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Oncogenicity of lncRNA FOXD2-AS1 and its molecular mechanisms in human cancers

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ABSTRACT

Objectives: Long non-coding RNAs (lncRNAs) are a group of noncoding RNAs with length larger than 200 nucleotides. LncRNAs have limited or no protein-coding capacity because of lack of obvious open reading frame. An increasing number of researches have shown that lncRNAs participate in the complex regulation network of cancer and play an important role in tumourigenesis and progression such as proliferation, migration and invasion. LncRNA FOXD2 adjacent opposite strand RNA 1 (FOXD2-AS1), located on chromosome 1p33 and with a transcript length of 2527 nucleotides, is a novel cancer-related lncRNA. FOXD2-AS1 was recently found to exhibit aberrant expression in various malignancies, including gastric, lung, bladder, colorectal, nasopharyngeal, esophageal, hepatocellular, thyroid and skin cancer, and its deregulation might be related to survival and prognosis of cancer patients. Pertinent to clinical practice, FOXD2-AS1 might act as a feasible biomarker or therapeutic target in human cancers. In this paper, we made a summary on the current findings concerning the biological functions and molecular mechanisms of FOXD2-AS1 in tumor progression.
Materials and methods: In this paper, we summarized and figured out recent studies about the expression and molecular biological mechanisms of FOXD2-AS1 in tumor progression. Existing relevant studies were obtained through a systematic search from PubMed, Embase, BioMedNet, GEO database and Cochrane Library.
Results: FOXD2-AS1 was a valuable tumor-associated lncRNA. Its expression level was up-regulation in various malignancies, including gastric, lung, bladder, colorectal, nasopharyngeal, esophageal, hepatocellular, thyroid and skin cancer. In addition, the aberrant expressions of FOXD2-AS1 have shown to contribute to proliferation, migration and invasion of cancer cells, and its deregulation is related to carcinogensis, overall survival, disease free survival, prognosis and tumor progression.
Conclusions: LncRNA FOXD2-AS1 is an oncogene and probably represents a feasible biomarker or therapeutic target in human cancers.

1. Introduction

Cancer is the leading cause death worldwide, which is a group of malignancy diseases with hundreds of types. This serious disease, threatening human health, consuming economic budgets and occupying medical resources, has a large amount of susceptible population worldwide [1–3]. It is estimated that 90.5 million people were diagnosed with cancer in 2015. There is 14.1 million new cases per year and 15.7% of all human deaths are caused by cancer [4]. In recent years, even though surgical techniques, targeted drugs, and radiochemotherapy have a great development, cancer patients tend to have advanced diagnosis and poor prognosis due to the lack of early and

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Abbreviations: BC, bladder cancer; CDC42, cell division control 42; ceRNA, competing endogenous RNA; CRC, colorectal cancer; EC, esophageal cancer; EA, esophageal adenocarcinoma; E2F1, Adenovirus E2 factor 1; EMT, epithelial-mesenchymal transition; EphB3, ephrin type-B receptor 3; ESCC, esophageal squamous cell carcinoma; EZH2, enhaner of zeste homolog 2; GC, gastric cancer; GEO, gene expression omnibus; HCC, hepatocellular carcinoma; KLK7, Kallikrein-related peptidase 7; LC, lung cancer; lncRNA, long non-coding RNAs; LSD1, lysine specific demethylase 1; miRNAs, microRNAs; MTT, mission trial test; NcRNAs, noncoding RNAs; NPC, nasopharyngeal carcinoma; NSCLCs, non-small cell lung cancers; OS, overall survival; PTC, papillary thyroid carcinoma; rRNA, ribosomal RNA; SCLCs, small cell lung cancers; snoRNA, small nucleolar RNAs; snRNA, small nuclear RNA; TC, thyroid cancer; TCF1, T cell factor-1; tRNA, transfer RNA; TRIB3, Tribbles pseudokinase 3

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efficient biomarkers [5]. Therefore, to control cancer better, identification of these potential efficient biomarkers is necessary for early diagnosis and favourable prognosis.

