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Nutrient Control of mRNA Translation

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Abstract

The emergence of genome-wide analyses to interrogate cellular DNA, RNA, and protein content has revolutionized the study of control networks that mediate cellular homeostasis. mRNA translation represents the last step of genetic flow and primarily defines the proteome. Translational regulation is thus critical for gene expression, in particular under nutrient excess or deficiency. Until recently, it was unclear how the global effects of translational control are orchestrated by nutrient signaling pathways. An emerging concept of translational reprogramming addresses how to maintain the expression of specific proteins during nutrient stress by translation of selective mRNAs. In this review, we describe recent advances in our understanding of translational control principles; nutrient-sensing mechanisms; and their dysregulation in human diseases such as diabetes, cancer, and aging. The mechanistic understanding of translational regulation in response to different nutrient conditions may help identify potential dietary and therapeutic targets to improve human health.

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INTRODUCTION

Following transcription, genomic information in the nucleotide sequences begins a long journey toward translation into the amino acids of a protein. Protein synthesis consumes the lion's share of energy and cellular resources, so translation is tightly coupled with nutrient status and environmental cues. A fundamental question is how cells respond to the availability of nutrients and adapt to nutrient deficiencies by changing the flow of genomic information. Recent studies using comparative genomic and proteomic profiling of cells have documented a lack of correlation between the mRNA and protein levels of numerous genes (134). It is becoming increasingly evident that the regulation of translation provides the cell with the plasticity to respond to rapid changes in the environment (149). Recent advances in next-generation sequencing enable the determination of gene regulation at an unprecedented scale and resolution (139). The development of ribosome profiling technology has reignited research interest in the translation field (66). This innovative technique enables monitoring of ribosome dynamics with subcodon resolution at the genome-wide scale (13).

Enabling swift regulation of gene expression, translational control can be quantitative (all-or-none versus graded), qualitative (enabling a single mRNA to produce several different proteins), or selective (activating subsets of mRNAs for translation) (91). By permitting rapid and selective changes in the proteome landscape, translational regulation plays a crucial role in cell growth, differentiation, stress response, and organismal development (48, 148). We argue that translational reprogramming lies at the heart of the cellular adaptation in response to nutrient stress (91). The mechanistic details of translational reprogramming, however, are only beginning to be unfurled. In

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this review, we discuss mechanisms underlying global translational regulation as well as selective translation in response to nutrient stress. We start with an overview of translation control and then discuss recent progress in nutrient-sensing pathways. In addition to describing the well-established amino acid response and mechanistic target of rapamycin (mTOR) signaling pathway, we cover the emerging concepts of *O*-GlcNAcylation and RNA modification. Given the breadth of these topics, we focus on the functional interpretation of nutrient response from the perspective of translational control and discuss its implications for human disease.

m^7G: 7-methylguanylate

IRES: internal ribosome entry site

TC: ternary complex

TISs: translation initiation sites

uORF: upstream open reading frame

TRANSLATIONAL REGULATION

Current Understanding of mRNA Translation

Tremendous progress has been made over the past several decades in understanding the molecular mechanisms of mRNA translation, fueled by advances in structural biology and high-throughput sequencing. To better illustrate nutrient control of mRNA translation, we briefly describe our current understanding of protein synthesis in eukaryotic cells. In general, mRNA translation can be divided into four distinct stages: initiation, elongation, termination, and recycling (59, 60). Although all translational stages are subject to regulation, under most circumstances the rate-limiting step is the initiation stage (59). Under normal growth conditions, eukaryotic cells employ a cap-dependent mechanism to initiation translation for most mRNAs. It typically starts with the binding of eukaryotic initiation factor 4F (eIF4F) to the 7-methylguanylate (m^7G) cap found on the 5′ end of the majority of mRNAs. The heterotrimeric complex eIF4F consists of eIF4E (cap binding), eIF4G (scaffold), and eIF4A (RNA helicase) (59, 106). Recent studies revealed alternative eIF4F complexes comprising variants of these components depending on the environmental and physiological conditions of the cell (61). Indeed, eIF4F inactivation only partially inhibits the overall translational capacity (24). Alternative mechanisms include internal ribosome entry site (IRES)-mediated cap-independent translation (57, 106). Additionally, translation that is neither cap dependent nor IRES mediated exists in cells (21, 24, 86, 94), expanding the scope of translational regulation.

Cap recognition is followed by assembly of the 43S preinitiation complex (43S PIC), which is composed of the 40S ribosome; initiation factors eIF1, eIF1A, eIF3, and the ternary complex (TC) of methionine-charged tRNA; GTP; and eIF2. PIC is recruited to mRNA via the scaffold eIF4G within the cap-associated eIF4F complex, forming the 48S complex (71). The DEAD-box RNA helicase eIF4A is believed to prepare a single-stranded region near the 5′ end of mRNA, thereby facilitating PIC attachment. However, recent studies suggest a more generic role for eIF4A in promoting recruitment of mRNAs regardless of their structural features (147, 169). The assembled PIC then scans the 5′ untranslated region (5′ UTR) until it encounters an initiation codon. Although the proposed scanning process in start codon selection has long been appreciated, the topology and operational mechanism of the scanning PIC are poorly understood (143). Noncanonical scanning mechanisms such as shunting have been proposed for the PIC to bypass secondary structures of the 5′ UTR (170). However, molecular details of the scanning process, let alone its regulatory pathways, remain obscure.

Proper selection of the translation initiation site (TIS) on mRNAs is crucial for the production of desired protein products. It is commonly assumed that the first AUG codon encountered by the scanning ribosome serves as the start site for translation (80). However, one or more potential initiation sites could exist upstream of the main start codon, forming upstream open reading frames (uORFs) (75). Likewise, AUG codons downstream of the main start codon may also serve as initiators (87). Many factors influence the start codon selection. For instance, the initiator AUG

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RPFs: ribosome-protected mRNA fragments

triplet is usually in an optimal context with a purine at position −3 and a guanine at position +4 (80). The presence of mRNA secondary structure at or near the start codon also influences the recognition efficiency. In addition to these *cis* sequence elements, the stringency of start codon selection is subject to regulation by *trans*-acting factors such as eIF1 and eIF1A (102). Inefficient recognition of an initiator codon results in a portion of PIC continuing to scan and initiating at a downstream site, a process known as leaky scanning. Many recent studies have uncovered a surprising variety of potential translation start sites in addition to the annotated start codons (70, 76, 167). Nearly half of the transcripts in the eukaryotic transcriptome possess multiple initiation sites (15). Intriguingly, many non-AUG codons, especially CUG, act as alternative start codons for initiating translation (76). Despite the prevailing alternative translation initiation, the dynamic selection of noncanonical start codons under differential growth conditions remains incompletely understood.

A signature of successful start codon recognition is the joining of the 60S subunit and dissociation of initiation factors. Once the 80S ribosome is engaged at the start codon, elongation ensues. Translation elongation is mediated by elongation factors eEF1 and eEF2, which deliver amino-acid-charged tRNA to the ribosomal A site and catalyze ribosomal translocation, respectively (29). During elongation, the ribosome does not move at a constant speed but rather in a stop-and-go traffic manner. Both *cis* sequence elements and *trans*-regulatory factors contribute to the variations of elongation speed. It is widely believed that rare codons with low cognate tRNAs tend to slow down ribosome elongation (37). Intriguingly, codon optimality seems to contribute to differential mRNA translation in response to amino acid starvation (128). When the ribosome decoding center reaches a stop codon, termination occurs via the concerted action of release factors eRF1 and eRF3 (29). Notably, peptide release, tRNA dissociation, and ribosome separation do not take place simultaneously (30). In some cases, the 40S subunit remains associated with mRNA and could start a second round of translation from the downstream start codon, a process called reinitiation (168). Strikingly, posttermination ribosomes could migrate bidirectionally along mRNA, resulting in promiscuous translation initiation (146).

