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REVIEW

Translational regulator eIF2α in tumor

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Abstract The eukaryotic translation initiation factor 2α (eIF2α) is the regulatory subunit of eIF2 which can be inactivated by phosphorylation. In the adaptive response to various microenvironmental stresses, phosphorylation of eIF2α (p-eIF2α) by specific kinases significantly downregulates global protein synthesis while selectively upregulates the activating transcription factor 4 (ATF4) translation. The ATF4 is a transcription activator that can translocate into nucleus and upregulate genes involved in amino acid synthesis, redox balance, protein maturation, and degradation which lead to the activation of both autophagy and apoptosis. During tumor progression, adaptive response facilitates tumor cell survival and growth under severe stresses. Therefore, eIF2α phosphorylation significantly promotes tumor progression and resistance to therapy. However, there is also evidence showing that p-eIF2α exerts suppressive effects on tumorigenesis. Current understanding of the roles eIF2α plays in tumor is still incomplete and needs further investigation. This review addresses on the past and current efforts to delineate the molecular mechanisms of eIF2α in tumorigenesis, tumor progression, resistance to therapy, and tumor cachexia as well as the translational promise of therapeutic applications targeting eIF2α-related signaling pathway.

Keywords EIF2α · Tumor · Translation initiation · Stress response · Tumor therapy

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Introduction

The eukaryotic translation initiation factor 2 (eIF2), which is composed of α-, β-, and γ-subunits, plays an essential role in the translation initiation of eukaryotic cells. Phosphorylation on Ser51 of the α regulatory subunit (p-eIF2α) effectively reduces the level of active eIF2, suppressing the initiation of mRNA translation [1]. For the dynamic and primary control of protein abundance which occurs during the process of mRNA translation [2], the p-eIF2α significantly inhibits global protein synthesis. Over the last decade, the function of p-eIF2α has been found to be of critical importance for promoting cellular adaptation and tolerance to stresses. Phosphorylation of eIF2α significantly reduces global mRNA translation, thus allowing cells to conserve resources to effectively manage stress conditions. On the other hand, some specific transcripts, in particular ATF4, are translationally upregulated to reduce stress-related damage [3].

During tumor progression, the cancer cells are characterized by remarkable tolerance to nutrient deprivation and hypoxia, which result from insufficient perfusion by the dysfunctional tumor microvasculature [4, 5]. P-eIF2α plays a pivotal role in response to those cellular stresses, thus facilitating tumor progression. Mounting evidence has demonstrated that the level of expression and phosphorylation status of eIF2α are significantly associated with tumor development and progression. However, the roles of p-eIF2α in the pathogenesis of cancer still remain controversial, because some studies have indicated that p-eIF2α could also provide protection against tumorigenesis. In this review, we will summarize the tumor-suppressive and tumor-promoting properties of eIF2α during different stages of cancer development and progression, and propose therapeutic implications on targeting eIF2α-related signaling pathway.

EIF2α in translational initiation

The eIF2 complex consists of three subunits, namely α-, β-, and γ-subunits. The α subunit regulates the level of active eIF2 complex, while the eIF2γ central subunit is the ribosome-dependent GTPase and binds to GTP or GDP. Subunit β, containing several polylysine repeats, interacts with mRNA and other eukaryotic translation initiation factors [6]. In eukaryotic translation initiation, GTP-bound eIF2 binds to the initiator methionyl-tRNA (Met-$tRNA_i$) and the 40S small ribosomal subunit, forming the eIF2-ternary complex (eIF2-TC). Some of the other translation initiation factors recruited include the eIF4F, eIF3, eIF1, eIF1A, and eIF5, as well as mRNA binding proteins. This initiation factor complex scans the 5′-untranslated region (5′-UTR) of mRNA in a processive 5′ to 3′ manner to the start codon [7–9]. Once the start codon is encountered, eIF2-bound GTP is irreversibly hydrolyzed, and eIF2 is subsequently released from the initiation complex. The guanine nucleotide exchange factor (GEF) eIF2B converts eIF2 from a GDP-bound form to the active eIF2-GTP form for further recruitment in translation initiation. However, this process can be significantly inhibited by the phosphorylation of eIF2α on Ser51 (p-eIF2α), which acts as a competitive inhibitor of the GEF eIF2B [10]. Thus, p-eIF2α effectively suppresses the global protein synthesis in eukaryotic cells. A schematic illustration of the eukaryotic translation initiation is shown in Fig. 1.

