



FOXM1 and Cancer: Faulty Cellular Signaling Derails Homeostasis

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Forkhead box transcription factor, FOXM1 is implicated in several cellular processes such as proliferation, cell cycle progression, cell differentiation, DNA damage repair, tissue homeostasis, angiogenesis, apoptosis, and redox signaling. In addition to being a boon for the normal functioning of a cell, FOXM1 turns out to be a bane by manifesting in several disease scenarios including cancer. It has been given an oncogenic status based on several evidences indicating its role in tumor development and progression. FOXM1 is highly expressed in several cancers and has also been implicated in poor prognosis. A comprehensive understanding of various aspects of this molecule has revealed its role in angiogenesis, invasion, migration, self-renewal and drug resistance. In this review, we attempt to understand various mechanisms underlying FOXM1 gene and protein regulation in cancer including the different signaling pathways, post-transcriptional and post-translational modifications. Identifying crucial molecules associated with these processes can aid in the development of potential pharmacological approaches to curb FOXM1 mediated tumorigenesis.

Keywords: FOXM1, cell signaling, post-transcriptional regulation, post-translational regulation, miRNA

INTRODUCTION

A Conspectus on Forkhead Transcription Factors

The evolutionarily conserved, winged helix group of transcription factors are derivatives of bacterial helix-turn-helix motif. In eukaryotes, it was initially identified in the homeotic gene- forkhead, whose discovery led to the generation of a plethora of significant findings. Mutation of this gene caused defects in cephalic development of drosophila leading to a forkhead appearance and hence the name forkhead (1). Albeit winged helix transcription factors are conserved throughout evolution, during the course of its progression these groups of transcription factors have

Abbreviations: ANO2, Anoctamin 2; CTNBL1, Catenin Beta Like 1; DCP1B, Decapping mRNA 1B; DOT1L, DOT1 Like Histone Lysine Methyltransferase; ECT2, Epithelial Cell Transforming 2; EPS8, Epidermal Growth Factor Receptor Pathway Substrate 8; FBX, F-Box and WD repeat Domain; FOXM1, Forkhead transcription factor M1; KLF, Kruppel Like Factor; METTL3, Methyltransferase Like 3; MTSS1, Metastasis Suppressor 1; OTUB1, OTU Deubiquitinase, Ubiquitin Aldehyde Binding 1; PBD, PLK1 Binding Domain; PDA, Pancreatic Adenocarcinoma; PQC, Protein Quality Control; RASSF1A, Ras Association Domain Family Member 1; RNF, Ring Finger Protein; RTK, Receptor Tyrosine Kinase; SETD3, SET Domain Containing 3, Actin Histidine Methyltransferase; SLC2A14, Solute Carrier Family 2 Member 14; SRP20, Serine and Arginine rich Splicing factor; STUB1, SUMO-targeted Ubiquitin Ligases; TAD, Transcriptional Activation domain; TCGA, The Cancer Genome Atlas Program; UCA1, Urothelial Cancer Associated 1; UCHL3, Ubiquitin C-Terminal Hydrolase L3; USP, Ubiquitin Specific Peptidase.

emerged with different binding specificities. Marsden et al. pointed out that the difference in binding specificities is the consequence of structural variations in the amino acid residues which lie in the immediate vicinity of the DNA binding motif (2). All forkhead transcription factors possess a characteristic 100 amino acid DNA binding domain which consists of three α -helices, three β -sheets and two large loops or wings that flank the third β -sheet (3).

Formerly, FOX proteins were designated as HFH, FREAC, and FKH. Subsequently, based on the phylogenetic analysis, these proteins have been divided into different subclasses (designated by a letter) and sub-subclass (denoted by an Arabic numeral). A unified nomenclature was introduced in 2000 which grouped the FOX proteins into different subclasses (FOXA-FOXS) based on sequence conservation. Human forkhead transcription factors are represented by uppercase letters whereas only the first letter is capitalized for mouse (4). FOXA, FOXC, FOXM, FOXP, FOXD, FOXE, FOXF, and FOXL have been shown to have a wide array of functions ranging from development to tumorigenesis (3, 5, 6).

Forkhead Transcription Factor M1 (FOXM1)

FOXM1, previously named as HNF-3, HFH-11, MPP2, TGT3, INS1, PIG29, FKHL16, MPHOSPH2, LOC2305, or Trident is a member of the Forkhead Box (Fox) family of transcription factors (7). Human *FOXM1* gene consists of 10 exons which span approximately 25 kb on the 12p13.33 chromosomal band (7). *FOXM1* has four major splice variants namely *FOXM1A*, *B*, *C* and *D* which arise by differential splicing of exon Va and VIIa (Figure 1A). Among these, *FOXM1B* contain neither of the alternative exons whereas *FOXM1C* has retained the exon Va and *FOXM1D* has retained VIIa (8). *FOXM1B*, *FOXM1C*, and *FOXM1D* act as transcriptional activators, but *FOXM1A* which has retained both the exons has been reported to be the inactive variant, suggesting some dominant negative effect as it has retained the DNA binding capability (9). FOXM1 protein consists of N terminal repressor domain, forkhead box domain and C terminal transcriptional activation domain (Figure 1B). FOXM1 maintains cell homeostasis by controlling diverse biological processes such as proliferation, cell cycle progression,

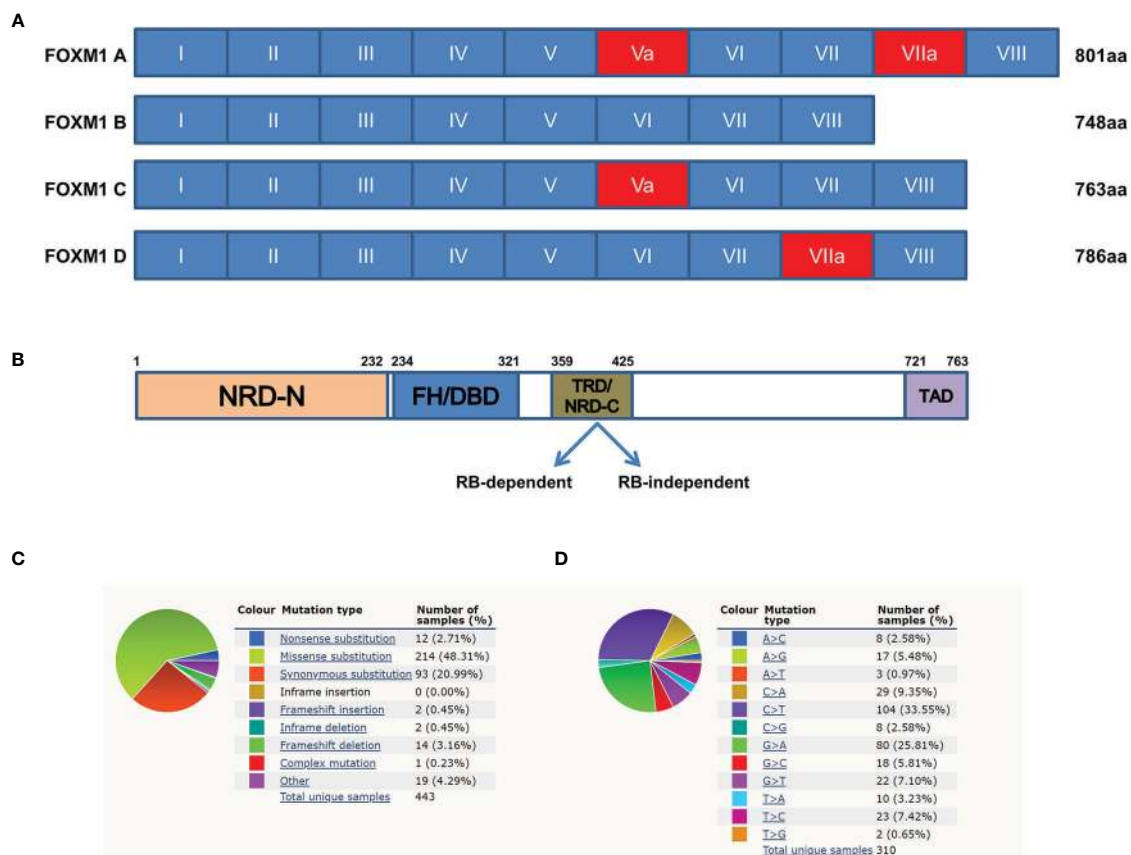


FIGURE 1 | Structure of Forkhead transcription factor M1 (FOXM1) and its mutational overview. **(A)** Schematic representation of the human FOXM1 showing 10 exons (I–VIII), of which Va and VIIa (red) are alternatively spliced. **(B)** Domain structure of FOXM1C protein. TRD mediated repression of FOXM1 can be either Rb-dependent or independent. NRD-N, N-terminal repressor domain; FH/DBD, Forkhead box DNA Binding Domain; TRD/NRD-C, Trans-Repressor Domain/C-terminal Repressor Domain; TAD, Trans-Activation Domain. Numerical indicate amino acid positions. **(C, D)** COSMIC data (<https://cancer.sanger.ac.uk/cosmic>) showing summary of the types of mutation and frequency of substitution mutations for the base pair changes on the coding strand. Sample size used in the analysis from the database is 443 and 310 respectively.

differentiation, DNA damage repair (DDR), tissue homeostasis, angiogenesis, apoptosis, redox signaling and drug resistance (10).

FOXM1 is involved in several pathophysiological conditions such as chronic obstructive pulmonary disease (COPD), asthma, acute lung injury (ALI), pulmonary fibrosis, pulmonary arterial hypertension (PAH) and cancer (11). This review mainly addresses the mechanisms by which FOXM1 is deregulated in cancer. A large amount of literature exists regarding FOXM1's role in homeostasis and tumorigenesis, which the current review summarizes by primarily focusing on the altered upstream and downstream regulatory mechanisms in cancer. It is necessary to understand the various oncogenic pathways leading to the modulation of FOXM1 in response to environmental cues or oncogenic insults. This review sheds light on how integral and inherent FOXM1 is in the pathogenesis of cancer. As the review progresses the readers would obtain a clear view on multiple facets of FOXM1 in cancer and its impact on the homeostasis with special emphasis on the regulatory aspect of FOXM1 in cellular transformation.

Genetic Alteration of FOXM1

FOXM1 is regarded as an oncogene due to its contribution in tumor initiation and progression whose expression has been shown to be elevated in various cancers (12) (13). Crucial mutations and gene copy amplification of FOXM1 have been observed at its loci 12p13.33 (<https://cancer.sanger.ac.uk/cosmic>) (14). Copy number alteration was observed in 29% of malignant peripheral nerve sheath tumors (MPNSTs) and also in breast cancers (15, 16). Barger et al. showed that mRNA and protein level alterations correlated with the copy number changes using the TCGA databases. Frequent amplification of FOXM1 was seen in various cancers among which testicular germ cell tumor had the maximum. Their analysis also revealed a correlation between aneuploidy and FOXM1 expression in TCGA pan-cancer aneuploidy clusters. Another study from the same group demonstrated that FOXM1 was found to be amplified in high-grade serous ovarian cancer (HGSOC) (17, 18).

