Pathology - Research and Practice 245 (2023) 154486

Contents lists available at ScienceDirect

Pathology - Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

A review on the role of ZEB1-AS1 in human disorders

Soudeh Ghafouri-Fard [a], Arian Askari [b], Kimia Behzad Moghadam [c], Bashdar Mahmud Hussen [d], Mohammad Taheri [e,f,*], Mohammad Samadian [g,**]

[a] Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Phytochemistry Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] School of Pharmacy, University of California, SF, USA
[d] Department of Pharmacognosy, College of Pharmacy, Hawler Medical University, Erbil, Iraq
[e] Institue of Human Genetics, Jena University Hospital, Jena, Germany
[f] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[g] Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
ZEB-AS1
Cancer
LncRNA
MicroRNA

ABSTRACT

ZEB1 Antisense RNA 1 (ZEB1-AS1) is a type of RNA characterized as long non-coding RNA (lncRNA). This lncRNA has important regulatory roles on its related gene, Zinc Finger E-Box Binding Homeobox 1 (ZEB1). In addition, role of ZEB1-AS1 has been approved in diverse malignancies such as colorectal cancer, breast cancer, glioma, hepatocellular carcinoma and gastric cancer. ZEB1-AS1 serves as a sponge for a number of microRNAs, namely miR-577, miR-335–5p, miR-101, miR-505–3p, miR-455–3p, miR-205, miR-23a, miR-365a-3p, miR-302b, miR-299–3p, miR-133a-3p, miR-200a, miR-200c, miR-342–3p, miR-214, miR-149–3p and miR-1224–5p. In addition to malignant conditions, ZEB1-AS1 has functional role in non-malignant conditions like diabetic nephropathy, diabetic lung, arthrosclerosis, Chlamydia trachomatis infection, pulmonary fibrosis and ischemic stroke. This review outlines different molecular mechanisms of ZEB1-AS1 in a variety of disorders and highlights its importance in their pathogenesis.

1. Introduction

After a long time of debate on whether long non-coding RNAs (lncRNAs) should be considered as junk DNA or functional ones, it is now concluded that these molecules have important biological characteristics [12,13,47,51]. In general, an lncRNA is a type of RNA that is not translated to protein, is longer than 200 bp and is usually transcribed by RNA POL II [14]. Although they are called "non-coding", recent investigations have proved that a number of lncRNAs can actually encode proteins or small peptides [4]. Regarding their critical role in the pathogenesis of both malignant and non-malignant disorders, uprising studies are being published every day to emphasize on the function of lncRNAs, and how these molecules can revolutionize therapeutic approaches for treatment of different conditions.

ZEB1 Antisense RNA 1 (ZEB1-AS1, also known as HSALNG0077083 in LNCipedia database), is a classified lncRNA. ZEB1-AS1 usually resides in nucleus and according to NCBI, its significant expression has been verified in endometrium, thyroid and ovary. Its genomic position is on the short arm of chromosome 10 (10p11.22) (Fig. 1). According to ensembl genome browser, alternative splicing contributes to 12 different transcripts of ZEB1-AS1 (https://asia.ensembl.org/Homo_sapiens/Gene/Summary?db=core;g=ENSG00000237036;r = 10:31206278–31320447). Different studies have verified that ZEB1-AS1 has a positive correlation with ZEB1 via epigenetics modifications and induces its stability [36,54]. Altogether, ZEB1-AS1 has been shown to have oncogenic roles in different cancers such as glioma, non-small cell lung cancer, colorectal, gastric and prostate cancer. In addition to malignant conditions, ZEB1-AS1 plays a central position in the pathogenesis of non-malignant disorder like atherosclerosis, ischemic stroke and even Chlamydia trachomatis infection. Several studies also correlate levels of ZEB1-AS1 to diabetes complications, including diabetic nephropathy. In this review, we aim to pinpoint molecular mechanisms of ZEB1-AS1 in different disorders and highlight its importance in pathogenesis.

* Corresponding author at: Institue of Human Genetics, Jena University Hospital, Jena, Germany.
** Corresponding author.
E-mail addresses: Mohammad.taheri@uni-jena.de (M. Taheri), mdsamadian@gmail.com (M. Samadian).

https://doi.org/10.1016/j.prp.2023.154486
Received 13 February 2023; Received in revised form 19 April 2023; Accepted 24 April 2023
Available online 26 April 2023

2. Role of ZEB1-AS1 in cancers

2.1. In vitro studies

Amongst different types of cancer, functional role of ZEB1-AS1 has been studied to a greater extent in colorectal cancer (CRC). In the case of drug sensitivity, it has been shown that knockdown of ZEB1-AS1 in CRC cell lines HT-29 and HCT116 increases 5-fluorouracil sensitivity [28]. Two major signaling pathways in CRC are affected by ZEB1-AS1. In SW480 and HCT116 cell lines, downregulation of ZEB1-AS1 inhibits PI3K/AKT signaling pathway and contributes to decreased colony formation and epithelial-mesenchymal transition (EMT) [57]. In another study conducted by Lv S.Y et al., ZEB1-AS1 can positively affect β-catenin and TCF4 expression, so if downregulated, Wnt/ β-catenin signaling pathway is attenuated and apoptosis is induced [38]. One of the main regulatory mechanisms of lncRNAs is molecular sponging [46]. In SW480, LOVO, HT29 and PKO cell lines, ZEB1-AS1 acts as a molecular sponge for miR-141–3p. After knocking down ZEB1-AS1, miR-141–3p levels rises and inhibits proliferation of cancer cells [66].

Similar to CRC, ZEB1-AS1 has an oncogenic role in hepatocellular carcinoma (HCC) and its downregulation is in favor of benign features. Interestingly, ZEB1-AS1 can regulate levels of both E2F1 and E2F2 in HCC [26,44]. With regards to E2F1 regulation, miR-299–3p/E2F1 axis has been approved as a functional axis. ZEB1-AS1 sponges miR-299–3p, and this microRNA targets 3′-UTR of E2F1, so E2F1 levels rises [44]. Considering transforming roles of E2F1 [9], mentioned axis contributes to malignant features like increased proliferation, migration and invasiveness in HCC cells [44]. E2F2 is another transcription factor acting a promoter or inhibitor of proliferation [8]. In HCC cell lines HepG2, 293 T and HCCLM6, ZEB1-AS1 downregulation contributes to upregulation of miR-365a-3p and subsequent targeting of E2F2, ultimately resulting in favorable (normal-like) properties of cancer cells [26].

Zinc Finger E-Box Binding Homeobox 1 (ZEB1) is known as master regulator of EMT and its dysregulation contributes to different types of cancer [45,56]. Identical to many lncRNAs, ZEB1-AS1 can regulate expression of its related gene ZEB1 in a positive manner. For instance, in glioma cell lines U87 and U251, interference of ZEB1-AS1 contributes to reduction of ZEB1 via miR-200c/141 and as expected, reduced levels of ZEB1 is associated with absence of malignant properties (Fig. 2) [42]. Relation of ZEB1-AS1 and ZEB1 is also explicated in pancreatic cancer cell lines, in which depletion of HIF-1α is followed by reduction of ZEB1-AS1 and ZEB1 expression [23].

One of the exact molecular mechanisms in relation to ZEB1-AS1/ ZEB1 axis was demonstrated by Su W et al. in DU145 and PC3 prostate cancer cells [55]. Compellingly, ZEB1-AS1 can recruit MLL1 to the promoter region of ZEB1, induce H3K4me3 modifications and thereby

