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Mini-review

FOXK transcription factors: Regulation and critical role in cancer

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ABSTRACT

Growing evidence suggests that alterations of gene expression including expression and activities of transcription factors are closely associated with carcinogenesis. Forkhead Box Class K (FOXK) proteins, FOXK1 and FOXK2, are a family of evolutionarily conserved transcriptional factors, which have recently been recognized as key transcriptional regulators involved in many types of cancer. Members of the FOXK family mediate a wide spectrum of biological processes, including cell proliferation, differentiation, apoptosis, autophagy, cell cycle progression, DNA damage and tumorigenesis. Therefore, the deregulation of FOXKs can affect the cell fate and they promote tumorigenesis as well as cancer progression. The mechanisms of FOXKs regulation including post-translational modifications (PTMs), microRNAs (miRNAs) and protein–protein interactions are well demonstrated. However, the detailed mechanisms of FOXKs activation and deregulation in cancer progression are still inconclusive. In this review, we summarize the regulatory mechanisms of FOXKs expression and activity, and their role in the development and progression of cancer. We have discussed whether FOXKs act as tumor suppressors/oncoproteins in tumor cells and their therapeutic applications in malignant diseases are also discussed. This review may assist in designing experimental studies involving FOXKs and it would strength the therapeutic potential of FOXKs as targets for cancers.

1. Introduction

Cancer is the second leading cause of death in both developed and developing countries [1–3]. According to global cancer statistics in 2018, the new cancer cases will rise to more than 18.1 million per year and cancer related death will be more than 9.6 million worldwide [4]. The number of new cases is rapidly increasing due to the improved awareness and new screening technologies in recent years. Although continuous efforts have been made in biomedical research to cure cancer, still it is a major health problem around the world. This could be due to unknown side of mechanisms of carcinogenesis as well as less knowledge about the gene alterations including the role of transcription factors. Forkhead box (FOX) proteins are a superfamily of evolutionarily conserved transcription factors that are characterized by their "forkhead" or "winged-helix" DNA binding domain (DBD), which can specifically bind to the well conserved sequence 5′-TTGTTTAC-3' [5–11]. Currently, more than 54 or 50 members of FOX family are identified in mammals or human genome, respectively [12]. FOX family is further grouped into 19 subfamilies (FOXA to FOXS) based on their sequence homology [13–17]. They regulate the expression of many genes, thereby controlling diverse cellular functions including cell cycle [18], cell growth [19], proliferation [20], apoptosis [21], autophagy [22], stress resistance [23], metabolism [24], DNA damage [7], drug resistance [25], angiogenesis [26,27], and carcinogenesis [28–30]. Thus, they play important roles in human health and disease, particularly in cancer. A large number of studies have demonstrated that FOX transcription factors are involved in the occurrence and development of human cancers [31–35].

The forkhead box class K (FOXK) transcription factors are ubiquitously expressed in various tissues and organs and they play vital roles in cellular functions of higher organisms. In mammalian species, the FOXK family includes two members, namely FOXK1 and FOXK2, which are regulated by PTMs, post-transcriptionally by miRNAs and protein–protein interactions [35–38]. FOXK family can regulate cell proliferation, survival, skeletal muscle regeneration and myogenic differentiation as well as carcinogenesis [39–42]. All these functions are

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Abbreviations

FOXK	forkhead box Class K
PTMs	post-translational modifications
miRNAs	microRNAs
DBD	DNA binding domain
FHA	forkhead-associated domain
MNF	myocyte nuclear factor
Sds3	suppressor of defective silencing 3
SID	Sin3b-interacting domain
BARD1	BRCA1 associated ring domain 1
Fhl3	four-and-a-half LIM domain 3
ncRNAs	noncoding RNAs
DMR	DNA methylated region
SBE	Sox binding element
tRNAs	transfer RNAs
rRNAs	ribosomal RNAs
siRNAs	small interfering RNAs
piRNAs	piwi-interacting RNAs
circRNAs	circular RNAs
lncRNAs	Long non-coding RNAs
RISC	RNA-induced silencing complex
3′ UTR	3′-untranslated region
PI3K	Phosphatidylinositol 3-kinase
GSK3	Glycogen synthase kinase 3
mTORC1	mammalian target of rapamycin complex 1
PP2A	protein phosphatase 2A
Sin3	SWI-independent-3
Adv	adenovirus
SM	smooth muscle
JLP	JNK associated leucine zipper protein
DVL	disheveled
BAP1	BRCA associated protein 1
ERα	estrogen receptor α
VEGF	Vascular endothelial growth factor
PDGF	platelet-derived growth factor
EMT	Epithelial to mesenchymal transition

mediated by specific activation of a coordinated transcriptional program. Therefore, deregulation of FOXKs function can affect cell fate and they can also promote malignancies. The present review focuses on the detailed mechanisms of FOXKs regulation, and their critical role in the development and progression of cancer. We have discussed the impact of activation and expression of FOXKs during oncogenesis or tumor suppression. Finally, we have discussed the future research directions of targeting FOXKs for cancer therapy.

2. Structures and functions of FOXKs

FOXK family consists of two members, FOXK1 and FOXK2, which share similar structures. FOXK1 and FOXK2 contain two domains, a forkhead winged helix-turn-helix DNA binding domain (FOX) and a forkhead-associated domain (FHA), which mediates its interaction with other proteins and regulates cell-cycle kinetics (Fig. 1). These two domains are highly conserved between FOXK1 and FOXK2. *FOXK1* gene is mapped to human chromosome 7p22.1 and it produces a functional FOXK1 protein composed of 733 amino acid [43,44]. The FOXK1 transcription factor, also called myocyte nuclear factor (MNF), is a DNA-binding protein. The FOX domain of FOXK1 is primarily responsible for its direct interaction with DNA, while the FHA domain mediates its interaction with suppressor of defective silencing 3 (Sds3) [45]. It also contains a Swi-independent 3b-interacting domain (SID) in the N-terminus, which mediates the direct interaction between FOXK1 and Sin3 [46]. The amino acids region of 95–420 in FOXK1 mainly mediates its interaction with FOXO4 and MEF2C [47]. Moreover, the N-terminal portions (amino acids 1–234) including FHA domain mediates its interaction with BRCA associated protein 1 (BAP1) [48]. *FOXK2* gene is located at human chromosome 17q25.3, which produces a functional FOXK2 protein with 660 amino acids [44,49]. FOXK2 is a DNA-binding protein, which is also known as ILF or ILF1. Similar to FOXK1, the FOX domain of FOXK2 mediates its interaction with DNA, whereas the amino acids region of 1–128 consists FHA domain, which is required for FOXK2 interaction with BRCA1 associated ring domain 1 (BARD1) [50]. The FOX domain in the amino acids region of 129–153 mediates the interaction between FOXK2 and estrogen receptor α (ERα) [50], while the region of amino acids 54–171, which includes FHA domain mediates the interaction of FOXK2 with dishevelled (DVL) and Sds3 [51]. In addition, the N-terminal portions (amino acids 8–190) including FHA domain are required for the interaction of FOXK2 with BAP1 [48]. It is quite interesting that the mRNAs of FOXKs in human undergo alternative splicing, which yield different isoforms of FOXK1 (FOXK1a and FOXK1b) [44] and FOXK2 (three isoforms) [52,53]. This

