The regulation of protein translation and its implications for cancer

Ping Song1, Fan Yang2, Hongchuan Jin3 and Xian Wang1

INTRODUCTION

Cancer is a major global public health problem and the second leading cause of death worldwide.1 It has been recognized as a disease resulting from the accumulation for multiple genetic and epigenetic changes. Genetic mutations mainly alter the functions of corresponding proteins, while epigenetic changes will change the expression of potential oncogenes and tumor suppressor genes. The regulation and function of these alterations have been substantially explored.2–7 However, the relevance of protein translation or the production of nascent proteins from mRNAs to the initiation and progression of human cancers used to be largely overlooked. With the recent development of experimental technologies, the regulation of protein translation has been gradually revealed. It could be affected by various factors including well-recognized players such as translation initiation factors and RNA-binding proteins, as well as new players such as noncoding RNAs and m6A modification of mRNAs (Fig. 1). In this review, we aimed to summarize the new advances in the regulation of protein translation, especially the contribution of dysregulated ncRNAs to the aberrant protein translation in cancers and facilitate a better understanding of the mechanism of carcinogenesis.

OVERVIEW OF THE PROTEIN TRANSLATION PROCESS

Translation steps

In general, protein translation can be divided into three main steps: initiation, extension, and termination. Initiation is the rate-limiting step in translation, and the formation of the translation initiation complex (eIF4F) is the most critical process.8 eIF4F consists of eIF4A, eIF4E, and eIF4G. Among them, eIF4A is a helicase that expands RNA into a single strand through the RNA-binding protein eIF4B. eIF4E is a cap-binding protein and eIF4G is a scaffolding protein used for mechanical assembly. eIF4F assembles on the structure of 5' m7G-capped of RNA and interacts with polyA tail-binding protein (PABP). However, the cap-independent mRNA translation process, which is IRES (internal ribosome entry site)-dependent translation, is triggered when the mTOR signaling pathway is inhibited by rapamycin, nutritional deficiencies, or hypoxia. As a result, activated 4EGBP1 (dephosphorylation) binds to eIF4E and inhibits cap-dependent translation. Meanwhile, eIF4G expression increases and mediates IRES-dependent translation. After the translation initiation complex is assembled, the 40S ribosomal subunit binds to other initiation factors, including eIF5 and the ternary complex (eIF2-GTP-Met-tRNAi) to form a 43S ribosome, thus enabling the progression into the extension stage.9,10 The initiation complex of cap-dependent translation scans the mRNA from the 5' end to find the first start codon (AUG), and enters the ribosomal P-site via initiator methionyl tRNA (Met-tRNAi). After that, the 43S ribosome was recruited to the 5' cap structure of mRNA to form a 48S ribosomal complex via eIF3 complex interacting with eIF4G. Meanwhile, GTP bound by eIF2 (composed of α-, β-, and γ-subunits) is activated by hydrolysis, leading to the release of eIF2-GDP after 60S ribosomes are recruited, leaving the active 80S ribosomes (40S and 60S subunits) to enter the extension phase.11,12 Termination: when the mRNA with stop codon (UAG, UGA, UAA) enters the ribosomal A-site, it can’t be recognized by activated amino acid (aa-tRNA). Instead, the protein releasing factor binds to the A-site, leading to the termination of protein synthesis13 (Fig. 2).

Translation components

In addition to mRNA as a template for protein translation, ribosomal RNA is required to provide translation sites, and...
transfer RNA (tRNA) as a tool for amino acid transport.\textsuperscript{14,15} tRNA carries specific amino acids to the ribosome under the action of aminoacyl tRNA synthetase, and accurately recognizes the codon sequence on mRNA by its anticodon, and adds specific amino acids into the peptide.\textsuperscript{16} Aberrant expression of rRNA and tRNA during tumorigenesis is frequently found in different tumors, including colorectal cancer,\textsuperscript{17} rhabdomyosarcoma,\textsuperscript{18} and retinoblastoma.\textsuperscript{19} There are only 61 types of tRNAs involved in the process of protein translation in eukaryotic cells. Due to the complexity of the secondary structures of tRNAs, it is difficult to design the primer and the research on tRNAs has been greatly restricted. However, with the development of high-efficiency reverse transcriptase enzymes,\textsuperscript{20} the exploration of tRNAs such as tRNA sequencing and quantification gradually became possible and popular.

The role of translation initiation factors in carcinogenesis
Increased abundance of components of translation initiation complex is prevalent in various kinds of tumors.\textsuperscript{21} For example, in BRAF-mutated tumors, increased expression of elf4F complex leads to anti-BRAF therapy resistance and more metastasis. Blocking the elf4E-elf4G interaction or targeted-inhibition of elf4A synergized BRAF-targeting therapy. Therefore, elf4F can be used as an indicator of acquired resistance to BRAF (V600) targeting therapy.\textsuperscript{22}

The binding of elf4E to the 5′ m7G-capped of the mRNA is the rate-limiting step for translation initiation. The genome-wide translation profiling reveals that the content of elf4E is critical for the translation of mRNAs that regulate the reactive oxygen species (ROS), which promotes cancer cell survival.\textsuperscript{23} By degrading the mRNA of elf4E-BP2, which negatively regulates elf4E, IGF2BP3 promotes elf4E-mediated translation activation, and ultimately leading to tumor cell proliferation.\textsuperscript{24} Phosphorylated elf4E promotes protein translation and also plays an important role in antitumor immunotherapy. In a liver cancer model induced by MYC overexpression combined with KRAS mutation (G12D), cancer cells escape immune surveillance and suppress the cytotoxicity of CD8\textsuperscript{+} T cells by increasing PD-L1 protein translation. While, eFT508, in phase 2 clinical trials (NCT02937675, NCT02605083 and NCT03258398), inhibits elf4E phosphorylation to reduce the translation of PD-L1 protein, reverses the aggressive and metastatic characteristics.\textsuperscript{25} In summary, activated elf4E promotes the RNA translation to accelerate the development of cancer by enhancing proliferation, inducing resistance to chemotherapy and anti-immune therapy. Encouragingly, there are small-molecule inhibitors available to target elf4E in the clinical trials, such as elf4E antisense oligonucleotides (ASOs), in phase 2 clinical trials (NCT02605083), targeted the elf4E mRNA for destruction, proven to inhibit tumor growth.\textsuperscript{26,27}