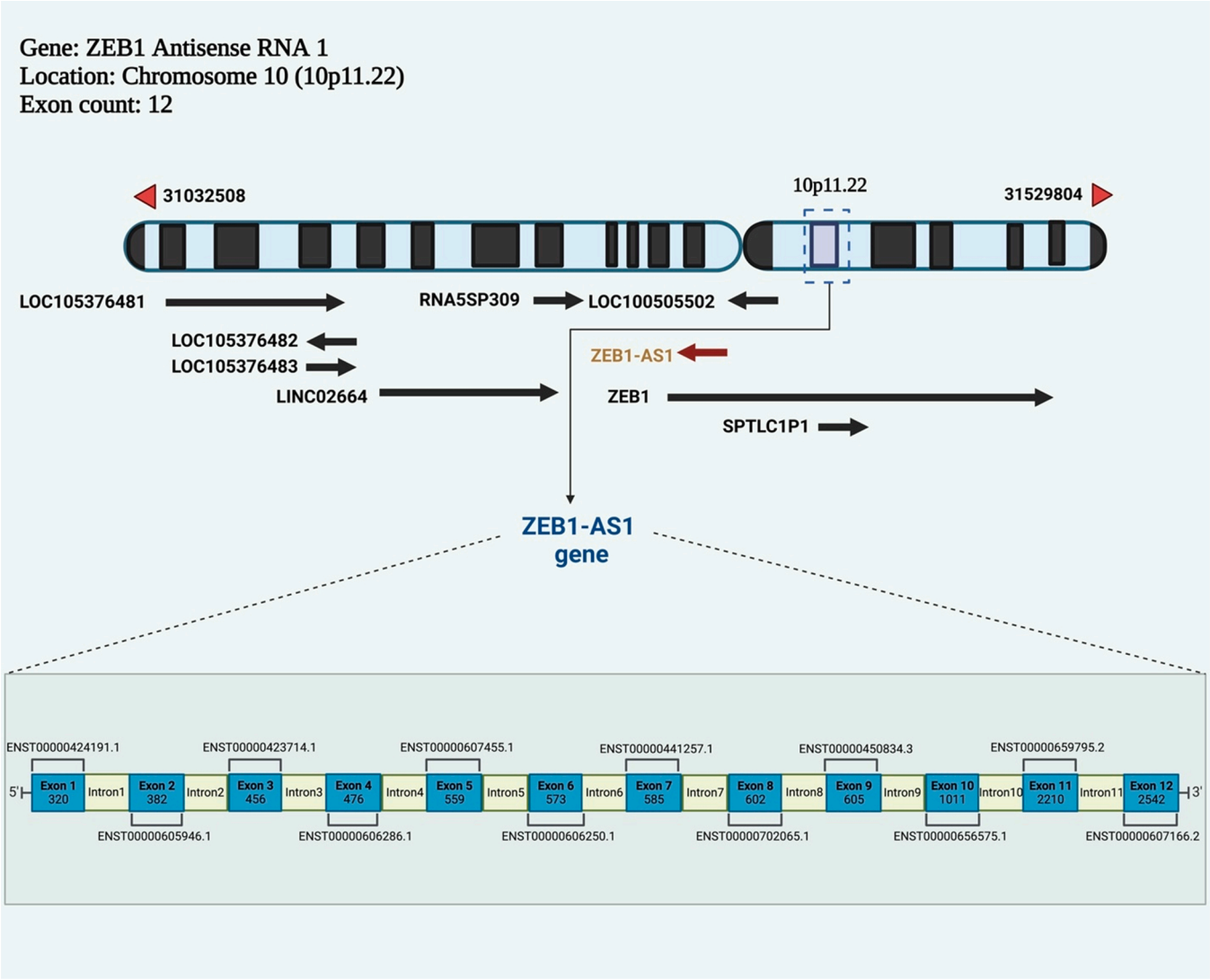

Fig. 1. Illustrates newly discovered lncRNA ZEB1-AS1 has a coding gene with 12 exons and located on short arm of chromosome 10 (10p11.22).

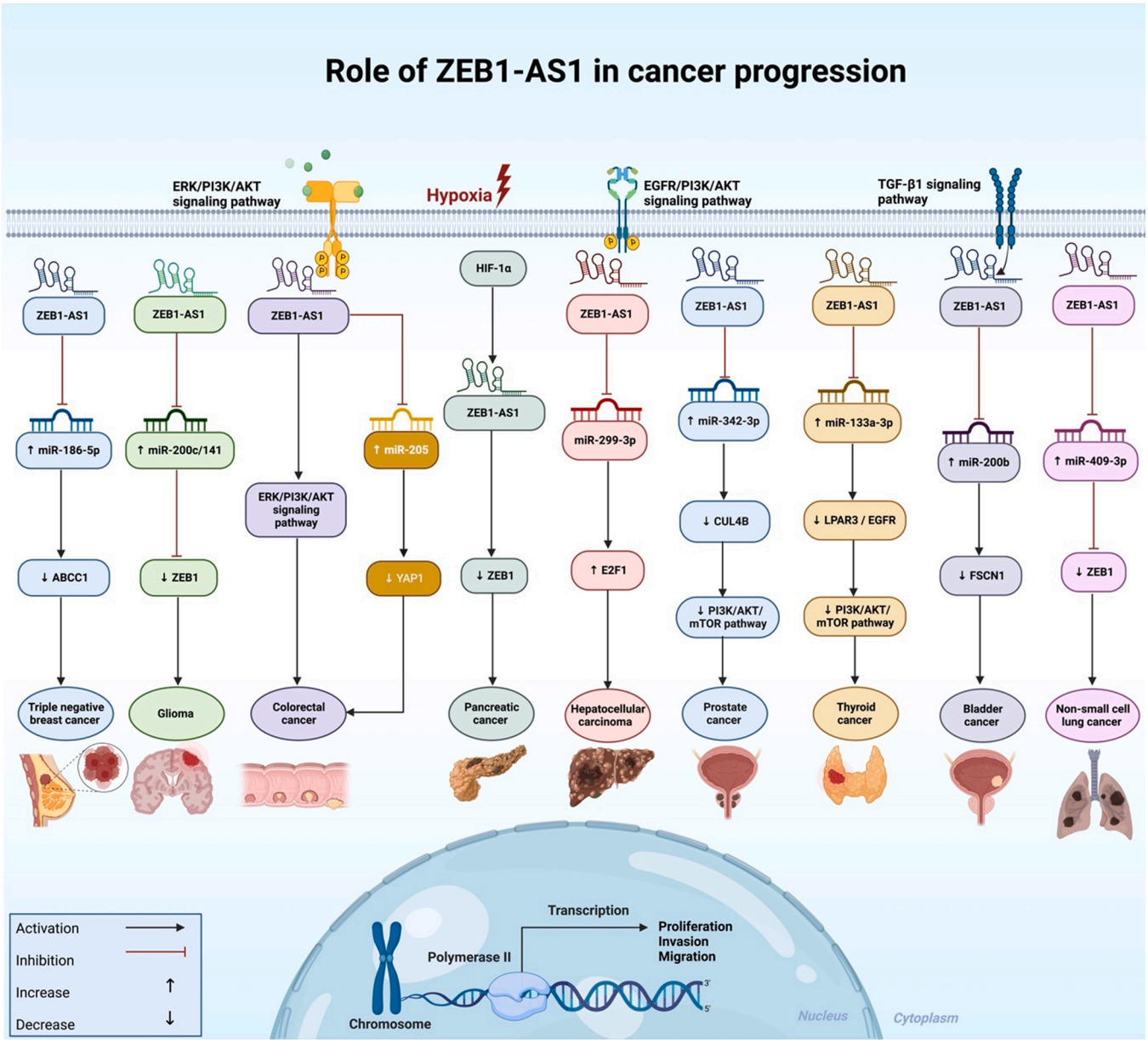

Fig. 2. The progression of ZEB1-AS1 in various tumors is depicted, which promotes tumor cell proliferation, invasion, migration, and survival by targeting certain genes and sponging distinct types of miRNAs.

inducing ZEB1. After forced inhibition of ZEB1-AS1, reduced level of ZEB1 is observed and this phenomenon is intertwined with reduced proliferation and migration in prostate cancer [55].

Without a doubt, ZEB1-AS1 acts as a transforming lncRNA and downregulation of it could be beneficial and in favor of benign properties. Table 1 summarizes functional studies on impact of ZEB1-AS1 in different types of cancer cell line.

2.2. *In vivo studies*

Analogous to in in vitro assays, ZEB1-AS1 has been shown to be a transforming lncRNA in xenograft models, specifically mice models. Two different studies in non-small cell lung cancer have supported this view. After knocking down ZEB1-AS1, tumor growth and weight reduces in comparison to control group in BALB/c nude mice [22,25].

In intrahepatic cholangiocarcinoma, after subcutaneous injection of HuCCT1 cells in which ZEB1-AS1 was knocked down, distant metastasis to lung was inhibited, recommending an anti-metastatic role for this lncRNA in vivo [21]. This phenomenon has also been affirmed in pancreatic cancer [23], oral squamous cell carcinoma [62] CRC [15] and HCC [41].

Cumulatively, different in vivo studies in different malignancies suggest an oncogenic role for ZEB1-AS1. Table 2 summarizes functional role of ZEB1-AS1 in vivo.

2.3. *Studies in clinical samples*

Different studies in a wide variety of clinical samples have proved the oncogenic roles of ZEB1-AS1 (Table 3). An *in silico* analysis of RNA transcriptome dataset of TCGA and related clinical characteristics of CRC patients obtained from the USCS Xena website has revealed that ZEB1-AS1 is among m6A-related prognostic lncRNAs that confer risk of CRC [28]. Expression of this lncRNA has been higher in high risk group of CRC compared with low risk group [28]. Moreover, expression of

Table 1
Role of ZEB1-AS1 in cancer cell lines (**Δ**: knock-down or deletion, ↑: overexpression, →: results in, EMT: Epithelial-mesenchymal transition, DOX: doxorubicin, UA: Ursolic acid, 5-FU: 5-fluorouracil, DDP: cisplatin, PTX: paclitaxel).

