FOXK2 transcription factor and its roles in tumorigenesis (Review)

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Abstract. Forkhead box K2 (FOXK2) is a central transcriptional regulator of embryonic development and cell homeostasis. Since its discovery, evidence has shown that FOXK2 mediates a variety of biological processes involving in genomic stability, DNA repair, cancer stem cell maintenance, cell proliferation, apoptosis and cell metabolism. The inherent structural characteristics of FOXK2 enable it as a transcriptional factor (TF) to cooperate with other active molecules in cancer development. FOXK2 mediates several significant chromatin events that are necessary for some chromatin accessibility and protein-protein interaction. FOXK2 is involved in the pathogenesis of a number of types of cancer as an oncoprotein or tumor suppressor depending on its interactive partners. Therefore, the loss of FOXK2 and its functions directly or indirectly affect the fate of cells. FOXK2 expresses differentially in a number of types of cancer and is involved in a number of aspects of carcinogenesis. However, its roles in tumorigenesis remain largely unexplored. The present review focused on the latest findings and evidence on the broad roles and possible mediating mechanisms of FOXK2 in carcinogenesis. The recent findings about FOXK2 may shed light on the direction of future FOXK2 research in tumorigenesis.

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1. Introduction

Forkhead box K2 (FOXK2), a central transcriptional regulator of embryonic development and cell homeostasis, was initially recognized as an essential member of the FOX family. Since its identification, evidence available has shown that FOXK2 mediates a diverse range of biological processes, such as cancer genetics and biology (1-4). However, the biological functions of FOXK2, especially functional redundancy and non-functional redundancy, remain largely unexplored. Functional redundancy is a property of transcription factors (TFs) that allows one TF to compensate for another due to their protein sequence homology, or the shared molecular chaperone (5-7). Non-functional redundancy of TFs serves a more important role in the cell fate conversions. Thus, loss of FOXK2 function or the absence of gain-of-function, directly and indirectly, affect tumorigenesis. Over the past 30 years, the hallmarks of cancer are defined as the collection of acquired biological capabilities during the multistep development of human tumors (8-10). It is well known that TFs are actively involved in the acquisition of biological capabilities in human tumors. As, to date, there is neither commercially available FOXK2 inhibitors/drugs nor convincing clinical trials of its use as a therapeutic target, the present review outlined the broad roles and possible mediating mechanisms of FOXK2 in carcinogenesis. Finally, it highlighted that the functional redundancy and non-functional redundancy of FOXK2 maps to tumor pathogenesis. This relationship may influence the direction of future FOXK2 research in tumorigenesis.

2. Structure of FOXK2

FOXKs are members of an evolutionarily conserved TF family that share a forkhead DNA-binding domain with their binding partners. The binding occurs at a conserved core sequence (TTGTTTAC) and mediates various chromatin events (11-14). For example, FOXK2 recognizes and binds to a purine-rich motif in the long terminal repeats of the

human immunodeficiency virus and is identified as an interleukin-enhancing factor-binding factor (ILF). This behavior was demonstrated in a study of genes encoding cytokines (15).

The *FOXK2* gene is located on human chromosome 17q25.3. As shown in Fig. 1, the gene is translated into a functional FOXK2 protein including 660 amino acids with a FOX domain containing a nuclear localization signal (NLS) that can bind to DNA minor groove and a forkhead-associated (FHA) domain (15,16). A phospho-threonine-containing polypeptide FHA domain in FOXK2 and FOXK1 serves as a defining differentiator from other FOX TFs (17,18). Such phospho-threonine/serine-binding domains are essential in metazoans as their interaction targets are primarily involved in cell cycle and DNA damage responses (19).

The role of alternative splicing in cancer is multifaceted and the activity of tumor suppressors and oncogenes is altered by alternative splicing (20,21). These changes are preferentially found in cancer cells and often manifest at the protein level as structural changes (22), removal of phosphorylation sites (23), or changes in subcellular localization (24). As with most human genes, *FOXK2* mRNA undergoes some degree of alternative splicing (25) and three isomers have been identified. The three isomers, termed ILF-1, ILF-2 and ILF-3, encode proteins with lengths of 655, 609 and 323 amino acids, respectively. The GenBank database (https://www.ncbi.nlm.nih.gov/genbank) labels them as FOX protein K2 isoforms X1, X2 and X3.

Structurally, all three proteins contain a signature proline-rich FHA domain. However, in contrast to ILF-1 and ILF-2, which contain a complete forkhead domain (FKH), ILF-3 contains a partially missing FKH (NCBI; https://www.ncbi.nlm.nih.gov). Although the significance of the complete FKH domain existence or absence is unclear, ILF-3 does lose the majority of potential phosphorylation sites in the COG5025 (GenBank, Ser180 to Gln577) region (26). There is evidence that alternative splicing alters protein phosphorylation, thereby limiting the effect of the kinase cascade signal (27-30). However, there is still a lack of research data on FOXK2 alternative splicing. Chromatin immunoprecipitation followed by sequencing (ChIP-seq) allows analysis of chromatin binding to TF and this particular technique may help answer a number of open questions about FOXK2 functions. The function of FOXK2 proteins is also closely related to their dynamic allocation in different subcellular structures. Therefore, understanding this new aspect and studying the regulatory mechanism help to elucidate its dynamic transcriptional role in mRNA expression of target genes. This understanding is critical to evaluating how it promotes health and disease (28,31).

The NLS is a motif that allows for active nuclear import of large proteins. However, the nuclear translocation of certain proteins does not appear to be dependent on the NLS of FOXK2. For example, FOXK2 mediates Disheveled (DVL) nuclear translocation according to its FHA and adjacent region (residue Arg129-Pro171) (32). Thus, there is no credible evidence to support the effect of NLS on FOXK2 functionality.

Over the past decade, the unexpected functional redundancies and non-functional redundancies of FOXK2 have become increasingly attractive prospects for researchers to explore. There is growing evidence that FOXK2 serves a vital role in various biological processes, especially in cancer cells, including in proliferation, differentiation, cell cycle progression, apoptosis and metabolic reprogramming.

3. Molecular mechanisms underlying the regulation of FOXK2

The regulation of FOXK2 activity has been extensively studied. In addition to regulation of mRNA expression, post-translational modifications (PTMs; Fig. 1), non-coding RNA (ncRNAs) and protein interactions also serve important roles in the loss or gain of FOXKs functions (4,33) (Figs. 2-4). PTMs affect the stability of transcriptionally active proteins. PTMs also control how these proteins interact with other molecules and serve different roles in various developmental processes in both internal and external settings, whether favorable or unfavorable (34-39). The most common PTMs are glycosylation modification, phosphorylation, methylation, acetylation, ubiquitination, sulphuration and reduction/oxidation (redox) modifications (40). Notably, epigenetic mechanisms including DNA cytosine modifications, histone modifications and regulation by ncRNAs are prominent epigenetic regulatory elements (41,42).

FOXK2 and methylation. DNA methylation is an evolutionarily ancient epigenetic modification that regulates FOXKs at the transcriptional level (43,44). These epigenetic modifications are closely associated with the aging process and regulate the transcriptional profile of DNA fragments by packaging them (43,44).

A considerable body of evidence suggests that ~1% of the human genome is methylated and methylated markers of gene promoter regions control gene expression (45-47). In addition, DNA methylation has been implicated in mediating transcriptional silencing, although the particular molecular pathways are not fully understood (48). Transcriptional silencing serves a vital role in critical biological processes such as replication, division, development survival, aging, genomic imprinting and embryonic development as facultative chromatin, especially in cancer development (49-54).

Several studies have demonstrated a preference for methylated markers for genomic site selection (55-57). Methyl groups are attached to 5-methylcytosine (5mC) throughout the genome, typically between cytosine and guanine (CpG) or within CpG islands polymerized by CpGs (55). This finding was further exemplified in a global causal analysis involving firefighters exposed to various environmental hazards. As expected, this controlled analysis revealed differential methylation loci in *FOXK2*. Three CpG loci in *FOXK2* were shown to be located in CpG islands and they exhibited reduced methylation (56).

FOXK2 is an effector of DNA methylation. FOXK2 methylation is a meaningful indicator of fertility. High levels of FOXK2 methylation are closely associated with male infertility (58). Furthermore, FOXK2 hypomethylation induced by dioxin exposure can also negatively affect male reproductive health (59).

