

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

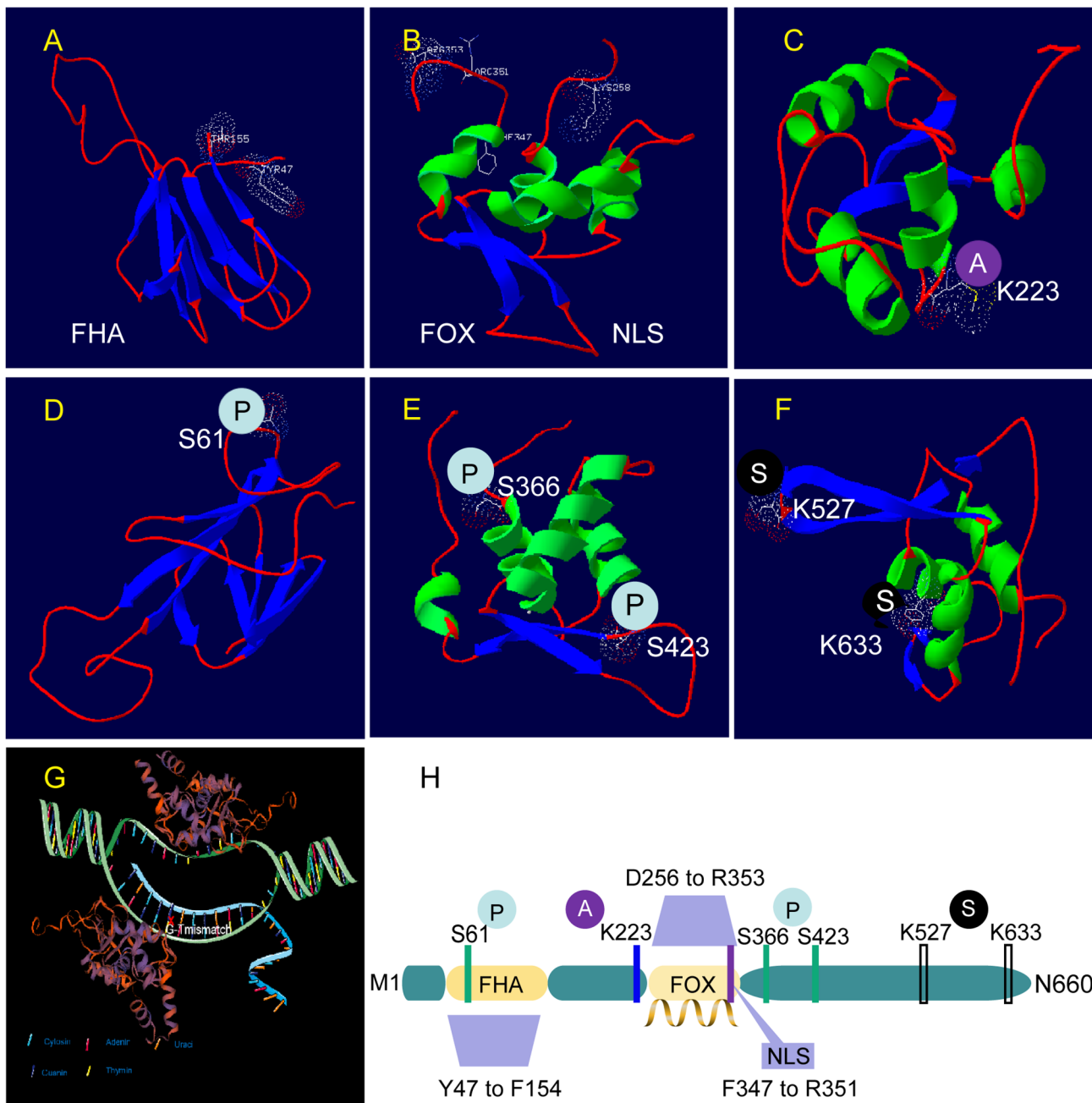


Figure 1. Illustration of the FOXK2 protein domain, PTM sites and G/T mismatches. (A) FOXK2 consists of a FHA domain (Tyr47 to Phe154). (B) FOXK2 also contains a highly conserved forked DNA-binding domain (FOX, Asp256 to Arg353) containing a NLS that can bind to DNA minor groove. (C-F) FOXK2 PTMs are 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

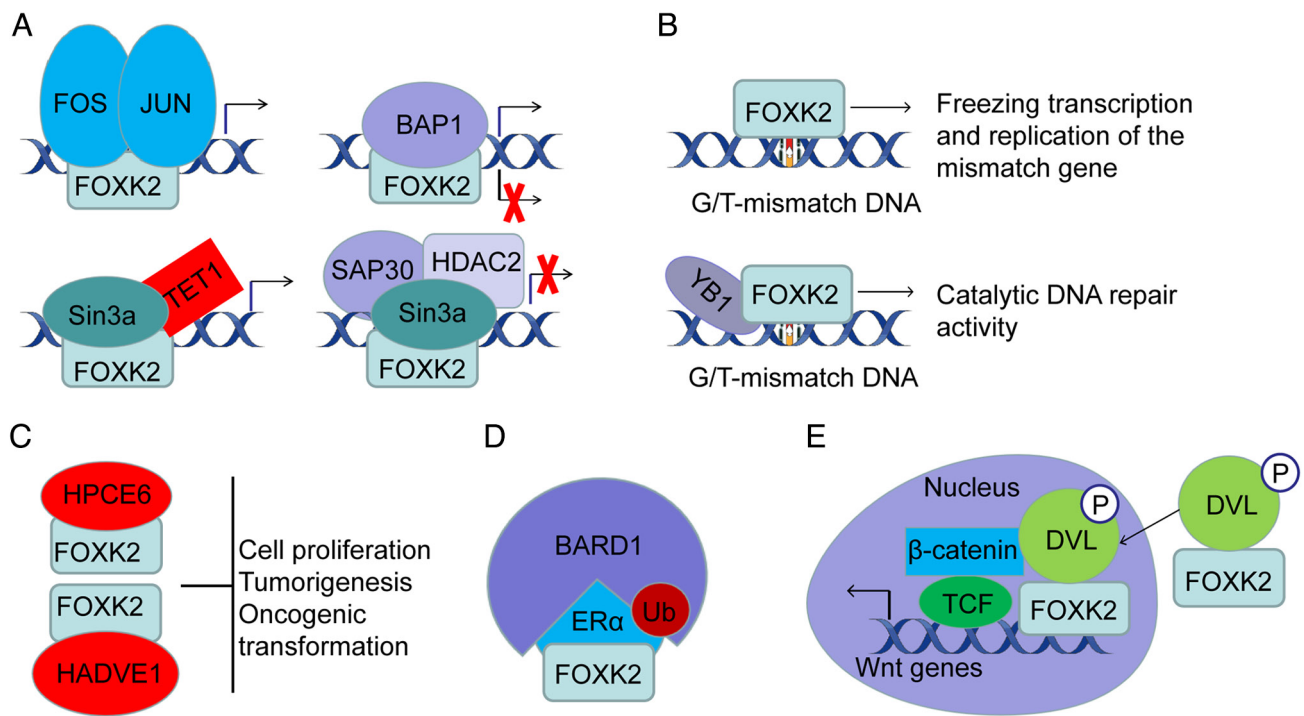


Figure 2. Protein interactions serve an important role in the loss or gain of FOXKs function. (A) FOXK2, as an important component of transcription co-inhibitory complex or transcription activation complex, inhibits or activates its target genes. (B) As a novel G/T mismatch DNA binding protein, FOXK2 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.

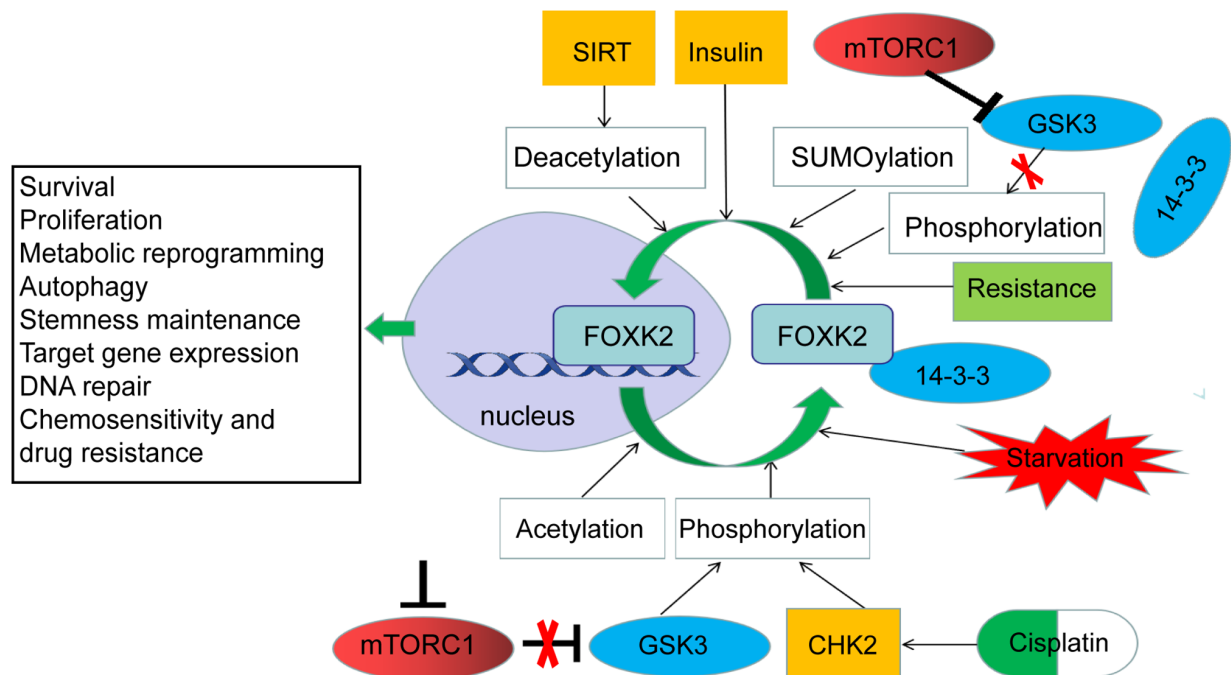


Figure 3. PTMs and other factors influence and regulate the nuclear-plasma shuttle of FOXK2 and control its interactions with other biomolecules and regulation of target genes. PTM, post-translational modifications; FOXK2, Forkhead box K2; SIRT, silencing of information regulator 2-related enzyme; mTORC1,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