In mammals, there exist four kinases that phosphorylate eIF2α on Ser51 in response to various microenvironmental stresses. The RNA-dependent protein kinase (PKR)-related endoplasmic reticulum (ER) kinase (PERK) responds to the accumulation of unfolded proteins in the ER. The PKR, an interferon (IFN)-inducible protein, is activated by binding to double-stranded RNA (dsRNA). The general control nonderepressible 2 kinase (GCN2) is activated by amino acid deprivation or by ultraviolet (UV) irradiation. The heme-regulated inhibitor kinase (HRI) is activated by heme deficiency [11]. These kinases also have important roles in affecting tumor development and progression via phosphorylation of eIF2α.

EIF2α in tumor

EIF2α in tumor initiation and development

EIF2α plays critical roles during tumor initiation and development. The higher expressions of eIF2α have been detected in tumor samples compared to matched normal tissues by immunohistochemistry (IHC), including bronchioloalveolar carcinomas of the lung [12], Hodgkin lymphoma [13], gastrointestinal carcinomas [14], and malignant melanoma [15]. EIF2α has a dual nuclear and cytoplasmic localization in tumor cells, rather than weak cytoplasmic distribution in normal tissues [14, 16]. These differential expressions of eIF2α may contribute to increased abnormal protein synthesis, which is associated with tumorigenesis.

Notably, the phosphorylation of eIF2α potently suppresses translation initiation and would further suppress tumorigenesis. Inhibition of eIF2α phosphorylation facilitated the malignant transformation of human NIH 3T3 cells by the expression of a dominant-negative form of PKR or by a mutant form of eIF2α that could not be phosphorylated [17, 18]. Several subsequent studies confirmed the tumor suppressor properties of p-eIF2α in mice and human tumor cells [19–22]. Furthermore, lower levels of p-eIF2α were found in human osteosarcoma versus normal tissue, while increased PKR levels were associated with increased tumor cell differentiation [17, 18, 23]. Another report demonstrated that the combination of p-eIF2α and PKR could be new prognostic markers for non-small cell lung cancer patients. They revealed that patients with high expressions of both PKR and p-eIF2α had longer survival [24].

As noted above, considerable evidence indicates that p-eIF2α exhibits tumor-suppressive effects during tumor initiation. Since large amounts of proteins are needed during tumorigenesis, p-eIF2α might play a negative role via inhibition of global mRNA translational initiation and is suggested to be an attractive target for antitumor modalities.

EIF2α in tumor progression

Mounting evidence has elucidated that p-eIF2α plays a protective role in tumor progression. As tumor increases in size, the dysfunctional microvasculature results in insufficient blood perfusion, which is associated with hypoxia, low nutrient concentrations, and low extracellular pH in tumor microenvironment [5, 4, 25]. Cancer cells could respond to stresses in various ways and achieve a more aggressive phenotype through eIF2α pathway (Fig. 2) [26].

Under severe hypoxia, the unfolded protein response (UPR) sensor PERK is activated in response to accumulation of unfolded or misfolded proteins in the ER lumen [22, 27, 28]. Exposure of human diploid fibroblasts and transformed cells to hypoxia led to hyperphosphorylation of both PERK and eIF2α. Such modification could be readily reversed upon reoxygenation or overexpression of wild-type PERK. In addition, cells with dominant-negative PERK exhibited attenuated phosphorylation of eIF2α and lower survival rate after exposing to hypoxia [28]. Another study consistently confirmed the protective role of PERK and p-eIF2α in tumor growth. Tumor cells with a nonphosphorylatable mutation of eIF2α or dominant-negative PERK displayed reduced hypoxia tolerance. Tumor allografts derived from nude mice bearing the mutant mouse embryonic fibroblasts (MEFs) grew slower and showed higher

