

# Eukaryotic translation initiation factor 5A in the pathogenesis of cancers (Review)

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**Abstract.** Cancer is the leading cause of death worldwide. The absence of obvious symptoms and insufficiently sensitive biomarkers in early stages of carcinoma limits early diagnosis. Cancer therapy agents and targeted therapy have been used extensively against tissues or organs of specific cancers. However, the intrinsic and/or acquired resistance to the agents or targeted drugs as well as the serious toxic side effects of the drugs would limit their use. Therefore, identifying biomarkers involved in tumorigenesis and progression represents a challenge for cancer diagnosis and therapeutic strategy development. The eukaryotic translation factor 5A (eIF5A), originally identified as an initiation factor, was later shown to promote translation elongation of iterated proline sequences. There are two eIF5A isoforms (eIF5A1 and eIF5A2). eIF5A2 protein consists of 153 residues, and shares 84% amino acid identity with eIF5A1. However, the biological functions of these two isoforms may be significantly different. Recently, it was demonstrated that eIF5A is widely involved in the pathogenesis of a number of diseases, including cancers. In particular, eIF5A plays an important role in regulating tumor growth, invasion, metastasis and tumor microenvironment. It was also shown to serve as a potential biomarker and target for the diagnosis and treatment of cancers. The present review briefly discusses the latest findings of eIF5A in the pathogenesis of certain malignant cancers and evolving clinical applications.

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## 1. Introduction

It was estimated that there will be an ~18.1 million new cancer cases and 9.6 million cancer deaths in 2018 worldwide (1). Lung cancer is a major global health problem, with a poor 5-year survival of ~15% and is the major cause of cancer-related deaths (2). Diagnosis at an advanced stage is the major reason for this low survival rate (2). Chemotherapy and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are used for advanced or recurrent disease, whose efficacy has been limited by emergence of resistance mechanisms (3). Breast, prostate and colorectal cancers are the second, third, and fourth cancers with the highest incidence worldwide, respectively. Colorectal cancer, gastric cancer and hepatocellular carcinoma are the three cancers with the highest mortality rate beyond lung cancer (1). Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide due to lack of appropriate diagnosis, treatment and cataloging of cancer cases (4). Despite advances in prevention techniques, screening and new technologies in both diagnosis and treatment, incidence and mortality rates continue to rise. Due to the lack of sensitive and specific biomarkers for early cancer detection and proper monitoring of patients' response to therapy (5), the therapeutic effects for invasion-related and metastasis-related cancers are still very poor (6). Therefore, improved tools for diagnosis, treatment and prognosis of cancers are crucial for improving patient outcomes.

The eukaryotic translation initiation factor 5A (eIF5A), the only known protein containing a spermidine derivative, such as hypusine, functions at the level of translation (7). Hypusine is formed by conjugation of the aminobutyl moiety of spermidine to a specific lysine residue of this protein (8). Modification with hypusine is critical requirement for eIF5A activity (9). The post-translational synthesis of hypusine involves two enzymatic steps, catalyzed by deoxyhypusine synthase (DHPS) and deoxyhypusine hydroxylase (DOHH), which selectively uses the polyamine spermidine as a substrate to generate hypusinated eIF5A (10). Two eIF5A isoforms, eIF5A1 and eIF5A2, are generated from distinct but related genes, which in humans contain 84% amino acid sequence identity (11). eIF5A1 is abundantly expressed in most cells and functions as a translation elongation factor. It was also shown that eIF5A1 is implicated in certain human diseases, including diabetes, several human cancer types, viral

