LncRNA-ATB: An indispensable cancer-related long noncoding RNA

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Abstract

Objectives: Long non-coding RNAs (lncRNAs) are a group of non-protein-coding RNAs that are greater than 200 nucleotides in length. Increasing evidence indicates that lncRNAs, which may serve as either oncogenes or tumour suppressor genes, play a vital role in the pathophysiology of human diseases, especially in tumourigenesis and progression. Deregulation of lncRNAs impacts different cellular processes, such as proliferation, dedifferentiation, migration, invasion and anti-apoptosis. The aim of this review was to explore the molecular mechanism and clinical significance of long non-coding RNA-activated by transforming growth factor β (lncRNA-ATB) in various types of cancers.

Materials and methods: In this review, we summarize and analyze current studies concerning the biological functions and mechanisms of lncRNA-ATB in tumour development. The related studies were obtained through a systematic search of Pubmed, Web of Science, Embase and Cochrane Library.

Results: Long non-coding RNAs-ATB is a novel cancer-related lncRNA that was recently found to exhibit aberrant expression in a variety of malignancies, including hepatocellular carcinoma, colorectal cancer, gastric cancer, and lung cancer. Dysregulation of lncRNA-ATB has been shown to contribute to proliferation, migration and invasion of cancer cells. Long non-coding RNAs-ATB promotes tumourigenesis and progression mainly through competitively binding miRNAs to induce epithelial-mesenchymal transition (EMT).

Conclusions: Long non-coding RNAs-ATB likely represents a feasible cancer biomarker or therapeutic target.

1 | INTRODUCTION

According to the draft of the human genome project (HGP), the human genome contains only approximately 20 000 protein-coding genes, which accounts for less than 2% of the entire genome. Generally, at least 70% of the sequences are transcribed into RNAs in higher eukaryotic genomes. To our knowledge, most of these transcripts are noncoding RNAs (ncRNAs), which were originally regarded as transcriptional noise and attracted limited attention.¹⁻⁵ Thanks to recent advances in sequencing technology and large-scale genome sequencing projects, both short ncRNAs (<200 nucleotides) and long ncRNAs (>200 nucleotides) have been implicated as critical regulators in diverse human diseases.⁶⁻⁸

Long noncoding RNAs (lncRNAs), which are mainly transcribed by RNA polymerase II and lack an obvious open reading frame, are a group of ncRNAs that are greater than 200 nucleotides in length.⁹⁻¹² lncRNAs can be involved in the regulation of gene expression at epigenetic, transcriptional and post-transcriptional levels.¹³⁻¹⁶ lncRNAs are widely reported to regulate pathophysiological processes by mechanisms (Figure 1) such as gene imprinting, histone modification, chromatin remodelling, transcriptional activation, transcriptional interference, nuclear transport, and cell cycle regulation.¹⁷⁻²¹ The recently proposed competing endogenous RNA (ceRNA) regulatory network also suggests that lncRNAs may work as sponges by binding competitively to microRNAs (miRNAs) and consequently repressing their

FIGURE 1 An increasing number of studies focus on lncRNAs. A PubMed search result using the keyword "lncRNA" is shown as a column diagram

function (ie, blocking interactions with target mRNAs).^{22,23} Multiple lncRNAs are aberrantly expressed in different disease types, particularly in refractory tumours with unclear pathogenesis.²⁴⁻²⁶ lncRNA dysregulation generally contributes to cancer progression by promoting malignant biological behaviours in tumour cells, such as proliferation, invasion and metastasis.^{27,28} Additionally, lncRNAs may serve as potential therapeutic targets and biomarkers for diagnosis or prognosis due to high tissue specificity, high efficiency and elevated stability.^{29,30}

Long noncoding RNA-activated by transforming growth factor β (lncRNA-ATB), which is located on chromosome 14, is a promising candidate among all tumour-associated lncRNAs and is overexpressed in numerous human cancers but downregulated in pancreatic cancer.

The present review summarizes current evidence regarding the abnormal expression, molecular mechanism and clinical significance of lncRNA-ATB, which is one of the most important regulatory RNAs in human cancer (Table 1) (Figure 2).