Tumor types	Targets/Regulators and signaling pathways	Cell lines	Functions	Ref
Triple negative breast cancer	miR-186–5p/ ABCC1 axis	DOX-resistant MDA-MB-468 and MDA-MB-436	Treatment with UA: ↓ ZEB1-AS1 → ↑ miR-186–5p → ↓ ABCC1: ↓ proliferation ↑ sensitivity to DOX	[34]
	ZEB1/ELAVL1	MDA-MB-436, MDA-MB-453, MCF-7 and MDA-MB-231	Δ ZEB1-AS1(which binds to ELAVL1) → ↓ ZEB1: ↓ proliferation ↑ apoptosis	[36]
Glioblastoma	-	U87MG	Δ ZEB1-AS1: ↓ proliferation ↓ migration ↑ apoptosis	[74]
Glioma	miR-200c/141/ZEB1 axis	U87, U251, LN18, U118, and T98G	Δ ZEB1-AS1 → ↑ miR-200c/141 → ↓ ZEB1: ↓ proliferation ↓ migration ↓ colony formation ↓ motility	[42]
	miR-577	A172, U87, T98G and SHG44	Δ ZEB1-AS1 (which acts as a molecular sponge) → ↑ miR-577: ↓ proliferation ↓ migration ↓ invasion	[65]
	ZEB1	HS683, T98G, U87, and U251	Δ ZEB1-AS1 → ↓ ZEB1: ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis	[37]
Colorectal cancer	-	HT-29 and HCT116	Δ ZEB1-AS1 ↓ proliferation ↓ 5-FU resistance ↓ EMT process	[28]
	-	Caco-2, HT-29, HCT116	Up-regulated ZEB1-AS1 is associated with ↑↑ sensitivity to: nelarabine, palbociclib, fluphenazine, asparaginase, LEE-011, Ifosfamide, hydroxyurea and dexrazoxane	[6]
	ERK/PI3K/AKT	SW480 and HCT116	Δ ZEB1-AS1 → ↓ ERK/PI3K/AKT ↓ colony formation ↓ EMT process	[57]
	miR-335–5p/APOC1 axis	HCT116	Δ ZEB1-AS1 → ↑ miR-335–5p → ↓ APOC1: ↓ invasion ↓ migration	[33]
	miR-141–3p	SW480, LOVO, HT29 and PKO	Δ ZEB1-AS1 (which acts as a molecular sponge) → ↑ miR-141–3p: ↓ proliferation ↑ cell cycle arrest	[66]
	miR-101/ZEB1 axis	SW480, DLD-1, HCT116, SW620, and HT29	Δ ZEB1-AS1(which acts as a molecular sponge) → ↑ miR-101 → ↓ ZEB1: ↓ proliferation ↓ migration	[69]
	p15	SW480, DLD-1, HCT116, SW620	Δ ZEB1-AS1 → ↑ p15 ↓ proliferation ↑ apoptosis	[15]
Colorectal cancer (continued)	miR-205/YAP1 Axis	SW620, SW480, HT29, and HCT116	Δ ZEB1-AS1 (which sponges miR-205) → ↑ miR-205 → ↓ YAP1: ↓ proliferation ↑ apoptosis	[24]
	miR-455–3p/PAK2 axis	SW480, HT29, LS174T, HCT116 and DLD-1	Δ ZEB1-AS1 (which acts as a molecular sponge) → ↑ miR-455–3p → ↓ PAK2: ↓ proliferation ↓ migration ↓ invasion	[20]
	miR-181a-5p/ Wnt/β-catenin (TCF4)	RKO, Caco2, DLD1, HCT116, LOVO and SW480	↑ miR-181a-5p → ↓ ZEB1-AS1 → ↓ β-catenin & TCF4: ↓ proliferation ↑ apoptosis	[38]
B-cell acute lymphoblastic leukemia	IL-11/STAT3	hBMSC-TERT and HS-5	Δ ZEB1-AS1 → ↓ IL-11 → ↓ STAT3 : ↓ proliferation	[60]
Pancreatic cancer	HIF-1α/ZEB1	PANC-1, BXPC-3, AsPC-1, SW1990, and MIAPaCa-2	Δ HIF-1α →Δ ZEB1-AS1 → ↓ ZEB1: ↓ proliferation ↓ migration ↓ invasion	[23]
	miR-505–3p/TRIB2 axis	SW1990, Capan-1 and CFPAC-1	Δ ZEB1-AS1 (which acts as a molecular sponge) → ↑ miR-505–3p → ↓ TRIB2: ↓ viability	[64]

(*continued on next page*)

Table 1 (*continued*)

Tumor types	Targets/Regulators and signaling pathways	Cell lines	Functions	Ref
			↓ migration ↓ invasion	
Hepatocellular carcinoma	miR-299–3p/E2F1 axis	Huh7, Hep3B, HepG2, MHCC97H and SMMC7721	↑ ZEB1-AS1 (which sponges miR-299–3p) → ↑ E2F1: ↑ proliferation ↑ migration ↑ invasion	[44]
	miR-23c	Huh7, SK-HEP-1, SNU-387, JHH-7, and HCCLM3	Δ ZEB1-AS1 → ↓ miR-23c: ↓ proliferation ↓ invasion	[71]
	miR-302b /EGFR/PI3K/AKT axis	PLC, MHCC-97 H, Hep3B, and Huh7	Δ ZEB1-AS1 (which targets miR-302b) → ↑ miR-302b → ↓ EGFR → ↓ PI3K/AKT pathway: ↓ proliferation ↓ migration ↓ invasion	[17]
	miR-365a-3p/E2F2 axis	HepG2, 293 T and HCCLM6	Δ ZEB1-AS1 (which targets miR-365a-3p) → ↑ miR-365a-3p → ↓ E2F2: ↓ proliferation ↓ viability ↑ cell cycle arrest	[26]
Epithelial ovarian cancer	MMP19	A2780 (including chemoresistant A2780)	↑ ZEB1-AS1 → ↑ MMP19: ↑ sensitivity to DDP and PTX	[7]
Oral Squamous Cell Carcinoma	miR-23a	SCC9, SCC25, TSCCA, HN4, and CAL27	Δ ZEB1-AS1 (which sponges miR-23a) → ↑ miR-23a: ↓ proliferation ↑ cell cycle arrest ↓ migration ↓ invasion ↓ EMT process	[62]
Esophageal squamous cell carcinoma (ESCC)/ Esophageal cancer (EC)	ZEB1 (ESCC)	EC9706, TE1, Eca109, Kyse70 and Kyse450	Δ ZEB1-AS1 → ↓ ZEB1: ↓ proliferation ↓ invasion	[78]
	miR-214/ZEB1 axis (EC)	EC109	Δ ZEB1-AS1 (which acts as molecular sponge) → ↑ miR-214 → ↓ ZEB1: ↓ proliferation	[75]
Prostate cancer	miR-342–3p/CUL4B axis | PI3K/AKT/mTOR Signaling pathway	DU145 and LNCaP	Δ ZEB1-AS1 (which acts as molecular sponge) → ↑ miR-342–3p → ↓ CUL4B → ↓ PI3K/AKT/mTOR pathway: ↓ proliferation ↓ migration ↓ invasion	[40]
	ZEB1 miR-200c/BMI1	DU145 and PC3	Δ ZEB1-AS1 (which recruits MLL1 to the promoter region of ZEB1) → ↓ ZEB1 + ↑ miR-200c → ↓ BMI1: ↓ proliferation ↓ migration	[55]
Intrahepatic cholangiocarcinoma	miR-200a/ ZEB1 axis	HuH28, HuCCT1, RBE, CCLP-1 and HCCC-9810	Δ ZEB1-AS1 (which acts as molecular sponge) → ↑ miR-200a → ↓ ZEB1: ↓ proliferation ↓ migration ↓ invasion ↓ EMT process	[21]
Cholangiocarcinoma	AR/ miR-133b/HOXB8 axis	QBC939, CCLP-1, RBE and TFK-1	Δ ZEB1-AS1(which is activated by AR) → ↑ miR-133b → ↓ HOXB8: ↓ proliferation ↓ stemness ↓ migration ↓ invasion ↓ EMT process	[20]
Thyroid cancer	miR-133a-3p/ LPAR3 /EGFR | PI3K/AKT/mTOR signaling pathway	SW579, TPC-1, BCPAP and KAT18	Δ ZEB1-AS1 (which acts as molecular sponge) → ↑ miR-133a-3p) → ↓ LPAR3 & EGFR → ↓ PI3K/AKT/mTOR: ↓ proliferation ↓ colony formation ↑ apoptosis	[67]
Melanoma	-	Primary and metastatic melanoma cell lines	Over expressed ZEB1-AS1 in melanoma, especially metastatic cell lines	[52]
	miR-1224–5p	SK-MEL-2, WM35, A375 and SK-MEL-5	Δ ZEB1-AS1(which acts as molecular sponge) → ↑ miR-1224–5p ↓ proliferation ↓ migration ↓ invasion	[61]
Bladder cancer	miR-200b/FSCN1/ TGF-β1axis	SW780, BIU, 5637, J82, T24, TCC-SUP, UM-UC3 and RT4	Δ ZEB1-AS1 (which is overexpressed by TGF-β1) → ↑ miR-200b → ↓ FSCN1: ↓ proliferation ↓ migration	[11]

(*continued on next page*)

Table 1 (*continued*)

Tumor types	Targets/Regulators and signaling pathways	Cell lines	Functions	Ref
			↓ invasion ↑ apoptosis	
	-	5637 and SW780	Δ ZEB1-AS1 ↓ proliferation ↓ migration ↑ apoptosis	[29]
Gastric cancer	miR-149–3p	SGC-7901 and MGC-803	Δ ZEB1-AS1 → ↑ miR-149–3p: ↓ proliferation ↓ migration ↓ invasion	[39]
	-	MKN28, MKN45, BGC823, MGC803, KATOIII, and SGC7901	Δ ZEB1-AS1: ↓ migration ↓ invasion	[32]
	miR-335–5p	SGC7901, HGC27, BGC823, MKN45, MKN28, and AGS	Δ ZEB1-AS1(which acts as molecular sponge) → ↑ miR-335–5p: ↓ proliferation ↓ migration ↓ invasion	[73]
	ZEB1	NCI-N87, SNU-1, AGS and MKN-45	Δ ZEB1-AS1 → ↓ ZEB1: ↓ migration ↓ invasion ↓ EMT process	[27]
Non-small cell lung cancer (NSCLC)	ID1	PC9, H1299, H1975, H460, and A-427	Δ ZEB1-AS1 → ↑ ID1 ↓ proliferation ↓ migration ↑ apoptosis ↑ cell cycle arrest	[22]
	miR-409–3p/ZEB1		Δ ZEB1-AS1 → ↑ miR-409–3p → ↓ ZEB1: ↓ proliferation ↑ apoptosis	[49]
	ZEB1	A549, H1975, H1299, and SPCA1 (adenocarcinoma) H1703 and SK-MES-1 (squamous carcinoma)	Δ ZEB1-AS1 → ↓ ZEB1: ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis ↑ cell cycle arrest ↓ EMT process	[25]
Cervical cancer	ZEB1	HeLa, C33A and SiHa	Δ ZEB1-AS1 → ↓ ZEB1: ↓ proliferation ↑ apoptosis ↓ invasion ↓ EMT process	[5]
Osteosarcoma	miR-200/ZEB1	HOS and Saos-2	Δ ZEB1-AS1 (which acts as molecular sponge) → ↑ miR-200 → ↓ ZEB1: ↓ proliferation ↓ migration	[31]
	ZEB1	HOS, U-2 OS, MG-63, and Saos-2	Δ ZEB1-AS1 → ↓ ZEB1: ↓ proliferation ↓ migration	[30]

ZEB1-AS1 has been related to the pathologic stage, and its over-expression has been associated with poor prognosis in CRC patients [28]. Other studies in this type of cancer has validated association between ZEB1-AS1 level and clinical stage [72], metastasis [33], histological grade [38], tumor invasion, microvascular invasion and lymph node metastasis [15].

