Annual Review of Cancer Biology
The Role of Translation Control in Tumorigenesis and Its Therapeutic Implications
Yichen Xu¹ and Davide Ruggero¹,²

¹Department of Urology and Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California 94157, USA; email: davide.ruggero@ucsf.edu
²Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California 94158, USA

Keywords
translation control, cancer initiation and metastasis, translation machinery, signaling transduction pathway, tumor immunology, translation inhibitors

Abstract
As a convergent mechanism downstream of most oncogenic signals, control of mRNA translation has emerged as a key driver in establishing and tuning gene expression at specific steps in cancer development. Translation control is the most energetically expensive molecular process in the cell that needs to be modulated upon adaption to limited cellular resources, such as cellular stress. It thereby serves as the Achilles’ heel for cancer cells, particularly in response to changes in the microenvironment as well as to nutrient and metabolic shifts characteristic of cancer cell growth and metastasis. In this review, we discuss emerging discoveries that reveal how cancer cells modulate the translation machinery to adapt to oncogenic stress, the mechanisms that guide mRNA translation specificity in cancer, and how this selective mode of gene regulation provides advantages for cancer progression. We also provide an overview of promising preclinical and clinical efforts aimed at targeting the unique vulnerabilities of cancer cells that rely on the remodeling of mRNA translation for their infinite growth and survival.
INTRODUCTION
Aberrant control of protein synthesis is a central driver of cellular transformation and tumor development. Compared to other means of gene expression regulation, such as transcription or protein stability, the regulation of protein synthesis is especially energy consuming, as over 20% of the total cellular energy is directly or indirectly invested in this process (Buttgereit & Brand 1995). This raises the outstanding question: Why is translational control so essential for cancer development? As the ultimate step of protein production, translation is clearly a significant node of gene expression. However, the reasons as to why cancer cells are required to frequently regulate this process rather than other means of gene expression, such as transcription, remain unknown. One explanation can be found in recent studies showing that a group of mRNAs (messenger RNAs) under frequent translational regulation are implicated in the ability of cancer cells to adapt to stress, which can be induced by changes in the tumor microenvironment, such as hypoxia, nutrient shortage, and the delivery of anticancer drugs. Overcoming this critical barrier is essential for cancer cell survival, and the reprogramming of mRNA translation serves as a major mechanism for cancer cell adaptation to acute microenvironment changes (Yamasaki & Anderson 2008). For example, cellular stress triggers mRNAs to be recruited into cytosolic stress granules (Buchan & Parker 2009), where they are temporarily translationally silenced. Once cell stress abates, this translational suppression can be relieved, resulting in the immediate translation of these mRNAs. Another important explanation is that tumor cells can also promptly produce proteins by selectively translating mRNAs that are urgently needed to respond to beneficial stimuli (i.e., growth signals) or to overcome an antitumor immune response (Xu et al. 2019). This temporal specificity in gene expression is a key advantage of translation regulation that helps tumor cells adapt to microenvironment signals. In this review, we highlight exciting research that may shed light on the mechanisms by which cancer cells manipulate translation as a fast and highly selective type of gene expression control. Specifically, we explore how cancer cells hijack the existing translational machinery through the cooperation of various oncogenic signals, and what mechanisms enable cancer cells to determine which specific mRNAs to translate. Lastly, we summarize existing cancer therapies that target components of the translation machinery and discuss possibly overlooked therapeutic opportunities that can be gained from targeting the last step in gene expression: protein production.

THE CANCEROUS TRANSLATIONAL MACHINERY
Alterations of Translation Factors in Cancer
Initiation of cap-dependent translation relies on the activity of the eukaryotic initiation factor 4F complex (eIF4F) that recruits ribosomes to the 5' end of mRNAs. There are three major components of this complex: eIF4E (the major cap-binding protein), eIF4G (the key complex scaffold), and eIF4A (a helicase that is responsible for unwinding secondary structures of mRNAs), all of which have been shown to be genetically amplified or transcriptionally increased in various human cancers (Bauer et al. 2001, De Benedetti & Graff 2004, Eberle et al. 1997). Genetic loss of the negative regulators of eIF4E, the eIF4E-binding proteins (4E-BPs), is frequently found in patients with pancreatic and head and neck cancers (Martineau et al. 2014, Wang et al. 2019), suggesting a tumor-suppressive role for 4E-BPs in certain cancers. Moreover, Eif4e and Eif4g are bona fide oncogenes themselves, whose overexpression promotes cellular transformation (Lazaris-Karatza et al. 1990, Ruggiero et al. 2004, Silvera et al. 2009). One of the most fundamental discoveries over the last several years has been the realization that reducing the levels of these translation factors, long conceived as housekeeping genes, surprisingly does not alter normal cellular homeostasis or embryonic development. For example, Eif4e haploinsufficiency in mice...
does not perturb normal development or cellular physiology, whereas it remarkably suppresses oncogenic transformation (Truitt et al. 2015). These findings support the notion that increased eIF4E activity and its partners are specifically utilized for cancer development. eIF6, another key translation factor responsible for 80S ribosome assembly and translation initiation, whose activity drives cell transformation and tumorigenesis, is also found amplified and overexpressed in human malignancies (Gandin et al. 2008, Gatza et al. 2014, Miluzio et al. 2011). Another translation factor important for cancer development is the eIF3 multiprotein factor, which is composed of 10–13 proteins involved in bridging the eIF4F-bound mRNA with the translation preinitiation complex (PIC), a ribonucleoprotein complex containing the small ribosomal subunit (40S) bound by a few initiation factors, including eIF1 and the eIF2–methionyl initiator transfer RNA (tRNA\textsubscript{Met}) ternary complex (eIF2-TC). Specifically, the eIF3h subunit is amplified in breast cancer and malignant prostate cancer (Nupponen et al. 1999, Saramaki et al. 2001), whereas the expressions of other subunits, such as eIF3e and eIF3f, are downregulated in various cancers (Marchetti et al. 2001, Shi et al. 2006). While understanding the distinct roles of eIF3 subunits in cancer remains an outstanding question, recent data suggest that specific subunits of this complex can regulate the translation of different mRNAs, which may have either oncogenic or tumor-suppressive properties (Lee et al. 2015, 2016). Recently, another translation initiation factor, eIF1A, responsible for the assembly of PIC and start codon selection, has been found to be mutated in thyroid cancer (Krishnamoorthy et al. 2018). In this context, the translation initiation factor eIF2A, also involved in start codon recognition, has been discovered to be both amplified in human squamous cell carcinomas and correlated with poor prognosis (Sendoe et al. 2017). The expression not only of translation initiation factors but also of elongation factors is widely altered in human cancers. For example, the expression of eIF5A, a translation factor involved in the elongation step of protein synthesis, is increased in a variety of cancers (Guan et al. 2004, He et al. 2011, Tang et al. 2010).

At present, although clear examples of genetic alterations in translation factors have been observed in cancers, by far the most prevalent changes are found instead at the level of their activity. In fact, almost all oncogenic signals that are frequently deregulated in cancer (PI3K, RAS, MYC, and pRB) directly control the activity of translation initiation and elongation factors at the level of their posttranslational modifications (PTMs; see below). Therefore, the large-scale genomics efforts aimed at identifying cancer mutations and drivers of cancer initiation are likely to miss these important changes. Moreover, as the translation factors may be essential genes, their alterations at the posttranslational level may represent a unifying mechanism for how their activities are controlled in cancer cells, for example, at the level of hypomorphic loss or increase in activity, rather than full deletions, which would compromise the fitness of even normal cells.

**Upstream Oncogenic Pathways that Regulate the Translational Machinery**

Cancer is a disease of aberrant signaling (Yaffe 2019). In this context, major signal transduction pathways, when abnormally activated, become key drivers of tumorigenesis by manipulating the activity of specific translation factors (**Figure 1b**). One of the best examples is the master transcription factor MYC, which is hyperactivated in most human cancers and is a key regulator of protein synthesis (Iritani & Eisenman 1999). MYC controls mRNA translation by increasing the transcription of many components of the translational machinery, such as ribosomal RNA (rRNA) (Grandori et al. 2005); ribosomal proteins (RPs) (Boon et al. 2001); translation initiation factors such as eIF4E, eIF4G, and eIF4A (Schmidt 2004); and the RNA guanine-7-methyltransferase responsible for the functional mRNA cap structure (Cole & Cowling 2009). Importantly, genetic
Alterations of the translation machinery and its upstream signals in cancer. (a) Translation initiation and elongation factors are frequently genetically altered in cancer. The complex eIF4F, composed of eIF4E, eIF4G, and eIF4A, is upregulated or amplified in various cancers; whereas their inhibitory proteins such as PDCD4 are downregulated. The expression of individual subunits of eIF3 and eIF2 in cancer can be different. Other factors including eIF1A, eIF5A, eEF1A, and eEF2 are also genetically altered. (b) RAS-MAPK and PI3K-AKT signaling transduction pathways are activated in most human cancers. The oncogenic activities of these pathways converge on the regulation of the translational machinery, mostly through the activation of mTOR, which phosphorylates and inactivates 4E-BPs. mTOR also phosphorylates and activates S6Ks. MNK downstream of RAS-MAPK directly phosphorylates eIF4E, promoting the translation of mRNAs crucial for cancer progression. In response to stress, the AMPK pathway is activated to suppress mTOR activity, whereas eIF2 kinases (PERK, HRI, PKR, and GCN2) phosphorylate the α subunit of eIF2, repressing global protein synthesis while increasing the translation of specific mRNAs that are critical to overcome the stress and promote cancer progression. In the nucleus, key oncogenic transcription events (e.g., activation of MYC and loss of p53 and pRB) contribute to the transcription of translation factors, RPs, and RNAs. (c) Alterations in ribosome components in cancer include RPs and enzymes responsible for rRNA modifications (e.g., DKC1, which catalyzes pseudo-uridination, and FBL, which mediates 2′-O-methylation) that are either upregulated, downregulated, or mutated specifically in cancers. Abbreviations: 40S, small ribosomal subunit; 60S, large ribosomal subunit; 4E-BPs, eIF4E-binding proteins; eIF4F, eukaryotic initiation factor complex 4F; met, methionyl; MNK, MAPK-interacting kinase; mRNA, messenger RNA; RPs, ribosomal proteins; rRNA, ribosomal RNA; S6Ks, S6 kinases; eEF2, elongation factor 2.

studies have firmly established that MYC’s oncogenic potential lies in its control of protein synthesis to drive cancer initiation. For example, MYC oncogenic activity is significantly compromised when the increased protein synthesis levels in a tumor are restored to normal by the deletion of one copy of the protein RPL24 (Barna et al. 2008). In particular, the MYC-driven elevation in protein synthesis is responsible for increased cell growth, division, and genomic instability in cancer.

