Journal of Cancer Research and Clinical Oncology (2025) 151:14
https://doi.org/10.1007/s00432-024-06047-z

REVIEW

# Role of the Forkhead box family protein *FOXF2* in the progression of solid tumor: systematic review

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Received: 8 April 2024 / Accepted: 22 November 2024


## Abstract

**Background** *FOXF2* was reported to involve in a variety of biological behaviors that include the development of the central nervous system, tissue homeostasis, epithelia-mesenchymal interactions, regulation of embryonic development, and organogenesis.

**Purpose** Understanding how *FOXF2* influences the growth and development of cancer could provide valuable insights for researchers to develop novel therapeutic strategies.

**Results** In this review, we investigate the underlying impact of *FOXF2* on tumor cells, including the transformation of cellular phenotype, capacity for migration, invasion, and proliferation, colonization of circulating cells, and formation of metastatic nodules. In addition, we discuss the molecular mechanisms of *FOXF2* in different cancers, including hepatocellular, esophageal, breast, colon, lung, prostate gland, as well as its role in embryonic development.

**Conclusion** *FOXF2* is a gene encoding a forkhead transcription factor belonging to the Forkhead Box family. The protein functions by recruiting activation transcription factors and basic components to activate the transcription of genes that interact with the complex. This review provides an in-depth analysis of the *FOXF2*'s function and pleiotropic roles in cancer development and progression.

**Keywords** FOX2 · Cancer · Signal pathway · Cancer development · Cancer progression

## Introduction

The Forkhead protein was first discovered in fruit fly (*Drosophila melanogaster*) more than two decades ago, marking the inception of the FOX protein family (Weigel et al. 1989). Subsequently, researchers identified similar proteins, leading to the formation of various subfamilies within the FOX protein family, including FOXA, FOXB, FOXC, FOXD, FOXE, and FOXF (Baumler and Hantke 1992; Nelson et al. 1992; Zaffran, Kuchler, Lee, et al., 2001). Forkhead box ((Forkhead Box F2, FOX) proteins comprise a superfamily of transcription regulators that are characterized by existing an evolutionarily conserved "fork head" or "wing helix" DNA-binding domain (Aitola et al. 2000; Blixt et al. 1998; Dou et al. 2017). Strikingly, more than 50 FOX proteins of 19 FOX gene subfamilies have been identified, ranging from lower organisms (*Caenorhabditis elegans*) to humans (Jackson, Carpenter, Nebert, et al., 2010; Raharjo et al. 2010). FOX family proteins have been found to regulate a number of biological functions that include embryonic development, cell differentiation, metabolism, proliferation, apoptosis, migration, invasion and longevity (Barr 2001; Cao et al. 2023; Jin et al. 2020).

*FOXF2* is a transcription factor that plays a key role in maintaining cell homeostasis and tumorigenesis (Lu et al. 2020). It is indicated that, *FOXF2* is primarily expressed in the fibroblasts within the lamina propria of the small intestine. Loss of *FOXF2* promotes adenomas formation by

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Published online: 26 December 2024

activating Wnt signaling (Nik, Reyahi, Ponten, et al., 2013). Similarly, *FOXF2* is predominantly expressed in the stromal cells of the transition zone in the prostate, and deficiency of *FOXF2* may contribute to the development and progression of prostate cancer through epithelial-mesenchymal transition (van der Heul-Nieuwenhuijsen et al. 2009). In addition, *FOXF2* is mainly expressed in pulmonary stromal cells and is involved in regulating extracellular matrix synthesis. In normal expression, it can inhibit the activity of matrix metalloproteinases and suppress epithelial-mesenchymal transition, thereby inhibiting the occurrence and progression of lung cancer (Seok et al. 2017). Besides, in the breast, *FOXF2* is predominantly expressed in basal-like cells. Decreased expression of *FOXF2* would promote epithelial-mesenchymal transition for basal-like cells and accelerate tumor formation and metastasis (Wang et al. 2015). Furthermore, *FOXF2* is highly expressed in the nucleus of stomach and functions as a tumor suppressor gene by inhibiting the Wnt singaling pathway (Higashimori et al. 2018). Details on the expression of *FOXF2* in various organs can be found in Supplementary Fig. 1.

Cancer immunotherapy is a strategy designed to exploit the patient's own immune system to recognize and eradicate cancer cells, but in some patients, the therapeutic effect is limited, underscoring the need for identifying novel therapeutic targets to enhance clinical outcomes. *FOXF2* is involved in regulating the activity of immune cells by regulating the expression of multiple immune-related genes (Kundu et al. 2022). Studies have found that *FOXF2* plays a positive role in anti-tumor immunity, and its expression level is closely correlated to the immune status of patients (Jia et al. 2022). The normal expression of *FOXF2* helps to stimulate the anti-tumor immune response by improving the ability of immune cells to recognize and attack cancer cells. In addition, *FOXF2* can also modulate the tumor microenvironment, inhibiting the production of tumor-related immunosuppressive factors, and reducing tumor immune evasion. Studies have revealed that *FOXF2* reduces tumor immune escape by regulating the infiltration and activity of immune cells, thereby improving the efficacy of cancer immunotherapy (Jia et al. 2022; Kundu et al. 2022; Leick, Obeid, Bekiranov, et al., 2019).