In patients with oral squamous cell carcinoma (OSCC), ZEB1-AS1 expression has been elevated and miR-23a expression level has been lower in cancerous tissues compared to non-cancerous tissues. Notably, ZEB1-AS1 expression levels has been substantially higher in tissues obtained from patients with advanced TNM stages. However, its expression has been similar in different pathological grades [62]. Most notably, expression of ZEB1-AS1 in serum samples of these patients has been decreased after tumor resection. Besides, over-expression of ZEB1-AS1 has been associated with poor survival of patients based on a Kaplan-Meier analysis [62].

In esophageal cancer, up-regulation of ZEB1-AS1 has been verified in both tumor tissues [77] and serum samples [75]. Notably, both peripheral and tumor tissue expressions have been correlated with poor survival. Moreover, its expression in tumoral tissues has been associated with TNM stage, lymph node metastasis [78], tumor grade and depth of invasion [63].

Associations between up-regulation of ZEB1-AS1 and malignant features have also been verified in other types of cancers, including HCC [44], pancreatic cancer [64], prostate cancer [55] and cholangiocarcinoma [20]. Table 3 summarizes these findings.

Diagnostic role of ZEB1-AS1 has been assessed in gastric cancer [39] and colorectal cancer [10] (Table 4). While in the former type of cancer, ZEB1-AS1 can distinguish between tumoral and normal samples with AUC value of 79% [39], in the latter type of cancer, it can separate tumoral and adjacent non-tumoral samples with AUC value of 0.84 [10].

Table 2
Impact of ZEB1-AS1 the in carcinogenesis in animal models (Δ: knock-down or deletion, SCID: severe combined immune deficiency).

Tumor type	Animal models	Results	Ref
Pancreatic cancer	BALB/c mice	Δ ZEB1-AS1: ↓ tumor growth ↓ metastasis (lung/liver)	[23]
Oral Squamous Cell Carcinoma	BALB/c nude mice	Δ ZEB1-AS1: ↓ tumor growth ↓ metastasis	[62]
Triple negative breast cancer	Mice	Δ ZEB1-AS1: ↓ tumor size, tumor volume & tumor weight	[36]
Hepatocellular carcinoma	Mice	Δ ZEB1-AS1: ↓ micro metastasis	[17]
Intrahepatic cholangiocarcinoma	BALB/c nude mice	Δ ZEB1-AS1: ↓ metastasis (liver/lung) ↓ tumor growth	[21]
Thyroid cancer	Nude mice	Δ ZEB1-AS1: ↓ tumor growth	[67]
Cholangiocarcinoma	BALB/c nude mice	Δ ZEB1-AS1: ↓ tumor growth	[20]
Colon adenocarcinoma/colorectal cancer	mice	Δ ZEB1-AS1: ↓ metastasis ↓ tumor growth	[20]
	BALB/c athymic nude mice	Δ ZEB1-AS1: ↓ tumor growth	[15]
Esophageal Squamous Cell Carcinoma	BALB/c nude mice	Δ ZEB1-AS1: ↓ tumor growth	[78]
Bladder cancer	BALB/c nude mice	↑ ZEB1-AS1: ↑ tumor growth	[11]
Glioma	SCID mice	Δ ZEB1-AS1: ↓ metastasis ↓ tumor weight & size	[42]
Cervical cancer	BALB/c athymic nude mice	Δ ZEB1-AS1: ↓ tumor growth	[5]
Gastric cancer	Nude mice	Δ ZEB1-AS1: ↓ tumor growth ↓ tumor weight	[73]
Non-small cell lung cancer (NSCLC)	BALB/c nude mice	Δ ZEB1-AS1: ↓ tumor growth ↓ tumor volume and weight	[22]
	BALB/c nude mice	Δ ZEB1-AS1: ↓ tumor growth	[25]

3. Role of ZEB1-AS1 in non-malignant conditions

3.1. Cell line studies

Different in vitro studies have assessed function of ZEB1-AS1 in non-malignant conditions. For instance, the impact of this lncRNA in the pathophysiology of diabetic lung has been investigate in vitro. Expression of ZEB1-AS1 in lung cells has been found to be decreased after exposure to high concentration of glucose. Moreover, up-regulation of ZEB1-AS1 has led to inhibition of apoptosis in lung cells in association with downregulation of p53. Overexpression of p53 has reduced the effect of ZEB1-AS1 up-regulation on apoptosis of these cells showing that ZEB1-AS1 controls lung cancer cell apoptosis through decreasing expression of p53 [16].

In addition, ZEB1-AS1 has been found to be over-expressed in persistent *Chlamydia trachomatis* infection. This lncRNA participates in the regulation of apoptosis, since its knock-down enhances apoptosis rate in the persistently infected cells. From a mechanistical point of view, ZEB1-AS1 silencing leads to reduction of the Bcl-2/Bax ratio and suppression of the mitochondrial membrane potential leading to cytochrome c release and enhancement of caspase-3 activation. In fact, ZEB1-AS1 acts as a sponge for miR-1224–5p to affect expression of MAP4K4. Moreover, ZEB1-AS1 suppresses apoptosis of *Chlamydia*-infected cells through activation of MAPK/ERK axis [35].

ZEB1-AS1 has also been shown to be upregulated in TGF-β1-induced RLE-6TN cells in correlation with the level of ZEB1, a master regulator of EMT. ZEB1-AS1 can enhance fibrogenesis in RLE-6TN cells via modulation of miR-141–3p and activation of ZEB1 in RLE-6TN cells [48]. In addition, ZEB1-AS1 contributes to the pathogenesis of atherosclerosis through modulation of miR-590–5p/ETS1 [3], miR-590–5p/HDAC9 [79] and miR-942/HMGB1 [18] axes. Table 5 summarizes these observations.

The function of ZEB1-AS1 in the pathogenesis of ischemic stroke, diabetic nephropathy and pulmonary fibrosis has been assessed in animal models (Table 6). Expression of ZEB1-AS1 has been shown to be increased in the lungs of BLM-induced rats in correlation with ZEB1 levels. ZEB1-AS1 silencing has relieved BLM-induced fibrogenesis in animal models through suppression of EMT [48]. ZEB1-AS1 has also been shown to aggravate cerebral ischemia/reperfusion injury in animal models through modulation of HMGB1/TLR-4 axis [58].

3.2. Studies in clinical samples

ZEB1-AS1 has been shown to be decreased in the plasma samples of patients with diabetic lung compared with both diabetic persons without this complication and healthy subjects. Notably, downregulated levels of ZEB1-AS1 can distinguish patients with diabetic lung from healthy subjects [16]. On the other hand, ZEB1-AS1 levels have been increased in serum of patients with atherosclerosis relative to normal controls, which has been accompanied by ox-LDL-associated endothelial cell injury in a dose dependent manner [79]. Finally, three independent studies have revealed down-regulation of ZEB1-AS1 in kidney tissues of

Table 3
Dysregulation of ZEB1-AS1 in clinical specimens (ANT: adjacent normal tissue, O-S: overall survival, DFS: disease-free survival, RFS: relapse-free survival, BM: bone marrow, PFS: progression-free survival, GEPIA: Gene Expression Profiling Interactive Analysis, TCGA: the cancer genome atlas, ICGC: The International Cancer Genome Consortium).

