Signaling in and out: long-noncoding RNAs in tumor hypoxia
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Abstract
Over the past few years, long non-coding RNAs (lncRNAs) are recognized as key regulators of gene expression at chromatin, transcriptional and posttranscriptional level with pivotal roles in various biological and pathological processes, including cancer. Hypoxia, a common feature of the tumor microenvironment, profoundly affects gene expression and is tightly associated with cancer progression. Upon tumor hypoxia, the central regulator HIF (hypoxia-inducible factor) is upregulated and orchestrates transcription reprogramming, contributing to aggressive phenotypes in numerous cancers. Not surprisingly, lncRNAs are also transcriptional targets of HIF and serve as effectors of hypoxia response. Indeed, the number of hypoxia-associated lncRNAs (HALs) identified has risen sharply, illustrating the expanding roles of lncRNAs in hypoxia signaling cascade and responses. Moreover, through extracellular vesicles, lncRNAs could transmit hypoxia responses between cancer cells and the associated microenvironment. Notably, the aberrantly expressed cellular or exosomal HALs can serve as potential prognostic markers and therapeutic targets. In this review, we provide an update of the current knowledge about the expression, involvement and potential clinical impact of lncRNAs in tumor hypoxia, with special focus on their unique molecular regulation of HIF cascade and hypoxia-induced malignant progression.

Keywords: Tumor hypoxia, Long non-coding RNA, lncRNA, HIF-1α, Hypoxia-associated lncRNAs, HAL, Extracellular vesicles

Background
Hypoxia-associated lncRNAs (HALs) emerging as newly driving factors in tumorigenesis
In rapidly growing solid tumors, hypoxia is a common, microenvironmental characteristics, caused by insufficient vascularization, and the high tumor metabolic demands [1]. Accumulating evidence has demonstrated that tumor hypoxia is involved in the initial oncogenic transformation, but is also closely linked to aggressive cancer phenotypes, such as metastases, recurrences and resistance to therapy [2–4]. Upon hypoxia, to survive, cancer cells co-opt the fundamental adaptive responses to this stress through modulating the central mediator of hypoxic response, the hypoxia-inducible factor-1 (HIF-1) complex.

The HIF-1 complex is a heterodimeric assembly of bHLH-PAS (basic helix-loop-helix DNA binding proteins of the PER-ARNT-SIM family) transcriptional factors, comprised of a constitutively expressed, stable HIF-1β subunit and an oxygen-sensitive HIF-1α subunit that determines HIF-1 activity [5, 6]. In mammals, two HIF-1α homologs, HIF-2α and HIF-3α (also known as IPAS-1, inhibitory PAS (Per/Arnt/Sim) domain protein), have been identified. Similar to HIF-1α, HIF-2α is also sensitive to oxygen concentration and can interact with HIF-1β to form the HIF-2 heterodimeric complex. Due to the structural similarity in DNA binding and dimerization domains as well as the difference in their transactivation domains,
HIF-1α and HIF-2α regulate both common as well as distinct sets of target genes. Meanwhile, HIF-3α, an isoform lacking the transactivation domain, has a dominant negative effect on HIF-dependent gene transcription [7, 8].

In the presence of sufficient oxygen, HIF-1α subunits are post-translationally modified by a family of dioxygenases (prolyl hydroxylase domain-containing dioxygenases PHD1, 2 and 3, also known as EGLN1-3, Egl-9 family hypoxia inducible factor 1-3). Upon hydroxylation, HIF-1α subunits are recognized by the E3 ubiquitin ligase, VHL (von Hippel-Lindau tumor suppressor protein), leading to the poly ubiquitination and subsequent rapid degradation through the ubiquitin-proteasome pathway (Fig. 1a). Under hypoxic conditions, the PHD dioxygenase activity is inhibited, and the accumulated HIF-1α subunit translocates into the nucleus, dimerizing with HIF-1β and binding to the HREs (hypoxia response elements; the consensus 5′-(A/G)CGTG-3′ nucleotide sequence) within the promoter regions of HIF target genes to stimulate downstream transcriptional activation of multiple hypoxia responsive genes (Fig. 1a), eliciting a wide spectrum of cellular adaptations, such as decreased apoptosis, enhanced angiogenesis, proliferation, migration and invasion [1, 9–11]. In addition to protein coding genes, it has been widely acknowledged that the non-coding transcriptome is also responsive to hypoxia and play critical roles in the hypoxic response and HIF-1 associated cancer progression [12–16].

With recent advances in high-throughput sequencing, it is recognized that only a small fraction (< 2%) of the transcriptional output encodes proteins whereas the vast majority encode a variety of non-coding RNAs. Among these non-coding RNA species, long (> 200 bp) non-coding RNAs (lncRNAs) are a large class of regulatory transcripts [17], including lincRNAs (long intergenic RNAs), long intronic ncRNAs, pseudogenes, TCRs (transcribed ultra-conserved regions), asRNAs (antisense RNAs) and eRNAs (enhancer RNAs) [18]. According to the latest human genome annotation (GRCh38, GENCODE release 33, January 2020; www.gencodegenes.org), 48,438 transcripts originating from 17,952 loci were identified as lncRNAs. Although less than 1% has been functionally annotated, growing evidence suggested the vital roles of these lncRNAs in regulation of gene expression at various stages, such as imprinting, transcription, RNA interference, RNA splicing, and translation control [19–23]. It is now believed that the distinctive RNA biochemical properties, such as base-pairing ability, dynamic expression and flexible structure, endow these lncRNAs with multi-functionality [24–28]. Collectively, it is now well appreciated that, through acting as signals, decoys, guides or scaffolds, lncRNA could act as a crucial player of biological regulation [23–25, 27, 29–33].

Over the last few years, a large number of dysregulated lncRNAs have been associated with numerous diseases, including cancer [34–37]. While a few cancer-associated lncRNAs have been well characterized [27, 38], the functions of most remain largely unknown. Dysregulation of many cancer-associated lncRNAs is linked to both clinicopathological features and survival outcomes of patients, suggesting that functional annotation of these lncRNAs will eventually identify new venues for early diagnosis and therapy of cancer [39]. Several studies have shown that the modulation of lncRNAs in response to hypoxia could play a regulatory role in HIF signaling cascade [14–16, 40, 41]. Here, we refer to these unique transcripts as "hypoxia-associated lncRNAs" (HALs). These RNA molecules are involved in multiple hypoxia-driven cancer progression pathways. In this review, we provide an updated summary of the tumor HALs, with a specific emphasis on the crosstalk between these lncRNA species and cellular hypoxia response (Table 1 and Additional file 1: Table S1). We address current models describing the functional involvement of these new players in cancer progression, highlighting their relevant clinical potential as cancer biomarkers or therapeutic targets. Our discussion is centered on tumor hypoxia. For the functional roles of lncRNAs in hypoxia-induced kidney/hepatic/myocardial injury and neuromuscular or cardiovascular diseases, interested readers are referred to a number of comprehensive reviews published in recent years [127–132].

**Review**

**LncRNAs as emerging driving forces in cancer progression upon tumor hypoxia**

Given the pivotal roles of lncRNA in hypoxia-associated tumorigenesis pathways, multiple approaches have been applied in the identification of hypoxia-regulated lncRNAs [87, 90]. A comprehensive analysis coupling RNA-seq with ChIP-seq [12] revealed the extensive involvement of HIF-1α and HIF-2α in the transcriptional regulation of lncRNAs upon hypoxia. In recent years, the rapid expansion of research on lncRNAs has provided additional insights into those associated with cellular hypoxia response. Table 1 presents an updated list of these hypoxia-associated lncRNAs (HALs). Upon hypoxia, most HALs are up-regulated. HIF could directly promote the expression of these hypoxia inducible lncRNAs through binding to the HREs (hypoxia response elements) located in their promoter (Table 1) [41]. LncRNA-LET [93], CF129 [54] and CRPAT4 [56] are among the few which are down-regulated in hypoxic conditions. Notably, lncRNA-SARCC is able to respond to hypoxic stress differentially in a VHL-dependent manner [94].

