Role of CDK1 in translational regulation in the M-phase

Jaroslav Kalous1*, Denisa Jansová1 and Andrej Šušor1

1 Institute of Animal Physiology and Genetics, Academy of Sciences of the Czech Republic, Rumburska 89, 27721 Libechov, Czech Republic

* Author to whom correspondence should be addressed

Abstract: Cyclin dependent kinase 1 (CDK1) has been primarily identified as a key cell cycle regulator in both mitosis and meiosis. Recently, an extramitotic function of CDK1 emerged when evidence was found that CDK1 is involved in many cellular events that are essential for cell proliferation and survival. In this review we summarize the involvement of active CDK1 in the initiation and elongation steps of protein synthesis in eukaryotes. During its activation CDK1 influences the initiation of protein synthesis, promotes the activity of specific translational initiation factors and affects the functioning of a subset of elongation factors. Our review provides insights into gene expression regulation during the transcriptionally silent cell cycle/M-phase and describes quantitative and qualitative translational changes based on the extramitotic role of the cell cycle master regulator CDK1, to optimize temporal synthesis of proteins to sustain division-related processes: mitosis and cytokinesis.

Keywords: CDK1, eIF4F, mTOR, mRNA translation, M-phase

1. Introduction

Cyclin dependent kinase 1 (CDK1) is a subunit of M phase-promoting factor (MPF)

CDK1 is a key player in driving the M-phase in both meiosis and mitosis [1,2]. CDK1 activity sharply increases at the beginning of the M-phase and CDK1 is inactivated at the exit from the M-phase [3–5] (Figure 1).
Figure 1. Dynamics of cyclin dependent kinase 1 (CDK1) activity, global translation and inactivation of the eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1) in the M-phase. At the beginning of the M-phase the intensity of global translation is at high levels and CDK1 activity sharply increases, accompanied by nuclear envelope breakdown. CDK1 activity peaks during the assembly of the spindle and 4E-BP1 becomes hyperphosphorylated which results in its inactivation as a translational repressor. At the exit of the M-phase CDK1 activity drops and 4E-BP1 phosphorylation is lowered. The intensity of global translation decreases gradually during the time course of the M-phase. Immunoblot image using pan 4E-BP1 antibody shows an exclusive phosphorylation shift in the M-phase. Dashed green line depicts intensity of global translation; brown curved line depicts CDK1 activity; orange bars depict intensity of 4E-BP1 intensity phosphorylation in the G2, M and inter-phases.

CDK1, a serine/threonine kinase, is a catalytic subunit of a complex known as MPF which is essential for cell cycle control at the G1-S and G2-M phase transitions of eukaryotic cells. CDK1 is involved in the control of such events as DNA replication and segregation, mRNA transcription, DNA repair and cell morphogenesis (reviewed in [6]). Previous studies identified several translation-associated factors as direct substrates of CDK1 in mitosis and meiosis [7,8]. The association of CDK1 with one of several cyclins is a prerequisite of CDK1 activity (Figure 1, 2).
Figure 2. Activated (cyclin dependent kinase 1) CDK1 supports mRNA translation during the M-phase. During the G2-phase inactive CDK1 with minimal amount of regulatory cyclin B protein is present. Prior prophase cyclin B accumulates in the nucleus and binding of cyclin B to CDK1 results in an increase of CDK1 activity. Active CDK1 promotes the nuclear lamina and nuclear envelope breakdown (NEBD). Post NEBD active CDK1 influences a number of targets including members of the translation-initiation and elongation.

In addition to cyclin binding, CDK1 activation requires dephosphorylation on Thr14 and Tyr15 residues and phosphorylation at Thr161 [9,10]. At the onset of M-phase cyclin B1 become translated and plays a fundamental role in cells entering M-phase [11]. In oocytes cyclin B1 and cyclin B2 are involved in the control of the transition from the first to the second meiotic division and cyclin B2 is able to compensate for cyclin B1 in CDK1 activation during the M-phase transition in oocyte meiosis (Li et al. 2018). A similar compensatory ability for cyclin B2/CDK1 to interact with separase has been revealed suggesting that cyclin B2/CDK1 and cyclin B1/CDK1 complexes likely function together in oocytes [13]. Cyclin B3/CDK1 complex is required for the M-phase to anaphase transition in oocytes (Li et al. 2019; Karasu et al. 2019).

2. Global mRNA translation during the M-phase

The dynamic control mRNA translation has a great impact on many intracellular processes. According to the published data, it is considered that global translation is substantially decreased during the M-phase (Figure 1) [16–19]. Five decades ago a 50 - 70% reduction of global protein synthesis in synchronized mammalian cells undergoing mitosis was described [20,21] and more recent data present a 35% decrease of translation rate during mitosis [19].

It has been documented that the intensity of protein synthesis suppression in cells undergoing mitosis is related to the method of cell synchronization [22,23]. An objection has been raised that the data of downregulation of protein translation in mitotic cells were built on the effects of cellular stress associated with cell cycle synchronization protocol (Anda and Grallert 2019). The reduction of global translation in cells undergoing cell division is believed to result from phosphorylation changes in translation initiation factors. Namely, the increased phosphorylation of an α subunit of eukaryotic initiation factor 2α (eIF2α) induced in synchronized cells by cell cycle progression through the G2/M phase was determined as a cause of the downregulation of mRNA translation (Kim et al. 2014; Silva et al. 2015). An intense and long-term eIF2α phosphorylation on Ser51 can suppress global translation and induce cell death (Hara et al. 2002; Yu et al. 2019). When the possible effect of synchronization on translation rates was eliminated, the flow cytometry data revealed that there were no significant variations in global translation rates throughout the cell cycle (Stonyte, Boye, and Grallert 2018).

On the other hand, oocytes isolated from mammalian ovaries are arrested in the prophase of the first meiotic division and naturally resume meiosis without chemical induction [29,30]. We and others [31,32] found that global translation decreases during meiotic progression and postfertilization. Although mitosis in synchronized cells is reported to be associated with reduced cap-dependent mRNA translation [19,21] in oocytes the cap-dependent translation is initiated at the resumption of meiosis as documented in in vitro matured porcine (Ellederova et al. 2006; Ellederova et al. 2008), bovine [33] and mice [17] oocytes (Figure 1).
3. M-phase and reprograming of translation

Ribosomes are considered as executors of the translational program although ribosomes can also control the translation of specific mRNAs. In eukaryotes, ribosome assembly is a complex process involving more than 200 assembly factors and taking place in the nucleolus, nucleoplasm and cytoplasm (reviewed in [34]). It has been shown that CDK1 is a pronounced activator of 5'TOP mRNA translation, which includes the synthesis of all ribosomal proteins [13]. The authors considered that CDK1 possibly stimulates global translation by phosphorylating additional ribosomal proteins or proteins associated with the ribosome. CDK1 plays a role in the ribosome assembly that requires rDNA transcription, pre-rRNA processing and assembly of mature rRNAs with ribosomal proteins [13]. Ribosome assembly involves several events relying on the rDNA transcription and processing of 47S pre-rRNA into 18S, 5.8S, and 28S mature rRNAs [35,36]. Transcription of rDNA is repressed during mitosis by the CDK1-directed phosphorylation of components of the rDNA transcription machinery [37,38].

