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DLX6-AS1: a putative lncRNA candidate in multiple human cancers

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Abstract

Long non-coding RNAs (lncRNAs) have important roles in regulating the expression of genes and act as biomarkers in the initial development of different cancers. Increasing research studies have verified that dysregulation of lncRNAs occurs in various pathological processes including tumorigenesis and cancer progression. Among the different lncRNAs, DLX6-AS1 has been reported to act as an oncogene in the development and prognoses of different cancers, by affecting many different signalling pathways. This review summarises and analyses the recent research studies describing the biological functions of DLX6-AS1, its overall effect on signalling pathways and the molecular mechanisms underlying its action on the expression of genes in multiple human cancers. Our critical analysis suggests that different signalling pathways associated to this lncRNA may be used as a biomarker for diagnosis, or targets of treatment in cancers.

Introduction

It has been estimated that about 18.1 million people suffer from cancer while almost 9.6 million of them have died of cancer in 2018 (Ref. 1). Although various factors are involved in cancer incidence, recently, it has been revealed that non-coding RNAs (ncRNAs) are important factors in cancer prevalence (Ref. 2). NcRNAs can be categorised into housekeeping and regulatory RNAs based on their functions (Ref. 3). Also, regulatory RNAs can be sub-grouped into small ncRNA and long ncRNA (lncRNA) according to transcript size (Ref. 3). lncRNAs have a length larger than 200 nucleotides and are thought to be unable to encode proteins (Refs 4, 5). Recent studies, however, have shown that some lncRNAs can encode small peptides or small proteins (Refs 6–8).

lncRNAs regulate gene transcription through three main mechanisms (Ref. 9). Firstly, lncRNAs act as chromatin regulators; in this pathway, lncRNAs often function as important cis- and trans-acting modulators for the expression of protein-coding genes (Ref. 10). Furthermore, they can mediate epigenetic modification by recruiting chromatin remodelling complex to a specific chromatin locus (Ref. 11). Secondly, lncRNAs are also involved in transcriptional regulation; where they act as cofactors to modify the activity of transcription factors (Ref. 12). Various developmental genes are regulated in a similar fashion by transcribing the enhancers in the cells in which they are active (Ref. 12). lncRNAs can modify RNA polymerase II activity by interplaying with the initiation complex to steer the promoter (Ref. 13). For example, lncRNA dihydrofolate reductase (DHFR) forms a triplex structure with the major promoter of DHFR, inhibiting the binding of the transcriptional cofactor transcription initiation factor IID (TAFII31) (Refs 14, 15). In addition, lncRNAs may affect global changes by interacting with some basic components of the RNA polymerase II-dependent transcription machinery (Ref. 13). Lastly, post-transcriptional regulation; the ability of lncRNAs to identify complementary sequences allows some specific interactions capable of regulating post-transcriptional processing of mRNAs like capping, splicing, editing, transport, translation, degradation, and stability at various control sites (Ref. 16).

Basically, cancer is a genetic disease in which genetic changes lead to aberrant gene expression (Ref. 17). lncRNAs play critical roles in several cancer-related cellular biological processes such as cell proliferation, apoptosis, migration, invasion and tumorigenesis (Refs 18, 19). Many lncRNAs have been shown to be expressed aberrantly in several cancers and play key regulatory roles in cancer, including oncogenic and tumour suppressor (Ref. 17). Furthermore, the oncogenic and tumour suppressor roles of lncRNAs include many biological processes such as DNA damage, angiogenesis, metastasis, cell stemness, immune escape, therapeutic resistance, and metabolic disorders (Fig. 1) (Ref. 17).

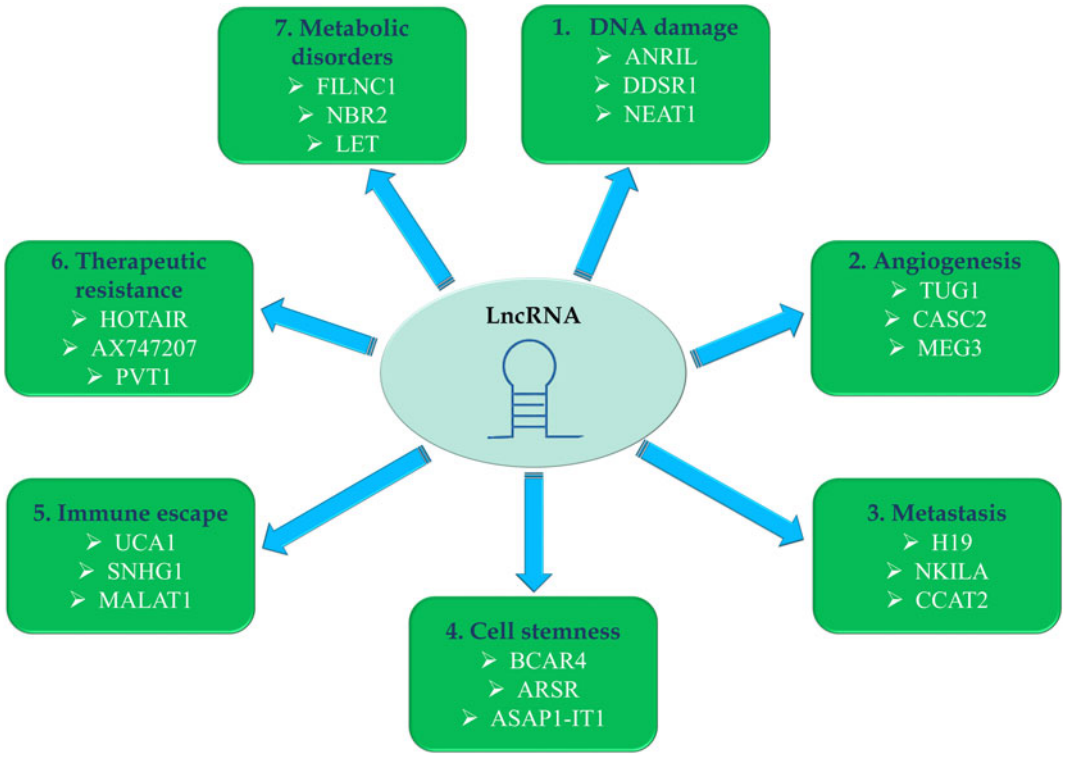

Fig. 1. The roles of lncRNAs in cancer (Ref. 17). In the figure are schematically shown the functions of the oncogenic and tumour suppressor of lncRNAs include many biological processes such as DNA damage, angiogenesis, metastasis, cell stemness, immune escape, therapeutic resistance, and metabolic disorders. lncRNAs, long non-coding RNAs.

Identification and characterisation of the detailed lncRNAs involved in the initiation and progression of different types of cancers would be extremely beneficial for cancer diagnosis and therapy (Ref. 20). Changes in expression of various lncRNAs were described to occur in different cancers, with lncRNAs being nowadays regarded as taking part in tumorigenesis and cancer development (Refs 21, 22). Given that lncRNAs can be easily detected from the body fluid by reverse transcription-polymerase chain reaction (RT-PCR), they can be utilised as appropriate diagnostic biomarkers to cancer diseases (Ref. 23). A number of lncRNAs are significantly up-regulated or down-regulated in different cancers (Ref. 24). In this study, the authors focused on collecting data on one important functional lncRNA (DLX6-AS1) that is usually found to be up-regulated in various cancers (Ref. 24).

DLX6-AS1 with gene ID number NONHSAG048270.3 in the NONCODE databases (http://www.noncode.org) is located on human chromosomal region 7q21.3 (Fig. 2a) and the change of its expression induces different cancers. The start site and end site are 96955140 and 97014065 respectively, and its sequence length is 15364 nucleotides (Refs 25, 26). Also, DLX6-AS1 gene expression in the Genotype-Tissue Expression (GTEx) database (https://www.gtexportal.org) is demonstrated in 54 tissues (Fig. 2b). According to information provided by the Ensembl database (http://www.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000231764;r=7:96955141-97014088), as of September 2020, DLX6-AS1 gene has 11 transcripts. DLX6-AS1 has different roles in cancer progression (i.e., tumour cell proliferation, growth, migration, epithelial-mesenchymal transition (EMT), invasion, aggressiveness and etc.) in different cancer types (Tables 1 and 2). Herein, it is our purpose to provide a concise review on current evidence associated with the role of DLX6-AS1 in different cancers, by firstly discussing the abnormal expression of this lncRNA in patient samples, followed by the description of its molecular mechanism of action and overall impact on signalling pathways leading to cancer development and progression.

