REVIEW

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Targeting HIF-1α signaling pathway for gastric cancer treatment

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Gastric cancer is a common malignancy with high mortality and limited therapeutic options. Hypoxia inducible factor-1 α (HIF-1α) is the key responser adapted to tumor hypoxia. Under hypoxia conditions, HIF-1α signaling is activated and responsible for cell biology associated with metabolism, inflammation, vascular homeostasis and tumorigenesis. Activation of HIF-1α signaling has been observed in a series of cancers including gastric cancer. Moreover, a variety of oncogene products may be induced by HIF-1α expression. Pharmacologic manipulation of HIF-1α may provide a novel therapeutic approach to gastric cancer. In this review, we summarize the recent information on HIF-1α in gastric cancer with special focus on the mechanism underlying HIF-1α signaling effects on proliferation, apoptosis, angiogenesis, EMT and drug-resistance of cancer cells, thereby predicting new therapeutic agents for better management of this malignancy.

1. Introduction

Gastric cancer is one of the leading causes of cancer-related death worldwide (Bertuccio et al. 2009). Despite of advances in the detection and treatment of gastric cancer including surgery, chemotherapy and targeted therapies, many metastatic gastric cancers still persist after primary therapy and eventually become resistant to chemotherapy (Karimi et al. 2014). For these refractory diseases, new drugs specifically inhibiting critical signaling pathways which promote tumorigenesis and tumor development are needed to improve the prognosis of patients.

As a common feature of many cancers, hypoxia contributes to the regulation of cell metabolism and chemoradiotherapy resistance leading to therapeutic failure (Huang et al. 2014; Pucci et al. 2018). In response to tumor hypoxia, upregulation of hypoxia-inducible factor 1 (HIF-1) activates the downstream genes participated in crucial aspects of cancer biology comprising angiogenesis, cell survival, glucose metabolism and invasion (Wang et al. 2014). As a subunit, HIF-1α is responsible for the function of HIF-1 and its overexpression is observed in a variety of cancer tissues compared with the respective normal tissues, including colorectal, breast, lung and gastric carcinomas (Cai et al. 2016; Kitajima and Miyazaki 2013; Li et al. 2016; Yan et al. 2017). However, the role of HIF-1α in tumor development as a promoter or inhibitor remains controversial. On one hand, HIF-1α was verified to be positively correlated with tumor metastasis and negatively with prognosis of patients (Chen et al. 2014; Liu et al. 2018). On the contrary, Carmeliet et al. (1998) showed that HIF-1α inhibits tumor growth through reducing proliferation and increasing apoptosis of embryonic stem cells due to its association with p53 (An et al. 1998).

Along with the significant progress in our understanding of HIF-1α, its roles in gastric cancer development have become increasingly clear. At the same time, precise treatment is gradually replacing traditional chemotherapy due to its better therapeutic effects and slighter side effects. Appearance of many HIF-1α inhibitors significantly improves the prognosis of advanced gastric cancer patients, indicating that HIF-1α may become a prospective target for gastric cancer treatment.

2. HIF-1α signaling pathway

HIF-1 consists of alpha (α) and beta (α) subunits which are both helix-loop-helix transcription factors. Among these two subunits, the expression of HIF-1α

can be high-induced by hypoxia leading to promotion of tumor growth, while HIF-1α protein levels remain constant and not concerned with oxygen concentrations, implying that HIF-1α is the decisive factor of HIF-1 transcriptional activity and hypoxia response (Huang et al. 1996). When oxygen is available, HIF-1α is targeted to be disrupted by hydroxylases, the key oxygen sensor including prolyl-hydroxylases (PHD1-3, especially PHD2) and asparaginyl hydroxylase (such as factor inhibiting HIF-1 (FIH-1)) which mediate ubiquitination and proteasomal degradation of HIF-1α (Berra et al. 2003; Kaelin and Ratcliffe 2008; Lando et al. 2002; Mahon et al. 2001; Townley-Tilson et al. 2015). Activities of prolyl and asparaginyl hydroxylase can be inhibited by hypoxia, resulting in relief of inhibition on HIF-1α (Jaakkola et al. 2001; Kaelin and Ratcliffe 2008; Maxwell et al. 1999). Activated HIF-1α is transferred to the nucleus and acts as a transcription factor with binding to HIF-1α to form a heterodimer. This heterodimer subsequently binds to hypoxia response elements (HREs) containing the recognizing sequence of 5'-(A/G)CGTG-3', leading to transactivation or inhibition of down-stream target genes associated with metabolism, inflammation, vascular homeostasis and tumorgenesis (Fig. 1). Hundreds of genes are discovered to be regulated by HIF-1α, of them several genes are found to establish close network with HIF-1α including NFkB1, BRCA1, STAT3, STAT1, MMP1, TIMP1, TLR2, FCGR3A, IRF1, FAS, and TFF3 (Wang et al. 2014).

