Review Article

The role of hypoxia-induced long noncoding RNAs (lncRNAs) in tumorigenesis and metastasis

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Long noncoding RNAs (lncRNAs) are noncoding RNAs with length greater than 200 nt. The biological roles and mechanisms mediated by lncRNAs have been extensively investigated. Hypoxia is a proven microenvironmental factor that promotes solid tumor metastasis. Epithelial-mesenchymal transition (EMT) is one of the major mechanisms induced by hypoxia to contribute to metastasis. Many lncRNAs have been shown to be induced by hypoxia and their roles have been delineated. In this review, we focus on the hypoxia-inducible lncRNAs that interact with protein/protein complex and chromatin/epigenetic factors, and the mechanisms that contribute to metastasis. The role of a recently discovered lncRNA RP11-390F4.3 in hypoxia-induced EMT is discussed. Whole genome approaches to delineating the association between lncRNAs and histone modifications are discussed. Other topics related to hypoxia-induced tumor progression but require further investigation are also mentioned. The clinical significance and treatment strategy targeted against lncRNAs are discussed. The review aims to identify suitable lncRNA targets that may provide feasible therapeutic venues for hypoxia-involved cancers.

Long noncoding RNAs (lncRNAs) and cancer

Long noncoding RNAs (lncRNAs) are non-coding RNAs that have the length of >200 nucleotide [1,2]. LncRNAs have been demonstrated to possess multiple biological functions, including cell differentiation, lineage determination, organogenesis, and tissue homeostasis [2]. One of the important biological aspects regulated by lncRNAs is tumorigenesis [3–7]. LncRNAs have been discovered in many different types of human cancers [3–7]. Dysregulations of lncRNAs have been shown to regulate tumorigenesis and cancer metastasis.

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through different mechanisms (see the following paragraph for detailed description) [3–7]. Different aspects of tumorigenesis, including cell proliferation, cell survival, immortalization, growth suppression, angiogenesis, cancer stemness, motility/cancer metastasis, tumor metabolism, treatment resistance, etc have been shown to be regulated by lncRNAs [3–7]. From the above functions regulated by lncRNAs, it is obvious that lncRNAs could have oncogenic or tumor suppressor roles [3–7]. Recent profiling of lncRNAs in different types of human cancers showed that the expression and dysregulation of lncRNAs are cancer-type specific and can be altered at transcriptional, genomic and epigenetic levels [8]. LncRNAs can also serve as diagnostic markers, prognostic markers, and therapeutic targets [4,6]. Therefore, lncRNAs have become major players in regulating tumorigenesis and tumor progression.

Mechanisms mediated by lncRNAs for their functions

The mode of actions of lncRNAs can be classified through different kinds of interactions between lncRNAs and other players, including mRNAs/miRNAs, proteins, and chromatin to perform their specific functions [3,7,9]. These mechanisms exerted by lncRNAs can be mediated through transcriptional regulation, post-transcriptional regulation, epigenetic regulation, mRNA stability, protein stability, disruption of protein–protein interaction, miRNA sponges, and higher order complex formation (for detailed description, see Refs. [10,11]). Depending on the locations of these lncRNAs, different mechanisms can be utilized. For example, transcriptional/epigenetic regulation and mRNA stability are carried out inside the nucleus, whereas protein stability, disruption of protein–protein interaction, and miRNA sponges are carried out in the cytoplasm [10,11]. For interactions between lncRNA and mRNAs/miRNAs, different aspects including sequestering miRNAs, regulation of mRNA processing (e.g. splicing), or mRNA post-transcriptional control (stability, translation) have been observed [3,7,9]. For interactions between lncRNA and proteins, promotion of protein complexes, disruption of protein–protein interactions, and nuclear localization have been shown [3,7,9]. For interactions between lncRNA and chromatin, lncRNAs can control local chromatin looping or recruit regulatory molecules to specific loci through scaffolding of chromatin complexes [3,7,9]. However, although scaffolding of chromatin complex has long been characterized as one of the major roles mediated by lncRNAs, the precise role of lncRNAs regulating a specific histone mark is only starting to be elucidated. Finally, lncRNAs could also serve as signaling molecules when they reside in exosomes [7]. Therefore, the role of lncRNAs to carry out different biochemical functions to modulate different biological outcomes is multiple and very diversified. For a specific lncRNA, there may be many different targets that can interact with this lncRNA and different biological phenotypes can be regulated. Therefore, to summarize the key aspects of regulation by lncRNAs, we will only focus on the interaction between lncRNAs and protein/protein complex as well as the interaction between lncRNAs and chromatin/epigenetic regulators. For the aspect of epigenetic regulators that are regulated by lncRNAs, we will focus on the different epigenetic players and the effects or outcomes regulated by lncRNAs. We will also focus on the tumorigenesis and metastasis phenotypes that could be regulated by various lncRNAs [3–7]. For other aspects of biology (e.g. cardiovascular biology), the role of lncRNAs in these fields will not be discussed. Since there may be many different miRNAs that could be sequestered by a single lncRNA, this part of results will only be briefly described in this review.