The effect of DLX6-AS1 on digestive system cancers

Esophageal squamous cell carcinoma (ESCC)

ESCC is a fatal malignancy. Despite various treatments, the prognosis of ESCC is still poor. (Ref. 75). A recent study revealed that DLX6-AS1 expression is up-regulated in ESCC compared to normal cells and is positively associated with differentiation grade and metastatic stage (Ref. 39). Furthermore, it was reported that upregulated DLX6-AS1 expression was occurred in both ESCC tissue and cells and could be regarded as a poor prognosis in ESCC (Ref. 40). Based on the mentioned evidence, DLX6-AS1 may affect metastasis and the growth of ESCC (Ref. 39). It was validated that DLX6-AS1 could be influenced as a reliable biomarker for the diagnosis and treatment of ESCC (Ref. 76).

Gastric cancer (GC)

The expression of DLX6-AS1 was up-regulated in GC cells in advanced clinical stages where DLX6-AS1 can promote cancer cell proliferation as an oncogene (Ref. 43). The silencing of DLX6-AS1 can suppress mitogen-activated protein kinase kinase kinase kinase 1 (MAP4K1) by regulating FUS RNA binding protein (FUS) expression and thus inhibiting GC cell proliferation (Ref. 44). Qian *et al.* (Ref. 46) reported that DLX6-AS1 was overexpressed in GC tissues and cell lines and it modulates glucose metabolism and cell growth in GC by targeting miR-4290 (Ref. 46). miR-4290 was confirmed as a downstream target of DLX6-AS1, and their expression levels were inversely correlated (Ref. 46). In their study, the suppressed GC cell malignancy upon DLX6-AS1 knockdown could be prominently reversed by 3-phosphoinositide-dependent protein kinase 1 (PDK1) overexpression (Ref. 46). In a mouse xenograft model inoculated with GC cells the knockdown of DLX6-AS1 significantly delayed the tumour growth (Ref. 46). Also, DLX6-AS1 might increase cell proliferation through DLX6-AS1/miR-204-5p/ organic cation

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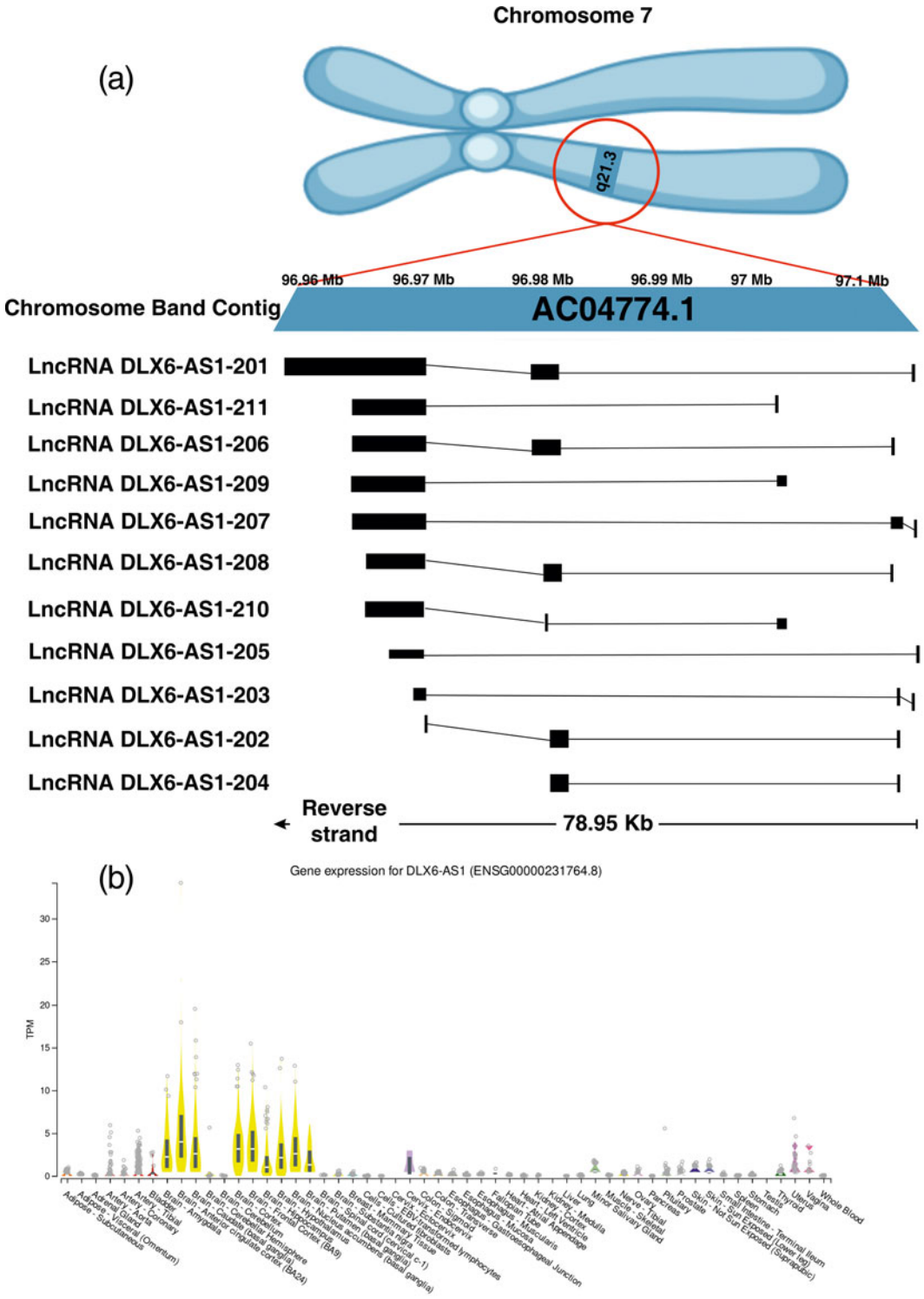

Fig. 2. DLX6-AS1 lncRNA genomic information. (a) an illustrated figure displaying DLX6-AS1 transcript information in humans. (b) a GTEx screenshot displaying DLX6-AS1 expression analysis in different cancers (https://www.gtexportal.org).

transporter 1 (OCT1) pathway in GC (Ref. 45). In the light of the available evidence, it can be suggested that DLX6-AS1 can be a crucial agent for the growth and proliferation of GC (Refs 44, 45).

Colorectal cancer (CRC)

DLX6-AS1 can promote the proliferation and migration of CRC cells. Zhang *et al.* (Refs 35, 55, 59, 61) reported that DLX6-AS1 was highly expressed in CRC with up-regulation of phosphoinositide 3-kinase (PI3 K)/AKT/mammalian target of rapamycin (mTOR) protein levels, and higher DLX6-AS1 expression was associated with both CRC proliferation and progression (Ref. 35). Kong *et al.* (Ref. 36) showed that CRC patients at advanced stage or with lymphatic metastasis had higher DLX6-AS1 expression (Ref. 36). One of the mechanisms was the regulation of the growth and aggressiveness of CRC cells *via* mediating miR-26a and a significant negative correlation between DLX6-AS1 and miR-26a was observed (Ref. 36). It was found that, miR-26a is a tumour suppressor gene, and can inhibit the malignant biological features of CRC cells (Ref. 36). Furthermore, with transfection of DLX6-AS1 siRNA, the growth and metastasis of CRC cells were suppressed (Ref. 36).

