lncRNA HIF1A-AS2: A potential oncogene in human cancers (Review)

YANG LIU[1], YUNYAN ZHANG[2], CHA CHEN[1] and YOUQIANG LI[3]

[1]The Second Clinical College of Guangzhou University of Chinese Medicine, Guangzhou, Guangdong 510006; [2]Department of Stomatology, Guangzhou Women and Children's Medical Center, Guangzhou, Guangdong 510000; [3]Department of Laboratory Medicine, The Affiliated Hexian Memorial Hospital of Southern Medical University, Guangzhou, Guangdong 511400, P.R. China

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Abstract. Long non-coding RNAs (lncRNAs) are transcripts that are >200 nucleotides, but with no open reading frame. An increasing number of lncRNAs have been identified following the development of second-generation sequencing technologies, and they have since become a research hotspot. Functionally, they play a vital role in tumor progression, including in tumor proliferation, migration, invasion, apoptosis and acquisition of drug resistance. They regulate gene expression primarily through interaction with DNA, RNA and proteins at the epigenetic, transcriptional and post-transcriptional levels. Endogenous hypoxia-inducible factor 1α antisense RNA 2 (lncRNA HIF1A-AS2) is aberrantly expressed and involved the development/progression of various types of tumors, such as bladder cancer, glioblastoma, breast cancer and osteosarcoma. It plays a vital role in the proliferation, apoptosis, migration, invasion and epithelial-mesenchymal transformation of various tumor cells. This review summarizes the current body of knowledge on the biological functions and related molecular mechanisms of lncRNA HIF1A-AS2 in the development/progression of human tumors and other diseases.

Correspondence to: Dr Youqiang Li, Department of Laboratory Medicine, The Affiliated Hexian Memorial Hospital of Southern Medical University, 2 Qinghe East Road, Guangzhou, Guangdong 511400, P.R. China
E-mail: liyouqiang21@126.com

Abbreviations: PHLDA1, pleckstrin homology like domain, family A, member 1; LSD1, lysine-specific demethylase 1; EMT, epithelial-mesenchymal transformation; IGF2BP2, insulin-like growth factor 2; DHX9, ATP-dependent RNA helicase A; HMGA1, high mobility group AT-hook 1; lncRNA, long non-coding RNA; HIF1A-AS2, hypoxia-inducible factor 1α antisense RNA 2

Key words: lncRNA, HIF1A-AS2, cancer, microRNA, biomarker

Contents

1. Introduction

Technological advances have driven an improved understanding of protein-coding genes; however, the functional roles of non-coding (nc)RNAs are relatively less well understood. ncRNAs account for >90% of the human genome, whereas protein-coding genes account for only 1.5% (1,2). Based on transcript size, ncRNAs are divided into two groups: Small ncRNAs with transcripts <200 nucleotides and long ncRNAs (lncRNAs) with transcripts >200 nucleotides in length (3). lncRNAs, first discovered in the sequencing of cDNA libraries in mouse cells (4), are mRNA-like transcripts that are likely transcribed by RNA polymerase II (RNA pol II), but which lack a stable open reading frame (5). Initially, these non-coding RNAs were viewed as by-products and noise of the transcription process (4). However, with the continuous development of gene technologies, a large number of studies have found that lncRNAs are involved in various physiological and pathological processes.

lncRNA HIF1A-AS2, also known as HIF1A-AS2, is the endogenous antisense transcript of hypoxia-inducible factor 1α (HIF1α), and 3'aHIF, termed HIF1α antisense RNA 2 (HIF1A-AS2), is localized at chromosome 14q23.2, and is 2,052 nucleotides in length. In 1999, it was first discovered to be abnormally expressed in clear cell renal carcinoma by Thrash-Bingham and Tartof (6), and was identified as the endogenous antisense transcript, which could bind to the 3' untranslated region (3'UTR) of HIF1α mRNA in a complementary manner (Fig. 1), and this bound form is referred to as aHIF. In 2002, Rossignol *et al* (7) reported that HIF1A-AS2 was expressed in several human tissues, both physiologically, and when the tissues had become cancerous. These findings attracted increased focus on HIF1A-AS2. Further studies demonstrated that HIF1A-AS2 was aberrantly expressed in