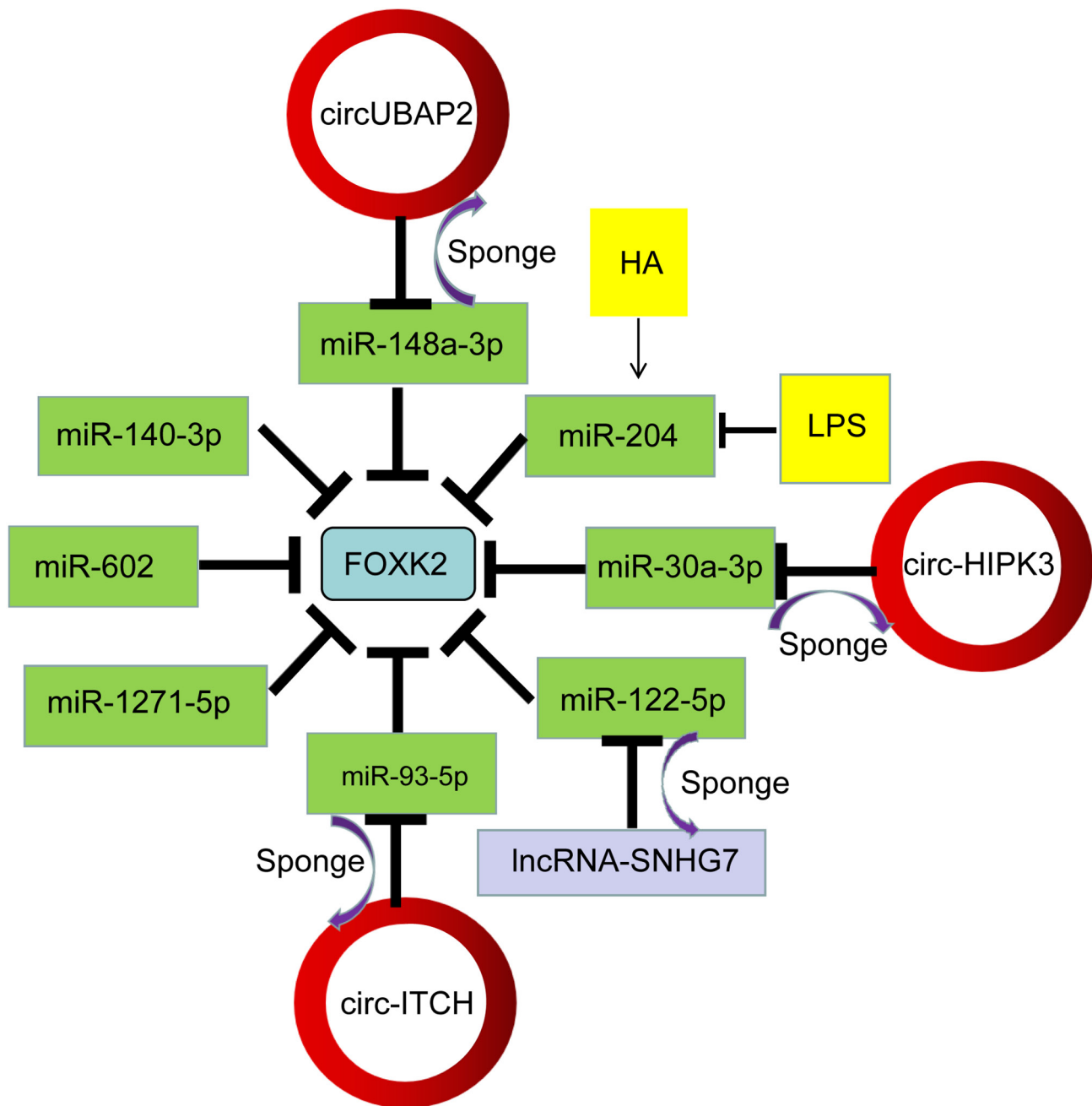


Figure 4. ncRNAs serve an important role in the loss or gain of FOXK2 function. ncRNAs, non-coding RNAs; FOXK2, Forkhead box K2; miR, microRNA; circ, circular RNA; lncRNA, long non-coding RNA.

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 14-3-3 γ 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* promoters 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-GlcNAcase, 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), hypomethylation 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- κ B 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- κ B 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 BRCA1-associated RING domain protein 1 (BARD1) and estrogen receptor α (ER α), resulting in enhanced degradation of ER α 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

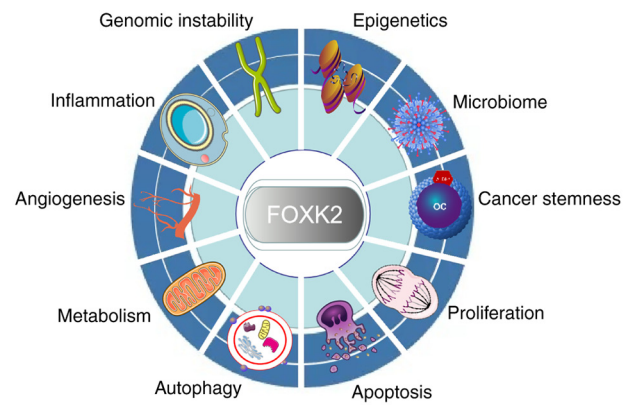


Figure 5. FOXK2 and the hallmarks of cancer. FOXK2 has shown a remarkable ability to regulate several fundamental biological processes involved in genomic stability, DNA repair, cancer stem cell maintenance, cell proliferation, apoptosis and cell metabolism. FOXK2, Forkhead box K2.

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- κ B 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- κ B. For example, epidermal growth factor (EGF) promotes FOXK2 expression through the NF- κ B 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- κ B, 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-1 α and STAT3 signaling pathways (89).

The NF- κ B 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- κ B pathway, thereby reducing apoptosis and increasing cell viability (136,247,248). The NF- κ B 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 relocation 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 ER α . FOXK2 enhances ubiquitin-mediated degradation of ER α , downregulation of ER α target gene transcription and inhibition of ER α 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 ER α 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 1 α (IRE1 α , *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-1 β 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 neuropilin-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-1 α 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-1 α , resulting in its inactivation. This inactivation inhibits the conversion of pyruvate to acetyl-CoA and increases lactic acid production (290). Additionally, HIF1 α 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 of 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.

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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.

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Competing interests

The authors declare that they have no competing interests.

References

1. Chen Y, Wu J, Liang G, Geng G, Zhao F, Yin P, Nowsheen S, Wu C, Li Y, Li L, *et al*: CHK2-FOXK axis promotes transcriptional control of autophagy programs. *Sci Adv* 6: eaax5819, 2020.
2. He L, Gomes AP, Wang X, Yoon SO, Lee G, Nagiec MJ, Cho S, Chavez A, Islam T, Yu Y, *et al*: mTORC1 promotes metabolic reprogramming by the suppression of GSK3-dependent Foxk1 phosphorylation. *Mol Cell* 70: 949-960.e4, 2018.
3. Hackmann K, Stadler A, Schallner J, Franke K, Gerlach EM, Schrock E, Rump A, Fauth C, Tinschert S and Oexle K: Severe intellectual disability, west syndrome, Dandy-Walker malformation, and syndactyly in a patient with partial tetrasomy 17q25.3. *Am J Med Genet A* 161A: 3144-3149, 2013.
4. Nestal de Moraes G, Carneiro LD, Maia RC, Lam EW and Sharrocks AD: FOXK2 transcription factor and its emerging roles in cancer. *Cancers (Basel)* 11: 393, 2019.
5. Gitter A, Siegfried Z, Klutstein M, Fornes O, Oliva B, Simon I and Bar-Joseph Z: Backup in gene regulatory networks explains differences between binding and knockout results. *Mol Syst Biol* 5: 276, 2009.
6. Dai Z, Dai X, Xiang Q and Feng J: Robustness of transcriptional regulatory program influences gene expression variability. *BMC Genomics* 10: 573, 2009.
7. Wu WS and Lai FJ: Functional redundancy of transcription factors explains why most binding targets of a transcription factor are not affected when the transcription factor is knocked out. *BMC Syst Biol* 9 (Suppl 6): S2, 2015.
8. Hanahan D and Weinberg RA: The hallmarks of cancer. *Cell* 100: 57-70, 2000.
9. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. *Cell* 144: 646-674, 2011.
10. Hanahan D: Hallmarks of cancer: New dimensions. *Cancer Discov* 12: 31-46, 2022.
11. Kaestner KH, Knochel W and Martinez DE: Unified nomenclature for the winged helix/forkhead transcription factors. *Genes Dev* 14: 142-146, 2000.