Most of the HALs identified have impacts on cancer progression, although the mechanistic details are not all clear. Table 1 shows an overview of the tumor HALs. We summarize in the table, their potential molecular target related to hypoxic responses as well as their reported functions and signaling pathways. These HALs...
Fig. 1 Regulations of HIF-1 activity by HALs. a Regulation of HIF-1. Under normoxia (green arrows), HIF-1α subunit is hydroxylated by PHDs (prolyl hydroxylase domain proteins). Hydroxylation residues within HIF-1α facilitates interaction of HIF-1α with the E3 ubiquitin ligase VHL protein, targeting HIF-1α for polyubiquitination and subsequent proteasome-dependent degradation. Upon hypoxia (red arrows), the PHDs and other prolyl hydroxylases are inhibited, leading to HIF-1α stabilization and translocation into nucleus. After dimerization with its transcriptional partner HIF-1β and recruitment of co-activators (e.g. CBP/p300), the HIF-1 heterodimer binds the HRE (hypoxia response element) of target genes to regulate transcription. b Transcriptional co-activator. Hypoxia-induced LncHIFCAR could directly interact with HIF-1α and facilitate the recruitment of HIF-1α and p300 cofactor to the target loci, thereby upregulating HIF-1 target genes. c Recruitment of transcription factor. HIF-1α-induced LncRNA-MTA2TR could recruit ATF3 to the promoter area of MTA2, thereby transcriptionally upregulating the expression of oncogenic MTA2. MTA2 can subsequently enhance HIF-1α protein accumulation via deacetylation, forming a feedback loop to amplify HIF-1 signaling. d mRNA stability control. The expression of LncRNA-LET is repressed through hypoxia-induced HDAC3, which reduces the histone H3 and H4 acetylation at the LncRNA-LET promoter. Decreased LncRNA-LET expression reduces the LncRNA-LET-mediated degradation of HIF-1α negative regulator NF90, leading to HIF-1α accumulation. e LncRNA/miRNA sponge. Hypoxia-induced H19 could upregulate HIF-1α expression by absorbing miRNA let-7 and nullifying let-7-mediated HIF1A mRNA suppression. f Molecular decoy, lincRNA-p21 is able to disrupt the interaction between HIF-1α and its negative regulator VHL via separate binding to both HIF-1α and VHL, thereby blocking VHL-dependent HIF-1α degradation. g Complex scaffold. LINK-A-mediated recruitment and enzymatic activation of BRK and LRRK2 kinases could facilitate phosphorylation of HIF-1α at specific residues. These phosphorylation modifications prevent subsequent HIF-1α degradation and enhance the association between HIF-1α and cofactor p300, thereby upregulating HIF-1 target genes. See text for a more detailed discussion.
| lncRNA                | Status upon hypoxia                                                                 | HIF involvement                                                                 | Cancer Types                                                                 | Clinical association                                                                                   | Functional Impact                                                                                   | Interactor                  | Target/Effect                                                                                     | Mechanistic Classification                                                                 | Refs   |
|----------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------|
| aHIF (HIF1A-AS2)     | Not further induced in nonpapillary disease, but can be induced in lymphocytes     | N.D. (2 Putative HREs)                                                          | Renal carcinoma                                                               | • Up-regulated in non-papillary clear-cell renal carcinoma                                           | N.D.                                                                                               | HIF1A mRNA stability          | mRNA stability control                                                              | (Binding of HIF1A-AS2 to the HIF1A mRNA 3′-UTR could possibly expose AU-rich elements and thus increase the degradation of HIF1A mRNA) | [42, 43]|
|                      |                                                                                    |                                                                                 |                                                                              |                                                                                                     |                                                                                                     |                                |                                                                            |                                                                                                                                         |        |
| Up-regulated         | N.D.                                                                               |                                                                                 | Human umbilical vein endothelial cells (HUVECs)                                | • Up-regulated in HUVECs in hypoxia                                                                 | HUVECs viability ↑                                                                                   | miR-153-3p                   | The expression of HIF-1α                                                       | Sequestration of miRNAs                                                  | [44]   |
| Up-regulated         | N.D.                                                                               |                                                                                 | Bladder cancer                                                                | • Up-regulated in bladder cancer after cisplatin treatment                                       | Cisplatin resistance ↑                                                                               | N.D.                         | Promoting HMGA1 expression                                                        | Transcriptional regulation (HIF1A-AS2 promoting the expression of HMGA1, which physically interacts with p53, p63, and p73, and therefore inhibits their transcriptional activity on Box) | [45]   |
|                      | Up-regulated                                                                      |                                                                                 | Mesenchymal Glioblastoma Stem-like Cells (M-GSCs)                              | • Up-regulated in M-GSCs                                                                          | Growth of M-GSCs ↑                                                                                  | IGF2BP2 and DHX9              | Maintenance of expression of HMGA1                                                                 | Complex scaffold (The direct interaction among HIF1A-AS2, IGF2BP2 and DHX9 is needed for HMGA1 expression) | [46, 47]|
|                      | HIF-1α and/or HIF-2α dependent (2 HREs identified)                                 |                                                                                 | Epithelial ovarian cancer (EOC)                                                | • Up-regulated in EOC                                                                             | Cell apoptosis ↓                                                                                  | N.D.                         | N.D.                                                                      | Unclear mechanism (May partially through the aHIF-mediated regulation of certain key mitochondrial apoptosis pathway-related genes, including Bcl-2, Bax, Caspase-7, and Caspase-9) | [48]   |
|                      |                                                                                    |                                                                                 |                                                                              |                                                                                                     | Cell proliferation ↓                                                                                 | N.D.                         | N.D.                                                                      |                                                                                                                                         |        |
|                      |                                                                                    |                                                                                 |                                                                              |                                                                                                     | Tumorigenesis ↑                                                                                     | N.D.                         | N.D.                                                                      |                                                                                                                                         |        |
|                      |                                                                                    |                                                                                 |                                                                              |                                                                                                     | Tumor growth ↑                                                                                      | N.D.                         | N.D.                                                                      |                                                                                                                                         |        |
| AGAP2-AS1            | Up-regulated                                                                       |                                                                                 | Hepatocellular carcinoma (HCC)                                                 | • Up-regulated in HCC                                                                             | Cell proliferation ↑                                                                                | miR-16-5p                    | The expression of ANXA11                                                        | Sequestration of miRNAs                                                                 | [49]   |
|                      |                                                                                    |                                                                                 | • Correlated with adverse clinical features and poor prognosis of HCC          |                                                                                                     | Migration and invasion ↑                                                                            |                                              |                                                                            | (Down-regulation of miR-16-5p-mediated repression of ANXA11)                                                                      |        |
Table 1 | HAL-mediated HIF signaling control and cancer progression (Continued)