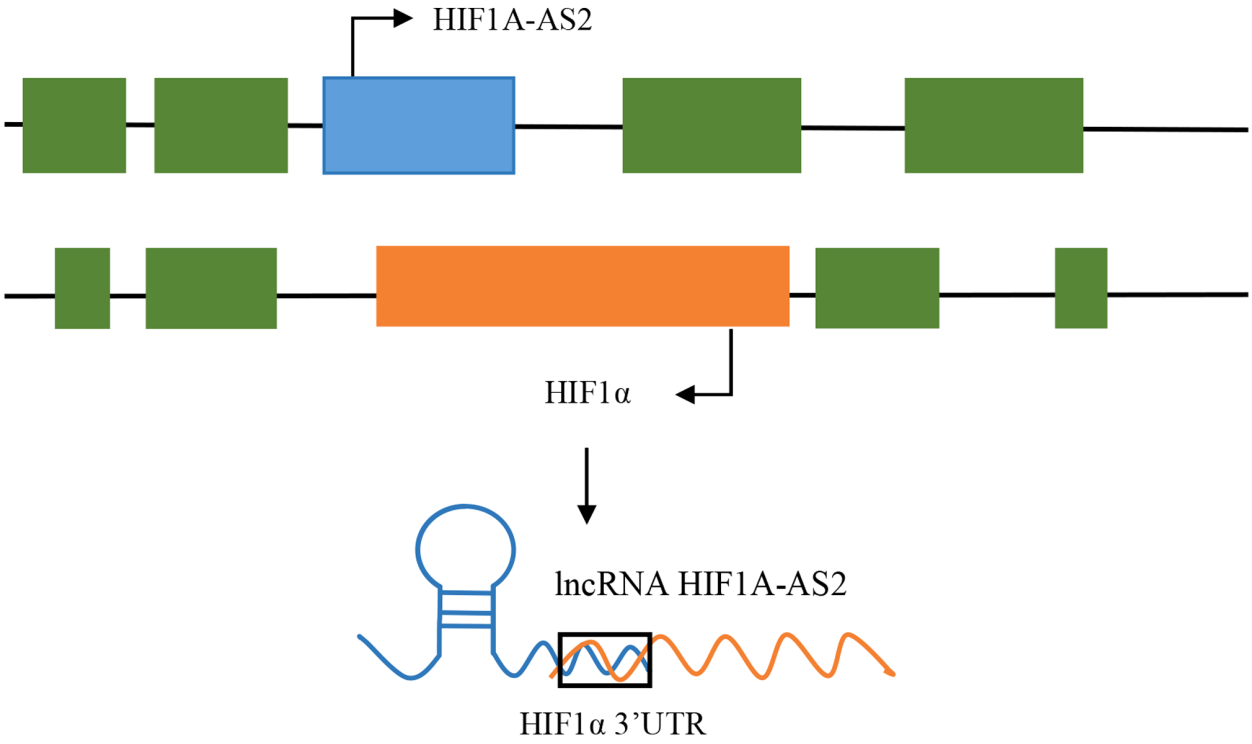

Figure 1. Location of HIF1A-AS2 and HIF1α in chromosome 14. HIF1α, hypoxia-inducible factor 1α; HIF1A-AS2, HIF1α antisense RNA.

various human diseases, including preeclampsia (PE), epithelial ovarian cancer (EOC), colorectal cancer (CRC), gastric cancer (GC), breast cancer (BC), bladder cancer, osteosarcoma (OS), renal cell carcinoma, non-small cell lung cancer (NSCLC) and glioblastoma (GBM). Chen *et al* (8) reported that the expression levels of HIF1A-AS2 were upregulated in GC tissues and cells, and this upregulated expression was correlated with Tumor-Node-Metastasis stage, tumor invasion, lymph node metastasis and a poor prognosis. Lin *et al* (9) also demonstrated upregulated expression of HIF1A-AS2 in 60 OS tissues compared with the adjacent healthy tissues. Thus, HIF1A-AS2 may serve as a promising target for treatment of several types of cancer.