LncRNAs, hypoxia and tumorigenesis

Solid tumor hypoxia has been shown to promote metastasis and tumor progression [12,13]. Intratumoral hypoxia can mediate these tumor-aggressiveness functions through stabilization of hypoxia-inducible factor-1α (HIF-1α) [12,13]. Hypoxia as a microenvironmental factor can be used as a good model system to study cancer metastasis [12,13]. Different transcriptional and epigenetic mechanisms have been shown to regulate hypoxia-induced gene expression and tumor metastasis [12–15]. LncRNAs regulated by hypoxia has been one of the hot topics in hypoxia-regulated biology since lncRNAs are capable of regulating multiple biological processes related to tumorigenesis and metastasis [10,11,16–18]. LncRNAs regulated by hypoxia have been shown to regulate tumor growth/proliferation, anti-apoptosis, migration/invasion, angiogenesis, and tumor metabolism [10,11,16–18]. In contrast, lncRNAs can also be used to regulate hypoxia-signaling through stabilization of HIF-1α by different mechanisms [19]. However, there are still many unidentified lncRNAs that are capable of mediating or regulating hypoxia signaling. Therefore, the new lncRNAs regulated by hypoxia or regulating hypoxia-signaling still remain to be identified and fully characterized.

Epithelial-mesenchymal transition (EMT) and hypoxia

Epithelial-mesenchymal transition (EMT) has been one of the major cancer metastasis-inducing mechanisms that received extensive attention for the past decade [20–22]. The migration, invasion, stem-like property, and treatment-resistant characteristics of tumor cells can be linked to EMT [20–22]. Different signaling pathways have been shown to trigger EMT, including TGF-β, hypoxia, Wnt, Notch, etc [20–23]. Among these signaling pathways, hypoxia stands out as one of the major driving forces that regulate EMT to promote cancer metastasis [23]. Hypoxia also activates the “core” EMT transcription regulators (Snail, Twist1, ZEB1, ZEB2, Slug) [24]. Various transcriptional and epigenetic mechanisms that control hypoxia-induced EMT have also been revealed [21,25,26]. For the role of lncRNAs that plays in tumorigenesis and metastasis [10,11,16–18], it is obvious that lncRNAs should play a significant role in regulating hypoxia-induced EMT. From the different mechanisms that could be mediated by lncRNAs [3,7,9], many different levels of regulation mediated by lncRNAs could be used to regulate hypoxia-induced
EMT. For this review, we will focus on lncRNAs induced by hypoxia that play a significant role in regulating hypoxia-induced tumorigenesis, EMT, and metastasis. The two aspects of regulation by hypoxia-induced lncRNAs that will be discussed will be the interaction between lncRNAs and proteins as well as between lncRNAs and chromatin/epigenetic regulators [3,11]. We will also discuss the role of a new hypoxia-induced lncRNA **RP11-390F4.3** and its specific epigenetic role in hypoxia-induced EMT [27].

**Hypoxia-inducible lncRNAs that interact with protein or protein complex to regulate gene expression and/or protein levels**

Interactions between lncRNA and protein/protein complex could result in the stabilization/degradation of proteins, formation of a cellular structure (e.g. paraspeckle), disruption of protein–protein interaction, dissociation of protein binding to a promoter, recruitment of kinase, nuclear localization, protein glycosylation, serving as a co-activator, regulation of RNA alternative splicing, etc [10,11]. LncRNA **NEAT1** is essential for paraspeckle formation that sequester transcriptionally active proteins and RNA transcripts [28]. **NEAT1** drives tumor initiation and progression by modulating the expression of many molecules involved in cell proliferation, survival, migration, invasion, EMT, metastasis, cancer stemness, and therapy resistance [29]. LncRNA **MALAT1** inhibits the association between VHL and HIF-1α/HIF-2α, causing the decreased degradation of HIF-1α/HIF-2α [30,31]. **MALAT1** also releases the binding of PTB-associated splicing factor (PSF) to the promoter of GAGE6 gene, thus promoting proliferation and migration/invasion in lung adenocarcinoma cells [32]. LncRNA **LINK-A** recruits BRK to the EGFR:GPNMB complex to activate BRK and induce Tyr 565 phosphorylation of HIF-1α, which interferes with Pro 564 hydroxylation of HIF-1α and cause normoxic HIF-1α stabilization [33]. **LncRNA LINK-A** also recruits LRRK2 to mediate Ser 797 phosphorylation of HIF-1α to potentiate its transcriptional activity [33]. Both events trigger normoxic HIF-1α signaling. LncRNA-p21 binds to HIF-1α and VHL to disrupt the interaction between HIF-1α and VHL, causing a positive feedback loop of HIF-1 signaling and is responsible for hypoxia-induced glycolysis [34]. LncRNA **CASC3** interacts with HIF-1α to stabilize HIF-1α, leading to increased glycolysis and tumorigenesis of nasopharyngeal cancer cells [35,36]. LncRNA **H19** is required for nuclear translocation of HIF-1α [37,38]. LncRNA **MTA2TR** recruits ATF3 to the promoter of MTA2 to induce its expression [39]. LncRNA **NDRG-OT1** induces NDRG1 degradation through
Hypoxia-induced lncRNAs that interact with chromatin/epigenetic regulators

