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Translational control and the cancer cell response to stress

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The evidence for the importance of aberrant translation in cancer cells is overwhelming. Reflecting the wealth of data, there are excellent reviews delineating how ribosomes and initiation factors are linked to cancer [1–3], and the therapeutic strategies being devised to target them [4]. Changes in translational efficiency can engender a malignant phenotype without the need for chromatin reorganization, transcription, splicing and mRNA export [5,6]. Thus, cancer-related modulations of the translational machinery are ideally suited to allow cancer cells to respond to the various stresses encountered along the path of tumorigenesis and organism-wide dissemination [7•,8,9,10•]. Emerging findings supporting this notion are the focus of this review.

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Translational control: critical determinant of (cancer) cell fate

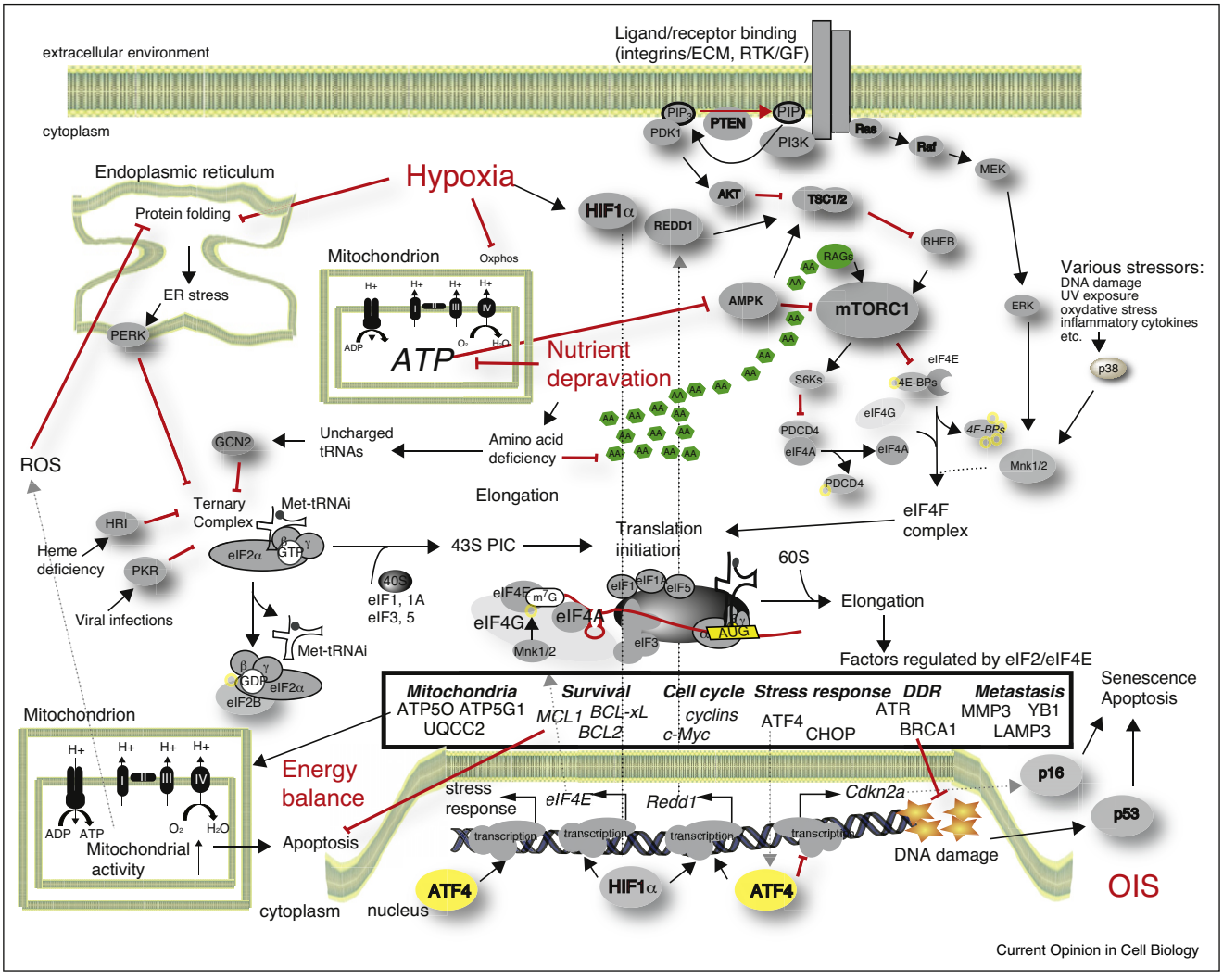
The translation of mRNAs into proteins is the most energy consuming step in the process of gene expression, more than gene transcription, mRNA degradation and proteasome-mediated protein degradation combined [11,12]. Translation has been reported as the greatest contributor to variations in gene expression levels [13–15]. While this proposition is still debated, it remains clear that translational control has a profound impact on gene expression in certain contexts. For example, embryotic stem cells (ESCs), as well as several adult stem cells, undergo drastic changes in global translation and in the translation of specific mRNAs at early stages of differentiation [16,17]. Our group recently demonstrated such an example, where a transcriptional regulator of cardiac lineage commitment, YY2, is translationally repressed in ESCs to maintain self-renewal [18]. Thus, in some conditions, translational control is the major mechanism regulating the expression of specific genes of critical importance. The most striking example of this paradigm is probably ATF4, which is efficiently translated only in stress conditions. ATF4 is the major transcription factor initiating the integrated stress response, however, its expression depends on translational regulation by eIF2α phosphorylation, which is mediated by upstream open reading frames (uORFs) [19] (see references [2,20] for more information on this and the scanning mechanism of translation).

