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Original Article

Clinical effects and molecular mechanisms of lncRNA MNX1-AS1 in malignant tumors

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Abstract: With continuous disclosure of the significance of long non-coding RNAs (lncRNAs) in gene expression, the role of lncRNAs in malignant tumors has attracted extensive attention of scholars. Many types of studies found that lncRNA MNX1-AS1 is an over-expressed lncRNA in various malignant tumors. Results also indicate that MNX1-AS1 participates in the biological processes of cancers. Recent studies found that lncRNA MNX1-AS1 has high sensitivities and specificities in tumor tissues and plasma and may be a potential diagnostic biomarker and prognostic predictor. The biological functions of lncRNA MNX1-AS1 and its mechanisms of function in tumors were comprehensively reviewed in this article to lay a molecular foundation for future clinical applications of MNX1-AS1.

Keywords: Tumors, lncRNA, MNX1-AS1, biomarker, molecular mechanism

Introduction

LncRNAs are a specific category of non-coding RNA molecules with transcriptional lengths of more than 200 nucleotides. Although they cannot encode proteins, lncRNAs have essential roles in multiple cellular processes, such as proliferation, migration, invasion, and differentiation [1, 2]. Additionally, lncRNAs are increasingly found and their functions have been further studied [3]. LncRNA regulation occurs during all steps of RNA metabolism, including chromosome modification [4], RNA transport, transcription [5], splicing [6], and translation [7]. LncRNAs are associated with important biological processes, including dose compensation effects genomic imprinting, epigenetic and cell cycle regulation, cell differentiation and tumorigenesis. If lncRNA is abnormally expressed during the above processes, tumor cells will resist cell death and develop the characteristic of unlimited proliferation. Abnormal activation of signaling pathways can also lead to tumor occurrence. LncRNAs can become crucial signal transduction mediums in tumor signal transduction pathways through interaction with RNAs or proteins. They can promote occurrence and development of tumors by affecting the transcription process [8]. The roles of many lncRNAs in different tumors have been evaluated. Expression levels differ greatly in different tumor stages and tissue grades [9]. Occurrence and development of tumors are closely related to lncRNAs, and study of these RNA molecules can provide new information for the diagnosis, treatment, and control of malignant tumors.

LncRNA MNX1-AS1 is the natural anti-sense transcription of MNX1, close to the 5' terminal of its protein-coding gene. MNX1-AS1 (i.e., CCAT5) was found for the first time to be a highly expressed gene in colorectal cancer. Although lncRNA MNX1-AS1 is a newly discovered lncRNA, study findings indicate that it exerts a pro-oncogenic effect in various cancers [10, 11]. It promotes tumor development via participation in multiple signaling pathways [12, 13]. In this article, we will review clinical functions and specific mechanisms of MNX1-AS1 in different malignant tumors.

Abnormal expression of MNX1-AS1 in different malignant tumors

Many researchers have used qRT-PCR assay and other methods to confirm that lncRNA

MNX1-AS1 is over-expressed in a variety of cancer tissues in the way of interfering proliferation, apoptosis, metastasis, and invasion of cancer cells (**Table 1**). MNX1-AS1 functions as an oncogene and is commonly upregulated in various kinds of malignant tumors. Down-regulation of MNX1-AS1 suppresses cell proliferation, cell migration and invasion ability, and promotes apoptosis of cancer cells. Oncogene expression is not only required for cancer initiation, but also for disease maintenance. Oncogenes are being extensively studied by researchers as anti-cancer therapeutic targets. Relationships between lncRNA MNX1-AS1 and the prognosis of patients are apparent (**Table 2**). Results from clinical studies indicate that up-regulation of lncRNA MNX1-AS1 is a predictor of shorter overall survival time, larger tumor size, more advanced TNM stage and metastasis.

