1 | INTRODUCTION

The genome-wide studies showed that greater than 70% of the human genome is transcribed into RNAs, while only approximately 2% of the sequences have the capacity to encode proteins.1,2 The non-coding RNAs (ncRNAs), which were long assumed to be transcriptional noise, comprise the most proportion of the transcripts.3 The ncRNAs are divided into diverse types according to their size, such as microRNAs (miRNAs), small nucleolar RNAs (snoRNAs), PIWI-interacting RNAs (piRNAs), and long non-coding RNAs (lncRNAs).4-7 Among them, miRNAs have been extensively investigated to understand their properties for clinical application, and the focus of research is recently shifting to lncRNAs.

LncRNAs mainly transcribed by RNA polymerase II are generally defined as a group of non-protein-coding RNAs, which are more than 200 nucleotides in length.8-10 LncRNAs have been confirmed to regulate gene expression and chromatin structure at epigenetic, transcriptional and post-transcriptional levels, and participate in physiological and pathological processes generally through gene imprinting, histone modification, chromatin remodelling, transcriptional activation, transcriptional interference, alternative splicing and cell cycle control.11-18 Increasing studies indicate that numerous lncRNAs, which may function as either oncogenes or tumor suppressor genes, are aberrantly expressed in a variety of human cancers, and contribute to the initiation and progression of malignancies.19,20 LncRNAs dysregulation can promote proliferation, invasion and metastasis of tumor cells and inhibit cellular senescence and apoptosis by multiple mechanisms, including working as miRNA sponges, protein scaffolds, regulatory signals or transcript decoys.21-25 Notably, lncRNAs may be used as feasible tumor biomarkers and potential therapeutic targets for diagnosis and treatment of cancers due to high tissue specificity and elevated efficiency.26,27
expression signature, functional feature, regulatory mechanism and clinical significance of ZEB1-AS1 during the occurrence and development of tumors (Tables 1 and 2).

2 | DISCOVERY AND CHARACTERIZATION OF ZEB1-AS1

ZEB1-AS1, which is mainly located in the nucleus, was originally discovered as the most efficient IncRNA to boost cellular proliferation in human HCC by Li in 2015. Both GSE55191 and GSE58043, which are two human IncRNA microarray datasets, were used to analyze aberrantly expressed IncRNAs in HCC, and the results showed that 573 IncRNAs were consistently upregulated and 19 IncRNAs were consistently downregulated in both microarray datasets. Among them, ZEB1-AS1 was identified as a central IncRNA by co-expression network analysis, and exhibited excellent characteristics. ZEB1-AS1 is located on chromosome 10p11.22 with approximately 2535 nucleotides in length, including two exons and one intron between the two exons. In addition, ZEB1-AS1 is an antisense transcript deriving from the promoter region of ZEB1, which is a critical transcription factor in tumor development.

3 | ZEB1-AS1 DEREGULATION IN HUMAN CANCERS

3.1 | Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths and the sixth most commonly diagnosed cancer worldwide. Although recent advances have been made in radical hepatectomy and liver transplantation, the postoperative 5-year survival
rate is still low due to the high recurrence rate and distant metastasis. Therefore, finding competent biomarkers for early diagnosis and prognosis evaluation will contribute to reduce the mortality of HCC patients.

Li et al demonstrated that ZEB1-AS1 expression was significantly upregulated in 102 HCC specimens compared with that in paired non-tumor tissues and healthy liver tissues, and was further upregulated in metastatic HCC tissues. Meanwhile, ZEB1-AS1 was also significantly overexpressed in HCC cell lines compared with expression in normal liver cell line in vitro. Furthermore, increased ZEB1-AS1 was markedly correlated with microvascular invasion, shorter overall survival and higher recurrence rates. Multivariate analysis showed that elevated ZEB1-AS1 expression was an independent predictor of poor prognosis. Functionally, increased ZEB1-AS1 promoted proliferation, migration and invasion of HCC cells in vitro, and facilitated tumor growth and metastasis in vivo. Taken together, ZEB1-AS1 plays an oncogenic role in HCC progression, suggesting that ZEB1-AS1 may work as a valuable molecular marker for prognosis prediction and a powerful target for HCC treatment.

3.2 Esophageal squamous cell carcinoma

Esophageal squamous cell carcinoma (ESCC) is the most common category of esophageal cancer, which is the sixth main cause of cancer deaths worldwide, and its incidence rates remain quite high in China. ESCC patients often reach the advanced stage when diagnosed, and the overall 5-year survival rate is less than 10%. The unfavorable prognosis is mainly due to the lack of sensitive and specific indicator for early detection. As a result, the identification of the biomarkers that contribute to early diagnosis of ESCC is extremely meaningful.

