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Forkhead Box M1 transcription factor: A novel target for cancer therapy

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Abstract

FoxM1 signaling has been reported to be associated with carcinogenesis. Therefore, the FoxM1 may represent a novel therapeutic target, and thus the development of agents that will target FoxM1 is likely to have significant therapeutic impact on human cancer. This review describes the mechanisms of signal transduction associated with FoxM1 and provides emerging evidence in support of its role in the carcinogenesis. Further, we summarize data on several FoxM1 inhibitors especially "chemopreventive agents" and these agents could be useful for targeted inactivation of FoxM1, which indeed could become a novel approach for the prevention and/or treatment of human cancer.

Keywords

FoxM1; cancer; cell signaling pathway; chemopreventive agents

Introduction

Forkhead box protein M1 (FoxM1) belongs to a family of evolutionary conserved transcriptional regulators that were characterized by the presence of a DNA-binding domain called the forkhead box or winged helix domain 1›2. In recent years, the sudden explosion in the literature provides emerging evidence in support of the biological significance of FoxM1 (previously known as HFH-11, MPP2, Win, and Trident) in tumor aggressiveness. It has been accepted that FoxM1 is involved in cell proliferation and apoptosis which affects the developmental function of many organs 3-5. It has been reported that FoxM1 is a key cell cycle regulator of both the transition from G_1 to S phase and the progression to mitosis [6-9]. Loss of FoxM1 expression generates mitotic spindle defects, delays cells in mitosis, and induces mitotic catastrophe [8]. Moreover, FoxM1 has been shown to regulate transcription of cell cycle genes essential for G_1-S and G_2-M progression, including Cdc25A, Cdc25B, cyclin B, cyclin D1, $p21^{cip1}$ and $p27^{kip1}$ 2›9-11. Recently, FoxM1 was found to bind mammalian mitotic kinase polo-like kinase 1 (Plk1), resulting in mediating Plk1-dependent regulation of cell-cycle progression [12].

Studies have shown that FoxM1 signaling also plays important roles in cellular developmental pathways including the maintenance of homeostasis between cell proliferation and apoptosis,

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and thus alterations in FoxM1 signaling has been reported to be associated with carcinogenesis [2,13]. These observations suggest that dysfunction of FoxM1 prevents differentiation, ultimately guiding undifferentiated cells toward malignant transformation. Emerging evidence suggest that the FoxM1 signaling network is frequently deregulated in human malignancies with up-regulated expression of FoxM1 in lung cancer, glioblastomas, prostate cancer, basal cell carcinomas, hepatocellular carcinoma, and primary breast cancer and pancreatic cancer [2,3,7, 13-18]. Moreover, it has been shown that higher expression of FoxM1 was associated with poor prognosis of breast cancer patients [19]. Furthermore, studies have shown that FoxM1b expression could serve as an independent predictor of poor survival in gastric cancer [20]. These results suggest that FoxM1 may have a crucial role in the development and progression of human cancers. Therefore, it is believed that inactivation of FoxM1 could represent a promising strategy for the development of novel and selective anti-cancer therapies.

The molecular mechanism(s) by which FoxM1 signaling induces tumor growth has not been fully elucidated. However, multiple oncogenic pathways, such as phosphatidylinositol 3-kinase (PI3K)/Akt, nuclear factor-κB (NF-κB), Sonic hedgehog (Shh), extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK), cyclooxygenase-2 (COX-2), epidermal growth factor receptor (EGFR), estrogen receptor (ER), vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMP), c-myc, p53, reactive oxygen species (ROS), and hypoxia inducible factor-1 (HIF-1) signaling have been reported to cross-talk with FoxM1 pathway, and thus it is believed that the cross-talk between FoxM1 and other signaling pathways plays important roles in tumor aggressiveness. Here, we discuss the recent advances in the understanding on the role of FoxM1 in tumor progression.

