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Review

A review on the role of FOXD2-AS1 in human disorders

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ABSTRACT

FOXD2 adjacent opposite strand RNA 1 (FOXD2-AS1) is a long non-coding RNA being transcribed from a locus on chromosome 1p33. This transcript has been found to be up-regulated in tumor samples of almost all types of malignancies in association with a significant increase in malignant features. FOXD2-AS1 can affect activity of PI3K/AKT, AKT/mTOR, Hippo/YAP, Notch, NRf2, Wnt/β-catenin, NF-ĸB and ERK/MAPK pathways. Furthermore, it can enhance stem cell properties in cancer cells and prompt epithelial-mesenchymal transition. It is also involved in induction of resistance to a variety of anticancer agents such as adriamycin, cisplatin, 5-fluorouracil, temozolomide and gemcitabine. This article summarizes the impact of FOXD2-AS1 in diverse human disorders.

1. Introduction

Long non-coding RNAs (lncRNAs) are a class of non-coding RNAs whose transcript size exceeds 200 nucleotides [16,44]. Depending on where they are localized in the cell, lncRNAs exert a variety of regulatory activities that have a significant impact on cellular functions [1,17,30,52]. In general, lncRNAs are considered as regulators of target gene expression or downstream processes [27], and they exert their regulatory functions through direct interaction with DNA, RNA, and proteins [20]. LncRNAs may also contribute to the development of malignancies [18,19,56]. As "RNA sponges" or competing endogenous RNA (ceRNAs), they can modulate tumor-related biological processes, including cell proliferation, metastasis, and apoptosis [55]. Dysregulation of lncRNAs has been related to various disorders, so lncRNAs are considered as candidates for therapeutic strategies [52].

LncRNA FOXD2 adjacent opposite strand RNA1 (FOXD2-AS1) is a recently identified lncRNA with a size of 2527 nucleotides that is located on chromosome 1p33 (https://www.ncbi.nlm.nih.gov/nuccore/NR_026878). FOXD2-AS1 is an lncRNA that is related to malignancies. It plays a critical role in the development of tumors and is upregulated in many different cancer types. Dysregulation of FOXD2-AS1 has an oncogenic impact, and it promotes the growth and metastasis of tumor cells [8,23]. The effect of FOXD2-AS1 in regulation of cancer cell proliferation, migration, invasion, and apoptosis proposes that it is a potential biomarker or therapeutic target in malignancies [46].

The involvement of FOXD2-AS1 in several malignancies has been demonstrated in recent investigations. Therefore, this lncRNA is an appropriate target for design of novel therapeutic methods. The present article provides a comprehensive overview of the studies that emphasized on the roles of FOXD2-AS1 in human disorders, notably malignant ones. The evidence for the functions of FOXD2-AS1 is categorized based on the type of studies, including cell line experiments, studies on animal models, and analyses of clinical specimens.

2. Cancers

2.1. Cell line studies

Several in vitro studies have evaluated function and expression level of FOXD2-AS1 in cancer cell lines. As an example, FOXD2-AS1 has been shown to stimulate proliferation, migration, and invasive attributes of bladder cancer cells. Furthermore, FOXD2-AS1 could down-regulate

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expression of TRIB3, a negative regulator of Akt. From a mechanistical viewpoint, FOXD2-AS1 can establish an RNA-DNA complex with the promoter of this gene to repress its transcriptional activity, leading to activation of Akt. Akt can in turn increase expression of E2F1, an important transcription factor participating in the G/S transition. Remarkably, E2F1 can bind to the promoter of FOXD2-AS1 and increase its transcriptional activities. Therefore, a feedback loop is established between FOXD2-AS1, Akt and E2F1 [53]. FOXD2-AS1 has also been reported to be highly expressed in gemcitabine-resistant bladder cancer cells. Its silencing has induced sensitivity to gemcitabine, reduced expression of drug-resistance associated genes (MDR1, MRP2, LRP1), and inhibited invasive properties of these cells. Notably, FOXD2-AS1 has been found to regulate expression of ABCC3 protein via adsorbing miR-143 [2].

Similarly, FOXD2-AS1 is over-expressed in breast cancer cells and increase cell drug resistance to adriamycin. FOXD2-AS1 silencing has suppressed invasiveness and migration of adriamycin resistance MCF-7 cells, induced their apoptosis, and suppressed activity of PI3K/AKT signals in the mentioned cells [43]. FOXD2-AS1 can also regulate progression of breast cancer through up-regulation pf the S100 calcium binding protein A1 and inhibition of Hippo/yes-associated protein signaling [26]. FOXD2-AS1 has also been upregulated in sphere subpopulation of breast cancer cells. Besides, FOXD2-AS1 silencing has decreased proliferative, migratory and invasive aptitudes of breast cancer cells, reduced proportion of CD44 + /CD24- breast cancer stem cells, and diminished expression of several stem factors such as Nanog, Oct4, and SOX2. Moreover, FOXD2-AS1 silencing has inhibited epithelial-mesenchymal transition (EMT). Being mainly located in the cytoplasm, FOXD2-AS1 sponges miR-150-5p to increase expression of its target PFN2 [29].

FOXD2-AS1 could also promote migration and proliferation of cervical cancer cells (Fig. 1). Mechanistical studies have shown that m^6A methyltransferase-like 3 (METTL3) could enhance FOXD2-AS1 stability and preserve its expression. Besides, FOXD2-AS1 has a role in recruitment of LSD1 to p21 promoter to decrease its expression. Cumulatively, METTL3/FOXD2-AS1 has been suggested to accelerate progression of cervical cancer through a m^6A-dependent route [28]. This lncRNA can also promotes malignant features of cervical cancer cells through sponging miR-760 and increasing expression of hepatoma-derived growth factor [11]. Moreover, it can downregulate expression of CDX1 in these cells [7]. Table 1 summarizes the impact of FOXD2-AS1 in carcinogenesis according to studies in cell lines.