Wang et al confirmed that ZEB1-AS1 was significantly overexpressed in 87 ESCC tissues compared with that in paired adjacent non-tumor tissues. Furthermore, increased ZEB1-AS1 expression was observably interrelated with tumor grade, depth of invasion and lymph node metastasis. Kaplan-Meier analysis uncovered that ESCC patients with elevated ZEB1-AS1 levels had a poorer overall survival and disease-free survival. Further study revealed that high ZEB1-AS1 expression was regarded as an independent prognostic factor for decreased survival of ESCC patients. Hence, ZEB1-AS1, which likely acts as a specific therapeutic target in ESCC, may provide a golden opportunity for anticancer therapy. Further investigations are warranted to clarify the biological function and regulatory mechanism of ZEB1-AS1 in ESCC.

3.3 Prostate cancer

Prostate cancer, which leads to approximately 1-2% of deaths in men annually, is the most commonly diagnosed tumor in males worldwide. The incidence rates of prostate cancer are gradually increasing largely due to the high-fat diet and prolongation of life expectancy. The management of prostate cancer remains a tremendous medical challenge as a result of the lack of efficient therapeutic methods. Thus, elucidating novel molecular mechanisms involved in the development of prostate cancer is an indispensable step to overcome this refractory malignancy.

Su et al reported that ZEB1-AS1 expression levels were significantly enforced in prostate cancer tissues and cell lines compared with those in non-tumor controls. Moreover, upregulated ZEB1-AS1 was remarkably associated with later clinical stage and perineural invasion. In addition, ZEB1-AS1 knockdown inhibited proliferation and migration of prostate cancer cells. Accordingly, ZEB1-AS1 plays an important role in the initiation and progression of prostate cancer, implying that ZEB1-AS1 may function as a prospective biomarker to improve early diagnosis rate of prostate cancer.

3.4 Glioma

Glioma is the most serious type of primary tumor in central nervous system, and causes exceedingly high death rates each year. Despite considerable improvement in combination treatments including surgical resection, chemotherapy and radiation therapy, the average life expectancy of glioblastoma multiforme, which is the most malignant glioma, is only approximately 15 months. Therefore, identifying new molecular abnormalities concerning glioma progression to establish a specific target is necessary for individual therapeutic strategy of glioma.

Lv et al corroborated that ZEB1-AS1 was highly expressed in glioma tissues compared with that in normal brain tissues, and was also overexpressed in three high-degree glioblastoma cell lines than expression in low-degree glioma cell line. Furthermore, upregulated ZEB1-AS1 was significantly related to clinical stage of glioma and reduced overall survival of glioma patients. In addition, increased ZEB1-AS1 expression was showed as an independent poor prognostic marker for glioma patients by multivariate analysis. Biologically, silencing ZEB1-AS1 dramatically suppressed proliferation, migration and invasion of glioma cells, and promoted cellular apoptosis. In general, ongoing and in-depth exploration for ZEB1-AS1 may make a new breakthrough in the diagnosis and treatment of glioma.

3.5 Osteosarcoma

Osteosarcoma, a highly aggressive cancer, is the most common group of malignant bone tumors in children and adolescents, and occurs nearly 20% lung metastases at the time of original diagnosis. The prognosis of patients with distant metastasis remains extremely poor, and their 5-year survival rate is approximately 20-30%. Hence, exploring appropriate biomarkers for early diagnosis of osteosarcoma is urgently needed.

Liu et al observed upregulated ZEB1-AS1 expression in both osteosarcoma tissues and cell lines compared with expression in adjacent non-tumor tissues and normal osteoblast cell line, respectively. The correlation between ZEB1-AS1 expression level and clinicopathologic characteristics of osteosarcoma patients was also been analysed, and the results showed that elevated ZEB1-AS1 expression was closely associated with larger tumor size, advanced Enneking stage, tumor metastasis, poorer recurrence-free survival
and overall survival. In addition, functional experiments revealed that increased ZEB1-AS1 promoted proliferation and migration of osteosarcoma cells. These findings illustrate that ZEB1-AS1 exhibits a crucial role in the pathogenesis of osteosarcoma, and displays favorable features as an indicator for diagnosis and treatment of osteosarcoma.

3.6 | Bladder cancer

Bladder cancer is the ninth most frequent malignancy worldwide, leading to approximately 52,395 cancer deaths annually. The effectiveness of chemotherapy in advanced bladder cancer is quite limited, and the recurrence rate of bladder cancer remains greatly high. Lin et al discovered that ZEB1-AS1 expression levels were significantly upregulated in bladder cancer tissues compared with those in paired noncancerous tissues. Moreover, ZEB1-AS1 expression was also elevated in bladder cancer cell lines. In addition, enforced ZEB1-AS1 expression was positively correlated with higher histological grade and advanced tumor stage. Pertinent to biological function, knocking down ZEB1-AS1 not only suppressed cellular proliferation and migration, but also promoted apoptosis of bladder cancer cells. Thus, increased ZEB1-AS1 is involved in carcinogenesis and progression of bladder cancer, and may become a promising diagnostic and prognostic biomarker and a potential therapeutic target.

