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Original Article

Interactions between hypoxia-inducible factor-1α and other molecules in cancer: a literature review

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Abstract: Hypoxia is a critical characteristic for malignant tumor progression. Transcription factor hypoxia-inducible factor-1α (HIF-1α) plays a fundamental role, assisting with adaption to a hypoxic microenvironment. Multiple target genes can be regulated by HIF-1α, further participating in a variety of biological events of tumorigenesis and tumor progression, including tumor cell proliferation, migration, invasion, metastasis, and angiogenesis. It is worth mentioning that the activity of HIF-1α interacts with several different kinds of molecules and regulators, such as transcription factors, microRNAs, long non-coding RNAs, and signaling pathways. These molecular interactions increase the complexity and difficulty of cancer research. A better understanding of the regulatory mechanisms of HIF-1α with other molecules in cancer will provide deeper insight into HIF-1α and cancer research.

Keywords: Hypoxia-inducible factor 1α, transcription factor, tumor-associated signaling pathway, microRNAs, long non-coding RNAs

Introduction

Hypoxia, a condition of insufficient oxygen supply, is one of the most common characteristics of the tumor microenvironment. It regulates a series of biological events of tumor cells and drives tumorigenesis [1]. Cellular responses to hypoxia are regulated by the hypoxia-inducible factor (HIF) family. Regarding HIF family members, the structures and functions of HIF-1 have been well characterized. HIF-1 is composed of an oxygen-regulated subunit, HIF-1α, and a constitutively-expressed subunit, HIF-1β. The stability of HIF-1 has been closely associated with expression of HIF-1α. Under normoxia, HIF-1α is degraded by ubiquitin proteasome system (UPS) after generation. Hypoxia leads to the failure of HIF-1α degradation through UPS pathways, resulting in the subsequent nuclear translocation of HIF-1α from cytosol. Within the nucleus, HIF-1α dimerizes with its constitutively expressed HIF-1β subunit and forms heterodimeric and stabilized HIF-1. HIF-1 activates downstream genes by binding to hypoxia-responsive elements (HREs) in the promoters of the genes [2, 3]. At present, approximately more than 100 downstream genes of HIF-1α have been identified. These genes are known to participate in a variety of biological events of tumorigenesis and tumor progression, including tumor cell proliferation, migration, invasion, metastasis, and angiogenesis [4].

Hypoxia in the tumor microenvironment, induced by various stimuli, such as microorganism infections, chronic inflammation, or the presence of bioactive mediators, upregulates expression of HIF-1α [5]. Several molecules, including transcriptional factors, small non-coding RNAs (microRNAs), and long non-coding RNAs (lncRNA), mediate the activation of HIF-1α at transcriptional, post-transcriptional, or translational levels. However, disturbed activity or abnormal expression levels of HIF-1α may lead to tumorigenesis and progression.

Key downstream genes of HIF-1α have been proven to influence the biological activities of tumor cells. For instance, downstream effector vascular endothelial growth factor (VEGF) is

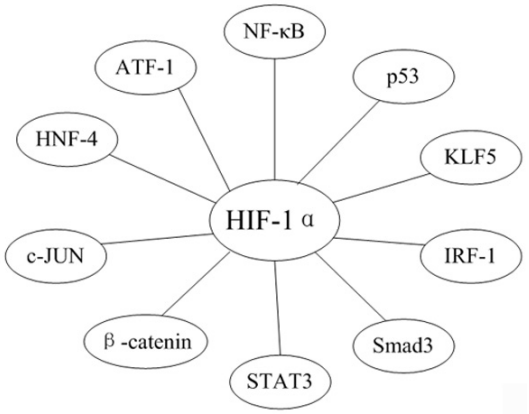

Figure 1. Crosstalk between HIF-1(α) and other transcription factors. NF-κB: Nuclear factor kappa-B; p53: p53 tumor suppressor; KLF5: Krüppel-like factors 5; IRF-1: Interferon regulatory factor-1; Smad3: SMAD family member 3; STAT3: Signal transducer and activator of transcription-3; β-catenin: beta-catenin; c-JUN: member of AP-1 family transcription factor; HNF-4: Hepatocyte nuclear factor-4; ATF-1: Activating transcription factor-1.

known to trigger angiogenesis. Glucose transporter-1 (GLUT-1) induces glycolysis [6, 7]. In addition, the activity of HIF-1α is also mediated by many upstream regulators. Emerging lines of evidences have highlighted the importance of HIF-1α in tumorigenesis and progression. Therefore, the current study summarized recent advances regarding the interaction between HIF-1α and other molecules in tumor development. The current study aimed to provide valuable insight in understanding the critical roles of HIF-1α in tumors.

