MINI-REVIEW

FoxM1 as a Novel Therapeutic Target for Cancer Drug Therapy

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Abstract

Background: Current cancer therapy mainly focuses on identifying novel targets crucial for tumorigenesis. The FoxM1 is of preference as an anticancer target, due to its significance in execution of mitosis, cell cycle progression, as well as other signal pathways leading to tumorigenesis. FoxM1 is partially regulated by oncoproteins or tumor suppressors, which are often mutated, lost, or overexpressed in human cancer. Since sustaining proliferating signaling is an important hallmark of cancer, FoxM1 is overexpressed in a series of human malignancies. Alarge-scale gene expression analysis also identified FoxM1 as a differentially-expressed gene in most solid tumors. Furthermore, overexpressed FoxM1 is correlated with the prognosis of cancer patients, as verified in a series of malignancies by Cox regression analysis. Thus, extensive studies have been conducted to explore the roles of FoxM1 in tumorigenesis, making it an attractive target for anticancer therapy. Several antitumor drugs have been reported to target or inhibit FoxM1 expression in different cancers, and down-regulation of FoxM1 also abrogates drug resistance in some cancer cell lines, highlighting a promising future for FoxM1 application in the clinic.

Keywords: FoxM1 - expression - prognosis - mechanism - drug resistance

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Introduction

Forkhead box M1 (FoxM1), a nuclear protein that influences multiple proteins and enzymes required for mitosis and cytokines, is essential for normal cell cycle execution during G1-S, G2 and M phase transitions (Myatt and Lam, 2007). Since rapid traverse of the cell cycle is essential for tumorigenesis, most cancer would thus produce large amounts of FoxM1 to sustain their rapid growth, enabling FoxM1 as one of the most stable tumor markers. In addition, clinical investigations revealed that overexpressed FoxM1 was correlated with tumor features, such as size, stage, differentiation, invasion, metastasis, and eventually, correlated with the prognosis of cancer patients (Sun et al., 2011b).

Great efforts have been put to explore the underlying mechanisms of FoxM1 in tumorigenesis. The current studies of FoxM1 were mainly focused on the cell cycle progression, apoptosis, senescence, angiogenesis, invasion, migration and proliferation (Koo et al., 2012). Thus, many anticancer drugs targeting or inhibiting FoxM1 were subsequently developed.

This present review will focus on the literature describing the expression of FoxM1 in human tumors, investigating the clinical prognostic roles of FoxM1 expression, or indicating the potential use of anti-cancer drugs targeting/inhibiting FoxM1. Furthermore, we also tried to explore the possible mechanisms of FoxM1 involved in tumorigenesis, summarizing the FoxM1 molecular pathway raised by current studies. Results showed that FoxM1 plays significant roles in the process of tumorigenesis, indicating the potential clinical application of FoxM1 in the near future.

Overexpression of FoxM1 in Human Cancers

FoxM1 is essential for cell growth and survival. Previous studies showed that organ defects in FoxM1 -/- mice was probably due to lack of progenitor cell proliferation, suggesting that FoxM1 was not only expressed in proliferating cells, but might also be required for proliferation in normal cells (Korver et al., 1998). Similarly, with respect to the FoxM1 ubiquitously expressed model, the overexpressed FoxM1 was correlated with the lung cell proliferation after tissue injury, indicating the potential proliferating roles of FoxM1 in different cell lines (Kalinichenko et al., 2003).

Since sustaining proliferation signaling was recognized as one of the most important hallmarks of cancer, increasing expression of such related genes and the signals manifested in their products would result in increased cancer proliferation and tumor growth. Thus, there were consensus that FoxM1 were up-regulated in most malignancies. Advances in high-throughput technologies such as microarray and next-generation sequencing for gene expression profiles have reinforced the discovery of predictive biomarkers (Dang et al., 2014). Accordingly, a large-scale gene expression analysis identified FoxM1