3.7 | Colorectal cancer

Colorectal cancer (CRC) is the fourth main cause of tumor-related mortality and the third most commonly diagnosed cancer worldwide. Gong et al demonstrated that ZEB1-AS1 expression was significantly increased in CRC tissues and cell lines compared with that in non-tumor controls, and upregulated ZEB1-AS1 was remarkably correlated with depth of tumor invasion, microvascular invasion and lymph node metastasis. Kaplan-Meier analysis showed that CRC patients with elevated ZEB1-AS1 expression had poorer overall survival and lower recurrence-free survival rate. In addition, silencing ZEB1-AS1 inhibited cellular proliferation and facilitated apoptosis of CRC cells. These data suggest that ZEB1-AS1 is an oncogenic lncRNA in CRC, and is expected to serve as a beneficial molecular marker to predict clinical outcome.

3.8 | B-lymphoblastic leukemia

B-lymphoblastic leukemia is one of the most lethal hematological malignancies. Wang et al reported that ZEB1-AS1 was significantly overexpressed in bone marrow tissues of B-lymphoblastic leukemia patients compared with that in healthy controls, and increased ZEB1-AS1 was indicated to predict poor survival of B-lymphoblastic leukemia patients by Kaplan-Meier analysis. Intriguingly, ZEB1-AS1 was confirmed lowly expressed in B-lymphoblastic leukemia cells but highly expressed in bone marrow stromal cells (BMSCs). Moreover, silencing ZEB1-AS1 had little effect on the viability of B-lymphoblastic leukemia cells. Nevertheless, B-lymphoblastic leukemia cells exhibited the inhibition of proliferation, when the cancer cells were fed with supernatants that derived from ZEB1-AS1-inhibited BMSCs. These results suggest that ZEB1-AS1-controlled microenvironment may be greatly required for the initiation and development of B-lymphoblastic leukemia. The regulatory method of ZEB1-AS1 in B-lymphoblastic leukemia is different from that in the above solid cancers probably due to the heterogeneity between hematological malignancies and solid tumors.

4 | REGULATORY MECHANISMS OF ZEB1-AS1

4.1 | ZEB1-AS1 promotes ZEB1 expression

ZEB1-AS1 is located in physical contiguity with ZEB1, which is a momentous regulatory factor involved in the EMT. To our knowledge, the antisense transcripts may function as a positive regulator for corresponding gene expression. For example, fibroblast growth factor receptor 3 antisense 1 (FGFR3-AS1) increases FGFR3 mRNA stability and upregulates FGFR3 expression in osteosarcoma; proliferating cell nuclear antigen antisense 1 (PCNA-AS1) increases PCNA mRNA stability by forming RNA hybridization with PCNA in HCC. Herein, Li et al confirmed lowly expressed in B-lymphoblastic leukemia patients by Kaplan-Meier analysis. Intriguingly, ZEB1-AS1 significantly enforced ZEB1 expression by increasing its promoter activity, thereby inducing the EMT and HCC metastasis. Su et al uncovered that ZEB1-AS1 epigenetically increased ZEB1, indirectly inhibited miR200c, and subsequently upregulated BMI1 to facilitate proliferation and migration of prostate cancer cells, suggesting the ZEB1-AS1/ZEB1/miR200c/BMI1 pathway may exert pivotal effects on the occurrence and development of prostate cancer.

The detailed regulatory mechanisms between ZEB1-AS1 and ZEB1 are quite sophisticated. Su and colleagues demonstrated that ZEB1-AS1 boosted ZEB1 expression by recruiting mixed-lineage leukemia 1 (MLL1) to the promoter region of ZEB1. MLL1 is a pivotal histone methyltransferase, and can induce H3K4me3 transition in promoter region of ZEB1. Similarly, Liu et al discovered that ZEB1-AS1 upregulated ZEB1 expression through recruiting p300 to the promoter region of ZEB1. p300, a histone acetyltransferase, can mediate an open and active chromatin status in promoter region of ZEB1. Thus, the epigenetic regulation clearly participates in ZEB1-AS1-induced ZEB1 transcription. In addition, another study indicated that ZEB1-AS1 upregulated ZEB1 expression through competitively binding to miR-200s, which directly targeted ZEB1 to repress its expression in various cancers.

