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Regulation of global and specific mRNA translation by the mTOR signaling pathway

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Abbreviations: 4E-BP, eIF4E-binding protein; TOP, terminal oligopyrimidine; eEF, eukaryotic elongation factor; eIF, eukaryotic initiation factor; ERK, extracellular signal-regulated kinase; mTOR, mammalian/mechanistic target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; PDCD4, programmed cell death protein 4; PI3K, phosphatidylinositol 3-phosphate kinase; PKC, protein kinase C; Raptor, regulatory-associated protein of mTOR; Rictor, rapamycin-insensitive companion of mTOR; rp, ribosomal protein; S6K, p70 ribosomal S6 kinase

The translation of mRNA into polypeptides is a key step in eukaryotic gene expression. Translation is mostly controlled at the level of initiation, which is partly regulated by the mammalian/mechanistic target of rapamycin (mTOR) signaling pathway. Whereas mTOR controls global protein synthesis through specific effector proteins, its role in the translation of select groups of mRNAs, such as those harboring a terminal oligopyrimidine (TOP) tract at their 5′ end, remains more enigmatic. In this article, we describe the current knowledge on the role of mTOR in global mRNA translation, but also focus on the potential molecular mechanisms underlying the regulation of specific translational programs.

Introduction

The translation of mRNA into polypeptides requires substantial cellular resources,[1] and as such, cells have evolved complex mechanisms to tightly regulate this process. Protein synthesis is frequently deregulated in cancer cells to support aberrant cell growth and proliferation.[2] Consistent with this, intense efforts are currently being deployed to identify therapeutic agents that would target components of the translational machinery.[3] Translation is mostly controlled at the initiation step, during which the eukaryotic small 40S ribosomal subunit is recruited to the 5'-terminal m^{7}G[5']ppp[5']N-cap structure of mRNA (where N can be any nucleotide).[4] This step is facilitated by several eukaryotic translation initiation factors (eIFs) and is partly regulated by the mammalian/mechanistic target of rapamycin (mTOR) signaling pathway.[5] The latter senses and responds to nutrient availability, energy sufficiency, stress and mitogens to modulate protein synthesis.[6] In this article, we will cover the mechanisms of cap-dependent translation, but also discuss what is known about the role of mTOR in the translation of specific subsets of mRNAs in light of recent findings.

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Regulation of cap-dependent translation by mTOR signaling

Under favorable growth conditions, mTOR promotes assembly of the eukaryotic translation initiation factor 4F (eIF4F) complex at the 5' end of mRNA (**Fig. 1**), which facilitates the recruitment of the ribosome and subsequent translation of the transcript.[7] eIF4F is a heterotrimeric protein complex, consisting of the cap-binding protein eIF4E, the large scaffolding protein eIF4G and the DEAD (Asp-Glu-Ala-Asp)-box RNA helicase eIF4A (also known as DDX2).[8] eIF4E directly binds to the m^{7}G-cap structure and is required for the cap-dependent translation of all nuclear-encoded transcripts.[9] eIF4G interacts with several proteins, including the large multisubunit protein eIF3 within the 43S pre-initiation complex (PIC), thereby bridging the small ribosomal subunit to the mRNA.[7] Following recruitment and formation of a 48S complex, the ribosome scans the mRNA towards the initiation codon, a process that is facilitated by the ability of eIF4A to unwind potential secondary structures in the 5' untranslated region (5' UTR) of mRNA.[10,11] Whereas the intrinsic helicase activity of eIF4A is weak,[12] this can be stimulated by its association with the eIF4F complex, as well as with its regulatory factors eIF4B and eIF4H.[13] eIF4G also interacts with the poly (A)-binding protein (PABP), which associates with the 3' end of mRNA and allows circularization of the transcript to promote its translation.[14] Recruitment of the 60S ribosomal subunit at the initiation codon results in formation of a translation-competent 80S ribosome that begins the elongation of a new polypeptide chain. Translation elongation is also partly regulated at the level of the eukaryotic elongation factor 2 (eEF2) by mTOR signaling, but this has been thoroughly reviewed elsewhere.[15]