3. The role of HIF-1α signaling in gastric cancer

3.1. HIF-1α and proliferation

Accelerated proliferation is an essential character of almost all types of cancer cells leading to a rapid growth of the tumor. Based on recent study results, we identified three major mechanisms by which HIF-1α induces proliferation of gastric cancer cells: acti-

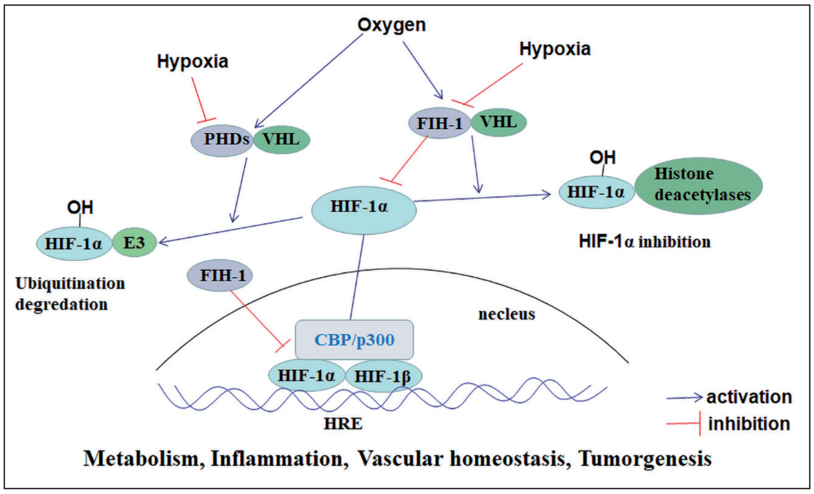

Fig. 1: HIF-1α signaling activation. When oxygen is available, HIF-1α is targeted to be disrupted by hydroxylases, the key oxygen sensor including prolyl-hydroxylases (PHDs) and asparaginyl hydroxylase (such as factor inhibiting HIF-1 (FIH-1)). PHDs mediate HIF-1α ubiquitination degradation through binding to the von Hippel-Lindau (VHL) protein and recruitment of an E3 ubiquitin-protein ligase. FIH-1 inhibits HIF-1α via the following ways: preventing combination of HIF-1α to the transcriptional co-activators CBP and p300; binding to HIF-1α directly and inhibiting its transactivation; binding to the transcriptional corepressor VHL which recruit histone deacetylases to inhibit HIF-1α. Activities of prolyl and asparaginyl hydroxylase can be inhibited by hypoxia, which resulting in activation of HIF-1α. Activated HIF-1α is transfered to nucleus and bind to HIF-1α to form a heterodimer which binds to hypoxia response elements (HREs) containing the recognizing sequence of 5'-(A/G)CGTG-3', leading to transactivation or inhibition of down-stream target genes associated with metabolism, inflammation, vascular homeostasis and tumorigenesis.

vating PI3K/AKT pathway (Ardyanto et al. 2006; Zhang et al. 2018); upregulating Forkhead box M1 (FoxM1)/PARI pathway (Bai et al. 2018; Zhang et al. 2018), and interaction with long non-coding RNAs (lncRNAs) (Huang et al. 2017; Liu et al. 2016; Zhang et al. 2015). For example, dysregulation of lncRNA related to HIF-1α has been recognized in many kinds of cancers. In gastric cancer, lncRNAs associated with promoted proliferation induced by HIF-1α consist of GAPLINC and PVT1. HIF-1α can increase proliferation activities of gastric cancer cells by inducing high expression of GAPLINC, it can also be a target gene of lncRNA PVT1 which contributes to enhanced cell proliferation (Huang et al. 2017; Liu et al. 2016; Zhang et al. 2015). What's more, several studies suggest that downregulation of HIF-1α or its activator inhibits proliferative activity of gastric cancer cells (Li et al. 2016; Wang et al. 2017; Zhang et al. 2018). In conclusion, apart from the traditional proliferation-associated pathways, lncRNAs have shown its unique role in HIF-1α pathway by promoting cell proliferation as well as metastasis of gastric cancer.