However, several studies demonstrated that the expression levels of HIF1A-AS2 in tumor tissues was abnormal, indicating the potential correlation between HIF1A-AS2 and cancer. Therefore, this review summarizes the current body of knowledge regarding the aberrant expression of this lncRNA (Table I), its function and the regulatory mechanisms of HIF1A-AS2 in several types of cancer.

2. Expression and function of lncRNA HIF1A-AS2 in several types of cancer

PE. PE is one of the leading causes of maternal death and a pregnancy-specific disease, affecting 3-14% of parturients worldwide (10). Although PE has been extensively studied (11), the underlying pathogenesis of PE remains elusive. However, it is hypothesized that inadequate trophoblastic invasion may cause PE (12,13). Wu *et al* (14) reported that HIF1A-AS2 expression was significantly downregulated in the tissues of 52 patients with PE compared with the adjacent normal samples. Knockdown of HIF1A-AS2 expression significantly inhibited proliferation, migration and invasion, as well as inducing G0/G1 cell cycle arrest and increased cell apoptosis in two trophoblast cell lines (HTR/SVneo and JAR). In contrast, overexpression of HIF1A-AS2 exerted the opposite effect. Mechanistically, a subcellular localization assay indicated that HIF1A-AS2 was primarily localized in the cell nucleus; thus, it may play a role in regulation of transcription. Further experiments showed that HIF1A-AS2 inhibited the transcription of pleckstrin homology like domain, family A, member 1 (PHLDA1), which plays a significant role in the activation-induced apoptosis following binding to lysine-specific demethylase (LSD1) at the epigenetic level. Furthermore, chromatin immunoprecipitation assays showed LSD1 and H3K4 me2 enrichment in the promoter region of the PHLDA1 gene (Fig. 2A) after transfection with small-interfering (si)-HIF1A-AS2. Thus, HIF1A-AS2 may be a useful diagnostic biomarker for PE.

EOC. Ovarian cancer (OC) is one of the most common types of malignant tumors in females, with EOC being the most common, accounting for 80-90% of OC cases (15,16) . Although EOC treatments have improved notably, even in developed countries, such as the United States and Canada, the overall survival remains at only 47% 5 years after diagnosis (17). Therefore, investigating the molecular mechanism and finding effective therapeutic targets for management of EOC is of great importance. Qiu *et al* (18) reported that the expression of HIF1A-AS2 in EOC tissues was significantly higher compared with the normal controls, and HIF1A-AS2 was a lncRNA that was upregulated under hypoxic conditions. Thus, the following assays were performed under hypoxic conditions. Functional assays revealed that knockdown of HIF1A-AS2 promoted cell apoptosis and weakened tumorigenesis in nude mice. In

Table I. Expression and function of long non-coding RNA HIF1α antisense RNA in PE and various types of cancer.

Disease	Change in expression	Role	Biological function	Related genes	Refs.
PE	Down	Pathogenic	Proliferation, migration, invasion, pro-apoptosis, cell cycle arrest	LSD1, PHLDA1	(14)
Epithelial ovarian cancer	Up	Oncogenic	Proliferation, migration and invasion	Bax, caspase-7, caspase-9, BCL-2, caspase-3	(18)
Colorectal cancer	Up	Oncogenic	Proliferation, migration and invasion	miR-129-5p, miR-33b-5p DNMT3A	(23)
Gastric cancer	Up	Oncogenic	Proliferation, migration and invasion	-	(8)
Breast cancer	Up	Oncogenic	Proliferation, migration and invasion	miR-548c-3p, HIF1α, VEGF	(30)
Bladder cancer	Up	Oncogenic	Proliferation, migration, invasion and anti-apoptosis	-	(35)
Osteosarcoma	Up	Oncogenic	Proliferation, migration, invasion and anti-apoptosis	miR-33b-5p, SIRT6, miR-129-5p	(9,40)
Glioblastoma	Up	Oncogenic	Neurosphere formation	IGF2BP2, DHX9, HMGA1	(43)
Renal cancer	Up	Oncogenic	Proliferation, migration, invasion and anti-apoptosis	HIF1α, miR-130-5p	(6,50)
Non-small cell lung cancer	Up	Oncogenic	Proliferation, migration, invasion and anti-apoptosis	miR-153b-5p, S100A14	(54)