The protein Ser/Thr kinase mTOR is the catalytic subunit of 2 functionally and structurally distinct multiprotein complexes

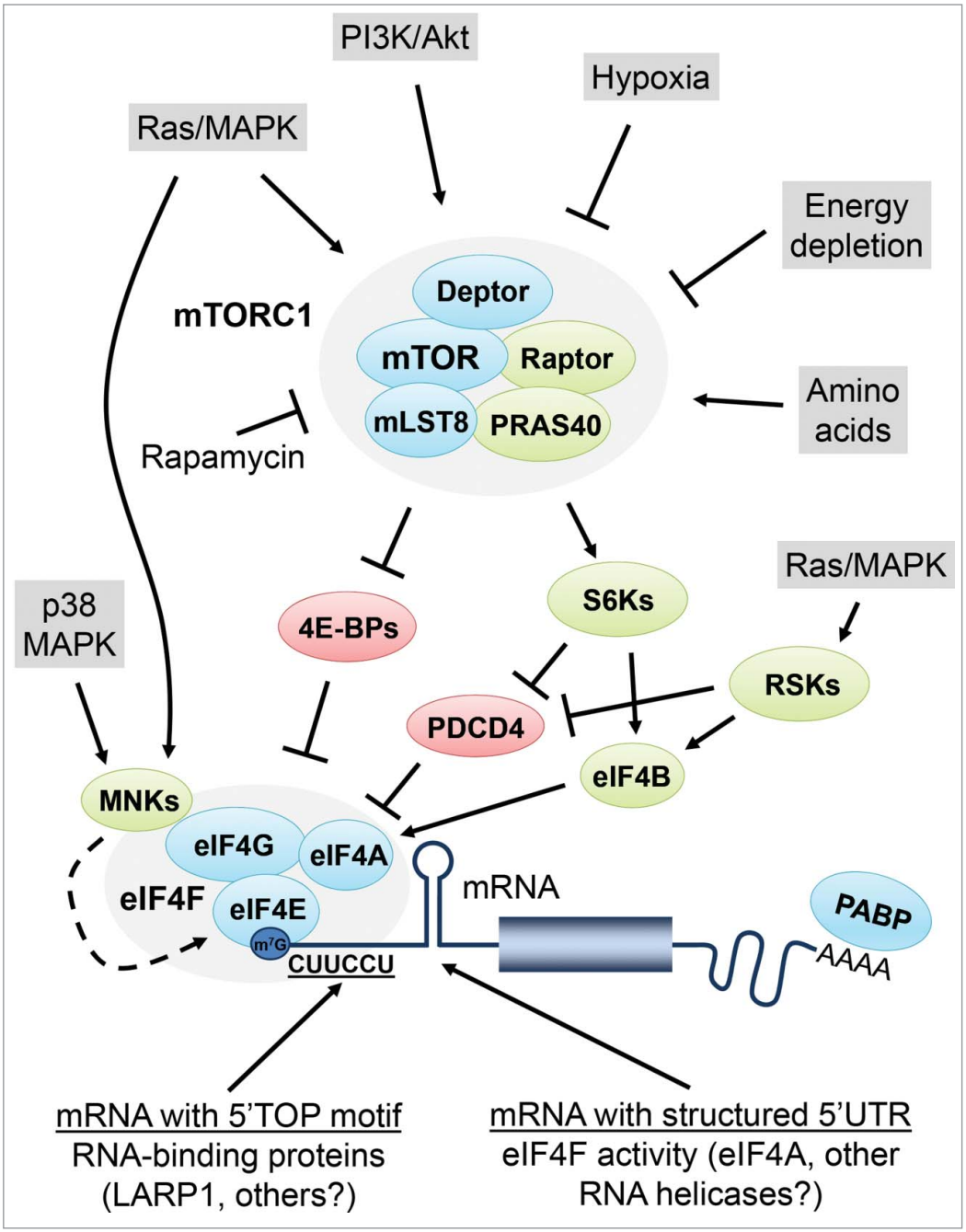

Figure 1. Schematic representation of mTORC1 signaling to the translational machinery. Growth factors and hormones stimulate mTORC1 activity via the Ras/MAPK and PI3K/Akt signaling pathways. mTORC1 is also activated by amino acids, and inactivated by energy depletion and hypoxia. mTORC1 promotes mRNA translation by regulating the 4E-BPs and S6Ks, which in turn modulate downstream effector proteins such as PDCD4 and eIF4B. Phosphorylation of the 4E-BPs by mTORC1 leads to their dissociation from eIF4E, thereby stimulating assembly of the eIF4F complex. The helicase activity associated with the eIF4F complex is thought to be critical for the unwinding of secondary structures within the mRNA 5′UTR, thereby facilitating scanning of the ribosome toward the initiation codon. The S6Ks and RSKs are thought to modulate eIF4A activity by phosphorylating eIF4B and the tumor suppressor PDCD4. The MNKs are recruited via eIF4G and directly phosphorylate eIF4E. mRNAs which contain a 5′ terminal oligopyrimidine (TOP) motif are dependent on mTORC1 activity for their translation. Several RNA-binding proteins were suggested to bind to the TOP motif and regulate TOP mRNA translation, including the La-related protein 1 (LARP1).

known as mTOR complex 1 (mTORC1) and complex 2 (mTORC2), which are defined by the components Raptor (regulatory-associated protein of mTOR) and Rictor (rapamycin-insensitive companion of mTOR), respectively.[16,17] Both Raptor and Rictor serve as necessary scaffolds that contribute to the integrity of each complex and facilitate the recruitment of mTOR substrates. Whereas mTORC1 controls several anabolic processes required for cell growth and proliferation, such as protein, lipid and nucleotide synthesis,[6,18] mTORC2 regulates the activity of several AGC (protein kinase A, G and C) family members (e.g., Akt, SGK1, PKCα) that are involved in cell survival and cytoskeletal reorganization.