CDK1 regulates ribosome assembly by targeting specific ribosomal proteins. During the G2/M phase, CDK1 phosphorylates ribosomal protein S3 (RPS3), which is a multifunctional protein involved in translation, DNA repair, and apoptosis. Phosphorylation of RPS3 by CDK1 is important for the nuclear accumulation of RPS3 [39]. RPS3 is localized evenly in the cytoplasm of GV oocytes and with higher concentration at the newly forming spindle in NEBD oocytes and mitotic cells [40,41].

It was documented that CDK1 co-sediments in the polysome fraction, and mass spectrometry revealed that CDK1 is associated with ribosomes [42]. This finding is in line with the notion that ribosomal protein L12 (RPL12) is a known substrate of CDK1 (Table 1), and RPL12 phosphorylation was shown to enhance a mitotic translation program [43].

| **Substrate**                  | **Reference**                     |
|-------------------------------|-----------------------------------|
| mTOR (Ser2448)                | Jansova et al., 2017              |
| Raptor (Ser696, Thr706)       | Gwinn et al., 2010, Ramírez-Valle et al., 2010 |
| 4E-BP1 (Thr37/Thr46)          | Shuda et al., 2015                |
| 4E-BP1 (Thr70)                | Heesom et al., 2001; Jansová at al., 2017 |
| 4E-BP1 (Ser83)                | Velásquez et al., 2016            |
| p70S6K (Ser411, Thr421, Ser424) | Papst et al., 1998; Shah et al., 2003 |
| elf4G1 (Ser1232)              | Dobrikov et al., 2014             |
| elf2α                         | Haneke et al., 2020               |
| eEF1B                         | Monnier et al., 2001; Sivan et al., 2011 |
| eEF1D                         | Mulner-Lorillon et. 1994         |
| eEF2K                         | Smith and Proud, 2008             |
| LARP1                         | Haneke et al., 2020               |
| RPL12                         | Imami et al., 2018                |
Table 1. Known cyclin dependent kinase 1 (CDK1) substrates involved in the translation. CDK1 controls the phosphorylation status and activity of proteins involved in the initiation [mammalian target of rapamycin (mTOR)], regulatory-associated protein of mTOR (Raptor), eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1 (4E-BP1), ribosomal protein S6 kinase B1 (p70S6K)] and elongation [eukaryotic elongation factor 2 kinase (eEF2K)] steps of mRNA translation.

RPL12 has been reported to be phosphorylated on Ser38 in different species [44]. Phosphorylation of RPL12 regulates the translation of specific subsets of mRNAs during mitosis [43]. In HeLa cells phosphorylation of RPL12 at Ser38 peaks in mitosis and reaches the lowest level during the S phase [43,45]. In eukaryotes the sequence surrounding Ser38 is highly conserved and matches a consensus motif for CDK1 substrates [43]. Inhibition of CDK1 induced a progressive decrease in the percentage of heavy polysomes and a decline in polypeptide synthesis [13].

The nucleolus, the large nuclear domain assembled around ribosomal genes (rDNAs), is the site of ribosome assembly. The assembly and disassembly of the nucleolus is dependent on the equilibrium between the phosphorylation/dephosphorylation of the transcription machinery and on the pre-ribosomal ribonucleoprotein (RNP) complexes processing under the control of the CDK1 and PP1 phosphatases [46]. CDK1 regulates the activity of the nucleolar phosphoprotein nucleophosmin/B23 involved in the regulation of rRNA transcription through its histone chaperone activity [47]. B23/nucleophosmin associates with rRNA chromatin to stimulate rRNA transcription [48]. It has been shown that B23/nucleophosmin interacts with maturing ribosomal subunits and is involved in their nuclear export (Yu et al. 2006). During mitosis phosphorylation of B23/nucleophosmin by CDK1 at specific sites induces a release of B23/nucleophosmin from chromatin and inactivates its RNA binding activity [48,50]. It has been suggested that CDK1 is an obvious activator of cap 5’TOP mRNA translation including the synthesis of all ribosomal proteins [13].

Above mentioned results couple CDK1 activity and cell cycle progression to ribosome biogenesis.

4. CDK1 activity and localization in the cell

One insight into how one kinase can coordinate so many different events is that cyclin B1-CDK1 is targeted to different structures as the cell enters meiosis/mitosis. Cyclin B1-CDK1 is activated on centrosomes [51], and a large fraction immediately moves into the nucleus preceding the breakdown of the nuclear envelope [52,53]. Subsequently, Cyclin B1-CDK1 binds to the microtubules, to chromosomes, and to unattached kinetochores in prometaphase [8,54]. These observations indicate that the localization of Cyclin B1-CDK1 may be an important determinant of how specific substrates are recognized at specific times. In connection, we previously found that distinct translational areas are present in the oocyte post NEBD which are influenced by the mammalian target of rapamycin (mTOR)/4F axis [8,17,55].

5. Cap-dependent mRNA translation

Translation of mRNA is regulated mostly during the initiation phase by initiation factors interacting with a specific structure bound to the 5’UTR of an mRNA molecule, the 5’ cap (m7GppN) [56]. The cap structure is specifically recognized by the eukaryotic initiation factor complex (eIF4F), comprised of the cap-binding eukaryotic translation initiation factor 4E
(eIF4E), the RNA helicase eIF4A and the scaffold protein eIF4G (Sonenberg et al. 1978; Imataka, Gradi, and Sonenberg 1998). EIF4G1 also binds the poly(A)-binding protein (PABP) [59], thereby enabling the circularization of the mRNA [60].

Suppression of cap-dependent translation coincides with eIF4E dephosphorylation [61] and occurs together with the increased level of hypophosphorylated 4E-BP1 [18]. The phosphorylation status of 4E-BP1 depends on nutrients, extracellular signals and stress factors (reviewed in [62]) (Figure 3).

**Figure 3.** Interaction of eukaryotic translation initiation factor 4E (eIF4E) and eIF4E-binding protein 1 (4E-BP1) is regulated by different cellular conditions. eIF4E interaction to 4E-BP1 is regulated by diverse conditions i.e. entry to meiosis or mitosis, extracellular signals (growth factors etc.), nutrient availability (amino acids) and stress.