According to the genome-wide studies, only about 2% of the human genome is transcribed into protein-coding RNAs, and approximately 98% consists of noncoding RNAs (NcRNAs) [6]. NcRNAs were often considered as ‘noises’ during transcriptional and post-transcriptional regulatory levels in the past [7,8]. However, ncRNAs play an important role in many of the vital and highly conversed protein-coding feedback functions. NcRNAs can be classified into long non-coding RNA (long ncRNA, lncRNA), transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNA (snoRNA), small nuclear RNA (snRNA) and microRNA (miRNA) and others [9–12]. Among them, lncRNAs have already been the focus of research in recent years. The main difference between lncRNAs and other members of non-coding RNAs family is that lncRNAs are greater than 200 nucleotides in length and are a key regulator in the process of cell transcription, while others are not [13]. LncRNAs, which are mainly transcribed by RNA polymerase II and lack an obvious open reading frame, are usually divided into five categories including sense, antisense, bidirection, intron and intergenic region [14,15]. Characteristically, lncRNAs have the following features, including (1) with or without very low protein-coding potential; (2) the length of transcript is between 200 and 100,000nts; (3) low conservation; (4) tissue-specific (the amount of lncRNAs expressed in different tissues is different) and spatiotemporal-specific (the expression of lncRNAs is different in the same tissues but different status) [16–18]. Functionally, lncRNAs are involved in regulation of many cellular processes, including gene imprinting, histone modification, nuclear transport, chromatin remodeling, transcriptional activation, transcriptional interference, and cell cycle regulation [19–23]. Now, an increasing number of studies have demonstrated that the abnormal expression of many lncRNAs was found in unclear pathogenesis and refractory tumors [24]. Dysregulation of LncRNAs generally contributes to tumor-pertinent cellular processes such as cell promotion, proliferation, invasion and metastasis by controlling gene expression in multiple levels including working as miRNA sponges, protein scaffolds, regulatory signals or transcript decoys [25,26]. Related to clinical practice, lncRNAs are emerging as new biomarkers and therapeutic targets for cancer diagnosis/prognostication due to high tissue specificity and elevated efficiency [27–29].

Long noncoding RNA FOXD2 adjacent opposite strand RNA1 (lncRNA FOXD2-AS1), which is a 2527-bp lncRNA located on chromosome 1p33, is a promising candidate among all tumor-related lncRNAs. FOXD2-AS1 expression is upregulated in various human malignancies, including gastric, lung, bladder, colorectal, nasopharyngeal, esophageal, hepatocellular, thyroid and skin cancer. (Tables 1 and 2). In this review, we summarized current evidences concerning the abnormal expression, functions and regulation mechanisms of lncRNA FODX2-AS1 and discussed its potential clinical value as a prognostic biomarker and therapeutic target.

2. LncRNA FOXD2-AS1 dysregulation and potential clinical value in cancers

2.1. Gastric cancer

Gastric cancer (GC), which is ranked as one of the most common cancer, is the second leading cause of cancer-related death worldwide [30]. Nearly 1 million people are diagnosed with GC worldwide each year, 700,000 of them are from developing countries and more than 500,000 from East Asia, mainly Japan and China. Although surgery and systemic chemotherapy have advanced considerably, the overall prognosis of GC remains poor with only 1/5 of patients surviving for 5 years or more after diagnosis, indicating that lack of biomarkers with high specificity and sensibility [31]. Consequently, it is urgent to find novel GC molecular markers and therapeutic targets for improving patient outcomes. One research from Xu et al. [32] revealed that lncRNA FOXD2-AS1 overexpression could be observed in GC tissues comparing to normal gastric tissues in microarray datasets from gene expression omnibus (GEO) and closely correlated with a large tumor size, later pathologic stage, and poor prognosis. Moreover, further comprehensive analysis through loss-and-gain-of-function experiments both in vitro and in vivo identified that knockdown of FOXD2-AS1 induced G1 phase arrest and S phase reduction, leading to a significant decrease in tumorigenicity, whereas FOXD2-AS1 overexpression promoted cell cycle progression and accelerated cell proliferation. Taken together, FOXD2-AS1 may serve as a crucial tumor-promoting gene in GC and may be a novel biomarker and therapeutic target for diagnosis and prognosis.