Chromatin regulation has been a prominent part of gene regulation research for more than two decades [48]. Epigenetic control through lncRNAs to regulate invasion and metastasis (one of the hallmarks of cancer) has been demonstrated [49]. The most prominent example of lncRNAs interacting with a chromatin complex is that lncRNA HOTAIR interacts with PRC2 and LSD1 chromatin modifying complexes simultaneously [50]. LncRNA HOTAIR is induced by hypoxia and plays an oncogenic role in non-small cell lung cancer [51]. LncRNA WT1-AS regulates hypoxia-induced WT-1 expression through modulating histone methylation [52]. LncRNA PVT1 scaffolds KAT7A to mediate H3K9 acetylation and recruit nuclear receptor binding protein TIF1β to activate NF90 expression, causing the stability of HIF-1α [53]. LncRNA MEG3 recruits DNMT3a, DNMT3b, and MBD1 to induce the hypermethylation of the TIMP2 promoter, promoting tumorigenesis [54]. Hypoxia-induced lncRNA GATA6-AS inhibits LOXL2 that removes H3K4me3 mark, inducing the expression of angiogenesis-related genes (peristin and COX-2) [55]. TGF-β also induces the expression of GATA6-AS that is essential for TGF-β-mediated EMT [56]. LncRNA HIF1A-AS2 interacts with IGFBP2 and DHX9 which are required for HMGAI expression [57]. This interaction is crucial for glioblastoma stem cell growth, cell renewal and survival [56]. LncRNA AK058803 causes hypomethylation of the SNCG promoter and induces its expression [57]. LncRNA BC005927 regulates the expression of EPH through its neighboring localization [58]. All the above lncRNAs described mediate their functions through ubiquitin-mediated proteolysis [40]. LncRNA HIF2PUT positively regulates HIF-2α levels and there is tight correlation between HIF2PUT and HIF-2α levels [41]. LncRNA HINCUT-1 is required for OGT mRNA expression and global O-GlcNAcylation of proteins [42]. LncRNA DARS-AS1 interacts with RNA binding protein 39 (RBM39) to inhibit its interaction with its ubiquitin ligase RNF147 and decrease the degradation of RBM39 [43]. LncRNA-SARCC promotes androgen receptor (AR) degradation through ubiquitin-mediated proteolysis of AR/HIF-1α/c-Myc signaling axis [44]. LncRNA BX111887 recruits YB1 to the promoter of ZEB1 to induce its expression [45]. Finally, a very unique function of lncRNAs is to serve as a co-activator for a transcription factor. In this case, lncRNA IncHIFCAR/MIR31HG directly interacts with HIF-1α and facilitates the recruitment of p300 to target gene promoters [46]. Overexpression of IncHIFCAR induces a pseudohypoxic signature and is critical for HIF-1α-induced sphere-forming ability, metabolic shift, and metastatic potential in vitro and in vivo [46]. Therefore, lncRNA IncHIFCAR functions as a HIF-1α co-activator to mediate HIF-1α-induced phenotypes [46]. Hypoxia-inducible lncRNA LUCAT1 interacts with poly-pyrimidine tract binding protein 1 (PTBP1) followed by recruitment of a set of DNA damage genes, resulting in altered alternative splicing of these genes [47]. Overexpression of lncRNA LUCAT1 causes chemoresistance of tumor cells to DNA damage drugs [47]. A summary of different mechanisms mediated by the lncRNAs described above is shown [Fig. 1 and Table 1].