Methods of Studying mRNA Translation

The emergence of genome-wide analyses to interrogate cellular DNA, RNA, and protein content has revolutionized the study of control networks that mediate cellular homeostasis. The advent of ribosome profiling (Ribo-seq) facilitates our understanding of mRNA translation from the global perspective (66). By capturing the entire set of ribosome-protected mRNA fragments (RPFs), Ribo-seq provides a snapshot of ribosome positions and density across the transcriptome at subcodon resolution. This powerful approach has been leveraged to measure ribosome dynamics and reveal the hidden coding potential of transcriptome from a broad range of species. Since its original development in the budding yeast *Saccharomyces cerevisiae*, Ribo-seq has been continuously modified for different purposes (**Figure 1**). For instance, selective Ribo-seq was developed to study cotranslational folding by using epitope-specific antibodies or pulling down binding partners of the newly synthesized polypeptide (52, 118, 142). To investigate local translation inside cells, proximity-specific Ribo-seq was used to isolate ribosomes associated to the endoplasmic reticulum (ER) (72) through coexpression of a spatially restricted biotin ligase fusion protein together with ribosomes containing an AviTag. In vivo biotinylation enables the recovery of ribosomes from defined locations such as the ER. A similar approach was also successfully applied to enrich ribosomes associated with the mitochondrial outer surface (162).

Regular Ribo-seq captures all the ribosomes engaged on mRNAs. It has long been a challenge to separate translating ribosomes at different stages. Collection of initiating ribosomes, for

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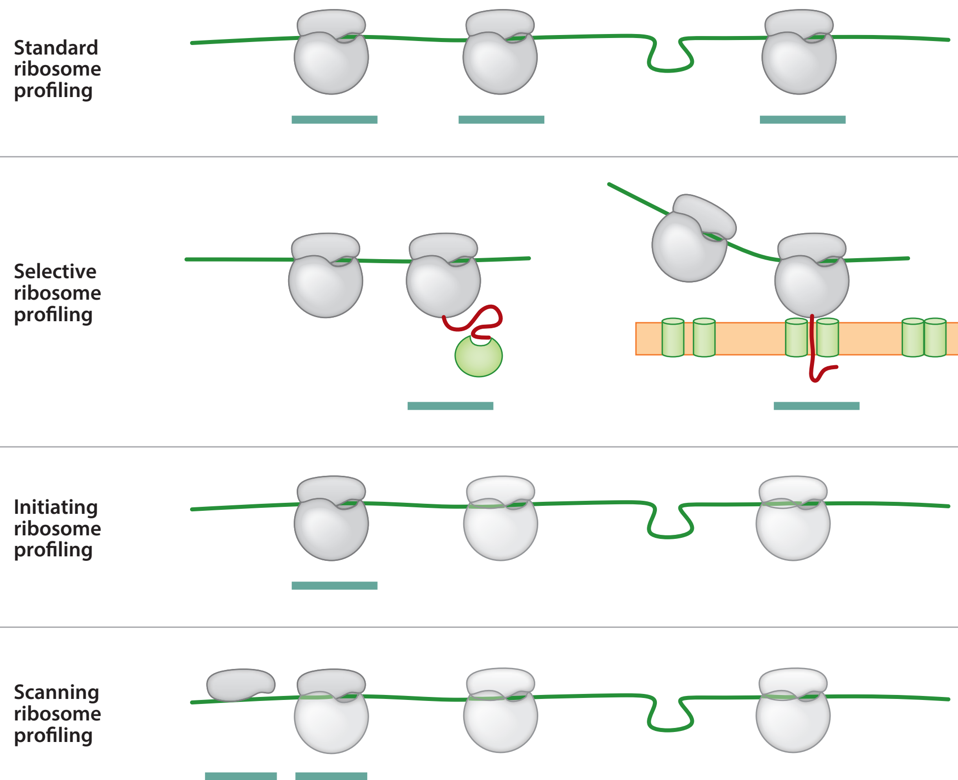

Figure 1

Diverse ribosome profiling strategies. Modified ribosome profiling protocols have been developed for different purposes. Selective ribosome profiling is designed to capture ribosomes synthesizing nascent chains interacting with chaperones or targeting different locations such as the endoplasmic reticulum. Initiating ribosome profiling captures ribosomes engaged at start codons. Scanning ribosome profiling captures 40S ribosomes before the assembly of 80S at start codons. Ribosome-protected mRNA fragments are shown below the captured ribosomes.

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instance, would permit experimental identification of TISs. This is particularly important because multiple TISs exist on a single mRNA. Several strategies have been employed for efficient capture of initiating ribosomes. Translation inhibitors such as harringtonine act on the first round of peptide bond formation. A short incubation period enables the runoff of elongating ribosomes, thereby specifically halting ribosomes at all possible TIS codons (67). Lee et al. (87) utilized a different translation inhibitor, lactimidomycin, to specifically capture the initiating ribosomes. Through coupling with puromycin, global translation initiation sequencing can be further modified into quantitative profiling of initiating ribosomes, permitting direct capture of initiating ribosomes from cell lysates (44, 45). Together with profiling of elongating ribosomes by use of cycloheximide (CHX), high-resolution profiling of initiating ribosomes greatly facilitates understanding of translation heterogeneity.

More recently, translational complex profile sequencing (TCP-seq) was developed to monitor the scanning process of the PIC (5). Following formaldehyde cross-linking of live cells, scanning ribosomes bound to mRNAs can be separated from 80S ribosomes. Although highly informative, the static picture of PIC positions in the 5′ UTR is still far from depicting the dynamic scanning process. Given the involvement of many initiation factors in the scanning process, TCP-seq

CHX: cycloheximide

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can be coupled with immunoprecipitation of various initiation factors to determine the role of these factors in the scanning process. A similar approach has been adopted to address ribosome heterogeneity, the concept that ribosomes differ in their protein content (165). In those cases, individual ribosome subunits are immunoprecipitated for isolation of specific ribosome complexes, followed by Ribo-seq (141). Results showed that distinct ribosome subunits were enriched on different mRNAs, suggesting that different ribosome complexes may be used to translate different mRNAs.

AAR: amino acid response

GCN2: general control nonderepressible 2

ISR: integrated stress response

Nevertheless, concerns have been raised regarding the interpretation of Ribo-seq results, as details of sample preparation may introduce bias and artifacts. During library preparation, for instance, the efficiency of circularization or linker ligation could be influenced by the 5′ end nucleotide identity of RPFs (83). As a result, technically inflated or depleted RPFs could alter the overall pattern of ribosome footprints. Additionally, pretreatment with the translation inhibitor CHX skews codon densities and induces unwanted cellular responses (131). Although omitting CHX pretreatment has become a common practice, eliminating artifacts introduced by varied protocols remains challenging. Finally, great caution must be taken because ribosome binding is not synonymous with protein production. Thus, it is important to apply independent approaches to validate translational output individually and globally. In this vein, quantitative proteomic analysis methods such as pulsed SILAC (stable isotope labeling by amino acids in cell culture) are highly desirable to corroborate proteome diversity and complexity (93).

