

REVIEW

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# Regulation of the master regulator FOXM1 in cancer



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## Abstract

FOXM1 (forkhead box protein M1) is a critical proliferation-associated transcription factor that is widely spatiotemporally expressed during the cell cycle. It is closely involved with the processes of cell proliferation, self-renewal, and tumorigenesis. In most human cancers, FOXM1 is overexpressed, and this indicates a poor prognosis for cancer patients. FOXM1 maintains cancer hallmarks by regulating the expression of target genes at the transcriptional level. Due to its potential role as molecular target in cancer therapy, FOXM1 was named the Molecule of the Year in 2010. However, the mechanism of FOXM1 dysregulation remains indistinct. A comprehensive understanding of FOXM1 regulation will provide novel insight for cancer and other diseases in which FOXM1 plays a major role. Here, we summarize the transcriptional regulation, post-transcriptional regulation and post-translational modifications of FOXM1, which will provide extremely important implications for novel strategies targeting FOXM1.

**Keywords:** FOXM1, Regulation, Transcriptional, Post-transcriptional, Post-translational

## Background

Forkhead box M1 (FOXM1), previously named HNF-3, HFH-11 or Trident, is a transcription factor of the Forkhead box (Fox) protein superfamily which is defined by a conserved winged helix DNA-binding domain [1]. The human FOXM1 gene consists of 10 exons, of which exons Va and VIIa can be alternatively spliced [2]. In the past, VIIa was treated as a repressor until a novel isoform (FOXM1d) that could promote the epithelial–mesenchymal transition (EMT) and metastasis by activating ROCKs in colorectal cancer was identified [3, 4]. Accordingly, there are four isoforms of human FOXM1 identified to date (Fig. 1a). FOXM1a contains both exons Va and VIIa and lacks transactivation activity, while the rest of the three, FOXM1b (which contains neither exon Va nor VIIa), FOXM1c (no VIIa) and FOXM1d (no Va) are transcriptionally active. The FOXM1 protein contains a conserved forkhead DNA-binding domain (DBD), an N-terminal repressor domain (NRD), and a C-terminal transactivation domain (TAD). The transactivation activity of TAD can be suppressed by direct

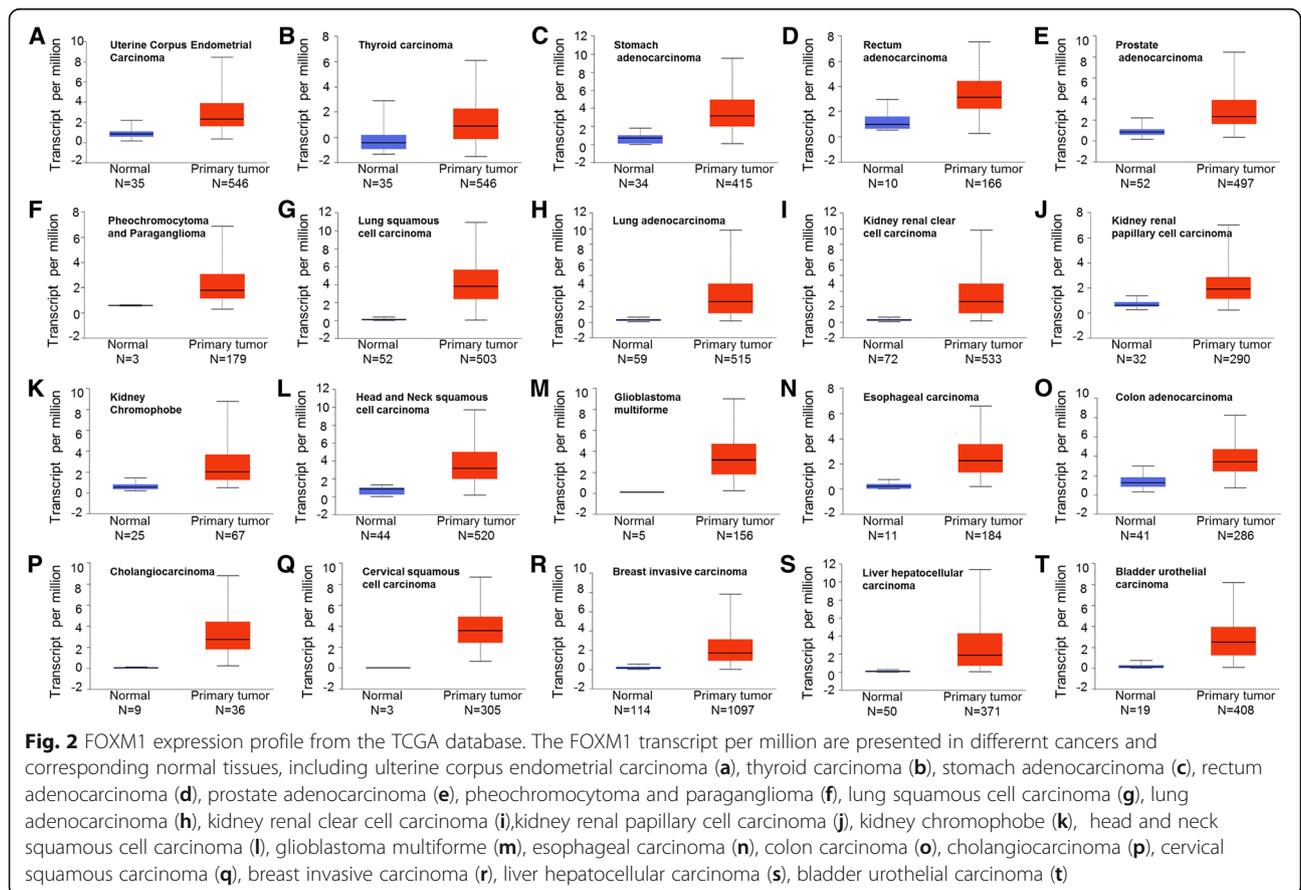
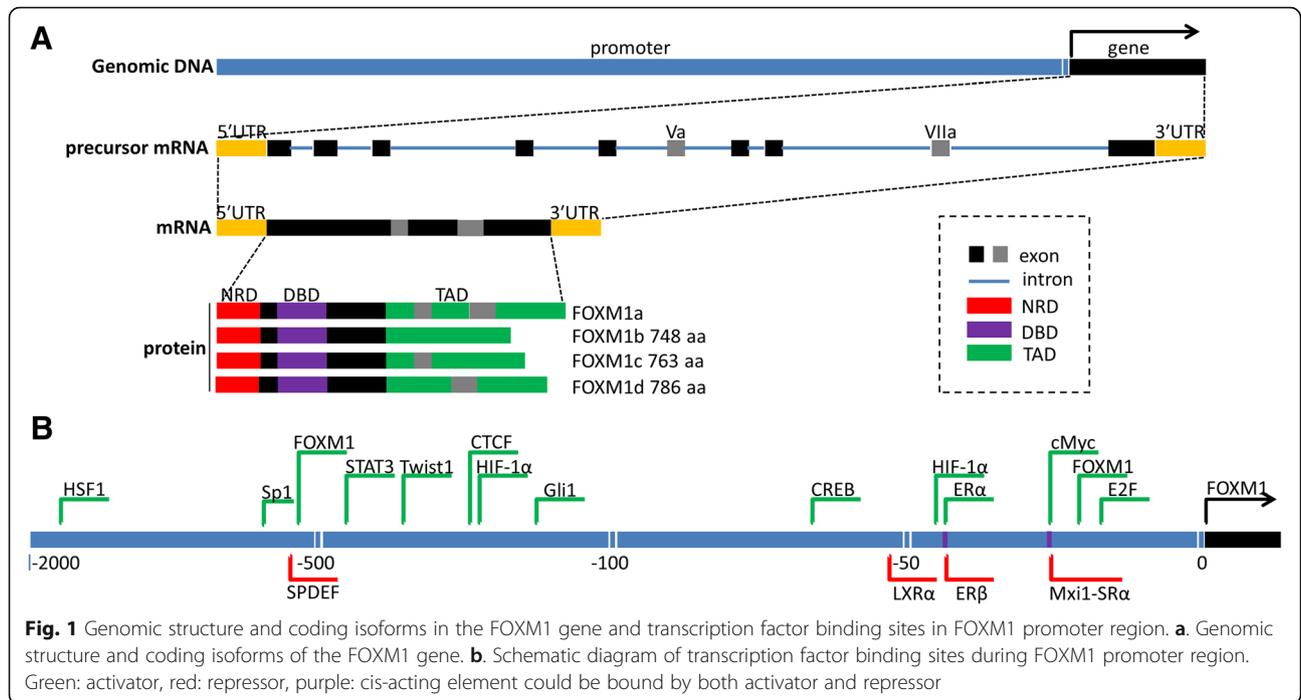
interaction with the NRD [5, 6]. In addition, murine FOXM1 splice variants display the same DNA-binding specificity as human FOXM1 and bind to DNA-binding sites with the consensus sequence 5'-A-C/T-AAA-C/T-AA-3' [7]. The study of murine FOXM1 may also be applied to human FOXM1. For example, it has been demonstrated that Gli1 regulates FOXM1 in murine stem cells [8]. In human basal cell carcinomas and colorectal cancer cells, FOXM1 is also a direct target of Gli1 [9, 10]. This may be due to the evolutionary conservation between the DNA binding domain of both human and murine FOXM1, suggesting the FOXM1 of the two species may share target genes. As such, investigating the regulation of murine FOXM1 may provide significant implications into the dysregulation of human FOXM1. Furthermore, a mouse model is a suitable experimental model for the development of novel FOXM1 inhibitors.

