REVIEW

Eukaryotic initiation factor 5A2 and human digestive system neoplasms

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Abstract

Eukaryotic initiation factor 5A2 (eIF5A2), as one of the two isoforms in the family, is reported to be a novel oncogenic protein that is involved in multiple aspects of many types of human cancer. Overexpression or gene amplification of *EIF5A2* has been demonstrated in many cancers. Accumulated evidence shows that eIF5A2 initiates tumor formation, enhances cancer cell growth, increases cancer cell metastasis, and promotes treatment resistance through multiple means, including inducing epithelial–mesenchymal transition, cytoskeletal rearrangement, angiogenesis, and metabolic reprogramming. Expression of eIF5A2 in cancer correlates with poor survival, advanced disease stage, as well as metastasis, suggesting that eIF5A2 function is crucial for tumor development and maintenance but not for normal tissue homeostasis. All these studies suggest that eIF5A2 is a useful biomarker in the prediction of cancer prognosis and serves as an anticancer molecular target. This review focuses on the expression, subcellular localization, post-translational modifications, and regulatory networks of eIF5A2, as well as its biochemical functions and evolving clinical applications in cancer, especially in human digestive system neoplasms.

Key words: Eukaryotic translation initiation factor 5A2; Hypusine modification;

Acetylation modification; Drug resistance; Cancer therapeutics

Core tip: Eukaryotic initiation factor 5A2 (eIF5A2) is one of only two cellular proteins that contain the unusual amino acid hypusine. eIF5A2 initiates tumor formation, enhances cancer cell growth, increases metastasis, and promotes treatment resistance through inducing epithelial–mesenchymal transition, cytoskeletal rearrangement, angiogenesis, and metabolic reprogramming. Isoform eIF5A2 represents a promising target for treatment of human digestive system cancer. Our objective was to consolidate the current literature to better understand the expression, subcellular localization, post-translational modifications, and regulatory networks of eIF5A2, as well as its biochemical functions and evolving clinical applications in human digestive system cancer.

INTRODUCTION

In 2000, *EIF5A2* was first sequenced and isolated as a novel candidate oncogene from human chromosome 3q26.2[1,2]. Eukaryotic initiation factor 5A2 (eIF5A2) is one of only two eIF5A family members that undergo an unusual post-translational hypusine modification[3]. Unlike isoform eIF5A1, which is ubiquitously expressed, eIF5A2 protein is normally not detected and its mRNA is expressed in a tissue-dependent manner in human tissues[1]. eIF5A2 protein has been shown to be overexpressed in many cancers, including cervical cancer[4,5], ovarian cancer[6-8], colorectal cancer[9,10], gastric cancer[11,12], liver cancer[13,14], melanoma[15,16], lung cancer[17], nasopharyngeal carcinoma[18], bladder cancer[19,20] and esophageal squamous cell carcinoma (ESCC)[21]. Accumulated evidence shows that eIF5A2 plays important roles as a regulatory molecule in many biological processes, including tumor formation, cancer cell growth, metastasis, maintenance of cancer stem cells (CSCs) and treatment resistance through multiple means including epithelial–mesenchymal transition (EMT), cytoskeletal rearrangement, angiogenesis, and metabolic reprogramming.

In this article, we review eIF5A2-related studies, particularly those about the discovery, subcellular location, functions, upstream and downstream regulation, and modification of eIF5A2, as well as its role as a biomarker and its therapeutic potential for human digestive system cancer.

LITERATURE SEARCH

A literature search was conducted using PubMed Library for "eIF5A2", "eIF-5A2", "eIF-5A-2", "eIF5A-2", "EIF5A2", "eukaryotic translation initiation factor 5A2", "eukaryotic initiation 5A2" or "human eukaryotic initiation factor 5A2".

PROPERTIES AND EXPRESSION

Human eIF5A2 is a small (approximately 17 kDa) universally conserved acidic protein that contains 153 amino acids and is encoded by *EIF5A2* gene, which is located on chromosome 3q26.2; a chromosomal region that is frequently amplified in several human cancers[2,3]. Multiple forms of *EIF5A2* mRNA (5.6, 3.8, 1.6 and 0.7 kb, with one at 3.8 kb being the major form) are the products of one gene with various lengths of 3'-untranslated region (UTR), resulting from the use of different polyadenylation (AAUAAA) signals in various human cancer cell lines[22]. In short, for the structure of eIF5A2, the C-terminal domain consists of a three-turn α-helix α2 and five strands of β7-β11 and the N-terminal domain is dominated by β-strands[23].