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GENERAL NUTRIENT-SENSING MECHANISMS

Integrated Stress Response

Protein synthesis is one of the most energy-consuming cellular processes, and translation capacity is tightly coupled to nutrient availability. In response to a shortage of amino acids, cells rapidly activate a pathway called amino acid response (AAR) that is essential for cell survival (77). AAR involves the activation of general control nonderepressible 2 (GCN2), which also serves as an amino acid sensor. This regulatory mechanism relies on the binding of amino acids to tRNAs, a process that is catalyzed by aminoacyl–tRNA synthase. Amino acid depletion leads to increased concentration of nonaminoacylated (uncharged) tRNAs, which activates GCN2 by binding to the histidyl–tRNA synthetase domain. Activated GCN2 kinase then phosphorylates eIF2α at serine residue 51 (human). eIF2α is a subunit of eIF2, which is part of the TC (59). Phosphorylation of eIF2α inhibits eIF2B, a GTP exchange factor essential for TC recycling. As a result, the reduced availability of TC causes attenuation of general protein synthesis (17, 82). eIF2α can be phosphorylated by additional mammalian protein kinases, such as heme-regulated kinase when iron levels are low; PKR (protein kinase activated by double-stranded RNA), which is activated by double-stranded RNAs; and PERK (PKR-like ER kinase), which is stimulated by ER stress due to misfolded proteins in the ER lumen. All four kinases converge on eIF2α to shut down global protein synthesis, forming integrated stress response (ISR) (**Figure 2**).

As TC is a necessary component of the 43S PIC, reduced TC levels delay the binding of 43S PIC to mRNAs and suppress global translation. Paradoxically, translation of a subset of mRNAs is promoted during ISR; the best-known example is GCN4 in yeast or ATF4 in mammals (58, 96). ATF4 acts as a transcription factor (TF) by binding to *cis*-regulatory motifs called CAAT. ATF4-targeted genes encode amino acid biosynthesis enzymes as well as amino acid transporters (2). Although activation of AAR increases transcription of the *ATF4* gene by approximately twofold, regulation of *ATF4* expression occurs primarily through translational control of preexisting mRNA. The mature *ATF4* mRNA contains two uORFs in the 5′ UTR: one near the 5′ terminus and the

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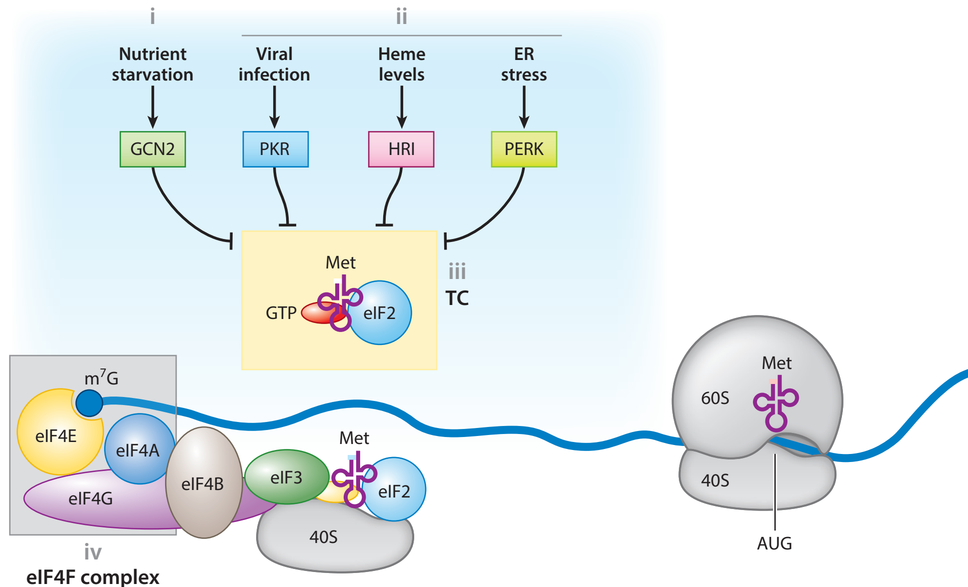

Figure 2

Translational consequences of integrated stress response. (*i*) In response to amino acid deprivation, the activated GCN2 phosphorylates eIF2α, which inhibits TC formation. In addition to the GCN2 kinase, other kinases integrate many stress conditions by phosphorylating eIF2α, thereby forming an integrated stress response targeting translation initiation (*ii*). Both the TC (*iii*) and the eIF4F complex (*iv*) are depicted. Abbreviations: eIF, eukaryotic initiation factor; ER, endoplasmic reticulum; GCN2, general control nonderepressible 2; HRI, heme-regulated kinase; m^7G, 7-methylguanylate; PERK, PKR-like ER kinase; PKR, protein kinase activated by double-stranded RNA; TC, ternary complex.

other overlapping with the main ORF but in different reading frames (158). On the basis of the leaky scanning model, the presence of uORFs is thought to suppress the translation efficiency of the main ORFs (11). Under normal growth conditions, the TC is abundant and ribosomes decode uORF1 as well as uORF2. Termination of uORF2 does not allow initiation of the main ORF because of sequence overlap. Upon amino acid starvation that triggers eIF2α phosphorylation, reduced TC formation leads to longer scanning time. As a result, more ribosomes bypass uORF2 and become available to initiate from the downstream main ORF (62). Notably, translation of the ATF4 main ORF relies on the reinitiation mechanism, which is fundamentally different from leaky scanning (176). Despite the prevailing view that it is TC availability that controls the efficiency of ATF4 translation, the timing of TC acquisition by reinitiating ribosomes remains to be determined.

mTOR Signaling Pathways

All organisms, including mammals, continuously monitor their immediate environment and respond to nutrient fluctuations. At the level of individual cells, a broad spectrum of adaptive mechanisms have evolved to sense and respond to nutrient deprivation. mTOR is a highly conserved serine/threonine kinase that is named for its inhibitor, rapamycin (39). mTOR assembles into two functionally and structurally distinct complexes in the cytoplasm: mTORC1 and mTORC2. As a major hub that integrates multiple signaling pathways, mTORC1 is a master regulator of protein synthesis that couples nutrient signaling to cell growth and proliferation (98). When the

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cellular nutrient level is ample, amino acids and growth factors activate mTORC1, which in turn promotes translation through two prominent downstream effectors: ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4E–binding proteins (4EBPs) (36). Activated mTORC1 phosphorylates S6K, which phosphorylates and activates ribosomal protein S6 (8). Similar to S6K, mTORC1 also phosphorylates 4EBP1, which in turn prevents it from binding to and inhibiting eIF4E. When 4EBP1 dissociates from eIF4E, eIF4E binds to cap structures on mRNAs and promotes cap-dependent translation (51). Interestingly, inhibition of eIF4E strongly affects a group of mRNAs containing a 5′ terminal oligopyrimidine tract; many of them encode ribosomal proteins and elongation factors (64, 155).