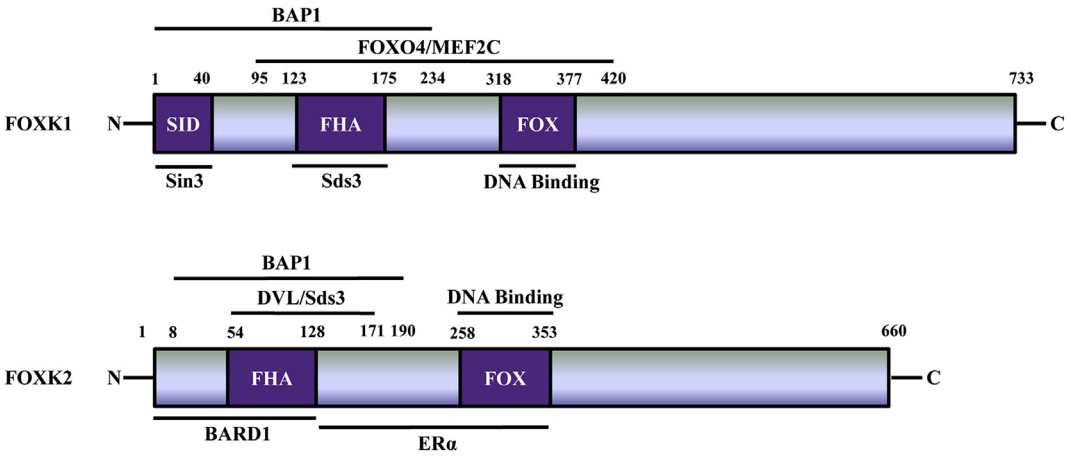

Fig. 1. Structure of human FOXKs. The two members of FOXK family are shown with their sizes and domain arrangement. Letters within the bar indicate structural domains. The well-known proteins interacting with FOXK1 and FOXK2 are shown above the lines at the corresponding domains. Only representatives of FOXKs-interacting proteins are shown. FOX, forkhead winged helix-turn-helix DNA binding domain; FHA, forkhead-associated domain; SID, Sin3b-interacting domain; BAP1, BRCA associated protein 1; Sds3, suppressor of defective silencing 3; Sin3, SWI-independent-3; FOXO4/MEF2C, Forkhead Box Class O4/Myocyte Enhancer Factor-2C; DVL, dishevelled; BARD1, BRCA1 associated ring domain 1; ERα, estrogen receptor α.

variation could be responsible for the differential binding affinities and interaction of FOX and FHA domains as well as distinct functions of FOXK1 and FOXK2. Currently, there is no clear evidence showing the specific functions of these isoforms to support this notion.

Members of the FOXK family are vital transcription factors that regulate a wide spectrum of biological processes, including cell proliferation, survival, differentiation, cell cycle progression, DNA damage and antivirus [39,47,54–56]. Additionally, FOXK proteins are also involved in the regulation of starvation-induced atrophy and autophagy programs as well as aerobic glycolysis. FOXK1/2 specifically recruits Sin3A–HDAC complexes to restrict the expression of its downstream target genes (such as *Tcfap4*, *Junb*, *Ccne2*, and *Fbxo32*), which are crucial atrophy and autophagy genes. The starvation induces translocation of FOXK1 from the nucleus to the cytoplasm and leads to up-regulation of these genes expression [40]. Moreover, FOXK1 and FOXK2 are shown to induce aerobic glycolysis through upregulating the expression of key target proteins such as hexokinase-2, phosphofructokinase, pyruvate kinase, and lactate dehydrogenase, which are enzymatic machinery required for the progression of glycolysis process. This finding indicates that FOXK1 and FOXK2 are critical regulators of glycolysis process and they can reprogram cellular metabolism [57]. FOXK1 also plays an important role in the process of skeletal muscle regeneration. Its expression is restricted to myogenic progenitor cells of adult skeletal muscle, and it controls the cell-cycle progression of myogenic progenitors through repressing its downstream target protein p21 expression, which is a cyclin-dependent kinase inhibitor that acts as an inhibitor of cell cycle progression [58]. Further study indicated that Sox15 transcriptionally activate FOXK1 expression by recruiting four-and-a-half LIM domain 3 (Fhl3) in the myogenic progenitor cell population [41]. FOXK2 promotes the efficient recruitment of AP-1 to chromatin, leading to the up-regulation of its target genes expression, such as *JAG1*, *IER3* and *SERPINE1* [59]. The multiple functions of FOXKs indicate that deregulation of FOXKs can lead to various diseases including cancer. However, further extensive investigations will provide valuable insight into their physiological function.

3. Molecular mechanisms of FOXKs regulation

There are several different mechanisms involved in the regulation of FOXKs activity in normal and cancer cells, such as noncoding RNAs (ncRNAs), PTMs and protein–protein interactions. Here, we present several modes of regulation of FOXKs during physiological and pathological condition with particular focus on the regulation of FOXKs in cancers.

3.1. Regulation of FOXKs at transcription level

DNA methylation is one of the most important epigenetic modifications, which is defined as modifications of the activity of a DNA segment without changing the DNA sequence by packaging those particular segment [60,61]. It is well known that the methylation of DNA in genes promoter regions suppress the expression of genes at transcription level [62–64]. It is closely associated with normal development and a number of critical processes, including aging, repression of transposable elements, and carcinogenesis [65–67]. FOXK1 promoter is methylated in multiple types of tumors cells. A molecular study using *pCpGL* reporter vector system and dual luciferase reporter assay revealed that the methylation of FOXK1 promoter negatively regulates its gene transcription. In that study, they found that the expression of luciferase is significantly higher in cells transfected with *pCpGL* reporter vector containing unmethylated FOXK1 DNA methylated region (DMR) than that in cells transfected with methylated reporter vector, which clearly show that the methylation of FOXK1 promoter suppresses its gene transcription. In addition, the FOXK1 promoter shows a trend for accelerated demethylation in blood samples from patients with autism [68].