infections and diseases of the nervous system (12). Meanwhile, eIF5A2 is overexpressed in numerous cancers, expressed few normal tissues, is a candidate oncogene and plays an important role in the development and progression of cancers (13). eIF5A1 does not only act as an oncogene but also functions as a tumor suppressor (14). eIF5A2 acts as an oncogene in several cancers (13). Both eIF5A1 and eIF5A2 are involved in cancer development and progression and can be a useful marker for diagnosis and prognosis (14). eIF5A1 and eIF5A2 exert their roles in promoting cancer cell growth, invasion and metastasis ability via a variety of cellular processes (15). The exact molecular mechanisms of these two proteins in cancer development and progression still remain unclear. One potential mechanism may be implicated in translational control of specific mRNAs, since more reports disclosed that eIF5A1 can promote the translation elongation of mRNA with ribosome stalling motifs (16-18), and it was also revealed that eIF5A1 can promote the translation of mRNA by promoting its nuclear export (19). Another potential mechanism is as a transcription factor in the nucleus, eIF5A2 was observed to bind to the promoter region of hypoxia-inducible factor (HIF) 1 $\alpha$  and regulate HIF1 $\alpha$  transcription in esophageal squamous cell carcinoma (ESCC) cell lines (20).

Inhibition of DHS and DOHH activity also provides the possibility of pharmacological control of eIF5A activity and expression of eIF5A-dependent genes (21-23). These findings suggested that eIF5A is a potential target and biomarker for the diagnosis and prediction of prognosis of malignant tumors. In the present review, the role of eIF5A in tumorigenesis and mechanisms in the pathogenesis of malignancy was evaluated and the specific functions of eIF5A are also briefly discussed. eIF5A is suggested to be a high priority target for cancer therapeutics.

## 2. Role of eIF5A in malignant tumors

*Cancerous nervous system diseases.* Glioblastoma (GBM). GBM is the most frequently occurring and invariably fatal primary brain tumor in adults (24). Despite a broad range of new and more specific treatment strategies, therapy of glioblastomas remains challenging and tumors relapse in all cases (25). The current treatment strategy for patients with GBM consists of surgery, radiotherapy and chemotherapy, but <3-5% of patients survive >5 years post-diagnosis (26). Thus, novel therapeutic and diagnostic approaches for GBMs are urgently needed. In an effort to find novel approaches to GBM treatment, recent studies have focused on molecular phenotyping of GBM subtypes to identify new targets for biomarkers and therapeutics (24,27-30).

Altered activities of eIF5A have been associated with cancer development. eIF5A, as well as the DHS and DOHH, were reported to be highly overexpressed in GBM patient samples, and the majority of the normal/healthy glia cells did not express eIF5A (21), suggesting that eIF5A might be a potential biomarker for GBM. Using an *in vitro* assay, Preukschas *et al* (21) found that targeting eIF5A and its hypusine modification with N1-guanyl-1,7-diaminoheptane (GC7) showed a strong antiproliferative effect in GBM cell lines. Although delivery of small interfering RNA (siRNA) to suppress GBM growth is a hurdle due to the critical obstacles

of the blood-brain barrier, combined treatment with clinically relevant alkylating agents and GC7 had an additive anti-proliferative effect in GBM cell lines (21). This suggested that pharmacological inhibition of eIF5A may represent a novel concept to treat GBM and may help to substantially improve the clinical course of this tumor.

The protein forkhead box D1 (FOXD1) is an oncogene. Short hairpin RNA-mediated attenuation of FOXD1 in glioma stem-like cells reduces their clonogenicity *in vitro* and *in vivo* (31). The long non-coding RNA FOXD1-AS1 (FOXD1-AS1) is the antisense transcript of the gene encoding for FOXD1. FOXD1-AS1 silencing caused glioma cells to exert suppressive effects *in vitro* and *in vivo* via targeting eIF5A, a direct target of FOXD1-AS1 (32). The data further indicated that eIF5A may be a target for glioma treatment.

*Neuroblastoma (NB).* NB is the most common extracranial solid tumor of childhood that affects the age group <15 years (33). Despite intensive multi-modal treatment, NB can spontaneously regress without treatment or actively give rise to metastases, and the 5-year survival rate remains <50% among high-risk patients, characterized by certain features, such as metastasis, >1 year of age and amplified *MYCN* oncogene (40-50%), despite intensive treatment protocols (34,35). Chimeric monoclonal GD2-specific antibodies, the targeted immunotherapy for NB, is clinically used today. However, acute pain side effect and application limit for large doses limit its clinical application (36). Hence, the search for novel therapeutic targets is crucial. Studies have demonstrated that elevated mRNA levels of the two target enzymes deoxyhypusine synthase (DHPS) and ornithine decarboxylase (ODC) correlate with poor prognosis in patients with NB (37). Targeting eIF5A expression using the DHPS inhibitor GC7 and the ODC inhibitor difluoromethylornithine induced p21/retinoblastoma (Rb) or p27/Rb-mediated G1 cell cycle arrest and activated caspase-3/7/9-mediated apoptosis in NB cells (38), suggesting that eIF5A is an effective target for improved NB drug therapy.

