Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj

Review Article

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

Pei-Hua Peng [a,1], *Kai-Wen Hsu* [b,1], *Joseph Chieh-Yu Lai* [c], *Kou-Juey Wu* [a,d,e,*]

[a] *Cancer Genome Research Center, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*
[b] *Research Center for Cancer Biology, Institute of New Drug Development, China Medical University, Taichung, Taiwan*
[c] *Institute of Biomedical Science, China Medical University, Taichung, Taiwan*
[d] *Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan*
[e] *Institute of Clinical Medical Sciences, Chang Gung University, Taoyuan, Taiwan*

Kou-Juey Wu

ARTICLE INFO

Article history:
Received 12 January 2021
Accepted 18 March 2021
Available online 24 March 2021

Keywords:
lncRNAs
Hypoxia
Epithelial–mesenchymal transition
Metastasis
Epigenetics
LncRNA *RP11-390F4.3*

ABSTRACT

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

* *Corresponding author*. Cancer Genome Research Center, Chang Gung Memorial Hospital at Linkou, 5, Fusing St., Gueishan, Taoyuan 333, Taiwan.
E-mail address: wukj@cgmh.org.tw (K.-J. Wu).
Peer review under responsibility of Chang Gung University.
[1] These authors contributed equally to this work.
https://doi.org/10.1016/j.bj.2021.03.005

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

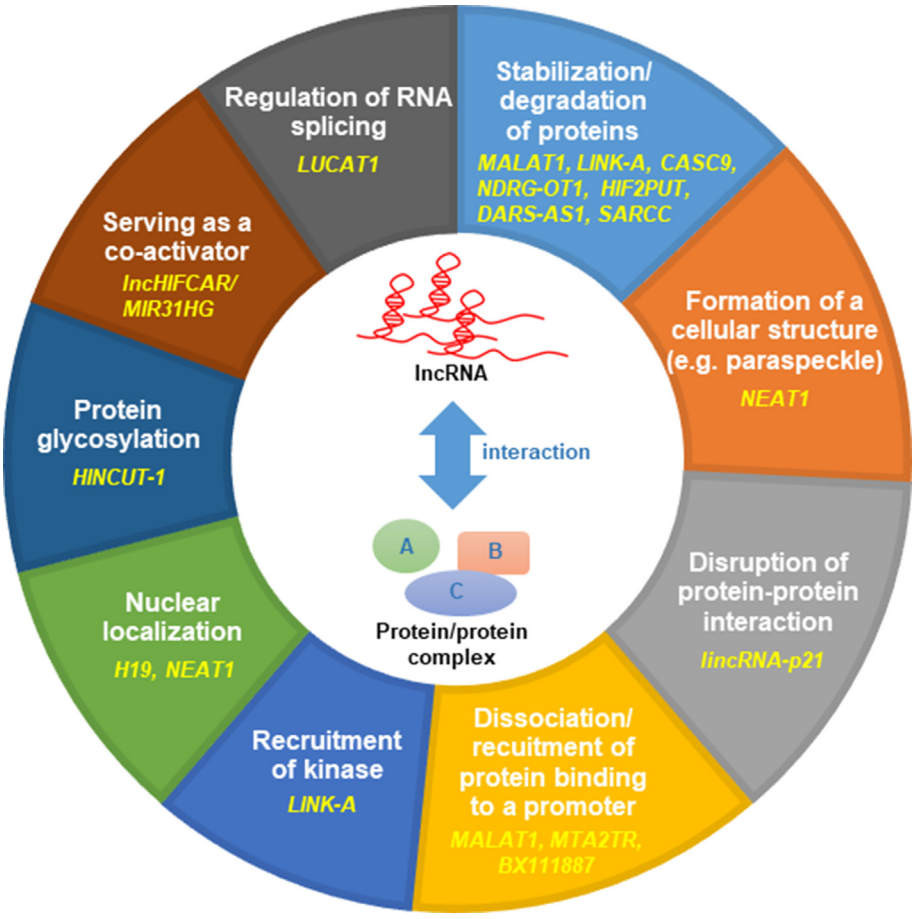

Fig. 1 Summary of hypoxia-induced lncRNAs that interact with protein/protein complex, leading to different outcomes.

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. *LincRNA-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 *CASC9* 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

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

	Hypoxia-induced lncRNA	Regulate by HIF-1α	Interaction protein or protein complex	Mechanism	Biological significances	Reference
1	*NEAT1*	v	EZH2	Complex scaffold	Paraspeckle formation	[29]
2	*MALAT1*	v	HIF-1α/HIF-2α	Post-Translational modification	Glycolysis	[30,31]
		v	GAGE6	Recruitment of protein binding to a promoter	Promoting cell proliferation, migration, invasion, and metastasis	[32]
3	*LINK-A*	v	BRK and LRRK2 kinase	HIF-1α phosphorylation	Glycolysis and tumor growth	[33]
4	*lincRNA-p21*	v	HIF-1α and VHL	Protein–Protein interaction	Glycolysis	[34]
5	*CASC9*	v	HIF-1α	Protein stability	Glycolysis and tumorigenesis	[35]
6	*H19*	v	HIF-1α	Nuclear localization	Cell Dissemination	[38]
7	*MTA2TR*	v	ATF3 and MTA2	Recruitment of protein binding to a promoter	Tumorigenesis	[39]
8	*NDRG-OT1*	v	NDRG1	Post-Translational modification	Protein degradation	[40]
9	*HIF2PUT*	v	HIF-2α	Transcriptional regulation	Decrease cell proliferation and migration	[41]
10	*HINCUT-1*	v	N.D.	Transcriptional regulation	Cell proliferation	[42]
11	*DARS-AS1*	v	RBM39	Post-Translational modification	Tumorigenesis	[43]
12	*lncRNA-SARCC*	v	Androgen receptor	Post-Translational modification	AR/HIF-1α/c-Myc signaling axis	[44]
13	*ZEBTR (BX111887)*	v	YB1 and NEB1	Recruitment of protein binding to a promoter	Promoting cell proliferation, migration, invasion, and metastasis	[45]
14	*LncHIFCAR (MIR31HG)*	v	HIF-1α	Transcriptional regulation	Glycolysis	[46]
15	*LUCAT1*	v	PTBP1	Scaffold	Promote Chemoresistance	[47]