Two additional notable pathways that regulate protein synthesis in human cancers are the PI3K-AKT and RAS-MAPK pathways. The most well-studied mechanism of action of the PI3K-AKT pathway in protein synthesis control is mediated by the inactivating phosphorylation of the tuberous sclerosis tumor-suppressor TSC1/2 complex, which is a negative regulator of the mammalian target of rapamycin complex 1 (mTORC1) (Zoncu et al. 2011). mTORC1 activation subsequently induces the phosphorylation of the RP S6 kinase 1/2 (S6K1/2) and 4E-BPs, promoting translation initiation. In addition, S6K phosphorylation also controls translation elongation via direct inhibition of the eEF2 kinase, a negative regulator of the elongation factor eEF2. Similar to the PI3K-AKT node, the RAS-MAPK pathway also modulates mRNA translation by blocking TSC2 activity (Ma et al. 2005, Roux et al. 2004). In addition, MAPK interacting kinases (MNK1/2), downstream of ERK and p38 kinases, phosphorylate eIF4E at serine 209 (Waskiewicz et al. 1999). Although the underlying mechanism by which eIF4E phosphorylation impacts translation remains poorly understood, compelling studies have shown that phosphorylated eIF4E promotes mRNA translation in hormone- or growth factor–treated cells (Gingras et al. 1999) and positively regulates the translation of specific mRNAs critical for tumor development and metastatic dissemination (Furic et al. 2010, Robichaud et al. 2015, Xu et al. 2019). Importantly, RAS-induced cell transformation and tumorigenesis are markedly abolished when TSC2 or eIF4E can no longer be phosphorylated by the RAS-MAPK pathway (Ma et al. 2005, Ueda et al. 2010), suggesting that RAS-mediated control of mRNA translation contributes significantly to its oncogenic activity.

Translational control is an integral part of these survival adaptive pathways. Under stress conditions, cancer cells reroute energetic resources by attenuating global protein synthesis, while translating the distinct mRNAs essential to mitigating the stress and promoting survival (Figure 1b). For example, an energy-sensing kinase, AMPK, is expressed in various cancers. AMPK can directly phosphorylate TSC1/2 (Ma et al. 2005), as well as the mTORC1 component Raptor (Gwinn et al. 2008), to shut down mTOR-mediated mRNA translation when necessary. The activation of AMPK also activates eIF2 kinase (eEF2K), which in turn phosphorylates and inhibits the function of eEF2 in translation elongation, enabling cancer cells to escape nutrition deprivation–induced apoptosis (Leprivier et al. 2013).
While phosphorylation is the most studied type of key PTM on translation factors, new exciting studies have discovered additional PTMs on translation factors induced by oncogenic pathways that are important for cancer progression. One remarkable example is a recent work discovering that the elongation factor eEF1A is methylated by methyltransferase-like 13 (METTL13), which is hijacked by oncogenic RAS signaling to elevate protein synthesis and promote tumorigenesis (Liu et al. 2019). Another unique PTM is hypusination on lysine 53 of the eIF5A translation factor. Hypusination is the transfer of an amino-butyl residue to lysine mediated by two enzymes, deoxyhypusine synthase (DHPS) and deoxyhypusine hydroxylase (DOHH), using polyamine spermidine as a substrate to generate hypusinated eIF5A. Interestingly, eIF5A and its isoform eIF5A2, as well as DHPS and DOHH, are upregulated in several cancers and are associated with unfavorable prognostic clinical outcomes (Nakanishi & Cleveland 2016). However, the role of eIF5A and of the hypusination modification in cancer are still poorly understood. Elucidating how unique PTMs modulate the activity of specific translation factors in cancer is essential not only to unveil new mechanisms of posttranscriptional regulation underlying tumor growth, but also to provide a rationale for new therapeutic intervention. This is illustrated by the fact that drugs targeting enzymes responsible for these PTMs have the potential to expose a novel point of vulnerability in cancer cells. For example, a compound that inhibits DHPS (GC-7) shows antiproliferative effects in mouse melanoma cells both in vitro and in vivo (Jasiulionis et al. 2007).

Cancer-Specific Ribosomes

Ribosomes were once considered indiscriminate protein production factories with identical composition across different cell and tissue types. However, exciting studies have now captured differences in the RNA and protein makeup of ribosomes. This variability and the identification of distinct mRNAs bound to variant ribosomes indicate that distinct ribosomal components may act as regulatory elements for the translation of specific mRNAs (reviewed by Genuth & Barna 2018). Indeed, recent studies have shown that translating ribosomes are heterogeneous at the level of both core RPs and ribosome-associated proteins, and that ribosomes with distinct protein compositions translate different subsets of mRNAs in embryonic stem cells (Shi et al. 2017, Simsek et al. 2017). In this respect, it is tempting to speculate that the composition of ribosomes in cancer cells may also change during tumorigenesis. PTMs of RPs, as well as chemical modifications in rRNAs such as methylation and pseudo-uridylation, are also commonly deregulated during cancer development from cellular transformation to tumor maintenance (Bellodi et al. 2010, Khalaileh et al. 2013, Marcel et al. 2013, McMahon et al. 2019, Montanaro et al. 2006). An important discovery supporting the concept that alterations in ribosomes function as drivers of human disease is the discovery of so-called ribosomopathies—inherited human syndromes caused by mutations in RPs and other factors that regulate ribosome activity, which are characterized by increased cancer susceptibility (Sulima et al. 2017). Examples include mutations in the DKC1 gene that encodes the dyskerin protein, an evolutionarily conserved enzyme responsible for the modification of specific uridine residues in rRNA (Heiss et al. 1998), and mutations of specific RPs (Drapchinskaia et al. 1999, Ebert et al. 2008). Importantly, patients affected by ribosomopathies have a high incidence of lymphomas and solid tumors (Lipton et al. 2001, Shimamura & Alter 2010). Moreover, genetic mutations or deletions of ribosomal components have been detected in several human cancers (Figure 1e) (Dave et al. 2014, De Keersmaecker et al. 2013, Ljungstrom et al. 2016, Rao et al. 2012). One example is a mutation of RPL10A at arginine 98 residue, which results in an altered expression of approximately 4% of the proteome, including the JAK/STAT signaling components in T cell acute lymphoblastic leukaemia (Girardi et al. 2018). Therefore, although a direct
connection has been established between alterations in the expression or activity of components of the ribosomes and susceptibility to cancer, further studies are required to directly assess whether cancer ribosomes exist—that is, whether the composition of the translation machinery itself is altered as a consequence of specific oncogenic lesions, and how these alterations influence translation control in cancer cells versus their untransformed counterparts. Another important connection between ribosomes and cancer is whether the total number of ribosomes and their composition may also be altered in the setting of cellular transformation. This is supported by findings from over 200 years ago that changes in the size and number of nucleoli (sites of ribosome production) could be used as biomarkers distinguishing normal cells from cancer cells. Often, such changes may only be proxies for the number and translational status of ribosomes in a cell. Therefore, more selective means for quantifying ribosomes’ activity, composition, and number are required to investigate the biophysical properties of the translation machinery in cancer. These ribosome alterations have important therapeutic implications for whether certain cancers can be targeted with ribosome inhibitors. For example, new compounds that target Pol I, responsible for transcribing ribosomal DNA, recently entered the clinic and have shown antitumor effects in preclinical studies (Drygin et al. 2009, Peltonen et al. 2014).

FEATURES OF mRNA REGULATORY ELEMENTS THAT DRIVE REGULATION AT THE TRANSLATIONAL LEVEL IN CANCER

Structural Regulatory Elements

One of the first insights into how mRNAs are selectively translated in cancer cells stemmed from the discovery that some mRNAs, including those encoding for growth factor receptors, survival proteins, or oncogenes such as MYC, possess secondary structures in their 5′ UTR (untranslated region) that hinder ribosome scanning and translation initiation (Kozak 1986, Pelletier & Sonenberg 1985). As these proteins are critical regulators of cell growth, the translation of their mRNAs is limited and highly regulated in normal cells by these RNA structures, which serve as important mechanisms to restrain protein production of selective mRNAs in the genome. Cancer cells augment the translation efficiency of these mRNAs by hyperactivating the eIF4F complex, in particular via the eIF4A helicase, which unwinds secondary structures within the 5′ UTRs, enabling a selective increase in the translome of cancer cells (Koromilas et al. 1992, Ray et al. 1985). Indeed, these eIF4A-sensitive transcripts include growth factor receptors and key cell cycle regulators (Wolfe et al. 2014). Interestingly, other DEAD box RNA helicases, such as DDX3 (encoded by DDX3X), have recently been shown to translate a network of mRNAs contributing to tumor development (Oh et al. 2016). Notably, DDX3X is mutated in 36% and 21% of WNT group and SHH group medulloblastoma, respectively (Northcott et al. 2017, Robinson et al. 2012), and thereby represents a major oncogenic driver that directly controls mRNA translation (Figure 2a).