The hypophosphorylated form of elf4E-binding proteins (4E-BPs) competes with elf4G to bind elf4E, which affects the formation of elf4F complex and inhibits translation. 4E-BPs inhibit the translation of proliferation and cell cycle proteins to affect tumor cell proliferation and growth.\textsuperscript{28,29} As a small-molecule inhibitor of the elf4E/elf4G interaction, 4EGi-1 can mimic 4E-BP function to restrain cap-dependent translation and inhibit the

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**Fig. 1** The process of gene expression. Gene expression needs to be transcribed from DNA to RNA, translated into protein, and modified into mature protein to perform biological functions. This figure highlights the influence of RBPs, microRNAs, lncRNAs, circRNAs, and RNA m6A modification on the protein translation procedure in tumorigenesis.

**Fig. 2** The model of protein translation process. Translation is initiated by elf4F assembly, consists of elf4A, elf4E, and elf4G. The hypophosphorylated form of 4E-BPs competes with elf4G to bind elf4E, which affects the formation of elf4F complex and inhibits translation. 4E-BPs inhibit the translation of proliferation and cell cycle proteins to affect tumor cell proliferation and growth.\textsuperscript{28,29} As a small-molecule inhibitor of the elf4E/elf4G interaction, 4EGi-1 can mimic 4E-BP function to restrain cap-dependent translation and inhibit the
growth of multiple cancer cell lines, highlighting the potential for targeting protein translation in the design of novel approaches in cancer treatment.

elf2a plays an important role in the process of translation initiation. Once phosphorylated, it loses its activity to recover the GTP required for Met-trNAi, resulting in translation inhibition. Smad7 promotes the proliferation of colon cancer cells by activating elf2a to increase CDC25 protein translation, a phosphatase that dephosphorylates CDK2, controls progression of the cell cycle through the S phase. In melanoma, the tumor suppressor gene PTEN increases the phosphorylation of elf2a via PDZ binding motif, promoting tumor cell apoptosis and inhibiting tumor proliferation. In prostate cancer, proteasome inhibitors PDZ binding motif, promoting tumor cell apoptosis and inhibiting translation in tumorigenesis (Table 1). For example, Musashi-1 functionally, they play a pivotal role in regulating the RNA translation machinery, thus affecting its translation. However, as RBPs are nonenzymatic, their contribution to the regulation of protein translation remains controversial, depending on the particular proteins affected on different tumor types and grades. There are studies indicating that increased elf2a phosphorylation may promote cancer development by enhancing the translation of target mRNAs. For example, decreased expression of PKR (also known as EIF2AK2), which is an elf2a phosphatase, is associated with less aggressive human cancers. GCN2 phosphorylates elf2a, promotes ATF4 protein translation by delayed restart (two uORFs in mRNA leader), which enhances tumorigenicity of fibrosarcoma cells in nude mice. Because of the paradoxical functions of elf2a, directly inhibiting phosphorylation need to consider the specific microenvironment of tumors.

THE EFFECTS OF POST-TRANSCRIPTIONAL REGULATION ON PROTEIN TRANSLATION IN TUMORS

RNA-binding protein

As the most widely studied post-translational regulators, RNA-binding proteins (RBPs) are involved in all aspects of RNA biological processes, including RNA metabolism, transport, and localization. Mechanistically, it has been speculated that RBPs reshape the structure of certain mRNA to change the affinity for translation machinery, thus affecting its translation. However, the exact mechanism still needs to be explored and confirmed. Functionally, they play a pivotal role in regulating the RNA translation in tumorigenesis (Table 1). For example, Musashi-1 (MSI1) and Musashi-2 (MSI2) are highly expressed in a variety of tumors, and they can functionally inhibit or promote the translation of both essential oncogenes and tumor suppressor genes through their N-terminal RNA recognition sequence (RRM). Kawahara et al. found that MSI1 competed with elf4G to bind PABP to inhibit translation of downstream genes to maintain the stem cell status. Sun-Mi et al. found MSI2 controlled efficient translation of Hoxa9, Myc, and Ikar2 mRNAs to maintain the mixed-lineage leukemia (MLL) self-renewal program. In a research carried by Li and his colleagues, elf3 was highly expressed in liver cancer, playing an important role in the initiation of translation and promotes the development of cancer. In leukemia, SYNCRIPT is a new RBP that promotes HOXA9 translation and controls myeloid leukemia stem cell programs. CELF1 is a new RBP that promotes HOXA9 translation and controls myeloid leukemia stem cell programs. CELF1 (CUGBP Elav-like family member 1), inhibits MYC protein translation to reduce the renew and proliferation of small intestinal epithelial cells. In the colorectal cancer, Hur (ELAV-like RNA-binding protein 1), binds to the 5′UTR region of the proapoptotic gene caspase-2L, inhibiting its translation, and promoting tumor cell antiapoptosis activity. In RKO intestinal cancer cells of wild-type p53, under short-term UV irradiation, Hur can promote P53 translation. Moreover, Hur inhibits wt-5a protein translation in breast tumors. Meanwhile, there are reports indicating that CPEBs (cytoplasmic polyadenylation element binding protein) induce cytoplasmic polyadenylation with specific polyA polymerase to enhancing translation and facilitating tumorigenesis and metastasis. IMP-3, a member of the insulin-like growth factor II (IGF-II) mRNA-binding protein (IMP) family, promotes IGF-II protein translation to induce the tumor cell proliferation in leukemia. When IFN-γ is used to treat inflammation in bone marrow cells, GAIT complex inhibits VEGFA translation by binding to the 3′UTR of VEGFA, while under hypoxic conditions, HnRNP L (heteroribonucleoprotein) is activated, interacting with DRBIP76 (interleukin enhancer binding factor 3) and hnRNP A2/B1 to form a heterotrimer, which blocks GAIT-mediated translation inhibition, and promotes VEGFA expression. Based on these studies, it is evident that RBPs participate in tumor stemness, metastasis, proliferation, and immunity by influencing the translation of target genes. However, as RBPs are nonenzymatic, indicating the lack of hydrophobic pockets capable of binding small-molecule inhibitors, they are difficult to be therapeutic targets.