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Table 1. Functional characterisations of DLX6-AS1 in multiple human cancers

Cancer type	Number of case	Assessed cell lines	Expression	Functional roles	Approach of lncRNA function study	Downstream targets	Predicting prognosis	Reference
Bladder cancer	A total of 54 bladder cancer and matched adjacent non-neoplastic specimens	The human uroepithelial cells SV-HUC-1, and human bladder cancer cells 5637, J82 and T24	Up-regulated	Proliferation, invasion, migration, and epithelial-to-mesenchymal transition	Knockdown/ overexpression	Wnt/β-catenin	DLX6-AS1 overexpression was correlated with advance TNM stage, lymphatic node metastasis and distant metastasis.	(Ref. 27)
Bladder cancer	A total of 80 bladder cancer and matched adjacent non-neoplastic specimens	Human Bladder cancer cell lines T24 and SW780, and human normal human urothelial cell line SV-HUC-1	Up-regulated	Cell growth and invasiveness	Knockdown/ overexpression	miR-223/ HSP90B1	–	(Ref. 28)
Bladder cancer	A total of 60 bladder cancer and matched adjacent non-neoplastic specimens	The human bladder epithelium immortalised cell line SV-HUC-1, and Bladder cancer cell lines T24, RT4, 5637, J82, and SW780	Up-regulated	Proliferation, migration, and invasion	Knockdown/ overexpression	miR-195-5p/ VEGFA/Ras/Raf/ MEK/ERK	DLX6-AS1 had significant negative correlation with the 5-year survival in patients.	(Ref. 29)
Breast cancer	A total of 45 breast cancer and matched adjacent non-neoplastic specimens	Human Breast cancer cell lines MDA-MB-231, MCF-7, MDA-MB-468, T47D, BT-474, and normal 98 breast epithelial cell line MCF-10A	Up-regulated	Proliferation, invasion, migration, and apoptosis	Knockdown	miR-505-3p/ RUNX2	DLX6-AS1 expression was positively associated with poor prognosis.	(Ref. 30)
Breast cancer	–	–	Up-regulated	Migration and invasion	Knockdown	FUS	–	(Ref. 31)
Breast cancer	A total of 58 bone metastasis and matched adjacent non-neoplastic specimens	–	Up-regulated	Bone metastasis	Systems biology	–	–	(Ref. 32)
Breast cancer	A total of 47 breast cancer and 28 matched adjacent non-neoplastic specimens	Human breast fibroblast cell line CCD-1095Sk and human Triple-negative breast cancer cell lines HCC1599, MDA-MB-231, HCC1806, HS578 T and CAL-51	Up-regulated	Cell proliferation, epithelial-mesenchymal transition	Knockdown/ overexpression	miR-199b-5p/ Paxillin	–	(Ref. 33)

Cervical cancer	A total of 78 cervical cancer and matched adjacent non-neoplastic specimens	Human immortalised cervical epithelial cell lines NC104, and human cervical cancer cell lines CaSki, ME-180, C-33A, SiHa and HeLa	Up-regulated	Proliferation	Knockdown	miR-199a	DLX6-AS1 overexpression was associated with FIGO stage in patients with cervical cancer.	(Ref. 34)
Cervical cancer	–	Cervical cancer cells SiHa, HeLa, C-33A, and CaSki, and	Up-regulated	Proliferation, migration, epithelial–mesenchymal transition, and apoptosis	Knockdown	miR-16-5p and ARPP19	–	(Ref. 29)
Colorectal cancer	A total of 60 primary colorectal cancer and matched adjacent non-neoplastic specimens	The normal human colon epithelial cell line NCM460, and CRC cell lines HCT116, HT-29, and SW480 w	Up-regulated	Proliferation, invasion, and migration	Knockdown/ overexpression	PI3 K/AKT/ mTOR	DLX6-AS1 overexpression was significantly associated with advanced T stage and distant metastasis.	(Ref. 35)
Colorectal cancer	A total of 76 primary colorectal cancer and matched adjacent non-neoplastic specimens	Normal human colorectal epithelial cell line NCM460, and Colorectal cancer cell lines DLD-1, HCT-116, HT-29, SW480, and SW620 w	Up-regulated	Growth and Aggressiveness	Knockdown	miR-26a/EZH2	Patients at advanced stage or with lymphatic metastasis had higher DLX6-AS1 expression.	(Ref. 36)
Endometrial cancer cells	A total of 78 endometrial cancer and matched adjacent non-neoplastic specimens	Human endometrial cancer cell lines RL-952, HEC-1-B, HEC-1-A, HHUA and HEC-251, and human endometrial cell line PA	Up-regulated	Proliferation, invasion, and apoptosis	Knockdown	p300/E2F1	–	(Ref. 37)
Epithelial ovarian cancer cells	A total of 128 epithelial ovarian cancer cells and matched adjacent non-neoplastic specimens	Epithelial ovarian cancer cell lines HEY, SKOV3, and OVCAR-3, and normal ovarian epithelial cell line IOSE80	Up-regulated	Proliferation and metastasis	Knockdown	Notch1, p21, and Hes1	DLX6-AS1 overexpression was significantly associated with FIGO stage, lymph node metastasis and poor prognosis.	(Ref. 38)
Esophageal squamous cell carcinoma	A total of 73 primary esophageal squamous cell carcinoma and matched adjacent non-neoplastic specimens	Human Esophageal squamous cell carcinoma Cell lines EC109 and KYSE30	Up-regulated	Proliferation, apoptosis, and invasion	Knockdown	–	DLX6-AS1 expression was significantly increased in advanced tumour stages (III/ IV) compared with early-stage tumours (I/II).	(Ref. 39)
Esophageal squamous cell carcinoma	A total of 30 esophageal squamous cell carcinoma and matched adjacent non-neoplastic specimens	Human ESCC cell lines Eca109, Ec9706, TE-1, TE-10, TE-11, and KYSE-520, and normal esophageal epithelial cells NHBE cells, and HEK-293 T cells	Up-regulated	Proliferation and apoptosis	Knockdown	mTOR	DLX6-AS1 overexpression in tumour tissues and cells indicates a poor prognosis.	(Ref. 40)

(*Continued*)

Table 1. (*Continued.*)

Cancer type	Number of case	Assessed cell lines	Expression	Functional roles	Approach of lncRNA function study	Downstream targets	Predicting prognosis	Reference
Esophageal squamous cell carcinoma	–	oral squamous cell carcinoma cell line HSC3	Up-regulated	Cell proliferation, migration and invasion	Knockdown	miR-15b and PLD1	–	(Ref. 41)
Ewing's sarcoma	Not reported	Ewing sarcoma cell lines SK-ES-1, A673, RD-ES, and mesenchymal stem cells (MSCs)	Up-regulated	Proliferation and accelerate the apoptosis	Knockdown	miR-124-3p/ CDK4	–	(Ref. 42)
Gastric cancer	A total of 62 primary gastric cancer and matched adjacent non-neoplastic specimens	Normal human gastric mucosa epithelial cell line GES-1 and GC cell lines HGC27, BGC823, SGC7901 and AGS cells	Up-regulated	Proliferation, colony formation, cell cycle progression, migration, and invasion	Knockdown	–	DLX6-AS1 overexpression was significantly associated with advanced clinical stage, lymph node metastasis and distant metastasis.	(Ref. 43)
Gastric cancer	–	Human gastric cancer cell lines AGS, HGC-27, SGC-7901 and BGC-823 and normal gastric epithelial cell line GES-1	Up-regulated	Proliferation, migration, and epithelial-to-mesenchymal transition	Knockdown	MAP4K1 and FUS	–	(Ref. 44)
Gastric cancer	A total of 56 primary gastric cancer and matched adjacent non-neoplastic specimens	Gastric cancer cell lines MKN-7, MKN-28, MGC803, HGC-27, MKN-45, AGS and SGC-7901, and normal intestinal cell line GES-1 and human embryonic kidney cell line 293 T	Up-regulated	Tumour progression and epithelial–mesenchymal transition	Knockdown	miR-204-5p/ OCT1	DLX6-AS1expression was associated with T3/T4 invasion, distant metastasis and poor clinical prognosis.	(Ref. 45)
Gastric Cancer	A total of 60 primary gastric cancer and matched adjacent non-neoplastic specimens	Gastric Cancer cells lines HGC-27, MGC803, SGC7901, MKN45, human gastric epithelial cell line GES-1	Up-regulated	Glucose Metabolism and Cell Growth	Knockdown	miR-4290	DLX6-AS1expression was positively associated with tumour sizes, lymph node involvement and tumour-node-metastasis staging.	(Ref. 46)
Glioma	A total of 36 glioma and matched adjacent non-neoplastic specimens	Human glioma cell lines U251, U87MG, T98G, SHG44, and normal human astrocytes (NHA)	Up-regulated	Proliferation, invasion, and tumour growth	Knockdown/ overexpression	miR-197-5p and E2F1	DLX6-AS1 overexpression was clinically correlated with the poor outcome of glioma patients.	(Ref. 47)
Hepatocellular carcinoma	A total of 60 primary hepatocellular carcinoma and matched adjacent non-neoplastic specimens	Human HCC cell lines MHCC97L, HCCLM3, HepG2, Hep3B, Huh7, and normal liver cell lines LO2	Up-regulated	Proliferation, migration, and invasion	Knockdown	miR-203a, MMP-2	DLX6-AS1expression was correlated with poor prognosis for Hepatocellular carcinoma patients.	(Ref. 48)