*Digestive system neoplasms.* Pancreatic cancer. Pancreatic ductal adenocarcinoma (PDAC) is the fourth-leading cause of cancer-related deaths, with an overall survival rate of <5% due to its difficulties in early diagnosis and metastasis (39). PDAC is one of the most chemoresistant cancers, and most available treatments are palliative (40). Therefore, identification of novel diagnostic and prognostic biomarkers and exploring corresponding targeted therapeutic strategies are needed.

Preukschas *et al* (21) investigated how eIF5A regulated PDAC pathogenesis and found that eIF5A was overexpressed in human PDAC tissues compared with corresponding normal pancreatic duct tissues. The study also found that activated eIF5A1 was upregulated during early stages of PDAC progression in response to KRas activation (21). Furthermore, targeting eIF5A by siRNA or pharmacological inhibition reduces PDAC cell proliferation, migration, invasion, metastasis and orthotopic tumor growth *in vitro* and *in vivo* (23,41). Mechanistically, eIF5A mediates PDAC cell migration and invasion by regulating RhoA/Rho-associated protein kinase (ROCK) signaling (23), and by regulating eIF5A-inactive tyrosine-protein kinase PEAK1 (PEAK1)-YAP (Yes-associated protein) signaling to mediate tumorigenicity (42).

Gemcitabine is the standard chemotherapeutic drug for PDAC treatment, either alone or in combination with other chemotherapeutics (43). However, resistance to gemcitabine is inevitable during the initial phase or during the treatment (43). Wang *et al* (44) reported that eIF5A2 overexpression is involved in chemoresistance to gemcitabine in PDAC cells and targeting eIF5A2 enhances the sensitivity of PDAC cells to gemcitabine *in vitro* and *in vivo*. Moreover, eIF5A-mediated PEAK1 expression enhanced gemcitabine sensitivity in PDAC cells (45). These data indicated that targeting eIF5A2 could provide a unique mechanism for PDAC therapy in the clinic.

Hepatocellular carcinoma (HCC). (HCC) is the fifth most common cancer and one of the top causes of cancer mortality worldwide (46). Treatment options for advanced HCC remain limited and unsuccessful due to the high incidence and metastasis, resulting in poor prognosis (47). Therefore, precise and effective biomarkers are needed for early diagnosis and prognostic estimation.

Lee *et al* (48) reported that the two isoforms (eIF5A1 and eIF5A2) were expressed in HCC tissues; eIF5A1 overexpression was related with higher numbers of tumor nodules and eIF5A2 overexpression was related with tumor venous infiltration in HCC. Tang *et al* (49) reported that EIF5A2 mRNA expression was significantly increased in HCC tissues compared with nontumorous tissues; furthermore, metastatic or venous infiltrated HCC tissues showed significantly increased eIF5A2 expression compared with the HCC tissues without metastasis or venous infiltration. In addition, eIF5A2 overexpression was significantly associated with shorter survival time in patients with HCC (15,50). Although eIF5A1 mRNA was expressed in HCC and non-tumor tissues, eIF5A1 expression is positively correlated to the number of metastatic nodules in HCC (51). Thus, eIF5A1/2 may be potential prognostic and diagnostic markers for HCC. In addition, enforced eIF5A2 expression promoted HCC cell growth and accelerated glucose utilization and lipogenesis rates (47). Enforced eIF5A2 expression also promoted HCC cell metastasis and angiogenesis *in vivo* via the c-Myc/microRNA (miR/miRNA)-29b axis (52). While targeting eIF5A2 by siRNA decreased cell motility and reduced cell migration via reactive oxygen species (ROS)-related pathways (15), miR-125b can reverse the effect of eIF5A2 in HCC cells (53).