Abbreviation: N.D.: Not determined

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 *lncHIFCAR/MIR31HG* directly interacts with HIF-1α and facilitates the recruitment of p300 to target gene promoters [46]. Overexpression of *lncHIFCAR* 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 *lncHIFCAR* functions as a HIF-1α co-activator to mediate HIF-1α-induced phenotypes [46]. Hypoxia-inducible lncRNA *LUCAT1* interacts with polypyrimidine 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].

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 KAT2A 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 (*periostin* and *COX-2*) [55]. TGF-β also induces the expression of *GATA6-AS* that is essential for TGF-β-mediated EMT [55]. LncRNA *HIF1A-AS2* interacts with IGFBP2 and DHX9 which are required for *HMGA1* expression [56]. This interaction is crucial for glioblastoma stem cell growth, cell renewal and survival [56]. LncRNA *AK058003* causes hypomethylation of the *SNCG* promoter and induces its expression [57]. LncRNA *BC005927* regulates the expression of *EPH4* through its neighboring localization [58]. All the above lncRNAs described mediate their functions through

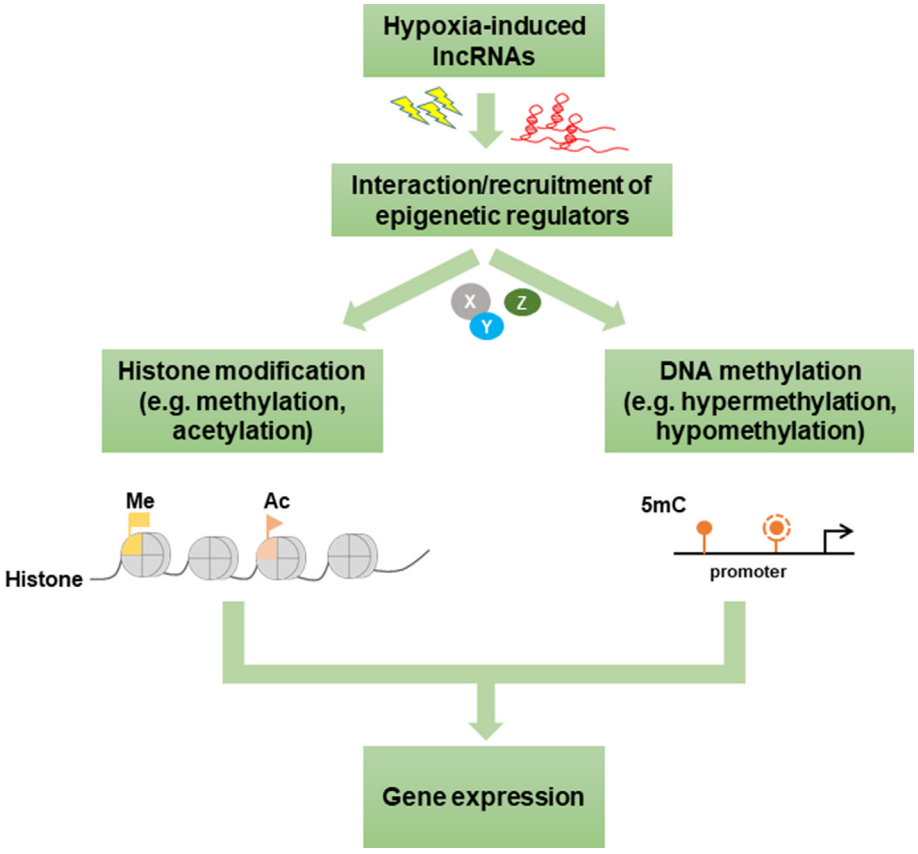

Fig. 2 A model of hypoxia-induced lncRNAs that interact with epigenetic regulators to regulate histone modifications or modulate DNA methylation, leading to changes in gene expression.

interacting with epigenetic factors and cause epigenetic outcomes (a model is shown in Fig. 2). A summary of all the results describe 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 result 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. ChRIP, chromatin RNA immunoprecipitation) [61,62]. Recent technologies based on ChIRP and ChRIP 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

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
1	*HOTAIR*	v	PRC2	Scaffolds	Histone modifications on target genes	[51]
2	*WT1-AS*	v	WT-1	Epigenetic regulation	Stem cell function	[52]
3	*PVT1*	v	KAT2A	Epigenetic regulation	Cell proliferation	[53]
4	*MEG3*	v	DNMT3a, DNMT3b, and MBD1	Epigenetic regulation	Promoting tumorigenesis	[54]
5	*GATA6-AS*	v	LOXL2	Epigenetic regulation	Angiogenesis	[55]
6	*HIF1A-AS2*	v	IGF2BP2, DHX9, and HMGA1	Epigenetic regulation	Stem cell growth, cell renewal and survival	[56]
7	*lncRNA-AK058003*	v	N.D.	Epigenetic regulation	Migration, invasion, and metastasis	[57]
8	*BC005927*	v	N.D.	Transcriptional regulation	Metastasis	[58]

Abbreviation: N.D.: Not determined

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.

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*, *lncRNA-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.