Other structured RNA elements in the 5′ UTR, known as internal ribosome entry sites (IRESs), regulate the translation of specific mRNAs in a cap-independent manner (Figure 2b). This mode of translation initiation is more prominent under distinct steps of cancer progression characterized by stress conditions, such as hypoxia, DNA damage, and amino acid starvation. Importantly, IRES-containing mRNAs encode for proteins associated with the hallmarks of cancer, such as prosurvival (e.g., HIF1A), antia apoptotic (e.g., BCL2 and XIAP), and proangiogenic (e.g., VEGFA and CTNND1) factors (Braunstein et al. 2007, Holcik et al. 2000, Silvera et al. 2009). The IRES structure, along with the activity of several IRES trans-acting factors including RNA-binding proteins (RBPs) and translational factors such as eIF4G or eIF3, recruits the 40S ribosome to the mRNA to promote translation initiation. It has also been reported that IRES-dependent translation of
specific protumor mRNAs can also be suppressed by certain RBPs, such as the tumor suppressor PDCD4, which directly represses the IRES-dependent translation of \textit{XIAP} and \textit{BCLXL} to block tumor growth (Liwak et al. 2012). Therefore, the successful translation of these IRES-containing mRNAs can enhance tumor initiation (Mizrachy-Schwartz et al. 2007), growth and angiogenesis (Braunstein et al. 2007), and therapy resistance (Gu et al. 2009).
mRNA features guiding translation specificity in cancer. (a–c) RNA elements including secondary structures (a), IRES elements (b), and protein-binding structural motifs (c) control the translation efficiency of specific mRNAs critical for tumorigenesis. (d) ATISs upstream of the main AUG start codon control the translation of key mRNAs during cancer development. An ATIS can lead to the production of long protein isoforms such as PTEN-L or the translation of a uORF that impacts the translation of the downstream mRNA. Dashed arrows indicate a less efficient translation initiation at the main AUG due to the initiation at ATIS or uORF. (e) Sequence motifs within UTRs can guide cap-dependent translation of protumor transcripts. (f) mRNA modifications (e.g., m^6^A) recognized by specific RBPs direct a preferential translation of oncogenic mRNAs for tumor progression. (g) Cancer-specific expression of a repertoire of tRNAs that match the cancer-mRNA codon sequences favors the translation of cancer mRNAs (e.g., mRNAs implicated in the cell cycle, invasion, and cancer angiogenesis) over other mRNAs (e.g., those implicated in differentiation and apoptosis). Abbreviations: 40S, small ribosomal subunit; 60S, large ribosomal subunit; ATIS, alternative translation initiation site; CPE, cytoplasmic polyadenylation element; IRES, internal ribosome entry site; ITAFs, IRES trans-acting factors; mRNA, messenger RNA; ORF, open reading frame; RBP, RNA-binding protein; tRNA, transfer RNA; uORF, upstream ORF; UTR, untranslated region.

Excitingly, new technologies, such as selective 2′-hydroxyl acylation analyzed by primer extension (SHAPE) and cross-linking immunoprecipitation (CLIP), have been instrumental in defining new RNA structures in the regulatory regions of selective mRNAs, unveiling new mechanisms for translation specificity. For example, recent studies have found that distinct components of the eIF3 complex such as eF3a and eF3c directly bind RNA hairpin structures in the 5′ UTR to regulate the translation of pro-oncogenic mRNAs such as c-JUN and BTG1 (Figure 2c) (Lee et al. 2015). Therefore, we are at the beginning of a new line of research that deciphers the structural topology of regulatory elements within mRNAs that may be directly involved in different steps of tumorigenesis and drug resistance.

**Alternative Translation Initiation Site**

Another example of a translation regulator located in the 5′ UTR of key oncogenic proteins is the alternative translation initiation site (ATIS), located upstream of the main AUG initiation codon. An ATIS can be in frame with the main open reading frame (ORF) and, if engaged by the 40S ribosome and the PIC, leads to a longer protein, which may have a new function. For instance, translation from an upstream ATIS present in the PTEN mRNA results in the synthesis of a long form of PTEN (PTEN-L), which is secreted to act as a tumor suppressor in neighboring cells that uptake PTEN-L. Notably, this tumor-suppressive translation event is lost in breast cancer (Hopkins et al. 2013). Alternatively, the ATIS may be part of a small ORF, known as an upstream ORF (uORF), which generally represses the translation efficiency of the main ORF (Figure 2d). The regulatory activity of uORFs has been an emerging example of how cells modulate the abundance of key proteins. Mechanistically, this can be achieved by (a) the ribosomes dissociating after translating the uORF or (b) the ribosomes stalling on the uORF and blocking the other incoming ribosomes (Lovett & Rogers 1996). Both scenarios impair the ability of ribosomes to translate the downstream main ORF. However, the translational barrier imposed by the uORF needs to be bypassed when cells need to translate the main ORF. The mechanistic details by which uORFs are circumvented, allowing the ribosome to engage the main start codon, are still poorly understood. Nevertheless uORF-mediated translation is likely exploited by cancer cells to favor the translation of specific mRNAs. For example, bypassing uORF-mediated translation suppression of the ERBB2 mRNA enhances the production of this oncogenic growth receptor (Mehta et al. 2006). Another recent example is the synthesis of programmed death ligand 1 (PD-L1), a key immune checkpoint that diminishes the antitumor T cell response. The PD-L1 mRNA is normally translationally repressed by uORFs located in its 5′ UTR. Importantly, this uORF-mediated translational repression is efficiently bypassed in aggressive cancer, leading to tumor immune
evasion and metastasis formation (Xu et al. 2019). Therefore, understanding the mechanisms by which cancer cells alter uORF regulatory activity should be of great interest to cancer biologists.

In this respect, one of the translation factors discovered to be involved in bypassing uORF-mediated translation repression is eIF2. eIF2 is the initiation factor that binds GTP and tRNA\textsubscript{Met} to form the eIF2-TC, which is important for delivering methionyl-tRNA\textsubscript{Met} onto the AUG start codon through GTP hydrolysis. Under different forms of cellular stress, such as endoplasmic reticulum stress, the \( \alpha \) subunit of eIF2 (eIF2\( \alpha \)) is phosphorylated at serine 51 by several eIF2\( \alpha \) kinases, including the double-stranded RNA-dependent protein kinase (PKR) and PKR-like endoplasmic reticulum kinase (PERK) (Wek 2018). eIF2\( \alpha \) phosphorylation modulates the propensity of eIF2 to recognize the start codon. It is noteworthy that cancer cells are usually under various stresses imposed by oncogenic insult–induced metabolic alterations or rapid changes in the tumor microenvironment. Therefore, increased eIF2\( \alpha \) phosphorylation in cancer cells is likely to trigger uORF bypass as a mechanism to control selective mRNA translation. Intriguingly, eIF2\( \alpha \) phosphorylation is characteristic of more aggressive cancers and is responsible, at least in part, for the bypass of uORF-mediated translational repression of PD-L1 in cancer (Xu et al. 2019). Furthermore, eIF2\( \alpha \) phosphorylation is essential for the growth of metastatic prostate cancer, and increased eIF2\( \alpha \) phosphorylation, in combination with loss of PTEN, is a strong predictor for prostate tumor recurrence and metastasis formation (Nguyen et al. 2018). PERK, which regulates eIF2\( \alpha \) phosphorylation, also controls the ability of cancer cells to undergo the epithelial-to-mesenchymal transition, which is responsible for both cancer metastasis and therapy resistance (Feng et al. 2014).

Intriguingly, a recent genome-wide study in the context of skin tumorigenesis showed that uORFs could also act as translation activators to fuel tumor growth (Sendoel et al. 2017). Although the underlying mechanism is unclear, this study proposed that engagement of these uORFs is likely mediated by an alternative translation initiation factor, eIF2A, which is upregulated in many cancers. Moreover, uORF-mediated translation regulation can be directly created or abolished by genetic mutations of upstream initiation codons, particularly in genes associated with cancer cell survival (McGillivray et al. 2018). The most prominent and functionally validated examples are mutations in the 5\textsuperscript{'} UTR that create new uORFs within the mRNAs CDKN2A (which encodes p16\textsuperscript{INK4A} and p14\textsuperscript{ARF}) (Liu et al. 1999) and CDKN1B (which encodes p27\textsuperscript{KIP1}) (Occhi et al. 2013). These newly generated uORFs induce the translation repression of these tumor suppressors in patients who are predisposed to melanoma and pituitary adenoma, respectively.

Important, the full repertoire of mRNAs that are translationally regulated in cancer cells when eIF2\( \alpha \) is phosphorylated is still unknown. In addition, elucidating the products of their uORFs in cancer cells would also be important for exploring potentially novel therapeutic strategies. For example, it has been proposed that the translation of a uORF can result in the production of a peptide that may be relevant for cell recognition by the immune system during the adaptive immune response (Starck et al. 2016). Indeed, silencing of the RPS28 protein promotes the translation of uORFs in melanoma cells. This results in the production of HLA-A2 antigen peptides that stimulate the antitumor CD8\textsuperscript{+} T cell response (Wei et al. 2019). In this scenario, an increase in the ribosome engagement of uORFs during early steps of cancer development may also lead to the production of small peptides that unintentionally appear on the surface of tumor cells. Therefore, these neoantigens could be employed for early cancer detection and as novel therapeutic targets.