Functional studies found that enforced eIF5A2 expression induced epithelial-mesenchymal transition (EMT) and enhanced the migrative and invasive ability of HCC cells *in vitro* and tumor metastasis *in vivo* in an experimental mouse model, while targeting eIF5A2 alleviates the tumorigenic properties of HCC cells *in vitro* and *in vivo* by inhibiting EMT (20,49,51). Therefore, eIF5A2 may be a potential therapeutic target for HCC. Wang *et al* (54) reported that targeting eIF5A2 enhanced the chemosensitivity of HCC cells to 5-fluorouracil (5-FU) by blocking p38 mitogen-activated protein kinase and JNK/c-Jun/matrix metalloproteinase (MMP)-2 signaling.

GC7 is a novel inhibitor of DHS, which is the key enzyme eIF5A2 activation and contributes to eIF5A2 inhibition (55). Accumulating evidence indicated that targeting eIF5A2 with GC7 significantly inhibited cell proliferation and promoted the cytotoxicity of cetuximab and doxorubicin in HCC cells (56,57). This data indicated that targeting eIF5A2 may be a chemotherapeutic strategy for the treatment of HCC.

miRNAs play a vital role in tumor chemoresistance via regulating eIF5A2 expression. Using an miRNA target prediction website, Xue *et al* (58) reported that the 3'-untranslated region of eIF5A2 was a potential target of miR-9. The study found that miR-9 enhanced the sensitivity of HCC cells to cetuximab via targeting eIF5A2. miR-9 can also enhance the sensitivity of HCC cells to cisplatin by targeting eIF5A2, resulting in inhibition of EMT signaling (59). Moreover, miR-383 underexpression-mediated doxorubicin resistance in HCC cells could be reversed by silencing eIF5A2 (60). The long non-coding RNA termed GAS6 antisense RNA 1 (GAS6-AS1)/miR-585/eIF5A2 pathway plays an important role in HCC progression and could be considered as a potential target for therapeutic approaches in HCC (61). These data indicated that targeting eIF5A2 directly or indirectly may serve as a potential therapeutic approach for HCC in the future.

Gastric cancer (GC). (GC) is one of the most common cancers with relatively poor prognosis and remains the second leading cause of cancer-related deaths worldwide (62). Abnormal gene or molecule expression is closely related to the occurrence and development of GC (63). Therefore, specific inhibitors or overexpression of these genes or molecules may be promising anticancer drugs for GC.

eIF5A2 was found to be overexpressed in human GC tissues and cell lines using immunohistochemical staining and western blot assays (64-67). Higher eIF5A2 expression was correlated with high pT/pN stage and lymphovascular invasion and poor overall survival in these patients with GC (64,65). Moreover, downregulation of eIF5A2 by siRNA was shown to inhibit GC cell proliferation and invasion via upregulating E-cadherin expression and downregulation of vimentin, cyclin D1, cyclin D3, c-Myc and metastasis-associated protein1 (MTA1) expression (65). These data indicated that eIF5A2 may be a prognostic marker and therapeutic target gene for GC.

It has been demonstrated that human miRNA expression contributed to the initiation and progression of GC. Tian *et al* (68) reported that miR-30b induced cell apoptosis and reduced cell migration and invasion *in vitro* via targeting eIF5A2 expression in GC cells. Sun *et al* (69) reported that miR-599 inhibited EMT and metastasis of GC cells *in vitro* and *in vivo* via targeting eIF5A2. Zhu *et al* (70) reported that eIF5A2 regulated cisplatin sensitivity in GC cells *in vitro* via eIF5A2-mediated EMT, suggesting that eIF5A2 may be a molecular target for anti-tumor therapy.

Colorectal cancer (CRC). CRC is the third leading cause of cancer-related deaths worldwide (71). Despite recent improvements in screening strategies and the development of more effective treatments for CRC, the prognosis of advanced CRC is still poor (72). Therefore, novel methods that would allow early detection and diagnosis of colorectal cancer are required.

eIF5A2 was found to be overexpressed in CRC tissues using an immunohistochemical assay, and higher eIF5A2 expression was correlated with CRC metastasis and short median survival time (73-76). Therefore, eIF5A2 could be as a novel prognostic marker for patients with CRC. eIF5A2 was also overexpressed in CRC cell lines (77), and enforced eIF5A2 expression induced EMT and enhanced cell motility and invasion in CRC cells

*in vitro* and lung metastasis *in vivo* (73). Another study showed that restoration of eIF5A2 in miR-203-overexpressing CRC cells reversed the suppressive effects of miR-203, indicating that eIF5A2 is a direct and functional target of miR-203 (75). Therefore, eIF5A2 could be an effective therapeutic target for CRC.

