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Cross-talk between protein synthesis, energy metabolism and autophagy in cancer

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Abstract

Translation is a pivotal step in the regulation of gene expression as well as one of the most energy consuming processes in the cell. Dysregulation of translation caused by the aberrant function of upstream signaling pathways and/or perturbations in the expression or function of components of the translation machinery is frequent in cancer. In this review, we discuss emerging findings that highlight hitherto unappreciated aspects of signaling to the translation apparatus with the particular focus on emerging connections between protein synthesis, autophagy and energy homeostasis in cancer.

Introduction

Dysregulation of mRNA translation is common in cancer. Oncogenes (e.g. MYC, RAS, PI3KCA) and tumor suppressors (PTEN, LKB1, TSC1/2, p53) impinge on the translation

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apparatus [1]. Changes in expression and/or mutations of the components of translational machinery (e.g. eIFs, ribosomal proteins) are also frequent in neoplasia [1]. Translation is an essential step in the regulation of gene expression. Although the contribution of the translatome to the composition of the proteome is debated, at least under certain conditions translation plays a major role in regulation of gene expression. For instance, various stressors (e.g. ER-stress) impede the ternary complex (TC) recycling [2]. Limited availability of TC (composed of the eIF2, GTP and initiator tRNA) results in reprograming of the translatome, whereby decrease in global protein synthesis is accompanied by translational activation of some uORF-containing mRNAs (e.g. ATF4) [2]. Cancer cells are exposed to various stressors (e.g. hypoxia, nutrient deprivation) as the neoplastic growth outstrips vascular supply, *ergo* it is reasonable to postulate that translation is important for shaping malignant proteomes. Translation is also one of the most energy costly processes [3]. Signaling nodes (e.g. mTOR and AMPK) are linked to both regulation of translation and energy homeostasis (Figure 1). Herein, we focus on recent findings highlighting the role of signaling pathways in the orchestration of protein synthesis and energy balance.

The mTOR/4E-BP/eIF4F axis coordinates translation and cancer energetics

Cancer cells must adjust their protein synthesis output to adapt to fluctuations in nutrient and oxygen availability. Initiation is thought to be the most regulated phase of protein synthesis [2]. One of the rate-limiting steps of initiation is the eIF4F complex assembly. eIF4F consists of the 5′mRNA cap-binding subunit eIF4E, the scaffold eIF4G and the DEAD-box helicase eIF4A [2]. eIF4F recruits mRNA to the ribosome and its levels are largely determined by mTOR, a serine/threonine kinase which integrates a number of stimuli (e.g. nutrients, growth factors, hormones) to adjust growth rates to cellular energy status [4]. In mammals, there are two functionally and structurally distinct mTOR complexes, mTORC1 and mTORC2 [4]. mTORC1 is a major stimulator of protein synthesis and other anabolic processes [4]. In addition to mTOR, AMPK plays a central role in maintenance of energy balance [5]. AMPK was thought to be activated when the AMP/ATP ratio is increased, but recently it was shown that AMPK may be activated by glucose withdrawal even before AMP/ATP ratios raise [6]. AMPK reduces anabolic processes while bolstering catabolism, in part by inhibiting mTORC1 [5].

mTORC1 phosphorylates translational inhibitors 4E-BPs (4E-BP1-3 in mammals) that block eIF4G:eIF4E binding [1]. 4E-BP phosphorylation dissociates them from eIF4E, which facilitates eIF4E:eIF4G interaction and eIF4F assembly. mTORC1 activity is frequently upregulated in cancer, which in addition to common overexpression of eIF4E results in elevated eIF4F levels in neoplasia [1]. High eIF4F levels are linked to resistance to both chemotherapy and targeted therapies, and predict poor patient outcome [1]. Hyperactivation of mTORC1 in cancer not only increases global protein synthesis, but also results in dramatic translational reprograming [1]. In part, mTORC1 stimulates translation of nuclear-encoded mRNAs which are translated into proteins with mitochondrial functions (e.g. TFAM, ETC complex components) [7,8]. Increase in energy consumption upon mTORC1 activation is thus compensated by enhanced translation of mRNAs that encode proteins that impact on mitochondrial number, function and dynamics. This is mediated by 4E-BPs [7–9]. These findings demonstrate that the mTORC1/4E-BP axis plays a major role in maintaining

energy balance by coordinating mitochondrial ATP production, and protein synthesis rates (Figure 1).