Tumor type	Samples	Expression (tumor vs normal)	Kaplan-Meier Analysis (ZEB1-AS1 dysregulation impact)	Univariate/ Multivariate cox regression	Association of ZEB1-AS1 expression with clinicopathologic characteristics	Ref
Colorectal cancer (CRC)/ colon adenocarcinoma (COAD)	6 CRC + 6 normal colon tissues	Upregulated	Poor survival rate	Independent prognostic factor	Associated with clinical stage	[28]
	TCGA database (429 COAD + 37 normal tissues)	Upregulated	-	-	Associated with advanced clinical stage	[72]
	30 CRC tissues + paired ANT	Upregulated	-	-	-	[19]
	TCGA database (647 CRC + 51 normal tissues)	Upregulated	Shorter survival rate	-	Associated with advanced TNM stage	[50]
	20 COAD + paired ANT	Upregulated	-	-	-	[2]
	30 CRC + paired ANT	Upregulated	-	-	Associated with metastasis	[33]
	27 CRC + paired ANT	Upregulated	Poor O-S	-	-	[66]
	50 CRC + paired ANT	Upregulated	-	-	-	[24]
	28 COAD + paired ANT	Upregulated	Poor survival rate		Associated with clinical stage, lymph node metastasis and distant metastasis	[20]
	50 CRC + paired ANT	Upregulated	-	-	Associated with TNM stage	[69]
	65 CRC + paired ANT	Upregulated			Associated with tumor histology grade, N grade, and M grade	[38]
	63 CRC + paired ANT	Upregulated	Shorter O-S	-	Associated with depth of tumor invasion, microvascular invasion and lymph node metastasis	[15]
	108 CRC + paired ANT	Upregulated	Shorter O-S	-	Associated with tumor size, differentiation degree, TNM stage, metastasis, depth of invasion and Dukes' classification	[10]
Esophageal Squamous Cell Carcinoma (ESCC)/ Esophageal cancer (EC)	TCGA (174 EC patients) + GSE53622 and GSE53624 (179 ESCC)	Upregulated	Poor survival rate	-	-	[77]
	56 ESCC + paired ANT	Upregulated	Poor survival rate		Associated with TNM stage and lymph node metastasis	[78]
	Serum of 21 EC patients + 21 healthy controls	Upregulated	-	-	-	[75]
	87 ESCC + paired ANT	Upregulated	Shorter O-S	Independent prognostic factors for O-S	Associated with tumor grade, depth of invasion, and lymph node metastasis	[63]
Oral Squamous Cell Carcinoma (OSCC)	30 OSCC + paired ANT	Upregulated	Shorter O-S		Associated with TNM stage	[62]
Hepatocellular carcinoma (HCC)	TCGA (319 HCC) + ICGC (230 HCC)	Upregulated	-	-	-	[76]
	60 HCC + paired ANT + GEPIA	Upregulated	Shorter O-S	-	Associated with TNM stage and lymph node metastasis	[44]
	32 HCC + paired ANT	Upregulated	-	-	-	[71]
	90 HCC + paired ANT + TCGA (362 HCC)	Upregulated	Shorter O-S and DFS	Independently associated with the risk of bone metastasis	Associated with metastasis	[41]
	32 HCC + paired ANT	Upregulated	Shorter O-S	-	-	[26]
Pancreatic cancer (PC)	119 PC + paired ANT	Upregulated	Shorter O-S	-	-	[23]
	30 PC + paired ANT	Upregulated	Shorter O-S	-	Associated with advanced clinical stage	[64]
Prostate cancer (PCa)	30 PCa + paired ANT	Upregulated	-	-	-	[40]
	114 paraffin embedded tissues	Upregulated	-	-	Associated with perineural invasion and advanced clinical stage	[55]
Triple-negative breast cancer (TNBC)	45 TNBC + paired ANT	Upregulated	-	-	-	[36]
Intrahepatic cholangiocarcinoma (IHCC)	118 IHCC + 20 paired tissues	Upregulated	Lower O-S and PFS	Independent risk factor for poor O-S and PFS	Associated with microvascular invasion, lymphatic metastasis and advanced TNM stage	[21]
Cholangiocarcinoma (CCA)	54 CCA + paired ANT	Upregulated	Poor O-S	Independent unfavorable prognostic factors for CCA	Associated with lymph node metastasis and TNM stage	[20]
Thyroid cancer (TC)	40 TC + paired ANT	Upregulated	-	-	-	[67]
Bladder cancer (BCa)	60 BCa + 23 paired ANT	Upregulated	Shorter DFS	-	-	[11]
	55 BCa + paired ANT	Upregulated	-	-	Associated with higher histological grade and advanced tumor stage	[29]
Gastric cancer (GC)	84 GC + 47 gastric dysplasia tissues + 59 healthy gastric mucous	Upregulated	Shorter O-S	Independent unfavorable prognostic factor for GC	Associated with lymph node metastasis, tumor size and TNM stage	[39]

(*continued on next page*)

Table 3 (*continued*)

Tumor type	Samples	Expression (tumor vs normal)	Kaplan-Meier Analysis (ZEB1-AS1 dysregulation impact)	Univariate/ Multivariate cox regression	Association of ZEB1-AS1 expression with clinicopathologic characteristics	Ref
	224 GC + paired ANT	Upregulated	Shorter O-S	Independent risk factors for poor prognosis	Associated with TNM stage	[1]
	75 GC + paired ANT	Upregulated	Poor survival rate	Independent prognostic factor	Associated with lymph node metastasis, invasion degree and TNM stage	[32]
	76 GC + paired ANT	Upregulated	Poor survival rate	-	Associated with TNM stage and lymph node metastasis	[73]
	124 GC + 20 paired ANT + 20 gastritis	Upregulated	Shorter O-S	Independent prognostic factor	Associated with lymph node metastasis, clinical stage, histological type and distant metastasis	[27]
Non-small cell lung cancer (NSCLC)	48 NSCLC + 26 pneumonia patients	Upregulated	Shorter O-S	Independent unfavorable prognostic factor	Associated with TNM stage and advanced clinical stage	[22]
	183 NSCLC + 85 paired ANT	Upregulated	Poor survival rate	-	Associated with TNM stage	[68]
	122 NSCLC + paired ANT	Upregulated	Shorter O-S	-	Associated with TNM stage, tumor size and lymph node metastasis	[25]
Melanoma	46 melanoma tissues + paired ANT	Upregulated	Poor survival rate	-	Associated with lymph node metastasis and TNM stage	[61]
Glioma	100 glioma tissues + 16 normal brain tissues	Upregulated	Poor survival rate	-	Associated with tumor size	[42]
	65 glioma tissues + paired ANT	Upregulated	Shorter O-S	Independent predictor of overall survival for glioma patients	Associated with tumor size, KPS and WHO grade	[65]
	82 glioma tissues + paired ANT	Upregulated	Shorter O-S	Independent prognostic factor for glioma patients	Associated with tumor grade	[37]
Cervical cancer (CC)	106 CC + paired ANT	Upregulated	Shorter O-S	-	Associated with FIGO stage and lymph node metastasis	[5]
B-cell acute lymphoblastic leukemia (B-ALL)	BM of 30 B-ALL + 30 healthy controls	Upregulated	Poor survival rate	-	-	[60]
Osteosarcoma (OS)	50 OS + paired ANT	Upregulated	Shorter O-S and RFS	-	Associated with tumor size advanced Enneking stage and metastasis	[30]

patients with diabetic nephropathy [43,53,59]. Table 7 shows human studies on the role of ZEB1-AS1 in non-malignant conditions.

4. Discussion

ZEB1-AS1 is an lncRNA with diverse functions in the pathophysiology of both malignant and non-malignant disorders. It has an important regulatory effect on ZEB1, the master regulator of EMT. Therefore, it can affect pathogenesis of disorders, particularly cancers through induction of EMT and metastasis. Mechanistically, ZEB1-AS1 acts as a sponge for a variety of miRNAs, namely miR-577, miR-335–5p, miR-101, miR-505–3p, miR-455–3p, miR-205, miR-23a, miR-365a-3p, miR-302b, miR-299–3p, miR-133a-3p, miR-200a, miR-200c, miR-342–3p, miR-214, miR-149–3p and miR-1224–5p. These miRNAs can affect carcinogenesis through modulation of expression of cancer-related genes.

Importantly, all conducted studies in the context of cancer have confirmed an oncogenic role for ZEB1-AS1. This lncRNA can increase cell proliferation, invasiveness, migratory potential and stemness properties. Based on this uniform effect of ZEB1-AS1 in diverse tissues, anti-ZEB1-AS1 strategies can be beneficial for reduction of tumor burden in almost all tissues. Different strategies such as siRNA-mediated gene silencing should be tested in different tissues.

ZEB1-AS1 has a diagnostic value for detection of cancers as revealed in the contexts of gastric cancer [39] and colorectal cancer [10]. Moreover, based on the observed down-regulation of ZEB1-AS1 in serum samples of patients after tumor resection [62], this lncRNA can be used as a marker in follow-up of patients after conduction of anti-cancer therapies.

ZEB1-AS1 has an important role in the induction of chemoresistance. Thus, it is a possible target for combating this phenotype. Combination of anti-ZEB1-AS1 therapies and chemotherapy might be a possible way to reduce chemoresistance.

In addition, up-regulation of ZEB1-AS1 has been linked with several

Table 4
Diagnostic value of ZEB1-AS1 in diseases (ANT: adjacent normal tissue).

Disease type	Samples	Distinguish between	Area under curve	Sensitivity (%)	Specificity (%)	Ref
Gastric cancer (GC)	84 GC + 47 gastric dysplasia tissues + 59 healthy gastric mucous	Tumor vs. normal	0.790	82.1	79.2	[39]
Colorectal cancer (CRC)	108 CRC + paired ANT	Tumor vs. normal	0.846	63	90	[10]

Table 5
Summary of cell line studies on the role of ZEB1-AS1 in non-malignant conditions (Δ: knock-down or deletion, HUVECs: human umbilical vein endothelial cells, ox-LDL: oxidized low-density lipoprotein, HCtAEC: Human carotid artery endothelial cell).

