ANTIOXIDANTS & REDOX SIGNALING
Volume 29, Number 9, 2018
Mary Ann Liebert, Inc.
DOI: 10.1089/ars.2017.7293

FORUM REVIEW ARTICLE

The Many Faces of Long Noncoding RNAs in Cancer

Xue Wu,[1,2] Oana M. Tudoran,[1,3] George A. Calin,[4,5] and Mircea Ivan[1,2]

Abstract

Significance: The emerging connections between an increasing number of long noncoding RNAs (lncRNAs) and oncogenic hallmarks provide a new twist to tumor complexity.
Recent Advances: In the present review, we highlight specific lncRNAs that have been studied in relation to tumorigenesis, either as participants in the neoplastic process or as markers of pathway activity or drug response. These transcripts are typically deregulated by oncogenic or tumor-suppressing signals or respond to microenvironmental conditions such as hypoxia.
Critical Issues: Among these transcripts are lncRNAs sufficiently divergent between mouse and human genomes that may contribute to biological differences between species.
Future Directions: From a translational standpoint, knowledge about primate-specific lncRNAs may help explain the reason behind the failure to reproduce the results from mouse cancer models in human cell-based systems. *Antioxid. Redox Signal.* 29, 922–935.

Keywords: cancer, non-coding RNA, metabolism, hypoxia, microenvironment

Introduction

Since the declaration of War on Cancer in 1971, increased efforts have been focused on characterizing the cellular and molecular changes associated with tumor progression and therapeutic response. Six key hallmarks have been highlighted to describe the mechanisms through which tumor cells proliferate, invade, and metastasize (39), and new emerging hallmarks are added as knowledge advances (40). Nevertheless, despite the progress in understanding the genetic programming of tumor cells, the overall decrease in mortality remains relatively modest. A major reason for therapeutic failure is tumor heterogeneity: advanced tumors being in fact a collection of dynamic subpopulations with different mutation spectra and vulnerabilities. Second, increasingly detailed molecular dissection of tumor-driving signals has revealed additional layers of complexity, with special attention being drawn by the expanding world of noncoding RNAs.

Over the past two decades, these cellular RNAs that translated into proteins have been gradually implicated in virtually all physiological, developmental, and disease processes, including cancer (6, 9, 25, 29, 57, 62). According to the classic dogma, RNA transcripts simply served as templates for protein synthesis (22), which led to decades of protein-centered research. However, successive waves of discovery identified multiple categories of functional noncoding transcripts, beginning with heterogeneous nuclear RNAs (45, 113), followed by introns (4, 5, 20), small nuclear RNAs (37, 38, 63, 81, 102), microRNAs (miRNAs) (61), and long noncoding RNAs (lncRNAs) (10). While the study of miRNAs dominated the first decade of the noncoding RNA revolution, in recent years, lncRNAs—generically defined as noncoding transcripts longer than 200 ribonucleotides—have moved to center stage.

The completion of human genome project and the parallel progress in RNA sequencing technology have been instrumental for identification of thousands of lncRNA transcripts (14, 17, 55, 97). In the latest Human GENCODE release (version 26, October 2016, GRCh38, Ensembl 88), 15,787 genes originating 27,720 RNA locus transcripts are identified as lncRNA genes. While the genome size tends to increase

Departments of [1]Medicine and [2]Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, Indiana.
[3]Department of Functional Genomics and Experimental Pathology, The Oncology Institute "Prof. Dr. I. Chiricuta," Cluj-Napoca, Romania.
[4]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas.
[5]Center for RNA Interference and Non-Coding RNA, The University of Texas MD Anderson Cancer Center, Houston, Texas.

during metazoan evolution toward increasingly complex life forms, the number of protein coding genes has remained relatively steady (105). In contrast, the number of noncoding elements, including lncRNAs, appears to have increased dramatically. As the term lncRNA is a generic designation based on size, additional classifications are required when dissecting their biological roles. A popular categorization is based on their genomic contexts (Fig. 1): (i) promoter-associated lncRNAs (Fig. 1a) (*e.g.*, promoter of *CDKN1A* antisense DNA damage-activated RNA); (ii) enhancer-associated lncRNAs (Fig. 1b) (*e.g.*, *Evf2*); (iii) natural antisense transcripts (NATs, Fig. 1c) (*e.g.*, hypoxia-inducible factor 1 alpha antisense 2 [*HIF1A-AS2*]); (iv) gene body-associated (sense) lncRNAs (Fig.1d) (*e.g.*, CCAAT/enhancer binding protein alpha - ecCEBPA); and (v) long intergenic ncRNAs (lincRNAs, Fig. 1e) (*e.g.*, *HOX* transcript antisense RNA [*HOTAIR*], metastasis-associated lung adenocarcinoma transcript 1 [*MALAT1*]) (8, 101).

From a cancer perspective, the ever-increasing number of connections between lncRNAs and oncogenic hallmarks adds a new twist to tumor complexity. lncRNAs tend to be less conserved during evolution and their expression exhibits higher tissue specificity compared with PCGs. Therefore, detailed knowledge about cancer-associated lncRNAs may explain some differences between neoplastic cells derived from different tissues or different species.

Despite the fundamental difference with respect to protein coding ability, lncRNAs exhibit important similarities with PCGs, including chromatin marks at their promoters or enhancers (35). Furthermore, lncRNA genes are also transcribed by RNA polymerase II, spliced at canonical splicing sites, and some undergo polyadenylation (93). Similarly to coding genes, lncRNAs are regulated, positively and negatively, by complexes of transcription factors, coregulators and corepressors, from proximal promoters or enhancers. It is predictable therefore that transcription factors that drive proliferation and survival programs in normal or tumor cells also engage lncRNAs that regulate specific aspects of tumor biology.

In addition to cell-autonomous regulatory mechanisms, the tumor microenvironment has a significant impact in shaping the lncRNA landscape. The combination of stress factors, including oxygen and nutrient depletion, favors the selection of populations with increased ability to survive by rewiring their molecular networks, including metabolism, apoptotic responses, and proliferative programs. As discussed below, it is predictable that tumor microenvironment-regulated lncRNAs should impact this set of basic cell responses.

How can a ribonucleotide stretch affect the survival and proliferation of a neoplastic cell? lncRNAs have been shown to regulate gene expression at multiple levels (epigenetic, transcriptional, and post-transcriptional) through interaction with other biomolecules, such as proteins, regulatory DNA regions, and miRNAs (Fig. 2). Subcellular localization appears to be a major determinant for lncRNA interactions and therefore functions. In particular, nuclear lncRNAs modulate gene expression in *cis* or *trans* by interacting with transcriptional coregulators and chromatin remodeling complexes. As shown by Rinn and colleagues, ~20% lncRNAs associate with the polycomb repressive complex 2 (PRC2), a multicomponent histone methyltransferase required for epigenetic silencing (56). A classic example is provided by *HOTAIR*, shown to reprogram PRC2 and LSD1-CoREST (lysine-specific demethylase 1 and REST corepressor 1 complex) occupancy within the homeobox D cluster (34, 108). Subsequent studies, however, indicated

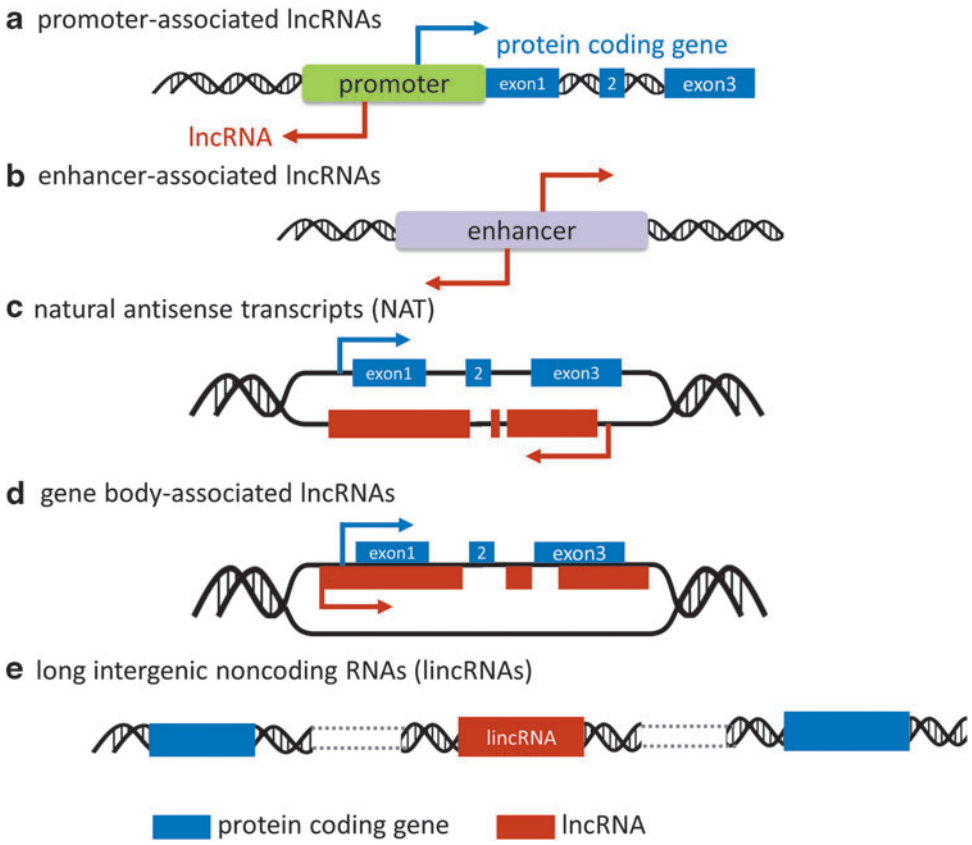

FIG. 1. lncRNA classification. Based on genomic context, lncRNA can be classified into five categories: **(a)** promoter-associated lncRNAs, **(b)** enhancer-associated lncRNAs, **(c)** natural antisense transcript, **(d)** gene body-associated lncRNAs, and **(e)** intergenic lncRNAs. lncRNA, long noncoding RNA.