12. Lam EW, Brosens JJ, Gomes AR and Koo CY: Forkhead box proteins: Tuning forks for transcriptional harmony. *Nat Rev Cancer* 13: 482-495, 2013.
13. Liu Y, Ao X, Ding W, Ponnusamy M, Wu W, Hao X, Yu W, Wang Y, Li P and Wang J: Critical role of FOXO3a in carcinogenesis. *Mol Cancer* 17: 104, 2018.
14. Nakagawa S, Gisselbrecht SS, Rogers JM, Hartl DL and Bulyk ML: DNA-binding specificity changes in the evolution of forkhead transcription factors. *Proc Natl Acad Sci USA* 110: 12349-12354, 2013.
15. Li C, Lai CF, Sigman DS and Gaynor RB: Cloning of a cellular factor, interleukin binding factor, that binds to NFAT-like motifs in the human immunodeficiency virus long terminal repeat. *Proc Natl Acad Sci USA* 88: 7739-7743, 1991.
16. Huang JT and Lee V: Identification and characterization of a novel human FOXK1 gene *in silico*. *Int J Oncol* 25: 751-757, 2004.
17. Mahajan A, Yuan C, Lee H, Chen ES, Wu PY and Tsai MD: Structure and function of the phosphothreonine-specific FHA domain. *Sci Signal* 1: re12, 2008.
18. Durocher D and Jackson SP: The FHA domain. *FEBS Lett* 513: 58-66, 2002.
19. Reinhardt HC and Yaffe MB: Phospho-Ser/Thr-binding domains: Navigating the cell cycle and DNA damage response. *Nat Rev Mol Cell Biol* 14: 563-580, 2013.
20. Kalnina Z, Zayakin P, Silina K and Linē A: Alterations of pre-mRNA splicing in cancer. *Genes Chromosomes Cancer* 42: 342-357, 2005.
21. Roy M, Xu Q and Lee C: Evidence that public database records for many cancer-associated genes reflect a splice form found in tumors and lack normal splice forms. *Nucleic Acids Res* 33: 5026-5033, 2005.
22. Bates DO, Cui TG, Doughty JM, Winkler M, Sugiono M, Shields JD, Peat D, Gillatt D and Harper SJ: VEGF165b, an inhibitory splice variant of vascular endothelial growth factor, is down-regulated in renal cell carcinoma. *Cancer Res* 62: 4123-4131, 2002.
23. Hu Y, Fang C and Xu Y: The effect of isoforms of the cell polarity protein, human ASIP, on the cell cycle and Fas/FasL-mediated apoptosis in human hepatoma cells. *Cell Mol Life Sci* 62: 1974-1983, 2005.
24. Wang L, Duke L, Zhang PS, Arlinghaus RB, Symmans WF, Sahin A, Mendez R and Dai JL: Alternative splicing disrupts a nuclear localization signal in spleen tyrosine kinase that is required for invasion suppression in breast cancer. *Cancer Res* 63: 4724-4730, 2003.
25. Nirula A, Moore DJ and Gaynor RB: Constitutive binding of the transcription factor interleukin-2 (IL-2) enhancer binding factor to the IL-2 promoter. *J Biol Chem* 272: 7736-7745, 1997.
26. Marais A, Ji Z, Child ES, Krause E, Mann DJ and Sharrocks AD: Cell cycle-dependent regulation of the forkhead transcription factor FOXK2 by CDK-cyclin complexes. *J Biol Chem* 285: 35728-35739, 2010.
27. Pan Q, Shai O, Lee LJ, Frey BJ and Blencowe BJ: Deep surveying of alternative splicing complexity in the human transcriptome by high-throughput sequencing. *Nat Genet* 40: 1413-1415, 2008.
28. Li C, Lusis AJ, Sparkes R, Nirula A and Gaynor R: Characterization and chromosomal mapping of the gene encoding the cellular DNA binding protein ILF. *Genomics* 13: 665-671, 1992.
29. Wang ET, Sandberg R, Luo S, Khrebtkova I, Zhang L, Mayr C, Kingsmore SF, Schroth GP and Burge CB: Alternative isoform regulation in human tissue transcriptomes. *Nature* 456: 470-476, 2008.
30. Merkin J, Russell C, Chen P and Burge CB: Evolutionary dynamics of gene and isoform regulation in mammalian tissues. *Science* 338: 1593-1599, 2012.
31. Clemente-González H, Porta-Pardo E, Godzik A and Eyraes E: The functional impact of alternative splicing in cancer. *Cell Rep* 20: 2215-2226, 2017.
32. Wang W, Li X, Lee M, Jun S, Aziz KE, Feng L, Tran MK, Li N, McCrea PD, Park JJ and Chen J: FOXKs promote Wnt/ β -catenin signaling by translocating DVL into the nucleus. *Dev Cell* 32: 707-718, 2015.
33. Liu Y, Ding W, Ge H, Ponnusamy M, Wang Q, Hao X, Wu W, Zhang Y, Yu W, Ao X and Wang J: FOXK transcription factors: Regulation and critical role in cancer. *Cancer Lett* 458: 1-12, 2019.
34. Giardina B, Messana I, Scatena R and Castagnola M: The multiple functions of hemoglobin. *Crit Rev Biochem Mol Biol* 30: 165-196, 1995.
35. Arbez N, Ratovitski T, Roby E, Chighladze E, Stewart JC, Ren M, Wang X, Lavery DJ and Ross CA: Post-translational modifications clustering within proteolytic domains decrease mutant huntingtin toxicity. *J Biol Chem* 292: 19238-19249, 2017.
36. Snider NT and Omary MB: Post-translational modifications of intermediate filament proteins: Mechanisms and functions. *Nat Rev Mol Cell Biol* 15: 163-177, 2014.
37. Richard SA, Jiang Y, Xiang LH, Zhou S, Wang J, Su Z and Xu H: Post-translational modifications of high mobility group box 1 and cancer. *Am J Transl Res* 9: 5181-5196, 2017.
38. Corujo D and Buschbeck M: Post-translational modifications of H2A histone variants and their role in cancer. *Cancers (Basel)* 10: 59, 2018.
39. Iavarone F, Desiderio C, Vitali A, Messana I, Martelli C, Castagnola M and Cabras T: Cryptides: Latent peptides everywhere. *Crit Rev Biochem Mol Biol* 53: 246-263, 2018.
40. Huang H, Arighi CN, Ross KE, Ren J, Li G, Chen SC, Wang Q, Cowart J, Vijay-Shanker K and Wu CH: iPTMnet: An integrated resource for protein post-translational modification network discovery. *Nucleic Acids Res* 46: D542-D550, 2018.
41. Yao B, Christian KM, He C, Jin P, Ming GL and Song H: Epigenetic mechanisms in neurogenesis. *Nat Rev Neurosci* 17: 537-549, 2016.
42. Liu MY, DeNizio JE, Schutsky EK and Kohli RM: The expanding scope and impact of epigenetic cytosine modifications. *Curr Opin Chem Biol* 33: 67-73, 2016.
43. Jones MJ, Goodman SJ and Kobor MS: DNA methylation and healthy human aging. *Aging Cell* 14: 924-932, 2015.
44. Bird A: Perceptions of epigenetics. *Nature* 447: 396-398, 2007.
45. Tsuchida T, Mano T, Koshi-Mano K, Bannai T, Matsubara T, Yamashita S, Ushijima T, Nagata K, Murayama S, Toda T, *et al*: Methylation changes and aberrant expression of FGFR3 in Lewy body disease neurons. *Brain Res* 1697: 59-66, 2018.
46. Pan XY, Yang Y, Meng HW, Li HD, Chen X, Huang HM, Bu FT, Yu HX, Wang Q, Huang C, *et al*: DNA methylation of PTGIS enhances hepatic stellate cells activation and liver fibrogenesis. *Front Pharmacol* 9: 553, 2018.
47. Hopp L, Löffler-Wirth H, Galle J and Binder H: Combined SOM-portrayal of gene expression and DNA methylation landscapes disentangles modes of epigenetic regulation in glioblastoma. *Epigenomics* 10: 745-764, 2018.
48. Lopez-Serra P and Esteller M: DNA methylation-associated silencing of tumor-suppressor microRNAs in cancer. *Oncogene* 31: 1609-1622, 2012.
49. Le TN, Schumann U, Smith NA, Tiwari S, Au PC, Zhu QH, Taylor JM, Kazan K, Llewellyn DJ, Zhang R, *et al*: DNA demethylases target promoter transposable elements to positively regulate stress responsive genes in Arabidopsis. *Genome Biol* 15: 458, 2014.
50. Jung M and Pfeifer GP: Aging and DNA methylation. *BMC Biol* 13: 7, 2015.
51. Bormann F, Rodríguez-Paredes M, Lasitschka F, Edelmann D, Musch T, Benner A, Bergman Y, Dieter SM, Ball CR, Glimm H, *et al*: Cell-of-Origin DNA methylation signatures are maintained during colorectal carcinogenesis. *Cell Rep* 23: 3407-3418, 2018.
52. Jaenisch R and Bird A: Epigenetic regulation of gene expression: How the genome integrates intrinsic and environmental signals. *Nat Genet* 33 (Suppl): S245-S254, 2003.
53. Egger G, Liang G, Aparicio A and Jones PA: Epigenetics in human disease and prospects for epigenetic therapy. *Nature* 429: 457-463, 2004.
54. Robertson KD: DNA methylation and human disease. *Nat Rev Genet* 6: 597-610, 2005.
55. Bird A, Taggart M, Frommer M, Miller OJ and Macleod D: A fraction of the mouse genome that is derived from islands of nonmethylated, CpG-rich DNA. *Cell* 40: 91-99, 1985.
56. Goodrich JM, Furlong MA, Caban-Martinez AJ, Jung AM, Batai K, Jenkins T, Beitel S, Littau S, Gulotta J, Wallentine D, *et al*: Differential DNA methylation by hispanic ethnicity among firefighters in the United States. *Epigenet Insights*: Mar 26, 2021 (Epub ahead of print).
57. Crujeiras AB, Pissios P, Moreno-Navarrete JM, Diaz-Lagares A, Sandoval J, Gomez A, Ricart W, Esteller M, Casanueva FF and Fernandez-Real JM: An epigenetic signature in adipose tissue is linked to nicotinamide N-methyltransferase gene expression. *Mol Nutr Food Res*: Apr 24, 2018 (Epub ahead of print).