COSMIC database has revealed several mutations and gene amplifications of FOXM1 across various cancers (**Figure 1C**). Synonymous mutation and missense substitution are observed to be the highest mutational events. Among the missense substitutions, C>T and G>A (**Figure 1D**) are found to be the most frequently occurring. These mutations have a wide range of FATHMM score (that predicts functional consequences of coding and non-coding variants). High FATHMM score (≥ 0.7) may predict a deleterious effect of these mutations. Most of these mutations may possibly alter the activity of FOXM1, but detailed studies need to be carried out to understand their effect at protein level, thereby the alterations in cellular physiology. The synonymous mutations do not have any deleterious effect on FOXM1 protein as this would not change the amino acid information. Nonsense mutations are observed in approximately 3% of the cases and these have a high pathogenic FATHMM score (>0.8). (<https://cancer.sanger.ac.uk/cosmic>) (14). Other genetic modifications of FOXM1 include gene fusion events like FOXM1/SLC2A14 (t (12;12)(p13;p13)), FOXM1/ANO2, FOXM1/DCP1B (19). Although SLC2A14 (hexose transporter),

ANO2 (calcium activated chloride channel), DCP1B (core component of the mRNA decapping complex) have been shown to be associated with various cancers, their functional role as gene fusion products need to be studied in detail (20, 21). Apart from these genetic alterations, FOXM1 has been shown to be altered by various transcriptional and translational deregulations.

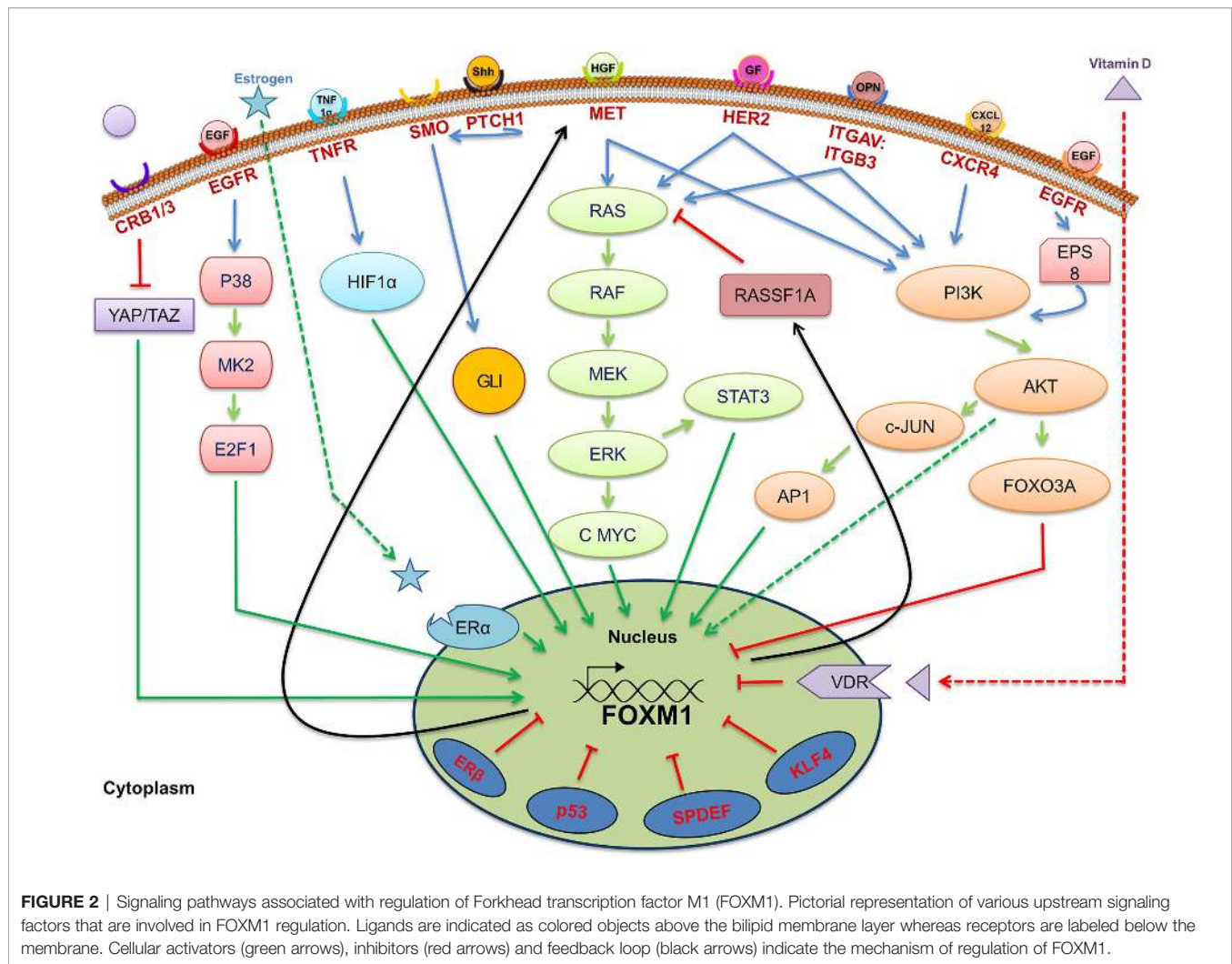
REGULATION OF FOXM1

In order to maintain a homeostatic environment, FOXM1 expression and activity needs to be tightly regulated and coordinated by diverse signaling pathways. This involves the regulation by transcription factors (activation), repressors (repression) and the epigenetic modifications (activation or repression). Following transcription, cellular cues drive the processing of pre-mRNA molecules by machineries involved in post-transcriptional modification. Various studies have revealed that several miRNAs target FOXM1 and regulate its expression (22, 23). The diverse functions of FOXM1 have been further manifested through various post-translational modifications. Activation and repression of FOXM1 protein is mediated primarily by the phosphorylation status of respective amino acid residues. Apart from this, acetylation, SUMOylation and ubiquitinylation also contribute toward its activity and stability.

Deregulated Cellular Signaling of FOXM1 in Tumorigenesis

FOXM1 is one of the major transcription factors altered in cancer by virtue of altered signal transduction pathways. Activation of FOXM1 *via* the altered KRAS signaling has been evident in the development of hepatocellular carcinomas and initiation of lung tumorigenesis in RAS driven tumors (24). Moreover existence of an inverse correlation between RASSF1A, a tumor suppressor of the RAS signaling pathway, and FOXM1 has been observed in the progression of colon cancer. Interestingly, a cross talk between FOXM1 transcription factor and RASSF1A (**Figure 2**) was also revealed from this study (25). RASSF1A, which is mainly altered *via* hypermethylation, protein degradation and point mutation has been widely observed in various cancers such as liver, breast, colon and bladder cancer (26–28). Another study has shown that FOXM1 is regulated by hepatocyte growth factor (HGF) *via* RAS/MEK/ERK, PI3K-AKT, and STAT molecules by the activation of mesenchymal epithelial transition (MET)-tyrosine kinase receptor. Interestingly, FOXM1 was observed to have direct binding site on MET promoter, thereby accelerating HGF/MET signaling. Presence of this positive FOXM1 and MET feedback loop accelerate pancreatic ductal adenocarcinoma (PDA) development (29). Whether FOXM1/MET overexpression have any association with metastasis of PDA need to be validated, however, its role in lymph node metastases of gastric cancer has already been established (30). Another signaling of FOXM1 *via* TGF- α /EGFR-STAT3-TESC was observed in cholangiocarcinoma progression (31).

One of the biomarkers for breast cancer detection is HER2, which has been shown to be altered in about 25% of the breast cancers. HER2 transmit the signals *via* RAS-MAPK or PI3K-



AKT pathway, whose overexpression in breast cancer patients activates the expression of FOXM1 (32). It has been shown that FOXM1 nuclear positivity is well correlated with HER2 expression in breast cancer patients. This study also established an existence of a link between ER positive expression and FOXM1 in HER2 positive cases (33). Subsequent studies revealed FOXM1 overexpression was associated with aggressive phenotypes and poor overall and disease free survival in ER positive breast cancer patients (34). Moreover, FOXM1 expression in breast cancer cells has been shown to be controlled by a nuclear receptor, ER α which directly bind to the ERE like element on FOXM1 promoter. ER α , which is situated on nuclear membrane, could be activated by direct binding of estrogen or through a ligand independent mechanism. The latter mechanism involves key residues in the AF-1 domain of ER being activated by phosphorylation in response to signal transmission through RTKs, thereby promoting cell growth and survival (35). Further, HER2 and FOXM1 expression has also been observed to have correlation in colorectal cancer (36).

P38MAPK Pathway has been shown to be associated with drug resistance *via* FOXM1 expression. Epirubicin treated, MCF-7 breast cancer cells have shown induction of FOXM1 expression through P38MAPK–E2F1 axis. However, epirubicin resistant cells have shown constitutively high level of E2F1 and FOXM1 expression leading to the loss of drug sensitivity. It may be due to the fact that phosphorylation of E2F1 at serine 364 residue by P38-MK2 (mitogen-activated protein kinase (MAPK)-activated protein kinase 2; MAPKAPK2) axis led to the stabilization of E2F1 thereby regulating the target gene expression (37). Additionally, it was also shown that P38 could enhance FOXM1 expression independent of E2F1 by repressing JNK1. In contrast to these observations by De Olano et al., an earlier study by Millour J et al. has shown down regulation of FOXM1 expression at the onset of epirubicin treatment in MCF-7 cells by the modulation of E2F activity on the FOXM1 promoter by P53 (38). Additionally FOXM1 was shown to be associated with sorafenib drug resistance in liver cancer cells *via* AKT-CJUN-AP1- FOXM1 signaling (39).

FOXM1 expression in glioblastoma stem like cells has been shown to be elevated *via* FGFR signaling, wherein the expression of FGFR has been found to be elevated *via* $\alpha 6$ -integrin and ZEB1/YAP1 transcription factor complex (40). A shorter overall survival was observed in glioblastoma multiforme (GBM) patients with the expression of $\alpha 6$ -integrin, ZEB1/YAP1, FGFR1 and FOXM1 (41). Integrin $\alpha \beta 3$ receptor activation by osteopontin (OPN) has been found to upregulate FOXM1 expression in pancreatic cancer cells. OPN promotes the epithelial mesenchymal transition (EMT) and cancer stem cells (CSC) like properties of pancreatic cancer cells (PCCs) by activating the integrin $\alpha \beta 3$ /Akt/Erk/FOXM1 cascade in a paracrine manner. The malignant phenotypes of PCCs could be induced by the OPN secreted from activated pancreatic stellate cells (PSC) in response to a hypoxic condition. Elevated OPN and FOXM1 expression reflects a poor clinical outcome in PCCs (42). Another study conducted in HEC1A cells also depicted the induction of FOXM1 expression by OPN (43).

A study by Chen et al. has shown that >60% of human breast cancer samples compared to adjacent normal breast tissues have high expression of epidermal growth factor receptor pathway substrate 8 (EPS8), enabling migration and motility (44). PI3K-AKT mediates, EPS8, dependent up regulation of FOXM1 which in turn leads to the activation of many of the cell cycle regulators, which includes CDC20, CDC25B, CDC25C phosphatases, Cyclin A, and Cyclin B among others. Additionally, FOXM1 regulates molecules associated with mitotic progression such as aurora-A kinase, polo-like kinase-1, centromere protein-A, E and F; stimulators of angiogenesis and motility including vascular endothelial growth factor (VEGF) and CXCL12. Chromatin immunoprecipitation assays in EPS8 overexpression background revealed an elevation in levels of acetylated histone H3 associated with the FOXM1 promoter (45). Recently EPS8 was shown as a novel interacting partner of FOXM1 which further established its role in enhanced cancer cell proliferation, migration and invasion (46). FOXM1 could also be activated *via* CXCL12 mediated PI3K/AKT-dependent mechanism in glioblastoma (47).