3.2. *HIF-1α and apoptosis*

Cell apoptosis is the rudimentary life phenomenon initiated with caspase activation which is induced by two main pathways: mitochondria-mediated apoptosis pathway and extracellular signal-mediated apoptosis pathway. Apoptosis-resistance, a common feature of cancer cells, serves as a promoter of gastric cancer malignance and chemo-resistance. A great deal of evidence suggests that HIF-1α can inhibit apoptosis of gastric cancer cells. In the first place, several studies establishing tumor xenograft models on mice show that HIF-1α inhibition can reduce the growth speed of gastric tumor by inducing apoptosis (Guan et al. 2017; Shen et al. 2012; Tanaka et al. 2015; Wakiyama and Kitajima 2017; Wang et al. 2017). The agonist of HIF-1α was discovered to significantly inhibit apoptosis of gastric cancer cells leading to reduced sensitivity to chemotherapeutic agents (Yan et al. 2015). Secondly, substantial evidences suggest that HIF-1α suppresses mitochondrial apoptosis via interplaying with microRNAs (miR-421, miR-18a) (Ge et al. 2016; Wu et al. 2015) and weakening reactive oxygen species (ROS)/mitochondria pathway which is responsible for the apoptosis of cancer cells (Li et al. 2014; Wakiyama and Kitajima 2017). Moreover, apart from mitochondrial apoptosis, HIF-1α can also inhibit extracellular signal-mediated apoptosis by activating MEK/ERK pathway *in vivo* and *in vitro* (Liu et al. 2010). Taken together, HIF-1α contributes to apoptosis-resistance by regulating both mitochondrial apoptosis and extracellular signal-mediated apoptosis. Fortunately, the treatment outcomes for gastric cancer are going to be improved with the development of studies in the apoptosis effect of HIF-1α inhibition.

3.3 *HIF-1α signaling and angiogenesis*

Angiogenesis is known as the sprouting of new capillaries from pre-existing vessels supported by hypoxia cancer cells to provide oxygen for rapid tumor growth (Rey and Semenza 2010). Ii is known that HIF-1α signaling is critical for gastric cancer angiogenesis through activating angiogenic growth factors (VEGF, SDF1, ANGPT2, PGF, PDGFB and SCF) (Bosch-Marce et al. 2007; Forsythe et al. 1996; Kelly et al. 2003) and microRNAs (such as miR-382, acting as an angiogenic oncogene) (Seok et al. 2014). A correlation analysis through immunohistochemical staining of resected gastric cancer specimens indeed verified the key role of HIF-1α in gastric tumor angiogenesis (Zhan et al. 2013). Several animal studies utilizing gastric cancer xenografts show that many HIF-1α inhibitors suppress tumor angiogenesis by reducing the expression of VEGF under hypoxia conditions (Fang et al. 2017; Kim et al. 2016; Ko et al. 2016; Lee et al. 2014). As the most common metastatic pattern in advanced gastric cancer, peritoneal dissemination is well-recognized to be positively correlated with tumor angiogenesis induced by HIF-1α (Miyake et al. 2013; Yoshikawa et al. 2006). However, Hiraki et al. (2012) suggested that knockdown of HIF-1α in gastric cancer cells promotes the progression of peritoneal dissemination by upregulating MMP-1, indicating that the role of HIF-1α signaling in peritoneal dissemination development is not simply *via* HIF-1α/VEGF pathway.

These data suggest that angiogenesis induced by HIF-1α is a main pathological characteristic of gastric cancer. HIF-1α mediates angiogenesis in gastric cancer mainly through two ways: HIF-1α/VEGF axis and HIF-1α/microRNAs pathway. The former has been studied extensively, while the relationship between HIF-1α and microRNAs in tumor angiogenesis is not fully realized. During the development of gastric cancer, HIF-1α can be an upstream-regulator or a downstream-target gene of microRNAs (Seok et al. 2014; Wu et al. 2015; Zheng et al. 2013), suggesting the microRNA/HIF-1α/microRNA pathway existing to regulate angiogenesis in gastric cancer.