4EBPs: eukaryotic initiation factor 4E–binding proteins

TSC: tuberous sclerosis complex

GAP: GTPase-activating protein

mTORC1 senses nutrient levels through a sophisticated system (79, 84). Amino acids promote the translocation of mTORC1 to the surface of the lysosome, where it can interact with the Ras homolog enriched in brain (Rheb) GTPase (129). At the lysosome surface, Rheb activity is subject to regulation by phosphoinositide 3 kinase (PI3K) pathways. Therefore, both the amino acid sensing system and the insulin signaling pathway converge on mTORC1. Rheb activity is negatively regulated by tuberous sclerosis complexes 1 and 2 (TSC1 and TSC2), in which TSC2 acts as a GTPase-activating protein (GAP) toward Rheb (68, 122). mTORC1, composed of the core mTOR, Raptor, and mLST8 subunits, docks on the lysosome through the direct interaction of Raptor with the lysosome-associated Rag GTPase–Regulator complex (**Figure 3**). The Rag GTPases form heterodimers RagA/B and RagC/D, which are necessary for mTORC1 signaling to respond quickly to changes in nutrient levels (78, 130). When amino acids are limited, Rag

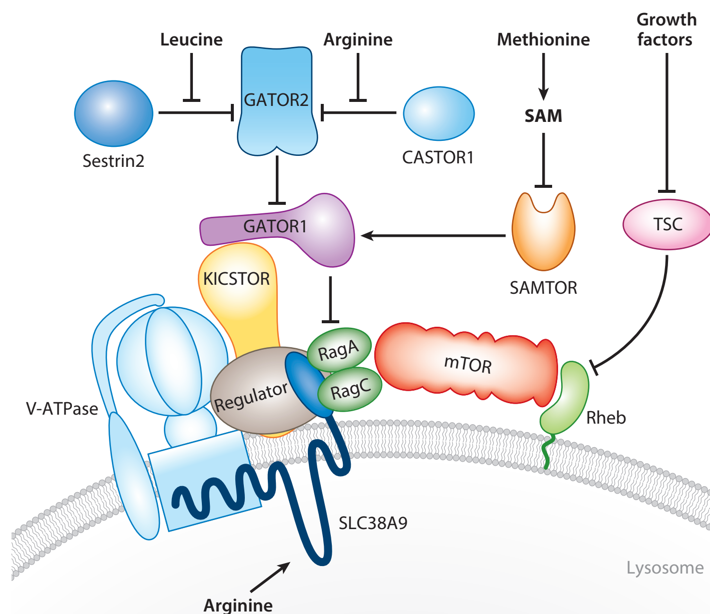

Figure 3

Cellular amino acid sensors for the mTORC1 signaling pathway. Schematic showing components of the nutrient-sensing pathway upstream of mTORC1, including many multiprotein complexes that regulate the Rag GTPases as well as the amino acid sensors Sestrin2, CASTOR1, SLC38A9, and the SAM sensor SAMTOR. The Rag GTPases promote the localization of mTORC1 to the lysosomal surface in response to nutrients, and at the lysosome the Rheb GTPase activates its kinase activity in response to insulin and energy levels. Abbreviations: mTOR, mechanistic target of rapamycin; mTORC, mTOR complex; Rheb, Ras homolog enriched in brain; SAM, *S*-adenosylmethionine; TSC, tuberous sclerosis complex.

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GTPases are inactivated, leading to GDP-coupled RagA/B and GTP-bound RagC/D, which are unable to recruit mTORC1 to the lysosome membrane. The Ragulator complex acts as a guanine nucleotide exchange factor (GEF) toward RagA and RagB, whereas another complex called GATOR1 has GAP activity (9, 10). Once recruited to the lysosome surface, mTORC1 is believed to be directly activated by Rheb.

GEF: guanine nucleotide exchange factor

Over the past decade, several proteins that help transmit individual amino acid availability to mTORC1 have been identified (**Figure 3**). The first validated amino acid sensor came with the discovery of Sestrin1 and Sestrin2 as leucine sensors (163). When leucine is depleted, Sestrin2 binds to GATOR2, a positive regulator of the nutrient-sensing arm of mTORC1, leading to GATOR2 inhibition. Upon leucine supplementation, the interaction between Sestin2 and GATOR2 is dissociated, which activates the mTORC1 pathways. Subsequently, proteins named CASTOR1/2 were identified as cytosolic arginine sensors for mTORC1; they also interact with GATOR2 (19). Under conditions where arginine is depleted, homodimers of CASTOR1 or heterodimers of CASTOR1 and CASTOR2 bind to GATOR2, thereby limiting the interaction of CASTOR proteins with cytoplasmic arginine. More recently, a protein called SAMTOR has been identified as an *S*-adenosylmethionine (SAM) sensor, which links mTORC1 to methionine levels (50). Although many other amino acid sensors remain elusive, these discoveries clearly indicate the existence of distinct pathways by which individual amino acids regulate mTORC1 activity.

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Individual Amino Acid Sensing Pathways

Amino acids are the building blocks of protein synthesis. The traditional view of AAR is mainly based on total amino acid starvation. The cellular response to individual amino acid deprivation remains surprisingly obscure. Current evidence suggests that the two major amino acid sensing pathways, mTORC1 and ISR, may differ depending on the specific amino acids that are missing. Recent research in mammalian cells suggests that deficiency of several essential amino acids, namely histidine, leucine, arginine, and methionine, resulted in different levels of eIF2α phosphorylation and subsequent translation attenuation (103). Also, the level of eIF2α phosphorylation does not necessarily correspond to the level of global translation. A mouse study found that GCN2 was not activated in the brain of mice whose diet lacked essential amino acids (88). Recent research using breast epithelial cells has shown that deprivation of single branched-chain amino acids (or glucose) for 30 min has the strongest inhibitory effect on global protein synthesis (43). The same study also found that deprivation of glycine or serine led to minimal translational changes.

Methionine is the initiating amino acid in the synthesis of virtually all eukaryotic proteins. Using Ribo-seq coupled with translation inhibitors specifically targeting the initiating ribosomes, several groups, including ours, have identified multiple initiation sites in almost half of the transcripts in the human and mouse transcriptomes (44, 67). Intriguingly, many non-AUG codons, especially CUG, act as alternative start codons for initiating uORF translation (150). It remains unclear whether these non-AUG start codons are initiated by methionine-charged tRNA. Methionine is also a key component in the generation of SAM, which is the primary methyl donor in biological reactions. As a result, methionine and its metabolic derivatives participate in several diverse metabolic pathways, including the biosynthesis of polyamines, purines, and creatine. Methionine deprivation inhibits methylation reactions and subsequently reduces the methylation of many macromolecules (153). In addition to DNA and histone methylation (the epigenome), RNA methylation has been discovered on all RNA species across many living organisms (125). These dynamic and reversible RNA modifications constitute the epitranscriptome, a tunable layer influencing nearly all aspects of RNA metabolism, including mRNA splicing, export, degradation, and

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translation (see the section titled Nutrient Sensing by RNA Modification). Therefore, methionine starvation has much broader impacts on cellular metabolism.

SLC7A11: solute carrier family 7 member 11

GPX4: glutathione peroxidase 4

Cysteine is among the rarest and most functionally diverse of all the amino acids. By virtue of its ability to form disulfide bonds, cysteine plays a crucial role in protein structure and in protein-folding pathways. Additionally, cysteine is a redox-sensitive amino acid that plays roles in thiolation and the oxidative stress response (151). Acting as the limiting amino acid for the production of glutathione (GSH), cysteine is crucial in maintaining the redox balance. Lowered GSH is one of the indices of oxidative stress, which has been implicated in various diseases including metabolic disorders, immune dysfunction, and cancer (156). Like many other amino acids, cells rely on transporters to maintain intracellular cysteine levels (104). The amino acid transport system x_c^- is an antiporter that imports extracellular cystine coupled to the efflux of intracellular glutamate (132). The transport system x_c^- exists as a heterodimer, consisting of solute carrier family 7 member 11 (SLC7A11, also known as xCT), the catalytic subunit of the transport system x_c^-, and SLC3A2, the chaperone that recruits SLC7A11 to the plasma membrane. Because of the reduced microenvironment inside cells, intracellular cystine is quickly converted to cysteine. Notably, cystine is highly enriched in the lysosome, as revealed by lysosomal metabolomic profiling (1). Blocking of V-ATPase resulted in depletion of cystine from lysosome.