Regulation of synthesis of nuclear-encoded mitochondrial proteins

Allosteric mTOR inhibitors (rapamycin and rapalogs) are employed for a variety of oncological indications, whereas second-generation mTOR inhibitors that target its active site are undergoing clinical trials [10]. Third-generation bivalent mTOR inhibitors that target both allosteric and active site have also been developed [11]. In most cell lines, however, mTOR inhibitors exert anti-proliferative, but not cytotoxic effects. This may be explained by emerging data that show that although mTOR inhibition results in decreased energy production, it concomitantly leads to reduced energy consumption, thereby resulting in a state of metabolic dormancy [8]. Accordingly, anti-neoplastic effects of anti-diabetic biguanides (e.g. metformin), which induce stress by decreasing mitochondrial ATP production, are potentiated in LKB1-deficient cells as they fail to induce AMPK, inhibit mTOR, and reduce energy consumption, thus resulting in energy crisis and cell death [12,13]. mTOR inhibition leads to simultaneous suppression of translation of mRNAs that encode proteins with mitochondrial function (i.e. subunits of ETC) and those that protect mitochondrial integrity (i.e. BCL-2 family members) [14]. This results in reduction in mitochondrial respiration and number, which is compensated by reduction in protein synthesis, and stimulation of autophagy, a vital cytoplasmic recycling process[14].

A large proportion of the transcripts which encode ETC subunits are characterized by short 5′UTRs (<30 nucleotides), whereas most transcripts encoding pro-survival factors harbor long 5′UTRs (>150 nucleotides). Transcripts with long, but not short 5′UTRs exhibit enhanced sensitivity to eIF4A inhibition [14]. eIF4A inhibitors induce cell death through translational suppression of BCL-2 family members and survivin, without reducing translation of ETC component-encoding mRNAs, or mTORC1 activity [14,15]. This induces mitochondrial depolarization and Bax/Bak-mediated apoptosis [14]. Hence, while mTOR inhibitors concurrently suppress translation of mRNAs that encode proteins involved in mitochondrial functions and protection of mitochondrial integrity, resulting in metabolic dormancy and cytostatic effects, eIF4A inhibitors induce apoptosis at least in part by selective inhibition of synthesis of proteins that maintain mitochondrial integrity without reducing mTOR activity, which results in energy crisis and cell death (Figure 1).

TISU element and coordination of transcriptional and translational mechanisms

The precise mechanism of how metabolic stress impacts on the translatome remains to be determined. A subset of short 5′UTR mRNAs contains a Translation Initiator of Short 5′UTR (TISU) element (C/GAAC/GATGGCGGC) which also serves as YY1 transcription regulatory element [16]. TISU mRNAs are actively translated under glucose deprivation despite reduction in global protein synthesis [17,18]. mTOR inhibitor rapamycin suppresses translation of TISU mRNAs [18]. Mechanistically, eIF4G:eIF1 interaction is thought to stimulate eIF4F release upon 48S complex formation on TISU mRNAs [18], followed by eIF1A-directed interaction between RPS3 and TISU and subsequent RPS3/RPS10e

exchange upon 80S assembly [19]. Simultaneous monitoring of the effects of glucose starvation on transcription start site selection and translation suggested that whereas 5′UTR length plays a role in regulation of mRNA translation in unstressed cells, this appears to be mostly mediated by the nature of cap-proximal nucleotides in glucose-deprived cells [20]. Intriguingly, glucose starvation appeared to induce alternative promoter selection in genes encoding translation factors including eIF4A1 and PABP. This appears to stimulate their translation under stress and results in eIF4A1 and PABP proteoforms with altered function [20]. Although the generality and physiological significance of these findings remains to be established, these data suggest the presence of complex orchestration of transcriptional and translational reprograming during adaptation to energy stress that is likely to play a major, yet underexplored role in neoplasia.