Noncoding RNAs

The noncoding RNA described in this review mainly includes small RNA (microRNA), long noncoding RNA (lncRNA), and circular RNA (circRNA), which have an important effect on tumors. In Table 2, we summarized the effects of noncoding RNA on translation procedure in tumors.

microRNA

MicroRNA is small noncoding RNA containing about 22 nucleotides. By complementary base pairing, microRNAs bind to the 3′UTR region or 5′UTR region of mRNA, thus mediating the degradation or translation of target mRNAs. It’s widely recognized that miRNAs inhibit cap-dependent translation at the
### Table 2. Noncoding RNAs involved in translation regulation

| Protein | Clinical correlates in cancers |
|---------|------------------------------|
| miR-10b inhibits HOXD10 translation | promotes the migration and invasion of breast cancer |
| miR-125 inhibits IGF1R translation | inhibits cell proliferation and metastasis in lung cancer |
| miR-146a inhibits c-met translation | inhibits colorectal cancer liver metastasis |
| miR-125b inhibits PiGF translation | inhibits the angiogenesis of liver cancer |
| miR-143-3p inhibits BRD2 translation | increases the therapy sensitivity to cisplatin in gastric cancer |
| miR-648 inhibits MGMT translation | sensitizes gliomas to temozolomide treatment |
| miR-675-5p inhibits TP53 translation | promotes the development of colorectal cancer |
| miR-10a promotes RP translation | promotes the overall protein translation |
| miR-143 and MSI2 regulates KRAS protein translation | affects the tumor growth of bladder cancer |
| miR-155-5p and HuR promotes HuR translation | supports the metastasis of colorectal cancer |
| miR-330 and HuR regulates STAT3 translation | cachexia |
| miR-17-19b and HuR regulates the translation of MYC | ensure the optimal growth of B-cell lymphoma |
| lncRNA-GMAM promotes ephrin A1 translation | enhances the invasion ability of gastric cancer |
| lncRNA-GMAM regulates BCL-2, BCL-6, XIAP, e-cadherin, n-cadherin, vimentin, and snail translation | promotes the development of liver cancer |
| lncRNA-MALAT1 increases TC7F2 translation | promotes aerobic glycolysis in liver cancer |
| LncNB1 promotes E2F1 translation | induces neuroblastoma cell proliferation and survival. |
| RP1-SO6.5 (RP1) attenuates p27kip1 translation | promotes breast cancer cell proliferation and metastasis |
| PYCARD-AS1 regulates PYCARD translation | antiapoptosis of breast cancer |
| OCC-1 and HuR regulates the translation of HuR targets | colorectal cancer |
| 7SL and HuR attenuates P53 translation | HeLa |
| lncRNA-p21 and HuR regulates the translation of JUNB and CTNBB1 | cervical carcinoma |
| IncRNA-TRMP and PTBP1 regulates P27 translation | A549 cell |
| AFAP1-AS1 and AUFI promote translation of ERBB2 | breast cancer |
| Lnc-LBCS and hnRNPK regulates AR translation | prostate cancer |
| Lnc-HITT and YB-1 regulates HIF-1α translation | colon cancer |
| LNC00460 and miR-149-5p regulates CUL4A translation | colorectal cancer |
| LINC0346 and miR-34a-5p regulates the translation of CD44, NOTCH1, and AXL proteins | gastric cancer |
| HOXA11-AS and miR-1297 regulates EZH2 protein translation | gastric cancer |
| IncRNA H19 and miR-29b-3p regulates MCL-1 translation | myeloma |
| circRNA | |
| circj-catenin generates a new 370 amino acid j-<a href=# category='protein'>catenin</a> isoform | liver cancer |
| Circ-FBXW7 encodes a new 21-kDa protein called FBXW7-185aa | gliomas |
| circ-SHPRH translates a new 17 kDa protein, SHPRH-146aa | gliomas |
| circ Yap inhibit the translation of Yap protein | breast cancer |
| circPABPN1 and HuR regulates the translation of PABPN1 | Hela |
| OIP5-AS1 and HuR regulates target genes of HuR | — |
| circRNA-MTO1 and TRAF4 inhibits the translation of Eg5 | breast cancer |
| circ-MALAT1 and miR-6887-3p enhances JAK2 expression | liver cancer |
| circELF4G2 and miR-218 increases HOXA1 translation | cervical cancer |
initiation step by dissociating the translation initiation factors from targeted mRNAs. Over the past decades, a bunch of researches demonstrated that microRNA plays an important role in tumorigenesis and development. In terms of influencing the translation process alone, microRNA-10b (miR-10b) is highly expressed in metastatic breast cancer. miR-10b inhibits HOXD10 translation via interaction with its 3′UTR and promotes the migration and invasion. miR-12528 inhibits insulin-like growth factor 1 receptor (IGF1R) translation to inhibit cell proliferation and metastasis in lung cancer. miR-146a inhibits tumor formation, and colorectal cancer liver metastasis by limiting c-Met translation. The expression of miR-125b is low in liver cancer tissue comparing to normal liver tissue, and overexpression miR-125b can inhibit the translation of placentation growth factor (PIGF) protein to reduce the angiogenesis. Comparing to normal gastric tissue, the expression of mir-143-3p is significantly lower in gastric cancer tissues. Overexpression of mir-143-3p inhibits BRD2 protein translation, thereby inhibiting cancer cell proliferation and increasing the therapy sensitivity to cisplatin.

