Biochimica et Biophysica Acta 1849 (2015) 845–860

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagrm

Review

Stress-mediated translational control in cancer cells ☆

Gabriel Leprivier [a,b], Barak Rotblat [c], Debjit Khan [a,b], Eric Jan [d], Poul H. Sorensen [a,b,*]

[a] Department of Molecular Oncology, British Columbia Cancer Research Centre, Vancouver, British Columbia V5Z 1L4, Canada
[b] Department of Pathology, University of British Columbia, Vancouver, British Columbia V6T 2B5, Canada
[c] Department of Life Science, Ben-Gurion University of the Negev, Beer-Sheva 84105, Israel
[d] Department of Biochemistry and Molecular Biology, University of British Columbia, Vancouver, British Columbia V6T1Z3, Canada

ARTICLE INFO

Article history:
Received 22 August 2014
Received in revised form 31 October 2014
Accepted 4 November 2014
Available online 10 November 2014

Keywords:
mRNA translation control
Stress response
Tumor adaptation
eIF2alpha
mTORC1
eEF2K

ABSTRACT

Tumor cells are continually subjected to diverse stress conditions of the tumor microenvironment, including hypoxia, nutrient deprivation, and oxidative or genotoxic stress. Tumor cells must evolve adaptive mechanisms to survive these conditions to ultimately drive tumor progression. Tight control of mRNA translation is critical for this response and the adaptation of tumor cells to such stress forms. This proceeds though a translational reprogramming process which restrains overall translation activity to preserve energy and nutrients, but which also stimulates the selective synthesis of major stress adaptor proteins. Here we present the different regulatory signaling pathways which coordinate mRNA translation in the response to different stress forms, including those regulating eIF2α, mTORC1 and eEF2K, and we explain how tumor cells hijack these pathways for survival under stress. Finally, mechanisms for selective mRNA translation under stress, including the utilization of upstream open reading frames (uORFs) and internal ribosome entry sites (IRESes) are discussed in the context of cell stress. This article is part of a Special Issue entitled: Translation and Cancer.

1. Introduction

Tumors often grow within hostile microenvironments characterized by different stress conditions such as hypoxia and nutrient deprivation (ND) due to defective tumor vasculature, or genotoxic and oxidative stress induced by rapid cell division or therapy [1–4]. Tumor cells must manage these and other stresses, and their ability to respond to each stress form will determine tumor progression and ultimately patient outcome. At the cellular level, the stress response relies on both energy preservation and the generation of an adaptive response, which combine to maintain cell survival. However, the mechanisms of stress adaptation proceed at the expense of tumor proliferation, representing a dilemma for tumor cells during tumor progression.

One major path to adaptively respond to stress is through the tight control of mRNA translation [2,4]. Indeed, mRNA translation is a highly energy-consuming process [5] which is typically inhibited in response to a number of stress forms in most tumor cells [1,2], allowing them to preserve energetic balance. In addition to saving energy, reducing overall mRNA translation prevents the synthesis of proteins that would otherwise interfere with the adaptive stress response [6]. However, the global decrease in translation occurs in conjunction with the selective synthesis of specific proteins which are involved in the adaptive response to stress [1,2]. Reduced mRNA translation activity under stress occurs predominantly at the initiation step [2,7], which is the rate-limiting step of mRNA translation, but in few notable cases it occurs at the elongation step [8–11]. In this review we will discuss how tumor cells control overall protein synthesis in response to various stresses, as compared to normal cells.

1.1. Stress signaling pathways and translational control

There are several highly conserved signaling pathways which control mRNA translation activity to couple overall translation rates to rapid changes in the extracellular milieu, and which tumor cells hijack to adapt to stress. These regulatory pathways orchestrate adaptive responses to stress by restraining overall translation and by stimulating selective synthesis of stress adaptive proteins [1,2]. Historically, most of the current understanding of translational control under cell stress has been from earlier investigations of endoplasmic reticulum (ER) stress and the unfolded protein response (UPR). ER stress is induced by an accumulation of unfolded or misfolded proteins in the ER lumen [12]. This leads to activation of the UPR, which collectively induces three parallel signaling pathways to effectively decrease global mRNA translation, degrade misfolded proteins, and increase synthesis of molecular chaperones and other factors in order to reduce ER stress and regain protein folding homeostasis [12,13]. The UPR induces three main effectors, namely the three ER transmembrane proteins, protein kinase RNA-like endoplasmic reticulum kinase (PERK), activating transcription

☆ This article is part of a Special Issue entitled: Translation and Cancer.

* Corresponding author at: Department of Molecular Oncology, British Columbia Cancer Research Centre, Vancouver, British Columbia V5Z 1L4, Canada. Tel.: +1 604 675 8202; fax: +1 604 675 8218.
E-mail address: psor@mail.ubc.ca (P.H. Sorensen).

http://dx.doi.org/10.1016/j.bbagrm.2014.11.002
1874-9399/

factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1), which collaborate to reprogram gene expression to increase protein quality control capacity through selective synthesis of chaperones, 78 kDa glucose-regulated protein (GRP78)/binding immunoglobulin protein (BiP), X-box binding protein 1 (XBP1), CCAAT-enhancer-binding protein homologous protein (CHOP), ATF4, and other factors, as has been expertly reviewed elsewhere [12,14]. If ER stress is severe and the UPR cannot compensate, this can lead to apoptosis, such as occurs with enhanced protein synthesis rates accompanying rapid proliferative rates, or as a result of high mutational burden in tumor cells. Indeed, ER stress is induced following diverse stress forms [15–17], and is increasingly viewed as a convergent downstream consequence of multiple stress types [18]. Therefore we will not further discuss ER stress in this review, focusing instead on other microenvironmental stress forms that can act upstream to induce ER stress, including hypoxia and nutrient deprivation, as well as oxidative and genotoxic stress.

Common to the regulation of mRNA translation under different stress types, including ER stress, is the translation initiation factor, eukaryotic translation initiation factor 2α (eIF2α). The activity of eIF2α is directly restricted by four stress-sensing kinases, namely PERK, which as mentioned is activated under ER stress as part of the UPR, as well as protein kinase RNA-activated (PKR), general control non-derepressible 2 (Gcn2) and heme-regulated inhibitor (HRI), each of which senses and responds to specific cellular stresses such as ER stress, hypoxia, ND, and oxidative stress [1,15]. Activation of these kinases directly leads to phosphorylation of eIF2α, in turn reducing the ability of this protein to recruit methionyl-initiator tRNA to the 40S ribosomal subunit, thus compromising the assembly of the translation initiation complex [19]. Paradoxically, eIF2α phosphorylation favors the selective translation of subsets of transcripts, depending on the stress type, through alternative translation regulatory mechanisms (see below) [1]. Another common and critical regulator of mRNA translation under stress is mammalian target of rapamycin complex 1 (mTORC1), which stimulates cap-dependent translation initiation by preventing the binding of eIF4E binding protein (4EBP) to the translation initiation factor eIF4E, and by inducing the phosphoprotein 70 ribosomal protein S6 kinase (p70S6K) which controls ribosomal protein S6 activity [20]. The mTORC1 complex is inactivated by nutrient deprivation, hypoxia and oxidative and genotoxic stress through different mechanisms, which restricts global protein synthesis [21]. However, the reduction in cap-dependent translation activity that occurs as a consequence of mTORC1 inhibition promotes cap-independent translation to support selective mRNA translation [22]. Finally, the other major regulator of protein synthesis in response to stress is the eukaryotic elongation factor 2 (eEF2) kinase (eEF2K) which directly controls the activity of the translation elongation factor eEF2 [23–25]. In response to ND, hypoxia and oxidative and genotoxic stress, eEF2K is activated, leading to phosphorylation and inactivation of eEF2, in turn preventing protein synthesis [26]. This pathway allows for the strict regulation of mRNA translation specifically at the elongation step in response to cell stress.

1.2. Selective translation mechanisms under cell stress

Several alternative translation mechanisms have emerged to circumvent the overall translation arrest that occurs under cell stress, in order to support the selective synthesis of stress adaptive proteins [1,2,4,27,28]. This translational reprogramming is exploited by tumor cells to enhance their protection against stress [22,29,30]. One key mRNA which undergoes selective translation is ATF4, a ER stress-induced transcription factor that activates transcription of downstream stress-response genes such as CHOP, components of the endoplasmic-reticulum-associated protein degradation (ERAD) machinery, and molecular chaperones [14,31]. Translational inhibition due to eIF2α phosphorylation leads to selective translation of ATF4, therefore reprogramming gene expression under stress. Analysis of the mechanism led to the identification of upstream open reading frames (uORFs) in the 5′ untranslated region (UTR) of the ATF4 message [27]. It is now estimated that ~50% of mammalian transcripts may possess at least one uORF [32,33]. In general, under homeostatic conditions, uORFs are inhibitory by preventing the scanning ribosomes from translating the main ORFs [34,35]. However, under stress conditions, for some uORF-containing mRNAs, ribosomes can bypass the uORFs via a reinitiation mechanism to allow translation of the main ORF [34–36]. Mechanistically, stress-mediated phosphorylation of eIF2α lowers the pool of functional eIF2, thereby allowing time for reinitiating ribosomes to assemble a translation initiation complex after scanning past the uORFs [34,35]. As a consequence, increased numbers of ribosomes are available to initiate translation from downstream main ORFs.

Other uORF-containing mRNAs are also selectively translated under stress, such as GADD34, CHOP and ATF5 [34,37,38]. For some mRNAs, translation proceeds via a re-initiation mechanism such as for ATF4, which is regulated by two uORFs in its 5′UTR. However, other mRNAs such as GADD34 are regulated by a single uORF, thus precluding the use of a re-initiation mechanism [37]. How can scanning ribosomes bypass a regulatory uORF within a 5′UTR? It has been proposed that the single uORF within the 5′UTR may use a leaky scanning whereby scanning ribosomes may under certain conditions circumvent the AUG start codon of the uORF and proceed to initiate translation at the main ORF [14]. Alternatively, a recent paper revealed that density regulated protein (DENR) and multiple copies in T-cell lymphoma-1 (MCT-1) factors can promote re-initiation of uORFs, thus providing another mechanism of uORF ribosome bypass [39]. Moreover, it was shown that DENR and MCT-1 factors are required for proliferation and control translation of a subset of uORF-containing mRNAs [39]. It remains to be seen whether DENR and MCT-1 proteins have a wider role in the translation of other uORF-containing mRNAs during cellular stress. In contrast, some uORFs are selectively translated under specific conditions such as genotoxic and oxidative stress, although the mechanisms remain unknown [8,40].

Another key mechanism of alternative translation in response to stress is through cap-independent translation using an internal ribosome-entry site (IRES). Such elements are present in the 5′UTRs of specific transcripts such as cellular inhibitor of apoptosis protein-1 (cIAP1), X-linked inhibitor of apoptosis protein (XIAP), and p53. These elements allow direct recruitment of ribosome subunits without requiring the presence of certain cap-dependent initiation factors such as eIF4E [1,6,41]. Even though some authors support that 3-5% of all cellular mRNAs may contain IRES elements [42], their ability to support efficient translation in eukaryotes is still a matter of debate [43–45]. Under stress conditions when cap-dependent translation is blocked (due to mTORC1 inhibition), cap-independent translation may become prevalent [2,22]. Together, such mechanisms allow tumor cells to synthesize proteins required for stress adaptation, even though overall translation is attenuated [46–48]. In this review, we will focus on translational control that occurs under stress forms induced within the tumor microenvironment, namely hypoxia, nutrient deprivation, and oxidative and genotoxic stress. For these stress forms, each of which can induce ER stress, we will describe their impact on overall translation activity as well as the signaling pathways which link stress sensing to the control of mRNA translation. Finally, the selective translation mechanisms employed under each of stress type will be presented.

2. Control of translation under hypoxia

The translational response to prototypical stress forms is exemplified by growth of cells under reduced oxygen tension, or hypoxia, and so we will first discuss the effects of hypoxia on tumor cell mRNA translation.

2.1. Tumor hypoxia

Hypoxia is a common feature of the tumor microenvironment and one which tumors must manage in order to progress. At early stages

of cancer, when tumors are avascular, hypoxia occurs as a consequence of limitations in oxygen diffusion within the tumor milieu [3,49]. At later stages, tumors remain intermittently under hypoxia as the developing tumor vasculature is highly abnormal and leaky [3,49]. As a result, areas of extreme hypoxia (less than 0.02% O_2) to moderate hypoxia (0.5–1% O_2) are typically found within the same tumor tissues [50]. Hypoxia exerts a selective pressure on tumor cells to favor the emergence of hypoxia-resistant tumor cells. These latter cells are defective in apoptosis, and concomitantly acquire resistance to chemo- and radio-therapy [51,52]. In addition, the level of hypoxia in tumors is associated with poor prognosis [50], together supporting the notion that hypoxia contributes to tumor aggressiveness. A well-described adaptive response of tumor cells to hypoxia is the induction of hypoxia-inducible factor 1α (HIF1α), whose levels are upregulated in most tumors as compared to normal tissues [53,54]. This transcription factor induces metabolic reprogramming for supporting survival under hypoxia, as well as stimulating neoangiogenesis and tumor invasion [55]. As will now be discussed, another major component of the adaptive response of the tumor cell to hypoxia is through the control of mRNA translation.

2.2. Effects of hypoxia on overall translation rates

Hypoxia exerts significant effects on the control of mRNA translation by affecting rates of overall translation. Given that hypoxia lowers ATP production [56] and that mRNA translation is a highly energy-consuming process [5], its rate needs to be properly reduced to preserve energy under conditions of low oxygen levels [57]. Such a response is critical to promote survival of both tumor and normal cells subjected to prolonged hypoxia [58,59]. When considering how hypoxia might impact overall translation rates, it is important to distinguish the effects of moderate (0.5%–1% O_2) from those of severe hypoxia (≤0.02% O_2). Indeed, severe hypoxia induces a rapid inhibition of overall translation (i.e. 1–4 h) in both tumor and normal cells [60–63]. Specifically, a 40–60% reduction in protein synthesis rates is observed as little as 1 h following severe hypoxic treatment. In contrast, under moderate hypoxia, the translation rate is only affected after prolonged treatment (i.e. 20–24 h) [61]. In addition, while normal cells exhibit translation arrest upon moderate hypoxia, tumor cells show a wide array of responses. Indeed, few tumor cells are refractory to the translation block induced under these conditions [64], whereas in most tumor cells examined the translation rate is inhibited (by 40% to 80%) by moderate hypoxia [64–66]. As discussed above, overall translation is primarily blocked at the initiation step under hypoxia, as assessed by polysome profiling and the inhibition of the eIF2α translation initiation factor (see Section 2.3) [60,62,67]. Translation elongation may also be inhibited in addition to initiation, based on the moderate retention of polysomes in tumor cells in response to hypoxia [60,62,67] and on the inhibition of the main translation elongation factor, eEF2, under these conditions (see Section 2.3).

2.3. Signaling pathways impacting mRNA translation and cell survival under hypoxia

Specific signaling pathways induced by hypoxia, following distinct kinetics, contribute to block mRNA translation both at the initiation and elongation steps, to promote cell survival and to support tumor growth under hypoxia. Here, we will discuss more specifically these signaling pathways in the context of tumor cells.