FOXK1 is a downstream target gene of several transcription factors, such as SOX15 and C-Jun. A database analysis showed that FOXK1 gene contains the Sox binding element (SBE) in its promoter. SOX15 interacts with Fhl3 and forms a complex, which transcriptionally activates the expression of FOXK1 through directly binding to SBE of FOXK1. The mutagenesis of the SBE attenuates FOXK1 expression in cells such as muscle myoblast [41]. Transcription factor C-Jun is recognized as an oncogene due to its ability to provide signals for cell survival [69,70]. It is well documented that C-Jun is highly expressed in multiple invasive cancers [71–73]. C-Jun directly binds to FOXK1 gene promoter and transcriptionally activates its expression, and the deregulation C-Jun leads to the development of gastric cancer [74]. The bioinformatics analysis reveals that the promoter of FOXK1 contains other transcription factors binding sequence, such as HMAG1, Sp1, smad3 and smad4 suggesting that FOXK1 expression may also be triggered by many transcription factors [74].

3.2. ncRNAs contribute to post-transcriptional regulation of FOXKs

ncRNAs are RNA molecules that are not translated into a protein. They are involved in many cellular processes through regulating gene expression at transcriptional or post-transcriptional level [75–79]. ncRNAs are classified as transfer RNAs (tRNAs) [80], ribosomal RNAs (rRNAs) [81], small RNAs such as miRNAs [82], small interfering RNAs (siRNAs) [83], piwi-interacting RNAs (piRNAs) [84], circular RNAs (circRNAs) [85] and long non-coding RNAs (lncRNAs) [86]. Currently, several studies revealed that ncRNAs function as tumor regulators by targeting transcription factors including FOXKs (Table 1).

miRNAs comprised of 18–25 nucleotides are able to regulate the translation of mRNA involved in biological processes including cell proliferation, apoptosis, differentiation and transformation [93–96]. They combine with other proteins to form the RNA-induced silencing complex (RISC), and then bind to the 3′-untranslated region (3′UTR) of mRNAs to regulate their translation [97–100]. miR-646 is aberrantly expressed in multiple human cancers [101–104]. miR-646 is able to inhibit the proliferation and EMT-induced metastasis of gastric cancer

Table 1
ncRNAs targeting FOXKs in cancer.

Cancer types	ncRNA	FOXKs	Function of the interaction	Ref.
Gastric cancer	miR-646	FOXK1	Inhibits proliferation and Epithelial to mesenchymal transition (EMT)-induced metastasis of gastric cancer cells.	[87]
	miR-593–3p	FOXK1	Inhibits growth and invasion of gastric cancer cells	[88]
	LINC02163	FOXK1	Promotes growth and invasion of gastric cancer cells.	[88]
Osteosarcoma	miR-186–5p	FOXK1	Inhibits proliferation, cell cycle, EMT, migration and invasion of osteosarcoma as well as in-vivo tumor growth.	[89]
Lung cancer	miR-1275	FOXK1	Inhibits proliferation and invasion of lung cancer cells.	[37]
	circMAN2B2	FOXK1	Promotes proliferation and invasion of lung cancer cells.	[37]
Colorectal cancer	miR-4492	FOXK1	Inhibits proliferation and invasion of colorectal cancer cells.	[90]
	LINC01503	FOXK1	Promotes proliferation and invasion of colorectal cancer cells.	[90]
Glioma	miR-137	FXOK1	Inhibits proliferation and induces apoptosis of glioma cells.	[91]
Hepatocellular carcinoma	miR-1271	FOXK2	Promotes cell growth and migration in hepatocellular carcinoma.	[92]

cells through directly targeting the FOXK1 3′UTR. Consistent with this, inverse correlations are observed between the expression of miR-646 and FOXK1 in patients with gastric cancer [87]. FOXK1 is also a potential target of miR-593–3p in gastric cancer cell lines. miR-593–3p decreases both mRNA and protein expression of FOXK1 [105]. miR-1275 possesses anti-tumor activity in lung cancer. The data from luciferase reporter assay indicates that FOXK1 is a direct target of miR-1275. miR-1275 can inhibit the proliferation and invasion of lung cancer cells by mainly inhibiting FOXK1 expression. Similar to miR-646, there is a reverse relationship between the expression of miR-1275 and FOXK1 in lung cancer [37]. Moreover, FOXK1 is identified as a novel target of miR-137. Its expression is inversely correlated with miR-137 in glioma tissues [91]. In human osteosarcoma, miR-186–5p directly targets FOXK1 3′-UTR and negatively regulates its expression. Silencing of FOXK1 expression enhances the inhibitory role of miR-186–5p on proliferation, migration and invasion of osteosarcoma cells [89]. FOXK2 is also regulated by miRNAs. In hepatocellular carcinoma, FOXK2 is directly targeted by miR-1271. Overexpression of miR-1271 leads to significant reduction of FOXK2 at both mRNA and protein levels, whereas miR-1271 inhibitor markedly increases the expression of FOXK2. The expression of miR-1271 is inversely associated with FOXK2 mRNA in human hepatocellular carcinoma tissues [92].

CircRNAs refer to a class of circular RNA molecules that form a covalently closed continuous loop, which make them more stable than most linear RNAs [106]. Several studies show that many circRNAs are aberrantly expressed in cancer tissues and they are involved in the regulation of carcinogenesis [107,108], but the mechanisms of their gene regulatory function is still largely unknown. It is well defined that circRNAs act as miRNAs sponge to regulate the expression of target genes [109–112]. FOXKs expression can be regulated by circRNAs. For instance, aberrant expression of circMAN2B2 promotes the proliferation and invasion of lung cancer cells through up-regulation of FOXK1 expression by sponging miR-1275. The inhibition of cell proliferation and invasion by restoration of FOXK1 in circMAN2B2 knockdown cells confirmed the circMAN2B2-miR1275-FOXK1 axis in lung carcinoma [37].

LncRNAs are a class of ncRNAs with a length of > 200 nucleotides [86]. Growing studies demonstrated that certain lncRNAs are involved in cancer progression through sponging miRNAs [113]. LncRNAs can also regulate the expression of FOXK1. In colorectal cancer, lncRNA LINC01503 sponges miR-4492 and upregulating FOXK1 to promote the proliferation and invasion of colorectal cancer cells [90]. Similarly, lncRNA LINC02163 regulates the growth and EMT phenotype of gastric cancer cells via inhibiting the binding of miR-593–3p to FOXK1 [88]. These findings indicate that there is a comprehensive network of ncRNAs and FOXKs are involved in cancer development and invasion. Therefore, it is important to deeply understand the association between ncRNAs and FOXKs for the designing of FOXKs based strategies.

