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Review

Hypoxia and lncRNAs in gastrointestinal cancers

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ABSTRACT

Objectives: Hypoxia is a hallmark of the tumor microenvironment, and hypoxia regions are frequently found in gastrointestinal cancers, which are associated with worse patients' survival and therapy resistance. However, the potential mechanisms of hypoxic tumor microenvironment still need to be further elucidated, especially about the roles of long non-coding RNAs (lncRNAs) in hypoxic tumor regions. In recent years, a great mount of independent research showed that many lncRNAs were modulated by hypoxia, and these lncRNAs were named as "hypoxia-regulated lncRNAs". In this review, the recent developments in the expression, regulation and functions of hypoxia-regulated lncRNAs in gastrointestinal cancers were summarized.

Materials and methods: In this review, we summarized and figured out recent studies concerning the expression and biological mechanisms of hypoxia-regulated lncRNAs in gastrointestinal cancers. The related studies were obtained through a systematic search of PubMed, Embase and Cochrane Library.

Results: Hypoxia-regulated lncRNAs have various roles in the regulation of metabolism, autophagy, invasion and metastasis in the hypoxic microenvironment. More importantly, hypoxic-regulated lncRNAs have a variety of potential mechanisms in gastrointestinal tumors, including epigenetic, lncRNA-miRNA interaction, lncRNA-protein interactions.

Conclusions: Hypoxia-regulated lncRNAs will undoubtedly be developed as targets and promote the progress in ideal therapies for gastrointestinal cancer patients.

1. Introduction

Gastrointestinal cancers is the leading cause of death in China and is the major public health problem [1]. To fight gastrointestinal cancers, various efforts have already been taken in studying cancer-related genetic mutations [2], but limited achievement has been made. The emphasis of cancer research is not only intrinsic (proto-oncogene and anti-oncogene), but also extrinsic (tumor microenvironment). Hypoxia is a hallmark of the tumor microenvironment, which could play protumorigenic roles [3]. When tumor cells proliferate out of control, cells inside tumors are exposed to hypoxia [4]. However, in the context of gastrointestinal cancers, hypoxic areas perpetuate and expand due to the aberrant activation of angiogenesis which gives rise to abnormal tumor vessels and the dysfunctional tumor vasculature [5]. In fact, the importance of hypoxic regions for prognosis has been recognized, with increasing studies implicating that tumor hypoxia have relevance to key aspects of cancer progression including metastases [6], recurrences [7] and resistance to therapy [8].

With the development of high-throughput sequence technology, long non-coding RNAs (lncRNAs) have been revealed in the identification and characterization [9], which is a type of non-coding RNA (ncRNA) over 200 nt in length [10–12]. LncRNAs have been found being dysregulated in a wide range of human diseases and disorders, including gastrointestinal cancers [13–15]. More importantly, a great mount of independent research showed that a specific group of lncRNAs were modulated by hypoxia [16–20], which were named as "hypoxia-regulated lncRNAs". HIF-1α-stabilizing long noncoding RNA (HISLA) blocked the interaction of PHD2 and HIF-1α to inhibit the hydroxylation and degradation of HIF-1α in breast cancer [17]. LncHIFCAR forms a complex with HIF-1α via direct binding and facilitates the recruitment of HIF-1α and p300 cofactor to the target promoter driving oral cancer progression [19]. Hypoxia causes demethylation of the CpG island, which consequently leads to the expression of both WT1 mRNA and WT1 lncRNA in acute myeloid leukaemia (AML) [21]. Recent research gradually revealed the response of lncRNAs to hypoxia and its regulatory role in cancers, which was helpful to seek potential tumor targets of digestive system tumors.

The aim of this review is to give the overview of the roles of

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lncRNAs in gastrointestinal cancer under hypoxia and briefly outline the underlying mechanisms. Knowledge about the functional roles of hypoxia-regulated lncRNAs in tumorigenesis may advance the understanding of gastrointestinal cancers progression and unveil novel diagnostic and therapeutic opportunities.