The human *FOXF2* gene encodes the human FOXF2 proteins, which is a member of the FOX superfamily. It has two independent activation domains, located in the C-terminal and the center part of the protein (He et al. 2020). Recently, *FOXF2* has been implicated as an important regulator for tumorigenesis and progression in various human cancers (He et al. 2020). In this review, we will focus on the elucidation of *FOXF2* function in the regulation of tumorigenesis and development.

## Biology of the *FOXF2* gene

### Bioinformatic analysis of the *FOXF2* gene

Over the years, several groups have explored the function and mechanisms of *FOXF2* in the gene regulatory network through bioinformatics analysis. For instance, Pierre et al. investigate gene expression across various species, including chickens, mice, rabbits, and humans, through Lawrence Livermore Institute Laboratory website (www.llnl.gov). It is found that, *FOXF2* is a highly conserved gene throughout biological evolution and plays an important regulatory role in the KATP channel and energy metabolism (Philip-Couderc et al. 2008). Consequently, Seselgyte et al. conducted whole-exome sequencing for familial ptyaloid hypoplasia and found that a missense mutation (p.Q433P) in the activation domain of the *FOXF2* gene may be the cause (Seselgyte et al. 2019). Through UALCAN and JASPAR data analysis, Fang et al. found that FOXF2-LOXL1 axis might be a crucial regulator for the development and progression of thyroid cancer(Fang et al. 2024). Similarly, based on bioinformatic analysis on TCGA database, Wang et al. revealed that *FOXF2* is a significant regulator for colorectal cancer progression(Wang et al. 2019). Toghther, these sudies reveal that *FOXF2* can interact with various upstream and downstream genes, playing a key role in regulating gene expression and organ function.

### General role of the *FOXF2* gene in organ development

*FOXF2* is highly expressed in the lungs (fetal and adult) and placenta, but has low expression in the prostate, colon, small intestine, and fetal brain. In the course of development, *FOXF2* is mainly expressed in endodermal- and ectodermal-derived mesenchyme organs (Aitola et al. 2000; Wu et al. 2021). These two specified tissues give rise to systems including the gastro-intestinal respiratory and urogenital system, as well as structures like the tooth, eye, ear, limbs and backbone. In addition, *FOXF2* is expressed in the developing central nervous system primarily originated from neuroectoderm. While *FOXF2* is more uniformly expressed in the mesenchyme, FOXF1 exhibits higher expression beneath the epithelium and mesothelium (Xu et al. 2016). *FOXF2* play a key role in the process of organogenesis, including palatogenesis and tongue morphology (J. Xu, Liu, Lan, et al., 2022). Loss of *FOXF2* is significantly associated with congenital malformations of various organs, such as megacolon, colorectal muscle hypoplasia and aganglionitis (Ormestad et al. 2006). It is reported that, *FOXF2* would regulate the process of epithelial proliferation and apoptosis resistance through β-catenin and the Wnt pathway

(Lu et al. 2022). Furthermore, *FOXF2* can be expressed in the pericytes of the central nervous system, and inactivation of which would lead to the destruction of the blood-brain barrier (Ben-Zvi and Liebner 2022).

## General role of the *FOXF2* gene in cancer progression

*FOXF2* has been implicated to be a key factor for tumorigenesis and cancer progression. Multiple studies have confirmed the relationship between the *FOXF2* gene and various malignancies, such as hepatocellular, gastric, esophageal, breast, colon, lung and prostate cancer (Chen et al. 2017a; Higashimori et al. 2018; Hirata et al. 2013; Lu et al. 2020; Zheng et al. 2015). In basal-like breast cancer (BLBC) cells, *FOXF2* interact with the VEGF-c/VEGFR3 signaling pathway, promoting lymphatic metastasis of BLBC cells (Wang et al. 2018). Additionally, *FOXF2* was identified as a directly functional target of mir-182, thereby contributing to the proliferation, invasion and metastasis of triple-negative breast cancer (TNBC) cells (X. Zhang, Ma, Liu, et al., 2017). Research shows that *FOXF2* might inhibit Wnt expression and suppress the growth rate of gastric cancer cells through the FOXF2-IRF2BPL-β-catenin axis. However, it is still unclear whether *FOXF2* can exert the similar effect in other malignant tumors, and thus further investigation is warranted(Higashimori et al. 2018).

It has been demonstrated that, the single-nucleotide polymorphism (SNP) of *FOXF2* rs1711972A > C in genes is significantly associated with poor prognosis in patients with resected non-small cell lung cancer (NSCLC), which might be attributed to its interaction with epithelial-mesenchymal transition (EMT) (Seok et al. 2017). Overall, these studies demonstrate that the *FOXF2* gene plays an important role in tumor progression through multiple pathways.