The effect of FOXK2 methylation can also be observed in the following examples of interaction with a range of environmental factors. A recent study analyzed genome-wide DNA methylation profiles of white blood cells. It found that FOXK2 hypermethylation levels were strongly associated with
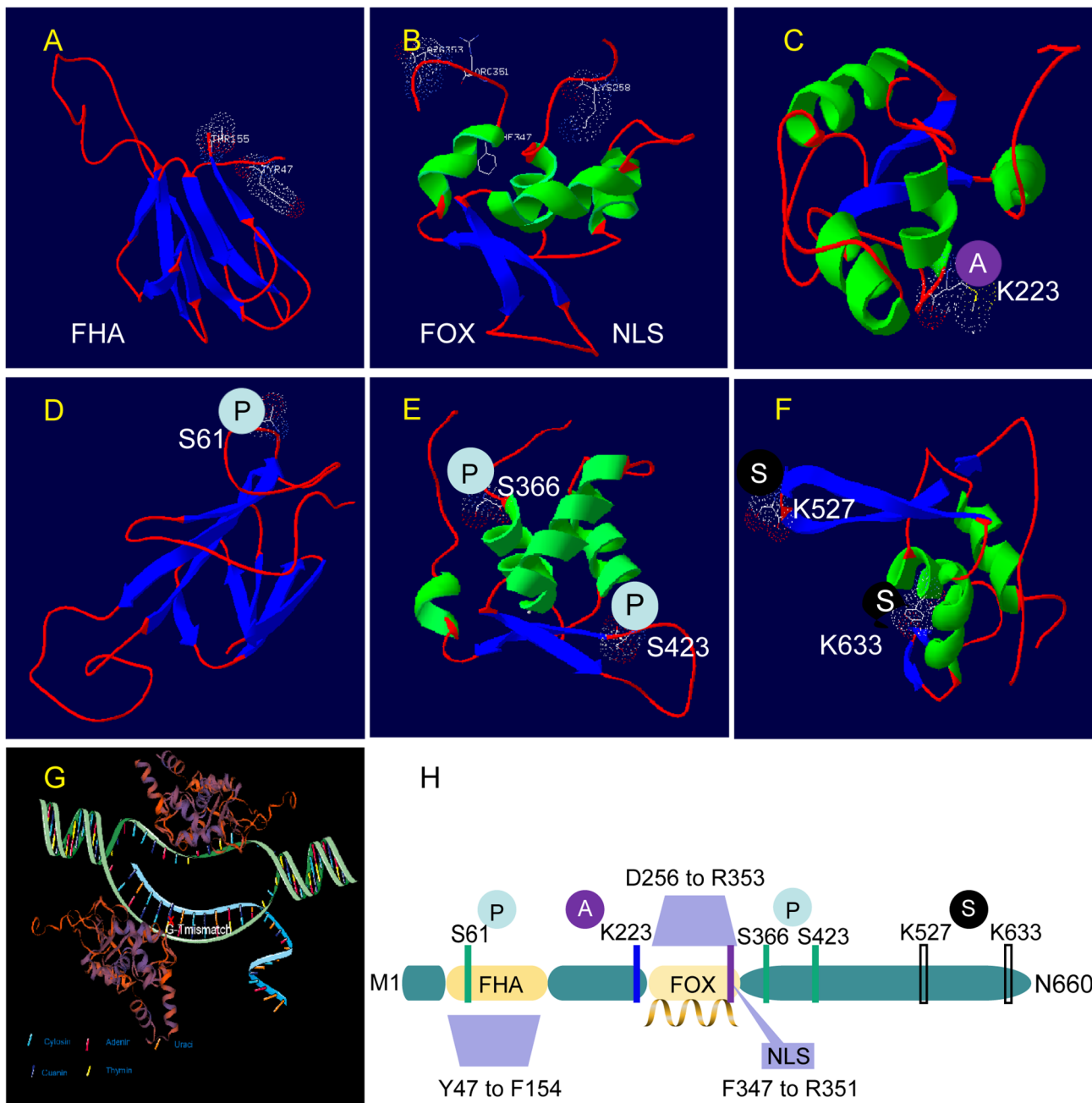
Figure 1. Illustration of the FOXK2 protein domain, PTM sites and G/T mismatches. (A) FOXK2 consists of a FHA domain (Tyr47 to Phe154). (B) FOXK2 also contains a highly conserved forked DNA-binding domain (FOX, Asp256 to Arg353) containing a NLS that can bind to DNA minor groove. (C-F) FOXK2 PTMs are illustrated, with acetylation, phosphorylation and SUMOylation sites shown. (G) FOXK2 binds to a consensus sequence with a GTAAACA core motif and FOXK2 recognizes G/T mismatches. (H) A 2D diagram of the structure of FOXK2. FOXK2, Forkhead box K2; PTM, post-translational modifications; FHA, forkhead-associated; NLS, nuclear localization signal.

smoking levels and also varied across racial/ethnic groups (60). Notably, hypermethylation can be observed in patients with severe psychophysiological trauma (61) and arsenic toxicity *in vivo* (62). The potential implication of this meaningful evidence is that FOXK2 methylation levels are associated with physiological stresses caused by environmental exposure. However, there is a lack of research on the relationship between changes in FOXK2 methylation levels and psychological stress and toxic transformation.

There is also considerable interest towards understanding the effects of certain lifestyle factors on FOXK2 methylation modification. In CpG islands of adipose tissue, methyltransferase

nicotinamide n-methyltransferase (NNMT) levels are influenced by diet and exercise. FOXK2 methylation levels are inversely correlated with NNMT (57), further supporting the link between environment and methylation levels.

Abnormal increases in methylation are associated with the inactivation of tumor related genes (63,64). A study examining genome-wide DNA methylation profiles of fibromatoid-like fibroma tumors involving FOXK2 showed that hypermethylation reduced FOXK2 mRNA expression (65).

Additionally, FOXK2 has also been identified as a dynamic reader of DNA methylation, mediating the interaction of methylated binding domain (MBD) deficient transcription
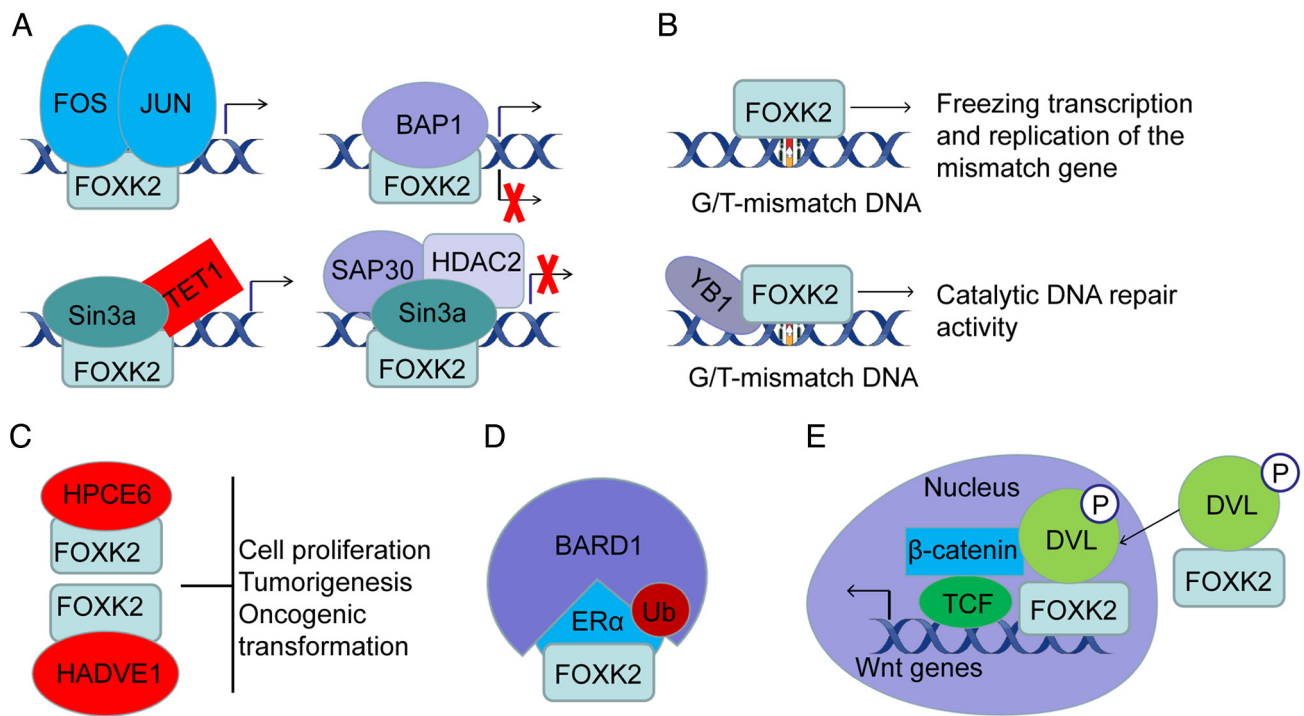
Figure 2. Protein interactions serve an important role in the loss or gain of FOXKs function. (A) FOXK2, as an important component of transcription co-inhibitory complex or transcription activation complex, inhibits or activates its target genes. (B) As a novel G/T mismatch DNA binding protein, FOXK2 serves an important role in determining the future of G/T mismatch DNA. (C) FOXK2 can bind to E1A and E6 viral proteins as a tumor suppressor protein. (D) FOXK2 acts as ERα and BARD1 scaffold protein and negatively regulates the expression of ERα and target genes. (E) FOXK2 interacts with DVL as a transfer protein and promotes nuclear translocation of DVL, which in turn activates the Wnt signaling pathway. FOXKs, Forkhead box K; ERα, estrogen receptor α; BARD1, BRCA1-associated RING domain protein 1.
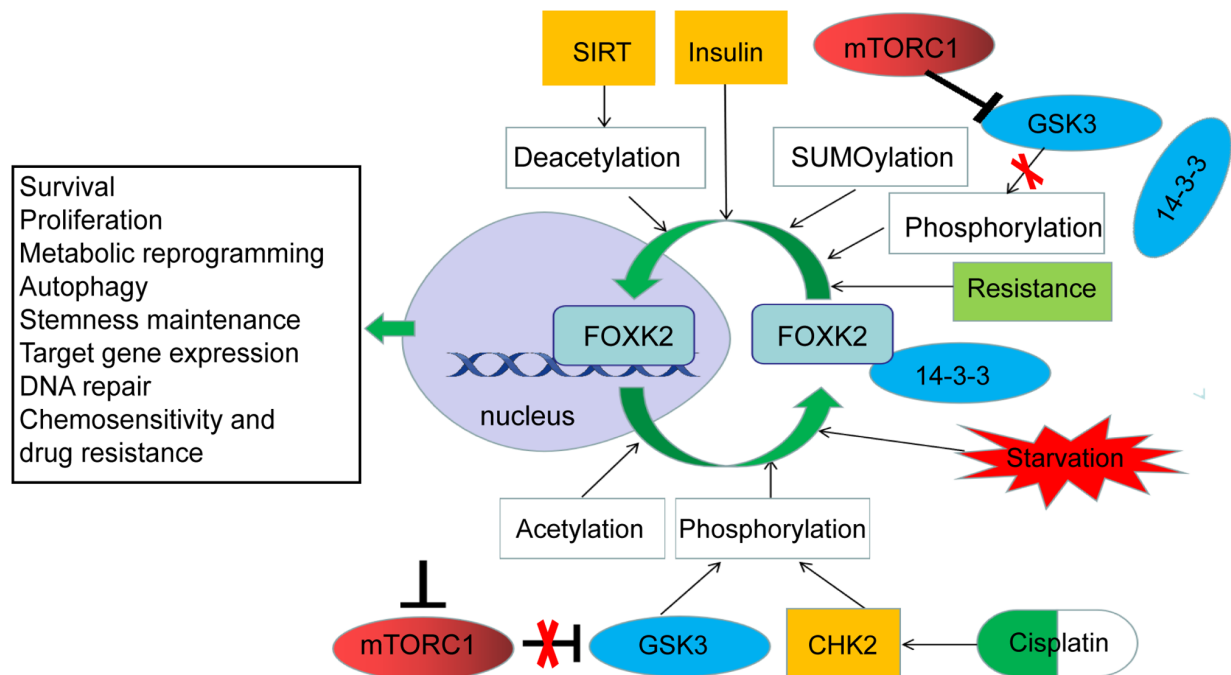