2 | LNCRNA-ATB DEREGLATION IN HUMAN CANCERS

2.1 | Hepatocellular carcinoma

Hepatocellular carcinoma (HCC), which causes approximately 600 000 deaths each year, is the third leading cause of cancer deaths

TABLE 1 Functional characterization of lncRNA-ATB in cancers

Cancer types	Expression	Functional role	Related gene	Role	References
Hepatocellular carcinoma	Upregulated	EMT, cell invasion, organ colonization	TGF- β , miR-200s, ZEB1, ZEB2, IL-11, STAT3	Oncogenic	32,36
Gastric cancer	Upregulated	EMT, invasion, metastasis, proliferation	miR-200s, ZEB, miR-141-3p, TGF- β 2	Oncogenic	38,39
Colorectal cancer	Upregulated	EMT	E-cadherin, ZO-1, ZEB1, N-cadherin	Oncogenic	41,42
Lung cancer	Upregulated	Migration, invasion, apoptosis		Oncogenic	44
Renal cell carcinoma	Upregulated	Proliferation, migration, invasion, apoptosis		Oncogenic	47
Breast cancer	Upregulated	EMT, growth, migration, invasion, apoptosis, trastuzumab resistance	miR-200c, ZEB1, ZNF-217	Oncogenic	50
Glioma	Upregulated	Proliferation, colony formation, migration, invasion	miR-200a, TGF- β 2	Oncogenic	52
Keloid	Upregulated		miR-200c, ZNF-217, TGF- β 2	Oncogenic	54
Prostate cancer	Upregulated	EMT, proliferation	cyclin E, cyclin D1, p27, p21, ERK, PI3K/AKT	Oncogenic	55
Pancreatic cancer	Downregulated			Tumour suppressor	57

EMT, epithelial-mesenchymal transition; TGF- β , transforming growth factor β ; ZEB1/2, zinc finger E-box binding homeobox 1/2; IL-11, interleukin-11; STAT3, signal transducer and activator of transcription 3; ZO-1, zonula occludens 1; ZNF-217, zinc finger protein 217; ERK, extracellular signal-regulated kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B.

FIGURE 2 The clinical significance of lncRNA-ATB in various tumours. The marked squares indicate the link between lncRNA-ATB deregulation and clinicopathological parameters in the corresponding cancer type. PSA, prostate specific antigen

worldwide. Both hepatitis B and C virus infections are significant factors involved in the development of HCC. The poor prognosis and high recurrence rates are largely attributed to intrahepatic and extrahepatic metastases in early HCC.³¹ Exploring the key molecular mechanisms involved in the initiation and progression of HCC is therefore required to discover novel biomarkers and therapeutic targets.

Yuan et al³² initially demonstrated that lncRNA-ATB transcript levels were significantly increased in 86 HCC tissues compared with those in paired adjacent noncancerous hepatic tissues and were further increased in portal vein tumour thrombus. Moreover, lncRNA-ATB overexpression was significantly correlated with liver cirrhosis, microvascular invasion, encapsulation, low recurrence-free survival rate and overall survival rate. Thus, high lncRNA-ATB levels clearly promote the invasion-metastasis cascade of HCC. Hepatic fibrosis is a crucial factor in the development of liver cirrhosis, which significantly contributes to the development of HCC.³³ Fu et al^{34,35} confirmed that lncRNA-ATB was dramatically upregulated in liver tissues and plasma from patients with HCV-related fibrosis. These data suggest that lncRNA-ATB may serve as a specific biomarker and therapeutic target for HCC and liver fibrosis patients. Notably, the efficacy and therapeutic potential of ultrasound-targeted microbubble destruction-mediated siRNA transfection against lncRNA-ATB to suppress HCC migration and invasion has been reported.³⁶

2.2 | Gastric cancer

Gastric cancer (GC) represents a major health burden worldwide, being the second main cause of cancer-related deaths. Although early treatment of GC has achieved considerable success, the long-term survival rate of GC is still low given the lack of appropriate biomarkers for early detection. Both carcinoembryonic antigen (CEA) and CA125 are frequently used as indicators in clinical practice, with dissatisfactory sensitivity and specificity, even when used in combination.³⁷ Therefore, identifying novel molecular abnormalities is crucial for the early diagnosis of this deadly disease.

Saito et al³⁸ corroborated findings that lncRNA-ATB expression levels were significantly elevated in GC tissues compared with those in adjacent nontumour tissues and closely correlated with vascular invasion and overall survival rate. Moreover, upregulated lncRNA-ATB was indicated as an independent poor prognostic factor for GC patients by multivariate analyses. Subsequently, Lei et al³⁹ similarly uncovered that lncRNA-ATB was upregulated in GC tissues and that silencing lncRNA-ATB inhibited proliferation in vitro. Hence, lncRNA-ATB shows potential for the diagnosis and treatment of GC and is expected to serve as a novel diagnostic and prognostic biomarker and therapeutic target.