3. Animal studies

Oncogenic effect of FOXD2-AS1 has been confirmed in xenograft

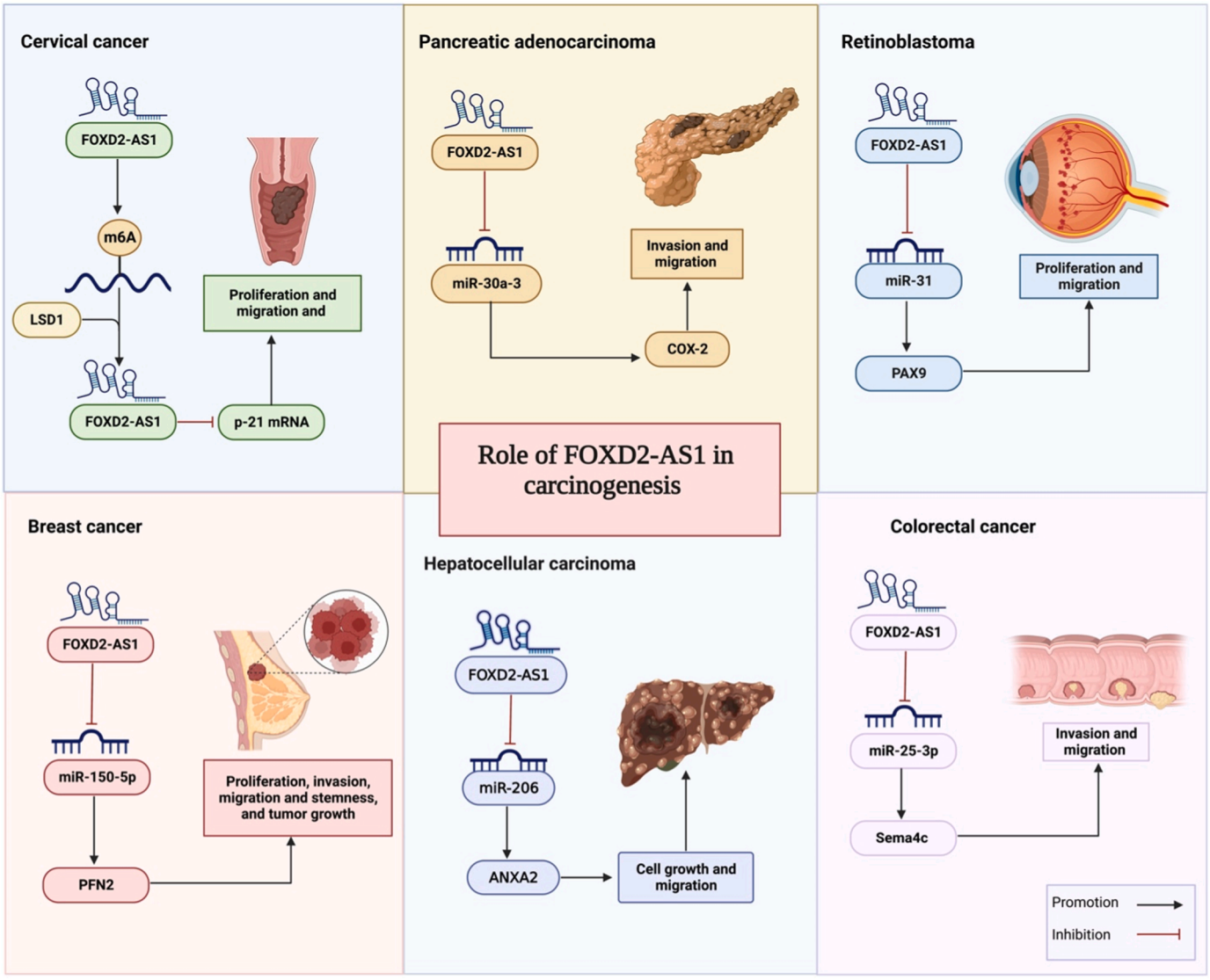

Fig. 1. Impacts of lncRNA FOXD2-AS1 in different types of cancer with its targets and signaling pathways.

Table 1
Impact of FOXD2-AS1 in carcinogenesis according to studies in cell lines (TCLs: tumor cell lines, NCL: normal cell line, Δ: knockdown or deletion, GSCs: glioma stem cells, ADR: Adriamycin, DDP: cisplatin, TE-1/DDP: DDP-resistant TE-1, 5-FU: 5-fluorouracil, TMZ: temozolomide, GEM: gemcitabine, SP: side population, BCSC: breast cancer stem cell, EMT: epithelial-mesenchymal transition).

Cancer type	Cell lines	Expression level of FOXD2-AS1	Regulators of FOXD2-AS1	Targets/Signaling pathways	Biological functions	Reference
Bladder cancer	TCLs: UM-UC-3, T24	_	E2F1	hnRNP L/TRIB3/ AKT /E2F1	↑FOXD2-AS1: ↑cell viability and colony formation, ↑G1 to S phase transition, ↑migration, ↑invasion ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓invasion	[53]
	TCLs: 5637, T24	Up (GEM-resistant TCLs vs. parental TCLs)	_	miR-143/ABCC3	ΔFOXD2-AS1: ↓GEM-resistance (↓MDR1, ↓MRP2, ↓LRP1, ↓ABCC3), invasion	[2]
Breast cancer	TCLs: MCF-7 and ADR-resistant TCLs (MCF-7/ADR) NCL: MCF-10A	Up (TCLs vs. NCLs, MCF-7/ADR vs. MCF-7)	_	PI3K/AKT signaling pathway	ΔFOXD2-AS1(in MCF-7/ADR): ↓migration, ↓invasion, ↑apoptosis, ↑chemosensitivity to ADR, DDP and 5-FU	[43]
	TCLs: MCF-7, MDA-MB-468, MDA-MB-453, BT-549 NCL: MCF-10A	Up (TCLs vs. NCLs)	_	LATS1, S100A1, Hippo/YAP signaling pathway	ΔFOXD2-AS1: ↓proliferation, ↑G1 phase cells and ↓S phase cells (↓cyclin E1, ↓CDK2 and ↑p21), ↓migration and ↓invasion (↓MMP-2 and MMP-9)	[26]
	TCLs: MCF-7, MDA-MB-468, MDA-MB-453, MDA-MB-231 NCL: MCF-10A	Up (TCLs vs. NCLs and tumor sphere cells vs. parental cells)	_	miR-150-5p/PFN2	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓invasion ΔFOXD2-AS1(in BCSCs): ↓CD44 + /CD24- cells, ↓stemness markers (Nanog, Oct4, SOX2)	[29]
Luminal breast cancer	TCLs: MCF7, T47D NCL: MCF10A	Up (TCLs vs. NCLs)	_	_	_	[3]
Cervical cancer	TCLs: CaSKi, HT-3, SiHa, C33A NCL: HaCaT	Up (TCLs vs. NCLs)	METTL3	LSD1/p21	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↑apoptosis ↑FOXD2-AS1: ↑proliferation, ↑migration, ↓apoptosis	[28]
	TCLs: CaSKi, HeLa, SiHa, C-33A NCL: Ect1/E6E7	Up (TCLs vs. NCLs)	_	miR-760/HDGF	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓invasion, ↑apoptosis	[11]
	TCLs: HeLa, SiHa NCL: H8	Up (TCLs vs. NCLs)	_	CDX1	ΔFOXD2-AS1: ↓cell viability and proliferation	[7]
Cholangiocarcinoma	TCLs: CCLP-1, QBC939, HuCCT1, RBE NCL: HIBEC	Up (TCLs vs. NCLs)	_	miR-760/E2F3	ΔFOXD2-AS1: ↓cell viability, ↓colony formation ability, ↓migration, ↓invasion ↑FOXD2-AS1: ↑cell growth, ↑colony formation ability, ↑migration, ↑invasion	[25]
Colorectal cancer	TCLs: HCT116, SW-620, LOVO, HCT-15, SW480 NCL: CCD-18Co	Up (TCLs vs. NCLs)	_	miR-4306	ΔFOXD2-AS1(in HCT116): ↓cell viability and proliferation, ↓Ki-67, ↓PCNA, ↑G0/G1 cell cycle arrest ↑FOXD2-AS1 (in LOVO): ↑viability and proliferation, ↑Ki-67, ↑PCNA, ↓G1 phase cells	[65]
	TCL: CR4	_	_	miR-25-3p/ sema4c	↑FOXD2-AS1: ↑migration, ↑invasion	[69]
	TCLs: HCT116, SW-620, LOVO, HT-29 NCL: CCD-18Co	Up (TCLs vs. NCLs)	_	miR-185-5p, CDC42	↑FOXD2-AS1: ↑proliferation, ↑migration, ↑invasion ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓invasion	[77]
	TCLs: RKO, HCT28, HCT116, HCT-15, SW480 NCL: CRL-1831	Up (TCLs vs. NCLs)	_	Notch signaling pathway, EMT pathway	ΔFOXD2-AS1: ↓cell viability, ↓migration, ↓invasion, ↓EMT (↑E-cadherin, ↓N-cadherin, ↓Snail), ↓Hes-1 and NICD (Notch signaling proteins)	[64]
Cutaneous melanoma	TCLs: A2058, A-375, SK-MEL-2, MeWo NCL: HEMa-LP	Up (TCLs vs. NCLs)	_	Akt	ΔFOXD2-AS1: ↓cell viability, ↓migration, ↓invasion	[46]
Esophageal squamous cell carcinoma	TCLs: TE-1 NCL: HEEC	Up (TCLs vs. NCLs and TE-1/DDP vs. parental TE-1 cells)	_	miR-195, AKT/ mTOR pathway	ΔFOXD2-AS1 (in TE-1/DDP cells): ↓colony formation and proliferation, ↑apoptosis, ↓invasion (↓MMP-9) ↑FOXD2-AS1 (in TE-1/DDP cells): ↑colony formation, ↑survival, ↓apoptosis, ↑invasion (↑MMP-9)	[37]
	TCLs: KYSE510, KYSE520, KYSE140, KYSE30, KYSE150 NCL: NE1	Up (TCLs vs. NCLs)	_	_	_	[4]