Nutrient depletion induces metabolic stress and eventually causes cell death (49). Deficiency of cellular cysteine induces a unique cell death program known as ferroptosis, a peroxidation-driven and iron-catalyzed form of nonapoptotic cell death (33). Ferroptosis is morphologically, genetically, and biochemically distinct from other forms of regulated cell death, such as apoptosis and necroptosis. Glutathione peroxidase 4 (GPX4) reduces lipid hydroperoxides to lipid alcohols at the expense of reduced GSH, thereby protecting cells against membrane lipid peroxidation and inhibiting ferroptosis (152). It has been proposed that deficiency of intracellular cysteine induces ferroptosis primarily as a result of failure to synthesize GSH. Consistently, inhibition of cellular cysteine uptake by use of erastin (an inhibitor of the transport system x_c^-) depleted GSH and induced ferroptosis (33). It is clear that cysteine deprivation triggers a unique cellular response pathway.

While protein production typically involves the incorporation of the 20 canonical amino acids, a handful of proteins incorporate nontraditional amino acids during protein synthesis. One such example is selenocysteine encoded by a UGA stop codon (25). Selenium can be found on at least 25 mammalian proteins, known as selenoproteins. Most of them have important cellular functions, especially in maintaining cellular redox balance (55). Mechanistically, it requires recognition of the *sec* insertion sequence located at the 3′ UTR of selenoproteins (35). When dietary selenium is insufficient, UGA will trigger mRNA decay via the NMD pathway, decreasing the availability of selenoproteins (137). However, selenoproteins that are stress inducible seem to be disproportionately affected by the lack of dietary selenium in comparison to housekeeping selenoproteins. On the other side of the spectrum, excessive dietary selenium does not seem to increase the synthesis of selenoproteins.

NUTRIENT SENSING BY *O*-GlcNAcYLATION

O-GlcNAc Biology

Nutrient-sensing mechanisms are not limited to amino acid signaling pathways. *O*-GlcNAcylation is a posttranslational modification in which *O*-GlcNAc, a monosaccharide, is added to serine or threonine residues of nuclear, cytoplasmic, and mitochondrial proteins (171). Unlike *N*-glycosylation, which often serves as a localization or recognition signal for proteins in the

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secretory pathway, *O*-GlcNAcylation usually has a regulatory role similar to that of phosphorylation (89). While phosphorylation status is controlled by many kinases and phosphatases, *O*-GlcNAcylation is modified by a single pair of enzymes, *O*-GlcNAc transferase (OGT) and *O*-GlcNAcase (OGA). Recent studies have shown that, in addition to possible regulation of OGT and OGA activities, *O*-GlcNAcylation is regulated by intracellular levels of UDP-GlcNAc, the sugar donor of the modification (54). Interestingly, the biogenesis of UDP-GlcNAc involves the hexamine biosynthesis pathway, which requires intermediates from glucose, amino acid, fatty acid, and nucleic acid metabolism. As a result, *O*-GlcNAcylation is highly dependent on the cellular nutrient environment. Many studies have since shown that changes in cellular nutrient conditions and stress conditions rapidly trigger changes in *O*-GlcNAcylation on targeted proteins (28, 90, 173). Due to *O*-GlcNAc's fundamental roles as a nutrient and stress sensor, it is not surprising that *O*-GlcNAcylation plays an important role in the etiologies of human diseases including diabetes, cancer, and neurodegenerative diseases.

OGT: *O*-GlcNAc transferase

OGA: *O*-GlcNAcase

Although *O*-GlcNAcylation was discovered several decades ago, identifying targeted proteins and mapping modification sites remain a formidable task. With advanced mass spectrometry and genetic and biochemical technologies, hundreds of proteins have been found to be modified by *O*-GlcNAc (97). Many of these proteins are actively involved in cellular processes such as transcription, the cell cycle, and metabolism (54). In this section, we discuss the current understanding of how *O*-GlcNAcylation regulates mRNA translation under various nutrient conditions.

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O-GlcNAc in Translational Regulation

To date, only a handful of papers have discussed the role of *O*-GlcNAc in translation regulation. In 1989, well before *O*-GlcNAc could be detected by mass spectrometry, Datta et al. (26) elegantly demonstrated that an eIF2-associating protein, p67, is *O*-GlcNAcylated and that its *O*-GlcNAcylation regulates mRNA translation in vitro. Specifically, they showed that p67 is necessary to protect eIF2 from eIF2 kinase, which phosphorylates eIF2 and inhibits its function. More than a decade later, the authors revisited this protein and found that the serine/threonine cluster of p67 (60SGTS63) is *O*-GlcNAcylated and that overexpression of a non-*O*-GlcNAcylable mutant of p67 in mammalian cells causes an increase in endogenous eIF2 phosphorylation and a reduction in global translation (27). In addition to regulating the checkpoint of eIF2, *O*-GlcNAcylation regulates the cap-binding ability of eIF4E through *O*-GlcNAcylation and 4EBP1 proteolysis (28, 32). As mentioned above, phosphorylated 4EBP1 releases eIF4E and allows it to bind to the mRNA cap to initiate translation. Studies of the liver and retina of diabetic mice revealed that hyperglycemia leads to increased protein *O*-GlcNAcylation and decreased global translation (28, 32). Mechanically, these effects could contribute in part to the *O*-GlcNAcylation of p53, which stabilizes and increases its activity (32). Interestingly, 4EBP1 itself is also *O*-GlcNAcylated, and the level of the modification is higher in diabetic mice (28). The increased *O*-GlcNAc level coincides with reduced binding of eIF4E to eIF4G. The subsequent reduction in global protein synthesis suggests that *O*-GlcNAcylation of 4EBP1 may regulate the interaction of eIF4E with eIF4G.

In addition to eIF4E, the other two subunits of the eIF4F complex, eIF4A and eIF4GI, can be *O*-GlcNAcylated (90). Using click chemistry, Li et al. (90) reported that both eIF4A and eIF4GI purified from mammalian cells are *O*-GlcNAcylated. Using m^7G cap immunoprecipitation, these authors showed that most modified eIF4A and eIF4GI are associated with the cap, suggesting that *O*-GlcNAcylation of these proteins may be functionally significant. Mass spectrometry revealed that eIF4A undergoes modification at sites S322 and S323, and an eIF4A modification mimic mutant (S322, 323Y) has significant less interaction with eIF4GI. This mutant also greatly reduced the helicase activity of eIF4A, further decreasing translation and cell proliferation. Using

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similar methods, the authors found that *O*-GlcNAcylation of eIF4GI does not affect eIF4F assembly. However, overexpression of a non-*O*-GlcNAcylable mutant of eIF4GI (S61A) reduced global translation, partly as a result of its decreased interaction with PABP1. However, another study reported that eIF4GI in mammalian cells undergoes minimal modification under physiological conditions (173). Instead, *O*-GlcNAcylation of eIF4GI was induced by heat shock stress. Given the different modes of mRNA translation under normal and stress conditions, it is possible that *O*-GlcNAcylation of eIF4GI serves as a functional switch in selective mRNA translation as well as in stress granule formation.

m^6A: N^6-methyladenosine

Apart from translation initiation factors, ribosomal proteins are subject to *O*-GlcNAc modification. The Anderson lab (119, 172) discovered that several ribosome proteins, including RACK1, RPS3, and RPL13a, are *O*-GlcNAcylated. A follow-up study by another group found that approximately 20 ribosomal proteins undergo *O*-GlcNAcylation, and their modification sites were identified via mass spectrometry (172). Notably, overexpression of OGT, but not OGA, increases the ratio of 60S to 80S ribosomes and decreases polysomes, suggesting a reduction of global translation. However, the underlying mechanism remains unclear. Finally, OGT has been reported to interact with active translating ribosomes (177). Not surprisingly, *O*-GlcNAcylation may occur on newly synthesized polypeptides in a cotranslational manner. Since OGT inhibition reduces the level of targeted proteins, it has been proposed that cotranslational *O*-GlcNAcylation stabilizes nascent peptide chains. It is clear that *O*-GlcNAcylation has broad effects on protein synthesis, forming an additional layer of cross talk between nutrient signaling and translational control.