FOXM1 is detected primarily in progenitor and regenerating tissues, as well as tumor cells, which are all highly proliferative [11]. As a classic proliferation-associated transcription factor, FOXM1 directly or indirectly activates the expression of target genes at the transcriptional level and exhibits a spatiotemporal pattern whose dysregulation is involved in almost all hallmarks of

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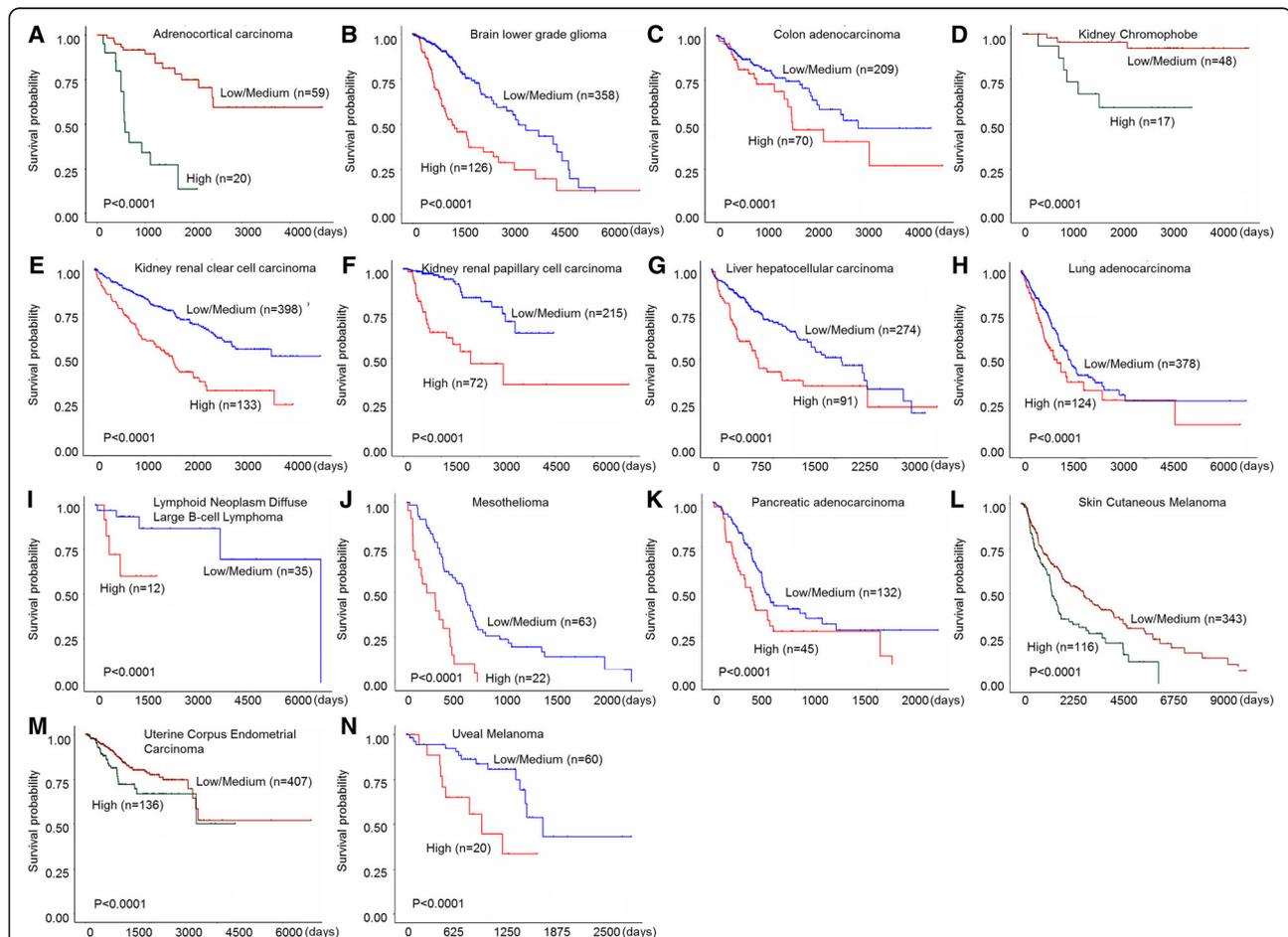
tumor cells [3, 12]. Increased expression of FOXM1 is observed in a variety of human cancers, such as ovarian cancer, breast cancer, prostate cancer, hepatoma, angiosarcoma, colorectal cancer, melanoma, lung cancer, and gastric cancer [13–21], which is consistent with the results obtained from the TCGA database (Fig. 2). Inhibition of FOXM1 in cancer cells leads to decreased cell proliferation and migration, metastasis, angiogenesis, EMT, and drug resistance [22–26]. Furthermore, a recent meta-analysis revealed that elevated FOXM1 expression is related to poor prognosis in most solid tumors [27], which is also further confirmed by the TCGA database (Fig. 3) [28]. These results clearly showed the important role of FOXM1 in tumorigenesis and cancer development. Therefore, FOXM1 has been identified as a potential therapeutic target for the treatment of cancers. Although a few drugs and inhibitors have been shown to be effective at inhibiting the activity of FOXM1 *in vitro*, they've yet to pass successfully into clinical use [29]. This is likely due in major part to the poor current understanding of the regulation of

FOXM1. Hence, a comprehensive review of FOXM1 regulation will thus contribute to the extensive effort and research into the gene as a therapeutic target for a number of FOXM1-dependent conditions, such as the cancers mentioned previously.