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Table 1 (*continued*)

Cancer type	Cell lines	Expression level of FOXD2-AS1	Regulators of FOXD2-AS1	Targets/Signaling pathways	Biological functions	Reference
	TCLs: KYSE150, KYSE30, TE-1, EC9706, EC109 NCL: HEEC	Up (TCLs vs. NCLs)	_	miR-204-3p	ΔFOXD2-AS1: ↓cell viability and proliferation (↓Ki-67 and PCNA), ↓migration and invasion (↓MMP-2 and MMP-9), ↑cell apoptosis (↓Bcl-2,↑Bax, ↑cleaved caspase 3 and 9)	[40]
Gallbladder cancer	TCLs: GBC-SD, SGC-996, QBC939, NOZ, OCUG1 NCL: HGBEC	Up (TCLs vs. NCLs)	_	DNMT1/MLH1	ΔFOXD2-AS1: ↓proliferation (↓Ki-67 and PCNA), ↓migration, ↓invasion, ↑apoptosis, ↑cell senescence	[12]
Gastric cancer	TCLs: BGC823, MGC803, AGS, SGC790, MKN45 NCL: GES-1	Up (TCLs vs. NCLs)	_	EZH2 and LSD1/ EphB3	ΔFOXD2-AS1: ↓cell growth, ↓cell cycle progression ↑FOXD2-AS1: ↑proliferation, ↑cell cycle progression	[63]
	TCLs: MKN-45, AGS, IM95 NCL: GES-1	Up (TCLs vs. NCLs)	_	miR-1913/ SETD1A	ΔFOXD2-AS1: ↑radiosensitivity: ↓efficiency of HR repair (↑cell death), ↓G2/M cell cycle arrest, ↓cell viability and proliferation (↓Ki-67 and PCNA), ↑apoptosis (↓Bcl-2, ↑Bax)	[22]
Glioma	TCLs: U251, LN18, T98G, A172, U-138 NCL: HA-1800	Up (TCLs vs. NCLs and in GSCs)	_	TAF-1/NOTCH1, NOTCH signaling pathway	ΔFOXD2-AS1 (in U251 GSCs): ↓sphere formation, ↓stemness (↓stemness markers including OCT4, SOX2, Nanog, Nestin, CD133), ↓CD133 + cells, ↓proliferation, ↑apoptosis, ↑GFAP (astrocyte marker), ↑differentiation	[60]
	TCLs: U251, A172 NCL: NHA	Up (TCLs vs. NCLs) Low-expressed (Curcumol-treated TCLs vs. parental TCLs)	_	_	↑FOXD2-AS1→ ↓Curcumol effects: ↑cell viability, ↑cell metastasis, ↓apoptosis, ↑self-renewal ability (↑neurosphere formation, ↑CD133, ↑Nanog, ↑Nestin, ↑SOX2), ↑TMZ resistance	[41]
	TCLs: U251, LN229, T98G, SHG44 NCL: HA	Up (TCLs vs. NCLs)	_	miR-506-5p	ΔFOXD2-AS1: ↓cell viability (↑p21, ↓CDK2, ↓cyclinE1), ↓EMT (↓N-cadherin, ↓vimentin, ↑E-cadherin), ↓migration and invasion (↓MMP7 and ↓MMP9)	[72]
	TCLs: U251, LN229, U87 NCL: HEB	Up (TCLs vs. NCLs)	_	EZH2/P53	ΔFOXD2-AS1: ↓colony formation ability	[74]
	TCLs: U251, LN229, U87, A172 NCL: HEB	Up (TCLs vs. NCLs and drug-resistant TCLs vs. parental cells)	_	miR-98-5p/CPEB4	ΔFOXD2-AS1: ↓proliferation and colony formation, ↓migration, ↓invasion, ↓EMT (↑E-cadherin, ↓N-cadherin, ↓vimentin), ↑apoptosis in drug-resistant TCLs: ΔFOXD2-AS1: ↓proliferation, ↓drug resistance, ↑apoptosis ↑FOXD2-AS1: ↑proliferation, ↑drug resistance, ↓apoptosis	[21]
	TCLs: U251, U87, A172, T98G NCL: HEB	Up (TCLs vs. NCLs)	_	miR-185-5p/ HMGA2, PI3K/ AKT signaling	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↑apoptosis	[42]
	TCLs: U251, U87, T98 NCL: SVG p12	Up (TCLs vs. NCLs)	_	miR-31/CDK1	ΔFOXD2-AS1: ↓cell viability, ↓proliferation, ↓colony formation, ↑G1 cell cycle arrest	[58]
	TCLs: U251, U87 NCL: HA-1800	Up (TCLs vs. NCLs)	_	miR-185-5p/ CCND2	ΔFOXD2-AS1: ↓CD44 + /CD133 + cells, ↓colony formation, ↓stemness factors (Nanog, Oct4, SOX2), ↓proliferation, ↓migration, ↓invasion, ↓EMT (↓N-cadherin and vimentin, ↑E-cadherin)	[51]
	TCLs: U251, LN229, A172, T98G, LN18 NCL: NHA	Up (TCLs vs. NCLs)	CREB1	miR-185/AKT1	ΔFOXD2-AS1: ↓proliferation and colony formation ability, ↑apoptosis, ↓migration, ↓invasion, ↓EMT (↓N-cadherin and vimentin)	[10]
	TCLs: U251, A172	_	_	MGMT promoter (methylation status)	ΔFOXD2-AS1 (in TMZ-treated cells): ↑TMZ sensitivity, ↓cell viability, ↓colony formation, ↓migration, ↓invasion, ↑apoptosis	[50]
Head and neck squamous cell carcinoma	TCLs: CAL27, FADU, TSCCA NCL: HOK	Up (TCLs vs. NCLs)	_	_	ΔFOXD2-AS1: ↓proliferation, ↓wound healing, ↓migration, ↓invasion	[57]
	TCLs: Cal-27, SCC-9	_	_	HMGA2	ΔFOXD2-AS1: ↓migration, ↓invasion, ↓EMT	[68]
Hemangioma	TCLs: HDEC, EOMA NCLs: HUVECs	Up (TCLs vs. NCLs)	_	miR-324-3p/ PDRG1	ΔFOXD2-AS1: ↓cell growth, ↓PCNA, ↓migration, ↓invasion, ↓MMP-2, ↓MMP-9, ↓N-cadherin, ↑E-cadherin ↑FOXD2-AS1: ↑proliferation and ↑colony formation ability,	[75]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Cell lines	Expression level of FOXD2-AS1	Regulators of FOXD2-AS1	Targets/Signaling pathways	Biological functions	Reference
					↑PCNA, ↑migration, ↑invasion, ↑MMP-2, ↑MMP-9, ↑N-cadherin, ↓E-cadherin	
Hepatocellular carcinoma	TCLs: HepG2, MHCC-97 L, MHCC-97 H, SNU449 NCL: LO2	Up (TCLs vs. NCLs)	_	miR-206/MAP3K1	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓invasion, ↑apoptosis	[24]
	TCLs: HepG2, Huh-7, SMMC-7721, Bel-7402, Hep3B NCL: L-02	Up (TCLs vs. NCLs)	_	miR-185/AKT	ΔFOXD2-AS1: ↓proliferation, ↑apoptosis, ↓migration, ↓invasion	[9]
	TCLs: HepG2, Huh-7 Sorafenib-resistant TCLs: SR-HepG2, SR-Huh-7	Low-expressed (SR-resistant cells vs. parental cells)	_	miR-150-5p/ TMEM9, NRf2 pathway	In SR-resistant cells ↑FOXD2-AS1: ↑sorafenib sensitivity, ↑apoptosis ΔFOXD2-AS1: ↑sorafenib resistance, ↓apoptosis	[54]
	TCLs: HepG2, SMMC-7721, Hep3B, LM3 NCL: L-02	Up (TCLs vs. NCLs)	EGR1	EZH2/DKK1, Wnt/ β-catenin signaling pathway	ΔFOXD2-AS1: ↓cell viability and proliferation, ↑apoptosis, ↓migration, ↓EMT	[31]
	TCLs: MHCC97-L, MHCC97-H, Hep3B, HCCLM3, SK-HEP1 NCL: HL7702	Up (TCLs vs. NCLs)	_	miR-206/ANXA2	↑FOXD2-AS1: ↑cell growth, ↑migration ΔFOXD2-AS1: ↓cell viability, ↓migration	[6]
	TCLs: HCCLM3, HepG2, MHCC97H, Huh7, SK NCL: L02	Up (TCLs vs. NCLs)	_	EZH2/CDKN1B	ΔFOXD2-AS1: ↓proliferation, ↓colony formation, ↓S phase cells, ↑G0/G1 cell cycle arrest(↓CDK2, ↓CDK4, ↓cyclin D1, ↓cyclin E1)	[61]
Laryngeal squamous cell carcinoma	TCLs: Hep2, TU-212	_	_	STAT3	↑FOXD2-AS1: ↓chemosensitivity to cisplatin, ↑sphere formation (↑size and number), ↑SP cells, ↑CD133 + cells, ↑stemness markers (↑OCT4, SOX2 and Nanog) ΔFOXD2-AS1: ↓cisplatin resistance, ↓sphere formation, ↓CD133 + cells, ↓stemness markers (↓OCT4, SOX2 and Nanog)	[34]
Nasopharyngeal carcinoma	TCLs: SUNE-1, CNE-1, CNE-2, HNE-1, C666-1, HONE-1 NCL: NP69	Up (TCLs vs. NCLs)	_	miR-363-5p/ S1001A	ΔFOXD2-AS1: ↓cell proliferation	[8]
Non-small-cell lung cancer	TCLs: A549, H1299 DDP-resistant TCLs: A549/DDP, H1299/DDP	Up (DDP-resistant cells vs. parental cells)	_	miR185-5p/SIX1	In DDP-resistant cells ΔFOXD2-AS1: ↓colony formation, ↓proliferation, ↓migration, ↓invasion, ↓drug-resistance (↓MRP1, ↓LRP, ↓Pgp)	[15]
	TCLs: A549, H1299, H1650, H2291 NCL: BEAS-2B	Up (TCLs vs. NCL)	_	Wnt/β-catenin signaling pathway	ΔFOXD2-AS1: ↓cell growth, ↓colony formation, ↑apoptosis ↑FOXD2-AS1: ↑cell growth, ↑colony formation, ↓apoptosis	[49]
Oral squamous cell carcinoma	TCLs: Cal27, HN6, SCC9 NCL: NOK	Up (TCLs vs. NCLs)	_	_	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓EMT (↓N-cadherin, ↓Snail1, ↑E-cadherin)	[39]
	TCLs: Cal27	_	_	_	ΔFOXD2-AS1: ↓proliferation and colony formation, ↓cell cycle signaling (↑p21, ↓CDK2 and ↓CDK4)	[35]
Osteosarcoma	TCLs: MG63, Saos-2 NCL: hFOB	Up (TCLs vs. NCLs)	WTAP (m^6A methyltransferase)	FOXM1	↑FOXD2-AS1 (in MG63): ↑proliferation, ↑migration ΔFOXD2-AS1 (in Saos-2): ↓proliferation, ↓migration	[48]
	TCL: U2-OS (cisplatin-resistant cells and control cells)	Up (cisplatin-resistant cells vs. controls)	_	miR-143	ΔFOXD2-AS1: ↑cisplatin-sensitivity ΔFOXD2-AS1 (in cisplatin-resistant cells): ↓proliferation, ↓migration, ↓invasion, ↑apoptosis (↑Bax, ↓Bcl-2)	[70]
	TCLs: MG63, Saos-2, 143B, U2-OS NCL: hFOB	Up (TCLs vs. NCLs)	HIF-1α	EZH2/p21	ΔFOXD2-AS1: ↓proliferation, ↓invasion, ↑apoptosis	[47]
	TCLs: MG63, SAOS2, U2OS, SOSP-9607 NCL: hFOB1.19	Up (TCLs vs. NCLs)	_	PHGDH, RRM2	ΔFOXD2-AS1: ↓proliferation, ↓colony formation, ↓S phase cells, ↓migration, ↓invasion	[67]