6. **CDK1 substitutes for mTOR control of cap-dependent translation**

mTOR, a serine/threonine protein kinase, is the main regulator of 4E-BP1 activity [63], thereby releasing eIF4E and activating translation (Gingras et al. 2001). Raptor, a binding partner of mTOR, mediates the functioning of mTOR [27]. Upon inhibition of mTOR, 4E-BP1 is dephosphorylated and the affinity of 4E-BP1 for eIF4E increases (Sonenberg and Hinnebusch 2009). mTOR enhances the translation of mRNAs containing the 5' TOP motif coding for ribosomal proteins, translation-related proteins, and wider variety of proteins, such as lysosome-related proteins and metabolism-related proteins, playing pivotal roles in gene expression controls in the majority of cellular mRNAs [66,67]. It has been documented that overexpression of rapamycin-resistant mTOR mutant restored the rapamycin-inhibited activity of mTOR effectors ribosomal protein S6 kinase B1 (p70S6K) and 4E-BP1 and removed the rapamycin induced inhibition of cell cycle progression [68]. Although mTOR is considered to be the main kinase phosphorylating 4E-BP1, several other kinases are involved in the phosphorylation of various 4E-BP1 residues [69,70].

The main substrates of mTOR, p70S6K and 4E-BP1, are phosphorylated by CDK1 during mitosis [70,71] (Table 1) and CDK1 can substitute for mTOR kinase in the activation of cap-dependent translation in mitotic cells, suggesting that an alternate pathway for the regulation of cap-dependent translation exists [19,23,72]. It has been observed in mouse prophase
lymphoblasts that CDK1 promotes mitotic growth through the increased phosphorylation of 4E-BP1 and cap-dependent protein synthesis [73].

When 4E-BP1 is hyperphosphorylated at Thr37/Thr46, Thr70 and Ser65 the elf4G:elf4E interaction is enabled and the initiation of cap-dependent translation begins (Gingras, Raught, and Sonenberg 1999; Gingras et al. 2001). It has been proposed that phosphorylation of 4E-BP1 at Thr37/Thr46 is rather constitutive, and phosphorylation at Ser65 is more related to its effect on cap-dependent translation [75]. Although the priming phosphorylation sites Thr-37/Thr-46 of 4E-BP1 are targeted by mTOR [63], the Thr37/Thr46 residues can be also phosphorylated by CDK1 [23]. CDK1 also phosphorylates 4E-BP1 at the Thr70 residue, which is one of several phosphorylation sites required for the inactivation of 4E-BP1 (Gingras et al. 2001; Heesom et al. 2001; Schalm et al. 2003). It has been suggested that mTOR may act in concert with CDK1 to generate fully inactivated/phosphorylated 4E-BP1 isoforms during mitosis [78].

Increased phosphorylation of 4E-BP1 occurs during meiotic M-phase in porcine, bovine and mouse oocytes (Ellederova et al. 2006; Ellederova et al. 2008; Romasko et al. 2013; Susor 2015). Although it is also diffusely located in the oocyte cytoplasm, the presence of phosphorylated 4E-BP1 at the meiotic spindle poles, kinetochores and along the polar microtubules suggests that it represents a possible means of supporting spatially localized protein production [79]. CDK1 and mTOR are the main positive regulators of 4E-BP1 phosphorylation during meiosis in mouse oocytes and CDK1 affects the activity of mTOR localized in the vicinity of chromosomes and on the MII spindle proposing that CDK1 acts indirectly on 4E-BP1 phosphorylation via mTOR activation [8].

It can be concluded that phosphorylation of 4E-BP1 promotes translation during the M-phase to support spindle assembly, highlighting the important role of CDK1 and mTOR kinase in this process.

During the M-phase CDK1 also phosphorylates and inactivates p70S6K, the other mTOR substrate [69,70]. It has been proposed that p70S6K is involved in the regulation of the TOP mRNA translation because the substrates of p70S6K include the eukaryotic translation elongation factor (eEF1A), eukaryotic elongation factor 2 (eEF2) and several ribosomal proteins [66]. Therefore, the CDK1 activity could be involved in the regulation of translation during the M-phase by decreasing the amount of translation factors available. Although p70S6K is phosphorylated by CDK1 at several sites, CDK1 does not phosphorylate p70S6K at Thr389, the mTOR phosphorylation site [70]. In HeLa cells the inhibition of CDK1 resulted in a reduced phosphorylation of the ribosomal protein S6 (RP56), a p70S6K substrate, indicating that CDK1 supports the initiation of translation through the p70S6K signaling pathway, however, CDK1 likely does not act via mTOR as CDK1 inhibition did not alter the integrity of the cap binding complex [13].

7. CDK1 modulates LARP1 activity

The translation and stability of 5’TOP mRNAs can be also regulated by the mTOR dependent phosphorylation of RNA-binding La-related protein 1 (LARP1) since LARP1 functions as a repressor of ribosomal protein mRNA translation downstream of mTOR [80,81]. In LARP1-depleted mitotic Hela cells elevated levels of cyclin B and chromosomes scattered on the mitotic spindle were detected [82]. Structural analysis revealed that LARP1 recognizes the m7Gppp cap moiety and the adjacent 5’ terminal oligopyrimidine sequence found in mRNAs [83]. Binding of LARP1 to the m7Gppp cap of ribosomal protein mRNAs precludes the binding of eukaryotic initiation factor 4E (eIF4E), thus blocking the assembly of the eIF4F
complex on ribosomal protein mRNAs [81,83]. The activity of LARP1 is regulated in an mTOR dependent manner (Hsu et al. 2011; Yu et al. 2011). It has been reported that LARP1 phosphorylation is also dependent on the activity of CDK1 and translation of 5'TOP mRNAs is strongly enhanced by CDK1 via LARP1 [13].

8. CDK1 regulates the elongation step of translation

In eukaryotes, the culmination of translation initiation coincides with the formation of an 80S initiation complex in which Met-tRNAi Met is bound to the P (peptidyl) site of the ribosome. The anticodon of the Met-tRNAi Met is base-paired with the start codon of the mRNA, and the second codon of the open reading frame (ORF) is localized on the A (aminoacyl) site of the ribosome. Elongation is initiated when the cognate elongating aminoacyl-tRNA is delivered to the A site of the ribosome. The eukaryotic translation elongation factor eEF1A is activated upon binding to GTP and creates a ternary complex upon binding to aminoacyl-tRNA [86,87].

CDK1 modulates the activity of elongation factors (Table 1). Translation elongation in eukaryotes is mediated by the determined actions of elongation factor 1A (eEF1A); elongation factor 1B (eEF1B) complex, and elongation factor 2 (eEF2). In HeLa cells and in sea urchin embryos the translation elongation rate declines in synchrony with an increase of CDK1 activity [88,89]. The eEF2 kinase (eEF2K) which inactivates eEF2 is inhibited by phosphorylation at Ser359 and CDK1 has been identified as the kinase phosphorylating eEF2K at Ser359 indicating that CDK1 stimulates the activity of eEF2 during mitosis [90].