Disease type	Interactions	Cell line	Function	Ref
Chlamydia trachomatis infection	miR-1224–5p / MAP4K4 axis	HeLa 229 (infected with C. trachomatis)	↑ ZEB1-AS1 → sponging of miR-1224–5p → ↑ MAP4K4: ↓ mitochondria-mediated apoptosis	[35]
Pulmonary fibrosis	miR-141–3p/ ZEB1 axis	RLE-6TN and 293 T	ZEB1-AS1 acts as a molecular sponge for miR-141–3p → ↑ ZEB1 → ↑ fibrosis	[48]
Diabetic nephropathy	miR-216a-5p/BMP7 axis	HK-2 (Treated with high glucose)	↑ ZEB1-AS1 (which targets miR-216a-5p) → ↑ BMP7 ↓ EMT process ↓ fibrogenesis	[43]
	miR-217/ MAFB axis	HK-2 (Treated with high glucose)	↑ ZEB1-AS1 (which sponges miR-217) → ↑ MAFB → attenuated fibrosis	[53]
Atherosclerosis	miR-590–5p/ ETS1 Axis | TGF-β/Smad Pathway	HUVECs treated with ox-LDL	ZEB1-AS1 sponges miR-590–5p → ↑ EST1: ↑ cell injuries & inflammation	[3]
	miR-590–5p/ HDAC9 axis	HUVECs treated with ox-LDL	Δ ZEB1-AS1 (which sponges miR-590–5p) → ↑ miR-590–5p → ↓ HDAC9 ↑ proliferation ↓ apoptosis	[79]
	miR-942/ HMGB1/	HCtAEC THP-1 treated with ox-LDL	ZEB1-AS1 sponges miR-942 and upregulates HMGB1 → ↑ cell injuries	[18]
	NOD2	HUVECs treated with ox-LDL	Δ ZEB1-AS1 (which upregulates NOD2 through recruiting LRPPRC) ↓ cell injuries ↓ cell death induced by ox-LDL	[70]

Table 6
In vivo studies on the role of ZEB1-AS1 in non-malignant conditions.

Disease type	Animal model	Function	Ref
Ischemic stroke	Sprague Dawley Rat (ischemia/ reperfusion injury models)	↑ ZEB1-AS1 → ↑ HMGB1/ TLR-4 axis: ↑ cognitive impairment ↑ brain fluid -aggravation of disease	[58]
Diabetic nephropathy	C57BL/KsJ mice (diabetic db/db)	↑ ZEB1-AS1 → reduced renal dysfunction and fibrosis	[53]
Pulmonary fibrosis (PF)	Sprague-Dawley rats PF models	Δ ZEB1-AS1 reduces fibrosis	[48]

malignant features indicating a prognostic role for this lncRNA.

In addition to malignant conditions, ZEB1-AS1 is involved in the pathophysiology of diabetic nephropathy, diabetic lung, arthrosclerosis, *Chlamydia trachomatis* infection, pulmonary fibrosis and ischemic stroke through regulation of several miRNA/mRNA axes and signaling pathways.

Taken together, ZEB1-AS1 represents an appropriate target for design of novel therapeutics particularly for cancers where it exerts explicit oncogenic roles. Future studies are needed to assess safety and applicability of ZEB1-AS1-targeting strategies in the clinical setting.

Table 7
Summary of human studies on the role of ZEB1-AS1 in non-malignant conditions.

Disease type	Number of clinical samples	Expression (case vs. control)	Method	Ref
Atherosclerosis (AS)	Blood sample of 30 AS + 30 healthy controls	Upregulated	qRT-PCR	[79]
Diabetic lung (DL)	Plasma of 78 DL + 78 diabetic patients + 78 healthy controls	Downregulated in DL	qRT-PCR	[16]
Diabetic nephropathy (DN)	20 DN kidney tissues + 20 healthy controls tissues	Downregulated	qRT-PCR	[43]
	26 DN kidney tissues + 10 normal kidney tissues (from patients with kidney carcinoma)	Downregulated	qRT-PCR	[53]
	8 DN kidney tissues + 8 minimal change disease tissues	Downregulated	qRT-PCR	[59]

Ethics approval and consent to Participant

Not applicable.

Consent of publication

Not applicable.

Funding

Not applicable.

CRediT authorship contribution statement

SGF wrote the draft and revised it. MT designed and supervised the study. AA, KBM, BMH and MS collected the data and designed the figures and tables. All the authors read the submitted version and approved it.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Acknowledgement

The authors would like to thank the clinical Research Development Unit (CRDU) of Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran for their support, cooperation and assistance throughout the period of study.

References

[1] H. Chai, C. Sun, J. Liu, H. Sheng, R. Zhao, Z. Feng, The relationship between ZEB1-AS1 expression and the prognosis of patients with advanced gastric cancer receiving chemotherapy, Technol. Cancer Res. Treat. 18 (2019), 1533033819849069.
[2] X.K. Chai, W. Qi, C.Y. Zou, C.X. He, M. Su, D.Q. Zhao, Potential prognostic value of a seven m6A-related LncRNAs signature and the correlative immune infiltration in colon adenocarcinoma, Front. Genet. 12 (2021), 774010.
[3] D. Chen, K. Wang, Y. Zheng, G. Wang, M. Jiang, Exosomes-mediated LncRNA ZEB1-AS1 facilitates cell injuries by miR-590-5p/ETS1 axis through the TGF-β/Smad pathway in oxidized low-density lipoprotein-induced human umbilical vein endothelial cells, J. Cardiovasc Pharmacol. 77 (2021) 480–490.

[4] Y. Chen, W. Long, L. Yang, Y. Zhao, X. Wu, M. Li, F. Du, Y. Chen, Z. Yang, Q. Wen, T. Yi, Z. Xiao, J. Shen, Functional peptides encoded by long non-coding RNAs in gastrointestinal cancer, Front. Oncol. 11 (2021), 777374.

[5] R. Cheng, N. Li, S. Yang, L. Liu, S. Han, Long non-coding RNA ZEB1-AS1 promotes cell invasion and epithelial to mesenchymal transition through inducing ZEB1 expression in cervical cancer, Onco Targets Ther. 11 (2018) 7245–7253.

[6] G. Cui, J. Liu, C. Wang, R. Gu, M. Wang, Z. Sun, F. Wei, Comprehensive analysis of the prognostic signature and tumor microenvironment infiltration characteristics of cuproptosis-related lncRNAs for patients with colon adenocarcinoma, Front. Oncol. 12 (2022) 1007918.

[7] C. Dai, P. Xu, S. Liu, S. Xu, J. Xu, Z. Fu, J. Cao, M. Lv, J. Zhou, G. Liu, H. Zhang, X. Jia, Long noncoding RNA ZEB1-AS1 affects paclitaxel and cisplatin resistance by regulating MMP19 in epithelial ovarian cancer cells, Arch. Gynecol. Obstet. 303 (2021) 1271–1281.

[8] I. Delgado, O. Fresnedo, A. Iglesias, Y. Rueda, W.-K. Syn, A.M. Zubiaga, B. Ochoa, A role for transcription factor E2F2 in hepatocyte proliferation and timely liver regeneration, Am. J. Physiol. Gastrointest. Liver Physiol. 301 (2011) G20–G31.

[9] P.-D. Denechaud, L. Fajas, A. Giralt, E2F1 a novel regulator of metabolism, Front. Endocrinol. 8 (2017).

[10] J. Fu, Y. Cui, Long noncoding RNA ZEB1-AS1 expression predicts progression and poor prognosis of colorectal cancer, Int J. Biol. Markers 32 (2017) e428–e433.

[11] R. Gao, N. Zhang, J. Yang, Y. Zhu, Z. Zhang, J. Wang, X. Xu, Z. Li, X. Liu, Z. Li, J. Li, C. Kong, J. Bi, Long non-coding RNA ZEB1-AS1 regulates miR-200b/FSCN1 signaling and enhances migration and invasion induced by TGF-β1 in bladder cancer cells, J. Exp. Clin. Cancer Res. 38 (2019) 111.

[12] S. Ghafouri-Fard, A. Abak, H. Shoorei, M. Mohaqiq, J. Majidpoor, A. Sayad, M. Taheri, Regulatory role of microRNAs on PTEN signaling, Biomed. Pharmacother. 133 (2021).

[13] S. Ghafouri-Fard, H. Shoorei, M. Taheri, Non-coding RNAs are involved in the response to oxidative stress, Biomed. Pharmacother. 127 (2020).

[14] S. Ghafouri-Fard, H. Shoorei, M. Taheri, The Role of Long Non-coding RNAs in Cancer Metabolism: A Concise Review, Front. Oncol. 10 (2020).

[15] H. Gong, H. Wen, X. Zhu, Y. Lian, X. Yang, Z. Qian, J. Zhu, High expression of long non-coding RNA ZEB1-AS1 promotes colorectal cancer cell proliferation partially by suppressing p15 expression, Tumour Biol. 39 (2017), 1010428317705336.

[16] L. Gu, H. Sun, Z. Yan, lncRNA ZEB1-AS1 is downregulated in diabetic lung and regulates lung cell apoptosis, Exp. Ther. Med. 20 (2020) 225.

[17] A.-E.E. Hridoy, M. Naim, N.U. Emon, I.H. Tipo, S. Alam, A. Al Mamun, M.S. Islam, Forecasting COVID-19 Dynamics and Endpoint in Bangladesh: A Data-driven Approach. medRxiv (2020) 2020.2006.2026.20140905.

[18] Z. Hua, K. Ma, S. Liu, Y. Yue, H. Cao, Z. Li, LncRNA ZEB1-AS1 facilitates ox-LDL-induced damage of HCtAEC cells and the oxidative stress and inflammatory events of THP-1 cells via miR-942/HMGB1 signaling, Life Sci. 247 (2020), 117334.