FoxM1 and PI3K/Akt signaling

FoxM1 has been reported to cross-talk with one of the major cell growth and apoptotic regulatory pathway, namely PI3K/Akt 21,[22]. Akt (also known as protein kinase B) is an evolutionarily conserved serine/threonine kinase. Three isoforms, Akt 1, Akt 2 and Akt 3, are expressed in mammals, which are encoded by the genes PKBα, PKBβ and PKBγ, respectively [23]. Akt is activated by phospholipid binding and phosphorylation at Thr^{308} by 3-phosphoinositide-dependent protein kinase 1 (PDK1), and also by phosphorylation within the C-terminus at Ser^{473} by PDK2. Specifically, PI3K activates Akt, which transmits signals from cytokines, growth factors, and oncoproteins to multiple targets [23]. Activation of PI3K localizes Akt to the plasma membrane *via* the pleckstrin homology domain of Akt, where Akt is activated by phosphorylation at Thr^{308} and Ser^{473}. Activated Akt functions to promote cell survival by inhibiting apoptosis through inactivation of several pro-apoptotic factors including Bcl-xL/Bcl-2-Associated Death (BAD), Forkhead transcription factors and caspase-9 [23].

Recently, FoxM1 has been shown to cross-talk with the PI3K/Akt pathway. Inhibition of PI3K by its inhibitor LY294002 caused a significant reduction of FoxM1b in human U2OS osteosarcoma cells 21. We also found that LY294002 and Wortmanin, the PI3K inhibitors, eliminated the expression of FoxM1 in PC-3 and LnCaP prostate cancer cell lines (unpublished data). However, blocking the Akt pathway with either dominant negative Akt plasmid or the Akt kinase inhibitor did not alter FoxM1 expression in human U2OS osteosarcoma cells [21]. Interestingly, we found that FoxM1 was decreased significantly in Akt knock-out mouse embryo fibroblasts (MEF), which showed decreased pAkt pathway (unpublished data). Recently, it was found that tumor cells expressing activated Akt1 are addicted to FoxM1 for proliferation and clonogenic survival 22. Further research in exploring the mechanisms how PI3K/Akt regulates FoxM1 is urgently needed.

FoxM1 and NF-κB signaling

Several studies have also shown that Akt regulates the NF-κB pathway *via* the phosphorylation and activation of molecules in the NF-κB pathway 24. NF-κB plays important roles in the control of cell growth, differentiation, apoptosis and stress–response. Without stimulation, NF-κB is sequestered in the cytoplasm through tight association with the impeding IκB proteins. Following stimulation, IκB protein is phosphorylated and degraded, allowing the NF-κB to translocate to the nucleus, bind to the NF-κB-specific DNA-binding sites or interact with other transcription factors, and thus regulate gene transcription [24]. A key regulatory step in the NF-κB pathway is the activation of IKK (IκB kinase) complex in which catalysis is thought to be *via* kinases, including IKKα and IKKβ, which directly phosphorylate IκB proteins [24,25]. It has been reported that the interplay between the NF-κB and forkhead transcription factors, such as Foxj1, Foxo3a and Foxp3 is biologically important. For example, Foxo3a promotes cell apoptosis through regulation of IκBβ and suppression of NF-κB [26]. Recently, Penzo et al reported that inhibition of NF-κB by IκBα super repressor in the MEFs abrogated both the IKKβ mediated induction of direct NF-κB targets and the repression effect on the FoxM1 targets [27]. Further in-depth studies are needed to ascertain the precise molecular regulation of FoxM1 and NF-κB and their cross-talks for elucidating the role of FoxM1 in cell growth, invasion and angiogenesis of cancer cells, some of the most important hallmarks of tumor aggressiveness.