In human cells a conserved consensus phosphorylation site for mitotic CDK1 is present on the catalytic δ subunit of eEF1B (termed “eEF1D”). The eEF1D and eEF1By subunits are physiological substrates for CDK1 during the resumption of meiosis in Xenopus oocytes [91,92]. In monkey kidney epithelial cells two eEF1D consensus CDK1 target sites were identified, Ser-133 and Thr-147, whilst eEF1D has been reported to be phosphorylated by CDK1 on Ser-133 in vitro [93]. Phosphorylation of Ser-133 during mitosis in HeLa cells is necessary for the reduced interaction of eEF1D with its substrate eEF1A and leads to a slowdown of translation elongation [87]. It has been proposed that phosphorylation of eEF1D by CDK1 leads to the reduced interaction of the catalytic subunit eEF1D with its substrate eEF1A·GDP, causing a decrease of guanine nucleotide exchange rate by the eEF1B complex followed by a lower level of active eEF1A·GTP during mitosis. Subsequently, less eEF1A·GTP is available for binding and delivering aa-tRNA to ribosomes, inducing a translational slowdown [87]. The above-mentioned data provide clear evidence of the importance of CDK1 in the regulation of elongation step of translation in eukaryotes.

9. Perspectives

Here we summarized findings that point to an extramitotic role of CDK1 in the cell to couple M-phase progression with protein expression. The challenge here is to experimentally uncouple the timing of M-phase progression from the extramitotic function of CDK1. Applying novel [(e.g. imaging, next generation sequencing (NGS)] methods to the naturally cycling cells will shed light to tightly coupled cellular processes. An interesting feature of CDK1-cyclin B is its localization in the cell which might be involved in the regulation of various substrates and the spatio-temporal coupling of two conserved molecular modules, CDK1-cyclin B for the cell cycle and translational regulation for gene expression. This might shed light on the physiological role on localized translation in the newly forming spindle. Future research is needed to elucidate more precisely the role of CDK1 in the regulation of mRNA translation.
Next generation sequencing of the polysomal fractions and cutting edge proteomics approach can contribute to the identification of translational changes in a positive and negative way. Additionally, detailed genome-wide analyses might reveal a subclass of transcriptome or their regulatory motives which are specifically influenced by CDK1 activity.

The direct effect of CDK1 activity on translational regulation is difficult to pinpoint because experimental manipulation of CDK1 activity might influence the timing of cell cycle progression and moreover, the number of CDK1 substrates might play an intermediate role in this process. We expect that more and more substrates with direct/indirect roles in protein synthesis will emerge in the coming years.

CDK1 has an effect on NEBD which leads to the release of numerous components from the nucleoplasm which might radically effect RNA binding proteins, ribosome assembly and/or translational activity.

Further research should be oriented to the extramitotic functioning of kinases in the regulation of translation. Description of the broader role of kinases will provide a new insight into the specialized translation and translational control in human diseases such as cancer. Dysregulation of CDK1 which leads to increased cell proliferation has been identified in various cancers. Accordingly, regulation of CDK1 and usage of CDK-inhibitors have been associated with encouraging results in the treatment of cancer.

Acknowledgments
We thank to Rajan Iyyappan and Michal Dvoran for critical reading of the manuscript. This research was funded by MSMT (EXCELLENCECZ.02.1.01/0.0/0.0/15_003/0000460 OP RDE), GACR (18-19395S; 19-13491S), PPLZ to D.J. (L200451901) and by Institutional Research Concept VO67985904.

Conflicts of Interest
The authors have no conflict of interest to declare.

References:
1. Adhikari, D.; Zheng, W.; Shen, Y.; Gorre, N.; Ning, Y.; Halet, G.; Kaldis, P.; Liu, K. Cdk1, but not Cdk2, is the sole Cdk that is essential and sufficient to drive resumption of meiosis in mouse oocytes. *Hum. Mol. Genet.* 2012, 21, 2476–84, doi:10.1093/hmg/ddq061.
2. Diril, M. K.; Ratnacaram, C. K.; Padmakumar, V. C.; Du, T.; Wasser, M.; Coppola, V.; Tessarollo, L.; Kaldis, P. Cyclin-dependent kinase 1 (Cdk1) is essential for cell division and suppression of DNA re-replication but not for liver regeneration. *Proc. Natl. Acad. Sci.* 2012, 109, 3826–3831, doi:10.1073/pnas.1115201109.
3. Dorée, M.; Peaucellier, G.; Picard, A. Activity of the maturation-promoting factor and the extent of protein phosphorylation oscillate simultaneously during meiotic maturation of starfish oocytes. *Dev. Biol.* 1983, 99, 489–501, doi:10.1016/0012-1606(83)90298-1.
4. Picard, A.; Labbe, J. C.; Doree, M. The cell cycle can occur in starfish oocytes and embryos without the production of transferable MPF (maturation-promoting factor). *Dev. Biol.* 1988, 128, 129–135, doi:10.1016/0012-1606(88)90274-6.
5. Wasserman, W.; Masui, Y. Effects of cycloheximide on a cytoplasmic factor initiating meiotic maturation in Xenopus oocytes. *Exp. Cell Res.* 1975, 91, 381–388, doi:10.1016/0014-4827(75)90118-4.
6. Enserink, J. M.; Kolodner, R. D. An overview of Cdk1-controlled targets and processes. *Cell Div.* 2010, 5, 1–43, doi: 10.1186/1747-1028-5-11.
7. Velásquez, C.; Cheng, E.; Shuda, M.; Lee-Oesterreich, P. J.; Von Strandmann, L. P.; Gritsenko, M. A.; Jacobs, J. M.; Moore, P. S.; Chang, Y. Mitotic protein kinase CDK1 phosphorylation of
mRNA translation regulator 4E-BP1 Ser83 may contribute to cell transformation. *Proc. Natl. Acad. Sci. U. S. A.* **2016**, *113*, 8466–8471, doi:10.1073/pnas.1607768113.

8. Jansova, D.; Koncicka, M.; Tetkova, A.; Cerna, R.; Malik, R.; del Llano, E.; Kubelka, M.; Susor, A. Regulation of 4E-BP1 activity in the mammalian oocyte. *Cell Cycle* **2017**, *16*, 927–939, doi:10.1080/15384101.2017.1295178.

9. Krek, W.; Nigg, E. A. Mutations of p34cdc2 phosphorylation sites induce premature mitotic events in HeLa cells: evidence for a double block to p34cdc2 kinase activation in vertebrates. *EMBO J.* **1991**, *10*, 3331–3341, doi:10.1002/j.1460-2075.1991.tb04897.x.