In addition to the eIF2α pathway, translation is regulated in stress conditions by the cap-binding protein eIF4E (Figure 1). Regulation of this initiation factor has been most extensively studied in cancer, as its oncogenic properties were first reported in 1990 [21]. While overexpression of eIF4E leads to a mild increase in global protein synthesis, a specific subset of mRNAs is particularly sensitive to the levels of eIF4E [22]. Such sensitivity has been reported to be conferred by a variety of features present in the mRNA, the details of which are discussed in other reviews [2,20]. While there is no consensus on the relative importance of each of these sequence elements, the overwhelming wealth of data indicates that regulated mRNAs disproportionately encode oncoproteins such as c-MYC, anti-apoptotic proteins such as BCL-xL and pro-angiogenic factors such as VEGFA [2–4,20,22]. It is therefore not surprising that cancer cells deregulate translation to promote their growth. Consistent with this concept are the findings that eIF4E is overexpressed in a wide variety of malignant diseases, including cancers of the breast, prostate, head and neck, colon, leukemias and lymphomas [3]. The list of cancers with dysregulation of eIF4E is growing, with the most recent additions of melanoma, hepatocellular carcinoma, diffuse infiltrating astrocytomas, malignant peripheral nerve sheath tumors and vestibular schwannomas [23–26].

Cancer strategies to deregulate translation

In addition to the aforementioned overexpression of eIF4E, cancer cells take many routes to deregulate translation. The two major regulatory branches are formation of the eIF4F complex, which binds to the mRNA 5′ cap structure, and formation of the ternary complex, which regulates the availability of initiator methionine tRNA for scanning 40S ribosomal subunits (Figure 1). The activity of eIF4F can be modulated by eIF4E levels, eIF4E