3.3. Importance of PTMs in regulating FOXKs

PTMs are important mechanisms for regulating the functions of

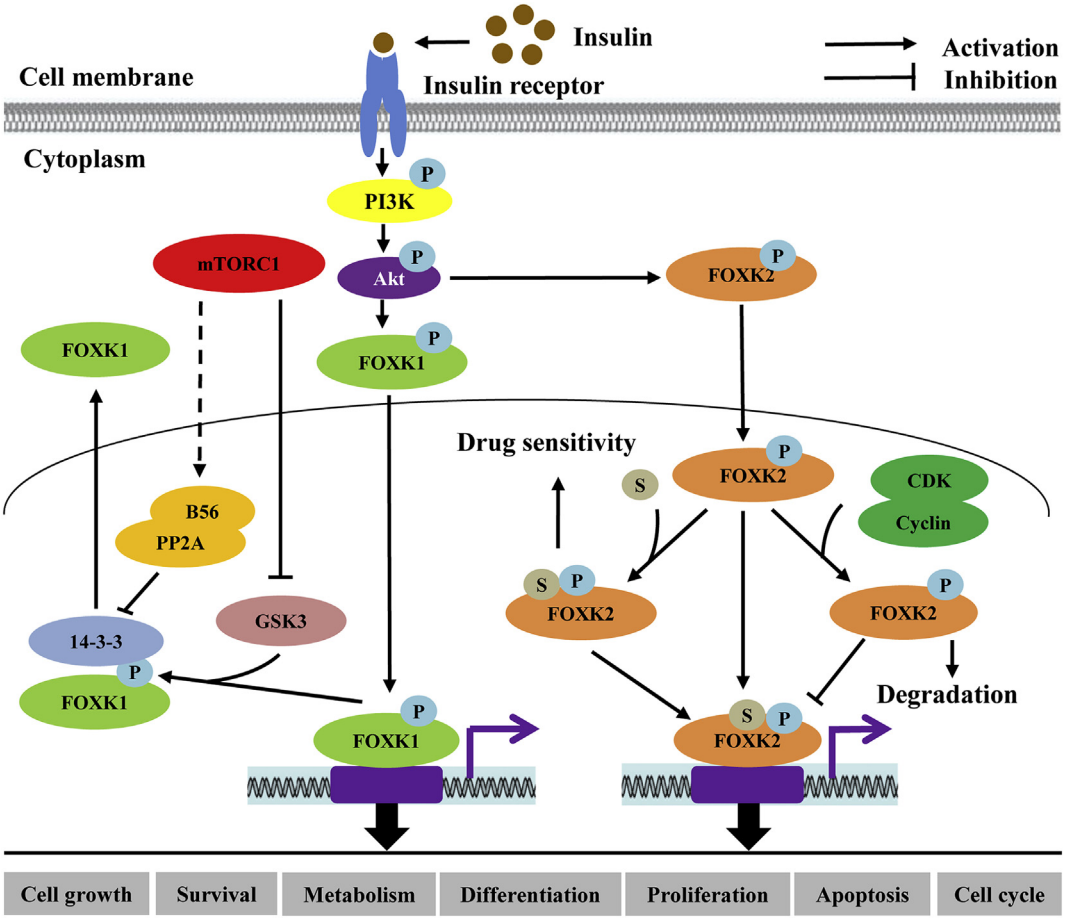

Fig. 2. Regulation of FOXK transcription factors by PTMs. Stimulation with insulin results in the phosphorylation of FOXK1 and FOXK2 through phosphatidylinositol 3-kinase (PI3K)-mediated activation of Akt that leads to the translocation of FOXK1/FOXK2 to the nucleus. FOXK1 is also phosphorylated by GSK3, which leads to its interaction with 14-3-3 factors and nuclear export. mTORC1 mediates the dephosphorylation of FOXK1 through inhibiting GSK3 activity, which results in enhanced binding of FOXK1 to DNA. CDK/cyclin complex induced phosphorylation of FOXK2 promotes its degradation and the decline of repressive activity. FOXK2 is sumoylated by SUMO2. Sumoylation of FOXK2 increases its transcriptional activity and mediates the cytotoxic response to paclitaxel through FOXO3a.

proteins that alter their stability, subcellular location, transcriptional activity and their interaction with other biomolecules [114–117]. The most common PTMs include phosphorylation, acetylation, glycosylation, methylation, ubiquitination and sumoylation [118]. Accumulating evidence reveals that the functions of FOXKs are altered by several posttranslational modifications (Fig. 2), such as phosphorylation and sumoylation [36,119,120], which can influence their target genes expression.

Phosphorylation is the major PTM regulates the translocation of several members of FOX family between nucleus and cytoplasm through influencing their interaction with chaperone proteins, including 14-3-3 and exportin/importin accessory proteins [121–123]. FOXK1 is a substrate of Glycogen synthase kinase 3 (GSK3), which is implicated in a number of diseases, including cancer [124]. The phosphorylation of FOXK1 by GSK3 promotes its interaction with 14-3-3 and leads to the reduction of DNA binding and nuclear exclusion of FOXK1. However, GSK3-dependent FOXK1 phosphorylation is inhibited by mammalian target of rapamycin complex 1 (mTORC1) [120]. Hyperactivation of mTORC1 is frequently observed in various types of cancer [125]. In mice model of cancer, the dephosphorylation of FOXK1 mediated by mTORC1 promotes the transactivation of its target gene *CCL2*, which leads to recruitment of tumor-associated monocytes-macrophages and tumor progression [126]. A molecular study found that B56, the regulatory subunit of protein phosphatase 2A (PP2A), is involved in mTORC1-dependent dephosphorylation of FOXK1 [127]. FOXK1 and FOXK2 also act as downstream signaling molecules of Akt in insulin signaling. FOXK1 and FOXK2 are phosphorylated by Akt-mTOR pathway after insulin stimulation and leads to their translocation to the nucleus in which they control the expression of genes associated with mitochondrial metabolism and cell proliferation. However, their localization to the cytoplasm in the basal state is dependent on GSK3 [128]. In addition, FOXK2 can be phosphorylated by CDK/cyclin complex at serine 368 and 423 sites, and its phosphorylation levels exhibit a periodic rise during the cell cycle. The hyperphosphorylation of FOXK2 occurs in mitotic cells. Moreover, phosphorylation of FOXK2 promotes its degradation and reduces its repressive activity, which consequently leads to the inhibition of apoptosis in human osteosarcoma cells [36].

Like phosphorylation, sumoylation also regulates various functions of FOX proteins by changing their subcellular location, DNA-binding activity, stability and interaction with other proteins [129–133]. In breast cancer cells, FOXK2 is sumoylated at lysine 527 and 633 sites by SUMO2. Sumoylation of FOXK2 positively regulates its transcriptional activity and it plays an important role in mediating the cytotoxic response to paclitaxel through the tumor suppressor FOXO3a [119]. Our recent study showed that FOXK2 activity is also modified by SUMO1

Table 2
Functional roles of FOXKs pathway in different types of cancer.