10. Solomon, M. J.; Glotzer, M.; Lee, T. H.; Philippe, M.; Kirschner, M. W. Cyclin activation of p34cdc2. *Cell* **1990**, *63*, 1013–1024, doi:10.1016/0022-8091(90)90504-8.

11. Tachibana, K.; Ishiura, M.; Uchida, T.; Kishimoto, T. The starfish egg mRNA responsible for meiosis reinitiation encodes cyclin. *Dev. Biol.* **1990**, *140*, 241–252, doi:10.1016/0012-1606(90)90074-S.

12. Li, J.; Tang, J. X.; Cheng, J. M.; Hu, B.; Yung, Y. Q.; Aalia, B.; Li, X. Y.; Jin, C.; Wang, X. X.; Deng, S. L.; Zhang, Y.; Chen, S. R.; Qian, W. P.; Sun, Q. Y.; Huang, X. X.; Liu, Y. X. Cyclin B2 can compensate for Cyclin B1 in oocyte meiosis I. *J. Cell Biol.* **2018**, *217*, 3901–3911, doi:10.1083/jcb.201802077.

13. Hanke, K.; Schott, J.; Lindner, D.; Hollensen, A. K.; Damgaard, C. K.; Mongis, C.; Knop, M.; Palm, W.; Ruggieri, A.; Stoeccklin, G. CDK1 couples proliferation with protein synthesis. *J. Cell Biol.* **2020**, *219*, e201906147, doi:10.1083/jcb.201906147.

14. Li, Y.; Wang, L.; Zhang, L.; He, Z.; Feng, G.; Sun, H.; Wang, J.; Li, Z.; Liu, C.; Han, J.; Mao, J.; Li, P.; Yuan, X.; Jiang, L.; Zhang, Y.; Zhou, Q.; Li, W. Cyclin B3 is required for metaphase to anaphase transition in oocyte meiosis I. *J. Cell Biol.* **2019**, *218*, 1553–1563, doi:10.1083/jcb.201808088.

15. Karasu, M. E.; Bouftas, N.; Keeney, S.; Wassmann, K. Cyclin B3 promotes anaphase onset in oocyte meiosis. *J. Cell Biol.* **2019**, *218*, 1265–1281, doi:10.1083/jcb.201808091.

16. Ellederova, Z.; Kovarova, H.; Melo-Sterza, F.; Livingstone, M.; Tomek, W.; Kubelka, M. Suppression of translation during in vitro maturation of pig oocytes despite enhanced formation of cap-binding protein complex eIF4F and 4E-BP1 hyperphosphorylation. *Mol. Reprod. Dev.* **2006**, *73*, 68–76, doi:10.1002/mrd.20368.

17. Susor, A.; Jansova, D.; Cerna, R.; Danylevska, A.; Anger, M.; Toralova, T.; Malik, R.; Supolíkova, J.; Cook, M. S.; Oh, J. S.; Kubelka, M. Temporal and spatial regulation of translation in the mammalian oocyte via the mTOR-eIF4F pathway. *Nat. Commun.* **2015**, *6*, 6078, doi:10.1038/ncomms7078.

18. Pyronnet, S.; Dostie, J.; Sonenberg, N. Suppression of cap-dependent translation in mitosis. *Genes Dev.* **2001**, *15*, 2083–2093, doi:10.1101/gad.889201.

19. Tanenbaum, M. E.; Stern-Ginossar, N.; Weissman, J. S.; Vale, R. D. Regulation of mRNA translation during mitosis. *Elife* **2015**, *4*, doi:10.7554/eLife.07957.

20. Fan, H.; Penman, S. Regulation of protein synthesis in mammalian cells. II. Inhibition of protein synthesis at the level of initiation during mitosis. *J. Mol. Biol.* **1970**, *50*, 655–670, doi:10.1016/0022-2836(70)90091-4.

21. Tarnowska, M. A.; Baglioni, C. Regulation of protein synthesis in mitotic HeLa cells. *J. Cell. Physiol.* **1979**, *99*, 359–67, doi:10.1002/jcp.1040990311.

22. Coldwell, M. J.; Cowan, J. L.; Vlasak, M.; Mead, A.; Willett, M.; Perry, L. S.; Morley, S. J. Phosphorylation of eIF4GII and 4E-BP1 in response to nocodazole treatment: A reappraisal of translation initiation during mitosis. *Cell Cycle* **2013**, *12*, 3615–3628, doi:10.4161/cc.26588.

23. Shuda, M.; Velásquez, C.; Cheng, E.; Corde, D. G.; Kwun, H. J.; Chang, Y.; Moore, P. S. CDK1 substitutes for mTOR kinase to activate mitotic cap-dependent protein translation. *Proc. Natl. Acad. Sci. U. S. A.* **2015**, *112*, 5875–5882, doi:10.1073/pnas.1505787112.

24. Kim, Y.; Lee, J. H.; Park, J. E.; Cho, J.; Yi, H.; Kim, V. N. PKR is activated by cellular dsRNAs during mitosis and acts as a mitotic regulator. *Genes Dev.* **2014**, *28*, 1310–1322, doi:10.1101/gad.242644.114.
25. Silva, R. C.; Dautel, M.; Di Genova, B. M.; Amberg, D. C.; Castilho, B. A.; Sattlegger, E. The Gcn2 Regulator Yih1 Interacts with the Cyclin Dependent Kinase Cdc28 and Promotes Cell Cycle Progression through G2/M in Budding Yeast. *PLoS One* **2015**, *10*, e0131070, doi:10.1371/journal.pone.0131070.

26. Stonyte, V.; Boye, E.; Grallert, B. Regulation of global translation during the cell cycle. *J. Cell Sci.* **2018**, *131*, doi:10.1242/jcs.220327.

27. Hara, K.; Maruki, Y.; Long, X.; Yoshino, K. ichi; Oshio, N.; Hidayat, S.; Tokunaga, C.; Avruch, J.; Yonezawa, K. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. *Cell* **2002**, *110*, 177–189, doi:10.1016/S0092-8674(02)00833-4.

28. Yu, C. L.; Yang, S. F.; Hung, T. W.; Lin, C. L.; Hsieh, Y. H.; Chiou, H. L. Inhibition of elf2α dephosphorylation accelerates pterostilbene-induced cell death in human hepatocellular carcinoma cells in an ER stress and autophagy-dependent manner. *Cell Death Dis.* **2019**, *10*, doi:10.1038/s41419-019-1639-5.

29. De La Fuente, R.; Viveiros, M. M.; Burns, K. H.; Adashi, E. Y.; Matzuk, M. M.; Eppig, J. J. Major chromatin remodeling in the germinal vesicle (GV) of mammalian oocytes is dispensable for global transcriptional silencing but required for centromeric heterochromatin function. *Dev. Biol.* **2004**, *275*, 447–458, doi:10.1016/j.ydbio.2004.08.028.

