archetypal and specialized cell cycles. Many crucial regulators of archetypal cell cycles evolved complex 5′ UTRs that may require specialized translational initiation factors. This additional layer of gene-expression regulation allows even tighter control of the levels of critical cell cycle players. Interestingly, temporal and spatial translational control of the proteins that regulate progression through meiosis or early embryogenesis is exerted mostly through their 3′ UTRs and 3′ UTR-binding proteins. However, recent work suggests that additional mechanisms of translational control, such as differential polyadenylation and microRNA-mediated repression, control the levels of key cell cycle regulators. Furthermore, the list of transcripts whose translation is affected by certain cell cycle or developmental transitions has recently expanded owing to new genome-wide approaches, although the roles that these factors play in mediating cell cycle progression remain to be discovered. Answers to the many open questions regarding the interplay between translational regulation and cell cycle progression will ultimately make a major contribution to our understanding of the principles of cell cycle control.

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