2.3.1. PERK–eIF2α

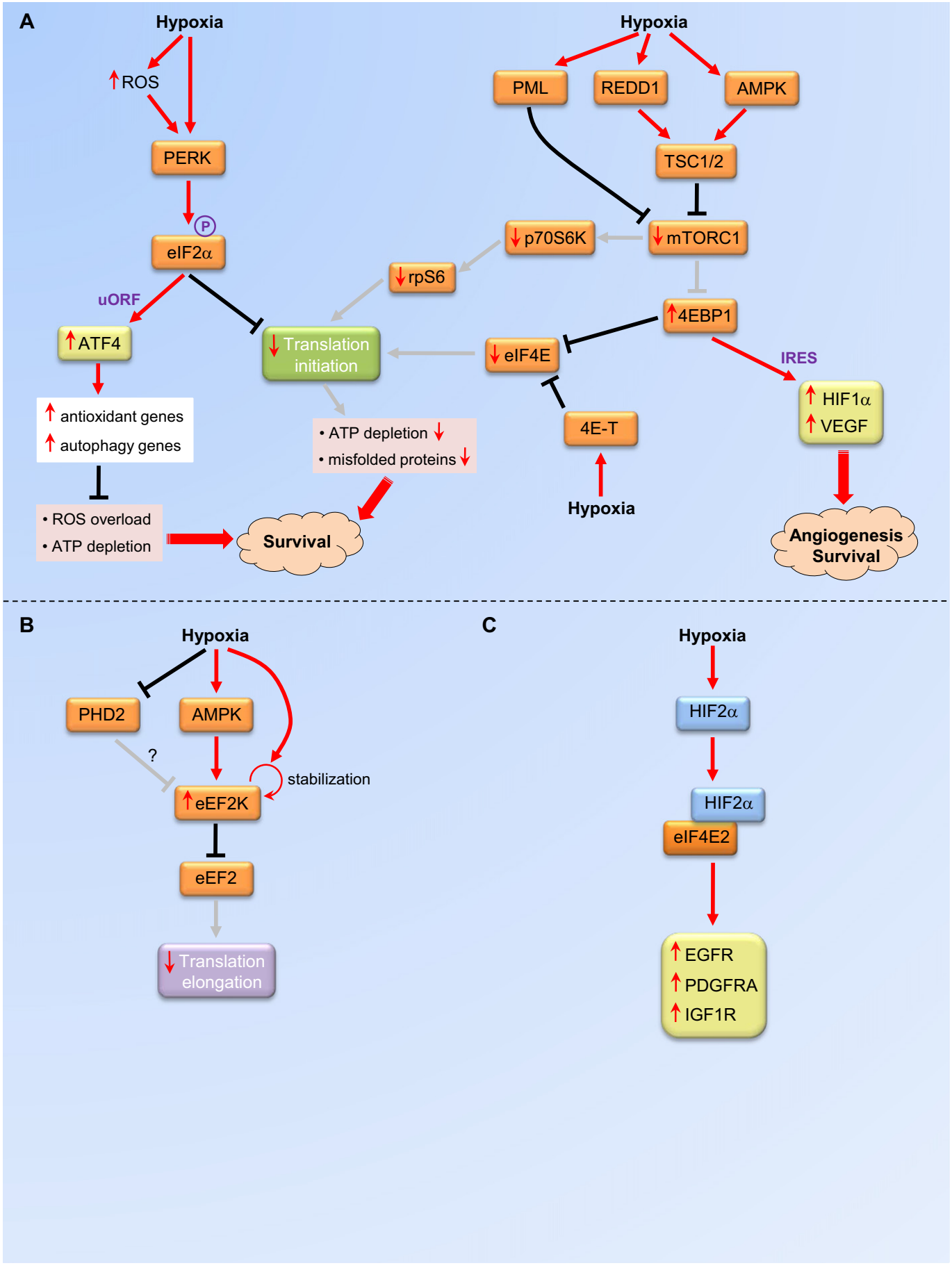
During the early phase of the hypoxic response, eIF2α rapidly becomes phosphorylated in tumor cells, leading to a block of translation initiation. Under severe hypoxia, eIF2α phosphorylation occurs extremely rapidly (in less than 1 h) [60,63,67], while under moderate hypoxia this occurs at later time points (by 6 h) [63,65]. Inhibition of eIF2α activity through its phosphorylation by PERK is a critical step leading to mRNA translation arrest in response to severe hypoxia [29,60,61,63,68]. The PERK–eIF2α pathway is thought to be induced by reactive oxygen species (ROS) under hypoxia [68], and independently of HIF1α [63]. Indeed, moderate hypoxia leads to increased intracellular ROS [69,70], and antioxidant treatment prevents eIF2α phosphorylation under these conditions [68] (Fig. 1A). How ROS specifically induces PERK remains unknown, although induction of increased misfolded protein load and UPR activation is a possibility.

Induction of the PERK–eIF2α axis is exploited by tumors to favor cell survival and tumor growth under hypoxia. Thus, blocking either PERK or eIF2α phosphorylation prevents survival of K-Ras^{V12}-transformed mouse embryonic fibroblasts (MEFs) and U373 glioblastoma cells under both moderate and severe hypoxia [29,30], and inhibition of this axis significantly reduces growth of tumor xenografts in mice [29,46]. The latter is associated with higher rates of cell death in hypoxic regions of tumors [29,30], supporting the notion that the PERK–eIF2α axis supports tumor resistance to hypoxic conditions in vivo. In keeping with this, eIF2α phosphorylation was found to be higher in breast, lung and liver tumor samples as compared to corresponding normal tissues [71]. The basis for PERK–eIF2α-mediated protection under hypoxia may rely on the ability of eIF2α phosphorylation to inhibit overall mRNA translation, thus preserving ATP levels and reducing accumulation of misfolded proteins and preventing ROS overload, as well as by promoting selective translation of adaptive stress response transcripts (see Section 2.4) (Fig. 1A).

2.3.2. mTORC1

Another mechanism to block translation in tumor cells under hypoxia is through mTORC1 inhibition [72,73]. During prolonged hypoxia (i.e. 4–16 h), mTORC1 becomes inactivated in response to severe hypoxia [60,74]. MTORC1 inhibition leads to a mRNA translation blockade at the initiation step [47,68,74]. Different mechanisms account for hypoxia-mediated inhibition of mTORC1 activity. Tuberous sclerosis 1 and 2 (TSC1/TSC2), which are negative regulators of mTORC1 (for review [75]), are required for this process, as both are necessary to block p70S6K and 4EBP1 phosphorylation under hypoxia [60,68,73]. The TSC1/TSC2 complex is controlled by regulated in development and DNA damage response 1 (REDD1), which is required for mTORC1 inhibition under hypoxia [73], and whose gene transcription is upregulated by HIF1α in response to hypoxia [73,76] (Fig. 1A). More specifically, REDD1 activates TSC2 by sequestration of 14-3-3 proteins, leading to stabilization of the TSC2 protein [77]. In addition, the energy sensor AMP-activated protein kinase (AMPK) is activated by hypoxia where it restrains mTORC1 activity in both pre-tumorigenic and tumor cells [68,78]. AMPK blocks mTORC1 activity by activating TSC2 [79], on one hand, and also by inhibiting the mTORC1 subunit Raptor [80] (Fig. 1A). In contrast, hypoxia-induced mTORC1 inhibition is independent of AMPK in normal cells [73]. The basis for this difference remains unexplained and warrants further investigation. Another mechanism, independent of TSC2 and REDD1 or AMPK, has been proposed in which mTORC1 blockade under hypoxia occurs through promyelocytic leukemia (PML). More specifically, PML interacts with mTOR under hypoxia, leading to accumulation of the latter in the nucleus, therefore preventing its activity in the cytoplasm [81] (Fig. 1A). Finally, it was shown that prior to mTORC1 inhibition, eIF4E activity is blocked under severe hypoxia through a 4EBP1-independent mechanism [60]. Under these conditions, eIF4E is predominantly localized to the nucleus, preventing its association with the cytoplasmic translation machinery, potentially due to the action of its transporter 4E-T [60] (Fig. 1A). Thus, multiple mechanisms converge to block translation initiation under hypoxia in tumor cells.

The control of mTORC1 activity under hypoxia influences the survival response but with different outcomes in normal versus tumor cells. Whereas mTORC1 inhibition reduces survival of normal cells under hypoxia [74], it supports the emergence of tumor cells that are resistant to hypoxia. For example, REDD1 overexpression (to force mTORC1


A
Hypoxia
ROS
PERK
P
eIF2α
uORF
ATF4
antioxidant genes
autophagy genes
• ROS overload
• ATP depletion
Translation initiation
• ATP depletion
• misfolded proteins
Survival
Hypoxia
PML
REDD1
AMPK
TSC1/2
p70S6K
mTORC1
rpS6
4EBP1
eIF4E
4E-T
Hypoxia
IRES
HIF1α
VEGF
Angiogenesis
Survival
B
Hypoxia
PHD2
AMPK
?
stabilization
eEF2K
eEF2
Translation elongation
C
Hypoxia
HIF2α
HIF2α
eIF4E2
EGFR
PDGFRA
IGF1R

inhibition) enhances tumor cell protection under hypoxia [76]. Conversely, failure to inhibit mTORC1, such as after TSC2 knockdown or p70S6K overexpression, increases sensitivity of various tumor cells to hypoxia [82,83]. Furthermore, this phenotype is dependent on translational arrest downstream of mTORC1 inhibition, given that p70S6K overexpression or 4EBP1 knockdown (both of which uncouple mTORC1 inhibition from attenuating translation) decreases resistance of tumor cells to hypoxia [58,82]. Moreover, mTORC1 activity is poorly detected in hypoxic regions of tumors in vivo, in contrast to normoxic regions of tumor xenografts and human tumors [74,78]. As with the PERK–eIF2α pathway, the protective effect of mTORC1 inhibition in tumor cells under hypoxia appears to maintain ATP levels [82] as well as redox balance [76,83] (Fig. 1A), although the exact advantages to the hypoxic tumor cell remain to be determined. Moreover, under moderate hypoxia, while most cells exhibit mTORC1 inhibition [72,73], some tumor cells are refractory to this blockade [64,78], due to mutations in negative regulators of mTORC1 such as phosphatase and tensin homolog (PTEN) or TSC1, leading to sustained mTORC1 activity under hypoxia [64,74]. How this contributes to tumor selection for aggressive phenotypes remains unknown, and warrants further investigation to determine whether mTORC1 should be targeted in such refractory tumor cells.

2.3.3. eEF2K–eEF2

In addition to the PERK–eIF2α and mTORC1 pathways, which regulate translation initiation, eEF2, the major regulator of mRNA translation elongation, is also strongly affected by hypoxia. In most cells, severe and moderate hypoxia lead to very rapid phosphorylation of eEF2 (within ~15 min) [64,84–86]. Phosphorylation of eEF2, which leads to its inactivation, contributes to hypoxia-induced translation shut down by restraining the elongation step of translation [64]. A number of mechanisms have been reported to account for the inactivation of eEF2 in response to hypoxia (Fig. 1B). One mechanism relies on the stabilization of its kinase, eEF2K, upon hypoxia, through inhibition of eEF2K degradation [64]. In addition, AMPK, which phosphorylates eEF2K at residue Ser-398 to activate it [87], as discussed in Section 3.2, contributes to increased eEF2K activity and eEF2 phosphorylation in response to prolonged hypoxia [68]. Moreover, under acute hypoxia, eEF2 phosphorylation is induced independently of AMPK by prolyl hydroxylases (PHD), which are O_2 sensors that get inactivated under hypoxia [88]. Indeed, forced expression of PHD2 attenuates eEF2 phosphorylation under acute hypoxia through an unknown mechanism [86]. The fine control of eEF2 activity under hypoxia may be important for tumor cell survival, as it was shown that targeted inhibition of eEF2 in normal tissues provides protection against hypoxia in vivo [59]. How this facilitates cell survival is unknown, and remains to be demonstrated in tumor cells.

2.4. Selective mRNA translation under hypoxia

Another observed phenomenon under hypoxia is that of selective mRNA translation. As discussed above, whereas most transcripts are poorly translated under hypoxia, specific transcripts can escape translational repression. The use of polysomal fractionation combined with microarrays technology allowed to identify few dozen transcripts whose translation is upregulated in tumor cells in response to hypoxia [62,65,67]. Several mechanisms facilitating selective translation have been defined for a limited number of transcripts.

2.4.1. eIF4E2 and eIF4E1

While mTORC1 is predominantly inhibited under hypoxia in most tumor cells, limited protein synthesis remains under these conditions. One mechanism results from increased activity of eIF4E2, a paralog of eIF4E, which supports selective cap-dependent translation initiation under moderate hypoxia [66]. Under these conditions, HIF2α is induced and binds to a specific element in the 3′UTR of some transcripts and thus recruits eIF4E2 to allow selective translation initiation of those transcripts (Fig. 1C). Transcripts activated through this mechanism include epidermal growth factor receptor (*EGFR*), platelet-derived growth factor receptor alpha (*PDGFRA*) and insulin-like growth factor 1 receptor (*IGF1R*); therefore this mechanism of selective translation may be important for supporting proliferation under hypoxia [66]. However, in tumor cells in which mTORC1 is not blocked under hypoxia (see above; [64]), another mechanism for selective translation has been proposed. In such cells, eIF4E1 is still active under hypoxia and its expression is maintained by HIF1α which controls *eIF4E1* transcription [89]. In this context, eIF4E1 may potentially promote translation of specific transcripts such as *c-Myc*, *cyclin D1* and *eIF4G1* under hypoxia, which can be critical for driving proliferation under hypoxia [89].

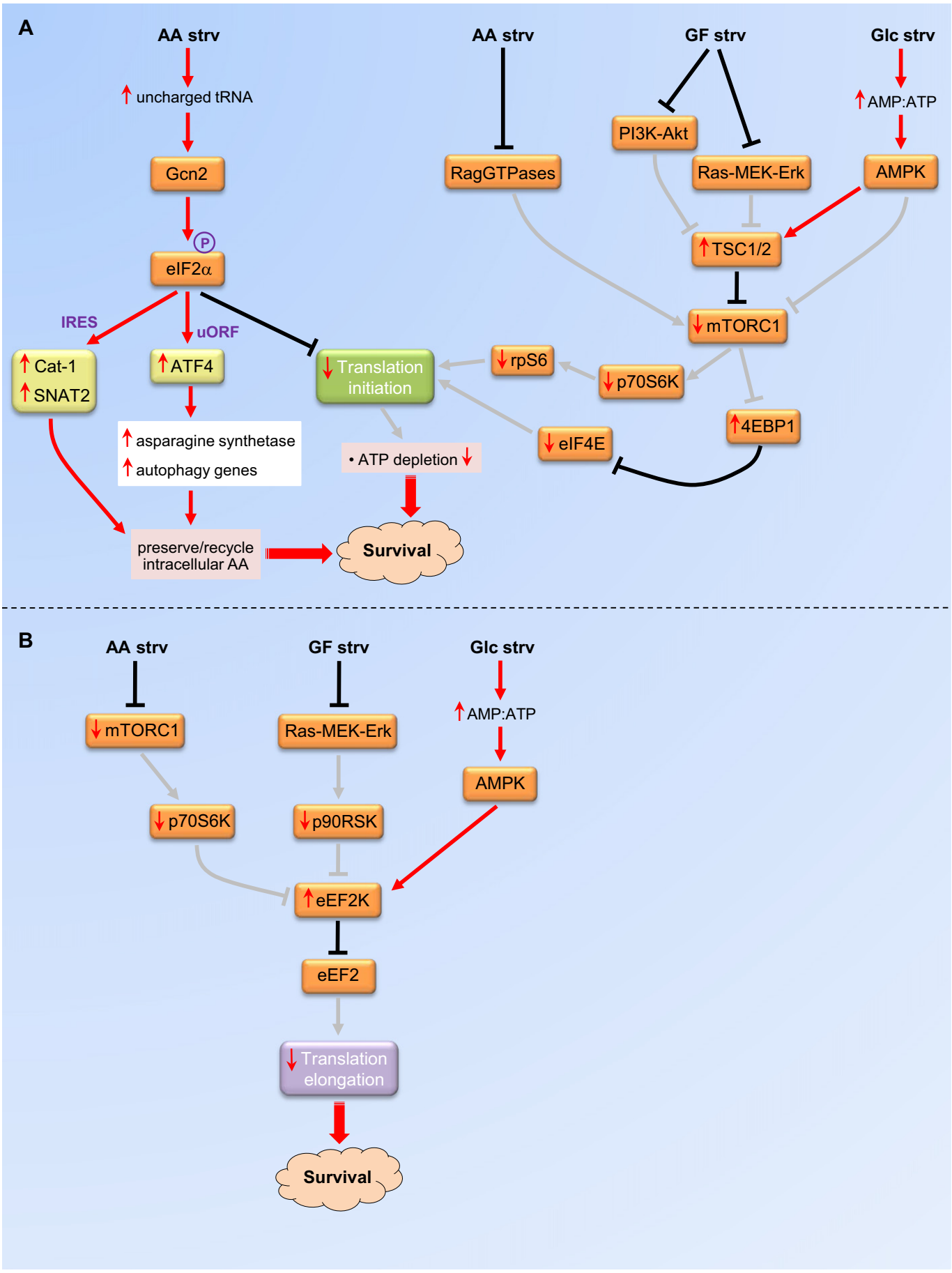
2.4.2. uORFs

Another important mechanism for selective mRNA translation under hypoxia is through the deployment of uORFs as an alternative translation initiation mechanism. Under hypoxia, uORF-mediated translation is enhanced due to an increase in eIF2α phosphorylation by PERK [90]. Transcripts possessing uORF in their 5′UTRs, such as ATF4, CHOP and GADD34 components of the UPR and ER stress response [27,37], are translationally induced under hypoxia in both tumor and normal cells, which is dependent on eIF2α phosphorylation [36,60,62,91]. More specifically, ATF4, which is a transcription factor acting as a major downstream mediator of the PERK–eIF2α axis (for review [31]), is critical for supporting cell survival under hypoxia and for promoting tumor growth. Indeed, targeted inhibition of ATF4 severely compromises survival of both tumor and normal cells under hypoxia [29,71,92], and prevents growth of tumor xenografts [93]. The ability of ATF4 to favor survival under hypoxia relies on its direct control of genes involved in autophagy, such as microtubule-associated protein 1 light chain 3 beta (*LC3B*) and unc-51 like autophagy activating kinase 1 (*ULK1*), and potentially of genes involved in anti-oxidative stress response (see below), including *cystathionase* [30,92,94,95]. Such transcriptional regulation contributes to preserve ATP levels and anti-oxidant capacity under hypoxia [30,92] (Fig. 1A). In vivo, ATF4 upregulation was detected in hypoxic regions of tumor xenografts, which was not observed when eIF2α phosphorylation was prevented [29]. In addition, ATF4 was found to be overexpressed in various tumor types (breast, brain, cervix and skin) compared to the respective normal tissues [29,91].