Hepatocellular carcinoma and liver cancer stem cells	A total of 48 primary hepatocellular carcinoma and matched adjacent non-neoplastic specimens	Hepatocellular carcinoma cell lines of SMMC-7721, HCCLM3, Hep3B, HepG2 and Huh7 and an immortalised normal L02 liver cell line	Up-regulated	Proliferation, and tumour formation	Knockdown	STAT3 and CADM1	–	(Ref. 49)
Laryngeal Cancer	A total of 43 laryngeal cancer carcinoma and matched adjacent non-neoplastic specimens	The human laryngeal cancer cell lines HEp-2 and Tu-177	Up-regulated	Proliferation	Knockdown	miR-26a/TRPC3	DLX6-AS1 expression was higher in advanced clinical stages compared with lower stages and was associated with poor prognosis.	(Ref. 50)
Laryngeal squamous cell carcinoma	A total of 23 laryngeal squamous cell carcinoma and matched adjacent non-neoplastic specimens	Laryngeal squamous cell carcinoma cell line Hep2	Up-regulated	Growth and invasion	Knockdown	miR-376c	–	(Ref. 51)
Liver cancer	A total of 60 primary hepatocellular carcinoma and matched adjacent non-neoplastic specimens	Human HCC cell lines MHCC97L, HCCLM3, SK-HEP-1, Hep3B, and Huh7, and normal human liver cell line LO2, and HEK293t cells	Up-regulated	Proliferation, migration, and invasion	Knockdown	miR-424-5p and WEE1	–	(Ref. 52)
Liver cancer	A total of 48 hepatocellular carcinoma and matched adjacent non-neoplastic specimens	Hepatocellular carcinoma cell lines of SMMC-7721, HCCLM3, Hep3B, HepG2 and Huh7, and immortalised normal L02 liver cell line	Up-regulated	Growth and differentiation	Knockdown	STAT3	–	(Ref. 49)
Lung adenocarcinoma	A total of 72 primary lung adenocarcinoma and matched adjacent non-neoplastic specimens	Human lung adenocarcinoma cell lines A549 and H1650	Up-regulated	–	Knockdown	–	DLX6-AS1 overexpression was significantly associated with both histological differentiation and TNM stage.	(Ref. 26)
LungSquamous Cell Carcinoma	Not reported	–	Up-regulated	Survival	Systems biology	–	–	(Ref. 53)
Nasopharyngeal carcinoma	A total of 72 nasopharyngeal carcinoma and matched adjacent non-neoplastic specimens	Nasopharyngeal epithelial cells NP69, NPC cell lines S18, S26, CNE-1, CNE-2, HONE-1, and 5-8F	Up-regulated	Promotes the malignant phenotypes	Knockdown/ overexpression	miR-199a-5p, and HIF-1α	–	(Ref. 54)

(*Continued*)

Table 1. (*Continued.*)

Cancer type	Number of case	Assessed cell lines	Expression	Functional roles	Approach of lncRNA function study	Downstream targets	Predicting prognosis	Reference
Neuroblastoma	A total of 36 neuroblastoma and matched adjacent non-neoplastic specimens	Human Neuroblastoma cell lines NB-1643, NB-1691, SK-N-AS, IMR-32, SH-SY5Y and SK-N-SH	Up-regulated	Tumour progression, invasion, metastasis, and apoptosis	Knockdown	miR-107/BDNF	DLX6-AS1 overexpression was positively correlated with advanced TNM stage and poor differentiation.	(Ref. 55)
Neuroblastoma	A total of 70 neuroblastoma and matched adjacent non-neoplastic specimens	Human Neuroblastoma cell lines SK – N -SH, SH -SY5Y, SK – N -AS, and SK – N -BE(Ref. 2)	Up-regulated	Proliferation, migration, invasion and epithelial–mesenchymal transition	Knockdown	YAP1/ miR-497-5p	DLX6-AS1 overexpression was positively correlated with advanced clinical stage and poor survival.	(Ref. 56)
Neuroblastoma	A total of 31 neuroblastoma and matched adjacent non-neoplastic specimens	Neuroblastoma cell lines SK-N-SH and LAN-6	Up-regulated	Cell proliferation, cell cycle and glycolysis	Knockdown/ overexpression	miR-506-3p/ STAT2	–	(Ref. 57)
Neuroblastoma	A total of 20 neuroblastoma and matched adjacent non-neoplastic specimens	Neuroblastoma cell lines SK-N-SH and SK-N-AS NB cells, and Human umbilical vein endothelial cells	Up-regulated	Cell migration, and invasion	Knockdown	miR-513c-5p/ PLK4	–	(Ref. 58)
Non-small cell lung cancer	A total of 27 primary non-small cell lung cancer and matched adjacent non-neoplastic specimens	Human non-small cell lung cancer cell lines A549, H1299 and 95D, and normal human epithelial cell line BEAS-2B	Up-regulated	Proliferation and migration	Knockdown	–	The higher serum *DLX6-AS1* level was associated with advanced disease stage, positive lymph node metastasis and poor tumour differentiation.	(Ref. 59)
Non-small cell lung cancer	A total of 48 primary non-small cell lung cancer and matched adjacent non-neoplastic specimens	Non-small cell lung cancer cell lines H1975 and A549, and human bronchial epithelial cell line 16HBE	Up-regulated	Proliferation, migration, and invasion	Knockdown	proline rich 11 (PRR11), miR-144	–	(Ref. 60)
Non-small cell lung cancer	A total of 51 primary non-small cell lung cancer and matched adjacent non-neoplastic specimens	Non-small cell lung cancer cell lines CALU3, CALU6, A549, and H1299 and human bronchial epithelial cell line HBE	Up-regulated	Proliferation, invasion, and migration	Knockdown	miR-27b-3p and GSPT1	*DLX6-AS1* overexpression was associated with tumour size and advanced clinical stage in patients.	(Ref. 25)
Osteosarcoma	A total of 40 osteosarcoma and matched adjacent non-neoplastic specimens	The human Osteosarcoma cell lines MG-63, Saos-2 and U2OS, and the hFOB cell line	Up-regulated	Proliferation and metastasis	Knockdown	miR-641 and HOXA9	DLX6-AS1 overexpression was significantly correlated with advanced TNM stage, high tumour grade, and distant metastasis of patients.	(Ref. 61)

Osteosarcoma	–	Human osteosarcoma cell lines MG63 and U2OS	Up-regulated	Stemness	Knockdown	miR-129-5p and DLK1	DLX6-AS1 overexpression was correlated with advanced clinical stage and poor histological grade. DLX6-AS1 was positively correlated with poor overall survival in osteosarcoma.	(Ref. 62)
Osteosarcoma	A total of 25 femoral osteosarcoma and matched adjacent non-neoplastic specimens	Human OS cell lines U2OS (HTB-96) and MG-63 (CRL-1427), and normal human osteoblast cell line NHost	Up-regulated	Proliferation, migration, and invasion	Knockdown	miR-141-3p/ Rab10	DLX6-AS1 overexpression was associated with advanced disease stage, positive lymph node metastasis and poor tumour differentiation	(Ref. 59)
Ovarian cancer	A total of 50 ovarian cancer and matched adjacent non-neoplastic specimens	Ovarian cancer cell lines SKOV3 and A2780, and normal ovarian epithelial cell line IOSE80, and human embryonic kidney cell 293 T	Up-regulated	Proliferation, migration, invasion, and apoptosis	Knockdown	miR-195-5p/ FHL2	–	(Ref. 63)
Ovarian Cancer Patients with Wild-Type BRCA1/ 2	A total of 459 ovarian cancer and matched adjacent non-neoplastic specimens	–	Up-regulated	Proliferation	Systems biology	BRCA1/2	–	(Ref. 64)
Pancreatic cancer	A total of 84 primary pancreatic cancer and matched adjacent non-neoplastic specimens	Human pancreatic duct epithelial cell Line HPDE6-C7, and human pancreatic cancer cell lines CAPAN-1, BxPC-3, SW 1990 and PANC-1	Up-regulated	Proliferation and invasion	Knockdown	miR-181b	DLX6-AS1 overexpression was positively correlated with larger tumour size, advanced TNM stage and lymph node metastasis.	(Ref. 65)
Pancreatic cancer	A total of 60 primary pancreatic cancer and matched adjacent non-neoplastic specimens	The normal human pancreatic ductal epithelial cells and Pancreatic cancer cell lines Panc-1, Bxpc-3, AsPC-1, Capan-1, CFPAC-1, and MIA PaCa-2	Up-regulated	Proliferation, cell cycle, migration, invasion, and apoptosis of cells	Knockdown/ overexpression	miR-497-5p, FZD4, FZD6, Wnt and β-catenin	DLX6-AS1 expression was negatively correlated with the survival of patients.	(Ref. 66)
Pancreatic cancer	A total of 96 primary pancreatic cancer and matched adjacent non-neoplastic specimens	–	Up-regulated	–	–	–	DLX6-AS1 can evaluate the chemotherapeutic effect and predict the prognosis.	(Ref. 67)
Prostate cancer	Not reported	The benign immortalised prostate cell lines BPH1 and PNT2, and Prostate cancer Cell lines LNCaP, PC3, DU145, VCaP and 22RV1	Up-regulated	–	–	cis protein-coding gene DLX6	–	(Ref. 68)