[19] While the central role of mTOR in protein synthesis is largely attributed to mTORC1,[5,20] mounting evidence suggests that mTORC2 may play a role in cotranslational processing or maturation of nascent polypeptides as they emerge from the ribosome.[21,22] mTORC1 coordinates mRNA translation by phosphorylating components of the translational machinery, including its 2 best characterized substrates: the eIF4E-binding proteins (4E-BPs) and the ribosomal S6 kinases (S6Ks) 1 and 2 (**Fig. 1**).[5,23,24] Using pharmacological inhibitors and genetic models, the functions of the 4E-BPs and S6Ks can be separated in cells, with the 4E-BPs playing comparatively more

important roles in the regulation of cell proliferation.[25] Mammals have 3 4E-BP isoforms (4E-BP1, 2 and 3) which are small proteins that repress mRNA translation at the initiation step by interfering with eIF4F complex assembly.[26,27] In quiescent cells, the 4E-BPs are kept in a hypophosphorylated state and strongly associate with eIF4E, thereby preventing eIF4G binding and eIF4F assembly. Once activated, mTORC1 phosphorylates Thr37/46 in human 4E-BP1, which are priming sites for subsequent phosphorylation at Ser65 and Thr70.[28,29] These phosphorylation events lead to 4E-BP1 release from eIF4E and subsequent initiation of translation.[27] While these regulatory events are thought to be the principal means by which mTORC1 controls global protein synthesis, cells do not respond equally to the inhibition of mTOR.[30,31] A potential explanation for this comes from findings that the level of expression of the 4E-BPs respective to eIF4E determines the response of cells to mTOR inhibitors.[25,32] Given that the ratio of eIF4E to the 4E-BPs may differ between cell types, this provides a likely explanation for the differing susceptibility of cancer cells to mTOR inhibitors.[32] Additional protein kinases have been shown to regulate phosphorylation of the 4E-BPs, including GSK3β and CK1ε,[33,34] but their relevance in oncogene- and growth factor-induced protein synthesis remains unknown at the moment.