In glioma, miR-648 inhibits O6-methylguanine-DNA methyltransferase (MGMT) protein translation, reducing the production of MGMT and thus sensitizing MGMT-expressing gliomas to temozolomide treatment. In colorectal cancer, overexpressed prostaglandin E2 (PGE2) upregulates miR-675-5p expression to inhibits TP53 translation, thus promoting tumor development. In research carried out by Orom et al., miR-10a could bind to the 5′UTR of ribosomal protein (RP) mRNA to promote the translation under amino acid starvation conditions, and regulated the overall protein translation. In conclusion, microRNAs can inhibit the proliferation, metastasis, angiogenesis of tumors and sensitize tumors to chemotherapy drugs by decreasing the protein synthesis of certain target genes.

MicroRNAs can also interact with RBPs to jointly regulate protein translation. For example, miR-143 inhibits MSI2 protein translation through 3′UTR base pairing to reduce the translation of KRAS which interacts with MSI2, thereby inhibiting tumor growth in bladder cancer. In colorectal cancer, MiR-155-5p promotes Huh7 translation to support cell metastasis. In tumor-induced cachexia, HuR promotes translation of STAT3 mRNA by preventing miR-330-mediated translation inhibition. In B-cell lymphoma, miR-17-19b indirectly reduces the translation efficiency of MYC by down-regulating Chek2 and increasing the binding of HuR to MYC mRNA.

Taken together, these studies highlight the balance between RBPs and microRNAs has an important impact on the translation of target genes. Indeed, antitumor therapies targeting microRNAs by miRNA mimics and inhibitors have shown promise in preclinical development.

LncRNA LncRNAs contain about 200 nucleotides, and play an important role in tumor progression by regulating the chromatin organization, transcription, mRNA stability, protein translation, and post-translational modification. As the scaffold of nuclear bodies involved in the translation regulation, LncRNAs play a crucial part in gene expression.

Gastric cancer metastasis-associated long noncoding RNA (GMAN) promotes the translation of ephrin A1 by binding with antisense GMAN RNA (GMAN-AS), enhancing the invasion ability of gastric cancer cells. Furthermore, it is highly expressed in liver cancer and interacts with eIF4B. By inhibiting the dephosphorylation of PPP2R2A, it promotes phosphorylation of serine 422 at eIF4B, and subsequent phosphorylated eIF4B increases the antiapoptotic proteins BCL-2, BCL-6, XIAP and migration-related proteins e-cadherin, n-cadherin, vimentin, and snail translation to promote the development of liver cancer. LncRNA-MALAT1 increases TCF7L2 translation by activating the mTOR-4EBP1 signal axis and SRSF1, and promotes aggressive glycosis in liver cancer. LncNB1 is overexpressed in MYCN-amplified neuroblastoma and induces neuroblastoma cell proliferation and survival. In mechanism, LncNB1 promotes the translation of DEPDC1B and translation of E2F1 mRNA, leading to phosphorylation of N-MYC and stable protein expression. The combination of RP1 and p-4E-BP1/eIF4E can prevent eIF4E from interacting with eIF4G, thus attenuating the translation of p27kip1 mRNA, and increasing the expression of snail to improve the invasiveness.

In breast cancer cells, LncRNA-AS1, the antisense LncRNA of proapoptotic gene PYCARD, overlaps and interacts with PYCARD at the 5′ UTR end, inhibiting ribosome assembly in the cytoplasm to limit the translation efficiency of PYCARD.

LncRNAs also play a role in protein translation by interacting with RBPs. LncRNA OCC-1 plays as suppressor in colorectal cancer. By binding to the E3 ligase β-TRCP, it increases the ubiquitination of Huh7, which leads to a decrease in the expression of downstream genes. LncRNA 7SL1, highly expressed in tumor cells, attenuates the translation of the tumor suppressor protein P53 by binding to the 3′UTR of P53 mRNA and squeezing HuR binding. On the other hand, HuR recruits let-7Ago2 to LncRNA- p21, reducing its stability. The decreased binding of LncRNA-p21 to mRNAs of JUNB and CTNNB1 promotes their protein translation in HeLa cells. LncRNA-TRMP promotes cancer cell proliferation and G1/S cycle progression when P53 is activated, the authors test the cycle-related proteins and find that TRMP negatively regulates P27. By inhibiting PTBP1, P27 mRNA-binding protein, TRMP ultimately inhibits IRES-dependent translation of P27 protein.

In terms of chemotherapy response, the expression level of actin filament-related protein 1 antisense RNA 1 (AFAP1-AS1) is higher in trastuzumab-resistant cells than that in sensitive cells. Exosomal AFAP1-AS1 can induce trastuzumab resistance. Mechanically, AFAP1-AS1 interacts with the AUU1 to promote translation of ERBB2, which is used to represent the RNA encoding the HER-2 protein. Lnc-lBCS expression is low in castration-resistant prostate cancer (CRPC) cell lines and tissues. In the absence of androgens, knockdown of lBCS is sufficient to activate androgen receptor (AR) signaling, consequently increasing AR protein translation. In terms of mechanism, lBCS directly interacts with hnRNPK to inhibit the formation of hnRNPK-AR complex and thus reduces AR translation. The low expression of H1TT (translation level HIF-1α inhibitor) is related to the advanced stage of colon cancer. After the expression is restored, H1TT inhibits tumor angiogenesis and tumor growth. Mechanistically, the direct binding of H1TT and YB-1 deceives and prevents YB-1 from binding to 5′UTR of HIF-1α mRNA, which relieves the translation promotion effect of YB-1on HIF-1α.