(*Continued*)

Table 1. (*Continued.*)

Cancer type	Number of case	Assessed cell lines	Expression	Functional roles	Approach of lncRNA function study	Downstream targets	Predicting prognosis	Reference
Prostate cancer	A total of 32 prostate cancer And A total of 28 benign prostatic hyperplasia	The prostate cancer cell lines CWR22rv1, LAPC-9, DU145, LNCaP, and PC-3 M, and normal human prostate epithelial cell line PrEC	Up-regulated	Malignant Phenotype and Lymph Node Metastasis	Knockdown/ overexpression	MMP-9, DNMT1, and LARGE	–	(Ref. 69)
Prostate cancer	A total of 20 prostate cancer and matched adjacent non-neoplastic specimens	Healthy human prostate cell line WPMY1, and Prostate cancer cell lines LNCap, DU145, PC-3, and VCap	Up-regulated	Cell proliferation and apoptosis	Knockdown	miR-497-5p/ SNCG	–	(Ref. 70)
Renal cell carcinoma	A total of 52 renal cell carcinoma and matched adjacent non-neoplastic specimens	The human renal cancer cell lines A498, ACHN, Caki-1, Caki-2, 786-O and G401, and normal kidney cell line HK-2	Up-regulated	Growth	Knockdown	miR-26a and PTEN	DLX6-AS1 expression in metastatic samples was shown higher level than that in non-metastatic samples.	(Ref. 71)
Thyroid cancer	A total of 108 thyroid cancer and adjacent normal thyroid tissue specimens	The human thyroid cancer cell lines K1, BCPAP, IHH4 and TPC1 and human normal thyroid epithelial cell line Nthyori3-1	Upregulated	Cell growth and autophagy	Knockdown/ overexpression	miR-193b-3p/ HOXA1	DLX6-AS1 was up-regulated, and miR-193b-3p was down-regulated in thyroid cancer tissues compared with adjacent normal thyroid tissue.	(Ref. 72)

Table 2. DLX6-AS1 as a competing endogenous RNA (CeRNA) for miRNAs in multiple human cancers

Cancer type	Targeting miRNA	Reference
Bladder cancer	miR-223	(Ref. 28)
Bladder cancer	miR-195-5p	(Ref. 73)
Breast cancer	miR-505-3p	(Ref. 30)
Breast cancer	miR-199b-5p	(Ref. 33)
Cervical cancer	miR-199a	(Ref. 34)
Cervical cancer	miR-16-5p	(Ref. 29)
Colorectal cancer	miR-26a	(Ref. 36)
7Esophageal squamous cell carcinoma	miR-15b	(Ref. 41)
Ewing's sarcoma	miR-124-3p	(Ref. 42)
Gastric cancer	miR-204-5p	(Ref. 45)
Gastric Cancer	miR-4290	(Ref. 46)
Glioma	miR-197-5p	(Ref. 47)
Hepatocellular carcinoma	miR-203a	(Ref. 48)
Hepatocellular carcinoma	miR-513c	(Ref. 74)
Laryngeal Cancer	miR-26a	(Ref. 50)
Laryngeal squamous cell carcinoma	miR-376c	(Ref. 51)
Liver cancer	miR-424-5p	(Ref. 52)
Nasopharyngeal carcinoma	miR-199a-5p	(Ref. 54)
Neuroblastoma	miR-107	(Ref. 55)
Neuroblastoma	miR-497-5p	(Ref. 56)
Neuroblastoma	miR-506-3p	(Ref. 57)
Neuroblastoma	miR-513c-5p	(Ref. 58)
Non-small cell lung cancer	miR-144	(Ref. 60)
Non-small cell lung cancer	miR-27b-3p	(Ref. 25)
Osteosarcoma	miR-641	(Ref. 61)
Osteosarcoma	miR-129-5p	(Ref. 62)
Osteosarcoma	miR-141-3p	(Ref. 59)
Ovarian cancer	miR-195-5p	(Ref. 63)
Pancreatic cancer	miR-181b	(Ref. 65)
Pancreatic cancer	miR-497-5p	(Ref. 66)
Prostate cancer	miR-497-5p	(Ref. 70)
Renal cell carcinoma	miR-26a	(Ref. 71)
Thyroid cancer	miR-193b-3p	(Ref. 72)

According to the previous data, DLX6-AS1 has a critical function in colorectal cell proliferation and migration (Refs 35, 36).

Hepatocellular carcinoma (HCC)

HCC have rapid progress and metastasis so it shows poor clinical characteristics (Ref. 77). Recent studies indicated that DLX6-AS1 has an up-regulated expression in HCC (Refs 48, 52). It was identified that DLX6-AS1 stimulates liver cancer via enhancing the WEE1 kinase expression by an effect on miR-424-5p (Ref. 52). Additionally, DLX6-AS1 promotes HCC carcinogenesis through the regulation of miR-203a/ matrix metalloproteinase-2 (MMP-2) pathway (Ref. 48). Furthermore, DLX6-AS1 induces liver cancer tumorigenesis by modulating the signal transducer and activator of transcription 3 (STAT3) signalling pathway through hypo-methylation of the cell adhesion molecule 1 (CADM1) promoter (Ref. 49). In addition, an in vivo study conducted by Liu *et al.* (Refs 2, 32, 50, 74) reported that DLX6-AS1 triggered the invasion, and migration of HCC via a mechanistic regulation among miR-513c, cullin 4A (Cul4A), and annexin A10 (ANXA10). Thus, the knockout of lncRNA DLX6-AS1 hindered miR-513c-mediated Cul4A suppression and eventually enhanced the ubiquitination-dependent degradation of ANXA10, thereby inhibiting the incidence and progress of HCC (Ref. 74). Thus, DLX6-AS1 can be used as a potential biomarker in this cancer (Refs 48, 49, 52, 78). Additionally, an in vivo experiment conducted by Wang *et al.* (Ref. 79) demonstrated that exosomal DLX6-AS1 regulates C-X-C motif chemokine ligand 17 (CXCL17) in HCC via competitively binding to miR-15a-5p to stimulate M2 macrophage polarisation, thus inducing HCC invasion, migration, and EMT (Ref. 79).

Pancreatic cancer

Because of the difficulty in diagnosing pancreatic cancer in its early stages, this cancer has a poor prognosis with a 5-year survival rate (Ref. 80). Recent studies revealed that DLX6-AS1 is expressed at high levels in several cancers such as pancreatic cancer, and it is involved in tumorigenesis and metastasis (Refs 65, 66). A study has shown that high expression of DLX6-AS1 was positively correlated with larger tumour size, advanced tumour/node/metastasis (TNM) stage and lymph node metastasis, where its knockdown dramatically impaired cancer cell proliferation, migration and invasion in pancreatic cancer (Ref. 65). Furthermore, the knockdown of miR-181b as the downstream target of DLX6-AS1, reversed the suppression of cell viability, migration and invasion abilities caused by DLX6-AS1 knockdown (Ref. 65). In addition, DLX6-AS1/miR-497-5p/ Frizzled Class Receptor 4 (FZD4)/ Frizzled Class Receptor 6 (FZD6)/Wnt/ β-catenin signalling pathway is involved in the development of pancreatic cancer, and DLX6-AS1 may be used as a biomarker in pancreatic cancer diagnosis and treatment (Ref. 66).

The effect of DLX6-AS1 on respiratory system cancers

Lung cancer

It has been described that expression levels of DLX6-AS1 were significantly increased in lung cancer and this high expression related to differential stages of the disease (Ref. 26). Huang *et al.* (Ref. 60) showed that DLX6-AS1 induces cell proliferation and invasion while inhibits apoptosis through regulating miR-144 and up-regulation of PRR11 in non-small cell lung cancer (NSCLC) (Ref. 60). Besides, the levels of lncRNA DLX6-AS1 as a carcinogenic marker was increased in NSCLC cells and it promoted the growth, migration and invasion of NSCLC cells *in vivo* and *in vitro* (Ref. 25). Furthermore, Zhang *et al.* (Refs 35, 55, 59, 61) demonstrated that DLX6-AS1 is a potential diagnostic biomarker for NSCLC. In their study, the expression levels of DLX6-AS1 were significantly increased in tumour tissues and NSCLC cell lines compared to adjacent normal tissues and normal cell lines, respectively (Ref. 59). Moreover, serum DLX6-AS1 level was significantly higher in patients with NSCLC compared to healthy controls (Ref. 59). Another study showed that DLX6-AS1 promotes NSCLC progression by targeting the miR-27b-3p/ G1 to S phase transition 1 (GSPT1) axis, and its knockdown played a positive role in NSCLC treatment *in vivo* (Ref. 25). Taken together, DLX6-AS1 may play an important role in the proliferation and invasion of lung cancer, and targeting it using biological molecules could be one of the strategies for lung cancer treatment.