2. Molecular mechanisms of hypoxia response in cancer

Hypoxia, a phenomenon with reduced tissue oxygen tension due to insufficient oxygen supply, is closely associated with signaling pathways promoting tumor growth [22]. Oxygen is essential for the respiration of eukaryotic cells, and cells cannot survive for long period of time without oxygen. However, tumor cells underwent a series of adaptive "pro-survival" changes in the anoxic environment, including a shift from aerobic to anaerobic metabolism, an elevation in erythropoietin to promote the increase in hemoglobin, and an increase in growth factors that lead to angiogenesis. When the proliferation of tumor cells is out of control, the oxygen-deficient microenvironment occurs, and cancer cells need to adapt to this environment [23–25]. During the adaptation process, neovascular growth (angiogenesis) and metabolic recombination are keys to cope with hypoxic tension [26,27]. Cells also have an essential and complex system to adapt to it. Hypoxia inducible factors (HIFs) are key players to response to cellular hypoxia [28,29], with multiple feedbacks and checkpoint signaling loops [30–33]. HIFs transcription factors are heterodimers composed of two subunits, an oxygen-sensitive α-subunit and a stable expressed β-subunit. As our knowledge, HIF-1α and HIF-2α independently regulated hypoxia-related genes containing partially overlapping transcription of target genes, while certain splice variants of HIF-3α exert dominant negative effects on HIF dependent gene transcription [34,35]. During hypoxia, the HIF-1α subunit accumulates in the nucleus, and forms the stable complex with the β-subunit. This complex binds DNA at specific sites within the hypoxia response elements (HREs) in the promoter regions of HIF-1 targeted genes to stimulate downstream transcription. The activation of HIF pathways is associated with an aggressive tumor phenotype and poor clinical outcome in numerous cancer types. Active HIF regulates the transcription of hundreds of coding and noncoding genes [36]. Accumulating evidences showed the involvement of hypoxia-regulated lncRNAs in gastrointestinal cancer cells (Table 1). The functional effects of several hypoxic-regulated lncRNAs in gastrointestinal tumors were reviewed, and reasonable strategies were proposed for future studies.

3. Hypoxia-regulated lncRNAs in gastric cancer

Li et al. [37] investigated the expression profile of non-coding RNAs (circRNAs, lncRNAs and miRNAs) in gastric cancer (GC) cells under hypoxic conditions via sequencing and subsequent bioinformatic analyses, the results showed that there were 69 lncRNAs differentially expressed (29 lncRNAs were up-regulated and 40 were downregulated by hypoxia). Although most of the hypoxic- regulated lncRNAs had not been mechanically studied in detail, a few that have been mechanically studied may provide clues to their biological role in hypoxic responses. Li et al. [38] expounded that lncRNA-AK123072 was up-regulated by hypoxia in GC, and epidermal growth factor receptor (EGFR) was positively correlated with that of AK123072 in the GC samples. Intriguingly, EGFR expression was also increased by hypoxia, AK123072 promoted metastasis of gastric cancer cells by upregulation of EGFR under hypoxia. Some lncRNAs indirectly affected HIF activity in GC. Wang and his colleagues [39] found a new hypoxia-upregulated lncRNA, AK058003, which was a regulator of hypoxia signal promoting GC migration and invasion. In addition, the expression of γ-synuclein (SNCG) was positively correlated with that of AK058003, and the SNCG gene CpG island methylation was significantly increased in GC cells depleted of AK058003. Another study [40] elucidated that a hypoxia-upregulated lncRNA BC005927 expression was correlated with a higher tumor-node-metastasis stage of GC, and BC005927 might accelerate expression of EPHB4 induced by DNA demethylation. In GC, lncRNA GAPLINC, short for gastric adenocarcinoma associated positive CD44 regulator, was upregulated and played the oncogenic role [41]. It was confirmed that HIF-1α could bind to the promoter region of GAPLINC and activated transcription. Downregulation of GAPLINC inhibited hypoxia-induced tumor proliferation. Recently, Huang et al. [42] further elucidated that lncRNA PVT-1 was strongly induced by hypoxia in BCG-823, SGC-7901 and AGS cells, and functioned as a critical mediator of hypoxia-enhanced mediated by HIF-1α. Besides, knockdown ZEB2-AS1 suppressed GC cell proliferation and invasion [43]. Without the sequence complementarity to HIF-1α, ZEB2-AS1 could not interact directly with HIF-1α mRNA. ZEB2-AS1 regulated the expression level of HIF-1α by modulating the expression of miR-143-5p, functioning as an endogenous miR-143-5p sponge [43]. The lncRNA prostate cancer gene expression marker 1 (PCGEM1) was located in the GC cell cytoplasm,

Table 1
The characteristics of hypoxia-regulated lncRNAs in gastrointestinal cancers.