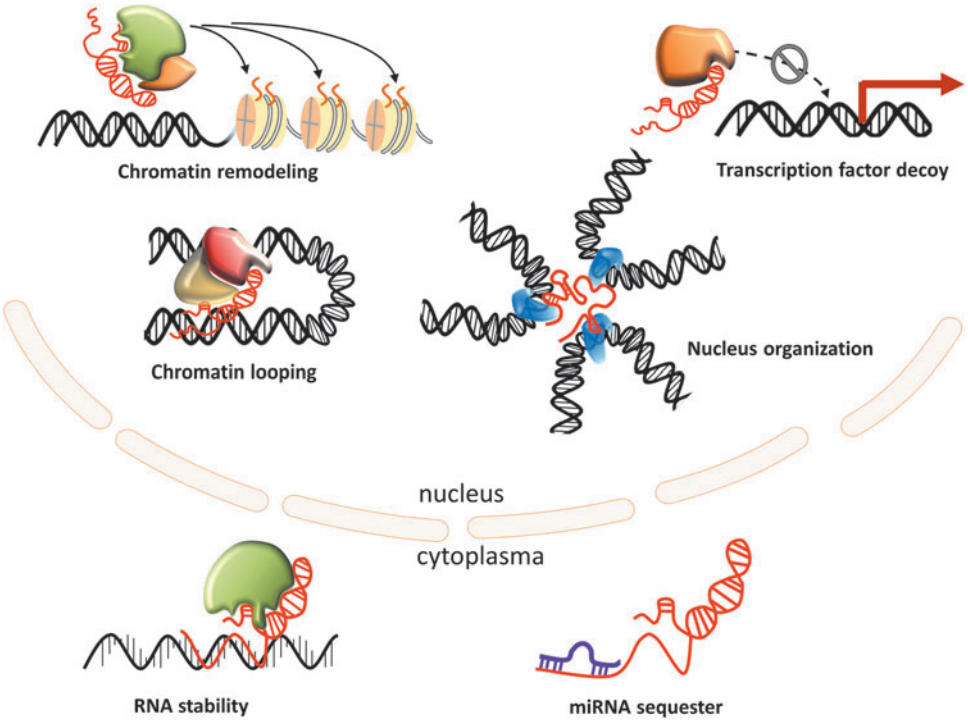

FIG. 2. lncRNA functions. A diverse range of mechanisms have been described for lncRNA regulation of their targets depending on their subcellular localization: assembly and recruitment of chromatin-modifying complexes to their DNA targets in *cis*; some lncRNAs act as RNA decoys, tethering transcription factors away from their DNA targets by directly binding to them as target mimics; and guiding of the physical looping that occurs between enhancers and targeted promoters (enhancer lncRNAs). Many lncRNAs bind to various protein partners to regulate RNA splicing, degradation, and translation; others act as microRNA target site decoys. miRNA, microRNA.

that the lncRNA-based PRC2 guiding model needs to be revised (23, 54). Furthermore, Portoso *et al.'s* recent results suggest that *HOTAIR*-PRC2 interactions are dispensable for *HOTAIR*-mediated transcriptional silencing (90).

A significant proportion of lncRNAs are thought to act in *cis* by enhancing or, conversely, repressing the expression of nearby genes (89). How exactly these lncRNAs perform these functions remains a debated topic. Some of these noncoding transcripts may reorganize the local architecture of chromatin and stoichiometry of transcriptional complexes by specific RNA-protein interactions. Recently, however, Engreitz *et al.* (26) provided a surprising twist to the function of lncRNAs. Their results indicate that (at least in some cases) the lncRNA transcript itself is not critical for the regulation of a neighboring gene as long as there is active transcription of this noncoding locus. In other words, the sequence and interactions of the noncoding RNA product take a backseat to the actual process that generates it. Based on the large number of lncRNAs and the enormous diversity of contexts in which they function, it seems reasonable to assume that these mechanisms are not mutually exclusive.

A puzzling characteristic of lncRNAs is that most of them exhibit very low expression in a particular cell context, including tumors. Many are often considered transcriptional noise and tend to be discounted by arbitrarily set expression cutoff. For lncRNAs, however, low expression should not automatically be viewed as lack of significance as they may achieve biologically meaningful concentrations in specific subcellular compartments; for example, the physical looping mediated by a specific lncRNA bringing together an enhancer and a promoter (66, 89). Supporting evidence has been presented linking lncRNAs to the three-dimensional organization of the nucleus, such as paraspeckle formation or multichromosomal structure (21, 36). These highly specific and localized interactions may support therefore the compatibility between low expression and tissue specificity (84).

At the post-transcriptional level, lncRNAs have been shown to be involved in virtually all steps of RNA metabolism, including stability, processing, and decay. The upregulation of natural antisense (NAT) type of lncRNAs often affects gene expression on the opposite strand by generating RNA duplexes, either by transcript stabilization or degradation *via* RNA interference. Several other effects such as alternative splicing lncRNA-mediated RNA processing have been described as well as an mRNA degradation process called Staufen-mediated decay, which involves lncRNAs binding to the 3′UTR of Staufen-targeted genes (58, 59). Furthermore, lncRNAs can also directly bind proteins, mostly transcription factors, to disrupt their interaction with targeted DNA or other proteins (49).

We will now apply the interactions and functions summarized to the specific case of tumors and highlight how lncRNAs can be integrated in the network of classic neoplastic determinants.

Tumor Microenvironment and lncRNAs; the Effect of Hypoxia

It is estimated that more than half of solid tumors contain hypoxic regions (75) (11, 110) that represent sources of cells with aggressive phenotype and high resistance to therapy (42, 94, 98, 99). The imbalance between high oxygen consumption of fast proliferating tumor cells and impaired oxygen delivery due to abnormalities in tumor vasculature (30) triggers signaling pathways that regulate tumor cell survival, angiogenesis, metastasis, immune response, and metabolic reprogramming.

Hypoxia-mediated cellular response is primarily driven through the HIF pathway, a complex regulatory network, with multiple feedbacks and checkpoint signaling loops. HIF transcription factors are heterodimers comprising two subunits: an oxygen-sensitive α-subunit (hypoxia-inducible factor 1 alpha [HIF-1α], HIF-2α, and HIF-3α) and a constitutively expressed β-subunit (HIF-1β/ARNT, HIF-2β/

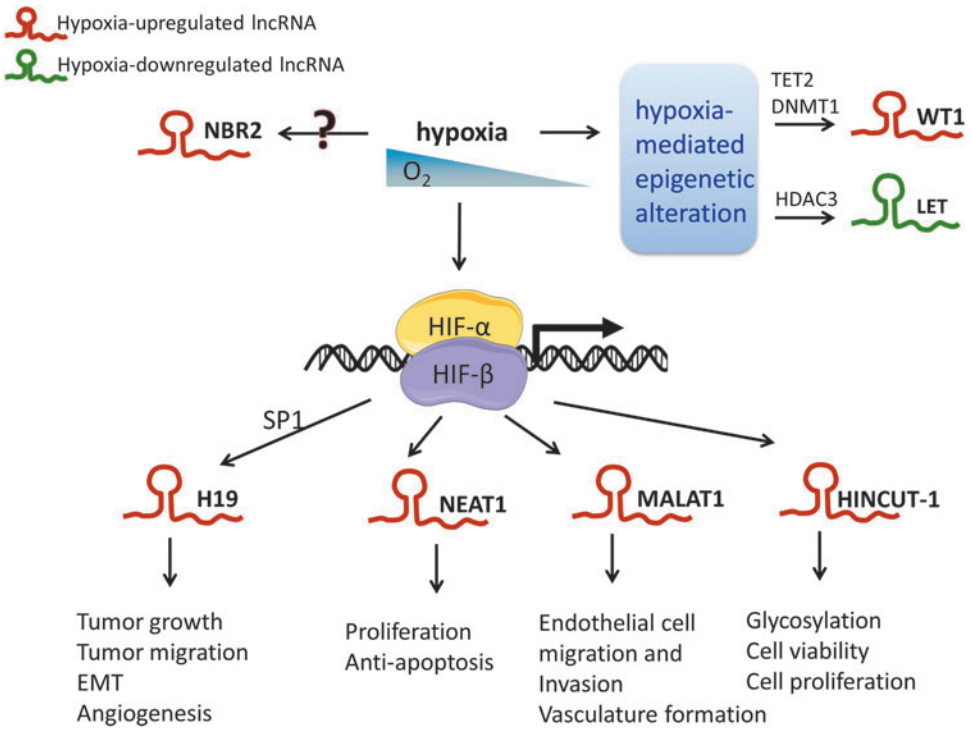

FIG. 3. Examples of hypoxia-regulated lncRNAs. lncRNAs can be regulated by hypoxia through direct or indirect manner. Some lncRNAs, such as *NEAT1*, *MALAT1*, and *HINCUT-1*, *etc*. have been identified as direct HIF targets. HIF is also involved in upregulation of *H19*, but most likely *via* an indirect signaling through SP1. Hypoxia-mediated epigenetic alterations also play important roles in the expression of some hypoxia-responsive lncRNAs such as *lncRNA WT1* and *LET*. DNMT1, DNA methyltransferase 1; EMT, epithelial-to-mesenchymal transition; *H19*, imprinted maternally expressed lncRNA; HIF, hypoxia-inducible factor; *HINCUT-1*, hypoxia-induced noncoding ultraconserved transcript 1; LET, low expression in tumor; *MALAT1*, metastasis-associated lung adenocarcinoma transcript 1; NBR2, neighbor of the BRCA1 gene 2; *NEAT1*, nuclear paraspeckle assembly transcript 1; TET2, tet methylcytosine dioxygenase 2; WT1, Wilms' tumor 1.

ARNT2). While HIF-1β/ARNT is ubiquitously expressed, HIF-2β/ARNT2 is mainly localized in neural tissue and kidney. Three prolyl hydroxylases, EGLN 1–3/PHD 1–3, hydroxylate two proline residues of HIF-α (12, 27, 51), thus favoring the binding of von Hippel-Lindau tumor suppressor protein (pVHL) to HIF-α, which subsequently targets HIF-α for ubiquitination-mediated proteasomal degradation (52, 53, 82). Under hypoxic conditions, the activity of EGLN enzymes decreases, resulting in increased abundance of non-hydroxylated HIF-α subunits, which cannot be recognized by the pVHL complex, thus able to form an active transcriptional complex.

Active HIF regulates the transcription of hundreds of coding and noncoding genes. While a large set of miRNAs have been reported as hypoxia responsive (31), a smaller number of lncRNAs have been identified that respond with at least some consistency to oxygen availability. However, it should not be interpreted that miRNAs are generally more responsive to oxygen deprivation. First, miRNAs have been systematically investigated for a longer period of time (103). Second, multiple nomenclatures coexisted for lncRNAs and one could speculate that the same lncRNA may have been identified by different screens under different names. Finally, omission of non-polyadenylated transcripts from library preparation may have led to the loss of hypoxia-responsive lncRNAs.

Overall, two types of lncRNA-HIF connections have been described: lncRNAs that are regulated in response to hypoxia and HIF signaling subsequently and lncRNAs that regulate HIF signaling (Fig. 3). Many hypoxia-inducible lncRNAs reported to date are direct transcriptional HIF targets (18, 19, 28, 79, 85, 86, 121, 124, 130). Chromatin immunoprecipitation sequencing studies of HIF-DNA binding have revealed that $\sim$30% of HIF binding sites are close to noncoding gene loci; correlations with hypoxic gene regulation revealed significant associations between HIF binding and transcription of lncRNA. Nevertheless, several lncRNAs such as nuclear paraspeckle assembly transcript 1 *(NEAT1), MALAT1, HIF1A-AS2*, imprinted maternally expressed lncRNA *(H19)*, hypoxia-induced noncoding ultraconserved transcript 1 *(HINCUT-1)*, and urothelial cancer-associated 1 have been identified as hypoxia-responsive lncRNAs (18, 19, 85, 86). A selection of hypoxia-regulated lncRNAs and their impact on tumor biology are summarized in Table 1.