| IncRNA | Status upon hypoxia | HIF involvement | Cancer Types | Clinical association | Functional Impact | Interactor | Target/Effect | Mechanistic Classification | Refs |
|--------|---------------------|-----------------|--------------|---------------------|-------------------|------------|---------------|---------------------------|------|
| ANRIL (CDKN2B-AS1) | Up-regulated | HIF-1α dependent (1 HRE identified) | Osteosarcoma | • Up-regulated in osteosarcoma | Apoptosis ↓ | N.D. | N.D. | Unclear mechanism (Possibly through epigenetic modification) | [50] |
| BCO05927 | Up-regulated | HIF-1α dependent (2 HREs identified) | Gastric cancer (GC) | • Up-regulated in GC • Correlated with higher tumor-node-metastasis stages and poorer prognoses | Metastasis ↑ | N.D. | N.D. | Transcriptional regulation (The neighboring gene, EPHB4, a metastasis-related gene, is regulated by BCO05927) | [51] |
| BX111887 (ZEBTR) | Up-regulated | HIF-1α dependent (1 HRE identified) | Pancreatic cancer (PC) | • Up-regulated in PC • Correlated with late TNM stage, lymphatic invasion and distant metastasis | Proliferation ↑ Migration ↑ Invasion ↑ | YB1 | ZEB1 promoter | Transcriptional regulation (BX111887 promotes ZEB1 transcription by recruiting YB1 to ZEB1 promoter) | [52] |
| CASC9 | N.D. | N.D. | Nasopharyngeal carcinoma (NPC) | Up-regulated in NPC tissues | Glycolysis and tumorigenesis ↑ Cell growth ↑ | HIF-1α | The stability of HIF-1α | Protein Stability (CASC9 interacts with HIF-1α and enhances the stabilization of HIF-1α) | [53] |
| CF129 (IncRNA-CF129145.1) | Down-regulated by binding of HIF-1α/HDAC1 complex to CF129 promoter | Down-regulated in PC | Pancreatic cancer (PC) | • Down-regulated in PC • Low CF129 expression predicted short overall survival | Invasion and metastasis ↓ | p53 and E3 ligase MKRN1 | FORC2 transcripion | Post-Translational modification (CF129 directly binds to p53 and E3 ligase MKRN1, inducing p53 protein ubiquitination and degradation, and thereby suppressing FORC2 transcription) | [54] |
| CPS1-JT1 | Down-regulated (treatment of hypoxia mimetic, CoCl₂) | N.D. | Colorectal cancer | Down-regulated in colorectal cancer | EMT and autophagy ↓ | N.D. | N.D. | Unclear mechanism (May partially through suppressing expression levels of HIF-1α, LC3-1, LC3-2, Beclin-1 and EMT associated proteins under hypoxia) | [55] |
| CRPATA4 (RP11-225B17) | Down-regulated | HIF-1α dependent, HIF-2α independent | Clear cell renal cell carcinoma (ccRCC) | • Up-regulated in ccRCC • Associated with poor overall survival and progression-free | Cell migration ↑ Proliferation ↑ | N.D. | N.D. | Unclear mechanism (May partially through the CRPATA4-mediated regulation of migration-
| IncRNA       | Status upon hypoxia | HIF involvement | Cancer Types                               | Clinical association                                                                 | Functional Impact | Interactor | Target/Effect | Mechanistic Classification                                                                 | Refs |
|--------------|---------------------|-----------------|-------------------------------------------|---------------------------------------------------------------------------------------|-------------------|------------|--------------|---------------------------------------------------------------------------------------------|------|
| DANCR        | N.D.                | N.D.            | Nasopharyngeal carcinoma (NPC)            | Up-regulated in NPC • Associated with poor prognosis                                   | Metastasis ↑ ❌ Invasion ↑ | NF90/NF45 complex | HIF-1α mRNA stability                                                                      | [57] |
| DARS-AS1     | Up-regulated        | HIF-1α dependent, But HIF-2α independent (2 HREs identified) | Myeloma                                  | Up-regulated in myeloma • Correlated with poor prognosis                               | Survival ↑ ❌ Tumorigenesis ↑ | RBM39      | RBM39 stability                                                                        | [58] |
| EIF3J-AS1    | (EIF3J-DT) Up-regulated | N.D.          | Hepatocellular carcinoma (HCC)            | Up-regulated in HCC tissues • Correlated with tumor size, vascular invasion, tumor stage and poor prognosis | Cell proliferation ↑ ❌ Migration ↑ ❌ Invasion ↑ | miR-122-5p | The expression of CTNND2                                                                  | [59] |
| ENST00000480739 (RPL13AP23) | N.D.                | N.D.            | Pancreatic ductal adenocarcinoma (PDAC)    | Down-regulated in PDAC • Associated with tumor node metastasis (TNM) stage and lymph node metastasis • Independent risk factor for PDAC survival following surgery | Invasion ↓ ❌ OS-9 mRNA & protein ↑ | N.D.       | Transcription of OS-9 (Negative regulation of HIF-1α)                                      | [60] |
| FALEC        | Up-regulated        | HIF-1α inducible | Prostate cancer (PCa)                     | Up-regulated in PCa • Independent prognostic factor                                    | Cell proliferation ↑ ❌ Migration and invasion ↑ | N.D.       | N.D.                                                   | Unclear mechanism                                                                 | [61] |
| FAM201A      | N.D.                | N.D.            | Non-small cell lung cancer (NSCLC)        | Up-regulated in tissues obtained from NSCLC patients resistant to radiotherapy          | Cell proliferation ↑ ❌ Apoptosis (under X-ray irradiation) ↓ | miR-370    | The expression of EGFR                                                                      | [62] |
| FEZF1-AS1    | N.D.                | N.D.            | Pancreatic cancer                         | Upregulated in                                                                           | Cell proliferation ↑ ❌ miR-142 and | miR-142          | The expression of EGFR                                                                      | [63] |
| IncRNA | Status upon hypoxia | HIF involvement | Cancer Types | Clinical association | Functional Impact | Interactor | Target/Effect | Mechanistic Classification | Refs |
|---------|----------------------|----------------|-------------|----------------------|------------------|------------|--------------|--------------------------|------|
| GAPLINC | Up-regulated | HIF-1α (2 HREs identified) (2 HREs) | Gastric cancer | • Upregulated in GC • High expression of GAPLINC correlates with poorer survival • GAPLINC correlates with CD44 activation | Proliferation ↑ Apoptosis ↓ Invasion ↑ Migration ↑ | miR-211-3p | The expression of CD44 | Sequestration of miRNAs (Down-regulation of miR-211-3p-mediated repression of CD44) | [64, 65] |
| H19 | Up-regulated | N.D. | Breast cancer stem cells (BCSCs) | • H19 expression strongly correlates with PDK1 in primary breast carcinomas | Glycolysis ↑ BCSC maintenance ↑ | let-7 | The expression of HIF-1α | Sequestration of miRNAs (Down-regulation of let-7-mediated repression of HIF-1α expression) | [66] |
| | Up-regulated | N.D. | Multiple Myeloma (MM) | N.D. | The expression of the hypoxia induced genes ↑ Adhesion on stromal cells ↑ | N.D. | N.D. | N.D. | Sequestration of miRNAs (HIF-1α nuclear translocation (H19 is required for HIF-1α nuclear translocation and the expression of the hypoxia-induced genes, such as CXCR4 and Snail)) | [67] |
| | Up-regulated | HIF-1α dependent (3 HREs identified) | Glioblastoma (GBM) | • Up-regulated in GBM • Correlated with poor prognosis • The HIF-1α levels were positively correlated with H19 levels in GBM specimens | Migration and invasion ↑ Tumor growth ↑ EMT ↑ | miR-181d | The expression of β-catenin | Sequestration of miRNAs (Down-regulation of miR-181d-mediated repression of β-catenin expression) | [68–71] |
| | Up-regulated | N.D. | Prostate Cancer | • Upregulated by estrogen or hypoxia • Reduced upon combined treatment | Cell motility ↓ Invasion ↓ | N.D. | Repression of β3 and β4 Integrins | Unclear mechanism (Combined Estrogen and Hypoxia treatment could cause H19 down-regulation, followed by up-regulation of both β3 and β4 Integrins and E-cadherin) | [72] |
| | Up-regulated | N.D. | Breast cancer, Non-small cell lung carcinoma (NSCLC) | • Up-regulated in NSCLC with chronic obstructive pulmonary disease (COPD) • Up-regulated in all | Migration and invasion ↑ Tumor growth ↑ EMT ↑ | N.D. | Up-regulation of miR-675-5p | Unclear mechanism (H19 could induce upregulation of miR-675-5p, whereas PS3 is a target gene of | [73, 74] |
| lncRNA       | Status upon hypoxia | HIF involvement       | Cancer Types                      | Clinical association                                                                 | Functional Impact                                                                 | Interactor | Target/Effect                      | Mechanistic Classification                                                                 | Refs |
|--------------|---------------------|-----------------------|-----------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------|------------------------------------|------------------------------------------------------------------------------------------|------|
| HAS2-AS1     | Up-regulated        | HIF-1α dependent (1 HRE identified) | Oral squamous cell carcinoma (OSCC) | • Up-regulated in OSCC                                                                  | EMT ↑                                                                             | N.D.       | N.D.                               | Unclear mechanism (HAS2-AS1-mediated hypoxia-induced EMT is dependent on cell-adhesion molecule CD44 and RHAMM) | [75] |
| HIF2PUT      | N.D.                | N.D.                  | Osteosarcoma                      | • Expression of HIF2PUT is correlated with HIF2A mRNA                                 | Cell proliferation and migration ↓ Expression of CSC marker CD133 ↓ Sphere-forming ability ↓ | N.D.       | Transcription of HIF2A             | Transcriptional regulation (HIF-2α was positively regulated by lncRNA HIF2PUT)           | [76] |
|              | N.D.                | N.D.                  | Osteosarcoma cancer stem cell     | • Down-regulated in osteosarcoma cell lines                                           | Proliferation ↓ Migration and invasion ↓ Sphere-formation ↓                         | N.D.       | N.D.                               | Unclear mechanism (May partly through HIF2PUT-mediated regulation of HIF-2 expression)   | [77] |
| HINCUT-1 (uc.475) | Up-regulated        | HIF-1α dependent (3 HREs identified) | Colon and breast cancer cell lines | N.D.                                                                                 | Hypoxic cell proliferation ↑                                                     | N.D.       | N.D.                               | Transcriptional regulation (HINCUT-1 is required for the expression of OGT mRNA expression and global O-GlcNAcylation of proteins) | [78] |
| HOTAIR       | N.D.                | N.D.                  | Renal cell carcinoma              | • Upregulated and correlated with tumor progression                                   | RCC proliferation ↑ Migration and EMT ↑ Apoptosis ↓                                | miR-217    | The expression of HIF-1α/AXL       | Sequestration of miRNAs (Down-regulation of miR-217-mediated repression of HIF-1α/AXL expression) | [79] |
|              | Up-regulated        | HIF-1α dependent (1 HRE identified) | Non-small cell lung carcinoma (NSCLC) | • High level of HOTAIR is associated with poor clinical outcome in multiple cancers | Cell proliferation under hypoxia ↑ Invasion & migration under hypoxia ↑ Apoptosis under hypoxia ↓ | N.D.       | N.D.                               | Unclear mechanism (Possibly through HOTAIR-mediated epigenetic modification)              | [80, 81] |
| IncRNA       | Status upon hypoxia | HIF involvement | Cancer Types                          | Clinical association                                                                 | Functional Impact               | Interactor | Target/Effect                          | Mechanistic Classification                                                                 | Refs  |
|--------------|---------------------|-----------------|---------------------------------------|----------------------------------------------------------------------------------------|---------------------------------|------------|----------------------------------------|--------------------------------------------------------------------------------------------|-------|
| HOT1P        | Up-regulated        | HIF-1α dependent | Glioma                               | • Up-regulated in glioma • Associated with metastasis and poor patient survival        | EMT ↑ Invasion ↑ Migration ↑   | miR-101    | The expression of ZEB1                | Sequestration of miRNAs (Down-regulation of miR-101-mediated repression of ZEB1)           | [82]  |
| IDH1-AS1     | N.D.                | N.D. (c-Myc-mediated repression) | Multiple cell lines (HeLa, HCT116, H1299, P498, and 293 T) | N.D.                                                                                  | Glycolysis ↓                   | IDH1       | IDH1 dimerization                      | Protein Dimerization (IDH1-AS1 interacts with IDH1 and promotes its Homo-dimerization)       | [83]  |
| UNC01436     | Up-regulated        | N.D.            | Non-small cell lung cancer (NSCLC)    | • Up-regulated in NSCLC • Associated with poor overall survival                        | Cell growth ↑ Migration and invasion ↑ | miR-30a-3p | The expression of EPAS1                | Sequestration of miRNAs (Down-regulation of miR-30a-3p-mediated repression of EPAS1)         | [84]  |
| lincRNA-p21 (TP53COR1) | Up-regulated | HIF-1α dependent & preference (2 HREs identified) | Cervical, lung and breast cancer cell lines | N.D.                                                                                  | Hypoxic glycolysis ↑ Tumor growth ↑ | HIF-1α and VHL | The disruption of the VHL-HIF-1α interaction | Protein-Protein Interaction Decay (Stabilization of HIF-1α by disrupting the VHL-HIF-1α Interaction) | [85]  |
| linc-ROR     | Up-regulated        | N.D.            | Hepatoma, glioma                      | Apoptosis ↓ Cell proliferation and motility ↑ Autophagy ↑                               | N.D.                            | N.D.       | N.D.                                  | Unclear mechanism (lincRNA-p21 could promote autophagy of hypoxic tumor cells by up-regulating HIF-1α protein levels and suppressing Akt/mTOR/p70S6K signaling pathways) | [86]  |
| linc-HIFCAR (MIR31HG) | Up-regulated | HIF-1α dependent | Oral cancer                           | • Up-regulated in oral cancer                                                         | Hypoxic glycolysis ↑           | HIF-1α     | Activation of HIF-1 signaling          | Transcriptional regulation                                                           | [89]  |