Table 1 Summary of hypoxia-inducible lncRNAs that interact with protein complexes.

| LncRNA       | Mechanism                                                                                       | Biological significances                                                                                     | Reference |
|--------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------|
| NEAT1        | Paraspeckle formation                                                                           | Glycolysis and tumor growth                                                                                 | [29]      |
| MALAT1       | Post-Translational modification                                                                 | Promoting cell proliferation, migration, invasion, and metastasis                                           | [30,31]  |
| LINK-A       | Post-Translational modification                                                                 | Promoting cell proliferation and migration                                                                   | [32]      |
| H19          | Nuclear localization                                                                            | Cell Dissemination                                                                                         | [38]      |
| H21          | Complex scaffold                                                                              | Paracrine formation                                                                                        |           |
| G3a          | Complex scaffold                                                                              | Paracrine formation                                                                                        |           |
| HIF1-α       | Complex scaffold                                                                              | Paracrine formation                                                                                        |           |
| Rho2         | Complex scaffold                                                                              | Paracrine formation                                                                                        |           |
| HIF2-α       | Complex scaffold                                                                              | Paracrine formation                                                                                        |           |
| MALAT1       | Complex scaffold                                                                              | Paracrine formation                                                                                        |           |
| NDRG-OT1     | Post-Translational modification                                                                 | Protein degradation                                                                                        | [40]      |
| HIF2PUT      | Post-Translational modification                                                                 | Promoting cell proliferation, migration, invasion, and metastasis                                           |           |
| CASC9        | Post-Translational modification                                                                 | Cell Dissemination                                                                                         | [35]      |
| lincRNA-p21  | Post-Translational modification                                                                 | Promoting cell proliferation and migration                                                                   | [34]      |
| CASC9        | Post-Translational modification                                                                 | Promoting cell proliferation and migration                                                                   | [34]      |
| LUCAT1       | Post-Translational modification                                                                 | Promoting cell proliferation and migration                                                                   | [47]      |

Abbreviation: N.D.: Not determined

Hypoxic HIF-1α expression causes hypomethylation of the IGFBP2 and DHX9 which are required for HMGAI expression [57]. This interaction is crucial for glioblastoma stem cell growth, cell renewal and survival [56]. LncRNA AK058803 causes hypomethylation of the SNCG promoter and induces its expression [57]. LncRNA BC005927 regulates the expression of EPH through its neighboring localization [58]. All the above lncRNAs described mediate their functions through
interacting with epigenetic factors and cause epigenetic outcomes (a model is shown in Fig. 2). A summary of all the results described above is shown in Table 2.

**LncRNA RP11-390F4.3 in hypoxia-induced EMT**

Various lncRNAs have been shown to regulate the expression of different EMT transcription regulators [44,59,60]. However, the ability of a specific lncRNA to regulate the expression of multiple EMT regulators has not been demonstrated. Recent results showed that hypoxia-inducible lncRNA RP11-390F4.3 is able to regulate the expression of multiple EMT regulators, including Snail, Twist1, ZEB1, and ZEB2 [27]. Since these EMT regulators represent four out of five “core” EMT regulators [24,27], the role of lncRNA RP11-390F4.3 appears to be important for the induction of hypoxia-induced EMT. Since lncRNA RP11-390F4.3 is induced by hypoxia and directly regulated by HIF-1α, these results further confirm its essential role in hypoxia-induced EMT [27]. Experimental evidence showed that lncRNA RP11-390F4.3 plays a crucial role in hypoxia-induced EMT and cancer metastasis from in vitro migration/invasion and in vivo metastatic assays [27]. It will be crucial in the next step to identify the histone-modifying complex that is scaffolded by lncRNA RP11-390F4.3 and test whether this lncRNA-protein complex specifically regulates a histone mark to regulate the expression of these four “core” EMT regulators (a model is shown in Fig. 3).

**LncRNAs associated with histone marks**

Although lncRNAs (e.g. HOTAIR) have been shown to be able to scaffold chromatin modifying complexes [1,3,7,9], the ability of lncRNAs to specifically regulate a histone mark has only been demonstrated recently. Although lncRNA HOTAIR has been shown to be induced by hypoxia and scaffolds PRC2 and LSD1 complexes [50,51], its ability to regulate a specific histone mark has not been demonstrated. The only hypoxia-inducible lncRNA shown to globally regulate a specific histone mark (H3K4me3) is lncRNA GATA6-AS that interacts with LOXL2, a protein shown to remove H3K4me3 mark [55]. Knockdown of LOXL2 in HUVEC cells increases the global levels of H3K4me3 and knockdown of lncRNA GATA6-AS reduces the H3K4 trimethylation of angiogenesis-related genes (periostin and cyclooxygenase-2) [55]. To solve the question of how lncRNAs-chromatin interactions regulate gene expression, technologies were developed using two different approaches: 1) pulling down RNA to profile chromatin signature (e.g. ChIRP, chromatin isolation by RNA purification), and 2) chromatin immunoprecipitation (ChIP) followed by gathering chromatin-associated RNA fragments (e.g. ChIRP, chromatin RNA immunoprecipitation) [61,62]. Recent technologies based on ChIRP and ChIRP were developed to obtain genome-wide information of RNA/chromatin interactome. GRID-seq (capturing in situ global RNA interactions with DNA by deep sequencing) was used to construct global RNA-chromatin