30. Eppig, J. J.; Schroeder, A. C. Capacity of Mouse Oocytes from Preantral Follicles to Undergo Embryogenesis and Development to Live Young after Growth, Maturation, and Fertilization in Vitro1. *Biol. Reprod.* **1989**, *41*, 268–276, doi:10.1095/biolreprod41.2.268.

31. Ellederová, Z.; Cais, O.; Šušor, A.; Uhlířová, K.; Kovářová, H.; Jelínková, L.; Tomek, W.; Kubelka, M. ERK1/2 map kinase metabolic pathway is responsible for phosphorylation of translation initiation factor eIF4E during in vitro maturation of pig oocytes. *Mol. Reprod. Dev.* **2008**, *75*, 309–317, doi:10.1002/mrd.20690.

32. Šušor, A.; Jelínková, L.; Karabinová, P.; Torner, H.; Tomek, W.; Kovářová, H.; Kubelka, M. Regulation of cap-dependent translation initiation in the early stage porcine parthenotes. *Mol. Reprod. Dev.* **2008**, *75*, 1716–1725, doi:10.1002/mrd.20913.

33. Tomek, W.; Sterza, F. A. M.; Kubelka, M.; Wollenhaupt, K.; Torner, H.; Anger, M.; Kanit, W. Regulation of Translation During In Vitro Maturation of Bovine Oocytes: The Role of MAP Kinase, elf4E (Cap Binding Protein) Phosphorylation, and elf4E-BP11. *Biol. Reprod.* **2002**, *66*, 1274–1282, doi:10.1095/biolreprod66.5.1274.

34. Fromont-Racine, M.; Senger, B.; Saveau, C.; Fasiolo, F. Ribosome assembly in eukaryotes. *Gene* **2003**, *313*, 17–42, doi: 10.1016/s0378-1119(03)00629-2.

35. Scheer, U.; Hock, R. Structure and function of the nucleolus. *Curr. Opin. Cell Biol.* **1999**, *11*, 385–390, doi: 10.1016/S0955-0674(99)80054-4.

36. Shaw, P. J.; Jordan, E. G. The Nucleolus. *Annu. Rev. Cell Dev. Biol.* **1995**, *11*, 93–121, doi:10.1146/annurev.cb.11.111019.000521.

37. Heix, J.; Vente, A.; Voit, R.; Budde, A.; Michaelidis, T. M.; Grummt, I. Mitotic silencing of human rRNA synthesis: inactivation of the promoter selectivity factor SL1 by cdc2/cyclin B-mediated phosphorylation. *EMBO J.* **1998**, *17*, 7373–81, doi:10.1093/emboj/17.24.7373.

38. Sirri, V.; Roussel, P.; Hernandez-Verdun, D. In vivo release of mitotic silencing of ribosomal gene transcription does not give rise to precursor ribosomal RNA processing. *J. Cell Biol.* **2000**, *148*, 259–70, doi:10.1083/jcb.148.2.259.

39. Yoon, I. S.; Chung, J. H.; Hahm, S. H.; Park, M. J.; Lee, Y. R.; Ko, S. I; Kang, L. W.; Kim, T. S.; Kim, J.; Han, Y. S. Ribosomal protein S3 is phosphorylated by Cdk1/cdc2 during G2/M phase. *BMB Rep.* **2011**, *44*, 529–534, doi:10.5483/BMBRep.2011.44.8.529.

40. Susor, A.; Kubelka, M. Translational regulation in the mammalian oocyte. In *Results and Problems in Cell Differentiation*; Springer Verlag, **2017**; Vol. 63, pp. 257–295, doi:10.1007/978-3-319-60855-6_12.

41. Jang, C. Y.; Kim, H. D.; Zhang, X.; Chang, J. S.; Kim, J. Ribosomal protein S3 localizes on the mitotic spindle and functions as a microtubule associated protein in mitosis. *Biochim. Biophys. Res. Commun.* **2012**, *429*, 57–62, doi:10.1016/j.bbrc.2012.10.093.
42. Simsek, D.; Tiu, G. C.; Flynn, R. A.; Byeon, G. W.; Leppke, K.; Xu, A. F.; Chang, H. Y.; Barna, M. The Mammalian Ribonome Reveals Ribosome Functional Diversity and Heterogeneity. *Cell* **2017**, *169*, 1051-1065.e18, doi:10.1016/j.cell.2017.05.022.

43. Imami, K.; Milek, M.; Bogdanow, B.; Yasuda, T.; Kastelic, N.; Zauber, H.; Ishihama, Y.; Landthaler, M.; Selbach, M. Phosphorylation of the Ribosomal Protein RPL12/uL11 Affects Translation during Mitosis. *Mol. Cell* **2018**, *72*, 84-98.e9, doi:10.1016/j.molcel.2018.08.019.

44. Gnädig, F.; Gunawardena, J.; Mann, M. PHOSIDA 2011: the posttranslational modification database. *Nucleic Acids Res.* **2011**, *39*, D253-60, doi:10.1093/nar/gkq1159.

45. Olsen, J. V.; Vermeulen, M.; Santamaria, A.; Kumar, C.; Miller, M. L.; Jensen, L. J.; Gnädig, F.; Cox, J.; Jensen, T. S.; Nigg, E. A.; Brunak, S.; Mann, M. Quantitative phosphoproteomics reveals widespread full phosphorylation site occupancy during mitosis. *Sci. Signal.* **2010**, *3*, doi:10.1126/scisignal.2000475.

46. Hernandez-Verdun, D. Assembly and disassembly of the nucleolus during the cell cycle. *Nucleus* **2011**, *2*, 189–194, doi:10.4161/ncl.2.3.16246.

47. Murano, K.; Okuwaki, M.; Hisaoka, M.; Nagata, K. Transcription Regulation of the rRNA Gene by a Multifunctional Nucleolar Protein, B23/Nucleophosmin, through Its Histone Chaperone Activity. *Mol. Cell. Biol.* **2008**, *28*, 3114–3126, doi:10.1128/mcb.02078-07.

48. Okuwaki, M.; Matsumoto, K.; Tsujimoto, M.; Nagata, K. Function of nucleophosmin/B23, a nucleolar acidic protein, as a histone chaperone. *FEBS Lett.* **2001**, *506*, 272–276, doi:10.1016/S0014-5793(01)02939-8.

49. Yu, Y.; Maggi, L. B.; Brady, S. N.; Apicelli, A. J.; Dai, M.-S.; Lu, H.; Weber, J. D. Nucleophosmin Is Essential for Ribosomal Protein L5 Nuclear Export. *Mol. Cell. Biol.* **2006**, *26*, 3798–3809, doi:10.1128/mcb.26.10.3798-3809.2006.