Figure 3. PTMs and other factors influence and regulate the nuclear-plasma shuttle of FOXK2 and control its interactions with other biomolecules and regulation of target genes. PTM, post-translational modifications; FOXK2, Forkhead box K2; SIRT, silencing of information regulator 2-related enzyme; mTORC1, mTOR complex 1; GSK3, glycogen synthase kinase-3; CHK2, checkpoint kinase 2 protein.

factors with methylated DNA (66,67). Several specific homologous framework proteins and proteins with wing-like helix domains, including FOXK2, can recognize methylated CpG

(mCpG) (66,68,69). FOXK2 has been shown to bind methylated DNA 5mC and the oxidative derivative 5-formylcytosine to recruit relevant functional proteins in mouse embryonic stem

Figure 4. ncRNAs serve an important role in the loss or gain of FOXK2 function. ncRNAs, non-coding RNAs; FOXK2, Forkhead box K2; miR, microRNA; circ, circular RNA; lncRNA, long non-coding RNA.

cells (66,67). Although FOXK2 can be used for MBD screening and serves an important role in coordinating transcriptional replication and DNA repair, it is not clear how a number of MBD-deficient TFs might be recruited by FOXK2 (70).

FOXK2 and phosphorylation. The dynamic regulation of phosphorylation is undoubtedly the most common and well-studied PTM (71,72). Phosphorylation with rapid and reversible properties profoundly modulates a wide range of proteins at a relatively small dynamic cost, controlling the balance between phosphorylation and dephosphorylation events (73,74).

The unique FHA domain of FOXK2 makes it an 'intelligent' sensor in complex networks related to cell signal cascades. It contributes to genomic stability, cell growth maintenance,

cell cycle regulation and signal transduction (75). These functions have been partially validated in yeast. The yeast FOX proteins Fkh1 and Fkh2 (homologs of human FOXK1 and FOXK2 proteins) are phosphorylated by Cdc28p, the primary cycle-dependent kinase in yeast, in a cell cycle-dependent manner (76,77). Changes in Fkh2 activity can affect pseudomycelia growth through transcriptional regulation of genes involved in M-phase transition (76). The cyclin-dependent kinase 1 (CDK1) phosphorylates FOXK2 at Ser368 and Ser423 in the COG5025 domain. The phosphorylation fluctuates periodically and reaches its peak in the M phase (26). In human osteosarcoma cells, CDK1-mediated phosphorylation of FOXK2 (S368/S423) negatively regulates its stability and inhibitory activity and thus inhibits tumor cell apoptosis (26).

Additionally, phosphorylation exerts a regulatory effect by modulating the subcellular localization and translocation of FOX family members and also regulates their interaction with chaperone proteins (78-80), such as 14-3-3, a hub-protein of complex network of protein-protein interaction that has several hundred identified protein interaction partners and is therefore involved in cellular processes and diseases (81). A recent study on autophagy showed that ataxia-telangiectasia mutation (ATM) mediates phosphorylation of checkpoint kinase 2 protein (CHK2) at Thr68 after DNA damage, which is critical for binding to the FHA domain of FOXK. This binding enables FOXK1 and FOXK2 to be phosphorylated by CHK2 at Ser130 and Ser61, respectively. Then, the phosphorylated FOXK protein is captured in the cytoplasm by 14-3-3γ and this affects the transcription of autophagy-related (ATG) genes (1). Phosphorylation-induced subcellular localization affecting cell metabolic reprogramming has also been demonstrated. By blocking mTOR complex 1 (mTORC1) and then eliminating its inhibitory effect on glycogen synthase kinase 3, both FOXK1 phosphorylation and its interactions with 14-3-3 ε are increased, resulting in reduced expression of multiple genes involved in glycolysis related pathways (2). However, whether all 14-3-3 subtypes or some of them indiscriminately trap FOXK2 remains unclear. Nutrition-related signals such as insulin and amino acids activate mTORC1 to induce protein phosphatase 2A (PP2A)-mediated dephosphorylation of the FOXK1 (82). This effect reduces the production of insulin-induced C-C chemokine ligand 2 (CCL2) (83). FOXK1 and FOXK2, like their FOXO subfamily partners, are downstream targets of insulin action (82). However, unlike FOXO1, insulin stimulation directs the translocation of FOXK proteins from the cytoplasm to the nucleus in an AKT-mTOR pathway-dependent manner (84). This translocation controls the expression of genes involved in regulating mitochondrial β-oxidation and biogenesis in the nucleus (85). Descriptions of FOXK2 translocation between nucleus and cytoplasm are helpful in understanding the functions of FOXK2 in signal transduction and gene expression regulation, but studies on this shuttle mechanism are scarce.

It is important to note that although some studies only investigated FOXK1, the results have practical reference significance for FOXK2 due to their high degree of similarities in the domain and protein sequence, with amino acid homology approaching 50% (86,87). Furthermore, studies on the clustering of FOXK1 and FOXK2 samples support the hypothesis of functional overlap of FOXKs. For example, one study found that single and double knockdowns of FOXK1/FOXK2 upregulated the expression of apoptosis-related genes and downregulated the expression of genes related to cell cycle and lipid metabolism (84). Additionally, FOXK1 and FOXK2 have a significant positive effect on the regulation of glycolysis, as they share a common regulatory substrate preference (glucose and fatty acid) and can upregulate the expression of enzymes required in glycolysis, which in turn regulate lactic acid production (88).

In addition to the examples mentioned above, in FOXK1 knock-out (KO) cells, several genes that participate in hormone biosynthesis, monoamine transport regulation, hematopoietic stem cell differentiation and integrin activation are downregulated. This gene regulatory profile is similar to that of FOXK2

KO cells, suggesting functional similarities between FOXK1 and FOXK2 in regulatory targets (89). However, the extent to which they cause physiological or pathological overlap, as well as non-redundant functions, remain to be elucidated.

FOXK2 and SUMOylation and ubiquitination. Several studies have shown that FOX-protein stability, DNA binding activity and interactions with chaperones are also regulated by SUMOylation (90-94). These regulatory activities are well represented in breast cancer cells, where FOXK2 SUMOylation serves a key role in mediating chemical sensitivity and resistance to paclitaxel. Paclitaxel treatment of breast cancer cells requires the SUMOylation of FOXK2 at the K527 and K633 sites for their cytotoxic function. The SUMOylation of FOXK2 significantly increased its binding to the *FOXO3* promoter, leading to upregulation of FOXO3 mRNA and protein levels. Conversely, FOXK2 accumulates in the nucleus of paclitaxel-resistant breast cancer cells, but recruitment to endogenous *FOXO3* promotors is impaired (95). FOXK2 does this by dynamically regulating subcellular localization and binding to target genes such as tumor suppressor FOXO3. However, the more detailed regulatory mechanisms remain to be elucidated.