A comparative analysis of *FOXF2* expression in tumor tissues and adjacent tissues in pancarcinoma revealed significant differences. The results showed that *FOXF2* expression was markedly down-regulated in tumor tissues, showing a decrease compared with relatively normal paracancer tissues. Additionally, a study of survival curves showed that *FOXF2* may be useful for predicting how long a pancarcinoma patient will live, as there was a strong link between *FOXF2* expression levels and patient survival. These findings suggest that *FOXF2* may play a key role in tumorigenesis and progression, and its low expression may be associated with poor pathobiological features and a poor prognosis (He et al. 2020; Higashimori et al. 2018; Wang et al. 2018b). This study inspires the further studies of *FOXF2's* role in the progression of pancarcinoma and lays the foundation for *FOXF2* as a potential therapeutic target and prognostic marker (Supplementary Fig. 2). The *FOXF2* expression in various cancer patients are summarized in Supplementary Table 1.

## Role of the *FOXF2* gene in tumor cell proliferation

Several studies have confirmed the association of *FOXF2* with various malignancies, particularly breast and prostate cancer, as well as involvement in the interstitial of the cranial nerve (Hirata et al. 2013; Lu et al. 2020; Reyahi et al. 2015). The downregulation of *FOXF2*, *RECK* and *MTSS1* gene expression in prostate cancer can promote cell invasion and proliferation (Hirata et al. 2013). MAZ plays dual roles in BLBC in a subtype-specific manner: suppressing cancer progression but promoting cell proliferation. *FOXF2*, as a transcriptional target of MAZ, at least partially mediates the functions of MAZ in BLBC. The MAZ-FOXF2-TWIST1 transcriptional regulation axis may serve an EMT-regulating pathway in BLBC and act as an attractive therapeutic target for aggressive BLBC. The *MAZ* mRNA level, particularly in combination with the *FOXF2* mRNA level, may serve as a prognostic marker for BLBC patients. The dual functions of the MAZ-FOXF2 axis in supporting all stages of cancer development and progression reflect the pleiotropic effects of multifunctional transcription factors, contributing to the complexity of cancer diagnosis and treatment (Yu et al. 2017). In addition, *Mir-182* can significantly accelerate the process of proliferation, invasion and metastasis of TNBC cells by directly targeting *FOXF2* (Lu et al. 2020). Overall, these studies suggest that the *FOXF2* gene plays a key role in mediating cell proliferation by regulating various pathways.

## Role of *FOXF2* in tumor metastasis

Tumor metastasis is complex, multi-step process that typically involves the following stages: detachment of cancer cell from the primary tumor; intracellular metastasis; cancer cell circulation; adhesion to the vessel wall; tumor extravasation; and subsequent tumor growth. As cell phenotypes change, EMT plays an essential role in the tumorigenic process. Increasing studies have shown EMT can suppress the adhesion of cells through involvement of key factors such as E-cadherin, SNAIL, TWIST1, ZEB and others (Noubissi Nzeteu et al. 2022). In this complex process, *FOXF2* has been implicated in metastasis of cancers of liver, breast, lung, esophageal, colon and cervix (He et al. 2020).

The loss of *FOXF2* can enhance the metastability of BLBC cells by increasing the transcriptional activation EMT program of TWIST1 (Wang et al. 2015). In Huh7 cell, the *FOXF2* deficiency might facilitate the colonization of circulating tumor cells and the formation of metastasis by inducing mesenchymal-epithelial transition (MET), (Dou

et al. 2017). Collectively, increasing studies have pointed that the *FOXF2* gene plays a pivotal role in mediating tumor metastasis by modulating various pathways. The low expression of *FOXF2* in tumors is closely related to tumor metastasis, and it inhibits the spread of malignant tumors by regulating epithelial-mesenchymal transformation and cell migration. Furthermore, *FOXF2* also affects ATP energy metabolism by regulating pathways related to energy supply in tumor cells, such as glycolysis and oxidative phosphorylation (Wang et al. 2019). When FOXF2 is lost, tumor cells are more likely to undergo glycolysis, a process generates ATP to fuel invasion and metastasis (Seok et al. 2017). Understanding the regulatory mechanisms of FOXF2 in tumor progression provides valuable insights for developing targeted therapeutic strategies. Further investigation into these pathways will be crucial for advancing cancer treatment.

The signal transduction network of *FOXF2* involves several critical pathways. First, *FOXF2* is involved in the regulation of cell proliferation and differentiation by regulating the activity of the Wnt/β-catenin signaling pathway. Secondly, *FOXF2* interacts with the TGF-β signaling pathway and influences epithelial-mesenchymal transformation and cell migration (Meyer-Schaller et al. 2018). Thirdly, *FOXF2* is also involved in the PI3K/AKT pathway, which regulates cell survival and proliferation (Jain et al. 2016). Finally, in terms of immune regulation, *FOXF2* affects the activity of immune cells through its interaction with the NF-κB signaling pathway (Zheng et al. 2018). In summary, *FOXF2* is involved in the regulation of various cellular processes, including proliferation, differentiation, migration, and immune response, through cross-regulation with multiple signaling pathways (Fig. 1).