Arguably the first reported hypoxia-inducible noncoding RNA is the transcript generated by the imprinted oncofetal gene *H19* (77, 79, 80). While details remain to be elucidated, Wu *et al.* provided evidence that HIF-1, while required, is not the direct activator of *H19* transcription. They proposed that HIF-1 activates SP1, which in turn activates the *H19* promoter (117). Functionally, *H19* has been shown to promote tumor growth and regulate anchorage-independent growth after hypoxia recovery (77, 79).

H19 exerts broader proneoplastic effects unrelated to its response to hypoxia. The *H19* gene is highly expressed in common metastatic sites regardless of tumor primary origin. *H19* enhances cell migration *in vitro* and stimulates tumor

Table 1. Hypoxia-Regulated Long Noncoding RNAs and Their Role in Cancer

lncRNA	*Hypoxia response*	*Transcription regulation*	*Cancer type*	*Cancer impact*	*Refs.*
H19	Up	HIF/MYC/SP1	HCC Bladder cancer CRC Esophageal cancer Breast cancer Gastric cancer	Cell survival and proliferation Migration Angiogenesis EMT	(13, 46, 73, 76–80, 87, 117, 122)
HINCUT1/ uc.475	Up	HIF	Colon cancer	Cell proliferation	(28)
UCA1/CURD	Up	HIF	Bladder cancer	Cell proliferation Migration and invasion Apoptosis	(121)
NEAT1	Up	HIF	Breast cancer	Cell survival Apoptosis	(18)
MALAT1	Up	HIF	Breast cancer Lung cancer	Cell cycle Angiogenesis Tumor metastasis	(18, 19, 85, 107)
lncRNA-NUTF2P3-001	Up	HIF	Pancreatic cancer	Proliferation, invasion	(67)
HIF1A-AS2	Up	HIF	Glioblastoma Breast cancer	Maintain mesenchymal glioblastoma stem-like cells in hypoxia niches	(7, 86)
SARCC	Up	HIF	RCC	Proliferation	(128)
ANRIL	Up	HIF	Osteosarcoma	Invasion, apoptosis	(114)
GAPLINC	Up	HIF	Gastric cancer	Proliferation	(70)
PVT1	Up	HIF	Cervical cancer Gastric cancer	Proliferation, apoptosis, migration, invasion, cisplatin cytotoxicity	(47, 50)
NBR2	Up	—	Breast cancer	Cell cycle Apoptosis/autophagy Metabolic checkpoint under energy stress	(72, 116)
EFNA3 lncRNA	Up	—	Breast cancer	Tumor metastasis	(32)
AK058003	Up	—	Gastric cancer	Modulate DNA methylation at *SNCG* CpG island Migration and invasion Tumor metastasis	(111)
AK123072	Up	—	Gastric cancer	Migration, invasion, metastasis	(125)
linc-ROR	Up	—	HCC	RNA sponge (*miR145*) Upregulate *HIF1A* mRNA Cell survival	(106)
HOTAIR	Up	HIF	Breast cancer Lung cancer	Cell viability Invasion Apoptosis Metastasis	(34, 130)
lncRNA-LET	Down	Hypoxia-mediated epigenetic alteration: HDAC3	Gallbladder cancer SCLC HCC CRC	Inhibit invasion and metastasis	(74, 123)
WT1 lncRNA	Up	Hypoxia-mediated epigenetic alteration: DNMT1, TET2	AML	Modulate histone methylation at *WT1* TSS	(83)

AML, acute myeloid leukemia; *ANRIL, CDKN2B* antisense RNA 1; CRC, colorectal cancer; DNMT1, DNA methyltransferase 1; EMT, epithelial-to-mesenchymal transition; H19, imprinted maternally expressed lncRNA; HCC, hepatocellular carcinoma; HIF, hypoxia-inducible factor; *HIF1A-AS2*, hypoxia-inducible factor 1 alpha antisense 2; *HINCUT-1*, hypoxia-induced noncoding ultraconserved transcript 1; *HOTAIR, HOX* transcript antisense RNA; lncRNA, long noncoding RNA; *MALAT1*, metastasis-associated lung adenocarcinoma transcript 1; *NBR2*, neighbor of the *BRCA1* gene 2; *NEAT1*, nuclear paraspeckle assembly transcript 1; *PVT1*, PVT1 plasmacytoma variant translocation 1 lncRNA; RCC, renal cell carcinoma; *SARCC*, suppressing androgen receptor in renal cell carcinoma; SCLC, squamous-cell lung cancer; TET2, tet methylcytosine dioxygenase 2; *UCA1/CUDR*, urothelial cancer-associated 1; WT1, Wilms' tumor 1.

metastasis *in vivo* (95). In ovarian carcinoma cells, *H19* overexpression is associated with chemoresistance and epithelial-to-mesenchymal transition phenotype (80). *H19* knockdown leads to decreased expression of genes with antiapoptotic function, such as microphthalmia-associated transcription factor, immediate early response 3, protein kinase C, zeta, B cell CLL/lymphoma 3, and serine/threonine kinase 1, and upregulation of proapoptotic genes such as DNA damage-inducible transcript 3 also known as *GADD153* (77). *H19* also plays an important and multipronged role in tumor angiogenesis (77) by regulating the production of proangiogenic factors such as angiogenin, fibroblast growth factor 18, prolylcarboxypeptidase, tumor necrosis factor α-induced protein 1, calponin 2, and inhibitor of DNA binding 2.

Although much remains to be understood about how these complex regulatory effects are set in motion, *H19* actions most likely involve a multitude of interactions, including proteins and RNA interactions. For example, *H19* can modulate chromatin structure within the imprinted gene network through interaction with methyl-CpG-binding domain protein 1 (87). Other studies provided evidence that *H19* functions as an endogenous miRNA sponge for *let-7* tumor suppressor miRNAs (118).

Choudhry *et al.* reported *NEAT1* and *MALAT1* as the main lncRNAs induced in hypoxic MCF7 breast cancer cells (18). *NEAT1* is predominantly controlled by HIF-2, rather than by HIF-1, and is involved in paraspeckle formation (21). One of the paraspeckle functions is to sequester hyperedited RNAs into the nucleus, thus impeding their translocation to the cytoplasm (3). Interestingly, elimination of these lncRNAs in the mouse embryo is compatible with life; therefore, it is conceivable that these transcripts play fine-tuning rather than essential roles in proliferation. However, in tumor cells, hypoxic induction of *NEAT1* promotes proliferation and suppresses apoptosis (18). Protumorigenic roles have been described for *MALAT1* as well. In the highly angiogenic neuroblastomas, upregulation of *MALAT1* promotes endothelial cell migration, invasion, and vasculature formation through fibroblast growth factor 2 upregulation (107). In breast cancer, *MALAT1* regulates critical processes such as tumor growth, differentiation, and metastasis (1). Genetic loss or antisense oligonucleotide (ASO)-mediated knockdown in MMTV-PyMT mouse mammary carcinoma models leads to gene expression alterations and splicing patterns of genes involved in pathogenesis, resulting in reduced branching morphogenesis in MMTV-PyMT- and Her2/neu-amplified tumor organoids, increased cell adhesion, and loss of migration (1). Many miRNAs, including *miR-205*, *miR-200c*, and *miR-204*, have been reported to interact with *MALAT1* and thus contribute to its tumor-promoting mechanism in various cancer types (44, 65, 120). However, these studies often provide little significant molecular proof and require further validation.

HINCUTs are a family of lncRNAs that are transcribed from regions exhibiting extremely high conservation between human, rat, and mouse genomes (2). Our groups have shown that *HINCUT-1* (originally termed *uc.475*) is an lncRNA transcribed as a retained intron of *O*-linked *N*-acetylglucosamine transferase (*OGT*) mRNA and is induced by hypoxia in an HIF-dependent manner (28). Although details are unclear, *HINCUT-1* appears to play an important role in steady-state *OGT* expression and overall cellular glycosylation and its inactivation has detrimental effects on cell viability and proliferation (28).

Recently, suppressing androgen receptor in renal cell carcinoma (*SARCC*) lncRNA was reported as an HIF-2 target in clear cell renal carcinoma. The authors provide preliminary evidence that *lncRNA-SARCC* binds and destabilizes androgen receptor (AR), which results in suppression of AR/HIF-2α/c-MYC signaling (128).

Another lncRNA probably driven by HIF is plasmacytoma variant translocation 1 lncRNA, which appears to be a multifaceted player in cancer. On the one hand, it promotes cell migration and invasion, and on the other hand, it was shown to correlate with immune response stimulation in cervical cancer (50).

Neighbor of breast cancer 1 (*BRCA1*) gene 2 (*NBR2*) lncRNA is a transcript expressed in the opposite orientation from the bidirectional *BRCA1* promoter that has recently been shown to regulate AMP-activated protein kinase under energy stress (72). Wiedmeier *et al.* have recently shown that *NBR2* is induced under prolonged hypoxia in MCF7 cells, while *BRCA1* is repressed. These results suggest that the two transcripts driven by the *BRCA1* promoter are differentially regulated in response to hypoxia, although the regulatory element(s) required for induction of *NBR2* appear to reside outside of the BRCA1 minimal promoter (116).

A rare case of lncRNA reported as downregulated in hypoxia is *lncRNA-LET* (74, 123), which exhibits the behavior of a tumor-suppressing element. In primary hepatocellular carcinoma, *lncRNA-LET* expression is inversely correlated with the prototypical hypoxia marker carbonic anhydrase 9, and experimentally, *lncRNA-LET* downregulation leads to hypoxia-induced cancer cell invasion in hepatocellular carcinoma cells (123). In a different tumor context, ectopic expression of *lncRNA-LET* leads to G0/G1 cell cycle arrest and induction of apoptosis under hypoxic conditions and suppresses gallbladder tumor growth *in vivo* (74).

Occasionally, hypoxia-dependent lncRNA regulation may occur through epigenetic regulators rather than direct HIF activation. In acute myeloid leukemia cells, induction of Wilms' Tumor 1 (WT1) lncRNA, an antisense-oriented lncRNA overlapping with intron 1 CpG island of the *WT1* gene, appears to be the result of demethylation through hypoxia-regulated expression of DNA methyltransferase 1 and tet methylcytosine dioxygenase 2 (83).

lncRNAs are not only direct targets of HIF transcriptional activation but also have been demonstrated to regulate the transcription of HIF genes themselves, through direct or indirect interactions. This mechanism creates complex signaling networks with positive and negative feedback loops that integrate multiple signaling pathways to control HIF response to hypoxia. HIF-1α antisense transcripts have long been known to be induced in response to hypoxia (7, 86) and have been shown to negatively regulate HIF expression by chromatin inactivation or mRNA degradation (7) (Fig. 4). More recently, in mesenchymal glioblastoma stem-like cells, *HIF1A-AS2* was found to be the most significantly upregulated lncRNA, playing a protumorigenic role. The authors identified DExH-box helicase 9 and insulin-like growth factor 2-binding protein 2 proteins as major interactors of *HIF1A-AS2* and this interaction in turn drives the expression of tumor-promoting downstream targets, in particular the high-mobility group AT-hook 1 (86). Preliminary evidence suggests that *HIF1A-AS2* may be relevant in a broader context as its knockdown was found to inhibit gastric cancer cell proliferation (16).