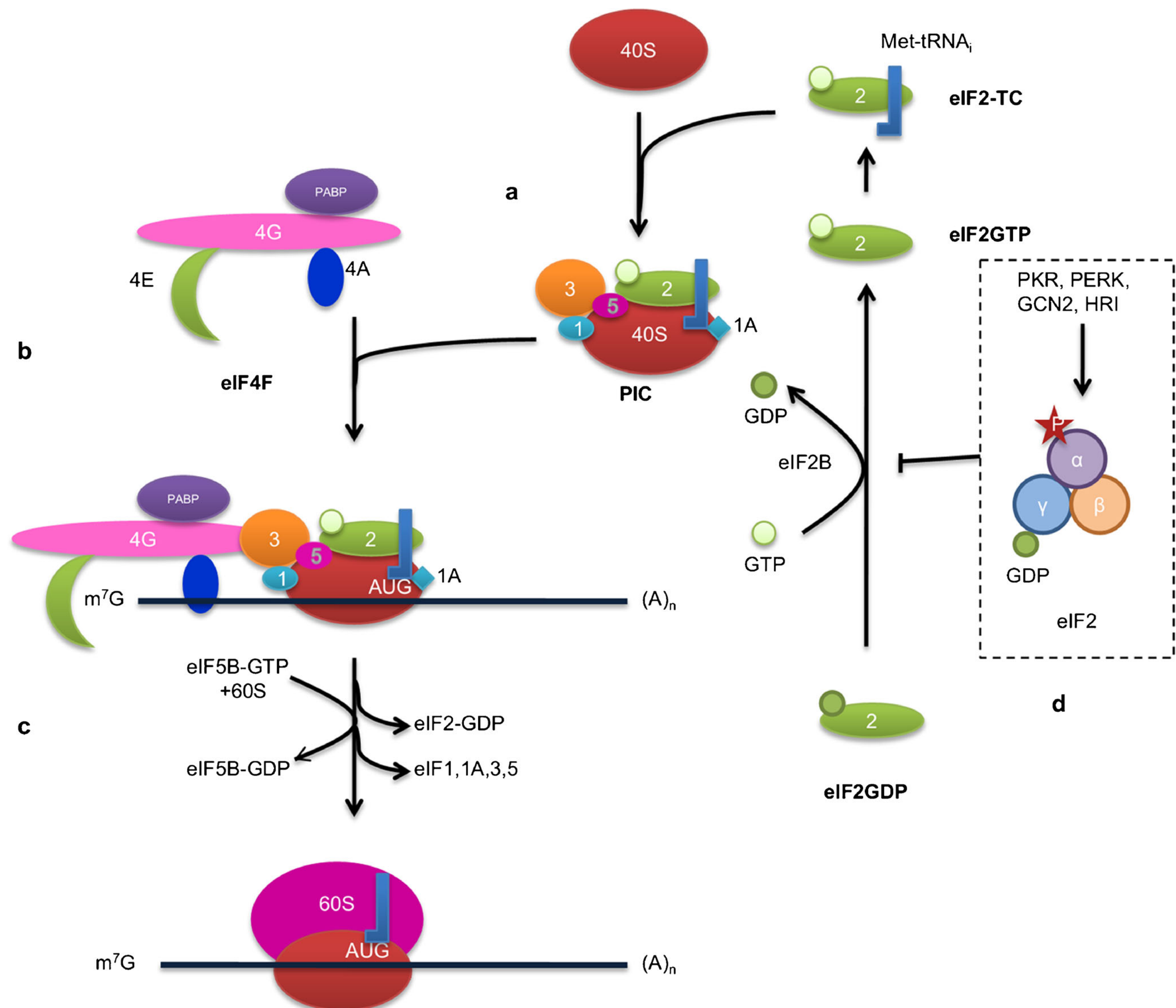

Fig. 1 A schematic illustration of involvement of eIF2α in translational initiation. **a** The eIF2-ternary complex (eIF2-TC) is formed by the 40S ribosomal subunit that binds eIF2-GTP, and the initiator Met-tRNA$_i$. EIF1, eIF1A, eIF3, and eIF5 are recruited to the eIF2-TC, producing the 43S ribosomal pre-initiation complex (PIC). **b** The cap-binding complex eIF4F binds to the mRNA m^{7}G-cap structure through the cap-binding protein eIF4E, while interaction between eIF4G and eIF3 brings the PIC to mRNA leading to formation of the initiation factor complex, which scans the 5′-UTR of mRNA in a processive 5′ to 3′ manner to the initiation codon. **c** Once the initiation codon is encountered, eIF5B-GTP assists in recruitment of the 60S subunit to the initiation complex. During 80S ribosome assembly, together with other initiation factors, eIF2 is released from the ribosome with irreversible hydrolysis of GTP. **d** The guanine nucleotide exchange factor (GEF) eIF2B converts eIF2 from a GDP-bound form to the active eIF2-GTP form for recruitment. However, this process can be inhibited by kinase-mediated phosphorylation of eIF2α in response to various stimulus. *1*, *1A*, *2*, *3*, *4A*, *4E*, *4G*, and 5 stand for eIF1, eIF1A, eIF2, eIF3, eIF4A, eIF4E, eIF4G, and eIF5, respectively