### Role of *FOXF2* in tumor drug resistance

The role of *FOXF2* in drug resistance is currently under investigation, with pre-clinical evidence suggesting that *FOXF2* is involved in inducing chemoresistance. One study found *FOXF2* can mediate multiple chemotherapy drug resistance in BLBC cells. Inhibition of *FOXF2* contributed to the multidrug resistance; while, inhibition of *FOXC2* can revert the drug-resistance induced by *FOXF2* depletion (Cai et al. 2015). As a consequence, exogenous *FOXF2* can serve as a potential strategy to revert multidrug resistance and improve outcomes of BLBC patients (Cai et al. 2015). Tamoxifen is considered as the most commonly used endocrine therapy drug for the treatment of estrogen receptor positive (ER+) breast cancer over forty years. One study on breast cancer, based on cell lines and clinical observations, reveals that miR-301 can enhance tamoxifen resistance by modulating the PTEN/Akt pathway. Luciferase reporter assays identified *FOXF2* as a target of miR-301 in the regulation of tamoxifen sensitivity, in cooperation with SKA2 (Shi et al. 2011).

In addition, the low expression of *FOXF2* in solid tumors is closely associated with the regulation of the extracellular matrix (ECM), which adversely affects the treatment efficiency of solid tumors. *FOXF2* plays a role in maintaining normal tissue structure and inhibiting tumor metastasis, but its low expression leads to abnormal remodeling of the ECM and increases the malignancy of solid tumors (Kong et al. 2013; Zhang et al. 2015). This change hinders the penetration of therapeutic drugs into tumor tissue, limiting drugs effectiveness and reducing treatment efficiency.

## Method of analysis

The *FOXF2* gene has been shown to play various roles in the development of cancer. The latest developments in this field are summarized in this section (Tables 1 and 2).

### Breast cancer

Based on immunohistochemistry, breast cancer can be divided into three types: luminal breast cancer (endocrine-type breast cancer), HER2-positive breast cancer, and triple-negative breast cancer (TNBC). Most BLBC belong to triple-negative breast cancer(Orrantia-Borunda et al. 2022).

The impact of *FOXF2* on breast cancer remains controversial. Studies have shown that *FOXF2* is primarily expressed in the stroma of breast cells and is generally restrained in breast cancer due to methylation of the *FOXF2* promoter region (Kong et al. 2013; Yu et al. 2017). In addition, *FOXF2* expression level appears to vary depending on the pathological subtype. For instance, BLBC often shows higher levels of *FOXF2* expression than those with non-basal-like breast cancer (Wang et al. 2015; T. Zhang, Wan, Liu, et al., 2017). This suggests that *FOXF2* may play different regulatory roles in different types of breast cancer.

Kong and colleagues collected tissue samples from 306 breast cancer patients and observed higher recurrence risk among patients with lower *FOXF2* expression (Kong et al. 2013). Shi et al. noted that upregulation of miR-301 inhibits *FOXF2* expression, which in turn activates the Wnt5α signaling pathway, thereby enhancing breast cancer proliferation and migration (Shi et al. 2011). Yu et al. reported that *FOXF2*- deficiency could activate the epithelial-mesenchymal transition (EMT) and accelerate metastasis (Yu et al. 2017). Wang et al. suggested that *FOXF2*-deficiency would activate EMT by suppressing TWIST1 expression (Wang et al. 2015). It is indicated that BLBC with lower *FOXF2* expression presented a higher risk of lymph node