In addition, LncRNAs can also serve as competitive endogenous RNAs (ceRNAs) to sponge or decoy on microRNAs to regulate protein translation. For example, LINC00346 recruits argonaute 2 ( Ago2), which acts as a molecular sponge, antagonizes miR-34a-5p to inhibit the translation of CD44, NOTCH1, and AXL proteins, and promotes the development of gastric cancer. LINC00460 is highly expressed in colorectal cancer cells. As ceRNA, it antagonizes miR-149-5p to inhibit cullin 4A (CUL4A) translation and affects cell growth and apoptosis. HOXA11-AS acts as a sponge of miR-1297, antagonizing its ability to inhibit the translation of EZH2 protein and increasing EZH2 protein into the nucleus to inhibit the transcription of PRSS8 and KLF2. In conclusion, HOXA11-AS/miR-1297/EZH2 crosstalk promotes the proliferation, migration and invasion of gastric cancer cell. LncRNA H19 is highly expressed in multiple myeloma and promotes tumor cell growth and bortezomib resistance via inhibiting miR-29b-3p expression and enhancing MCL-1 translation.
that a large amount of circular RNAs (circRNAs) are endogenous, conservative, and stable in eukaryotic cells. CircRNAs are a new type of noncoding RNA, characterized with covalent closed loop formed by reverse splicing of precursor mRNA. Recent studies have demonstrated the relation between circRNAs and polysomes. Some circRNAs contain the start codon AUG and the recognized open reading frame (ORF), indicating that circRNAs have a potential protein coding function. Circβ-catenin, abundantly expressed in liver cancer, generates a 370 amino acid β-catenin isoform, which utilizes the start codon as linear β-catenin RNA transcription and translation ends with a new termination caused by circularization codon. This newly born β-catenin can resist GSK3 phosphorylation, and finally stabilize expression and activate WNT signaling pathway. Circ-FBXW7 is highly expressed in the normal human brain. It relies on the IRES to cross the open reading frame and encode a 21 kDa protein, FBXW7-185aa. In gliomas, the upregulation of FBXW7-185aa inhibits proliferation and cell cycle. In addition, circ-SHPRH can also translate a 17 kDa protein, SHPRH-146aa, through IRES-driven open reading frames (ORF), and both are low expressed in gliomas. Overexpression of them can inhibit gliomas development.

In addition to being able to regulate translation by itself, circRNAs can also regulate other protein translation by regulating translation initiation. For example, overexpression of circ-YAP inhibits the assembly of the translation initiation complex (eIF4G and PABP), thus inhibiting the translation of Yap protein. As a consequence, overexpression of circYap inhibits the proliferation, migration, and colony formation of breast cancer cells. Furthermore, circRNAs interact with RBPs or act as ceRNA through sponge microRNAs to affect translation and play an important role in tumorigenesis and development. In HeLa cells, circPABPN1 (hsa_circ_0031288) prevents HuR from binding to PABPN1 mRNA and inhibits the translation of PABPN1 protein. Similarly, OIP5-A51 inhibits tumor cell proliferation by preventing HuR from binding to target genes. In breast cancer, circRNA-MTO1 (hsa-circRNA-007874) binds to the tumor necrosis factor receptor-associated factor 4 (TRAF4), thereby inhibiting the translation of mitogenic kinesin (Eg5) and reversing Monastrol (kinesin inhibitor) resistance. circ-MALAT1 combines with ribosomes and tumor suppressor gene PAX5 to form a complex, hindering the translation of PAX5 and helping maintain cancer stem cell characteristics. It is also found that circ-MALAT1 promotes liver cancer stem cell self-renewal by acting as the miR-6887-3p sponge, enhancing JAK2 expression and activating the JAK2/STAT3 signaling pathway. In cervical cancer, highly expressed circEIF4G2 acts as a sponge for miR-218 which promotes HOXA1 protein translation, and consequently promotes cancer cell proliferation and migration.

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**Fig. 3** m6A modification regulates protein translation. The m6A modification is catalyzed by the writers (METTL3/METTL14/WTAP, WETTL16) and demethylated by erasers (FTO, ALKBH5). The m6A modification is recognized by the readers (YTHDF1/2/3, YTHDC1/2, IGF2BP1/2/3, and HuR). The translation procedure of target genes can be influenced by the m6A modification level
tumorigenesis and metastasis. In HeLa cells, sequencing results combined with experiments have shown that YTHDF3 can coordinate with YTHDF1 to regulate translation. The mechanisms include YTHDF3’s regulation on translation initiation without directly binding translation initiation factors, and cooperation with YTHDF1 to jointly regulate translation.

In addition, leucine-rich pentapeptide repeat (LRPPRC) may also act as m6A recognition protein, affects mitochondrial protein translation. In fragile X syndrome, X fragile mental retardation protein (FMRP) inhibits translation by binding to the LS protein on the 80S ribosome directly. In autism spectrum disorders, FMR1 affects mRNA metabolism by recognizing m6A modifications, including protein translation. M6A modification can also affect mRNA conditions and translation extension steps, thus altering translation kinetics. However, the exact mechanism of these genes has not been studied in tumors. Most of the m6A modifications of mRNA and small noncoding RNAs depend on the sequences and structures of mRNAs to work, and they will inevitably have a competitive or cooperative relationship in the translation process of mRNAs.