(*continued on next page*)

Table 1 (*continued*)

Cancer type	Cell lines	Expression level of FOXD2-AS1	Regulators of FOXD2-AS1	Targets/Signaling pathways	Biological functions	Reference
Ovarian cancer	TCLs: SKOV3, A2780, OVCAR3 NCL: IOSE80	Up (TCLs vs. NCLs)	_	miR-4492	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓invasion	[13]
Pancreatic adenocarcinoma	TCL: Capan-2	_	_	miR-30a-3/COX-2	↑FOXD2-AS1: ↑migration, ↑invasion	[66]
Papillary thyroid carcinoma	TCLs: BHP5-16, CGTH-W3, BCPAP, TPC-1 NCL: Nthy-ori3-1	Up (TCLs vs. NCLs)	_	miR-185-5p	ΔFOXD2-AS1: ↓proliferation, ↓colony formation, ↓division cells, ↓invasion, ↑apoptosis (↓Bcl-2, ↑Bax, ↑Bak, ↑cleaved caspase 3, ↑cytochrome c), ↓ cell cycle genes expression (CK2, cyclin D2 and cyclin B1)	[32]
	TCLs: BHP5-16, K1, BHP2-7, BCPAP NCL: Nthy-ori3-1	Up (TCLs vs. NCLs)	_	miR-485-5p/KLK7	ΔFOXD2-AS1: ↓cell viability and proliferation, ↓migration, ↑apoptosis	[71]
Retinoblastoma	TCLs: SO-RB50, Y79, Weri-RB1 NCL: ARPE-19	Up (TCLs vs. NCLs)	_	miR-31/PAX9	↑FOXD2-AS1: ↑proliferation, ↑migration	[36]
Thyroid cancer	TCLs: TT, B-CPAP, BHT101, CAL-62, 8305 C, K1, TPC-1 NCL: PTFE	Up (TCLs vs. NCLs)	_	miR-7-5p/TERT	ΔFOXD2-AS1: ↓spheroids formation, ↓SP cells, ↓CD133 + cells, ↓ABCG2, SOX2, NANOG, and BMI-1 expression, ↓anoikis resistance and ↓cell survival (↑apoptosis, ↓mitochondrial potential, ↑CytoC, ↑caspase-3 and caspase-9 activity)	[38]
Tongue squamous cell carcinoma	TCLs: CAL-27, SCC-9	_	_	NF-kB and ERK/MAPK	ΔFOXD2-AS1: ↓migration, ↓invasion	[76]