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| lncRNA | Status upon hypoxia | HIF involvement | Cancer Types | Clinical association | Functional Impact | Interactor | Target/Effect | Mechanistic Classification | Refs |
|--------|---------------------|-----------------|--------------|----------------------|------------------|------------|--------------|---------------------------|------|
| IncRNA-AK058003 | Up-regulated | N.D. | Gastric cancer | Up-regulated in GC | A strong correlation between high EFNA3 expression and shorter metastasis-free survival in breast cancer patients | Cell extravasation ↑ | Metastatic dissemination ↑ | Epigenetic regulation ([90]) | |
| IncRNA-EFNA3 | Up-regulated | HIF-1α dependent (1 HRE identified) | Breast cancer | A strong correlation between high EFNA3 expression and shorter metastasis-free survival in breast cancer patients | Hypoxic cell proliferation ↑ | Sphere-forming ability ↑ | Sequestration of miRNAs ([91]) | |
| IncRNA-HAL (Inc-METTL16-2) | Up-regulated | HIF-1α dependent (3 putative HREs found) | Breast cancer | Up-regulated in triple negative breast cancer | Migration ↑ | Cancer stem cell phenotype ↑ | Unclear mechanism ([92]) | |
| IncRNA-LET (NPTN-IT1) | Down-regulated | HIF-1α dependent (Indirect: Histone deacetylation) | Lung squamous-cell cancer (LSCC), hepatocellular carcinoma (HCC) and colorectal cancer (CRC) | A strong correlation between hypoxia, histone acetylation disorder and metastasis in HCC | Metastasis ↓ | Hypoxic cell cycle progression↑ | mRNA stability control ([93]) | |
| IncRNA-SARCC (Inc-P2RY1-1) | VHL-dependent | HIF-2α dependent (1 HRE identified) | Renal cell carcinoma | Differentially regulated by hypoxia in a von Hippel-Lindau (VHL)-dependent manner in RCC clinical specimens | Hypoxic cell cycle progression (VHL-restored RCC cells) ↑ | Hypoxic cell cycle progression (VHL-mutant RCC cells) ↓ | Post-Translational modification ([94]) | |
| IncTCF7 (WSPAR) | Up-regulated | N.D. | Glioma | Up-regulated in glioma | Cell migration ↑ | Proliferation ↑ | Unclear mechanism ([95]) | |
| IncRNA | Status upon hypoxia | HIF involvement | Cancer Types | Clinical association | Functional Impact | Interactor | Target/Effect | Mechanistic Classification | Refs |
|--------|---------------------|-----------------|--------------|----------------------|-------------------|------------|--------------|--------------------------|------|
| MALAT1 | Up-regulated        | HIF-2α dependent & preference (1 HRE) | Hepatocellular carcinoma | N.D. | Cell growth ↑ | N.D. | N.D. | ↑ | Post-Translational modification (MALAT1 decreases hydroxylation of HIF-1α/HIF-2α, possibly through dissociation of the VHL protein from HIF-1α/HIF-2α) | [96, 97] |
|        | Up-regulated        | N.D.            | Lung adenocarcinoma | N.D. | Proliferation ↑, Migration ↑, Invasion ↑ | PTB-associated splicing factor (PSF) | GAG66 promoter | Transcriptional regulation (The physical interaction of MALAT1 and PSF released the binding of PSF to GAG66 promoter) | [98, 99] |
| MEAT3  | Up-regulated        | N.D.            | Hepatocellular carcinoma | N.D. | Proliferation ↑, Migration and invasion ↑, Apoptosis ↓ | | | Sequestration of miRNAs (Down-regulation of mir-200a) | [100] |
|        | Up-regulated        | N.D.            | Pheochromocytoma | N.D. | Hypoxia-induced PC12 cell injury ↑ | Methylation proteins (DNMT3a, DNMT3b, and MBD1) | TIMP2 promoter methylation | Epigenetic regulation (MEAT3 recruited methylation proteins DNMT3a, DNMT3b, and MBD1 and accelerated TIMP2 promoter methylation, which in turn inhibited its expression) | [101] |
| MTA2TR | Up-regulated        | HIF-1α dependent (1 HRE identified) | Pancreatic cancer (PC) | Upregulated in PC tissues | Cell proliferation ↑, Invasion ↑ | Activating transcription factor 3 (ATF3) | | Transcriptional regulation (MTA2TR transcriptionally upregulates MTA2 expression by recruiting ATF3 to the promoter area of MTA2) | [102] |
| NEAT1  | Up-regulated        | HIF-2α dependent | Non-small cell lung cancer (NSCLC) | • Up-regulated in NSCLC, • Associated with TNM stage and metastasis | Cell proliferation ↑, Migration and invasion ↑ | mir-101-3p | SOX9/Wnt/β-catenin signaling pathway | Sequestration of miRNAs (Down-regulation of mir-101-3p-mediated repression of SOX9/Wnt/β-catenin signaling pathway) | [103] |
|        | Up-regulated        | HIF-2α           | Breast cancer | High expression of NEAT | Proliferation ↑ | N.D. | N.D. | Complex scaffold | [12, |
| lncRNA         | Status upon hypoxia | HIF involvement            | Cancer Types                  | Clinical association                                                                 | Functional Impact                                                                 | Interactor         | Target/Effect                                                                 | Mechanistic Classification                                                                 | Refs  |
|---------------|---------------------|----------------------------|-------------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------|
| NDRG-OT1 (Inc-NDRG1-1) | Up-regulated         | N.D.                       | Breast cancer                 | N.D.                                                                                  | N.D.                                                                            | NDRG1 degradation | Apoptosis ↓                                                                   | (Induces paraspeckle formation, thereby enhancing cancer cell survival in hypoxia)           | 104-106 |
| NORAD         | Up-regulated         | N.D.                       | Pancreatic cancer (PC)         | Upregulated in PC                                                                   | Migration ↑                                                                      | miR-125a-3p       | The expression of RhoA                                                          | Post-Translational modification (NDRG-OT1 could promote NDRG1 degradation via ubiquitin-mediated proteolysis) | 107   |
| NUT2P3-001 (NUT2P3) | Up-regulated         | HIF-1α-dependent           | Pancreatic cancer (PC)         | Upregulated in pancreatic cancer                                                      | Cell viability, proliferation ↑, Invasion ↑, EMT ↑, Metastasis ↑                  | miR-3923           | The expression of KRAS                                                          | Sequestration of miRNAs (Down-regulation of miR-125a-3p-mediated repression of RhoA)          | 108   |
| PCGEM1        | Up-regulated         | N.D.                       | Gastric cancer (GC)            | Up-regulated in GC                                                                   | Invasion and metastasis ↑                                                       | N.D.               | N.D.                                                                            | Unclear mechanism (Partially through regulating SNAIL, a key transcription factor of EMT)   | 110   |
| PVT1          | N.D.                 | N.D.                       | Nasopharyngeal carcinoma (NPC) | Up-regulated in NPC, associated with a poor prognosis in NPC patients                | NPC cell proliferation ↑, Colony formation ↑, In vivo tumorigenesis ↑            | KAT2A (chromatin modification factor)                                             | Transcription of NF90 (RNA-binding protein)                                                   | 111   |
|               |                      | N.D.                       | Hepatocellular carcinoma (HCC) | Up-regulated in HCC tissues and cell lines                                           | Cell proliferation ↑, Migration ↑, Invasion and iron uptake ↑, Apoptosis ↓       | miR-150            | The expression of HIG2 (Hypoxia-inducible protein 2)                           | Sequestration of miRNAs (Down-regulation of miR-150-mediated repression of HIG2)               | 112   |
|               |                      | N.D.                       | Gastric cancer                 | Upregulated in GC                                                                   | GC cell                                                                         | miR-186            | The expression of miR150                                                         | Sequestration of miRNAs (Down-regulation of miR-150-mediated repression of HIG2)               | 113   |
| IncRNA               | Status upon hypoxia | HIF involvement | Cancer Types                          | Clinical association                                                                 | Functional Impact                  | Interactor target/Effect | Mechanistic Classification                      | Refs |
|---------------------|---------------------|-----------------|---------------------------------------|--------------------------------------------------------------------------------------|------------------------------------|---------------------------|-----------------------------------------------|-------|
| RERT-lncRNA (RAB4B-EGUN2) | N.D.                | N.D.            | Hepatocellular carcinoma (HCC)        | The expression levels of RERT-lncRNA and EGUN2 were significantly correlated in HCC   | N.D.                               | N.D.                      | Transcriptional regulation (RERT-lncRNA induces EGUN2/PHD1 expression at the transcriptional level) | [116] |
| UBE2CP3             | N.D.                | N.D.            | Hepatocellular carcinoma (HCC)        | • Up-regulated in HCC, especially in high EV (endothelial vessel) density tissues     | Proliferation ↑ Migration ↑ Tube formation ↑ | N.D.                      | Unclear mechanism (May partially through UBE2CP3-induced increase in the secretion of VEGFA into the supernatant via activation of the ERK/HIF-1α signaling pathway) | [117] |
| UCA1                | Up-regulated        | HIF-1α-dependent | Estrogen receptor (ER)-positive breast cancer | N.D.                                                                                | Tamoxifen resistance ↑ miR-18a The expression of HIF-1α | N.D.                      | Sequestration of miRNAs (Down-regulation of miR-18a-mediated repression of HIF-1α expression) | [118] |
|                     |                     |                 | Hypoxia-resistant gastric cancer (HRGC) | Upregulated in HRGC cells                                                              | Migration ↑ miR-7-5p The expression of EGFR | N.D.                      | Sequestration of miRNAs (Down-regulation of miR-7-5p-mediated repression of EGFR) | [119] |
| IncRNA | Status upon hypoxia | HIF involvement | Cancer Types | Clinical association | Functional Impact | Interactor | Target/Effect | Mechanistic Classification | Refs |
|--------|---------------------|----------------|--------------|---------------------|------------------|------------|--------------|--------------------------|------|
|        | Up-regulated        | N.D.           | Acute myeloid leukemia (AML) | Upregulated following ADR (adriamycin)-based chemotherapy | Cytotoxic effect of ADR | miR-125a | The expression of HK2 | Sequestration of miRNAs (Down-regulation of miR-125a-mediated repression of HK2) | [120] |
|        | Up-regulated        | HIF-1α dependent (2 HREs) | Bladder cancer | Upregulated in bladder cancer | Cell proliferation under hypoxia | N.D. | N.D. | Unclear mechanism (UCA1 could modulate the expression of several genes involved in tumorigenic potential, drug resistance and embryonic development) | [121, 122] |
|        | Up-regulated        | HIF-1α dependent (1 HRE identified) | Osteosarcoma | N.D. | Cell growth | N.D. | N.D. | Unclear mechanism (May partially through inactivating the PTEN/AKT signaling pathway) | [123] |
| WTI-AS | Up-regulated        | HIF-1 dependent (DNA demethylation of the CpG island) | Myeloid Leukemia | Upregulated in Wilms’ tumors | N.D. | N.D. | N.D. | Epigenetic regulation (WTI-AS mediates hypoxia-induced WT-1 mRNA upregulation through modulating histone methylation) | [124, 125] |
| ZEB2-AS1 | Up-regulated       | HIF-1α dependent (GC) | Gastric cancer | Upregulated in GC | Cell proliferation and growth | miR-143-5p | The expression of HIF-1α | Sequestration of miRNAs (Down-regulation of miR-143-5p-mediated repression of HIF-1α expression) | [126] |