2.2. Non-small cell lung cancer

Lung cancer (LC), including small cell lung cancers (SCLCs) and non-small cell lung cancers (NSCLCs) in pathological classification, is the leading cause of cancer-related mortality worldwide. The 5-years survival rate is less than 11%, and approximately 1.4 million people are diagnosed with LC each year [33,34]. NSCLCs, which account for about 80%–85% of all LC cases, are the predominant form of LC [35]. Despite recent advance in treatment such as chemotherapy, prognosis of LC is still poor due to early metastasis. Thus, reliable biomarkers and therapeutic targets for LC would facilitate early detection and improve the survival of patients. Rong et al. [36] found through microarray data that lncRNA FOXD2-AS1 was significantly up-regulated in NSCLC tumor tissues compared with that in paired adjacent normal tissues. In addition, increased lncRNA FOXD2-AS1 was markedly correlated with

Table 1
Functional characterization of lncRNA FOXD2-AS1 in various cancers.

Cancer types	Expression	Functions	Related genes	Role	Refs.
Gastric cancer	Upregulated	proliferation	EZH2, LSD1, EphB3	Oncogene	32
Non-small cell lung cancer	Upregulated	proliferation	β-catenin, TCF1, Wnt/β-catenin	Oncogene	36
Bladder cancer	Upregulated	proliferation, migration, invasion	MDR1, MRP2, LRP1, ABCC3, miR-143, Akt, E2F1, TRIB3	Oncogene	39,40
Nasopharyngeal carcinoma	Upregulated	proliferation	miR-363-5p, S100A1	Oncogene	43
Colorectal cancer	Upregulated	proliferation, migration, invasion	EMT, Notch, E-cadherin, Hes-1, N-cadherin, Snail, NICD, miR-185-5p, CDC42	Oncogene	49,50
Esophageal cancer	Upregulated	–	–	Oncogene	54
Hepatocellular carcinoma	Upregulated	migration	ANXA2	Oncogene	56,58
Thyroid cancer	Upregulated	Proliferation, migration	miR-485-5p, KLK7	Oncogene	60,61
Cutaneous melanoma	Upregulated	proliferation, migration, invasion	Akt	Oncogene	63

ABCC3: ATP-binding cassette, subfamily C3; ANXA2: annexin A2; CDC42: cell division control 42; E-cadherin: epithelial-cadherin; E2F1: Adenovirus E2 factor 1; EMT: epithelial-mesenchymal transition; EphB3: ephrin type-B receptor 3; EZH2: enhaner of zeste homolog 2; Hes^{-1}: hairy and enhancer of split-1; KLK7: Kallikrein-related peptidase 7; LRP1: low density lipoprotein receptor-related protein 1; LSD1: lysine specific demethylase 1; MDR1: multi-drug resistance gene; MRP2: multidrug resistance-associated protein 2; N-cadherin: neural-cadherin; NICD: Notch1 intracellular domain; S100A1: S100 calcium-binding protein A1; TCF1: T cell factor-1; TRIB3: Tribbles pseudokinase 3.

Table 2
Clinical significance of lncRNA FOXD2-AS1 in diverse cancers.

Cancer types	Overexpression of lncRNA FOXD2-AS1	Refs
Gastric cancer	larger tumour size, later pathologic stage and poor prognosis	[32]
Non-small cell lung cancer	poor prognosis	[36]
Bladder cancer	later tumor stage, recurrence and poor prognosis	[39,40]
Nasopharyngeal carcinoma	shorter survival and poor prognosis	[43]
Colorectal cancer	shorter overall survival	[49,50]
Esophageal cancer	poor prognosis, shorter overall survival and disease free survival	[54]
Hepatocellular carcinoma	shorter overall survival	[56,58]
Thyroid cancer	poor prognosis, shorter overall survival	[60,61]
Cutaneous melanoma	deep Breslow thickness, present ulceration, high Clark level, distant metastasis	[63]

lower overall survival (OS) and was independent predictors of OS in NSCLC patients. Functionally, knocking down lncRNA FOXD2-AS1 inhibited the NSCLC cells growth and induced apoptosis of NSCLC cells. Taken together, lncRNA FOXD2-AS1 acts as an carcinogenic lncRNA, suggesting its potential clinical value as a novel therapeutic target for NSCLC treatment.