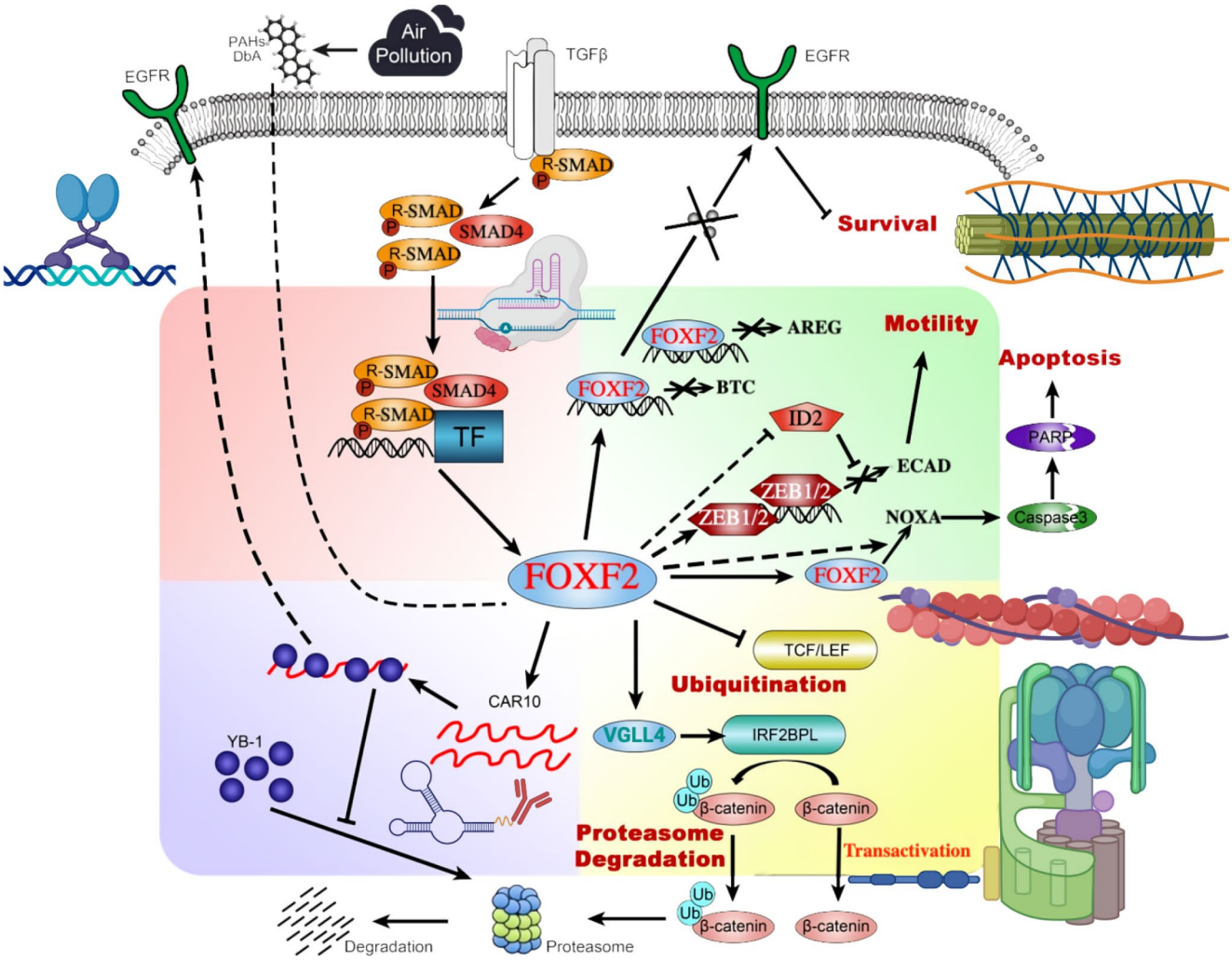


**Fig. 1** The signaling pathway of FOXF2 in tumor progression. TGFβ receptor activates and induces the receptor-bound SMADS phosphorylation followed by subsequent SMAD complex formation. The SMAD complex activates FOXF2 expression with the transcription of EGFR ligands betacellulin (BTC) and amphiregulin (ATEG) repression. FOXF2 also transcriptionally activates NOXA (proapoptotic gene) and induces the caspase-dependent apoptosis. FOXF2 could downregulate the E-cadherin through upregulating ZEB1/ZEB2 and downregulating ID2, affecting the motility of cells. FOXF2 upregulates E3 ligase IRF2BPL and induces β-catenin ubiquitination and degradation. FOXF2 can downregulate the transcription of TCF/LEF. Air pollution can induce DbA upregulation and consequently induced up-regulation of CAR10 and EGFR through FOXF2-YB-1 signal cascade. (Biorender licence number: EH27E0WTW0)

metastasis. Experimental data also supported that, the VEGFR3 expression is suppressed under *FOXF2*-dificient environment, which facilitates lymphatic-like structures formation and lymph node metastasis (Q. S. Wang, He, Yang, Wang et al. 2018a, b). However, the role of *FOXF2* on tumor progression seems to be dependent on pathological subtype. For BLBC, the baseline *FOXF2* expression is higher than endocrine-type breast cancer, and lower *FOXF2* expression is associated with tumor invasion. In contrast, for endocrine-type breast cancer, higher *FOXF2* expression may enhance stem-like characteristics and promote tumor progression (Zhang et al. 2022). Furthermore, *FOXF2* may also play a role in mediating multidrug resistance (MDR) in breast cancer. For example, Cai and colleagues found that the loss of *FOXF2* enhances MDR in breast cancer cells through transcriptional repression of FOXC2 (Cai et al. 2015). However, another study by Kang et al. showed that MDR phenomenon occurs in breast cancer cell with high *FOXF2* expression, potentially mediated by the suppression of FOXO1 (Kang et al. 2019). These conflicting observations indicate that the regulation of *FOXF2* on breast cancer is highly complicated.