FoxM1 and EGFR signaling

EGFR signaling pathways play critical roles in the control of cell growth, apoptosis, migration, invasion, and many other physiological processes, and has been shown to be activated in various cancers [28]. EGFR family consists of HER-1/EGFR, HER-2/ErbB-2, HER-3/ErbB-3, and HER-4/ErbB-4 transmembrance receptors. Each receptor is activated by one or more EGF-related peptides, such as EGF, transforming growth factor (TGF)-α, heparin-binding EGF (HB-EGF), and amphiregulin. After binding of the ligands, EGFR dimerizes, either as a homodimer or heterodimer with other members of the EGFR family [28]. EGFR is then auto-phosphorylated or trans-phosphorylated at specific tyrosine residues for its activation, resulting in the activation of multiple downstream signaling cascades, including PI3K/Akt, and ERK, ultimately leading to increased cell proliferation and the prevention of programmed cell death 28. Indeed, there is increasing evidence to support the concept that many human tumors are causally linked with deregulated activation of one or more of these growth factor receptors. A significant correlation between FoxM1 expression and the HER2 status has been reported in breast cancer 19,29. Specifically, HER2 protein levels directly correlated with FoxM1 expression in both breast carcinoma cell lines and breast cancer samples from patients [29]. Further evidence suggest that HER2 regulates the FoxM1 expression at mRNA, protein and gene promoter levels in breast cancer [29]. Moreover, studies are underway to analyze the potential interaction between FoxM1 and HER2, especially how HER2 activates FoxM1 expression in our laboratory and perhaps in others as well.

FoxM1 and Raf/MEK/MAPK signaling

The MAPK is another important transduction signaling pathway that plays a critical role in controlling the balance between cell survival and apoptosis. The MAPK cascade is activated by a variety of cellular stimuli to influence cell growth and apoptosis 30. It has been reported that the activation of the MAPK pathways may cause the induction of phase II detoxifying enzymes, and conversely inhibition of MAPK pathways may inhibit AP-1-mediated gene expression [30]. MAPK pathway consists of three-tiered kinase core where a MAP3K activates MAP2K that in turn activates MAPK (ERK, JNK, and p38), resulting in the activation of NF-κB, cell growth, and cell survival [30]. It has been well documented that activation of MAPK

found in several types of cancer are also linked with cancer angiogenesis, invasion, and metastasis 30,31. Recent evidence suggest that FoxM1 is an effector of Raf/MEK/MAPK signaling in G2/M regulation 21,32. Ma et al. found that the activity of the Raf/MEK/MAPK is necessary and sufficient for the nuclear translocation of FoxM1. Moreover, activation of the Raf/MEK/MAPK pathway enhances the transactivating activity of FoxM1 on the cyclin B1 promoter 32. Interestingly, Major et al. reported that blocking the MAPK pathway could diminish FoxM1 transcriptional activity 21, suggesting that the cross-talks between Raf/MEK/MAPK and FoxM1 is mechanistically important in human malignancies and thus inactivation of these pathways rather than a single pathway would be therapeutically important.

FoxM1 and ERK signaling

ERK1 and ERK2 are members of the MAPK super family that can mediate cell proliferation and apoptosis. ERK activation has been commonly associated with protection against apoptosis induced by a variety of agents. It is well known that multiple phosphatases (such as MAPK phosphatases) inactivate ERKs, suggesting that the duration and extent of ERK activation is controlled by the balanced activities of (MAPK/ERK) kinase MEKs and respective phosphatases 30. ERK activities were found to be elevated in many human tumors, and higher activity in tumors was associated with a poor prognosis, suggesting the crucial role of ERK in tumor progression 33-35. Recently, Calvisi et al. found that FoxM1 is a major ERK effector in human hepatocellular carcinoma (HCC) 36. They found that ERK achieves its activation by triggering the degradation of its specific inhibitor, dual-specificity phosphatase 1 (DUSP1), via the synergistic activity of S-phase kinase-associated protein 2 (SKP2), CDC28 protein kinase 1b (CKS1) and ERK 36. In this context, FoxM1 triggers the degradation of the DUSP1 through transcriptional activation of CKS1 and SKP2, thus sustaining ERK activity in human HCC 36. These limited yet important studies clearly suggest an important regulatory role of FoxM1 in the activation of ERK.