HIF1α, hypoxia-inducible factor 1α; LSD1, lysine-specific demethylase 1; PHLDA1, pleckstrin homology like domain, family A, member 1; IGF2BP2, insulin-like growth factor 2; DHX9, ATP-dependent RNA helicase A; HMGA1, high mobility group AT-hook 1; VEGF, vascular endothelial growth factor; BCL-2, B-cell lymphoma 2; BAX, Bcl-2-associated X protein; miRNA, microRNA; PE, preeclampsia.

contrast, overexpression of HIF1A-AS2 inhibited EOC cell apoptosis and enhanced cell proliferation.

Further mechanistic experiments showed that HIF1A-AS2 functions by regulating the mitochondrial apoptosis pathway-related genes (Fig. 2B). Briefly, HIF1A-AS2 knockdown resulted in increased expression of Bax, Bcl-2, caspase-7, and caspase-9 at the mRNA level under hypoxic conditions. Thus, overexpression of HIF1A-AS2 may serve as a diagnostic biomarker for EOC.

CRC. CRC is the third most common type of cancer and the fourth leading cause of cancer-associated death globally (19,20). At present, chemotherapy is an essential treatment for CRC; however, both the incidence and death rate of CRC is increasing rapidly (21,22). Thus, it is crucial to identify novel critical genes involved in the pathogenesis of CRC to develop effective treatments. Lin *et al* (23) observed upregulated expression of HIF1A-AS2 in CRC tissues and cells compared with the healthy controls. Moreover, high expression of HIF1A-AS2 was strongly associated with a poor prognosis and advanced TNM stages in patients with CRC. Functionally, knockdown of HIF1A-AS2 inhibited the proliferation, invasion and epithelial-mesenchymal transformation (EMT) of CRC cells *in-vitro*. HIF1A-AS2 mechanistically functioned as a competing endogenous (ce)RNA binding to microRNA (miR)-129-5p (Fig. 2C), a tumor suppressor. Consistent with this, DNMT3A was identified to be a target of miR-129–5p. The critical role of the HIF1A-AS2/miR-129-5p/DNMT3A axis in the proliferation, invasion and EMT of CRC cells was further confirmed by reverse transcription-quantitative PCR and dual- luciferase reporter assays. Thus, due to its oncogenic role and clinical significance in colorectal cancer, HIF1A-AS2 may be considered a diagnostic biomarker and prognostic indicator for CRC.

GC. GC is the third leading cause of cancer-associated death worldwide, with ~1,000,000 newly diagnosed cases each year, and a higher rate of occurrence in East Asia (24,25). The majority of patients are diagnosed with advanced stage GC, and thus, GC has a high mortality rate (26). Therefore, it has been a central issue to study the pathogenic mechanisms of GC and identify effective tumor markers to improve early diagnosis. Chen *et al* (8) reported that HIF1A-AS2 was upregulated in 38 GC samples and four human GC cell lines compared with the matched paracarcinoma tissues or a normal GC cell line (GES-1), respectively. The high expression of HIF1A-AS2 was significantly associated with a more advanced TNM stage, tumor invasion, lymph node metastasis and a poor prognosis. Functionally, knockdown of HIF1A-AS2 suppressed the proliferative ability of GC cells *in-vitro* and restrained tumor