eIF2 and nutrient sensing

Cells in solid tumors are exposed to limited nutrients (e.g. glucose, amino acids) and in this context eIF2α phosphorylation is thought to act as a pro-survival mechanism [21,22]. eIF2α phosphorylation limits TC recycling and is stimulated via four kinases: GCN2, PERK, PKR, and HRI [2]. GCN2 is a major eIF2α kinase which senses nutritional stress [2]. In yeast, GCN2 is activated by binding directly to uncharged tRNAs via a protein domain related to histidyl-tRNA synthetase, which induces autophosphorylation and derepression of its kinase domain [23]. eIF2α phosphorylation inhibits GEF activity of eIF2B, thereby limiting TC levels [2]. This suppresses global translation while inducing synthesis of proteins encoded by uORF mRNAs, including the transcription factor ATF4 [2]. ATF4 upregulates expression of amino acid transporters and aminoacyl-tRNA synthetases [24]. Prostate cancer cells appear to depend on increased expression of multiple amino acid transporters, including LAT family (L-type amino acid transporters) members which are involved in uptake of amino acids with neutral side chains, including L-leucine [25]. LAT1 is required for growth of androgen-insensitive PC3 cells [26] and ATF4 stimulates its expression. ATF4 also stimulates expression of genes encoding autophagic factors (see below) to increase amino acid availability. Accordingly, ATF4 has been suggested as a potential target in various malignancies [27]. Importantly, a number of studies have suggested a cross-talk between mTOR, eIF2α phosphorylation [28–30] and/or ATF4 [31,32]. This positions eIF2 and ATF4 as central nodes of regulatory networks which orchestrate protein synthesis, autophagy and energy metabolism to maintain energy balance of cancer cells (Figure 1).

Emerging roles of elongation in cancer energetics

Cross-talk between the translation machinery and energetics also occurs at the elongation step, which is the most energy consuming translation phase. Each elongation cycle consumes two GTPs, one during delivery of aminoacyl (aa)-tRNA to the ribosomal A-site by eEF1A, and another during translocation of the ribosome which is mediated by eEF2 [33]. In addition, elongation consumes aa-tRNAs, whereby aminoacylation of tRNAs requires hydrolysis of ATP to AMP, which is equivalent of 2 ATPs [33].

eEF2K, a member of the atypical α-kinase family, phosphorylates eEF2 (T56 in humans) which interferes with its ribosomal association and reduces elongation rates[34]. Under

physiological conditions eEF2K is regulated by insulin and Ca^{2+}. In muscle, reduction in ATP levels releases Ca^{2+}, which stimulates eEF2K association with calmodulin, eEF2K activation and eEF2 phosphorylation [35]. This shuts down protein synthesis, thereby reducing energy consumption and allowing for ATP replenishment.

mTORC1 phosphorylates and inactivates eEF2K (S366 in humans) via S6K, which leads to increased elongation rates [36]. S366 is also phosphorylated by ERK/p90RSK pathway [36]. In addition, mTORC1 has been shown to directly phosphorylate eEF2K (S78 in humans), which interferes with calmodulin binding and also leads to inactivation of eEF2K [36]. AMPK phosphorylates eEF2K (S398 in humans), thereby leading to an overall decrease in protein synthesis [37]. eEF2K activity is also stimulated in hypoxia in an HIF-independent manner that appears to involve reduction in hydroxylation of Pro98 (in humans). Hydroxylation of Pro98 likely compromises calmodulin:eEF2K association[38].

Since mTORC1 and ERK are upregulated in neoplasia, it is plausible that increased protein synthesis rates in cancer are at least in part caused by eEF2K inactivation. Considering that elevated protein synthesis rates parallel autonomous growth observed in neoplasia, it is thus expected that inactivation of eEF2K endows cancer cells with proliferative advantage. Indeed, in a model of APC-loss-driven intestinal carcinogenesis, eEF2K inactivation by the mTORC1/S6K axis reprograms elongation to increase cyclin D3 levels and support aberrant WNT signaling [39]. Ablation of eEF2K alleviated the effects of mTORC1 inactivation on proliferation of enterocytes [39], which suggests that eEF2K exhibits tumor suppressive properties. In contrast, eEF2K is thought to prevent energy crisis and cancer cell death under conditions when energy resources are limiting. For instance, it has been demonstrated that eEF2K may exhibit tumor protective effects in cell culture and xenograft models under the conditions of nutrient starvation [40,41]. This seemingly contradictory role of eEF2K in cancer is reminiscent of AMPK function in tumor initiation and progression. AMPK appears to impede tumor formation, but when the tumors reach the size whereby the nutrients and oxygen become limiting, AMPK takes a cytoprotective role [42]. By analogy, it is plausible that eEF2K is involved in suppressing tumor formation (e.g. in the APC loss-driven colorectal cancer model), while promoting tumor survival via reducing energy consumption by the translational machinery when the tumors reach certain mass and the nutrients become scarce. Since eEF2K is not an essential gene [43], there is a heightened interest to delineate the precise role of eEF2K in neoplasia to facilitate employment of eEF2K inhibitors in the clinic.