58. Camprubí C, Salas-Huetos A, Aiese-Cigliano R, Godo A, Pons MC, Castellano G, Grossmann M, Sanseverino W, Martin-Subero JJ, Garrido N and Blanco J: Spermatozoa from infertile patients exhibit differences of DNA methylation associated with spermatogenesis-related processes: An array-based analysis. *Reprod Biomed Online* 33: 709-719, 2016.
59. Nwanaji-Enwerem JC, Jenkins TG, Colicino E, Cardenas A, Baccarelli AA and Boyer EW: Serum dioxin levels and sperm DNA methylation age: Findings in Vietnam war veterans exposed to agent orange. *Reprod Toxicol* 96: 27-35, 2020.
60. Park SL, Patel YM, Loo LW, Mullen DJ, Offringa IA, Maunakea A, Stram DO, Siegmund K, Murphy SE, Tiirikainen M and Le Marchand L: Association of internal smoking dose with blood DNA methylation in three racial/ethnic populations. *Clin Epigenetics* 10: 110, 2018.
61. Yehuda R, Daskalakis NP, Bierer LM, Bader HN, Klengel T, Holsboer F and Binder EB: Holocaust exposure induced inter-generational effects on FKBP5 methylation. *Biol Psychiatry* 80: 372-380, 2016.
62. Hughes MF: Arsenic toxicity and potential mechanisms of action. *Toxicol Lett* 133: 1-16, 2002.
63. Jones PA and Baylin SB: The fundamental role of epigenetic events in cancer. *Nat Rev Genet* 3: 415-428, 2002.
64. Jones PA and Baylin SB: The epigenomics of cancer. *Cell* 128: 683-692, 2007.
65. Timmergen MJM, Boers R, Vriend ALM, Boers J, van Ijcken WFJ, Lavrijsen M, Grünhagen DJ, Verhoef C, Sleijfer S, Smits R, *et al*: Differentially methylated regions in desmoid-type fibromatosis: A comparison between CTNNB1 S45F and T41A tumors. *Front Oncol* 10: 565031, 2020.
66. Spruijt CG, Gnerlich F, Smits AH, Pfaffeneder T, Jansen PW, Bauer C, Münzel M, Wagner M, Müller M, Khan F, *et al*: Dynamic readers for 5-(hydroxy)methylcytosine and its oxidized derivatives. *Cell* 152: 1146-1159, 2013.
67. Iurlaro M, Ficiz G, Oxley D, Raiber EA, Bachman M, Booth MJ, Andrews S, Balasubramanian S and Reik W: A screen for hydroxymethylcytosine and formylcytosine binding proteins suggests functions in transcription and chromatin regulation. *Genome Biol* 14: R119, 2013.
68. Hu S, Wan J, Su Y, Song Q, Zeng Y, Nguyen HN, Shin J, Cox E, Rho HS, Woodard C, *et al*: DNA methylation presents distinct binding sites for human transcription factors. *Elife* 2: e00726, 2013.
69. Baymaz HI, Fournier A, Laget S, Ji Z, Jansen PW, Smits AH, Ferry L, Mensinga A, Poser I, Sharrocks A, *et al*: MBD5 and MBD6 interact with the human PR-DUB complex through their methyl-CpG-binding domain. *Proteomics* 14: 2179-2189, 2014.
70. Du Q, Luu PL, Stirzaker C and Clark SJ: Methyl-CpG-binding domain proteins: Readers of the epigenome. *Epigenomics* 7: 1051-1073, 2015.
71. Li X, Wilmanns M, Thornton J and Köhn M: Elucidating human phosphatase-substrate networks. *Sci Signal* 6: rs10, 2013.
72. Sacco F, Perfetto L, Castagnoli L and Cesareni G: The human phosphatase interactome: An intricate family portrait. *FEBS Lett* 586: 2732-2739, 2012.
73. Fukami Y and Lipmann F: Reversal of Rous sarcoma-specific immunoglobulin phosphorylation on tyrosine (ADP as phosphate acceptor) catalyzed by the src gene kinase. *Proc Natl Acad Sci USA* 80: 1872-1876, 1983.
74. Kole HK, Abdel-Ghany M and Racker E: Specific dephosphorylation of phosphoproteins by protein-serine and -tyrosine kinases. *Proc Natl Acad Sci USA* 85: 5849-5853, 1988.
75. Almawi AW, Matthews LA and Guarné A: FHA domains: Phosphopeptide binding and beyond. *Prog Biophys Mol Biol* 127: 105-110, 2017.
76. Zhu G, Spellman PT, Volpe T, Brown PO, Botstein D, Davis TN and Futcher B: Two yeast forkhead genes regulate the cell cycle and pseudohyphal growth. *Nature* 406: 90-94, 2000.
77. Pic-Taylor A, Darieva Z, Morgan BA and Sharrocks AD: Regulation of cell cycle-specific gene expression through cyclin-dependent kinase-mediated phosphorylation of the forkhead transcription factor Fkh2p. *Mol Cell Biol* 24: 10036-10046, 2004.
78. Ma RY, Tong TH, Cheung AM, Tsang AC, Leung WY and Yao KM: Raf/MEK/MAPK signaling stimulates the nuclear translocation and transactivating activity of FOXM1c. *J Cell Sci* 118: 795-806, 2005.
79. Myatt SS and Lam EW: The emerging roles of forkhead box (Fox) proteins in cancer. *Nat Rev Cancer* 7: 847-859, 2007.
80. Li A, Wang J, Wu M, Zhang X and Zhang H: The inhibition of activated hepatic stellate cells proliferation by arctigenin through G0/G1 phase cell cycle arrest: Persistent p27(Kip1) induction by interfering with PI3K/Akt/FOXO3a signaling pathway. *Eur J Pharmacol* 747: 71-87, 2015.
81. Aitken A: 14-3-3 proteins: A historic overview. *Semin Cancer Biol* 16: 162-172, 2006.
82. Nakatsumi H, Oka T, Higa T, Shirane M and Nakayama KI: Nuclear-cytoplasmic shuttling protein PP2AB56 contributes to mTORC1-dependent dephosphorylation of FOXK1. *Genes Cells* 23: 599-605, 2018.
83. Nakatsumi H, Matsumoto M and Nakayama KI: Noncanonical pathway for regulation of CCL2 expression by an mTORC1-FOXK1 axis promotes recruitment of tumor-associated macrophages. *Cell Rep* 21: 2471-2486, 2017.
84. Sakaguchi M, Cai W, Wang CH, Cederquist CT, Damasio M, Homan EP, Batista T, Ramirez AK, Gupta MK, Steger M, *et al*: FoxK1 and FoxK2 in insulin regulation of cellular and mitochondrial metabolism. *Nat Commun* 10: 1582, 2019.
85. Amaya MJ, Oliveira AG, Guimarães ES, Casteluber MC, Carvalho SM, Andrade LM, Pinto MC, Mennone A, Oliveira CA, Resende RR, *et al*: The insulin receptor translocates to the nucleus to regulate cell proliferation in liver. *Hepatology* 59: 274-283, 2014.
86. Katoh M and Katoh M: Identification and characterization of human FOXK1 gene *in silico*. *Int J Mol Med* 14: 127-132, 2004.
87. Bowman CJ, Ayer DE and Dynlacht BD: Foxk proteins repress the initiation of starvation-induced atrophy and autophagy programs. *Nat Cell Biol* 16: 1202-1214, 2014.
88. Sukonina V, Ma H, Zhang W, Bartsaghi S, Subhash S, Heglin M, Foyn H, Betz MJ, Nilsson D, Lidell ME, *et al*: FOXK1 and FOXK2 regulate aerobic glycolysis. *Nature* 566: 279-283, 2019.
89. Xia YK, Zeng YR, Zhang ML, Liu P, Liu F, Zhang H, He CX, Sun YP, Zhang JY, Zhang C, *et al*: Tumor-derived neomorphic mutations in ASXL1 impairs the BAP1-ASXL1-FOXK1/K2 transcription network. *Protein Cell* 12: 557-577, 2021.
90. Danciu TE, Chupreta S, Cruz O, Fox JE, Whitman M and Iñiguez-Lluhi JA: Small ubiquitin-like modifier (SUMO) modification mediates function of the inhibitory domains of developmental regulators FOXC1 and FOXC2. *J Biol Chem* 287: 18318-18329, 2012.
91. Sutinen P, Rahkama V, Rytinki M and Palvimäki JJ: Nuclear mobility and activity of FOXA1 with androgen receptor are regulated by SUMOylation. *Mol Endocrinol* 28: 1719-1728, 2014.
92. Song JG, Xie HH, Li N, Wu K, Qiu JG, Shen DM and Huang CJ: SUMO-specific protease 6 promotes gastric cancer cell growth via deSUMOylation of FoxM1. *Tumour Biol* 36: 9865-9871, 2015.
93. Meredith LJ, Wang CM, Nascimento L, Liu R, Wang L and Yang WH: The key regulator for language and speech development, FOXP2, is a novel substrate for SUMOylation. *J Cell Biochem* 117: 426-438, 2016.
94. Rocca DL, Wilkinson KA and Henley JM: SUMOylation of FOXP1 regulates transcriptional repression via CtBP1 to drive dendritic morphogenesis. *Sci Rep* 7: 877, 2017.
95. Nestal de Moraes G, Ji Z, Fan LY, Yao S, Zona S, Sharrocks AD and Lam EW: SUMOylation modulates FOXK2-mediated paclitaxel sensitivity in breast cancer cells. *Oncogenesis* 7: 29, 2018.
96. Shmueli A and Oren M: Life, death and ubiquitin: Taming the mule. *Cell* 121: 963-965, 2005.
97. López-Otín C and Hunter T: The regulatory crosstalk between kinases and proteases in cancer. *Nat Rev Cancer* 10: 278-292, 2010.
98. Ikeda F and Dikic I: Atypical ubiquitin chains: New molecular signals. 'Protein modifications: Beyond the usual suspects' review series. *EMBO Rep* 9: 536-542, 2008.
99. Suryadinata R, Roesley SN, Yang G and Sarčević B: Mechanisms of generating polyubiquitin chains of different topology. *Cells* 3: 674-689, 2014.
100. Rajalingam K and Dikic I: SnapShot: Expanding the ubiquitin code. *Cell* 164: 1074-1074.e1, 2016.
101. Deng L, Meng T, Chen L, Wei W and Wang P: The role of ubiquitination in tumorigenesis and targeted drug discovery. *Signal Transduct Target Ther* 5: 11, 2020.
102. Scheuermann JC, de Ayala Alonso AG, Oktaba K, Ly-Hartig N, McGinty RK, Fraterman S, Wilm M, Muir TW and Müller J: Histone H2A deubiquitinase activity of the polycomb repressive complex PR-DUB. *Nature* 465: 243-247, 2010.

103. Abdel-Wahab O, Gao J, Adli M, Dey A, Trimarchi T, Chung YR, Kusc C, Hricik T, Ndiaye-Lobry D, Lafave LM, *et al*: Deletion of *Asxl1* results in myelodysplasia and severe developmental defects in vivo. *J Exp Med* 210: 2641-2659, 2013.
104. LaFave LM, Béguelin W, Koche R, Teater M, Spitzer B, Chramiec A, Papalexli E, Keller MD, Hricik T, Konstantinoff K, *et al*: Loss of BAP1 function leads to EZH2-dependent transformation. *Nat Med* 21: 1344-1349, 2015.
105. Micol JB and Abdel-Wahab O: The role of additional sex combs-like proteins in cancer. *Cold Spring Harb Perspect Med* 6: a026526, 2016.
106. Campagne A, Lee MK, Zielinski D, Michaud A, Le Corre S, Dingli F, Chen H, Shahidian LZ, Vassilev I, Servant N, *et al*: BAP1 complex promotes transcription by opposing PRC1-mediated H2A ubiquitylation. *Nat Commun* 10: 348, 2019.
107. Ji Z, Mohammed H, Webber A, Ridsdale J, Han N, Carroll JS and Sharrocks AD: The forkhead transcription factor FOXK2 acts as a chromatin targeting factor for the BAP1-containing histone deubiquitinase complex. *Nucleic Acids Res* 42: 6232-6242, 2014.
108. Abdel-Wahab O and Dey A: The ASXL-BAP1 axis: New factors in myelopoiesis, cancer and epigenetics. *Leukemia* 27: 10-15, 2013.
109. Carbone M, Yang H, Pass HI, Krausz T, Testa JR and Gaudino G: BAP1 and cancer. *Nat Rev Cancer* 13: 153-159, 2013.
110. Chittock EC, Latwiel S, Miller TC and Müller CW: Molecular architecture of polycomb repressive complexes. *Biochem Soc Trans* 45: 193-205, 2017.
111. Okino Y, Machida Y, Frankland-Searby S and Machida YJ: BRCA1-associated protein 1 (BAP1) deubiquitinase antagonizes the ubiquitin-mediated activation of FoxK2 target genes. *J Biol Chem* 290: 1580-1591, 2015.
112. Ivanov GS, Ivanova T, Kurash J, Ivanov A, Chuikov S, Gizatullin F, Herrera-Medina EM, Rauscher F III, Reinberg D and Barlev NA: Methylation-acetylation interplay activates p53 in response to DNA damage. *Mol Cell Biol* 27: 6756-6769, 2007.
113. Li G, Margueron R, Hu G, Stokes D, Wang YH and Reinberg D: Highly compacted chromatin formed in vitro reflects the dynamics of transcription activation in vivo. *Mol Cell* 38: 41-53, 2010.
114. Wang XW, Guo QQ, Yu Y, Zhou TT, Zhang SY, Wang Z, Liu JW, Tang J, Jiang XY, Wang SS, *et al*: The deacetylation of Foxk2 by Sirt1 reduces chemosensitivity to cisplatin. *J Cell Mol Med* 26: 491-506, 2022.
115. Bejerano G, Pheasant M, Makunin I, Stephen S, Kent WJ, Mattick JS and Haussler D: Ultraconserved elements in the human genome. *Science* 304: 1321-1325, 2004.
116. Johnsson P, Lipovich L, Grandér D and Morris KV: Evolutionary conservation of long non-coding RNAs; sequence, structure, function. *Biochim Biophys Acta* 1840: 1063-1071, 2014.
117. Cech TR and Steitz JA: The noncoding RNA revolution-trashing old rules to forge new ones. *Cell* 157: 77-94, 2014.
118. Kentwell J, Gundara JS and Sidhu SB: Noncoding RNAs in endocrine malignancy. *Oncologist* 19: 483-491, 2014.
119. Lieberman J: Tapping the RNA world for therapeutics. *Nat Struct Mol Biol* 25: 357-364, 2018.
120. Gomes CPC, Schroen B, Kuster GM, Robinson EL, Ford K, Squire IB, Heymans S, Martelli F, Emanueli C and Devaux Y: EU-CardioRNA COST Action (CA17129): Regulatory RNAs in heart failure. *Circulation* 141: 313-328, 2020.
121. Ebert MS and Sharp PA: Roles for microRNAs in conferring robustness to biological processes. *Cell* 149: 515-524, 2012.
122. Yamamura S, Imai-Sumida M, Tanaka Y and Dahiya R: Interaction and cross-talk between non-coding RNAs. *Cell Mol Life Sci* 75: 467-484, 2018.
123. Anastasiadou E, Jacob LS and Slack FJ: Non-coding RNA networks in cancer. *Nat Rev Cancer* 18: 5-18, 2018.
124. Bartel DP: MicroRNAs: Genomics, biogenesis, mechanism and function. *Cell* 116: 281-297, 2004.
125. Bartel DP: MicroRNAs: Target recognition and regulatory functions. *Cell* 136: 215-233, 2009.
126. Fabian MR, Mathonnet G, Sundermeier T, Mathys H, Zipprich JT, Svitkin YV, Rivas F, Jinek M, Wohlschlegel J, Doudna JA, *et al*: Mammalian miRNA RISC recruits CAF1 and PABP to affect PABP-dependent deadenylation. *Mol Cell* 35: 868-880, 2009.
127. Min KW, Jo MH, Shin S, Davila S, Zealy RW, Kang SI, Lloyd LT, Hohng S and Yoon JH: AUF1 facilitates microRNA-mediated gene silencing. *Nucleic Acids Res* 45: 6064-6073, 2017.
128. Sun M, Ding J, Li D, Yang G, Cheng Z and Zhu Q: NUDT21 regulates 3'-UTR length and microRNA-mediated gene silencing in hepatocellular carcinoma. *Cancer Lett* 410: 158-168, 2017.
129. Chen D, Wang H, Chen J, Li Z, Li S, Hu Z, Huang S, Zhao Y and He X: MicroRNA-129-5p regulates glycolysis and cell proliferation by targeting the glucose transporter SLC2A3 in gastric cancer cells. *Front Pharmacol* 9: 502, 2018.
130. Cui Z, Liu L, Kwame Ameyor F, Zhu Q, Wang Y, Li D, Shu G, Tian Y and Zhao X: High expression of miR-204 in chicken atrophic ovaries promotes granulosa cell apoptosis and inhibits autophagy. *Front Cell Dev Biol* 8: 580072, 2020.
131. Lin MF, Yang YF, Peng ZP, Zhang MF, Liang JY, Chen W, Liu XH and Zheng YL: FOXK2, regulated by miR-1271-5p, promotes cell growth and indicates unfavorable prognosis in hepatocellular carcinoma. *Int J Biochem Cell Biol* 88: 155-161, 2017.
132. Chen S, Jiang S, Hu F, Xu Y, Wang T and Mei Q: Foxk2 inhibits non-small cell lung cancer epithelial-mesenchymal transition and proliferation through the repression of different key target genes. *Oncol Rep* 37: 2335-2347, 2017.
133. Harada K, Baba Y, Ishimoto T, Shigaki H, Kosumi K, Yoshida N, Watanabe M and Baba H: The role of microRNA in esophageal squamous cell carcinoma. *J Gastroenterol* 51: 520-530, 2016.
134. Liu M, Yu J, Wang D, Niu Y, Chen S, Gao P, Yang Z, Wang H, Zhang J, Zhang C, *et al*: Epigenetically upregulated MicroRNA-602 is involved in a negative feedback loop with FOXK2 in esophageal squamous cell carcinoma. *Mol Ther* 27: 1796-1809, 2019.
135. Wang D, Wang H, Liu C, Mu X and Cheng S: Hyperglycemia inhibition of endothelial miR-140-3p mediates angiogenic dysfunction in diabetes mellitus. *J Diabetes Complications* 33: 374-382, 2019.
136. Li S, Zhao L, Li X, Shang G, Gao L, Song Z and Li T: Mir-204 regulates LPS-induced A549 cell damage by targeting FOXK2. *J Healthc Eng* 2021: 7404671, 2021.
137. Kristensen LS, andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB and Kjems J: The biogenesis, biology and characterization of circular RNAs. *Nat Rev Genet* 20: 675-691, 2019.
138. Chen LL: The expanding regulatory mechanisms and cellular functions of circular RNAs. *Nat Rev Mol Cell Biol* 21: 475-490, 2020.
139. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, Evantal N, Memczak S, Rajewsky N and Kadener S: circRNA biogenesis competes with pre-mRNA splicing. *Mol Cell* 56: 55-66, 2014.
140. Kristensen LS, Hansen TB, Venø MT and Kjems J: Circular RNAs in cancer: Opportunities and challenges in the field. *Oncogene* 37: 555-565, 2018.
141. Patop IL and Kadener S: circRNAs in cancer. *Curr Opin Genet Dev* 48: 121-127, 2018.
142. Zhang M and Xin Y: Circular RNAs: A new frontier for cancer diagnosis and therapy. *J Hematol Oncol* 11: 21, 2018.
143. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK and Kjems J: Natural RNA circles function as efficient microRNA sponges. *Nature* 495: 384-388, 2013.
144. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, *et al*: Circular RNAs are a large class of animal RNAs with regulatory potency. *Nature* 495: 333-338, 2013.
145. Hu W, Bi ZY, Chen ZL, Liu C, Li LL, Zhang F, Zhou Q, Zhu W, Song YY, Zhan BT, *et al*: Emerging landscape of circular RNAs in lung cancer. *Cancer Lett* 427: 18-27, 2018.
146. Hua Q, Chen Y, Liu Y, Li M, Diao Q, Xue H, Zeng H, Huang L and Jiang Y: Circular RNA 0039411 is involved in neodymium oxide-induced inflammation and antiproliferation in a human bronchial epithelial cell line via sponging miR-93-5p. *Toxicol Sci* 170: 69-81, 2019.
147. Han D, Wang Y, Wang Y, Dai X, Zhou T, Chen J, Tao B, Zhang J and Cao F: The tumor-suppressive human circular RNA CircITCH sponges miR-330-5p to ameliorate doxorubicin-induced cardiotoxicity through upregulating SIRT6, survivin and SERCA2a. *Circ Res* 127: e108-e125, 2020.
148. Yang C, Yuan W, Yang X, Li P, Wang J, Han J, Tao J, Li P, Yang H, Lv Q and Zhang W: Circular RNA circ-ITCH inhibits bladder cancer progression by sponging miR-17/miR-224 and regulating p21, PTEN expression. *Mol Cancer* 17: 19, 2018.
149. Li J, Guo R, Liu Q, Sun J and Wang H: Circular RNA Circ-ITCH inhibits the malignant behaviors of cervical cancer by microRNA-93-5p/FOXK2 axis. *Reprod Sci* 27: 860-868, 2020.