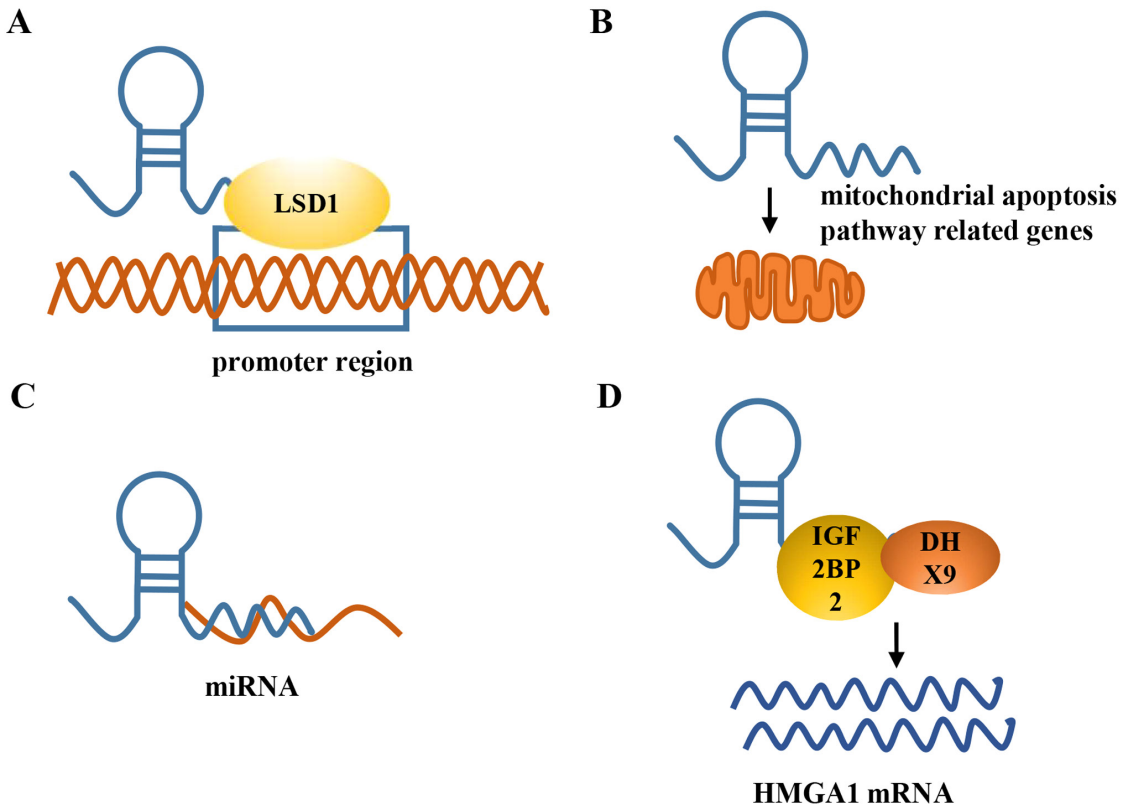

Figure 2. Mechanistic model of HIF1A-AS2 in cancer. (A) HIF1A-AS2 recruits LSD1 to the promoter of the target gene and regulates gene transcription at the epigenetic level. (B) HIF1A-AS2 can regulate expression of mitochondrial apoptosis pathway-related genes. (C) HIF1A-AS2 can function as a competing endogenous RNA to sponge miRNA in cancer. (D) HIF1A-AS2 can bind to IGF2BP2 and DHX9 to modulate the expression of HMGA1. HIF1A-AS, hypoxia-inducible factor 1α antisense RNA; LSD1, lysine-specific demethylase 1; IGF2BP2, insulin-like growth factor 2; DHX9, ATP-dependent RNA helicase A; HMGA1, high mobility group AT-hook 1; miRNA, microRNA.

weight and volume in nude mice. In addition, it was found that HIF1A-AS2 had value in the early diagnosis of GC and could be used as a potential diagnostic marker for detection of GC. Therefore, HIF1A-AS2 is a potential tumorigenic gene in GC, but its molecular mechanisms have not been studied, to the best of our knowledge.