Cross-talk between autophagy and protein synthesis

While mTORC1 stimulates protein synthesis, it is a major negative regulator of autophagy (Figure 1). Nutrient deprivation, which causes mTORC1 inhibition, induces autophagy, thereby supplying the free amino acids needed for the synthesis of crucial proteins [4]. Indeed, as shown in yeast, autophagy maintains protein synthesis when amino acids are limiting [44]. ULK1 is a serine/threonine kinase that resides in an initiatory complex baring its name and regulates other autophagy factors such as AMBRA, ATG9, and BECN1, thereby stimulating autophagosome formation [45–47]. mTORC1 inhibits ULK1 function by phosphorylating it at S758 and S638 (in human), whereas phosphorylation by AMPK on

Ser317 and Ser556 (in human) results in ULK1 activation [48,49]. mTORC1 also phosphorylates and inactivates other autophagy proteins including AMBRA and ATG13 [50,51].

Autophagy proteins also feedback to regulate mTORC1, and therefore indirectly affect protein synthesis. For example, the autophagy receptor protein SQSTM1/p62, which brings ubiquitinated substrates to the autophagosome, has been reported to interact with mTOR, raptor and RAG GTPases, and is important for amino acid sensing [52]. Once the autophagosome is formed, it must fuse with lysosomes to degrade its contents which results in release of free amino acids [53]. This implies that autophagy can self-regulate via its later stages through modulation of mTORC1 and stimulation of protein synthesis, once sufficient cytoplasmic contents are recycled.

Changes in eIF levels and/or activity have also been demonstrated to impact on autophagy. For instance, increased eIF4G1 levels are paralleled by translational activation of mRNAs implicated in cell survival that consequently prevent autophagy and apoptosis [54]. Moreover, the eIF2α/ATF4 axis upregulates transcription of many autophagy genes, including p62, ATG16L, LC3B, ATG12, ATG3, and BECN1 [55]. Cross-regulation of mTOR and eIF2α phosphorylation also impacts on autophagy. mTORC1 inhibition results in eIF2α phosphorylation via PP6C phosphatase dependent activation of GCN2. Depletion of PP6C attenuates autophagy in response to mTORC1 inhibition, whereas PP6C mutations present in melanoma increase autophagy [29].

Post-transcriptional regulation of autophagy mRNAs has also been reported. HuD binds to the 3′-UTR of ATG5 mRNA and increases its translation [56]. In Drosophila, deadenylation by Orb-regulated CCR4 represses translation of ATG12 mRNA, which consequently inhibits autophagy [57]. Decapping of autophagy protein-encoding mRNAs was reported to inhibit their synthesis when nutrients are not limiting [58]. Others have however reported the opposite effects of mRNA capping on autophagy rates in other experimental systems [59].

Therefore, autophagy generates amino acids for protein synthesis, which consequently consumes them. Both cellular processes are both controlled by the same signaling hubs (mTORC1, AMPK, and GCN2) to maintain energy balance (Figure 1).