Sonic Hedgehog (Shh) Signaling activates FOXM1 expression through its effector molecule GLI1, a zinc finger transcription factor (48). Expression of FOXM1 correlates directly with the expression of patched-1 (PTCH1), smoothened (SMO) and GLI1 in various cancers (49, 50). Wang et al. have proved GLI1-FOXM1 interaction by depicting the direct binding of GLI1 to the FOXM1 promoter (51). Alteration in Hh signaling, thereby the expression of FOXM1 has been evident from reports on various cancers. It has also been observed that in some of the cancer cases even though GLI1 is altered at the initial stages, FOXM1 and GLI1 correlation is seen only when lymph node metastasis occurs. Hh and FOXM1 overexpression have been observed in cervical cancer tissue, wherein Shh, PTCH1 and GLI1 correlated with the pathological grade of the tumors and GLI1 and SMO correlated with the clinical stage of the tumors (50). Colorectal cancer cell proliferation was also enhanced in the background of Hh signaling and FOXM1 expression (51).

Salvador/Warts/Hippo (SWH) Pathway or in short Hippo signaling pathway regulates cell proliferation and apoptosis thus

controlling the organ size in animals. Mechanical stress, G-protein-coupled receptor signaling, and oxidative stress are some of the upstream signaling for hippo pathway. This pathway also has been shown to be altered in cancer (52). The major protein kinase involved in the pathway is Hippo (Hpo) whose phosphorylation of downstream YAP is inactive during growth stimulation. Unphosphorylated YAP translocate to nucleus and interacts with TEAD to control gene transcription (53). In malignant mesothelioma, YAP/TEAD directly binds to the FOXM1 promoter enhancing its gene expression (54). Moreover, FOXM1 upregulation has been observed in various soft tissue sarcoma subtypes which led to an increased cell proliferation (55). ROCK/YAP/FOXM1 axis has been observed in airway smooth muscle cell proliferation, migration, and contraction which is induced by S1P binding to S1PR_{2/3} (56). YAP/TEAD-FOXM1 signaling axis has also been associated with the expression of chromosomal instability signature genes CIN25 and CIN70 expression in hepatocellular carcinoma (HCC) (57). Studies in breast cancer cells MDAMB 231 have also shown FOXM1 to modulate proliferation, clonal expansion, migration and stemness in YAP1 dependent manner (58). Through an integrated transcriptomic, proteomic, and drug screening approach, YAP-FOXM1 axis was identified as the driver of EMT-associated EGFR-TKI (Tyrosine Kinase Inhibitor) resistance by increased abundance of spindle assembly checkpoint (SAC) proteins, including polo-like kinase 1 (PLK1), aurora kinases, survivin, and kinesin spindle protein (KSP).

FOXM1 is also regulated by another stress signaling pathway, TNF α /ROS/HIF-1 in hepatocellular carcinoma. The existence of a positive correlation between HIF1 α and FOXM1 in HCC patients reflects poor prognosis, aggressive tumors, and high recurrence rate (59). An increased incidence rate of cancer in colon, breast, prostate and ovarian has been inversely correlated with the vitamin D deficiency (60). An inverse correlation between vitamin D receptor expression and FOXM1 in pancreatic ductal carcinoma patients was observed by Li Z et al. Pharmacological activation of Vitamin D receptor (VDR) by vitamin D and its analog has led to the suppression of FOXM1 signaling as evidenced from the expression of its downstream targets such as cyclin D1, CMYC, SKP2, CD44 and c-MET (61). Overall representation of the upstream signaling of FOXM1 has been given in **Figure 2**.

Post-Transcriptional Alterations of FOXM1 in Cancer

The fate of mRNAs is decided by various intricate mechanisms which include capping, splicing, polyadenylation and rate of nuclear export. All these processes are controlled by various protein complexes and enzymes to maintain homeostasis.

Deregulation in Splicing Machinery

Pre-mRNA molecules undergo splicing to generate various isoforms of a particular gene. Approximately 70% of the human genes undergo splicing events and generate diversity in the protein profile. SRp20 (SFR S3), a splicing factor that regulates FOXM1, PLK1, and Cdc25 B transcripts, has been

observed to be overexpressed in ovarian, cervical, AML, lung, breast, stomach, skin, bladder, colon, liver, thyroid, and kidney cancers (62, 63). Precise regulation by splicing is quintessential to maintain cellular homeostasis by FOXM1 as evidenced from the G2/M phase arrest due to SRp20 downregulation. Accumulation FOXM1A and downregulation of both FOXM1B and FOXM1C have been observed upon knockdown of SRp20 (63). In addition, USP39, a component of the spliceosome, also regulates FOXM1 pre-mRNA processing. High expression of USP39 has been observed in human HCC and FOXM1 is found to be one of the molecules overexpressed (64). Inhibition of USP39 by siRNA has downregulated FOXM1 and in turn led to tumor volume reduction in xenograft model of HCC (65). Another protein involved in FOXM1 splicing is a nuclear protein, CTNNB1 which has been found to be associated with the Prp19 complex of the spliceosome. This protein is involved in regulating the splicing events of FOXM1 in ovary and its elevated expression was reported in ovarian cancer. FOXM1B and C protein levels were high in CTNNB1 overexpressed cells, whereas a decreased expression has been observed in knockdown ovarian cancer cells (66). These splicing mechanisms have been illustrated in **Figure 3A**.

Deregulation in Epi-Transcriptomics

Incorporation of N6-Methyladenosine (m6A) into the pre-mRNA molecules by m6A methyltransferases-METTL3 is one

of the most important epi-transcriptomic modifications present in eukaryotes that play important role in various physiological processes and disease states. This modification could be removed either by FTO (fat-mass and obesity-associated protein) or ALKBH5 (α -ketoglutarate-dependent dioxygenase alkB homolog 5) (67). ALKBH5 expression has been reported to be high in breast cancer, GBM, ovarian cancer, pancreatic cancer and gastric cancer (68). A study by Zhang et al. had demonstrated FOXM1 as a target of ALKBH5 and also identified a long non-coding RNA antisense to FOXM1. Interaction of long noncoding RNA with FOXM1 promotes the recruitment of ALKBH5 to the FOXM1 nascent transcripts. This in turn leads to the binding of HUR, an RNA binding protein thereby resulting in protein translation (**Figure 3B**). Blockade of these molecules by shRNA interrupted the proliferation of GSCs and GBM (69). So it would be speculated that the deregulation on these molecules in cancer may affect the expression of FOXM1 transcription factor.

Deregulation of FOXM1 by miRNA and lncRNA

Approximately 60% of genes encoded in the human genome are regulated by miRNAs (70). It has been shown that many physiological processes such as development, apoptosis, EMT, proliferation and stem cell maintenance are tightly regulated by miRNAs (71). Studies related to FOXM1 and miRNA so far has generated ample knowledge regarding potential miRNAs which inhibit FOXM1 post-transcriptionally.

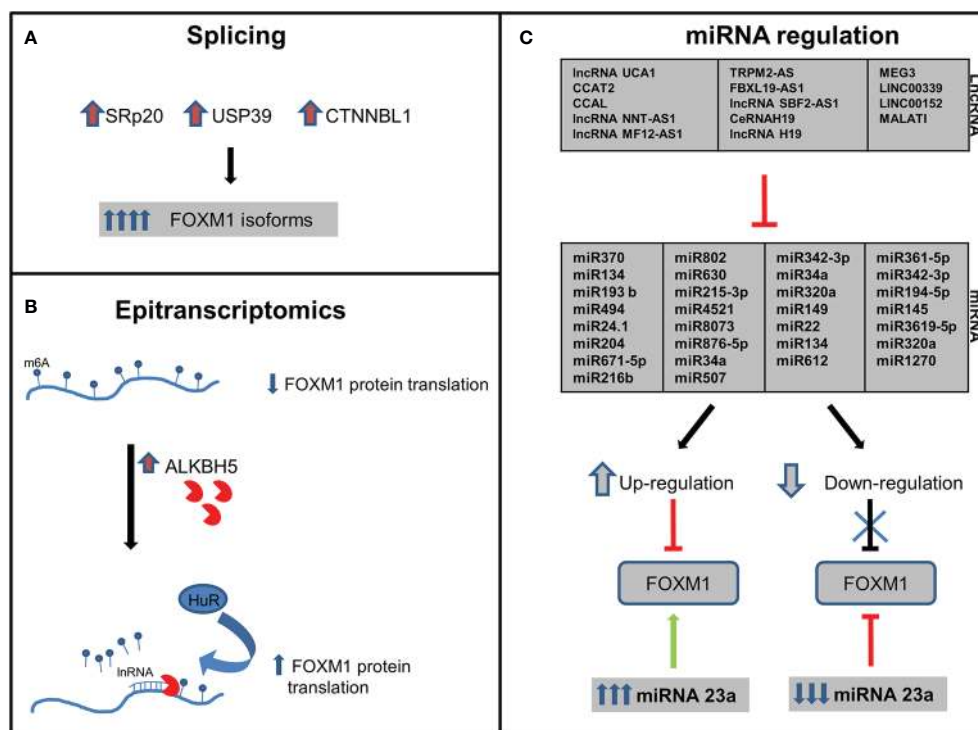


FIGURE 3 | Post-transcriptional regulation of Forkhead transcription factor M1 (FOXM1). FOXM1 regulation by (A) Splicing-elevation of splicing factors lead to upregulation of FOXM1 isoforms (B) Epitranscriptomics-upregulation of ALKBH5 leads to increased FOXM1 translation and (C) lncRNA/miRNA-FOXM1 gene expression is regulated by miRNA which in turn are regulated by lncRNA (details of specificity are described in **Table 1**).

The miRNA which target and regulate FOXM1 expression has widely been altered in various cancers. These miRNAs either function as tumor suppressors or oncogenes. FOXM1 is not only altered through the direct binding of miRNA to the 3'UTR but also by indirect effect of miRNAs on upstream regulatory molecules of FOXM1. Upregulation of FOXM1 by inhibiting its miRNA reflected in phenotypes such as proliferation, invasion and migration (**Table 1**). CagA, a virulence factor of *Helicobacter pylori* promotes the expression of FOXM1 by downregulating miRNA 370 in gastric cancer (73). Another mechanism of FOXM1 miRNA downregulation is by the hypermethylation of its own promoter (78).

Recent studies on FOXM1 miRNAs have revealed several prospective targets for cancer treatment. It has been shown that miRNA inhibitors have the ability to re-sensitize drug resistance cells to chemotherapy. This could have positive implications as FOXM1 is a major molecule in drug resistance mechanism. The drug resistance phenotype in cancer cells has been observed to be reversed by the overexpression of miRNA 134 (75), whereas miRNA 320 enhanced radiosensitivity by directly targeting FOXM1. Majority of the reported miRNAs has a potential to be considered as a prognostic and diagnostic marker. **Table 1** shows an overview of the reported miRNAs of FOXM1. Despite several miRNA studies revealing its association with cancer, only few have reported the regulatory mechanisms of miRNA. A study indicated miR 135a has been found to be transcribed by FOXM1 transcription factor and metastasis suppressor1 (MTSS1) (114). It also transcriptionally enhanced the expression of miR-1306-3p, a plausible biomarker for clinical prognosis of HCC.