150. Shi X, Liu TT, Yu XN, Balakrishnan A, Zhu HR, Guo HY, Zhang GC, Bilegsaikhan E, Sun JL, Song GQ, *et al*: microRNA-93-5p promotes hepatocellular carcinoma progression via a microRNA-93-5p/MAP3K2/c-Jun positive feedback circuit. *Oncogene* 39: 5768-5781, 2020.
151. Ma DH, Li BS, Liu JJ, Xiao YF, Yong X, Wang SM, Wu YY, Zhu HB, Wang DX and Yang SM: miR-93-5p/IFNAR1 axis promotes gastric cancer metastasis through activating the STAT3 signaling pathway. *Cancer Lett* 408: 23-32, 2017.
152. Chen X, Chen S, Xiu YL, Sun KX, Zong ZH and Zhao Y: RhoC is a major target of microRNA-93-5P in epithelial ovarian carcinoma tumorigenesis and progression. *Mol Cancer* 14: 31, 2015.
153. Li J, Chu ZP, Han H, Zhang Y, Tian F, Zhang JQ and Huang XH: Suppression of miR-93-5p inhibits high-risk HPV-positive cervical cancer progression via targeting of BTG3. *Hum Cell* 32: 160-171, 2019.
154. Li Y, Ge YZ, Xu L and Jia R: Circular RNA ITCH: A novel tumor suppressor in multiple cancers. *Life Sci* 254: 117176, 2020.
155. Sun J, Yin A, Zhang W, Lv J, Liang Y, Li H, Li Y and Li X: CircUBAP2 inhibits proliferation and metastasis of clear cell renal cell carcinoma via targeting miR-148a-3p/FOXK2 pathway. *Cell Transplant* 29: 963689720925751, 2020.
156. Xu Q, Cheng D, Li G, Liu Y, Li P, Sun W, Ma D and Ni C: CircHIPK3 regulates pulmonary fibrosis by facilitating glycolysis in miR-30a-3p/FOXK2-dependent manner. *Int J Biol Sci* 17: 2294-2307, 2021.
157. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, Barrette TR, Prensner JR, Evans JR, Zhao S, *et al*: The landscape of long noncoding RNAs in the human transcriptome. *Nat Genet* 47: 199-208, 2015.
158. St Laurent G, Wahlestedt C and Kapranov P: The landscape of long noncoding RNA classification. *Trends Genet* 31: 239-251, 2015.
159. Kitagawa M, Kitagawa K, Kotake Y, Niida H and Ohhata T: Cell cycle regulation by long non-coding RNAs. *Cell Mol Life Sci* 70: 4785-4794, 2013.
160. Ballarino M, Morlando M, Fatica A and Bozzoni I: Non-coding RNAs in muscle differentiation and musculoskeletal disease. *J Clin Invest* 126: 2021-2030, 2016.
161. Brazão TF, Johnson JS, Müller J, Heger A, Ponting CP and Tybulewicz VL: Long noncoding RNAs in B-cell development and activation. *Blood* 128: e10-e19, 2016.
162. Delás MJ, Sabin LR, Dolzhenko E, Knott SR, Munera Maravilla E, Jackson BT, Wild SA, Kovacevic T, Stork EM, Zhou M, *et al*: lncRNA requirements for mouse acute myeloid leukemia and normal differentiation. *Elife* 6: e25607, 2017.
163. Sirey TM, Roberts K, Haerty W, Bedoya-Reina O, Rogatti-Granados S, Tan JY, Li N, Heather LC, Carter RN, Cooper S, *et al*: The long non-coding RNA Cerox1 is a post transcriptional regulator of mitochondrial complex I catalytic activity. *Elife* 8: e45051, 2019.
164. Esteller M: Non-coding RNAs in human disease. *Nat Rev Genet* 12: 861-874, 2011.
165. Yuan JH, Yang F, Wang F, Ma JZ, Guo YJ, Tao QF, Liu F, Pan W, Wang TT, Zhou CC, *et al*: A long noncoding RNA activated by TGF- β promotes the invasion-metastasis cascade in hepatocellular carcinoma. *Cancer Cell* 25: 666-681, 2014.
166. Huarte M: The emerging role of lncRNAs in cancer. *Nat Med* 21: 1253-1261, 2015.
167. Liao D, Liu X, Yuan X, Feng P, Ouyang Z, Liu Y and Li C: Long non-coding RNA tumor protein 53 target gene 1 promotes cervical cancer development via regulating microRNA-33a-5p to target forkhead box K2. *Cell Cycle* 21: 572-584, 2022.
168. Diaz-Lagares A, Crujeiras AB, Lopez-Serra P, Soler M, Setien F, Goyal A, Sandoval J, Hashimoto Y, Martinez-Cardús A, Gomez A, *et al*: Epigenetic inactivation of the p53-induced long noncoding RNA TP53 target 1 in human cancer. *Proc Natl Acad Sci USA* 113: E7535-E7544, 2016.
169. Chen B, Lan J, Xiao Y, Liu P, Guo D, Gu Y, Song Y, Zhong Q, Ma D, Lei P and Liu Q: Long noncoding RNA TP53TG1 suppresses the growth and metastasis of hepatocellular carcinoma by regulating the PRDX4/ β -catenin pathway. *Cancer Lett* 513: 75-89, 2021.
170. Pan J, Fang S, Tian H, Zhou C, Zhao X, Tian H, He J, Shen W, Meng X, Jin X and Gong Z: lncRNA JPX/miR-33a-5p/ Twist1 axis regulates tumorigenesis and metastasis of lung cancer by activating Wnt/ β -catenin signaling. *Mol Cancer* 19: 9, 2020.
171. Lin C, Xiang Y, Sheng J, Liu S, Cui M and Zhang X: Long non-coding RNA CRNDE promotes malignant progression of hepatocellular carcinoma through the miR-33a-5p/CDK6 axis. *J Physiol Biochem* 76: 469-481, 2020.
172. Sasaki M, Ishikawa T, Ishiguro M, Okazaki S, Yamauchi S, Kikuchi A, Matsuyama T, Kawada K, Tokunaga M, Uetake H and Kinugasa Y: The effectiveness of plasma miR-33a-5p as a predictive biomarker for the efficacy of colorectal cancer chemotherapy. *Oncol Lett* 21: 489, 2021.
173. Zhao Z, Gao J and Huang S: lncRNA SNHG7 promotes the HCC progression through miR-122-5p/FOXK2 axis. *Dig Dis Sci* 67: 925-935, 2022.
174. van der Heide LP, Wijchers PJ, von Oerthel L, Burbach JP, Hoekman MF and Smidt MP: FoxK2 is required for cellular proliferation and survival. *J Cell Physiol* 230: 1013-1023, 2015.
175. Qian Y, Xia S and Feng Z: Sox9 mediated transcriptional activation of FOXK2 is critical for colorectal cancer cells proliferation. *Biochem Biophys Res Commun* 483: 475-481, 2017.
176. Ji Z, Donaldson IJ, Liu J, Hayes A, Zeef LA and Sharrocks AD: The forkhead transcription factor FOXK2 promotes AP-1-mediated transcriptional regulation. *Mol Cell Biol* 32: 385-398, 2012.
177. Meehan RR, Lewis JD, McKay S, Kleiner EL and Bird AP: Identification of a mammalian protein that binds specifically to DNA containing methylated CpGs. *Cell* 58: 499-507, 1989.
178. Hendrich B and Bird A: Identification and characterization of a family of mammalian methyl-CpG binding proteins. *Mol Cell Biol* 18: 6538-6547, 1998.
179. Chen X, Ji Z, Webber A and Sharrocks AD: Genome-wide binding studies reveal DNA binding specificity mechanisms and functional interplay amongst forkhead transcription factors. *Nucleic Acids Res* 44: 1566-1578, 2016.
180. Komorek J, Kuppuswamy M, Subramanian T, Vijayalingam S, Lomonosova E, Zhao LJ, Mymryk JS, Schmitt K and Chinnadurai G: Adenovirus type 5 E1A and E6 proteins of low-risk cutaneous beta-human papillomaviruses suppress cell transformation through interaction with FOXK1/K2 transcription factors. *J Virol* 84: 2719-2731, 2010.
181. Tang F, Cao F, Lu C, He X, Weng L and Sun L: Dvl2 facilitates the coordination of NF- κ B and Wnt signaling to promote colitis-associated colorectal progression. *Cancer Sci* 113: 565-575, 2022.
182. Good MC, Zalatan JG and Lim WA: Scaffold proteins: Hubs for controlling the flow of cellular information. *Science* 332: 680-686, 2011.
183. Pan CQ, Sudol M, Sheetz M and Low BC: Modularity and functional plasticity of scaffold proteins as p(l)acemakers in cell signaling. *Cell Signal* 24: 2143-2165, 2012.
184. Kagan JC, Magupalli VG and Wu H: SMOs: Supramolecular organizing centres that control innate immunity. *Nat Rev Immunol* 14: 821-826, 2014.
185. Langeberg LK and Scott JD: Signalling scaffolds and local organization of cellular behaviour. *Nat Rev Mol Cell Biol* 16: 232-244, 2015.
186. Liu Y, Ao X, Jia Z, Bai XY, Xu Z, Hu G, Jiang X, Chen M and Wu H: FOXK2 transcription factor suppresses ER α -positive breast cancer cell growth through down-regulating the stability of ER α via mechanism involving BRCA1/BARD1. *Sci Rep* 5: 8796, 2015.
187. Parsons R, Li GM, Longley MJ, Fang WH, Papadopoulos N, Jen J, de la Chapelle A, Kinzler KW, Vogelstein B and Modrich P: Hypermutability and mismatch repair deficiency in RER+ tumor cells. *Cell* 75: 1227-1236, 1993.
188. Fishel R, Lescoe MK, Rao MR, Copeland NG, Jenkins NA, Garber J, Kane M and Kolodner R: The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. *Cell* 75: 1027-1038, 1993.
189. Leach FS, Nicolaides NC, Papadopoulos N, Liu B, Jen J, Parsons R, Peltomäki P, Sistonen P, Aaltonen LA, Nyström-Lahti M, *et al*: Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. *Cell* 75: 1215-1225, 1993.
190. Katoh M, Igarashi M, Fukuda H, Nakagama H and Katoh M: Cancer genetics and genomics of human FOX family genes. *Cancer Lett* 328: 198-206, 2013.
191. Michailidou K, Lindström S, Dennis J, Beesley J, Hui S, Kar S, Lemaçon A, Soucy P, Glubb D, Rostamianfar A, *et al*: Association analysis identifies 65 new breast cancer risk loci. *Nature* 551: 92-94, 2017.
192. Fujii Y and Nakamura M: FOXK2 transcription factor is a novel G/T-mismatch DNA binding protein. *J Biochem* 147: 705-709, 2010.