2.4.3. IRESes

The presence of potential IRES elements in the 5′UTRs of specific transcripts allows cells to circumvent the blocking of cap-dependent translation induced by hypoxia. Indeed, cap-independent (IRES-mediated) translation is increased by hypoxia in tumor cells, paralleling the inhibition of cap-dependent translation due to mTORC1 inactivation [47]. More specifically, hypoxia induces translation of major hypoxia adaptive factors such as HIF1α, vascular endothelial growth factor (VEGF),

Fig. 1. Translational control under hypoxia. A, eIF2α and mTORC1 pathways respond to hypoxia to regulate mRNA translation. On one hand, hypoxia induces PERK to mediate eIF2α phosphorylation (i.e. inhibition), shutting down overall translation (at the initiation step) to prevent ATP depletion and accumulation of misfolded proteins. In addition, eIF2α phosphorylation stimulates ATF4 synthesis through a uORF-based mechanism, supporting transcription of antioxidant and autophagy genes to prevent ROS overload and ATP depletion. Altogether, this promotes cell survival in response to hypoxia. On the other hand, hypoxia inhibits mTORC1 activity through induction of AMPK, REDD1 or PML. Consequently, overall translation (at the initiation step) is attenuated, which favors cell survival by preventing ATP depletion and accumulation of misfolded proteins. However, activation of 4EBP1 due to mTORC1 inhibition leads to increased IRES-mediated translation of HIF1α and VEGF under hypoxia, which stimulates angiogenesis and cell survival. B, the eEF2K pathway responds to hypoxia to control mRNA translation elongation. Hypoxia induces eEF2K activation, either through inhibition of prolyl hydroxylase 2 (PHD2), by induction of AMPK, or by stabilizing eEF2K. This leads to phosphorylation and inhibition of eEF2 and thus restrains translation elongation. C, eIF4E2 mediates selective translation under hypoxia. HIF2α is induced by hypoxia and recruits eIF4E2 to specific elements present in the 3′UTR of a subset of transcripts. This allows for the selective synthesis of proteins such as EGFR, PDGFRA and IGF1R, which support cell growth under hypoxia. Gray arrows and bars indicate release from regulatory effects of upstream pathways.


A
AA strv
uncharged tRNA
Gcn2
P
eIF2α
IRES
uORF
Cat-1
SNAT2
ATF4
asparagine synthetase
autophagy genes
preserve/recycle intracellular AA
Translation initiation
• ATP depletion
Survival
AA strv
RagGTPases
GF strv
PI3K-Akt
Ras-MEK-Erk
Glc strv
AMP:ATP
AMPK
TSC1/2
mTORC1
rpS6
p70S6K
4EBP1
eIF4E
B
AA strv
mTORC1
p70S6K
GF strv
Ras-MEK-Erk
p90RSK
Glc strv
AMP:ATP
AMPK
eEF2K
eEF2
Translation elongation
Survival

and VEGF & type I collagen inducible protein (VCIP) through IRESes [46,47]. Moreover, it was proposed that 4EBP activation in response to hypoxia and mTORC1 inhibition dictates a switch from cap-dependent to cap-independent translation to support tumor growth and angiogenesis [47] (Fig. 1A). Indeed, 4EBP overexpression increases growth of breast tumor xenografts in correlation with higher blood vessel density and enhanced VEGF IRES activity [47]. Of relevance, 4EBP expression was found to be upregulated in advanced breast tumors compared to normal tissues [47]. In addition, the IRES-mediated translation of VCIP, an integrin binding protein involved in angiogenesis, is dependent on PERK expression, and PERK-deficient tumors exhibit reduced functional vessel formation [46]. However, others studies assessing IRES activities of HIF1α and VEGF using various assays showed only very low translation activity from these elements, suggesting that cryptic promoter activity in constructs used for those studies may interfere [96,97]. Of note, Young et al. confirmed that VEGF transcripts are selectively translated under hypoxia, even without significant IRES-mediated translation, suggesting that selective translation mechanisms other than IRES sustain VEGF synthesis under hypoxia. The debate regarding the existence and efficiency of cellular IRESes is not restricted to the VEGF IRES, and has been reviewed elsewhere [43–45].

3. Control of translation under nutrient deprivation

In addition to hypoxia, tumor cells are also often subjected to ND, both at early stages of tumor development before the formation of new blood vessels and at later stages due to the defective nature of the tumor vasculature [3]. In addition, the high requirement of tumor cells for specific nutrients such as glucose and glutamine [98,99] further increases the state of nutritional depletion within the tumor microenvironment. Metabolic measurements in vivo have shown that a number of tumor tissues exhibit a severe reduction in glucose levels compared to normal tissues [100,101]. ND acts primarily as a barrier against tumor development, by inducing cell cycle arrest and necrosis [102]. Indeed, oncogenic activating mutations dramatically sensitize cells to ND, while stimulating proliferation and protein synthesis [98,103,104]. This is in part due to the inability of oncogene-transformed cells to both restrain energy-consuming (anabolic) processes (including protein synthesis) and activate energy-generating (catabolic) processes in nutrient-poor environments [98,103,104]. However, tumor cells have evolved mechanisms to circumvent oncogene-induced hypersensitivity to ND and to adapt to such stress conditions [71,105–107]. These mechanisms are critical for tumor expansion, and therefore represent potential therapeutic targets. At the cellular level, the response to ND proceeds through a coordinated reprogramming of cellular metabolism governed by the action of specific nutrient-sensing signaling pathways [108]. This response includes the tight control of mRNA translation through regulation of overall translation rates as well as through selective mRNA translation [4].

3.1. Overall translation rates under ND

Proper control of overall translation activity is essential for the survival response to ND. Indeed, failure to inhibit overall mRNA translation under ND leads to cell death [103,105]. Restricting global protein synthesis when nutrients are scarce is critical to preserve the energetic balance, as protein synthesis is a highly energy-consuming process [5], as well as to prevent synthesis of unwanted proteins interfering with the adaptive response [104]. The combined deprivation of growth factors, glucose and amino acids leads to a severe and rapid block in overall translation, indeed by more than 70% as compared to control conditions, in both tumor and normal cells [104]. Similarly, withdrawal of glucose or amino acids alone attenuates overall translation but with slower kinetics than when both nutrient types are depleted. Glucose starvation reduces global protein synthesis by up to 50% in both normal and tumor cells [84,109,110]. On the other hand, amino acid deprivation leads to a similar decrease of protein synthesis rate as observed in tumor cells [110–112]. As discussed in the next section, translation arrest under ND is mediated at the initiation step by mTORC1 inhibition [105,110]. However, translation elongation is also inhibited by nutrient withdrawal through specific negative regulation of the eEF2 translation elongation factor [105,113–115]. While a block at the elongation step does not further reduce overall protein synthesis under ND, as initiation is already inhibited, it is required to preserve cell survival under these conditions [105], highlighting the complexity of regulating mRNA translation in the survival response to ND, as will now be discussed.

3.2. Signaling pathways impacting mRNA translation under ND

Few key nutrient sensing pathways are responsible for coordinating the rate of protein synthesis under nutrient availability. Strict regulation of these pathways is critical for promoting cell survival under nutrient deprived conditions. Tumor cells exploit these nutrient sensing pathways for adapting to nutritional stress.

3.2.1. Gcn2–eIF2α

The activity of the translation initiation factor eIF2α is tightly controlled by nutrient levels, especially of amino acids. Indeed, eIF2α is rapidly phosphorylated in response to amino acid starvation in tumor cells (~1 h) [111,116,117], exhibiting even a faster response in normal cells (i.e. starting at 15 min) [27]. Reports also describe the induction of eIF2α phosphorylation in response to glucose starvation at later time points (i.e. 10–24 h) in both tumor and normal cells [71,109], most likely due to indirect effects (see below). Inhibition of eIF2α in response to amino acids or glucose starvation contributes to reduced global protein synthesis induced under these conditions, given that eIF2α activity is absolutely required for assembly of the translation initiation complex [19].

Phosphorylation of eIF2α in response to amino acid depletion occurs through the Gcn2 kinase in both tumor and normal cells [27,71,116,118]. Gcn2 becomes phosphorylated and directly activated by accumulation of uncharged tRNAs following amino acid starvation [119] (Fig. 2A). In response to glucose starvation, both Gcn2 and PERK mediate eIF2α phosphorylation, at least in normal cells [71]. However, the effect of glucose deprivation is indirect as in these conditions Gcn2 is induced by an indirect reduction in specific amino acids, and PERK is activated by accumulation of misfolded proteins (ER stress) [71]. The Gcn2–eIF2α axis exerts a protective effect against amino acid depletion in tumor cells, given that targeted disruption of *Gcn2* or inhibition of eIF2α phosphorylation severely compromises cell survival when

Fig. 2. Translational control under nutrient deprivation. A, eIF2α and mTORC1 pathways respond to nutrient deprivation to regulate mRNA translation. On one hand, amino acid starvation (AA strv) induces Gcn2 which mediates eIF2α phosphorylation (i.e. inhibition), shutting down overall translation at the initiation step to prevent ATP depletion. In addition, eIF2α phosphorylation leads to the selective synthesis of the amino acid transporters Cat-1 and SNAT2 (via IRESes), and of ATF4 (through a uORF-based mechanism) which drives transcription of asparagine synthetase and of autophagy genes. This preserves and recycles amino acids. Together with the reduction in overall translation, this promotes cell survival in response to amino acid starvation. On the other hand, mTORC1 activity is inhibited by nutrient deprivation through distinct regulatory pathways: i) amino acid starvation (AA strv) prevents RagGTPase activation which is normally required for mTORC1 activity; ii) growth factor starvation (GF strv) blocks PI3K–Akt and Ras–MEK–Erk pathways activation therefore releasing TSC1/2 inhibition; iii) glucose starvation (Glc strv) activates AMPK which stimulates TSC1/2 as well as inhibiting mTORC1 more directly. As a consequence of mTORC1 inhibition, overall translation (at the initiation step) is restricted, which favors cell survival by preventing ATP depletion under nutrient deprivation. B, the eEF2K pathway responds to nutrient deprivation to control mRNA translation elongation. EEF2K is activated by nutrient deprivation through distinct regulatory pathways: i) amino acid starvation (AA strv) inhibits mTORC1 activity, thus releasing p70S6K-mediated inhibition of eEF2K; ii) growth factors starvation (GF strv) blocks the Ras–MEK–Erk pathway, releasing p90RSK-mediated blockage of eEF2K; iii) glucose starvation (Glc strv) activates AMPK due to increases in the intracellular AMP:ATP ratio. This leads to phosphorylation and inhibition of eEF2, thus restraining translation elongation to promote cell survival under nutrient deprivation. Gray arrows and bars indicate release from regulatory effects of upstream pathways.

amino acids are depleted [71]. This has relevance for tumor survival and development in vivo, as targeted inhibition of *Gcn2* prevents growth of tumor xenografts in immunocompromised mice, which is associated with reduced blood vessels and lower VEGF levels within tumor tissues [71,120]. Expression of Gcn2 is specifically upregulated in a number of human tumor types compared to corresponding normal tissues [71,120]. In addition, high phosphorylated levels of Gcn2 were detected in colon and breast tumor tissues in contrast to corresponding normal tissues [71]. Altogether, these suggest a model whereby tumor cells exploit the Gcn2–eIF2α axis to adapt to nutrient deprived conditions in order to support tumor progression. This function likely relies on the ability of the Gcn2–eIF2α axis to block global protein synthesis to preserve energy and to stimulate selective translation of mediators of the nutrient stress response such as ATF4 (see Section 3.3).

3.2.2. mTORC1

The mTORC1 complex is a central hub for integrating the levels of available nutrients to the control of protein synthesis. The activity of mTORC1 is distinctly regulated by growth factors, glucose, and amino acid levels through different upstream regulatory mechanisms [20] (Fig. 2A). Growth factors lead to mTORC1 activation by induction of the PI3K–Akt and Ras–MEK–Erk pathways which both inactivate TSC1 and TSC2 (for review [21]). Given that activating mutations found in a number of tumors (such as in *RAS* or *PTEN*) support constitutive activation of these signaling pathways, mTORC1 activity may be maintained in the absence of growth factors in tumors. Under glucose-deprived conditions, ATP levels are depleted leading to mTORC1 inhibition in both tumor and normal cells [79,105,121]. This is mediated by AMPK, which is directly activated by increases in the ratios of AMP:ATP and ADP:ATP (for review [122]). In response to reduced glucose levels, AMPK blocks mTORC1 activity by activating TSC2 [79] and by inhibiting Raptor [80] (Fig. 2A). Amino acid levels are other key regulators of mTORC1 activity (for review [123]). Amino acids stimulate Rag GTPases activation through complex regulatory mechanisms, which in turn recruit mTORC1 to the lysosomal surface where it interacts with its activator, Rheb [124,125]. Consequently, withdrawal of amino acids leads to rapid mTORC1 inhibition, as observed in both tumor and normal cells [125–130].

Reduced mTORC1 activity following ND directly contributes to the mRNA translation block observed under these conditions, and is critical for cell survival under ND. Cells with overactive mTORC1 (such as *TSC2* −/− MEFs) fail to restrict overall translation under glucose starvation, which leads to an ATP crisis and ultimately to cell death [103,131,132]. Strikingly, chemical inhibition of global protein synthesis in *TSC2* −/− cells reduces glucose starvation-induced cell death by preserving the ATP balance [103,132] (Fig. 2A). In addition, failure to restrict mTORC1 activity under glucose starvation leads to inadequate stimulation of p53 synthesis, which exerts pro-apoptotic functions under these conditions [131]. Altogether, these data support the notion that proper control of mRNA translation in response to glucose deprivation through inhibition of mTORC1 is critical for cell survival. In keeping with this, targeted inhibition of *TSC2* sensitizes *Rb* mutant tumor cells, such as Saos-2 osteosarcoma, DU145 prostate tumor and MDA-MB-468 breast tumor cells, to nutrient deprived conditions [83]. The inability to block mTORC1 in vivo correlates with reduced growth of tumor xenografts from *Rb* mutant tumor cells [83], consistent with mTORC1 inhibition being important for the development of at least some tumors within a nutrient-deprived tumor microenvironment.

3.2.3. eEF2K–eEF2

Another major nutrient sensing node that regulates protein synthesis is the eEF2K–eEF2 pathway. Activity of the eEF2K is controlled by various nutritional signals through distinct upstream signaling pathways (for review [26]) (Fig. 2B). Growth factors block eEF2K activity through the action of the Ras–MEK–Erk-p90RSK pathway, whereas amino acids prevent eEF2K activity by stimulating the mTORC1–p70S6K pathway [115]. In response to glucose depletion, AMPK mediates direct activation of eEF2K through its phosphorylation on residue Ser-398 [87]. This further emphasizes the fundamental role of AMPK in coupling energy levels to translation control, as it regulates both translation initiation (through mTORC1) and translation elongation (through eEF2K) in response to ND. The activity of eEF2K is induced by ND both in normal and tumor cells, leading to eEF2 inactivation and inhibition of translation elongation [105,113–115]. However, initial oncogenic activation such as through *RAS* mutations or oncogenic tyrosine kinases such as ETV6-NTRK3 (EN), prevents eEF2K activation under ND, as constitutive activation of Ras sustains the Erk–p90RSK pathway under these conditions [105]. In addition, oncogenic Ras and EN restrict eEF2K induction by unexpectedly preventing AMPK activation in response to ND [105]. Remarkably, following cellular adaptation to nutrient-deprived conditions, Ras- or EN-transformed cells restore activation of eEF2K under ND through re-induction of AMPK [105].