Expression of lncRNA MNX1-AS1 in lung cancer

As deep sequencing has been extensively applied in medical research, gene chip, qRT-PCR, and in situ hybridization, the expression disorders of some lncRNAs have gradually come into our sight. LncRNA CCAT1, lncRNA HOTAIR, and lncRNA PVT1 can transform healthy bronchial epithelial cells into malignant cells [14-16]. Many lncRNAs are unusually expressed in non-small cell lung cancer (NSCLC) tissues and plasma and can be used as biomarkers for diagnosis of NSCLC. Gaofeng Liu et al. found that expression levels of lncRNA MNX1-AS1 in NSCLC tissues and cells were remarkably higher than those in adjacent healthy lung epithelial cells and tissues. Correlations between expression levels of MNX1-AS1 and TNM stage and lymph node metastasis of patients are significantly greater, and patients with higher expression levels of MNX1-AS1 have a poorer prognosis. Taken together, these study results support the hypothesis that MNX1-AS1 is an independent prognostic factor for patients with NSCLC. In one study, A549 cells with MNX1-AS1 gene knocked-out were used for cell proliferation assay, transwell assay, plate clone formation assay, and flow cytometry [17]. The results suggested that MNX1-AS1 knock-out could inhibit NSCLC cell proliferation, clone formation, metastasis, and promote apoptosis. Study results of Ronghua Yang et al. indicated the presence of discrepancies in MNX1-AS1 expression between lung adenocarcinoma and healthy lung tissues [18]. At the same time, no such difference was found between lung squamous cell carcinoma and healthy lung tissues. Further studies should pay attention to the differences in expression levels of MNX1-AS1 in different pathological types of lung cancer.

Expression of lncRNA MNX1-AS1 in gastric cancer

Due to its complex pathogenesis, the early symptoms are not apparent, and patients pay little attention to it, resulting in a low early diagnosis rate [19]. You Shuai et al. analyzed the expression levels of lncRNA MNX1-AS1 in GC tissue samples using gene chip and qRT-PCR. The results indicated that the expression of lncRNA MNX1-AS1 was significantly upregulated in GC tissue samples and GC cell lines, while over-expression of MNX1-AS1 predicted a poor outcome of GC patients. Proliferation assay, flow cytometry, and transwell assay results indicated that lncRNA MNX1-AS1 promoted the proliferation, metastasis, and invasion of tumor cells. Findings of xenograft models also indicated that deletion of MNX1-AS1 inhibited growth of xenograft tumors [20]. Wei Zhang et al. obtained similar results, but the tumor-promoting mechanisms of MNXA-AS1 in the two studies were different [21].

Expression of lncRNA MNX1-AS1 in esophageal cancer

Esophageal cancer is a common cancer type. It ranks seventh in morbidity and sixth in the leading cause of cancer-related deaths globally [22]. Although current diagnostic methods and techniques have improved, most patients are already in the advanced stages of diagnosis. They cannot undergo early surgical resection due to the easily overlooked early symptoms of esophageal cancer; and their 5-year survival rate is only about 15% [23]. We aim to improve the early diagnosis rates and therapeutic effects by finding new diagnostic markers and therapeutic targets of esophageal cancer and improve the outcomes of patients with esophageal cancer [24]. Jie Chu et al. found that the expression levels of lncRNA MNX1-AS1 in esophageal cancer tissues were remarkably upregulated, compared with heal-