Collectively, the abnormal regulation of m6A methylation is closely related with the development of cancers ranging from metabolism, cell self-renewal, differentiation, and metastasis. Increasing evidences show that m6A modification of mRNA plays a dual role in cancer. On the one hand, methyltransferase complex increases the m6A modification of oncogenes to promote cancer development. On the other hand, FTO and ALKBH5 also promote tumor progression by reducing the modification of target genes. Therefore, the exact role of m6A in tumors needs to be judged according to the cellular contexts.

The effects of codons and tRNAs on protein translation in tumors The factors discussed above, including RBPs, noncoding RNAs and RNA m6A modification, perform function by regulating the mRNA structure and translation initiation complex. In addition to those factors, codons are one of the factors that affect the translation extension. Different codons were translated at different speeds. For example, GAA was found translated with a rate of 21.6 codons while GAG at 6.4 codons per second. Codon extension mainly depends on the entry of tRNA into the ribosome A-site through anticodon recognition. Therefore, the abundance of tRNA also plays a role in translation efficiency. Growing evidence demonstrated that dysregulation of tRNA was involved in tumor progression. Compared with normal cells, breast cancer cells have a 3-fold increase in nuclear-encoded tRNA expression and a 5-fold increase in mitochondrial-encoded tRNA to facilitate the translation of a subset of regulatory genes. For example, tRNAGluUUC and tRNAArgCCG were upregulated in breast cancer and promoted metastasis by increasing the ribosome occupancy of transcripts enriched for their cognate codons. Further researches identified two different subsets of tRNA pool between proliferation and differentiation, of which one is induced in proliferating cells and inhibited in other cases, and the other exhibiting the opposite characteristics. Subsequently, if this program hijacked by tumor cells to selectively upregulate proliferative tRNA, it will likely promote the translation of precancerous transcripts. In the future, tRNA may serve as a biomarker for cancer.

CONCLUSION
Translation is an essential procedure for the protein expression, in this review we summarized the common factors affecting this procedure, including translation initiation factors, RBPs, noncoding RNAs (microRNAs, IncRNAs and circRNAs), and RNA m6A modification. In addition, codons and tRNAs play important role on the translation elongation rate. The past decades have witnessed the rapid development of experimental techniques for research of translation, such as isotope or puromycin labeling, polysome profiling experiments using ultracentrifugation and density gradient separation, and these up-to-date techniques paved a wider path for researchers to investigate the potential molecular mechanism of tumor biology. After detecting abnormal translation in tumorigenesis induced by the above influencing elements, m6A and noncoding RNAs may potentially contribute to the prediction of the prognosis of tumor patients and the clinical application of antitumor therapy. Because of the widespread existence of RBPs, noncoding RNAs, m6A modification and tRNAs in eukaryotic cell, clarifying their relationship with aberrant protein translation is of great significance for the tumor treatment.

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ADDITIONAL INFORMATION
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REFERENCES
1. Siegel, R. L., Miller, K. D. & Jemal, A. Cancer statistics, 2019. CA Cancer J. Clin. 69, 7–34 (2019).
2. Stillman, B. Histone modifications: insights into their influence on gene expression. Cell 175, 6–9 (2018).
3. Bourgeois, C. F., Mortreux, F. & Auboeuf, D. The multiple functions of RNA helicases as drivers and regulators of gene expression. Nat. Rev. Mol. Cell Biol. 17, 426–438 (2016).
4. Darzykiewicz, E. et al. Beta-globin mRNAs capped with m7G, m2.7(2)G or m2.2.7(3)G differ in intrinsic translation efficiency. Nucleic Acids Res. 16, 8953–8962 (1988).
5. Xu, F. & Cohen, S. N. RNA degradation in Escherichia coli regulated by 3′ ade- nylation and 5′ phosphorylation. Nature 374, 180–183 (1995).
6. Tudek, A., Lloret-Llinares, M. & Jensen, T. H. The multitasking polyA tail: nuclear RNA maturation, degradation and export. Philos. Trans. R. Soc. Lond. B Biol. Sci. 373, 2018 https://doi.org/10.1098/rstb.2018.0169.
7. Mowen, K. A. & David, M. Unconventional post-translational modifications in immunological signaling. Nat. Immunol. 15, 512–520 (2014).
8. Silvera, D., Formenti, S. C. & Schneider, R. J. Translational control in cancer. Nat. Rev. Cancer 10, 254–266 (2010).
9. Spriggs, K. A., Bushell, M. & Willis, A. E. Translational regulation of gene expression during conditions of cell stress. Mol. Cell. 40, 228–237 (2010).
10. Bhat, M. et al. Targeting the translation machinery in cancer. Nat. Rev. Drug Discov. 14, 261–278 (2015).
11. Hershey, J. W. B., Sonenberg, N. & Mathews, M. B. Principles of translational control. Cold Spring Harb. Perspect. Biol. 19, 2017 https://doi.org/10.1101/cshperspect.a032607.
12. Jackson, R. J., Hellen, C. U. & Pestova, T. V. The mechanism of eukaryotic translation initiation and principles of its regulation. Nat. Rev. Mol. Cell Biol. 11, 113–127 (2010).
13. Hellen, C. U. Translation termination and ribosome recycling in Eukaryotes. Cold Spring Harb. Perspect. Biol. 10, 2018 https://doi.org/10.1101/cshperspect.a032655.
14. Jung, H., Glogkas, C. G., Sonenberg, N. & Holt, C. E. Remote control of gene function by local translation. Cell 157, 26–40 (2014).
15. Frye, M., Harada, B. T., Behm, M. & He, C. RNA modifications modulate gene expression during development. Science 361, 1346–1349 (2018).
16. Dever, T. E., Dinnar, J. D. & Green, R. Translation elongation and recoding in Eukaryotes. Cold Spring Harb. Perspect. Biol. 10, 2018 https://doi.org/10.1101/cshperspect.a032649.
17. Pogue-Geile, K. et al. Ribosomal protein genes are overexpressed in colorectal cancer: isolation of a cDNA clone encoding the human S3 ribosomal protein. Mol. Cell Biol. 11, 3842–3849 (1991).
18. Williamson, D. et al. Nascent pre-rRNA overexpression correlates with an adverse prognosis in alveolar rhabdomyosarcoma. Genes Chromosomes Cancer 45, 839–845 (2006).
19. White, R. J. et al. Repression of RNA polymerase III transcription by the retino- blastoma protein. Nature 382, 88–90 (1996).
20. Preinacker, V. et al. Codon optimality is a major determinant of mRNA stability. Cell 160, 1111–1124 (2015).
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21. Bjornsti, M. A. & Houghton, P. J. Lost in translation: dysregulation of core-dependent translation and cancer. *Cancer Cell* 5, 519–523 (2004).