3.4. *HIF-1α and EMT*

Epithelial to mesenchymal transition (EMT) appears as reduced epithelial markers like E-cadherin, desmoplankins, claudins, cytokeratins and the gain of mesenchymal markers such as N-cadherin, vimentin, Snail, etc. Hypoxia is one of the conditions able to trigger EMT which plays a vital role in cancer metastasis. The induction role of HIF-1α on EMT was assigned to many human cancers (Deng et al. 2018; Kim et al. 2018). In gastric cancer, HIF-1α is demonstrated to enhance invasion and metastasis of gastric cancer *via* inducing EMT (Liu et al. 2014; Yang et al. 2017; Zhang et al. 2017). Plenty study results confirm that HIF-1α upregulates EMT

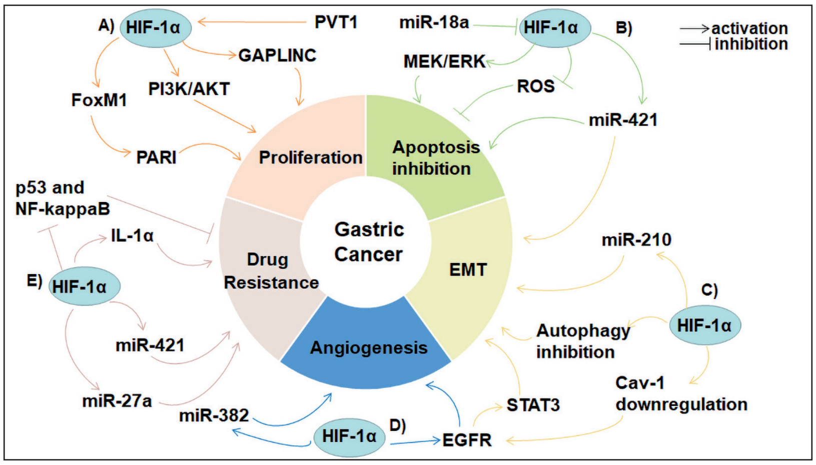

Fig. 2: HIF-1α signaling pathway in regulating gastric cancer development. A) Activated by lncRNA PVT1, HIF-1α promotes proliferation of gastric cancer cells through activating PI3K/AKT, FoxM1/PARI pathways and lncRNA GAPLINC. B) Apoptosis of gastric cancer cells can be inhibited by HIF-1α which activates MEK/ERK pathway and miR-421 as well as controlling production of reactive oxygen species (ROS). MiR-18a was hypothesized to induce apoptosis through antagonism to HIF-1α. C) HIF-1α involves in EMT though upregulating miR-210 and inhibiting autophagy. Besides, HIF-1α/caveolin-1(Cav-1)/EGFR/STAT3 pathway also contributes to EMT initiation. D) Angiogenesis developed in gastric cancer is mainly induced through HIF-1α/EGFR and HIF-1α/miR-382 pathway. E) MiR-421, miR-27a and IL-1α upregulated by HIF-1α contribute to enhanced chemo-resistance. What's more, HIF-1α can reduce sensitivity of gastric cancer cells to chemotherapeutic agents by suppressing p53 and NF-kappaB activity.

by mediating EMT-associated transcription factors and signaling pathways in gastric cancer. First, HIF-1α/microRNAs pathway serves as a promising activator of EMT. Studies *in vivo* and *in vitro* show that miR-421 and miR-210 upregulated by HIF-1α both promote metastasis or chemo-resistance of gastric cancer by regulating EMT-related proteins (Ge et al. 2016; Yu et al. 2015; Zhang et al. 2016). MiR-224, upregulated by HIF-1α, is responsible for migration of gastric cancer and is confirmed to induce EMT in other type of cancers including malignant melanoma and colorectal cancer (Amankwatia et al. 2015; He et al. 2017; Knoll et al. 2014). These data indicate that the HIF-1α/mircoRNAs/EMT pathway is involved in metastasis of gastric cancer. Second, tumor-associated macrophages (TAMs) and autophagy are associated with EMT induced by HIF-1α (Qin et al. 2015; Zhang et al. 2017). What's more, many transcription factors targeted by HIF-1α are suggested to activate EMT covering Snail, Rab11-FIP2, KLF8, caveolin-1 (Cav-1) and RhoE (Dong et al. 2016; Kannan et al. 2014; Liu et al. 2014; Yang et al. 2017; Zhou et al. 2011).

Except for microRNAs, lncRNAs also exhibit important roles during the HIF-1α-induced tumor EMT process (Cai et al. 2017). With more and more studies discovering the function of microRNA or lncRNA in tumor progression, the impact of these non-coding RNAs on invasiveness of gastric cancer will be better known.