LncRNA	Expression	Tumor type	Biological function	Refs.
AK058003	Up	GC	Regulates SNCG and promotes gastric cancer metastasis.	[39]
AK123072	Up	GC	Regulates EGFR and promotes gastric cancer metastasis.	[38]
BC005927	Up	GC	Regulates EPHB4 and promotes gastric cancer metastasis.	[40]
GAPLINC	Up	GC	Correlates with CD44 activation in GC tissues, HIF-1α binds to the promoter region of GAPLINC and activates its transcription.	[41]
PVT1	Up	GC, HCC	Interacts with miR-143-5p in GC cells and this interaction lead to the inhibition of downstream of HIF-1α expression. Regulates the expression of miR-150 and HIG2 to suppress tumorigenesis and iron metabolism disorder.	[42,53]
ZEB2-AS1	Up	GC	Interacts with miR-186 in GC cells and this interaction lead to the inhibition of downstream of HIF-1α expression.	[43]
PCGEM1	Up	GC	Regulates SNAI1 and promotes gastric cancer metastasis.	[44]
HIF1α-AS2	Up	GC	Promotes cell proliferation and tumorigenesis.	[45]
UCA1	Up	GC	Interacts with miR-7-5p and this interaction lead to the inhibition of EGFR.	[46]
linc00152	Up	GBC, CRC	Interacts with miRNAs (miR-138 and miR-193) and this interaction lead to the inhibition of HIF-1α expression.	[50,62]
lncRNA-LET	Up	GBC	Promotes cell proliferation.	[48]
linc-ROR	Up	HCC	Interacts with miR-145 and this interaction lead to the inhibition of phosphorylation of p70S6K1.	[51]
CPS1-IT1	Down	HCC, CRC	Acts as a co-chaperone and alters Hsp90 and HIF-1α binding affinity.	[52,60]
lincRNA-p21	Up	HCC	Enhances hypoxic tumor cell radiosensitivity through HIF-1/Akt/mTOR/P70S6K pathway.	[54]
NUTF2P3-001	Up	PC	Interacts with miR-3923 and this interaction lead to the inhibition of KRAS.	[74]
BX111	Up	PC	Activates transcription of ZEB1 via recruiting transcriptional factor YB1 to its promoter region.	[55]
NORAD	Up	PC	Functions as a ceRNA to regulate the expression of the RhoA through competition for miR-125a-3p.	[56]
ENST00000480739	Down	PC	Targets HIF-1α expression by upregulating OS-9.	[57]
FEZF1-AS1	Up	PC	Promotes cell proliferation and invasion through miR-142/HIF-1α axis under hypoxic condition.	[58]
HIF2PUT	Up	CRC	Functions as a promoter upstream transcript of HIF-2α.	[62]
linc01234	Up	CRC		[75]

and the expression of PCGEM1 was associated with HIF-1α. PCGEM1 also involved in the invasion and metastasis of GC by participating in EMT [44]. Owing to the reason known to all the antisense transcripts might function as a regulator for corresponding gene expression. LncRNA HIF1α-AS2 was a natural antisense transcript of HIF-1α, and HIF1α-AS2 played a crucial role in cancer development by regulating the cancer-relevant HIF-1α pathway [45]. The expression of HIF1α-AS2 was upregulated in GC tumorous tissues compared with the adjacent normal tissues. Knockdown of HIF1α-AS2 expression could inhibit cell proliferation and tumorigenesis [45]. Besides, lncRNA UCA1 was upregulated in both the plasma and tumor tissues of patients with GC. UCA1 was upregulated in hypoxia-resistant gastric cancer cells (MGC-803/Hypo and BGC-823/Hypo) [46], and elevated UCA1 was an independent poor prognostic indicator for GC.

4. Hypoxia-regulated lncRNAs in gallbladder cancer

Gallbladder cancer (GBC) was the common biliary tract cancer and the fifth most common gastrointestinal malignancy [47]. LncRNA-LET played an important role in the stability of nuclear factor 90 protein, thus leading to hypoxia-induced invasion of GBC. The ectopic expression of lncRNA-LET led to the arrest of cell cycle at G0/G1 phase and to the induction of apoptosis under hypoxic conditions in GBC [48]. Besides, lincRNA00152 was upregulated in GBC and associated with poor prognosis. Moreover, Cai et al. [49] demonstrated that SP1/linc00152/PI3K/AKT might be a potential therapeutic target for GBC. Other research reported that linc00152 dramatically promoted cell migration, invasion and epithelial-mesenchymal transition (EMT) progression. Mechanistic analyses indicated that linc00152, miR-138 and HIF-1α formed the competing endogenous RNAs (ceRNAs) relationship, and linc00152/miR-138/HIF-1α pathway potentiated the progression of GBC [50]. However, the expression level of linc00152 under hypoxia conditions was not clear, further study was needed to explore its role in GBC under hypoxia conditions.