Cancer types	Members of FOXK family	Key message(s)	Ref.
Breast cancer	FOXK1	High FOXK1 expression is associated with better prognosis. FOXK1 regulates breast cancer angiogenesis through inhibition of vascular endothelial growth factor.	[136]
	FOXK2	FOXK2 promotes ubiquitin-mediated degradation of ERα by enhancing the interaction of ERα with an E3 ubiquitin ligase, BRCA1/BARD1 that leads to inhibition of breast cancer cell growth.	[50]
		FOXK2 inhibits the proliferation and invasion of breast cancer cells and suppresses the growth and metastasis of breast cancer. Low FOXK2 expression is strongly correlated with poor prognosis.	[137]
		Deregulation of FOXK2 contributes to drug resistance. FOXK2 regulates epirubicin and paclitaxel sensitivity through FOXO3a in breast cancer.	[138]
		FOXK2 transcriptional activity is positively regulated by sumoylation, which plays a key role in mediating the cytotoxic response to paclitaxel through FOXO3a.	[119]
Colon cancer	FOXK1	Knockdown of FOXK1 significantly induces apoptosis, inhibits tumorigenesis and tumor growth and strongly enhances the antitumor activity of 5-fluorouracil (5-FU) *in vitro* and *in vivo*.	[139]
		Co-expression of FOXK1 and FHL2 promotes proliferation, invasion and metastasis in colorectal cancer.	[140]
		FOXK1 induces EMT and promotes the invasion of colorectal cancer cells *in vitro* and *in vivo*. High expression of FOXK1 is associated with poor prognosis in colorectal cancer patients.	[90]
		FOXK1 promotes RUFY3-mediated metastasis via orthotopic implantation. Knockdown of FOXK1 in RUFY3-overexpressing colorectal cancer cells reversed EMT and metastatic phenotypes.	[136]
	FOXK2	FOXK2 promotes the proliferation of colorectal cancer cells. High expression of FOXK2 is significantly correlated with poor survival.	[141]
	FOXK1/2	FOXK1 and FOXK2 positively regulate Wnt/b-catenin signaling by promoting translocation of DVL into the nucleus. FOXK1 and FOXK2 protein levels are elevated in human colorectal cancers and correlate with DVL nuclear localization.	[51]
Lung cancer	FOXK1	FOXK1 expression is up-regulated by circMAN2B2 through sponging miR-1275 in lung cancer cells, which leads to the proliferation and invasion of cells.	[37]
	FOXK2	FOXK2 inhibits non-small cell lung cancer cell growth by suppressing the expression of cyclin D1 and CDK4. FOXK2 plays major roles in the inhibition of EMT of non-small cell lung cancer cell by directly targeting N-cadherin and Snail	[142]
Glioma	FOXK1	High expression of FOXK1 is associated with metastasis and increased tumor size of glioblastoma. Knockdown of FOXK1 significantly inhibits EMT and metastasis of GBM cells, while ectopic expression of FOXK1 promotes them.	[91]
	FOXK2	FOXK2 suppresses the proliferation, migration, and invasion of human glioma cells and predicts a favorable prognosis.	[143]
Hepatocellular carcinoma (HCC)	FOXK1	FOXK1 significantly increases the proliferation, migration and invasion of HCC, partly through activation of the Wnt/b-catenin signaling pathway.	[42]
	FOXK2	FOXK2 promotes cell growth and indicates unfavorable prognosis in HCC. High FOXK2 expression is associated with poor overall and disease-free survival in patients with HCC.	[92]
Ovarian cancer	FOXK1	FOXK1 promotes cell proliferation through regulating the expression of p21, and it promotes metastasis in ovarian cancer. The expression of FOXK1 is associated with tumor size, metastasis and poor prognosis.	[144]
Clear-cell renal cell carcinoma	FOXK2	FOXK2 inhibits the malignant phenotype and induces apoptosis of clear-cell renal cell carcinoma by inhibiting EGFR	[145]
Gastric cancer	FOXK1	FOXK1-directed regulation by C-jun facilitates the proliferation, invasion and metastasis of human gastric cancer.	[74]
Esophageal cancer	FOXK1	FOXK1 inhibits apoptosis and promotes the proliferation and migration of esophageal cancer cells. High FOXK1 expression is related to poor differentiation of esophageal cancer.	[146]

and SUMO3, and sumoylation enhances the stability of FOXK2 and plays a negative role in the proliferation of ERα-positive breast cancer cells (data not published). Bioinformatics analysis shows that FOXKs contains several potential PTM sites such as methylation, acetylation and ubiquitination apart from phosphorylation, suggesting that those PTMs could also involve in the regulation of FOXKs activity. It is well defined that PTMs interact with each other. Such modifications influence the functions of FOXKs by synergistic manner or compete with each other. Therefore, extensive studies on PTMs of FOXKs are required to further understand the molecular functions and regulatory mechanism of FOXKs.

3.4. Alternative protein–protein interactions modulate FOXKs activity

The activity of FOXKs can be modulated by other proteins through protein-protein interactions. As a transcription factor, FOXKs interact with a variety of proteins to promote or inhibit the expression of their target genes. Therefore, the co-regulators and general transcription factors expressed in a particular cell types are critical in determining the FOXKs activity. FOXK1 plays an important role in skeletal muscle regeneration through regulating the cell-cycle progression of myogenic progenitors [47]. Xiaozhong et al. revealed that FHL2, a LIM-only protein, directly interacts with FOXK1 via its LIM domain and forms a complex to repress the transcriptional activity of FOXO4 in myogenic progenitor cells [134]. Moreover, Sin3 binds to FOXK1 through its PAH2 domain and their interaction promotes cell cycle activity. The knockdown of Sin3 results in the cell cycle arrest and upregulation of cell cycle inhibitor genes [46], which indicates its critical role in the upregulation of FOXK1-mediated cell cycle progression. Sds3 is an adaptor protein, which is required to mediate the interaction between Sin3 and FOXK1. Sds3 directly binds to FOXK1 via phospho-Thr^{49}. Similar to Sin3, the knockdown of Sds3 also leads to decreased activity of FOXK1 and cell-cycle arrest in myogenic progenitor cells [45].