**Sequence Motifs**

Several sequence-specific elements in mRNA 5\textsuperscript{'} UTRs are functionally associated with the translation efficiency of distinct mRNAs in response to oncogenic signals (Figure 2c). One of the earliest examples is the 5\textsuperscript{'}-terminal oligopyrimidine tract (TOP) motif, which is identified as a
translational regulator of mRNAs encoding for components of the translation machinery, including RPs (Levy et al. 1991), and translational factors themselves (Iadevaia et al. 2008). The specific translation of TOP-containing mRNAs contributes to the increase in protein synthesis and cell growth downstream of mTOR activation (Hsieh et al. 2012, Jefferies et al. 1994, Tang et al. 2001, Thoreen et al. 2012). Using genome-wide ribosome profiling experiments in prostate cancer cells treated with mTOR ATP active site inhibitors, researchers have also identified so-called TOP-like sequences such as the pyrimidine-rich translational element (PRTE) in proinvasive transcripts, including Y box–binding protein 1 (YBX1) and metastasis-associated 1 (MTA1) (Hsieh et al. 2012). Furthermore, the PRTE is responsible for the translation of phosphoribosyl pyrophosphate synthetase 2, a rate-limiting nucleotide biosynthesis enzyme necessary for increasing the nucleotide pool in MYC-induced tumorigenesis (Cunningham et al. 2014). Another sequence motif that confers sensitivity to translation in an eIF4E-dependent manner during the early steps of cellular transformation is the cytosine-enriched regulator of translation (CERT) motif, which promotes translation initiation of specific mRNA networks. These mRNAs include the antioxidant proteins ferritin and glutathione, which are essential for cellular transformation and tumor progression by counteracting the toxic increases of reactive oxygen species (Truitt et al. 2015).

Although researchers understand the functional relevance of these sequence motifs (e.g., TOP, TOP-like, PRTE, CERT) in regulating the translation of specific transcripts during tumorigenesis, the mechanistic details by which they interact with the translation machinery remain elusive. A working hypothesis is that oncogenic signaling coordinates the recruitment of distinct RBPs and specific translational factors to these sequence motifs to promote translation initiation. In line with this hypothesis, La-related protein 1 (LARP1) binds to the 5′ TOP motif and regulates the translation of mTOR-sensitive mRNAs (e.g., RP mRNAs) (Fonseca et al. 2015, Tcherkezian et al. 2014). Another example is the splicing factor U2AF1, a noncanonical translation regulator that binds mRNA at a specific RNA motif near the AUG start codon, which normally suppresses the translation of hundreds of mRNAs, including IL-8. Importantly, mutations in U2AF1 at serine 34 (S34F), which are found in many human cancers, relieve this suppression and may contribute to cancer metastasis through derepression of the translation of specific mRNA networks (Palangat et al. 2019).

Interestingly, the interaction of RBPs with regulatory elements located in the 3′ UTR may also control the translation of oncogenic mRNAs. For example, the cytoplasmic polyadenylation element (CPE) is located in the 3′ UTR of hundreds of mRNAs involved in important cellular processes (e.g., cell proliferation, chromosome segregation). The CPE is bound by a group of RBPs known as CPE-binding proteins (CPEBs) including CPEB4, which is overexpressed in pancreatic ductal adenocarcinoma. The binding of CPEB4 to the CPE induces the translation of several protumor mRNAs, such as tPA (tissue plasminogen activator), mediating tumor progression (Ortiz-Zapater et al. 2011). The precise mechanism by which putative RBPs may impact translation specificity through their binding with 5′ or 3′ UTRs remains an outstanding question in cancer biology. However, it is intriguing that some of these RBPs themselves may be altered during tumor development, and their expression levels can also serve as indicators of poor prognosis (Pereira et al. 2017).

**RNA Modifications**

Although RNA modifications were discovered in the 1960s, the importance of the RNA epitranscriptome, particularly in cancer, has only recently come under investigation. Similar to genomic DNA epigenetics, modifications of an mRNA influence translation control and mRNA stability. N6-methyladenosine (m6A) is the most common modification in cells, which is mediated by
methyltransferases METTL3 and METTL14, known as writers; recognized by a cluster of RBPs, known as readers [e.g., YTH family proteins (Wang et al. 2015)]; and erased by demethylases, including FTO and ALKBH5. The gain or loss of function of these proteins affects mRNA translation. In the cancer setting, both m^6^A writers (Vu et al. 2017) and readers (e.g., YTHDF1) (Han et al. 2019, Nishizawa et al. 2018) remarkably impact cancer progression. Deletion of METTL3 abrogates oncogenesis by suppressing the translation efficiency of oncogenic mRNAs encoding for proteins involved in either signal transduction (e.g., \textit{EGFR}) or gene transcription (e.g., \textit{BRD4} and \textit{SP1}), all of which possess m^6^A within their CDS (coding sequence) or 3' UTR (Barbieri et al. 2017, Choe et al. 2018, Lin et al. 2016, Vu et al. 2017). As these proteins linked to m^6^A can be inhibited by small molecules, they may represent novel therapeutic targets. Mechanistically, it has been suggested that METTL3 facilitates 5'-3' mRNA looping, in which METTL3 bound on the 3' UTR interacts with the initiation factor eIF3 to directly influence the binding of the 40S subunit on the 5' UTR (Choe et al. 2018). This mRNA looping is believed to promote translation reinitiation after ribosomes are disassembled following translation termination (Figure 2f). The m^6^A modification is pervasive and present throughout the transcriptome of mRNAs (5' UTR, CDS, and 3' UTR). Whether m^6^A modifications change during cancer development and if these changes support the translation selection of oncogenic mRNAs during cancer progression are outstanding questions that remain unanswered.

**Codon Usage**

Cancer cells may have an increased demand for translating selective mRNA networks that, in some instances, are composed of transcripts harboring a unique codon usage (Figure 2g). Exciting recent studies support the notion that tumor cells preferentially increase the expression of specific tRNA (transfer RNA) species to enhance the translation elongation of transcripts enriched for their cognate codons (Goodarzi et al. 2016, Pavon-Eternod et al. 2009). The codon-biased translation of specific mRNAs in cancer cells is controlled at the level of not only tRNA abundance but also tRNA modifications (Begley et al. 2007, Chan et al. 2012, Delaunay et al. 2016). Interestingly, mRNAs involved in cell proliferation, cell invasion, and metastasis appear to harbor distinct codon usage frequencies compared to other mRNAs (Gingold et al. 2014, Goodarzi et al. 2016). In this context, codon usage–mediated translation control regulates the synthesis of key oncogenes such as RAS. Compared to HRAS, KRAS mRNAs contain relatively rare codons that are low in abundance, resulting in reduced translational efficiency of this specific isoform of RAS. Replacing these rare codons with common ones significantly enhances KRAS protein synthesis (Lampson et al. 2013). More recently, it has been proposed that codon usage in translational control may also impact therapeutic resistance. For example, the codon-specific translation of a DNA damage repair kinase, ATR, renders cancers resistant to DNA damage agents (Li et al. 2018).

**FROM THE BENCH TO THE CLINIC: TARGETING TRANSLATIONAL CONTROL**

It is now clear that translational remodeling of critical mRNA networks regulates important steps in cancer development. This cancer-specific translational remodeling may now provide a therapeutic window for new inhibitors of mRNA-selective translation control. Major efforts have been made to target oncogenic drivers (e.g., MYC amplification and RAS mutations), which are often undruggable. In contrast, cancer-specific translational control is an emerging example of a nononcogene addiction, a dependency common to multiple oncogenic signals. Therefore, targeting the translation machinery represents a novel therapeutic intervention for cancer (Figure 3).
Figure 3

Drugs and therapeutic strategies (blue text) targeting the translation machinery and its upstream signaling in cancer. TKis and compounds inhibiting the RAS-MAPK, PI3K-AKT, and mTOR signaling pathways can result in the suppression of translation initiation. Drugs targeting the enzymes regulating the posttranslational modifications of translation factors [e.g., eIF4E or eIF2 phosphorylation (Chen et al. 2011, Zhao et al. 2016) and eIF5A hypusination] can also alter the activity of these translation factors. The activity of translation factors can be targeted by the compounds that are directly bound to them (e.g., eIF4A and eEF1A inhibitors, the eIF2B activator ISRIB, and 4EGI, which blocks the eIF4E-eIF4G interaction). The abundances of translation components can also be regulated (e.g., antisense oligonucleotides, which degrade eIF4E mRNA, and the Pol I inhibitor, which blocks ribosome biogenesis). Many of these compounds block the translation of specific protumor mRNAs and show potential preclinical or clinical efficacies.

Abbreviations: 40S, small ribosomal subunit; 60S, large ribosomal subunit; ISRIB, integrated stress response inhibitor; met, methionyl; MNK, MAPK-interacting kinase; mRNA, messenger RNA; PIC, preinitiation complex; TKi, tyrosine kinase inhibitor; tRNA, transfer RNA.