Unlike *EIF5A1*, which is ubiquitously expressed, *EIF5A2* is normally not detected and its mRNA is expressed in a tissue-dependent and cell-type-specific manner, and is mainly found in testes, parts of adult brain, human cancer tissues (such as primary ovarian cancers) and some cancer cell lines (such as SW480 and UACC-1598)[1,2,24]. Clement *et al*[3] described the identification of eIF5A2 protein in human colorectal (SW-480) and ovarian (UACC-1598) cancer cell lines, and were first to report that eIF5A2 has an important role in eukaryotic cell survival similar to that of the ubiquitous eIF5A1. Overexpression of *EIF5A2* and/or eIF5A2 protein is observed in several human cancer tissues and/or cell lines such as cervical cancer[4,5,25], ovarian cancer[7,8], colorectal cancer[9,10,26-28], gastric cancer[11,12,29,30], ESCC[21,31], liver cancer[13,14,32-35], nasopharyngeal cancer[18], oral squamous cell carcinoma[36,37], pancreatic cancer[38-40], non-small cell lung cancer[17,41-43], melanoma[15,16], bladder cancer[34,44,45], and breast cancer[46,47]. In contrast, eIF5A2 is not generally overexpressed in glioblastoma[48] and chronic myeloid leukemia[49]. These observations suggest that eIF5A2 overexpression is not an invariable hallmark of cancer. Pällmann *et al*[50] reported high levels of *EIF5A2* mRNA in brain, epididymis, lung, prostate and testis tissues of wild-type mice, as assessed by quantitative real-time polymerase chain reaction.

POST-TRANSLATIONAL MODIFICATIONS

Hypusine modification and activation of eIF5A2

In humans, isoforms eIF5A1 and eIF5A2 are the only two cellular proteins that experience a post-translational hypusination by two essential enzymatic steps involving deoxyhypusine synthase (DHS) and deoxyhypusine hydroxylase (DOHH), which selectively catalyze the polyamine spermidine- to finish eIF5A hypusi-nation[22,51-53]. eIF5A exists mainly as the fully hypusination form in mammalian tissues and cells[54]. First, the 4- aminobutyl moiety of spermidine are transferred to the - amino group of Lys50 to form a deoxyhypusine-containing intermediate by DHS[3,22,51,55]. Second, DOHH catalyzes the hydroxylation of the deoxyhypusine residue to generate hypusine-containing eIF5A and activates it[22,51]. It has been reported that the endogenous activity of DHS and/or DOHH appears to be insufficient for modification of the excess precursors of mature eIF5A2 and eIF5A1[22], and exogenously expressed eIF5A2 and eIF5A1 is largely unhypusinated, and can be hypusinated only when DHS and DOHH are coexpressed[56,57]. Therefore, transfection studies with eIF5A2 expression vectors, such as our previous study[11] and others[7,9,13,26,27,31], should be re-assessed by evaluating the real changes in the concentrations of the hypusinated eIF5A2 or its precursor to determine the true cause of the biological effects. Hypusine modification not only activates eIF5A2, but also regulates its subcellular localization. However, in contrast to DHS- and DOHH-mediated hypusination of eIF5A1, which is crucial for embryonic development as well as for viability in adult mice, the cancer-associated isoform eIF5A2 is dispensable for embryonic development and viability in adult organisms[50]. Future work will be needed to determine the contribution of hypusine biosynthetic enzymes of eIF5A2 in tumorigenesis and metastasis.

Acetylation modification

In addition to unique hypusination, eIF5A2 also undergoes reversible acetylation modification at Lys-47, like eIF5A1 does[56,57]. Histone deacetylase 6 and sirtuin 2 have been identified as the major deacetylases of eIF5A2[56]. Acetylation of eIF5A2 at Lys-47 plays an important role in its subcellular localization. It is also reported that acetylation of the hypusine side chain in the N-terminal domain by a key polyamine catabolic enzyme, spermidine/spermine-N1-acetyltransferase 1 (SSAT1) inactivates eIF5A, which suggests regulation of eIF5A activity by reversible acetylation/deacetylation at this site though SSAT1 catalysis[58].