Mass spectrometric analysis revealed that FOXK1 and FOXK2 are targets of adenovirus (Adv) oncoprotein E1A, which directly interacts with FOXK1 and FOXK2 through a Ser/Thr-containing domain. A viral oncoprotein E6 also interacts with FOXK1 and FOXK2 through a motif similar to that of E1A. A molecular study found that E1A and E6 inhibit oncogenic transformation through their interaction with FOXK1 and FOXK2 [56]. MADS-box transcription factors SRF can also interact with FOXK1 and this interaction is required to regulate the expression of SRF target genes such as *smooth muscle (SM) α-actin* and *PPGB* [135]. FOXK1 acts as a transcriptional repressor of p21 during mitosis. The interaction of FOXK1 with a scaffolding protein, JNK associated leucine zipper protein (JLP) and PLK1 is essential to regulate the cell cycle dependent gene expression, which was confirmed by reduction of p21 at transcript level and increased level of FOXK1 protein upon knockdown of JLP [38], suggesting a novel mechanism of JLP dependent regulation of FOXK1 activity. In addition, RUFY3 is a RUN domain containing protein, which interacts with FOXK1, and this interaction stabilizes FOXK1 and promotes metastasis in colorectal cancer cells [136]. In contrast, the interaction of TET1 and FOXK1 in breast cancer cells suppresses the expression of FOXK1 target genes (such as *Twist*), leading to negative regulation of tumorigenesis [136]. FOXK1 and FOXK2 positively modulate Wnt/β-catenin signaling by interacting with DVL in colon cancer and this interaction promotes translocation of DVL to nucleus. In experimental animals, the overexpression of FOXK2 induces hyper-proliferation of intestinal cells by enhancing DVL nuclear localization and upregulation of Wnt/β-catenin signaling [51]. In lung cancer cells, BAP1 directly binds to FOXK2 via its Thr(P)-493 and recruits HCF-1 to repress the expression of FOXK2 target genes [48].

4. Implication of FOXKs in cancer progression

A tightly controlled expression and activity of FOXKs provide a balanced transcriptional network to ensure appropriate cell function and tissue development. Therefore, deregulation of FOXKs affect cell proliferation, differentiation, apoptosis, autophagy, migration, invasion and DNA repair, which are closely associated with cancer initiation, development, metastasis, angiogenesis and drug resistance (Table 2). A thorough understanding of FOXKs function in cancer progression will contribute to the development of better diagnostics and treatments for cancer.

4.1. Roles of FOXKs in cancer proliferation and initiation

The most remarkable characteristic of cancer is the constant proliferation and resistance to apoptosis of malignant cells. The oncogenic role of FOXK1 is closely associated with promoting cell proliferation and inhibition of apoptosis in a variety of cancers, including colorectal, gastric, esophageal, ovarian and lung cancer as well as hepatocellular carcinoma and glioblastoma [37,42,74,139,144,146,147]. FOXK1 expression is shown to be significantly up-regulated in multiple cancer tissues compared with that of in corresponding non-tumor tissues [74,139,146], which clearly indicates the oncogenic function of FOXK1. The oncogenic characteristic of FOXK1 may be partially due to its involvement in the positive modulation of cell cycle process. For instance, FOXK1 contributes to the G1 to S phase transition of ovarian cancer cells through targeting the expression of p21 [144]. In fact, FOXK1 regulates a large-scale network of genes critically involved in cell cycle progression, such as *PRC1*, *CDCA5*, *DHFR*, *CCNB1*, *GTSE1*, *TYMS*, *GSDMD*, and *TFDP1*. The knockdown of FOXK1 results in cell cycle arrest in many tumor cells including U2OS cells [54]. Moreover, the knockdown of FOXK1 significantly increases the percentage of in the G0/G1 phase, and decreases the percentage of glioblastoma cells in the S-phase [147]. Similar results have been reported in colorectal [139] and esophageal cancer [146], indicating the crucial role of FOXK1 in driving cancer initiation through regulating the cell cycle progression and proliferation.

Likewise FOXK1, FOXK2 acts as an oncoprotein by positively promoting the proliferation of colorectal cancer [141]. FOXK2 facilitates cell proliferation in hepatocellular carcinoma through targeting PI3K/AKT signaling pathway [92]. However, FOXK2 plays a negative role in cancer progression by suppressing tumor growth in other types of cancer [137,142,143,145]. *Cyclin D1* is a classical target gene of ERα, which plays an important role in governing the cell cycle entry and proliferative stage of a cell. In our previous study, we found that FOXK2 significantly decreases the expression of *Cyclin D1* in ERα-positive breast cancer cell line MCF-7, and it inhibits the cell cycle progression of MCF-7 by blocking transition from G0/G1 phase to S phase. FOXK2 suppresses the transcriptional activity of ERα by promoting its ubiquitin-mediated degradation, which results in the repression of MCF-7 cells proliferation [50]. In addition, FOXK2 suppresses proliferation and induces apoptosis of carcinoma cells through inhibiting the expression of its downstream target EGFR in clear-cell renal cell carcinoma [145]. Similar observations have been made in glioma [143] and non-small cell lung cancer [142]. These findings indicate that the function of FOXK2, as an oncoprotein or tumor suppressor, depends on the upstream regulations, and its diversity of functions in the cancer cell. Therefore, further studies are required in more types of cancer to determine whether FOXKs are suppressor or activator oncogenes, which would help to precisely utilize FOXKs-based therapeutics in particular type of cancer.

4.2. Roles of FOXKs in cancer angiogenesis

Angiogenesis is a physiological process that is indispensable in the formation of new blood vessels. A sustained angiogenesis is the crucial factor for cancer progression and it is critically involved in tumor growth and metastatic spread [148]. The angiogenic factors (e.g., vascular endothelial growth factor, VEGF) and oncoproteins are essential for the maintenance of an angiogenic phenotype of vessel cells that

contributes to cancer progression [149–151]. However, the detailed mechanism is still inconclusive. VEGF belongs to the platelet-derived growth factor (PDGF)/VEGF superfamily that is required for the vasculogenesis [152] and increased availability of these growth factors in pathological conditions, such as cancer accelerate angiogenic processes [153]. The stimulation of vascular endothelial cells by VEGF is a key step of angiogenesis, which promotes their proliferation and the formation of tubes [154]. FOXK1 is involved in this process, but its role in tumor angiogenesis is not clearly elucidated yet. In breast cancer cells, knockdown of FOXK1 results in the up-regulation of VEGF expression, whereas overexpression of FOXK1 decreased VEGF expression, indicating that *VEGF* is a downstream target gene of FOXK1. A molecular study found that FOXK1 inhibits the transcription of VEGF through directly binding to the promoter of VEGF in endothelial cells. This subsequently leads to the suppression of tube formation [155]. In addition, a significant increase of tumor vessel density was found in FOXK1-overexpressed colorectal cancer xenograft tumor [139,140]. Similar results also observed in gastric cancer [74]. Currently, the influence of FOXK2 on angiogenesis is still unclear. Although some progress has been made in investigating the functional mechanism of FOXKs on angiogenesis, further studies are still required to address the role of FOXK2 in angiogenesis.