4.2 | ZEB1-AS1 activates IL-11/STAT3 signalling

The tumor microenvironment is composed of extracellular matrix, diverse non-tumor cells around cancer cells and a variety of surrounding biological active molecules. These cells and
their secretory molecules interact with each other and establish an exceedingly complicated signal network to impact cancer progression. Signal transducer and activator of transcription 3 (STAT3) as an oncogene can be constitutively activated in diverse tumors, and elevated STAT3 expression has been shown to be promoted by upregulated interleukin-11 (IL-11), which is a well-known component of tumor microenvironment. IL-11/STAT3 signalling exerts a critical role in transferring extracellular signal into the nucleus, and leads to uncontrolled proliferation, metastasis and anti-apoptosis of cancer cells by affecting various tumor-related genes, such as Bcl-2 and Bax. Wang et al revealed that ZEB1-AS1 directly bound to IL-11 protein and promoted IL-11 protein stability in BMSCs of B-lymphoblastic leukemia patients. Further study confirmed that silencing ZEB1-AS1 in BMSCs caused a decrease of IL-11 protein and the inhibition of IL-11/STAT3 signalling in B-lymphoblastic leukemia cells by the co-culture system of B-lymphoblastic leukemia cells and corresponding ZEB1-AS1-inhibited BMSCs (Figure 1). These findings suggest that upregulated ZEB1-AS1 in BMSCs can activate IL-11/STAT3 signalling in a tumor microenvironment dependent manner. However, the detailed mechanisms involved in the tumor progression remain to be further investigated.

4.3 Other regulatory mechanisms

DNA methylation is one of the most important epigenetic modifications, and DNA methylation in lncRNAs promoters likely represents an epigenetic modulator of lncRNAs expression. The methylation frequency of ZEB1-AS1 gene is found dramatically decreased during HCC progression, and hypomethylation of ZEB1-AS1 promoter is significantly associated with ZEB1-AS1 overexpression, implying that aberrant methylation of ZEB1-AS1 promoter may exhibit a vital role in ZEB1-AS1 expression and HCC development. Both apoptosis-related proteins (e.g., Bcl-2 and Bax) and cell cycle regulators (e.g., Cyclin D1, CDK2 and p15) play a key role in tumorigenesis and progression. Gong et al reported that ZEB1-AS1 boosted proliferation of CRC cells partly through repressing p15 expression. Lv et al demonstrated that ZEB1-AS1 promoted proliferation of glioma cells in part by decreasing Bax expression and increasing the expression of matrix metalloproteinase 2 (MMP2), MMP9, N-cadherin and integrin-β1, and decreasing E-cadherin expression in glioma.

5 Conclusion and future directions

An increasing number of IncRNAs are found to exert important regulatory functions in gene expression, and the aberrant expression of IncRNAs is gradually recognized as a hallmark feature in cancer. Investigating these molecules as biomarkers or therapeutic targets will be a promising field for cancer treatment. At present, some well-characterized IncRNAs have been detected not only in tumor tissues but also in body fluids, such as blood plasma and urine. For instance, both urinary prostate cancer antigen 3 (PCA3) and plasma H19 are regarded as reliable biomarkers in prostate cancer and gastric cancer, respectively. Notably, IncRNA-mediated cis regulation of
target genes greatly enriches the gene regulatory network of IncRNAs, and exhibits its complexity and diversity. For example, lincRNA-p21, a neighboring gene of p21, functions in cis to upregulate p21 expression; and ZEB1-AS1 herein increases ZEB1 expression by cis regulation. The cis regulating mechanism of lncRNAs indicates a viable research direction in this field.

ZEB1-AS1 is identified as an oncogenic lncRNA in diverse malignancies, and upregulated ZEB1-AS1 promotes malignant phenotypes, such as proliferation, invasion and migration by inducing the EMT, activating signalling pathways and regulating cell cycle (Figure 2). However, the precise molecular mechanisms upstream and downstream of ZEB1-AS1 are not thoroughly understood, and remain to be systematically investigated. ZEB1-AS1 dysregulation is significantly associated with multiple poorer clinicopathological characteristics such as distant metastasis and reduced survival rate, suggesting its potential clinical utility as a favorable biomarker for diagnosis and prognosis. Nevertheless, the expression and function of ZEB1-AS1 in body fluids remains quite obscure, and needs to be further validated. Furthermore, ZEB1-AS1 is extremely prospective to be a feasible drug target due to forceful tumor specificity and reduced systemic toxicity. Despite recent efforts to explore the functions and mechanisms of ZEB1-AS1, its research is still at the preliminary stage. Further systematic studies in larger patient cohorts are warranted to accelerate its clinical application.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.
AUTHOR CONTRIBUTIONS
Jinglin Li and Zhenglong Li: Study idea, design and manuscript preparation. Kaiming Leng and Yi Xu: Data collection and interpretation. Lining Huang and Daolin Ji: Data analysis. Xingming Jiang and Yunfu Cui: Final correction and review.

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