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Nasopharyngeal carcinoma (NPC)

In a study by Yang *et al.* (Refs 23, 51, 54, 66), the expression of lncRNA DLX6-AS1 was up-regulated in NPC tissues and cells (Ref. 54). The proliferation, migration, and invasion of NPC were enhanced by overexpression of DLX6-AS1 but inhibited by DLX6-AS1 knockdown (Ref. 54). Furthermore, DLX6-AS1 can act as a competing endogenous RNA (ceRNA) to regulate miR-199a-5p expression and, thereby increasing hypoxia-inducible factor 1-alpha (HIF-1α) expression as a direct target of miR-199a-5p (Ref. 54). HIF-1α expression is notably increased in the hypoxic microenvironment of solid tumours, facilitating tumour cell proliferation and metastasis (Ref. 54). Increased expression of HIF-1α in tumour tissues may be related to the up-regulation of DLX6-AS1 and thereby inhibiting miR-199a/b-5p expression, indicating a relationship between non-coding RNAs and the tumour microenvironment (Ref. 54).

Laryngeal squamous cell carcinoma (LSCC)

LSCC is the second most common neck and head malignancy (Ref. 81). Although LSCC in the early stages can be successfully treated, treatment is impossible at the advanced stages (Ref. 82). So, the identification of lncRNAs involved in LSCC development can help to achieve rapid diagnosis and treatment (Ref. 82). A study showed that the expression levels of DLX6-AS1 in LSCC tissues are increased and that DLX6-AS1 knockdown enhanced the expression of miR-376c in the Hep2 cells, suppressing cell growth (Ref. 51). Liu *et al.* (Refs 2, 32, 50, 74) demonstrated that DLX6-AS1 had increased expression in tumour tissues compared with adjacent normal tissues and in higher clinical stages compared with lower stages (Ref. 50). DLX6-AS1 knockdown decreased cell proliferation and affected key mitochondrial metabolic parameters in both HEp-2 and Tu-177 cells (Ref. 50). In addition, DLX6-AS1 knockdown suppressed transient receptor potential cation channel subfamily c member 3 (TRPC3)-mediated mitochondrial calcium uptake and ROS production (Ref. 50). They also showed that DLX6-AS1 regulates mitochondrial calcium homoeostasis, respiration, and tumour proliferation *via* modulating the miR-26a/TRPC3 axis in laryngeal cancer (Ref. 50). It was suggested that DLX6-AS1 could be influenced as an effector agent for LSCC growth and development.

The effect of DLX6-AS1 on reproductive system cancers

Endometrial cancer

In a recent study, researchers found that DLX6-AS1 and DLX6 both are highly expressed in endometrial cancer cells and tissues (Ref. 37). DLX6-AS1 formed a triplex structure with DLX6 *via* interaction with p300/ E2F transcription factor 1 (E2F1) acetyltransferase and up-regulation of DLX6-AS1 and DLX6 can promote endometrial cancer progression *via* this novel triplex mechanism. Silencing of DLX6-AS1 and DLX6 weakened the proliferation and invasion of endometrial cancer cells and tumours, while promoting apoptosis (Ref. 37).

Cervical cancer (CC)

Despite reinforced screening, CC is the fourth most common cancer in women (Ref. 83). Additionally, the occurrence rate of CC is significantly increasing in women (Ref. 83). Therefore, understanding the molecular characteristics and causes of this cancer is very important to improve its treatment (Ref. 84). Numerous studies have shown that lncRNAs play a regulatory role in the development of CC (Refs 34, 84, 85). It has been proven that silencing DLX6-AS1 can inhibit cell proliferation and increase apoptosis in cervical cells, and the possibility of miR-199a being a target of DLX6-AS1 (Ref. 34). Thus, it acts as a sponge for miR-199a and promotes the development and expansion of CC (Ref. 34). Moreover, the stimulating effect of DLX6-AS1 on the progression of CC may also occur *via* increased expression of cAMP-regulated phosphoprotein 19 (ARPP19) upon sponging of miR-16-5p, as reported by Xie *et al.* (Ref. 29). It was validated that serum exosomal lncRNA DLX6-AS1 could be considered as a prognostic biomarker for the diagnosis and treatment of CC (Ref. 86).

Ovarian cancer (OC)

Molecular research of DLX6-AS1 verified that overexpression of this marker predicts poor prognosis in OC and DLX6-AS1 acted as a tumour promoter in cell proliferation and metastasis by modulating Notch and miRNA signalling pathway (Ref. 61). Therefore, it is suggested that up-regulated expression of DLX6-AS1 can lead to proliferation and metastasis of OC (Ref. 61). lncRNA DLX6-AS1 exacerbates the proliferation, migration, and invasion of OC *via* modulating four and a half lim domains 2 (FHL2) by sponging miR-195-5p (Ref. 63).

Breast cancer

A recent study confirmed that DLX6-AS1 acts as a biomarker in breast cancer cell growth compared to non-tumour cells (Ref. 30). DLX6-AS1 could enhance cell migration and invasion in breast cancer through up-regulation of FUS (Ref. 31). In addition, DLX6-AS1 lncRNA acts as a sponge for miR-505-3p. DLX6-AS1 may lead to proliferation and invasion of breast cancer cells *via* miR-505-3p/ Runt-related transcription factor 2 (RUNX2) axis, which can be considered as a therapeutic target to cure breast cancer (Ref. 30). It was also identified that lncRNA DLX6-AS1, as a ceRNA of miR-199b-5p and paxillin, induces tumorigenesis and cisplatin resistance in Triple-negative breast cancer cells by down-regulating miR-199b-5p (Ref. 33).

The effect of DLX6-AS1 on urinary system cancers

Renal cancer

Many studies had demonstrated that lncRNAs' expression is dramatically dysregulated in renal cancer when compared to normal renal cells (Ref. 87). A study revealed that lncRNA DLX6-AS1 expression was increased in renal cell cancer compared with normal cells (Ref. 71). In this study, DLX6-AS1 was shown to act *via* suppressing miR-26a expression (Ref. 71). However, further research is necessary to understand the exact function of DLX6-AS1 in renal cancer occurrence and progression.

Prostate cancer

Recent studies confirmed that DLX6-AS1 is highly expressed in prostate cancer tissues and cells and has an important role in the progression of prostate cancer (Refs 69, 70). It was found that DLX6-AS1 recruits DNA methyltransferase 1 (DNMT1) to like-acetylglucosaminyltransferase (LARGE) promoter and induces the methylation of LARGE promoter to down-regulate the expression of LARGE, which finally enhances the proliferation, invasion, and metastasis of prostate cancer cells (Ref. 69). It was also identified that lncRNA DLX6-AS1 acts as a ceRNA of miR-497-5p and promotes the proliferation of prostate cancer cells and tumours through modulating the downstream target gene of miR-497-5p, synuclein gamma (SNCG), *in vitro* and *in vivo* (Ref. 70).

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Bladder cancer

Bladder cancer happens more commonly in males than females and although there are different treatments for bladder cancer, the prognosis is still poor after treatment (Ref. 88). A study reported that up-regulation of DLX6-AS1 was observed in bladder cancer tissues. The results showed that DLX6-AS1 accelerates cell proliferation in bladder cancer by the activity of the Wnt/ β-catenin signalling pathway (Ref. 27). Another study showed that there is an inverse relationship in the expression of DLX6-AS1 and miR-223 in bladder cancer cells, since silencing of DLX6-AS1 and overexpression of miR-223 stopped tumour growth (Ref. 28). By using the DLX6-AS1 knockdown, Wang *et al.* (Ref. 31) demonstrated that lncRNA DLX6-AS1 significantly affects miR-195-5p-mediated vascular endothelial growth factor A (VEGFA)/Rat sarcoma (Ras)/ rapidly accelerated fibrosarcoma (Raf/MEK)/ extracellular signal-regulated kinase (ERK) pathway, and higher DLX6-AS1 expression is associated with both bladder cancer development and progression (Ref. 73). Therefore, it seems that this lncRNA may play a function in the bladder cancer growth process.