Table 1. Functional characterization of lncRNA MNX1-AS1 in different cancers

Cancer types	Roles	Expression	Function	Related Genes	Related pathways	References
Bladder cancer	Oncogene	Upregulated	Proliferation, migration, Invasion, and epithelial-mesenchymal transition (EMT)	miR-218-5, RAB1A	Not determined	[4]
Breast cancer	Oncogene	Upregulated	Proliferation, migration, and invasion	AKT, mTOR	AKT/mTOR pathway	[12]
Cervical cancer	Oncogene	Upregulated	Proliferation and anti-apoptosis	ERK1/2, JNK	MAPK pathway	[16]
Colon carcinoma	Oncogene	Upregulated	Proliferation, migration, and invasion	miR-218-5, SEC61A1	Not determined	[15]
Esophageal cancer	Oncogene	Upregulated	Proliferation, migration, and invasion	miR-34a, SIRTI, IGF2	Not determined	[7, 23]
Gastric cancer	Oncogene	Upregulated	Proliferation, migration, and invasion	TEAD4, miR-6785-5P, BCL2, CDKN1A, PCNA, EMT	Not determined	[2, 6, 11]
Glioblastoma	Oncogene	Upregulated	Proliferation, migration, and invasion	miR-4443	Not determined	[21]
Hepatocellular carcinoma	Oncogene	Upregulated	Proliferation, migration, and invasion	miR-218-5p, COMMD8	Not determined	[9]
Lung cancer	Oncogene	Upregulated	Proliferation, migration, invasion, and anti-apoptosis	miR-527, BRF2	Not determined	[8, 13, 14]
Osteosarcoma	Oncogene	Upregulated	Proliferation and invasion	KISS1	Not determined	[22]
Ovarian cancer	Oncogene	Upregulated	Proliferation, migration and anti-apoptosis	Not determined	Not determined	[18, 19]
Prostate cancer	Oncogene	Upregulated	Proliferation, migration and invasion	Not determined	Not determined	[10]

Table 2. Clinical characterization of lncRNA MNX1-AS in different cancers

Cancer types	Clinical characterization of lncRNA MNX1-AS	References
Bladder cancer	Not determined	[4]
Breast cancer	Not determined	[12]
Cervical cancer	Shorter overall survival time	[16]
Colon carcinoma	Not determined	[15]
Esophageal cancer	Lymph node metastasis	[7, 23]
Gastric cancer	Shorter overall survival time, lager tumor size, higher TNM stage and advanced metastasis	[2, 6, 11]
Glioblastoma	Not determined	[21]
Hepatocellular carcinoma	Shorter overall survival time, higher TNM stage and advanced metastasis	[9]
Lung cancer	Shorter overall survival time, higher TNM stage and advanced metastasis	[8, 13, 14]
Osteosarcoma	Lower differentiated degree, higher clinical stage, lager tumor size and advanced metastasis	[22]
Ovarian cancer	Shorter overall survival time and progression-free survival, higher FIGO stage and advanced metastasis	[18, 19]
Prostate cancer	Not determined	[10]

thy esophageal tissues. The high expression levels of lncRNA MNX1-AS1 was associated with lymph node metastasis. Deletion of lncRNA MNX1-AS1 significantly restrained cell proliferation, migration, and invasion. Flow cytometry assay revealed that lncRNA MNX1-AS1 regulated the esophageal cancer cell cycle and apoptosis [13, 25].

Expression of lncRNA MNX1-AS1 in ovarian cancer

The morbidity of ovarian cancer ranks sixth among gynecological tumors. It is the most common malignant tumor of the female reproductive system [26]. Li AH et al.'s qPCR results indicated that expression levels of lncRNA MNX1-AS1 in ovarian epithelial carcinoma cells were remarkably higher than in healthy ovarian epithelial tissues ($P<0.01$). LncRNA MNX-AS1 expression has significant correlations with FIGO stage ($P=0.005$), grade ($P=0.040$), and distant metastasis ($P<0.01$). Kaplan-Meier analyses revealed that progression-free survival (PFS) ($P<0.0001$) and overall survival (OS) ($P=0.0003$) times of patients with tumors with higher lncRNA MNX1-AS1 expression were significantly shorter than those of other patients. COX-regression analysis revealed that FIGO stage, distant metastasis, and lncRNA MNX1-AS1 expression levels were independent prognostic factors of PFS and OS [27]. Yan Lv et al. had similar results using OVCA433 and SKOV-3 ovarian cancer cell lines [28].

Expression of lncRNA MNX1-AS1 in breast cancer

LncRNA HOTAIR, lncRNA FBXL19-AS1, lncRNA H19, and other lncRNAs are related to the occurrence and development of breast cancer [29, 30]. Yue Cheng et al. found that the levels of expression of lncRNA MNX1-AS1 in breast cancer tissues were remarkably higher than in healthy breast tissues. Over-expression of lncRNA MNX1-AS1 promoted proliferation, migration, and invasion of breast cancer cells. In breast cancer tissues, lncRNA MNX1-AS1 is synergistically expressed with its natural transcription MNX1 [31].