Abbreviation: CRC colorectal cancer; CSC cancer stem cell; EMT epithelial–mesenchymal transition; GC Gastric cancer; HCC hepatocellular cancer; HRE hypoxia response element; HUVECs human umbilical vein endothelial cells; ICC Immunocytochemistry, LC lung cancer, M-GSCs Mesenchymal glioblastoma multiforme stem-like cells, N.D. Not determined, NSCLC non-small cell lung carcinoma, OSCC Oral squamous cell carcinoma, PDAC pancreatic ductal adenocarcinoma, RCC Renal Cell Carcinoma, RNP ribonucleic protein, TNM tumor, node, metastasis, VHL von Hippel-Lindau protein, WHO World Health Organization
may also have hypoxia-independent functions. For the sake of conciseness, those targets are not included in the table. In addition, some of these lncRNAs can be captured by exosomes and transmitted to tumor microenvironment to exert their functions and further propagate the hypoxic responses (Table 2). Notably, several HALs, such as UCA1, PVT1, H19 and MALAT1, might adapt more than one action mode in different cancer types. In the discussion below, we highlight the selected few HALs to illustrate their mechanisms of actions.

**HAL-mediated epigenetic and transcriptional regulation**

A large number of lncRNAs are localized in the nucleus, participating in various biological processes, including chromatin organization, nuclear structure, transcriptional and post-transcriptional regulation of gene expression. With regard to chromatin organization, the pangenomic investigations of RNA–protein interactions have shown that two hypoxia-inducible, oncogenic antisense RNAs ANRIL (also known as CDKN2B antisense RNA 1) and HOTAIR (HOX transcript antisense RNA) could interact with different histone-modifying complexes, and have thus been proposed to impact the chromatin modification and transcriptional state [138]. However, whether these two antisense RNAs are involved in modulating gene expression in response to hypoxia via epigenetic modification or chromatin reorganization remains to be characterized. In addition, WT1-AS could mediate hypoxia-induced upregulation of oncogenic transcription factor WT-1 in cis through modulating histone H3K4 and H3K9 methylation around the transcription start site of WT1 mRNA, contributing to acute myeloid leukemia (AML) progression [124]. Similarly, in gastric cancer, lncRNA-AK058003, which could be profoundly induced by hypoxia, resides upstream of SNCG (synuclein gamma, a synuclein family member, promotes migration, invasion and metastasis) and enhances SNCG expression in cis through demethylation of SNCG promoter CpG islands, thereby driving hypoxia-induced metastasis [90]. In the context of nasopharyngeal carcinoma (NPC), up-regulated PVT1 could serve as a scaffold for a transcriptional activator, the histone acetyltransferase KAT2A, to activate transcription of NF90. NF90, a RNA-binding protein, has been reported to stabilize many target mRNAs, including HIF1A mRNA. Indeed, the upregulated NF90 increased HIF1A mRNA stability and promoted malignant transformation of NPC cells [111]. In addition, in hypoxia-injured pheochromocytoma cells, up-regulated MEG3 (maternally expressed gene 3) could recruit methylation proteins DNMT3a, DNMT3b and MBD1 to facilitate TIMP2 promoter methylation, which in turn inhibited the expression of this cell cycle arrest inducer TIMP2. Moreover, a HIF-1α negative regulator, OS-9, is reported to facilitate HIF-1α hydroxylation and subsequent proteasomal degradation through tethering the interaction between HIF-1α and prolyl hydroxylases (PHDs) [139]. Interestingly, in pancreatic ductal adenocarcinoma (PDAC), another

### Table 2 | HALs identified extracellularly

| lncRNA | Extracellular space identified | Cell to Cell Transfer | Functional Impact | Mechanism | Ref |
|--------|--------------------------------|----------------------|-------------------|-----------|----|
| aHIF (HIF1A-AS2) | Serum (aHIF level in serum correlates with its expression in matched ectopic endometria) | Endometriotic cyst stromal cells (ECSCs)-derived exosomes to human umbilical vein endothelial cells (HUVECs) | Elicits proangiogenic behavior in HUVECs, thus facilitating endometriosis angiogenesis. | Activates VEGF-A, VEGF-D, and b-FG in HUVECs | [133] |
| CCAT2 | Exosomes secreted from cultured glioma cells | U87-MG glioma cells to HUVECs | Promotes HUVEC angiogenesis and inhibits apoptosis induced by hypoxia | Promotes VEGF-A, TGF-β and Bcl2 expression. Inhibits BAX and caspase 3 expression | [134] |
| H19L (LINC01146) | Extracellular vesicles secreted by tumor associated fibroblasts (TAMs) | TAMs to breast cancer cells | Enhances aerobic glycolysis and apoptotic resistance of cancer cells | Stabilizes HIF-1α | [135] |
| PVT1 | Exosomes secreted from cultured colon cancer cells. Cancer cells with more aggressive phenotypes have more extracellular PVT1 | Not determined | Promotes cell proliferation and inhibits apoptosis. | | [136] |
| linc-ROR | Exosomes secreted from cultured hepatocellular carcinoma cells | HCC cancer cells to cancer cells | Promotes cell survival of recipient cells | Through a miR-145–HIF-1α signaling module to increase HIF-1α expression | [87] |
| UCA1 | Exosomes secreted from cultured bladder cancer cells & serum | Bladder cancer 5637 cells with high expression of UCA1 to bladder cancer UMUC2 cells with low expression of UCA1 | Promotes cell proliferation, migration and invasion of recipient cells | Promotes xenograft growth | [137] |
In conclusion, IncRNA ENST00000480739 could inhibit HIF-1α by up-regulating OS9 (osteosarcoma amplified-9) expression through enhancing the acetylation of H3K27 within OS9 gene promoter [60]. Of note, in PDAC, the level of ENST00000480739 is markedly downregulated, and negatively correlated with lymph node metastasis, in agreement with its negative regulatory role in HIF-1 signaling [60]. As ENST00000480739 resides upstream of the OS9 promoter region, this IncRNA also act in cis to induce OS9 transcription.