HIF-1α and other transcription factors

Under hypoxia conditions, abnormal expression of genes and proteins related to cellular metabolism frequently occurs. These changes are closely related with the alteration activities of key transcription factors (TFs), including HIF-1α and other TFs that interact with HIF1, such as NF-κB. Importantly, HIF-1 expression and activity can be modulated by NF-κB. NF-κB is also induced in response to hypoxia [8, 9]. Moreover, other transcription factors, including ATF-1, c-JUN and STAT3, can interact with HIF-1 [10]. As a cAMP response element binding protein (CREB) transcription factor, ATF-1 (activating transcription factor-1) can be activated in hypoxia conditions [11]. The interaction of ATF-1 with HIF is necessary to some targets of transactivation of HIF [12]. Transcription factor c-JUN belongs to the activator protein 1 (AP-1) family. Its interaction with HIF1α requires the posttranslational modification of c-Jun, which is a hypoxia-dependent procedure [13]. STAT3 is a key member of the signal transducer and activator of transcription family (STATs). Its activation will be upregulated by several stresses, including hypoxia and growth factor-mediated/inflammatory cytokines-mediated signaling [14, 15]. Previous studies have shown that nuclear retention and target expression levels of STAT3 were increased under hypoxia conditions. In a study of breast cancer, expression of several HIF-1 targets depended greatly on the activity of STAT3 in cancer cells [16]. As a tumor suppressor protein, dysfunction of p53 can be seen in various human tumors. P53 has been shown to negatively regulate the activity of HIF-1α [17]. Transfection of p53 downregulates expression of HIF-1α and VEGF. HIF-1α accumulation is blocked by p53 overexpression or activation [18]. These results indicated the interaction relationships between HIF-1 and other TFs, which are critical regulators in cancer pathogenesis. **Figure 1** summarizes the interaction of these TFs involved in HIF-1 regulation, including ATF-1, NF-κB, p53, KLF5 [19, 20], IRF-1 [21], Smad3 [22-24], STAT3, β-catenin [25-27], c-JUN, and HNF-4 [28, 29].

HIF-1α and tumor-associated signaling pathways

Although the current study has collected transcription factors, indicating their crosstalk with HIF-1, it should be noted that these are not the only factors that interact with HIF-1 in cells. Other critical disorders, including reactive oxygen species (ROS), alteration AKT activity, disregulated cytokines and chemokines, and autocrine signaling pathways, are important factors that can influence the cell microenvironment. They can subsequently regulate HIF-1α expression and activity [30, 31]. Several signaling pathways, closely related with tumorigenesis, are involved in HIF-1α regulation.

HIF-1α and PI-3K pathways

Phosphoinositide 3-kinase (PI-3K) is divided into three subgroups, class I, class II, and class III PI-3K. These are based on its structure and regulation, as well as the *in vitro* lipid substrate specificity. PI-3K is responsible for the recruit-

ment of different upstream signaling. It also contributes to activation of signaling transduction pathways. PI-3K has been implicated to be involved in cell survival and metabolism. In tumor cells, the activity of PI-3K is generally overactivated [32, 33]. PI-3K-Akt pathways have been shown to regulate HIF-1α activity in response to growth factors and other signals. In a study of breast cancer cells, results indicated that HIF-1α and VEGF expression can be induced by bFGF (basic fibroblast growth factor) in a time- and dose-dependent manner. Moreover, the mechanisms were shown to be related with bFGF-regulated phosphorylation of Akt. Cells treated with LY294002 (the PI-3K inhibitor) showed a suppression of bFGF-induced VEGF increases. This indicated that PI-3K/Akt pathways can regulate HIF-1α activation by bFGF [34]. Some growth factors can be regulated by inflammatory cytokines. IL-1β (interleukin-1 beta) has been shown to induce the production of SCF (stem cell factor) in breast cancer cell MCF-7, dependent on HIF-1α activity. Other studies have discovered a crucial role of PI-3K/mTOR pathways in IL-1β-induced HIF-1α accumulation in MCF-7 cells [35]. Importantly, mTOR was also found to play a role in IL-1β-induced SCF production.