Long noncoding RNA (lncRNA) are transcripts with lengths exceeding 200 nucleotides. They are critical in tumorigenesis, chromatin remodeling, and post-transcriptional regulation. Last few years have shown growing evidence of lncRNA-miRNA-mRNA axis in regulation of several proteins. miRNA 507 and lncRNA UCA1 cooperatively regulate FOXM1 expression in melanoma cells. UCA1 has a direct binding site on miRNA 507 and has led to the existence of a negative correlation between lncRNA and miRNA 507 (100). FRLnc1, a long non coding RNA has been shown to be upregulated in 49% (20/41) of gastric cancer cases by positively regulating the expression of FOXM1 leading to enhanced cell migration. Apart from these, many lncRNA like H19, LINC00339, LINC01410, Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), SBF2-AS1, FBXL19-AS1, MEG3, TRPM2-AS, MFI2-AS1, NNT-AS1, CCAL, modulate the expression of FOXM1 *via* miR-342-3p and miR-194, miR-145, miR-3619, miR-320a, miR-361-5p, miR-876-5p, miR-612, miR-194-5p, miR-134, miR-22, and miR-149 respectively in various cancers. Few studies also demonstrated a positive feedback loop between FOXM1 and lncRNA like LINC01410, CCAT2, PVT1 and TUG1 (112, 115, 116) (**Table 1** and **Figure 3C**).

Post-Translational Modification of FOXM1 in Cancer

Post-translational modification (PTM) of FOXM1 includes methylation, phosphorylation, acetylation, SUMOylation and

ubiquitination. Appropriate activation, inactivation and degradation of this protein are vital for the execution of various cellular processes and maintenance of homeostasis. As FOXM1 plays a major role in many cellular processes, any deregulation in its activity by way of faulty PTMs may facilitate the process of tumorigenesis. Overall view of the FOXM1 PTMs and the factors associated are depicted in **Figure 4**.

Methylation

Methylation is a PTM in which methyl groups are added to the lysine and arginine residues of proteins. Methyltransferase-SETD3 modify FOXM1 under normoxic conditions and hamper its transcriptional activity (117). A proteomic study had revealed K278 and K282 as the plausible sites of methylation on FOXM1 (118). On the other hand, increased transcriptional activity of FOXM1 was mediated through the dimethylation of H3K27 by DOT1L in pancreatic and colon cancer. The tumor promoting effect in these cancers was mediated *via* WNT5A, a downstream target of FOXM1 (119).

Phosphorylation

Phosphorylation is a process in which phosphate group is covalently attached to the respective amino acid of a protein substrate by an enzymatic reaction catalyzed by various protein kinases. Major protein kinases involved in this process are serine threonine protein kinase, tyrosine protein kinase, protein kinase A, B, and C. FOXM1 phosphorylations are mostly carried out by ERK, Cyclin dependent kinases (CDK), Polo like Kinase, and protein kinase A, B, and C (**Figure 5**). Transcriptional activity of FOXM1 mostly depends on the activation by Ras-mitogen-activated protein kinase (MAPK) signaling pathway, which activates FOXM1 through Cyclin-CDKs (120). Phosphorylation of FOXM1 at various residues happens to be in a cell cycle dependent manner (121). It has been shown that FOXM1B phosphorylation starts at the G₁ phase (4 h post serum addition) and progresses through the S phase (12 h) and G₂ phase (18 to 22 h) of the cell cycle which directly correlated with the transcriptional activity of this protein (122). Another study also has reported FOXM1 activity to be low in cells synchronized at the G₁/S transition and increased only as the cells entered the G₂ phase after release from the G₁/S block (10 to 12 h after release), whereas expression of FOXM1 was relatively constant. Induction of FOXM1 activity in G₂ was not due to enhanced DNA binding, but due to differences in its phosphorylation status as FOXM1 was already bound to its target promoters in G₁/S phase of the cell cycle (123).

CyclinD1/D3 and CDK4/6 complexes play a role in phosphorylating FOXM1 at initial stages of cell cycle and they have also been found to be associated with neoplastic growth. These phosphorylation events aid to suppress the senescence program hence they may accelerate tumorigenesis (124). When cells enter S and G₂ phase, Cyclin E/A and CDK2 complex phosphorylates FOXM1C at Thr600, Thr611 and Ser638 and regulate the transcriptional activity (125). Three potential CDK 1/2 sites were observed in the FOXM1B protein which includes amino acid residues at 585, 596 and 657. Among these T596

TABLE 1 | List of miRNAs that regulate Forkhead transcription factor M1 (FOXM1).

Sl. No.	miRNA	Loci	D/U	Associated Cancer	Highlights
1.	miR370	14q32	↓	Osteosarcoma (72), Gastritis and Gastric cancer (73), Acute myeloid leukemia (22)	Regulates cell proliferation, invasion and migration (72). Downregulation in 77% (37/48) of patient samples (AML) (73). Epigenetic silencing of miR370 in leukemic cells (22).
2.	miR134	14q32.31	↓	Esophageal Squamous cell carcinoma (ESCC) (74), Lung adenocarcinoma (75), Non-small-cell lung carcinoma (NSCLC) (76) Hepatocellular carcinoma (HCC)	Could inhibit the migration and invasion of ESCC cells (74). Regulates proliferation and metastasis via LncRNA MF12-AS1 /miR134/FOXM1. LncRNA MF12 overexpression associated with poor prognosis and advanced stage among patients (77).
3.	miR193b	16p13.12	↓	Prostate cancer	Hypermethylation of the promoter has been observed in cancer. Inhibits migration and invasion in prostate cancer cell lines (78).
4.	miR494	14q32.1	↓	Pancreatic cancer	PDAC metastasis and reduced survival times of patients correlated with reduced expression of miR 494. Could efficiently inhibit cell migration and invasion in pancreatic cells (79).
5.	miR24-1	9q22.32	↓	Bladder cancer	Induction of miR24-1 resulted in inhibition of cell proliferation, cell cycle arrest and increased apoptosis (80).
6.	miR204	r9q21.12	↓	Esophageal cancer (EC)	Inverse correlation with EMT phenotype of EC cells (81). Functions as tumor suppressor or oncogenes (82).
7.	miR671-5p	7q36.1.	↓	Breast cancer cells	Expression is inversely proportional to the invasive and metastatic properties of the cancer cell (83). Gradual reduction of mRNA in progression of normal epithelial to atypical ductal hyperplasia (ADH), to ductal carcinoma <i>in situ</i> (DCIS), and then invasive ductal carcinoma (IDC) (84).
8.	miR216b	2p16.1	↓	Hepatocellular carcinoma Cervical cancer (85)	Administration to HepG2 cells has produced a prominent cell cycle arrest phenotype and apoptosis (86).
9.	miR802	21q22.12	↓	Breast tissues	Proliferation of MCF7 breast cancer cells (87).
10.	miR23a	19q13.10	↑	Breast cancer	Function as tumor suppressor or Oncogenes. Potential putative biomarker of breast cancer (88).
11.	miR630	15q24.1	↓↑	Hepatocellular and bladder cancer (89–91) (Overexpression) Gastric cancer (downregulation)	Function as oncogene or tumor suppressor gene
12.	miR215-3p	1q41	↓	Colorectal cancer	Functions as oncogene as well as tumor suppressor gene. Inversely proportional to lymph node metastasis in colon cancer (92).
13.	miR4521	17p	↓	Medulloblastoma	Accelerates proliferation and invasion of several medulloblastoma cell lines (93).
14.	miR8073	13q34	↓	Colon, breast, and pancreatic cancer	Increased tumor growth (94).
15.	miR876-5p	9p21.1	↓	Glioblastoma (GBM) Breast cancer	Accelerated cell proliferation, reduced apoptosis and increased migration and invasion capabilities of GBM cells (95). Regulates cell proliferation and cell apoptosis via FBXL19-AS1 /miR876-5p/FOXM1 axis (96).
16.	miR34a	1p36.22	↓	Esophageal Squamous cell carcinoma (ESCC), Liver cancer (LC) Hepatocellular carcinoma (HCC)	Accelerates cell proliferation and cell migration (97). DNMT1 causes miR34a promoter methylation and suppression, leading to FOXM1 upregulation and promotes LC stemness (98). Regulates cell differentiation, and metastasis via CCAT2 /miR-34a/FOXM1. FOXM1 activates CCAT2 transcription (99).
17.	miR507	Xq27.3	↓	Melanoma cells	Regulates FOXM1 expression via lncRNA UCA 1 /miR 507/FOXM1 axis (100).
18.	miR342-3p	14q32.2	↓	Cervical Cancer GBC tissues Gallbladder cancer	Control cell proliferation, migration and invasion in cervical cells by regulating the expression of FOXM1 (101). lncRNA H19 and miR-342-3p expression are inversely proportional (102). CeRNA H19 expression regulates cell proliferation and invasion via H19/miR342-3P/FOXM1 axis (102).
19.	miR320a	8p21.3 8p21.3	↓	Renal Cell Carcinoma (RCC) Human umbilical vein endothelial cells (HUEVCs)	RCC cell proliferation, invasion and migration (103). Regulates HUVEC proliferation via MALAT1 /miR-320a/FOXM1 (104).
20.	miR149	2q37.3	↓	Gastric cancer	Regulates proliferation and metastasis via CCAL /miR-149/FOXM1 axis (105).
21.	miR22	17p13.3	↓	Lung Squamous cell carcinoma	Regulates proliferation, invasion, migration and metastasis via lncRNA NNT-AS1 /miR 22 (106).
22.	miR612	11q13.1	↓	Gastric Cancer	Regulates proliferation, migration, invasion and radioresistance via TRPM2-AS /miR 612/FOXM1 axis (107).

(Continued)

TABLE 1 | Continued

Sl. No.	miRNA	Loci	D/U	Associated Cancer	Highlights
23.	miR361-5p	Xq21.2	↓	Cervical Cancer Osteosarcoma cells	Regulates cell proliferation via lncRNA SBF2-AS1 /miR361-5p/ <i>FOXM1</i> . Elevated expression of lncRNA SBF2-AS1 was associated with advanced FIGO stage and lymph node metastasis of CC patients (108). Regulates proliferation and migration via MEG3 /miR-361-5p/ <i>FOXM1</i> axis (109).
24.	miR194-5p	1q41	↓	Gastric cancer, Colorectal adenocarcinoma	Regulates proliferation invasion, and migration via lncRNA H19 /miR-194-5p/ <i>FOXM1</i> axis (110).
25.	miR145	5q32	↓	Non-small-cell lung carcinoma (NSCLC)	Regulates proliferation, invasion and apoptosis via LINC00339 /miR145/ <i>FOXM1</i> axis (111).
26.	miR3619-5p	22q13.31	↓	Thyroid cancer	Regulates proliferation and apoptosis through LINC01410 /miR-3619-5p/ <i>FOXM1</i> (112)
27.	miR1270	19p12	↓	Rheumatoid arthritis (RA)	Regulates proliferation and apoptosis via LINC00152 /miR-1270/ <i>FOXM1</i> (113).