2.3 | Colorectal cancer

Colorectal cancer (CRC), which affects greater than 1.2 million people annually, is a common disease worldwide, and approximately one-fifth of patients exhibit metastases when diagnosed. CRC patients with metastases typically exhibit a survival rate of less than 5 years.^{24,40} As such, the development of sensitive and specific biomarkers for the early diagnosis of CRC would represent a momentous step towards reducing mortality.

Iguchi et al⁴¹ demonstrated that lncRNA-ATB was significantly overexpressed in CRC tissue specimens compared with expression in paired non-neoplastic specimens, and increased lncRNA-ATB was significantly associated with greater tumour size, depth of tumour invasion, lymphatic invasion, vascular invasion, lymph node metastasis, haematogenous metastasis, and poorer outcomes. Yue and colleagues⁴² also reported that lncRNA-ATB expression was significantly increased in colon cancer tissues compared with that in matched adjacent mucosa. Moreover, univariate and multivariate analyses indicated that elevated lncRNA-ATB levels are an independent prognostic factor for increased tumour recurrence and decreased survival. Pertinent to noninvasive diagnosis, the plasma lncRNA-ATB expression levels were significantly increased in colon cancer patients 1 month after surgery. These results suggest that lncRNA-ATB, a potential oncogenic lncRNA in CRC, may provide a

promising diagnostic and therapeutic option for suppressing CRC progression.

2.4 | Lung cancer

Lung cancer remains the major cause of cancer-related deaths and the most commonly diagnosed cancer worldwide. Nonsmall cell lung cancer (NSCLC), which accounts for approximately 80% of all lung cancer cases, is the primary category of lung cancer, and its prognosis is poor despite recent progress in chemotherapy.⁴³ Therefore, reliable prognostic biomarkers and molecular targets for lung cancer are urgently needed.

Ke et al⁴⁴ reported that lncRNA-ATB expression was significantly upregulated in NSCLC tissues and cell lines compared with that in paired adjacent normal tissues. In addition, increased lncRNA-ATB was markedly correlated with larger tumour size, lymph node metastasis, and distant metastasis in NSCLC patients. Functionally, knocking down lncRNA-ATB inhibited migration and invasion and promoted apoptosis in NSCLC cell lines. Notably, patients with elevated lncRNA-ATB presented lower survival rates. Obviously, increased lncRNA-ATB exerts oncogenic effects in NSCLC. Coal workers' pneumoconiosis (CWP), an occupational disease with a high incidence, is apt to develop into lung cancer. Ma et al⁴⁵ demonstrated that lncRNA-ATB was significantly upregulated in plasma from CWP patients compared with that in healthy controls and healthy coal miners and negatively correlated with vital capacity (VC) and forced vital capacity (FVC). Furthermore, elevated lncRNA-ATB was related to CWP risk. Taken together, lncRNA-ATB acts as an oncogenic lncRNA, suggesting its potential clinical value as a biomarker and target in NSCLC and CWP.

2.5 | Renal cell carcinoma

Renal cell carcinoma (RCC) is one of the most lethal urologic cancers. Patients with RCC often present with distant metastases at the time of diagnosis due to the lack of early indicators for detection.⁴⁶ As a result, identifying effective biomarkers is essential to not only predict the prognosis of RCC but also to help expand innovative targeted therapies for RCC.

Xiong et al⁴⁷ observed elevated lncRNA-ATB expression in RCC tissues and cell lines compared with that in nontumour controls, especially in RCC patients with metastasis. Moreover, high lncRNA-ATB expression was correlated with tumour stage, histological grade, vascular invasion, lymph node metastasis and distant metastasis. Functionally, knocking down lncRNA-ATB could suppress cellular proliferation, migration and invasion, and triggered apoptosis in RCC cells. Renal transplantation is the principal treatment available for RCC patients, and acute renal allograft rejection is considered a major risk factor for renal allograft loss. Qiu and colleagues⁴⁸ indicated that lncRNA-ATB was strongly upregulated in kidney biopsy samples from patients with acute rejection compared with in control transplant patients. In addition, lncRNA-ATB overexpression might impact renal cell phenotypes and the nephrotoxicity of postoperative pharmaceutical immunosuppression therapy. These results suggest that lncRNA-ATB as a biomarker is a potential oncogenic

lncRNA in RCC that can identify patients with acute rejection after renal transplantation.