HIF-1α and MAPK pathways

Mitogen-activated protein kinase (MAPK) is a group of serine/threonine kinases that drive cell response to diverse stimuli [36, 37]. Three subgroups of MAPK, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, have been shown to manipulate multiple biologic processes. The consistent activation of MAPK signaling pathways has been noted in primary tumors, as well as in *in vitro* cultured cancer cell lines. Importantly, HIF-1α is known to interact with MAPK signaling pathways in tumor development [36, 38]. It has been reported that YC-1 can inhibit HIF-1α and HIF-1α-mediated gene expression. Moreover, MAPK pathways are involved in YC-1-mediated inhibition of HIF-1α to regulate cell proliferation and migration activity. This induces apoptosis in human bladder transitional carcinoma cells [39]. One study of sporadic renal cell carcinoma confirmed that MAPK pathways plays key roles in expression of HIF-1α. This study approved the interaction of MAPK pathways and HIF-1α [40].

HIF-1α and Notch pathways

Notch is a highly conserved signaling pathway that presents in multiple organisms. Many reports have revealed that Notch signaling pathways are closely associated with cell proliferation, differentiation, adhesion, and apoptosis. They are also linked to tumorigenesis and progression [41-43]. The interaction between Notch and HIF-1α in malignant tumors has been extensively studied. HIF-1α can lead to the activation of Notch pathways in different types of cancer tissues, further regulating cell proliferation, migration, and cell cycle procedures [44]. In a study of glioblastoma stem cells, HIF-1α induced the activation of Notch pathways [45]. Inactivation/blocked HIF-1α expression or suppression of Notch signaling pathways can inhibit hypoxia-induced maintenance of glioblastoma stem cells. Results indicated that there was an interaction between HIF-1α and the intracellular domain of Notch, further activating Notch pathways.

HIF-1α and autocrine signaling pathways

IL-11 is a cytokine belonging to the IL-6 family. It is expressed in multiple human cancers. Studies have shown that IL-11 autocrine was induced by hypoxia-stimulation and expression of IL-11 mRNA was partly dependent upon HIF-1 activity [46]. In a study of glioblastomas, expression of pro-inflammatory cytokine IL-1β was upregulated in tumor samples and glioma cells. IL-1β-induced HIF-1α formed a HIF-1α-IL-1β autocrine system to maintain the elevation of IL-1β expression in tumors [47]. Another study investigated the roles of Flt1 (the "fms-like tyrosine kinase" receptor) in neuroblastoma progression [48]. They found that inhibition of Flt1 autocrine signaling reduced HIF-1α phosphorylation, further leading to down-expression of bFGF (basic fibroblast growth factor, the target of HIF-1α). This indicated that the hypoxia-driven Flt1 autocrine loop interacts with HIF-1α, playing a critical role in the tumorigenesis and progression of neuroblastomas.

HIF-1α and microRNAs

Transcriptional factors and microRNAs (miRNA) mediate gene expression at transcriptional and post-transcriptional levels, respectively. Moreover, crosstalk between transcriptional factors and miRNAs has also been noted. For

instance, transcriptional factors bind to and affect the transcription of miRNAs. Moreover, the mRNA of transcriptional factors may serve as target effectors for certain miRNAs. The complex regulatory network, composing transcriptional factors, miRNAs, and target genes, stabilizes the gene regulation system in cells. Increasing evidence has emphasized the crosstalk between transcriptional factors and miRNAs in tumor development.

Many studies have discovered miRNAs that are aberrantly regulated in response to hypoxia, named hypoxia-regulated-miRNAs (HRMs) [49]. Since miRNAs are transcribed from miRNA genes that involve RNA polymerase, transcription factors play crucial roles in regulating expression of miRNAs. HIF-1α is the most critical TF that regulates expression of these HRMs in hypoxia conditions. In addition, a panel of microRNAs can target HIF-1α to regulate its activity and protein expression. These complex regulatory mechanisms regulate a set of biological activities in cancer cells, directly or indirectly. For example, mir-210 is one of the HRMs that has been investigated extensively in different types of cancer [49]. Elevation of miR-210 by EGCG in lung cancer cell lines is mediated by the stabilization of HIF-1α [50]. Other miRNAs have been reported to interact with HIF-1α in tumor progression. **Table 1** summarizes recent findings on the roles of interaction between HIF-1α and microRNAs in human cancer, illustrating the mechanisms and effects of these interactions in tumor cells.