Translational Regulation of "eIF4E-sensitive" Transcripts

Whereas mTORC1 controls global protein synthesis by regulating eIF4F assembly, it also preferentially stimulates the translation of select groups of mRNAs through mechanisms that remain elusive. Among these mRNA subsets are transcripts that contain relatively long and structured 5' UTRs, also referred to as "eIF4E-sentitive" mRNAs (**Fig. 1**).[35] These include several mRNAs encoding proteins involved in cell survival and proliferation,[25] such as cyclins,[36] ornithine decarboxylase (ODC),[37] VEGF[38] and Myc.[39] Unlike housekeeping mRNAs, which typically do not possess structured 5' UTRs (e.g.,, GAPDH and β-actin), the majority of eIF4E-sensitive mRNAs have long and highly structured 5' UTRs.[35,40,41] This feature makes them more dependent on the unwinding activity of eIF4A within the eIF4F complex,[42] and thus highly sensitive to the levels of eIF4E in the cell. eIF4E was also found to promote eIF4A activity by binding to an autoinhibitory domain of eIF4G, providing additional means by which eIF4E selectively stimulates the translation of highly structured mRNAs.[43] Consistent with this, eIF4E has been shown to be overexpressed in many types of cancer, and its expression often correlates with disease progression.[44] Recently, another subset of mRNAs encoding proteins involved in mitochondrial function and biogenesis has been shown to be sensitive to eIF4E,[45] but these do not appear to have long 5'UTRs and the mechanisms responsible for their eIF4E sensitivity remains mostly uncharacterized.

As mTORC1 directly controls assembly of the eIF4F complex, its activity is thought to be particularly important for the translation of "eIF4E-sensitive" transcripts. In addition to the 4E-BPs, mTORC1 regulates eIF4A activity via the S6Ks.[5] Programmed cell death protein 4 (PDCD4) is a binding partner of eIF4A that inhibits translation initiation by preventing assembly of eIF4F complexes.[46] Phosphorylation of a phosphodegron motif within PDCD4 by the S6Ks was shown to promote its ubiquitination and proteasomal degradation.[47] The S6Ks also phosphorylate eIF4B, a co-factor of eIF4A.[48] It was found that eIF4B phosphorylation promotes its recruitment to the eIF4F complex and thereby facilitates cap-dependent translation.[49-51] These regulatory events were shown to promote the translation of several mRNAs with structured 5'UTRs, including those transcripts encoding proteins involved in cell proliferation (Cdc25C, Myc, ODC) and survival (Bcl-2 and XIAP).[52] Additional AGC family members have been shown to similarly regulate both PDCD4 and eIF4B, including RSK (p90 ribosomal S6 kinase) and Akt,[50,53,54] underscoring the importance of regulating eIF4F activity in the promotion of different gene expression programs.

In higher eukaryotes, eIF4E is phosphorylated on Ser209 in response to stress and mitogen stimulation,[55] and this phosphorylation event was shown to be mediated by the MAPK-interacting kinases (MNK1 and 2).[56,57] To phosphorylate eIF4E, the MNKs are recruited to the eIF4F complex via a direct interaction with the C-terminal region of eIF4G.[58] Although phosphorylation of eIF4E does not have a major impact on global translation rates, it was found to stimulate the translation of a subset of mRNAs encoding proteins involved in survival (e.g., Mcl1)[59] and tumor invasion (e.g.,, Snail, MMP-3).[60,61] Translational regulation of *Snail* and *MMP-3* mRNAs was found to promote epithelial-to-mesenchymal transition (EMT), pointing to a role for eIF4E phosphorylation in cancer metastasis.[60] However, the precise mechanisms by which eIF4E phosphorylation affects the translation of these transcripts remain to be determined.