50. Hisaoka, M.; Ueshima, S.; Murano, K.; Nagata, K.; Okuwaki, M. Regulation of Nucleolar Chromatin by B23/Nucleophosmin Jointly Depends upon Its RNA Binding Activity and Transcription Factor UBF. *Mol. Cell. Biol.* **2010**, *30*, 4952–4964, doi:10.1128/mcb.00299-10.

51. Jackman, M.; Lindon, C.; Nigg, E. A.; Pines, J. Active cyclin B1–CdK1 first appears on centrosomes in prophase. *Nat. Cell Biol.* **2003**, *5*, 143–148, doi:10.1038/ncb918.

52. Karabinova, P.; Kubelka, M.; Susor, A. Proteasomal degradation of ubiquitinated proteins in oocyte meiosis and fertilization in mammals. *Cell Tissue Res.* **2011**, *346*, 1–9, doi:10.1007/s00441-011-1235-1.

53. Gavet, O.; Pines, J. Progressive Activation of CyclinB1-Cdk1 Coordinates Entry to Mitosis. *Dev. Cell* **2010**, *18*, 533–543, doi:10.1016/j.devcel.2010.02.013.

54. Pines, J.; Hunter, T. Cyclin-dependent kinases: a new cell cycle motif? *Trends Cell Biol.* **1991**, *1*, 117–21, doi:10.1016/0962-8924(91)90116-q.

55. Bischof, J.; Brand, C. A.; Somogyi, K.; Májer, I.; Thome, S.; Mori, M.; Schwarz, U. S.; Lénárt, P. A cdk1 gradient guides surface contraction waves in oocytes. *Nat. Commun.* **2017**, *8*, 1–10, doi:10.1038/s41467-017-00979-6.

56. Shatkin, A. J. Capping of eucaryotic mRNAs. *Cell* **1976**, *9*, 645–653, doi:10.1016/0092-8674(76)90128-8.

57. Sonenberg, N.; Morgan, M. A.; Merrick, W. C.; Shatkin, A. J. A polypeptide in eukaryotic initiation factors that crosslinks specifically to the 5‘-terminal cap in mRNA. *Proc. Natl. Acad. Sci. U. S. A.* **1978**, *75*, 4843–4847, doi:10.1073/pnas.75.10.4843.

58. Imataka, H.; Gradi, A.; Sonenberg, N. A newly identified N-terminal amino acid sequence of human elf4g binds poly(A)-binding protein and functions in poly(A)-dependent translation. *EMBO J.* **1998**, *17*, 7480–9, doi:10.1093/emboj/17.24.7480.

59. Sachs, A. B.; Davis, R. W. The poly(A) binding protein is required for poly(A) shortening and 60S ribosomal subunit-dependent translation initiation. *Cell* **1989**, *58*, 857–867, doi:10.1016/0092-8674(89)90938-0.

60. Wells, S. E.; Hillner, P. E.; Vale, R. D.; Sachs, A. B. Circularization of mRNA by eukaryotic translation initiation factors. *Mol. Cell* **1998**, *2*, 135–140, doi:10.1016/S1097-2765(00)80122-7.
61. Bonneau, A. M.; Sonenberg, N. Involvement of the 24-kDa cap-binding protein in regulation of protein synthesis in mitosis. *J. Biol. Chem.* **1987**, *262*, 11134–11139.

62. Sengupta, C.; Peterson, T. R.; Sabatini, D. M.; Sengupta, S. Regulation of the mTOR Complex 1 Pathway by Nutrients, Growth Factors, and Stress. *Mol. Cell* **2010**, *40*, 310–322, doi:10.1016/j.molcel.2010.09.026.

63. Burnett, P. E.; Barrow, R. K.; Cohen, N. A.; Snyder, S. H.; Sabatini, D. M. RAFT1 phosphorylation of the translational regulators p70 S6 kinase and 4E-BP1. *Proc. Natl. Acad. Sci. U. S. A.* **1998**, *95*, 1432–1437, doi:10.1073/pnas.95.4.1432.

64. Gingras, A. C.; Raught, B.; Gygi, S. P.; Niedzwiecka, A.; Miron, M.; Burley, S. K.; Polakiewicz, R. D.; Wyslouch-Cieszynska, A.; Aebersold, R.; Sonenberg, N. Hierarchical phosphorylation of the translation inhibitor 4E-BP1. *Genes Dev.* **2001**, *15*, 2852–2864, doi:10.1101/gad.912401.

65. Sonenberg, N.; Hinnebusch, A. G. Regulation of Translation Initiation in Eukaryotes: Mechanisms and Biological Targets. *Cell* **2009**, *136*, 731–745, doi:10.1016/j.cell.2009.01.042.

66. Meyuhas, O.; Kahan, T. The race to decipher the top secrets of TOP mRNAs. *Biochim. Biophys. Acta* **2015**, *1849*, 801–11, doi:10.1016/j.bbagrm.2014.08.015.

67. Yamashita, R.; Suzuki, Y.; Takeuchi, N.; Wagakuri, H.; Ueda, T.; Sugano, S.; Nakai, K. Comprehensive detection of human terminal oligo-pyrimidine (TOP) genes and analysis of their characteristics. *Nucleic Acids Res.* **2008**, *36*, 3707–3715, doi:10.1093/nar/gkn248.

68. Fingar, D. C.; Richardson, C. J.; Tee, A. R.; Cheatham, L.; Tsou, C.; Blenis, J. mTOR Controls Cell Cycle Progression through Its Cell Growth Effectors S6K1 and 4E-BP1/Eukaryotic Translation Initiation Factor 4E. *Mol. Cell. Biol.* **2004**, *24*, 200–216, doi:10.1128/mcb.24.1.200-216.2004.

69. Papst, P. J.; Sugiyama, H.; Nagasawa, M.; Lucas, J. J.; Maller, J. L.; Terada, N. Cdc2-cyclin B phosphorylates p70 S6 kinase on Ser411 at mitosis. *J. Biol. Chem.* **1998**, *273*, 15077–15084, doi:10.1074/jbc.273.24.15077.

70. Shah, O. J.; Ghosh, S.; Hunter, T. Mitotic regulation of ribosomal S6 kinase 1 involves Ser/Thr, Pro phosphorylation of consensus and non-consensus sites by Cdc2. *J. Biol. Chem.* **2003**, *278*, 16433–16442, doi:10.1074/jbc.M300435200.

71. Heesom, K. J.; Avison, M. B.; Diggle, T. A.; Denton, R. M. Insulin-stimulated kinase from rat fat cells that phosphorylates initiation factor 4E-binding protein 1 on the rapamycin-insensitive site (serine-111). *Biochem. J.* **1998**, *336*, 39–48, doi:10.1042/bj3360039.