HIF-1α and lncRNA

Long non-coding RNAs (lncRNA) are a group of RNA with lengths greater than 200 nt. They do not have the function of encoding protein [68]. They have been documented as having a critical role in cancer development and progression [69, 70]. Hypoxia has long been linked to the Warburg effect. Yet, the underlying mechanisms remain largely unclear. It is not known if lncRNAs are involved in the contribution of hypoxia to the Warburg effect.

Recently, scientists have found that lncRNAs are involved in hypoxia-induced metastasis. Studies have also confirmed the existence of regulation mechanisms between lncRNA and HIF-1α. Documents have reported that lncRNA-p21 is able to bind HIF-1α, as well as VHL. This disrupts the VHL-HIF-1α interaction. The disassociation attenuates VHL-mediated HIF-1α ubiquitination and causes HIF-1α accumulation [71]. Expression and transcriptional activity levels of HOX transcript antisense intergenic RNA (HOTAIR), an oncogenic long noncoding RNA, were enhanced upon hypoxia conditions. This effect could be regulated by HIF-1α through binding to hypoxia-responsive elements (HRE) of HOTAIR promoters, which finally influenced proliferation, migration, and invasion of tumor cells in non-small cell lung cancer [72]. Another study found that frequently downregulated lncRNA-ENST00000480739 in pancreatic ductal adenocarcinoma (PDAC) contributes to tumor metastasis and progression by regulating HIF-1α. They demonstrated that ENST-00000480739 may target HIF-1α expression by upregulating osteosarcoma amplified-9 (OS-9) [73]. Results of these studies have indicated the existence of a positive feedback loop between HIF-1α and lncRNAs.

In addition, HIF-1α can also target lncRNAs to regulate the development and progression of cancer. 57. Matsumine et al. found that urothelial carcinoma associated 1 (USA-1) is a HIF-1a-targeted lncRNA that enhances hypoxic bladder cancer cell proliferation, migration, and invasion. The underlying mechanism was that HIF-1α specifically bound to hypoxia response elements (HREs) in the lncRNA-UCA1 promoter [74]. Furthermore, the study published in oncogene shows that the coding EFNA3 mRNA levels remained relatively stable in response to hypoxia. However, HIFs drove the expression of previously unknown lncRNAs from EFNA3 locus. These lncRNAs caused Ephrin-A3 protein accumulation to contribute to metastatic spread of breast cancer [75]. These studies showed the existence of a complex regulatory interaction between HIF-1α and lncRNAs. **Table 2** summarizes research concerning HIF-1α and lncRNAs, suggesting that lncRNAs will be a novel target for cancer research in the future.

Conclusion

HIF-1α-mediated hypoxia response can generally regulate hundreds of target genes, affecting tumor cell behavior under hypoxia conditions. HIF-1α expression and/or activity can be regulated by other molecules and/or regulators, including transcription factors, microRNAs, long non-coding RNAs, and signaling path-