Translational control of TOP mRNAs

A second group of mRNAs, harboring a terminal oligopyrimidine (TOP) tract at their 5' end, was shown to be particularly sensitive to mTOR inhibitors.[62] These mRNAs encode for components of the translational apparatus, such as ribosomal proteins and elongation factors.[63,64] The 5'TOP sequence consists of a cytosine at the penultimate nucleotide position followed by a stretch of 4–14 pyrimidines (**Fig. 1**).[63,64] The translation of TOP mRNAs is highly sensitive to stress and growth conditions, and behaves as an "all-or-none" phenomenon. Recent studies using high-resolution transcriptome-scale ribosome profiling have confirmed that the translation of TOP mRNAs is highly sensitive to mTOR inhibitors,[30,31] but the mechanisms by which this occurs still remain unclear.[65] These studies demonstrated that the selective regulation of TOP mRNAs by mTORC1 depends on the regulation of eIF4E by the 4E-BPs, as the deletion of the latter rendered TOP mRNA translation resistant to mTORC1 inhibition.[30,31] While these data suggest that the 4E-BPs are required for TOP mRNA translation, another study has shown that hypoxia and other types of stresses suppress TOP mRNA translation independently of the 4E-BPs.[66] The variance

between studies can be partially explained by differing experimental conditions, nevertheless it does suggest that additional factors may be required for TOP mRNA translation in a context-dependent manner.[65]

Several candidate proteins have been proposed over the years as potential modulators of TOP mRNAs, including the abundant La antigen (also known as La-related protein 3 [LARP3]).[67-69] LARP3 was shown to directly interact with mRNAs containing a 5'TOP motif within actively translating polysomes, suggesting that it plays a positive role in TOP mRNA translation.[67] The RNA-binding protein AUF1 (AU-rich element RNA-binding protein 1) was also found to interact with the 5'TOP sequence, but in this case AUF1 binding correlated with translational repression of TOP mRNAs.[70] Similarly, the stress granule-associated TIA-1 (T-cell-restricted Intracellular Antigen-1) and TIAR (TIA-1-related protein) were found to assemble at the 5' end of TOP mRNAs and inhibit their translation.[71] This translational suppression required the inactivation of mTOR signaling, suggesting a molecular mechanism by which availability of nutrients may redirect limited cellular resources during suboptimal growth conditions.

In a recent report from our group, we showed that the La-related protein 1 (LARP1) associates with TOP mRNAs and facilitates their translation in cells.[72] This protein was previously shown to associate with and promote the stability of TOP mRNAs,[73] suggesting that LARP1 may regulate TOP mRNAs at different levels to control their expression in cells. Interestingly, 2 studies aiming to characterize the mTOR phosphoproteome repertoire have identified LARP1 as a potential mTORC1 phosphorylation substrate.[74,75] This finding was recently corroborated using both *in vitro* and *in vivo* phosphorylation assays,[76] confirming LARP1 as a *bona fide* mTORC1 substrate.[77] Consistent with this, LARP1 was found to interact with the mTORC1-specific component Raptor, suggesting that LARP1 is an mTORC1-specific cell growth effector.[72] At this point in time, the biological significance of LARP1 phosphorylation by mTORC1 remains unknown, but results suggest that these phosphorylation events may positively regulate LARP1 function, perhaps by modulating its interaction with mRNA. LARP1 may be one of the many unrecognized regulators of specific mRNA translation downstream of mTORC1, which may provide additional means for promoting or suppressing the translation of specific subsets of mRNAs.