The activation of eEF2K and the subsequent block of translation elongation are critical for promoting cell survival under nutrient-deprived conditions (Fig. 2B). Indeed, targeted inhibition of *eEF2K* leads to severe cell death under ND in both normal and tumor cells, as well as in whole organisms [105]. Ras- or EN-transformed cells that fail to activate eEF2K are hypersensitive to these stress conditions, while eEF2K overexpression in these cells restores cell survival [105]. In addition, AMPK also promotes survival of tumor cells under ND by attenuating both translation initiation (through mTORC1 blockage) and translation elongation (through activation of eEF2K) [105]. This was similarly observed following cell detachment, a stress condition leading to both hypoxia and nutrient deprivation in which anoikis is prevented in tumor cells by an AMPK-mediated block in translation initiation [132]. Of note, the pro-survival function of eEF2K under ND occurs even under conditions when mTORC1 and global protein synthesis are already blocked through amino acid withdrawal [105]. This argues that inhibition of translation at the initiation step is insufficient to support cell survival even though it restricts global protein synthesis, and that blockade at the elongation step is also required. Instead, eEF2K-mediated inhibition of translation elongation may help to preserve intracellular protein homeostasis or prevent the synthesis of specific unwanted transcripts such as pro-apoptotic proteins [104]. Finally, both eEF2K and AMPK activities are critical for tumor development in vivo. Overexpression of eEF2K prevents caloric restriction-induced tumor necrosis in tumor xenografts [105], and AMPK overactivation enhances tumor growth in immunocompromised mice [133]. The clinical relevance of eEF2K functions is highlighted by our recent findings that *eEF2K* expression is upregulated in brain tumors compared to normal tissues and that *eEF2K* expression positively correlates with poor prognosis [105]. In keeping with this, high eEF2K activity was detected in tumor tissues but not in normal surrounding tissues [105]. Remarkably, eEF2K function is evolutionarily conserved as the *Caenorhabditis elegans eEF2K* ortholog, *efk-1*, is required for maintaining worm viability when nutrients are scarce [105]. Overall, eEF2K control of mRNA translation elongation appears to be an essential pro-survival pathway under ND which is hijacked by tumor cells to support their adaptation to nutritional stress within the tumor microenvironment.

3.3. Selective translation mechanisms under ND

As with hypoxia, a number of transcripts escape the overall translation blockade induced by ND. Genome-wide analyses of mRNA translation have facilitated the identification of subsets of mRNAs which are still translated under ND in normal in vivo tissues. Hundreds of such mRNAs have been reported, with predominance for transcripts whose products are involved in the electron transport chain and lipid metabolism [134,135], highlighting the importance of translational reprogramming of metabolism for the adaptive response to nutrient deprived conditions in vivo. A number of the identified transcripts possess 5′UTRs which are shorter and less structured, and this may support their

preferential translation under ND [135]. In addition, mechanisms for selective translation under nutrient-deprived conditions have been characterized for specific transcripts in tumor and normal cells.

3.3.1. uORFs

Similar to the response to hypoxia, eIF2α phosphorylation by different kinases can stimulate translation of uORF-containing transcripts in response to amino acid starvation. One well characterized uORF-containing transcript is *ATF4*, whose translation is induced by the Gcn2–eIF2α axis following amino acid deprivation in both tumor and normal cells [27,116] (Fig. 2A). Synthesis of ATF4 provides cells with protection under this condition [71]. Indeed, inhibition of ATF4 expression severely restricts the survival of HT1080 fibrosarcoma and DLD1 colon adenocarcinoma cells, as well as MEFs under amino acid restricted conditions [71,136]. In addition, ATF4 targeted inactivation prevents the growth of human tumor xenografts in vivo [71], highlighting the importance of the Gcn2–eIF2α–ATF4 axis for supporting tumor expansion within the nutrient-deprived conditions of the tumor microenvironment. The pro-survival function of ATF4 under amino acid deprivation results from the activation of specific ATF4 target genes involved in amino acid biosynthetic pathways, such as asparagine synthetase [71, 136,137] (Fig. 2A). Induction of asparagine synthetase by ATF4 under these conditions is potentially critical for maintaining intracellular levels of asparagine, an amino acid which supports proliferation of some tumor cells [71]. Notably, asparagine synthetase overexpression rescues the growth inhibition of ATF4-deficient tumor xenografts [71]. In response to amino acid starvation, and as a result of the induction of the Gcn2–eIF2α axis, ATF4 also leads to transcriptional induction of autophagy genes such as *p62/SQSTM1*, *LC3B* and *beclin1* [138] (Fig. 2A). Potential autophagic degradation by ATF4 under amino acid limited conditions may function to recycle amino acids [139]. Together with the observed overactivation of Gcn2 in tumors (see Section 3.2), upregulation of ATF4 in various tumor types [29,91] further reinforces the importance of this axis for tumor adaptation to nutrient-restricted conditions.

In addition to ATF4, another important mediator of the response to ND translationally controlled by a uORF is carnitine palmitoyltransferase 1 C (*CPT1C*). This transcript encodes an enzyme involved in fatty acid oxidation, a metabolic process which is critical for cell survival under glucose deprived conditions [98,133]. In tumor cells, the main *CPT1C* ORF gets translated in response to glucose deprivation, as the inhibitory uORF is ineffective under these stress conditions, thus allowing the selective translation of CPT1C under glucose depletion [140]. This is important for tumor adaptation to nutritional stress, as CPT1C was shown to mediate survival of tumor cells under glucose starvation and to contribute to tumor growth in vivo [107].

3.3.2. IRESes

Translation of specific transcripts in response to ND also proceeds through cap-independent mechanisms. Specifically, synthesis of two amino acid transporters, namely cationic amino acid transporter-1 (Cat-1) and sodium-coupled neutral amino acid transporter 2 (SNAT2), is controlled by IRESes under ND. Translation of the lysine/arginine transporter *cat-1* transcript is induced by amino acid or glucose starvation through an IRES [111,141]. Under amino acid deprivation, the translational control of the *cat-1* IRES is dependent upon induction of the Gcn2–eIF2α axis in tumor cells [142] (Fig. 2A). It was proposed that eIF2α phosphorylation may stimulate the synthesis of an IRES trans-acting factor (ITAF) which stabilizes *cat-1* IRES [143]. In contrast, under glucose starvation, the PERK–eIF2α axis is responsible for induction of *cat-1* IRES activity in tumor cells [141]. These studies highlight the involvement of different stress sensing kinases such as Gcn2 and PERK for regulating *cat-1* cap-independent translation in response to different types of nutrient stress conditions. In addition, the translation of the neutral amino acid transporter *SNAT2* transcript is governed by an IRES which is increased under amino acid deprivation [48]. Similar to the regulation of *cat-1* IRES, phosphorylation of eIF2α by Gcn2 in response to amino acid deprivation induces *SNAT2* IRES-mediated translation [48] (Fig. 2A).

Cap-independent translation can also serve to support selective translation under growth factor deprived conditions. Indeed, the translation of the sterol regulatory element-binding transcription factor 1 (*SREBP-1*) mRNA is maintained in the absence of growth factors in tumor cells, and this is mediated by an IRES [144]. Additionally, cap-independent translation of the X-linked inhibitor of apoptosis protein (*XIAP*) transcript supports the induced synthesis of XIAP under growth factor starvation through an IRES, thus protecting cells from apoptosis [145]. Translation regulation of these and other transcripts still to be identified may preserve cell survival under nutritional stress, which tumor cells could take advantage of.

4. Control of translation under oxidative and genotoxic stress

Maintaining redox state and integrity of the chromatin under conditions of oxidative and genotoxic stress is essential for all biological organisms. Pathways that are impaired in the anti-oxidative stress and DNA damage responses are linked to several human pathologies, in particular with ones that are associated with aging [146]. Furthermore, oxidative stress and DNA damage are implicated in the mechanism of action of many anti-cancer drugs and their toxicities [147]. When cells accumulate damaged macro- and other biomolecules, they often either initiate apoptosis or repair programs. For example, the tumor suppressor p53 is known to play a key role in this decision-making process [148], as well as in promoting the expression of anti-oxidative stress enzymes [149]. It is therefore not surprising that cancer cells exploit endogenous oxidative stress detoxification pathways in order to facilitate their resistance to therapy [150] or to inhibit apoptosis [151,152]. Indeed, a number of mechanisms that promote adaptation and tolerance to oxidative stress have been described, especially those that are mediated by transcription factors such as NF-E2 related factor 2 (NRF2) and p53 which directly induce the expression of gene products that function as anti-oxidants and promote cellular anti-oxidative stress metabolic programs [153].

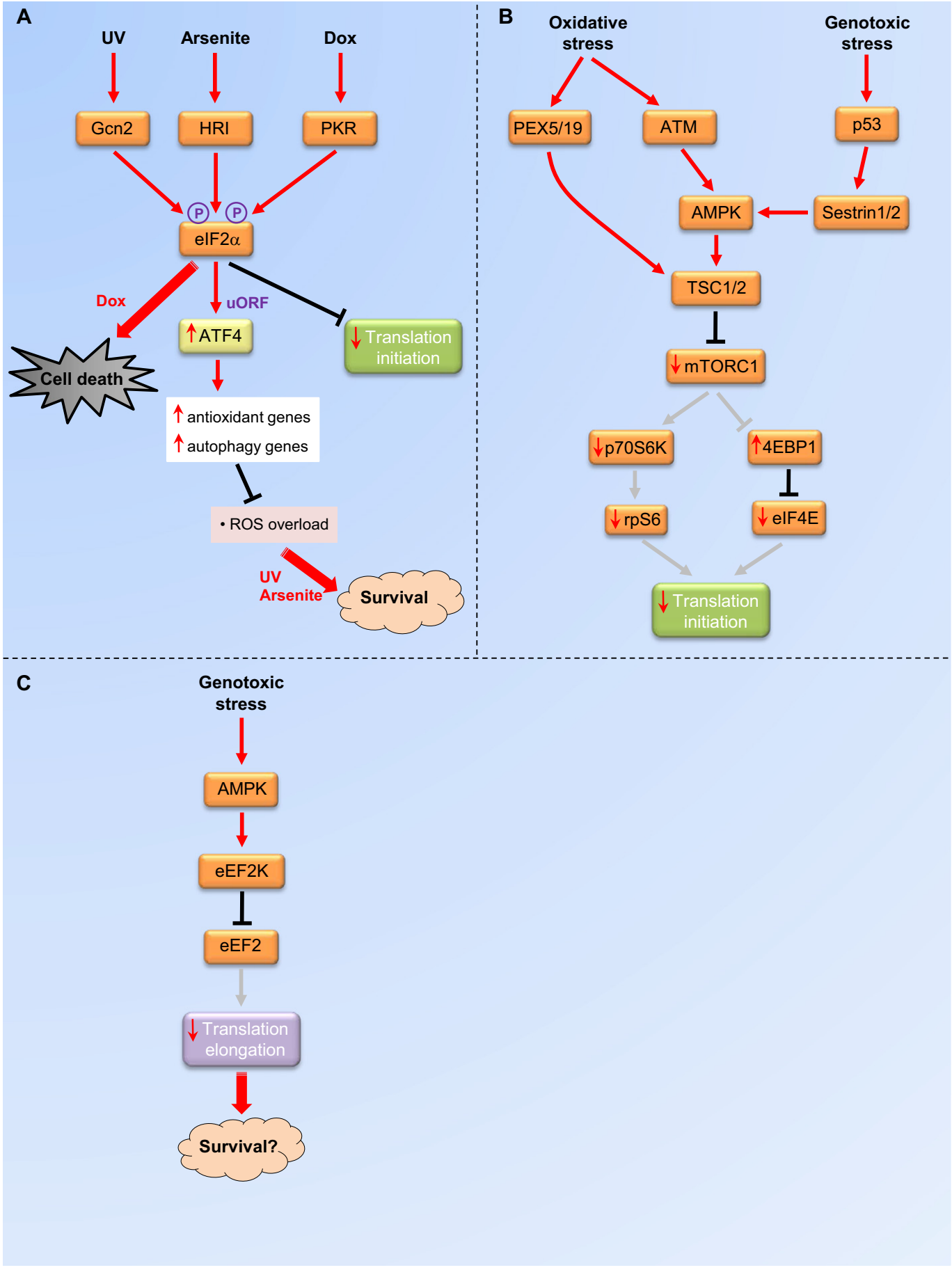
An important aspect of the cellular response to oxidative and genotoxic stress occurs at the translational level, whereby overall translation is restricted while the translation of specific subsets of messages is promoted. As is the case with the other stress forms described above, this translational response may facilitate rapid changes of the cellular proteome to adapt to oxidative and genotoxic stress. Consequently, tumor cells, by taking advantage of such translational reprogramming, can acquire resistance to chemo- and radio-therapy.

4.1. Overall translation rates under oxidative and genotoxic stress

Global mRNA translation is profoundly reduced by oxidative and genotoxic stress. More specifically, oxidative stress, such as H_2O_2 or arsenite, induces a severe inhibition of global protein synthesis rates in both tumor and normal cells [8,154–156]. In addition, genotoxic stress, including etoposide, doxorubicin and UV treatments, leads to striking reductions in overall translation activity in both tumor and normal cells [9,40,157–163]. This block in global translation occurs at the initiation step in a number of instances under oxidative and genotoxic stress [154,155,162]. However, translation elongation is also attenuated in some cases, such as in response to H_2O_2 in yeast [8] or under doxorubicin treatment in tumor cells (see Section 4.2) [9].

4.2. Signaling pathways and translational control under oxidative and genotoxic stress

Translational control in response to oxidative and genotoxic stress is orchestrated by specific signaling pathways, many of which are also involved in the response to hypoxia and ND. These pathways


A
UV
Arsenite
Dox
Gcn2
HRI
PKR
P
P
eIF2α
Dox
uORF
ATF4
Translation initiation
Cell death
antioxidant genes
autophagy genes
• ROS overload
UV
Arsenite
Survival
B
Oxidative stress
Genotoxic stress
PEX5/19
ATM
p53
AMPK
Sestrin1/2
TSC1/2
mTORC1
p70S6K
4EBP1
rpS6
eIF4E
Translation initiation
C
Genotoxic stress
AMPK
eEF2K
eEF2
Translation elongation
Survival?

accommodate overall translation activity, at both the initiation and elongation steps, in response to oxidative and genotoxic stress which may be decisive to preserve cell survival.

4.2.1. eIF2α

In response to oxidative or genotoxic stress, eIF2α is rapidly phosphorylated in both tumor and normal cells as shown for UV, arsenite, doxorubicin and etoposide treatments [154,155,158,161,164,165], thus contributing to translational arrest [154,155,158,160,161,164]. Gcn2 is responsible for inducing eIF2α phosphorylation and restraining overall translation in both tumor and normal cells in response to UV [158,160,161] (Fig. 3A). However, another report indicates the involvement of the ER-resident kinase PERK in this process [164]. Under oxidative stress such as arsenite treatment, HRI is activated to induce eIF2α phosphorylation and translational arrest [155] (Fig. 3A). Activation of these kinases supports cell survival under stress as shown in normal cells. In response to UV stress, apoptosis is enhanced when *Gcn2* is lost [160] and genetic deletion of *HRI* dramatically compromises survival of MEFs under arsenite treatment [155]. In addition, eIF2α phosphorylation may prevent cell death under UV stress. Notably, in UV-stressed cells, translational arrest by eIF2α phosphorylation decreases the synthesis of nuclear factor of kappa light polypeptide gene enhancer in B-cells (NFκB)-inhibitor alpha (IκBα), an inhibitor of NFκB, thereby leading to NFκB activation [160]. NFκB activation exerts a protective role under UV stress [160], likely through transcriptional induction of anti-oxidative stress genes [166]. In contrast, phosphorylation of eIF2α in response to doxorubicin, which occurs due to p53-mediated upregulation of PKR, results in cell apoptosis along with translational inhibition [165] (Fig. 3A). Notably, targeted inhibition of *PKR* renders HCT116 colon cancer cells more resistant to doxorubicin and etoposide in a tumor xenograft model [165]. Overall, these studies indicate that different eIF2α kinases become activated depending on the type of oxidative and genotoxic stress, leading to distinct biological responses.