Figure 1



Regulation of translation initiation in response to stress. This figure depicts the major signaling pathways regulating translation initiation and their modulation by various stressors. (Upper right) The PI3K/AKT/mTOR pathway is activated in response to signals such as receptor tyrosine kinases (RTK) binding to growth factors (GF) and integrins binding to components of the extracellular matrix (ECM). This results in phosphorylation of inhibitory eIF4E binding proteins (4E-BPs) and availability of eIF4E to form the eIF4F complex in conjunction with eIF4G and eIF4A. Following formation of the eIF4F complex, MNKs may bind to eIF4G and phosphorylate eIF4E. MNKs are activated by MEK/ERK and p38 MAPK pathways in response to a wide range of stimuli including RTK signaling, inflammatory cytokines, and UV exposure. (Middle left) Formation of the ternary complex, consisting of eIF2, GTP and initiator methionine tRNA, is regulated via phosphorylation by the eIF2α kinases, resulting in stabilization of the eIF2-GDP-eIF2B complex and inhibition of translation. Stimuli activating these kinases include viral infections (PKR), heme deficiency (HRI), ER stress (PERK) and uncharged tRNAs (GCN2). (Middle) Ternary complex joins with the 40S ribosomal subunit and other initiation factors to form the 43S pre-initiation complex (PIC), which interacts with the eIF4F complex to promote the scanning of 5′UTRs and AUG recognition, and thus, translation initiation. (Black box) Examples of important factors translationally regulated by eIF4E and eIF2. (Nucleus) Depiction of relevant transcription factors and their targets. Also shown is the importance of DNA damage in oncogene-induced senescence (OIS). (Endoplasmic reticulum) Protein misfolding leads to ER stress and activation of PERK, which phosphorylates eIF2α. (Mitochondrion, top) Oxidative phosphorylation in mitochondria is the major source of cellular energy. The ATP produced maintains adequate AMP/ATP levels to prevent AMPK activation. When nutrients and energy are scarce, AMPK is activated and inhibits the AKT/mTOR pathway. (Mitochondrion, bottom left) Mitochondrial activity is itself regulated by translation, as components of the electron transport chain are regulated by the eIF4F complex. Overactive mitochondria produce excessive ROS, which can lead to protein misfolding in the ER, as well as to apoptosis. The eIF4E-regulated survival factors can counteract the pro-apoptotic effects of overactive mitochondria by maintaining the integrity of their membranes. This delicate balance between energy production and apoptosis is assured by co-regulation of survival and mitochondrial proteins by eIF4E. (Top) Hypoxia inhibits oxidative phosphorylation, as oxygen is the final electron acceptor in this process. As a result, mitochondrial ATP production decreases, leading to AMPK activation and mTOR inhibition. Furthermore, hypoxia activates HIF1α, which translocates to the nucleus and activates the transcription of eFI4E, as well as REDD1. In turn, REDD1 inhibits the mTOR pathway via activation of TSC2. Hypoxia also leads to affects protein folding, leading to ER stress and PERK activation. Black arrows represent activation, red bar-headed lines indicate inhibition, dotted grey arrows follow molecules across subcellular compartments.

phosphorylation via the MAP Kinase Integrating Kinases (MNK1/2), or by the activity of the inhibitory eIF4E binding proteins (4E-BPs). These events occur downstream of oncogenic signaling, specifically through the MAPK and mTOR signaling pathways. These pathways are hyperactive in the vast majority of cancers, particularly due to activating mutations of RAS, BRAF and PI3K, or loss of function mutations of the tumor suppressor PTEN, which are among the most frequent genetic perturbations in cancer [27]. Changes in eIF4F complex formation mildly affect global protein synthesis, but have particularly pronounced effects on the translation of mRNAs encoding proteins which are important for proliferation, metabolism and survival, providing cancer cells a selective advantage [2–4,20,22,28••]. Regulation of eIF2α in cancer is more complex: its phosphorylation results in the inhibition of global protein synthesis and cancer cell proliferation, but is required for adaptation to stress conditions [29]. Thus, a delicate balance must be achieved, which depends heavily on the extent and duration of eIF2α phosphorylation, as well as on the identity of the kinase involved [29]. Notwithstanding these peculiarities, eIF2α has been reported to be overexpressed in some hematological and solid tumors [30,31], as have its upstream kinases [32,33]. Regulation of eIF2 can also be achieved through sequestration by eIF5 and eIF5 mimic proteins (5MP1/2) [34•].