[19] E. Huang, T. Ma, J. Zhou, N. Ma, W. Yang, C. Liu, Z. Hou, S. Chen, Z. Zong, B. Zeng, Y. Li, T. Zhou, A novel senescence-associated LncRNA signature predicts the prognosis and tumor microenvironment of patients with colorectal cancer: a bioinformatics analysis, J. Gastrointest. Oncol. 13 (2022) 1842–1863.

[20] X. Jiang, J. Li, W. Wang, Z. Hu, C. Guan, Y. Zhao, W. Li, Y. Cui, AR-induced ZEB1-AS1 represents poor prognosis in cholangiocarcinoma and facilitates tumor stemness proliferation and invasion through mediating miR-133b/HOXB8, Aging 12 (2020) 1237–1255.

[21] M. Jiao, S. Ning, J. Chen, L. Chen, M. Jiao, Z. Cui, L. Guo, W. Mu, H. Yang, Long non-coding RNA ZEB1–AS1 predicts a poor prognosis and promotes cancer progression through the miR-200a/ZEB1 signaling pathway in intrahepatic cholangiocarcinoma, Int J. Oncol. 56 (2020) 1455–1467.

[22] J. Jin, H. Wang, J. Si, R. Ni, Y. Liu, J. Wang, ZEB1-AS1 is associated with poor prognosis in non-small-cell lung cancer and influences cell migration and apoptosis by repressing ID1, Clin. Sci. 133 (2019) 381–392.

[23] Y. Jin, Z. Zhang, Q. Yu, Z. Zeng, H. Song, X. Huang, Q. Kong, H. Hu, Y. Xia, Positive reciprocal feedback of lncRNA ZEB1-AS1 and HIF-1α contributes to hypoxia-promoted tumorigenesis and metastasis of pancreatic cancer, Front. Oncol. 11 (2021), 761979.

[24] Z. Jin, B. Chen, LncRNA ZEB1-AS1 regulates colorectal cancer cells by MiR-205/YAP1 axis, Open Med. 15 (2020) 175–184.

[25] J. Li, Z. Liang, J. Zheng, X. Zhang, J. Fu, Long noncoding RNA ZEB1-AS1 predicts an unfavorable prognosis of non-small lung cancer and regulates epithelial to mesenchymal transition through reducing ZEB1 expression, Int. J. Clin. Exp. Pathol. 10 (2017) 10910–10917.

[26] M. Li, H. Guan, Y. Liu, X. Gan, LncRNA ZEB1-AS1 reduces liver cancer cell proliferation by targeting miR-365a-3p, Exp. Ther. Med. 17 (2019) 3539–3547.

[27] Y. Li, X. Wen, L. Wang, X. Sun, H. Ma, Z. Fu, L. Li, LncRNA ZEB1-AS1 predicts unfavorable prognosis in gastric cancer, Surg. Oncol. 26 (2017) 527–534.

[28] Z. Li, Y. Liu, H. Yi, T. Cai, Y. Wei, Identification of N6-methylandenosine related lncRNA signatures for predicting the prognosis and therapy response in colorectal cancer patients, Front. Genet. 13 (2022), 947747.

[29] J. Lin, Y. Zhan, Y. Liu, Z. Chen, J. Liang, W. Li, A. He, L. Zhou, H. Mei, F. Wang, W. Huang, Increased expression of ZEB1-AS1 correlates with higher histopathological grade and promotes tumorigenesis in bladder cancer, Oncotarget 8 (2017) 24202–24212.

[30] C. Liu, J. Lin, Long noncoding RNA ZEB1-AS1 acts as an oncogene in osteosarcoma by epigenetically activating ZEB1, Am. J. Transl. Res. 8 (2016) 4095–4105.

[31] C. Liu, C. Pan, Y. Cai, H. Wang, Interplay between long noncoding RNA ZEB1-AS1 and miR-200s regulates osteosarcoma cell proliferation and migration, J. Cell Biochem. 118 (2017) 2250–2260.

[32] X.J. Liu, S.L. Li, J.S. Li, H. Lu, L.L. Yin, W.F. Zheng, W.C. Wang, Long non-coding RNA ZEB1-AS1 is associated with poor prognosis in gastric cancer and promotes cancer cell metastasis, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 2624–2630.

[33] C. Lu, X. Luo, C. Xing, Y. Mao, Y. Xu, W. Gao, W. Wang, T. Zhan, G. Wang, Z. Liu, C. Yu, Construction of a novel mRNA-miRNA-lncRNA network and identification of potential regulatory axis associated with prognosis in colorectal cancer liver metastases, Aging 13 (2021) 14968–14988.

[34] Q. Lu, W. Chen, Y. Ji, Y. Liu, X. Xue, Ursolic acid enhances cytotoxicity of doxorubicin-resistant triple-negative breast cancer cells via ZEB1-AS1/miR-186-5p/ABCC1 Axis, Cancer Biother Radio. 37 (2022) 673–683.

[35] F. Luo, Y. Wen, L. Zhao, S. Su, W. Lei, L. Chen, C. Chen, Q. Huang, Z. Li, LncRNA ZEB1-AS1/miR-1224-5p / MAP4K4 axis regulates mitochondria-mediated HeLa cell apoptosis in persistent Chlamydia trachomatis infection, Virulence 13 (2022) 444–457.

[36] N. Luo, K. Zhang, X. Li, Y. Hu, ZEB1 induced-upregulation of long noncoding RNA ZEB1-AS1 facilitates the progression of triple negative breast cancer by binding with ELAVL1 to maintain the stability of ZEB1 mRNA, J. Cell Biochem. 121 (2020) 4176–4187.

[37] Q.L. Lv, L. Hu, S.H. Chen, B. Sun, M.L. Fu, C.Z. Qin, Q. Qu, G.H. Wang, C.J. He, H. H. Zhou, A. Long, Noncoding RNA ZEB1-AS1 promotes tumorigenesis and predicts poor prognosis in glioma, Int. J. Mol. Sci. 17 (2016).

[38] S.Y. Lv, T.D. Shan, X.T. Pan, Z.B. Tian, X.S. Liu, F.G. Liu, X.G. Sun, H.G. Xue, X. H. Li, Y. Han, L.J. Sun, L. Chen, L.Y. Zhang, The lncRNA ZEB1-AS1 sponges miR-181a-5p to promote colorectal cancer cell proliferation by regulating Wnt/β-catenin signaling, Cell Cycle 17 (2018) 1245–1254.

[39] M.H. Ma, J.X. An, C. Zhang, J. Liu, Y. Liang, C.D. Zhang, Z. Zhang, D.Q. Dai, ZEB1-AS1 initiates a miRNA-mediated ceRNA network to facilitate gastric cancer progression, Cancer Cell Int. 19 (2019) 27.

[40] T. Ma, H. Chen, P. Wang, N. Yang, J. Bao, Downregulation of lncRNA ZEB1-AS1 represses cell proliferation, migration, and invasion through mediating PI3K/AKT/mTOR signaling by miR-342-3p/CUL4B axis in prostate cancer, Cancer Biother Radio. 35 (2020) 661–672.

[41] Z.J. Ma, Y. Wang, H.F. Li, M.H. Liu, F.R. Bi, L. Ma, H. Ma, H.L. Yan, LncZEB1-AS1 regulates hepatocellular carcinoma bone metastasis via regulation of the miR-302b-EGFR-PI3K-AKT axis, J. Cancer 11 (2020) 5118–5128.

[42] L. Meng, P. Ma, R. Cai, Q. Guan, M. Wang, B. Jin, Long noncoding RNA ZEB1-AS1 promotes the tumorigenesis of glioma cancer cells by modulating the miR-200c/141-ZEB1 axis, Am. J. Transl. Res. 10 (2018) 3395–3412.

[43] Q. Meng, X. Zhai, Y. Yuan, Q. Ji, P. Zhang, lncRNA ZEB1-AS1 inhibits high glucose-induced EMT and fibrogenesis by regulating the miR-216a-5p/BMP7 axis in diabetic nephropathy, Braz. J. Med. Biol. Res. 53 (2020), e9288.

[44] B. Mu, C. Lv, Q. Liu, H. Yang, Long non-coding RNA ZEB1-AS1 promotes proliferation and metastasis of hepatocellular carcinoma cells by targeting miR-299-3p/E2F1 axis, J. Biochem. 170 (2021) 41–50.

[45] T. Ohira, R.M. Gemmill, K. Ferguson, S. Kusy, J. Roche, E. Brambilla, C. Zeng, A. Baron, L. Bemis, P. Erickson, E. Wilder, A. Rustgi, J. Kitajewski, E. Gabrielson, R. Bremnes, W. Franklin, H.A. Drabkin, WNT7a induces E-cadherin in lung cancer cells, Proc. Natl. Acad. Sci. 100 (2003) 10429–10434.

[46] G. Olgun, O. Sahin, O. Tastan, Discovering lncRNA mediated sponge interactions in breast cancer molecular subtypes, BMC Genom. 19 (2018) 650.

[47] R. Policarpo, A. Sierksma, B. De Strooper, C. d'Ydewalle, From junk to function: LncRNAs in CNS health and disease, Front. Mol. Neurosci. 14 (2021).