**Esophageal cancer (EC).** EC ranks as the sixth most common cause of cancer-related deaths worldwide (78). There are two major histological forms for EC, adenocarcinoma (EAC) and ESCC, the latter of which comprises up to 90% of EC, and is a common type of EC in developing countries, including China (79). The five-year survival rate for ESCC is 15-25%, mainly due to late diagnosis and propensity for metastasis (20). Therefore, understanding of the molecular mechanisms underlying ESCC progression could improve early diagnosis, treatment strategy and overall prognosis of ESCC.

Reverse transcription-quantitative PCR (RT-qPCR) and immunohistochemical analyses showed that >40% of ESCC tissues showed increased eIF5A2 mRNA and protein expression compared with matched nontumor tissues (80). Furthermore, eIF5A2 overexpression was significantly associated with tumor invasion and lymph node metastasis and shorter survival times for patients with ESCC (80). In ESCC cells *in vitro* and *in vivo*, enforced eIF5A2 expression induced EMT and enhanced cell migratory and invasive abilities via HIF1 $\alpha$ -mediated signaling pathway (20). Yang *et al* (80) reported that enforced eIF5A2 expression induced chemoresistance of ESCC cells to 5-FU, docetaxel and taxol *in vitro*, while targeting eIF5A2 could reverse the effect. In addition, eIF5A2 overexpression was related with shorter survival for patients with ESCC who underwent taxane-based chemotherapy after esophagectomy (80). These data indicated that eIF5A2 maybe as an effective biomarker for predicting prognosis and chemotherapy response for patients with ESCC. In addition, based on GSE6188, GSE13937 and GSE43732 microarray assays obtained from the Gene Expression Omnibus database (<http://www.ncbi.nlm.nih.gov/geo/>), eIF5A2 was overexpressed in EC tissues compared with matched nontumor tissues, suggesting that eIF5A2 could be as a promising biomarker for the diagnosis of esophageal cancer (81). Moghanibashi *et al* (82) reported that eIF5A1 participated in nucleocytoplasmic transport, which plays a role in esophageal carcinogenesis. However, whether eIF5A1 could be a diagnostic and therapeutic target needs further investigation. In addition, no related research has been found investigating the association between EAC and in the literature.

**Breast cancer.** Breast cancer is a strong heterogeneous disease, and its pathogenesis remains unclear in most cases (83). More than 90% of breast cancer-related deaths are associated with metastasis, however, the critical molecular controls underlying tumor metastasis are poorly understood (84). Current treatments for metastatic breast cancer are based on a strategy of systemic chemotherapy and endocrine therapies, but the intrinsic resistance and acquired resistance to chemotherapy and endocrine therapies are inevitable, of which the molecular resistance mechanisms are still unknown (85). Therefore, the identification of metastasis-related factors and molecular resistance mechanisms warrants further investigation.

Liu *et al* (86) reported that higher eIF5A2 expression correlated with doxorubicin resistance in breast cancer cells and targeting eIF5A2 could effectively restore the sensitivity of breast cancer cells to doxorubicin treatment in breast cancer cells *in vitro* and *in vivo*. Sirtuin 2 (SIRT2) is a cytoplasmic protein in the family of sirtuins that are NAD<sup>+</sup>-dependent class III histone deacetylases (87). Increasing evidence implied the dynamic role of SIRT2 in regulating tumorigenesis (88-91). Shah *et al* (92) reported that targeting eIF5A2 using the small molecule inhibitor of SIRT2 reduced cell viability by inhibiting c-Myc expression in human breast cancer cells *in vitro*. These data indicated that eIF5A could be an effective target for breast cancer therapy. Liu *et al* (93) reported that eIF5A2 was identified as a candidate target gene of miR-375, which was suggested to serve as a tumor suppressor in breast cancer. However, to the best of our knowledge, the expression of eIF5A in breast cancer tissues and its association with the clinicopathology of patients with breast cancer have not been reported.