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

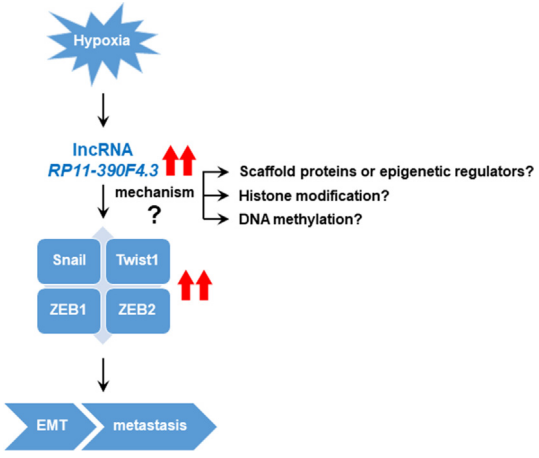

Fig. 3 A model of hypoxia-induced lncRNA *RP11-390F4.3* that regulates four "core" EMT transcriptional regulators to mediated hypoxia-induced EMT, metastasis, and tumor progression.

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	Associating with miRNAs	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*	Giloma	[60]
		miR-615-3p	HMGB3	NSCLC cells	[70]
5	*linc-ROR*	miR-145	*p70S6K1 (RPS6KB1)*	HCC	[71]
6	*lncRNA-EFNA3*	miR-210	EFNA3	BC	[72]
		miR-101a	ROCK2	PC-12	[73]
7	*NORAD*	miR-125a-3p	RhoA	PC	[74]
		miR-205	EGLN2	Melanoma	[75]
		miR-590-3p	VEGFA, FGF1, and FGF2	HUVEC cells	[76]
8	*NUTF2P3*	miR-3923	KRAS	PC	[77]
9	*UCA1*	miR-18a	HIF-1α	BC	[78]
		miR-7-5p	EGFR	GC	[79]
		miR-125a	HK2	AML	[80]
10	*ZEB2-AS1*	miR-143-5p	HIF-1α	GC	[81]
	Hypoxia-induced lncRNA	**Associating with miRNAs, protein/protein complex or epigenetic regulators**	**Target gene**	**Cancer type**	**Reference**
11	*FAM201A*	miR-370	EGFR	NSCLC	[82]
12	*FEZF1-AS1*	miR-142 and miR-133a	HIF-1α and VEGF	PC	[83]
13	*H19*	miR-181d	β-catenin	GBM	[84]
		miR-675-5p	p53	NSCLC	[85,86]
		miR-675	Slug	H358 cells	[86]
		let-7	HIF-1α	BCSCs	[87]
14	*HIF1A-AS2*	miR-153-3p	HIF-1α/VEGFA/Notch1	HUVEC cells	[88]
		miR-665	IL6	ASC cells	[89]
15	*HOTAIR*	miR-217	HIF-1α/AXL	RCC	[90]
		miR-130a-3p	HIF-1α	HCC	[91]
		miR-204	FAK	MDA-MB-231 cells	[92]
16	*LINC01436*	miR-30a-3p	EPAS1	NSCLC	[93]
17	*MALAT1*	miR-200a	N.D.	HCC	[94]
18	*NEAT1*	miR-101-3p	SOX9/Wnt/β-Catenin pathway	NSCLC	[95]
		Mir-370-3p	HMGA2/HIF-1α	GBM	[96]
19	*PVT1*	miR-186	HIF-1α	GC	[97]
		miR-199a-5p	HIF-1α	NSCLC	[98]
		miR-150	HIG2	HCC	[99]

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]
4	*HOTAIR*	promotion	Sponge	miR-217	[90]
5	*HOTTIP*	promotion	Sponge	miR-101	[60]
6	*NEAT1*	promotion	Sponge	miR-101-3p	[95]
		promotion	Sponge	miR-370-3p	[96]
7	*NORAD*	promotion	Sponge	miR-125a-3p	[74]
8	*RP11-390F4.3*	promotion	N.D.	*Twist1, snail, ZEB1 and ZEB2*	[27]
9	*ZEBTR (BX111887)*	promotion	Transcriptional regulation	*ZEB1*	[45]

Abbreviation: N.D.: Not determined

Table 5 Summary of all the hypoxia-inducible lncRNAs described in the text.

	lncRNA	EMT	Interaction protein or protein complex	Interaction chromatin/epigenetic regulators	Associating with miRNAs	Mechanism	Biological significances	Reference
1	*AGAP2-AS1*	v			v	Sequestration of miRNAs	Promoting cell proliferation, migration, and invasion	[67]
2	*CASC9*	v	v			Protein stability	Promoting glycolysis and tumor progression	[35,36]
3	*H19*	v	v		v	HIF-1α nuclear translocation/ Sequestration of miRNAs	Promoting migration, invasion, and tumor progression/Cell Dissemination/Glycolysis	[38,84–87]
4	*HOTAIR*	v		v	v	Epigenetic regulation/ Sequestration of miRNAs	Promoting cell proliferation and migration/Glycolysis/Histone modifications on target genes	[51,90–92]
5	*HOTTIP*	v			v	Sequestration of miRNAs	Promoting migration and invasion	[60,70]
6	*NEAT1*	v	v		v	Complex scaffold/Sequestration of miRNAs	Promoting cell proliferation, migration, invasion, and tumorigenesis/Paraspeckle formation	[29,95,96]
7	*NORAD*	v			v	Sequestration of miRNAs	Promoting migration, invasion, and tumor progression	[74–76]
8	*RP11-390F4.3*	v				Transcriptional regulation	Promoting migration, invasion, and tumor progression	[27]
9	*ZEBTR (BX111887)*	v	v			Transcriptional regulation	Promoting cell proliferation, migration, and invasion	[45]
10	*MALAT1*		v		v	Transcriptional regulation/ Sequestration of miRNAs	Promoting cell proliferation, migration, invasion, and tumor progression/Glycolysis	[30–32,94]
11	*LINK-A*		v			Complex scaffold	Glycolysis and tumorigenesis	[33]
12	*lincRNA-p21*		v			Protein–Protein interaction	Glycolysis	[34]
13	*MTA2TR*		v			Transcriptional regulation	Tumorigenesis	[39]
14	*NDRG-OT1*		v			Post-Translational modification	Protein degradation	[40]
15	*HIF2PUT*		v			Transcriptional regulation	Decrease cell proliferation and migration	[41]
16	*HINCUT-1*		v			Transcriptional regulation	Cell proliferation	[42]
17	*DARS-AS1*		v			Post-Translational modification	Tumorigenesis	[43]
18	*lncRNA-SARCC*		v			Post-Translational modification	AR/HIF-1α/c-Myc signaling axis	[44]
19	*LncHIFCAR (MIR31HG)*		v			Transcriptional regulation	Glycolysis	[46]
20	*LUCAT1*		v			Scaffold	Promote Chemoresistance	[47]
21	*WT1-AS*			v		Epigenetic regulation	Stem cell function	[52]
22	*PVT1*			v	v	Epigenetic regulation/ Sequestration of miRNAs	Promoting cell proliferation, migration, and invasion	[53,97–99]
23	*MEG3*			v		Epigenetic regulation	Tumorigenesis	[54]
24	*GATA6-AS*			v		Epigenetic regulation	Angiogenesis	[55]
25	*HIF1A-AS2*			v	v	Epigenetic regulation/ Sequestration of miRNAs	Stem cell growth, cell renewal and survival/Angiogenesis/Promote ASC osteogenic differentiation	[56,88,89]