22. Bousssemart, L. et al. elf4F is a nexus of resistance to anti-BRAF and anti-MEK cancer therapies. *Nature* 513, 105–109 (2014).

23. Truit, M. L. et al. Differential requirements for elf4E dose in normal development and cancer. *Cell* 162, 59–71 (2015).

24. Mitautu, R. et al. Oncofetal protein IGFBP3 facilitates the activity of proto-oncogene protein elf4E through the destabilization of elf4E-BP2 mRNA. *Oncogene* 35, 13495–13502 (2016).

25. Xu, Y. et al. Translation control of the immune checkpoint in cancer and its therapeutic targeting. *Nat. Med.* 25, 301–311 (2019).

26. Graff, J. R. et al. Therapeutic suppression of translation initiation factor eIF4F expression reduces tumor growth without toxicity. *J. Clin. Invest.* 117, 2635–2648 (2007).

27. Reich, S. H. et al. Structure-based design of pyridone-aminal eFT508 targeting translational activator of insulin-like growth factor II leader-3 mRNA during response to ultraviolet light irradiation. *J. Med. Chem.* 61, 3516–3540 (2018).

28. Dowling, R. J. et al. mTORC1-mediated cell proliferation, but not cell growth, is inhibited by elf4F. *Science* 328, 1172–1176 (2010).

29. Martineau, Y., Arar, R., Bousquet, C. & Pyronnet, S. Anti-oncogenic potential of the elf4F-encoding proteins. *Oncogene* 32, 671–677 (2013).

30. Moerke, N. J. et al. Small-molecule inhibition of the interaction between the translation initiation factors elf4F and elf4G. *Cell* 128, 257–267 (2007).

31. Stoll, C. et al. A functional role for Smad7 in sustaining colon cancer cell growth and survival. *Cell Death Dis.* 5, e1073 (2014).

32. Mounir, Z. et al. Tumor suppression by PTEN requires the activation of the PKR-elf4alpha phosphorylation pathway. *Sci. Signal.* 2, ra85 (2008).

33. Zhu, K. et al. Control of HIF-1alpha expression by elf2alpha phosphorylation-mediated translational repression. *Cancer Res.* 69, 1836–1843 (2009).

34. Pathak, S. S. et al. The elf4alpha kinase GCN2 modulates period and rhythmicity of the circadian clock by translational control of Atf4. *Neuron* 104, 724–735 (2019).

35. Kozel, C. et al. Overexpression of elf5 or its protein mimic 5MP perturbs elf2 function and induces ATF4 translation through delayed re-initiation. *Nucleic Acids Res.* 44, 8704–8713 (2016).

36. Martinez-Salas, E. et al. RNA-binding proteins impacting on internal initiation of translation. *Int. J. Mol. Sci.* 14, 27105–27126 (2013).

37. Zhang, B. et al. A comprehensive expression landscape of RNA-binding proteins (RBPs) across 16 human cancer types. *RNA Biol.* 17, 211–226 (2020).

38. Kudinov, A. E., Karanicolos, J., Golemis, E. A. & Bounemer, Y. Musashi RNA-binding proteins as cancer drivers and novel therapeutic targets. *Clin. Cancer Res.* 23, 2143–2153 (2017).

39. Kawahara, H. et al. Neural RNA-binding protein Musash1 inhibits translation initiation by competing with elf4G for PABP. *J. Cell Biol.* 181, 639–653 (2008).

40. Park, S. M. et al. Musashi2 sustains the mixed-lineage leukemia-driven stem cell regulatory program. *J. Clin. Invest.* 125, 1286–1298 (2015).

41. Li, T. et al. Transcriptomic analyses of RNA-binding proteins reveal elf3c promotes cell proliferation in hepatocellular carcinoma. *Cancer Sci.* 108, 877–885 (2017).

42. Yu, L. P. et al. Functional screen of MS2 interferes identifies an essential role for SYNCRIP in myeloid leukemia stem cells. *Nat. Genet.* 49, 866–875 (2017).

43. Liu, L. et al. Competition between RNA-binding proteins CELF1 and HuR modulates MYC translation and intestinal epithelial renewal. *Mol. Biol. Cell.* 26, 1797–1810 (2015).

44. Winkler, C. et al. Attenuation of the ELAV-like protein HuR sensitizes adenocarcinoma cells to the intrinsic apoptotic pathway by increasing the translation of caspase-2L. *Cell Death Dis.* 5, e1322 (2014).

45. Mazan-Mamczarz, K. et al. RNA-binding protein HuR enhances p53 translation in response to ultraviolet light irradiation. *Proc. Natl Acad. Sci. USA* 100, 8354–8359 (2003).