Local translation of TOP mRNAs in Activity-dependent Protein Synthesis

In addition to playing roles in determining the type of transcripts to be translated, mTORC1 regulates mRNA translation in space and time.[78,79] This is likely to be particularly important for synaptic plasticity, such as during the late phase of long-term potentiation (L-LTP), which requires local increases in protein synthesis in response to synaptic activity.[80-82] Neuronal mTORC1 becomes activated in response to different stimulation paradigms (i.e., forskolin, high-frequency stimulation, mGluR agonists), and its inhibition by rapamycin was found to block long-lasting synaptic changes and memory consolidation in different animal models.[78] Notably, a number of studies have documented an elevation in the levels of elongation factors eEF1A and eEF2, as well as ribosomal protein S6, in response to synaptic activity in both mammals and *Aplysia*.[83-88] All of these proteins are encoded by TOP mRNAs,[64] suggesting that mTORC1 may participate in synaptic plasticity by locally increasing the availability of translation factors and other components of the translational apparatus.[78] Evidence for this comes from the observation that TOP mRNAs are transported into dendrites and axons where they are locally translated in an mTORC1-dependent manner.[88,89] In fact, TOP mRNAs represent some of the most abundant transcripts localized within these structures.[90,91]

While it seems unlikely that new ribosomes are assembled in this compartment, as this process is thought to strictly occur in the nucleolus,[92] the translation of TOP mRNAs may serve to selectively replace or replete translation factors and ribosomal proteins during times of increased demand in protein synthesis.[78] Another possibility is that certain elongation factors encoded by TOP mRNAs may be present in dendrites and axons in limiting amounts, such that increasing their expression by promoting TOP mRNA translation would significantly increase overall translation rates. Alternatively, certain proteins encoded by TOP mRNAs may serve extraribosomal functions that may or may not be specific to neuronal cells.[78] Our results implicating LARP1 in TOP mRNA translation suggest that this protein may also be involved in local mRNA translation.[72] Based on mRNA expression profiles, LARP1 is ubiquitously expressed with relatively high expression levels in the nervous system. One possibility is that LARP1 may be required for TOP mRNA translation in specific compartments, such as dendrites and axons, but the potential role of LARP1 in the nervous system remains highly speculative at the moment.

mTORC1 Regulates the Cap Recruitment of a Network of Translational Regulators

Using m^7G-cap affinity chromatography and quantitative mass spectrometry (MS), our group has globally surveyed proteins that directly or indirectly interact with the 5' mRNA cap structure.[72] This search has led to the identification of ~160 distinct proteins, from which a majority was found to co-purify based on protein-protein interactions (their purification was resistant to nuclease treatment). This characterization was performed under conditions where mTOR activity was either increased by insulin treatment or reduced using an mTOR inhibitor, which revealed an orchestrated network of interactions to the 5' mRNA cap structure that is dependent on mTOR activity. As expected, we found that many known translational regulators were recruited to the 5' mRNA cap in a manner that was dependent on mTOR activity, including eIF4G, eIF4A, and eIF3 isoforms, as well as PABP. We identified 4E-BP1 and 2 as the only 2 proteins whose interactions negatively correlated with mTOR activity,[72] suggesting that they may be responsible for the

displacement of all eIF4E-dependent proteins upon mTOR inhibition. To address this, we compared mTOR responsiveness between wild-type and double *4E-BP1/2* knockout fibroblasts, and found that all mTOR-dependent regulations were lost in cells lacking the 4E-BPs.[72] These results underscore the role of the 4E-BPs in regulating proteins' access to eIF4E, and suggest that the effects of mTOR inhibitors on global protein synthesis are highly dependent on the 4E-BPs, as reported.[25] As indicated above, this may help in explaining some of the discrepancies in the literature regarding the effects of mTOR inhibitors.

In addition to known translational regulators, our results indicate that many proteins with uncharacterized roles in translation are recruited to eIF4E in response to mTOR stimulation.[72] Notably, many of these proteins were found to contain a RNA recognition motif, suggesting that they regulate some aspects of mRNA metabolism in a manner that is dependent on mTOR activity. These include several hnRNPs (heterogeneous nuclear ribonucleoproteins), such as hnRNP A1, F, U and R, which are RNA-binding proteins with multiple roles in mRNA metabolism.[93] A key characteristic of hnRNPs is that they undergo nucleo-cytoplasmic shuttling and thus likely participates in mRNA transport.[94] Each hnRNP binds to specific ribonucleotide sequences and therefore associates with distinct subsets of mRNA.[93] Our results indicate that mTOR stimulates the recruitment of some hnRNP isoforms to the 5' mRNA cap,[72] which may provide a regulated mechanism for the selective recruitment of mRNAs to the translational machinery. Consistent with this possibility, is the fact that hnRNP A1 and F have been shown to regulate the translation of specific mRNAs[95,96]; however, the involvement of mTOR in this process is currently unknown.