26	*lncRNA-AK058003*	v	Epigenetic regulation		Promoting migration, invasion, and tumor progression	[57]		
27	*BC005927*	v	Epigenetic regulation		Tumor progression	[58]		
28	*EIF3J-AS1*		Sequestration of miRNAs	v	Promoting cell proliferation, migration, and invasion	[68]		
29	*GAPLINC*		Sequestration of miRNAs	v	Promoting cell proliferation, migration, and invasion	[69]		
30	*linc-ROR*		Sequestration of miRNAs	v	Tumorigenesis	[71]		
31	*lncRNA-EFNA3*		Sequestration of miRNAs	v	Tumor progression	[72,73]		
32	*NUTF2P3*		Sequestration of miRNAs	v	Promoting cell proliferation, invasion, and tumor progression	[77]		
33	*UCA1*		Sequestration of miRNAs	v	Promoting cell proliferation, migration, invasion, and tumor progression/Drug resistance	[78–80]		
34	*ZEB2-AS1*		Sequestration of miRNAs	v	Promoting cell proliferation, invasion/Tumorigenesis	[81]		
35	*FAM201A*		Sequestration of miRNAs	v	Promoting cell proliferation	[82]		
36	*FEZF1-AS1*		Sequestration of miRNAs	v	Promoting cell proliferation and invasion	[83]		
37	*LINC01436*		Sequestration of miRNAs	v	Promoting cell migration and invasion	[93]		

carcinoma [100]. 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 modifed 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 ciplatin in cervical cancer cells [106]. Antisense oligonucleotides against lncRNA *LUCAT1* induces chemosensititivity 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, RNAi, 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.

Funding

This work was supported in part to K.J.W. by Ministry of Science and Technology Summit and Frontier grants (MOST 108-2321-B-182A-005, MOST 109-2326-B-182A-002), Chang Gung Memorial Hospital (OMRPG3I0012, NMRPG3J6192, CORPG3J0232, NMRPG3J0672); to K.W.H. by Ministry of Science and Technology (MOST 108-2628-B-039-003; MOST 109-2628-B-039-006), China Medical University (CMU109-MF-12), and the "Drug Development Center, China Medical University" from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project (Ministry of Education, Taiwan); and to P.H.P. by Ministry of Science and Technology (MOST 109-2320-B-182A-022), Chang Gung Memorial Hospital (NMRPG3K0511).

Conflicts of interest

There is no competing interest among the authors.

Acknowledgements

Due to the limitation of space, we apologize to the authors whose papers are not cited in the manuscript.