models of different cancers (Table 2). For instance, depletion of FOXD2-AS1 expression in UM-UC-3 bladder cancer cells has resulted in the reduction of tumor growth in xenograft models. Furthermore, this intervention has led to down-regulation of CCND1 and Ki-67 in tumors of animals [53]. Besides, experiments in animal models of breast cancer created by subcutaneous administration of MDA-MB-468 cells into axillary lymph node of BALB/c nude mice have shown that FOXD2-AS1 silencing inhibits tumor growth, and leads to up-regulation of phosphorylated YAP and LATS1, demonstrating that suppression of FOXD2-AS1 activates Hippo/yes-associated protein signaling [26]. Another study in xenograft models of breast cancer has shown that FOXD2-AS1 silencing not only decreases tumor volume and weight, but also reduces expression levels of Nanog, Oct4 and SOX2. Moreover, FOXD2-AS1 knockdown could decrease N-cadherin expression, and increase levels of E-cadherin and vimentin [29]. Similarly, FOXD2-As1 silencing in animal models of glioma has resulted in the reduction of tumor growth, enhancement of mice survival, decrease in the activity of Notch pathway and down-regulation of stemness markers [60].

The impact of FOXD2-AS1 on response to chemotherapeutic has also been investigated in animal models of cancer. Experiments in cisplatin-treated model of laryngeal squamous cell carcinoma have shown that up-regulation of FOXD2-As1 increases chemoresistance and tumor growth, while its silencing enhances chemosensitivity, decreases tumor volume and increases survival of animals [34].

4. Studies in human tissues

Expression assays have revealed up-regulation of FOXD2-AS1 in almost all types of malignant tissues. For instance, FOXD2-AS1 has been shown to be over-expressed in bladder cancer tissues in association with tumor stage, recurrence, and poor prognosis [53]. Similarly, in patients with breast cancer, FOXD2-AS1 high levels have been associated with poor prognosis [29]. Moreover, FOXD2-AS1 expression has been associated with expressions of estrogen receptor and Her2, distant and lymphatic metastases, and TNM stage [29]. FOXD2-AS1 has also been found to be significantly upregulated in luminal A and B breast cancer specimens in association with progesterone receptor-positive status and p53 protein level [3].

Up-regulation of FOXD2-AS1 expression in cervical cancer tissue has also been correlated to the unfavorable prognosis of patients [28], FIGO stage, lymph node metastasis and depth of tumor invasion [11].

In melanoma samples, over-expression of FOXD2-AS1 has been noticeably correlated with deep Breslow thickness, present ulceration, high Clark level and distant metastases. Yet, no association has been detected between its levels and disease-free or overall survival of patients in this type of cancer [46]. However, in esophageal squamous cell carcinoma, FOXD2-AS1 expression has been shown to be a predictor of both overall and disease-free survival times [4].

In gastric cancer samples, expression of FOXD2-AS1 has been associated with tumor dimension, invasion deepness, lymphatic metastasis, tumor stage [63] as well as pathological differentiation [67]. Table 3 summarizes the results of studies about expression of FOXD2-AS1 in different cancers.

5. Non-malignant disorders

Among non-malignant conditions, contribution of FOXD2-AS1 to the pathoetiology of osteoarthritis, preeclampsia, rheumatoid arthritis and pterygium has been assessed (Fig. 2). Expression assays have revealed up-regulation of FOXD2-AS1 and CCND1 in osteoarthritis cartilage tissues, parallel with down-regulation of miR-206. Functional studies have shown that FOXD2-AS1 promotes chondrocyte viability. Moreover, suppression of FOXD2-AS1 in chondrocytes has led to G0/G1 arrest and induction of cells apoptosis. From a mechanistical viewpoint, FOXD2-AS1 functions as a sponge for miR-206 to increase expression of CCND1. FOXD2-AS1 inhibition could suppress expression of CCND1 in chondrocytes. Cumulatively, these observations have indicated that FOXD2-AS1 can induce chondrocyte growth through influencing miR-206/CCND1 axis [5]. Another study has shown positive association between FOXD2-AS1 expression and the severity of osteoarthritis. Expression of FOXD2-AS1 has been found to be stimulated by IL-1β and/or TNF-α in chondrocytes. Up-regulation of FOXD2-AS1 in chondrocytes has been associated with induction of cell proliferation, inflammatory responses and extracellular matrix degradation. These effects are mediated through miR-27a-3p/TLR4 axis [59].

Moreover, FOXD2-AS1 has been shown to affect trophoblasts

Table 2
Animal studies on the effects of FOXD2-AS1 carcinogenesis (Δ: knockdown or deletion, GSC: glioma stem cell, DDP: cisplatin, TIC: tumor initiating cells).

Cancer type	Animal model	Results	Reference
Bladder cancer	NOD-SCID female mice	ΔFOXD2-AS1: ↓tumor growth, ↓tumor volume, ↓tumor weight, ↓CCND1 and Ki-67 (proliferation markers)	[53]
	BALB/c nude mice	ΔFOXD2-AS1: ↓tumor growth, ↓tumor volume, ↓tumor weight	[2]
Breast cancer	Male BALB/c nude mice	ΔFOXD2-AS1: ↓tumor size, ↓body weight increasing rate, ↓tumor volume increasing rate, ↑p-YAP and p-LATS1 expression	[26]
	Female BALB/c nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓tumor volume, ↓Nanog, ↓Oct4, ↓SOX2, ↓N-cadherin, ↑E-cadherin and vimentin	[29]
Cervical cancer	Male BALB/c nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓tumor volume ↑FOXD2-AS1→ ↓p21 overexpression effects: ↑proliferation, ↑migration, ↓apoptosis	[28]
	Female BALB/c nude mice	ΔFOXD2-AS1: ↓tumor growth, ↓tumor weight, ↑miR-760, ↓HDGF	[11]
Esophageal squamous cell carcinoma	BALB/c nude mice	In DDP-treated ESCC mice model ΔFOXD2-AS1: ↓tumor growth ↑FOXD2-AS1: ↑tumor weight, ↑tumor volume	[37]
	BALB/c nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓tumor volume	[40]
Gallbladder cancer	BALB/c nude mice	↑FOXD2-AS1: ↑tumor growth, ↑tumor weight, ↑tumor volume, ↑Ki-67, ↑PCNA	[12]
Gastric cancer	Athymic nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓tumor volume, ↓PCNA, ↑EphB3	[63]
Glioma	Nude mice	ΔFOXD2-AS1: ↓tumor growth, ↓tumor weight, ↑survival, ↓Notch signal (↓JAG1,↓PS1, ↓HES1), ↑GSC apoptosis, ↓NOTCH1, ↓stemness markers (↓Nestin, ↓SOX2, ↓CD133), ↑GFAP	[60]
	BALB/c nude mice	In drug-resistant glioma models ΔFOXD2-AS1: ↓tumor weight ↑FOXD2-AS1: ↑ tumor weight	[21]
	SPF BALB/c nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓tumor volume, ↑miR-185-5p	[42]
	Female BALB/c nude mice	ΔFOXD2-AS1: ↓tumor volume, ↓tumor weight, ↓CCND2	[51]
Hepatocellular carcinoma	Nude mice	ΔFOXD2-AS1: ↓tumor growth, ↓Ki-67	[24]
	Female BALB/c nude mice	↑FOXD2-AS1: ↑tumor growth, ↑tumor volume, ↑tumor weight	[6]
	Nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓tumor volume, ↓Ki-67, ↑CDKN1B	[61]
Laryngeal squamous cell carcinoma (LSCC)	BALB/c nude mice	in cisplatin-treated LSCC model ↑FOXD2-AS1: ↑chemo-resistance, ↑tumor growth, ↑cell proliferation, ↓apoptosis ΔFOXD2-AS1: ↑chemo-sensitivity, ↓tumor volume, ↑mice survival	[34]
Nasopharyngeal carcinoma	Male BALB/c nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓Ki-67	[8]
Non-small-cell lung cancer	Male BALB/c nude mice	In DDP-resistant in vivo models ΔFOXD2-AS1: ↓tumor growth, ↓tumor weight, ↑miR185-5p, ↓SIX1	[15]
	BALB/c nude mice	↑FOXD2-AS1: ↑tumor volume, ↑tumor weight, ↑tumor growth	[49]
Oral squamous cell carcinoma	SPF nude mice	ΔFOXD2-AS1: ↓tumor growth, ↓tumor volume, ↓tumor weight	[39]
Osteosarcoma	BALB/c nude mice	↑FOXD2-AS1: ↑tumor growth	[48]
	Nude mice	ΔFOXD2-AS1: ↓tumor growth	[47]
	Female BALB/c nude mice	ΔFOXD2-AS1: ↓tumor growth, ↓tumor volume, ↓lung metastasis	[67]
Papillary thyroid carcinoma	Male BALB/c nude mice	ΔFOXD2-AS1: ↓tumor growth, ↓tumor weight, ↓tumorigenesis, ↓Ki-67 expression	[32]
Thyroid cancer	BALB/c nude mice	ΔFOXD2-AS1: ↓tumor weight, ↓tumor volume, ↑TIC required,↑miR-7-5p, ↓TERT	[38]