In this review, we provide an overview of how FOXM1 is regulated and focus on the transcriptional, post-transcriptional, post-translational, and protein-protein/RNA interaction levels. Though many biomolecules regulate the expression of FOXM1, we emphasize the biomolecules that directly interact with or modify the promoter, RNA, or protein of FOXM1. At the same time, we will discuss briefly the pharmacological inhibition of FOXM1.

### Transcriptional regulation of FOXM1

The core promoter regions of the FOXM1 gene contain several classic regulatory elements, such as E-boxes, and other cis-acting elements that can function as responsive elements to other transcription factors. Here, we mainly



**Fig. 3** Kaplan–Meier analyses of overall survival according to FOXM1 expression levels in different cancer suffers, including adrenocortical carcinoma (a), glioma (b), colon adenocarcinoma (c), kidney chromophobe (d), kidney renal clear cell carcinoma (e), kidney renal papillary cell carcinoma (f), liver hepatocellular carcinoma (g), lung adenocarcinoma (h), uterine corpus endometrial carcinoma (m), uveal melanoma (n)

discuss the transcription factors that directly bind to the promoter regions (which are verified by electrophoretic mobility shift assays and/or chromatin immunoprecipitation assays) (Fig. 1b).

Most responsive elements are located adjacent to FOXM1's transcriptional start sites, though the furthest element is found approximately 2000 bp away. More than 75% of these binding sites act as cis-activation elements, but they do not all function through the same basic mechanisms. For example, glioma-associated oncogene homolog 1 (Gli1), CCCTC-binding factor (CTCF), cAMP responsive element-binding protein (CREB), signal transducer and activator of transcription 3 (STAT3), and E2F interact directly with their binding sites and up-regulate FOXM1 expression [9, 30–34]. In human colorectal cancer (CRC), Gli1 regulates FOXM1 by directly binding to its promoter at BS4 (GCCACCCCA), which contributes to the proliferation of CRC cells [9]. The DNA-binding protein, CTCF, may regulate the motility and invasiveness of primary hepatocellular carcinoma (HCC) cells via interaction with the CTCF-binding site(s) located in the proximal promoter of FOXM1 [30]. In HBV-associated HCC, CREB directly bound to the FOXM1 promoter in response to HBx and facilitates hepatoma cell invasion and metastasis [33]. In the chronic myeloid leukemia K562 cell line, FOXM1 is transcriptionally dependent on STAT3 and crucial for its cell proliferation, cell cycle checkpoints and viability [32]. However, twist-related protein 1 (Twist1) may not be sufficient to enhance FOXM1 gene transcription unless it recruits the coactivator p300 to form a complex. In gastric cancer, Twist 1 could bind to the promoter region of FOXM1, and subsequently recruit p300 to induce its mRNA transcription [35]. Other transcription factors are stress-dependent. For example, under normoxic conditions, HIF-1 $\alpha$  is unstable because specific proline residues are hydroxylated. Under hypoxic conditions, HIF-1 $\alpha$  directly binds to the promoter of FOXM1 and activates its expression. Consequently, the upregulation of FOXM1 promotes the proliferation of hepatoma cells and enhances their resistance to apoptosis [36, 37]. Moreover, Dai B et al. reported that upon heat shock stress HSF1 was released from Hsp90 and translocated from cytoplasm to nucleus. Then HSF1 directly bound to FOXM1 promoter and increased FOXM1 promoter activity [38]. They also revealed that overexpression of a constitutively active HSF1 up-regulated FOXM1 expression in Hs683 cells, indicating that HSF1 may also regulate FOXM1 expression in glioma cell lines under normal conditions [38]. Taken together, the evidence suggests that HSF1 regulates the FOXM1 expression under both heat shock stress and normal conditions.

The FOXM1 promoter region also contains sites that can function as cis-suppression elements. For example,

liver X receptor a (LXR $\alpha$ ) functions as a transcriptional repressor for FOXM1 expression by binding to an inverted repeat IR2 (-52CCGTCAcgTGACCT-39) in the FOXM1 promoter region, and suppresses the proliferation of HCC cells [39]. Barsotti AM et al. reported that p53-mediated inhibition of FOXM1 is partially p21 and retinoblastoma (RB) family dependent in MCF-7 cells [40], while FOXM1 was demonstrated as direct target gene of p53 in mice hepatocytes [41]. Some responsive elements have dual roles, such as the ERE (estrogen-response element) and the E-box within the proximal promoter region of the FOXM1 gene. In ER $\alpha$ -positive breast cancer cells, ER $\alpha$  can upregulate FOXM1 expression by binding to the ERE. Conversely, ER $\beta$  binding to the ERE down-regulates FOXM1 expression [42, 43]. In a similar fashion, the E-box is a competitive binding site for c-Myc (activator) and Mxi1-SR $\alpha$  (repressor) [44, 45].

It is worth noting that, there exists a positive auto-regulation loop of FOXM1. In 2009, Marianna Halasi first found that siomycin A and thiostrepton, transcriptional inhibitors of FOXM1, downregulated both the transcriptional activity and expression levels of FOXM1 [46]. The phenomenon indicates the existence of an auto-regulation loop for FOXM1. Subsequently, a research study showed that disruption of FOXM1 binding site inhibited FOXM1 promoter activity, confirming that the -745/-738 bp region is required for the auto-regulatory activation of the FOXM1 promoter [47, 48]. Furthermore, it has been reported that nuclear AURKA can be recruited by FOXM1 as a co-factor to transactivate FOXM1 target genes in a kinase-independent manner [49]. AURKA and FOXM1 participated in a tightly coupled positive feedback loop to enhance BCSC phenotype. Moreover, AURKA can effectively transactivate the FOXM1 promoter through a Forkhead response element, whereas FOXM1 can activate AURKA expression at the transcriptional level [49]. All these findings confirm the existence of an autoregulatory loop, suggesting that FOXM1 protein can potentially bind to FOXM1 promoter region.

Herein, we have summarized all the reported transcription activators and repressors that directly bound to FOXM1 core promoter (Table 1). This will not only benefit for the discovery of novel transacting factors during the regulatory region of FOXM1 promoter, but it will also provide important implications for the design of drugs targeting FOXM1.