Downregulation (D) or Upregulation (U) (indicated by arrows) of miRNAs alters FOXM1 expression in various cancers. List also shows the outcomes of altered miRNA expression and lncRNAs (in bold) that regulate miRNAs.

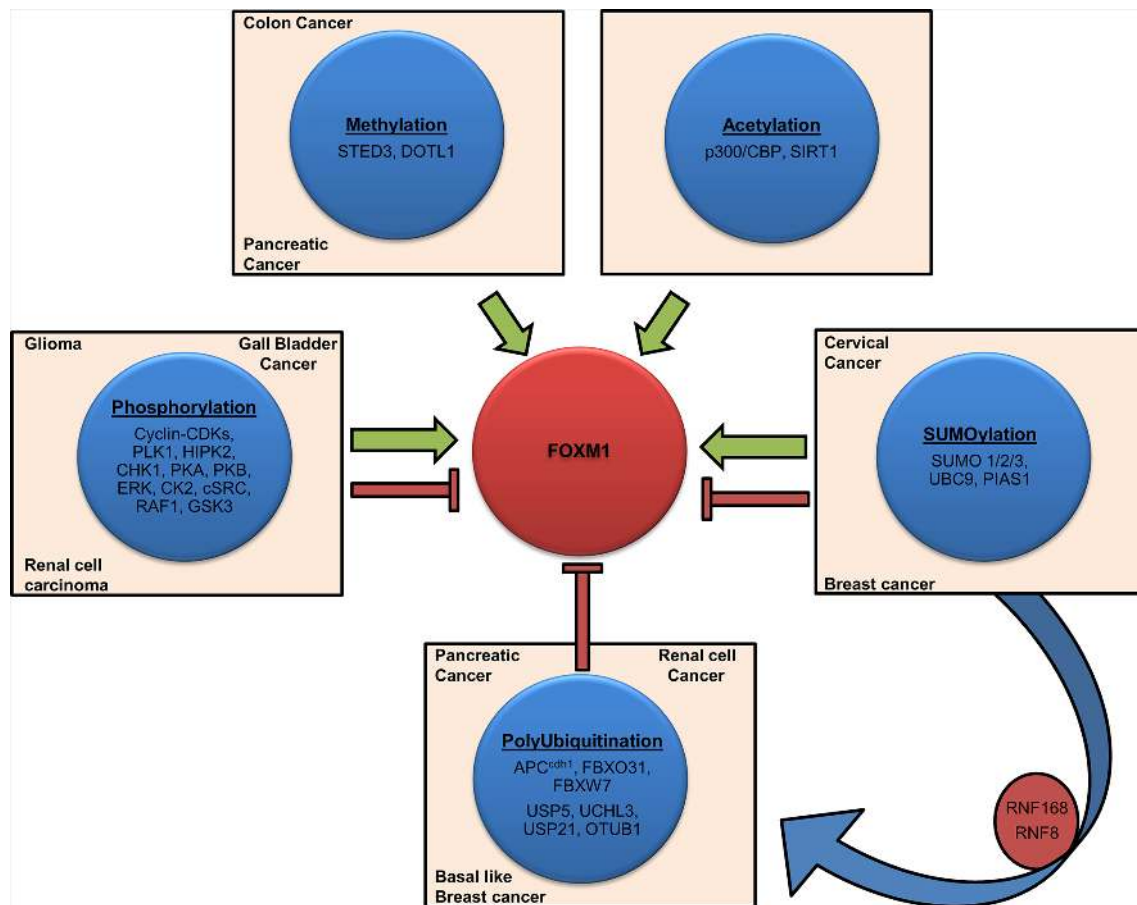


FIGURE 4 | Post-translational modifications of Forkhead transcription factor M1 (FOXM1). Schematic representation shows various factors involved in FOXM1 post-translational modifications (PTMs). Activation (Methylation, Acetylation), inhibition (Polyubiquitination), contextual (Phosphorylation, SUMOylation) and crosstalk are depicted by representative arrows. Cancers associated with the altered expression of these factors have also been indicated.

residue has been recognized as a critical CDK1 phosphorylation site within the activation domain of FOXM1B. CDK-dependent phosphorylation stimulates the FOXM1B transcriptional activity, which has correlated with binding to the CREB-

binding protein (CBP), the transcriptional co-activator. Mutation of T596 abolishes binding to CBP and inhibits transcriptional activity of FOXM1B (122). Mutation of the other two sites showed only a marginal decrease in the

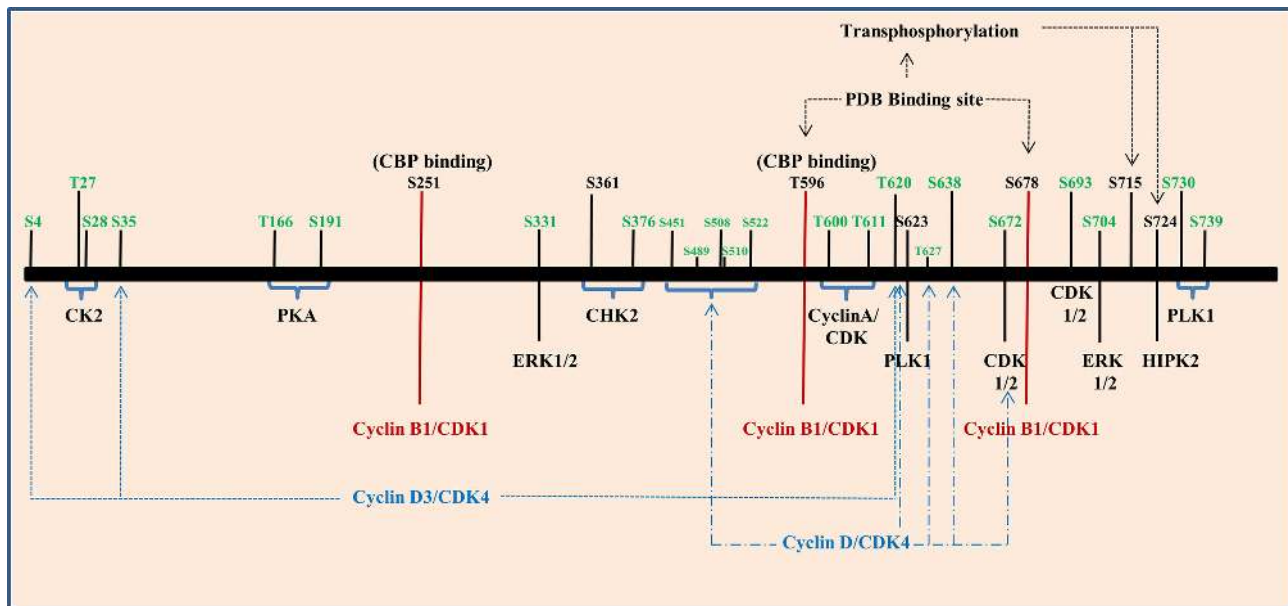


FIGURE 5 | Phosphorylation of Forkhead transcription factor M1 (FOXM1) is regulated by several kinases. Graphical representation of various kinases that regulate the different phosphorylation sites of FOXM1B (black) and C (green).

transcriptional activity of FOXM1B. Cyclin-binding motif (LXL motif) located at residues 639 to 641 has been responsible for the binding of CDK- Cyclin and both CDK1 and CDK2 were shown to be associated with FOXM1B. Mutation of the Cyclin-binding motif (Leu-641-Ala) has resulted in the elimination of both CDK1 and CDK2 binding. Phosphorylation of S251 in the forkhead box domain of FOXM1B stands as a critical event for activation of its transcriptional activity at the G₂/M phase by CDK1. Chen et al. also proved that S251 residue may be required for the nuclear localization of FOXM1 and its DNA binding. Disruption of these sites inhibits phosphorylation of FOXM1 and reduced transcriptional activity (126).

Entry of FOXM1 in to G₂/M triggers polo-like kinase 1 (PLK1) mediated phosphorylation. PLK1 Binding domain (PBD) recognizes S-pS/pT-P/X22,24 consensus sequence. By transferring phosphate group from ATP to substrates, PLK1 control various G₂/M associated cellular processes, namely centrosome maturation, checkpoint recovery, spindle assembly, cytokinesis, and apoptosis. Also, PLK1 phosphorylation sites in FOXM1B serves as a regulator for its repressor function in G₁ phase and activator function in S and G₂/M phase (127). FOXM1 has two potential PBD-binding sites (T596 and S678) at its C terminal region and phosphorylate S715 and S724 present within the TAD region of FOXM1 (128). It has been shown that PLK1 and FOXM1 expression were positively correlated in renal cell carcinoma cell lines. This study has also shown that the down regulation of PLK1 by siRNA resulted in reduced expression of FOXM1 (129). PLK1 mediated phosphorylation further promotes phosphorylation by MELK leading to increased expression of mitotic genes in glioma stem cells (130). It has been shown that

shorter overall survival of gall bladder cancer patients (GC) were significantly associated with FOXM1, PLK1, and NEK7 (131). Moreover, esophageal adenocarcinoma cell lines and tissues showed increased expression of FOXM1 and PLK1 than the normal counterpart and barrettes metaplasia. In addition they have also observed increased expression of FOXM1A and FOXM1B in most of the samples but heterogeneity was observed in FOXM1C's expression (132). The histological grading of renal cell carcinoma has been correlated with the expression of FOXM1 and HIPK2 wherein HIPK2 phosphorylates FOXM1 at S724 (133). Two ERK phosphorylation sites have been identified in FOXM1C at residues 331 and 704 respectively and its phosphorylation *via* MAPK signaling accelerate nuclear translocation of FOXM1C and bring its G₂/M regulatory effect (120).

The role of FOXM1 in DNA damage response has been evident from various studies. At the onset of DNA damage, phosphorylation of FOXM1 by CHK2 kinase ensures a proper DNA damage response through the stabilization of FOXM1. In FOXM1B, S361 residue marks the phosphorylation site for CHK2 and has been established to be conserved between mouse and humans (134). Apart from the role of Cyclin-CDK, CHK2 and PLK1, activation of FOXM1C was found to have occurred by the action of protein kinase CK2, cAMP dependent protein Kinase A, c-SRC and RAF-1. PKA phosphorylate substrates by recognizing R/K-R/K-X-S/T consensus sequence. FOXM1C has two such sequences around T160 and S190 at the N terminal region. Likewise, protein kinase CK2 recognizes the motif S/T-X-X-E/D. Phosphorylation of FOXM1C by CK2 at residues T27 and S28 results in its activation by removing the inhibitory phosphorylation. c-SRC and RAF1 are two other kinases also found to be involved in

the activation of FOXM1C through N terminal region (135). **Figure 5** summarizes various phosphorylation sites on FOXM1B and C that has been discussed.