Apart from chromatin structure remodeling, a series of HALs could modulate transcription and thereby fine-tune the HIF network. For instance, IncRNA HIF2PUII (HIF-2α promoter upstream transcript), RERT-lncRNA and hypoxia-inducible BC005927 are all found to act in cis to up-regulate neighboring protein-coding genes HIF2A (encodes HIF-2α), EGLN2 (encodes prolyl hydroxylase PHD1) and EPHB4 (encodes Ephrin type-B receptor 4, a metastasis-related gene), at the transcriptional level, respectively [51, 76, 116].

Moreover, HALs could directly act on specific transcription factors through physical interactions to modulate their transactivation activities. We recently identified a hypoxia-inducible IncRNA LncHIFCAR (long noncoding HIF-1α co-activating RNA, also known as MIR31HG) acting as a HIF-1α co-activator via direct interaction with HIF-1α, thereby enhancing the binding of HIF-1α and cofactor p300 to the target loci (Fig. 1b). As the abundance of the HIF complex increases, the hypoxia-induced HIF-1 signaling cascade is augmented to further promote subsequent cancer progression [89]. Meanwhile, in pancreatic cancer, HIF-1α-induced IncRNA-MTA2TR (MTA2 transcriptional regulator RNA) transcriptionally up-regulates the expression of oncogenic MTA2 (metastasis associated protein 2) by recruiting ATF3 (activating transcription factor 3) to the promoter area of MTA2 [102]. Subsequently, MTA2 can enhance the accumulation of HIF-1α protein via MTA2-mediated HIF-1α deacetylation and stabilization, which further activates HIF-1α transcriptional activity, forming feedback loops to augment HIF-1 signaling [102] (Fig. 1c).

In addition, through binding to PSF (PTB-associated splicing factor), hypoxia-induced IncRNA MALAT1 released PSF from its downstream proto-oncogene GAGE6 (proto-oncogene G antigen 6) and activated its transcription, thereby promoting proliferation, migration and invasion of lung adenocarcinoma cells [98, 99]. Given the extraordinary variety of transcriptional regulatory machinery discovered in the cell, it is anticipated that more IncRNAs-mediated regulation on hypoxia-induced transcriptional program will be unraveled in the imminent future.

**HAL-mediated post-transcriptional control**

HALs also participate in post-transcriptional regulation including mRNA stability and miRNA-mediated gene silencing.

**mRNA stability control** Three HALs, lncRNA-LET (Long noncoding RNA Low Expression in Tumor), DANCR (Differential Antagonizing Non-Protein Coding RNA) and HIF1A-AS2 (HIF1A Antisense RNA 2; also known as aHIF), have all been reported to affect HIF1A mRNA stability. lncRNA-LET expression is generally suppressed in various types of tumors, whereas hypoxia-induced HDAC3 (histone deacetylase 3) could repress its expression by reducing the histone acetylation of the lncRNA-LET promoter region [93, 140]. Mechanistically, lncRNA-LET is bound to NF90 (nuclear factor 90), which increases NF90 degradation by the proteasome. As RNA binding protein NF90 could stabilize HIF1A mRNA [93, 141], the downregulation of lncRNA-LET upon hypoxia plays a key role in the stabilization of NF90 protein, thereby increasing HIF-1α mRNA stability upon hypoxia and accordingly hypoxia-induced cancer cell invasion [93] (Fig. 1d). Likewise, in nasopharyngeal carcinoma, another oncogenic IncRNA DANCR was up-regulated and associated with lymph node metastasis and poor survival [57]. Through interaction with the NF90/NF45 complex, DANCR could increase HIF1A mRNA stability, leading to metastasis and disease progression.

In addition, another hypoxia-inducible antisense IncRNA HIFIA-AS2, was shown to be up-regulated in various tumors [42, 43, 46, 142, 143] and could differentially regulate HIF-1α and HIF-2α expression during long-term hypoxic conditions [43, 47]. Upon acute hypoxia, HIF-1α and HIF-2α were similarly induced. Interestingly, during prolonged hypoxia, these two proteins were differentially regulated as HIF-1α protein level gradually decreased due to a reduction in its mRNA stability, whereas HIF-2α protein remained upregulated. Meanwhile, long-term hypoxia also induced an increase in HIFIA-AS2, whose gene promoter harbors functional HREs. During prolonged hypoxia, HIF1A-AS2 could bind to its sense counterpart, the HIF-1α mRNA 3’-UTR, and possibly expose the AU-rich elements in this region, thereby destabilizing HIF-1α mRNA to convey target gene specificity [43, 47]. Paradoxically, HIF1A-AS2 was also shown to sequester miR153-3p (see next section) to enhance HIF-1α expression [44]. Thus, the mode of action of HIF1A-AS2 is complex and likely context-dependent.

**miRNA sponges** A wealth of IncRNAs adapt a well-characterized, common mechanism, “ceRNA (competing endogenous RNA)” or “RNA sponges”, to repress miRNA-mediated gene silencing. The ceRNAs compete...
for shared miRNAs, sequester these miRNAs and diminish their silencing effect on target mRNAs.

Functional manipulations have demonstrated that several HALs, such as lincRNA-ROR [87], PVT1 [113, 114], HIF1A-AS2 [44], UCA1 [118], HOXATIR [79], FEZF1-AS1 [63], ZEB2-AS1 [126] and H19 [66], could act as a ‘ceRNA’ to reduce individual specific miRNA-mediated HIF1A mRNA destabilization and thereby restoring HIF-1α levels and consequently promote cancer progression (Table 1). Specifically, in breast cancer stem cells, by absorbing endogenous miRNA let-7 and aborting let-7-mediated HIF1A mRNA suppression, hypoxia-induced H19 could stimulate HIF-1α expression [66] (Fig. 1e). In addition, in glioblastoma, hypoxia-induced H19 up-regulation has been shown to confer an aggressive behavior by sequestering miR-181d and nullifying its suppression on an oncogenic EMT-associated factor, β-catenin [68].

In a similar way, certain HALs could act as a ceRNA to modulate other hypoxia-responsive regulators than HIF-1α. In gastric cancer, GAPLINC (Gastric Adenocarcinoma Associated, Positive CD44 Regulator, Long Intergenic Non-Coding RNA) is a HIF-1α direct, transcriptional downstream target, and could promote invasive tumor progression [64]. Mechanistically, GAPLINC could serve as a decoy for miR-211-3p to restore the levels of cancer stem cell marker CD44, enhancing tumor progression [65]. Aside from GAPLINC, NORAD [108], UCA1 [119, 120], HOTTIP [82], EIF3J-AS1 [59], MALAT1 [100], FAM201A [62], AGAP2-AS1 [49], LINC01436 [84], NEAT1 [103], NUTF2P3 [109] IncRNAs were shown to function in this way (Table 1). Collectively, in response to hypoxia, the crosstalk among the IncRNA and miRNA transcriptomes build a reciprocal repression feedback network, eliciting concordant shift to transcriptional reprogram. Further exploration of this pertinent co-working group of IncRNAs and miRNAs under hypoxic conditions would help appreciate this emerging additional layer of post-transcriptional regulation governed by HALs.

**HAL-mediated control of protein activity, stability and/or higher-order complex formation**

In addition to acting as ceRNAs to modulate gene expression through interaction with miRNAs, HALs have multiple molecular modes to act at the protein level to further modulate gene expression. One of the hypoxia-induced IncRNAs, PVT1 (plasmacytoma variant translocation 1), was implicated in cervical cancer progression, likely through its interaction with a multifunctional shuttling protein, nucleolin [115]. In multiple cancer cell lines, HIF-1-induced lincRNA-p21 provides another example as to how HALs modulate hypoxia response by protein sequestration. Through separate binding to HIF-1α and VHL, lincRNA-p21 could increase HIF-1α accumulation by disruption of the VHL/HIF-1α interaction and subsequent attenuation of VHL-mediated HIF-1α ubiquitination and degradation [85] (Fig. 1f). Another HIF-1α binding IncRNA CASC9 (cancer susceptibility candidate 9) is highly expressed in nasopharyngeal carcinoma (NPC) tissues. CASC9 could interact with and stabilize HIF-1α, promoting the glycolysis and tumorigenesis of NPC cells [53].

Nevertheless, in addition to fine-tuning the activity of one single protein, HALs can also dynamically modulate higher-order protein organizations by serving as scaffolds or molecular decoys. In mesenchymal glioblastoma stem-like cells, through direct binding to two RNA binding proteins, DHX9 (ATP-dependent RNA helicase A) and IGF2BP2 (insulin-like growth factor 2 mRNA-binding protein 2), IncRNA HIF1A-AS2 could facilitate the interaction between this protein complex and their mRNA target HMGAI (high mobility group AT-hook 1), thereby enhancing HMGAI expression as well as the downstream molecular response to hypoxic stress [46, 47].