The mechanisms of ubiquitination have been extensively studied. Ubiquitination primarily consists of mono-ubiquitination and polyubiquitination and it regulates a diverse range of physiological and pathological activities (96,97). Ubiquitination and deubiquitination events of substrate proteins have significant effects on several aspects of cell life, such as cell cycle regulation, apoptosis, receptor downregulation and gene transcription (98-100). The ubiquitin-proteasome system include ubiquitin ligases (E1, E2 and E3), proteasomes and deubiquitination enzymes (DUBs) (96,97). The unique roles that these proteasomes and enzymes serve in tumor inhibition and tumor inhibition pathways are well documented, such as in tumor metabolism regulation, immune tumor microenvironment (TME) regulation and cancer stem cell maintenance (101).

The PcG-repressive (PR)-DUB complex catalyzes the deubiquitination of H2A at lysine 119 (102). Although several models for the PR-DUB complex's inhibitory function have been reported, how it mediates gene inhibition is still not fully understood (103-106). FOXK1 and FOXK2 are considered to be indispensable components of three mammalian PR-DUB complexes, including breast cancer type 1 susceptibility protein (BRCA1) associated protein-1 (BAP1, homolog of human Calypso), host cell factor C1 (HCFC1) and additional sex combs-like proteins (103). Notably, BAP1 DUB has been reported to function as a FOXK2 chaperone in human cells in a FOXK2 FHA-dependent manner (107). Furthermore, BAP1 functions as an important tumor suppressor protein in several different tumor types and can deubiquitinate histone H2A to regulate transcription (108-110). In the absence of BAP1, FOXK2 fails to recruit BAP1, losing the ability to inhibit oncogenesis by directing BAP1 to its target gene (111). The relationships between the various components of the PR-DUB complex have been extensively studied. However, the link between FOXK2 and enzymes responsible for regulating protein O-GlcNAc modification, including OGT and glycoside enzyme (O-Glcnase, OGA), has not been adequately studied.

FOXK2 and acetylation. Acetylation is involved in almost all cellular biological processes, including cancer. FOXK2 can affect the acetylation of proteins of interest and the transcription of target genes. A study of the FOXK proteins in hunger-induced atrophy and initiation of autophagy found that FOXK1 and FOXK2 restrict the acetylation of the target genomic protein H4 and the expression of essential autophagy genes. FOXK1 and FOXK2 achieve this restriction by recruiting the suppressor-interacting 3A (Sin3a) histone deacetylation enzyme (HDAC) complex (85). There is also evidence that FOXK2, as a transcription inhibitor, can interact with proteins in the Sin3a HDAC co-inhibitory complex in human cells (105). Despite growing evidence of non-histone acetylation affecting a range of cellular processes (112,113), the regulatory role of lysine acetylation in cancer cells remains to be elucidated. Lysine residue in FOXK2 can also be modified by acetylation. The acetylation levels at the K223 site in FOXK2 are directly related to the sensitivity of tumor cells to cisplatin. In cancer cells, cisplatin can enhance the acetylation of FOXK2 K223, reduce the nuclear distribution of FOXK2, significantly downregulate the expression of cell-cycle-related genes and significantly upregulate the expression of apoptosis-related genes. FOXK2 K223 hyperacetylation can even promote mitotic catastrophe (114). However, in cisplatin-treated cancer cells, the silencing of information regulator 2-related enzyme 1 reduces the effect of deacetylation of FOXK2 K233 on cell apoptosis (114). This finding has far-reaching implications for understanding chemical sensitivity and drug resistance in cancer and warrants further in-depth studies in the future.

FOXK2 and ncRNAs. Thanks to rapid advances in sequencing technologies, several unique ncRNA sequences have been identified. MicroRNAs (miRNAs/miRs), circular RNAs (circRNAs) and long ncRNAs (lncRNAs) control numerous molecular targets, mediate cellular processes and determine cell fate (115,116).

ncRNAs are RNA molecules lacking protein-coding regions responsible for regulating gene expression at the transcriptional or post-transcriptional level (117-120). These functional regulators link relevant genes into regulatory networks, with some ncRNAs, such as miRNAs and lncRNAs, possibly regulating the mRNAs of several target genes. Moreover, the mRNA of a specific gene can be regulated by multiple miRNAs (121,122). Notably, some ncRNA cross-talk imparts robustness to biological processes, supporting their role as crucial regulators. The noise of these complex interactions can profoundly impact cell fate, especially in cancer (121,123).

FOXK2 and microRNAs (miRNAs). miRNAs are endogenous and abundant. They are RNA sequences that are ~22 nucleotides long and can be associated with the corresponding miRNA response elements (124,125). These miRNAs, composed of 18-25 nucleotides, bind with other proteins to form RNA-induced silencing complexes that target the 3'-untranslated region (3'-UTR) of mRNA. This function regulates the translation of mRNAs involved in biological processes such as cell proliferation, apoptosis, differentiation and transformation (126-129). In a study involving granulosa cells (GC), miR-204, a downstream regulator of the phospho-inositol 3-kinase (PI3K)/AKT/mTOR signaling

pathway, directly targets FOXK2 and results in promoting GC proliferation and inhibiting apoptosis (130). In hepatocellular carcinoma (HCC), FOXK2 is a direct target of miR-1271, which negatively regulates FOXK2 at the mRNA and protein levels (131). A study assessing epithelial-mesenchymal transition and proliferation in non-small cell lung cancer (NSCLC) confirmed that the FOXK2 3'-UTR site (position 40-47) (GUGCCAA) is directly targeted and negatively regulated by miR-1271 (132).

Notably, miRNAs that regulate FOXK2 are affected by epigenetic and environmental changes. In various esophageal squamous cell carcinoma (ESCC) studies (133,134), hypo-methylation of the miR-602 promoter induced expression and negatively regulated the target gene *FOXK2*. It regulated the cell cycle by promoting the proliferation and metastasis of ESCC *in vitro* and *in vivo*. Notably, reduced FOXK2 expression significantly accelerated the biological pathway mediated by miR-602 overexpression (134).

Some metabolic substrates and drugs also induce miRNA expression. Under high glucose conditions, the expression of miR-140-3p in endothelial cells (ECs) was significantly decreased. The low level of miR-140-3p lost the inhibitory effect on the expression of FOXK2, thereby enhancing the angiogenic function of ECs (135). In hirsutanol A (HA)-pretreated A549 cells, upregulation of miR-204 directly targets FOXK2, promoting cell viability by reducing apoptosis and inhibiting the release of inflammatory factors by attenuating NF-κB activation (136).

FOXK2 and circRNAs. circRNAs possess a continuous loop of at least a few hundred nucleotides and a covalently closed loop, resulting in a higher degree of stability compared with most linear RNAs (137,138). Ashwal-Fluss *et al* showed that circRNAs are produced through co-transcription and competition with conventional splicing (139). Several circRNAs are closely associated with tumor development and progression; however, the details of their regulatory mechanisms remain inconclusive (140-142). Intriguingly, two studies conducted in 2013 showed that two circRNAs, CDR1-as (also known as CIRS-7) and sex-determining region Y (Sry), act as sponges for miRNAs that regulate transcription of specific miRNAs (143,144). That circRNAs act as sponges for miRNAs to influence the transcription of target genes is now widely accepted (145,146).

Circ-ITCH has been reported to significantly affect several biological characteristics of tumors by acting as a tumor suppressor (147,148). Knockdown of circ-ITCH expression in human cervical cancer (CC) tissues and cell lines attenuated the inhibitory effects of circ-ITCH on the malignancy of CC cells (149). The presence of a circ-ITCH/miR-93-5p/FOXK2 axis was further explored in that study; miR-93-5p has been shown to function as a tumor promoter in several types of cancer (150-152) and it is significantly upregulated in CC tissues and cell lines (153). The researchers confirmed that circ-ITCH could directly bind to miR-93-5p using bioinformatics tools and this was confirmed using a luciferase reporter assay. FOXK2 expression was significantly downregulated in CC tissues. The study also confirmed that FOXK2 was a target of miR-93-5p using TargetScan and this was verified using a luciferase reporter assay. miR-93-5p mimics significantly inhibit FOXK2 expression in HeLa cells and FOXK2

knockdown significantly reduced FOXK2 expression in HeLa cells transfected with a miR-93-5p inhibitor (153). In summary, circ-ITCH achieves its tumor-suppressive activity by sponging miR-93-5p to regulate FOXK2 expression and its role as a tumor suppressor in several types of cancer is well established and reviewed elsewhere (154).

Another example of a circRNA acting as a sponge can be found in clear cell kidney cells (ccRCC). The novel circRNA UBAP2 acts as a miRNA sponge to regulate miR-148a-3p, which itself affects FOXK2 mRNA and protein levels and influences ccRCC cell proliferation, migration and invasion (155). In addition, a study on pulmonary fibrosis showed that circHIPK3 enhances FOXK2 expression by sponging miR-30A-3p, thereby promoting fibroblast activation proliferation and glycolysis (156).