Expression of lncRNA MNX1-AS1 in colon adenocarcinoma

Colon cancer is a type of malignant tumor in the digestive system. Its morbidity and mortality rates rank third and fifth, respectively, among malignant tumors [32]. Yaqun Ye et al.'s study revealed the relationship between lncRNA MNX1-AS1 and colonic adenocarcinoma and its functional mechanism. LncRNA MNX1-AS1 is upregulated in colonic adenocarcinoma. JASPAR prediction tool results indicate that E2F1 can be combined with the promoter region of lncRNA MNX1-AS1. The interaction between lncRNA MNX1-AS1 and E2F1 was confirmed using luciferase reporter assay and chromatin immunoprecipitation assay. Subsequent functional tests revealed that down-regulated lncRNA MNX1-AS1 reduced cell proliferation, migration, and invasion in colonic adenocarcinoma; upregulated E2F1 reversed this effect [10].

Expression of lncRNA MNX1-AS1 in hepatocellular carcinoma

Alpha-fetoprotein (AFP) is often used as an essential serum marker for HCC, but its sensitivity and specificity are unsatisfactory [33]. Other biomarkers, such as Golgi protein 73,

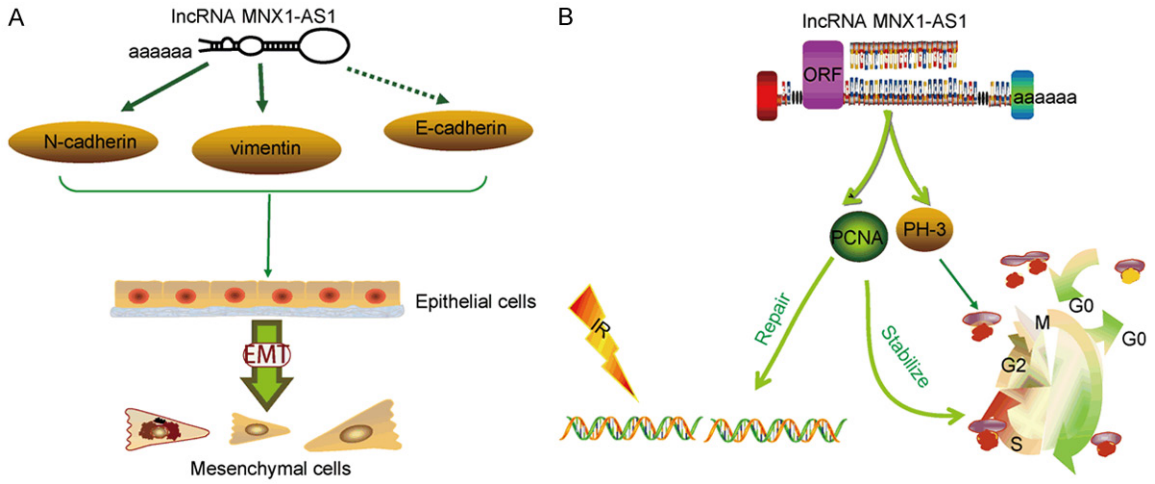

Figure 1. A. LncRNA MNX1-AS1 in various cancer cells can up-regulate expression of N-cadherin and vimentin while down-regulating expression of E-cadherin and induce the process of epithelial-mesenchymal transformation (EMT). B. PCNA is essential for stabilization of DNA synthesis and repair of DNA damage, and PH-3 participates in the G2 stage of the cell cycle. LncRNA MNX1-AS1 regulates the cell cycle via PCNA and PH-3.