viability in vitro through regulation of expression of miR-3127. Knockdown of FOXD2-AS1 has reduced the stimulating effect of miR-3127 inhibition on trophoblasts. Thus, FOXD2-AS1 has been suggested as a therapeutic marker in preeclampsia [76].

FOXD2-AS1 has also been found to promote proliferation and invasion of fibroblast-like synoviocytes through modulation of miR-331–3p/PIAS3 axis in rheumatoid arthritis [73].

Finally, expression of FOXD2-AS1 has been increased in recurrent pterygium samples. Besides, over-expression of FOXD2-AS1 has been related to advanced stages, higher microvessel density and short recurrent-free survival. Based on the results of ROC curve analysis, FOXD2-AS1 has been suggested to predict recurrence of pterygium. Mechanistically, FOXD2-AS1 induces proliferation and inhibits apoptosis through modulation of the miR-205/VEGF axis. Besides, H3K27 acetylation at the FOXD2-AS1 promoter has been found to be responsible for up-regulation of FOXD2-AS1 [14]. Tables 4 and 5 summarize the results of cell line studies and investigations in clinical samples about the role of FOXD2-AS1 in non-malignant disorders, respectively.

6. Discussion

FOXD2-AS1 has been found to be involved in the etiology of a variety of human disorders, including cancers and non-malignant conditions. From a mechanistical viewpoint, FOXD2-AS1 can serve as a molecular sponge for various miRNAs to regulate expression of downstream targets of these miRNAs. miR-143/ABCC3, miR-150–5p/PFN2, miR-760/HDGF, miR-760/E2F3, miR-25–3p/sema4c, miR-1913/SETD1A, miR-

Table 3
Dysregulation of FOXD2-AS1 in clinical samples from cancer patients (ANTs: adjacent normal tissues, TCGA: the cancer genome atlas, GEPIA: gene expression profiling interactive analysis, GEO: gene expression omnibus, OS: overall survival, DFS: disease-free survival, DSS: disease-specific survival, RFS: recurrence-free survival, PFS: progression-free survival, FIGO: international federation of gynecology and obstetrics, TANRIC: the atlas of noncoding RNAs in cancer, NCI REMBRANDT: national cancer institute repository for molecular brain neoplasia data, TMZ: temozolomide, DDP: cisplatin, ER: estrogen receptor, hEGFR2: human epidermal growth factor receptor 2, TNM: tumor-node-metastasis, T stage: tumor stage, PTAs: Pairs of tumor tissues and adjacent non-tumoral samples).

Cancer type	Specimens	Expression (tumor vs. normal)	Kaplan-Meier analysis (impact of high FOXD2-AS1 expression)	Univariate cox regression analysis	Multivariate cox regression analysis	Association of dysregulation of FOXD2-AS1 with clinicopathologic parameters	Reference
Bladder cancer	84 PTAs + TCGA dataset (19 sample pairs)	High	Shorter OS and PFS	_	_	Tumor stage, tumor recurrence	[53]
Breast cancer	60 PTAs	High	_	_	_	_	[43]
	TCGA dataset (1110 tumor samples and 246 normal samples)	High	_	_	_	_	[26]
	34 PTAs	High	Shorter OS	_	_	ER and hEGFR2 expression, distant and lymphatic metastasis, TNM stage	[29]
Luminal breast cancer	71 PTAs	High	_	_	_	P53 protein expression	[3]
Cervical cancer	30 pairs of tumor tissues and normal tissues	High	Shorter survival	_	_	_	[28]
	63 PTAs	High	Shorter OS	_	_	FIGO stage, lymph node metastasis, depth of cervical invasion	[11]
	35 PTAs	High	Shorter OS	_	_	Tumor size, tumor stage	[7]
Cholangiocarcinoma	57 PTAs	High	Shorter OS	TNM stage, lymph node invasion and FOXD2-AS1 expression (prognostic factors for OS)	TNM stage, FOXD2-AS1 expression (independent prognostic factors)	TNM stage, lymph node metastasis	[25]
Colorectal cancer	40 PTAs + GEPIA database	High	_	_	_	_	[65]
	60 PTAs + TCGA dataset	High	Shorter survival rate	_	_	_	[69]
	tumor tissues and ANTs	High	Shorter survival rate	_	_	_	[77]
	45 PTAs	High	_	_	_	_	[64]
Cutaneous melanoma	124 tumor tissues and 40 ANTs + TCGA dataset (460 tumor tissues and 558 normal tissues)	High	_	_	_	Breslow thickness, Ulceration, Clark level, distant metastasis	[46]
Esophageal squamous cell carcinoma	20 PTAs	High	_	_	_	_	[37]
	147 PTAs	High	Shorter OS and DFS	FOXD2-AS1 expression, TNM stage, lymph node metastasis (prognostic factors)	FOXD2-AS1 expression and TNM stage (independent predictors for OS) FOXD2-AS1 expression and lymph node metastasis (independent predictors for DFS)	_	[4]
	10 PTAs	High	There was no correlation with PFS (in 162 samples)	_	_	_	[40]
Gallbladder cancer	PTAs (from GEO database)	High	_	_	_	_	[12]
Gastric cancer (GC)	106 PTAs + GEO database	High (in ~70% GC tissues vs. ANTs)	Shorter DFS	Invasion depth, TNM stage, lymphatic metastasis and FOXD2-AS1 expression (prognostic factors for DFS)	TNM stage and FOXD2-AS1 expression (independent prognostic factors)	Tumor size, invasion depth, lymphatic metastasis, tumor stage	[63]
	109 plasma samples of patients	High	_	_	_	Pathological differentiation, lymph	[67]

(*continued on next page*)

Table 3 (*continued*)