FOXK2 and long non-coding RNAs (lncRNAs). lncRNAs are transcripts that do not encode proteins and are often >200 nucleotides (157,158). lncRNAs are presently hypothesized to serve vital roles in several cellular processes, including cell cycle regulation (159), differentiation (160-162), metabolism (163) and various diseases (164,165). One study has shown that certain lncRNAs are involved in cancer progression through the adsorption of miRNAs via sponging (166). lncRNAs can also regulate FOXK2 expression. Emerging evidence suggests that lncRNA tumor protein 53 target gene 1 (*TP53TG1*), enriched in CC, sponges the FOXK2-targeting miR-33a-5p and thus increases FOXK2 expression. This increase in FOXK2 expression promotes related protein activity, activates the PI3K/AKT/mTOR signaling pathway and increases tumor biological activity (167). It has been reported that *TP53TG1* functions as an oncogene in several types of cancer (168,169) and miR-33A-5P can function as a tumor suppressor gene in several other types of cancer (170-172). Similarly, lncRNA small nucleolar RNA host gene 7 (*SNHG7*) also functions as an oncogene to promote HCC tumor growth *in vivo* via a miR-122-5p/FOXK2 axis. In addition, lncRNA SNHG7 abrogated the negative regulation on FOXK2 through the sponging of miR-122-5p and promoted the occurrence and development of liver cancer (173). The mechanism of FOXK2 as a repressor and activator of gene transcription remains to be further studied.

FOXK2 and chaperones. A number of molecules have been shown to interact with FOXK2, which interacts with other transcription factors and active proteins as a key to carrying out its regulatory functions. Protein kinases are one of the most common partners that interact with FOXK2. Their interactions are involved in a variety of cellular functions, including metabolism (84,88), autophagy (1), cell cycle regulation (26), cell proliferation and survival (174) and changes in subcellular localization (2). FOXK2 binds to oncoproteins; Qian *et al* (175) reported that the sex-determining region Y box 9 (SOX9) oncoprotein directly binds to the FOXK2 promoter, significantly upregulating its mRNA expression levels. FOXK2 also interacts with activating and inhibiting proteins. For example, FOXK2 efficiently recruits activating protein-1 (AP-1) transcription factors to chromatin and binds to them, contributing to AP-1-dependent gene expression changes (176). In addition, FOXK1 and FOXK2 can recruit the Sin3a HDAC complex to inhibit the expression of essential autophagy genes (87). Notably, FOXK2 appears to recruit Sin3a HDAC complex and BAP1 impartially. The mechanism of this differential recruitment is unclear and further studies are necessary to elucidate the molecular mechanisms underlying the differing epigenetic modification preferences of local chromatin. FOXK2 functions well with proteins exhibiting similar functions. For example, methyl-CpG binding domain proteins (MBD6) and FOXK2 are prime candidates for MBD proteins and DNA methyl-dissociation reading. However, MBD6 is recruited to laser-induced DNA damage sites in a manner independent of its MBD domain and interacts with PR-DUB (69,70,177,178).

FOXK2 interacts with members of its family. An excellent example of FOX interfamily interactions is the dynamic occupancy model of FOXK2 and FOXO3a for shared binding modes. The two genes dynamically correlate and isolate rather than directly competing to control their FOXO-dependent gene expression functions (179).

FOXK2 binds to viral proteins. One study demonstrated that FOXK1 and FOXK2 interact with the c-terminal region of the adenovirus (HAdV) protein E1A, inhibiting HAdV E1A-induced proliferation and transformation in cells (180). DVL2, an adaptor protein of Wnt/β-catenin signaling, serves an important role in the development of colitis-associated colorectal cancer (CRC) by linking the inflammatory NF-κB signaling pathway to the Wnt/β-catenin signaling pathway (181). FOXK2 associates with DVL2 and migrates to the nucleus to positively regulate the Wnt/β-catenin signaling pathway (181). The PDZ domain of DVL2 and a four-amino acid motif named IVLT are necessary when binding to the FHA domain on FOXK2 and its adjacent region (residue ~129-171) (32).

FOXK2 acts as part of a scaffold protein complex. Scaffold proteins are high-order complexes that bind at least two protein partners together, specifically recruiting signaling proteins, within the delicate tissue framework to achieve temporal and spatial control of specific pathways (182-185). For example, a breast cancer study showed that FOXK2 interacts with BRCA1 as a scaffold protein for BReast-CAncer susceptibility gene 1 (BRCA1)/BRCA1-associated RING domain protein 1 (BARD1) and estrogen receptor α (ERα), resulting in enhanced degradation of ERα and ultimately reduced transcriptional activity (186).

Proteins typically do not function as single modules in the biological processes of living cells. Instead, they function with other proteins in dynamic networks, interacting with numerous biologically active substances. For example, in a recent study of tumor-derived morphological mutations, BAP1 was isolated from wild-type ASXL1 mutants whose C-terminus was truncated and whose regulation of target genes was lost through the ASXL1-BAP1-FOXK1/K2 axis (89). This example demonstrates that numerous proteins can interact amongst themselves in tandem within intricate complexes. Furthermore, their interactions occasionally span multiple complexes, giving fascinating and elaborate protein-protein relationships.

In conclusion, FOXK2 regulates target genes through a combination of multiple transcription factors. FOXK2 and chaperone proteins form various complexes and the specific interactions between FOXK2 and each component of the complex lead to the diversity of its regulatory functions.

However, the mechanisms by which FOXK2 interacts with other transcription factors and active factors are not well understood. The current studies neither reveal how FOXK2 selects for preferred interacting partner nor address the biological significance or evolutionary advantages of this selection.

4. FOXK2 and the hallmarks of cancer

FOXK2 is an active participant in the multistep process of tumor development (4). The role of FOXK2 varies across tumor types and in some contexts, FOXK2 either becomes a driving force or a bottleneck in cell proliferation, differentiation and death. Given that FOXK2 is involved in a broad range of regulatory pathways employed during physiological development as well as carcinogenesis, it makes sense to summarize its role in cancer.

In cancer, FOXK2 functions as a gatekeeper of DNA repair and mutation prevention. Studies have shown that genes mediating the DNA repair process are inextricably linked to potential mutations in cancer (187-189). Furthermore, FOX proteins regulate several aspects of cell biology by inducing the transcription of target genes (190,191). The ability of FOXK2 to regulate fundamental biological processes is evident in cell proliferation (132,174), DNA repair (192), apoptosis (193) and regulation of cell metabolism (84,88) (Fig. 5). Indeed, there is growing evidence that FOXK2 is closely related to the development of tumors, but it may also serve opposing roles based on the specific type of tumor. Several studies have reported that FOXK2 expression is low in breast cancer (186,194), NSCLC (132), glioma (195) and ccRCC (193). Its role as a tumor suppressor gene is not evident. Conversely, the increase in FOXK2 expression is closely related to the occurrence and development of tumors. Other studies have found that FOXK2 expression is upregulated in papillary thyroid carcinoma (PTC) (196), anaplastic thyroid cancer (ATC) (197), CRC (198) and HCC tissues (131). These conflicting findings suggest that tumor-specificity may determine the role of FOXK2 and dictate its function as an oncogene or tumor suppressor gene in tumorigenesis and progression. However, general rules cannot be extrapolated from current data and these results are far from helping the understanding of the general regulatory pattern of FOXK2.

FOXK2 and genomic instability. Enabling hallmarks are the precise molecular and cellular mechanisms that allow for the evolution of tumor-initiating cells to develop and acquire core signature capabilities, typically during tumor development and malignant progression. In addition, enabling hallmarks assist in the linkage of cancer marker phenotypes to the TME and explains various aspects relevant to cancer (9,10). These enabling features are present across all stages of cancer progression.

Genomic instability in cancer cells has been considered the primary hallmark, resulting in random mutations and chromosomal rearrangement (9,10,199,200). It has been reported that a patient with West syndrome, a severe intellectual disability and malformation, was identified as partial tetrasomy 17q25.3 and the breakpoint of chromosome 17q25.3 rearrangement was located in the *FOXK2* (3). Certain mutated genotypes confer advantages in subclonal selection and growth in the local
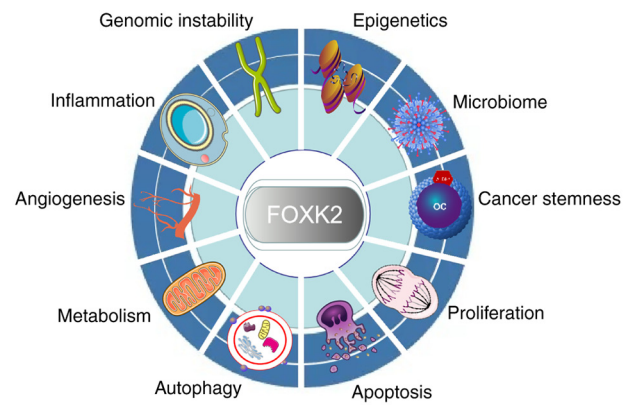

Figure 5. FOXK2 and the hallmarks of cancer. FOXK2 has shown a remarkable ability to regulate several fundamental biological processes involved in genomic stability, DNA repair, cancer stem cell maintenance, cell proliferation, apoptosis and cell metabolism. FOXK2, Forkhead box K2.

tissue environment (201). A roster of alterations in conditions of genomic instability have been suggested for DNA damage prevention, DNA repair system activation, DNA repair defects, centrosomes and telomerase (202).

Genomic stability is a prerequisite for high fidelity DNA and thus DNA is subject to precise and complex control mechanisms (9,10). Throughout the cell cycle of a normal cell, the integrity of the genome is protected by checkpoints (9,10). An abnormal number of chromosomes during cancer development indicates the failure of one or more cell cycle checkpoints (203). It is well established that CHK2 functions as an effector kinase of the ATM-CHk2-p53 pathway in DNA damage repair and its phosphorylation activity is critical for the DNA double-stranded break (DSB) response (204,205). A transcriptional control study of autophagy showed that Ser61 within FOXK2 is phosphorylated by CHK2, which inhibits apoptosis of cancer cells via DNA damage (1).