REFERENCES

[1] Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell 2013;152:1298–307.
[2] Schmitz SU, Grote P, Herrmann BG. Mechanisms of long noncoding RNA function in development and disease. Cell Mol Life Sci 2016;73:2491–509.
[3] Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. Cancer Cell 2016;29:452–63.
[4] Huarte M. The emerging role of lncRNAs in cancer. Nat Med 2015;21:1253–61.
[5] Evans JR, Feng FY, Chinnaiyan AM. The bright side of dark matter: lncRNAs in cancer. J Clin Invest 2016;126:2775–82.
[6] Li Y, Egranov SD, Yang L, Lin C. Molecular mechanisms of long noncoding RNAs-mediated cancer metastasis. Genes Chromosomes Cancer 2019;58:200–7.
[7] Geisler S, Coller J. RNA in unexpected places: long non-coding RNA functions in diverse cellular contexts. Nat Rev Mol Cell Biol 2013;14:699–712.
[8] Yan X, Hu Z, Feng Y, Hu X, Yuan J, Zhao SD, et al. Comprehensive genomic characterization of long non-coding RNAs across human cancers. Cancer Cell 2015;28:529–40.
[9] Yoon JH, Abdelmohsen K, Gorospe M. Posttranscriptional gene regulation by long noncoding RNA. J Mol Biol 2013;425:3723–30.
[10] Shih JW, Kung HJ. Long non-coding RNA and tumor hypoxia: new players ushered toward an old arena. J Biomed Sci 2017;24:53.
[11] Kuo TC, Kung HJ, Shih JW. Signaling in and out: long-noncoding RNAs in tumor hypoxia. J Biomed Sci 2020;27:59.
[12] Schito L, Semenza GL. Hypoxia-inducible factors: master regulators of cancer progression. Trends Cancer 2016;2:758–70.
[13] Semenza GL. The hypoxic tumor microenvironment: a driving force for breast cancer progression. Biochim Biophys Acta 2016;1863:382–91.
[14] Chen Y, Liu M, Niu Y, Wang Y. Romance of the three kingdoms in hypoxia: HIFs, epigenetic regulators, and chromatin reprogramming. Cancer Lett 2020;495:211–23.
[15] Li T, Mao C, Wang X, Shi Y, Tao Y. Epigenetic crosstalk between hypoxia and tumor driven by HIF regulation. J Exp Clin Cancer Res 2020;39:224.
[16] Chang YN, Zhang K, Hu ZM, Qi HX, Shi ZM, Han XH, et al. Hypoxia-regulated lncRNAs in cancer. Gene 2016;575:1–8.
[17] Wu X, Tudoran OM, Calin GA, Ivan M. The many faces of long noncoding RNAs in cancer. Antioxidants Redox Signal 2018;29:922–35.
[18] Kapinova A, Kubatka P, Zubor P, Golubnitschaja O, Dankova Z, Uramova S, et al. The hypoxia-responsive long non-coding RNAs may impact on the tumor biology and subsequent management of breast cancer. Biomed Pharmacother 2018;99:51–8.
[19] Wang X, Zhao D, Xie H, Hu Y. Interplay of long non-coding RNAs and HIF-1α: a new dimension to understanding hypoxia-regulated tumor growth and metastasis. Cancer Lett 2021;499:49–59.
[20] Nieto MA, Huang RY, Jackson RA, Thiery JP. EMT: 2016. Cell 2016;166:21–45.
[21] Lu W, Kang Y. Epithelial-mesenchymal plasticity in cancer progression and metastasis. Dev Cell 2019;49:361–74.
[22] Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol 2019;20:69–84.
[23] Yang MH, Wu MZ, Chiou SH, Chen PM, Chang SY, Liu CJ, et al. Direct regulation of TWIST by HIF-1α promotes metastasis. Nat Cell Biol 2008;10:295–305.
[24] Yang J, Antin P, Berx G, Blanpain C, Brabletz T, Bronner M, et al. Guidelines and definitions for research on epithelial-mesenchymal transition. Nat Rev Mol Cell Biol 2020;21:341–52.
[25] Lin YT, Wu KJ. Epigenetic regulation of epithelial-mesenchymal transition: focusing on hypoxia and TGF-β signaling. J Biomed Sci 2020;27:39.