Cancer type	Specimens	Expression (tumor vs. normal)	Kaplan-Meier analysis (impact of high FOXD2-AS1 expression)	Univariate cox regression analysis	Multivariate cox regression analysis	Association of dysregulation of FOXD2-AS1 with clinicopathologic parameters	Reference
	and 106 plasma samples of healthy controls					node metastasis, TNM stage	
	375 tumor tissues and 32 normal tissues (from TCGA)	High	Poor prognosis	_	_	_	[22]
	95 PTAs	High	_	_	_	Lymph node metastasis, Helicobacter pylori infection	[45]
Glioma	26 tumor tissues and 26 normal tissues + TCGA datasets	High	Shorter survival rate	_	_	_	[60]
	21 glioma tissues and 21 normal brain samples	High	_	_	_	Tumor size, tumor stage	[74]
	86 PTAs	High	_	_	_	Tumor diameter, WHO classification, lymph node metastasis, TMZ drug resistance	[21]
	48 tumor tissues and 24 normal controls	High	_	_	_	_	[42]
	30 tumor samples and 7 normal brain tissues + TCGA dataset	High	Shorter OS	_	_	_	[58]
	29 PTAs	High	Shorter OS	_	_	_	[51]
	Tumor tissues and ANTs + TCGA dataset	High	Shorter OS	FOXD2-AS1 expression (prognostic factor)	FOXD2-AS1 expression (independent prognostic factor)	KPS score, WHO grade	[10]
	TCGA, NCI REMBRANDT and GEO data set	High (recurrent tissues vs. non-recurrent tissues)	Shorter OS	_	_	IDH mutation status, MGMT promoter status, neoplasm histologic grade, tumor recurrence	[50]
	TCGA dataset (tumor tissues and ANTs)	High	Shorter OS	FOXD2-AS1 expression	FOXD2-AS1 expression (independent prognostic factor)	grade, T stage, N stage, TNM stage	[57]
	TCGA dataset (tumor tissues and ANTs) + GEO database	High	Shorter survival	_	_	Pathological stage	[68]
Hemangioma	16 proliferative hemangiomas and 14 involuting hemangiomas	High (proliferative hemangiomas vs. involuting hemangiomas)	_	_	_	_	[75]
Hepatocellular carcinoma (HCC)	60 PTAs +60 HCC serum samples and 60 controls	High	_	_	_	_	[24]
	18 PTAs (3 primary HCC, 10 stage I-II, 5 stage III-IV)	High (tumor tissues vs. ANTs and stage III-IV HCC samples vs. stage I-II HCC samples)	_	_	_	_	[9]
	88 PTAs	High	Shorter OS	_	_	_	[31]
	140 PTAs + TCGA dataset (360 tumor samples)	High	Shorter OS	_	_	_	[6]
	105 PTAs+ GEPIA database	High	Shorter OS and DFS	_	_	Tumor number, tumor size	[61]
Laryngeal squamous cell carcinoma (LSCC)	24 PTAs	High (21 out of 24 LSCC samples vs. ANTs)	_	_	_	Clinical stage, relapse status	[34]

(*continued on next page*)

Table 3 (*continued*)

Cancer type	Specimens	Expression (tumor vs. normal)	Kaplan-Meier analysis (impact of high FOXD2-AS1 expression)	Univariate cox regression analysis	Multivariate cox regression analysis	Association of dysregulation of FOXD2-AS1 with clinicopathologic parameters	Reference
Nasopharyngeal carcinoma	50 PTAs	High	Shorter survival rate	_	_	_	[8]
Non-small-cell lung cancer	20 DDP-sensitive tumor samples, 20 DDP-resistant tumor samples	High (DDP-resistant tissues vs. DDP-sensitive samples)	_	_	_	_	[15]
	45 PTAs	High (in 23 out of 45 sample pairs)	Shorter OS	_	FOXD2-AS1 expression, differentiation, advanced stage (independent prognostic factors for OS)	_	[49]
	Exosomal RNA from 26 patients, 26 smokers and 48 controls	High (patients and smokers vs. healthy controls)	_	_	_	_	[62]
Oral squamous cell carcinoma	25 PTAs + TCGA dataset (331 patients)	High	Shorter OS and DSS	Radiation therapy, lymphovascular invasion, perineural invasion and FOXD2-AS1 expression (prognostic factors for OS and DSS)	FOXD2-AS1 expression (independent prognostic factor)	Histologic grade, lymphovascular invasion, anatomic localization, radiation therapy	[39]
	290 tumor samples and 31 normal controls (from TANRIC platform)	High	Shorter OS	_	_	Pathological grade	[35]
Osteosarcoma	PTAs + TCGA dataset	High	Shorter OS	_	_	Clinical stage, metastasis	[48]
	35 PTAs + TCGA dataset	High	Shorter OS	_	_	Clinical stage, tumor size	[47]
	40 PTAs	High (in 32 out of 40 sample pairs)	Shorter survival time	_	_	_	[67]
Ovarian cancer	39 PTAs	High	_	_	_	_	[13]
Pancreatic adenocarcinoma	54 PTAs + TCGA dataset	High	Shorter OS	_	_	_	[66]
Papillary thyroid carcinoma	160 PTAs	High	Shorter OS	TNM stage, lymph node metastasis, FOXD2-AS1 expression (prognostic factors for OS)	FOXD2-AS1 expression (independent prognostic factor)	TNM stage, lymph node metastasis	[32]
	84 PTAs	High	Shorter survival rate	_	_	_	[71]
Retinoblastoma (RB)	38 RB tissue samples, 12 normal samples	High	_	_	_	Lymph node metastasis, IIRC stage	[36]
Stomach adenocarcinoma	6 PTAs + TCGA dataset + GEO dataset	High (based on qRT-PCR and TCGA Low (based on GEO)	No significant association with survival	_	_	_	[33]
Thyroid cancer	59 PTAs + TCGA dataset	High	Shorter RFS	_	_	Age, clinical stage, T and N classification, recurrence status	[38]
Tongue squamous cell carcinoma	41 PTAs +TCGA dataset	High	Shorter OS	_	_	Tumor stage, TNM stage, lymphatic metastasis	[76]

98–5p/CPEB4, miR-185–5p/HMGA2, miR-31/CDK1, miR-185–5p/CCND2, miR-185/AKT1, miR-324–3p/PDRG1, miR-206/MAP3K1, miR-185/AKT, miR-150–5p/TMEM9, miR-206/ANXA2, miR-363–5p/S1001A, miR185–5p/SIX1, miR-30a-3/COX-2, miR-485–5p/KLK7, miR-31/PAX9 and miR-7–5p/TERT are among miRNA/mRNA axes that are modulated by FOXD2-AS1. Besides, FOXD2-AS1 can affect activity of PI3K/AKT, AKT/mTOR, Hippo/YAP, Notch, NRf2, Wnt/β-catenin, NF-ƙB and ERK/MAPK signaling pathways. This lncRNA can enhance stem cell properties in cancer cells and induce EMT. Moreover, it is involved in induction of resistance to a variety of anticancer agents such as adriamycin, cisplatin, 5-fluorouracil, temozolomide and gemcitabine.

This lncRNA has been shown to be over-expressed in a range of tumor tissues compared with non-malignant tissues. The only exception is a single study in stomach cancer that reported up-regulation of FOXD2-AS1 in expression data provided by TCGA database, while its down-regulation based on GEO data [33]. Typically, up-regulation of FOXD2-AS1 has been associated with poor survival of patients with different types of cancers. Moreover, its up-regulation has been correlated with malignant features such as advanced clinical stage, poor differentiation, as well as lymph node and distant metastases.