Other modifications

eIF5A can be modified by phosphorylation[59,60], ubiquitination[61] and trans-glutaminylation[62], but clear effects on its activity have not been fully detected. eIF5A dephosphorylation is required for translation arrest in stationary phase cells[60]. Shang *et al*[61] reported that the carboxyl terminus of Hsc70-interacting protein (CHIP) functions as a negative regulator of eIF5A to mediate its ubiquitination for degradation. This was the first report on regulation of eIF5A protein stability *via* a protein degradation mechanism. It is likely, therefore, that the CHIP–eIF5A2 axis mediates ubiquitination of eIF5A2 for degradation in human cancers. The potential role of eIF5A2 in human cancer development and metastasis has been found in recent years; therefore, the importance of eIF5A2 post-translational modifications in its

oncogenic properties should be elucidated in the future.

SUBCELLULAR LOCALIZATION OF eIF5A2

The nuclear membranes force nucleocytoplasmic exchange to proceed through nuclear pore complexes (NPCs)[63]. The NPC permeability barrier -allows free passage to small molecules, while limiting larger molecules that approach or exceed a limit of > 30kDa in mass or > 5nm in diameter[64]. Most evidence demonstrates s that eIF5A2, as a shuttling protein, is responsible for regulating protein translation in the cytoplasm, and only a few studies have shown that it is located and works in the nucleus[15,21,65]. More studies are necessary to address its role in the nucleus. eIF5A2 has an invariably small molecular mass of only 17 kDa and can thus cross the NPC permeability barrier rapidly, even without the help of an importin. The nuclear export of eIF5A may be mediated by the nuclear exporter exportin (XPO)4, which belongs to the importin-β family of nuclear transporters, in a hypusine-dependent manner[66,67]. In addition, the N-terminal 19 amino acids of eIF5A serve as a signal for nuclear localization of eIF5A[68]. Knockdown of XPO4 in murine hepatoma cells leads to nuclear accumulation of eIF5A2 as well as eIF5A1[65].

Post-translational modifications including acetylation at Lys-47 and hypusination at Lys-50 of eIF5A2 direct its subcellular localization[56]. Acetylation acts as a molecular switch for eIF5A2, allowing it to exert distinct functions in the cytoplasm and nucleus. The acetylated form of eIF5A2 is primarily enriched in the nucleus, suggesting that acetylation at Lys-47 induces nuclear accumulation[56]. In addition, the study also showed that unhypusinated eIF5A2 is highly acetylated but is significantly deacetylated upon hypusination, implying crosstalk between acetylation and hypusination[56]. Hypusination can reduce acetylation in eIF5A2, leading to its localization in the cytoplasmic compartment where it is required for protein synthesis. Inhibition of the deacetylases or impaired hypusination increases acetylation of eIF5A2, leading to nuclear accumulation. These findings provide strong evidence that cytoplasmic location of eIF5A2 requires not only hypusination but also hypo-acetylation.

REGULATION OF *EIF5A2* EXPRESSION IN HUMAN DIGESTIVE SYSTEM NEOPLASMS

Although the mechanisms of *EIF5A2* gene upregulation in tumor cells are not clear yet, most researchers believe that the main reason is genomic instability caused by copy number variation. To date, *EIF5A2* has been frequently found, but not always, to be amplified in human cancers and cancer cell lines[2,8,10,17,19,21,69]. Although tumors that exhibit gene amplification typically exhibit high eIF5A2 expression, many have high eIF5A2 levels without gene amplification, and thus other mechanisms, such as transcriptional regulation and/or post-transcriptional regulation, must exist in eIF5A2 upregulation. It has been demonstrated that K-ras activation upregulates eIF5A2 expression as well as hypusination *via* transcriptional regulation during the early stages of pancreatic ductal adenocarcinoma (PDAC) progression[38]. Another study has reported that hypoxia increases *EIF5A2* RNA levels, at least in part *via* hypoxia-inducible factor (HIF)-1α in ESCC cells[21].