2.3. Bladder cancer

Bladder cancer (BC), accounting for the ninth most frequent malignancy worldwide, lead to approximately 52,395 cancer deaths each year [30]. Although the treatments for BC have greatly developed with the progress of medical technology, the recurrence and mortality rate of BC patients are still pessimistic in both developing and developed countries [37,38]. Therefore, molecular mechanism of BC should be concerned to identify new therapeutic targets for BC patients. An et al. [39], utilizing RT-PCR assay, demonstrated that lncRNA FOXD2-AS1 expression was significantly upregulated in gemcitabine-resistant bladder cancer cells. Subsequently, loss-of-function experiments showed that FOXD2-AS1 knockdown inhibited the gemcitabine resistance of bladder cancer cells by inhibiting the expression levels of drug resistance genes. Furthermore, transwell invasion assay results revealed that FOXD2-AS1 knockdown suppressed BC cells invasion and tumor growth compared with negative control group. Similarly, Su et al. [40] demonstrated that FOXD2-AS1 was significantly upregulated in BC tissues according to analysis of 19 pairs of cancer and adjacent noncancerous samples. Thus, these results revealed that FOXD2-AS1 might provide a novel therapeutic target for BC.

2.4. Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC), one of the most general malignant head and neck neoplasms, occurs in the epithelial lining of the nasopharynx [41,42]. Although chemotherapy combined with radiotherapy can prolong the survival period of NPC patients, the detailed mechanisms of NPC tumorigenesis are still unclear. Hence, in order to discover effective diagnostic markers and targets, a deeper understanding of the molecular mechanisms about development and progression of NPC is required. Chen et al. [43] found that FOXD2-AS1 was not only upregulated in NPC patients but significantly associated with worse survival rate. Further evaluation confirmed that knockdown of FOXD2-AS1 repressed NPC cells proliferation in vitro and tumor growth in vivo [43]. Therefore, these results and findings facilitate the development of lncRNA-directed diagnostics and therapeutics against this disease. However, these results need to be supported by further and larger sample studies.

2.5. Colorectal cancer

Colorectal cancer (CRC), which is the third most common cancer and the fourth leading cause of cancer-related deaths worldwide, affects greater than 1.2 million people annually. Approximately 1/5 of patients presen ts with metastases before diagnosis [44,45]. CRC patients typically exhibit a survival rate less than 5 years due to early metastasis [46,47]. In spite of the treatment methods (such as surgery, radiation therapy, chemotherapy and targeted therapy) have advanced, the high recurrence and unfavourable prognosis remain the disturbing problems [48]. Consequently, it is vital to research the molecular mechanisms of CRC occurrence and development for exploring new therapeutic targets for CRC patients. A recent study showed that FOXD2-AS1 was a promising factor compared with other lncRNA candidates [49]. Afterwards, 45 CRC patients were selected and real-time reverse transcription-polymerase chain reaction (qRT-PCR) was performed to explore the transcriptional difference between paired tumor and adjacent normal tissues, showing that FOXD2-AS1 expression in CRC was upregulated. Further experiments in vitro assay in CRC cell lines displayed that FOXD2-AS1 was an aggressive role in proliferation, migration and invasion. In addition, Zhu et al. [50] also reported that expression of FOXD2-AS1 was increased. Upregulation of FOXD2-AS1 promoted proliferation, migration, and invasion in colon cancer cells. A 12-year follow-up study reported that High expression level of FOXD2-AS1 in CRC was closely associated with the shorter OS rate. Consequently, FOXD2-AS1 could effectively promote cell carcinogenesis, proliferation, invasion and metastases and be used as a potential biomarker for the diagnosis and therapy of CRC.