FoxM1 and Sonic hedgehog signaling

Hedgehog signaling is very important in the regulation of cell proliferation, survival, and apoptosis. Deregulation of hedgehog signaling pathway has been found in several cancers, including medulloblastoma, rhabdomyosarcoma, melanoma, basal cell carcinoma, breast, lung, liver, stomach, prostate, and pancreatic cancers 37. There are three members of the hedgehog family, named as Sonic hedgehog (Shh), Desert hedgehog (Dhh), and Indian hedgehog (Ihh). So far, the zinc-finger Gli is one of the key direct downstream targets of Shh signaling. It is all known that vertebrates have three Gli proteins (Gli1, Gli2, and Gli3). It has been found that FoxM1 is a downstream target of Gli1 in basal cell carcinomas 17. Over-expression of FoxM1 in non-small cell lung carcinomas (NSCLC) was found to be significantly correlated with Gli1 expression 38. In colorectal cancer, expression of Gli1 and FoxM1 mRNA was found to correlated with Shh expression 39, suggesting that FoxM1 cross-talks with Shh via Gli1 in many tumors. Therefore, targeted inactivation of either downstream or upstream molecules of Gli such as FoxM1 would be therapeutically important for human malignancies.

FoxM1 and Estrogen Receptor (ER)

The deregulated hormone receptor signaling is important in many human malignancies. It has been found that estrogen receptor (ER) signaling plays important roles in the carcinogenesis and tumor progression through regulation of transcription of estrogen-responsive genes 40. Many environmental chemicals have been found to be estrogenic and have been shown to stimulate the growth of ER-positive human breast cancer cells 40. The biological effects of estrogen are primarily mediated through two nuclear steroid receptors, estrogen receptors ER-α and ER-β. ER-α plays a major role in breast cancer initiation and progression, whereas ER-β appears to have an opposing function to ER-α in tumor growth. ER-α plays its role as a

classical transcription factor and a signal transducer. Estrogen binding activates ER-α through phosphorylation, its dissociates from chaperon proteins, alterations in its conformation, and finally activation of its target genes 40. Recently, it was found that FoxM1 can work as a physiological regulator of ER-α expression in breast carcinoma cells. FoxM1 regulates ER-α expression at the transcriptional and promoter levels primarily through binding directly to FHREs region of the ER-α promoter 41. It was recently shown that FOXO3a can interact with FoxM1 on ER-α promoter and regulate ER-α expression [41,42]. Moreover, FOXO3a may repress ER-α activity through an alternative mechanism by which FOXO3a down-regulates FoxM1 expression [43]. These provocative results need further in-depth investigation in order to gain mechanistic insight regarding the cross-regulation of FoxM1 and ER.

FoxM1 and Cyclooxygenase (COX-2) pathway

COX is a rate-limiting enzyme involved in the conversion of arachidonic acid to prostaglandins (PGs). There are two isoforms of COX: COX-1 is constitutively expressed in many tissues and is involved in the housekeeping function of prostanoids, while COX-2, the inducible isoform, accounts for the elevated production of prostaglandins in response to various inflammatory stimuli, hormones, and growth factors [44]. COX-2 appears to be involved in various aspects of carcinogenesis. Therefore, COX-2 has received more attention than COX-1 in cancer research 44. In recent years, COX-2 inhibitors and NSAIDs have been shown to decrease the risk of various cancers, including colon and lung cancers, suggesting that the down-regulation of COX-2 could be one of the molecular mechanisms for the treatment of human malignancies. Recently, it has been found that FoxM1 directly or indirectly regulates COX-2 expression 45. Inhibition of FoxM1 by either siRNA transfection or by its inhibitors reduces COX-2 expression in A549 human lung adenocarcinoma cells. Moreover, FoxM1 transgenic mice show higher expression of COX-2 in MCA/BHT-treated lungs. Abundant COX-2 expression was detected in FoxM1-positive lung tumors, whereas the FoxM1-negative tumors lacked detectable COX-2 expression, suggesting that FoxM1-deficiency is associated with reduced COX-2 expression 45. Furthermore, FoxM1 stimulates COX-2 promoter activity and directly binds to COX-2 promoter [45], and these results clearly suggest an intimate relationship between COX-2 and FoxM1.