Targeting Translation Initiation and Elongation in Cancer Cells

Most compounds that inhibit translation control in cancer target translation initiation. One of the first examples is rapamycin and its analogs (rapalogs, such as everolimus), which allosterically inhibit mTORC1 activity. However, these compounds are not strong inhibitors of the mTORC1-directed phosphorylation of 4E-BP1 in vivo and do not efficiently abrogate the translation upregulation downstream of this oncogenic pathway, and therefore their anticancer efficacy is limited (Fruman & Rommel 2014). Interestingly, next-generation mTOR inhibitors that block the ATP site activity of mTOR (currently in several phase II trials for different cancers, including glioma, prostate cancer, breast cancer, etc.) possess higher efficacy in tumor regression. This is due in large part to their ability to abrogate phosphorylation of 4E-BPs and the translation of oncogenic mRNA networks (Benjamin et al. 2011). However, dose-limiting toxicities (DLTs) exist in both types of mTOR inhibitors. For example, the major DLTs of rapalogs are stomatitis, fatigue, mucositis, and hyperlipemia, while ATP site inhibitors such as MLN0128 and AZD2014 have also exhibited rash, anemia, mucositis, and fatigue. Strategies for managing the DLTs are being implemented to improve the tolerability of these inhibitors.
An intense ongoing effort has been made to target the eIF4F complex directly. For example, an antisense oligonucleotide (ASO) that promotes Eif4e mRNA degradation has proven effective in suppressing tumor progression in preclinical mouse models; however, phase I/II clinical trials may fall short, most likely due to the inefficient delivery of ASOs into solid tumors (Duffy et al. 2016, Honget al. 2011). Other examples include compounds that block the Eif4e-Eif4g interaction (e.g., 4EGI-1, 4E1RCat, 4E2RCat), which have displayed varied efficacies in preclinical animal models (Chen et al. 2012, Ghosh et al. 2009). As researchers have uncovered the involvement of eIF4A in translation of cancer-specific transcripts, efforts have also been made to target this important RNA helicase. Preclinical compounds that target eIF4A include silvestrol (Bordeleau et al. 2008) and the newly discovered compound rocaglamide A, which converts eIF4A into a translational repressor by selectively trapping eIF4A on the polypurine RNA stretch in an ATP-independent manner and consequently blocking ribosome scanning (Iwasaki et al. 2016). eIF4A inhibition by these compounds results in tumor suppression in xenograft tumor models (Bordeleau et al. 2008, Cerezo et al. 2018, Manier et al. 2017, Wolfe et al. 2014).

eIF4E phosphorylation, mediated by the MNKs, positively controls cap-dependent translation. Several MNK inhibitors have been generated, such as cercosporamide and toivotosertib (also named eT508), which abrogate tumor progression and metastasis in xenograft and genetically engineered mouse models (Konicek et al. 2011, Xu et al. 2019). Importantly, toivotosertib is currently in several phase II clinical trials against colorectal and castration-resistant prostate cancers (https://clinicaltrials.gov identifiers NCT03690141, NCT03258398). Another exciting target is the hypusination of eIF5A, which is the only known protein to contain a hypusine amino acid. The inhibition of Eif5a hypusination using GC-7 induced cell apoptosis and melanoma regression in mice (Jasiulionis et al. 2007).

Recent studies have further highlighted the possibility of also targeting the translation elongation step in cancer cells. For example, the elongation factor eEF1A, amplified in malignancies including ovarian cancer, can be inhibited by the natural product ternatrin and its synthetic variants (Carelli et al. 2015), although the antitumor efficacy of these compounds remain at present unknown. The activity of another elongation factor, eEF2, which is overexpressed in gastrointestinal cancers, can be targeted by nelfinavir, an activator of the eEF2 kinase that blocks eEF2 activity. Nelfinavir treatment results in tumor growth suppression both in vitro and in vivo (De Gassart et al. 2016). However, the activation of the eEF2K-eEF2 axis as an anticancer therapy needs careful consideration. Since recent studies have shown that cancer cells under stress conditions such as nutrient deprivation surprisingly rely on eEF2K activity for cancer progression (Leprivier et al. 2013), eEF2K activation (for example by nelfinavir treatment) under certain circumstances could unwittingly favor cancer development.

**Targeting the Translational Control of Cancer-Immune Cross Talk**

Cancer cells are surrounded by several cell types that modulate tumor development, including cytotoxic T cells, which restrict tumor growth when activated. Cancer cells disable the toxicity activity of these lymphocytes by upregulating immune checkpoint proteins such as PD-L1, which acts as a “don’t eat me” signal to immune cells, enabling cancer immune evasion. In this context, translation control is one of the fastest modes of gene expression to change protein levels in response to environmental stimuli, several key oncogenic inflammatory products [e.g., COX2, TNF-α, IFN-γ (Mazumder et al. 2010)] and immune checkpoints are regulated at the translational level (Franchini et al. 2019, Xu et al. 2019). Indeed, targeting distinct translation factors in cancer blocks the selective translation of PD-L1 (Cerezo et al. 2018, Parsa et al. 2007, Xu et al. 2019), leading to the reactivation of the antitumor immune response. These findings have prompted the
use of translation inhibitors, such as tomivosertib, an inhibitor of eIF4E phosphorylation, in combination with anti-PD-1/PD-L1 inhibitors in clinical trials (NCT03616834). New opportunities may also arise for directly targeting the translation factors in tumor-infiltrating cells that support tumor progression. One example is the suppression of eIF4E phosphorylation, which leads to a decrease in the translation of antiapoptotic mRNAs such as BCL2 or MCL1 in the protumor neutrophils, inducing neutrophil cell death and preventing lung metastasis formation (Robichaud et al. 2018). Another example is the m6A reader YTHDF1, which increases the translation of lysosomal cathepsins in dendritic cells during cancer development (Han et al. 2019). Genetic deletion of YTHDF1 reduces cathepsin production, leading to enhanced neoantigen presentation by dendritic cells to antitumor T cells and increased therapeutic efficacy of the PD-L1 checkpoint blockade. Therefore, inhibiting the translation of these key immune mRNAs may provide additional immunotherapy opportunities.

SUMMARY

The translome of the cancer genome should be of great interest to cancer biologists. While the field has placed a heavy emphasis on deciphering how changes in mRNA abundance contributes to tumor development, there is now a growing realization that the deregulations in translational control act as key drivers of cancer initiation and progression. These changes in gene expression, which extend beyond the measurement of transcript levels, are often not fully appreciated, and this oversight hinders a more complete understanding of vital molecular features that distinguish a normal cell from a cancer cell. This realization is further reflected in the growing appreciation that, similar to distinct regulatory elements in specific genetic loci (such as enhancer elements or promoters), the UTRs of mRNAs are rich in sequence and structural information that facilitates rapid and highly selective changes in their translation efficiency in the cancer setting. Studies of post-transcriptional control in cancer are unveiling new, exciting mechanisms for gene expression and protein abundance regulation. Advances in new technologies that capture changes in translational control at a genome-wide scale, such as CLIP, SHAPE, and ribosome profiling, have significantly contributed to decoding the regulatory language of cancer mRNA translation. Ultimately, as the translation machinery is downstream of almost all oncogenic signals, targeting specific translation factors offers conceptually new strategies for cancer therapy, including not only first-line therapeutics but also strategies used in combination with existing clinical compounds, especially when patients develop resistance to the initial treatments.

DISCLOSURE STATEMENT

D.R. is a shareholder of eFFECTOR Therapeutics Inc., and a member of its scientific advisory board.

ACKNOWLEDGMENTS

We apologize to those important works we were unable to cite. We thank Maria Barna for critically reviewing this manuscript and Elisa Fazzari, Joanna Kovalski, and Krizly Jane Jayme for helpful discussions with this review. Y.X. is supported by the Damon Runyon Cancer Research Foundation. D.R. is a Leukemia and Lymphoma Society Scholar and has received research support from the National Institutes of Health (grants R01CA140456 and R35CA242986) and the American Cancer Society (grant American Cancer Society Research Professor Award).
LITERATURE CITED

Anand N, Murthy S, Amann G, Wernick M, Porter LA, et al. 2002. Protein elongation factor EEF1A2 is a putative oncogene in ovarian cancer. *Nat. Genet.* 31:301–5

Barbieri I, Tzelepis K, Pandolfini L, Shi J, Millan-Zambrano G, et al. 2017. Promoter-bound METTL3 maintains myeloid leukemia by m6A-dependent translation control. *Nature* 552:126–31

Barna M, Pusic A, Zollo O, Costa M, Kondrashov N, et al. 2008. Suppression of Myc oncogenic activity by ribosomal protein haploinsufficiency. *Nature* 456:971–75

Bauer C, Diesinger I, Brass N, Steinhart H, Iro H, Meese EU. 2001. Translation initiation factor eIF-4G is immunogenic, overexpressed, and amplified in patients with squamous cell lung carcinoma. *Cancer* 92:822–29

Begley U, Dyavaiah M, Patil A, Rooney JP, DiRenzo D, et al. 2007. Trm9-catalyzed tRNA modifications link translation to the DNA damage response. *Mol. Cell* 28:860–70

Bellodi C, Kopmar N, Ruggero D. 2010. Deregulation of oncogene-induced senescence and p53 translational control in X-linked dyskeratosis congema. *EMBO J.* 29:1865–76

Benjamin D, Colombi M, Moroni C, Hall MN. 2011. Rapamycin passes the torch: a new generation of mTOR inhibitors. *Nat. Rev. Drug Discov.* 10:868–80

Boon K, Caron HN, van Asperen R, Valentijn L, Hermus MC, et al. 2001. N-myc enhances the expression of a large set of genes functioning in ribosome biogenesis and protein synthesis. *EMBO J.* 20:1383–93

Bordeleau ME, Robert F, Lindqvist L, Chen SM, et al. 2008. Therapeutic suppression of translation initiation modulates chemosensitivity in a mouse lymphoma model. *J. Clin. Investig.* 118:2651–60

Braunstein S, Karpisheva K, Goldberg J, Hochman T, et al. 2007. A hypoxia-controlled cap-dependent to cap-independent translation switch in breast cancer. *Mol. Cell* 30:501–12

Buchan JR, Parker R. 2009. Eukaryotic stress granules: the ins and outs of translation. *Mol. Cell* 36:932–41

Buttgereit F, Brand MD. 1995. A hierarchy of ATP-consuming processes in mammalian cells. *Biochem. J.* 312(Pr. 1):163–67

