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REVIEW

EIF5A2 promotes tumor metastasis and angiogenesis

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The pathogenesis of solid tumors is a long-term process involving the accumulation of multiple genetic and epigenetic changes causing activation of oncogenes and inactivation of tumor suppressor genes. Gene amplification is one of the most common causes of oncogene activation that plays a critical role in the development and progression of various cancers because over expression of candidate oncogene(s) within the amplicon confers a selective growth advantage. Amplification of the long arm of chromosome 3, especially 3q26, is one of the most frequently detected genomic alterations in various cancers, such as lung cancer^[1, 2], esophageal carcinoma^[3], breast cancer^[4], ovarian cancer^[5] and nasopharyngeal carcinoma^[6], suggesting the existence of one or more important oncogenes at 3q26. To identify candidate oncogene(s) within the 3q26 amplicon, genomic DNA library of 3q26 was generated by chromosome micro dissection and a hybrid selection strategy was applied to isolate over expressed genes from the micro dissected DNA^[7]. One candidate oncogene at 3q26, eukaryotic translation initiation factor 5A2 (eIF5A2) was identified by this strategy. In the same time, Johansson and his colleagues also identified eIF5A2 as a phylogenetically conserved variant of eIF5A^[8]. EIF5A2 shares 83% amino acid identity with EIF5A including the critical functional domain necessary for maturation by hypusine modification at lysine-50 residue^[7, 9, 10]. Unlike EIF5A that is universally expressed in tissues, EIF5A2 is only found in testis, brain and tumor tissues^[8].

Since eIF5A2 was firstly reported to be amplified in ovarian cancer^[7], overexpression of eIF5A2 has been reported in many other solid tumors including hepatocellular carcinoma (HCC)^[10, 11], esophageal squamous cell carcinoma (ESCC)^[12], gastric cancer^[13], non-small cell lung cancer^[2], bladder cancer^[14, 15], melanoma^[16] and colorectal cancer^[17, 18]. Interestingly, overexpression of eIF5A2 has been closely associated with clinical stage and tumor metastasis in several cancers including ovarian cancer^[19], melanoma^[16], colorectal cancer^[18] and HCC^[10]. In addition, overexpression of eIF5A2 has been also closely correlated with poorer outcome of several cancers, such as ovarian cancer^[20], bladder cancer^[15], ESCC^[12] and pancreatic cancer^[21]. Metastasis consists of a series of rate limiting steps. Metastasis is the acquisition of motility by tumor cells in a process: epithelial-mesenchymal transition (EMT). Recent studies have demonstrated that eIF5A2 plays an important role in EMT through the down-regulation of epithelial markers (e.g. E-cadherin and β -catenin) and up-regulation of mesenchymal markers (e.g. fibronectin and vimentine)^[10, 12]. In addition, these studies find that overexpression of eIF5A2 is able to promote the formation of stress fiber and lamellipodia via the activation of RhoA/Rac1 signaling pathway^[10, 12]. Molecular studies indicate that eIF5A2 is able to promote tumor metastasis by enhancing the binding of c-myc on MTA1 promoter^[18], to induce EMT via activating STAT3/ TGF- β 1 signaling^[15] and to increase MMP-2 activity^[16].

Although 3q26 amplification is a major event for eIF5A2 over expression in ovarian cancer ^[7], amplification of 3q26 has not been frequently detected in many other cancers, such as HCC ^[22]. In ESCC, the copy number gain was detected in less than 40% of ESCCs with eIF5A2 over expression ^[12], suggesting that other mechanisms might contribute to the eIF5A2 over expression event. Further study finds that eIF5A2 expression can be induced by hypoxic culture condition ^[12]. Hypoxia is a powerful driving force to breakdown normal tissue homeostasis and rearrangement of tumor-stroma interactions in tumor invasion and metastasis ^[23]. Hypoxia-inducible factor-1 (HIF1) is one of the best characterized hypoxia response pathways. HIF1 α is one of the master regulators of tumor metastasis, which can be regulated through oxygen-dependent and -independent mechanisms in a cell specific manner ^[24]. Our study demonstrated that bidirectional regulation exists between EIF5A2 and HIF1 α ^[12]. The direct binding of EIF5A2 to the promoter region of HIF1 α has been verified by luciferase assay and chromatin immunoprecipitation ^[12]. Since HIF1 α also plays a very important role in tumor angiogenesis, the association of EIF5A2 over expression and angiogenesis has been studied. The results demonstrate that over expression of EIF5A2 can promote angiogenesis, and association study on clinical ESCC specimens indicates that over expression of EIF5A2 is positively correlated with HIF1 α and VEGF expressions ^[12]. In HCC, eIF5A2 has been reported to be associated with venous infiltration too ^[25].

eIF5A2 has been associated with chemo resistance in breast cancer ^[26], therefore, it is a potential therapeutic target for cancer treatment. shRNAs targeting eIF5A2 along or with the combination of chemotherapeutic agent docetaxel (TXT) or cisplatin (CDDP) can effectively reduce the tumor volume and tumor weight in animal models ^[12]. Inhibiting eIF5A2 activity with N1-guanyl-1, 7-diaminoheptane (GC7) has demonstrated to enhance the therapeutic efficacy of doxorubicin in HCC and bladder cancer cells ^[27, 28]. As eIF5A2 plays an important role in the multi-step progression of metastasis and angiogenesis, therapeutic targeting eIF5A2 may become a new useful approach to prevent and/or control tumor metastasis and angiogenesis in cancer treatment. Taken together, recent studies have demonstrated that eIF5A2 plays critical roles in tumor cell proliferation, invasion, metastasis, angiogenesis and drug resistance. As silencing eIF5A2 expression can dramatically inhibit its oncogenic function, targeting this oncogene might shed light on the effective treatment of cancer patients with eIF5A2 over expression.

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