levels of apoptosis in the hypoxic regions compared to tumors with an intact PERK-eIF2α pathway [29].

During amino acid deficiency, uncharged tRNA binds to GCN2 and triggers autophosphorylation in the activation loop of the enzyme, resulting in subsequent phosphorylation of eIF2α [3]. Loss of GCN2 in mice diminished p-eIF2α in liver when the mice were exposed to leucine starvation [30]. A recent study showed that the GCN2-eIF2α pathway confers survival and proliferative advantage under amino acid and glucose deprivation in transformed cells. GCN2 was verified as the molecular sensor of amino acid or glucose deprivation that induced eIF2α phosphorylation and facilitated upregulation of downstream effectors [31].

The p-eIF2α significantly limits the rate of translational initiation, represses the global mRNA translation and thus conserves energy under stress conditions. However, the translation of some specific mRNAs that encode proteins for cellular adaption is upregulated, particularly the activating

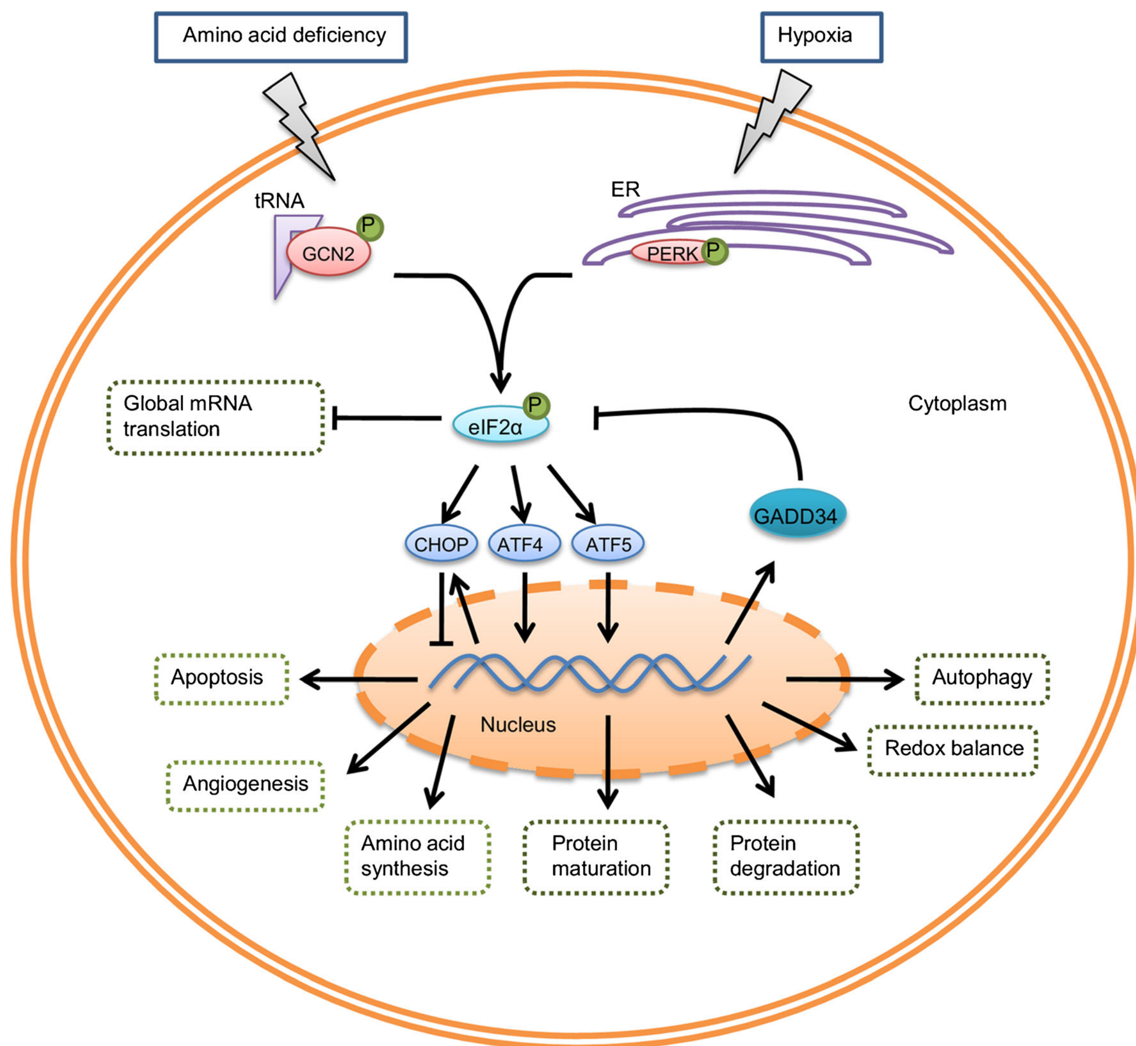

Fig. 2 Phosphorylation of eIF2α in response to microenvironmental stresses during tumor progression. EIF2α is phosphorylated by GCN2 and PERK in response to amino acid deficiency and hypoxia, respectively. Then, p-eIF2α inhibits global mRNA translation but enhances translation of ATF4, ATF5, and CHOP, which facilitate cellular response to stresses. Downstream effects include amino acid synthesis, redox balance, protein maturation and degradation, and activation of autophagy and apoptosis. Specially, GADD34 facilitates feedback dephosphorylation of p-eIF2α to restart global translation. CHOP, which could also be activated by ATF4 in response to prolonged and excessive stress, triggers apoptosis via downregulation of antiapoptotic proteins

transcription factor 4 (ATF4). The increased translation of ATF4 results from differential contribution of its two conserved upstream open reading frames (uORFs) in the 5’ region of the mRNA. In non-stressed cells, ribosomes translate the 5' proximal uORF1 and then scan downstream of mRNA reinitiating at the uORF2, an inhibitory element that blocks ATF4 expression. When the eIF2α is phosphorylated, the level of eIF2-GTP is reduced and ribosomes require increased time to become competent. The