Many studies have demonstrated that miRNAs (miRs) target the 3'-UTR of cytoplasmic mRNA of *EIF5A2* to post-transcriptionally regulate mRNA and protein levels[70] (Table 1). *EIF5A2* is a putative target for miR-203, miR-30b, miR-9, miR-125b, miR-599 and miR-588, which are predicted by the bioinformatic algorithm TargetScan (www.targetscan.org). miR-203 suppresses growth and invasion of colorectal cancer cells (SW620 and LOVO), at least partly, by binding the 3'-UTR of *EIF5A2* and repressing *EIF5A2* expression at both the mRNA and protein levels[26]. miR-30b[29], miR-599[71] and miR-588[72] suppress gastric cancer cell metastasis *via* binding to the 3'-UTR of *EIF5A2* and repressing eIF5A2 expression. miR-125b inhibits tumorigenic properties of hepatocellular carcinoma (HCC) cells *via* suppressing eIF5A2 expression, through binding to the 3'-UTR of *EIF5A2*[73]. miR-9 enhances sensitivity to cetuximab in epithelial phenotype HCC cells through regulation of eIF5A2[74].

Zender *et al*[65] has reported that eIF5A2 is a key downstream effector of XPO4 in tumor inhibition, and XPO4 is a negative regulator of eIF5A2, which may play a role in inhibiting cell proliferation in the nucleus. In murine hepatoma cells, knockdown of XPO4 leads to accumulation of eIF5A1 and eIF5A2 in the nucleus[65]. The sonic hedgehog-GLI family zinc finger 1 signaling pathway upregulates eIF5A2 in pancreatic cancer cells[28]. Moreover, hypoxia can induce eIF5A2 upregulation and

Table 1 miRNA action in regulation of *EIF5A2* gene expression

miRs	Ref.	Materials	Function
miR-203	Deng *et al*[26]	CRC cells (SW620 and LOVO)	Suppressing growth and invasion *via* miR-203/EIF5A2 axis
miR-599	Wang *et al*[71]	GC cells (BGC823 and MKN-45)	Inhibiting metastasis and EMT *via* miR-599/EIF5A2 axis
miR-588	Zhou *et al*[72]	GC cells (MGC803)	Regulating invasion, migration and EMT *via* miR-588/EIF5A2 axis
miR-30b	Tian *et al*[29]	GC cells (AGS and MGC803)	Downregulation of EIF5A2 by miR-30b inhibits EMT
miR-9	Xue *et al*[74]	HCC cells (Hep3B and Huh7)	Enhancing sensitivity to cetuximab *via* miR-9/EIF5A2 axis
miR-125b	Tsang *et al*[73]	HCC tissue and cells	Inhibiting tumorigenic properties *via* miR-125b/EIF5A2 axis

CRC: Colorectal cancer; GC: Gastric cancer.

promote eIF5A2 translocation from the cytoplasm to the nucleus in ESCC cell lines (KYSE140, KYSE180, KYSE410, KYSE510 and EC109)[21].

FUNCTIONS OF eIF5A2 IN HUMAN DIGESTIVE SYSTEM NEOPLASMS

The cancer-associated isoform eIF5A2 is not essential for normal development and viability, which has been confirmed *in vivo*[50]. Accumulating evidence shows that eIF5A2 plays important roles in tumor proliferation[11], metastasis[13], EMT[9,11,13,28-29,35,75,76], cytoskeletal rearrangement[13], angiogenesis[21], metabolic reprogramming[14], maintenance of CSCs[31,77] and drug resistance[33,38,74,75,78-80]*via* its subsequent signaling pathways. Additionally, eIF5A2 is associated with survival of many digestive cancer patients[9,11,12,14,21,32] (Figure 1).