**Ovarian cancer.** The most extensively investigated biomarker for screening of epithelial ovarian cancer (EOC) is serum CA-125, reported to distinguish malignant from benign pelvic masses, monitor therapeutic response and detect recurrent disease (94,95). However, serum CA-125 has only a modest ability to detect early stage ovarian cancer (96). Moreover, CA-125 screening is not reliable enough for routine monitoring (97). In addition, serum CA-125 has very low predictive value and a high false-positive rate in EOC diagnosis (96,98). Therefore, development of improved diagnostic tools for the early detection of ovarian cancer is urgently needed.

eIF5A2 was found to be overexpressed in EOC tissues, especially in the advanced stage of EOC, using tissue microarray and immunohistochemical assays (99,100), suggesting that eIF5A can be useful as stage-specific tissue biomarker for EOC. In addition, patients with EOC with higher eIF5A2 expression has short survival time compared to the EOC patients with lower IF5A2 expression (101), indicating that eIF5A2 could be a prognostic marker for EOC.

Experimental research found that targeting eIF5A2 inhibited cell growth in the ovarian cancer UACC-1598 cell line *in vitro* and *in vivo* (100). Furthermore, targeting eIF5A2 using siRNA increased the chemosensitivity of UACC-1598 cells to gemcitabine treatment (102). Further evidence showed that eIF5A also enhanced chemotherapeutic drug- and XPO1 inhibitor-induced ovarian cancer cell apoptosis *in vitro* and *in vivo* (103). Using immunohistochemical assays, eIF5A1 was also found to be overexpressed in EOC tissues, and higher eIF5A1 expression was associated with poor survival of EOC patients (104). In addition, enforced eIF5A1 expression enhanced cell proliferative and invasive capabilities in EOC cells, while targeting eIF5A1 could reverse the effect, implying that eIF5A1 is a potential therapeutic target for EOC (105).

**Cervical cancer.** Cervical cancer is the second most common cancer among females worldwide (106). Patients with advanced or recurrent cervical cancer have poor prognosis, and their 1-year survival of only 10-20% (107). Platinum-based chemotherapy in metastatic cervical cancer is palliative and associated with median overall survival of 9 months (108).

Therefore, it is crucial to explore the molecular mechanism of cervical cancer metastasis and to identify new therapeutic targets.

RT-qPCR assay showed that eIF5A2 mRNA levels were significantly higher in cervical cancer tissues compared with paired paratumor tissues (109). Targeting eIF5A2 inhibited cell proliferation and migration, and induced G1 phase cell cycle arrest in HeLa cells *in vitro* by targeting the RhoA/ROCK pathway (110). Mémin *et al* (23) reported that silencing of eIF5A2 inhibited proliferation and induced apoptosis in cervical cancer cell *in vitro* and *in vivo*, indicating that eIF5A2 is a potential therapeutic target for cervical cancer. eIF5A1 was also upregulated in human cervical cancer tissues compared with adjacent non-cancerous cervix samples (111). Silencing eIF5A1 or DOHH induced apoptosis of human papilloma virus 16 E6-infected cervical cancer cells *in vitro* (111). Therefore, targeting eIF5A1 may also provide a new approach for preventing and treating cervical cancer.

Yang *et al* (109) reported that eIF5A2 overexpression was related with higher Fédération Internationale de Gynécologie et d'Obstétrique staging, lymph node metastasis, postoperative recurrence and poor survival in patients with cervical cancer, suggesting that eIF5A2 is a potential prognosis biomarker for cervical cancer.