5. Hypoxia-regulated lncRNAs in hepatocellular cancer

A recent study found that linc-ROR was overexpressed by hypoxia in HCC [51], which was functionally linked to hypoxia signal in HCC through a miR-145/HIF-1α signaling. In fact, knockdown linc-ROR decreased p70S6K1 phosphorylation which was a critical regulator in protein synthesis, and inhibited PDK1 and HIF-1α protein expression via up-regulation of miR-145 [51]. In addition, lncRNA CPS1-IT1 acted as a tumor suppressor in HCC by reducing HIF-1α activation and suppressing EMT [52]. CPS1-IT1 interacted with heat shock protein 90 (HSP90) and reduced the binding affinity between HSP90 and HIF-1α, thereby resulting in reduced HIF-1α activation [52]. Another study indicated hypoxia-inducible protein 2 (HIG2) was found to be the target gene of miR-150, and PVT1 could directly bind to miR-150 [53]. Knockdown PVT1 could inhibit the expression level of HIG2 through competitive binding miR-150 [53]. In the same manner, lincRNA-p21 was also induced by hypoxia [54], and knockdown lincRNA-p21 inhibited the autophagy of hypoxic tumor cells by downregulating HIF-1α protein level via activating Akt/mTOR/P70S6K signaling pathway [54]. This might be one of the mechanisms about radio sensitizing hypoxic tumor cells by lincRNA-p21 knockdown.

6. Hypoxia-regulated lncRNAs in pancreatic cancer

LncRNA BX111 was a novel lncRNA which was located adjacent to the ZEB1 gene. BX111 could modulate ZEB1 expression, as well as the proliferation and invasion ability of pancreatic cancer (PC) cells [55]. BX111 was transcriptionally regulated by HIF-1α during hypoxia condition in PC. After being treated with hypoxia, PC cells showed morphological transformation from epithelium to fibroblast, BX111 contributed to the hypoxia-induced EMT of pancreatic cells by regulating expression of ZEB1 and its downstream proteins E-cadherin and MMP2. In addition, Li et al. [56] used the robust multiarray average (RMA) algorithm to compare expression data from 55 pancreatic tumor tissues and their matched non-tumor tissues, and they identified 272 consistent non-coding RNAs that were significantly upregulated or down-regulated. And lncRNA NORAD was significantly increased after hypoxic stimulation [56]. NORAD could promote PC cells EMT and metastasis by regulating RhoA in a miR-125a-3p dependent manner. Furthermore, knockdown of NORAD could alleviate malignant phenomena caused by hypoxia [56]. Besides, a novel lncRNA ENST00000480739 expression level was remarkably decreased in PC [57] and ENST00000480739 positively regulated OS-9 by activating the transcription of the OS-9 promoter. Another study revealed that FEZF1-AS1 acted as an oncogene via promoting PC cell proliferation and invasion through miR-142/HIF-1α axis under hypoxic condition [58].

7. Hypoxia-regulated lncRNAs in colorectal cancer

Han's group [59] analyzed the lncRNAs and mRNAs expression profile in colorectal cancer (CRC) cell SW480 by RNA sequencing, the results showed that 77 lncRNAs and 1327 mRNAs were abnormally expressed and several novel hypoxia-regulated lncRNAs were firstly discovered in CRC, including RP11-126K1.2, RP3-438O4.4, linc01119, CTB-22K21.2, RP11-798M19.6, and RP11-2B6.3. LncRNA CPS1-IT1 was a hypoxia-regulated lncRNA, and the relative expression of CPS1-IT1 was notably decreased in CRC tissues compared with their adjacent non-cancerous tissues [60]. Under hypoxia, CPS1-IT1 expression was significantly reduced, however, the expression of LC3-II, which was a protein associated with autophagy, was increased. Further study found that CPS1-IT1 suppressed metastasis and EMT by inhibiting hypoxia-induced autophagy through inactivation of HIF-1α in CRC [60]. Another research showed that linc00152 was overexpressed in CRC under hypoxic condition [61], and linc00152 could combine with miR-138 and miR-193. Linc00152 could function as a competing endogenous RNA that can augment HIF1 translation in the cytoplasm of hypoxic colorectal cancer cells [61]. Besides, Yao et al. [62] found a lncRNA which was the promoter upstream transcript of HIF-2α, named lncRNA-HIF2PUT. The expression level of lncRNA-HIF2PUT was significantly correlated with HIF-2α expression in CRC. Knockdown of lncRNA-HIF2PUT blocked the HIF-2α expression, and lncRNA-HIF2PUT might be a regulator of HIF-2α [62].