Table 1. Interaction of lncRNAs with HIF-1(α) in different cancer types

Cancer type	HIF-1α related regulatory mechanism	Biological effect	Ref
Lung cancer	The elevation of miR-210 by EGCG in lung cancer cell lines is mediated by the stabilization of HIF-1α	Overexpression of miR-210 reduced cell proliferation rate and anchorage-independent growth, reduced sensitivity to EGCG	[50]
Lung cancer	miR-210-dependent targeting of SDHD was able to activate HIF-1	miR-210 regulate cell metabolism, survival and modulation of HIF-1 activity	[51]
Lung cancer	HIF-1α mRNA is a target of miR-622	Overexpression of miRNA-622 suppresses tumor metastasis by repressing HIF-1α	[52]
Hepatocarcinoma	miR-199a reduced the endogenous protein level of HIF-1α in hypoxia	Overexpression of microRNA-199a inhibits cell proliferation	[53]
Hepatocarcinoma	miR-138 directly targeted HIF-1α	HIF-1α reversed the miR-138-mediated suppression of cell invasion	[54]
Hepatocarcinoma	miR-338-3p inhibited HIF-1α activity and HIF-1α protein levels	miR-338-3p inhibits HCC tumor growth and sensitizes HCC cells to sorafenib	[55]
Nasopharyngeal cancer	HIF-1α is a direct target of miR-338-3p and miR-338-3p regulates HIF-1α expression in NPC cells	Inhibits migration and proliferation of nasopharyngeal cancer	[56]
Pancreatic cancer	miR-21 is induced by hypoxia via HIF-1α upregulation	miR-21 allows cells to avoid apoptosis in a hypoxic microenvironment	[57]
Colon cancer	Over-expression of miR-22 inhibits HIF-1α expression during hypoxia	Over expression miR-22 induce less endothelial cell growth and invasion	[58]
Ovarian cancer	miR-145 inhibits p70S6K1 post-transcription, HIF-1α is the downstream of p70S6K1 and is decreased by miR-145 overexpression	P70S6K1 rescues miR-145-suppressed HIF-1 and VEGF levels, tumorigenesis and tumor angiogenesis	[59]
Bladder cancer	miR-145 is a direct target of HIF-1α in and two HREs have been identified in the promoter region of miR-145 in RT4 cells	miR-145 regulates apoptosis of RT4 cells under hypoxia condition	[60]
Breast cancer	Downregulation of VEGF mRNA by miR-20b was associated with reduced levels of nuclear HIF-1α and STAT3	VEGF expression mediated by HIF-1 and STAT3 in a miR-20b-dependent manner	[61]
Prostate cancer	Down of miR-128 restored the RPS6KB1/HIF-1α/PKM2 pathway	miR-128 inhibited cell growth, reduced glucose consumption & lactate production	[62]
Prostate cancer	miR-21 enhancing HIF-1α expression	Inducing tumor angiogenesis	[63]
Prostate cancer	Over-expression of miR199b down-regulated HIF-1α	Reduced cell growth and increased cell death	[64]
Melanoma	HIF-1α, target of miR-155, was increased in miR-155 deficient cells	miR-155 deficiency promoted solid tumor growth	[65]
Multiple Myeloma	Thehypoxia\AKT/miR-199a-5p loop as a potential molecular mechanism responsible of miR-199a-5p down-regulation in hypoxic condition	miR-199a-5p negatively affected MM cells migration, increased the adhesion of MM cells to bone marrow stromal cells (BMSCs) in hypoxic conditions	[66]
Gastric carcinoma	HIF-1α was the target genes of miR-18a	miR-18a could induce apoptosis through the HIF-1α apoptosis pathway	[67]

Table 2. Interaction of lncRNAs with HIF-1(α) in different cancer types

Cancer type	HIF-1α related regulatory mechanism	Biological effect	Ref
Non-small cell lung cancer	HIF-1α directly target at HOTAIR through interaction with putative HREs in the upstream region of HOTAIR	Under hypoxia conditions, HIF-1α knockdown or inhibition could prevent HOTAIR upregulation, suppression of HOTAIR could be a novel therapeutic strategy	[72]
Pancreatic ductal adenocarcinoma	Long non-coding RNA ENST00000480739 may target HIF-1α expression by upregulating OS-9	The downregulated ENST00000480739 in PDAC contributes to tumor metastasis and progression by regulating HIF-1α	[73]
Bladder cancer	HIF-1α specifically bound to HREs in the lncRNA-UCA1 promoter	UCA1 is involved in bladder cancer progression and acts as a diagnostic biomarker	[74]
Breast cancer	HIFs drove the expression of lncRNAs from EFNA3 locus caused Ephrin-A3 protein accumulation in hypoxia	Hypoxia could contribute to metastatic spread of breast cancer via HIF-mediated induction of EFNA3 lncRNAs	[75]

way proteins. The interplay between HIF-1α and other molecules can partly determine if the net effects of the HIF-mediated hypoxia response are oncogenic or tumor suppressive. Thus, these regulators may indirectly regulate cell physiologic processes, including angiogenesis, cell proliferation, differentiation, and cell cycle.

Recently, HIF-1α has been analyzed as a therapeutic target for cancer research [76, 77]. Ideally, the HIF-1α inhibitor could exhibit effective anti-tumor roles. However, results have not been ideal. Since HIF-1α can be regulated by several kinds of molecules, it is suspected that these regulators may influence the character of HIF-1α in cells, as well as in the microenvironment. Examining the interactions between HIF-1α and other molecules may be an important supplement for cancer research and tumor therapy.

Disclosure of conflict of interest

None.

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