Carelli JD, Sethofer SG, Smith GA, Miller HR, Simard JL, et al. 2015. Ternatin and improved synthetic variants kill cancer cells by targeting the elongation factor-1A ternary complex. *eLife* 4:e10222

Cerezo M, Guemiri R, Druillenec S, Girault I, Malka-Mahieu H, et al. 2018. Translational control of tumor immune escape via the eIF4F-STX1-PD-L1 axis in melanoma. *Nat. Med.* 24:1877–86

Chen L, Aktas BH, Wang Y, He X, Sahoo R, et al. 2011. Chemical genetics identify eIF2α kinase heme-regulated inhibitor as an anticancer target. *Nat. Chem. Biol.* 7:610–16

Choe J, Lin S, Zhang W, Liu Q, Wang L, et al. 2018. mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis. *Nature* 561:556–60

Cole MD, Cowling VH. 2009. Specific regulation of mRNA cap methylation by the c-Myc and E2F1 transcription factors. *Onkogene* 28:1169–75

Cunningham JT, Moreno MV, Lodi A, Ronen SM, Ruggero D. 2014. Protein and nucleotide biosynthesis are coupled by a single rate-limiting enzyme, PRPS2, to drive cancer. *Cell* 157:1088–103

Dave B, Granados-Principal S, Zhu R, Benz S, Rahizadeh S, et al. 2014. Targeting RPL39 and MLF2 reduces tumor initiation and metastasis in breast cancer by inhibiting nitric oxide synthase signaling. *PNAS* 111:8838–43

De Benedetti A, Graff JR. 2004. eIF-4E expression and its role in malignancies and metastases. *Onkogene* 23:1899–99

De Gassart A, Demaria O, Panes R, Zaffalon L, Ryazanov AG, et al. 2016. Pharmacological eEF2K activation promotes cell death and inhibits cancer progression. *EMBO Rep.* 17:1471–84

De Keersmaecker K, Arak ZK, Li N, Vicente C, Patchett S, et al. 2013. Exome sequencing identifies mutation in *CNOT3* and ribosomal genes *RPL3* and *RPL10* in T-cell acute lymphoblastic leukemia. *Nat. Genet.* 45:186–90
Delaunay S, Rapino F, Tharun L, Zhou Z, Heukamp L, et al. 2016. Elp3 links tRNA modification to IRES-dependent translation of LEF1 to sustain metastasis in breast cancer. J. Exp. Med. 213:2503–23

Draptchinskaia N, Gustavsson P, Andersson B, Pettersson M, Willig TN, et al. 1999. The gene encoding ribosomal protein S19 is mutated in Diamond-Blackfan anaemia. Nat. Genet. 21:169–75

Drygin D, Siddiqui-Jain A, O’Brien S, Schwaebe M, Lin A, et al. 2009. Anticancer activity of CX-3543: a direct inhibitor of rRNA biogenesis. Int. J. Cancer 139:1648–57

Eberle J, Krasagakis K, Orfanos CE. 1997. Translation initiation factor eIF-4A1 mRNA is consistently overexpressed in human melanoma cells in vitro. Int. J. Cancer 71:396–401

Ebert BL, Pretz J, Bosco J, Chang CY, Tamayo P, et al. 2008. Identification of RPS14 as a 5q− syndrome gene by RNA interference screen. Nature 451:335–39

Feng YX, Sokol ES, Del Vecchio CA, Sanduja S, Claessen JH, et al. 2014. Epithelial-to-mesenchymal transition activates PERK-eIF2α and sensitizes cells to endoplasmic reticulum stress. Cancer Discov. 4:702–15

Fonseca BD, Zakaria C, Jia JJ, Gruber TE, Svitkin Y, et al. 2015. La-related protein 1 (LARP1) represses terminal oligopyrimidine (TOP) mRNA translation downstream of mTORC1. J. Biol. Chem. 290:15996–6020

Franchini DM, Lanvin O, Tosolini M, Patras de Campaigno E, Cammas A, et al. 2019. Microtubule-driven stress granule dynamics regulate inhibitory immune checkpoint expression in T cells. Cell Rep. 26:94–107.e7

Fruman DA, Rommel C. 2014. PI3K and cancer: lessons, challenges and opportunities. Nat. Rev. Drug Discov. 13:140–56

Ghosh B, Benyumov AO, Ghosh P, Jia Y, Avdulov S, et al. 2009. Nontoxic chemical interdiction of the epithelial-to-mesenchymal transition by targeting cap-dependent translation. ACS Chem. Biol. 4:367–77

Gingga S, Miluzio A, Barbieri AM, Beugnet A, Kiyokawa H, et al. 2008. Eukaryotic initiation factor 6 is rate-limiting in translation, growth and transformation. Nature 455:684–88

Gatza ML, Silva GO, Parker JS, Fan C, Perou CM. 2014. An integrated genomics approach identifies drivers of proliferation in luminal-subtype human breast cancer. Nat. Genet. 46:1051–59

Genuth NR, Barna M. 2018. The discovery of ribosome heterogeneity and its implications for gene regulation and organismal life. Mol. Cell 71:364–74

Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, et al. 2008. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol. Cell 30:214–26

Han DL, Liu J, Chen CY, Dong LH, Liu Y, et al. 2019. Anti-tumour immunity controlled through mRNA m6A methylation and YTHDF1 in dendritic cells. Nature 566:270–74

Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, et al. 2008. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol. Cell 30:214–26

Han DL, Liu J, Chen CY, Dong LH, Liu Y, et al. 2019. Anti-tumour immunity controlled through mRNA m6A methylation and YTHDF1 in dendritic cells. Nature 566:270–74

Genuth NR, Barna M. 2018. The discovery of ribosome heterogeneity and its implications for gene regulation and organismal life. Mol. Cell 71:364–74

Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, et al. 2008. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol. Cell 30:214–26

Han DL, Liu J, Chen CY, Dong LH, Liu Y, et al. 2019. Anti-tumour immunity controlled through mRNA m6A methylation and YTHDF1 in dendritic cells. Nature 566:270–74
He LR, Zhao HY, Li BK, Liu YH, Liu MZ, et al. 2011. Overexpression of eIF5A-2 is an adverse prognostic marker of survival in stage I non-small cell lung cancer patients. *Int. J. Cancer* 129:143–50

Heiss NS, Knight SW, Vulliamy TJ, Klauck SM, Wiemann S, et al. 1998. X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions. *Nat. Genet.* 19:32–38

Holcik M, Yeh C, Korneluk RG, Chow T. 2000. Translational upregulation of X-linked inhibitor of apoptosis (XIAP) increases resistance to radiation induced cell death. *Oncogene* 19:4174–77

Hong DS, Kurzrock R, Oh Y, Wheler J, Naing A, et al. 2011. A phase 1 dose escalation, pharmacokinetic, and pharmacodynamic evaluation of eIF-4E antisense oligonucleotide LY2275796 in patients with advanced cancer. *Clin. Cancer Res.* 17:6582–91

Hopkins BD, Fine B, Steinbach N, Dendy M, Rapp Z, et al. 2013. A secreted PTEN phosphatase that enters cells to alter signaling and survival. *Science* 341:399–402

Hsieh AC, Liu Y, Edlind MP, Ingolia NT, Janes MR, et al. 2012. The translational landscape of mTOR signalling steers cancer initiation and metastasis. *EMBO J.* 11:4153–58

Iadevaia V, Caldarola S, Tino E, Amaldi F, Loreni F. 2008. All translation elongation factors and the e,f,and h subunits of translation initiation factor 3 are encoded by 5’-terminal oligopyrimidine (TOP) mRNAs. *RNA* 14:1730–36

Iritani BM, Eisenman RN. 1999. c-Myc enhances protein synthesis and cell size during B lymphocyte development. *PNAS* 96:13180–85

Iwaski S, Floor SN, Ingolia NT. 2016. Rocaglates convert DEAD-box protein eIF4A into a sequence-selective translational repressor. *Nature* 534:558–61

Jasulionis MG, Luchessi AD, Moreira AG, Souza PP, Suenaga AP, et al. 2007. Inhibition of eukaryotic translation initiation factor 5A (eIF5A) hypusination impairs melanoma growth. *Cell Biochem. Funct.* 25:109–14

Jeffries HBJ, Reinhard C, Kozma SC, Thomas G. 1994. Rapamycin selectively represses translation of the “polypyrimidine tract” mRNA family. *PNAS* 91:4441–45

Khalaileh A, Dreazen A, Khatib A, Apel R, Swisa A, et al. 2013. Phosphorylation of ribosomal protein S6 attenuates DNA damage and tumor suppression during development of pancreatic cancer. *Cancer Res.* 73:1811–20

Koromilas AE, Lazaris-Karatzas A, Sonenberg N. 1992. mRNAs containing extensive secondary structure in their 5’ non-coding region translate efficiently in cells overexpressing initiation factor eIF-4E. *EMBO J.* 11:4153–58

Kozak M. 1986. Influences of mRNA secondary structure on initiation by eukaryotic ribosomes. *PNAS* 83:2850–54

Krishnamoorthy GP, Davidson NR, Leach SD, Zhao Z, Lowe SW, et al. 2018. EIF1AX and RAS mutations cooperate to drive thyroid tumorigenesis through ATF4 and c-MYC. *Cancer Discov.* 9:264–81

Lampson BL, Persing NL, Prinz JA, Lascina JR, Marzluff WF, et al. 2013. Rare codons regulate KRas oncogenesis. *Curr. Biol.* 23:70–75

Lazaris-Karatzas A, Montine KS, Sonenberg N. 1990. Malignant transformation by a eukaryotic initiation factor subunit that binds to mRNA 5’ cap. *Nature* 345:544–47

Lee ASY, Kranzusch PJ, Cate JH. 2015. eIF3 targets cell-proliferation messenger RNAs for translational activation or repression. *Nature* 522:111–14