FoxM1 and MMP

Tumor metastasis occurs by a series of steps including cell invasion, degradation of basement membranes and the stromal extracellular matrix, ultimately leading to tumor cell invasion and metastasis 46. The MMPs are a family of related enzymes that degrade extracellular matrix, which are considered to be important factors in facilitating tumor invasion. Among these MMPs, MMP-9 and MMP-2 have been considered to be important factors in facilitating invasion and metastases in human cancers because of their roles in the degradation of basement membrane collagen 46. It has been reported that MMP-9 expression is elevated in the liver of FoxM1b transgenic mice [47]. Recently, it has been shown that MMP-2 inhibition abrogates FoxM1 transcriptional activity and down-regulate its downstream signaling effectors such as checkpoint kinase (Chk2)-mediated DNA repair response in irradiated lung cancer cells [48]. We also reported that down-regulation of FoxM1 inhibited MMP-9 and MMP-2 expression in pancreatic cancer cell lines 18, suggesting that FoxM1 could regulated MMPs. Recently, in our recent studies we also found that FoxM1 siRNA inhibited the expression of MMP-9 and MMP-2 in breast cancer cell lines 49, suggesting the role of FoxM1 and MMP's regulation in human malignancies

FoxM1 and Reactive oxygen species (ROS)

ROS, continuously generated from mitochondrial respiratory chain, include superoxide radical (O^{2-}), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$) and singlet oxygen [50]. ROS are

produced continuously *in vivo* under aerobic conditions. Mammalian cells possesses an efficient antioxidant defense system, mainly composed of the enzymes such as glutathione peroxidase (GPx), glutathione S-transferase (GST), superoxide dismutase (SOD), catalase and peroxidases, and also some small molecules of antioxidants, like glutathione (GSH), which can scavenge the excessive ROS produced through cellular metabolism, and make ROS level relatively stable under physiological conditions in order to maintain cellular homeostasis [50]. Very recently, Park et al reported that FoxM1 is a critical regulator of oxidative stress during oncogenesis 22. These authors have identified a negative feedback loop involving FoxM1 that regulates ROS. Specifically, oncogenic Ras requires ROS to induce FoxM1. Moreover, elevated FoxM1 was found to significantly up-regulated the expression of ROS scavenger genes, such as MnSOD and catalase 22. These results suggest a promising strategy in which FoxM1 inhibitor could be useful for reducing the higher levels of endogenous ROS and thereby may prevent carcinogenesis or will cause reduction in the severity of cancer.

FoxM1 and vascular endothelial growth factor (VEGF)

Many studies have shown that VEGF is a critical mediator of angiogenesis and it regulates most of the steps in the angiogenic cascade including proliferation, migration, and tube formation of endothelial cells [51]. In addition, studies have shown that VEGF promotes migration and invasion of human cancer cells [51]. The results of these investigations also suggested a trend towards an association between the expression of VEGF and distant metastasis. It has been reported that FoxM1 regulates VEGF signaling in various cell types [52]. Li et al reported that FoxM1b expression was significantly correlated with VEGF expression in human gastric cancer. Moreover, FoxM1b directly regulates the expression of the *VEGF* gene at the transcriptional level, which seemed to require intact Sp1 signaling [20]. Zhang et al also reported similar results in glioma cells, suggesting that FoxM1 contributes to glioma progression by enhancing VEGF expression and thereby inducing tumor angiogenesis [53]. Interestingly, we recently found a significant reduction of VEGF expression and secretion in pancreatic cancer cells by FoxM1 down-regulation. We also found a marked increase in the activity of VEGF in FoxM1 cDNA transfected cells [18] and these results are consistent with our findings in breast cancer cells [49]. These provocative results clearly suggest that the inhibition of FoxM1 could be useful for the inhibition of VEGF, which is likely to have a significant impact in the inhibition of angiogenesis and tumor pregression.

FoxM1 and c-Myc

Almost all types of human cancers show high frequencies of c-Myc amplification or over-expression of its protein product, c-Myc [54]. c-Myc can induce cyclin D1 which interacts with CDK4 and CDK6 to promote cell cycle progression [54]. FoxM1c has been found to transactivate the human c-myc promoter directly via the two TATA boxes P1 and P2 [55]. Moreover, FOXM1c transactivates the P1 and P2 promoters synergistically with Sp1, a transcription factor known to bind and transactivate these two promoters [56]. Furthermore, the key proliferation signal cyclin E/Cdk2 could enhance the transactivation of the c-myc promoter by FoxM1c, but P/CAF and the adenoviral oncoprotein E1A repressed this transactivation [57]. Recently, it was found that FoxM1c activated Bmi-1 expression via c-Myc [58] and interestingly, Zeng et al found that c-myc is a downstream gene of FoxM1 in gastric cancer [59]. These results clearly suggest a link between c-myc and FoxM1; however further in-depth molecular investigations are needed for exploiting these pathways for targeted cancer therapy.