8. Hypoxia-regulated lncRNAs functions in gastrointestinal cancers

8.1. Epigenetic regulation

The expression of lncRNAs was abnormal in cancer cells and they could mediate transcriptional regulation at epigenetic level through DNA methylation [63–65], acetylation [66–68] and phosphorylation [69,70]. In hypoxia condition, EGFR expression was increased and methylation of EGFR gene CpG island was significantly upregulated in GC cells depleted of AK123072 [38]. Tumor oncogene SNCG was a target gene of AK058003 which was located 8.6 kb down-stream of AK058003 [39]. Compared with control group, more methylated CpG dinucleotides were shown when GC cells were transduced with AK058003 siRNA transfection [39]. AK058003 upregulated the expression of SNCG in GC cells via SNCG DNA methylation. Besides, EPHB4 which was a metastasis-associated oncogene, was located 300 kb upstream of BC005927 [40]. Knockdown of BC005927 could downregulate the expression of EPHB4 in GC cells by regulating EPHB4 DNA methylation [40]. Another example as follow, lncRNA-LET was also involved in hypoxia signal transduction in GBC [48], Yang et al. [71] demonstrated that hypoxia-induced histone deacetylase 3 repressed lncRNA-LET by reducing the histone acetylation-mediated

modulation of the lncRNA-LET promoter region in HCC.

8.2. Function as "ceRNAs"

"CeRNA" mechanisms and network construction have been widely reported in the field of cancer research [72,73]. In fact, there were a group of typical examples among hypoxia-regulated lncRNAs. ZEB2-AS1 could not interact directly with HIF-1α mRNA to modulate transcript levels. ZEB2-AS1 inhibited the expression of HIF-1α mRNA by sequestering and modulating the expression of miR-143-5p, functioning as an endogenous miR-145 sponge [43]. In addition, linc-ROR [51], linc00152 [50], NORAD [56] and FEZF1-AS1 [58] also functioned in this way. Likewise, some of the lncRNAs might regulate other hypoxia-associated proteins more than HIF-1α via functioning as "ceRNAs". GAPLINC was shown to enhance tumor migration and invasion by acting as a molecular sponge for miR-211-3p to suppress CD44 expression [41].

8.3. Interaction with protein

LncRNAs could also directly regulate protein expression to participate in cellular behaviors. RNA transcripts could combine with proteins to form ribonucleoprotein particles (RNPs) to play significant roles. LncRNA CPS1-IT1 was able to interact with HSP90, which was a double-stranded RNA-binding protein that had been implicated in the stabilization, transport and translational control of HIF-1α [52,60]. LncRNA-LET could also interact with protein in GBC [48], knockdown lncRNA-LET increased an abundance of NF90 protein. Surprisingly, NF90 could also increase the expression of HIF-1α and contribute to decrease lncRNA-LET expression level. Above results might provide a positive feedback loop that augments the HIF-1α response under hypoxic conditions in GBC.

9. Conclusions

Increasing evidences have indicated that hypoxia-regulated lncRNAs played important roles in the development of gastrointestinal cancers. In this review, some examples of lncRNAs involved in hypoxia-related processes were outlined, various mechanisms and functions of hypoxia-regulated lncRNAs were illustrated. Hypoxia-regulated lncRNAs had an extremely wide range of biological functions in gastrointestinal cancers, including initiation, progression, invasion, and metastasis. Although a huge list of hypoxia-regulated lncRNAs have been identified thus far, it was still a strenuous task to reveal the functional relevance of lncRNAs in cancers. In order to solve this problem, in-depth detection of lncRNA candidate genes were needed to make clear the roles of lncRNAs in apoptosis, metastasis, metabolism and other aspects. Due to the limited understanding of the roles of hypoxia-regulated lncRNAs, further research are needed about the regulatory mechanisms of lncRNAs in response to hypoxia. In the near future, more hypoxia-regulated lncRNAs will undoubtedly be developed as targets and promote the progress in ideal therapies for gastrointestinal cancer patients.

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Author contribution

Huang and Wang designed and wrote this manuscript. Hu and Guan collected and analyzed related researches. Jiang and Li corrected and reviewed this final manuscript. All authors read and approved the final manuscript. Special thanks to the editor's excellent work.

Declaration of Competing Interest

Authors have no conflicts of interest to report.

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