Acetylation

Acetylation of histones or transcription factors represents a transcriptionally active state in most cases. This process involves the transfer of acetyl group from donors to the α -amino group of the first amino acid residue of a protein or to the ϵ -amino group of a lysine residue by lysine acetyl transferases. Apart from the role in the transcriptional activation, acetylation has also been associated with subcellular localization and stability of the protein. Acetylation of FOXM1 by p300/CBP at lysines K63, K422, K440, K603 and K614 has been noted to be essential for its transactivation of the target genes. This modification of FOXM1 increases during the S phase and remains elevated throughout the G2 and M phases (136). Apart from its increased transcriptional activity, acetylation of FOXM1 resulted in stabilization of the protein. Acetylation of FOXM1 follows a peak curve; levels increased initially in the S phase (4 h), elevated in the early G2 phase (8–10 h), reached maximum levels at the late G2/M phases (12–14 h), and then drops down when entering G1 phase (16–22 h). Observation of Lv et al. indicated that although the interaction between FOXM1 and p300 was initiated at the S phase, it reached the peak at G2/M phase. Notably, optimal binding of FOXM1 and CDK1 depends upon the acetylation of FOXM1 which further contributes toward its activation by phosphorylation. FOXM1 Thr 596 CDK phosphorylation site can recruit p300/CBP to the FOXM1B transcriptional activation domain. This interaction leads to acetylation of FOXM1 and thereby it's increased transcriptional activity. Moreover, FOXM1-dependent transcription is negatively affected by deacetylases like SIRT1. Tumor growth potential was significantly reduced in acetylation deficient mutants compared to wildtype FOXM1 (136).

SUMOylation

SUMOylation is a highly dynamic and reversible post translational modification that modulates FOXM1 activity in a context dependent manner. It involves covalent attachment of small ubiquitin-related modifier (SUMO) to specific lysine residues and thus regulating various aspects such as its subcellular localization, cell cycle progression, transcription, and DNA repair events (137). ψ KXE consensus motifs for SUMOylation are present throughout FOXM1 at amino acid positions 201, 218, 341, 445, 463, and 480. SUMOylation of ψ KXE motifs on the transactivation domain of FOXM1C promoted cytoplasmic accumulation and degradation by APC^{Cdh} ubiquitin ligase in breast cancer cells. It was also reported that epirubicin resistant cells are refractory to the SUMOylation, hence its transcriptional activation rather than destabilization (138). SUMO1 mediated inactivation of FOXM1 was shown to be reverted by PLK1 activity (139).

A study by Jaiswal et al. reported that SUMO conjugating enzymes, UBC9 and PIAS1 accelerates destabilization and nucleo-cytoplasmic shuttling of FOXM1. They also reported that HPV16 E7 oncoprotein can prevent SUMOylation of FOXM1B by impairing its interaction with UBC9 leading to its increased transcriptional activity in HPV positive cervical cancer cell lines

(140). In contrast to the above mentioned studies, Wang et al. showed an increased activity of FOXM1 by SUMO1 mediated SUMOylation in breast cancer cells (141). In addition, Schimmel et al. demonstrated transcriptional activation of FOXM1 by SUMO2 in wild type compared to the SUMOylation deficient FOXM1 mutant. Their results indicated that SUMOylation blocks the dimerization of FOXM1, thereby relieving FOXM1 auto repression (142).

Ubiquitination

Orderly synthesis and degradation of proteins are necessary for the proper functioning of the cell. Degradation of the proteins is initiated by the addition of ubiquitin molecules (polyubiquitination) to the lysine residue by ubiquitin activating and conjugating enzymes (E1 and E2), and their recognition by E3 ubiquitin ligases (143). Studies on APC^{Cdh1}, an E3 ubiquitin ligase, showed its involvement in degrading FOXM1 in late M and early G1 phase of cell cycle. This degradation is brought about by D box and KEN box APC^{Cdh1} recognition motifs present at the N terminal region of FOXM1 (144). Role of other ubiquitin ligases like FBXO31's in ubiquitinating and degrading FOXM1 have also been demonstrated in G2/M transition (145). Additionally, the role of deubiquitinase enzymes like USP5, UCHL3 and USP21 have been demonstrated to stabilize FOXM1 in pancreatic cancer, and basal like breast cancer (BLBC) respectively (146–148). Deubiquitination of FOXM1 by UCHL3 was also shown to promote pancreatic cancer progression and gemcitabine resistance (146). Also, a recent study showed that OTUB1 mediated deubiquitination of FOXM1 promotes renal cell carcinoma *via* upregulation of ECT 2 (149).

Protein quality control (PQC) mostly relies on an efficient spatiotemporal regulation of proteins by crosstalk between various cellular machineries. Kongsema et al. showed that SUMOylation was a prerequisite to recruit RNF168, an E3 ubiquitin ligase, to degrade FOXM1 in response to genotoxic stress in MCF-7 breast cancer cells. Further, their study also revealed that RNF168 works in cooperation with RNF8 as it only has a conventional ubiquitin-interacting motif and not a SUMO interacting motif (150). Chen et al. also showed that FOXM1 degradation was induced by FBXW7 dependent ubiquitination upon S474 phosphorylation by the GSK3- α complex. However this process was inhibited by the Wnt signaling activation and subsequent interaction with USP5 thereby leading to the stabilization of FOXM1 in glioblastoma multiforme (151).

REGULATION BY FOXM1

FOXM1 transcriptionally regulates the expression of a plethora of genes involved in various cellular processes such as cell cycle, DDR, senescence, apoptosis, migration, invasion, oxidative stress, and drug resistance. This protein has been found to be altered in various cancers by contributing to all the hallmarks of cancer. Thus it can be considered to be a potential target for precision cancer treatment modalities.

FOXM1 maintains sustained proliferation by modulating the expression of crucial cell cycle proteins. FOXM1 was shown to mediate G1 and S phase transitions by activation of CyclinD1

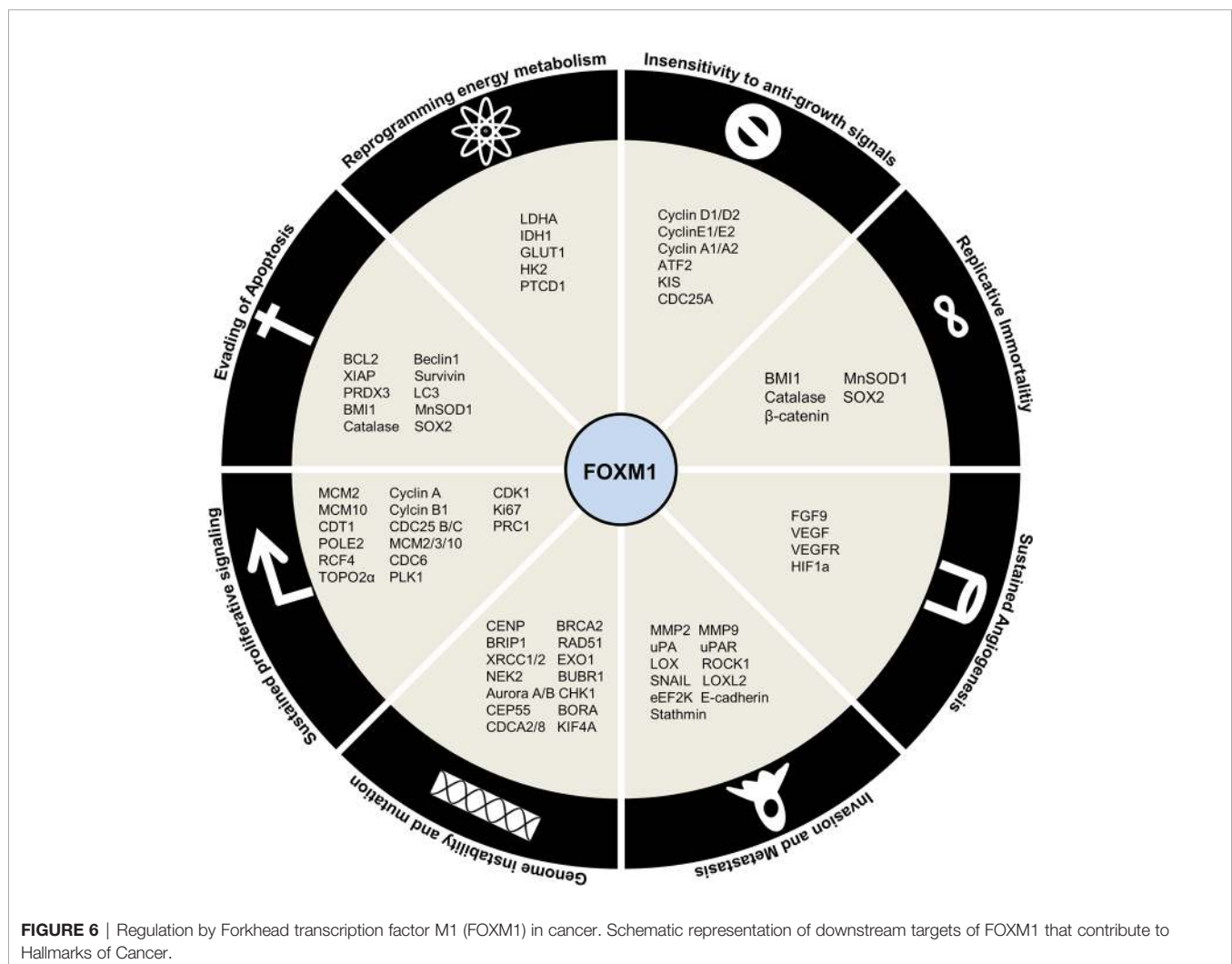
(152), Cyclin E2 (124), Cyclin A2 (153), ATF2 (154), KIS (155), CDC25A (156) and reduction of CDK inhibitors p16, p27^{Kip1}, p21^{Cip1} (insensitivity to anti-growth signals) through its degradation by SKP2 and CSK1 (SCF ubiquitin ligase complexes) (**Figure 6**) (157). It also regulates DNA replication initiation by MCM2, MCM3, MCM10, CDT1 (124), CDC6 (158) and progression by POLE2, RFC4 (159), TOP2A (160), whose deregulation could lead to loss of fidelity. G2/M transition was mediated by Cyclin A, Cyclin B1 (161), CDK1 (162, 163), PLK1 (128), Ki67, PRC1 (164) and CDC25A/B (165) (sustained proliferative signaling). Additional to developing insensitivity to growth signal inhibitors (Cip, Kip proteins), FOXM1 could also keep proliferative signals like TGF α (166), JNK1 (154), IGF1 (167), and NEDD4-1 (168), continuously switched on (self-sufficiency in growth signals).

FOXM1 has been shown to be involved in generation of genomic instability by altered DNA damage response (CHK1) and repair (BRCA2, EXO1, RAD51, BRIP1, XRCC1/2) (169, 170). Apart from this, its role in execution of mitosis by genes such as

BUBR1, NEK2 (171), Aurora A/B (172, 173), KIF4A (174), CENP-A/B/E/F, CEP55, BORA and CDCA2/8 (175) ensures high fidelity of cell division process (genome instability and mutation).

Supplemental to uncontrolled proliferation and development of a full blown cancer is resisting cell death. Affirming to its role in cancer development and progression, FOXM1 inhibits apoptosis by BCL2 (176), XIAP, survivin (177) and enhance autophagy by LC3 and Beclin1 (178). Moreover, FOXM1 was shown to avoid senescence by activation of BMI1 and ROS scavengers' catalase, MnSOD1, and PRDX3 (179) (evading apoptosis). It has been found that FOXM1 depletion sensitizes the cells to premature senescence thus slowing down cancer progression. Overcoming replicative senescence by activation of hTERT mediated telomeric activity further established FOXM1 as an oncogene (limitless replicative potential).