72. Pyronnet, S.; Pradayrol, L.; Sonenberg, N. A cell cycle-dependent internal ribosome entry site. *Mol. Cell* **2000**, *5*, 607–616, doi:10.1016/S1097-2765(00)00240-3.

73. Miettinen, T. P.; Kang, J. H.; Yang, L. F.; Manalis, S. R. Mammalian cell growth dynamics in mitosis. *Elife* **2019**, *8*, doi:10.7554/elife.44700.

74. Gingras, A.-C.; Raught, B.; Sonenberg, N. elf4 Initiation Factors: Effectors of mRNA Recruitment to Ribosomes and Regulators of Translation. *Annu. Rev. Biochem.* **1999**, *68*, 913–963, doi:10.1146/annurev.biochem.68.1.913.

75. Shah, O. J.; Anthony, J. C.; Kimball, S. R.; Jefferson, L. S. 4E-BP1 and S6K1: Translational integration sites for nutritional and hormonal information in muscle. *Am. J. Physiol. - Endocrinol. Metab.* **2000**, *279*:E715-E729, doi:10.1152/ajpendo.2000.279.A.E715.

76. Heesom, K. J.; Gampel, A.; Mellor, H.; Denton, R. M. Cell cycle-dependent phosphorylation of the translational repressor elf-4E binding protein-1 (4E-BP1). *Curr. Biol.* **2001**, *11*, 1374–1379, doi:10.1016/S0960-9822(01)00422-5.

77. Schalm, S. S.; Fingar, D. C.; Sabatini, D. M.; Blenis, J. TOS Motif-Mediated Raptor Binding Regulates 4E-BP1 Multisite Phosphorylation and Function Drosophila or specific inhibition of mammalian TOR (mTOR) by the immunosuppressant rapamycin results in reduced cell size and cell proliferation [2-4]. The best. *Curr. Biol.* **2003**, *13*, 797–806, doi: 10.1016/S0960-9822(03)00329-4.

78. Sun, R.; Cheng, E.; Velásquez, C.; Chang, Y.; Moore, P. S. Mitosis-related phosphorylation of the eukaryotic translation suppressor 4E-BP1 and its interaction with eukaryotic translation initiation factor 4E (eIF4E). *J. Biol. Chem.* **2019**, *294*, 11840–11852, doi:10.1074/jbc.RA119.008512.
93. Phosphorylation Site in Eukaryotic Elongation Factor 1 Protein Kinases Encoded by Herpesviruses and Cellular Protein Kinase cdc2 Target the Same

Kawaguchi, R.; Bellé, R. Elongation factor EF-M1 protein respectively homologous to elongation factors EF-

Mulner complex from Xenopus oocytes contains a p47 protein, an in vivo substrate of MPF, and a p30

acid Sm

Nucleic Acids Res. regulation of protein synthesis at the elongation step by CDK1/cyclin B phosphorylation.

Monnier, A.; Bellé, R.; Morales, J.; Cormier, P.; Boulben, S.; Mulner

2008 doi:10.1074/jbc.M111.255810.

to hindered tRNA delivery to ribosomes.

Sivan, G.; Aviner, R.; Elroy-Stein, O. Mitotic modulation of translation elongation factor 1 leads to hindered tRNA delivery to ribosomes. J. Biol. Chem. 2011, 286, 27927–35, doi:10.1074/jbc.M111.255810.

84. Hsu, P. P.; Kang, S. A.; Rameseder, J.; Zhang, Y.; Ottina, K. A.; Lim, D.; Peterson, T. R.; Choi, Y.; Gray, N. S.; Yaffe, M. B.; Marto, J. A.; Sabatini, D. M. The mTOR-regulated phosphoproteome reveals a mechanism of mTORC1-mediated inhibition of growth factor signaling. Science 2011, 332, 1317–1322, doi:10.1126/science.1199498.

85. Yu, Y.; Yoon, S. O.; Poulogiannis, G.; Yang, Q.; Ma, X. M.; Villén, J.; Kubica, N.; Hoffman, G. R.; Cantley, L. C.; Gygi, S. P.; Blenis, J. Phosphoproteomic analysis identifies Grb10 as an mTORC1 substrate that negatively regulates insulin signaling. Science 2011, 332, 1322–1326, doi:10.1126/science.1199484.

86. Jakobsson, M. E.; Malecki, J.; Falnes, P. Regulation of eukaryotic elongation factor 1 alpha (eEF1A) by dynamic lysine methylation. RNA Biol. 2018, 15, 314–319, doi:10.1080/15476286.2018.1440875.

87. Sivan, G.; Aviner, R.; Elroy-Stein, O. Mitotic modulation of translation elongation factor 1 leads to hindered tRNA delivery to ribosomes. J. Biol. Chem. 2011, 286, 27927–35, doi:10.1074/jbc.M111.255810.

88. Sivan, G.; Elroy-Stein, O. Regulation of mRNA Translation during cellular division. Cell Cycle 2008, 7, 741–4, doi:10.4161/cc.7.6.5596.

89. Monnier, A.; Bellé, R.; Morales, J.; Cormier, P.; Boulben, S.; Mulner-Lorillon, O. Evidence for regulation of protein synthesis at the elongation step by CDK1/cyclin B phosphorylation. Nucleic Acids Res. 2001, 29, 1453–7, doi:10.1093/nar/29.7.1453.

90. Smith, E. M.; Proud, C. G. cdc2-cyclin B regulates eEF2 kinase activity in a cell cycle- and amino acid-dependent manner. EMBO J. 2008, 27, 1005–1016, doi:10.1038/emboj.2008.39.

91. Bellé, R.; Derancourt, J.; Pouleux, R.; Capony, J. P.; Ozon, R.; Mulner-Lorillon, O. A purified complex from Xenopus oocytes contains a p47 protein, an in vivo substrate of MPF, and a p30 protein respectively homologous to elongation factors EF-1γ and EF-1β. FEBS Lett. 1989, 255, 101–104, doi:10.1016/0014-5793(89)81069-5.

92. Mulner-Lorillon, O.; Minella, O.; Cormier, P.; Capony, J. P.; Cavadore, J. C.; Morales, J.; Pouleux, R.; Bellé, R. Elongation factor EF-1 delta, a new target for maturation-promoting factor in Xenopus oocytes. J. Biol. Chem. 1994, 269, 20201–7.

93. Kawaguchi, Y.; Kato, K.; Tanaka, M.; Kanamori, M.; Nishiyama, Y.; Yamanashi, Y. Conserved Protein Kinases Encoded by Herpesviruses and Cellular Protein Kinase cdc2 Target the Same Phosphorylation Site in Eukaryotic Elongation Factor 1. J. Virol. 2003, 77, 2359–2368,
doi:10.1128/jvi.77.4.2359-2368.2003.