**Lung cancer.** Lung cancer is the leading cause of cancer-related deaths worldwide, and non-small cell lung cancer (NSCLC) constitutes >80-90% of all lung malignancies (112). Despite advances in treatment options including surgery, radiation, chemotherapy and targeted therapies, the 5-year overall survival rate for patients with metastatic NSCLC is <5% (113). In human lung adenocarcinoma, eIF5A2 overexpression was related with positive lymphocytic response and relatively poorer survival of patients (114). Furthermore, tissues with poor differentiation or 12th/13th codon K-Ras mutations or p53 nuclear accumulation showed higher eIF5A2 expression (114), suggesting that eIF5A2 may be as a prognostic marker for lung adenocarcinoma. Jin *et al* (115) has demonstrated that adenovirus-mediated eIF5A1 overexpression induced apoptosis in A549 cells *in vitro* and improved the survival time in mice bearing A549 xenograft tumors *in vivo*, possibly modulated by NF- $\kappa$ B in a p53-dependent manner (116). However, Taylor *et al* (117) reported that eIF5A1 induced A549 cell apoptosis via a p38 and JNK/MAP-dependent pathway and ap53-independent pathway,

eIF5A2 was also found to be overexpressed in NSCLC tissues (118); furthermore, eIF5A2 overexpression was related with advanced T stage and local invasion in patients with NSCLC (118), suggesting that eIF5A2 might serve as a poor prognostic marker. Xu *et al* (119) reported that eIF5A2 expression was upregulated in A549 cells following human transforming growth factor (TGF)- $\beta$ 1 treatment, which induced EMT phenotypical changes, resulting in enhanced tumor invasion and metastatic capabilities. However, eIF5A2 downregulation could reverse the effect of TGF- $\beta$ 1 in A549 cells (119,120). In addition, targeting eIF5A2 significantly inhibited cell proliferation and induced apoptosis, and enhanced cisplatin or cetuximab cytotoxicity in NSCLC cells (121,122). In NSCLC cells, eIF5A2 was reported to control cell growth, apoptosis and chemotherapy sensitivity by

regulating miR-9 (123-125). These data indicated that eIF5A2 may serve as a therapeutic target for the treatment of NSCLC.

**Malignant tumors of the urinary system.** Bladder cancer. Bladder cancer is the fourth most common cancer in males and the ninth most common cancer in females in the Western world (126). A total of 70% patients with bladder cancer present with superficial tumors, and >30% of patients present with muscle-invasive disease, resulting in metastasis and ultimately causing death (127). Moreover, 50-70% of superficial tumors will recur, and 10-20% of superficial tumors will progress to muscle-invasive disease (128,129). It is difficult to diagnose bladder cancer accurately and sensitively at an early stage due to the lack of disease-specific symptoms (117). The prognosis of muscle-invasive bladder cancer is poor, and recurrence is common after radical surgery or chemotherapy (130). Therefore, the development of molecular assays that could diagnose bladder cancer accurately at an early stage would be a significant advantage. Numerous reports demonstrated that eIF5A2 was overexpressed in bladder cancer tissues by immunohistochemical and enzyme-linked immunosorbent assays (131-135). Bladder cancer tissues with higher eIF5A2 expression predicted short survival using Kaplan Meier curves, recurrence, progression and chemotherapy response in patients with bladder cancer (131-133). Therefore, eIF5A2 may be a potential marker of bladder cancer diagnosis or progression. Furthermore, eIF5A2 knockdown inhibited cell proliferation and invasion both *in vitro* and *in vivo*, whereas eIF5A2 overexpression promoted cell proliferation *in vitro* (131,135). In addition, targeting eIF5A2 with GC7 enhanced the therapeutic efficacy of doxorubicin in bladder cancer via preventing EMT (135,136), indicating that eIF5A2 may be a potential target for bladder cancer therapy.