In triple-negative breast cancer (TNBC), LINK-A (long intergenic non-coding RNA for kinase activation) has a critical role in the growth factor-induced HIF-1α signaling under normoxic conditions [88]. LINK-A is required for the recruitment of BRK (breast tumor kinase) and subsequent enzymatic activation, which is stimulated by HB-EGF (Heparin-binding EGF-like growth factor) signal. HB-EGF mediates the heterodimerization of EGFR (epidermal growth factor receptor) and GPNNMB (transmembrane glycoprotein NMB) to form 'EGFR-GPNNMB' complex. Due to its direct interaction with BRK and LRRK2 (leucine-rich repeat kinase 2), LINK-A could recruit these two kinases to EGFR-GPNNMB heterodimer, thereby inducing their kinase activities, resulting in HIF-1α phosphorylation: BRK-mediated HIF-1α phosphorylation at Tyr565, a phosphorylation preventing the adjacent Pro564 hydroxylation of HIF-1α and subsequent HIF-1α degradation under normoxic conditions; and LRRK2-mediated HIF-1α phosphorylation at Ser797, which facilitates the interaction of HIF-1α with the transcriptional cofactor p300 [88] (Fig. 1g). In TNBC samples, both LINK-A abundance and HIF-1 signaling activation are correlated with cancer progression and shorter survival, revealing potential therapeutic targets for TNBC [88].

An additional novel function of IncRNAs is their structural role in the assembly of nuclear domains. For instance, MALAT1 (metastasis-associated lung adenocarcinoma transcript 1, also known as NEAT2) and NEAT1 (nuclear enriched abundant transcript 1) are located in two well-characterized nuclear bodies, nuclear speckles and paraspeckles, respectively. Also known as SC35 splicing domains, nuclear speckles are membrane-less.
compartments and their formation involves “phase-separation” mediated by aggregated lncRNAs and proteins. Being an abundant component of the nuclear speckles, MALAT1 associates with numerous splicing factors and other SR (serine/arginine-rich) proteins, and is required for their correct localization to the nuclear speckles, although the overall nuclear speckle assembly is not dependent on the abundance of MALAT1 [144, 145]. So far, the functional involvement of MALAT1 in RNA splicing in response to hypoxia remains to be determined. In contrast, lncRNA NEAT1 is shown to be an essential architectural component of nuclear paraspeckles [144, 145]. The precise function of paraspeckles remains largely elusive, but proposed to regulate gene expression via the retention of hyper-edited RNA and other multifunctional factors in the nucleus [104]. Given the functional involvement of both MALAT1 and NEAT1 in nuclear structure, further investigation of the extent to which these nuclear structures and their associated transcription reprogramming respond to hypoxia will deepen our understanding of the cellular dynamic response to hypoxia.

**HAL-mediated control of hypoxia response via unclear mechanism**

As listed in Table 1, most of the HALs identified with profound impact on tumorigenesis have not yet been examined in mechanistic detail. However, other reports regarding the same lncRNA with functional characterization might reveal clues about their biological roles in response to hypoxia. For instance, lncRNA PCGEM1 was found to be overexpressed in gastric cancer, and could be induced by hypoxia [110]. In gastric cancer cells, PCGEM1 could promote the invasion and metastasis through activating the expression of SNAI1, a key transcription factor of EMT, though the underlying mechanism remains elusive [110]. Notably, in prostate cancer, our group previously reported that the oncogenic PCGEM1 could promote chromatin recruitment of c-Myc and enhances its transactivation activity through direct physical interaction [146]. As SNAI1 is a well-characterized downstream gene of c-Myc, the possible functional role of the PCGEM1/c-Myc/SNAI1 signaling axis in hypoxia-associated cancer progression warrants further investigation.

In summary, as noted in the above sections, given the relatively large size and the structural flexibility of lncRNAs, it is to be expected that they interact with multiple RNA or protein components and have multifunctions, perhaps in a context-dependent manner. As such, their roles in hypoxia responses and in tumor progression may differ appreciably in different cancer types.

**LncRNAs as predictive biomarkers and therapeutic targets for hypoxic tumor**

**Extracellular vesicles-containing HALs and their biologic effects on tumorigenesis**

Extracellular vesicles are effective devices for transporting biomolecules among various cells types [147, 148]. Based on the difference in size and biogenesis, cell-derived extracellular vesicles can be broadly divided into two main categories: exosomes (30–100 nm in diameter) and microvesicles. Together with proteins and other non-coding RNAs, emerging evidence has shown that lncRNAs are packaged into exosomes [149, 150], and the abundance of lncRNAs in exosomes correlates with their expression level in the cell of origin [151]. Through exosomal transfer, several lncRNAs are shown to potentiate cell responses to hypoxia between cancer cells and normal cells [87], as well as between cancer cell and the associated microenvironment [150]. Table 2 summarizes hypoxia-associated lncRNAs identified extracellularly. For example, linc-ROR was found abundant in tumor cells as well as in exosomes derived from tumor cells [87]. It is increased both in cells or exosomes during hypoxia, and it up-regulates HIF-1α expression by absorbing miR-145. By co-culture systems, linc-ROR-containing exosomes increase HIF-1α transcription in recipient cells [87]. Hypoxia can shape and fine tune specific macrophage phenotypes in the tumor milieu that are known to promote tumor progression [152]. Chen et al found lncRNA HISLA (also known as LINC01146), secreted by tumor-associated macrophages, stabilized HIF-1α and enhanced aerobic glycolysis in cancer cells, leading to contagious metabolic reprogramming within tumor regions [150]. PVT1, a lncRNA that often co-amplifies with c-myc and functions as miRNA sponge to upregulate HIF-1α expression [153, 154], is another example of exosomal transfer between TAMs (tumor associated macrophages) and cancer cells. PVT1 is detected in exosomes derived from colon cancer cells, particularly in more aggressive cells [136]. In granulocytic myeloid-derived suppressor cells (G-MDSCs), PVT1 was up-regulated by HIF-1α under hypoxia and contributed to immunosuppression, given its depletion reduced the suppression of these cells on T-cells and delayed tumor progression [155]. Other exosomal transferred lncRNAs that are implicated in cancer cells during hypoxia include UCA1 in bladder cancer for promoting tumor growth and EMT [137], and CCAAT2 for glioma’s resistance to apoptosis and angiogenesis [134].

The functions of lncRNAs in exosomes for tumor progression await to be explored given a significant level of non-coding RNAs are revealed in exosomes (and elevated upon hypoxia) whereas only a small fraction has been studied [149, 150, 156]. Accordingly, it is conceivable that multiple tumor phenotypes and signaling
pathways are affected upon exosomal loading. Indeed, by microarray analyses, Mao et al showed hundreds of lncRNAs, together with other transcripts, are changed in endothelial cell recipients of exosomes derived from squamous cancer cells [157]. Importantly, they found exosomes obtained from hypoxic condition facilitate angiogenesis and metastasis better than those obtained from normoxic condition in a xenograft model. Similar effects between normoxic exosomes and hypoxic exosomes on angiogenesis were found in a mouse xenograft model of glioblastoma, with additional effect on accelerating tumor expansion at later stage [158]. The elevation in transcripts by exosomes could result from direct gene transfer, or sequential effects mediated by the transferred genes. By which mechanism lncRNAs are selected to be packaged in the exosomes upon stimuli is not known; nevertheless, these studies revealed exosomes as a means by which hypoxia in the tumor microenvironment facilitates tumor cells to spread and progress.

**Diagnostic potential of HALs**

Several HALs with known oncogenic functions have been detected in patient-derived exosomes, including H19 in serum from patients with bladder cancer [159], HOTAIR in urinary exosomes from patients with urothelial bladder cancer [156], UCA1 in serum from bladder cancer patients [137], and HIF1A-AS2 in patients with endometriosis [133]. Future studies aimed at identifying hypoxia-responsive transcripts in extracellular vesicles would surely reveal more players in this aspect. Bearing differential expression patterns between normal and malignant stages and/or tumor size, oncogenic lncRNAs that can be detected extracellularly would potentially serve as non-invasive biomarkers for early detection, prognosis prediction, and disease surveillance. PCA3, up-regulated in > 90% of men with prostate cancer, is an example of this [160]. A urine-based assay has been approved by the United States Food and Drug Administration (FDA) since 2012 as an alternative diagnostic test for patients undergoing repeat prostate biopsy or with previous negative prostate biopsy.

As described above, there is considerable evidence indicating hypoxia as a progression factor for tumor development [161]. Hypoxia promotes angiogenesis, tumor metastasis, immune evasion and therapy-resistance. The oxygenation status of tumor was reported to influence local tumor response to radiation treatment, as well as overall survival in a variety of tumors [162–164]. Chemotherapeutic drugs, such as Docetaxel and Sorafenib, also tend to be more effective in normoxic conditions [165, 166]. The hypoxic regions in tumors are infiltrated with cells which promote tumor tolerance (regulatory T-cells, myeloid-derived suppressor cells, and macrophages), while antitumor T-cells are devoid and inhibited by HIF-1α-mediated accumulation of extracellular adenosine [167–169]. PD-L1 (Programmed death-ligand 1), a ligand expressed by tumor cells or myeloid-derived suppressor cells to suppress T-cell’s anti-tumor immunity, is up-regulated by and a direct target of HIF-1α during hypoxia [170]. It has become increasingly apparent that hypoxia in tumors fosters immune suppression and prevents effective immunotherapy. Considering the ill-effects of hypoxia, it is important to detect and to overcome tumor hypoxia even before therapy starts, for the best of patient care.

By far, while there has been a great deal of interest in methodologies to measure hypoxia in patients, an efficient, non-invasive, while sensitive method to detect small regions of hypoxia that frequently occur in the tumors is still lacking [163]. A few metabolic markers (HIF-1α, HIF-2, CA9 and GLUT1) have been used to assess low oxygen tensions by immunohistochemistry [171, 172]; however, the application of them in clinic is limited given that their expressions can be triggered by factors other than hypoxia and that biopsies only represent a small sampling of the tumor. As exosome composition mirrors the hypoxia status of tumors [158], a hypoxia signature may be formulated based on the exosomal hypoxia-responsive transcripts including HALs to evaluate oxygenation in the body for clinical exploitation, once our knowledge is advanced.