[48] W. Qian, X. Cai, Q. Qian, W. Peng, J. Yu, X. Zhang, L. Tian, C. Wang, lncRNA ZEB1-AS1 promotes pulmonary fibrosis through ZEB1-mediated epithelial-mesenchymal transition by competitively binding miR-141-3p, Cell Death Dis. 10 (2019) 129.

[49] R. Qu, X. Chen, C. Zhang, LncRNA ZEB1-AS1/miR-409-3p/ZEB1 feedback loop is involved in the progression of non-small cell lung cancer, Biochem. Biophys. Res. Commun. 507 (2018) 450–456.

[50] L. Ruan, W. Chen, X. Zhao, N. Fang, T. Li, Predictive potentials of ZEB1-AS1 in colorectal cancer prognosis and their correlation with immunotherapy, J. Oncol. 2022 (2022) 1084555.

[51] A. Safa, A. Abak, H. Shoorei, M. Taheri, S. Ghafouri-Fard, MicroRNAs as regulators of ERK/MAPK pathway: a comprehensive review, Biomed. Pharmacother. 132 (2020).

[52] D.D. Siena Á, J.R. Plaça, L.F. Araújo, B. de, II, K. Peronni, G. Molfetta, C.A.O. de Biagi, Jr, E.M. Espreafico, J.F. Sousa, W.A. Silva, Jr, Whole transcriptome analysis reveals correlation of long noncoding RNA ZEB1-AS1 with invasive profile in melanoma, Sci. Rep. 9 (2019) 11350.

[53] Y. Song, C. Miao, J. Wang, LncRNA ZEB1-AS1 inhibits renal fibrosis in diabetic nephropathy by regulating the miR-217/MAFB axis, RSC Adv. 9 (2019) 30389–30397.

[54] W. Su, M. Xu, X. Chen, N. Chen, J. Gong, L. Nie, L. Li, X. Li, M. Zhang, Q. Zhou, Long noncoding RNA ZEB1-AS1 epigenetically regulates the expressions of ZEB1 and downstream molecules in prostate cancer, Mol. Cancer 16 (2017) 142.

[55] W. Su, M. Xu, X. Chen, N. Chen, J. Gong, L. Nie, L. Li, X. Li, M. Zhang, Q. Zhou, Long noncoding RNA ZEB1-AS1 epigenetically regulates the expressions of ZEB1 and downstream molecules in prostate cancer, Mol. Cancer 16 (2017) 142.

[56] Y. Takeyama, M. Sato, M. Horio, T. Hase, K. Yoshida, T. Yokoyama, H. Nakashima, N. Hashimoto, Y. Sekido, A.F. Gazdar, J.D. Minna, M. Kondo, Y. Hasegawa, Knockdown of ZEB1 a master epithelial-to-mesenchymal transition (EMT) gene suppresses anchorage-independent cell growth of lung cancer cells, Cancer Lett. 296 (2010) 216–224.

[57] Q. Tang, X. Hu, Q. Guo, Y. Shi, L. Liu, G. Ying, Discovery and validation of a novel metastasis-related lncRNA prognostic signature for colorectal cancer, Front. Genet. 13 (2022), 704988.

[58] J. Wang, X. Chen, L. Sun, X. Chen, H. Li, B. Xiong, H. Wang, Long noncoding RNA ZEB1-AS1 aggravates cerebral ischemia/reperfusion injury in rats through the HMGB1/TLR-4 signaling axis, Nan Fang Yi Ke Da Xue Xue Bao 42 (2022) 1134–1142.
[59] J. Wang, J. Pan, H. Li, J. Long, F. Fang, J. Chen, X. Zhu, X. Xiang, D. Zhang, lncRNA ZEB1-AS1 was suppressed by p53 for renal fibrosis in diabetic nephropathy, Mol. Ther. Nucleic Acids 12 (2018) 741–750.
[60] Q. Wang, X. Du, M. Yang, S. Xiao, J. Cao, J. Song, L. Wang, LncRNA ZEB1-AS1 contributes to STAT3 activation by associating with IL-11 in B-lymphoblastic leukemia, Biotechnol. Lett. 39 (2017) 1801–1810.
[61] Q. Wang, R. Zhang, D. Liu, Long non-coding RNA ZEB1-AS1 indicates poor prognosis and promotes melanoma progression through targeting miR-1224-5p, Exp. Ther. Med. 17 (2019) 857–862.
[62] X. Wang, Y. Guo, C. Wang, Q. Wang, G. Yan, Long noncoding RNA ZEB1-AS1 downregulates miR-23a promotes tumor progression, and predicts the survival of oral squamous cell carcinoma patients, Onco Targets Ther. 14 (2021) 2699–2710.
[63] Y.L. Wang, Y. Bai, W.J. Yao, L. Guo, Z.M. Wang, Expression of long non-coding RNA ZEB1-AS1 in esophageal squamous cell carcinoma and its correlation with tumor progression and patient survival, Int. J. Clin. Exp. Pathol. 8 (2015) 11871–11876.
[64] G. Wei, T. Lu, J. Shen, J. Wang, LncRNA ZEB1-AS1 promotes pancreatic cancer progression by regulating miR-505-3p/TRIB2 axis, Biochem Biophys. Res. Commun. 528 (2020) 644–649.
[65] N. Wei, H. Wei, H. Zhang, Long non-coding RNA ZEB1-AS1 promotes glioma cell proliferation migration and invasion through regulating miR-577, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 3085–3093.
[66] G. Wu, M. Xue, Y. Zhao, Y. Han, C. Li, S. Zhang, J. Zhang, J. Xu, Long noncoding RNA ZEB1-AS1 acts as a sponge of miR-141-3p to inhibit cell proliferation in colorectal cancer, Int. J. Med. Sci. 17 (2020) 1589–1597.
[67] W. Xia, W. Jie, ZEB1-AS1/miR-133a-3p/LPAR3/EGFR axis promotes the progression of thyroid cancer by regulating PI3K/AKT/mTOR pathway, Cancer Cell Int. 20 (2020) 94.
[68] J. Xie, Y. Wu, X. Bian, D. Chen, Q. Gui, J. Huang, Increased expression of lncRNA ZEB1-AS1 in non-small cell lung cancer is associated with poor prognosis, Int. J. Clin. Exp. Pathol. 11 (2018) 3703–3707.
[69] W.C. Xiong, N. Han, N. Wu, K.L. Zhao, C. Han, H.X. Wang, G.F. Ping, P.F. Zheng, H. Feng, L. Qin, P. He, Interplay between long noncoding RNA ZEB1-AS1 and miR-101/ZEB1 axis regulates proliferation and migration of colorectal cancer cells, Am. J. Transl. Res 10 (2018) 605–617.
[70] X. Xu, C. Ma, Z. Duan, Y. Du, C. Liu, lncRNA ZEB1-AS1 mediates oxidative low-density lipoprotein-mediated endothelial cells injury by post-transcriptional stabilization of NOD2, Front. Pharmacol. 10 (2019) 397.
[71] S. Xue, F. Lu, C. Sun, J. Zhao, H. Zhen, X. Li, LncRNA ZEB1-AS1 regulates hepatocellular carcinoma progression by targeting miR-23c, World J. Surg. Oncol. 19 (2021) 121.
[72] J. Zhang, Y. Wu, J. Mu, D. Xin, L. Wang, Y. Fan, S. Zhang, Y. Xu, Glycosyltransferase-related long non-coding RNA signature predicts the prognosis of colon adenocarcinoma, Front. Oncol. 12 (2022), 954226.
[73] L.L. Zhang, L.F. Zhang, X.H. Guo, D.Z. Zhang, F. Yang, Y.Y. Fan, Downregulation of miR-335-5p by long noncoding RNA ZEB1-AS1 in gastric cancer promotes tumor proliferation and invasion, DNA Cell Biol. 37 (2018) 46–52.
[74] W. Zhang, L. Xiong, Effect of lncRNA ZEB1-AS1 on proliferation invasion and apoptosis of glioma U87 cells, Oncol. Lett. 17 (2019) 5120–5124.
[75] Y.G. Zhang, M.W. Zhou, L. Bai, R.Y. Han, K. Lv, Z. Wang, Extracellular vesicles promote esophageal cancer progression by delivering lncZEB1-AS1 between cells, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 2662–2670.
[76] Z. Zhang, F. Wang, J. Zhang, W. Zhan, G. Zhang, C. Li, T. Zhang, Q. Yuan, J. Chen, M. Guo, H. Xu, F. Yu, H. Wang, X. Wang, W. Kong, An m6A-Related lncRNA signature predicts the prognosis of hepatocellular carcinoma, Front. Pharmacol. 13 (2022), 854851.
[77] X. Zhao, Y. Wang, F. Meng, Z. Liu, B. Xu, Risk stratification and validation of eleven autophagy-related lncRNAs for esophageal squamous cell carcinoma, Front. Genet. 13 (2022), 894990.
[78] Y. Zhao, N. Wang, X. Zhang, H. Liu, S. Yang, LncRNA ZEB1-AS1 down-regulation suppresses the proliferation and invasion by inhibiting ZEB1 expression in oesophageal squamous cell carcinoma, J. Cell Mol. Med. 23 (2019) 8206–8218.
[79] J. Zhong, B. Cheng, L. Yang, G. Li, Y. Yuan, G. Luo, Z. Shu, H. Jiang, LncRNA ZEB1-AS1 knockdown alleviates oxidative low-density lipoprotein-induced endothelial cell injury via the miR-590-5p/HDAC9 axis, Cent. Eur. J. Immunol. 46 (2021) 325–335.