FoxM1 and p53

The p53 is a stress response protein that acts primarily as a transcription factor to regulate a large number of genes involved in a variety of cellular insults, including oncogene activation and DNA damage [60]. It is well known that p53 plays a role as tumor suppressor in human.

Many studies have shown the connection between p53 and FoxM1 in human cancer. For example, it is known that the induction of FoxM1c expression markedly suppressed senescence and expression of p53 and $p21^{cip1}$ [58], whereas down-regulation of FoxM1 increased transcriptional activity of p53 and $p21^{cip1}$ [61]. It has been shown that p53 is required for the down-regulation of FoxM1. Specifically, p53 facilitates the repression of FoxM1 expression after DNA damage. Moreover, p53-mediated inhibition of FoxM1 is partially $p21^{cip1}$ and Rb family dependent [62]. FoxM1 inhibotors, such as siomycin A and thiostrepton, stabilize the expression of p53 [63]. However, in gastric cancer cells, FoxM1 depletion leads to cellular senescence and consequently impaired clonogenic growth, which was significantly dependent on $p27^{kip1}$ induction, with and without inactivation of p53 and/or p16 [59].

FoxM1 and HIF-1

HIF-1 consists of α and β subunits and is a major transcription factor involved in cell response to hypoxia [64]. Cellular levels of HIF-1α and APE1/Ref-1 (apurinic/apyrimidinic endonuclease 1/redox factor-1) redox stabilization of the HIF-1α protein are critical for its nuclear translocation and DNA binding and transcriptional activity [64]. Recently, it has been found that hypoxia up-regulates FoxM1 expression at both mRNA and protein levels in several cancer cells 65. Up-regulation of FoxM1 was due to direct binding of HIF-1 to the HIF-1 binding sites in the FoxM1 promoter. Moreover, FoxM1 was essential for growth and proliferation of hypoxic cancer cells. Furthermore, this induction of FoxM1 leads to promotion of tumor cell proliferation by increased cyclin B1 and cyclin D1 expression and decreased nuclear levels of p21 protein 65. These studies suggest that the FoxM1 is induced by hypoxia, and is required for tumor progression.

FoxM1 and proteasome pathway

The ubiquitin-proteasome pathway has been extensively studied in human cancers due to its important role in regulating cell proliferation and cell death [66]. It has been well known that the balance of cell proliferation and cell death was regulated by cell growth inducers and growth inhibitors. In cancer cells, an altered balance between cell growth inducers and inhibitors leads to deregulated growth and inhibition of apoptotic pathways. Thus, proteasome inhibition is a desirable targeted approach for the treatment of human malignancies. Proteasome inhibitors are found to induce cell death rapidly and selectively in oncogene-transformed but not normal or untransformed cells [66]. Many natural and synthetic inhibitors of proteasome have been developed, which include bortezomib, MG115, MG132, lactacystin, peptide aldehydes, peptide boronates, etc. [66]. Recently, it was found that FoxM1 is a general target for proteasome inhibitors [63]. MG115, MG132 and bortezomib inhibit FoxM1 transcriptional activity and FoxM1 expression. Moreover, over-expression of FoxM1 specifically protected cells against cell death induced by proteasome inhibitors [63], suggesting that inhibition of FoxM1 may be required for the antitumor activity of proteasome inhibitors.