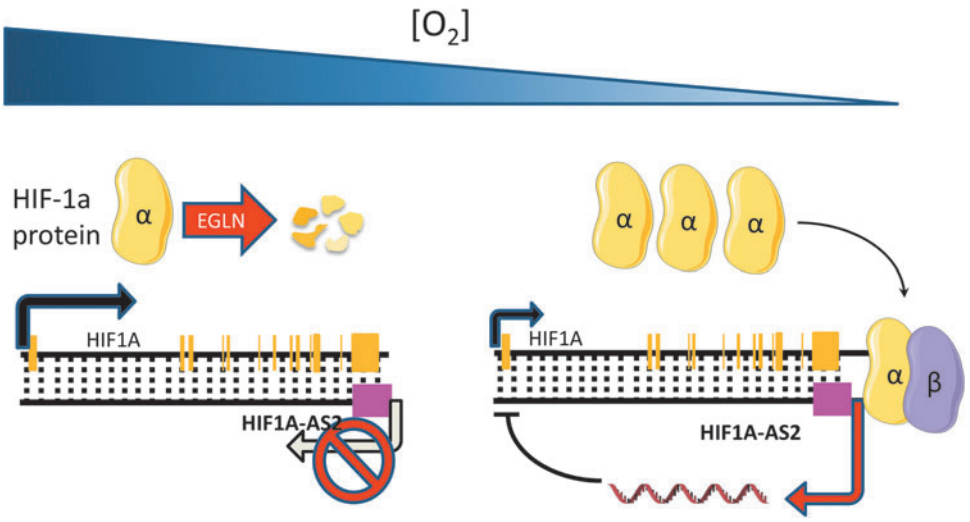

FIG. 4. *HIF1A* antisense transcript forms negative feedback loops to control HIF response to hypoxia. *HIF1A-AS2* is an HIF-target lncRNA. Under hypoxia, HIF directly binds to the *HIF1A-AS2* promoter, driving the expression of an antisense transcript to *HIF1A*, which in return negatively regulates *HIF1A* expression level as a negative feedback mechanism. *HIF1A-AS2*, hypoxia-inducible factor 1 alpha antisense 2.

A more recent, and incompletely understood, mechanism appears to involve HIF-2 and is based on HIF-2α promoter upstream transcript lncRNA. This is an lncRNA transcribed from the upstream of the HIF-2α promoter, which induces *cis* HIF-2α activation in osteosarcoma (112) and colorectal cancer (126).

Several lncRNAs have been reported to regulate HIF signaling through indirect mechanisms (Fig. 5). Long intergenic noncoding RNA for kinase activation mediates heparin-binding epidermal growth factor-like growth factor-triggered, epidermal growth factor receptor: glycoprotein nonmetastatic melanoma protein B heterodimer-dependent HIF-1α phosphorylation leading to HIF-1α stabilization, HIF-1α-p300 interaction, and activation of hypoxic programs, including glycolysis under normal oxygen conditions in breast cancer (68). In pancreatic ductal adenocarcinoma, lncRNA ENST00000480739 has been demonstrated to increase the levels of endoplasmic reticulum lectin protein (104), which is known to increase the affinity between HIF-1α and EGLN hydroxylases, therefore leading to HIF-1α destabilization. Somewhat similarly, *RAB4B-EGLN2* read-through lncRNA appears to suppress HIF-1α signaling through *EGLN* transcription activation (132).

Other Cancer-Associated lncRNAs

Colon cancer-associated transcripts (CCATs), 1 (119) and 2 (69), are lncRNAs transcribed from the highly conserved 8q24 region that has been shown to enhance the transcription of MYC oncogene and promote cancer progression, invasion, and metastasis. *CCAT1* is involved in maintaining chromatin looping between the *MYC* promoter and its enhancers in

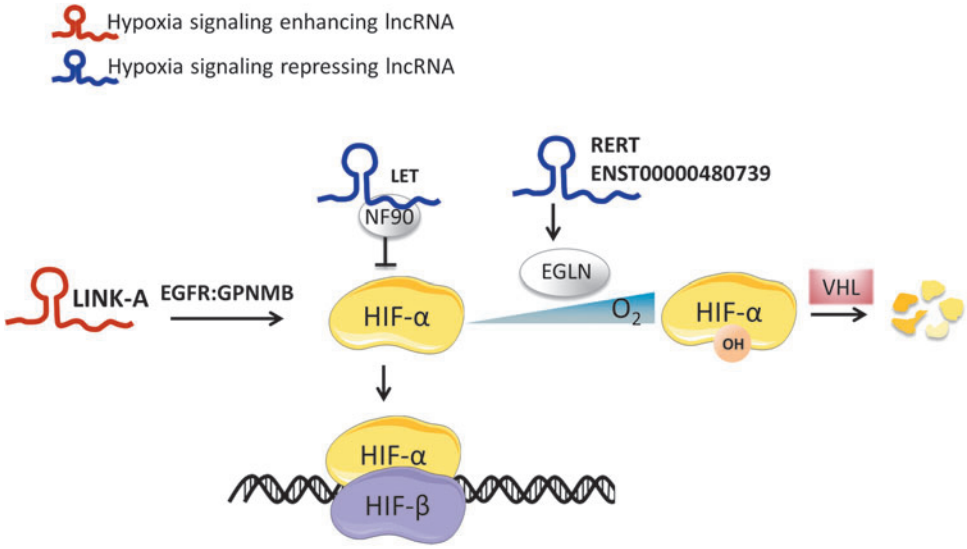

FIG. 5. Examples of lncRNAs that regulate hypoxia signaling. Several lncRNAs have been reported to regulate hypoxia signaling through indirect mechanisms. *LINK-A* stabilizes HIF-1α through an EGFR:GPNMB heterodimer-dependent HIF-1α phosphorylation and thus activates HIF-1α transcriptional programs. *lncRNA LET* reduces the protein levels of HIF-1α through its association with NF90. *lncRNA RERT* and ENST00000480739 downregulate hypoxia signaling through modulation of EGLN. EGFR, epidermal growth factor receptor; EGLN 1–3/PHD 1–3, prolyl hydroxylases 1–3; GPNMB, glycoprotein nmb; HIF-1α, hypoxia-inducible factor 1 alpha; *LINK-A*, long intergenic noncoding RNA for kinase activation; *RERT*, *RAB4B-EGLN2* read-through lncRNA.

coordination with the CCCTC-binding factor. *CCAT2* increases chromosomal instability through transcription factor 7-like 2-mediated transcriptional regulation. Thus, both CCAT1 and CCAT2 have been associated with increased risk of cancer and have been shown to regulate multiple molecular pathways to promote cell proliferation, metastasis, and cancer metabolism (96).

lincRNA-p21 is a p53 transcriptional target that has been shown to repress p53 transcriptional response through heterogeneous nuclear ribonucleoprotein K and trigger apoptosis (48). While in coordination with RNA-binding protein HuR, it inhibits the translation of p53 targets such as jun B proto-oncogene and catenin beta 1 (127). In nonsmall cell lung cancer, tumor samples with high *lincRNA-p21* levels show higher microvascular density. *lincRNA-p21* induces angiogenesis *in vitro*, while lincRNA-p21 inhibition leads to downregulation of angiogenesis-related genes, such as vascular endothelial growth factor A (15).

Prostate cancer-associated ncRNA transcript 1 (*PCAT-1*), although initially reported as a *PCAT* (91), has been described to associate with multiple types of cancers. *PCAT-1* is a target of the PRC2 and represses the transcription of genes involved in cell proliferation, invasion, and metastasis.

CDKN2B antisense RNA 1 (*ANRIL*) is transcribed in the opposite direction from the *INK4b-ARF-INK4a* cluster and it is one of the most frequently altered lncRNAs in cancer. The molecular mechanisms through which *ANRIL* mediated cancer development and progression are still uncertain; however, it is hypothesized that aberrant expression levels of *ANRIL* may block the DNA damage response mechanism, leading to genomic instability. In addition, *ANRIL* promotes tumor cell proliferation by regulating target genes in *trans*. *ANRIL* promotes the epigenetically silencing of *miR-99A/miR-449A*, therefore upregulating mechanistic target of rapamycin and cyclin-dependent kinase 6/E2F transcription factor 1 pathways (129).

lncRNAs: Are Diagnostic and Therapeutic Applications Feasible?

As functional molecules, the lncRNA expression levels may serve as better prognostic and diagnostic indicators of diseases than mRNAs. Additional, their highly specific spatial and temporal expression signatures could lead to a more accurate disease diagnosis and classification. Potential applications of lncRNAs in clinical oncology have been proposed, such as diagnostic biomarkers and therapy response predictors. Prostate cancer-associated 3 (*PCA3/DD3*) lncRNA, for example, has already been tested in controlled clinical settings based on its much higher expression in prostate tumors compared with normal prostate and other tissues. However, based on the available data, *PCA3/DD3* does not appear to be superior to the routinely used prostate-specific antigen (24, 60). Another potentially valuable marker may be *HOTAIR*, which was found to be upregulated dramatically in metastatic breast cancer tissue compared with normal breast tissue (34).

The therapeutic relevance of lncRNAs is currently under exploration, but critical hurdles need to be overcome. Due to their size, transduction of tumor suppressor lncRNAs necessitates delivery systems (*e.g.*, viruses) that have yet to prove their value in clinical settings. On the other hand, oncogenic lncRNAs may be targetable with synthetic RNAs, such as siRNAs, ASOs, or miRNAs. While siRNA-mediated knockdown of cytoplasmic lncRNAs is highly efficient, targeting nuclear lncRNAs is more challenging. Thus, the ASO technology has been optimized to target nuclear lncRNAs for RNase H1-mediated RNA degradation. Promising *in vivo* results have been reported for several lncRNAs such as *MALAT1* (1) and *SAMSSON* (64).

Another approach for lncRNA targeting may be based on lessons learned from the study of vault RNAs (vtRNAs) as mediators of multidrug resistance (33). It was shown that vtRNAs directly bind to chemotherapeutic agents, indicating that it would also be possible to design small molecules that interact with lncRNAs (33). vtRNAs are technically short RNAs, ranging from 80 to 90 nucleotides; however, examples of longer RNAs involved with drug interactions exist, such as aptamers (41, 43, 88, 115). Targeting transcripts the size of lncRNAs may appear challenging, but there is a precedent for fragmenting large ribonucleoprotein complexes into more manageable sizes. This strategy has been applied to design ligands for the expanded rCUG and rCAG repeats expressed in myotonic dystrophy type 1 that interact with Muscleblind-like 1 protein (92). Moreover, unbiased methods such as systematic evolution of ligands by exponential enrichment have the potential to be used to identify molecules that interact with lncRNAs (109).

The clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9-based technologies have revolutionized the study of genetic reprogramming by being developed into a genome-wide editing tool with large applications, including noncoding transcriptome functionality (71, 131). However, CRISPR-Cas9-directed lncRNA genomic deletions do not necessarily induce repression of biological activity (100, 131). The CRISPR interference has been reported as a better approach for lncRNA functionality studies as this technology uses a nuclease-dead dCAS9-KRAB repressor fusion protein to repress gene transcription. This protein can be recruited by single-guided RNA pools to the lncRNA transcriptional start sites, and association with a specific phenotype (71) can be selected based on specific markers as a readout.

In conclusion, multidisciplinary approaches continue to provide critical insights into the involvement of lncRNAs in various aspects of cancer biology. While many lncRNAs already show significant potential as therapeutic targets or cancer biomarkers, transitioning from basic knowledge to viable clinical applications remains challenging. Future studies will need to clarify which, if any, lncRNAs are truly essential for cancer cell viability and to develop more efficient tools for their inactivation in clinical tumors. Furthermore, it would be highly impactful to identify lncRNAs that inform about tumor vulnerability to specific therapeutic agents, potentially in a defined genetic context.

Acknowledgments

Work in Dr. Ivan's laboratory is supported by a National Institutes of Health (NIH/NCI) grant R01CA155332; Dr. Calin's laboratory is supported by National Institutes of Health (NIH/NCATS) grant UH3TR00943-01 through the NIH Common Fund, Office of Strategic Coordination (OSC); the NIH/NCI grant 1 R01 CA182905-01; U54 grant—UPR/MDACC Partnership for Excellence in Cancer Research 2016 Pilot

Project; CLL Moonshot Flagship project; and the Estate of C.G. Johnson, Jr.; and Dr. Tudoran's work is supported by the Romanian National Grant Program PN-II-RU-TE-2014-4-1984.

References

1. Arun G, Diermeier S, Akerman M, Chang KC, Wilkinson JE, Hearn S, Kim Y, MacLeod AR, Krainer AR, Norton L, Brogi E, Egeblad M, and Spector DL. Differentiation of mammary tumors and reduction in metastasis upon Malat1 lncRNA loss. *Genes Dev* 30: 34–51, 2016.
2. Bejerano G, Pheasant M, Makunin I, Stephen S, Kent WJ, Mattick JS, and Haussler D. Ultraconserved elements in the human genome. *Science* 304: 1321–1325, 2004.
3. Ben-Zvi M, Amariglio N, Paret G, and Nevo-Caspi Y. F11R expression upon hypoxia is regulated by RNA editing. *PLoS One* 8: e77702, 2013.
4. Berget SM and Sharp PA. A spliced sequence at the 5′-terminus of adenovirus late mRNA. *Brookhaven Symp Biol* 12–20: 332–344, 1977.
5. Berk AJ and Sharp PA. Sizing and mapping of early adenovirus mRNAs by gel electrophoresis of S1 endonuclease-digested hybrids. *Cell* 12: 721–732, 1977.
6. Bernstein E, Caudy AA, Hammond SM, and Hannon GJ. Role for a bidentate ribonuclease in the initiation step of RNA interference. *Nature* 409: 363–366, 2001.
7. Bertozzi D, Iurlaro R, Sordet O, Marinello J, Zaffaroni N, and Capranico G. Characterization of novel antisense HIF-1alpha transcripts in human cancers. *Cell Cycle* 10: 3189–3197, 2011.
8. Bonasio R and Shiekhattar R. Regulation of transcription by long noncoding RNAs. *Annu Rev Genet* 48: 433–455, 2014.
9. Bracken CP, Gregory PA, Khew-Goodall Y, and Goodall GJ. The role of microRNAs in metastasis and epithelial-mesenchymal transition. *Cell Mol Life Sci* 66: 1682–1699, 2009.
10. Brannan CI, Dees EC, Ingram RS, and Tilghman SM. The product of the H19 gene may function as an RNA. *Mol Cell Biol* 10: 28–36, 1990.
11. Brown JM and Giaccia AJ. The unique physiology of solid tumors: opportunities (and problems) for cancer therapy. *Cancer Res* 58: 1408–1416, 1998.
12. Bruick RK and McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. *Science* 294: 1337–1340, 2001.
13. Cai X and Cullen BR. The imprinted H19 noncoding RNA is a primary microRNA precursor. *RNA* 13: 313–316, 2007.
14. Carninci P, Kasukawa T, Katayama S, Gough J, Frith MC, Maeda N, Oyama R, Ravasi T, Lenhard B, Wells C, Kodzius R, Shimokawa K, Bajic VB, Brenner SE, Batalov S, Forrest AR, Zavolan M, Davis MJ, Wilming LG, Aidinis V, Allen JE, Ambesi-Impiombato A, Apweiler R, Aturaliya RN, Bailey TL, Bansal M, Baxter L, Beisel KW, Bersano T, Bono H, Chalk AM, Chiu KP, Choudhary V, Christoffels A, Clutterbuck DR, Crowe ML, Dalla E, Dalrymple BP, de Bono B, Della Gatta G, di Bernardo D, Down T, Engstrom P, Fagiolini M, Faulkner G, Fletcher CF, Fukushima T, Furuno M, Futaki S, Gariboldi M, Georgii-Hemming P, Gingeras TR, Gojobori T, Green RE, Gustincich S, Harbers M, Hayashi Y, Hensch TK, Hirokawa N, Hill D, Huminiecki L, Iacono M, Ikeo K, Iwama A, Ishikawa T, Jakt M, Kanapin A, Katoh M, Kawasawa Y, Kelso J, Kitamura H, Kitano H, Kollias G, Krishnan SP, Kruger A, Kummerfeld SK, Kurochkin IV, Lareau LF, Lazarevic D, Lipovich L, Liu J, Liuni S, McWilliam S, Madan Babu M, Madera M, Marchionni L, Matsuda H, Matsuzawa S, Miki H, Mignone F, Miyake S, Morris K, Mottagui-Tabar S, Mulder N, Nakano N, Nakauchi H, Ng P, Nilsson R, Nishiguchi S, Nishikawa S, Nori F, Ohara O, Okazaki Y, Orlando V, Pang KC, Pavan WJ, Pavesi G, Pesole G, Petrovsky N, Piazza S, Reed J, Reid JF, Ring BZ, Ringwald M, Rost B, Ruan Y, Salzberg SL, Sandelin A, Schneider C, Schonbach C, Sekiguchi K, Semple CA, Seno S, Sessa L, Sheng Y, Shibata Y, Shimada H, Shimada K, Silva D, Sinclair B, Sperling S, Stupka E, Sugiura K, Sultana R, Takenaka Y, Taki K, Tammoja K, Tan SL, Tang S, Taylor MS, Tegner J, Teichmann SA, Ueda HR, van Nimwegen E, Verardo R, Wei CL, Yagi K, Yamanishi H, Zabarovsky E, Zhu S, Zimmer A, Hide W, Bult C, Grimmond SM, Teasdale RD, Liu ET, Brusic V, Quackenbush J, Wahlestedt C, Mattick JS, Hume DA, Kai C, Sasaki D, Tomaru Y, Fukuda S, Kanamori-Katayama M, Suzuki M, Aoki J, Arakawa T, Iida J, Imamura K, Itoh M, Kato T, Kawaji H, Kawagashira N, Kawashima T, Kojima M, Kondo S, Konno H, Nakano K, Ninomiya N, Nishio T, Okada M, Plessy C, Shibata K, Shiraki T, Suzuki S, Tagami M, Waki K, Watahiki A, Okamura-Oho Y, Suzuki H, Kawai J, Hayashizaki Y, FANTOM Consortium, and RIKEN Genome Exploration Research Group and Genome Science Group (Genome Network Project Core Group).The transcriptional landscape of the mammalian genome. *Science* 309: 1559–1563, 2005.
15. Castellano JJ, Navarro A, Vinolas N, Marrades RM, Moises J, Cordeiro A, Saco A, Munoz C, Fuster D, Molins L, Ramirez J, and Monzo M. LincRNA-p21 Impacts prognosis in resected non-small cell lung cancer patients through angiogenesis regulation. *J Thorac Oncol* 11: 2173–2182, 2016.
16. Chen WM, Huang MD, Kong R, Xu TP, Zhang EB, Xia R, Sun M, De W, and Shu YQ. Antisense long noncoding RNA HIF1A-AS2 is upregulated in gastric cancer and associated with poor prognosis. *Dig Dis Sci* 60: 1655–1662, 2015.
17. Cheng J, Kapranov P, Drenkow J, Dike S, Brubaker S, Patel S, Long J, Stern D, Tammana H, Helt G, Sementchenko V, Piccolboni A, Bekiranov S, Bailey DK, Ganesh M, Ghosh S, Bell I, Gerhard DS, and Gingeras TR. Transcriptional maps of 10 human chromosomes at 5-nucleotide resolution. *Science* 308: 1149–1154, 2005.
18. Choudhry H, Albukhari A, Morotti M, Haider S, Moralli D, Smythies J, Schodel J, Green CM, Camps C, Buffa F, Ratcliffe P, Ragoussis J, Harris AL, and Mole DR. Tumor hypoxia induces nuclear paraspeckle formation through HIF-2alpha dependent transcriptional activation of NEAT1 leading to cancer cell survival. *Oncogene* 34: 4546, 2015.
19. Choudhry H, Schodel J, Oikonomopoulos S, Camps C, Grampp S, Harris AL, Ratcliffe PJ, Ragoussis J, and Mole DR. Extensive regulation of the non-coding transcriptome by hypoxia: role of HIF in releasing paused RNApol2. *EMBO Rep* 15: 70–76, 2014.
20. Chow LT, Roberts JM, Lewis JB, and Broker TR. A map of cytoplasmic RNA transcripts from lytic adenovirus type 2, determined by electron microscopy of RNA:DNA hybrids. *Cell* 11: 819–836, 1977.
21. Clemson CM, Hutchinson JN, Sara SA, Ensminger AW, Fox AH, Chess A, and Lawrence JB. An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. *Mol Cell* 33: 717–726, 2009.
22. Crick FH. On protein synthesis. *Symp Soc Exp Biol* 12: 138–163, 1958.
23. Davidovich C, Zheng L, Goodrich KJ, and Cech TR. Promiscuous RNA binding by polycomb repressive complex 2. *Nat Struct Mol Biol* 20: 1250–1257, 2013.