Concluding remarks and future challenges

Recent data indicate that mTOR, AMPK and eIF2α kinases coordinate translation with cellular energetics and autophagy, which allows simultaneous modulation of the proteome and maintenance of energy balance. As understanding of the molecular underpinnings of the crosstalk between translation and energy metabolism is expanding, new regulatory nodes are starting to emerge. For example, eIF6, which binds to 60S ribosome and interferes with subunit joining, stimulates translation of transcriptional factors which increase lipogenesis and glycolysis in a mTOR-independent manner [60]. Similarly, eIF3, a large multiprotein complex that plays a role in recruitment of the mRNA to the ribosome, increases translation of mRNAs encoding mitochondrial components [61]. Changes in mRNA methylation also impact on the translatome [62]. Cancer-specific metabolic perturbations, including increase

in D-2HG in tumors harboring IDH1/2 mutations (e.g. glioma and leukemia) are expected to disrupt mRNA methylation patterns and alter translation by inhibiting mRNA demethylases (e.g. ALKBH5) [63]. Collectively, findings outlined in this review show complex cross-regulation of nutrient sensing, metabolism, translation and autophagy via signaling pathways. Future research is required to dissect the molecular mechanisms which orchestrate these processes in homeostasis and when dysregulated result in cancer.

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Highlights

- Protein synthesis is one of the most energy consuming processes in the cell
- Nutrient availability modulates growth signaling and protein synthesis rates
- Autophagy is a survival mechanism providing metabolic substrates during stress
- Nutrient sensing, protein synthesis and autophagy are coordinated via mTORC1

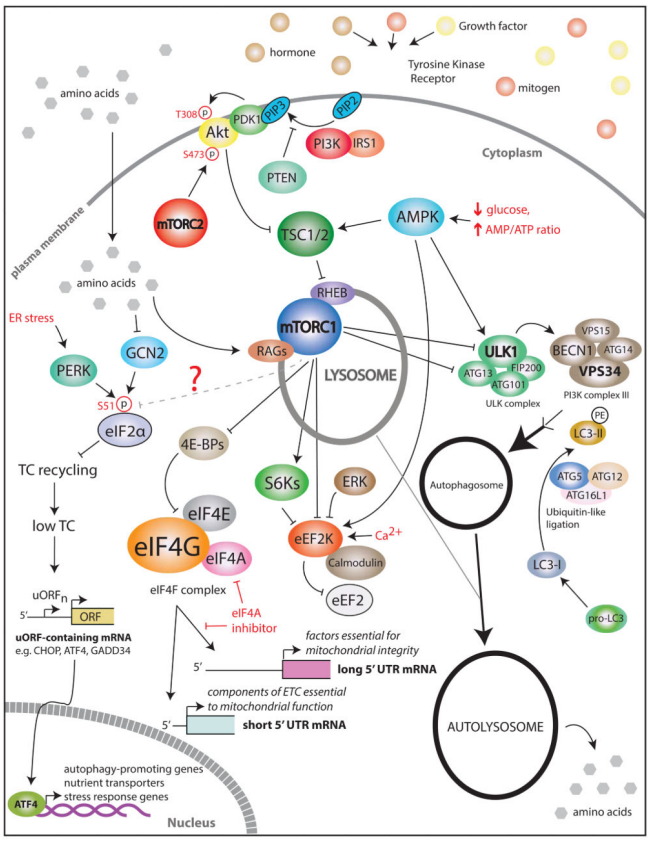

Figure 1. Schematic presentation of the orchestration of protein synthesis, energy metabolism and autophagy

mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) are two functionally and structurally distinct complexes. In response to growth factors (e.g. IGFs) and hormones (e.g. insulin), mTORC1 is activated via the PI3K/AKT/TSC/RHEB pathway, whereas amino acids activate mTORC1 via RAG GTPases (reviewed in [4]). mTORC1 phosphorylates and inactivates translational inhibitor 4E-BPs, which then allows eIF4F complex assembly. Increased levels of eIF4F lead to reprogramming of the translatome which in part leads to selective increase in translation of long 5′UTR mRNAs that encode factors that protect mitochondrial integrity, and short 5′UTR mRNAs which encode components of the electron transport chain (ETC) complex. When energy resources are limiting, AMPK is activated to reduce anabolic processes, while stimulating catabolic ones (reviewed in [5]. This is in part achieved by inhibition of mTORC1. eEF2K phosphorylates eEF2 which interferes with its ribosomal association and reduces elongation rates. This suppresses protein synthesis and reduces energy consumption. mTORC1 and ERK inactivate eEF2K thereby increasing protein synthesis, whereas AMPK activates eEF2K and reduces translation rates. GCN2 and PERK are major eIF2α kinases that sense nutritional (e.g. limited glucose, amino acids etc.) and endoplasmic reticulum (ER) stress, respectively. eIF2α phosphorylation coincides with reduction in ternary complex (TC) levels. This leads to the suppression of global translation while translationally activating some of the upstream open reading frame (uORF) containing mRNAs including CHOP, ATF4, GADD34. ATF4 induces upregulation of amino acid transporters and aminoacyl-tRNA synthetases as well as a number of autophagy protein-