Lee ASY, Kranzusch PJ, Doudna JA, Cate JHD. 2016. eIF3d is an mRNA cap-binding protein that is required for specialized translation initiation. *Nature* 536:96–99

Leprivi G, Renke M, Rotblat B, Dubuc A, Mateo AR, et al. 2013. The eEF2 kinase confers resistance to nutrient deprivation by blocking translation elongation. *Cell* 153:1064–79

Levy S, Avni D, Hariharan N, Perry RP, Meyuhas O. 1991. Oligopyrimidine tract at the 5’ end of mammalian ribosomal-protein mRNAs is required for their translational control. *PNAS* 88:3319–23

Li M, Kao E, Malone D, Gao X, Wang JYJ, David M. 2018. DNA damage-induced cell death relies on SLFN11-dependent cleavage of distinct type II tRNAs. *Nat. Struct. Mol. Biol.* 25:1047–58
Lin SB, Choe J, Du P, Triboulet R, Gregory RI. 2016. The m^6A methyltransferase METTL3 promotes translation in human cancer cells. *Mol. Cell* 62:335–45

Lipton JM, Federman N, Khazzas Y, Schwartz CL, Hilliard LM, et al. 2001. Osteogenic sarcoma associated with Diamond–Blackfan anemia: a report from the Diamond–Blackfan Anemia Registry. *J. Pediatr.* Hematol. Oncol. 23:39–44

Liu L, Dilworth D, Gao L, Monzon J, Summers A, et al. 1999. Mutation of the CDKN2A 5′ UTR creates an aberrant initiation codon and predisposes to melanoma. *Nat. Genet.* 21:128–32

Liu S, Hausmann S, Carlson SM, Fuentes ME, Francis JW, et al. 2019. METTL13 methylation of eEF1A increases translational output to promote tumorigenesis. *Cell* 176:491–504.e21

Liwak U, Thakor N, Jordan LE, Roy R, Lewis SM, et al. 2012. Tumor suppressor PDCD4 represses internal ribosome entry site-mediated translation of antiapoptotic proteins and is regulated by S6 kinase 2. *Mol. Cell. Biol.* 32:1818–29

Ljungstrom V, Cortese D, Young E, Pandzic T, Mansouri L, et al. 2016. Whole-exome sequencing in relapsing chronic lymphocytic leukemia: clinical impact of recurrent RPS15 mutations. *Blood* 127:1007–16

Lovett PS, Rogers EJ. 1996. Ribosome regulation by the nascent peptide. *Microbiol. Rev.* 60:366–85

Ma L, Chen Z, Erdjument-Bromage H, Tempst P, Pandolfi PP. 2005. Phosphorylation and functional inactivation of TSC2 by Erk implications for tuberous sclerosis and cancer pathogenesis. *Cell* 121:179–93

Manier S, Huynh D, Shen YJ, Zhou J, Yusufzai T, et al. 2017. Inhibiting the oncogenic translation program is an effective therapeutic strategy in multiple myeloma. *Sci. Transl. Med.* 9:eaal2668

Marchetti A, Buttitta F, Pellegrini S, Bertacca G, Callahan R. 2001. Reduced expression of INT-6/eIF3-p48 in human tumors. *Int. J. Oncol.* 18:175–79

Martineau Y, Azar R, Muller D, Lasfargues C, El Khawand S, et al. 2014. Pancreatic tumours escape from translational control through 4E-BP1 loss. *Oncogene* 33:1367–74

Mazummer B, Li X, Barik S. 2010. Translation control: a multifaceted regulator of inflammatory response. *J. Immunol.* 184:3311–19

McGillivray P, Ault R, Prawashe M, Kitchen R, Balasubramanian S, Gerstein M. 2018. A comprehensive catalog of predicted functional upstream open reading frames in humans. *Nucleic Acids Res.* 46:3326–38

McMahon M, Contreras A, Holm M, Uechi T, Forester CM, et al. 2019. A single H/ACA small nucleolar RNA mediates tumor suppression downstream of oncogenic RAS. *eLife* 8:e48847

Mehta A, Trotta CR, Peltz SW. 2006. Derepression of the Her-2 uORF is mediated by a novel post-transcriptional control mechanism in cancer cells. *Genes Dev.* 20:939–53

Mikuzio A, Beugnet A, Grosso S, Brina D, Mancino M, et al. 2011. Impairment of cytoplasmic eIF6 activity restricts lymphomagenesis and tumor progression without affecting normal growth. *Cancer Cell* 19:765–75

Mizrahi-Schwartz S, Kravchenko-Balasha N, Ben-Bassat H, Klein S, Levitzki A. 2007. Optimization of energy-consuming pathways towards rapid growth in HPV-transformed cells. *PLOS ONE* 2:e628

Montanaro L, Brigotti M, Clohessy J, Barbieri S, Cecarelli C, et al. 2006. Dyserkerin expression influences the level of ribosomal RNA pseudo-uridylation and telomerase RNA component in human breast cancer. *J. Pathol.* 210:10–18

Nakamura J, Aoyagi S, Nanchi I, Nakatsuka S, Hirata E, et al. 2009. Overexpression of eukaryotic elongation factor eEF2 in gastrointestinal cancers and its involvement in G2/M progression in the cell cycle. *Int. J. Oncol.* 34:1181–89

Nakanishi S, Cleveland JL. 2016. Targeting the polyamine-hypusine circuit for the prevention and treatment of cancer. *Amino Acids* 48:2533–62

Nguyen HG, Conn CS, Kye Y, Xue L, Forester CM, et al. 2018. Development of a stress response therapy targeting aggressive prostate cancer. *Sci. Transl. Med.* 10:eaaar2036

Nishizawa Y, Konno M, Asai A, Koseki J, Kawamoto K, et al. 2018. Oncogene c-Myc promotes epitranscriptome m^6A reader YTHDF1 expression in colorectal cancer. *Oncotarget* 9:7476–86
Northcott PA, Buchhalter I, Morrissy AS, Hovestadt V, Weischenfeldt J, et al. 2017. The whole-genome landscape of medulloblastoma subtypes. *Nature* 547:311–17

Nupponen NN, Porkka K, Kakko E, Tanner M, Persson K, et al. 1999. Amplification and overexpression of p40 subunit of eukaryotic translation initiation factor 3 in breast and prostate cancer. *Am. J. Pathol.* 154:1777–83

Occhi G, Regazzo D, Trivellin G, Boaretto F, Ciato D, et al. 2013. A novel mutation in the upstream open reading frame of the CDKN1B gene causes a MEN4 phenotype. *PLoS Genet.* 9:e1003350

Oh S, Flynn RA, Floor SN, Purzner J, Martin L, et al. 2016. Medulloblastoma-associated DDX3 variant selectively alters the translational response to stress. *Oncotarget* 7:28169–82

Ortiz-Zapater E, Pineda D, Martinez-Bosch N, Fernandez-Miranda G, Iglesias M, et al. 2011. Key contribution of CPEB4-mediated translational control to cancer progression. *Nat. Med.* 18:83–90

Palangat M, Anastasakis DG, Fei DL, Lindblad KE, Bradley R, et al. 2019. The splicing factor U2AF1 contributes to cancer progression through a noncanonical role in translation regulation. *Genes Dev.* 33:482–97

Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, et al. 2007. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nat. Med.* 13:84–88

Pavon-Eternod M, Gomes S, Geslain R, Dai Q, Rosner MR, Pan T. 2009. tRNA over-expression in breast cancer and functional consequences. *Nucleic Acids Res.* 37:7268–80

Pelletier J, Sonenberg N. 1985. Insertion mutagenesis to increase secondary structure within the 5′ noncoding region of a eukaryotic mRNA reduces translational efficiency. *Cell* 40:515–26

Peltonen K, Colis L, Liu H, Trivedi R, Moubarack MS, et al. 2014. A targeting modality for destruction of RNA polymerase I that possesses anticancer activity. *Cancer Cell* 25:77–90

Pereira B, Billaud M, Almeida R. 2017. RNA-binding proteins in cancer: old players and new actors. *Trends Cancer* 3:506–28

Rao S, Lee SY, Gutierrez A, Perrigoue J, Thapa R, et al. 2012. Inactivation of ribosomal protein L22 promotes transformation by induction of the stenness factor, Lin28B. *Blood* 120:3764–73

Ray BK, Lawson TG, Kramer JC, Cladaras MH, Grifo JA, et al. 1985. ATP-dependent unwinding of messenger RNA structure by eukaryotic initiation factors. *J. Biol. Chem.* 260:7651–58

Robichaud N, del Rincon SV, Huor B, Alain T, Petrucelli LA, et al. 2015. Phosphorylation of eIF4E promotes EMT and metastasis via translational control of SNAIL and MMP-3. *Oncogene* 34:2032–42

Robichaud N, Hsu BE, Istomine R, Alvarez F, Blagih J, et al. 2018. Translational control in the tumor microenvironment promotes lung metastasis: phosphorylation of eIF4E in neutrophils. *PNAS* 115:E2202–9

Robinson G, Parker M, Kranenburg TA, Lu C, Chen X, et al. 2012. Novel mutations target distinct subgroups of medulloblastoma. *Nature* 488:43–48

Roux PP, Ballif BA, Anjum R, Gygi SP, Blenis J. 2004. Tumor-promoting phorbol esters and activated Ras inactivate the tuberous sclerosis tumor suppressor complex via p90 ribosomal S6 kinase. *PNAS* 101:13489–94

Ruggero D, Montanaro L, Ma L, Xu W, Londei P, et al. 2004. The translation factor eIF-4E promotes tumor formation and cooperates with c-Myc in lymphomagenesis. *Nat. Med.* 10:484–86