4. HIF-1α and chemo-resistance of gastric cancer

Chemotherapeutic drugs effective for gastric cancer treatment embrace 5-fluorouracil (5-FU), platinum compounds, anthracyclines, taxanes and irinotecan. Although this therapy was observed to be well tolerated and had yielded good responses in clinical trials, acquired resistance is common in clinical practice.

Involvement of HIF-1α in chemo-resistance during gastric cancer treatment has been well recognized. Combined with recent study data, HIF-1α is suggested to induce anti-cisplatin effects through three major mechanisms: first, dysregulating microRNAs (such as miR-421, miR-27a) and lncRNAs (such as PVT1) (Ge et al. 2016; Zhang et al. 2015; Zhao et al. 2015); second, upregulating inflammatory factors (such as IL-1α) (Xuan and Wang 2017); third, suppressing activities of p53 and NF-kappaB (Rohwer et al. 2010). Through these three main pathways, cisplatin-induced apoptosis is significantly abrogated. In addition, HIF-1α is considered as an independent risk factor for gastric cancer relapse after 5-FU chemotherapy because of its function with inhibiting 5-FU-mediated apoptosis (Nakamura et al. 2010). Recent studies reveal that glycolysis inhibitors can reverse HIF-1α-induced resistance to 5-FU (Chen et al. 2015; Xuan et al. 2014), indicating that a high level of glycolysis under hypoxia is conducive to 5-FU-resistance. Finally, drug sensitivity can be enhanced by HIF-1α knockdown (Zhao et al. 2016). Except for cisplatin and 5-FU, HIF-1α also induces resistance to oxaliplatin, vincristine, epirubicin, oxaliplatin and capecitabine during chemotherapy (Liu et al. 2008; Mangia et al. 2015). All evidence suggests that the efficacy of chemotherapeutic drugs can be impaired by HIF-1α, which has become a main obstacle during the therapy of gastric cancer.

5. Contribution of HIF-1α inhibitors to prevent gastric cancer

Due to the pivotal role of HIF-1α in promoting gastric carcinogenesis and progression as well as inducing resistance to chemotherapy (Fig. 2), the effect of HIF-1α inhibitors on gastric cancer treatment aroused our concern. There are many kinds of HIF-1α inhibitors exhibiting anti-gastric cancer effect in recent studies through the following mechanisms. Firstly, with deep understanding of the relationship between HIF-1α and microRNAs, HIF-1α inhibitors are discovered to achieve an anticancer function by suppressing the release of microRNAs. The representative drug class of this category is that of proton-pump inhibitors (PPIs), which have been already applied for clinical treatment of peptic ulcer and gastro-esophageal reflux disease (Guan et al. 2017; Shen et al. 2012). Secondly, HIF-1α inhibitors can prevent progression of gastric cancer by anti-proliferative and pro-apoptotic effects. Low dose YC-1, an inhibitor of HIF-1α combined with glucose (G) and insulin (I) treatments is established targeting hypoxic gastric cancer cells (Tanaka et al. 2015; Wakiyama and Kitajima 2017). What's more, angiogenesis of gastric cancer can be obstructed by HIF-1α inhibitors such as celecoxib or berberine (Lin et al. 2004; Wang et al. 2006). Finally, some natural compounds like quercetin and curcumin are discovered to suppress gastric cancer by inhibiting HIF-1α (Wang et al. 2011, 2017).

These preclinical trials offer promises for the anti-cancer effects of drugs inhibiting HIF-1α in gastric cancer, in addition to established therapeutic options for gastric cancer.

6. Conclusion and future perspectives

HIF-1α signaling has been considered as a promoter of gastric cancer progression through mediating enhanced proliferation, angiogenesis, EMT, drug-resistance and inhibited apoptosis of cancer cells. Despite the impressive progress of HIF-1α signaling in gastric cancer, there are several challenges for a systematic clinical application of HIF-1α inhibitors. First, although non coding RNAs (microRNAs and lncRNAs) have been confirmed to be a vital factor in HIF-1α-induced cancer progression, its regulating mode with HIF-1α is still unclear and worth to be explored more deeply. Second, a phase I clinical trial of drugs targeting HIF-1α combined with conventional chemotherapy is still underway (ClinicalTrials.gov Identifier: NCT01049620). Further evaluation is necessary for safety and effectiveness of HIF-1α-targeted drugs. Finally, novel drugs aimed at molecules in HIF-1α signaling need to be developed due to the limited range of drugs directly targeting for HIF-1α. New therapeutic strategy with HIF-1α signaling inhibitors is predictable to be developed for gastric cancer clinical trials in the future.

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