The effect of DLX6-AS1 on central nervous system cancers

Glioma

A recent study has explained the role of DLX6-AS1 in the disease of glioma, revealing that the expression of this lncRNA was enhanced in glioma patients' cells resulting in a poor prognosis (Ref. 47). Due to the role of DLX6-AS1 in glioma, silencing of DLX6-AS1 expression by siRNAs inhibited tumour growth *in vitro* and *in vivo* (Ref. 47). Additionally, DLX6-AS1 could bind to miR-197-5p as a ceRNA, thereby increasing E2F1 expression, which leads to glioma tumorigenesis (Ref. 47). However, there are not many studies available on the role of DLX6-AS1 in glioma growth, and only one study has been published. Therefore, more studies are needed in this regard.

Neuroblastoma (NB)

NB is the most common extracranial solid malignant tumour in children and accounts for 15% of all childhood cancer deaths (Ref. 89). The lncRNA DLX6-AS1 was up-regulated in NB tissues and cell lines, and its expression was positively correlated with advanced stages and poor outcome of NB (Ref. 55). Proliferation rate, migration and invasion ability, as well as EMT process of NB cells were inhibited after DLX6-AS1 knockdown, meanwhile, *in vivo* tumour growth was impaired after DLX6-AS1 inhibition (Ref. 55). In addition, DLX6-AS1 could bind directly to miR-497-5p and negatively regulate its expression, which suggested that DLX6-AS1 functioned as a ceRNA for miR-497-5p in NB (miR-497-5p has also been suggested as a tumour suppressor in other cancers) (Ref. 56). Furthermore, it was observed that the expression of signal transducer and activator of transcription 2 (STAT2) is regulated by miR-506-3p at the post-transcriptional level (Ref. 57). On the other hand, DLX6-AS1 could bind to miR-506-3p and inhibit its expression to induce NB cell proliferation, cell cycle and glycolysis *in vitro* and tumour growth *in vivo via* STAT2 activation (Ref. 57). Zhang *et al.* (Refs 35, 55, 59, 61) found that DLX6-AS1 inhibits the expression of miR-107, thereby increasing the expression of brain-derived neurotrophic factor (BDNF), as a target of miR-107 and an oncogene in NB, which leads to the progression of NB (Ref. 55). In addition, DLX6-AS1 promotes the progression of NB by affecting miR-513c/PLK4 axis (Ref. 58). So, DLX6-AS1 might act as a promising therapeutic target for NB (Ref. 56).

The effect of DLX6-AS1 on other cancers

Ewing's sarcoma

It has been proven that high expression of DLX6-AS1 can lead to Ewing's sarcoma development. Ewing's sarcoma is a malignancy that is observed in children and adolescents and DLX6-AS1 could lead to tumorigenesis of Ewing's sarcoma *via* miR-124-3p/ cyclin-dependent kinase 4 (CDK4)-related mechanism (Ref. 42). DLX6-AS1 acts as the sponge of miR-124-3p (Ref. 42). miR-124-3p targets the 3'-untranslated region (UTR) of CDK4 mRNA and its expression is decreased in Ewing's sarcoma specimens and cells (Ref. 42). Silencing of DLX6-AS1 increased the expression of miR-124-3p and inhibited the proliferation of Ewing's sarcoma cells, while promoting apoptosis (Ref. 42).

Osteosarcoma (OS)

A study has shown that DLX6-AS1 was significantly up-regulated in OS cell lines and that it functions as a ceRNA by targeting miR-641/homeobox A9 (HOXA9) signalling pathway to promote OS cell proliferation and metastasis (Ref. 61). Zhang *et al.* (Ref. 62) showed that high expression of DLX6-AS1 induces OS and it is a marker of poor prognosis in OS, acting by the activation of Wnt signalling (Ref. 62). Results of Guo *et al.*'s (Ref. 27) study showed that high expression of DLX6-AS1 enhanced Rab10 by inhibiting miR-141-3p expression and this up-regulation can subsequently increase tumorigenesis in OS (Ref. 59). Studies have confirmed the effect of DLX6-AS1 as an efficient agent for the OS tumorigenesis, proliferation and metastasis by targeting HOXA9/Wnt signalling pathway and verified the stimulatory ability of DLX6-AS1 in various cancer types, especially OS (Refs 59, 62).

Thyroid cancer (TC)

Many lncRNAs play an important role in the occurrence and progression of TC (Ref. 72). In one study, Feng *et al.* (Ref. 72) provide evidence that DLX6-AS1 silencing could be led to prevent thyroid carcinoma cell growth and stimulates autophagy through miR-193b-3p up-regulating and homeobox A1 (HOXA1) down-regulating (Ref. 72). The study indicated that DLX6-AS1 exerts as a ceRNA for miR-193b-3p to target HOXA1, promoting TC tumorigenesis (Ref. 72). Thus, DLX6-AS1 promotes TC tumorigenesis by inducing TC cell progression and suppressing autophagy and may act as an oncogene in TC (Ref. 72).

Biological and pathological functions of DLX6-AS1 in different cancers

DLX6-AS1 has different molecular mechanisms of action as well as different functions in cancer (Figs 3 and 4; Table 1).

DLX6-AS1 has involved in cancer epigenetics. DLX6-AS1 could induce hypo-methylation of the CADM1 promoter in HCC. Methylation of the CADM1 promoter can reduce the expression of CADM1, a tumour-suppressor gene that suppresses STAT3 activation, and induce liver cancer tumorigenesis (Ref. 49). In a similar way, DLX6-AS1 could induce methylation of the LARGE promoter and finally induce down-regulation of the expression of LARGE in prostate cancer, which enhances the proliferation, invasion, and metastasis (Ref. 69).

DLX6-AS1 could act as a ceRNA and competitively bind to miRNAs in different cancers to inhibit their functions (Table 2). Some of these binding partners are similar in different cancers. For example, DLX6-AS1 could bind to miR-26a and inhibit its functions in CRC, LSCC, and renal cancer to promote

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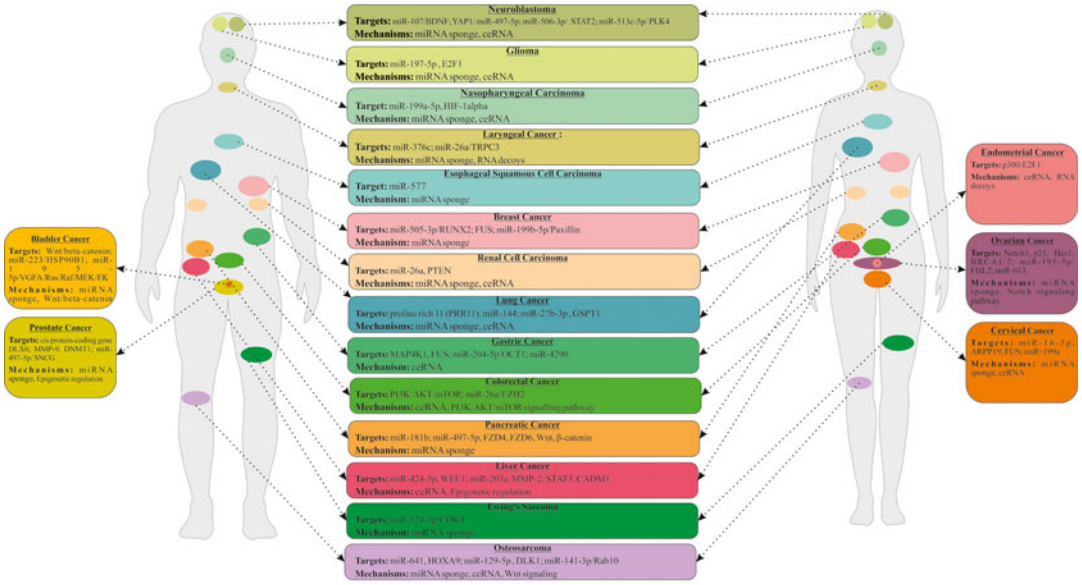

Fig. 3. Schematic image displaying the different organs of the body where DLX6-AS1 is involved in cancer and the associated mechanisms and targets.