24. Day JR, Jost M, Reynolds MA, Groskopf J, and Rittenhouse H. PCA3: from basic molecular science to the clinical lab. *Cancer Lett* 301: 1–6, 2011.
25. Doi N, Zenno S, Ueda R, Ohki-Hamazaki H, Ui-Tei K, and Saigo K. Short-interfering-RNA-mediated gene silencing in mammalian cells requires Dicer and eIF2C translation initiation factors. *Curr Biol* 13: 41–46, 2003.
26. Engreitz JM, Haines JE, Perez EM, Munson G, Chen J, Kane M, McDonel PE, Guttman M, and Lander ES. Local regulation of gene expression by lncRNA promoters, transcription and splicing. *Nature* 539: 452–455, 2016.
27. Epstein AC, Gleadle JM, McNeill LA, Hewitson KS, O'Rourke J, Mole DR, Mukherji M, Metzen E, Wilson MI, Dhanda A, Tian YM, Masson N, Hamilton DL, Jaakkola P, Barstead R, Hodgkin J, Maxwell PH, Pugh CW, Schofield CJ, and Ratcliffe PJ. *C. elegans* EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. *Cell* 107: 43–54, 2001.
28. Ferdin J, Nishida N, Wu X, Nicoloso MS, Shah MY, Devlin C, Ling H, Shimizu M, Kumar K, Cortez MA, Ferracin M, Bi Y, Yang D, Czerniak B, Zhang W, Schmittgen TD, Voorhoeve MP, Reginato MJ, Negrini M, Davuluri RV, Kunej T, Ivan M, and Calin GA. HINCUTs in cancer: hypoxia-induced noncoding ultraconserved transcripts. *Cell Death Differ* 20: 1675–1687, 2013.
29. Fernandez-Valverde SL, Taft RJ, and Mattick JS. MicroRNAs in beta-cell biology, insulin resistance, diabetes and its complications. *Diabetes* 60: 1825–1831, 2011.
30. Fukumura D and Jain RK. Tumor microvasculature and microenvironment: targets for anti-angiogenesis and normalization. *Microvasc Res* 74: 72–84, 2007.
31. Gee HE, Ivan C, Calin GA, and Ivan M. HypoxamiRs and cancer: from biology to targeted therapy. *Antioxid Redox Signal* 21: 1220–1238, 2014.
32. Gomez-Maldonado L, Tiana M, Roche O, Prado-Cabrero A, Jensen L, Fernandez-Barral A, Guijarro-Munoz I, Favaro E, Moreno-Bueno G, Sanz L, Aragones J, Harris A, Volpert O, Jimenez B, and del Peso L. EFNA3 long noncoding RNAs induced by hypoxia promote metastatic dissemination. *Oncogene* 34: 2609–2620, 2015.
33. Gopinath SC, Matsugami A, Katahira M, and Kumar PK. Human vault-associated non-coding RNAs bind to mitoxantrone, a chemotherapeutic compound. *Nucleic Acids Res* 33: 4874–4881, 2005.
34. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, Wang Y, Brzoska P, Kong B, Li R, West RB, van de Vijver MJ, Sukumar S, and Chang HY. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. *Nature* 464: 1071–1076, 2010.
35. Guttman M, Amit I, Garber M, French C, Lin MF, Feldser D, Huarte M, Zuk O, Carey BW, Cassady JP, Cabili MN, Jaenisch R, Mikkelsen TS, Jacks T, Hacohen N, Bernstein BE, Kellis M, Regev A, Rinn JL, and Lander ES. Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. *Nature* 458: 223–227, 2009.
36. Hacisuleyman E, Goff LA, Trapnell C, Williams A, Henao-Mejia J, Sun L, McClanahan P, Hendrickson DG, Sauvageau M, Kelley DR, Morse M, Engreitz J, Lander ES, Guttman M, Lodish HF, Flavell R, Raj A, and Rinn JL. Topological organization of multichromosomal regions by the long intergenic noncoding RNA Firre. *Nat Struct Mol Biol* 21: 198–206, 2014.
37. Hadjiolov AA, Venkov PV, and Tsanev RG. Ribonucleic acids fractionation by density-gradient centrifugation and by agar gel electrophoresis: a comparison. *Anal Biochem* 17: 263–267, 1966.
38. Hamm J, Darzynkiewicz E, Tahara SM, and Mattaj IW. The trimethylguanosine cap structure of U1 snRNA is a component of a bipartite nuclear targeting signal. *Cell* 62: 569–577, 1990.
39. Hanahan D and Weinberg RA. The hallmarks of cancer. *Cell* 100: 57–70, 2000.
40. Hanahan D and Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 144: 646–674, 2011.
41. Hanson S, Berthelot K, Fink B, McCarthy JE, and Suess B. Tetracycline-aptamer-mediated translational regulation in yeast. *Mol Microbiol* 49: 1627–1637, 2003.
42. Harris AL. Hypoxia—a key regulatory factor in tumour growth. *Nat Rev Cancer* 2: 38–47, 2002.
43. Hermann T and Patel DJ. Adaptive recognition by nucleic acid aptamers. *Science* 287: 820–825, 2000.
44. Hirata H, Hinoda Y, Shahryari V, Deng G, Nakajima K, Tabatabai ZL, Ishii N, and Dahiya R. Long Noncoding RNA MALAT1 promotes aggressive renal cell carcinoma through Ezh2 and interacts with miR-205. *Cancer Res* 75: 1322–1331, 2015.
45. Holmes DS, Mayfield JE, Sander G, and Bonner J. Chromosomal RNA: its properties. *Science* 177: 72–74, 1972.
46. Huang C, Cao L, Qiu L, Dai X, Ma L, Zhou Y, Li H, Gao M, Li W, Zhang Q, Han K, and Lv H. Upregulation of H19 promotes invasion and induces epithelial-to-mesenchymal transition in esophageal cancer. *Oncol Lett* 10: 291–296, 2015.
47. Huang T, Liu HW, Chen JQ, Wang SH, Hao LQ, Liu M, and Wang B. The long noncoding RNA PVT1 functions as a competing endogenous RNA by sponging miR-186 in gastric cancer. *Biomed Pharmacother* 88: 302–308, 2017.
48. Huarte M, Guttman M, Feldser D, Garber M, Koziol MJ, Kenzelmann-Broz D, Khalil AM, Zuk O, Amit I, Rabani M, Attardi LD, Regev A, Lander ES, Jacks T, and Rinn JL. A large intergenic noncoding RNA induced by p53 mediates global gene repression in the p53 response. *Cell* 142: 409–419, 2010.
49. Hung T, Wang Y, Lin MF, Koegel AK, Kotake Y, Grant GD, Horlings HM, Shah N, Umbricht C, Wang P, Wang Y, Kong B, Langerod A, Borresen-Dale AL, Kim SK, van de Vijver M, Sukumar S, Whitfield ML, Kellis M, Xiong Y, Wong DJ, and Chang HY. Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. *Nat Genet* 43: 621–629, 2011.
50. Iden M, Fye S, Li K, Chowdhury T, Ramchandran R, and Rader JS. The lncRNA PVT1 contributes to the cervical cancer phenotype and associates with poor patient prognosis. *PLoS One* 11: e0156274, 2016.
51. Ivan M, Haberberger T, Gervasi DC, Michelson KS, Gunzler V, Kondo K, Yang H, Sorokina I, Conaway RC, Conaway JW, and Kaelin WG, Jr. Biochemical purification and pharmacological inhibition of a mammalian prolyl hydroxylase acting on hypoxia-inducible factor. *Proc Natl Acad Sci U S A* 99: 13459–13464, 2002.
52. Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, Salic A, Asara JM, Lane WS, and Kaelin WG, Jr. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O_2 sensing. *Science* 292: 464–468, 2001.
53. Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, von Kriegsheim A, Hebestreit HF, Mukherji