DNA mismatch repair (MMR) is vital in ensuring replication fidelity and maintaining genomic stability and is critical in the prevention of mutations (206). MMR defects that lead to a high mutational burden were exemplified in a study of breast cancer (207). Researchers have modeled the initiation of MMR (208). FOXK2, as a novel G/T mismatch-specific binding protein, may sense G/T mismatches and recruit BAP1 to trigger the DNA repair mechanism (192,209). The phosphorylation of BAP1 and its catalytic activity are necessary prerequisites for its repair function (209). Mechanistically, FOXK2 may act as a DNA-binding protein that binds to the distorted conformation of DNA resulting from mismatches, facilitating the recruitment of other repair proteins (210). In response to laser micro-irradiation, MBD6 was recruited to laser-induced DNA damage sites independently of PR-DUB. It was also found that FOXK2/PR-DUB and MBD6 share a genome target gene subset (69). A study of yeast FOX proteins showed that lexa-FHA fusion proteins bind to chromatin, induced by DSBs, and subsequently recruit donors in an FHA-domain-dependent manner (211). Importantly, the presence or absence of the N-terminal coding region (139-459 bp) of the FHA domain determines whether FOXK2 binds specifically to the G/T mismatch. This specific binding either recruits DNA repair proteins such as YB-1 to form complexes

that initiate DNA mismatch repair, or freezes transcription and replication of mismatched genes leading to cell death (192). Together, these findings suggest that FOXK2 serves an important role in the regulatory mechanisms of DNA repair.

Loss of telomere protection can lead to a telomere crisis, a widespread state of genomic instability that can amplify or drive aging-related cancer development (212,213). Conversely, telomerase activation provides an opportunity to eliminate the telomere crisis, leading to the formation of cancer clones with genomic rearrangements (212,213). Although the relationship between FOXK2 and telomeres or telomerase has not been studied in-depth, studies have implicated FOXK1 in cellular telomere fusion (33,214).

FOXK2 and cancer epigenetics. Epigenetic effects serve a significant role in regulating the interactions between genomes and the environment and this has attracted considerable research interest (215). These epigenetic effects may also influence gene expression patterns and drive cancer development (64,216,217). Non-mutational epigenetic regulation of gene expression was initially interpreted, a decade ago, as a powerful mechanism that mediates development and differentiation (218,219). This concept has received increased attention in recent years regarding its significance in cancer biology (10,220,221). It has been shown that crucial regulatory elements constitute a set of epigenetic regulations (44). The emerging field of epitranscriptomics, involving modifications of mRNAs and lncRNAs as well as newly identified DNA cytosine modifications, is a key mechanism of epigenetic regulation promoting cancer progression (222). As described earlier, epigenetic modification of FOXK2 mediates several chromatin events critical in the multi-step process of cancer development. The present review highlighted a possible link between environmental exposure to cancer risk and epigenetic modifications of DNA. One study focusing on differences in DNA methylation amongst ethnic firefighters showed that FOXK2 hypomethylation partly explains the differences in epigenetic susceptibility to cancer risk associated with toxic exposure between ethnic groups (56). Chemical exposure, including but not limited to polycyclic aromatic hydrocarbons, may lead to differential methylation of FOXK2 CpG sites across ethnic groups (56). Other suitable examples are the hypermethylation of leukocytes caused by smoking, which is positively correlated with smoking level (60). Certain lifestyles, such as exercise and bariatric surgery, reduce NNMT expression and lead to increased levels of FOXK2 methylation (57). However, the relationship between more environmental factors, lifestyle and psychological stress and FOXK2 methylation has not been well explored. In addition, few studies have been published on the regulatory mechanism of FOXK2 methylation and its effect on downstream target genes.

FOXK2 and tumor-promoting inflammation. The link between chronic inflammation and the development and progression of cancer has been long established (223,224). Inflammatory mediators and cell effectors promote tumor development by changing the local TME. The altered microenvironment disrupts the immune response and contributes to the proliferation and survival of malignant cells (224). Inflammation in the TME is mainly characterized by the accumulation of innate and adaptive immune cells (223,225), both of which promote tumor progression (226,227). However, the association of these immune cells with FOXK2 has not been fully studied. Encouragingly, a study of early immune networks suggested that FOXK2 is involved in immune regulation in early life (the 1st, 2nd, 3rd trimester of gestations, birth, newborn and infant periods) (228). Other studies have also shown that FOXK2 affects the activation of T lymphocytes and serves a role in the development of immune networks (229,230). NF-κB is a TF involved in the inflammation and immune response cellular pathways (231) and it has been shown to be involved in tumorigenesis (232,233). FOXK2 expression is positively regulated by NF-κB. For example, epidermal growth factor (EGF) promotes FOXK2 expression through the NF-κB pathway (198). Alterations in TME caused by cellular inflammation can also induce DNA damage, which in turn assists tumor cells to acquire a variety of biological abilities (227,234,235). As previously described, FOXK2 functions as a G/T mismatch-specific binding protein that initiates DNA damage repair or freezes transcription and replication of mismatched genes. However, this function in cancer is still poorly characterized. Together, these studies suggest that the immune networks are closely related to FOXK2 and serves a crucial role in oncogenesis. Studies have shown that the adaptive immune system can promote tumor suppressor gene inactivation (224,236); however, whether FOXK2 is involved in this regulation is unknown.

FOXK2 and viruses. The relationship between the microbiome and human cancer is complex and contested and the relationships are well described elsewhere (237,238). Recently, polymorphic variations in an organism's microbial community have been suggested as constituting a uniquely advantageous trait for acquiring signature abilities (10). This view is becoming increasingly compelling. Since human HAdVs were first isolated from an adenoid tissue nearly 70 years ago (239), the ability of specific categories of viruses to induce tumor growth has been demonstrated in different mammalian models (240,241). The possible role of HAdVs in malignant diseases in humans has been continuously explored, but their role in human cancer remains unclear (242). One study found that the binding and interaction of the c-terminal region of the viral E1A protein with FOXK2 is essential for suppressing HAdV-mediated tumor formation *in vivo* and *in vitro* (180). Furthermore, HAdV E1A protein interaction with FOXK1 and FOXK2 is dependent on the levels of phosphorylated E1A.

Human papillomavirus (HPV) is another interesting virus in relation to FOXK2. The E6 protein of HPV 21/14 exerts its antitumor effects by targeting FOXK1 and FOXK2 in tandem with a conserved Thr-Ser motif (180). In addition, the interaction of the E6 protein with FOXK1 and FOXK2 in epithelial cells may drive viral infection replication and differentiation rather than transformation (180). However, the relationship between FOXK2 and more viruses has not received sufficient attention.

FOXK2 and sustained proliferative signaling. The most fundamental characteristic of cancer cells is their ability to maintain chronic proliferation. The degree of proliferation is directly related to the development and progression of cancer (9).

During development, growth factor signaling pathways induce proliferation, migration, differentiation and death in select populations of cells to ensure adherence to programmed organ sizes and functions. The expression of cycle-related proteins and signaling pathways in cancer cells is often altered, resulting in oncogenic activation of growth factor signals or inhibition of cell death, leading to pathological proliferation and tumor growth. These shared signaling pathways primarily include hypoxia-inducible factor-1 (HIF-1), CDKs, NF-κB, PI3K/AKT, insulin-like growth factor receptor (IGF-1R) and estrogen receptor signaling (201).

Different studies have assessed the effects of FOXK2 on the signaling pathways aforementioned. FOXK2 knockdown induces non-neoplastic immortal cell death, proliferation and survival as FOXK2 deletion leads to increased expression of p53 up-regulated modulator of apoptosis (PUMA) and NOXA (174).

The transcription factor HIF-1 structurally acts as a heterodimer and regulates inducible genes that respond to changes in oxygen levels (243,244). Nuclear localization of this molecule in conditions of low oxygen concentrations induces transcription of several genes responsible for tumor invasiveness (245). The network crosstalk between FOXK2 and HIF-1 is complex. FOXK2 interacts with ASXL1, a vital component of PR-DUB, to regulate HIF-1α and STAT3 signaling pathways (89).

The NF-κB pathway is regulated by EGF and induces FOXK2 expression (198). FOXK2 promotes colorectal cancer proliferation and metastasis by increasing the expression of Zinc finger E-box binding homeobox 1 and EGFR (198). Studies have shown that miR-204 is a novel regulator of the innate immune response (246) that targets FOXK2 by inhibiting the NF-κB pathway, thereby reducing apoptosis and increasing cell viability (136,247,248). The NF-κB pathway has been shown to be activated in colon cancer, controlling the expression of multiple target genes, promoting cell proliferation and linking immunomodulatory, inflammatory and carcinogenic responses (249).