NUTRIENT SENSING BY RNA MODIFICATION

To date, more than 170 different RNA chemical modifications have been found on RNAs across all living organisms (114). Most modifications have been identified in abundant cellular RNAs, such as tRNA and rRNA molecules. The recent resurgence of interest in modifications of mRNA has been fueled by technological advances that reveal chemical modifications of nucleotides in a qualitative and quantitative manner. In addition to the well-documented $2'O$-methylation ($2'O$-Me) and m^7G modifications, mRNA may be marked by *N*6-methyladenosine (m^6A), m^1A, m^6Am, m^5C, pseudouridine (ψ), and so forth. These dynamic and reversible RNA modifications constitute the epitranscriptome, a tunable layer influencing nearly all aspects of RNA metabolism, including mRNA splicing, export, degradation, and translation (125). Representing a new nutrient-sensing mechanism, RNA modification is reshaping our understanding of the nutritional regulation of gene expression.

mRNA m^6A Methylation

Among all modifications, m^6A is the most abundant internal mRNA modification (42). First discovered in the 1970s, this modification has only been appreciated since the development of transcriptome-wide m^6A sequencing techniques. Intriguingly, global m^6A mapping revealed an asymmetric distribution of mRNA methylation, with most m^6A sites enriched near the stop codon (34, 109). A consensus sequence, RRACH (R = adenine or guanine; H = adenine, uracil, or cytosine), has been widely recognized, and its primary readers, writers, and erasers have been identified (41, 107). This dynamic modification is written by a multicomponent methyltransferase complex consisting of methyltransferase-like 3 (METTL3), methyltransferase-like 14, Wilms tumor 1–associated protein, KIAA1429, RNA-binding motif protein 15, and zinc finger CCH domain–containing protein 13 (92, 159). While METTL3 is the sole component harboring methyltransferase activity, other proteins provide structural and regulatory roles that are critical

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for the methylation process. Once methylated, the modification can be removed by m^{6}A demethylases such as fat mass and obesity–associated protein and α-ketoglutarate-dependent dioxygenase alkB homolog 5 (73, 174). The dynamics of m^{6}A modification is consistent with the finding that the mRNA m^{6}A levels fluctuate in response to varied nutrient status and stress conditions.

The YTH domain family proteins serve as the major m^{6}A readers (42). While YTHDC1 is located in the nucleus, YTHDC1, YTHDF1, YTHDF2, and YTHDF3 are primarily cytoplasmic m^{6}A readers. Indeed, YTHDF1 and, to a lesser extent, YTHDF3 promote protein translation by binding to methylated mRNA near the stop codon (140, 160). The primary function of YTHDF2 is apparently to mediate mRNA decay, although other functions likely exist. YTHDC2, the only RNA helicase–containing m^{6}A reader, appears to promote mRNA translation by resolving secondary structures in the coding region (100). Other m^{6}A-binding proteins may also act as potential readers. For instance, both eIF3 and HNRNPA2B1 interact with methylated mRNAs (3, 108). Additionally, m^{6}A installation could repel certain RNA-binding proteins, presumably via altered RNA secondary structures (38).

By affecting nearly all aspects of mRNA metabolism, m^{6}A marks an ever-growing list of cellular and physiological functions. The translational effect of m^{6}A could be complex, depending on the methylated mRNA regions as well as the involved m^{6}A readers (**Figure 4**). The asymmetric m^{6}A deposition suggests that regional methylation may have distinct functional consequences. Previous studies reported that the cytosolic m^{6}A readers YTHDF1 and YTHDF3 promote cap-dependent mRNA translation, presumably via 3′ UTR methylation (140, 160). Intriguingly, m^{6}A promotes translation by facilitating mRNA looping via METTL3–eIF3H interaction (21). In addition to m^{6}A in the UTRs, approximately 35% of m^{6}A residues are located within the coding sequence (CDS). Using an elegant single-molecule-based in vitro translation system, investigators have demonstrated that m^{6}A interferes with the decoding process by affecting tRNA accommodation, thereby slowing down translation elongation (22). We recently reported that m^{6}A in the CDS promotes mRNA translation via the helicase-containing YTHDC2 (100). Interestingly, m^{6}A in the 5′ UTR could facilitate cap-independent translation through a process involving eIF3

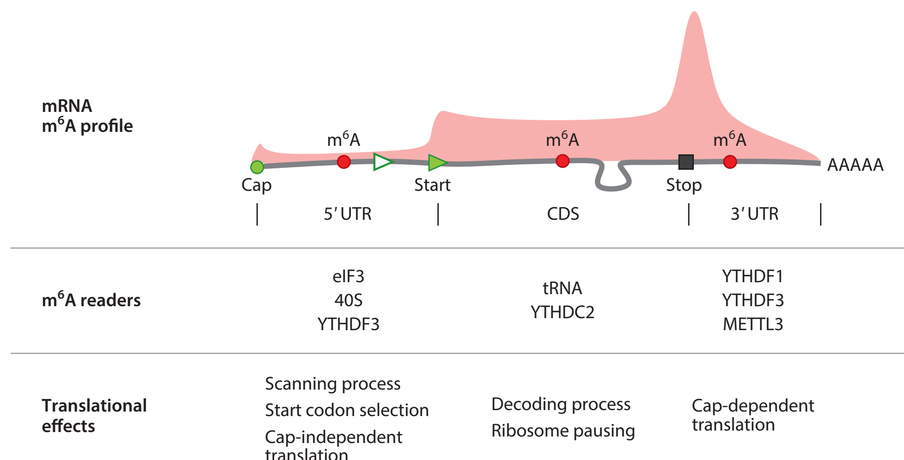

Figure 4

Regional effects of mRNA m^{6}A modification on translation. The asymmetric distribution of m^{6}A is shown above the mRNA. Depending on m^{6}A-interacting factors or readers, regional m^{6}A marks may have distinct effects on mRNA translation. Abbreviations: CDS, coding sequence; eIF, eukaryotic initiation factor; m^{6}A, *N*6-methyladenosine; UTR, untranslated region.

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(108, 175), although the exact nature of this process remains unclear. In support of this idea is the finding that methylation of circRNAs in the form of m^6A promotes their translation (166). Additionally, m^6A could mediate mRNA translation that is neither cap nor IRES dependent, possibly involving ABCF1 (24). In response to amino acid starvation, the reduced mRNA methylation promotes ATF4 translation (176). It has also been suggested that 5′ UTR m^6A affects ribosome scanning, which would influence start codon selection. Given the distinct regional effects of mRNA methylation, it is highly desirable to distinguish the contributions of individual m^6A modifications. More recently, we have developed site-specific m^6A editing tools by fusing m^6A enzymes to the catalytically dead CRISPR/Cas9 (94). Programmable m^6A editing enables functional dissection of single-site methylation in different mRNA regions.