encoding genes, including p62, ATG16L, LC3B, ATG12, ATG3, and BECN1. AMPK is a major positive regulator of the autophagy protein ULK1, while mTORC1 is a major negative regulator of autophagy. The ULK1 complex functions to initiate autophagosome formation along with the PI3K complex. This increased autophagic flux allows for cytoplasmic components to be recycled during acute nutrient starvation to feed back into the synthesis of vital proteins. Collectively, mTOR, AMPK, and eIF2α kinases coordination show multifaceted signaling nodes of nutrient sensing, translation, and autophagy. Of note, this representation of the pathways is simplified to highlight the mechanisms of coordination of mRNA translation, metabolism and autophagy. Detailed representation of mTOR, AMPK pathways and autophagy can be found in [4,5,64].

Table 1

List of Abbreviations

	Definition
4E-BP	Eukaryotic initiation factor 4E-binding protein
AKT	Protein Kinase B
ALKBH5	Alpha-Ketoglutarate-Dependent Dioxygenase AlkB Homolog 5
AMBRA	Activating Molecule In BECN1-Regulated Autophagy Protein 1
AMPK	Adenosine Monophosphate-activated Protein Kinase
APC	Adenomatous polyposis coli
ATF4	Activating Transcription Factor 4
ATG	Autophagy Related
ATG16L1	Autophagy Related 16 Like 1
BCL-2	B-Cell CLL/Lymphoma 2
BECN1	Beclin1
CCR4	C-C motif Chemokine Receptor 4
D-2HG	D-2-hydroxyglutarate
eEF2	Eukaryotic Elongation factor 2
eEF2K	Eukaryotic Elongation factor 2 kinase
eIF	Eukaryotic Initiation Factor
ER	Endoplasmic Reticulum
ERK	Extracellular Signal–regulated kinase
ETC	Electron Transport Chain
GCN2	General Control Nonderepressible 2
GDP	Guanosine diphosphate
GEF	Guanine nucleotide exchange factor
HIF	Hypoxia-inducible factor
HRI	Heme-regulated Eukaryotic Initiation Factor 2α kinase
HuD	Hu Antigen D
IDH1/2	Isocitrate Dehydrogenase (NADP+) 1/2
LAT	L-type Amino Acid Transporter
LAT1	L-type Amino Acid Transporter 1
LC3B	Microtubule Associated Protein 1 Light Chain 3 Beta
LKB1/STK11	Serine/Threonine Kinase 11
mRNA	Messenger RNA
mTOR	Mammalian Target of Rapamycin
mTORC1	Mammalian Target of Rapamycin complex 1
mTORC2	Mammalian Target of Rapamycin complex 2
P90RSK	90 KDa Ribosomal Protein S6 Kinase
PABP	Poly-A binding protein
PC-3	Prostate cancer cells

	Definition
PERK	protein kinase R (PKR)-like endoplasmic reticulum kinase
PI3KCA	Phosphatidylinositol 3-kinase
PKR	Protein Kinase R
PP6C	Protein Phosphatase 6 Catalytic Subunit
Pro98	Proline residue 98
PTEN	Phosphatase and Tensin Homolog
RPS10e	Ribosomal protein S10e
RPS3	Ribosomal protein S3
S6K	Ribosomal Protein S6 Kinase
SQSTM1/p62	Sequestome 1/p62
TC	Ternary complex
TFAM	Transcription Factor A, Mitochondrial
TFEB	Transcription Factor EB
TISU	Translation Initiator of Short 5′Untranslated Region
tRNA	Transfer RNA
TSC1/2	Tuberous sclerosis 1/2
ULK1	Unc-51 Like Autophagy Activating Kinase 1
uORF	Upstream Open Reading Frame
UTR	Untranslated region