eIF5A2 and EMT
Over the past 10 years, many studies have evaluated the role of eIF5A2 in activating EMT in human cancer cells. Tang *et al*[13] first reported that eIF5A2 induces EMT; an important event in tumor invasion and metastasis that is chiefly characterized by upregulation of mesenchymal markers (Vimentin, fibronectin, E-cadherin and α-smooth muscle actin) and downregulation of epithelial markers (E-cadherin and β-catenin) in HCC. Shek *et al*[35] and Lou *et al*[75] confirmed that eIF5A2 enhances the aggressiveness of HCC cells by inducing EMT. Zhu *et al*[9] found that overexpression of eIF5A2 also promotes colorectal carcinoma cell aggressiveness by upregulating Metastasis-associated protein 1 through C-myc to induce EMT[76]. In addition, eIF5A2 induces EMT of other human digestive system neoplasms such as gastric cancer[11,29] and pancreatic cancer[28].

eIF5A2 and cytoskeletal rearrangement
In HCC, eIF5A2 stimulates rearrangement of the cytoskeleton through activation of the RhoA/Rac1 GTPase signaling pathway[13]. That study showed that overexpression of eIF5A2 in human liver LO2 cells provokes the formation of stress fibers and lamellipodia, without affecting expression level of Rho/Rac GTPase in the cells[13]. However, the precise mechanism underlying EIF5A2-mediated Rho-GTPase activation requires further investigation.

eIF5A2 and angiogenesis
Increased expression of eIF5A2, *via* hypoxia or gene amplification, contributes to angiogenesis in ESCC *via* the HIF-1α-mediated signaling pathway[21]. *In vitro* and *in vivo* assays have both indicated that eIF5A2 increases angiogenesis by enhancing matrix metalloproteinase 2 activity *via* activation of the p38 mitogen-activated protein kinase pathway, and eIF5A2 silencing increases tumor vessel wall continuity, increases blood perfusion, and improves tumor oxygenation in HCC[33].

eIF5A2 and metabolic reprogramming
A recent study reported that eIF5A2 triggers cellular metabolic reprogramming, including glucose metabolism, by promoting aerobic glycolysis and fatty acid biosynthesis *via* upregulation of *FASN* and *ACSS2* in human liver cancer cells[14].

eIF5A2 and maintenance of stemness of cancer cells
CSCs are suggested to be responsible for driving resistance to conventional therapies and for cancer metastasis and/or recurrence. It has been reported that eIF5A2
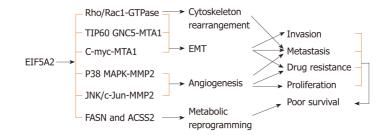
Figure 1 unctions and subsequent pathways of eukaryotic initiation factor 5A2 in human digestive system neoplasms. Overexpression of Eukaryotic initiation factor 5A2 (eIF5A2) induces epithelial–mesenchymal transition (EMT) by enhancing RhoA/Rac1-GTPase and ITP60 GNC5-MTA1 activity in hepatocellular carcinoma (HCC). Overexpression of *EIF5A2* also promotes colorectal carcinoma and gastric cancer cell aggressiveness by upregulating the C-myc/MTA axis to induce EMT. Increased expression of eIF5A2 contributes to angiogenesis in esophageal squamous cell carcinoma *via* the P38 MAPK/MMP2 pathway. eIF5A2 promotes cell proliferation and triggers cellular metabolic reprogramming in HCC cells, including glucose metabolism and fatty acid biosynthesis *via* upregulation of *FASN* and *ACSS2*. In HCC, eIF5A2 stimulates rearrangement of the cytoskeleton through activation of the RhoA/Rac1 GTPase signaling pathway. eIF5A2: Eukaryotic initiation factor 5A2; EMT: Epithelial–mesenchymal transition.

overexpression increases the stemness of ESCC cells (KYSE510)[31]. A recent study showed that eIF5A2 also contributes to the maintenance of HCC CSCs (CD133+ HCC cells) *via* the c-Myc/miR-29b axis[77].

eIF5A2 and survival of patients

Overexpression of cytoplasmic eIF5A2 detected by immunohistochemistry is correlated with poor survival of patients with digestive system malignancies, including colorectal cancer[9], ESCC[21], gastric cancer[11,12] and liver cancer[14,32]. All these studies suggest that a high level of eIF5A2 expression in the cytoplasm is a potential prognostic indicator in many human cancers. However, a recent study demonstrated that nuclear eIF5A2 expression is also an independent prognostic marker in human melanoma[15]. Therefore, nuclear eIF5A2 may have the potential to serve as a therapeutic marker for some human cancers, and further study is needed to establish the subcellular localization of eIF5A2.