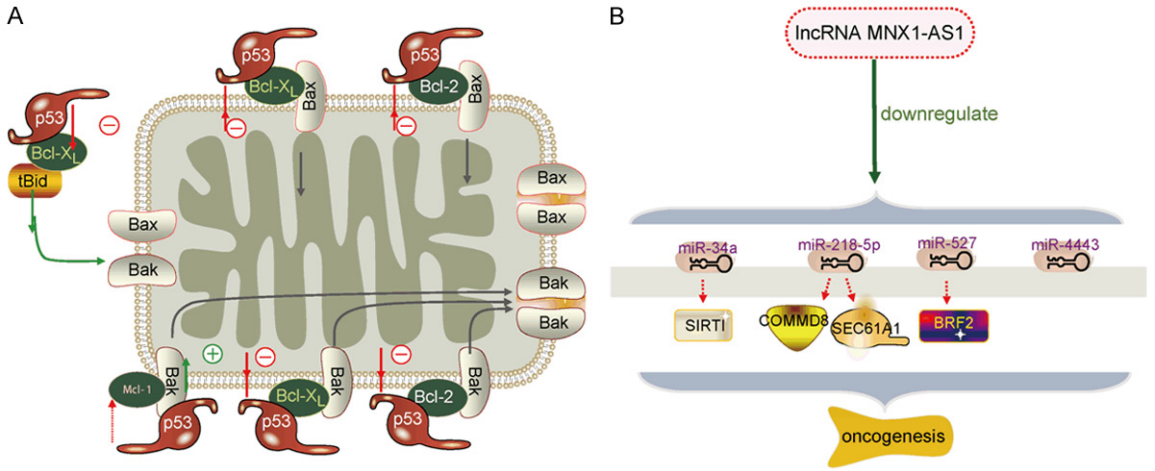

Figure 2. A. Bax and Bcl-2 have roles as pro-apoptotic proteins and anti-apoptotic proteins, respectively. MNX1-AS1 can regulate apoptosis via Bcl-2 and Bax. B. LncRNA MNX1-AS1 downregulates downstream miRNAs and induces oncogenesis.

abnormal thrombin, and phosphatidylinositol proteoglycan 3, do not have high diagnostic accuracies [34]. Therefore, new early detection and early intervention markers are of great significance to improve the prognosis and survival rates of patients with HCC. LncRNA MNX1-AS1 is noticeably upregulated in HCC tissues and HCC cell lines. Results of qRT-PCR and in situ hybridization (ISH) analyses indicate that lncRNA MNX1-AS1 levels are positively correlated with TNM stage. Expression levels of lncRNA MNX1-AS1 in metastatic HCC tissues are higher than those in lung metastatic HCC tissues. Results of function loss experiments indicate that lncRNA MNX1-AS1 down-regulation restrains the proliferation, migration, and invasion of HCC cells in vitro. Kaplan-Meier analyses reveal that HCC patients have higher lncRNA MNX1-AS1 expression levels and lower survival rates [35]. These results suggest that MNX1-AS1 is a prognostic marker of HCC.

Molecular mechanism of lncRNA MNX1-AS1

Four aspects of the molecular mechanism of MNX1-AS1 are described in this section (**Figures 1** and **2**).

LncRNA MNX1-AS1 induces metastasis and invasion of cancer cells by promoting epithelial-mesenchymal transformation

Epithelial-mesenchymal transformation (Endo-MT/EMT), a special phenotype of cancer cells, is closely correlated with the invasion and migration of various cancer cells [36]. During this period, expression levels of the mesenchymal phenotypic proteins N-cadherin and vimentin increase, while epithelial phenotypic protein E-cadherin decreases in epithelial cells [37]. Adhesion between epithelial cells and basal cell membranes decrease, while the migration and invasion phenotypes of mesenchymal cells increase and they acquire the ability to degrade extracellular matrix. In one study of MNX1-AS1 expression in NSCLC, Western-blot results indicated that expression levels of E-cadherin in lncRNA MNX1-AS1 knocked-out epithelial cells increased significantly, while expression of N-cadherin and vimentin remarkably decreased ($P<0.05$). This result suggested that loss of lncRNA MNX1-AS1 restrained migration and invasion of A549 cell lines by regulating the EMT process (**Figure 1A**) [17]. Similarly, using WB assays, other studies of correlations between lncRNA MNX1-AS1 and development of prostate cancer, gastric cancer, and breast cancer, found that lncRNA MNX1-AS1 might induce metastasis and invasion of cancer cells via the EMT [21, 31, 38].