mRNA Acetylation

Recent technologies have permitted the detection of other types of mRNA modifications. Acetylation of cytidine, for instance, has recently been found on mRNAs and has been proposed to promote translation efficiency (4). Prior to this study, *N*4-acetylcytidine (ac4C) had been found only on tRNAs, catalyzed by *N*-acetyltransferase 10 (NAT10) (56). NAT10 was later reported as a poly(A)-interacting factor, suggesting that mRNAs may be acetylated by NAT10. Indeed, liquid chromatography coupled with tandem mass spectrometry showed that ac4C exists on human poly(A) RNAs and that ac4C can be detected in poly(A)-isolated RNAs by use of an ac4C-specific antibody (4). The use of acetylated RNA immunoprecipitation of poly(A) RNAs coupled with deep sequencing enabled the discovery of more than 4,000 ac4C peaks in the transcriptome of HeLa cells. Unlike m^6A, most of these ac4C peaks are enriched in the 5′ UTR and CDS regions. Importantly, acetylated mRNAs tend to have higher translation efficiency. Mechanistically, the authors of this study (4) found that acetylation is disproportionately found on the third position of a codon, known as the wobble position. Silent mutation from wobble cytidine to noncytidine abolishes the increase in translation efficiency. The authors proposed that mRNA acetylation enhances translation by promoting interaction between mRNAs and cognate tRNAs. Since acetate is produced from carbohydrate and fat catabolism, changes in nutrient level could influence mRNA acetylation and subsequent translation.

tRNA Modification

Posttranscriptional modifications in the anticodon loop of tRNAs are critical for the decoding process. Depending on the associated tRNA isoacceptor and the organism, tRNA position 34 is subject to various modifications. Some of these modifications are important for the fine-tuning of protein translation and the subsequent maintenance of proteome integrity. Using a quantitative systematic approach, Chan et al. (18) reported signature changes in the spectrum of tRNA modifications in *S. cerevisiae* upon oxidative stress. Interestingly, there was an increase in the proportion of $tRNA^{Leu(CAA)}$ containing m^5C at the wobble position. This modification causes selective translation of mRNA from genes enriched in the TTG codon. In higher eukaryotes, m^5C–tRNA methylation is found at positions 48, 49, and 72, as well as positions 34 and 38 in the anticodon loop (6). The absence of a methyl group at these positions has been suggested to interfere with tRNA folding and stability, codon–anticodon interactions, and reading frame maintenance (116). Thiolation also occurs on tRNA wobble-uridine nucleotides, which is correlated with the intracellular availability of sulfur amino acids methionine and cysteine (85). Interestingly, changing tRNA thiolation regulates translational reprogramming and enables cells to modulate their translational capacity according to metabolic homeostasis (85).

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In addition to tRNA modifications, several recent studies have reported that oxidative stress triggers endonucleolytical cleavage of tRNAs around the anticodon, giving rise to small RNA species that may participate in various stress signaling pathways (127, 154). Finally, a recent study reported that an up-to-10-fold increase of methionine misacylation occurs at tRNAs when cells are exposed to oxidative stress. It has been proposed that misincorporation of methionine into cellular proteins could protect cells from reactive oxygen species–mediated damage (117). Given the diversity of tRNA modifications, much remains to be learned about the role of differential tRNA modification in translational regulation.

rRNA Modification

In eukaryotes, the translation machinery ribosome is composed of four rRNAs and approximately 80 ribosomal proteins arranged into small (40S) and large (60S) subunits. Ribosome biogenesis depends on the nutritional status of the cell. It has been reported that refed mice have an increased expression of mRNAs encoding ribosomal proteins, most likely in an effort to restore protein production (111). Like tRNAs, rRNAs are highly modified; approximately 2% of rRNA nucleotides are modified. There are three main types of rRNA nucleotide modifications: (*a*) conversion of uridine to pseudouridine (Ψ); (*b*) methylation of 2′ hydroxyls; and (*c*) alterations to bases, most of which undergo methylation at different positions (136). Similar to m^6A modification, rRNA methylation is dependent on the levels of methyl donors. Amino acid starvation experiments limit these modifications, thereby adding a new layer of translation regulation.

TRANSLATIONAL DEREGULATION IN DISEASE

The contribution of fundamental cellular processes to metabolic homeostasis has been intensively studied. Our understanding of the impact of translational dysregulation on metabolic disorders lags behind that of transcription and cell signaling pathways. Nevertheless, a growing body of evidence suggests that proteome imbalance has a crucial role in a wide range of human diseases, including diabetes, cancer, and aging (53).

Metabolic Disorders

Diabetes mellitus can be divided into two types: type 1 (T1DM), which is characterized by little to no insulin production, and type 2 (T2DM), which is characterized by resistance or nonresponse to insulin. In both cases, the production of insulin by pancreatic β cells is critical. The human proinsulin mRNA contains two downstream translation initiation sites (dTISs): an in-frame one at position 72 and an out-of-frame one at position 341. Using a reporter assay, Kracht et al. (81) found that both dTISs can initiate translation, suggesting the presence of a considerable degree of leaky scanning of the insulin mRNA. Interestingly, the translation from out-of-frame dTIS 341 is augmented under stress. Furthermore, the product of the out-of-frame translation is an autoantigen that activates β cell $CD8^+$ T cells, leading to apoptosis in T1DM patients. Insulin or proinsulin is known to be translated in the ER, processed in the Golgi apparatus by carboxypeptidase E (CPE), and secreted as the final cleaved insulin peptide. Jo et al. (74) reported that both insulin production and the protein level of CPE are reduced in OGT knockout β cells. They found that eIF4GI is less stable in the absence of *O*-GlcNAcylation. Moreover, the reduced CPE level, as well as reduced insulin production, can be rescued by overexpression of wild-type eIF4GI, suggesting that *O*-GlcNAcylation of eIF4GI is essential for CPE translation and the subsequent maturation of insulin. As a hormone, insulin regulates metabolic processes such as glucose metabolism and the

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production of key adipogenic TFs. Brina et al. (14) found that adipogenic TFs are not responsive to insulin in mice that have only one copy of eIF6. Further analysis revealed that eIF6 regulates the translation of the TFs by binding to the guanine/cytosine-rich or uORF sequences in the 5′ UTR of the TF transcripts. As a result of the reduced TF translation, levels of blood cholesterol and triacylglycerols are lower in heterozygous mice than in their wild-type littermates. This finding suggests that eIF6 is vital in insulin signaling and adipocyte metabolism.

One of the most prominent TFs that promotes fat metabolism in adipose tissues and the liver is CCAAT/enhancer-binding protein β, whose mRNA contains one uORF and is capable of producing three isoforms, LAP*, LAP, and LIP (178). LIP, which contains the DNA-binding domain but not the N-terminal transactivation domain, acts as a competitive inhibitor of LAP* and LAP. Interestingly, expression of LIP depends on mTORC1 signaling and uORF reinitiation. Inhibition of mTORC signaling or deletion of the uORF abolishes LIP expression, augmenting the effect of LAP and LAP*. Mice with reduced LIP expression had reduced total body fat and increased lean body mass despite consuming more food, making these mice metabolically healthier than their wild-type counterparts (178).

Cholesterol homeostasis is also essential for metabolic health. Mobin et al. (110) reported that an RNA-binding protein, vigilin, is upregulated in obese mice with fatty liver disease. PAR-CLIP (photoactivatable ribonucleoside-enhanced cross-linking and immunoprecipitation) revealed that vigilin binds to cytosine/uracil-rich regions in the mRNA-coding regions of *Apob* as well as other proatherogenic secreted cytokines. Knockdown of vigilin in hepatocytes deceases levels of low-density and very low-density lipoprotein and leads to the formation of atherosclerotic plaques in these mice, highlighting the critical role of vigilin-mediated translational control in hepatic metabolic health.

Lastly, micronutrients have been implicated in the development of metabolic disorders. For instance, dietary selenium has been associated with T2DM (63). As mentioned above, selenoproteins are essential for cellular redox response. Insufficient intake of selenium may lead to a reduction in the protein level of several selenoproteins, such as GPX4, which in turn results in increased levels of reactive oxygen species and possibly metabolic alterations.