Saramaki O, Willi N, Bratt O, Gasser TC, Koivisto P, et al. 2001. Amplification of EIF3S3 gene is associated with advanced stage in prostate cancer. *Am. J. Pathol.* 159:2089–94

Schmidt EV. 2004. The role of c-myc in regulation of translation initiation. *Oncogene* 23:3217–21

Sendelöv A, Dunn JG, Rodriguez EH, Naik S, Gomez NC, et al. 2017. Translation from unconventional 5′ start sites drives tumour initiation. *Nature* 541:494–99

Shi J, Kahle A, Hershey JW, Honchak BM, Warneke JA, et al. 2006. Decreased expression of eukaryotic initiation factor 3f deregulates translation and apoptosis in tumor cells. *Oncogene* 25:4923–36

Shi Z, Fujii K, Kovary KM, Genuith NR, Rost HL, et al. 2017. Heterogeneous ribosomes preferentially translate distinct subpools of mRNAs genome-wide. *Mol. Cell* 67:71–83.e7

Shimamura A, Alter BP. 2010. Pathophysiology and management of inherited bone marrow failure syndromes. *Blood Rev.* 24:101–22

Silvera D, Arju R, Darvishian F, Levine PH, Zolfaghari L, et al. 2009. Essential role for eIF4GI overexpression in the pathogenesis of inflammatory breast cancer. *Nat. Cell Biol.* 11:903–8
Simsek D, Tiu GC, Flynn RA, Byeon GW, Leppek K, et al. 2017. The mammalian ribo-interactome reveals ribosome functional diversity and heterogeneity. *Cell* 169:1051–65.e18

Starck SR, Tsai JC, Chen K, Shodiyaa M, Wang L, et al. 2016. Translation from the 5′ untranslated region shapes the integrated stress response. *Science* 351:aaed3867

Sulima SO, Hofman IJF, De Keersmaecker K, Dinman JD. 2017. How ribosomes translate cancer. *Cancer Discov.* 7:1069–87

Tang DJ, Dong SS, Ma NF, Xie D, Chen L, et al. 2010. Overexpression of eukaryotic initiation factor 5A2 enhances cell motility and promotes tumor metastasis in hepatocellular carcinoma. *Hepatology* 51:1255–63

Tang H, Hornstein E, Stolovich M, Levy G, Livingstone M, et al. 2001. Amino acid-induced translation of TOP mRNAs is fully dependent on phosphatidylinositol 3-kinase-mediated signaling, is partially inhibited by rapamycin, and is independent of S6K1 and rpS6 phosphorylation. *Mol. Cell. Biol.* 21:8671–83

Tcherkezian J, Cargnello M, Romeo Y, Huttlin EL, Lavoie G, et al. 2014. Proteomic analysis of cap-dependent translation identifies LARP1 as a key regulator of 5′TOP mRNA translation. *Genes Dev.* 28:357–71

Thoreen CC, Chantranupong L, Keys HR, Wang T, Gray NS, Sabatini DM. 2012. A unifying model for mTORC1-mediated regulation of mRNA translation. *Nature* 485:109–13

Truitt ML, Conn CS, Shi Z, Pang X, Tokuyasu T, et al. 2015. Differential requirements for eIF4E dose in normal development and cancer. *Cell* 162:59–71

Ueda T, Sasaki M, Elia AJ, Chio II, Hamada K, et al. 2010. Combined deficiency for MAP kinase-interacting kinase 1 and 2 (Mnk1 and Mnk2) delays tumor development. *PNAS* 107:13984–90

Vu LP, Pickering BF, Cheng Y, Zaccara S, Nguyen D, et al. 2017. The N6-methyladenosine (m6A)-forming enzyme METTL3 controls myeloid differentiation of normal hematopoietic and leukemia cells. *Nat. Med.* 23:1369–76

Wang X, Zhao BS, Roundtree IA, Lu ZK, Han DL, et al. 2015. N6-methyladenosine modulates messenger RNA translation efficiency. *Cell* 161:1388–99

Wang ZY, Feng XD, Molinolo AA, Martin D, Vitale-Cross L, et al. 2019. 4E-BP1 is a tumor suppressor protein reactivated by mTOR inhibition in head and neck cancer. *Cancer Res.* 79:1438–50

Waskiewicz AJ, Johnson JC, Penn B, Mahalingam M, Kimball SR, Cooper JA. 1999. Phosphorylation of the cap-binding protein eukaryotic translation initiation factor 4E by protein kinase Mnk1 in vivo. *Mol. Cell. Biol.* 19:1871–80

Wei J, Kishon RJ, Angel M, Conn CS, Dalla-Venezia N, et al. 2019. Ribosomal proteins regulate MHC class I peptide generation for immunosurveillance. *Mol. Cell* 73:1162–73.e5

Wek RC. 2018. Role of eIF2α kinases in translational control and adaptation to cellular stress. *Cold Spring Harb. Perspect. Biol.* 10:a032870

Wolfe AL, Singh K, Zhong Y, Drew P, Rajasekhar VK, et al. 2014. RNA G-quadruplexes cause eIF4A-dependent oncogene translation in cancer. *Nature* 513:65–70

Xu Y, Poggio M, Jin HY, Shi Z, Forester CM, et al. 2019. Translation control of the immune checkpoint in cancer and its therapeutic targeting. *Nat. Med.* 25:301–11

Yaffe MB. 2019. Why geneticists stole cancer research even though cancer is primarily a signaling disease. *Sci. Signal.* 12:eaaaw3483

Yamasaki S, Anderson P. 2008. Reprogramming mRNA translation during stress. *Curr. Opin. Cell Biol.* 20:222–26

Zhao X, Zhang C, Zhou H, Xiao B, Cheng Y, et al. 2016. Synergistic antitumor activity of the combination of salubrinal and rapamycin against human cholangiocarcinoma cells. *Oncotarget* 7:85492–501

Zoncu R, Efeyan A, Sabatini DM. 2011. mTOR: from growth signal integration to cancer, diabetes and ageing. *Nat. Rev. Mol. Cell Biol.* 12:21–35
Contents

AMP-Activated Protein Kinase: Friend or Foe in Cancer?
Diana Vara-Ciruelos, Madhumita Dandapani, and D. Grahame Hardie .................. 1

Metabolism in the Tumor Microenvironment
Allison N. Lau and Matthew G. Vander Heiden .................................... 17

Mitophagy and Mitochondrial Dysfunction in Cancer
Kay F. Madeo .............................................................................. 41

Targeting MYC Proteins for Tumor Therapy
Elmar Wolf and Martin Eilers .......................................................... 61

Metabolic Drivers in Hereditary Cancer Syndromes
Marco Sciacovelli, Christina Schmidt, Eamonn R. Maher, and Christian Frezza ....... 77

Investigating Tumor Heterogeneity in Mouse Models
Tuomas Tammela and Julien Sage ................................................... 99

Engineering T Cells to Treat Cancer: The Convergence of Immuno-Oncology and Synthetic Biology
Joseph H. Choe, Jasper Z. Williams, and Wendell A. Lim .............................. 121

Lactate and Acidity in the Cancer Microenvironment
Scott K. Parks, Wolfgang Mueller-Klieser, and Jacques Pouysségur .................... 141

Reactivation of Endogenous Retroelements in Cancer Development and Therapy
Charles A. Isbik and Daniel D. De Carvalho .......................................... 159

WNT and β-Catenin in Cancer: Genes and Therapy
Rene Jackstadt, Michael Charles Hodder, and Owen James Sansom .................. 177

The Epithelial-to-Mesenchymal Transition in Development and Cancer
Alexandre Francou and Kathryn V. Anderson ......................................... 197

RNA Modifications in Cancer: Functions, Mechanisms, and Therapeutic Implications
Huilin Huang, Hengyou Weng, Xiaolan Deng, and Jianjun Chen .................... 221
Is There a Clinical Future for IDO1 Inhibitors After the Failure of Epacadostat in Melanoma?
Benoit J. Van den Eynde, Nicolas van Baren, and Jean-François Baurain ............... 241

Deregulation of Chromosome Segregation and Cancer
Natalie L. Curtis, Gian Filippo Ruda, Paul Brennan, and Victor M. Bolanos-Garcia ........................................ 257

Acquired Resistance in Lung Cancer
Asmin Tulpule and Trever G. Bivona .......................................................... 279

Toward Targeting Antiapoptotic MCL-1 for Cancer Therapy
Gemma L. Kelly and Andreas Strasser .......................................................... 299

Nongenetic Mechanisms of Drug Resistance in Melanoma
Vito W. Rebecca and Meenhard Herlyn ..................................................... 315

Biomarkers for Response to Immune Checkpoint Blockade
Shridar Ganesan and Janice Mehnert .......................................................... 331

Immune-Based Approaches for the Treatment of Pediatric Malignancies
Kristopher R. Bosse, Robbie G. Majzner, Crystal L. Mackall, and John M. Maris .......... 353

The Neural Regulation of Cancer
Shawn Gillespie and Michelle Monje ......................................................... 371

Cancer-Associated Cachexia: A Systemic Consequence of Cancer Progression
Anup K. Biswas and Swarnali Acharyya ...................................................... 391

The Pleiotropic Role of the KEAP1/NRF2 Pathway in Cancer
Warren L. Wu and Thales Papagiannakopoulos ......................................... 413

The Role of Translation Control in Tumorigenesis and Its Therapeutic Implications
Yichen Xu and Davide Ruggero ................................................................. 437

Regulatory T Cells in Cancer
George Plitas and Alexander Y. Rudensky .................................................. 459

Errata

An online log of corrections to Annual Review of Cancer Biology articles may be found at http://www.annualreviews.org/errata/cancerbio