193. Zhang F, Ma X, Li H, Zhang Y, Li X, Chen L, Guo G, Gao Y, Gu L, Xie Y, *et al*: FOXK2 suppresses the malignant phenotype and induces apoptosis through inhibition of EGFR in clear-cell renal cell carcinoma. *Int J Cancer* 142: 2543-2557, 2018.
194. Shan L, Zhou X, Liu X, Wang Y, Su D, Hou Y, Yu N, Yang C, Liu B, Gao J, *et al*: FOXK2 elicits massive transcription repression and suppresses apatinib resistance in hypoxic response and breast cancer carcinogenesis. *Cancer Cell* 30: 708-722, 2016.
195. Wang B, Zhang X, Wang W, Zhu Z, Tang F, Wang D, Liu X, Zhuang H and Yan X: Forkhead box K2 inhibits the proliferation, migration, and invasion of human glioma cells and predicts a favorable prognosis. *Onco Targets Ther* 11: 1067-1075, 2018.
196. Li S, Wang P, Ju H, Zhu T, Shi J and Huang Y: FOXK2 promotes the proliferation of papillary thyroid cancer cell by down-regulating autophagy. *J Cancer* 13: 858-868, 2022.
197. Feng H, Jin Z, Liang J, Zhao Q, Zhan L, Yang Z, Yan J, Kuang J, Cheng X and Qiu W: FOXK2 transcriptionally activating VEGFA induces apatinib resistance in anaplastic thyroid cancer through VEGFA/VEGFR1 pathway. *Oncogene* 40: 6115-6129, 2021.
198. Du F, Qiao C, Li X, Chen Z, Liu H, Wu S, Hu S, Qiu Z, Qian M, Tian D, *et al*: Forkhead box K2 promotes human colorectal cancer metastasis by upregulating ZEB1 and EGFR. *Theranostics* 9: 3879-3902, 2019.
199. Baylin SB and Jones PA: Epigenetic determinants of cancer. *Cold Spring Harb Perspect Biol* 8: a019505, 2016.
200. Jones PA, Issa JP and Baylin S: Targeting the cancer epigenome for therapy. *Nat Rev Genet* 17: 630-641, 2016.
201. Block KI, Gyllenhaal C, Lowe L, Amedei A, Amin AR, Amin A, Aquilano K, Arbiser J, Arreola A, Arzumanyan A, *et al*: Designing a broad-spectrum integrative approach for cancer prevention and treatment. *Semin Cancer Biol* 35 (Suppl 1): S276-S304, 2015.
202. Duijff PHG, Nanayakkara D, Nones K, Srihari S, Kalimutho M and Khanna KK: Mechanisms of genomic instability in breast cancer. *Trends Mol Med* 25: 595-611, 2019.
203. Rusin M, Zajkowicz A and Butkiewicz D: Resveratrol induces senescence-like growth inhibition of U-2 OS cells associated with the instability of telomeric DNA and upregulation of BRCA1. *Mech Ageing Dev* 130: 528-537, 2009.
204. Falck J, Mailand N, Syljuåsen RG, Bartek J and Lukas J: The ATM-Chk2-Cdc25A checkpoint pathway guards against radioresistant DNA synthesis. *Nature* 410: 842-847, 2001.
205. Matsuoka S, Huang M and Elledge SJ: Linkage of ATM to cell cycle regulation by the Chk2 protein kinase. *Science* 282: 1893-1897, 1998.
206. Mas-Ponte D and Supek F: DNA mismatch repair promotes APOBEC3-mediated diffuse hypermutation in human cancers. *Nat Genet* 52: 958-968, 2020.
207. Barroso-Sousa R, Jain E, Cohen O, Kim D, Buendia-Buendia J, Winer E, Lin N, Tolane SM and Wagle N: Prevalence and mutational determinants of high tumor mutation burden in breast cancer. *Ann Oncol* 31: 387-394, 2020.
208. LeBlanc SJ, Gauer JW, Hao P, Case BC, Hingorani MM, Weninger KR and Erie DA: Coordinated protein and DNA conformational changes govern mismatch repair initiation by MutS. *Nucleic Acids Res* 46: 10782-10795, 2018.
209. Yu H, Pak H, Hammond-Martel I, Ghram M, Rodrigue A, Daou S, Barbour H, Corbeil L, Hébert J, Drobetsky E, *et al*: Tumor suppressor and deubiquitinase BAP1 promotes DNA double-strand break repair. *Proc Natl Acad Sci USA* 111: 285-290, 2014.
210. Kundert K and Fraser JS: DNA-binding proteins meet their mismatch. *Nature* 587: 199-200, 2020.
211. Li J, Coïc E, Lee K, Lee CS, Kim JA, Wu Q and Haber JE: Regulation of budding yeast mating-type switching donor preference by the FHA domain of Fkh1. *PLoS Genet* 8: e1002630, 2012.
212. Maciejowski J and de Lange T: Telomeres in cancer: Tumour suppression and genome instability. *Nat Rev Mol Cell Biol* 18: 175-186, 2017.
213. Chakravarti D, LaBella KA and DePinho RA: Telomeres: History, health and hallmarks of aging. *Cell* 184: 306-322, 2021.
214. Tang M, Feng X, Pei G, Srivastava M, Wang C, Chen Z, Li S, Zhang H, Zhao Z, Li X and Chen J: FOXK1 participates in DNA damage response by controlling 53BP1 function. *Cell Rep* 32: 108018, 2020.
215. Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A and Hemminki K: Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 343: 78-85, 2000.
216. Berdasco M and Esteller M: Aberrant epigenetic landscape in cancer: How cellular identity goes awry. *Dev Cell* 19: 698-711, 2010.
217. Esteller M: Cancer epigenomics: DNA methylomes and histone-modification maps. *Nat Rev Genet* 8: 286-298, 2007.
218. Bitman-Lotan E and Orian A: Nuclear organization and regulation of the differentiated state. *Cell Mol Life Sci* 78: 3141-3158, 2021.
219. Goldberg AD, Allis CD and Bernstein E: Epigenetics: A landscape takes shape. *Cell* 128: 635-638, 2007.
220. Nam AS, Chaligne R and Landau DA: Integrating genetic and non-genetic determinants of cancer evolution by single-cell multi-omics. *Nat Rev Genet* 22: 3-18, 2021.
221. Feng Y, Liu X and Pauklin S: 3D chromatin architecture and epigenetic regulation in cancer stem cells. *Protein Cell* 12: 440-454, 2021.
222. Toh TB, Lim JJ and Chow EK: Epigenetics in cancer stem cells. *Mol Cancer* 16: 29, 2017.
223. Dvorak HF: Tumors: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med* 315: 1650-1659, 1986.
224. Mantovani A, Allavena P, Sica A and Balkwill F: Cancer-related inflammation. *Nature* 454: 436-444, 2008.
225. Pagès F, Galon J, Dieu-Nosjean MC, Tartour E, Sautès-Fridman C and Fridman WH: Immune infiltration in human tumors: A prognostic factor that should not be ignored. *Oncogene* 29: 1093-1102, 2010.
226. Grivennikov SI, Greten FR and Karin M: Immunity, inflammation, and cancer. *Cell* 140: 883-899, 2010.
227. Qian BZ and Pollard JW: Macrophage diversity enhances tumor progression and metastasis. *Cell* 141: 39-51, 2010.
228. van Bilsen JHM, Dulos R, van Stee MF, Meima MY, Rouhani Rankouhi T, Neergaard Jacobsen L, Staudt Kvistgaard A, Garthoff JA, Knippels LMJ, Knipping K, *et al*: Seeking windows of opportunity to shape lifelong immune health: A network-based strategy to predict and prioritize markers of early life immune modulation. *Front Immunol* 11: 644, 2020.
229. Oh H and Ghosh S: NF- κ B: Roles and regulation in different CD4(+) T-cell subsets. *Immunol Rev* 252: 41-51, 2013.
230. Blanchett S, Boal-Carvalho I, Layzell S and Seddon B: NF- κ B and extrinsic cell death pathways-entwined do-or-die decisions for T cells. *Trends Immunol* 42: 76-88, 2021.
231. Gilmore TD: Introduction to NF-kappaB: Players, pathways, perspectives. *Oncogene* 25: 6680-6684, 2006.
232. Karin M and Greten FR: NF-kappaB: Linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol* 5: 749-759, 2005.
233. Li Q, Withoff S and Verma IM: Inflammation-associated cancer: NF-kappaB is the lynchpin. *Trends Immunol* 26: 318-325, 2005.
234. DeNardo DG and Coussens LM: Interactions between lymphocytes and myeloid cells regulate pro-versus anti-tumor immunity. *Cancer Metastasis Rev* 29: 309-316, 2010.
235. Ohnishi S, Ma N, Thanan R, Pinlaor S, Hammam O, Murata M and Kawanishi S: DNA damage in inflammation-related carcinogenesis and cancer stem cells. *Oxid Med Cell Longev* 2013: 387014, 2013.
236. Martin TD, Patel RS, Cook DR, Choi MY, Patil A, Liang AC, Li MZ, Haigis KM and Elledge SJ: The adaptive immune system is a major driver of selection for tumor suppressor gene inactivation. *Science* 373: 1327-1335, 2021.
237. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA and Knight R: The microbiome and human cancer. *Science* 371: eabc4552, 2021.
238. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A and Wargo JA: The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. *Cancer Cell* 33: 570-580, 2018.
239. Rowe WP, Huebner RJ, Gilmore LK, Parrott RH and Ward TG: Isolation of a cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture. *Proc Soc Exp Biol Med* 84: 570-573, 1953.
240. Trentin JJ, Yabe Y and Taylor G: The quest for human cancer viruses. *Science* 137: 835-841, 1962.
241. Javier RT: Adenovirus type 9 E4 open reading frame 1 encodes a transforming protein required for the production of mammary tumors in rats. *J Virol* 68: 3917-3924, 1994.