2.6. Esophageal cancer

Esophageal cancer (EC), which is more than 480,000 new cases and 400,000 deaths annually, is the sixth main cause of cancer deaths worldwide with a 5-year OS rate less than 10% [51,52]. EC can be devided into two major histological subtypes including esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EA), the former is the main histological type of EC in China with close relation to smoking and drinking. Although chemotherapy, radiotherapy and surgery have been proposed for the treatment of ESCC, prognosis of most cases is still unsatisfactory [53]. Therefore, searching ideal biomarkers and therapeutic targetsfor EC is urgent. Bao et al. [54] confirmed that expression of FOXD2-AS1 was significantly overexpressed in 147 ESCC tissues compared with their normal counterparts. Furthermore, Kaplan–Meier analysis uncovered that ESCC patients with high FOXD2-AS1 expression had a shorter OS and disease free survival. Hence, FOXD2-AS1, may provide a golden opportunity for anticancer therapy and serve as a predictive marker for ESCC patients' survival rate. However, further investigations are needed to clarify the underlying molecular mechanisms of this novel lncRNA in ESCC.

2.7. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC), has approximately 750,000 new cases worldwide each year, which causes approximately 600,000 deaths and ranks the second for long time. Hepatitis virus infection, alcoholic hepatic cirrhosis, aspergillus infection, parasitization and medication abuse are the major etiological factors of HCC [55,56].

Despite surgical advances, only 10%–20% of tumors can be surgically removed due to frequent intrahepatic and extrahepatic metastases [57]. Therefore, identifying novel biomarkers and therapeutic targets for early diagnosis and prognosis evaluation will contribute to reduce the mortality of HCC patients [56]. Chang et al. [58] found that FOXD2-AS1 was overexpressed in HCC tissues and overexpression of FOXD2-AS1 was markedly correlated with lower OS. MTT, wound healing and cell migration assays revealed that FOXD2-AS1 overexpression enhanced the metastasis of HCC cells both in vitro and vivo, suggesting that FOXD2-AS1 was concluded to function as an oncogene in HCC.

2.8. *Thyroid cancer*

Thyroid cancer (TC) is the most common type of malignancy in endocrine, which can be classified into four subtypes: papillary thyroid carcinoma (PTC), anaplastic thyroid carcinoma, follicular carcinoma, and medullary thyroid carcinoma [59]. Although early diagnosis and treatment with TC have improved, the prognosis of TC patients is unsatisfied. Thus, it is urgent to find more novel therapeutic targets for TC [60]. Zhang et al. [61] found that FOXD2-AS1 was high expression in PTC and associated with poor prognosis. Furthermore, FOXD2-AS1 accelerated the PTC proliferation, apoptosis, and migration through regulating the miR-485-5p/KLK7 (Kallikrein-related peptidase 7) axis. Similarly, Lu et al. [60] also found that FOXD2-AS1 was upregulation in TC and significantly associated with TC patients overall or recurrence-free survival time.

2.9. *Cutaneous melanoma*

Cutaneous melanoma is one of the most aggressive skin and mucosa cancers and a considerable threat to human health. Although treatments for melanoma has progressed tremendously in the past decade, the melanoma patients generally have low survival rate [62]. Ren et al. [63] confirmed that expression level of FOXD2-AS1 was upregulated in cutaneous melanoma tissue specimens and cell lines. FOXD2-AS1 promoted cutaneous melanoma cell proliferation, migration and invasion. Furthermore, high expression of FOXD2-AS1 was obviously correlated with the malignant status of the cutaneous melanoma patient. These results indicated that FOXD2-AS1 may be a novel therapeutic target for cutaneous melanoma.