Another hallmark of cancer is the reprogramming of energy metabolism by aerobic glycolysis. FOXM1 promotes this by direct activation of LDHA (180), IDH1 (181), GLUT1 (181), GLUT1 and HK2 (182). FOXM1 is also implicated in regulating the



expression of pentatricopeptide repeat domain 1 (PTCD1), a mitochondrial leucine-specific tRNA binding protein which inhibits oxidative phosphorylation (183) (deregulating cellular energetics). In order to maintain a constant nutrient supply for this energy metabolism altered cells, FOXM1 stimulated neovascularization by promoting expression of FGF9, VEGF/VEGFR triggered by HIF/ROS signaling (184) (sustained angiogenesis). Epithelial-mesenchymal transition events lead to the escape of cells from primary site to enable cancer progression. FOXM1 has been shown to facilitate this escape by activating invasion and migration (MMP2, MMP9 (185), uPA, UPAR (186), LOX, LOXL2 (187), ROCK1 (8), SNAIL (188), eEF2K (189), E-Cadherin (190)) (tissue invasion and metastasis).

Recent developments have revealed the role of stemness in sustaining cancer contrary to its physiological functions. They present with enhanced capacities for self-renewal, proliferation, differentiation, metastasis, homing and drug resistance. FOXM1 has been demonstrated to promote these functions of stemness through regulation of OCT4, NANOG and SOX2 (191). Drug resistance phenotypes in cancer cells have been gained by the action of FOXM1 regulating the expression of ABCB1 (192), ABCC4 (193), ABCC5 (194), NBS1 (195) and BRIP1 (169). **Figure 6** summarizes the downstream factors of FOXM1 in mediating Hallmarks of cancer.

In addition to the regulation of cancer by these various transcriptional mechanisms, FOXM1 has been shown to exert its role in cancer development by several critical protein-protein interactions. FOXM1 interaction with MELK, PIN1 and pSTAT3 induced neurosphere development, BRAFV600E stimulated melanoma progression and radioresistance in glioblastoma respectively (130, 196, 197). FOXM1-SMAD interaction occurs downstream of the TGF β signaling pathway and promotes tumor progression (198). Nucleophosmin (NPN) was shown to sustain FOXM1 nuclear localization in cancer cells, whose mutation in AML interestingly led to FOXM1 inactivation by cytoplasmic shuttling (199). Binding with β -catenin and NF κ B in CML led to development of self-renewal capacity and enhanced survival (200). Although FOXM1 is a master transcriptional factor, it was shown to be a cofactor of β -catenin in regulating Wnt signaling mediated tumorigenesis in glioma. FOXM1 was also found to be stabilized by its interaction with PHGDH, which results in proliferation, invasion and tumorigenesis (201). Additionally, FOXM1 was also shown to interact with lncRNA, PVT1 and promote tumor growth and metastasis in gastric cancer (116). Heat shock protein 70 (HSP70) was shown to be a direct biological inhibitor of FOXM1 by affecting its transactivation capabilities (202). **Table 2** lists various interacting molecules of FOXM1.

PHARMACOLOGICAL INHIBITORS OF FOXM1

In general, activity of a protein is regulated by effectors ranging from ions to large macromolecules. FOXM1 expression and

activity are tightly controlled by several inbuilt cellular mechanisms which include autoinhibition of N-terminal repressor domain, miRNAs and regulation by proteins like p19ARF, p53, RB, KLF4 and FOXO3. FOXM1 is overexpressed in most cancers and is also known to have implications in all hallmarks of cancer, primarily based on its ability to transcriptionally activate several downstream effectors. This necessitated the development of novel chemical interventions which have been significantly progressing over the last decade. Indirect targeting of FOXM1 have been established using inhibitors of upstream factors like PIN1 (DRI peptides), SP1 (Thiazolidinediones) and GIL1 (Diarylheptanoids) (196, 212, 213). Traditional medicinal derivatives like Honokiol and Casticin have also shown to suppress FOXM1 and thereby its target genes (214, 215). Druggability of transcription factors has to account for any undesired effects due to the wide array of processes regulated by it. Therefore, specific inhibitors like DRI and 9R-201 peptides, FOXM1 Aptamer and TFI-10 that bind to FOXM1 are more effective in reducing tumor growth and activating apoptotic pathways (196, 216, 217). Additionally, several proteasome inhibitors like MG132, Bortezomib (218, 219) and thiazol antibiotics have been shown to significantly reduce FOXM1 expression. Siomycin a and Thiostrepton have been widely used across various cancer cell lines due to its specificity to inhibit FOXM1 by interacting with the DNA binding domain and preventing any auto feedback *via* NFRM loop (220). Despite development of these inhibitors, their clinical outcomes have been limited due to several kinetic and clinical factors. High throughput screening and phage library preparation have led to the designing of specific inhibitors like 9R-201, FOXM1 Apt, FDI-6 and RCM1 (221, 222) that primarily bind to the FOXM1 DBD *via* an electron deficient sulfur atom (π -sulfur) to His-287 in the protein. Although several inhibitors have been developed for targeting FOXM1 at multiple levels, specific delivery to cancer cells is the need of the hour to avoid disbalance of cellular homeostasis. Novel strategies to target FOXM1 dependent cancers could include combinatorial therapies with inclusion of chemosensitizers. A summary of the inhibitors of FOXM1 have been listed in **Table 3**.

CONCLUSION AND FUTURE PERSPECTIVE

In this review, we have addressed various regulatory pathways and mechanisms by which FOXM1 is altered and its implications in modulating different hallmarks of cancer. Based on its role in controlling various aspects of cellular processes as discussed throughout this review, FOXM1 is reinforced as an oncogene. We have elaborately discussed several signaling pathways that are deregulated in cancer. RAS signaling pathway increase FOXM1 expression and also its nuclear translocation. FOXM1 further keep this signaling switched on through the inhibition of RASSF1A tumor suppressor protein. OPN activated α 6-integrin leads to a triggering of FOXM1-FGFR/MET loop that may culminate in metastasis. Additionally, activation of hedgehog signals *via* Gli1 correlate with FOXM1 expression and predict

TABLE 2 | List of various interacting partners of Forkhead transcription factor M1 (FOXM1).

Sl. No.	Interactors	Function	Physiological context
1.	APC ^{cdh1} , cdc27 subunit	Degradation of FOXM1	Cell proliferation (144)
2.	β-catenin	The interaction with FOXM1 leads to its nuclear translocation.	Proliferation, invasion and migration, control Wnt target gene expression (200)
3.	CDC25A	Interaction leads to activation FOXM1 transcriptional activity.	Regulate cell cycle (156)
4.	EPS8	Partnering factor in regulating G2/M progression.	Proliferation and migration/invasion (46)
5.	FBXO31	Destabilize FOXM1 by promoting degradation	Genomic instability (145)
6.	FBXW7	Stabilize FOXM1 by deubiquitination.	Cell proliferation, invasion, apoptosis (151) (203),
7.	GSK3A	Phosphorylate FOXM1. Wnt signaling hampers this process.	Cell proliferation, invasion, apoptosis (151) (203),
8.	HIPK2	Phosphorylation of FOXM1	Cell proliferation (133)
9.	HSP 70	Interact with FOXM1 during proteotoxic stress and inhibit FOXM1's DNA binding ability.	Provide resistance to cell death and chemotherapeutics (202)
10.	MELK	Phosphorylate FOXM1 and increase its transcriptional activity	Cell cycle progression (130)
11.	MTDH	Stabilization of FOXM1 and also increase its transcriptional activity	Cell proliferation, angiogenesis and invasion (204)
12.	NPM	Helps FOXM1 to localize in the nucleus in cancer cells	Cell proliferation (199), drug resistance (205).
13.	OTUB1	Suppress FOXM1 degradation by deubiquitination.	Cell proliferation (206, 207)
14.	P19ARF	Inhibit FOXM1 transcriptional activity	Cell proliferation (208)
15.	PHGDH	Stabilization of FOXM1	Proliferation, invasion (201)
16.	PIN1	Increase FOXM1 activity.	Proliferation, metastasis and drug resistance (196)
17.	PLK1	Increase transactivation capability of FOXM1 by phosphorylation.	Cell cycle progression (128)
18.		Phosphorylate FOXM1 and increase its transcriptional activity and aids mitotic progression.	Cell proliferation (128)
19.	PP2A/B55α	Dephosphorylate FOXM1 and negatively regulates FoxM1 activity	Cell proliferation
20.	RB1	Interaction with RB1 represses FOXM1. RB1 and DNMT3b interaction makes FOXM1 to function as repressor for some genes	Differentiation of luminal epithelial progenitors (209) (210)
21.	RNF168 RNF8	Ubiquitination and degradation of SUMOylated FOXM1.	Cell proliferation (150)
22.	SIRT1	Destabilize FOXM1 by activating APC cdh1 mediated degradation	Cell proliferation (136)
23.	SMAD 3	Its interaction with FOXM1 sustain SMAD3/SMAD4 complex activation	Metastasis (198)
24.	SP1	FOXM1 and SP1 interaction induce EGF dependent COX2 expression.	Cell proliferation (211)
25.	STAT3	FOXM1 interacts with FOXM1 following radiation treatment	Confers radio resistance (197)
26.	SUMO 1	Destabilization/Activation	Proliferation, invasion, metastasis (138) (141),
27.	USP21	Stabilize FOXM1 expression by deubiquitination.	Proliferation, Drug sensitivity (148).
28.	USP5	Stabilization of FOXM1	Proliferation, invasion, migration (147)

Role of FOXM1 interacting proteins and their physiological effects in context of cancer.

metastatic outcomes. We also emphasized the importance of Vitamin D in FOXM1 regulation, as dietary variations are an emerging area in cancer research.

Altered expression of FOXM1 transcription factor has been seen in majority of the cancers. The deregulation of FOXM1 observed during tumorigenesis may be traced back to its own miRNAs. miRNAs are categorized either as oncogenic or tumor suppressive based on their expression pattern in malignancy. They impart their effect through direct association with FOXM1 or indirectly through its regulatory factors. Identification of FOXM1 miRNAs as tumor biomarkers has necessitated the need for further studies on miRNAs regulation.

Hampered post-translational modifications like SUMOylation by infectious viral particles or resistance to chemotherapeutic drugs tactically modulate FOXM1 function leading to a growth advantage. However a word of caution here is that predicting the eventual direction of FOXM1 function in cancer progression would be dependent on elucidating the SUMOylation fate determining factors. Sustained FOXM1 activity in cancer may be promoted by deregulated expression of various kinases such as pERK as seen in high grade ovarian cancer (245). Existence of a positive feedback loop between FOXM1 and kinases such as PLK1

and CDK1 further support a sustained FOXM1 activation in various malignancies.