PI3Ks are a family of lipid kinases initially hypothesized to be involved in the transformational ability of viral oncoproteins. Subsequent studies found that PI3Ks were involved in regulating various cellular processes, including cell proliferation and differentiation (131,250). The effects of FOXK2 and PI3Ks are multi-dimensional. In certain clinical samples, such as patients who only received surgery without preoperative chemotherapy or radiotherapy, FOXK2 is negatively regulated by miR-1271-5p and exerts carcinogenic activity by activating the PI3K/AKT signaling pathway in HCC cells (131). TP53TG1 promotes the occurrence and development of CC by regulating miR-33A-5P targeting FOXK2 (167). FOXK2, as a downstream regulator of the PI3K/AKT/mTOR signaling pathway, promotes GC proliferation and inhibits apoptosis (130).

CDKs are serine/threonine kinases that rely on a cyclin regulatory subunit to initiate cell division and transcription, particularly in cancer progression (251). FOX TFs, including FOXKs, control cellular processes during physiological development and in the development and progression of cancer (190,252,253). Furthermore, in prokaryotes and metazoans, a fundamental process controlled by FOX TFs is cell cycle progression (76,254-257). In addition to regulating the transcription of target genes in the cell cycle, FOX TFs are regulated by cyclically regulated kinases. There are extensive and complex links between cell cycle-regulated kinases and the FOX transcription factor family (257). Studies involving the regulatory function of FKH2 (a homolog of human FOXKs) on the cell cycle support the link between cycle-regulated kinase and the FOX protein (76,77).

Furthermore, another study identified FOXK2 as a target of the CDK-cyclin complex in human cells and found that FOXK2 levels are cell cycle-dependent, reaching a maximum concentration during the M-phase (26). This study also found that FOXK2 mRNA levels did not change significantly during the cell cycle, suggesting that FOXK2 is regulated via PTMs. Notably, endogenous FOXK2 stably translocates to the nucleus of most asynchronously growing U2OS cells (26), while the subcellular localization of other FOX TFs varies with the stage of the cell cycle (257,258). FOXK2 relocalization away from the DNA during mitosis (26) also differs from the persistent association of FOXK1 with DNA (259). However, the significance of this small change in nuclear localization has not been thoroughly studied.

The relationship between estrogen and cancer has been extensively reviewed (260,261). Estrogen induces cell proliferation and increases the probability of mutations during DNA synthesis through ER-mediated signal transduction (262). A study showed that FOXK2 forms a complex with BARD1 and acts as a supportive protein of BRCA1/BARD1 and ERα. FOXK2 enhances ubiquitin-mediated degradation of ERα, downregulation of ERα target gene transcription and inhibition of ERα positive breast cancer cell proliferation (186). FOXK2 also inhibits the proliferation, invasion and metastasis of triple-negative breast cancer cells independent of ER expression (194,263). Notably, another breast cancer study reported that FOXK2 activity is negatively regulated by ERα levels (194).

Cancer stem cells are the source of tumor cells, granting them the ability to achieve a state of cell immortality. Recent research has shown that FOXK2, a highly expressed stem cell-specific TF in ovarian cancer, binds to an intron regulatory element of the sensor ERN1. This binding triggers an unfolded protein response that directly upregulates inositol-requiring enzyme 1α (IRE1α, *ERN1* gene) expression. In addition, it results in the X-box-binding selective active splicing of protein 1 (XBP1) and activation of stemness-related pathways (264). However, there is still a lack of broader studies on the effect of FOXK2 on cancer stem cell stemness and little is known about the regulatory mechanism of FOXK2 upstream regulatory signals in the maintenance of stemness.

FOXK2 and anti-growth signaling. High-throughput sequencing has proved to be an invaluable tool in cancer research. The ability to avoid anti-growth signals and the loss of tumor suppressor factors leads cancer cells to exhibit disorderly and uncontrolled growth, which is widely accepted as a hallmark of cancer (9,265). Several tumor suppressor genes function together to determine cell fate (265). In addition to BAP1, BRCA1 and DVL as aforementioned, the relationship between FOXKs and other tumor-related factors is discussed in the present review. Phosphatase and TENsin Homolog (PTEN) is a phosphatase that dephosphorylates

phosphatidylinositol-triphosphate (PIP3) to PIP2 (266-268). PTEN is a well-known tumor suppressor gene involved in several types of cancer, negatively regulating the PI3K/AKT signaling pathway (266). However, loss-of-function mutations of PTEN are often found in tumors (269). Through ChIP and dual luciferin reporter assays, FOXK1 was shown to directly bind to the miR-32 promoter. It was also shown to positively regulate the expression of miR-32 and transmembrane protein 245 gene (TMEM245). In CRC, FOXK1 was shown to inhibit the expression of PTEN through transcriptional regulation of TMEM245/miR-32, thereby enhancing the proliferation, migration and invasion of CRC cells and reducing the apoptosis of CRC cells (270). Another study further demonstrated the existence of a core promoter region in the -320 to -1 bp range of the 5' flanks of the TMEM245/miR-32 gene and inhibitory regulatory elements in the -606 to -320 bp range (271).

FOXK2 also interacts with other tumor suppressor proteins. For example, after S-phase DNA damage, FOXK1-53BP1 interaction is dependent on ATM/CHK2, which reduces the correlation between 53BP1 and its downstream factors RIF1 and PTIP (214). In addition, FOXK2 interacts with the transcriptional co-suppressor complex NCoR/SMRT Sin3a NuRD and REST/CoREST to exert its anti-tumor role. As a result, FOXK2 inhibits genes such as HIF-1β and EZH2 and modulates several signaling pathways, including the hypoxia response (194).

FOXK2 and resistance to apoptosis. Maintenance of the balance of pro-apoptotic and anti-apoptotic proteins is crucial in determining cell apoptosis development. The struggle between apoptosis and anti-apoptosis is present in all stages of cancer, from precancerous lesions to tumor formation. The deregulation of apoptosis is associated with the development and progression of cancer through unmoderated cell proliferation and cancer resistance to drug therapy (272). Therefore, the ability to evade apoptosis is considered a defining cancer hallmark (9). Among the several anti-apoptotic pathways, the overexpression of anti-apoptotic proteins is the primary strategy cancer cells use to avoid apoptosis (201). The role of the Bcl-2 family members in apoptosis is well established. The Bcl-2 homologous (BH) domain is the structural basis for interaction among its members and drives pro-apoptotic or anti-apoptotic functions (273,274).

One study found that knockdown of FOXK2 led to reduced proliferation and increased apoptosis in mouse NIH3T3 fibroblasts and mouse breast cancer NMuMG cells (174). After FOXK2 gene KO, expression of the pro-apoptotic proteins PUMA and NOXA was significantly upregulated (174) and PUMA and NOXA are members of the pro-apoptotic Bcl-2 family (275). A positive association between FOXK2 and increased phospho-AKT levels has been shown (131). Additional studies have demonstrated that AKT is phosphorylated by PDK1 on one or two specific sites, which is necessary for its full catalytic activity. Activated AKT inactivates the expression of pro-apoptotic proteins such as Bcl-2 and FOXO TFs, positively affecting cell survival (276,277). Although there is evidence suggesting that FOXK2 exerts an anti-apoptotic role, research on the effects of FOXK2 on cell proliferation and survival is limited. Thus, further studies are required to understand the function and

mechanism underlying the anti-apoptotic effects of FOXK2 are required.

FOXK2 and angiogenesis. Angiogenesis, defined as the growth of new capillaries from existing blood vessels, involves endothelial cell migration, invasion and duct formation. Angiogenesis is essential for dividing cells and this is especially true for tumor cells, as the new vessels provide oxygen and nutrients to maintain cell division (278,279). The activation of angiogenesis can result from the imbalance between pro-angiogenic and anti-angiogenic molecules (280,281). Of all the angiogenic factors, the most influential are VEGF, EGF and platelet-derived growth factor (PDGF) (282). VEGFA exerts an angiogenic effect by binding to VEGFR-1 and VEGFR-2 and its co-receptors neuropilin-1 and neuropil-2 (NRP-1 and NRP-2) (283,284). In addition, VEGFA regulates endothelial cell survival and enhances the mobilization of bone marrow-derived endothelial precursor cells (285,286). VEGFA/VEGFR-2 signaling is widely considered the most important angiogenic mechanism.

It has previously been reported that VEGFA expression is increased in ATC following apatinib treatment (287). Furthermore, the ChIP dual-luciferase reporter system and functional assays confirm that FOXK2 promotes ATC angiogenesis by inducing VEGFA transcription (197). When VEGFR-2 is blocked, VEGFA then binds to VEGFR-1, promoting angiogenesis by activating ERK, PI3K/AKT and P38/MAPK signaling in human umbilical vein endothelial cells, which compensates for VEGFR2 blockage (197,288). Notably, VEGFA binding to VEGFR-1 can promote FOXK2-mediated VEGFA transcription and angiogenesis through a positive feedback loop (197).

In a diabetes mellitus mouse model and in human ECs, miR-140-3p transcription inhibits FOXK2 signaling, promoting key angiogenic steps, including EC proliferation, cell migration and endovascular formation (135). Conversely, FOXK1 inhibits angiogenesis by inhibiting VEGFA transcription (289). However, the controversial works aforementioned also leave a number of unanswered questions. The key to solve these problems is to further study the regulatory mechanism of FOXK2 and angiogenesis related metabolic remodeling.

FOXK2 and metabolism. Tumor cells are especially adept at adapting to the environment and extracting energy. Their ability to increase glucose uptake and lactic acid production (the Warburg effect) is an excellent example of the evolution of substrate metabolic fate (290). This well-evolved flexibility is necessary to ensure enhanced biomass synthesis while maintaining redox equilibrium and cellular homeostasis (291,292). These properties reflect a balance between the availability of growth-signaling chemical nutrients, the subsequent adaptive metabolic remodeling and the everyday needs of the cell (293).