M, Schofield CJ, Maxwell PH, Pugh CW, and Ratcliffe PJ. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science* 292: 468–472, 2001.
54. Kaneko S, Son J, Shen SS, Reinberg D, and Bonasio R. PRC2 binds active promoters and contacts nascent RNAs in embryonic stem cells. *Nat Struct Mol Biol* 20: 1258–1264, 2013.
55. Kapranov P, Cawley SE, Drenkow J, Bekiranov S, Strausberg RL, Fodor SP, and Gingeras TR. Large-scale transcriptional activity in chromosomes 21 and 22. *Science* 296: 916–919, 2002.
56. Khalil AM, Guttman M, Huarte M, Garber M, Raj A, Rivea Morales D, Thomas K, Presser A, Bernstein BE, van Oudenaarden A, Regev A, Lander ES, and Rinn JL. Many human large intergenic noncoding RNAs associate with chromatin-modifying complexes and affect gene expression. *Proc Natl Acad Sci U S A* 106: 11667–11672, 2009.
57. Kim DH, Villeneuve LM, Morris KV, and Rossi JJ. Argonaute-1 directs siRNA-mediated transcriptional gene silencing in human cells. *Nat Struct Mol Biol* 13: 793–797, 2006.
58. Kretz M. TINCR, staufen1, and cellular differentiation. *RNA Biol* 10: 1597–1601, 2013.
59. Kretz M, Siprashvili Z, Chu C, Webster DE, Zehnder A, Qu K, Lee CS, Flockhart RJ, Groff AF, Chow J, Johnston D, Kim GE, Spitale RC, Flynn RA, Zheng GX, Aiyer S, Raj A, Rinn JL, Chang HY, and Khavari PA. Control of somatic tissue differentiation by the long non-coding RNA TINCR. *Nature* 493: 231–235, 2013.
60. Lee GL, Dobi A, and Srivastava S. Prostate cancer: diagnostic performance of the PCA3 urine test. *Nat Rev Urol* 8: 123–124, 2011.
61. Lee RC, Feinbaum RL, and Ambros V. The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 75: 843–854, 1993.
62. Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Radmark O, Kim S, and Kim VN. The nuclear RNase III Drosha initiates microRNA processing. *Nature* 425: 415–419, 2003.
63. Legrain P, Seraphin B, and Rosbash M. Early commitment of yeast pre-mRNA to the spliceosome pathway. *Mol Cell Biol* 8: 3755–3760, 1988.
64. Leucci E, Vendramin R, Spinazzi M, Laurette P, Fiers M, Wouters J, Radaelli E, Eyckerman S, Leonelli C, Vanderheyden K, Rogiers A, Hermans E, Baatsen P, Aerts S, Amant F, Van Aelst S, van den Oord J, de Strooper B, Davidson I, Lafontaine DL, Gevaert K, Vandesompele J, Mestdagh P, and Marine JC. Melanoma addiction to the long non-coding RNA SAMMSON. *Nature* 531: 518–522, 2016.
65. Li J, Wang J, Chen Y, Li S, Jin M, Wang H, Chen Z, and Yu W. LncRNA MALAT1 exerts oncogenic functions in lung adenocarcinoma by targeting miR-204. *Am J Cancer Res* 6: 1099–1107, 2016.
66. Li W, Notani D, Ma Q, Tanasa B, Nunez E, Chen AY, Merkurjev D, Zhang J, Ohgi K, Song X, Oh S, Kim HS, Glass CK, and Rosenfeld MG. Functional roles of enhancer RNAs for oestrogen-dependent transcriptional activation. *Nature* 498: 516–520, 2013.
67. Li X, Deng SJ, Zhu S, Jin Y, Cui SP, Chen JY, Xiang C, Li QY, He C, Zhao SF, Chen HY, Niu Y, Liu Y, Deng SC, Wang CY, and Zhao G. Hypoxia-induced lncRNA-NUTF2P3-001 contributes to tumorigenesis of pancreatic cancer by derepressing the miR-3923/KRAS pathway. *Oncotarget* 7: 6000–6014, 2016.
68. Lin A, Li C, Xing Z, Hu Q, Liang K, Han L, Wang C, Hawke DH, Wang S, Zhang Y, Wei Y, Ma G, Park PK, Zhou J, Zhou Y, Hu Z, Zhou Y, Marks JR, Liang H, Hung MC, Lin C, and Yang L. The LINK-A lncRNA activates normoxic HIF1alpha signalling in triple-negative breast cancer. *Nat Cell Biol* 18: 213–224, 2016.
69. Ling H, Spizzo R, Atlasi Y, Nicoloso M, Shimizu M, Redis RS, Nishida N, Gafa R, Song J, Guo Z, Ivan C, Barbarotto E, De Vries I, Zhang X, Ferracin M, Churchman M, van Galen JF, Beverloo BH, Shariati M, Haderk F, Estecio MR, Garcia-Manero G, Patijn GA, Gotley DC, Bhardwaj V, Shureiqi I, Sen S, Multani AS, Welsh J, Yamamoto K, Taniguchi I, Song MA, Gallinger S, Casey G, Thibodeau SN, Le Marchand L, Tiirikainen M, Mani SA, Zhang W, Davuluri RV, Mimori K, Mori M, Sieuwerts AM, Martens JW, Tomlinson I, Negrini M, Berindan-Neagoe I, Foekens JA, Hamilton SR, Lanza G, Kopetz S, Fodde R, and Calin GA. CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. *Genome Res* 23: 1446–1461, 2013.
70. Liu L, Zhao X, Zou H, Bai R, Yang K, and Tian Z. Hypoxia promotes gastric cancer malignancy partly through the HIF-1alpha dependent transcriptional activation of the long non-coding RNA GAPLINC. *Front Physiol* 7: 420, 2016.
71. Liu SJ, Horlbeck MA, Cho SW, Birk HS, Malatesta M, He D, Attenello FJ, Villalta JE, Cho MY, Chen Y, Mandegar MA, Olvera MP, Gilbert LA, Conklin BR, Chang HY, Weissman JS, and Lim DA. CRISPRi-based genome-scale identification of functional long noncoding RNA loci in human cells. *Science* 355, 2017.
72. Liu X, Xiao ZD, Han L, Zhang J, Lee SW, Wang W, Lee H, Zhuang L, Chen J, Lin HK, Wang J, Liang H, and Gan B. LncRNA NBR2 engages a metabolic checkpoint by regulating AMPK under energy stress. *Nat Cell Biol* 18: 431–442, 2016.
73. Luo M, Li Z, Wang W, Zeng Y, Liu Z, and Qiu J. Long non-coding RNA H19 increases bladder cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression. *Cancer Lett* 333: 213–221, 2013.
74. Ma MZ, Kong X, Weng MZ, Zhang MD, Qin YY, Gong W, Zhang WJ, and Quan ZW. Long non-coding RNA-LET is a positive prognostic factor and exhibits tumor-suppressive activity in gallbladder cancer. *Mol Carcinog* 54: 1397–1406, 2015.
75. Manoochehri Khoshinani H, Afshar S, and Najafi R. Hypoxia: a double-edged sword in cancer therapy. *Cancer Invest* 34: 536–545, 2016.
76. Matouk I, Raveh E, Ohana P, Lail RA, Gershtain E, Gilon M, De Groot N, Czerniak A, and Hochberg A. The increasing complexity of the oncofetal h19 gene locus: functional dissection and therapeutic intervention. *Int J Mol Sci* 14: 4298–4316, 2013.
77. Matouk IJ, DeGroot N, Mezan S, Ayesh S, Abu-lail R, Hochberg A, and Galun E. The H19 non-coding RNA is essential for human tumor growth. *PLoS One* 2: e845, 2007.
78. Matouk IJ, Halle D, Gilon M, and Hochberg A. The non-coding RNAs of the H19-IGF2 imprinted loci: a focus on biological roles and therapeutic potential in lung cancer. *J Transl Med* 13: 113, 2015.
79. Matouk IJ, Mezan S, Mizrahi A, Ohana P, Abu-Lail R, Fellig Y, Degroot N, Galun E, and Hochberg A. The oncofetal H19 RNA connection: hypoxia, p53 and cancer. *Biochim Biophys Acta* 1803: 443–451, 2010.

80. Matouk IJ, Raveh E, Abu-lail R, Mezan S, Gilon M, Gershtain E, Birman T, Gallula J, Schneider T, Barkali M, Richler C, Fellig Y, Sorin V, Hubert A, Hochberg A, and Czerniak A. Oncofetal H19 RNA promotes tumor metastasis. *Biochim Biophys Acta* 1843: 1414–1426, 2014.
81. Maxwell ES and Fournier MJ. The small nucleolar RNAs. *Annu Rev Biochem* 64: 897–934, 1995.
82. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, Wykoff CC, Pugh CW, Maher ER, and Ratcliffe PJ. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature* 399: 271–275, 1999.
83. McCarty G and Loeb DM. Hypoxia-sensitive epigenetic regulation of an antisense-oriented lncRNA controls WT1 expression in myeloid leukemia cells. *PLoS One* 10: e0119837, 2015.
84. Mele M and Rinn JL. ''Cat's Cradling'' the 3D genome by the act of LncRNA transcription. *Mol Cell* 62: 657–664, 2016.
85. Michalik KM, You X, Manavski Y, Doddaballapur A, Zornig M, Braun T, John D, Ponomareva Y, Chen W, Uchida S, Boon RA, and Dimmeler S. Long noncoding RNA MALAT1 regulates endothelial cell function and vessel growth. *Circ Res* 114: 1389–1397, 2014.
86. Mineo M, Ricklefs F, Rooj AK, Lyons SM, Ivanov P, Ansari KI, Nakano I, Chiocca EA, Godlewski J, and Bronisz A. The long non-coding RNA HIF1A-AS2 facilitates the maintenance of mesenchymal glioblastoma stem-like cells in hypoxic niches. *Cell Rep* 15: 2500–2509, 2016.
87. Monnier P, Martinet C, Pontis J, Stancheva I, Ait-Si-Ali S, and Dandolo L. H19 lncRNA controls gene expression of the imprinted gene network by recruiting MBD1. *Proc Natl Acad Sci U S A* 110: 20693–20698, 2013.
88. Nahvi A, Sudarsan N, Ebert MS, Zou X, Brown KL, and Breaker RR. Genetic control by a metabolite binding mRNA. *Chem Biol* 9: 1043, 2002.
89. Orom UA, Derrien T, Beringer M, Gumireddy K, Gardini A, Bussotti G, Lai F, Zytnicki M, Notredame C, Huang Q, Guigo R, and Shiekhattar R. Long noncoding RNAs with enhancer-like function in human cells. *Cell* 143: 46–58, 2010.
90. Portoso M, Ragazzini R, Brencic Z, Moiani A, Michaud A, Vassilev I, Wassef M, Servant N, Sargueil B, and Margueron R. PRC2 is dispensable for HOTAIR-mediated transcriptional repression. *EMBO J* 36: 981–994, 2017.
91. Prensner JR, Iyer MK, Balbin OA, Dhanasekaran SM, Cao Q, Brenner JC, Laxman B, Asangani IA, Grasso CS, Kominsky HD, Cao X, Jing X, Wang X, Siddiqui J, Wei JT, Robinson D, Iyer HK, Palanisamy N, Maher CA, and Chinnaiyan AM. Transcriptome sequencing across a prostate cancer cohort identifies PCAT-1, an unannotated lincRNA implicated in disease progression. *Nat Biotechnol* 29: 742–749, 2011.
92. Pushechnikov A, Lee MM, Childs-Disney JL, Sobczak K, French JM, Thornton CA, and Disney MD. Rational design of ligands targeting triplet repeating transcripts that cause RNA dominant disease: application to myotonic muscular dystrophy type 1 and spinocerebellar ataxia type 3. *J Am Chem Soc* 131: 9767–9779, 2009.
93. Quinn JJ and Chang HY. Unique features of long noncoding RNA biogenesis and function. *Nat Rev Genet* 17: 47–62, 2016.
94. Rankin EB and Giaccia AJ. The role of hypoxia-inducible factors in tumorigenesis. *Cell Death Differ* 15: 678–685, 2008.
95. Raveh E, Matouk IJ, Gilon M, and Hochberg A. The H19 long non-coding RNA in cancer initiation, progression and metastasis—a proposed unifying theory. *Mol Cancer* 14: 184, 2015.
96. Redis RS, Vela LE, Lu W, Ferreira de Oliveira J, Ivan C, Rodriguez-Aguayo C, Adamoski D, Pasculli B, Taguchi A, Chen Y, Fernandez AF, Valledor L, Van Roosbroeck K, Chang S, Shah M, Kinnebrew G, Han L, Atlasi Y, Cheung LH, Huang GY, Monroig P, Ramirez MS, Catela Ivkovic T, Van L, Ling H, Gafa R, Kapitanovic S, Lanza G, Bankson JA, Huang P, Lai SY, Bast RC, Rosenblum MG, Radovich M, Ivan M, Bartholomeusz G, Liang H, Fraga MF, Widger WR, Hanash S, Berindan-Neagoe I, Lopez-Berestein G, Ambrosio AL, Gomes Dias SM, and Calin GA. Allele-specific reprogramming of cancer metabolism by the long non-coding RNA CCAT2. *Mol Cell* 61: 520–534, 2016.
97. Rinn JL, Euskirchen G, Bertone P, Martone R, Luscombe NM, Hartman S, Harrison PM, Nelson FK, Miller P, Gerstein M, Weissman S, and Snyder M. The transcriptional activity of human chromosome 22. *Genes Dev* 17: 529–540, 2003.
98. Schindl M, Schoppmann SF, Samonigg H, Hausmaninger H, Kwasny W, Gnant M, Jakesz R, Kubista E, Birner P, Oberhuber G, Austrian B, and Colorectal Cancer Study Group. Overexpression of hypoxia-inducible factor 1alpha is associated with an unfavorable prognosis in lymph node-positive breast cancer. *Clin Cancer Res* 8: 1831–1837, 2002.
99. Semenza GL. Intratumoral hypoxia, radiation resistance, and HIF-1. *Cancer Cell* 5: 405–406, 2004.
100. Shalem O, Sanjana NE, Hartenian E, Shi X, Scott DA, Mikkelsen TS, Heckl D, Ebert BL, Root DE, Doench JG, and Zhang F. Genome-scale CRISPR-Cas9 knockout screening in human cells. *Science* 343: 84–87, 2014.
101. Sigova AA, Mullen AC, Molinie B, Gupta S, Orlando DA, Guenther MG, Almada AE, Lin C, Sharp PA, Giallourakis CC, and Young RA. Divergent transcription of long noncoding RNA/mRNA gene pairs in embryonic stem cells. *Proc Natl Acad Sci U S A* 110: 2876–2881, 2013.
102. Singh R and Reddy R. Gamma-monomethyl phosphate: a cap structure in spliceosomal U6 small nuclear RNA. *Proc Natl Acad Sci U S A* 86: 8280–8283, 1989.
103. St. Laurent G, Wahlestedt C, and Kapranov P. The landscape of long noncoding RNA classification. *Trends Genet* 31: 239–251, 2015.
104. Sun YW, Chen YF, Li J, Huo YM, Liu DJ, Hua R, Zhang JF, Liu W, Yang JY, Fu XL, Yan T, Hong J, and Cao H. A novel long non-coding RNA ENST00000480739 suppresses tumour cell invasion by regulating OS-9 and HIF-1alpha in pancreatic ductal adenocarcinoma. *Br J Cancer* 111: 2131–2141, 2014.
105. Taft RJ, Pheasant M, and Mattick JS. The relationship between non-protein-coding DNA and eukaryotic complexity. *Bioessays* 29: 288–299, 2007.
106. Takahashi K, Yan IK, Haga H, and Patel T. Modulation of hypoxia-signaling pathways by extracellular linc-RoR. *J Cell Sci* 127: 1585–1594, 2014.
107. Tee AE, Liu B, Song R, Li J, Pasquier E, Cheung BB, Jiang C, Marshall GM, Haber M, Norris MD, Fletcher JI, Dinger ME, and Liu T. The long noncoding RNA MALAT1 promotes tumor-driven angiogenesis by up-regulating pro-angiogenic gene expression. *Oncotarget* 7: 8663–8675, 2016.