BC. BC is the most common malignancy and the leading cause of cancer-related death in women (27). Breast cancer tumors usually express a combination of the following receptors: Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2). Cases that lack expression of these three receptors are termed triple-negative breast cancer (TNBC). TNBC accounts for ~20% of all breast cancer cases, ad is most common in women >40 (28). TNBC is highly invasive, with high mortality and recurrence rates. Current treatments for TNBC include surgery, chemotherapy, radiotherapy and targeted therapy. However, the median overall survival rarely extends beyond 18 months in patients with advanced BC (29). Therefore, it is essential to study the molecular mechanism and identify novel biomarkers for management of TNBC. Guo *et al* (30) showed that HIF1A-AS2 was significantly overexpressed in four BC cell lines compared with a normal mammary epithelial cell line. Knockdown of HIF1A-AS2 levels effectively suppress proliferation, invasion, EMT and senescence of MCF-7 cell lines *in-vitro*. *In vivo* studies also showed that tumor growth was reduced after the knockdown of HIF1A-AS2 by short hairpin (sh)RNA targeting HIF1A-AS2 *in-vivo*, thus indicating that HIF1A-AS2 functions as an oncogene. Mechanistically, a HIF1A-AS2/miR-548c-3p/HIF1a/VEGF axis was confirmed to regulate the proliferation, invasion, migration and EMT of BC cells. Jiang *et al* (31) also reported that expression of HIF1A-AS2 was increased in 33 TNBC tissues compared with the adjacent normal breast tissues. Knockdown of HIF1A-AS2 functionally suppressed TNBC cell proliferation. These results indicated that HIF1A-AS2 was involved in the pathogenesis of TNBC, suggesting that it could be a prognostic indicator or therapeutic target for TNBC.

Bladder cancer. Bladder cancer is one of the most common malignancies of the urinary system worldwide, posing a severe threat to human health (32). Surgery, radiotherapy and chemotherapy are the primary modes of treatment for bladder cancer; however, the 5-year overall survival rate is only 50-60% (33). Although several studies have demonstrated novel biomarkers for the early detection and diagnosis of bladder cancer, the survival rate of patients with bladder cancer remains very low (34). Therefore, it is necessary to identify novel biomarkers to improve the early diagnosis and prognosis of bladder cancer. Chen *et al* (35) revealed that the expression of HIF1A-AS2 was significantly upregulated in 44 bladder cancer samples and cancer cell lines (5637 and T24) compared with the matched normal peritumoral tissues or the SVHUC-1 normal bladder cell line. In addition, the upregulated HIF1A-AS2 expression was closely related to histological grade, tumor invasion depth and TNM stage. These results indicated that lncRNA

HIF1A-AS2 may function as an oncogene in bladder cancer. Functionally, knockdown of HIF1A-AS2 significantly inhibited bladder cancer cell proliferation and migration, and increased apoptosis. Conversely, overexpression of HIF1A-AS2 had the opposite effect.

Furthermore, a tetracycline-induced shRNA using medical synthetic biology techniques was designed, which could effectively inhibit the expression of HIF1A-AS2 in a dose-dependent manner, and in turn inhibited cell growth and migration, and induced apoptosis in bladder cancer cells. It also indicated that tetracycline-induced shRNA may be a novel approach for quantitatively controlling specific targets in human cancers, and may be an effective treatment method for bladder cancer. Thus, HIF1A-AS2 may serve as a target for the treatment of bladder cancer; however, the exact molecular regulatory mechanisms in bladder cancer require further study.

OS. OS is a skeletal system primary malignant tumor, common amongst the younger population, particularly children and adolescents (36,37). OS accounts for 60% of all sarcoma cases, characterized by early metastasis, high aggressiveness, a high rate of disability and a high recurrence rate (38). Despite advances in OS treatment, the overall survival of patients has not substantially increased, the 5-year overall survival still remains only 20% over the past 30 years (39). Thus, understanding the molecular mechanism of OS and identifying novel therapeutic targets is of great clinical significance to improve early diagnosis and survival rates of patients with OS. Lin *et al* (9) observed increased HIF1A-AS2 expression in 60 OS samples and four OS cell lines when compared with the 60 adjacent normal samples or the hFOB 1.19 cells, respectively. In addition, high expression of HIF1A-AS2 was significantly associated with a larger tumor size, higher tumor grade, advanced stage disease and distance of metastasis.