3. Regulatory mechanism of lncRNA FOXD2-AS1

LncRNA FOXD2-AS1 is located on chromosome 1p33 with a transcript length of 2527 nucleotides. The following studies shown that overexpression of FOXD2-AS1 had a leading role in malignancies and exhibited its oncogenic activity by multiple mechanisms inducing cancer cells proliferation, migration and invasion (Fig. 1). The epithelial-mesenchymal transition (EMT) is one crucial malignant mechanism tumorigenesis and progression [64]. Yang et al. [49] demonstrated that knockdown of FOXD2-AS1 decreased expression of N-cadherin and Snail protein and increased expression of the epithelial marker E-cadherin protein in CRC cells via western blot analysis of the phenotypic markers. Besides EMT method, the Notch signaling pathway was inactivated in the CRC cells after FOXD2-AS1 silencing, in which the Notch pathway marker protein Hes^{-1} and NICD overexpression driven by FOXD2-AS1 were demonstrated. These results revealed that FOXD2-AS1 might promote the proliferation, migration and invasion of CRC cells via the EMT and Notch signaling pathway.

The competing endogenous RNA (ceRNA) manner is a major mechanism of lncRNA FOXD2-AS1 in cancer development. LncRNA FOXD2-AS1 can serve as sponge for miRNAs and abolish miRNAs endogenous suppressive effect on key targets. Zhu et al. [50] reported that the cell division control 42 (CDC42), a key protein of cancer cell metastasis, was enriched in CRC cells by FOXD2-AS1 binding miR-185-5p, suggesting that the FOXD2-AS1/miR-185-5p/CDC42 axis participated in CRC progression. Similarly, Chen et al. [43] found that lncRNA FOXD2-AS1 functioned as a ceRNA for miR-363-5p to modulate expression of S100A1 (a calcium-binding protein belonging to the family of S100 proteins and high expression in several cancers), suggesting that a lncRNA FOXD2-AS1/miR-363-5p/S100A1 axiswas involved in NPC progression. Similarly, LncRNA FOXD2-AS1 acted as a molecular sponge of miR-485-5p to regulate KLK7 expression, indicating that FOXD2-AS1/miR-485-5p/KLK7 axis regulated PTC progression [61].

Furthermore, FOXD2-AS1 could bind with lysine (K)-specific demethylase 1 A (LSD1) and enhancer of zeste homolog 2 (EZH2) to regulate downstream target genes and modulate tumorigenesis and progression. Xu et al. [32] discovered that FOXD2-AS1 could recruit LSD1 and EZH2 to the EphB3 promoter and target both H3K4 demethylation and H3K27 methylation, thereby, inhibition transcription of target gene. The results indicated that FOXD2-AS1 promoted GC cells proliferation by silence EphB3 transcription by binding with LSD1 and EZH2. Moreover, lncRNA FOXD2-AS1 could also activate Wnt/β-catenin signalling pathway, which wasactivation pathway in various tumors and also played vital role in modulating cancer cells growth. Rong et al. [36] revealed, by western blot, that overexpression of FOXD2-AS1 in NSCLC cells induced expression of β-catenin and T cell factor-1 (TCF1), which were the key adaptors of Wnt/β-catenin signaling, and then promoted NSCLC cells growth. Su et al. [40] discovered that FOXD2-AS1 activated the TRIB3/Akt signaling pathway, which then promoted expression of Adenovirus E2 factor 1 (E2F1). Subsequently, E2F1 could bind to the FOXD2-AS1 promoter region and enhance its transcriptional activity, indicating that FOXD2-AS1/Akt/E2F1 formed a feedback loop. Futhermore, FOXD2-AS1 promoted cutaneous melanoma cell proliferation, migration and invasion through inhibition of phosphor-Akt expression [63].