A study showed that FOXK1 and FOXK2, experimentally associated with nutritional stress, may function as regulators to induce aerobic glycolysis reprogramming (88). Mechanistically, FOXK1 and FOXK2 induce aerobic glycolysis by upregulating hexokinase 2 (HK2), phosphofructokinase, pyruvate kinase (PK) and lactate dehydrogenase (LDH). These enzymes are associated with glucose metabolism and regulate the flow of glycolysis (88,294). Further studies have shown that

an increase in pyruvate dehydrogenase (PDH) kinases 1 and 4 activity prevents the conversion of pyruvate to acetyl-CoA in the mitochondria and pyruvate is instead reduced to lactic acid (88,290,294).

Thioredoxin interacting protein (TXNIP) is an α-inhibitory protein. TXNIP modulates glucose homeostasis through strong negative regulation of glucose uptake and aerobic glycolysis (295,296). FOXK1/FOXK2 can directly bind to the TXNIP promoter to exert an influence on aerobic glycolysis (89). It is also found that structurally and functionally deficient PR-DUB complexes, including the absence of FOXK1/FOXK2, significantly reduce TXNIP protein levels, resulting in increased glucose uptake and increased intracellular lactic acid and ATP levels (89).

The FOXK transcription factor regulates glucose consumption by altering its own subcellular localization and affecting HIF-1α gene expression through a process regulated by mTOR (2,87). PDH can be hyper-phosphorylated by pyruvate dehydrogenase kinases (PDKs), which are upregulated by HIF-1α, resulting in its inactivation. This inactivation inhibits the conversion of pyruvate to acetyl-CoA and increases lactic acid production (290). Additionally, HIF1α regulates several major glycolytic proteins, including the glycolytic enzymes HK2, phosphoglycerate kinase 1, LDHA and PKM2 (297,298).

FOXK2 and autophagy. Autophagy can inhibit the proliferation of tumor cells (299,300). In a state of nutritional deficiency or during chemotherapy, autophagy also serves as a means for tumor cells to resist apoptosis (301). The ATG proteins, including ULK1 and Vps34 complexes, act as critical regulators in the initiation and development of autophagy (302,303). It has been shown that FOXK2 promotes the proliferation of PTC cells by downregulating autophagy (196). The same study also found that the ATG proteins ULK1 and VPS34 were significantly upregulated after FOXK2 KO, but significantly downregulated after FOXK2 overexpression (196). Another study showed that in the context of DNA damage, the FOXK protein was phosphorylated by CHK2 and captured by 14-3-3 in the cytoplasm, resulting in an increase in the expression of ATG genes through transcriptional control, triggering autophagy and increasing chemotherapeutic resistance (1). Furthermore, it has been shown that FOXK1/FOXK2 explicitly recruits the Sin3a-HDAC complex to restrict the acetylation of histone H4 and the expression of essential autophagy genes (87). In conclusion, these findings illustrate the importance of FOXK2 in regulating autophagy and suggest a link between chromosomal events and autophagy regulation.

5. Discussion and conclusion

The present review examined the most influential roles of FOXK2 in cancer development. It highlighted the complexity of the function of FOXK2 and gave an outlook on what has to be investigated in future work. In addition, it described the current understanding of FOXK2 and its global capabilities, providing context for explaining how FOXK2 functions in cancer, both individually and as a part of numerous complex systems. The extensive expression of FOXK2 and inherent structural characteristics distinguish it from ~1,600 other human TFs (304).

FOXK2 functions in several different contexts by cooperating with other active molecules. The suggestion that TFs work together to achieve their function is widely accepted (305,306). The properties of FOXK2 and other members of the FOX family determine its precise function in biology. For example, there are also binding differences between FOXK2 and other members of the FOX family among functionally specific target genes partly influenced by the flanking region (179,307). Theoretical and practical observations show that synergistic binding and co-regulation are the primary synergistic modes of TFs, which help bioactive molecules bind to DNA, influencing chromatin accessibility and downstream gene transcription (308). However, specific modes of action of FOXK2 expression in different time and space under physiological and pathological conditions have not been clearly demonstrated and general principles cannot be inferred from the current study.

FOXK2 mediates several functionally significant chromatin events. This suggests that DNA-mediated cooperative binding is crucial for the function of TFs (309). TFs that can bind to target sites on nucleosome DNA are known as pioneer factors (310,311). These pioneer TFs are responsible for opening chromatin or changing the conformation of the nucleosome by initiating nucleosome displacement (312-314). The above are necessary prerequisites for recruiting other bioactive substances and other TFs (315). These pioneer TFs control cell fate by locally opening chromatin to initiate transcription (316,317). Its stability is partly influenced by steric hindrance (318) and nucleosome affinity for active chromatin remodeling (319). Members of the FOX family have been shown to function as pioneer factors as they can bind to nucleosome DNA and open chromatin, thereby exposing DNA binding modes allowing it to bind to other TFs and subsequently regulate gene expression (320,321). Based on this evidence and the regulation of chromatin events by FOXK2 described above, FOXK2 may be considered a pioneer factor. Unraveling local chromatin regions without the help of ATP-dependent chromatin remodeling factors (322,323) is a valuable characteristic for consideration of FOXK2 as a pioneer candidate.

Protein-protein interactions are regulatory mechanisms for TFs that are well understood. Studies using single-molecule imaging confirm that when multiple TFs bind with DNA at consistently spaced intervals with a consistent orientation, the binding sites are occupied for longer periods of time, conferring additional stability (324,325). FOXK2 has been shown to form complexes with several proteins to perform different functions. According to its nature, eukaryotic gene expression regulation can be divided into instantaneous (reversible) (326,327) and development (irreversible) regulation (328,329). Instantaneous regulation determines the fate of metabolic substrates and hormonal fluctuations in enzyme activity. It also dictates the substrate or hormonal concentrations at different stages of the cell cycle. Development regulation influences overall eukaryotic cell differentiation, growth and development processes. The present review provides an overview of the contribution of FOXK2 to transient and developmental regulation and highlights the role of epigenetic modifications in controlling chromatin accessibility and protein interactions.

The present review also discussed the multifaceted role of FOXK2 in cancer. FOXK2 is involved in the pathogenesis of numerous types of cancer. Whether FOXK2 functions as

an oncoprotein or tumor suppressor appears to be closely related to its partners and its spatio-temporal properties and is thus tumor-specific. A human cancer genome survey elucidated several salient features of oncogenes involving the types of sequence alterations identified, oncogenic mutations in cancer classes and protein domains encoded by cancer genes (330). Indeed, proteins encoded by cancer genes typically regulate cell proliferation, differentiation and death. A functional review of FOXK2 also supports the hypothesis of FOXK2 as an oncogene. However, the genes that have been reported with precise causal associations with tumorigenesis have been identified and initially reported based on sufficient genetic evidence. Mutated genes that provide cancer cells a growth advantage are highly suitable candidates for oncogenes. Genes with translocations or copy number alterations supported by convincing genetic data are another group of candidates. Genes whose expression levels are altered only in cancer cells are not suitable oncogene candidates, lacking any mutations in DNA that cannot be conclusively linked to tumorigenesis. However, FOXK2 mutations have not been reported previously to the best of the authors' knowledge. Based on the evidence, the biological regulatory functions of FOXK2, such as the regulation of glucose metabolism and autophagy, may be used as hijacking tools by tumor cells to enable unlimited proliferation and survival of tumor cells. Of course, these assumptions are contested and unproven. In the absence of more extensive research, one should be cautious about making conclusive claims. However, what is certain is that FOXK2 is vital in the development and progression of cancer. In the foreseeable future, in-depth studies targeting the regulatory features of FOXK2 may reveal its role in tumorigenesis.

Although a similar review was published in 2019 regarding FOXK2 and its roles in cancer (4), the present review has updated the recent findings about FOXK2 by a number publications since then. First, it detailed the nomenclature and structural differences of the three isoforms of FOXK2 and suggested that alternative splicing of FOXK2 may be related to the role of kinase cascade signaling. Second, for the regulatory mechanism of FOXK2, it considered both its roles as a regulator and being regulated, with systematically and clearly description in terms of gene level, post-translational modification and protein interaction. Third, it summarized the roles of FOXK2 as pioneer factor, G/T mismatch DNA-binding protein, virus-binding protein, scaffold protein and transfer vector and proposed that FOXK2 can be a candidate as a pioneer factor. Fourth, it used the widely accepted concept of cancer hallmarks to describe the broad role of FOXK2 in tumorigenesis in detail. Fifth, it took a cautious attitude toward the definition of FOXK2 as an oncogene or a tumor suppressor. FOXK2 may act as a hijacked molecular to achieve its spatiotemporal and tumor-specific functions. Finally, it objectively noted the shortcomings of current studies and the directions for future research on FOXK2 in the hope that the present review will provide useful information for researchers working in this field.

Availability of data and materials

Not applicable.

Authors' contributions

ZhaoW and XL developed the idea, and wrote and revised the manuscript. ZhanW and ZH supervised the study and contributed to critical reading and revising of the manuscript. All the authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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