Furthermore, Kaplan-Meier survival analysis showed that the 5-year survival rate of the high HIF1A-AS2 expression group was lower than the low HIF1A-AS2 expression group. Knockdown of HIF1A-AS2 resulted in decreased cell proliferation, migration and invasion, increased cell cycle arrest in the G0/G1-phase and an increased percentage of apoptotic cells. In *in-vivo* experiments, knockdown of HIF1A-AS2 resulted in reduced tumor size in nude mice. Mechanistically, HIF1A-AS2/miR-33b-5p/SIRT6 was confirmed to regulate OS cell proliferation, migration and apoptosis. Wang *et al* (40) also confirmed increased expression of HIF1A-AS2 in 30 OS samples and four OS cell lines compared with the adjacent normal tissues and osteoblast cell lines, respectively. Moreover, high HIF1A-AS2 expression was associated with poor survival rates. Functional assays revealed that HIF1A-AS2 overexpression promoted osteosarcoma cell proliferation, cell cycle progression and invasion. HIF1A-AS2 mechanistically served as a ceRNA to negatively regulate miR-129–5p (Fig. 2C). Thus, HIF1A-AS2 may be an effective diagnostic and prognostic indicator of OS.

GBM. GBM is the most common and aggressive primary malignant brain tumor, with a median patient survival time of 14-16 months (41). GBM is a highly proliferative and invasive tumor with a poor prognosis. Despite advances in GBM treatment, patients are still likely to face a poor prognosis (42). Therefore, new therapeutic methods and targets are required. lncRNAs are involved in the development of GBM. Mineo *et al* (43) reported that HIF1A-AS2 contributes to the formation of stem-like glioma cells (GSCs) in the tumor microenvironment and their adaptation to hypoxia. Based on characterization of the GBM genome and transcriptome, GBM can be divided into several cellular subtypes, including mesenchymal (M), proneural (P), neural (N), and classical (C) (44). Patients with the aggressive and predominant M subtype exhibit a particularly high degree of tumor necrosis (45). It was observed that HIF1A-AS2 expression was significantly increased in the GSCs of patients with the M subtype. Moreover, knockdown of HIF1A-AS2 led to reduced growth, decreased cellular activity and decreased neurosphere-forming capacity of M GSC cells (43).

Furthermore, the HIF1A-AS2 expression is increased under hypoxic conditions. In order to clarify the pro-oncogenic function of HIF1A-AS2, researchers revealed that knockdown of HIF1A-AS2 by shRNA resulted in smaller tumor sizes in nude mice. Mechanistic experiments showed that HIF1A-AS2 could bind to IGF2BP2 and DHX9 to directly modulate the expression of HMGA1 (Fig. 2D) and maintain the growth of M GSCs under hypoxic conditions (43). In addition, Liao *et al* (46) showed that the upregulated HIF1A-AS2 expression could mediate radiation resistance of the glioma, leading to tumor recurrence following radiotherapy by regulating expression of apoptotic proteins. Knockdown of HIF1A-AS2 increased the expression of the pro-apoptotic protein caspase 7 and the number of apoptotic cells. Thus, HIF1A-AS2 may be a novel diagnostic indicator and potential therapeutic target for the management of GBM.