[26] Wu CY, Tsai YP, Wu MZ, Teng SC, Wu KJ. Epigenetic reprogramming and post-transcriptional regulation during the epithelial-mesenchymal transition. Trends Genet 2012;28:454–63.
[27] Peng PH, Chieh-Yu Lai J, Hsu KW, Wu KJ. Hypoxia-induced lncRNA RP11-390F4.3 promotes epithelial-mesenchymal transition (EMT) and metastasis through upregulating EMT regulators. Cancer Lett 2020;483:35–45.
[28] Choudhry H, Albukhari A, Morotti M, Haider S, Moralli D, Smythies J, et al. Tumor hypoxia induces nuclear paraspeckle formation through HIF-2α dependent transcriptional activation of NEAT1 leading to cancer cell survival. Oncogene 2015;34:4482–90.
[29] Dong P, Xiong Y, Yue J, Hanley SJB, Kobayashi N, Todo Y, et al. Long non-coding RNA NEAT1: a novel target for diagnosis and therapy in human tumors. Front Genet 2018;9:471.
[30] Luo F, Sun B, Li H, Xu Y, Liu Y, Liu X, et al. A MALAT1/HIF-2α feedback loop contributes to arsenite carcinogenesis. Oncotarget 2016;7:5769–87.
[31] Luo F, Liu X, Ling M, Lu L, Shi L, Lu X, et al. The lncRNA MALAT1, acting through HIF-1α stabilization, enhances arsenite-induced glycolysis in human hepatic L-02 cells. Biochim Biophys Acta 2016;1862:1685–95.
[32] Hu L, Tang J, Huang X, Zhang T, Feng X. Hypoxia exposure upregulates MALAT-1 and regulates the transcriptional activity of PTB-associated splicing factor in A549 lung adenocarcinoma cells. Oncol Lett 2018;16:294–300.
[33] Lin A, Li C, Xing Z, Hu Q, Liang K, Han L, et al. The LINK-A lncRNA activates normoxic HIF1α signalling in triple-negative breast cancer. Nat Cell Biol 2016;18:213–24.
[34] Yang F, Zhang H, Mei Y, Wu M. Reciprocal regulation of HIF-1α and lincRNA-p21 modulates the Warburg effect. Mol Cell 2014;53:88–100.
[35] Su X, Li G, Liu W. The long noncoding RNA cancer susceptibility candidate 9 promotes nasopharyngeal carcinogenesis via stabilizing HIF1α. DNA Cell Biol 2017;36:394–400.
[36] Zhang Z, Fang E, Rong Y, Han H, Gong Q, Xiao Y, et al. Hypoxia-induced lncRNA CASC9 enhances glycolysis and the epithelial-mesenchymal transition of pancreatic cancer by a positive feedback loop with AKT/HIF-1α signaling. Am J Cancer Res 2021;11:123–37.
[37] Raveh E, Matouk IJ, Gilon M, Hochberg A. The H19 Long non-coding RNA in cancer initiation, progression and metastasis - a proposed unifying theory. Mol Canc 2015;14:184.
[38] Corrado C, Costa V, Giavaresi G, Calabrese A, Conigliaro A, Alessandro R. Long non coding RNA H19: a new player in hypoxia-induced multiple myeloma cell dissemination. Int J Mol Sci 2019;20:801.
[39] Zeng Z, Xu FY, Zheng H, Cheng P, Chen QY, Ye Z, et al. LncRNA-MTA2TR functions as a promoter in pancreatic cancer via driving deacetylation-dependent accumulation of HIF-1α. Theranostics 2019;9:5298–314.
[40] Lin HC, Yeh CC, Chao LY, Tsai MH, Chen HH, Chuang EY, et al. The hypoxia-responsive lncRNA NDRG-OT1 promotes NDRG1 degradation via ubiquitin-mediated proteolysis in breast cancer cells. Oncotarget 2018;9:10470–82.
[41] Wang Y, Yao J, Meng H, Yu Z, Wang Z, Yuan X, et al. A novel long non-coding RNA, hypoxia-inducible factor-2α promoter upstream transcript, functions as an inhibitor of osteosarcoma stem cells in vitro. Mol Med Rep 2015;11:2534–40.
[42] Ferdin J, Nishida N, Wu X, Nicoloso MS, Shah MY, Devlin C, et al. HINCUTs in cancer: hypoxia-induced noncoding ultraconserved transcripts. Cell Death Differ 2013;20:1675–87.
[43] Tong J, Xu X, Zhang Z, Ma C, Xiang R, Liu J, et al. Hypoxia-induced long non-coding RNA DARS-AS1 regulates RBM39 stability to promote myeloma malignancy. Haematologica 2020;105:1630–40.
[44] Zhai W, Sun Y, Jiang M, Wang M, Gasiewicz TA, Zheng J, et al. Differential regulation of LncRNA-SARCC suppresses VHL-mutant RCC cell proliferation yet promotes VHL-normal RCC cell proliferation via modulating androgen receptor/HIF-2α/C-MYC axis under hypoxia. Oncogene 2016;35:4866–80.
[45] Deng SJ, Chen HY, Ye Z, Deng SC, Zhu S, Zeng Z, et al. Hypoxia-induced LncRNA-BX111 promotes metastasis and progression of pancreatic cancer through regulating ZEB1 transcription. Oncogene 2018;37:5811–28.
[46] Shih JW, Chiang WF, Wu ATH, Wu MH, Wang LY, Yu YL, et al. Long noncoding RNA LncHIFCAR/MIR31HG is a HIF-1α co-activator driving oral cancer progression. Nat Commun 2017;8:15874.
[47] Huan L, Guo T, Wu Y, Xu L, Huang S, Xu Y, et al. Hypoxia induced LUCAT1/PTBP1 axis modulates cancer cell viability and chemotherapy response. Mol Canc 2020;19:11.
[48] Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. Nat Rev Genet 2016;17:487–500.
[49] Darwiche N. Epigenetic mechanisms and the hallmarks of cancer: an intimate affair. Am J Cancer Res 2020;10:1954–78.
[50] Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, et al. Long noncoding RNA as modular scaffold of histone modification complexes. Science 2010;329:689–93.
[51] Zhou C, Ye L, Jiang C, Bai J, Chi Y, Zhang H. Long noncoding RNA HOTAIR, a hypoxia-inducible factor-1α activated driver of malignancy, enhances hypoxic cancer cell proliferation, migration, and invasion in non-small cell lung cancer. Tumour Biol 2015;36:9179–88.
[52] McCarty G, Loeb DM. Hypoxia-sensitive epigenetic regulation of an antisense-oriented lncRNA controls WT1 expression in myeloid leukemia cells. PLoS One 2015;10:e0119837.
[53] Wang Y, Chen W, Lian J, Zhang H, Yu B, Zhang M, et al. The lncRNA PVT1 regulates nasopharyngeal carcinoma cell proliferation via activating the KAT2A acetyltransferase and stabilizing HIF-1α. Cell Death Differ 2020;27:695–710.
[54] Zheng XY, Lei BX, Lin YY, Sui MH, Zhang ML, Zhuang ZQ, et al. Long noncoding RNA MEG3 silencing protects against hypoxia-induced pheochromocytoma-12 cell injury through inhibition of TIMP2 promoter methylation. J Cell Physiol 2020;235:1649–62.
[55] Neumann P, Jae N, Knau A, Glaser SF, Fouani Y, Rossbach O, et al. The lncRNA GATA6-AS epigenetically regulates endothelial gene expression via interaction with LOXL2. Nat Commun 2018;9:237.
[56] Mineo M, Ricklefs F, Rooj AK, Lyons SM, Ivanov P, Ansari KI, et al. The long non-coding RNA HIF1A-AS2 facilitates the maintenance of mesenchymal glioblastoma stem-like cells in hypoxic niches. Cell Rep 2016;15:2500–9.
[57] Wang Y, Liu X, Zhang H, Sun L, Zhou Y, Jin H, et al. Hypoxia-inducible lncRNA-AK058003 promotes gastric cancer metastasis by targeting gamma-synuclein. Neoplasia 2014;16:1094–106.
[58] Liu X, Wang Y, Sun L, Min J, Liu J, Chen D, et al. Long noncoding RNA BC005927 upregulates EPHB4 and promotes gastric cancer metastasis under hypoxia. Cancer Sci 2018;109:988–1000.
[59] Zhang J, Jin HY, Wu Y, Zheng ZC, Guo S, Wang Y, et al. Hypoxia-induced LncRNA PCGEM1 promotes invasion and metastasis of gastric cancer through regulating SNAI1. Clin Transl Oncol 2019;21:1142–51.
[60] Zhang S, Wang W, Liu G, Xie S, Li Q, Li Y, et al. Long non-coding RNA HOTTIP promotes hypoxia-induced epithelial-mesenchymal transition of malignant glioma by regulating