### Post-transcriptional regulation of FOXM1

In addition to the normal processes of post-transcriptional splicing and modification, there are other mechanisms by which FOXM1 can be regulated post-transcriptionally. For example, there are a number of non-coding RNAs (ncRNAs) considered to be

**Table 1** Factors reported to bind directly to FOXM1 promoter and regulated its expression

Transcription factor	Responsive element	Act. / Rep.	Cell	Coactivator	Pos. / Neg. regulation
cMyc [109, 110]	E-Box	A	U-937 etc.		CAR [44]/–
Mxi1-SRa [45]	E-Box	R	DL23		–/FOXO3a [111]
HIF-1 $\alpha$ [36]	–271/– 267, – 47/– 42	A	HepG2		TNF- $\alpha$ [37]/–
ER $\alpha$ [42]	–45	A	MCF-7 ZR-75-1		–/HDACs
ER $\beta$ [43]	–45	R	MCF-7		
E2F [34]	–24	A	MCF-7		MnSOD [31]/P53 [34, 112]
STAT3 [32]	–440/– 432	A	K562		MAPK/–
CREB [33]	–60/– 36	A	HepG2		HBx/–
HSF1 [38]	– 1792/– 1767	A	U-87MG		
Twist1 [35]	– 375/– 352	A	NCI-N87	P300	
LXR $\alpha$ [39]	–52/– 39	R	HepG2		
Gli1 [9, 10]	–216/– 204	A	HT29		
Gli1, Gli2 [8]	Not clear	A	Murine NSCs		
SPDEF [47]	–670/– 660	R	TRAMP-C2R3		
FOXM1 [46, 47]	–745/– 660, – 27/– 22	A	TRAMP-C2R3, MCF-7		AURKA [49]/–
CTCF [30]	– 296/– 120	A	HepG2		
Sp1 [95]	– 891	A	HepG2		
P53 [41]	Not clear	R	mice hepatocyte		

Act. /Rep. Activator or repressor, Pos. /Neg. positive or negative regulatory factor, A activate, R repress

**Table 2** Non-coding RNAs interaction with FOXM1 transcript

MicroRNA	mechanism	CeRNA	Physiological context	Cancer
miR-216b	3'UTR		proliferation <sup>b</sup> , invasion <sup>b</sup>	Glioblastoma [113], melanoma [114], hepatocellular carcinoma [115]
MiR-214	3'UTR		proliferation <sup>b</sup> , invasion <sup>b</sup> , drug sensitivity <sup>a</sup>	cervical cancer [54]
miR-361-5p	3'UTR		proliferation <sup>b</sup> , invasion <sup>b</sup>	lung cancer [116]
miR-342	3'UTR		proliferation <sup>b</sup> , migration <sup>b</sup>	colorectal cancer [117]
miR-671-5p	3'UTR		proliferation <sup>b</sup> , invasion <sup>b</sup> , EMT <sup>b</sup>	breast cancer [118]
miR-149	3'UTR		drug sensitivity <sup>a</sup> , EMT <sup>b</sup>	Colorectal Cancer [55], non-small cell lung cancer [119]
miR-509-5p	3'UTR		proliferation <sup>b</sup> , migration <sup>b</sup> , invasion <sup>b</sup>	non-small cell lung cancer [120]
miR-802	3'UTR		proliferation <sup>b</sup>	breast cancer [121]
miR-34a	3'UTR	CCAT2 [58]	senescence <sup>a</sup>	hepatocellular carcinoma [122]
miR-370	3'UTR		proliferation <sup>b</sup> , apoptosis <sup>a</sup>	osteosarcoma [123], laryngeal squamous cell carcinoma [124], gastric carcinoma [125]
miR-877	3'UTR		proliferation <sup>b</sup>	hepatocellular carcinoma [126]
miR-320	3'UTR		drug sensitivity <sup>a</sup> , radiosensitivity <sup>a</sup>	colon cancer [127], Glioma [128]
miR-204	3'UTR		invasion <sup>b</sup> , EMT <sup>b</sup>	esophageal cancer [129]
miR-24-1	3'UTR		proliferation <sup>b</sup>	bladder cancer [130]
miR-342-3p	3'UTR	H19 [57]	proliferation <sup>b</sup> , migration <sup>b</sup> , invasion <sup>b</sup>	cervical cancer [56]

<sup>a</sup>: promoting

<sup>b</sup>: Inhibition

important in this regulation. MicroRNAs (miRNAs) are endogenous, highly conserved, non-coding RNAs of approximately 21–24 nucleotides that can guide mRNA degradation or repress translation by binding to complementary sequences in the 3' untranslated regions (3'UTRs) of targeted mRNAs [50]. Long non-coding RNAs (lncRNAs) are ncRNAs longer than 200 nucleotides that can act as competing endogenous RNAs (ceRNAs). The ceRNAs, known as miRNA “decoys” or “sponges”, are RNA transcripts that competitively bind to the same miRNA via base pair complementarity with miRNA recognition/response elements (MREs) [51]. MicroRNAs and lncRNAs regulate each other through the binding sites of their response elements (MREs) [52, 53].

To date, dozens of miRNAs have been found to regulate the proliferation, invasion, migration, senescence, apoptosis, epithelial-mesenchymal transition (EMT), and drug sensitivity of cancer cells through binding to the 3'UTRs of FOXM1 mRNA. For example, miRNA-214 acts as a tumor repressor during the process of migration, and invasion, and is associated with sensitivity to cisplatin in cervical cancer via directly binding to the 3'UTRs of FOXM1 mRNA [54]. miRNA-149 can inhibit EMT in non-small cell lung cancer cells (NSCLC cells) by the same mechanism (Table 2) [55]. Compared with miRNAs, few lncRNAs have been identified to regulate FOXM1 expression. In gallbladder cancer (GBC), lncRNA H19 upregulates FOXM1 expression and promotes its proliferation and invasion, through competitively ‘sponging’ miR-342-3p [56, 57]. Another lncRNA, colon cancer-associated transcript 2 (CCAT2), upregulates FOXM1 expression and promotes HCC cell growth through interaction with and suppression of miR-34a [58].

In addition, lncRNAs also regulate nascent FOXM1 transcripts. For example, lncRNA FOXM1-AS interacts with nascent FOXM1 transcripts, promoting the ALKBH5-mediated demethylation and subsequent FOXM1 up-regulation. Besides, with the emerging research of the non-coding RNAs, including the circular RNA, piwi-interacting RNA, snRNA and snoRNA, the possible regulation between these non-coding RNAs and FOXM1 require further study for determination.

### Post-translational modifications of FOXM1

Post-translational modifications (PTMs) are the chemical modifications of a protein after its translation, which can have broad effects on the targets. The FOXM1 protein is modified by multiple PTMs that include phosphorylation, ubiquitination, SUMOylation, acetylation and methylation, which may have activating or inhibiting effects. These modifications determine the cellular

localization, protein stabilization, and transcriptional activity of FOXM1 in normal or disease states (Table 3).