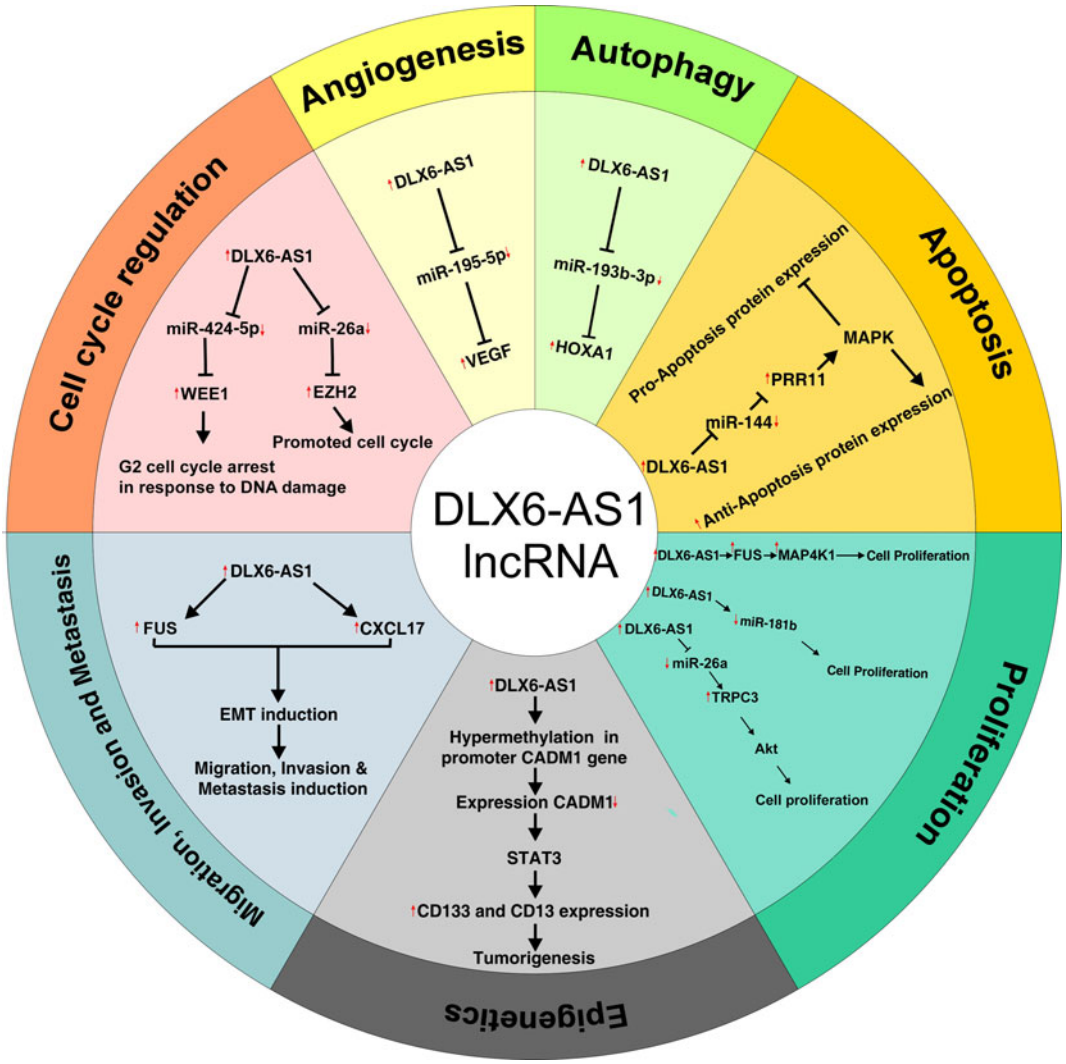

Fig. 4. The schematic diagram demonstrates the different functions of DLX6-AS1 in different human cancers. DLX6-AS1 is capable of regulating angiogenesis and tumour growth by inhibiting the miR-195-5p expression. DLX6-AS1 is able to promote cancer tumorigenesis by regulating the STAT3 signalling pathway via hypo-methylation of the CADM1 promoter. Also, DLX6-AS1 can alter proliferation, migration, invasion, and metastasis through the regulation of signalling pathways and targets related to cancer. Additionally, lncRNAs can alter tumorigenesis through the regulation of apoptosis.

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tumorigenesis (Refs 36, 50, 71). DLX6-AS1 acts as a ceRNA for miR-513c in HCC and NB (Refs 58, 74). In addition, DLX6-AS1 promotes the progression of pancreatic cancer, prostate cancer, and NB by sponging miR-497-5p (Refs 56, 66, 70). Moreover, DLX6-AS1 binds to and inhibits miR-195-5p in the bladder and ovarian cancer, leading to tumorigenesis (Refs 63, 73).

As mentioned above, DLX6-AS1 has involved in the pathogenesis of human cancers. DLX6-AS1 induces cell proliferation by regulation of miR-181b in pancreatic cancer (Ref. 65). DLX6-AS1 could enhance MAP4K1-mediated cell proliferation by positive regulation of FUS expression in GC cells (Ref. 44). In addition, DLX6-AS1 promotes tumour proliferation via modulating the miR-26a/TRPC3 axis in laryngeal cancer (Ref. 50).

DLX6-AS1 has involved in the migration and invasion of different human cancers. For example, DLX6-AS1 induces invasion, migration, and EMT in HCC and NB (Refs 55, 79). DLX6-AS1 could enhance migration and invasion of breast cancer cells through up-regulation of FUS (Ref. 31). Exosomal DLX6-AS1 could regulate CXCL17 in HCC via competitively binding to miR-15a-5p, inducing HCC invasion, migration, and EMT (Ref. 79).

DLX6-AS1 could inhibit cell apoptosis in cancer. Down-regulation of DLX6-AS1 can inhibit cell proliferation and increase apoptosis in endometrial cancer, CC, and Ewing's sarcoma (Refs 34, 37, 42). DLX6-AS1 inhibits apoptosis by regulating miR-144 and up-regulation of PRR11 in NSCLC (Ref. 60).

DLX6-AS1 inhibited autophagy by regulating miR-193b-3p and up-regulation of HOXA1 in TC cells (Ref. 72).

DLX6-AS1 could regulate the cell cycle in cancer cells. For example, DLX6-AS1 sponges miR-424-5p in HCC, leading to overexpression of WEE1 kinase, a G2 checkpoint kinase, leading to G_2 cell cycle arrest in response to DNA damage (Ref. 52). This arrest of the cell cycle allows for DNA repair before mitotic entry in cancer cells, which often lack the G1-S checkpoint for DNA repair (Ref. 90). In contrast, DLX6-AS1 promoted cell cycle and proliferation by up-regulating EZH2 through sponging miR-26a in CRC (Ref. 36).

DLX6-AS1 could up-regulate VEGFA, a vital factor of tumour angiogenesis, in bladder cancer through sponging miR-195-5p. Therefore, DLX6-AS1 may have a potential role in tumour angiogenesis (Ref. 73).

Conclusion

Recent studies have further confirmed that lncRNAs regulate gene expression and relates to cell invasion and tumorigenesis in different cancers. lncRNA DLX6-AS1 is overexpressed in multiple malignancies. Various studies verified that the expression of this lncRNA is correlated with advanced clinical stages, tumour size, metastasis, chemotherapeutic effect, and survival of patients in different cancers and may be used as a tumour marker for prognosis of these diseases (Table 1).

DLX6-AS1 knockdown decreased cell proliferation, migration and invasion in several cancers. The research studies demonstrated that various molecular mechanisms of lncRNAs are involved in cancer development by different signalling pathways. There seems to be a relationship between lncRNAs and miRNAs, where DLX6-AS1 acts as a ceRNA to bind to different miRNAs and inhibit their function (Table 2). Up-regulation of DLX6-AS1 results in an inhibition of the expression of different miRNAs.

Due to the lack of information about the function of DLX6-AS1 in blood cancers (Leukemias, lymphoma and myeloma), DLX6-AS1 seems to be mainly involved in solid cancers. However, more research studies are required to investigate the potential role of this molecule in blood cancers.

DLX6-AS1 is mainly overexpressed in a wide range of cancer types and it majorly acting as an oncogene in several different cancers. Knockdown of DLX6-AS1 in several cancers by using siRNAs or shRNAs reduces tumour growth or cancer cells proliferation, migration, and invasion and increases apoptosis. Targeting DLX6-AS1 using clustered regularly interspaced short palindromic repeat/caspase9 (CRISPR/ Cas9), siRNAs, shRNAs, and antisense oligonucleotides creates a new therapeutic strategy for various cancers. Finally, further investigations will promote the wider application of DLX6-AS1 in clinical prognosis and therapeutic strategies of various cancers.

Conflict of interest. The authors declare that there are no conflicts of interest.

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