the miR-101/ZEB1 axis. Biomed Pharmacother 2017;95:711–20.
[61] Chu C, Qu K, Zhong FL, Artandi SE, Chang HY. Genomic maps of long noncoding RNA occupancy reveal principles of RNA-chromatin interactions. Mol Cell 2011;44:667–78.
[62] Mondal T, Subhash S, Vaid R, Enroth S, Uday S, Reinius B, et al. MEG3 long noncoding RNA regulates the TGF-β pathway genes through formation of RNA–DNA triplex structures. Nat Commun 2015;6:7743.
[63] Li X, Zhou B, Chen L, Gou LT, Li H, Fu XD. GRID-seq reveals the global RNA-chromatin interactome. Nat Biotechnol 2017;35:940–50.
[64] Fang J, Ma Q, Chu C, Huang B, Li L, Cai P, et al. PIRCh-seq: functional classification of non-coding RNAs associated with distinct histone modifications. Genome Biol 2019;20:292.
[65] Mumbach MR, Granja JM, Flynn RA, Roake CM, Satpathy AT, Rubin AJ, et al. HiChIRP reveals RNA-associated chromosome conformation. Nat Methods 2019;16:489–92.
[66] Yu F, Zhang G, Shi A, Hu J, Li F, Zhang X, et al. LnChrom: a resource of experimentally validated lncRNA-chromatin interactions in human and mouse. Database, v 2018, 2018. https://doi.org/10.1093/database/bay039.
[67] Liu Z, Wang Y, Wang L, Yao B, Sun L, Liu R, et al. Long non-coding RNA AGAP2-AS1, functioning as a competitive endogenous RNA, upregulates ANXA11 expression by sponging miR-16-5p and promotes proliferation and metastasis in hepatocellular carcinoma. J Exp Clin Cancer Res 2019;38:194.
[68] Yang X, Yao B, Niu Y, Chen T, Mo H, Wang L, et al. Hypoxia-induced lncRNA EIF3J-AS1 accelerates hepatocellular carcinoma progression via targeting miR-122-5p/CTNND2 axis. Biochem Biophys Res Commun 2019;518:239–45.
[69] He Y, Wu Z, Qiu C, Wang X, Xiang Y, Lu T, et al. Long non-coding RNA GAPLINC promotes angiogenesis by regulating miR-211 under hypoxia in human umbilical vein endothelial cells. J Cell Mol Med 2019;23:8090–100.
[70] Shi J, Wang H, Feng W, Huang S, An J, Qiu Y, et al. Long non-coding RNA HOTTIP promotes hypoxia-induced glycolysis through targeting miR-615-3p/HMGB3 axis in non-small cell lung cancer cells. Eur J Pharmacol 2019;862:172615.
[71] Takahashi K, Yan IK, Haga H, Patel T. Modulation of hypoxia-signaling pathways by extracellular linc-RoR. J Cell Sci 2014;127:1585–94.
[72] Gomez-Maldonado L, Tiana M, Roche O, Prado-Cabrero A, Jensen L, Fernandez-Barral A, et al. EFNA3 long noncoding RNAs induced by hypoxia promote metastatic dissemination. Oncogene 2015;34:2609–20.
[73] Gong W, Qie S, Huang P, Xi J. Deletion of long noncoding RNA EFNA3 aggravates hypoxia-induced injury in PC-12 cells by upregulation of miR-101a. J Cell Biochem 2019;120:836–47.
[74] Li H, Wang X, Wen C, Huo Z, Wang W, Zhan Q, et al. Long noncoding RNA NORAD, a novel competing endogenous RNA, enhances the hypoxia-induced epithelial-mesenchymal transition to promote metastasis in pancreatic cancer. Mol Canc 2017;16:169.
[75] Chen Y, Cao K, Li J, Wang A, Sun L, Tang J, et al. Overexpression of long non-coding RNA NORAD promotes invasion and migration in malignant melanoma via regulating the MIR-205-EGLN2 pathway. Cancer Med 2019;8:1744–54.
[76] Zhao X, Wei X, Wang X, Qi G. Long noncoding RNA NORAD regulates angiogenesis of human umbilical vein endothelial cells via miR-590-3p under hypoxic conditions. Mol Med Rep 2020;21:2560–70.
[77] Li X, Deng SJ, Zhu S, Jin Y, Cui SP, Chen JY, et al. Hypoxia-induced lncRNA-NUTF2P3-001 contributes to tumorigenesis of pancreatic cancer by derepressing the miR-3923/KRAS pathway. Oncotarget 2016;7:6000–14.
[78] Li X, Wu Y, Liu A, Tang X. Long non-coding RNA UCA1 enhances tamoxifen resistance in breast cancer cells through a miR-18a-HIF1α feedback regulatory loop. Tumour Biol 2016;37:14733–43.
[79] Yang Z, Shi X, Li C, Wang X, Hou K, Li Z, et al. Long non-coding RNA UCA1 upregulation promotes the migration of hypoxia-resistant gastric cancer cells through the miR-7-5p/EGFR axis. Exp Cell Res 2018;368:194–201.
[80] Zhang Y, Liu Y, Xu X. Knockdown of LncRNA-UCA1 suppresses chemoresistance of pediatric AML by inhibiting glycolysis through the microRNA-125a/hexokinase 2 pathway. J Cell Biochem 2018;119:6296–308.
[81] Wu F, Gao H, Liu K, Gao B, Ren H, Li Z, et al. The lncRNA ZEB2-AS1 is upregulated in gastric cancer and affects cell proliferation and invasion via miR-143-5p/HIF-1α axis. OncoTargets Ther 2019;12:657–67.
[82] Liu AM, Zhu Y, Huang ZW, Lei L, Fu SZ, Chen Y. Long noncoding RNA FAM201A involves in radioresistance of non-small-cell lung cancer by enhancing EGFR expression via miR-370. Eur Rev Med Pharmacol Sci 2019;23:5802–14.
[83] Ou ZL, Zhang M, Ji LD, Luo Z, Han T, Lu YB, et al. Long noncoding RNA FEZF1-AS1 predicts poor prognosis and modulates pancreatic cancer cell proliferation and invasion through miR-142/HIF-1α and miR-133a/EGFR upon hypoxia/normoxia. J Cell Physiol 2019;234:15407–19.
[84] Wu W, Hu Q, Nie E, Yu T, Wu Y, Zhi T, et al. Hypoxia induces H19 expression through direct and indirect HIF-1α activity, promoting oncogenic effects in glioblastoma. Sci Rep 2017;7:45029.
[85] Zheng ZH, Wu DM, Fan SH, Zhang ZF, Chen GQ, Lu J. Upregulation of miR-675-5p induced by lncRNA H19 was associated with tumor progression and development by targeting tumor suppressor p53 in non-small cell lung cancer. J Cell Biochem 2019;120:18724–35.
[86] Matouk IJ, Raveh E, Abu-lail R, Mezan S, Gilon M, Gershtain E, et al. Oncofetal H19 RNA promotes tumor metastasis. Biochim Biophys Acta 2014;1843:1414–26.
[87] Peng F, Wang JH, Fan WJ, Meng YT, Li MM, Li TT, et al. Glycolysis gatekeeper PDK1 reprograms breast cancer stem cells under hypoxia. Oncogene 2018;37:1062–74.
[88] Li L, Wang M, Mei Z, Cao W, Yang Y, Wang Y, et al. lncRNAs HIF1A-AS2 facilitates the up-regulation of HIF-1α by sponging to miR-153-3p, whereby promoting angiogenesis in HUVECs in hypoxia. Biomed Pharmacother 2017;96:165–72.
[89] Wu R, Ruan J, Sun Y, Liu M, Sha Z, Fan C, et al. Long non-coding RNA HIF1A-AS2 facilitates adipose-derived stem cells (ASCs) osteogenic differentiation through miR-665/IL6 axis via PI3K/Akt signaling pathway. Stem Cell Res Ther 2018;9:348.
[90] Hong Q, Li O, Zheng W, Xiao WZ, Zhang L, Wu D, et al. LncRNA HOTAIR regulates HIF-1α/AXL signaling through inhibition of miR-217 in renal cell carcinoma. Cell Death Dis 2017;8:e2772.
[91] Hu M, Fu Q, Jing C, Zhang X, Qin T, Pan Y. LncRNA HOTAIR knockdown inhibits glycolysis by regulating miR-130a-3p/HIF1A in hepatocellular carcinoma under hypoxia. Biomed Pharmacother 2020;125:109703.
[92] Lozano-Romero A, Astudillo-de la Vega H, Terrones-Gurrola M, Marchat LA, Hernandez-Sotelo D, Salinas-Vera YM, et al. HOX transcript antisense RNA HOTAIR abrogates vasculogenic mimicry by targeting the AngiomiR-204/FAK Axis in triple negative breast cancer cells. Noncoding RNA 2020;6:19.