## Lung cancer

Studies have shown that *FOXF2* is expressed in the mesenchyme surrounding the bronchial epithelium (Yang et al. 2010). Over the past decade, the role of *FOXF2* in lung

**Table 1** Genes regulated by FOXF2 in cancer models

| Human Cancer | Genes Regulated | Proteins Encoded | Technique | Effect on Transcription | Function | Oncogene or Tumour Suppressor | Models | References |
|---|---|---|---|---|---|---|---|---|
| Breast cancer | FOXC2 | FOXC2 | Luciferase assay | Repression | regulated EMT phenotype, aggressive behavior, and multiple chemotherapy drug resistance | Oncogene | Cell lines | (Cai et al. 2015) |
| Breast cancer | ITGBL1, CSPG2, COMP, DSPG3, FST, OGN, POSTN, SPARC, SPON1, CTSK, LOXL2, PLAU | | ChIP | Activation | high FOXF2 expression have a propensity to metastasize to bone | Oncogene | Cell lines and primary breast cancer tissues | (Wang et al. 2019b) |
| Breast cancer | TWIST1 | TWIST1 | ChIP, Luciferase assays | Repression | FOXF2 deficiency promotes epithelial-mesenchymal transition and metastasis of basal-like breast cancer | Tumor suppressor | Cell lines; Xenograft mice; Human primary TNBC tissues | (Wang et al. 2015) |
| Breast cancer | VEGFR3 | | ChIP-PCR, Luciferase assays | Repression | FOXF2 deficiency promotes the lymphatic metastasis of BLBC | Tumor suppressor | Cell lines; SCID mice; primary TNBC tissue | (Wang et al. 2018b) |
| Lung cancer | CAR10 | | Luciferase assays | Activation | CAR10 is a downstream target of FOXF2 | Oncogene | Cell lines; SCID mice | (Zhang et al. 2018) |

cancer progression remains controversial. Laura et al. analyzed 1,715 NSCLC sample from the TCGA database and found that lower *FOXF2* expression was associated with poorer prognosis (Boyero et al. 2023). In another study, Kong et al. demonstrated that, the *FOXF2* mRNA expression is a negative prognostic marker for resected NSCLC and is generally suppressed in lung cancer compared with normal tissue (Kong et al. 2016). However, contradictory results were also reported in some studies. For instance, Xu et al. examined 48 paired lung cancer and normal tissue samples and observed higher *FOXF2* mRNA expression in lung cancer tissue. Lung cancer with higher *FOXF2* mRNA expression is associated with shorter survival time (Xu et al. 2019). Based on TCGA dataset, Kundu and colleagues found the *FOXF2* expression was widely elevated in lung cancer with high EMT score. According to in vivo and in vitro experiment, lung cancer with *FOXF2* knockdown presented limited invasion and migration ability. Mechanistically, the silenced *FOXF2* function could significantly activate E-cadherin and suppress Zeb1 expression, which in turn reverses the EMT process, impairing the lung cancer's invasion and migration capability (Kundu et al. 2016). Studies showed that, the function of *FOXF2* is influenced not only by its expression levels but also by various internal and external regulatory factors. For instance, it is reported that, under the stimulation of cigarette smoke, *FOXF2* exhibited a greater DNA binding ability and a stronger transcriptional regulatory activity (Tharappel et al. 2010). In addition, the hypoxic condition is reported to contribute to the suppression of *FOXF2* expression in lung cancer cell (Geng et al. 2016). Recently, the effect of *FOXF2* on single nucleotide polymorphisms (SNP) is reported. For instance, Seok and colleagues found that the *FOXF2* rs1711972 AC + CC genotype was associated with significantly better overall survival (OS) and disease-free survival (DFS) compared to the AA genotype. Based on in vitro experiments, the rs1711972C allele had significantly higher *FOXF2* promoter activity compared with the rs1711972A allele. Additionally,*FOXF2* rs1711972 CC genotype was significantly associated with increased *FOXF2* mRNA expression compared with AA + AC genotype (Seok et al. 2017). Given these findings, future research should focus on the interplay between gene expression, phenotype, and environment to better understand the impact of *FOXF2* on lung cancer progression.

## Colorectal cancer

Previous studies have suggested that *FOXF2* might modulate intestinal development by limiting mesenchymal Wnt signaling and promoting extracellular matrix production (Ormestad et al. 2006). Under normal physiological conditions, *FOXF2* efficiently inhibits the activation of the Wnt signaling pathway, thus maintaining cellular homeostasis. However, when *FOXF2* expression is suppressed, the Wnt signaling pathway becomes activated, leading to abnormal proliferation and anti-apoptotic characteristics in the