46. Leanderson, K., Riesbeck, K. & Andersson, T. Wnt-5a mRNA translation is suppressed by the Elav-like protein HuR in human breast epithelial cells. *Nucleic Acids Res.* 34, 3988–3999 (2006).

47. D’Ambrogio, A., Nagaoka, K. & Richter, J. D. Translational control of cell growth and malignancy by the CPEBs. *Nat. Rev. Cancer* 13, 283–290 (2013).

48. Liao, B., Hu, Y., Herrick, D. J. & Brewer, G. The RNA-binding protein IMP-3 is a translational activator of insulin-like growth factor II leader-3 mRNA during proliferation of human X562 leukemia cells. *J. Biol. Chem.* 280, 18517–18524 (2005).

49. Yao, P. et al. The HILDA complex coordinates a conditional switch in the 3′-untranslated region of the VEGFA mRNA. *PloS Biol.* 11, e1001635 (2013).

50. Beerermann, J., Piccoli, M. T., Viereck, J. & Thum, T. Non-coding RNAs in development and disease: background, mechanisms, and therapeutic approaches. *Physiol. Rev.* 96, 1297–1325 (2016).
The regulation of protein translation and its implications for cancer
Song et al.

80. Han, M. et al. Exosome-mediated lncRNA AFAP1-AS1 promotes trastuzumab resistance through binding with AUFI and activating ERBB2 translation. Mol. Cancer 19, 26 (2020).
81. Gu, P. et al. A novel AR translational regulator IncRNA LBCS inhibits castration resistance of prostate cancer. Mol. Cancer 18, 109 (2019).
82. Wang, X. et al. A novel lncRNA HHTT forms a regulatory loop with HIF-1alpha to modulate angiogenesis and tumor growth. Cell Death Differ. 27, 1431–1446 (2019).
83. Xu, T. P. et al. KLFS5 and MVC modulated LINCO0346 contributes to gastric cancer progression through acting as a competing endogenous RNA and indicates poor outcome. Cell Death Differ. 26, 2179–2193 (2019).
84. Liu, Y. et al. A novel lncRNA, LINCO0460, affects cell proliferation and apoptosis by regulating KLF2 and CUL4A expression in colorectal cancer. Mol. Ther. Nucleic Acids 12, 684–697 (2018).
85. Sun, M. et al. LncRNA HOXA11-AS promotes proliferation and invasion of gastric cancer by scaffolding the chromatin modification factors PRC2, LSD1, and DNMT1. Cancer Res. 76, 6299–6310 (2016).
86. Pan, Y. et al. LncRNA H19 overexpression induces bortezomib resistance in multiple myeloma by targeting MCL-1 via miR-29b-3p. Cell Death Dis. 10, 106 (2019).
87. Santner, L., Bar, C. & Thum, T. Circular RNAs: a novel class of functional RNA molecules with a therapeutic perspective. Mol. Ther. 27, 1350–1363 (2019).
88. Lei, M. et al. Translation and functional roles of circular RNAs in human cancer. Mol. Cancer 19, 30 (2020).
89. Liang, W. C. et al. Translation of the circular RNA circbeta-catenin promotes liver cancer cell growth through activation of the Wnt pathway. Genome Biol. 20, 84 (2019).
90. Yang, Y. et al. Novel role of FBXW7 circular RNA in repressing glioma tumorigenesis. J. Natl Cancer Inst. 110, 304–315 (2018).
91. Zhang, M. et al. A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis. Oncogene 37, 1805–1814 (2018).
92. Wu, N. et al. Translation of yis-associated protein (YAP) is antagonized by its circular RNA via suppressing the assembly of the translation initiation machinery. Cell Death Differ. 26, 2758–2773 (2019).
93. Ng, W. L., Mohd Mohidin, T. B. & Shukla, K. Functional role of circular RNAs in translation and functional roles of circular RNAs in human cancer. Mol. Cancer 19, 30 (2020).
94. Abdelmohsen, K. et al. Identification of HuR target circular RNAs uncovers suppression of PABPN1 translation by CircPABPN1. RNA Biol. 14, 361–369 (2017).
95. Kim, J. et al. LncRNA OIP5-AS1/cyano sponges RNA-binding protein HuR. Nucleic Acids Res. 44, 2378–2392 (2016).
96. Liu, Y. et al. Circular RNA NTMTO suppresses breast cancer cell viability and reverses monastrol resistance through regulating the TRAF4/Eg5 axis. Int. J. Oncol. 53, 1752–1762 (2018).
97. Chen, L. et al. Circ-MALAT1 functions as both an mRNA translation brake and a modulator of circular RNA biogenesis. Adv. Sci. (Weinh.) 7, 1900949 (2020).
98. Mao, Y. Zhang, L. & Li, Y. circEIF4G2 modulates the malignant features of cervical cancer via the miR218/HOXA1 pathway. Cell Death Dis. 19, 616 (2018).
99. Liu, J., Xu, Y., Stoleru, D. & Salic, A. Imaging protein synthesis in cells and tissues with an alkyne analog of puromycin. Proc. Natl Acad. Sci. USA 109, 413–418 (2012).
100. Su, K. H. et al. HSFI critically attunes proteotoxic stress sensing by mTORC1 to combat stress and promote growth. Nat. Cell Biol. 18, 527–539 (2016).
101. Chasse, H. et al. Analysis of translation using polynucleosome profiling. Nucleic Acids Res. 45, e15 (2017).
102. Santos, D. A., Shi, L., Tu, B. P. & Weissman, J. S. Cycloheximide can distort measurements of mRNA levels and translation efficiency. Nucleic Acids Res. 47, 4974–4985 (2019).
103. Murat, P. et al. RNA G-quadruplexes at upstream open reading frames cause DHX36- and DHX9-dependent translation of human mRNAs. Genome Biol. 19, 229 (2018).

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