![Fig. 2 A model of hypoxia-induced lncRNAs that interact with epigenetic regulators to regulate histone modifications or modulate DNA methylation, leading to changes in gene expression.](image-url)
interactome [63]. PIRCh-seq (profiling interacting RNAs on chromatin followed by deep sequencing) could be used to classify lncRNAs into enhancer, promoter, silencer, or insulator by comparing ChRIP datasets associated with distinct histone modifications [64]. HiChIRP (HiChIP protocol for chromatin purification using a specific RNA of interest) was developed to profile 3D conformation of chromatin with lncRNAs of interest [65]. Although these technological approaches could be used for RNA/chromatin interactome profiling (ChIRP-seq, ChRIP-seq, GRID-seq and PIRCh-seq) or high order chromatin conformation with lncRNAs (HiChIRP), it is still difficult to differentiate the function of lncRNAs between cis and trans. Another bioinformatics approach to classify lncRNA-chromatin interaction has been presented, which is designated as LnChrom [66]. This resource database collects experimentally validated 382,4,73 lncRNA-chromatin interactions from public datasets that will facilitate browsing, searching and retrieving of the interaction data [66]. The effects of lncRNA-chromatin interactions can be used to study epigenetic modifications and transcriptional expression. Although it is possible to classify cis or trans lncRNAs by the interactome information obtained from GRID-seq or ChIRP-seq, precise linkage between the chromatin modifying complex and lncRNA-histone mark provided by the sequencing methods described above still remains elusive. Further identification and characterization of histone modifying complex that specifically regulates a histone mark are still mandatory in order to fully understand the molecular mechanism of a lncRNA-histone modifying complex that specifically regulates a histone mark under hypoxia.

### Clinical relevance and therapeutic strategies

It is conceivable that hypoxia-inducible lncRNAs can serve as diagnostic and prognostic markers [4,6,100]. Among the examples, lncRNA NEAT1 is shown to be a marker for tumor grade and lymph node metastasis in clear cell renal cell

**Hypoxia-inducible lncRNAs that work through associating with miRNAs**

One of the important functions of lncRNAs is to associate with miRNAs and serve as miRNA sponge [3,7,9]. Sequestering of miRNAs by lncRNAs has been shown in many hypoxia-inducible lncRNAs [10,11,16−18]. The list includes lncRNAs AGAP2-AS1, EIF3J-AS1, GAPLINC, HOTTIP, lincROR, lincRNA-EFNA3, NORAD, NUTF2P3, UCA1, ZEB2-AS1 [10,11,16,60,67−81]. In addition, other lncRNAs that are able to interact with protein/protein complex or epigenetic regulators may also have miRNA sequestering function, including lncRNAs FAM201A, FEZF1-AS1, H19, HIF1A-AS2, HOTAIR, LINC01436, MALAT1, NEAT1, PVT1 [10,11,75,82−99]. The specific genes regulated by these lncRNAs and their tumor types have been summarized in Table 3. Therefore, multiple functions mediated by these lncRNAs have been demonstrated. However, the miRNA sponge function mediated by these hypoxia-inducible lncRNAs will not be discussed in details since many miRNAs could be sequestered by a lncRNA and the detailed results have been summarized in recent reviews [10,11]. A summary of all the results described above is shown in Table 3.

### Table 2 Summary of hypoxia-inducible lncRNAs that interact with chromatin or epigenetic factors.

| Hypoxia-induced lncRNA | Regulate by HIF-1α | Interaction chromatin/epigenetic regulators | Mechanism | Biological significances | Reference |
|------------------------|-------------------|-------------------------------------------|-----------|--------------------------|-----------|
| HOTAIR                 | v                 | PRC2                                      | Scaffolds | Histone modifications on target genes | [51]      |
| WT1-AS                 | v                 | WT-1                                      | Epigenetic regulation | Stem cell function | [52]      |
| PVT1                   | v                 | KAT2A                                     | Epigenetic regulation | Cell proliferation | [53]      |
| MEG3                   | v                 | DNMT3a, DNMT3b, and MBD1                  | Epigenetic regulation | Promoting tumorigenesis | [54]      |
| GATA6-AS               | v                 | LOXL2                                     | Epigenetic regulation | Angiogenesis       | [55]      |
| HIF1A-AS2              | v                 | IGF2BP2, DHX9, and HMGA1                  | Epigenetic regulation | Stem cell growth, cell renewal and survival | [56]      |
| IncRNA-AK058003        | v                 | N.D.                                      | Epigenetic regulation | Migration, invasion, and metastasis | [57]      |
| BC005927               | v                 | N.D.                                      | Transcriptional regulation | Metastasis | [58]      |