**Therapeutic potential of HALs (targeting hypoxia in cancer therapy, a lncRNA perspective)**

Several approaches have been proposed to target hypoxia in tumor [161, 163]. These include drugs that induce cell death selectively in hypoxic cells, e.g. hypoxia-activated prodrugs, or drugs sensitizing hypoxic cells to radiation. Since the adaptive response to hypoxia mainly orient from the transactivation of HIF signaling, some approaches seek to block hypoxia-induced responses by targeting HIFs and the related signaling, or to target pathways that also play pivotal roles in hypoxia adaptation, such as signaling involving mTOR, DNA damage response, and the unfolded protein response. In that regard, HALs that are elevated upon hypoxia and contribute to tumor progression in pre-clinical studies could potentially serve as molecular targets, e.g. PVT, LncHIFCAR, etc. (see Table 1) [41]. By contrast, HALs that are repressed in order to magnify hypoxia response, such as LncRNA-LET, could be induced for therapeutic intervention.

Various strategies have been developed to modulate RNAs. Silencing lncRNAs by small interfering RNAs, antisense oligonucleotides (ASOs), or ribozymes and deoxyribonucleotides are well demonstrated in pre-clinical studies. Until now, three ASOs and one aptamer therapies have been approved by the FDA for diseases and a handful of others are in clinical trials. The development of short oligonucleotides that fold into three-dimensional structures,
aptamers, offers a greater specificity as they target specific structure regions to either mediate RNA degradation or disrupt functional interactions between binding partners [173]. Small molecules that bind to lncRNA and hinder its interaction surface have similar advantages. Additionally, peptide nucleic acids (PNA)-based approach against lncRNAs have been described. HOTAI R-targeting PNA conjugated with pH-low insertion peptide (pHLIP) successfully delivered the anti-lncRNA to the acidic tumor. It blocked the interaction between HOT AI R and EZH2, subsequently inhibited HOTAI R-EZH2 activity and re-sensitized resistant ovarian tumors to platinum [174].

In any case, an issue all hypoxia-based therapeutics need to consider is the poorly perfused tissue in tumors. In response to their rapid growth, tumor cells secret pro-angiogenic factors such as VEGF to induce vascular formation, yet the constant stimulation leaves tumor vasculature ill-formed and leaky [175]. Simultaneous blockade of HIFs and pro-angiogenic factors has been proposed for targeting tumor hypoxia, in that targeting the angiogenic factors may allow vasculature to mature, resulting more effective blood supply and drug delivery. Another strategy is to relieve oxygen demand by drugs that alleviates oxygen tension in tumors. Papaverine, an FDA-approved drug as a smooth muscle relaxant, was found to inhibit mitochondria complex I and enhance the response to radiotherapy, while well-oxygenated normal tissues were not sensitized [176]. Accordingly, lncRNAs that regulate mitochondria respiration may be considered for targeting tumor hypoxia as an adjuvant treatment.

Conclusion and future perspectives

Decades of intensive scientific research on hypoxia and HIF biology has greatly contributed to our understanding of oxygen homeostasis. Over the past few years, a substantial increase in our knowledge of the noncoding transcriptomes, while putting on an additional layer of complexity in hypoxia regulation and responses, has advanced our comprehension of hypoxic biology. This review has presented an update of our current insights regarding lncRNAs involved in hypoxia-associated processes, highlighting the diverse mechanisms and functions of hypoxia-associated lncRNAs (HALs). These novel action modes unveil the un-anticipated predominance of HALs in the regulation of gene expression under hypoxic conditions and outline the elaborate network among the different types of RNA transcripts, chromatin DNA and protein factors. However, advancement in analytical methodologies and in structural and genomic technologies of RNA are required to open up new important directions for in-depth investigation. For the state-of-the-art methodologies to unveil the functions of lncRNAs, readers are directed to two excellent recent reviews [177, 178], as well as those in this special issue.

The role of HIF in hypoxia responses has been the central topic of most investigations. Indeed, HIF has been shown to be a central regulator of the coding and non-coding transcriptome and tightly associated with cancer risk [12, 179–181]. Most HALs, in particular, are highly responsive to hypoxia and HIF and, in turn, participate in the regulation of the protein-coding genome either in cis or in trans to offer multiple routes to HIF-mediated gene regulation, implementing both positive and negative feedback loops that either strengthen or repress the hypoxia response. Most notably, the extracellular vesicles-containing HALs could evoke peculiar response to specific cell population, affecting nearby cells and those at a great distance, diversifying the hypoxia response far beyond the previously recognized. The cellular adaptation to hypoxia requires the precisely coordinated regulatory network to cope with the acute, transient and dynamic oxygen deprivation stress in local regions, whereas lncRNAs, with their flexible structure for interaction and quick biogenesis nature, could be uniquely suited to provide rapid, precise and reversible responses to this insult. It is clear that HALs and their downstream targets are shown to confer a series of biological effective responses to hypoxia. Feasibly, this extensive molecular crosstalk between lncRNA and hypoxic signaling cascades may undergo co-evolution to maintain such an exquisite, orchestrated program.

Thus, for a comprehensive understanding of hypoxia-associated tumor biology, it is of relevance to characterize the long non-coding transcriptome involved in hypoxia adaptation.

Given the prominent pathological roles of HALs in hypoxia-associated cancer progression, these RNAs could be exploited as useful indicators to define the cancer intrinsic subtypes to aid in precision medicine. Importantly, HALs are often tissue specific and respond to hypoxia in a cell context dependent manner. As such, they are excellent markers for tissue and tumor hypoxia responses. Compared with other bio-molecules, lncRNAs are ideal biomarkers that provide specificity, stability, sensitivity and easy accessibility [38]. Most notably, cell-free lncRNAs or those packed in extracellular vesicles can be detectable in various body fluids [182]. Hence, the genome-wide annotation of tissue-specific HAL signatures could guide development of promising, non-invasive biomarkers for early diagnosis, prognosis and prediction. Although most lncRNA-targeted treatments are still in their infancy stages, the recent success in RNA-based therapeutics holds promises for future technical innovations. With in-depth characterization of the interplay among hypoxia microenvironment and lncRNA function, more HALs could surely accelerate the design of therapeutics for tumor patients, enabling the targeting of the previously undruggable transcriptome in the near future.
Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s12929-020-00654-x.

Additional file 1: Table S1. Hypoxia-associated IncRNAs.

Abbreviations
ASO: Antisense oligonucleotide; bHLH-PAS: Basic helix-loop-helix DNA binding proteins of the PER-ARNT-SIM family; BRK: Breast tumor kinase; ceRNA: competitive endogenous RNA; CRC: Colorectal cancer; CSC: Cancer stem cell; DHX9: ATP-dependent RNA helicase A; EGFR: Epidermal growth factor receptor; EMT: Epithelial-mesenchymal transition; FDA: Food and Drug Administration; GC: Gastric cancer; G-MDSCs: Granulocytic myeloid-derived suppressor cells; GPNMB: Transmembrane glycoprotein NMB; GSC: Glioblastoma stem-like cells; HB-EGF: Heparin-binding EGF; HCC: Hepatocellular cancer; HMGA1: High mobility group AT-hook 1; HAL: Hypoxia-associated IncRNAs; HUVECs: Human umbilical vein endothelial cells; IgG2BP2: Insulin-like growth factor 2 mRNA-binding protein 2; LC: Lung cancer; IncRNA: long non-coding RNA; LRKK2: Leucine-rich repeat kinase 2; M-GSCs: Mesenchymal glioblastoma multiforme stem-like cells; ncRNA: non-coding RNA; N.D.: Not determined; NF90: Nuclear factor 90; NSCLC: Non-small cell lung carcinoma; OGT: O-linked N-acetylglucosamine transferase; OS-9: Osteosarcoma amplified-9; OGT: Ornithine decarboxylase; RCC: Renal cell Carcinoma; SNCG: Synuclein gamma; TNBC: Triple-negative breast cancer; UTR: Untranslated region; VEGF: Vascular endothelial growth factor; VHL: Von Hippel-Lindau protein

Acknowledgements
None.

Authors’ contributions
TCK, JWS and HJK wrote the manuscript. All authors read and approved the final manuscript.

Funding
This work was financially supported by the “TMU Research Center of Cancer Translational Medicine” from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan (to JWS and HJK). It is also supported by grants MOST108-2321-B-010-013-MY2, MOST108-2320-B-038-011 and MOST107-2320-B-038-055-MY3 from Ministry of Science and Technology of Taiwan (to HJK); TMU106-AE1-B52 from Taipei Medical University and MOST107-2320-B-038-009-MY2 from Ministry of Science and Technology of Taiwan (to TCK). TCK was supported by an independent research scholar grant from Ministry of Science and Technology of Taiwan (MOST 105-2321-B-400-011-MY3), and is indebted to Ting-Feng Tsai (National Yang-Ming University) for her support after the end of the grant.

Availability of data and materials
Not Applicable.

Ethics approval and consent to participate
Not Applicable.

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 27 February 2020 Accepted: 22 April 2020

Published online: 05 May 2020

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