delayed reinitiation allows ribosomes to bypass the uORF2 and reinitiate at the ATF4 ORF [32–34]. ATF4 can then translocate into the nucleus, bind to target promoters via C/EBP-ATF response elements (CAREs), and transcriptionally regulate a number of genes involved in amino acid synthesis, redox balance, protein maturation and degradation, and activation of both autophagy and apoptosis [34]. Besides, several other basic region/leucine zipper motif (bZIP) transcription factors, such as ATF5 and C/EBP-homologous protein (CHOP), are also preferentially transcribed during p-eIF2α [35].

Asparagine synthetase (ASNS), which is one of the best characterized proteins activated by ATF4, catalyzes the conversion of aspartate to asparagine during limitations for essential amino acids [36–38]. Study has revealed that overexpression of ASNS increased survival and reversed the proliferation block in ATF4 knockdown cells [31]. During hypoxia, ATF4-dependent upregulated carbonic anhydrase 9 (CA9) promotes tumor invasion and metastasis by contributing to low extracellular pH [39–41]. CA9 was commonly overexpressed in human tumors and recognized as a poor prognostic

factor [42]. Additionally, another target of ATF4 activation, GADD34 facilitates feedback dephosphorylation of p-eIF2α to restart global translation after stress [3].

Notably, BIP (chaperone immunoglobulin heavy chain-binding protein), ORP15 (oxysterol-binding protein and oxysterol-binding protein-related protein 15) and GRP94 (glucose-regulated protein 94), as well as oxidoreductases such as ERO1L (endoplasmic oxidoreductin-1-like protein) and PDI (protein disulphide isomerase) are upregulated during UPR to facilitate protein maturation in ER [43–47]. Increased BIP levels permit retrograde transport of misfolded proteins back across the ER membrane to facilitate their degradation by the cytoplasmic 26S proteasome [48]. Moreover, CHOP and ATF4 induce autophagy via transcriptional upregulation of autophagy-related (Atg) genes, most notably Beclin1 [49]. Autophagic and proteasomal degradation enhances survival capacity of tumor cells under stress [50, 51]. CHOP, which could also be activated by ATF4 in response to prolonged and excessive stress, whereas, triggers apoptosis via downregulation of antiapoptotic proteins [52–55].