Role of eIF5A2 in treatment resistance of human digestive system neoplasms

Primary or secondary anticancer drug resistance is a clinical problem shared by both chemotherapy and targeted therapy. The development of resistance may be predicted from pre-existing genomic and proteomic profiles in patients[78]. eIF5A2 can be used as a biomarker for predicting drug resistance. N1-guanyl-1,7-diaminoheptane (GC7), an inhibitor of DHS, enhances the therapeutic efficacy of doxorubicin in epithelial HCC cells (Huh7, Hep3B and HepG2)[75,79] by preventing the doxorubicin-induced EMT through inhibition of eIF5A2 activation. GC7 can also enhance the sensitivity of oral cancer cells to cisplatin[37]. eIF5A2 promotes resistance to doxorubicin *via* regulation of EMT in colon cancer cells[27]. Downregulation of eIF5A2 increases tumor perfusion and reduces tumor hypoxia, thus increasing the chemosensitivity of HCC cells to 5-fluorouracil by remodeling tumor vessels[33]. eIF5A2 is significantly related to gemcitabine sensitivity in PDAC cells[38]. Recently, Xue *et al*[74] reported that eIF5A2 is associated with cytotoxicity of cetuximab in epithelial HCC cells[80]. A high level of eIF5A2 expression is related to drug resistance in many human digestive system cancers. However, other studies have shown no significant relationship between *EIF5A2* expression and effects of preoperative radiotherapy in human rectal cancer[81].

CONCLUSIONS AND PERSPECTIVES

Basic research and clinical evidence show that *EIF5A2* is a candidate oncogene and may be a key biomarker for the prognosis of various human digestive system cancers. There is growing evidence that inhibition of hypusination of eIF5A2 inhibits tumorigenesis. Hypusine modification of eIF5A by DHPS and DOHH forms an attractive platform for therapeutic intervention. Many studies have shown that GC7, as an inhibitor of DHS, enhances the sensitivity of drugs through inhibition of eIF5A2 activation in many kinds of human cancer cells[27,37,39,42,47,75,79,80,82,83]. However, hypusination takes place in all eukaryotic cells and has been shown to be necessary for proliferation of mammalian cell lines[52] and crucial for embryonic development as

well as viability in adult mice[50]. So, important questions remain regarding how to selectively target tumors and reduce adverse effects.

In contrast to *EIF5A1*, the of *EIF5A2* is limited to tissue such as testes and a few parts of the adult brain, but it is abundant in many human cancers. The eIF5A2 protein is associated with cancer metastasis by influencing the processes of EMT, angiogenesis, cytoskeletal rearrangement, and metabolic reprogramming. Thus, the isoform eIF5A2 represents a promising target for the treatment of malignant tumors. Moreover, in contrast to DHS or DOHH, the eIF5A2 isoform is not essential for embryonic development or for viability in an adult organism. So, we speculated whether eIF5A2, which is only expressed in a few tissues in the normal human body, but abundant in various tumor cells, might represent a better target for therapy. Therefore, we propose that specific inhibitors of eIF5A2 will exhibit selective toxicity toward eIF5A2-dependent cancer cells. Better understanding of the physiological and pathophysiological functions of eIF5A2 may lead to more effective management of many human digestive system cancers with high expression of *EIF5A2*, *via* early detection, precise prognostication, and molecular targeted treatment. A recent study demonstrated that Mg(II)-catechin nanocomposite particles (Mg(II)-Cat NPs) delivering siEIF5A2 inhibited bladder cancer cell growth *in vitro* and *in vivo*[45,84]. These results provide preclinical evidence for use of Mg(II)-Cat/siEIF5A2 combined therapeutic methods in cancer.

However, it is also clear that more researches are needed to clarify the underlying mechanisms that regulate eIF5A2 expression, for example, how does noncoding RNA regulate the UTR of *EIF5A2* and how is its promoter epigenetically modified. With regard to the downstream pathway, the exact mechanism of eIF5A2 in regulating its target and whether it can act as a transcriptional factor have not been elucidated.

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