**Prostate cancer (PCa).** PCa is the second most common cancer and the fifth most common cause of cancer-associated mortality worldwide in men (137). PCa is asymptomatic in the early stage of the disease. However, despite significant improvements in early detection due to routine prostate-specific-antigen (PSA) testing, the diagnostic accuracy is <75% (138). In addition, whether PSA testing effectively reduces the risk of death from PCa remains controversial. Advocates of testing argue that PSA testing may, in some cases, lower the stage and grade of cancer at diagnosis, and decrease the risk of being diagnosed with metastatic PCa, for which there is no cure (139). However, across the population of asymptomatic men, PSA testing does not decrease all-cause mortality, and some men will progress and develop metastatic disease despite screening and an earlier diagnosis (140). Therefore, it is critical to develop an individualized approach for early detection (141). Anti-androgen therapies are part of the standard of therapeutic regimen for advanced or metastatic PCa (142). However, PCa always develops resistance to androgen deprivation and progresses to castrate-resistant prostate cancer (143). Lu *et al* (144) reported that eIF5A2 was overexpressed in PCa tissues, and enhanced eIF5A2 expression was related with higher tumor stage, recurrence and short survival, indicating that eIF5A2 expression could be a candidate biomarker for prognosis assessment in prostate cancer. It was found that enforced eIF5A expression promoted prostate epithelial cell proliferation via



modulation of DOHH expression, which is a specific and direct target of the putative tumor suppressor miR-331-3p and miR-642-5p (145,146). However, whether eIF5A1/2 could be a target for PCa treatment needs further investigation.

**Tumor microenvironment.** The tumor microenvironment consists of stromal cells, the extracellular matrix and signaling molecules that communicate with cancer cells (147). The normal cellular microenvironment inhibits tumor cell growth, but alterations within the tumor microenvironment affect the regulation of both cancer and stromal cells (148). Most of the signals are related to the tumor microenvironment, such as Notch signaling (149), tumor-associated macrophages and neutrophils (150), CXCL12/CXCR4 (151), tumor-associated macrophages (152), tumor-related exosomes (153), hypoxia/HIF-1 $\alpha$ -driven factors (154) and MMPs (155). These signals have the ability to induce proliferation and inhibit apoptosis, induce angiogenesis and avoid hypoxia to influence the invasive phenotype (156). In addition, the tumor microenvironment is not only influenced by signals from tumor cells, but also stromal components, which contribute to tumor progression and metastasis by affecting cancer cell function (157,158). Therefore, targeting the tumor microenvironment to encapsulate or destroy cancer cells in their local environment has become mandatory for cancer invasion (159). Hence, identification of therapeutic targets and manipulation of the tumor microenvironment could be used as an approach to prevent and treat cancer.

Accumulating studies have demonstrated that eIF5A2 regulated numerous signals related to cell apoptosis, angiogenesis, invasion and metastasis, such as Akt/MMP-2 (160), MTA1 (70), ROS-related pathways (50), HIF1 $\alpha$ -mediated signaling pathway (20), (PEAK1) (15) and TGF- $\beta$  (161). eIF5A2 was able to induce EMT in CRC cells, a key event in tumor invasion and metastasis, characterized by downregulation of epithelial markers such as E-cadherin and  $\beta$ -catenin and upregulation of mesenchymal markers such as fibronectin, N-cadherin,  $\alpha$ -smooth muscle actin and vimentin (162). In addition, eIF5A2 could also activate RhoA/Rac1 to stimulate the formation of stress fiber and lamellipodia (17). Therefore, targeting eIF5A2 in the tumor microenvironment could be useful in the treatment and prevention of cancer.

### 3. Conclusion

Accumulative clinical and experimental evidence showed that eIF5A2 is overexpressed in a number of malignant tumor tissues. Upregulation of eIF5A2 is associated with poor survival, advanced disease stage, poor response to chemotherapeutic drugs and metastasis for patients with cancer, suggesting that eIF5A2 might be a potential prognostic biomarker for malignancies. Numerous evidence demonstrated that enforced eIF5A2 expression enhanced cancer cell growth, increased cancer cell metastasis and promoted chemotherapy resistance through multiple ways. Furthermore, targeting eIF5A2 or inactivating hypusination of eIF5A by DHPS and DOHH attenuated tumor growth and metastasis and overcomes chemotherapeutic resistance, suggesting that targeting eIF5A2 may provide an effective approach for the treatment of malignancies. However, the exact mechanism by which eIF5A2 regulates its target genes and whether it can

directly play a biological role as a transcription factor has not been elucidated.

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### Authors' contributions

XJ, LW, HZ and LN collaborated in data collection and literature review. DC wrote the manuscript. All authors read and approved the final version of the manuscript.

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Not applicable.

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### Competing interests

The authors declare that they have no competing interests.

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