EIF2α in tumor therapeutic resistance

Resistance to targeted cancer therapies is a major limitation in cancer treatment. Recently, p-eIF2α has been identified as a potential contributor to cancer therapy resistance. Due to the incomplete fixation of DNA damage as well as diffusion limits, tumor hypoxia significantly contributes to resistance to radiation and chemotherapy [56–59]. In response to hypoxia, hypoxia-inducible factor (HIF) and PERK-eIF2α pathway are activated to promote tumor cell survival. However, the p-eIF2α-dependent arm is uniquely required to determine tumor radioresistance of hypoxic cells. Transient p-eIF2α inhibition increased radiation response of hypoxic cells and enhanced median survival of mice under radiation. They also demonstrated that the p-eIF2α pathway protected cells from cycling hypoxia via the induction of cysteine, glutathione synthesis, and mitigation of effects of reactive oxygen species (ROS) [60]. Additionally, ASNS, a target of ATF4 activation in response to p-eIF2α, is associated with resistance to asparaginase therapy in certain tumors [61, 62].

Furthermore, dormant tumor cells would be resistant to cytotoxic chemotherapy that targets actively dividing cells [63]. Novel mechanisms underlying drug resistance in dormant cancer cells have been identified in a dormant cancer cell model. The dormant cells were resistant to drug-induced death by activation of PERK-eIF2α pathway. Accordingly, the apoptosis rate was significantly enhanced following inhibition of PERK-eIF2α pathway via RNA interference and dominant-negative expression [64].

EIF2α in tumor cachexia

In the terminal stage of cancer, half of cancer patients suffer from cachexia, including atrophy of adipose tissue and skeletal muscle. Both depressed protein synthesis and increased protein degradation contribute to muscle atrophy. The eIF2α is one of the key regulators of protein synthesis in skeletal muscle. Studies have elucidated that PKR was activated to phosphorylate eIF2α; thus, the subsequent decline in global protein translation partially led to cancer cachexia [65–67]. To develop more effective treatment, further studies are needed to finally clarify the molecular basis of cancer cachexia.

Implication for tumor therapy

Considering the important roles for eIF2α during different stages of cancer development and progression, there are several therapeutic approaches that have been proposed to target the eIF2α-related signaling pathway.

Inhibit tumor growth via induction of eIF2α phosphorylation

Recently, Aktas et al. firstly identified three small-molecular-weight compounds, namely clotrimazole (CLT), eicosapentaenoic acid (EPA), and troglitazone (TRO), which exerted distinct antitumor effects via induction of eIF2α phosphorylation and restriction of the availability of the eIF2-GTP-Met-tRNA$_i$ ternary complex both in vitro and in vivo. Through depletion of internal Ca^{2+} stores in cancer cells, CLT, EPA, and TRO induced the phosphorylation of eIF2α and inhibited global protein synthesis but enhanced the expression of ATF4-dependent genes. Notably, CLT, EPA, and TRO significantly inhibited cancer cell proliferation in vitro and tumor growth in mice models [68].

HIF-1α is the oxygen-regulated subunit of HIF-1, and HIF-1 facilitates tumor growth and angiogenesis under hypoxic conditions. Tirapazamine (TPZ), a well-characterized bioreductive anticancer agent, showed inhibitory effect on HIF-1α protein synthesis. Further study revealed that the inhibitory effect on HIF-1α synthesis was dependent on the phosphorylation of eIF2α [69].