Our results also indicate that several RNA helicases are recruited to the 5' mRNA cap structure in response to mTOR activation, including DDX3, DDX6, DHX9, DDX17 and DDX36.[72] These RNA helicases may assist eIF4A during the initiation step to enhance the process of ribosomal scanning on structured mRNAs,[97] as was recently described for the DEAH (Asp-Glu-Ala-His)-box protein DHX29.[98] The DEAD-box helicase DDX3 is not essential for global translation, but is required for the translation of specific transcripts (e.g., *Cyclin E1*) that contain secondary structures within their 5' UTRs.[99,100] We found that mTOR promotes the recruitment of DDX3 to the 5' mRNA cap in a 4E-BP1/2-dependent manner,[72] suggesting a mechanism whereby mTOR activity is required for the translation of DDX3-bound transcripts. DDX6 (also known as RCK or p54) is a highly conserved DEAD-box helicase that contributes to global and transcript-specific mRNA storage, translational repression, and decay.[101] Recently, DDX6 was found to participate in the miRNA-mediated silencing of specific transcripts,[102] suggesting that in this case mTOR may participate in the translational repression of DDX6-bound transcripts. The highly conserved protein DHX9 (also known as RNA helicase A; RHA) was also recognized to participate in translation initiation.[13] It was shown to assist eIF4A in the unwinding of secondary structures within the 5' UTR of specific mRNAs (e.g.,, *JUND*).[103,104] At present, there is no evidence that DDX17 or DDX36 participate in translational regulation, but our results highly suggest that they may be unrecognized modulators of translation initiation.

Conclusions and Perspectives

Recent studies of the transcriptome have demonstrated that steady-state mRNA levels show low concordance with the cellular proteome,[105,106] suggesting that translational regulation plays a major role in gene expression. Consistent with this, translational control was shown to regulate many aspects of life, including embryonic development, immunity, metabolism and the maintenance of normal physiology.[107-109] Based on the involvement of several oncogenic signaling pathways in the regulation of protein synthesis,[24] it is not surprising that deregulation of mRNA translation can contribute to cancer.[110,111] Many studies have reported the overexpression of different eIFs in cancer,[112] further suggesting that many components of the translational machinery represent potential targets for therapeutic intervention.[3]

In addition to global mechanisms of translational regulation, it is now clear that different *cis*-acting elements present on the RNA molecule and their cognate *trans*-acting factors greatly affect translational efficiency. While it has been known for some time that certain subsets of mRNAs are differently affected by mTORC1 signaling, including TOP mRNAs and eIF4E-sensitive transcripts,[35,62] the molecular properties dictating this selectivity are poorly defined. It goes without saying that many unrecognized mechanisms of specific translation must also exist, and these represent major challenges that would need to be addressed in order to fully understand the complexity of translational regulation. To this end, it will be important to globally determine the specificity of different RNA-binding proteins for their associated mRNAs using crosslinking approaches and high-throughput sequencing.[113] Another important avenue for future studies is to understand cell type-specific regulation of mRNA localization and translation. For example, the localization and upstream regulation of mRNA translation in differentiated neurons is likely to be different from that of highly proliferating cells. Indeed, accumulating evidence suggests that the spatial regulation of mRNA translation can determine biological consequences,[114] such as during synaptic plasticity.[115,116] Elucidation of the molecular mechanisms underlying specific mRNA translation will result in a better understanding of various human diseases, especially those characterized by deregulated mRNA translation, such as diabetes, obesity and cancer to name a few.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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