242. Sanchez-Prieto R, de Alava E, Palomino T, Guinea J, Fernandez V, Cebrian S, LLeonart M, Cabello P, Martin P, San Roman C, *et al*: An association between viral genes and human oncogenic alterations: The adenovirus E1A induces the Ewing tumor fusion transcript EWS-FLI1. *Nat Med* 5: 1076-1079, 1999.
243. Wang GL, Jiang BH, Rue EA and Semenza GL: Hypoxia-inducible factor 1 is a basic-helix-loop-helix-PAS heterodimer regulated by cellular O₂ tension. *Proc Natl Acad Sci USA* 92: 5510-5514, 1995.
244. Semenza GL: Hypoxia-inducible factor 1: Master regulator of O₂ homeostasis. *Curr Opin Genet Dev* 8: 588-594, 1998.
245. Vaupel P and Mayer A: Hypoxia in cancer: Significance and impact on clinical outcome. *Cancer Metastasis Rev* 26: 225-239, 2007.
246. Sui H, Fan S, Liu W, Li Y, Zhang X, Du Y and Bao H: LINC00028 regulates the development of TGFβ1-treated human tenon capsule fibroblasts by targeting miR-204-5p. *Biochem Biophys Res Commun*: Feb 19, 2020 (Epub ahead of print).
247. Wittstatt J, Weider M, Wegner M and Reiprich S: MicroRNA miR-204 regulates proliferation and differentiation of oligodendroglia in culture. *Glia* 68: 2015-2027, 2020.
248. Zhang J, Su M and Yin Z: Construction of inflammatory directed polymer micelles and its application in acute lung injury. *AAPS PharmSciTech* 21: 217, 2020.
249. Wang S, Liu Z, Wang L and Zhang X: NF-kappaB signaling pathway, inflammation and colorectal cancer. *Cell Mol Immunol* 6: 327-334, 2009.
250. Engelman JA, Luo J and Cantley LC: The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. *Nat Rev Genet* 7: 606-619, 2006.
251. Malumbres M: Cyclin-dependent kinases. *Genome Biol* 15: 122, 2014.
252. Greer EL and Brunet A: FOXO transcription factors at the interface between longevity and tumor suppression. *Oncogene* 24: 7410-7425, 2005.
253. Katoh M and Katoh M: Human FOX gene family (Review). *Int J Oncol* 25: 1495-1500, 2004.
254. Koranda M, Schleiffer A, Endler L and Ammerer G: Forkhead-like transcription factors recruit Ndd1 to the chromatin of G2/M-specific promoters. *Nature* 406: 94-98, 2000.
255. Pic A, Lim FL, Ross SJ, Veal EA, Johnson AL, Sultan MR, West AG, Johnston LH, Sharrocks AD and Morgan BA: The forkhead protein Fkh2 is a component of the yeast cell cycle transcription factor SFF. *EMBO J* 19: 3750-3761, 2000.
256. Kumar R, Reynolds DM, Shevchenko A, Shevchenko A, Goldstone SD and Dalton S: Forkhead transcription factors, Fkh1p and Fkh2p, collaborate with Mcm1p to control transcription required for M-phase. *Curr Biol* 10: 896-906, 2000.
257. Ho KK, Myatt SS and Lam EW: A number of forks in the path: Cycling with FoxO. *Oncogene* 27: 2300-2311, 2008.
258. Laoukili J, Stahl M and Medema RH: FoxM1: At the crossroads of ageing and cancer. *Biochim Biophys Acta* 1775: 92-102, 2007.
259. Yan J, Xu L, Crawford G, Wang Z and Burgess SM: The forkhead transcription factor FoxI1 remains bound to condensed mitotic chromosomes and stably remodels chromatin structure. *Mol Cell Biol* 26: 155-168, 2006.
260. Liang J and Shang Y: Estrogen and cancer. *Annu Rev Physiol* 75: 225-240, 2013.
261. Douglas CC, Johnson SA and Arjmandi BH: Soy and its isoflavones: The truth behind the science in breast cancer. *Anticancer Agents Med Chem* 13: 1178-1187, 2013.
262. Eroles P, Bosch A, Pérez-Fidalgo JA and Lluch A: Molecular biology in breast cancer: Intrinsic subtypes and signaling pathways. *Cancer Treat Rev* 38: 698-707, 2012.
263. Nestal de Moraes G, Khongkow P, Gong C, Yao S, Gomes AR, Ji Z, Kandola N, Delbue D, Man EP, Khoo US, *et al*: Forkhead box K2 modulates epirubicin and paclitaxel sensitivity through FOXO3a in breast cancer. *Oncogenesis* 4: e167, 2015.
264. Zhang Y, Wang Y, Zhao G, Tanner EJ, Adli M and Matei D: FOXK2 promotes ovarian cancer stemness by regulating the unfolded protein response pathway. *J Clin Invest* 132: e151591, 2022.
265. Amin ARMR, Karpowicz PA, Carey TE, Arbiser J, Nahta R, Chen ZG, Dong JT, Kucuk O, Khan GN, Huang GS, *et al*: Evasion of anti-growth signaling: A key step in tumorigenesis and potential target for treatment and prophylaxis by natural compounds. *Semin Cancer Biol* 35 (Suppl 1): S55-S77, 2015.
266. Milella M, Falcone I, Conciatori F, Cesta Incani U, Del Curatolo A, Inzerilli N, Nuzzo CM, Vaccaro V, Vari S, Cognetti F and Ciuffreda L: PTEN: Multiple functions in human malignant tumors. *Front Oncol* 5: 24, 2015.
267. Trinquand A, Tanguy-Schmidt A, Ben Abdelali R, Lambert J, Beldjord K, Lengliné E, De Gunzburg N, Payet-Bornet D, Lhermitte L, Mossafa H, *et al*: Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenetic risk classification of adult T-cell acute lymphoblastic leukemia: A group for research in adult acute lymphoblastic leukemia study. *J Clin Oncol* 31: 4333-4342, 2013.
268. Tesio M, Trinquand A, Macintyre E and Asnafi V: Oncogenic PTEN functions and models in T-cell malignancies. *Oncogene* 35: 3887-3896, 2016.
269. Liu Y, Easton J, Shao Y, Maciaszek J, Wang Z, Wilkinson MR, McCastlain K, Edmonson M, Pounds SB, Shi L, *et al*: The genomic landscape of pediatric and young adult T-lineage acute lymphoblastic leukemia. *Nat Genet* 49: 1211-1218, 2017.
270. Wu W, Chen Y, Ye S, Yang H, Yang J and Quan J: Transcription factor forkhead box K1 regulates miR-32 expression and enhances cell proliferation in colorectal cancer. *Oncol Lett* 21: 407, 2021.
271. Wu W, Tan W, Ye S, Zhou Y and Quan J: Analysis of the promoter region of the human miR-32 gene in colorectal cancer. *Oncol Lett* 17: 3743-3750, 2019.
272. Opel D, Schnaiter A, Dodier D, Jovanovic M, Gerhardinger A, Idler I, Mertens D, Bullinger L, Stilgenbauer S and Fulda S: Targeting inhibitor of apoptosis proteins by Smac mimetic elicits cell death in poor prognostic subgroups of chronic lymphocytic leukemia. *Int J Cancer* 137: 2959-2970, 2015.
273. Mergny JL, Lacroix L, Teulade-Fichou MP, Hounsou C, Guittat L, Hoarau M, Arimondo PB, Vigneron JP, Lehn JM, Riou JF, *et al*: Telomerase inhibitors based on quadruplex ligands selected by a fluorescence assay. *Proc Natl Acad Sci USA* 98: 3062-3067, 2001.
274. Yin XM, Oltvai ZN and Korsmeyer SJ: BHL and BH2 domains of Bcl-2 are required for inhibition of apoptosis and heterodimerization with Bax. *Nature* 369: 321-323, 1994.
275. Youle RJ and Strasser A: The BCL-2 protein family: Opposing activities that mediate cell death. *Nat Rev Mol Cell Biol* 9: 47-59, 2008.
276. Asnaghi L, Calastretti A, Bevilacqua A, D'Agnano I, Gatti G, Canti G, Delia D, Capaccioli S and Nicolini A: Bcl-2 phosphorylation and apoptosis activated by damaged microtubules require mTOR and are regulated by Akt. *Oncogene* 23: 5781-5791, 2004.
277. Van Der Heide LP, Hoekman MF and Smidt MP: The ins and outs of FoxO shuttling: Mechanisms of FoxO translocation and transcriptional regulation. *Biochem J* 380: 297-309, 2004.
278. Folkman J: Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1: 27-31, 1995.
279. Folkman J: What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 82: 4-6, 1990.
280. Baeriswyl V and Christofori G: The angiogenic switch in carcinogenesis. *Semin Cancer Biol* 19: 329-337, 2009.
281. Cao Y: Antiangiogenic cancer therapy. *Semin Cancer Biol* 14: 139-145, 2004.
282. Bergers G and Benjamin LE: Tumorigenesis and the angiogenic switch. *Nat Rev Cancer* 3: 401-410, 2003.
283. Song Y, Zeng S, Zheng G, Chen D, Li P, Yang M, Luo K, Yin J, Gu Y, Zhang Z, *et al*: FOXO3a-driven miRNA signatures suppresses VEGF-A/NRP1 signaling and breast cancer metastasis. *Oncogene* 40: 777-790, 2021.
284. Karaman S, Leppänen VM and Alitalo K: Vascular endothelial growth factor signaling in development and disease. *Development* 145: dev151019, 2018.
285. Ellis LM and Hicklin DJ: VEGF-targeted therapy: Mechanisms of anti-tumour activity. *Nat Rev Cancer* 8: 579-591, 2008.
286. El Atat O, Fakih A and El-Sibai M: RHOG activates RAC1 through CDC42 leading to tube formation in vascular endothelial cells. *Cells* 8: 171, 2019.
287. Jin Z, Cheng X, Feng H, Kuang J, Yang W, Peng C, Shen B and Qiu W: Apatinib inhibits angiogenesis via suppressing Akt/GSK3β/ANG signaling pathway in anaplastic thyroid cancer. *Cell Physiol Biochem* 44: 1471-1484, 2017.
288. Wang S, Xiao Z, Hong Z, Jiao H, Zhu S, Zhao Y, Bi J, Qiu J, Zhang D, Yan J, *et al*: FOXF1 promotes angiogenesis and accelerates bevacizumab resistance in colorectal cancer by transcriptionally activating VEGFA. *Cancer Lett* 439: 78-90, 2018.
289. Sun T, Wang H, Li Q, Qian Z and Shen C: Forkhead box protein k1 recruits TET1 to act as a tumor suppressor and is associated with MRI detection. *Jpn J Clin Oncol* 46: 209-221, 2016.