### Phosphorylation

The activity of FOXM1 is of great importance to the cell cycle, and phosphorylation of FOXM1 protein plays a key role in that activity. The transcriptional activity of FOXM1 is upregulated through the cell cycle and is consistent with its phosphorylation [59]. With the progress of the cell cycle, FOXM1 phosphorylation is constantly changing. The FOXM1 protein maintains a relative hypo-phosphorylation status in the G1/S phase, exhibits increased phosphorylation from the S phase to the G2/M transition, reaches hyper-phosphorylation status in the M phase, and is subsequently dephosphorylated in the late M phase. This dynamic and tight phosphorylation change is mediated by various kinases and their positive feedback loops.

The transactivation domain (TAD) of FOXM1 can be suppressed by direct interaction with the NRD (N-terminal repression domain). To a transcription factor such as FOXM1, sufficient protein levels, nuclear localization and exposure of the TAD are indispensable for maximizing transcriptional activity. In the G1/S phase, FOXM1 mRNA reaches its peak while the FOXM1 protein exhibits low transcriptional activity due to cytoplasmic localization and NRD inhibition of the TAD [60]. In the late G1 phase, Cyclin D-CDK4/6 complexes phosphorylate multiple sites of FOXM1, including T620, T627, and S672, which then triggers the G1 to S cell cycle transition [6]. Interestingly, during this process, B55 $\alpha$  (a subunit of protein phosphatase 2A) prevents premature activation of FOXM1 through contact with FOXM1 and repression of cyclin A-CDK [6, 61]. In the late S and G2/M phases, phosphorylation of both S331 and S704 of FOXM1 via the Raf/MEK/MAPK pathway stimulates FOXM1 nuclear translocation and thus promotes the transcriptional activity of FOXM1 [60]. During the G2 phase, cyclin A/E-CDK2 complexes phosphorylate FOXM1, including sites T600, S638, and especially T611, which relieves repression of TAD by NRD, and restores the TAD transactivation activity [62, 63]. In addition, phosphorylation at S251 is critical for cyclin-B1-Cdk1-dependent phosphorylation of FOXM1 [59]. The phosphorylation at T596 by cyclin-B1-Cdk1 on the one hand recruits Plk1 directly to phosphorylate FOXM1 at S715 and S724, which promotes the transcriptional activity of FOXM1 [64]. On the other hand, that phosphorylation recruits the transcriptional co-activator p300/CREB binding protein (CBP) to enhance its transcriptional activity [65].

In response to DNA damage, checkpoint kinase 2 (Chk2) phosphorylates FOXM1 at S361, inhibiting its degradation and increasing transcription of XRCC1 and

**Table 3** Post-translational modifications of FOXM1

PTM	Enzyme	Effect	Cell cycle	FOXM1 isoform
<b>Phosphorylation</b>				
T620,T627,S672	Cyclin D-CDK4/6[6]	Transcriptional activity <sup>a</sup> stabilization <sup>a</sup>	G1 → S	FOXM1c
S331	Raf/MEK/MAPK [60]	Nuclear translocation <sup>a</sup>	Late S	FOXM1c
S704	Raf/MEK/MAPK [60]	Transcriptional activity <sup>a</sup>	Late S	FOXM1c
T600,T611,S638	Cyclin A/E-Cdk2 [62, 63]	Transcriptional activity <sup>a</sup>	G2/M	FOXM1c
T596	Cyclin B1-Cdk1 [64]	Transcriptional activity <sup>a</sup>	G2/M	FOXM1b
S678	Cyclin B1-Cdk1 [65]	Transcriptional activity <sup>a</sup>	Late G2	FOXM1b
S507,S657, T585	Cyclin B1-Cdk1 [131]	Transcriptional activity <sup>a</sup>	G2/M	FOXM1b
S715,S724	Plk1 [64]	Transcriptional activity <sup>a</sup>	G2 → M/M	FOXM1b
S361	Chk2 [66]	stabilization <sup>a</sup>	DDR	FOXM1b
S251	<sup>c</sup> [59]	CDK1-dependent phosphorylation <sup>a</sup>	G2/M	FOXM1b
S474	GSK3 [67]	degradation <sup>a</sup>		FOXM1b
<b>Ubiquitination</b>				
-	APC/C-Cdh1 [71, 72]	degradation <sup>a</sup>	Late M/Early G1	FOXM1
-	CRL4-VprBP [73]	degradation <sup>a</sup>	G1/S	FOXM1
-	SCF/FBXO31 [74]	degradation <sup>a</sup>	G2 → M	FOXM1
-	SCF/FBXL2 [132]	degradation <sup>a</sup>		FOXM1
-(K48)	FBXW7 [67]	degradation <sup>a</sup>		FOXM1
-(K48)	RNF8,RNF168 [75]	degradation <sup>a</sup>	(DDR)	FOXM1
<b>De-ubiquitination</b>				
-	USP5 [67]	Nuclear translocation <sup>a</sup>		FOXM1
(K48)	OTUB1 [76, 77]	degradation <sup>b</sup>		FOXM1
<b>SUMOylation</b>				
Lys132,144,201,218,356,368,415,440,443,460,478,495(SUMO2)	<sup>c</sup> [78]	Transcriptional activity <sup>a</sup> Nuclear translocation <sup>a</sup>	G2/M	FOXM1c
Lys463(SUMO1)	PIASy [79]	Transcriptional activity <sup>a</sup>		FOXM1b
Lys201,218,460,478,495(SUMO1)	Ubc9 [80]	Cytoplasmic translocation <sup>a</sup> Cdh1-mediated degradation <sup>a</sup>	(CDR)	FOXM1c
-(SUMO1,2,3)	Ubc9,PIAS1 [81]	Cytoplasmic translocation <sup>a</sup> stabilization <sup>b</sup>		FOXM1b
Lys201,218,341,445,462,480(SUMO1)	<sup>c</sup> [68]	Cytoplasmic translocation <sup>a</sup> stabilization <sup>b</sup>	Late M	FOXM1b
<b>Acetylation</b>				
Lys63,422,440,603,614	CBP/p300 [82]	stabilization <sup>a</sup> DNA-binding ability <sup>a</sup> Transcriptional activity <sup>a</sup>	G2/M	FOXM1c
<b>Methylation</b>				
-	SETD3 [83]	Transcriptional activity <sup>b</sup>		FOXM1

K48 Lys48-linked poly-ubiquitin chains, DDR DNA-damage response, CDR cytotoxic drug response

<sup>a</sup>: Promoting

<sup>b</sup>: Inhibition

<sup>c</sup>: not clear

→ Transition

BRCA2 genes, which are required for repair of DNA damage [66].

FOXM1 phosphorylation is also linked to ubiquitination and SUMOylation. For example, GSK3 phosphorylates FOXM1 at the S474 site, which promotes its subsequent ubiquitin-mediated degradation by FBXW7 [67]. Plk1-mediated phosphorylation of FOXM1 antagonizes its SUMOylation and facilitates cell cycle progression [68].

### Ubiquitination and de-ubiquitination

Ubiquitin (Ub) is a 76-amino acid protein with seven lysine residues that can conjugate to substrate proteins and form a poly-ubiquitin chain, conferring a range of functions. For example, the K48- and K11-linked poly-ubiquitin chains lead to proteolysis of the substrate protein, while the K63-linked poly-ubiquitin chain functions in signal transduction [69]. Ubiquitination is an enzymatic PTM in which an ubiquitin protein is attached to a target protein. De-ubiquitination opposes the role of ubiquitination by removing ubiquitin from substrate proteins.