Abbreviation: N.D.: Not determined

Fig. 3 A model of hypoxia-induced lncRNA RP11-390F4.3 that regulates four “core” EMT transcriptional regulators to mediated hypoxia-induced EMT, metastasis, and tumor progression.

![Fig. 3 A model of hypoxia-induced lncRNA RP11-390F4.3 that regulates four “core” EMT transcriptional regulators to mediated hypoxia-induced EMT, metastasis, and tumor progression.](image-url)
Table 3 Summary of hypoxia-inducible lncRNAs that associate with miRNAs (some of them also interact with protein/protein complex and/or epigenetic factors/chromatin).

| Hypoxia-induced lncRNA | miRNAs Associated with | Target gene | Cancer type | Reference |
|-------------------------|------------------------|-------------|-------------|-----------|
| 1 AGAP2-AS1             | miR-16-5p              | ANXA11      | HCC         | [67]      |
| 2 EIF3J-AS1             | miR-122-5p             | CTNND2      | HCC         | [68]      |
| 3 GAPLINC               | miR-211                | Bcl2        | HUVEC cells | [69]      |
| 4 HOTTIP                | miR-101                | ZEB1        | Glioma      | [60]      |
|                        | miR-615-3p             | HMGB3       | NSCLC cells | [70]      |
| 5 linc-ROR             | miR-145                | p70S6K1 (RPS6KB1) | HCC | [71] |
| 6 IncRNA-EFNA3         | miR-210                | ROCK2       | PC-12       | [72]      |
|                        | miR-101a               | EFNA3       | BC          | [73]      |
|                        | miR-125a-3p            | RhoA        | PC          | [74]      |
|                        | miR-205                | EGLN2       | Melanoma    | [75]      |
|                        | miR-590-3p             | VEGFA, FGF1, and FGF2 | HUVEC cells | [76] |
| 7 NORAD                | miR-3923               | KRAS        | PC          | [77]      |
| 8 NUTF2P3              | miR-18a                | HIF-1α      | BC          | [78]      |
|                        | miR-7-5p               | EGFR        | GC          | [79]      |
|                        | miR-125a               | HK2         | AML         | [80]      |
| 9 UCA1                 | miR-143-5p             | HIF-1α      | GC          | [81]      |

Abbreviations: N.D.: Not determined; HCC: Hepatocellular Carcinoma; HUVEC: Human Umbilical Vein Endothelial cell; NSCLC: Non-Small Cell Lung Cancer; BC: Breast Cancer; PC-12: Rat Adrenal Pheochromocytoma; PC: Pancreatic Cancer; GC: Gastric Cancer; AML: Acute Myeloid Leukemia; EC: Endometrial Cancer; H358 cell: Human lung carcinoma cell; BCSCs: Breast Cancer Stem Cells; GBM: Glioblastomas; ASC: Adipose-derived Stem Cells; MDA-MB-231 cells: Breast Cancer cells; RCC: Renal Cell Carcinoma.

Table 4 Summary of hypoxia-inducible lncRNAs that are involved in the EMT phenotype.

| Hypoxia-induced lncRNA | EMT phenotype | Mechanism          | Regulated genes (or proteins) | Reference |
|-------------------------|---------------|--------------------|-------------------------------|-----------|
| 1 AGAP2-AS1             | promotion     | Sponge             | miR-16-5p                     | [67]      |
| 2 CASC9                 | promotion     | N.D.               | AKT/HIF-1α                    | [36]      |
| 3 H19                   | promotion     | Sponge             | miR-181d                      | [84]      |
|                        | promotion     | N.D.               | miR-675-5p                    | [85,86]   |
|                        | promotion     | let-7              | miR-675                       | [87]      |
| 4 HIF1A-AS2             | promotion     | Sponge             | miR-130a-3p                   | [88]      |
| 5 HOTAIR                | promotion     | HIF-1α/AXL         | miR-153-3p                    | [89]      |
| 6 LINC01436             | promotion     | EGFR               | miR-665                       | [90]      |
| 7 MALAT1                | promotion     | N.D.               | miR-204                       | [91]      |
| 8 NEAT1                 | promotion     | SOX9/Wnt/β-catenin pathway | miR-101-3p                   | [92]      |
|                        | promotion     | FAK                | miR-370-3p                    | [93]      |
| 9 PVT1                  | promotion     | HIF-1α             | miR-30a-3p                    | [94]      |
|                        | promotion     | HIF-1α             | N.D.                          | [95]      |
|                        |              |                    | miR-199a-5p                   | [96]      |
|                        |              |                    | miR-150                       | [97]      |