Inhibition of eIF2α phosphorylation

The second option might be to inhibit the eIF2α phosphorylation due to the ability of p-eIF2α to cope with cellular stress. 6-Shogaol, a compound derived from ginger (*Zingiber officinale* Rosc), exhibited antitumor activity both in vitro and in vivo. Cells treated with 6-Shogaol showed suppressed eIF2α phosphorylation and increased cell death rate. 6-Shogaol-mediated cell death was prevented by overexpression of eIF2α but enhanced by inhibition of p-eIF2α [70]. In

addition, another report suggested that imatinib-induced cell death in chronic myeloid leukemia (CML) was partially by the reduction of PERK-eIF2α pathway. Inhibiting apoptosis did not affect the inhibitory effects of imatinib on PERK-eIF2α pathway, thereby suggesting that p-eIF2α inhibition was a cause rather than an effect of cell death. Interestingly, inhibition of the PERK-eIF2α phosphorylation significantly increased imatinib-mediated cell death [71]. Thus, inhibiting the eIF2α kinases would be a promising new approach for development of anticancer agents. A number of elF2α kinase inhibitors have been identified; however, there are only a few published reports focusing on the anticancer properties of those inhibitors. GSK2656157 was recently identified as a potent and selective inhibitor of PERK enzyme. In vitro study showed treatment with GSK2656157 significantly inhibited the activation of PERK-eIF2α-ATF4 pathway. Importantly, it exhibits inhibitory effect on multiple human tumor xenografts growth in mice models [72]. Fewer studies, at present, have focused on other substrates of these kinases; it remains unknown if one or more kinases should be inhibited and what the results may be with these inhibitors on tumors.

Inhibition of downstream processing of p-eIF2α

P-eIF2α transcriptionally regulates a large number of genes by selective upregulation of several transcription factors such as ATF4 under UPR [3]. Notably, these downstream factors of p-eIF2α play important roles through several pathways, especially those in the proteasomal and autophagic pathways, in facilitating tumor growth and progression [34, 73]. The third approach may be suggested to target the downstream processing of p-eIF2α.

Proteasomal pathway plays a crucial role in cellular homeostasis after an increase in p-eIF2α during ER stress response [74]. Multiple myeloma (MM) cells constitutively express high levels of UPR components resulting in their sensitivity to proteasomal inhibitors. Bortezomib (BTZ), a specific inhibitor of the 26S proteasome, blocks proteasomal degradation of misfolded proteins and shows a favorable toxicity profile in MM patients. Although there is no evidence to indicate that is dependent on p-eIF2α, the in vitro study has demonstrated that the PERK-eIF2α-ATF4 pathway was rapidly activated and the UPR-induced apoptosis was augmented while the MM cells were treated with BTZ or other proteasomal inhibitors [75]. However, BTZ carries the potential for serious side effects and development of resistance. A recent study suggested that the inhibition of p-eIF2α dephosphorylation by salubrinal could suppress bortezomib-induced quiescence and survival of residual multiple myeloma cells [76]. In addition, another study identified sulforaphane, a dietary isothiocyanate derived from cruciferous vegetables, inhibited proteasomal degradation in a manner similar to BTZ. A combination of sulforaphane and arsenic trioxide (ATO), an agent with clinical activity in MM, induced synergistic cytotoxic effects [77]. Furthermore, a novel proteasome inhibitor MLN9708 was confirmed to inhibit tumor cell growth both in vitro and in vivo [78].

Autophagy, an intracellular degradation system by delivering portions of the cytoplasm and organelles to lysosomes, enables tumor growth during tumor progression. Therefore, pharmacological inhibitors that target autophagy have been proposed for the treatment of cancer, including 3-methyadenine, wortmannin, LY294002, chloroquine (CQ), hydroxychloroquine (HCQ), bafilomycin A1, and monensin [79, 80]. CQ and HCQ have augmented the efficacy of a variety of anticancer therapies both in experimental models and in clinical trials [81]. A dimeric CQ analog Lys01 was recently reported to be a more potent autophagy inhibitor than CQ or HCQ. Remarkably, in vivo study had showed that greater effects on autophagy inhibition and tumor growth reduction were induced by Lys05 which was a water-soluble salt of Lys01 [82]. However, whether the inhibition of autophagy abolishes the pro-survival effect of p-eIF2α is still unclear and needs to be further investigated.