108. Tsai MC, Manor O, Wan Y, Mosammaparast N, Wang JK, Lan F, Shi Y, Segal E, and Chang HY. Long noncoding RNA as modular scaffold of histone modification complexes. *Science* 329: 689–693, 2010.
109. Tsai MC, Spitale RC, and Chang HY. Long intergenic noncoding RNAs: new links in cancer progression. *Cancer Res* 71: 3–7, 2011.
110. Vaupel P and Mayer A. Hypoxia in cancer: significance and impact on clinical outcome. *Cancer Metastasis Rev* 26: 225–239, 2007.
111. Wang Y, Liu X, Zhang H, Sun L, Zhou Y, Jin H, Zhang H, Zhang H, Liu J, Guo H, Nie Y, Wu K, Fan D, Zhang H, and Liu L. Hypoxia-inducible lncRNA-AK058003 promotes gastric cancer metastasis by targeting gamma-synuclein. *Neoplasia* 16: 1094–1106, 2014.
112. Wang Y, Yao J, Meng H, Yu Z, Wang Z, Yuan X, Chen H, and Wang A. A novel long non-coding RNA, hypoxia-inducible factor-2alpha promoter upstream transcript, functions as an inhibitor of osteosarcoma stem cells in vitro. *Mol Med Rep* 11: 2534–2540, 2015.
113. Warner JR, Soeiro R, Birnboim HC, Girard M, and Darnell JE. Rapidly labeled HeLa cell nuclear RNA. I. Identification by zone sedimentation of a heterogeneous fraction separate from ribosomal precursor RNA. *J Mol Biol* 19: 349–361, 1966.
114. Wei X, Wang C, Ma C, Sun W, Li H, and Cai Z. Long noncoding RNA ANRIL is activated by hypoxia-inducible factor-1alpha and promotes osteosarcoma cell invasion and suppresses cell apoptosis upon hypoxia. *Cancer Cell Int* 16: 73, 2016.
115. Werstuck G and Green MR. Controlling gene expression in living cells through small molecule-RNA interactions. *Science* 282: 296–298, 1998.
116. Wiedmeier JE, Ohlrich A, Chu A, Rountree MR, and Turker MS. Induction of the long noncoding RNA NBR2 from the bidirectional BRCA1 promoter under hypoxic conditions. *Mutat Res* 796: 13–19, 2017.
117. Wu W, Hu Q, Nie E, Yu T, Wu Y, Zhi T, Jiang K, Shen F, Wang Y, Zhang J, and You Y. Hypoxia induces H19 expression through direct and indirect Hif-1alpha activity, promoting oncogenic effects in glioblastoma. *Sci Rep* 7: 45029, 2017.
118. Xia T, Liao Q, Jiang X, Shao Y, Xiao B, Xi Y, and Guo J. Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. *Sci Rep* 4: 6088, 2014.
119. Xiang JF, Yin QF, Chen T, Zhang Y, Zhang XO, Wu Z, Zhang S, Wang HB, Ge J, Lu X, Yang L, and Chen LL. Human colorectal cancer-specific CCAT1-L lncRNA regulates long-range chromatin interactions at the MYC locus. *Cell Res* 24: 513–531, 2014.
120. Xiao H, Tang K, Liu P, Chen K, Hu J, Zeng J, Xiao W, Yu G, Yao W, Zhou H, Li H, Pan Y, Li A, Ye Z, Wang J, Xu H, and Huang Q. LncRNA MALAT1 functions as a competing endogenous RNA to regulate ZEB2 expression by sponging miR-200s in clear cell kidney carcinoma. *Oncotarget* 6: 38005–38015, 2015.
121. Xue M, Li X, Li Z, and Chen W. Urothelial carcinoma associated 1 is a hypoxia-inducible factor-1alpha-targeted long noncoding RNA that enhances hypoxic bladder cancer cell proliferation, migration, and invasion. *Tumour Biol* 35: 6901–6912, 2014.
122. Yang C, Tang R, Ma X, Wang Y, Luo D, Xu Z, Zhu Y, and Yang L. Tag SNPs in long non-coding RNA H19 contribute to susceptibility to gastric cancer in the Chinese Han population. *Oncotarget* 6: 15311–15320, 2015.
123. Yang F, Huo XS, Yuan SX, Zhang L, Zhou WP, Wang F, and Sun SH. Repression of the long noncoding RNA-LET by histone deacetylase 3 contributes to hypoxia-mediated metastasis. *Mol Cell* 49: 1083–1096, 2013.
124. Yang F, Zhang H, Mei Y, and Wu M. Reciprocal regulation of HIF-1alpha and lincRNA-p21 modulates the Warburg effect. *Mol Cell* 53: 88–100, 2014.
125. Yang Z, Wang R, Zhang T, and Dong X. Hypoxia/lncRNA-AK123072/EGFR pathway induced metastasis and invasion in gastric cancer. *Int J Clin Exp Med* 8: 19954–19968, 2015.
126. Yao J, Li J, Geng P, Li Y, Chen H, and Zhu Y. Knockdown of a HIF-2alpha promoter upstream long noncoding RNA impairs colorectal cancer stem cell properties in vitro through HIF-2alpha downregulation. *Onco Targets Ther* 8: 3467–3474, 2015.
127. Yoon JH, Abdelmohsen K, Srikantan S, Yang X, Martindale JL, De S, Huarte M, Zhan M, Becker KG, and Gorospe M. LincRNA-p21 suppresses target mRNA translation. *Mol Cell* 47: 648–655, 2012.
128. Zhai W, Sun Y, Jiang M, Wang M, Gasiewicz TA, Zheng J, and Chang C. Differential regulation of lncRNA-SARCC suppresses VHL-mutant RCC cell proliferation yet promotes VHL-normal RCC cell proliferation via modulating androgen receptor/HIF-2alpha/C-MYC axis under hypoxia. *Oncogene* 35: 4866–4880, 2016.
129. Zhang EB, Kong R, Yin DD, You LH, Sun M, Han L, Xu TP, Xia R, Yang JS, De W, and Chen J. Long noncoding RNA ANRIL indicates a poor prognosis of gastric cancer and promotes tumor growth by epigenetically silencing of miR-99a/miR-449a. *Oncotarget* 5: 2276–2292, 2014.
130. Zhou C, Ye L, Jiang C, Bai J, Chi Y, and Zhang H. Long noncoding RNA HOTAIR, a hypoxia-inducible factor-1alpha activated driver of malignancy, enhances hypoxic cancer cell proliferation, migration, and invasion in non-small cell lung cancer. *Tumour Biol* 36: 9179–9188, 2015.
131. Zhu S, Li W, Liu J, Chen CH, Liao Q, Xu P, Xu H, Xiao T, Cao Z, Peng J, Yuan P, Brown M, Liu XS, and Wei W. Genome-scale deletion screening of human long non-coding RNAs using a paired-guide RNA CRISPR-Cas9 library. *Nat Biotechnol* 34: 1279–1286, 2016.
132. Zhu Z, Gao X, He Y, Zhao H, Yu Q, Jiang D, Zhang P, Ma X, Huang H, Dong D, Wan J, Gu Z, Jiang X, Yu L, and Gao Y. An insertion/deletion polymorphism within RERT-lncRNA modulates hepatocellular carcinoma risk. *Cancer Res* 72: 6163–6172, 2012.

Address correspondence to:
Dr. Mircea Ivan
Department of Medicine
Indiana University School of Medicine
980 W. Walnut Street, Room C225
Indianapolis, IN 46202

E-mail: mivan@iu.edu

Date of first submission to ARS Central, July 26, 2017; date of acceptance, August 2, 2017.

Abbreviations Used

AML = acute myeloid leukemia
ANRIL = CDKN2B antisense RNA 1
AR = androgen receptor
ASO = antisense oligonucleotide
BRCA1 = breast cancer 1
CCATs = colon cancer-associated transcripts
CRC = colorectal cancer
CRISPR = clustered regularly interspaced short palindromic repeat
DNMT1 = DNA methyltransferase 1
EGFR = epidermal growth factor receptor
EGLN 1–3/PHD 1–3 = prolyl hydroxylases 1–3
EMT = epithelial-to-mesenchymal transition
GPNMB = glycoprotein nmb
H19 = imprinted maternally expressed lncRNA
HCC = hepatocellular carcinoma
HIF = hypoxia-inducible factor
HIF-1α = hypoxia-inducible factor 1 alpha
HIF1A-AS2 = hypoxia-inducible factor 1 alpha antisense 2
HINCUT-1 = hypoxia-induced noncoding ultraconserved transcript 1
HOTAIR = HOX transcript antisense RNA
lincRNA = long intergenic ncRNA
LINK-A = long intergenic noncoding RNA for kinase activation
lncRNA = long noncoding RNA
MALAT1 = metastasis-associated lung adenocarcinoma transcript 1
miRNA = microRNA
NAT = natural antisense transcript
NBR2 = neighbor of the BRCA1 gene 2
NEAT1 = nuclear paraspeckle assembly transcript 1
OGT = *O*-linked *N*-acetylglucosamine transferase
PCA3/DD3 = prostate cancer-associated 3
PCAT-1 = prostate cancer-associated ncRNA transcript 1
PRC2 = polycomb repressive complex 2
pVHL = von Hippel-Lindau tumor suppressor protein
PVT1 = PVT1 plasmacytoma variant translocation 1 lncRNA
RCC = renal cell carcinoma
RERT = RAB4B-EGLN2 read-through lncRNA
SARCC = suppressing androgen receptor in renal cell carcinoma
SCLC = squamous-cell lung cancer
TET2 = tet methylcytosine dioxygenase 2
UCA1/CUDR = urothelial cancer-associated 1
VEGFA = vascular endothelial growth factor A
vtRNA = vault RNA
WT1 = Wilms' tumor 1