Overall perspectives on the role of FoxM1 as a novel target for cancer therapy

FoxM1 signaling has been demonstrated to maintain a balance between cell proliferation, differentiation and apoptosis. An abnormal activation of FoxM1 gene is one of the hallmarks of human malignancies [2]. A growing body of literature strongly suggests that increased expression of FoxM1 gene was detected in many human cancer cells and tissues such as those of the pancreas, breast, non-small cell lung cancers, basal cell carcinomas, hepatocellular carcinomas, glioblastomas, prostate cancer, and cervical cancer [2,3,7,13-18,67]. These results clearly suggest that inactivation of FoxM1 signaling by novel approaches would have a significant impact in cancer therapy. Therefore, FoxM1 appears to be an attractive target for therapy and given the emerging data describing the significant role of FoxM1 in the progression

of human cancers, Radhakrishnan et al. have rightly pointed out that, by inhibiting this single transcription factor, it should be possible to target multiple facets of tumorigenesis [68].

Recently, we have reported that docetaxel (taxotere) alone or in combination with estramustine down-regulated the expression of FoxM1 in prostate cancer leading to cell growth inhibition and induction of apoptosis [69,70]. Other investigators have reported FoxM1 down-regulation using drugs, namely antibiotic thiazole compound Siomycin A, thiostrepton, and EGFR inhibitor Gefitinib 68,71. Very recently, Bhat et al found that proteasome inhibitors, such as MG115, MG132 and bortezomib could inhibit FoxM1 transcriptional activity and its expression [63]. Moreover, the FoxM1 inhibitors including Siomycin A, thiostrepton also act as proteasome inhibitors [63]. These observations clearly suggest that chemical compounds that target FoxM1 may act as anticancer drugs; however further in-depth pre-clinical studies are needed to find the right combinations for the inactivation of FoxM1 and its intimate partners in the crime toward better treatment of human malignancies.

One of the major challenges is to eliminate unwanted toxicity associated with the chemical inhibitors, especially the cytotoxicity in the gastrointestinal tract. Therefore, we sought to find novel avenues by which FoxM1 could be inactivated, which may represent a promising strategy for the development of novel and selective anti-cancer therapies. Most of the known chemopreventive agents that are currently being studied were found in “natural products” or their synthetic derivatives 72, suggesting that the compounds found in the nature is a rich resource for cancer prevention and therapy. Many natural compounds, particularly plant products and dietary constituents, have been found to exhibit cancer chemopreventive activities 72,[73]. Studies from our laboratory have shown that chemopreventive agents such as 3,3′-diindolylmethane (non-toxic agents from dietary sources) may inhibit FoxM1 activation in breast cancer cells leading to apoptotic cell death [74]. These novel preliminary reports clearly demonstrate that chemopreventive agents could be useful for the inhibition of FoxM1 and is likely to have beneficial effects toward cancer therapy. However, further in-depth studies including mechanistic *in vitro* studies, *in vivo* animal experiments and clinical trials are needed to fully appreciate the consequence of the down-regulation of FoxM1 signaling by non-toxic dietary chemopreventive agents. We believe that this article could stimulate further research in this field for the development of non-toxic approaches for cancer therapy by targeting FoxM1 signaling by single agents or by using a combination approach for designing better treatment strategies for the prevention and/or treatment of human malignancies.

Conclusion

The emerging evidence from *in vitro* and *in vivo* studies reviewed above demonstrate that FoxM1 signaling plays important roles in the pathogenesis and progression of cancer by cross-talking with multiple cell signaling pathways (Figure-1). Therefore, the FoxM1 signaling pathway may be a promising therapeutic target, and thus the development of agents that will target FoxM1 is likely to have significant therapeutic impacts on for treatment of human cancers. It is important to note that several FoxM1 inhibitors could be useful for targeted inactivation of FoxM1 signaling, which indeed could become useful for the prevention and treatment of cancer. However further in-depth mechanistic studies, *in vivo* animal experiments, and novel clinical trials are needed to fully appreciate the effects of FoxM1 inhibitors in the combination treatment with conventional cancer therapies. Moreover, it is tempting to speculate that we are going to witness rapid developments in the areas assessing the biological significance of chemopreventive agents that could be a safer approach for targeted inactivation of FoxM1, which could be a novel strategy for the prevention of tumor progression and/or successful treatment of human malignancies in the future.