LncRNA MNX1-AS1 induces proliferation of cancer cells

In a series of studies, the results of CCK-8 assay, MTT assay, and tablet cloning assay indicated that lncRNA MNX1-AS1 exerted significant effects on cancer cell proliferation [13, 39-41]. Proliferating cell nuclear antigen (PCNA) participates in DNA synthesis and has a vital role in cell proliferation [42, 43]. In recent years, the relationships between PCNA and tumor development have become an active research field [44]. PCNA is highly expressed in many tumors (e.g., lung, cervical, oral, and breast) [45-47]. Phospho-histone H3 (PH-3), P53, and Ki-67 also have strong correlations with the proliferation of cancer cells [38]. Wei Zhang et al. found that PCNA expression levels decreased in gastric cancer cells when lncRNA MNX1-AS1 was knocked-out [21]. Therefore, lncRNA MNX1-AS1 may affect cancer cell proliferation by regulating expression of PCNA and PH-3 (**Figure 1B**).

LncRNA MNX1-AS1 regulates apoptosis of cancer cells

Flow cytometry results indicate that LncRNA MNX1-AS1 inhibits apoptosis of various cancer cells [17, 18, 28, 48]. There are various anti-apoptotic mechanisms of cancer cells. Studies of cancer cells found that MNX1-AS1 has an anti-apoptotic role via up-regulation of expression levels of anti-apoptotic proteins (e.g., Bcl-2) and down-regulation of ng the expression of pro-apoptotic proteins (e.g., Bax) (**Figure 2A**). Because expression of Bcl-2 and Bax is regulated by the tumor suppressor gene P53, Bcl-2 over-expression exists in some types of B-cell lymphomas [49]. Taken together, these findings strongly indicate that the failure of normal programmed death can cause cancerization. In one study, Gaofeng Liu et al. found that the expression level of Bax was remarkably downregulated in NSCLC cells. In contrast, the expression level of Bcl-2 was remarkably upregulated in NSCLC cells transfected with MNX1-AS1; the opposite results occurred in NSCLC cells with MNX1-AS1 knocked-out. Two other studies on ovarian and cervical cancer had similar conclusions [18, 48]. These results suggest that lncRNA MNX1-AS1 has an anti-apoptotic role by increasing the expression level of anti-apoptotic protein Bcl-2 and decreasing the expression level of pro-apoptotic protein Bax.

LncRNA MNX1-AS1 functions through downstream microRNAs

MicroRNAs (miRNAs) are non-coding single-stranded small RNAs with about 22 to 25 nucleotides in length. They regulate post-transcriptional processes by combining the 3'-untranslated region (3' UTR) of their target mRNAs. During the more than 20 years since the discovery of miRNAs, cancer has become the focus of research in this field. MiRNAs are related to tumor growth, invasion, angiogenesis, and immune avoidance [50]. They are divided into the tumor-promoting miRNAs (ONCO-miRNA) and tumor-suppressing miRNAs (TS-miRNAs) based on their different roles in cancer development. ONCO-miRNAs are usually upregulated in tumors and promote cancer