RCC. RCC is one of the most common malignancies of the urinary system, and accounts for 2-3% of all malignancies (47,48). The estimated number of new cases and deaths worldwide in 2018 were 403,262 and 175,098, respectively (49). Relatively fewer biomarkers for RCC have been identified when compared with other types of cancer. Thus, it is essential to identify novel and sensitive biomarkers to predict the progress and prognosis of the disease. In 1999, Thrash-Bingham and Tartof (6) first discovered a natural antisense transcript that could bind to the 3'UTR of HIF1α mRNA in non-papillary kidney cancer and termed it aHIF, for which the official gene symbol is now HIF1A-AS2. Expression of HIF1A-AS2 is increased in non-papillary renal carcinoma cells compared with the control cells, but not in papillary renal carcinoma cells. It is hypothesized that decreased HIF1a mRNA expression through HIF1A-AS2 may serve an important role in regulating P53 to regulate progression of cancer, but this mechanism requires further investigation (6). Zhu *et al* (50) also reported increased expression of HIF1A-AS2 in kidney cancer tissues and RCC cells compared with the non-cancerous tissues. In addition, knockdown of HIF1A-AS2 inhibited renal cancer cell proliferation, invasion and migration, whilst accelerating cell apoptosis. Overexpression of HIF1A-AS2 resulted in the opposite effect. HIF1A-AS2 mechanistically functions as a ceRNA, binding to miR-130a-5p (Fig. 2C) to modulate renal carcinoma progression. Thus, HIF1A-AS2 may be a promising diagnostic biomarker and a potential therapeutic target for management of renal cancer.

NSCLC. Lung cancer is the most common type of cancer and the leading cause of cancer-associated death worldwide. The

majority of patients are diagnosed with advanced stage disease in the first instance, and NSCLC accounts for nearly 85% of patients with lung cancer (51). Despite advances in cancer treatment, lung cancer has a high mortality rate, accounting for 18.4% of all cancer deaths (52,53). Thus, understanding the molecular mechanism of *NSCLC* and identifying novel therapeutic targets is of great clinical significance. Zhang *et al* (54) reported elevated expression levels of HIF1A-AS2 in NSCLC tissues and cell lines, and this increased expression was associated with a poor prognosis. However, knockdown of HIF1A-AS2 resulted in decreased cell proliferation, migration and invasion, and an increased percentage of apoptotic cells. Mechanistically, a HIF1A-AS2/miR-153–5p/S100A14 axis was confirmed to regulate NSCLC cell proliferation, migration and apoptosis (Fig. 2C). Thus, HIF1A-AS2 may be an effective diagnostic and prognostic indicator for NSCLC.

3. Conclusions and future perspective

A wealth of studies have shown that lncRNAs exert their functions through various mechanisms, such as associating with transcription factors, chromatin modifiers, signaling adapters, enzymes and miRNAs, to influence gene expression, post-translational modifications and protein activities (55).

HIF1A-AS2 has been reported to regulate cellular pathological processes, but is primarily focused on tumors. HIF1A-AS2 is primarily functions as a protein scaffold, protein decoy and a ceRNA. Mineo *et al* (43) reported that HIF1A-AS2 acts as a protein scaffold to bind both IGF2BP2 and DHX9 to modulate the expression of HMGA1. Wu *et al* (14) reported that HIF1A-AS2 functions as a protein decoy to inhibit the transcription of PHLDA1 by binding to LSD1, a histone demethylase. Additionally, HIF1A-AS2 acts as a molecular sponge to bind miRNAs to further affect expression of other genes (23,40,50,54,56). Although significant achievements have been obtained with regard to understanding the role of HIF1A-AS2 in various types of cancer, further studies are still required with regard to its regulatory function, as lncRNAs often exhibit several complex regulatory functions/mechanisms.

Studies have shown that HIF1A-AS2 may serve as a novel biomarker for the clinical diagnosis of several types of cancer. These data demonstrate that upregulated expression of HIF1A-AS2 is associated with poor overall survival and an unfavorable prognosis, such as in TNBC, OS and CRC. Nevertheless, the clinical diagnostic value of HIF1A-AS2 in these types of cancer needs to be validated using large-scale multicenter cohorts.

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Availability of data and materials

Not applicable.

Authors' contributions

YLi conceived and designed the study. YLiu, YZ and CC participated in drafting and revising the article. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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