4.3. Roles of FOXKs in cancer EMT

EMT is an essential process by which epithelial cells lose their characteristics including epithelial features, polarity and cell-cell adhesion, and gain migratory and invasive properties, which will eventually lead to increased metastasis ability of cells. EMT plays important roles in a number of developmental processes, such as mesoderm formation, myogenesis and neural tube formation [156–158]. EMT process is characterized by the up-regulation of several mesenchymal markers (e.g. Vimentin, N-Cadherin) and down-regulation of epithelial markers (e.g. E-cadherin) [159]. The aberrant activation of EMT is closely associated with the initiation of metastasis during cancer progression [160–163]. It is well documented that FOXKs are important regulators of EMT [74,137,140,142,143,147,155,164]. For example, FOXK1-overexpressing colorectal cancer cells exhibit a spindle-like fibroblastic morphology, which is a main characteristic of EMT. Moreover, ectopic FOXK1 expression up-regulates its target genes expression, including *Survivin*, *AP-1*, *ZEB1* and *TERT*, which are known to be involved in EMT. However, the knockdown of FOXK1 results in down-regulation of mesenchymal markers (vimentin and snail) and up-regulation of epithelial markers (E-cadherin and γ–catenin) in those cells indicating that FOXK1 can induce EMT in colorectal cancer cells [164]. Similarly, FOXK1 overexpression in gastric cancer cells induces the loss of cell-cell contact and the cobblestone-like phenotype. The expression of vimentin is upregulated, whereas E-cadherin expression is downregulated after a sustained expression of FOXK1 [74]. FOXK1 also promotes EMT in glioblastoma multiforme cells through activating its downstream target gene *Snail* transcription [147]. However, FOXK1 exhibits inhibitory role on EMT process in breast cancer cell line MCF-7 through suppressing its target Twis (EMT inducer) expression [155].

FOXK2 can inhibit the EMT process of MCF-7 cells through suppressing transcription of *Ezh2*. FOXK2-deficient MCF-7 cells exhibits a loss of cell-cell contacts, scattered appearance, and the cobble stone-like structure become a spindle-like fibroblastic morphology [137]. Molecular studies in non-small cell lung cancer and glioma cells found that FOXK2 inhibits EMT progress in those cells through the repression of its target genes, such as *N-cadherin* and *Snail* [142,143]. Collectively, these findings confirm the involvement of FOXKs in the regulation of EMT and they control the expression of EMT related genes, such as *Vimentin*, *E-cadherin*, *N-cadherin* and *Snail*.

4.4. Roles of FOXKs in cancer invasion and metastasis

Metastasis is a complex multistep pathological process, which plays a crucial role in the morbidity and mortality of cancer [148]. This process consists of several distinct steps including the degradation of the basement membrane and remodeling of stromal extra-cellular matrix, cell invasion and re-initiation of tumor cells at the secondary site [148,165]. During invasion and metastasis, the cancer cells migrate and colonize at secondary sites away from primary tumor. Although a considerable progress has been made in investigating the mechanisms of invasion and metastasis, the regulatory mechanisms of this process remain largely unknown.

In recent years, FOXK proteins are identified as the critical regulators of tumor invasion and metastasis. An increased expression of FOXK1 expression is highly correlated with metastasis. FOXK1 promotes the migration and invasion of ovarian cancer cells. This effect could depend on FOXK1-mediated regulation of MMP-9 expression [144]. In glioblastoma, the expression of FOXK1 is positively associated

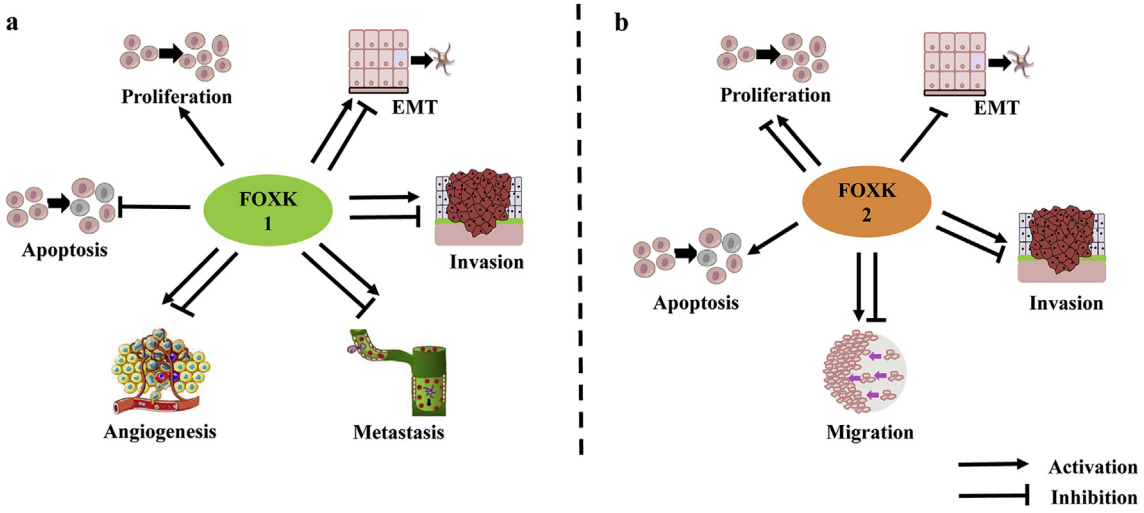

Fig. 3. Role of FOXKs in cancer progression. (a) FOXK1 mainly functions as an oncoprotein, and it facilitates cancer progression through promoting proliferation, EMT, invasion, metastasis, angiogenesis and inhibiting apoptosis in a variety of cancers. However, in breast cancer, it works as a tumor suppressor through inhibiting angiogenesis, EMT, invasion and metastasis. (b) FOXK2 mainly functions as a tumor suppressor through inhibiting proliferation, EMT, invasion and migration, and inducing apoptosis in most types of cancer. In colorectal and hepatocellular carcinoma, it works as an oncoprotein through promoting proliferation, invasion and migration.

with metastasis of this malignancy, and FOXK1 promotes metastasis of glioblastoma multiforme cells through activation of transcription of *Snail* [147]. Similarly, FOXK1 also promotes the invasion and metastasis of colorectal cancer through inducing EMT program [164]. Moreover, FOXK1 facilitates invasion and metastasis of colorectal cancer cells through interacting with FHL2 [140]. The FOXK1-dependent invasion and metastasis is also observed in hepatocellular carcinoma and gastric cancer [42,74]. However, FOXK1 inhibits invasion and metastasis of breast cancer cells through downregulation of EMT genes, such as *CDH2 (N-cadherin)*, *TWIST* and *VEGF* [155]. Similar to FOXK1, FOXK2 also exhibit differential effects on the invasion and metastasis of cancer depending on the malignant cell type. For example, a high FOXK2 expression is closely associated with vascular invasion of hepatocellular carcinoma. In experimental studies, the overexpression of FOXK2 promotes the cell migration, whereas silencing of FOXK2 results in the opposite phenotypes [92]. However, FOXK2 possesses negative effects in cancer invasion and metastasis in other types of malignancy including glioma, breast cancer, clear-cell renal cell carcinoma and non-small cell lung cancer [137,142,143,145]. Experimental studies using genetic ablation or overexpression of FOXK2 confirmed this notion in these types of cancer. The overexpression of FOXK2 inhibits cell migration and invasion, while FOXK2 knockdown enhances its migration and invasion in glioma [143], breast cancer [137], clear-cell renal cell carcinoma [145] and non-small cell lung cancer [142]. Collectively, these studies suggest that FOXKs is an effective target to prevent cancer invasion and metastasis as well as cancer progression.