Both of these facets of translational regulation can be modulated, together or separately, to affect protein synthesis in response to stress. Interestingly, Gandin *et al.* demonstrated a coordinated regulation of eIF2α and eIF4E via CK2 and mTORC1 [35•]. This study revealed a novel mechanism of translational adaptation to the microenvironment by which CK2 activates the mTOR pathway via PTEN inactivation, in addition to promoting eIF2α dephosphorylation, thus regulating both arms of translation initiation. A similar crosstalk was observed by Rajesh *et al.*, who implicated eIF2α phosphorylation in the activation of AKT and the response of cancer cells to oxidative stress [36•]. REDD1, which inhibits mTOR via TSC2 activation, has also been suggested to link eIF4F and ternary complex formation [37]. Thus, ATF4 promotes the transcription of REDD1 downstream of ER stress, purportedly to inhibit translation and thus the source of stress [37,38]. Taken together, these studies shed new light on the complex interplay between signaling pathways that endow cancer cells with the ability to modulate translation in response to environmental challenges (Figure 1). The nature of some of these challenges and the translational adaptations to them have been recently investigated and are described below.

Oncogene induced senescence (OIS)

A critical barrier to neoplastic transformation is the coupling of oncogenic stress with the pro-proliferative properties of oncogenes, resulting in senescence or apoptosis. This is related to accumulating DNA damage due to hyperactive proliferative signaling, and activation of the p53/p21 and p16INK4A tumor-suppressor pathways and growth arrest [39–41]. Overexpression or hyperactivation of eIF4E was previously reported to act as a classical oncogene by inducing senescence in mouse embryonic fibroblasts and in B cells [42,43]. In contrast, recent studies using breast cancer models describe eIF4E as an exception to this rule, as its overexpression promotes sustained proliferation without inducing OIS [10•,44]. While DNA damage occurs in cells overexpressing eIF4E [10•], they benefit from the concomitantly increased translation of DNA repair factors such as BRCA1 [45•], in addition to factors promoting survival and cell cycle progression [44,46]. As a result, they are able to overcome the anti-proliferative and pro-apoptotic signals associated with DNA damage and, thus, uncouple OIS from their oncogenic signaling [10•]. Beyond this apparent cell-type specificity of eIF4E-related OIS, it is well established that aberrant eIF4E expression can counteract RAS-mediated OIS and apoptosis induced by c-MYC, cooperating with these oncogenes to promote neoplastic transformation [42,47,48]. Alternatively, cells undergoing transformation can evade OIS and oxidative stress via the eIF2α-ATF4 axis [29,49,50]. Mechanistically, eIF2α phosphorylation promotes ATF4 mRNA translation, which in turn suppresses the transcription of the major senescence inducing gene Cdkn2a [29,50]. Consequently, levels of p16INK4 and p19ARF decrease, preventing senescence. The implication of both eIF4E and eIF2 in the escape from OIS is demonstrated by a proteome-wide study of ubiquitinylation by Bengsch *et al.*, where translational control was identified as critically important in this process [51]. Thus, cancer cells, even in pre-neoplastic stages, deregulate translation to evade senescence and achieve transformation.

Nutrient deprivation and hypoxia

As tumors grow, vascularization becomes limiting for maintaining nutrient and oxygen levels, challenging their survival. However, tumors develop mechanism to counteract this deficiency by using unique translational mechanisms that can function under hypoxia, and by engendering abnormal vasculature [52,53]. Consistent with this, both the eIF2α and eIF4E branches are independently inhibited during hypoxia and nutrient depravation to restrict protein synthesis, though the sensors of each stress vary (see Figure 1) [54]. Concomitantly, translation of the mRNAs encoding known players in the stress response, that is transcripts containing uORFs such as ATF4, is increased, with the recently discovered addition of $p21^{Cip1}$ [55•]. Indeed, Lehman *et al.* identified a transcript variant of the p21 mRNA possessing uORFs, conferring cell cycle arrest and survival in amino acid poor environments. A more controversial topic pertains to the mechanisms by which cancer cells adapt to mTOR inhibition during hypoxia [56]. IRES-dependent translation