Abbreviation: N.D.: Not determined
| IncRNA        | EMT | Interaction protein or protein complex | Interaction chromatin/epigenetic regulators | Associating with miRNAs | Mechanism                                      | Biological significances                                                                 | Reference |
|--------------|-----|---------------------------------------|---------------------------------------------|-------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------|-----------|
| AGAP2-AS1    | v   |                                       |                                              | v                       | Sequestration of miRNAs                        | Promoting cell proliferation, migration, and invasion                                | [67]      |
| CASC9        | v   |                                       |                                              | v                       | Protein stability                              | Promoting glycolysis and tumor progression                                              | [35,36]  |
| H19          | v   |                                       |                                              | v                       | HIF-1α nuclear translocation/Sequestration of miRNAs | Promoting migration, invasion, and tumor progression/Cell Dissemination/Glycolysis     | [38,84–87]|
| HOTAIR       | v   |                                       | v                                            | v                       | Epigenetic regulation/Sequestration of miRNAs | Promoting cell proliferation and migration/Glycolysis/Histone modifications on target genes | [51,90–92]|
| HOTTIP       | v   |                                       |                                              | v                       | Sequestration of miRNAs                        | Promoting migration and invasion                                                        | [60,70]  |
| NEAT1        | v   |                                       |                                              | v                       | Complex scaffold/Sequestration of miRNAs       | Promoting cell proliferation, migration, invasion, and tumorigenesis/Paraspeckle formation | [29,95,96]|
| NORAD        | v   |                                       |                                              | v                       | Sequestration of miRNAs                        | Promoting migration, invasion, and tumor progression                                   | [74–76]  |
| RP11-390F4.3 | v   |                                       |                                              | v                       | Transcriptional regulation                     | Promoting migration, invasion, and tumor progression                                   | [27]     |
| ZEBTR (BX111887) | v |                                       |                                              | v                       | Transcriptional regulation                     | Promoting cell proliferation, migration, and invasion                                  | [45]     |
| MALAT1       | v   |                                       |                                              | v                       | Transcriptional regulation/Sequestration of miRNAs | Promoting cell proliferation, migration, invasion, and tumor progression/Glycolysis    | [30–32,94]|
| LINK-A       | v   |                                       |                                              | v                       | Complex scaffold                               | Glycolysis and tumorigenesis                                                            | [33]     |
| lincRNA-p21  | v   |                                       |                                              | v                       | Protein–Protein interaction                    | Glycolysis                                                                               | [34]     |
| MTA2TR       | v   |                                       |                                              | v                       | Transcriptional regulation                     | Tumorigenesis                                                                          | [39]     |
| NDRG-OT1     | v   |                                       |                                              | v                       | Post-Translational modification                | Protein degradation                                                                     | [40]     |
| HIF2PUT      | v   |                                       |                                              | v                       | Transcriptional regulation                     | Decrease cell proliferation and migration                                              | [41]     |
| HINCUT-1     | v   |                                       |                                              | v                       | Transcriptional regulation                     | Cell proliferation                                                                     | [42]     |
| DARS-AS1     | v   |                                       |                                              | v                       | Post-Translational modification                | Tumorigenesis                                                                          | [43]     |
| lincRNA-SARCC | v |                                       |                                              | v                       | Post-Translational modification                | AR/HIF-1α/c-Myc signaling axis                                                         | [44]     |
| LncHIFCAR (MIR31HG) | v |                                       |                                              | v                       | Transcriptional regulation                     | Glycolysis                                                                              | [46]     |
| LUCAT1       | v   |                                       |                                              | v                       | Scaffold                                    | Promote Chemoresistance                                                               | [47]     |
| WTI1-AS      | v   |                                       |                                              | v                       | Epigenetic regulation                         | Stem cell function                                                                     | [52]     |
| PVT1         | v   |                                       | v                                            | v                       | Epigenetic regulation/Sequestration of miRNAs | Promoting cell proliferation, migration, and invasion                                  | [53,97–99]|
| MEG3         | v   |                                       |                                              | v                       | Epigenetic regulation                         | Tumorigenesis                                                                          | [54]     |
| GATA6-AS     | v   |                                       |                                              | v                       | Epigenetic regulation                         | Angiogenesis                                                                            | [55]     |
| HIF1A-AS2    | v   |                                       | v                                            | v                       | Epigenetic regulation/Sequestration of miRNAs | Stem cell growth, cell renewal and survival/Angiogenesis/Promote ASC osteogenic differentiation | [56,88,89]|