2.6 | Breast cancer

Breast cancer (BC) is the leading reason of cancer deaths in women, and its incidence rates are gradually increasing worldwide. Distant metastasis and drug resistance are major challenges in the treatment of BC.⁴⁹ Hence, the development of reliable biomarkers to predict drug responsiveness and tumour progression should be a priority. Shi et al⁵⁰ confirmed that lncRNA-ATB expression was significantly increased in trastuzumab-resistant BC tissues and cell lines. Functionally, knocking down lncRNA-ATB inhibited the growth, migration and invasion of trastuzumab-resistant cells and promoted cellular apoptosis, suggesting that lncRNA-ATB might be a prospective target for combating metastasis and reversing trastuzumab resistance in BC.

2.7 | Glioma

Glioma is the most lethal primary central nervous system tumour, leading to significant mortality worldwide annually.⁵¹ Ma et al⁵² reported that lncRNA-ATB expression was significantly increased in glioma tissues and cell lines compared with that in normal brain tissues and was associated with poor outcomes in glioma patients. In addition, knocking down lncRNA-ATB inhibited the malignant biological behaviour of glioma cells, including proliferation, colony formation, migration, and invasion. Thus, the discovery of lncRNA-ATB may provide a new direction for targeted glioma treatment.

2.8 | Keloid

Keloids, a subgroup of benign skin cancers, result from abnormal wound healing and never regress spontaneously. The treatment of keloids is a particular challenge.⁵³ Zhu et al⁵⁴ demonstrated that lncRNA-ATB expression was significantly increased in both keloid tissues and fibroblasts compared with that in normal skin tissues and fibroblasts, respectively. Thus, lncRNA-ATB might be a promising biomarker for the diagnosis of and a potential target for the treatment of keloids.

2.9 | Prostate cancer

Prostate cancer is the most frequently diagnosed malignancy in males worldwide.²⁵ Xu et al⁵⁵ discovered that lncRNA-ATB levels were significantly increased in prostate cancer tissues compared with levels in adjacent nontumour tissues. With regard to clinicopathological parameters, increased lncRNA-ATB levels were closely associated with histological grade, high preoperative prostate specific antigen (PSA) levels, pathological stage, high Gleason score, lymph node metastasis, angiolymphatic invasion and biochemical recurrence. In general, lncRNA-ATB displays advantageous characteristics as a novel biomarker for early diagnosis, prognosis evaluation, and as a therapeutic target in prostate cancer.

2.10 | Pancreatic cancer

Pancreatic cancer is the fourth primary cause of cancer-related deaths worldwide and is typically diagnosed at advanced stages as a result of its deep location and atypical symptoms.⁵⁶ Unlike the above studies, lncRNA-ATB is downregulated in pancreatic cancer tissues and cell lines compared with in controls. Moreover, low lncRNA-ATB expression was significantly correlated with lymphatic metastasis, neural invasion and clinical stage. Notably, multivariate analysis revealed that decreased lncRNA-ATB expression was an independent predictor of poor prognosis, highlighting lncRNA-ATB as a potential tumour suppressor in pancreatic cancer.⁵⁷ Nevertheless, the specific mechanism of lncRNA-ATB in pancreatic cancer needs to be further investigated. Perhaps, due to differences in tumour tissue origin, extracellular microenvironment, and upstream and downstream regulatory factors, lncRNA-ATB can function not only as an oncogene but also as a tumour suppressor.

3 | REGULATORY MECHANISMS OF LNCRNA-ATB

Transforming growth factor β (TGF- β) is a multifunctional cytokine that modulates tumourigenesis and progression in part by inducing the epithelial-mesenchymal transition (EMT).^{58,59} lncRNA-ATB, which is activated by TGF- β , enforced zinc finger E-box binding homeobox 1 (ZEB1) and ZEB2 expression by competitively binding the miR-200 family and subsequently promote EMT and HCC cell invasion in vivo and in vitro.³² Similarly, the lncRNA-ATB/miR-200s/ZEB axis played an important role in TGF- β -induced EMT to promote invasion and metastasis of GC.³⁸ Another study demonstrated that lncRNA-ATB acts as a ceRNA to promote trastuzumab resistance and the invasion-metastasis cascade in BC by competitively binding to miR-200c to upregulate ZEB1 and zinc finger protein 217 (ZNF-217), thereby inducing the EMT.⁵⁰ Interestingly, knocking down lncRNA-ATB decreased autocrine secretion of TGF- β 2 and expression of ZNF-217 in keloid fibroblasts but increased expression of miR-200c, which targets ZNF-217. This finding indicated that lncRNA-ATB facilitated the initiation and progression of keloids via a signalling loop involving lncRNA-ATB/miR-200c/ZNF-217/TGF- β 2.⁵⁴ A signalling loop was also found in glioma, and lncRNA-ATB promoted glioma malignancy by directly targeting miR-200a to upregulate TGF- β 2 expression.⁵²