has been proposed by some groups [57]. Others have reported that eIF4E2, also known as 4EHP, serves as an alternative cap-binding protein and recruits ribosomes via an alternative initiation complex [58]. Of note, 4EHP is expressed at lower levels and possesses much poorer affinity for the cap than eIF4E [59,60]; therefore, how 4EHP could compete with eIF4E for cap-binding remains to be demonstrated. Specialized translation by non-canonical cap-binding proteins has also been proposed for eIF3d and the c-Jun mRNA [61•]. An alternative model proposes that, in cancer cells, eIF4E-dependent translation is uncoupled from mTOR inhibition [62]. In this context, hypoxia, via HIF1α stabilization, increases eIF4E transcription to enable escape from mTOR/4E-BP1 inhibition of translation [63]. This model is supported by the fact that eIF4E promotes the translation of mRNAs encoding key hypoxia-response factors including the major hypoxia-related transcription factor, HIF1α, and growth factors promoting vascularization such as FGF2 and VEGFA [64–66]. Another possibility is differential recruitment of cap-binding proteins to RNA granules or their post-translational modifications [8,67], a concept that is not mutually exclusive with other hypotheses.

Energetic stress

Low levels of oxygen and/or nutrients can prevent proper energy production by cancer cells, as can mitochondrial damage and chemical inhibitors of oxidative phosphorylation [68]. The link between translation and energy status is mediated by AMPK, which is activated by an increase in the AMP/ATP ratio, leading to phosphorylation of TSC2 and inhibition of translation via the mTOR/4E-BP axis. Phosphorylation of eIF2α downstream of AMPK has also been implicated, specifically in the context of drugs targeting NAD+ synthesis [69]. Thus, energy deficits lead to the inhibition of translation and energy conservation. In turn, many mitochondrial proteins are regulated at the level of translation [70,71]. Interestingly, Gandin *et al.* demonstrated that translational co-regulation of these mitochondrial proteins and anti-apoptotic proteins constitutes a critical survival mechanism. As synthesis of proteins maintaining the integrity of the outer mitochondrial membrane (*e.g.* BCL2, MCL1, BIRC5) is decreased due to mTOR inhibition, mitochondrial activity is coordinately downregulated by preventing the synthesis of key electron transport chain components (*e.g.* ATP5O, ATP5G1, NDUFS6, UQCC2) [28••,70]. Such co-regulation allows cancer cells to rapidly adapt to changing energetic states, but may also confer a targetable weakness, due to differences in the 5′UTRs of the two groups of mRNAs. Oxidative phosphorylation-related mRNAs possess short 5′UTRs enriched for translation initiator of short 5′UTR (TISU) elements, whereas survival-related mRNAs possess long, structured 5′UTRs [28••]. Thus, only the latter group requires the helicase activity of eIF4A to unwind 5′UTR secondary structures. This key difference may explain why mTOR inhibitors are cytostatic, whereas eIF4A inhibitors are cytotoxic, as mitochondrial activity continues despite decreased ability to maintain membrane integrity [28••]. Another important mechanism linking energy status to translation has been reported, whereby energetic stress leads to alternative transcription start site selection, altering the 5′UTRs of a wide array of transcripts and therefore their potential for translational control [72]. Many regulated mRNAs are themselves involved in translation, thus adding to the complexity of the interplay between energy status and translation. For example, under glucose starvation, the gene encoding poly-A binding protein (PABP) is transcribed from an alternative promoter, resulting in a transcript with a shorter 5′UTR lacking autoinhibitory sequences and displaying increased translation [72]. Thus, there are several mechanisms that we are only beginning to uncover by which cancer cells can adapt translation to their energetic requirements. Whether this can be targeted in cancer patients remains to be seen, but it is an area of active investigation [4].

Drug resistance

One of the most studied and clinically dire attributes of translational deregulation is the ability to confer drug resistance on cancer cells. There are numerous reports of resistance to chemotherapy, radiation and targeted therapies being mediated by alterations in the translational machinery [73–76], which has been called a 'nexus of resistance' [75]. Some of the most recent observations include phosphorylated eIF4E-mediated resistance to radiation, DNA damage and alkylating agents [8,77,78], as well as resensitization of ovarian cancers to carboplatin by mTOR kinase inhibitors [45•]. Similar findings have been observed for eIF2α phosphorylation, in that use of salubrinal, a phosphatase inhibitor that prevents eIF2α dephosphorylation, enhances the efficacy of doxorubicin [79] and the proteasome inhibitor bortezomib [80]. These effects are thought to be mediated by increased translation of mRNAs encoding DNA repair and survival factors in the case of deregulated eIF4F complex formation [45•,73–76], and to the pro-apoptotic properties of long-term maintenance of eIF2α phosphorylation in the case of salubrinal [79,80].