**Table 2** Genes/miRNA regulated FOXF2 in cancer models

| Human Cancer | Regulatory genes/miRNA | Target genes | Technique | Effect on Transcription | Function | Oncogene or Tumor Suppressor | Models | References |
|---|---|---|---|---|---|---|---|---|
| Breast cancer | miRNA301 | FOXF2, BBC3, PTEN, and COL2A1 | Luciferase assays | Repression | miR-301 as a crucial oncogene in human breast cancer that acts through multiple pathways and mechanisms to promote nodal or distant relapses | Oncogene | Cell lines; immunodeficient mice (SCID) CB.17; Patients | (Shi et al. 2011) |
| Breast cancer | SP1 | FOXF2 | ChIP; Luciferase assays | Repression | SP1 regulated the transcriptional activity of FOXF2 through direct binding to the proximal promoter region | Tumor Suppressor | Cell lines; Patients | (Tian et al. 2015) |
| Breast cancer | miRNA182 | FOXF2 | Luciferase assays | Activation | FOXF2 was a direct target of miR-182. | Oncogene | Cell lines | (Yu et al. 2017a) |
| Breast cancer | miRNA182 | FOXF2 | Luciferase assays | Activation | FOXF2 was identified as a direct and functional target of miR-182 | Oncogene | Cell lines | (Zhang et al. 2017a, b) |
| Ovarian cancer | miR-182-5p | FOXF2 | Luciferase assays | Activation | LncRNA ADAMTS9-AS2 regulates ovarian cancer progression by targeting miR-182-5p/FOXF2 signaling pathway | Oncogene | Cell lines | (Wang et al. 2018a) |
| Rectal cancer | miRNA182 | FOXF2 | Luciferase assays | Activation | LncRNA ADAMTS9-AS2 was predicted to regulate the expression of FOXF2 gene through competitive binding to miR-182. | Oncogene | Cell lines | (Wang et al. 2019a) |
| Colorectal cancer | miR-182 | FOXF2 | Luciferase assays | Activation | miR-182-induced downregulation of FoxF2 partly accounts for increased activity of β-catenin signaling | Oncogene | Cell lines | (Zhang et al. 2015) |
| Lung cancer | miR-301b | FOXF2 | Luciferase assays | Activation | the overexpression of hsa-miR-301b and hsa-miR-769-5p significantly affected the cell cycle of A549 cells | Oncogene | Cell lines | (Geng et al. 2016) |
| Lung cancer | miR-200 family miR-183 ~ 96 ~ 182 | FOXF2 | Luciferase assays | Repression | miR-200 family and the miR-183 ~ 96 ~ 182 cluster inhibit lung cancer invasion and metastasis by targeting Foxf2 | Tumor Suppressor | Cell lines | (Kundu et al. 2016) |

intestinal epithelium, and potentially resulting in adenoma formation (Nik, Reyahi, Ponten, et al., 2013). It has been reported that *FOXF2* is generally downregulated in colorectal cancer and acts as a central regulatory node in various key signaling pathways that influence the onset and progression of the disease. Elevated levels of miR-182 are frequently observed in advanced colorectal cancer tissues. Knockdown of miR-182 reduces the invasive and metastatic potential of colorectal cancer cells. Mechanistically, this occurs through the elevation of *FOXF2* level following the miR-182 knockdown, which in turn reduces β-catenin expression and inhibits EMT (Wang et al. 2019a; Zhang et al. 2015). Similaryly, LSD1 overexpression mediated by the repression of *FOXF2* leads to an increased malignant phenotype in colorectal cancer (Chen et al. 2017). Liu et al. further discovered that among colorectal cancer patients, those with lower *FOXF2* expression levels were more likely to have a higher tendency for lymph node metastasis, more advanced

disease stages, and a higher risk of recurrence (Liu, Xiao, Wang, et al., 2022). These results demonstrate that *FOXF2* is a crucial biomarker influencing both the occurrence and progression of colorectal cancer.

## Esophageal cancer

Esophageal squamous cell carcinoma (ESCC) is a prevalent digestive cancer with a generally poor prognosis. Our research group examined 33 pairs of esophageal tumor and matched normal tissue samples, finding that *FOXF2* mRNA expression was significantly lower in the cancerous tissue compared to the normal esophageal tissue. In a subsequent analysis involving 188 surgically resected ESCC specimens, we observed that patients with reduced *FOXF2* mRNA expression were more likely to experience lymph node metastasis and had shorter survival times (Zheng et al. 2015). Additionally, Chen et al. investigated the effect of *FOXF2* promoter methylation on the prognosis of ESCC. They employed methylation-specific PCR to evaluate the methylation status of the *FOXF2* promoter in formalin-fixed, paraffin-embedded ESCC tissues, and observed that high levels of *FOXF2* promoter methylation independently predict a decreased overall survival rate for ESCC patients, consistent with results from cancer genome mapping. The authors proposed that the downregulation of *FOXF2* expression caused by *FOXF2* promoter methylation may contribute to the invasion and metastasis of esophageal squamous cell carcinoma (Chen et al. 2017). These results suggest that *FOXF2* may function as a tumor suppressor gene in the progression of esophageal cancer, though additional supporting data are still required.