**Table 5 Summary of all the hypoxia-inducible IncRNAs described in the text.**
LncRNA H19 is shown to be a marker for tumor size in breast cancer [100]. LncRNA PVT1 is shown to be a marker for clinical stage in pancreatic cancer [100]. LncRNA LINK-A expression and LINK-A-activated pathway correlate with the poor survival of triple negative breast cancer patients [33]. Many of the lncRNAs described in the review can become prognostic markers in different types of human cancers [33,100]. Due to space limitation, this subject will not be thoroughly discussed in this section.

Since certain lncRNAs are potential oncogenes, it is reasonable to try to target these lncRNAs to treat human cancers [100,101]. The methods that can be used include RNA-mediated interference (RNAi), uniformly modified single-stranded antisense oligonucleotides (ASOs), and morpholinos [101]. Both uniformly modified ASOs and morpholinos can be used to block the interface between lncRNA and protein and interfere with the function of lncRNAs. However, there are serious limitations of using these methods. These limitations include: (1) crossing of cell plasma membrane; (2) presence of cellular nucleases and innate immune response; (3) entrapment of ASOs in the endosomal compartment; (4) off-target effects caused by these ASOs [101]. Nanomedicine technology has also been developed. These technology includes: (1) lipid-based nanoparticles (liposomes); (2) polymer-based nanoparticles and micelles; (3) dendrimers; (4) carbon-based nanoparticles [102]. All these methods still require further confirmation of their feasibility. Fortunately, initial therapeutic successes have been achieved during the past few years [103,104]. Recently, CRISPR/Cas9 technology has been adapted to target lncRNAs (CRISPRi) [105]. An enzymatically inactive Cas9 is fused to a transcriptional repressor followed by guiding by guide RNA to a specific locus to achieve repression of a lncRNA gene [105]. From the discussions described above, many hypoxia-inducible oncogenic lncRNAs may be ideal targets for future therapy. For example, locked nucleic acids (LNAs) against lncRNA PVT1 has been shown to induce chemosensitivity to cisplatin in cervical cancer cells [106]. Antisense oligonucleotides against lncRNA LUCAT1 induces chemosensitivity of coloectal cancer cells [47]. From the recent development of technology, it will be optimistic to continue to look for possible therapeutic venues in order to target these oncogenic lncRNAs.

**Conclusions**

LncRNAs obviously play an important role in many biological processes, especially tumorigenesis [2–7]. For hypoxia-induced EMT and metastasis, certain hypoxia-induced lncRNAs have been described in this review article for their mechanistic function and a summary of specific lncRNAs regulating EMT has been shown in Table 4 [10,11,16]. Through interacting with protein/protein complex, chromatin/epigenetic factors, or sequestering various miRNAs, these hypoxia-induced lncRNAs have been shown to regulate hypoxia-induced metastatic phenotypes [10,11]. One of the prominent example is lncRNA RP11-390F4.3 that activates multiple “core” EMT transcription regulators [27]. A summary of the functions mediated by these hypoxia-inducible lncRNAs, their corresponding mechanisms, and
the physiological significance described in this review is shown [Table 5]. Further identification and characterizations of novel lncRNAs that can be regulated by hypoxia should continue in order to obtain a full spectrum of hypoxia-regulated lncRNAs and their mechanistic control of cancer metastasis. Other biological aspects that are worth investigation are cancer stemness and metabolic reprogramming induced by hypoxia. Major lncRNAs that regulate these two aspects should be pursued. Furthermore, lncRNAs that may regulate tumor microenvironment through paracrine effects or through exosome-mediated delivery of lncRNAs should be identified and characterized. Therefore, the non-coding transcriptome induced by hypoxia may be equally important as the coding transcriptome [10–13,16–18].

For clinical applications, hypoxia-induced lncRNAs have already been shown to be able to provide diagnostic and prognostic significance [4,6,100,101]. Future endeavors will focus on targeting these lncRNAs through different approaches (ASOs, RNAs, morpholinos, Nanoparticles, CRISPR/Cas9 technology) in order to antagonize the functions or repress the expression of these “oncogenic” lncRNAs [100–102]. More research efforts are required in order to achieve these therapeutic goals.

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Conflicts of interest
There is no competing interest among the authors.

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