Invasion and metastasis

Several challenges are encountered by cancer cells in the process of metastatic dissemination, as they migrate into the extra-cellular matrix (ECM), intravasate, circulate in the blood stream, extravasate and colonize distant organs. Nutrient concentrations change, as do the repertoire of growth factors present, and the composition of the ECM. Interestingly, different ECM components encountered by invading cells may increase mTOR signaling and override its inhibition by hypoxia [81,82]. Phosphorylation of eIF4E and 4E-BPs by MNKs and mTOR,

respectively, promotes the translation of a pro-metastatic program that favors epithelial-to-mesenchymal transition *in vitro* and metastasis *in vivo* [83–89]. In the clinic, deregulation of eIF4E is associated with invasive disease, metastasis and poor survival in prostate, breast, and lung cancers, melanoma, astrocytoma, renal cell carcinoma, and many others [24,26,90–93]. More generally, neo-vascularization due to increased *Vegfa* and *Fgf2* translation during hypoxia is associated with metastatic progression [64,65]. Much less is known about the role of eIF2 regulation in the metastatic process. One group has reported a mild increase in metastasis due to hypoxia-induced eIF2α phosphorylation and promotion of LAMP3 translation [94]. Hypothetically, the many changing environments encountered by cancer cells during invasion, intravasation, survival in circulation, extravasation and colonization should result in a number of stresses likely to affect ternary complex formation, though this remains to be investigated.

Conclusion and perspectives

In summary, studies exploring deregulated translation in cancer underscore the critical importance of translation control in the rapid response of cancer cells to various stresses present in different stages of cancer development and progression. Key translational targets have been identified, and technologies allowing genome-wide analysis of translation are opening new avenues of research and promising therapeutic strategies [28,85].

Despite the importance of translation in cancer, its targeting in cancer patients has not been achieved, notwithstanding some notable benefits of rapamycin analogs [4]. The only drug to target eIF4E directly, LY2275796/ISIS183750, is a second-generation antisense oligonucleotide. When administered intravenously to cancer patients in a phase 1 clinical trial, the eIF4E ASO reduced eIF4E RNA levels in tumor tissue [95,96••]. Importantly however, the reduction of eIF4E protein was delayed, likely reflecting the stability of eIF4E protein in tissue, and was evident only toward the end of cycle 1 [95,96••]. Accordingly, truly evaluating efficacy of the eIF4E ASO might have required additional time on therapy (Graff J, personal communication). Other promising drug candidates are being extensively explored, including inhibitors of the eIF4A helicase, cap-competitive inhibitors, inhibitors of the eIF4E:eIF4G interaction and inhibitors of ternary complex formation [4]. Most interesting is the possibility of utilizing inhibitors of translation in favorable combinations, based on the knowledge summarized herein. For example, proteasome inhibitors such cause apoptotic cell death due to ER stress and eIF2α phosphorylation, and are now being combined with compounds inhibiting eIF2α dephosphorylation, thus preventing cancer cell adaptation (NCT01775553) [80]. Furthermore, combinations of inhibitors of translation and metabolism are currently being investigated in pancreatic cancer, breast cancer, endometrial cancer and several others (NCT02048384, NCT01627067, NCT01529593, NCT00659568), considering the critical interplay between translation and energy status. While not yet in clinical development, inhibitors of eIF4A are particularly attractive in this regard. As their cytotoxicity is based on creating an imbalance between mitochondrial activity and stability, tumors with highly active mitochondria may be especially sensitive to these inhibitors. Finally, considering the importance of translational control in metastatic dissemination, it may be worthwhile to consider the development of inhibitors of translation in clinical settings where metastasis prevention is the main priority, rather than removal of the primary tumor. Prostate cancer patients under active surveillance may benefit from such a strategy.

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