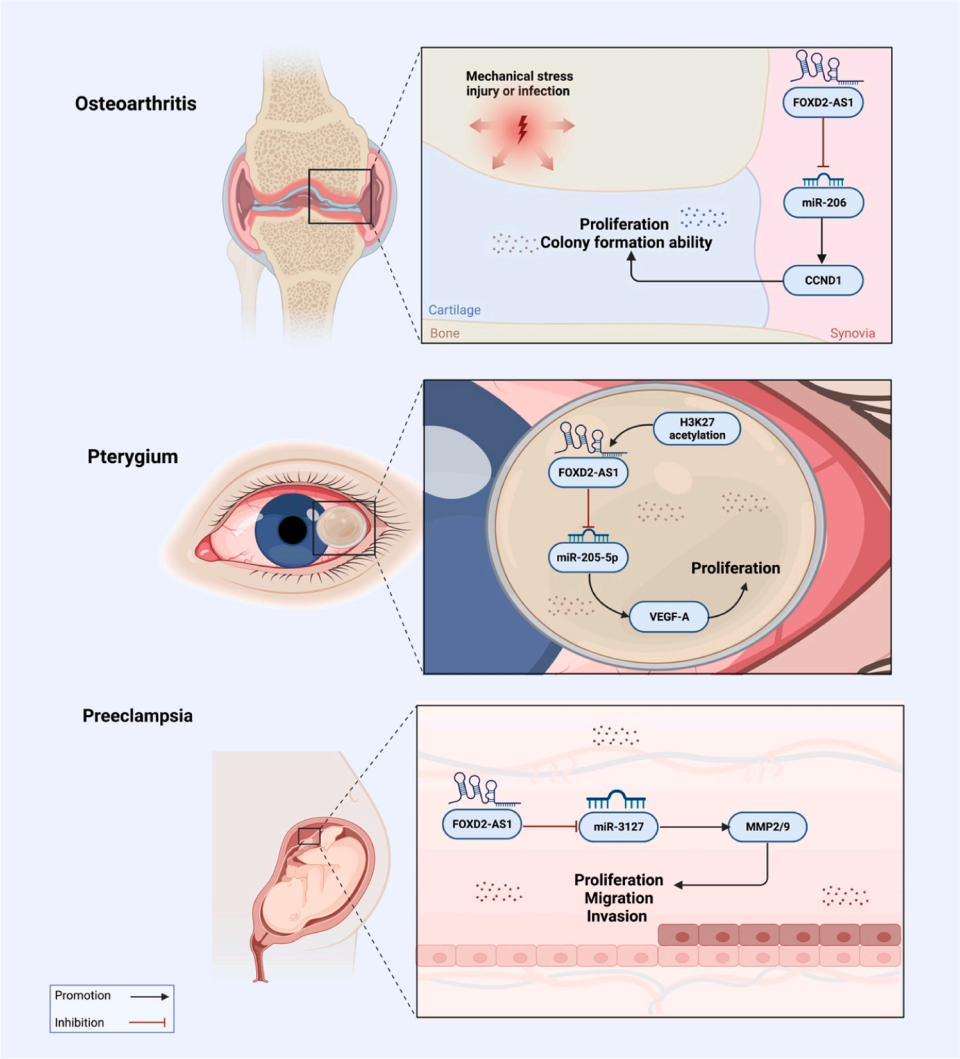

Fig. 2. The role of FOXD2-AS1 lncRNA in the development of osteoarthritis, pterygium, and preeclampsia with its targets and signaling pathways.

Table 4
Cell line experiments on the involvement of FOXD2-AS1 in non-malignant disorders (Δ: knockdown or deletion, ECM: extracellular matrix).

Disorder	Cell line	Expression level of FOXD2-AS1	Interactions	Description	Reference
Osteoarthritis (OA)	C28/12 cells	_	FOXD2-AS1/miR-206/CCND1	ΔFOXD2-AS1: ↓proliferation, ↓colony formation ability, ↑G0/G1 cell cycle arrest, ↑apoptosis	[5]
	C28/12 cells	_	FOXD2-AS1/miR-27a-3p/TLR4	↑ FOXD2-AS1: ↑cell viability, ↑inflammation (↑IL-6 and IL-8), ↑ECM degradation (↓collagen II, ↓aggrecan, ↑MMP-13)	[59]
Preeclampsia (PE)	HTR-8/SVneo cells	_	FOXD2-AS1/miR-3127	ΔFOXD2-AS1: ↓proliferation, ↓migration, ↓invasion (↓MMP-2 and MMP-9) ↑ FOXD2-AS1: ↑proliferation, ↑migration, ↑invasion (↑MMP-2 and MMP-9)	[76]
Rheumatoid arthritis (RA)	FLSs (RA-FLSs and normal FLSs)	High (RA-FLSs vs. FLSs)	FOXD2-AS1/miR-331-3p/PIAS3	ΔFOXD2-AS1(in RA-FLSs): ↓proliferation, ↑G1 phase cells, ↓S phase and G2 phase cells, ↓migration, ↓invasion ↑ FOXD2-AS1(in RA-FLSs): ↑proliferation, ↓G1 phase cells, ↑S phase and G2 phase cells, ↑migration, ↑invasion	[73]
Pterygium	HPF-R (isolated from recurrent tissues)	_	FOXD2-AS1 (activated by H3K27 acetylation)/miR-205-5p/VEGF-A	ΔFOXD2-AS1: ↓proliferation, ↑apoptosis ↑ FOXD2-AS1: ↑proliferation, ↓apoptosis	[14]

Table 5
Analysis of FOXD2-AS1 expression in clinical samples from non-malignant disorders.

Disorder	Samples	Expression level of FOXD2-AS1	Association of expression level of FOXD2-AS1 with clinicopathologic parameters	Reference
Osteoarthritis (OA)	26 OA cartilage tissues and 26 normal cartilage tissues	Up (OA cartilage tissues vs. normal tissues)	_	[5]
	35 OA cartilage tissues and 35 normal cartilage tissues	Up (OA cartilage tissues vs. normal tissues)	_	[59]
Preeclampsia (PE)	plasma samples from 52 patients and 52 controls	Down (patients vs. controls)	_	[76]
Rheumatoid arthritis (RA)	Synovial tissues and blood samples from 43 patients and 21 controls	Up (RA tissue and blood samples vs. normal controls)	_	[73]
Pterygium	126 pairs of pterygium tissues and adjacent conjunctiva tissue samples	Up (pterygium vs. conjunctiva and recurrent patients vs. primary patients)	Advanced stage, Microvessel density	[14]

In addition to different types of cancers, FOXD2-AS1 is involved in the pathoetiology of osteoarthritis, preeclampsia, rheumatoid arthritis and pterygium. Totally, data regarding expression profile and function of FOXD2-AS1 in non-malignant conditions is scarce as compared to cancers.

Moreover, contribution of genetic polymorphisms within FOXD2-AS1 to the pathetiology of human disorders has not been assessed. Theoretically, these polymorphisms can affect function or expression levels of FOXD2-AS1 in different tissues, thus conferring risk of diverse disorders, particularly cancers.

Taken together, FOXD2-AS1 is an oncogenic lncRNA in diverse tissues whose up-regulation contributes to the carcinogenic processes. Future studies are necessary to assess the efficacy of FOXD2-AS1-targtted therapies in the treatment of cancer.

Ethics approval and consent to Participant

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Author statement

SGF wrote the draft and revised it. MT and HP designed and supervised the study. AH and BMH collected the data and designed the figures and tables. All authors approved the submitted version and approved it.

CRediT authorship contribution statement

Hussen Bashdar Mahmud: Data curation, Formal analysis. **Taheri Mohammad:** Writing – original draft, Visualization, Investigation, Funding acquisition. **Pourmoshtagh Hasan:** Writing – original draft, Methodology, Investigation. **Harsij Atefe:** Methodology, Investigation. **Ghafouri-Fard Soudeh:** Writing – original draft, Visualization, Validation.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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