The N-terminus of the FOXM1 protein contains KEN box (K-E-N-X-X-X-N) and destruction box (R-X-X-L-X-X-X-X-N) sequences that are involved in its ubiquitin-mediated degradation. The KEN box was first found to be an anaphase promoting complex (APC) recognition signal [70], which is responsible for the Cdh1-APC-mediated ubiquitination. Both the KEN box and destruction box (D box) of FOXM1 can be recognized by some ubiquitin protein ligases. In the late M and early G1 phases, Cdh1 interacts with FOXM1 and recruits APC/C E3 ubiquitin ligases to degrade it, which inhibits cell cycle progression [71, 72]. The E3 ligase system is delicate in its regulation of FOXM1 during the cell cycle. For example, in the G1/S phases, E3 ubiquitin ligase CRL4 integrates with its receptor VprBP, which promotes FOXM1 degradation to maintain its relatively low level. In G2/M phase, when FOXM1 is indispensable, VprBP separates from CRL4, relinquishing its inhibition of FOXM1 [73]. During the G2/M transition, SCF/FBXO31 E3 ubiquitin ligases act as negative regulators of FOXM1 via ubiquitin-mediated degradation, which can maintain genomic stability [74].

FOXM1 ubiquitination is also linked to SUMOylation. For example, RNF168 can modulate DNA-damage response (DDR) by promoting protein ubiquitination. In breast cancer treated with epirubicin, FOXM1 is modified through SUMOylation, which leads to its ubiquitination and degradation by RNF168 E3 ubiquitin ligase [75].

In contrast, deubiquitinating enzymes (DUBs) can remove the poly-ubiquitin chains on FOXM1 protein. For instance, in epirubicin-resistant breast cancer and in ovarian cancer, OTUB1 catalyzes the cleavage of the

K48-specific ubiquitin linkage from FOXM1, which promotes cancer progression via facilitating cell proliferation and drug resistance [76, 77].

### SUMOylation

Small Ubiquitin-like Modifier (SUMO) proteins are small proteins that are covalently attached to other proteins and modify their function. In mammals, there are four SUMO isoforms, SUMO-1, SUMO-2, SUMO-3, and SUMO-4. SUMOylation is an important PTM of FOXM1 that regulates its activity, stability, and other PTMs. The functions of FOXM1 SUMOylation are diverse and may regulate its activity in an isoform-specific manner.

Multiple sites of FOXM1 are modified by SUMO-2, and this modification peaks in the M phase, which is consistent with its phosphorylation. This modification blocks the dimerization and relieves the auto-repression of FOXM1, thereby increasing its transcriptional activity [78]. Another SUMOylation of FOXM1 at K463 by SUMO-1 is also required for its transcriptional activity [79].

In contrast, SUMOylation of FOXM1 at different sites may inhibit its activity. For instance, FOXM1c is modified by SUMO-1 at multiple sites, which promotes the cytoplasmic translocation of FOXM1c and enhances APC/Cdh1-dependent ubiquitin-mediated degradation. This modification subsequently attenuates the transcriptional activity of FOXM1c [80]. This phenomenon has been confirmed with another FOXM1 isoform-FOXM1b [81].

### Other PTMs of FOXM1

FOXM1 is also regulated by acetyltransferases and methyltransferases. For instance, FOXM1 can be acetylated by p300/CBP at lysines K63, K422, K440, K603 and K614, which enhances its transcriptional activity by promoting its DNA binding affinity, protein stability, and phosphorylation sensitivity [82]. Under normoxic conditions, methyltransferase SETD3 specifically binds and methylates FOXM1, which inhibits its activity [83].

In general, we can conclude that the FOXM1 protein can be modified by multiple PTMs, including phosphorylation, ubiquitination, SUMOylation, acetylation, and so on. It has been demonstrated that these PTMs can result in the spatiotemporal control of target protein expression. This may provide new strategies for the modulation of FOXM1 expression utilizing the key enzymes involved in these PTMs.

### Protein/RNA directly interacts with FOXM1 protein

The protein-protein/RNA interactions of FOXM1 are discussed in detail in a recently published review [84].

**Table 4** proteins/RNA interact with FOXM1

Protein/RNA	Binding site	Effect	Cell cycle	FOXM1 isoform
B55a [61]	<sup>a</sup>	CyclinA CDK2 activity↓	G1	FOXM1c
RB [85]	359/425	Transcriptional activity↓	G1	FOXM1c
p19 <sup>ARF</sup> [86]	688/748	Transcriptional activity↓		FOXM1b
NPM [87]	195/688	Nuclear translocation↑		FOXM1b
CDC25A [89]	C-terminal	CDK1 activity↑		FOXM1
PHGDH [133]	N-terminal	Stabilization↑		FOXM1
MELK [88]	N-terminal	Plk1 activity↑	G2 → M/M	FOXM1
Pin1 [134]	S331,704	Transcriptional activity↑		FOXM1
MTDH [90]	N-terminal	Stabilization↑ transcriptional activity↑		FOXM1b
PVT1(lncRNA) [91]	<sup>a</sup>	Stabilization↑		FOXM1
HSP70 [135]	<sup>a</sup>	Transcriptional activity↓		FOXM1

CD central domain

<sup>a</sup> not clear

↓ Decrease

↑ Increase

→ Transition

This article revisits these interactions and focuses on molecules that directly interact with FOXM1 (Table 4).

In the G1 phase, RB acts as a repressor by binding directly to the central domain of FOXM1, which may recruit NRD to inhibit TAD. Cyclin D1/Cdk4 activates FOXM1 by releasing its TAD from repression by RB, which might lead to deregulated proliferation and cancer [85]. Another tumor suppressor p19<sup>ARF</sup> interacts directly with the C-terminal (688–748) of FOXM1, and decreases FOXM1 transcriptional activity. At the same time, the interaction also diminishes FOXM1 stimulation of colony formation of U2OS cells, suggesting that p19<sup>ARF</sup> may be an effective therapeutic inhibitor of FOXM1 transformation function [86].