4. Conclusion and perspective

LncRNA FOXD2-AS1 is a well-characterized cancer-related lncRNA involved in alteration of multiple cellular functions such as proliferation, migration and invasion.The dysregulation of FOXD2-AS1 has close relation with various human cancers including gastric, lung, bladder, nasopharyngeal, colorectal, esophageal, hepatocellular, thyroid and skin cancers. The regulatory mechanisms of FOXD2-AS1 were extremely complicated and extensive including activation EZH2 and LSD1; activating NOTCH, TRIB3/Akt and Wnt/β-catenin signalling pathways; inhibition of downstream gene expression by competitively binding miRNAs; and induction of the EMT (Fig. 1). However, the precise molecular mechanisms upstream and downstream of FOXD2-AS1 remain to be systematically investigated and confirmed. In terms of clinical application, overexpressed FOXD2-AS1 generally served as an undesirable factor linked to malignant clinicopathological characteristics and shorter OS, suggesting that it might function as a potential tumor biomarker for diagnosis and prognosis. Nevertheless, the expression level of FOXD2-AS1 in body fluids or serum have not been clearly validated. Molecular targeted therapy is extraordinarily promising because of its stronger tumor specificity and lower systemic toxicity. In short, as a viable drug target, the researches on FOXD2-AS1 are just getting started, further specific functions and mechanisms of FOXD2-AS1 should be deeply explored for ultimate clinical application.

Conflict of interest

All the authors declare that they have no conflicts of interest.

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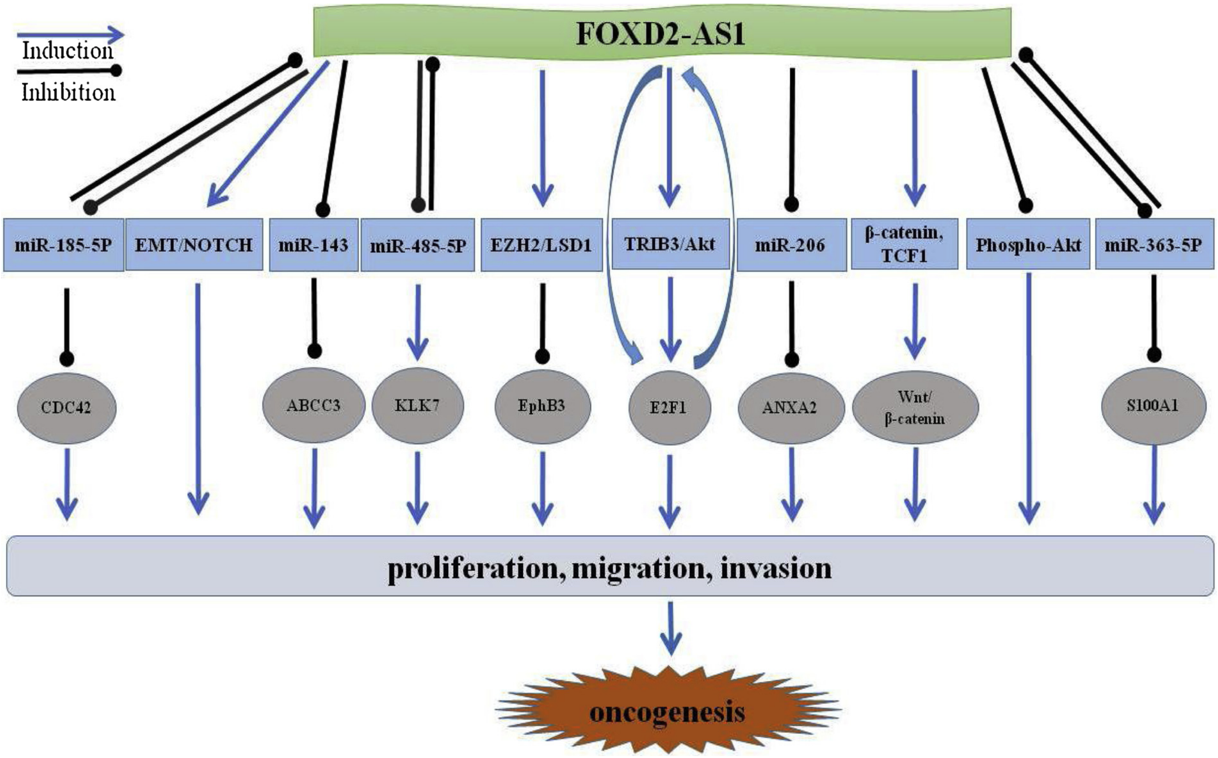

Fig. 1. FOXD2-AS1 mediates mechanisms involved in cancer progression.

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