The ceRNA regulatory network is a major mechanism of lncRNA-ATB in cancer development. The miR-200 family is the main target of the lncRNA-ATB sponge, but other miRNAs can interact with it as well. Lei et al³⁹ reported that lncRNA-ATB functions as a ceRNA for miR-141-3p to modulate TGF- β 2 expression, suggesting that a lncRNA-ATB/miR-141-3p/TGF- β 2 feedback loop participates in GC progression. Another study found that lncRNA-ATB overexpression in HCV-induced liver fibrogenesis activated hepatic stellate cells (HSCs) and increased collagen synthesis by competitively binding to miR-425-5p, which inhibited the expression of TGF- β type II receptor (TGF- β RII) and Sma- and Mad-related protein 2 (SMAD2).³⁴ In

addition, lncRNA-ATB overexpression might act on colon tumorigenesis by decreasing the expression of epithelial markers (eg, E-cadherin and zonula occludens 1) and increasing the expression of mesenchymal markers (eg, ZEB1 and N-cadherin) to promote the EMT.⁴²

In addition to acting as a ceRNA, lncRNA-ATB can also activate various signalling pathways. Xu et al⁵⁵ discovered that lncRNA-ATB overexpression promoted prostate cancer cell proliferation by up-regulating cyclin E and cyclin D1 and downregulating p27 and p21 expression. Further experimental results confirmed that lncRNA-ATB boosted the EMT by activating extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signalling. In addition, lncRNA-ATB boosted organ colonization of disseminated tumour cells in HCC by interacting with interleukin-11 (IL-11) mRNA, increasing IL-11 mRNA stability, causing autocrine induction of IL-11, and subsequently triggering signal transducer and activator of transcription 3 (STAT3) signalling.³² These findings reveal the complexity of these interactions, which contribute to malignant transformation and tumour progression. Understanding the mechanisms of lncRNA-ATB is conducive for practical applications to diagnose and treat cancers.

4 | CONCLUSION AND FUTURE PERSPECTIVES

lncRNA-ATB, a well-characterized cancer-related lncRNA, can alter cellular functions such as proliferation, migration and invasion in various human cancers. The mechanisms by which lncRNA-ATB promotes

FIGURE 3 lncRNA-ATB mediates mechanisms involved in cancer progression. lncRNA-ATB facilitates the EMT by competitively binding miR-200s and miR-141-3p; activates STAT3, ERK and PI3K/AKT signalling; and regulates feedback signalling with TGF- β to promote tumourigenesis. TGF- β , transforming growth factor β . lncRNA-ATB, long noncoding RNA-activated by transforming growth factor β . ERK, extracellular signal-regulated kinase. PI3K, phosphoinositide 3-kinase. AKT, protein kinase B. IL-11, interleukin-11. ZEB1/2, zinc finger E-box binding homeobox 1/2. ZNF-217, zinc finger protein 217. STAT3, signal transducer and activator of transcription 3. EMT, epithelial-mesenchymal transition

tumour development are extremely complicated and involve multiple steps, including induction of the EMT by competitively binding miRNAs; activating STAT3, ERK and PI3K/AKT signalling pathways; and feedback signalling between TGF- β and lncRNA-ATB (Figure 3). Nevertheless, the detailed regulatory mechanisms upstream and downstream of lncRNA-ATB remain to be systematically explored. In terms of clinical application, lncRNA-ATB may function as a potential biomarker for diagnosis and prognosis because its aberrant expression is closely interrelated with poorer clinicopathological parameters such as reduced survival rate and advanced stage. However, the expression level and chemical stability of lncRNA-ATB in biological samples, such as serum, have not been clearly validated. Compared with traditional cytotoxic chemotherapy, molecular targeted therapy has the advantages of strong tumour specificity and low systemic toxicity. As a viable drug target, lncRNA-ATB is extraordinarily promising. Ongoing efforts to clarify the underlying mechanisms promise that lncRNA-ATB will ultimately reach the clinic.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Jinglin Li: Study idea, design and manuscript preparation. Wangyang Zheng and Xinheng Li: Data collection and interpretation. Zhenglong Li and Zhidong Wang: Data analysis. Xingming Jiang and Yunfu Cui: Final correction and review.

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