4.2.2. mTORC1

mTORC1 is inactivated in response to oxidative and genotoxic stress in both tumor and normal cells, including H_2O_2, etoposide, cisplatin and camptothecin treatments [162,167–169]. Different mechanisms account for the inhibition of mTORC1 under these stresses (Fig. 3B). AMPK appears to be one critical factor for this process though its activation of TSC2, in turn leading to mTORC1 inhibition. Indeed, AMPK is activated by oxidative and genotoxic stress following two distinct mechanisms [167,168]. On one hand, AMPK is activated by the DNA damage response kinase ataxia telangiectasia mutated (ATM) under oxidative stress [167]. On the other hand, AMPK is induced by Sestrin1 and Sestrin2, which are themselves activated by p53 under genotoxic stress [168] (Fig. 3B). An alternative mechanism has been proposed for TSC2-mediated inhibition of mTORC1 in response to oxidative stress. Under these conditions, TSC1/2 and Rheb are recruited to peroxisomes through the peroxisomal biogenesis factors PEX19 and PEX5, resulting in mTORC1 inhibition and activation of autophagy [169] (Fig. 3B). However, whether mTORC1 inhibition contributes to translation arrest in vivo following oxidative and genotoxic stress needs to be further investigated. Finally, mTORC1 inhibition under oxidative stress was shown to induce autophagy in MCF-7 breast tumor cells [167,169], suggesting that negative mTORC1 regulation may contribute to cell survival under these conditions. Further investigations are warranted to establish the impact of mTORC1 regulation on the survival response to oxidative and genotoxic stress, and the involvement of mTORC1-mediated translational control in such biological responses.

4.2.3. eEF2K

The eEF2K–eEF2 pathway is also reported to respond to various oxidative and genotoxic stress forms. Activity of eEF2K, as detected by eEF2 phosphorylation, is induced by H_2O_2, doxorubicin and γ-irradiation in tumor and normal cells [9,68,157]. AMPK, which is also induced by genotoxic stress [167], is responsible of phosphorylating and activating eEF2K under doxorubicin treatment [9] (Fig. 3C), following similar mechanisms as characterized for the response to ND [87]. Notably, the eEF2K activation leads to a severe block in translation elongation in response to doxorubicin, which is a critical event for mediating overall translation arrest in both tumor and normal cells [9,157]. Indeed, targeted inhibition of *eEF2K* prevents overall translation inhibition under these conditions, suggesting that elongation is potentially the rate-limiting step of protein synthesis activity in the cellular response to doxorubicin [9,157]. Furthermore, during recovery from DNA damage (following release from doxorubicin treatment), translation elongation is resumed as a direct consequence of eEF2K degradation, supporting the re-initiation of global protein synthesis [9]. Thus, eEF2K is specifically targeted for proteosomal degradation following release from doxorubicin treatment by its interaction with the Skp1–cullin–F-box protein (SCF)-beta-transducin repeats-containing proteins (βTrCP) ubiquitin ligase complex [9]. Finally, the eEF2K pathway may potentially provide tumor cells with enhanced resistance to chemo- and radio-therapy. For instance, targeted inhibition of *eEF2K* was shown to sensitize breast tumor cells to the action of doxorubicin in a tumor xenograft model [170].

4.3. Selective translation mechanisms under oxidative and genotoxic stress

As described above for hypoxia and ND, several transcripts escape the translation block induced by oxidative and genotoxic stress. Global approaches such as polysomal fractionation combined with microarray analysis showed that hundreds of transcripts are still translated under UV treatment in tumor cells [40]. More specifically, the synthesis of several major oxidative stress response regulators such as NFκB, p53 and NRF2, is sustained under oxidative stress to support critical biological responses under stress [160,171,172]. The selective translation of subsets of transcripts under oxidative and genotoxic stress involve both uORF- and IRES-mediated translational mechanisms.

4.3.1. uORFs

In response to oxidative and genotoxic stress, the uORF-regulated transcript *ATF4* is translated following eIF2α phosphorylation in both tumor and normal cells [173,174]. Induction of this eIF2α-ATF4 axis enhances resistance to γ-irradiation in U373 glioblastoma cells and tumor xenografts [30,174]. This protective effect relies on induction of specific downstream ATF4 target genes involved in the antioxidant response, including *cystathionase*, and in autophagy, such as lysosomal-associated membrane protein 3 (*LAMP3*) [30,174] (Fig. 3A). In addition, a number of other uORF-containing transcripts are translated in response to UV treatment in tumor cells. For example, specific uORF-containing

Fig. 3. Translational control under oxidative and genotoxic stress. A, the eIF2α pathway responds to oxidative and genotoxic stress to regulate mRNA translation. These stresses lead to eIF2α phosphorylation (i.e. inhibition) through distinct upstream kinases: i) UV activates Gcn2, ii) arsenite treatment stimulates HRI, iii) doxorubicin (dox) treatment induces PKR. As a consequence, overall translation is shut down at the initiation step. In addition, eIF2α phosphorylation stimulates ATF4 synthesis through a uORF-based mechanism, mediating transcription of antioxidant and autophagy genes to prevent ROS overload. This transcriptional program supports cell survival in response to UV and arsenite. However, in response to doxorubicin, eIF2α phosphorylation leads to cell death. B, the mTORC1 pathway responds to oxidative and genotoxic stress. Activity of mTORC1 is inhibited by oxidative and genotoxic stress through distinct regulatory pathways: i) oxidative stress induces PEX5/19 to recruit TSC1/2 and mTORC1 to peroxisomes; ii) oxidative stress also activates AMPK, downstream of ATM, to stimulate TSC1/2; iii) genotoxic stress mediates p53 activation of Sestrin1/2 which in turn activates AMPK. As a consequence of mTORC1 inhibition, overall translation is restricted at the initiation step in response oxidative and genotoxic stress. C, the eEF2K pathway responds to genotoxic stress to control mRNA translation elongation. EEF2K is activated by genotoxic stress through induction of AMPK. This leads to phosphorylation and inhibition of eEF2, thus restraining translation elongation which may potentially favor cell survival under genotoxic stress. Gray arrows and bars indicate release from regulatory effects of upstream pathways.

transcripts encoding DNA repair enzymes, including xeroderma pigmentosum, complementation group A (*XPA*), excision repair cross-complementation group 5 (*ERCC5*), and damage-specific DNA binding protein 1 (*DDB1*), are efficiently translated under UV stress [40]. Moreover, this translational reprogramming is dependent on the activation of the DNA repair regulatory kinase DNA-PKcs, which is upstream of Gcn2 under these conditions [40]. Such selective translation mechanisms may facilitate DNA repair within tumor cells following UV treatment. Finally, the transcript encoding arsenite-inducible regulatory particle-associated protein (AIRAP) is translationally activated during arsenite treatment through the relief of an inhibitory uORF [175]. Indeed, the *AIRAP* transcript contains a single uORF in a non-optimal kozak context which, under basal conditions, restricts the initiation of the downstream main ORF [175]. However, under arsenite treatment, eIF1 becomes phosphorylated, leading to leaky scanning across the inhibitory uORF, supporting enhanced translation from the main ORF [175]. Notably, AIRAP exerts a protective function against the toxic effects of arsenite [176].

4.3.2. IRESes

The c-MYC protein is a cancer associated transcription factor that is activated by oxidative and genotoxic stress [177]. Work form the Willis lab has demonstrated that following genotoxic stress, *c-MYC* is translated through a cap-independent IRES mechanism [178], and this process plays a particularly important role in radio-resistance of tumor cells under oxidative and genotoxic stress. Notably, the anti-apoptotic protein XIAP is upregulated under γ-irradiation through enhanced translation via its 5′UTR IRES, rendering tumor cells resistant to radiotherapy [28,179]. Targeted inhibition of *XIAP* in myeloma cells compromises cell survival in response to chemotherapeutic drugs, demonstrating the importance of XIAP upregulation in tumor cell resistance to chemo- and radio-therapy [180]. Several other anti-apoptotic proteins are also translationally controlled by IRESes under oxidative and genotoxic stress. These include BCL2-associated athanogene (BAG-1), which promotes resistance of tumor cells to DNA damage-inducing drugs [181] and whose synthesis is induced by an IRES under genotoxic stress [182]. In addition, synthesis of cIAP1 and BCL2 are enhanced by etoposide and arsenite treatments through IRES-mediated mechanisms [183,184]. Together, the selective translational upregulation of these anti-apoptotic proteins further supports a model whereby tumor cells block apoptosis under oxidative and genotoxic stress conditions via selective IRES-mediated translation.

Transcriptional master regulators of the oxidative and genotoxic stress response such as p53 and NRF2 are also reported to be translationally controlled though IRESes. Indeed, translation of *p53* is controlled by an IRES in response to oxidative and genotoxic stress. The *p53* transcript has a dual IRES structure that controls the translation of full-length p53 and an N-terminally truncated isoform (Δ40p53) from the same mRNA [185,186]. Polypyrimidine tract-binding protein protein (PTB), an ITAF, stimulates IRES-mediated translation of p53 isoforms in response to doxorubicin, following PTB relocalization from the nucleus to the cytoplasm [187]. This regulation is altered in the presence of melanoma associated mutations in the *p53* 5′UTR [188]. In addition, human double minute 2 homolog (HDM2) and HDM4 (also known as HDMX) act as other ITAFs which synergistically increase p53 IRES activity under DNA damage following HDMX phosphorylation by ATM [189]. Other ITAFs have been reported as controlling p53 IRES activity, such as eIF4G2 (also known as DAP5), Annexin A2 and PTB associated Splicing Factor (PSF) [190,191]. NRF2 is another master regulator of the response to oxidative stress that is translationally induced through an IRES under oxidative stress [192–194]. While NRF2 synthesis is blocked under basal conditions due to the presence of a highly structured inhibitory hairpin element present in its 5′-UTR, its synthesis is enhanced by oxidative stress through stimulation of an IRES element also present within its 5′-UTR [192]. IRES-mediated translation of NRF2 requires the binding of the ITAF La autoantigen [194]. Synthesis of other transcription factors is also induced by oxidative and genotoxic stress through IRES. This includes octamer-binding protein 4 (OCT4), which is synthesized upon H_2O_2 treatment in MCF-7 breast cancer and HepG2 liver carcinoma cells [195], and runt-related transcription factor 2 (RUNX2), whose translation is stimulated by mitomycin C [196]. Another transcription factor, SREBP1, is translationally induced by H_2O_2 through an IRES, thus contributing to H_2O_2 stimulation of lipogenesis [197]. This indicates that SREBP1 IRES responds to different stresses, i.e. ND and oxidative stress. All together, this supports a model whereby under oxidative and genotoxic stress, IRES-mediated translation of key regulators and pro-survival factors provide tumor cells with mechanisms for attaining resistance to chemo- and radio-therapy.

5. Conclusions

The ability of tumor cells to respond and adapt to diverse stress conditions encountered in the tumor microenvironment, such as hypoxia, nutrient deprivation, and oxidative and genotoxic stress, is decisive for the selection of more aggressive tumor clones, and thus for driving tumor progression. The control of mRNA translation is a major strategy employed by tumor cells to support their adaptation to stress. Strikingly, the regulatory pathways which couple translation activity to the stress response are common across each stress form described in this review, and many of the involved pathways are inextricably linked to ER stress and the UPR. This supports a model by which there is a common cellular response to the many different stress conditions of the tumor microenvironment. Indeed, tumor cells hijack these common pathways to drive a translation reprogramming process to support their survival under diverse stress forms. From a therapeutic point of view, this opens up the possibility of targeting and neutralizing stress adaptive mechanisms by preventing the induction of key common pathways. It is therefore tempting to consider the major regulators of these pathways, including eIF2α kinases, ATF4, mTORC1, and eEF2K, as potential therapeutic targets in cancers. This warrants further studies to validate the use of such targets to treat cancers. Of note, in the case of mTORC1, activation of the protein will be warranted to interfere with tumor adaptation, which counters current therapeutic strategies which aim to inhibit mTORC1. Therefore the decision to either activate or inhibit mTORC1 to treat cancers should take into account the levels of stress within the tumor microenvironment of the targeted cancers. Overall, a better understanding of how tumor cells exploit mRNA translation to ensure their adaptation to stress holds great promise for developing new therapeutic options in clinical oncology.

Acknowledgements

This work was supported by funds from the Canadian Cancer Society Research Institute (2012-701353), and the British Columbia Cancer Foundation (Fund ID: OPDRG005) through generous donations from Team Finn and other riders in the Ride to Conquer Cancer.

References

[1] M. Holcik, N. Sonenberg, Translational control in stress and apoptosis, Nat. Rev. Mol. Cell Biol. 6 (2005) 318–327.
[2] B. Liu, S.B. Qian, Translational reprogramming in cellular stress response, Wiley Interdiscip. Rev. 5 (2014) 301–315.
[3] J.A. Nagy, S.H. Chang, A.M. Dvorak, H.F. Dvorak, Why are tumour blood vessels abnormal and why is it important to know? Br. J. Cancer 100 (2009) 865–869.
[4] K.A. Spriggs, M. Bushell, A.E. Willis, Translational regulation of gene expression during conditions of cell stress, Mol. Cell 40 (2010) 228–237.
[5] F. Buttgereit, M.D. Brand, A hierarchy of ATP-consuming processes in mammalian cells, Biochem. J. 312 (Pt 1) (1995) 163–167.
[6] U. Liwak, M.D. Faye, M. Holcik, Translation control in apoptosis, Exp. Oncol. 34 (2012) 218–230.
[7] J.W. Hershey, N. Sonenberg, M.B. Mathews, Principles of translational control: an overview, Cold Spring Harb. Perspect. Biol. 4 (2012).
[8] M.V. Gerashchenko, A.V. Lobanov, V.N. Gladyshev, Genome-wide ribosome profiling reveals complex translational regulation in response to oxidative stress, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 17394–17399.

[9] F. Kruiswijk, L. Yuniati, R. Magliozzi, T.Y. Low, R. Lim, R. Bolder, S. Mohammed, C.G. Proud, A.J. Heck, M. Pagano, D. Guardavaccaro, Coupled activation and degradation of eEF2K regulates protein synthesis in response to genotoxic stress, Sci. Signal. 5 (2012) ra40.

[10] B. Liu, Y. Han, S.B. Qian, Cotranslational response to proteotoxic stress by elongation pausing of ribosomes, Mol. Cell 49 (2013) 453–463.

[11] R. Shalgi, J.A. Hurt, I. Krykbaeva, M. Taipale, S. Lindquist, C.B. Burge, Widespread regulation of translation by elongation pausing in heat shock, Mol. Cell 49 (2013) 439–452.

[12] P. Walter, D. Ron, The unfolded protein response: from stress pathway to homeostatic regulation, Science 334 (2011) 1081–1086.

[13] T.K. Rainbolt, J.M. Saunders, R.L. Wiseman, Stress-responsive regulation of mitochondria through the ER unfolded protein response, Trends Endocrinol. Metab. 25 (2014) 528–537.

[14] G.D. Pavitt, D. Ron, New insights into translational regulation in the endoplasmic reticulum unfolded protein response, Cold Spring Harb. Perspect. Biol. 4 (2012).

[15] H.J. Clarke, J.E. Chambers, E. Liniker, S.J. Marciniak, Endoplasmic reticulum stress in malignancy, Cancer Cell 25 (2014) 563–573.

[16] D.E. Feldman, V. Chauhan, A.C. Koong, The unfolded protein response: a novel component of the hypoxic stress response in tumors, Mol. Cancer Res. 3 (2005) 597–605.

[17] J.D. Malhotra, R.J. Kaufman, Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? Antioxid. Redox Signal. 9 (2007) 2277–2293.

[18] B.G. Wouters, M. Koritzinsky, Hypoxia signalling through mTOR and the unfolded protein response in cancer, Nat. Rev. Cancer 8 (2008) 851–864.

[19] A.G. Hinnebusch, Mechanism and regulation of initiator methionyl-tRNA binding to ribosomes, in: N. Sonenberg, J.W.B. Hershey, M.B. Mathews (Eds.), Translational Control of Gene Expression, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2000, pp. 185–243.

[20] R. Zoncu, A. Efeyan, D.M. Sabatini, mTOR: from growth signal integration to cancer, diabetes and ageing, Nat. Rev. Mol. Cell Biol. 12 (2011) 21–35.