[93] Yuan S, Xiang Y, Wang G, Zhou M, Meng G, Liu Q, et al. Hypoxia-sensitive LINC01436 is regulated by E2F6 and acts as an oncogene by targeting miR-30a-3p in non-small cell lung cancer. Mol Oncol 2019;13:840–56.
[94] Zhao ZB, Chen F, Bai XF. Long noncoding RNA MALAT1 regulates hepatocellular carcinoma growth under hypoxia via sponging MicroRNA-200a. Yonsei Med J 2019;60:727–34.
[95] Kong X, Zhao Y, Li X, Tao Z, Hou M, Ma H. Overexpression of HIF-2α-Dependent NEAT1 promotes the progression of non-small cell lung cancer through miR-101-3p/SOX9/Wnt/β-Catenin signal pathway. Cell Physiol Biochem 2019;52:368–81.
[96] Lulli V, Buccarelli M, Ilari R, Castellani G, De Dominicis C, Di Giamberardino A, et al. Mir-370-3p impairs glioblastoma stem-like cell malignancy regulating a complex interplay between HMGA2/HIF1A and the oncogenic long non-coding RNA (lncRNA) NEAT1. Int J Mol Sci 2020;21:3610.
[97] Huang T, Liu HW, Chen JQ, Wang SH, Hao LQ, Liu M, et al. The long noncoding RNA PVT1 functions as a competing endogenous RNA by sponging miR-186 in gastric cancer. Biomed Pharmacother 2017;88:302–8.
[98] Wang C, Han C, Zhang Y, Liu F. LncRNA PVT1 regulate expression of HIF1α via functioning as ceRNA for miR-199a-5p in nonsmall cell lung cancer under hypoxia. Mol Med Rep 2018;17:1105–10.
[99] Xu Y, Luo X, He W, Chen G, Li Y, Li W, et al. Long non-coding RNA PVT1/miR-150/HIG2 Axis regulates the proliferation, invasion and the balance of iron metabolism of hepatocellular carcinoma. Cell Physiol Biochem 2018;49:1403–19.
[100] Wu M, Zhang X, Han X, Pandey V, Lobie PE, Zhu T. The potential of long noncoding RNAs for precision medicine in human cancer. Cancer Lett 2021;501:12–9.
[101] Arun G, Diermeier SD, Spector DL. Therapeutic targeting of long non-coding RNAs in cancer. Trends Mol Med 2018;24:257–77.
[102] Jiang MC, Ni JJ, Cui WY, Wang BY, Zhuo W. Emerging roles of lncRNA in cancer and therapeutic opportunities. Am J Cancer Res 2019;9:1354–66.
[103] Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Lancet 2016;388:3017–26.
[104] Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, et al. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. Lancet 2016;388:2239–53.
[105] Gilbert LA, Horlbeck MA, Adamson B, Villalta JE, Chen Y, Whitehead EH, et al. Genome-scale CRISPR-mediated control of gene repression and activation. Cell 2014;159:647–61.
[106] Iden M, Fye S, Li K, Chowdhury T, Ramchandran R, Rader JS. The lncRNA PVT1 contributes to the cervical cancer phenotype and associates with poor patient prognosis. PLoS One 2016;11:e0156274.