In summary, both FOXK1 and FOXK2 have dual effects on cancer, and this may be dependent on the varying upstream regulations and their diversity of function. FOXK1 generally functions as an oncoprotein due to its role in promoting proliferation, cell cycle progression, metastasis, and inhibiting apoptosis among a variety of cancers. However, it acts as a tumor suppressor in breast cancer. By contrast, FOXK2 generally functions as a tumor suppressor in most types of cancer, except colorectal cancer and hepatocellular carcinoma (Fig. 3).

5. FOXKs and their clinical significance in cancer

A rapid progress has been made in therapeutic strategies for various types of cancer in recent years. However, there is still a high incidence and mortality among cancer patients due to heavy economic burden to patients' family. A large number of cancer patients are diagnosed only at an advanced stage due to the absence of any disturbing clinical symptoms during carcinogenesis. Therefore, the identification of specific and sensitive biomarkers is required for the early detection and the selection of cancer patients for individualized treatment. In recent years, numerous studies have revealed the key role of FOXK proteins in the pathogenesis of various types of cancer. Additionally, the differential expression of FOXKs in many human tumor specimens encourages their potential use as biomarkers for the diagnosis, prognosis and treatment of multiple malignant tumors. For instance, FOXK1 overexpression can be used as a biomarker to identify subsets of colorectal cancer with a more aggressive phenotype [164]. In addition, FOXK1 expression is identified as an unfavorable prognostic biomarker in colorectal and esophageal cancer [74,140,146]. However, overexpression of FOXK1 acts as a better prognosis factor in breast cancer [155]. FOXK2 is also well recognized as a biomarker in the cancer progression. The expression of FOXK2 is progressively lost during breast cancer progression, and its lower expression is strongly associated with the indicators of poor prognosis, including higher histologic grades, positive lymph nodes, and $ER\alpha^{-}/PR^{-}/HER2^{-}$ status, which suggests its potential role as a prognosis biomarker [137]. In addition, FOXK2 is also identified as a promising prognostic biomarker for glioma, HCC and gastric cancer [92,143,166]. However, there are several challenges in translating FOXKs as biomarkers for the diagnosis, prognosis and treatment for various types of cancers. Firstly, the exact relationship between the expression levels of FOXKs and the degree of tumor progression has not yet been established. Secondly, the correlation of FOXKs expression with different subtypes of tumors requires further clarifications. Thirdly, it is important to fully understand the association between lower expression of FOXK2 and chemotherapeutic resistance should be completely delineated, since increased expression of FOXK2 can enhance the sensitivity of breast cancer cells to drugs such as paclitaxel and epirubicin [138]. The potential values of FOXKs as biomarkers has been validated in studies with small sample size. Thus, larger population-based studies are still needed to further confirm the utilization of FOXKs as biomarker in cancer.

FOXK proteins could be efficient and potential targets for cancer treatment due to their crucial role in cancer progression. The increased expression of FOXK1 has been reported to promote the proliferation, migration, invasion and metastasis of multiple types of cancer [42,74,140,144,146], indicating the potential role of FOXK1 as a therapeutic target for patients with these cancers. Similarly, a high expression of FOXK2 is observed in colorectal cancer. FOXK2 is transcriptionally activated by SOX9, and this activation promotes the proliferation of colorectal cancer cells, indicating its potential therapeutic value for colorectal cancer therapy [141]. In addition, FOXK2 inhibits the progression of breast cancer [137] and clear-cell renal cell carcinoma [145], in which FOXK2 can serve as a potential therapeutic target. Thus, the screening or synthesis of chemotherapeutic drugs targeting FOXK proteins could provide a novel and valuable therapeutic strategy for the cancer treatment. Given the fact that FOXK proteins is directly regulated by several ncRNAs [37,87,92], the therapeutic regulation of FOXK-targeting ncRNA could also be a valuable strategy for cancer treatment. Currently, the available reports and data emphasize the potential clinical utility of FOXKs, however further studies are required for the clear understanding of the role of FOXKs in the sensitivity and resistance of chemotherapeutic drugs as well as their differential effect on various cancers.

6. Future perspectives

Members of FOXK family are important regulators of multiple physiological and pathological processes due to their role in governing the expression of many genes involved in cellular proliferation, apoptosis, cell cycle progression, DNA damage and carcinogenesis. A tightly controlled expression and activity of FOXKs deliver a balanced transcriptional program to ensure appropriate development, homeostasis and regeneration of tissues. In contrast, the deregulation of FOXKs results in the initiation, development and progression of a variety of diseases, including cancer. FOXK proteins are regulated by a variety of signaling networks. The intricate regulatory networks involved in controlling FOXKs activity are significantly altered in a number of human cancers. Therefore, FOXKs exhibit a great potential as therapeutic targets for a wide range of cancers. The differential expression of FOXKs in multiple types of cancers offers exciting possibility for cancer-tissue-specific therapeutic strategies. In addition, the enhanced expression of FOXK2 is crucial for sensitizing cells to chemotherapeutic drugs (paclitaxel or epirubicin) in breast cancer cell lines [138], indicating the feasibility of targeting FOXKs for chemotherapy. ERα is an efficient target of endocrine therapy in breast cancer. The level of functional ERα is essential for successful endocrine treatment of breast cancer [167]. We previously found that FOXK2 decreases the protein level of ERα by enhancing its degradation [50]. This study reveals the key role of FOXK2 in determining the sensitivity or resistance of endocrine treatment. As the emerging evidences indicate that ncRNAs have crucial role in regulating FOXKs, the signaling axis of ncRNAs-FOXKs is also a promising target for cancer treatment. However, more extensive studies not only required to elucidate the regulatory mechanisms and differential functions in various cancer cells, but also prerequisite to develop an efficient FOXKs-based therapeutic strategies and translate them to clinical settings.

Conflicts of interest

The authors report no conflicts of interest in this work.

Author's contributions

All authors read and approved the manuscript. Y.L., W.D., X.A., and JX.W. initiated the topic and wrote the manuscript. H.G., M.P., Q.W., and XD.H. contributed to discussion and revision of the article. W.W., Y.Z., and WP.Y. generated the figures. X.A., and JX.W. conceived the idea for the review.

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