[21] S. Sengupta, T.R. Peterson, D.M. Sabatini, Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress, Mol. Cell 40 (2010) 310–322.

[22] D. Silvera, S.C. Formenti, R.J. Schneider, Translational control in cancer, Nat. Rev. Cancer 10 (2010) 254–266.

[23] U. Carlberg, A. Nilsson, O. Nygard, Functional properties of phosphorylated elongation factor 2, Eur. J. Biochem. 191 (1990) 639–645.

[24] A.G. Ryazanov, E.K. Davydova, Mechanism of elongation factor 2 (EF-2) inactivation upon phosphorylation. Phosphorylated EF-2 is unable to catalyze translocation, FEBS Lett. 251 (1989) 187–190.

[25] A.G. Ryazanov, E.A. Shestakova, P.G. Natapov, Phosphorylation of elongation factor 2 by EF-2 kinase affects rate of translation, Nature 334 (1988) 170–173.

[26] J.W. Kenney, C.E. Moore, X. Wang, C.G. Proud, Eukaryotic elongation factor 2 kinase, an unusual enzyme with multiple roles, Adv. Biol. regul. 55 (2014) 15–27.

[27] H.P. Harding, I. Novoa, Y. Zhang, H. Zeng, R. Wek, M. Schapira, D. Ron, Regulated translation initiation controls stress-induced gene expression in mammalian cells, Mol. Cell 6 (2000) 1099–1108.

[28] M. Holcik, C. Yeh, R.G. Korneluk, T. Chow, Translational upregulation of X-linked inhibitor of apoptosis (XIAP) increases resistance to radiation induced cell death, Oncogene 19 (2000) 4174–4177.

[29] M. Bi, C. Naczki, M. Koritzinsky, D. Fels, J. Blais, N. Hu, H. Harding, I. Novoa, M. Varia, J. Raleigh, D. Scheuner, R.J. Kaufman, J. Bell, D. Ron, B.G. Wouters, C. Koumenis, ER stress-regulated translation increases tolerance to extreme hypoxia and promotes tumor growth, EMBO J. 24 (2005) 3470–3481.

[30] K.M. Rouschop, L.J. Dubois, T.G. Keulers, T. van den Beucken, P. Lambin, J. Bussink, A.J. van der Kogel, M. Koritzinsky, B.G. Wouters, PERK/eIF2alpha signaling protects therapy resistant hypoxic cells through induction of glutathione synthesis and protection against ROS, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 4622–4627.

[31] D.C. Singleton, A.L. Harris, Targeting the ATF4 pathway in cancer therapy, Expert Opin. Ther. Targets 16 (2012) 1189–1202.

[32] S.E. Calvo, D.J. Pagliarini, V.K. Mootha, Upstream open reading frames cause widespread reduction of protein expression and are polymorphic among humans, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 7507–7512.

[33] S. Lee, B. Liu, S.X. Huang, B. Shen, S.B. Qian, Global mapping of translation initiation sites in mammalian cells at single-nucleotide resolution, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) E2424–E2432.

[34] L.R. Palam, T.D. Baird, R.C. Wek, Phosphorylation of eIF2 facilitates ribosomal bypass of an inhibitory upstream ORF to enhance CHOP translation, J. Biol. Chem. 286 (2011) 10939–10949.

[35] K.M. Vattem, R.C. Wek, Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 11269–11274.

[36] J.D. Blais, V. Filipenko, M. Bi, H.P. Harding, D. Ron, C. Koumenis, B.G. Wouters, J.C. Bell, Activating transcription factor 4 is translationally regulated by hypoxic stress, Mol. Cell. Biol. 24 (2004) 7469–7482.

[37] Y.Y. Lee, R.C. Cevallos, E. Jan, An upstream open reading frame regulates translation of GADD34 during cellular stresses that induce eIF2alpha phosphorylation, J. Biol. Chem. 284 (2009) 6661–6673.

[38] D. Zhou, L.R. Palam, L. Jiang, J. Narasimhan, K.A. Staschke, R.C. Wek, Phosphorylation of eIF2 directs ATF5 translational control in response to diverse stress conditions, J. Biol. Chem. 283 (2008) 7064–7073.

[39] S. Schleich, K. Strassburger, P.C. Janiesch, T. Koledachkina, K.K. Miller, K. Haneke, Y.S. Cheng, K. Kuchler, G. Stoecklin, K.E. Duncan, A.A. Teleman, DENR-MCT-1 promotes translation re-initiation downstream of uORFs to control tissue growth, Nature 512 (2014) 208–212.

[40] I.R. Powley, A. Kondrashov, L.A. Young, H.C. Dobbyn, K. Hill, I.G. Cannell, M. Stoneley, Y.W. Kong, J.A. Cotes, G.C. Smith, R. Wek, C. Hayes, T.W. Gant, K.A. Spriggs, M. Bushell, A.E. Willis, Translational reprogramming following UVB irradiation is mediated by DNA-PKcs and allows selective recruitment to the polysomes of mRNAs encoding DNA repair enzymes, Genes Dev. 23 (2009) 1207–1220.

[41] C.U. Hellen, P. Sarnow, Internal ribosome entry sites in eukaryotic mRNA molecules, Genes Dev. 15 (2001) 1593–1612.

[42] G. Johannes, P. Sarnow, Cap-independent polysomal association of natural mRNAs encoding c-myc, BiP, and eIF4G conferred by internal ribosome entry sites, RNA 4 (1998) 1500–1513.

[43] W.V. Gilbert, Alternative ways to think about cellular internal ribosome entry, J. Biol. Chem. 285 (2010) 29033–29038.

[44] R.J. Jackson, The current status of vertebrate cellular mRNA IRESs, Cold Spring Harb. Perspect. Biol. 5 (2013).

[45] M. Kozak, A second look at cellular mRNA sequences said to function as internal ribosome entry sites, Nucleic Acids Res. 33 (2005) 6593–6602.

[46] J.D. Blais, C.L. Addison, R. Edge, T. Falls, H. Zhao, K. Wary, C. Koumenis, H.P. Harding, D. Ron, M. Holcik, J.C. Bell, Perk-dependent translational regulation promotes tumor cell adaptation and angiogenesis in response to hypoxic stress, Mol. Cell. Biol. 26 (2006) 9517–9532.

[47] S. Braunstein, K. Karpisheva, C. Pola, J. Goldberg, T. Hochman, H. Yee, J. Cangiarella, R. Arju, S.C. Formenti, R.J. Schneider, A hypoxia-controlled cap-dependent to cap-independent translation switch in breast cancer, Mol. Cell 28 (2007) 501–512.

[48] F. Gaccioli, C.C. Huang, C. Wang, E. Bevilacqua, R. Franchi-Gazzola, G.C. Gazzola, O. Bussolati, M.D. Snider, M. Hatzoglou, Amino acid starvation induces the SNAT2 neutral amino acid transporter by a mechanism that involves eukaryotic initiation factor 2alpha phosphorylation and cap-independent translation, J. Biol. Chem. 281 (2006) 17929–17940.

[49] A.R. Pries, A.J. Cornelissen, A.A. Sloot, M. Hinkeldey, M.R. Dreher, M. Hopfner, M.W. Dewhirst, T.W. Secomb, Structural adaptation and heterogeneity of normal and tumor microvascular networks, PLoS Comput. Biol. 5 (2009) e1000394.

[50] M. Hockel, P. Vaupel, Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects, J. Natl. Cancer Inst. 93 (2001) 266–276.

[51] T.G. Graeber, C. Osmanian, T. Jacks, D.E. Housman, C.J. Koch, S.W. Lowe, A.J. Giaccia, Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours, Nature 379 (1996) 88–91.

[52] M. Weinmann, V. Jendrossek, D. Guner, B. Goecke, C. Belka, Cyclic exposure to hypoxia and reoxygenation selects for tumor cells with defects in mitochondrial apoptotic pathways, FASEB J. 18 (2004) 1906–1908.

[53] K.L. Talks, H. Turley, K.C. Gatter, P.H. Maxwell, C.W. Pugh, P.J. Ratcliffe, A.L. Harris, The expression and distribution of the hypoxia-inducible factors HIF-1alpha and HIF-2alpha in normal human tissues, cancers, and tumor-associated macrophages, Am. J. Pathol. 157 (2000) 411–421.

[54] H. Zhong, A.M. De Marzo, E. Laughner, M. Lim, D.A. Hilton, D. Zagzag, P. Buechler, W.B. Isaacs, G.L. Semenza, J.W. Simons, Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases, Cancer Res. 59 (1999) 5830–5835.

[55] G.L. Semenza, Regulation of mammalian O_2 homeostasis by hypoxia-inducible factor 1, Annu. Rev. Cell Dev. Biol. 15 (1999) 551–578.

[56] W.W. Wheaton, N.S. Chandel, Hypoxia. 2. Hypoxia regulates cellular metabolism, Am. J. Physiol. Cell Physiol. 300 (2011) C385–C393.

[57] P.W. Hochachka, L.T. Buck, C.J. Doll, S.C. Land, Unifying theory of hypoxia tolerance: molecular/metabolic defense and rescue mechanisms for surviving oxygen lack, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 9493–9498.

[58] L. Dubois, M.G. Magagnin, A.H. Cleven, S.A. Weppler, B. Grenacher, W. Landuyt, N. Lieuwes, P. Lambin, T.A. Gorr, M. Koritzinsky, B.G. Wouters, Inhibition of 4E-BP1 sensitizes U87 glioblastoma xenograft tumors to irradiation by decreasing hypoxia tolerance, Int. J. Radiat. Oncol. Biol. Phys. 73 (2009) 1219–1227.

[59] B. Scott, C.L. Sun, X. Mao, C. Yu, B.P. Vohra, J. Milbrandt, C.M. Crowder, Role of oxygen consumption in hypoxia protection by translation factor depletion, J. Exp. Biol. 216 (2013) 2283–2292.

[60] M. Koritzinsky, M.G. Magagnin, T. van den Beucken, R. Seigneuric, K. Savelkouls, J. Dostie, S. Pyronnet, R.J. Kaufman, S.A. Weppler, J.W. Voncken, P. Lambin, C. Koumenis, N. Sonenberg, B.G. Wouters, Gene expression during acute and prolonged hypoxia is regulated by distinct mechanisms of translational control, EMBO J. 25 (2006) 1114–1125.

[61] M. Koritzinsky, K.M. Rouschop, T. van den Beucken, M.G. Magagnin, K. Savelkouls, P. Lambin, B.G. Wouters, Phosphorylation of eIF2alpha is required for mRNA translation inhibition and survival during moderate hypoxia, Radiother. Oncol. 83 (2007) 353–361.

[62] M. Koritzinsky, R. Seigneuric, M.G. Magagnin, T. van den Beucken, P. Lambin, B.G. Wouters, The hypoxic proteome is influenced by gene-specific changes in mRNA translation, Radiother. Oncol. 76 (2005) 177–186.

[63] C. Koumenis, C. Naczki, M. Koritzinsky, S. Rastani, A. Diehl, N. Sonenberg, A. Koromilas, B.G. Wouters, Regulation of protein synthesis by hypoxia via activation of the endoplasmic reticulum kinase PERK and phosphorylation of the translation initiation factor eIF2alpha, Mol. Cell. Biol. 22 (2002) 7405–7416.

[64] E. Connolly, S. Braunstein, S. Formenti, R.J. Schneider, Hypoxia inhibits protein synthesis through a 4E-BP1 and elongation factor 2 kinase pathway controlled by mTOR and uncoupled in breast cancer cells, Mol. Cell. Biol. 26 (2006) 3955–3965.

[65] J.D. Thomas, G.J. Johannes, Identification of mRNAs that continue to associate with polysomes during hypoxia, RNA 13 (2007) 1116–1131.

[66] J. Uniacke, C.E. Holterman, G. Lachance, A. Franovic, M.D. Jacob, M.R. Fabian, J. Payette, M. Holcik, A. Pause, S. Lee, An oxygen-regulated switch in the protein synthesis machinery, Nature 486 (2012) 126–129.