Despite enormous amount of literature describing the various processes that associate FOXM1 with cancer, its potential as a target molecule for cancer treatment has been limited by the fact that it is a transcription factor. FOXM1 inhibition by siRNA or chemical inhibitors has shown to reduce the tumor size and also sensitized the tumor cells to chemotherapeutic agents. We envisage that developing targeted therapy by identifying interacting partners, pathways activated and various crosstalk mechanisms is the way forward in the quest for discovering inhibitors to halt the march of cancer. Furthermore, FOXM1 acts as a barrier for most of the existing chemotherapeutic regimes as evidenced from the drug resistance to Herceptin and taxol, mediated by degradation of p27 and *via* stathmin respectively (246, 247). FOXM1 expression and its modulation by various mechanisms in response to different cues have necessitated a thorough understanding of signaling molecules, various post transcriptional and translational mechanisms. This will pave the way for devising precise therapeutic target points of FOXM1 dependent cancer initiation, progression, genomic instability

TABLE 3 | List of inhibitors of Forkhead transcription factor M1 (FOXM1).

Sl. No.	Inhibitor	General Action	Indirect/Direct (I/D) mechanism	Cancer	Cell Lines
1.	Bortezomib	Proteasome inhibitor	I –	Osteosarcoma Pancreatic cancer Multiple myeloma Leukemia	U2OS (218) Mia PaCa-2 (219) U266 and RPMI8226 (218) HL-60 (218)
2.	Casticin	Anti-malarial sensitizer	I FOXO3a-FOXM1 (Inhibit FOXO3a)	Breast cancer Ovarian cancer Liver cancer	MDA-MB231, MCF-7 (223) SKOV3, A2780 (215) HEPG2, PLC/PRF/5 (224)
3.	Daunorubicin	Topoisomerase inhibitor	I p53-p21-FOXM1	Lung cancer Breast cancer Liver cancer	H1299 (225) MCF-7 (225) HepG2 (225)
4.	Diarylheptanoids	Anti-oxidants	I Shh-Gli-FOXM1 (Inhibit Gli1)	Pancreatic cancer	PANC-1 (213)
5.	DFOG	Genistein derivative	I –	Ovarian cancer Gastric cancer	CoC1, SKOV3 (226) AGS, SGC-7901 (227)
6.	DIM	Radioprotector	I –	Breast cancer Colorectal cancer Gastric cancer	MDA-MB231, MDA-MB468, SKBR3, MCF-7 (228) DLD-1 and HCT116 (229) SNU638 (230)
7.	FDI-6	FOXM1 specific drug	D Blocks FOXM1 DBD	Breast cancer Laryngeal Cancer	MCF-7, MDA-MB231 (231) Hep-2 (221)
8.	FOXM1 Apt	FOXM1-specific single stranded DNA aptamer generated by SELEX	D Target FOXM1 DBD	Breast cancer	MDA-MB436 (217)
9.	Fulvestrant (ICI182780)	Estrogen receptor antagonist	I ERβ1/ERα-FOXM1 axis (Inhibits ERα)	Breast cancer	MCF-7, ZR-75-1 (35)
10.	Genistein	Angiogenesis inhibitor	I –	Pancreatic cancer Lung cancer	BxPC-3, HPAC, MIAPaCa-2, PANC28 (232) IMR-90, H460, A549, H446 (233)
11.	Honokiol	Anti-inflammatory, anti-oxidant	D Interact with FOXM1	Osteosarcoma Prostate cancer Breast cancer	U2OS C3 (214) DU145 (214) MDA-MB231 (214)
12.	MG132	Proteasome inhibitor	I –	Pancreatic cancer Breast cancer Colorectal cancer	Mia PaCa-2 (219) MDA-MB231 (219) HCT-116 (219)
13.	Mithramycin A	DNA binding neuroprotective antibiotic	I Sp1-FOXM1 (Inhibit Sp1)	Liver cancer	HEPG2, PLC/PRF/5 (212)
14.	Monensin	Polyether antibiotic	D Interact with FOXM1 DBD	Prostate cancer	ENZR ⁺ -CRPC (234)
15.	Natura-α	STAT3 inhibitor	I –	Prostate cancer	LNCaP, LNCaP-AI, PC-3, and DU145 (235)
16.	Nutlin-3	MDM2-p53 interaction inhibitor	I MDM2-p53-FOXM1 (MDM2 inhibitor)	Osteosarcoma Lung cancer Ovarian cancer Colorectal cancer	U2OS (225), OVCAR10 NCI-H23 A2780 HCT-116 (225)
17.	Panepoxydone	Fungal NFκB pathway inhibitor	I –	Breast cancer	MCF7, MDA-MB231 (236)
18.	Peptide 9R-P201	High affinity peptides against FOXM1C from the phage random library	D Target FOXM1 DBD	Liver cancer	HepG2 (216)
19.	RCM-1	FOXM1 drug identified by high throughput screen	I Increase ubiquitination	Osteosarcoma Melanoma Prostate cancer Breast cancer Lung cancer Melanoma	U2OS C3 B16-F10 (mouse) (222) MyC-CaP (mouse) (222) 4T1 (mouse) (222) A549 (222) Colo829, Malme-3M (196)
20.	S331/704 DRI peptide	ATP competitive-BRAF Kinase	I Pin1-FOXM1 binding		
21.	Siomycin A	Thiazole antibiotic	D Interact with FOXM1 DBD and by NFRM loop	Liver cancer Lung cancer Colorectal cancer Melanoma	Huh7, Hep3B, SK-Hep (220) A549 (220) SW480, SW620 (220) DM443, DM366, DM833, DM646 (237)
22.	Thiazolidinediones	Anti-hyperglycemic	I Sp1-FOXM1 (Inhibit Sp1)	Leukemia Liver cancer	CEM, HL60, U937 (220) HepG2, PLC/PRF/5 (212)

(Continued)

TABLE 3 | Continued

Sl. No.	Inhibitor	General Action	Indirect/Direct (I/D) mechanism	Cancer	Cell Lines
23.	Thiostrepton	Thiazole antibiotic	D Interact with FOXM1 DBD and by NFRM loop	Breast cancer Ovarian cancer Colorectal cancer Melanoma Leukemia Laryngeal Squamous Ca Thyroid cancer	MCF-7, MDA-MB436, MDA-MB231 SKOB3, OVCAR3 (238) HCT-15, HT-29 (239) DM443, DM366, DM833, DM646 (237) MV4-11, THP1, CEM, HL60, U937 Hep-2
24.	TFI-10	Modified Thiazolidinediones	D Interact with FOXM1 DBD	Breast cancer	BCPAP, TCP-1
25.	TMPP	IER5 activator	I IER5-FOXM1 axis	Leukemia	MDA-MB231 (240) U937, YRK2 (241)
26.	U0126	MEK1/2 inhibitor	I MEK-ERK-FOXM1 axis	Ovarian cancer Breast cancer	OVCA433, A2780cp (242) MCF-7, ZR-75-30 (243)
27.	Ursolic acid	Anti-inflammatory, Anti-apoptotic	I –	Breast cancer	MCF-7 (244)
28.	Vemurafenib (PLX4032)	BRAF inhibitor	I BRAF-ERK-FOXM1-AuroraB	Melanoma	A375, 501mel (173)

Chemical inhibitors of FOXM1 and their mechanism of action, tested in respective cell lines.

TMPP, 2,3,4-tribromo-3-methyl-1-phenylphospholane 1-oxide; DIM, 3,3'-diindolylmethane; DFOG, 7-difluoromethoxyl-5,4'-di-n-octyl-genistein.

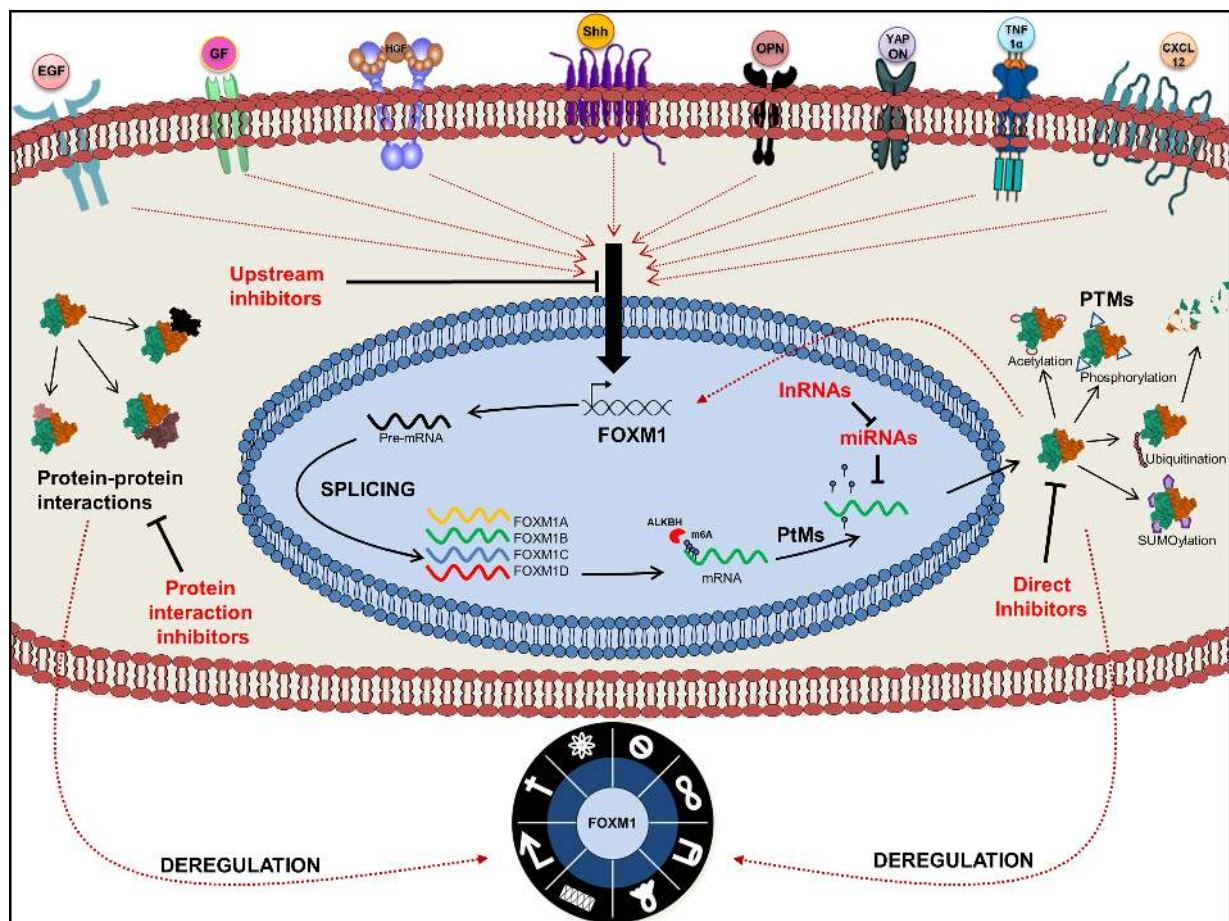


FIGURE 7 | Graphical abstract of Forkhead transcription factor M1 (FOXM1) regulation. Pictorial represents upstream regulators of FOXM1 and its various fates. Point of action of FOXM1 chemical inhibitors is also indicated.

and cancer cell drug resistance processes. Graphical abstract of the review has been represented in **Figure 7**.

AUTHOR CONTRIBUTIONS

DK, SJ, AN wrote the manuscript. DK, SJ designed the figures. AN provided guidance and revised the manuscript.

All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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