Induction of apoptosis

In the setting of severe/chronic stress, cells may undergo apoptosis, which would also be a promising option for cancer therapy. A study elucidated a central role of p-eIF2α in apoptotic effect triggered by pegylated-arginase I (peg-Arg I) in acute lymphoblastic T cell leukemia (T-ALL). Peg-Arg I phosphorylated eIF2α and induced apoptosis via activation of PERK and GCN2 as well as downregulation of phosphatase GADD34 [83]. Alkyl-lysophospholipid analog (ALP) edelfosine could accumulate in ER and induced apoptosis by pro-apoptotic factor CHOP which was induced by p-eIF2α [84]. Similarly, some pharmacological agents induce p-eIF2α through ER-stress, further trigger CHOP-mediated apoptosis, including tetradecylthioacetic acid [85], isoliquiritigenin (ISL) [86], capsaicin [87], luteolin [88], Platycodin D (PD) [89], and CCT020312 [90]. Moreover, artificial suppression of nc886, a non-coding RNA targeting PKR activation, results in the activation of PKR-eIF2α apoptosis pathway [91]. This could be a potential therapy in eliminating malignant cells during tumorigenesis and progression.

Combination therapy for tumor

Lastly, a combination therapy may also be considered a valid approach to combat with tumor. Aberrantly activated p-eIF2α in tumor cells could be inhibited for therapeutic intention. The oncolytic virotherapy is a promising experimental therapeutic approach for treating cancer. Sunitinib, a potent inhibitor of PKR and RNase L, impairs antiviral innate immunity [92]. Report suggested that a combination of oncolytic virotherapy with sunitinib leads to enhanced effect on the elimination of

prostate, breast, and kidney malignant tumors in mice, compared with either one alone. In excised mice tumors, the PKR-eIF2α pathway is significantly reduced [93].

On the other hand, some chemotherapeutic agents synergistically killed tumor cells partially by increased eIF2α phosphorylation, such as a combination of sorafenib with vorinostat or lapatinib with OSU-03012 (a small molecule derivative of the Cox-2 inhibitor celecoxib). Suppression of p-eIF2α function abolished the above drug combination lethality [94, 95].

Summary and future perspectives

Although the multiple roles of eIF2α in cancer require further elucidation, it is obvious that eIF2α is critical signaling protein involved in the regulation of translation initiation and integrated stress response (ISR). Both translational initiation and ISR are implicated in tumor development, thereby linking eIF2α directly to tumorigenesis and progression. The increased expressions of eIF2α have been observed in various types of solid tumors and hematologic neoplasms. Accordingly, increasing preclinical studies have suggested that eIF2α plays important roles in tumor initiation, progression, and resistance to therapy. However, the roles of eIF2α in cancer remain controversial, particularly the phosphorylated form of eIF2α. EIF2α is phosphorylated by several kinases to inhibit global mRNA translation but enhance expression of special proteins that cope with cellular stresses. In experimental models, p-eIF2α exhibits tumor-suppressive properties in tumor initiation and development. During tumor progression, however, eIF2α is phosphorylated to adapt to the hypoxia and nutrition deprivation and further contributes to tumor progression and therapy resistance. As tumor grows up, specific dephosphorylases are induced to dephosphorylate p-eIF2α and reinitiate the global mRNA translation and then supply sufficient proteins the tumor needed.

Although tremendous efforts have been made to elucidate the precise mechanism of eIF2α in tumorigenesis, the clinical study is still lacking. The expression and phosphorylation levels of eIF2α are promising prognostic factor for cancer patients, which need further investigations in clinical specimens. However, the differences in describing eIF2α expression and the lack of high-quality antibody for precisely detecting the phosphorylation on certain sites create difficulties in reaching a conclusion about eIF2α expression and its correlation with clinicopathological parameters. Clearly, further studies with specific antibodies and standardized methods are needed to establish the importance of eIF2α and p-eIF2α in tumor pathology and their roles as prognostic biomarkers.

A number of strategies targeting eIF2α-related pathway have been proposed including the induction of p-eIF2α, inhibition of p-eIF2α or downstream processing by pharmacological inhibitors, induction of apoptosis through p-eIF2α-CHOP pathway, and combination therapy for tumor. However, new drugs that target eIF2α pathway required further validation using appropriate in vitro and tumor models, considering the controversial roles of eIF2α in tumor at different stages. Up to date, most available drugs or molecules are used as sensitizers to other therapies in preclinical and/or clinical trials. No effective single agent is available, and further investigation is anticipated to make those new candidates enter clinic.

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Conflict of interests The authors have no conflict of interests.

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