[67] T. van den Beucken, M.G. Magagnin, B. Jutten, R. Seigneuric, P. Lambin, M. Koritzinsky, B.G. Wouters, Translational control is a major contributor to hypoxia induced gene expression, Radiother. Oncol. 99 (2011) 379–384.
[68] L. Liu, D.R. Wise, J.A. Diehl, M.C. Simon, Hypoxic reactive oxygen species regulate the integrated stress response and cell survival, J. Biol. Chem. 283 (2008) 31153–31162.
[69] N.S. Chandel, E. Maltepe, E. Goldwasser, C.E. Mathieu, M.C. Simon, P.T. Schumacker, Mitochondrial reactive oxygen species trigger hypoxia-induced transcription, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 11715–11720.
[70] K.D. Mansfield, R.D. Guzy, Y. Pan, R.M. Young, T.P. Cash, P.T. Schumacker, M.C. Simon, Mitochondrial dysfunction resulting from loss of cytochrome c impairs cellular oxygen sensing and hypoxic HIF-alpha activation, Cell Metab. 1 (2005) 393–399.
[71] J. Ye, M. Kumanova, L.S. Hart, K. Sloane, H. Zhang, D.N. De Panis, E. Bobrovnikova-Marjon, J.A. Diehl, D. Ron, C. Koumenis, The GCN2–ATF4 pathway is critical for tumour cell survival and proliferation in response to nutrient deprivation, EMBO J. 29 (2010) 2082–2096.
[72] A.M. Arsham, J.J. Howell, M.C. Simon, A novel hypoxia-inducible factor-independent hypoxic response regulating mammalian target of rapamycin and its targets, J. Biol. Chem. 278 (2003) 29655–29660.
[73] J. Brugarolas, K. Lei, R.L. Hurley, B.D. Manning, J.H. Reiling, E. Hafen, L.A. Witters, L.W. Ellisen, W.G. Kaelin Jr., Regulation of mTOR function in response to hypoxia by REDD1 and the TSC1/TSC2 tumor suppressor complex, Genes Dev. 18 (2004) 2893–2904.
[74] F. Kaper, N. Dornhoefer, A.J. Giaccia, Mutations in the PI3K/PTEN/TSC2 pathway contribute to mammalian target of rapamycin activity and increased translation under hypoxic conditions, Cancer Res. 66 (2006) 1561–1569.
[75] Y. Li, M.N. Corradetti, K. Inoki, K.L. Guan, TSC2: filling the GAP in the mTOR signaling pathway, Trends Biochem. Sci. 29 (2004) 32–38.
[76] T. Shoshani, A. Faerman, I. Mett, E. Zelin, T. Tenne, S. Gorodin, Y. Moshel, S. Elbaz, A. Budanov, A. Chajut, H. Kalinski, I. Kamer, A. Rozen, O. Mor, E. Keshet, D. Leshkowitz, P. Einat, R. Skaliter, E. Feinstein, Identification of a novel hypoxia-inducible factor 1-responsive gene, RTP801, involved in apoptosis, Mol. Cell. Biol. 22 (2002) 2283–2293.
[77] M.P. DeYoung, P. Horak, A. Sofer, D. Sgroi, L.W. Ellisen, Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling, Genes Dev. 22 (2008) 239–251.
[78] A. Schneider, R.H. Younis, J.S. Gutkind, Hypoxia-induced energy stress inhibits the mTOR pathway by activating an AMPK/REDD1 signaling axis in head and neck squamous cell carcinoma, Neoplasia 10 (2008) 1295–1302.
[79] K. Inoki, T. Zhu, K.L. Guan, TSC2 mediates cellular energy response to control cell growth and survival, Cell 115 (2003) 577–590.
[80] D.M. Gwinn, D.B. Shackelford, D.F. Egan, M.M. Mihaylova, A. Mery, D.S. Vasquez, B.E. Turk, R.J. Shaw, AMPK phosphorylation of raptor mediates a metabolic checkpoint, Mol. Cell 30 (2008) 214–226.
[81] R. Bernardi, A. Papa, A. Egia, N. Coltella, J. Teruya-Feldstein, S. Signoretti, P.P. Pandolfi, Pml represses tumour progression through inhibition of mTOR, EMBO Mol. Med. 3 (2011) 249–257.
[82] Y. Hamanaka, M. Mukai, M. Shimamura, T. Kitagawa, T. Nishida, F. Isohashi, T. Ito, Y. Nishizawa, M. Tatsuta, H. Matsuda, M. Inoue, Suppression of PI3K/mTOR pathway rescues LLC cells from cell death induced by hypoxia, Biochem. Biophys. Res. Commun. 330 (2005) 318–326.
[83] B. Li, G.M. Gordon, C.H. Du, J. Xu, W. Du, Specific killing of Rb mutant cancer cells by inactivating TSC2, Cancer Cell 17 (2010) 469–480.
[84] S. Horman, G. Browne, U. Krause, J. Patel, D. Vertommen, L. Bertrand, A. Lavoinne, L. Hue, C. Proud, M. Rider, Activation of AMP-activated protein kinase leads to the phosphorylation of elongation factor 2 and an inhibition of protein synthesis, Curr. Biol. 12 (2002) 1419–1423.
[85] J. Lin, N. Wang, Y. Li, Z. Liu, S. Tian, L. Zhao, Y. Zheng, S. Liu, S. Li, C. Jin, B. Xia, LEC-BiFC: a new method for rapid assay of protein interaction, Biotech. Histochem. 86 (2011) 272–279.
[86] A. Romero-Ruiz, L. Bautista, V. Navarro, A. Heras-Garvin, R. March-Diaz, A. Castellano, R. Gomez-Diaz, M.J. Castro, E. Berra, J. Lopez-Barneo, A. Pascual, Prolyl hydroxylase-dependent modulation of eukaryotic elongation factor 2 activity and protein translation under acute hypoxia, J. Biol. Chem. 287 (2012) 9651–9658.
[87] G.J. Browne, S.G. Finn, C.G. Proud, Stimulation of the AMP-activated protein kinase leads to activation of eukaryotic elongation factor 2 kinase and to its phosphorylation at a novel site, serine 398, J. Biol. Chem. 279 (2004) 12220–12231.
[88] A.C. Epstein, J.M. Gleadle, L.A. McNeill, K.S. Hewitson, J. O'Rourke, D.R. Mole, M. Mukherji, E. Metzen, M.I. Wilson, A. Dhanda, Y.M. Tian, N. Masson, D.L. Hamilton, P. Jaakkola, R. Barstead, J. Hodgkin, P.H. Maxwell, C.W. Pugh, C.J. Schofield, P.J. Ratcliffe, C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation, Cell 107 (2001) 43–54.
[89] T. Yi, E. Papadopoulos, P.R. Hagner, G. Wagner, Hypoxia-inducible factor-1alpha (HIF-1alpha) promotes cap-dependent translation of selective mRNAs through up-regulating initiation factor eIF4E1 in breast cancer cells under hypoxia conditions, J. Biol. Chem. 288 (2013) 18732–18742.
[90] J. Somers, T. Poyry, A.E. Willis, A perspective on mammalian upstream open reading frame function, Int. J. Biochem. Cell Biol. 45 (2013) 1690–1700.
[91] K. Ameri, C.E. Lewis, M. Raida, H. Sowter, T. Hai, A.L. Harris, Anoxic induction of ATF-4 through HIF-1-independent pathways of protein stabilization in human cancer cells, Blood 103 (2004) 1876–1882.
[92] L.R. Pike, D.C. Singleton, F. Buffa, O. Abramczyk, K. Phadwal, J.L. Li, A.K. Simon, J.T. Murray, A.L. Harris, Transcriptional up-regulation of ULK1 by ATF4 contributes to cancer cell survival, Biochem. J. 449 (2013) 389–400.
[93] M. Horiguchi, S. Koyanagi, A. Okamoto, S.O. Suzuki, N. Matsunaga, S. Ohdo, Stress-regulated transcription factor ATF4 promotes neoplastic transformation by suppressing expression of the INK4a/ARF cell senescence factors, Cancer Res. 72 (2012) 395–401.
[94] K.M. Rouschop, T. van den Beucken, L. Dubois, H. Niessen, J. Bussink, K. Savelkouls, T. Keulers, H. Mujcic, W. Landuyt, J.W. Voncken, P. Lambin, A.J. van der Kogel, M. Koritzinsky, B.G. Wouters, The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5, J. Clin. Invest. 120 (2010) 127–141.
[95] T. Rzymski, M. Milani, L. Pike, F. Buffa, H.R. Mellor, L. Winchester, I. Pires, E. Hammond, I. Ragoussis, A.L. Harris, Regulation of autophagy by ATF4 in response to severe hypoxia, Oncogene 29 (2010) 4424–4435.
[96] A.G. Bert, R. Grepin, M.A. Vadas, G.J. Goodall, Assessing IRES activity in the HIF-1alpha and other cellular 5′ UTRs, RNA 12 (2006) 1074–1083.
[97] R.M. Young, S.J. Wang, J.D. Gordan, X. Ji, S.A. Liebhaber, M.C. Simon, Hypoxia-mediated selective mRNA translation by an internal ribosome entry site-independent mechanism, J. Biol. Chem. 283 (2008) 16309–16319.
[98] M. Buzzai, D.E. Bauer, R.G. Jones, R.J. Deberardinis, G. Hatzivassiliou, R.L. Elstrom, C.B. Thompson, The glucose dependence of Akt-transformed cells can be reversed by pharmacologic activation of fatty acid beta-oxidation, Oncogene 24 (2005) 4165–4173.
[99] H. Shim, Y.S. Chun, B.C. Lewis, C.V. Dang, A unique glucose-dependent apoptotic pathway induced by c-Myc, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 1511–1516.
[100] A. Hirayama, K. Kami, M. Sugimoto, M. Sugawara, N. Toki, H. Onozuka, T. Kinoshita, N. Saito, A. Ochiai, M. Tomita, H. Esumi, T. Soga, Quantitative metabolome profiling of colon and stomach cancer microenvironment by capillary electrophoresis time-of-flight mass spectrometry, Cancer Res. 69 (2009) 4918–4925.
[101] T. Schroeder, H. Yuan, B.L. Viglianti, C. Peltz, S. Asopa, Z. Vujaskovic, M.W. Dewhirst, Spatial heterogeneity and oxygen dependence of glucose consumption in R3230Ac and fibrosarcomas of the Fischer 344 rat, Cancer Res. 65 (2005) 5163–5171.
[102] R.G. Jones, C.B. Thompson, Tumor suppressors and cell metabolism: a recipe for cancer growth, Genes Dev. 23 (2009) 537–548.
[103] A.Y. Choo, S.G. Kim, M.G. Vander Heiden, S.J. Mahoney, H. Vu, S.O. Yoon, L.C. Cantley, J. Blenis, Glucose addiction of TSC null cells is caused by failed mTORC1-dependent balancing of metabolic demand with supply, Mol. Cell 38 (2010) 487–499.
[104] G. Leprivier, P.H. Sorensen, How does oncogene transformation render tumor cells hypersensitive to nutrient deprivation? Bioessays 36 (2014) 1082–1090.
[105] G. Leprivier, M. Remke, B. Rotblat, A. Dubuc, A.R. Mateo, M. Kool, S. Agnihotri, A. El-Naggar, B. Yu, S. Prakash Somasekharan, B. Faubert, G. Bridon, C.E. Tognon, J. Mathers, R. Thomas, A. Li, A. Barokas, B. Kwok, M. Bowden, S. Smith, X. Wu, A. Korshunov, T. Hielscher, P.A. Northcott, J.D. Galpin, C.A. Ahern, Y. Wang, M.G. McCabe, V.P. Collins, R.G. Jones, M. Pollak, O. Delattre, M.E. Gleave, E. Jan, S.M. Pfister, C.G. Proud, W.B. Derry, M.D. Taylor, P.H. Sorensen, The eEF2 Kinase Confers Resistance to Nutrient Deprivation by Blocking Translation Elongation, Cell 153 (2013) 1064–1079.
[106] C. Mauro, S.C. Leow, E. Anso, S. Rocha, A.K. Thotakura, L. Tornatore, M. Moretti, E. De Smaele, A.A. Beg, V. Tergaonkar, N.S. Chandel, G. Franzoso, NF-kappaB controls energy homeostasis and metabolic adaptation by upregulating mitochondrial respiration, Nat. Cell Biol. 13 (2011) 1272–1279.
[107] K. Zaugg, Y. Yao, P.T. Reilly, K. Kannan, R. Kiarash, J. Mason, P. Huang, S.K. Sawyer, B. Fuerth, B. Faubert, T. Kalliomaki, A. Elia, X. Luo, V. Nadeem, D. Bungard, S. Yalavarthi, J.D. Growney, A. Wakeham, Y. Moolani, J. Silvester, A.Y. Ten, W. Bakker, K. Tsuchihara, S.L. Berger, R.P. Hill, R.G. Jones, M. Tsao, M.O. Robinson, C.B. Thompson, G. Pan, T.W. Mak, Carnitine palmitoyltransferase 1C promotes cell survival and tumor growth under conditions of metabolic stress, Genes Dev. 25 (2011) 1041–1051.
[108] A. Caro-Maldonado, C. Muñoz-Pinedo, Dying for something to eat: how cells respond to starvation, Open Cell Signal. J. 3 (2011) 42–51.
[109] H. Muaddi, M. Majumder, P. Peidis, A.I. Papadakis, M. Holcik, D. Scheuner, R.J. Kaufman, M. Hatzoglou, A.E. Koromilas, Phosphorylation of eIF2alpha at serine 51 is an important determinant of cell survival and adaptation to glucose deficiency, Mol. Biol. Cell 21 (2010) 3220–3231.
[110] K.A. Scorsone, R. Panniers, A.G. Rowlands, E.C. Henshaw, Phosphorylation of eukaryotic initiation factor 2 during physiological stresses which affect protein synthesis, J. Biol. Chem. 262 (1987) 14538–14543.
[111] J. Fernandez, I. Yaman, R. Mishra, W.C. Merrick, M.D. Snider, W.H. Lamers, M. Hatzoglou, Internal ribosome entry site-mediated translation of a mammalian mRNA is regulated by amino acid availability, J. Biol. Chem. 276 (2001) 12285–12291.
[112] J. Zhang, J. Fan, S. Venneti, J.R. Cross, T. Takagi, B. Bhinder, H. Djaballah, M. Kanai, E.H. Cheng, A.R. Judkins, B. Pawel, J. Baggs, S. Cherry, J.D. Rabinowitz, C.B. Thompson, Asparagine plays a critical role in regulating cellular adaptation to glutamine depletion, Mol. Cell 56 (2014) 205–218.
[113] L.E. Campbell, X. Wang, C.G. Proud, Nutrients differentially regulate multiple translation factors and their control by insulin, Biochem. J. 344 (Pt 2) (1999) 433–441.
[114] E.M. Smith, C.G. Proud, cdc2-cyclin B regulates eEF2 kinase activity in a cell cycle- and amino acid-dependent manner, EMBO J. 27 (2008) 1005–1016.
[115] X. Wang, W. Li, M. Williams, N. Terada, D.R. Alessi, C.G. Proud, Regulation of elongation factor 2 kinase by p90(RSK1) and p70 S6 kinase, EMBO J. 20 (2001) 4370–4379.
[116] G. Qing, B. Li, A. Vu, N. Skuli, Z.E. Walton, X. Liu, P.A. Mayes, D.R. Wise, C.B. Thompson, J.M. Maris, M.D. Hogarty, M.C. Simon, ATF4 regulates MYC-mediated neuroblastoma cell death upon glutamine deprivation, Cancer Cell 22 (2012) 631–644.
[117] P. Zhang, B.C. McGrath, J. Reinert, D.S. Olsen, L. Lei, S. Gill, S.A. Wek, K.M. Vattem, R.C. Wek, S.R. Kimball, L.S. Jefferson, D.R. Cavener, The GCN2 eIF2alpha kinase is