Several proteins can increase FOXM1 activity by promoting its stabilization, nuclear location, and phosphorylation or inhibiting its ubiquitination. For example, in cancer cells nucleophosmin (NPM) interacts with FOXM1 and their interaction is required for sustaining

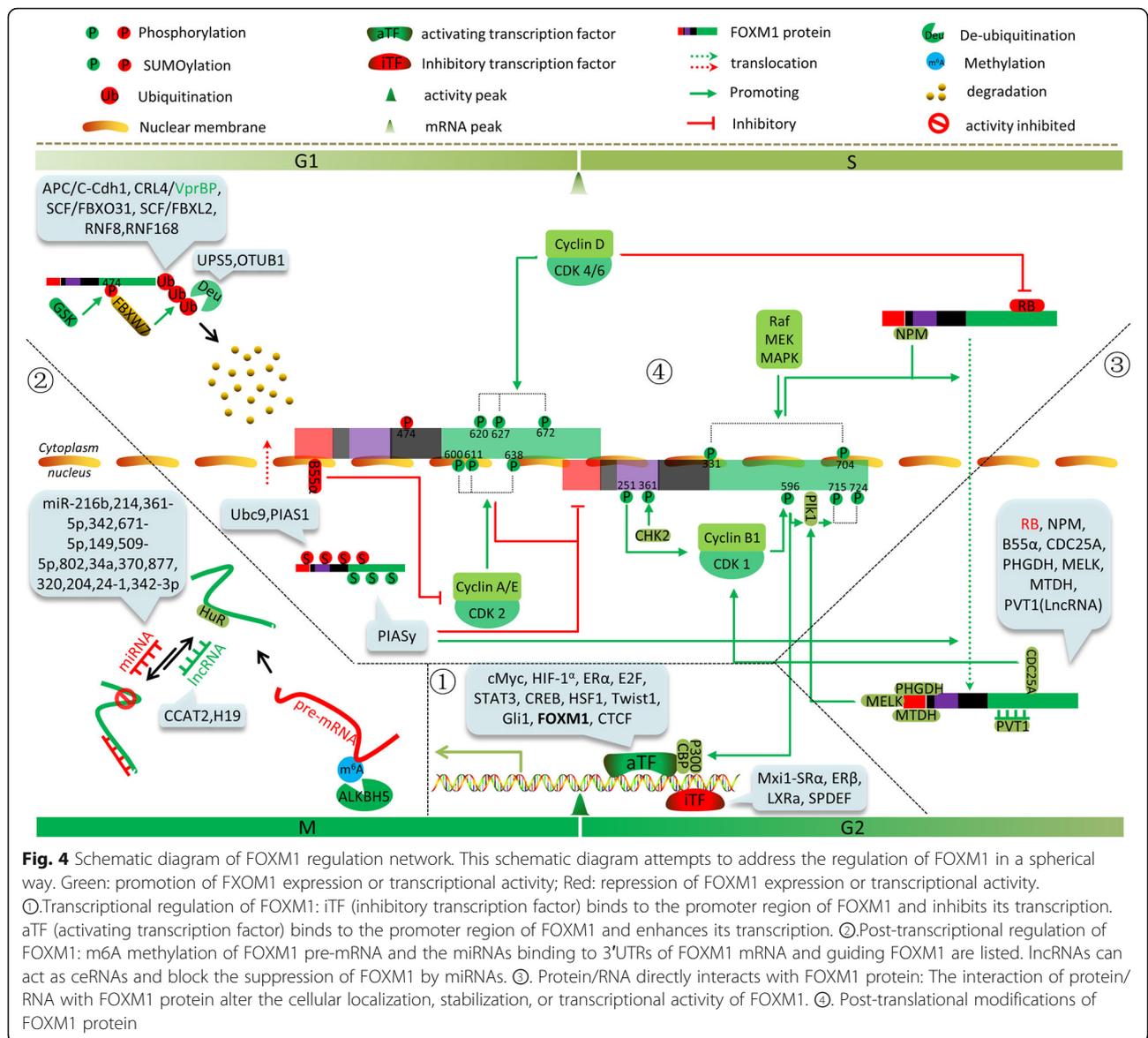
the level and nucleus localization of FOXM1 [87]. In glioma stem-like cell (GSC), maternal embryonic leucine-zipper kinase (MELK) increases the activity of FOXM1 by interaction with its N-terminus and promoting its phosphorylation by Plk1 [88]. As mentioned above, PLK1 binds and phosphorylates FOXM1 leading to its activation and increased gene expression, which are required for mitotic progression. In addition, cell division cycle 25A (CDC25A) interacts with the C-terminus and enhances CDK1-dependent phosphorylation of FOXM1 [89]. This phosphorylation is required to release the inhibitory function of the NRD during G2 phase (as mentioned above). Another protein, metadherin/astrocyte elevated gene-1 (MTDH), directly interacts with FOXM1 via the N-terminal inhibitory domain of MTDH, and this interaction disrupts the binding of Cdh-1 (mentioned above) to FOXM1, thus protecting FOXM1 from subsequent proteasomal degradation. At the same time, MTDH also binds to FOXM1 target gene

**Table 5** Inhibitors of FOXM1 whose mechanism has been elucidated

Inhibitors	Mechanism	Effect	Cancer cells
Thiazolidinediones	Inhibit Sp1	mRNA expression <sup>b</sup>	hepatoma [95]
Diarylheptanoids	Inhibit Gli1	mRNA and protein expression <sup>b</sup>	pancreatic cancer [96]
RCM-1	increase ubiquitination	protein degradation <sup>a</sup>	osteosarcoma [99]
Thiostrepton	Interact with FOXM1	binding of FOXM1 to target sites <sup>b</sup>	breast cancer [98]
honokiol	Interact with FOXM1	binding of FOXM1 to target sites <sup>b</sup>	osteosarcoma [100]
FDI-6	Block FOXM1 DBD	binding of FOXM1 to target sites <sup>b</sup>	MCF-7[128]
FOXM1 Apt	target FOXM1 DBD	binding of FOXM1 to target sites <sup>b</sup>	HEK 293 T [136]
Peptide 9R-P201	target FOXM1 DBD	FOXM1 and target gene expression <sup>b</sup>	HepG2 [137]

<sup>a</sup>: Promoting;

<sup>b</sup>: Inhibition



**Fig. 4** Schematic diagram of FOXM1 regulation network. This schematic diagram attempts to address the regulation of FOXM1 in a spherical way. Green: promotion of FOXM1 expression or transcriptional activity; Red: repression of FOXM1 expression or transcriptional activity. ①. Transcriptional regulation of FOXM1: iTF (inhibitory transcription factor) binds to the promoter region of FOXM1 and inhibits its transcription. aTF (activating transcription factor) binds to the promoter region of FOXM1 and enhances its transcription. ②. Post-transcriptional regulation of FOXM1: m6A methylation of FOXM1 pre-mRNA and the miRNAs binding to 3'UTRs of FOXM1 mRNA and guiding FOXM1 are listed. lncRNAs can act as ceRNAs and block the suppression of FOXM1 by miRNAs. ③. Protein/RNA directly interacts with FOXM1 protein: The interaction of protein/RNA with FOXM1 protein alter the cellular localization, stabilization, or transcriptional activity of FOXM1. ④. Post-translational modifications of FOXM1 protein

promoters and enhances its transcriptional activity. All these interactions promote cell cycle progression, angiogenesis, and cancer cell invasion in vitro and in vivo [90].

As mentioned above, lncRNA can act as an oncogenic factor through the regulation of the transcriptional level of FOXM1. Interestingly, the lncRNA PVT1 can bind to FOXM1 protein and elevate its levels by reducing its degradation and enhancing its stability, subsequently promoting the proliferation and invasion of gastric cancer cells [91]. This implies that noncoding RNA can not only function at the transcriptional level, but also play a role in other processes. The clarification of the interaction binding sites between FOXM1 and other proteins will provide implication for the design of short peptides and small molecular targeting FOXM1.