Cancer

Dysregulation of mRNA translation is frequently observed cancer cells (12, 145, 157). Many oncogenic signaling pathways (e.g., Ras, PI3K/mTOR, and MYC) converge to regulate the assembly and activity of eIF4F, a protein complex responsible for ribosome loading to the 5′ end cap of mRNAs (23, 98, 138). By controlling the translational efficiency of specific messages, eIF4F serves as a critical nexus for cancer development (121). As a result, malignant cells often become "addicted" to elevated protein synthesis. Over the last several years, there have been many efforts to target translation initiation in cancer treatment. However, recent clinical trials using inhibitors targeting eIF4F or its upstream regulators (e.g., mTOR) showed only limited efficacy (101). It is possible that the mechanistic linkage between dysregulated translation initiation and tumorigenesis is more complex than previously thought (120, 135). In various cancers, protein synthesis rates and translational components are significantly elevated (126). This enhanced global protein synthesis rate has been associated with enhanced formation of the eIF4F initiation complex.

The tumor microenvironment contains many stressors, including hypoxia, nutrient limitation, and inflammation. These can induce noncanonical translation mediated by IRES, the structural elements in 5′ UTR that permit cap-independent translation (57). Efficient IRES-mediated translation initiation requires RNA-binding proteins known as IRES *trans*-acting factors. A recent study reported that in breast cancer cells, protein production of tumor suppressor p120 is upregulated

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through IRES-mediated translation (144). Therefore, cap-independent translation can be hijacked by cancer cells to promote tumorigenesis. Due to a lack of nutrients within the interior of solid tumors, ISR is activated to promote tumor progression (31). In this context, mTORC1 inhibition appears to be beneficial for tumor growth because augmented autophagy and micropinocytosis facilitate internal nutrient supply (120). Tumor growth and metabolic adaptation may restrict the availability of certain amino acids for protein synthesis. Ribo-seq of kidney cancers revealed ribosome pausing at proline codons (95), implying a tumor-specific proline vulnerability that can be targeted for cancer treatment.

Cancer cells exploit multiple mechanisms to modulate translation, including deregulation of uORF translation (133). Repeated observations of uORF mutations associated with disease imply a crucial role of uORFs in pathogenesis. The *CDKN2A* gene encodes two proteins, p16INK4a and p14ARF, which act as tumor suppressors by regulating the cell cycle. In addition to mutations in the main ORF, a single point mutation in the 5′ UTR of *CDKN2A* creates a new TIS. Translation of this novel uORF decreases CDKN2A protein levels in hereditary melanoma (11). Human epidermal growth factor receptor 2 (HER2; also known as ERBB2) is overexpressed in approximately 15–30% of breast cancers (69). The translation of *HER2* is normally repressed by uORF translation. In tumor cells, however, the RNA-binding proteins HUR and hnRNPA1 overcome the inhibitory effect of this translation by binding to the 3′ UTR of *HER2* (20, 105). Deregulation of uORF translation also can occur in a global manner. A recent study reported that alternative translation initiation is globally elevated in embryonic skin cells from a mouse tumorigenesis model (135). It was hypothesized that the phosphorylation of eIF2α in the early stages of tumorigenesis leads to reprogrammed translation via eIF2A-dependent alternative initiation. Although translational control of cancer is multifaceted, several clinical efforts are under way to target specific components of the translation apparatus for cancer therapeutics (121).

Aging

Aging is characterized by deterioration in the maintenance of homeostatic processes over time, leading to functional decline and increased risk of disease and death. Protein homeostasis (or proteostasis) is orchestrated at multiple levels, but the importance of translational regulation has been increasingly appreciated. Multiple studies have demonstrated that the overall level of protein synthesis decreases with age in various invertebrates, mice, rats, and humans (e.g., 47). These studies observed reduced ribosome abundance and decreased levels of major initiation and elongation factors. A reduced abundance of translation elongation factor eEF1A was shown in aged *Drosophila melanogaster* (161). To investigate how translation is involved in the aging process, researchers downregulated the somatic isoform of eIF4E (IFE-2) in *Caenorhabditis elegans*, which enhanced the prolongevity effects of gene mutations (123). Downregulation of another initiation factor, eIF4G (IFG-1), increases the average life span of nematodes by more than 30% (124), while deletion of two subunits of eIF3 results in a 40% life-span extension (16). The nematode life span is also improved by downregulation of one of the subunits of the eIF2B initiation factor. These results support the idea that reduction of mRNA translation might be a conserved mechanism to extend life span in multiple species under different conditions.

A proper balance among synthesis, maturation, and degradation of cellular proteins is crucial for cells to maintain physiological functions (7). Various studies using yeast, *C. elegans*, *Drosophila*, and mammals have demonstrated that autophagy-related genes are essential for life-span extension (99), whereas autophagy deficiency suppresses normal life span (115). Autophagy induction depends on eIF5A, which is necessary for the translation of ATG3. mTORC1 inhibition enhances the association of eIF5A with ribosomes, enabling autophagy to proceed more readily (40).

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Molecular chaperones govern the integrity of the proteome as so-called cellular lifeguards. In mammalian cells, heat shock transcription factor 1 (HSF1) is the major transcriptional regulator of stress response (112, 164). In support of a role for a stress resistance mechanism that regulates life span, HSF1 overexpression induces longevity while HSF1 knockout shortens life span in *C. elegans* (46). Moreover, HSF1 is indispensable for life-span extension in classical long-lived insulin-signaling mutants (65, 113). Thus, a robust stress response is required for life-span extension in these organisms. It is likely that a decrease in global protein synthesis results in spare chaperone molecules in cells, which may contribute to the observed increase in organism life span.

HSF1: heat shock transcription factor 1

SUMMARY

Translational control in eukaryotic cells is critical for gene expression during nutrient deprivation and stress. The ability of cells to adapt to nutrient status is crucial for their survival. Regulation of global protein synthesis coupled with selective translation allows cells to rapidly respond to a variety of stress conditions. Although accumulating evidence has begun to reveal multiple signaling pathways in nutrient sensing, more questions than answers are brought up by studies of translational reprogramming in cellular adaptation. For instance, despite the essential role of amino acids in protein synthesis, why is the translation of individual mRNAs not equally affected by amino acid starvation? How are translational and nontranslational functions of amino acids coordinated in amino acid response? What is the precise mechanism by which only a subset of proteins undergo *O*-GlcNAcylation in response to nutrient stress? Given that uORFs are frequent in genes with critical biological functions, how does evolution exploit this element for regulatory purposes? With the prevailing mRNA modifications, how are differential epitranscriptomic marks integrated into translational reprogramming? It will be exciting to watch the unveiling of answers to these questions and to see the inevitable surprises that will emerge.

As we gain better insight into the mechanisms of translation, it is clear that a combination of emerging technologies will paint a multifaceted picture of this paramount cellular process. Elucidating the mechanisms underlying translational reprogramming during nutrient stress will not only shed light on the fundamental principles of translation but also provide deeper insight into the pathophysiology of human diseases. Dysregulated nutrient signaling pathways are often an underlying cause of metabolic disorders like diabetes. Translational control is a crucial component of cancer development and progression. Nutrient adaptation is deeply rooted in the aging process. Our hope is that, over the long term, cross-fertilization between high-throughput analysis and biochemical studies will allow for a better understanding of translational reprogramming in response to nutrient stress. Ultimately, elucidating nutrient control of mRNA translation might lead to the development of new therapeutic strategies for human diseases.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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