required for adaptation to amino acid deprivation in mice, Mol. Cell. Biol. 22 (2002) 6681–6688.
[118] T.G. Anthony, B.J. McDaniel, R.L. Byerley, B.C. McGrath, D.R. Cavener, M.A. McNurlan, R.C. Wek, Preservation of liver protein synthesis during dietary leucine deprivation occurs at the expense of skeletal muscle mass in mice deleted for eIF2 kinase GCN2, J. Biol. Chem. 279 (2004) 36553–36561.
[119] B.A. Castilho, R. Shanmugam, R.C. Silva, R. Ramesh, B.M. Himme, E. Sattlegger, Keeping the eIF2 alpha kinase Gcn2 in check, Biochim. Biophys. Acta 1843 (2014) 1948–1968.
[120] Y. Wang, Y. Ning, G.N. Alam, B.M. Jankowski, Z. Dong, J.E. Nor, P.J. Polverini, Amino acid deprivation promotes tumor angiogenesis through the GCN2/ATF4 pathway, Neoplasia 15 (2013) 989–997.
[121] M.N. Corradetti, K. Inoki, N. Bardeesy, R.A. DePinho, K.L. Guan, Regulation of the TSC pathway by LKB1: evidence of a molecular link between tuberous sclerosis complex and Peutz–Jeghers syndrome, Genes Dev. 18 (2004) 1533–1538.
[122] D.G. Hardie, AMP-activated protein kinase: an energy sensor that regulates all aspects of cell function, Genes Dev. 25 (2011) 1895–1908.
[123] L. Bar-Peled, D.M. Sabatini, Regulation of mTORC1 by amino acids, Trends Cell Biol. 24 (2014) 400–406.
[124] A. Efeyan, R. Zoncu, S. Chang, I. Gumper, H. Snitkin, R.L. Wolfson, O. Kirak, D.D. Sabatini, D.M. Sabatini, Regulation of mTORC1 by the Rag GTPases is necessary for neonatal autophagy and survival, Nature 493 (2013) 679–683.
[125] Y. Sancak, T.R. Peterson, Y.D. Shaul, R.A. Lindquist, C.C. Thoreen, L. Bar-Peled, D.M. Sabatini, The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1, Science 320 (2008) 1496–1501.
[126] A. Beugnet, X. Wang, C.G. Proud, Target of rapamycin (TOR)-signaling and RAIP motifs play distinct roles in the mammalian TOR-dependent phosphorylation of initiation factor 4E-binding protein 1, J. Biol. Chem. 278 (2003) 40717–40722.
[127] C. Demetriades, N. Doumpas, A.A. Teleman, Regulation of TORC1 in response to amino acid starvation via lysosomal recruitment of TSC2, Cell 156 (2014) 786–799.
[128] Y. Iiboshi, P.J. Papst, H. Kawasome, H. Hosoi, R.T. Abraham, P.J. Houghton, N. Terada, Amino acid-dependent control of p70(s6k) involvement of tRNA aminoacylation in the regulation, The Journal of biological chemistry 274 (1999) 1092–1099.
[129] M. Roccio, J.L. Bos, F.J. Zwartkruis, Regulation of the small GTPase Rheb by amino acids, Oncogene 25 (2006) 657–664.
[130] A.R. Tee, D.C. Fingar, B.D. Manning, D.J. Kwiatkowski, L.C. Cantley, J. Blenis, Tuberous sclerosis complex-1 and -2 gene products function together to inhibit mammalian target of rapamycin (mTOR)-mediated downstream signaling, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 13571–13576.
[131] C.H. Lee, K. Inoki, M. Karbowniczek, E. Petroulakis, N. Sonenberg, E.P. Henske, K.L. Guan, Constitutive mTOR activation in TSC mutants sensitizes cells to energy starvation and genomic damage via p53, EMBO J. 26 (2007) 4812–4823.
[132] T.L. Ng, G. Leprivier, M.D. Robertson, C. Chow, M.J. Martin, K.R. Laderoute, E. Davicioni, T.J. Triche, P.H. Sorensen, The AMPK stress response pathway mediates anoikis resistance through inhibition of mTOR and suppression of protein synthesis, Cell Death Differ. 19 (2012) 501–510.
[133] S.M. Jeon, N.S. Chandel, N. Hay, AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress, Nature 485 (2012) 661–665.
[134] A.N. Dang Do, S.R. Kimball, D.R. Cavener, L.S. Jefferson, eIF2alpha kinases GCN2 and PERK modulate transcription and translation of distinct sets of mRNAs in mouse liver, Physiol. Genomics 38 (2009) 328–341.
[135] B.M. Zid, A.N. Rogers, S.D. Katewa, M.A. Vargas, M.C. Kolipinski, T.A. Lu, S. Benzer, P. Kapahi, 4E-BP extends lifespan upon dietary restriction by enhancing mitochondrial activity in Drosophila, Cell 139 (2009) 149–160.
[136] H.P. Harding, Y. Zhang, H. Zeng, I. Novoa, P.D. Lu, M. Calfon, N. Sadri, C. Yun, B. Popko, R. Paules, D.F. Stojdl, J.C. Bell, T. Hettmann, J.M. Leiden, D. Ron, An integrated stress response regulates amino acid metabolism and resistance to oxidative stress, Mol. Cell 11 (2003) 619–633.
[137] H. Chen, Y.X. Pan, E.E. Dudenhausen, M.S. Kilberg, Amino acid deprivation induces the transcription rate of the human asparagine synthetase gene through a timed program of expression and promoter binding of nutrient-responsive basic region/leucine zipper transcription factors as well as localized histone acetylation, J. Biol. Chem. 279 (2004) 50829–50839.
[138] W. B'Chir, A.C. Maurin, V. Carraro, J. Averous, C. Jousse, Y. Muranishi, L. Parry, G. Stepien, P. Fafournoux, A. Bruhat, The eIF2alpha/ATF4 pathway is essential for stress-induced autophagy gene expression, Nucleic Acids Res. 41 (2013) 7683–7699.
[139] J.J. Lum, R.J. DeBerardinis, C.B. Thompson, Autophagy in metazoans: cell survival in the land of plenty, Nat. Rev. Mol. Cell Biol. 6 (2005) 439–448.
[140] I. Lohse, P. Reilly, K. Zaugg, The CPT1C 5′UTR contains a repressing upstream open reading frame that is regulated by cellular energy availability and AMPK, PLoS One 6 (2011) e21486.
[141] J. Fernandez, B. Bode, A. Koromilas, J.A. Diehl, I. Krukovets, M.D. Snider, M. Hatzoglou, Translation mediated by the internal ribosome entry site of the cat-1 mRNA is regulated by glucose availability in a PERK kinase-dependent manner, J. Biol. Chem. 277 (2002) 11780–11787.
[142] J. Fernandez, I. Yaman, W.C. Merrick, A. Koromilas, R.C. Wek, R. Sood, J. Hensold, M. Hatzoglou, Regulation of internal ribosome entry site-mediated translation by eukaryotic initiation factor-2alpha phosphorylation and translation of a small upstream open reading frame, J. Biol. Chem. 277 (2002) 2050–2058.
[143] I. Yaman, J. Fernandez, H. Liu, M. Caprara, A.A. Komar, A.E. Koromilas, L. Zhou, M.D. Snider, D. Scheuner, R.J. Kaufman, M. Hatzoglou, The zipper model of translational control: a small upstream ORF is the switch that controls structural remodeling of an mRNA leader, Cell 113 (2003) 519–531.
[144] F. Damiano, S. Alemanno, G.V. Gnoni, L. Siculella, Translational control of the sterol-regulatory transcription factor SREBP-1 mRNA in response to serum starvation or ER stress is mediated by an internal ribosome entry site, Biochem. J. 429 (2010) 603–612.
[145] A. Riley, L.E. Jordan, M. Holcik, Distinct 5′ UTRs regulate XIAP expression under normal growth conditions and during cellular stress, Nucleic Acids Res. 38 (2010) 4665–4674.
[146] T. Finkel, N.J. Holbrook, Oxidants, oxidative stress and the biology of ageing, Nature 408 (2000) 239–247.
[147] W. Zhu, M.H. Soonpaa, H. Chen, W. Shen, R.M. Payne, E.a. Liechty, R.L. Caldwell, W. Shou, L.J. Field, Acute doxorubicin cardiotoxicity is associated with p53-induced inhibition of the mammalian target of rapamycin pathway, Circulation 119 (2009) 99–106.
[148] a.J. Levine, P53, the cellular gatekeeper for growth and division, Cell 88 (1997) 323–331.
[149] K. Bensaad, A. Tsuruta, M.A. Selak, M. Vidal, K. Nakano, R. Bartrons, E. Gottlieb, K.H. Vousden, TIGAR, a p53-inducible regulator of glycolysis and apoptosis, Cell 126 (2006) 107–120.
[150] B. Rotblat, T.G. Grunewald, G. Leprivier, G. Melino, R.A. Knight, Anti-oxidative stress response genes: bioinformatic analysis of their expression and relevance in multiple cancers, Oncotarget 4 (2013) 2577–2590.
[151] G.I. Evan, K.H. Vousden, Proliferation, cell cycle and apoptosis in cancer, Nature 411 (2001) 342–348.
[152] E.C. LaCasse, D.J. Mahoney, H.H. Cheung, S. Plenchette, S. Baird, R.G. Korneluk, IAP-targeted therapies for cancer, Oncogene 27 (2008) 6252–6275.
[153] B. Rotblat, G. Melino, R.A. Knight, NRF2 and p53: Januses in cancer? Oncotarget 3 (2012) 1272–1283.
[154] K. Fujimura, A.T. Sasaki, P. Anderson, Selenite targets eIF4E-binding protein-1 to inhibit translation initiation and induce the assembly of non-canonical stress granules, Nucleic Acids Res. 40 (2012) 8099–8110.
[155] E. McEwen, N. Kedersha, B. Song, D. Scheuner, N. Gilks, A. Han, J.J. Chen, P. Anderson, R.J. Kaufman, Heme-regulated inhibitor kinase-mediated phosphorylation of eukaryotic translation initiation factor 2 inhibits translation, induces stress granule formation, and mediates survival upon arsenite exposure, J. Biol. Chem. 280 (2005) 16925–16933.
[156] F.H. Pham, P.H. Sugden, A. Clerk, Regulation of protein kinase B and 4E-BP1 by oxidative stress in cardiac myocytes, Circ. Res. 86 (2000) 1252–1258.
[157] H.P. Chu, Y. Liao, J.S. Novak, Z. Hu, J.J. Merkin, Y. Shymkiv, B.P. Braeckman, M.V. Dorovkov, A. Nguyen, P.M. Clifford, R.G. Nagele, D.E. Harrison, R.E. Ellis, A.G. Ryazanov, Germline quality control: eEF2K stands guard to eliminate defective oocytes, Dev. Cell 28 (2014) 561–572.
[158] J. Deng, H.P. Harding, B. Raught, A.-C. Gingras, J.J. Berlanga, D. Scheuner, R.J. Kaufman, D. Ron, N. Sonenberg, Activation of GCN2 in UV-irradiated cells inhibits translation, Curr. Biol. 12 (2002) 1279–1286.
[159] M.S. Iordanov, D. Pribnow, J.L. Magun, T.H. Dinh, J.A. Pearson, B.E. Magun, Ultraviolet radiation triggers the ribotoxic stress response in mammalian cells, J. Biol. Chem. 273 (1998) 15794–15803.
[160] H.-y. Jiang, R. Wek, GCN2 phosphorylation of eIF2alpha activates NF-kappaB in response to UV irradiation, Biochem. J. 380 (2005) 371–380.
[161] N.H. Kwon, T. Kang, J.Y. Lee, H.H. Kim, H.R. Kim, J. Hong, Y.S. Oh, J.M. Han, M.J. Ku, S.Y. Lee, S. Kim, Dual role of methionyl-tRNA synthetase in the regulation of translation and tumor suppressor activity of aminoacyl-tRNA synthetase-interacting multifunctional protein-3, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 19635–19640.
[162] a.R. Tee, C.G. Proud, DNA-damaging agents cause inactivation of translational regulators linked to mTOR signalling, Oncogene 19 (2000) 3021–3031.
[163] S. Wu, Y. Hu, J.L. Wang, M. Chatterjee, Y. Shi, R.J. Kaufman, Ultraviolet light inhibits translation through activation of the unfolded protein response kinase PERK in the lumen of the endoplasmic reticulum, J. Biol. Chem. 277 (2002) 18077–18083.
[164] R.J. Kaufman, D. Scheuner, M. Schroder, X. Shen, K. Lee, C.Y. Liu, S.M. Arnold, The unfolded protein response in nutrient sensing and differentiation, Nat. Rev. Mol. Cell Biol. 3 (2002) 411–421.
[165] C.H. Yoon, E.S. Lee, D.S. Lim, Y.S. Bae, PKR, a p53 target gene, plays a crucial role in the tumor-suppressor function of p53, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 7852–7857.
[166] M.J. Morgan, Z.G. Liu, Crosstalk of reactive oxygen species and NF-kappaB signaling, Cell Res. 21 (2011) 103–115.
[167] A. Alexander, S.-L. Cai, J. Kim, A. Nanez, M. Sahin, K.H. MacLean, K. Inoki, K.-L. Guan, J. Shen, M.D. Person, D. Kusewitt, G.B. Mills, M.B. Kastan, C.L. Walker, ATM signals to TSC2 in the cytoplasm to regulate mTORC1 in response to ROS, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 4153–4158.
[168] A.V. Budanov, M. Karin, p53 target genes sestrin1 and sestrin2 connect genotoxic stress and mTOR signaling, Cell 134 (2008) 451–460.
[169] J. Zhang, J. Kim, A. Alexander, S. Cai, D.N. Tripathi, R. Dere, A.R. Tee, J. Tait-Mulder, A. Di Nardo, J.M. Han, E. Kwiatkowski, E.a. Dunlop, K.M. Dodd, R.D. Folkerth, P.L. Faust, M.B. Kastan, E. Kwiatkowski, M.Sahin Sahin, C.L. Walker, A tuberous sclerosis complex signalling node at the peroxisome regulates mTORC1 and autophagy in response to ROS, Nat. Cell Biol. 15 (2013) 1186–1196.
[170] I. Tekedereli, S.N. Alpay, C.D. Tavares, Z.E. Cobanoglu, T.S. Kaoud, I. Sahin, A.K. Sood, G. Lopez-Berestein, K.N. Dalby, B. Ozpolat, Targeted silencing of elongation factor 2 kinase suppresses growth and sensitizes tumors to doxorubicin in an orthotopic model of breast cancer, PLoS One 7 (2012) e41171.
[171] K. Bourougaa, N. Naski, C. Boularan, C. Mlynarczyk, M.M. Candeias, S. Marullo, R. Fahraeus, Endoplasmic reticulum stress induces G2 cell-cycle arrest via mRNA translation of the p53 isoform p53/47, Mol. Cell 38 (2010) 78–88.
[172] S.E. Purdom-Dickinson, E.V. Sheveleva, H. Sun, Q.M. Chen, Translational control of nrf2 protein in activation of antioxidant response by oxidants, Mol. Pharmacol. 72 (2007) 1074–1081.

[173] E.J. Kim, Y.J. Lee, S. Kang, Y.B. Lim, Ionizing radiation activates PERK/eIF2alpha/ATF4 signaling via ER stress-independent pathway in human vascular endothelial cells, Int. J. Radiat. Biol. 90 (2014) 306–312.
[174] A. Nagelkerke, J. Bussink, A.J. van der Kogel, F.C. Sweep, P.N. Span, The PERK/ATF4/LAMP3-arm of the unfolded protein response affects radioresistance by interfering with the DNA damage response, Radiother. Oncol. 108 (2013) 415–421.
[175] L. Zach, I. Braunstein, A. Stanhill, Stress-induced start codon fidelity regulates arsenite-inducible regulatory particle-associated protein (AIRAP) translation, J. Biol. Chem. 289 (2014) 20706–20716.
[176] J. Sok, M. Calfon, J. Lu, P. Lichtlen, S.G. Clark, D. Ron, Arsenite-inducible RNA-associated protein (AIRAP) protects cells from arsenite toxicity, Cell Stress Chaperones 6 (2001) 6–15.
[177] G. Ott, A. Rosenwald, E. Campo, Understanding MYC-driven aggressive B-cell lymphomas: pathogenesis and classification, Blood 122 (2013) 3884–3891.
[178] T. Subkhankulova, S. Mitchell, A. Willis, Internal ribosome entry segment-mediated initiation of c-Myc protein synthesis following genotoxic stress, Biochem. J. 192 (2001) 183–192.
[179] M. Holcik, C. Lefebvre, C. Yeh, T. Chow, R.G. Korneluk, A new internal-ribosome-entry-site motif potentiates XIAP-mediated cytoprotection, Nat. Cell Biol. 1 (1999) 190–192.
[180] G. Desplanques, N. Giuliani, R. Delsignore, V. Rizzoli, R. Bataille, S. Barillé-Nion, Impact of XIAP protein levels on the survival of myeloma cells, Haematologica 94 (2009) 87–93.
[181] X. Yang, Y. Hao, A. Ferenczy, S.C. Tang, A. Pater, Overexpression of anti-apoptotic gene BAG-1 in human cervical cancer, Exp. Cell Res. 247 (1999) 200–207.
[182] H.C. Dobbyn, K. Hill, T.L. Hamilton, K.A. Spriggs, B.M. Pickering, M.J. Coldwell, C.H. de Moor, M. Bushell, A.E. Willis, Regulation of BAG-1 IRES-mediated translation following chemotoxic stress, Oncogene 27 (2008) 1167–1174.
[183] K.W. Sherrill, M.P. Byrd, M.E. Van Eden, R.E. Lloyd, BCL-2 translation is mediated via internal ribosome entry during cell stress, J. Biol. Chem. 279 (2004) 29066–29074.
[184] M.E. Van Eden, M.P. Byrd, K.W. Sherrill, R.E. Lloyd, Translation of cellular inhibitor of apoptosis protein 1 (c-IAP1) mRNA is IRES mediated and regulated during cell stress, RNA 10 (2004) 469–481.
[185] M.M. Candeias, D.J. Powell, E. Roubalova, S. Apcher, K. Bourougaa, B. Vojtesek, H. Bruzzoni-Giovanelli, R. Fahraeus, Expression of p53 and p53/47 are controlled by alternative mechanisms of messenger RNA translation initiation, Oncogene 25 (2006) 6936–6947.
[186] P.S. Ray, R. Grover, S. Das, Two internal ribosome entry sites mediate the translation of p53 isoforms, EMBO Rep. 7 (2006) 404–410.
[187] R. Grover, P.S. Ray, S. Das, Polypyrimidine tract binding protein regulates IRES-mediated translation of p53 isoforms, Cell Cycle 7 (2008) 2189–2198.
[188] D. Khan, A. Sharathchandra, A. Ponnuswamy, R. Grover, S. Das, Effect of a natural mutation in the 5′ untranslated region on the translational control of p53 mRNA, Oncogene 32 (2013) 4148–4159.
[189] L. Malbert-Colas, A. Ponnuswamy, V. Olivares-Illana, A.S. Tournillon, N. Naski, R. Fahraeus, HDMX folds the nascent p53 mRNA following activation by the ATM kinase, Mol. Cell 54 (2014) 500–511.
[190] A. Sharathchandra, R. Lal, D. Khan, S. Das, Annexin A2 and PSF proteins interact with p53 IRES and regulate translation of p53 mRNA, RNA Biol. 9 (2012) 1429–1439.
[191] S. Weingarten-Gabbay, D. Khan, N. Liberman, Y. Yoffe, S. Bialik, S. Das, M. Oren, A. Kimchi, The translation initiation factor DAP5 promotes IRES-driven translation of p53 mRNA, Oncogene 33 (2014) 611–618.
[192] W. Li, N. Thakor, E.Y. Xu, Y. Huang, C. Chen, R. Yu, M. Holcik, A.N. Kong, An internal ribosomal entry site mediates redox-sensitive translation of Nrf2, Nucleic Acids Res. 38 (2010) 778–788.
[193] K.P. Shay, A.J. Michels, W. Li, A.N. Kong, T.M. Hagen, Cap-independent Nrf2 translation is part of a lipoic acid-stimulated detoxification stress response, Biochim. Biophys. Acta 1823 (2012) 1102–1109.
[194] J. Zhang, T.N. Dinh, K. Kappeler, G. Tsaprailis, Q.M. Chen, La autoantigen mediates oxidant induced de novo Nrf2 protein translation, Mol. Cell Proteomics 11 (2012) (M111 015032).
[195] X. Wang, Y. Zhao, Z. Xiao, B. Chen, Z. Wei, B. Wang, J. Zhang, J. Han, Y. Gao, L. Li, H. Zhao, W. Zhao, H. Lin, J. Dai, Alternative translation of OCT4 by an internal ribosome entry site and its novel function in stress response, Stem Cells 27 (2009) 1265–1275.
[196] Z.S. Xiao, L.G. Simpson, L.D. Quarles, IRES-dependent translational control of Cbfa1/Runx2 expression, J. Cell. Biochem. 88 (2003) 493–505.
[197] A.M. Giudetti, F. Damiano, G.V. Gnoni, L. Siculella, Low level of hydrogen peroxide induces lipid synthesis in BRL-3A cells through a CAP-independent SREBP-1a activation, Int. J. Biochem. Cell Biol. 45 (2013) 1419–1426.