## Prostate cancer

*FOXF2* is primarily expressed in the stromal cells of the prostate, with significantly higher levels observed in the transition zone compared to the peripheral zone (van der Heul-Nieuwenhuijsen et al. 2009). Research suggests that *FOXF2* may play a crucial role in maintaining normal prostate tissue homeostasis by regulating the balance between cell proliferation, apoptosis, and differentiation. It has been reported that a lower expression level of FOXF2 is more frequently detected in prostatic hyperplasia and prostate cancer (Chen et al. 2023). Hiroshi et al. demonstrated that silencing *FOXF2* expression resulted in increased proliferation and migration of prostate cancer cells (Hirata et al. 2013). Wei et al. found that overexpression of miR-96 enhances the proliferative capability of prostate cancer cells, likely through the targeted inhibition of *FOXF2* (Wei et al. 2017). To better understand the role of *FOXF2* on prostate cancer, Jia et al. analyzed human genome databases and conducted immunohistochemical experiments on clinical samples. They found that *FOXF2* expression was negatively correlated with Gleason scores in prostate cancer; higher levels of *FOXF2* expression were associated with lower Gleason scores, suggesting characteristics of a less aggressive profile (Jia et al. 2022). In mouse models, researchers observed that increased *FOXF2* expression led to a reduction in the CAFs phenotype and downregulation of Cxcl5 expression. This alteration decreased the number of immunosuppressive myeloid cells, thereby enhancing T cell cytotoxicity and strengthening anti-tumor immunity, which in turn inhibited prostate cancer growth and metastasis (Jia et al. 2022). These findings suggest that *FOXF2* plays a significant tumor-suppressive role in the progression of prostate cancer. However, a study published in 2009 reported that knocking down *FOXF2* expression in normal prostate epithelial cells did not significantly promote cell proliferation (van der Heul-Nieuwenhuijsen et al. 2009). This indicates that the progression from normal prostate tissue to malignancy is a complex process involving the dysregulation of multiple signaling pathways, rather than changes in a single factor like *FOXF2*.

## Liver cancer

Dou et al. reported that *FOXF2* is generally downregulated in liver cancer tissues compared to normal liver tissues (Dou et al. 2017). The knockdown of *FOXF2* expression in hepatocellular carcinoma cells (HCC) using shRNA results in enhanced migration and invasion. In addition, nude mice injected with Huh7 cells that had undergone stable Foxf2 knockout exhibited a more pronounced tumor formation (Dou et al. 2017). Shi et al. analyzed *FOXF2* expression in tissue samples from 295 liver cancer patients and found that lower *FOXF2* expression is correlated with larger tumors and poorer cell differentiation. Therefore, lower expression status of *FOXF2* was identified as an independent risk factor for poor prognosis in liver cancer patients. According to experiments in vitro, overexpression of *FOXF2* induced a significant increase in cell apoptosis (Shi et al. 2016). These data suggest that *FOXF2* may play a crucial role as a tumor suppressor gene in the development and progression of liver cancer, warranting further investigation on *FOXF2's* therapeutic potential.

## Gynecologic cancer

To date, there have been limited reports on the role of *FOXF2* in gynecological cancers. Zhang et al. found that *FOXF2* is generally downregulated in cervical cancer tissues, with more pronounced downregulation observed in cases with lymph node metastasis, myometrial invasion,

and advanced disease stages (Zhang et al. 2018). Elevated *FOXF2* expression can reduce the proliferation, migration, and invasion capabilities of HeLa cells, likely through the inhibition of the Wnt signaling pathway and the epithelial-mesenchymal transition (EMT) process (Zhang et al. 2018). Wang et al. found that ADAMTS9-AS2 suppresses the growth of ovarian cancer through the targeted activation of *FOXF2* (Wang et al. 2018). In vitro experiments supported that overexpression of ADAMTS9-AS2 significantly inhibits the proliferation and invasion of ovarian cancer cells, but these effects were reversed when *FOXF2* was inhibited (Wang et al. 2018). Furthermore, *FOXF2* is essential for the regulation of the extracellular matrix in endometrial cells. Overexpression of *FOXF2* can alter the extracellular matrix, which in turn reduces the sensitivity of endometrial cancer to progesterone treatment and contributes to the development of resistance (Lomenick et al. 2006).

## Conclusion

*FOXF2* has been shown to contribute to the progression of the tumor. To conclude, we believe that *FOXF2* plays pleiotropic roles ranging from cancer initiation to metastasis, as evidenced by its association with clinical outcomes across various human cancers. However, further research is needed to clarify different molecular pathways and define the precise role of *FOXF2* in cancer progression. *FOXF2* holds promise as a new biomarker for evaluating prognosis and controlling tumor progression in various malignancies, offering the potential for early detection and treatment of cancer and metastasis.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00432-024-06047-z.

**Author contributions** YZ: supervision, conceptualization, writing—reviewing and editing. LW: writing—original draft preparation. ZH: writing—reviewing and editing. HL: supervision, conceptualization. XL: supervision, conceptualization, writing—reviewing and editing. All authors read and approved the final manuscript.

**Funding** This study was supported by the National Natural Science Foundation of China (No. 82102955), the Guangzhou Basic Research Project [grant number 202201011326], and Medical Scientific Research Foundation of Guangdong Province of China (Grant No. A2020150, A2018301).

**Data availability** Data is provided within the manuscript or supplementary information files.

## Declarations

**Ethics approval and consent to participate** Not applicable.

**Patient consent for publication** Not applicable.

**Competing interests** The authors declare no competing interests.



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