cell growth mainly by degrading tumor suppressor genes. TS-miRNAs are down-regulated in tumors and have an anti-tumor function [50, 51]. Compared with normal tissue, miRNA expression disorders are found in almost all stages of tumorigenesis (cell cycle [52], apoptosis [53], invasion [54], and angiogenesis [55]). Studies find that lncRNA MNX1-AS1 can regulate levels of downstream miRNAs. Jie Chu et al. searched in a bioinformatics database and found that lncRNA MNX1-AS1 has specific regions that bind to miRNA-34a. They thus can function as competing endogenous RNA (ceRNA) and regulate miRNA levels. Jie Chu et al. transfected KYSE 30 cell lines with lncRNA MNX1-AS1. Using qRT-PCR, they found that miRNA-34a levels were significantly decreased in KYSE 30 cells and that miRNA-34a levels in esophageal cancer tissues were significantly negatively correlated with lncRNA MNX1-AS1 levels. They found in the GEPIA database that SIRT1 might be a downstream signaling molecule of miRNA-34a, so they performed relevant experiments to confirm this hypothesis. In other words, lncRNA MNX1-AS1 can promote occurrence and development of esophageal cancer via the lncRNA MNX1-AS1/miRNA-34a/SIRT1 axis [13]. Similarly, Degang Ji et al. found that lncRNA MNX1-AS1 is the ceRNA of miRNA-218-5p. Luciferase reporter assay results indicated that the miRNA-218-5p analog significantly reduced lncRNA MNX1-AS1 levels in hepatocellular cancer cells. They then performed a luciferase reporter assay to examine whether COMMD8 is the downstream signaling molecule of miRNA-218-5p. LncRNA MNX1-AS1 can promote the occurrence and development of HCC via the lncRNA MNX1-AS1/miRNA-218-5p/COMMD8 axis [37]. Haiboo Liu et al. found that lncRNA MNX1-AS1 can promote the occurrence and development of lung cancer through the lncRNA MNX1-AS1/miRNA-527/BRF2 axis [11]. Wei Huang et al. found that MNX1-AS1 cab promote the occurrence and development of colorectal adenocarcinoma via the lncRNA MNX1-AS1/miRNA-218-5p/SEC61A1 axis [10]. Yan Gao et al. found that lncRNA MNX1-AS1 can promote the occurrence and development of malignant glioma through the lncRNA MNX1-AS1/miRNA-4443 axis [12]. MiRNAs are essential for the function of lncRNA MNX1-AS1 (**Figure 2B**). However, all the possible downstream signaling molecules found in these experiments are newly discovered miRNAs. Therefore, further experiments are needed to examine mechanisms between miRNAs and lncRNA MNX1-AS1.

Conclusions

The last 2 to 3 years have seen much progress in the research field of mechanisms of MNX1-AS1. MNX1-AS1 promotes the EMT process, which is closely related to the invasion and migration of various cancer cells. MNX1-AS1 also promotes unlimited proliferation of cancer cells by regulating some proliferation-related genes. There are also some studies of effects of MNX1-AS1 in cancer cell apoptosis. MNN1-AS1 seems to participate in multiple steps associated with the occurrence and development of malignant tumors. Further exploration of the mechanisms of MNN1-AS1 will be an arduous but meaningful task.

In this article, we comprehensively described clinical effects and mechanisms of MNX1-AS1 as an oncogene in various malignant tumors. In the first part, we described the effects of lncRNA MNX1-AS1 on cell proliferation, apoptosis, invasion, and metastasis in different malignant tumors. We listed the genes that have coordinating or antagonistic roles. We also summarized the effects of lncRNA MNX1-AS1 over-expression on tumor lesion size, stage, grade, distant metastasis, and patient prognosis. A higher expression level of lncRNA MNX1-AS1 is significantly related to a poorer prognosis. This relationship illustrates that lncRNA MNX1-AS1 can be used as a biomarker to predict prognosis. In the second part of the article, we described possible mechanisms of lncRNA MNXA-AS1 from four aspects by reviewing literature about MNX1-AS1. In addition to the above mechanisms, MNX1-AS1 also has a cancer-promoting role through the MAPK [44] and AKT/mTOR pathways [28]. Collectively, MNX1-AS1 is a newly discovered lncRNA, and study results support the hypothesis that it has non-negligible effects on the occurrence and development of various malignant tumors.

These studies had some limitations. First, most ignored differences between different tumor subtypes. For example, the pathological types of lung cancer include adenocarcinoma, squamous cell carcinoma, and small cell carcinoma.

Expression levels, effects, and mechanisms of lncRNA MNX1-AS1 may be different in different subtypes. The clinical and pathological characteristics of different pathological types of breast cancer vary greatly, so it is necessary to study differences between expression levels of MNX1-AS1. The mechanisms of most lncRNAs are complex, and the secondary structures and specific mechanisms of lncRNA MNX1-AS1 have not been fully elucidated. It may have roles that are completely different from those found by these studies. As a lncRNA with potential clinical value, lncRNA MNX1-AS1 needs to be studied comprehensively.

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Disclosure of conflict of interest

None.

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