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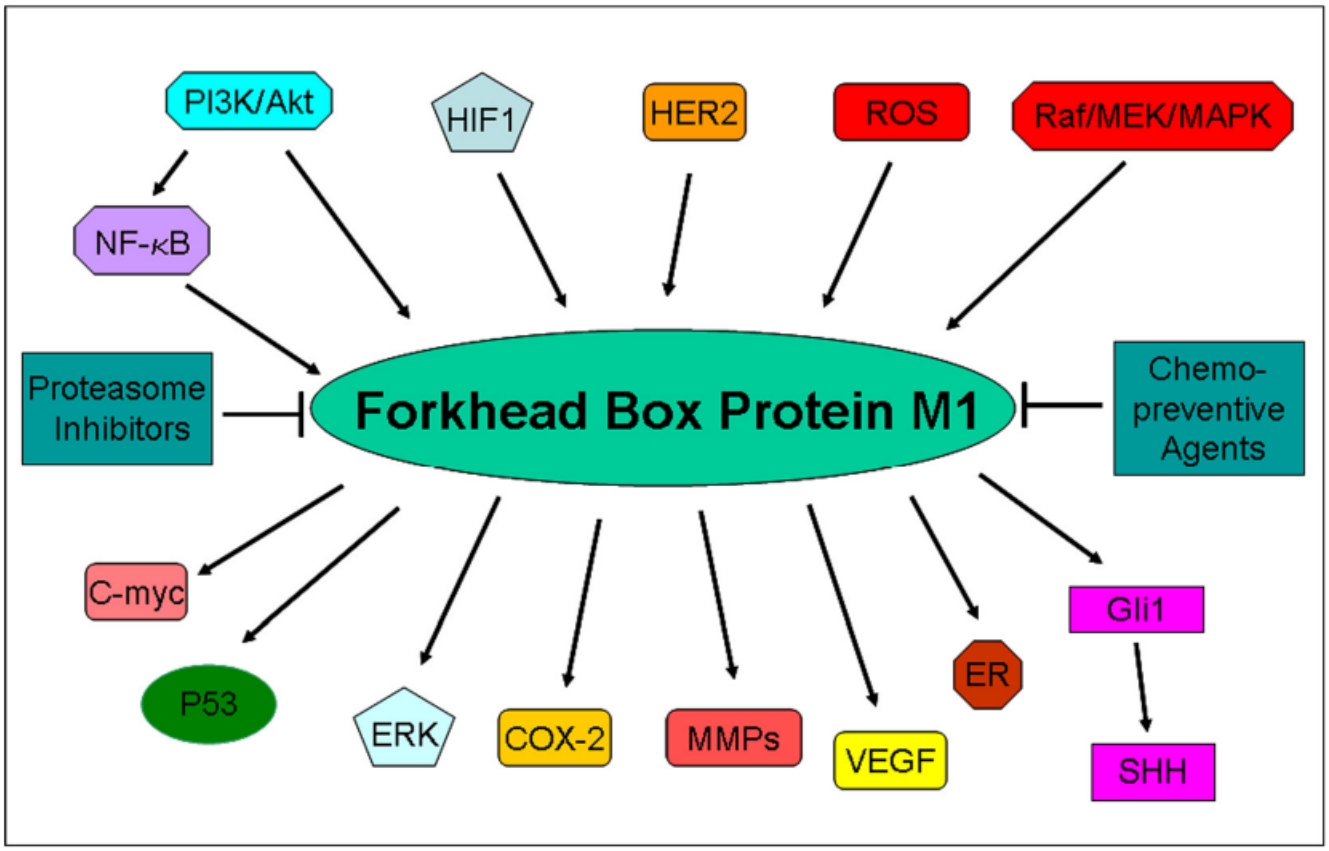

Figure-1.

Diagram of FoxM1 cross-talking with other pathways. COX-2: cyclooxygenase-2; ER: estrogen receptor; ERK: extracellular signal-regulated kinase; HIF1: hypoxia-inducible factor 1; MAPK: mitogen-activated proteinkinase; MMPs: matrix metalloproteinases; NF-κB: nuclear factor-κB; PI3K: phosphatidylinositol 3-kinase; ROS: reactive oxygen species; SHH: sonic hedgehog; VEGF: vascular endothelial growth factor.