**Pharmacological inhibition of FOXM1**

Significant progress has been accomplished over the last few years in terms of the pharmacological inhibition of FOXM1 in cancer [92–94]. It is apparent, as outlined in the above discussion, that the inhibition of FOXM1 expression (at the levels of transcription, translation, and post-translation) and/or its interactions with target sites (block DBD, nuclear localization, protein-protein interaction) may be an effective way to inhibit FOXM1-mediated biological effects (Table 5). For example, Sp1 directly binds to the promoter of FOXM1 and activates its transcription. Thiazolidinedione (TZD) inhibits FOXM1 expression through downregulation of Sp1, which may negatively regulate tumor cell growth and promote apoptosis [95]. Diarylheptanoids, from

medicinal plants, can also suppress FOXM1 and expression of its target genes by suppressing Gli1 in pancreatic cancer cells [96].

That said, the biological effects of targeting transcription factors are diversified, and it may not be the best therapeutic solution. The siRNA and ARF peptide target FOXM1 is relatively specific and effective, but the drug-targeted delivery and immune responses may be a major obstacle to be clinical use. Another classical FOXM1 inhibitor thiostrepton, a thiazole antibiotic, inhibits FOXM1 through interacting directly with FOXM1 protein and acting as a proteasome inhibitor [97, 98]. Several recent studies have found that small molecule inhibitors work well to inhibit FOXM1. Sun L et al. identified a small molecule RCM-1 by high-throughput screen, which blocks the nuclear localization and increases the proteasomal degradation of FOXM1 with less effect on other FOX family transcription factors [99]. Another small molecule, honokiol, inhibits FOXM1 by specific binding in a way that is structurally strict [100]. Although much work has been done, there is much more to accomplish to identify specific FOXM1 inhibitors and to validate them in clinical trials. These FOXM1 inhibitors may be used as single agents or in combination with low-dose chemotherapy for cancer treatment.

### FOXM1 in the tumor microenvironment

The tumor microenvironment is created by the tumor and dominated by tumor-induced interactions. Although various immune effector cells are recruited to the tumor site, their anti-tumor functions are suppressed. Infiltrates of inflammatory cells present in human tumors are chronic in nature and are enriched in regulatory T cells (Treg) as well as myeloid suppressor cells (MSC) [101]. Immunotherapeutic strategies, including cancer vaccines, oncolytic viruses, adoptive transfer of ex vivo activated T and natural killer cells, and administration of antibodies or recombinant proteins, are now being described at a breathtaking pace, especially after the clinical application of the monoclonal antibody blocking of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD1) [102]. Few research have revealed the role of FOXM1 in immune cells: FOXM1 may be involved in the determination of induced Tregs (iTreg) versus T<sub>H</sub>17 development during T cell differentiation [103]. Furthermore, latest reports revealed that FOXM1 modulates atherosclerosis by inducing macrophage proliferation [104]. However, little is known about the possible role of FOXM1 in tumor microenvironment. Interestingly, FOXM1 (362–370) (YLVPQFPV), FOXM1(373–382) (SLVLQPSVKV), and FOXM1(640–649) (GLMDLSTTPL) peptides primed HLA-A2-restricted cytotoxic T lymphocytes (CTLs) in

the HLA-A2 transgenic mice, suggesting that FOXM1 may be a suitable target for immunotherapy against cancers. However, the HLA-A2-restricted epitopes of FOXM1 identified need to be further clinically tested [105]. As the important role of FOXM1 in cell proliferation and determination of cell fate, more study is needed to reveal the possible role of FOXM1 in the tumor infiltrating immune cells.

### Conclusions and future perspectives

FOXM1 is a crucial regulator of many biological processes and tissues, and dysregulation of FOXM1 can significantly contribute to tumorigenesis and cancer progression. For its potential as a target for cancer therapies, FOXM1 was named the Molecule of the Year in 2010 [106]. Over the past few decades, understanding of the regulation and function of FOXM1 has rapidly increased, providing new insights into the roles of this transcription factor in cancer and other diseases. At the same time, some small molecule inhibitors that target FOXM1 have promising potential as drugs for cancer treatment [107, 108]. However, there are important challenges that limit the translation of promising drugs into clinical practice. Before the entry of FOXM1 inhibitors into clinical trials, more thorough preclinical studies on their anti-tumor efficacy are still needed. In addition, the toxicity of the above drugs should also be fully evaluated. It is not quite clear how the interaction and isoforms switch between FOXM1a and FOXM1b or FOXM1c or FOXM1d. It also remains unclear how the isoforms of FOXM1 interact and what role they may play in the regulation of FOXM1, in disease progression, or in response to relevant therapeutic strategies. Importantly, although the crystal structure of the FOXM1 DNA-recognition domain has been fully identified [7], it is vital that the complete structure of the FOXM1 protein be elucidated. This will be of utmost importance for the discovery of novel FOXM1 inhibitors.

In this review, we have summarized many of the activators and repressors that directly interact with or modify FOXM1 at multiple levels and drew the FOXM1-interaction network diagram (Fig. 4). The comprehensive understanding of the regulation of FOXM1 will provide a basis for further investigation, which may provide new potential therapeutic strategies.

### Abbreviations

APC/C: Anaphase-promoting complex-cyclosome; AURKA: Aurora kinase A; CCAT2: Colon cancer-associated transcript 2; CDC25A: Cell division cycle 25A; ceRNAs: Competing endogenous RNAs; Chk2: Checkpoint kinase 2; CRC: Colorectal cancer; CREB: cAMP responsive element-binding protein; CTCF: CCCTC-binding factor; DBD: Forkhead DNA-binding domain; EMT: Epithelial-mesenchymal transition; ERE: Estrogen-response element; FBXW7: F-box/WD repeat-containing protein 7; FDI-6: A small molecule compound; FOXM1 Apt: FOXM1-specific single stranded DNA aptamer; FOXM1: Human Forkhead Box M1; GBC: Gallbladder cancer; Gli1: Glioma-associated oncogene homolog 1; GSC: Glioma stem-like cell;

HCC: Hepatocellular carcinoma; HDAC: Histone deacetylases; HIF-1: Hypoxia-inducible factor 1; HSF1: Heat shock factor 1; lncRNAs: Long non-coding RNAs; LXRA: Liver X receptor  $\alpha$ ; MAPK: Mitogen-activated Protein Kinase; MELK: Maternal embryonic leucine-zipper kinase; miRNAs: MicroRNAs; MnSOD: Manganese-dependent superoxide dismutase; MREs: Response elements; MTDH: Metadherin/astrocyte elevated gene-1; ncRNA: Non-coding RNA; NPM: Nucleophosmin; NRD: N-terminal repressor domain; p19<sup>ARF</sup>: 19-kD alternative reading frame (ARF) protein; Peptide 9R-P201: A peptidomimetics from the phage random library; RCM-1: Robert Costa Memorial drug-1; SETD3: SET domain-containing protein; STAT3: Signal transducer and activator of transcription 3; SUMO: Small Ubiquitin-like Modifier; TAD: C-terminal transactivation domain; TNF- $\alpha$ : Tumor necrosis factor alpha; Twist1: Twist-related protein 1

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#### Authors' contributions

G-BL, X-ZL, SZ, CL, S-MY, LY, C-JH, and J-YB were involved in the conception, design and drafting of the manuscript. All authors read and approved the final manuscript.

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