290. Bensinger SJ and Christofk HR: New aspects of the Warburg effect in cancer cell biology. *Semin Cell Dev Biol* 23: 352-361, 2012.
291. Palm W and Thompson CB: Nutrient acquisition strategies of mammalian cells. *Nature* 546: 234-242, 2017.
292. Cairns RA, Harris IS and Mak TW: Regulation of cancer cell metabolism. *Nat Rev Cancer* 11: 85-95, 2011.
293. Vander Heiden MG, Cantley LC and Thompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science* 324: 1029-1033, 2009.
294. Tamada M, Suematsu M and Saya H: Pyruvate kinase M2: Multiple faces for conferring benefits on cancer cells. *Clin Cancer Res* 18: 5554-5561, 2012.
295. Waldhart AN, Dykstra H, Peck AS, Boguslawski EA, Madaj ZB, Wen J, Veldkamp K, Hollowell M, Zheng B, Cantley LC, *et al*: Phosphorylation of TXNIP by AKT mediates acute influx of glucose in response to insulin. *Cell Rep* 19: 2005-2013, 2017.
296. Sheth SS, Castellani LW, Chari S, Wagg C, Thippavong CK, Bodnar JS, Tontonoz P, Attie AD, Lopaschuk GD and Lusis AJ: Thioredoxin-interacting protein deficiency disrupts the fasting-feeding metabolic transition. *J Lipid Res* 46: 123-134, 2005.
297. Luo W, Hu H, Chang R, Zhong J, Knabel M, O'Meally R, Cole RN, Pandey A and Semenza GL: Pyruvate kinase M2 is a PHD3-stimulated coactivator for hypoxia-inducible factor 1. *Cell* 145: 732-744, 2011.
298. Denko NC: Hypoxia, HIF1 and glucose metabolism in the solid tumour. *Nat Rev Cancer* 8: 705-713, 2008.
299. Takamura A, Komatsu M, Hara T, Sakamoto A, Kishi C, Waguri S, Eishi Y, Hino O, Tanaka K and Mizushima N: Autophagy-deficient mice develop multiple liver tumors. *Genes Dev* 25: 795-800, 2011.
300. Sun T, Li X, Zhang P, Chen WD, Zhang HL, Li DD, Deng R, Qian XJ, Jiao L, Ji J, *et al*: Acetylation of beclin 1 inhibits autophagosome maturation and promotes tumour growth. *Nat Commun* 6: 7215, 2015.
301. Kimmelman AC and White E: Autophagy and tumor metabolism. *Cell Metab* 25: 1037-1043, 2017.
302. Nakatogawa H, Suzuki K, Kamada Y and Ohsumi Y: Dynamics and diversity in autophagy mechanisms: Lessons from yeast. *Nat Rev Mol Cell Biol* 10: 458-467, 2009.
303. Kim J, Kim YC, Fang C, Russell RC, Kim JH, Fan W, Liu R, Zhong Q and Guan KL: Differential regulation of distinct Vps34 complexes by AMPK in nutrient stress and autophagy. *Cell* 152: 290-303, 2013.
304. Lambert SA, Jolma A, Campitelli LF, Das PK, Yin Y, Albu M, Chen X, Taipale J, Hughes TR and Weirauch MT: The human transcription factors. *Cell* 172: 650-665, 2018.
305. Reiter F, Wienerroither S and Stark A: Combinatorial function of transcription factors and cofactors. *Curr Opin Genet Dev* 43: 73-81, 2017.
306. Wunderlich Z and Mirny LA: Different gene regulation strategies revealed by analysis of binding motifs. *Trends Genet* 25: 434-440, 2009.
307. Kuroyanagi H: Fox-1 family of RNA-binding proteins. *Cell Mol Life Sci* 66: 3895-3907, 2009.
308. Morgunova E and Taipale J: Structural perspective of cooperative transcription factor binding. *Curr Opin Struct Biol* 47: 1-8, 2017.
309. Klemm SL, Shipony Z and Greenleaf WJ: Chromatin accessibility and the regulatory epigenome. *Nat Rev Genet* 20: 207-220, 2019.
310. Iwafuchi-Doi M and Zaret KS: Pioneer transcription factors in cell reprogramming. *Genes Dev* 28: 2679-2692, 2014.
311. Soufi A, Garcia MF, Jaroszewicz A, Osman N, Pellegrini M and Zaret KS: Pioneer transcription factors target partial DNA motifs on nucleosomes to initiate reprogramming. *Cell* 161: 555-568, 2015.
312. Swinstead EE, Miranda TB, Paakinaho V, Baek S, Goldstein I, Hawkins M, Karpova TS, Ball D, Mazza D, Lavis LD, *et al*: Steroid receptors reprogram FoxA1 occupancy through dynamic chromatin transitions. *Cell* 165: 593-605, 2016.
313. Hughes AL, Jin Y, Rando OJ and Struhl K: A functional evolutionary approach to identify determinants of nucleosome positioning: A unifying model for establishing the genome-wide pattern. *Mol Cell* 48: 5-15, 2012.
314. Struhl K and Segal E: Determinants of nucleosome positioning. *Nat Struct Mol Biol* 20: 267-273, 2013.
315. Swinstead EE, Paakinaho V, Presman DM and Hager GL: Pioneer factors and ATP-dependent chromatin remodeling factors interact dynamically: A new perspective: Multiple transcription factors can effect chromatin pioneer functions through dynamic interactions with ATP-dependent chromatin remodeling factors. *Bioessays* 38: 1150-1157, 2016.
316. Zhu F, Farnung L, Kaasinen E, Sahu B, Yin Y, Wei B, Dodonova SO, Nitta KR, Morgunova E, Taipale M, *et al*: The interaction landscape between transcription factors and the nucleosome. *Nature* 562: 76-81, 2018.
317. Iwafuchi-Doi M and Zaret KS: Cell fate control by pioneer transcription factors. *Development* 143: 1833-1837, 2016.
318. Allis CD and Jenuwein T: The molecular hallmarks of epigenetic control. *Nat Rev Genet* 17: 487-500, 2016.
319. Dann GP, Liszczak GP, Bagert JD, Müller MM, Nguyen UTT, Wojcik F, Brown ZZ, Bos J, Panchenko T, Pihl R, *et al*: ISWI chromatin remodellers sense nucleosome modifications to determine substrate preference. *Nature* 548: 607-611, 2017.
320. Iwafuchi-Doi M, Donahue G, Kakumanu A, Watts JA, Mahony S, Pugh BF, Lee D, Kaestner KH and Zaret KS: The pioneer transcription factor FoxA maintains an accessible nucleosome configuration at enhancers for tissue-specific gene activation. *Mol Cell* 62: 79-91, 2016.
321. Iwafuchi M, Cuesta I, Donahue G, Takenaka N, Osipovich AB, Magnuson MA, Roder H, Seeholzer SH, Santisteban P and Zaret KS: Gene network transitions in embryos depend upon interactions between a pioneer transcription factor and core histones. *Nat Genet* 52: 418-427, 2020.
322. Cirillo LA, Lin FR, Cuesta I, Friedman D, Jarnik M and Zaret KS: Opening of compacted chromatin by early developmental transcription factors HNF3 (FoxA) and GATA-4. *Mol Cell* 9: 279-289, 2002.
323. Shim EY, Woodcock C and Zaret KS: Nucleosome positioning by the winged helix transcription factor HNF3. *Genes Dev* 12: 5-10, 1998.
324. Chen J, Zhang Z, Li L, Chen BC, Revyakin A, Hajj B, Legant W, Dahan M, Lionnet T, Betzig E, *et al*: Single-molecule dynamics of enhanceosome assembly in embryonic stem cells. *Cell* 156: 1274-1285, 2014.
325. Gebhardt JC, Suter DM, Roy R, Zhao ZW, Chapman AR, Basu S, Maniatis T and Xie XS: Single-molecule imaging of transcription factor binding to DNA in live mammalian cells. *Nat Methods* 10: 421-426, 2013.
326. Mazza D, Abernathy A, Golob N, Morisaki T and McNally JG: A benchmark for chromatin binding measurements in live cells. *Nucleic Acids Res* 40: e119, 2012.
327. Morisaki T, Müller WG, Golob N, Mazza D and McNally JG: Single-molecule analysis of transcription factor binding at transcription sites in live cells. *Nat Commun* 5: 4456, 2014.
328. Marchise C, Roudier F, Castaings L, Bréhaut V, Blondet E, Colot V, Meyer C and Krapp A: Nuclear retention of the transcription factor NLP7 orchestrates the early response to nitrate in plants. *Nat Commun* 4: 1713, 2013.
329. Rey G, Cesbron F, Rougemont J, Reinke H, Brunner M and Naef F: Genome-wide and phase-specific DNA-binding rhythms of BMAL1 control circadian output functions in mouse liver. *PLoS Biol* 9: e1000595, 2011.
330. Futreal PA, Coin L, Marshall M, Down T, Hubbard T, Wooster R, Rahman N and Stratton MR: A census of human cancer genes. *Nat Rev Cancer* 4: 177-183, 2004.



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