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as one of the most differentially-expressed genes in most solid tumors, enabling the FoxM1 as a consistent tumor marker in cancer (Okabe et al., 2001). Great efforts have then been put into identifying the expression level of FoxM1 in different types of cancer tissues. Usually, the definition of FoxM1 overexpression was based on the immunohistochemistry staining or realtime PCR. When the expression level of FoxM1 was significantly higher in cancer tissues than the corresponding paracancer or normal tissues, it was defined as overexpression. We have previously demonstrated the overexpression level of FoxM1 in hepatocellular carcinoma and gallbladder carcinoma by immunohistochemical staining. We also observed some relationship between the FoxM1 expression and specific clinical characteristics of cancer patients, which we will discuss later (Wu et al., 2010; Qu et al., 2013; Wang et al., 2013a). Similar studies have also verified the overexpressed FoxM1 level in a series of malignancies, including liver cancer, pancreatic cancer, gallbladder cancer, gastric cancer, colorectal cancer, esophageal cancer, laryngeal cancer, thyroid cancer, lung cancer, pleural mesothelioma, breast cancer, ovarian cancer, cervical cancer, bladder cancer, renal cancer, nerve sheath tumor, lymphoma and leukemia (Table 1). Mechanisms of such overexpression level has been extensively explored, and some suggested that the expression level of FoxM1 was partially regulated by oncogenes and tumor suppressors, which are often mutated, lost, or overexpressed in human cancer, such as P53, HER2, and c-Myc.

Correlation between FoxM1 Expression and Clinicopathological Features in Human Cancers

Clinical investigations revealed that the overexpressed FoxM1 was correlated with specific characteristics of tumors. By correlation analysis, FoxM1 was found to be overexpressed in the more aggressive tumors. For example, in lung cancer, liver cancer and thyroid cancer, FoxM1 was correlated with the more aggressive phenotypes, including poor differentiation, advanced stage, larger tumor size and more tumor numbers (Yang et al., 2009; Sun et al., 2011b; Ahmed et al., 2012; Xia et al., 2012b; Xu et al., 2012). In colon cancer, gastric cancer and lung cancer, higher expression of FoxM1 also accounted for the increased incidence of lymph node metastasis and distant metastasis (Li et al., 2009; Xu et al., 2012; Li et al., 2013a). Thus, the increased tumor progression and aggressiveness would eventually affect the prognosis of these cancer patients.

Series of studies have focused on the relationship between FoxM1 expression and prognosis, and got almost consistent results that higher FoxM1 expression level was correlated with poorer prognosis of cancer patients. We summarized the eligible studies that focused on the FoxM1 expression and prognosis by cox regression, the details of which were listed in Table 2 (Bektas et al., 2008; Li et al., 2009; Yang et al., 2009; Jiang et al., 2011; Priller et al., 2011; Sun et al., 2011a; 2011b; Yu et al., 2011; Chu et al., 2012; He et al., 2012; Xia et al., 2012a; 2012b; Xue et al., 2012; Li et al., 2013a; 2013b; Okada et al., 2013; Wang et al., 2013a; 2013b; Wu et al., 2013; Xu et al., 2013). Studies were eligible if they reported a risk estimate [e.g., hazard ratio (HR) or relative risk (RR) relating FoxM1 expression to subsequent death using survival analysis regression

Table 1. Disregulation of FoxM1 in Human Tumors

Tumor with FoxM1 Overexpression
Hepatocellular carcinoma, Intrahepatic cholangiocarcinoma, Gallbladder carcinoma, Pancreatic cancer, Gastric cancer, Colorectal cancer, Esophageal carcinoma, Laryngeal carcinoma, Nasopharyngeal carcinoma, Neck squamous cell carcinoma, Thyroid cancer, Lung cancer, Pleural mesothelioma, Glioblastoma, Medulloblastoma, Meningioma, Basal cell carcinoma, Renal cancer, Uterine cancer, Bladder cancer, Breast canccer, Ovarian cancer, Cervical cancer, Prostate cancer, Testicular cancer, Acute myeloid leukemia, Diffuse large B-cell lymphoma

Table 2. Characteristics of Eligible Studies Focusing on FoxM1 Expression and Prognosis by Cox Regression

Author	malignancy	treatment	No. of patients	FoxM1 evaluation
Xue YJ (YJ Xue et al. 2012)	renal cancer	nephrectomy	83	immunstaining
Wu XR (XR Wu et al. 2013)	renal cancer	nephrectomy	87	immunstaining
Xia JT (JT Xia et al. 2012)	pancreatic cancer	surgical resection	80	immunstaining
Yu JS (J Yu et al. 2011)	nerve sheath tumor	surgical resection	87	immunstaining
Xu N (N Xu et al. 2013)	lung cancer	lobectomy	175	immunstaining
Wang Y (Y Wang et al. 2013)	lung cancer	surgery, chemotherapy	162	immunstaining
Yang DK (DK Yang et al. 2009)	lung cancer	lobectomy	69	immunstaining
Jiang LZ (LZ Jiang et al. 2011)	laryngeal cancer	surgical resection	89	immunstaining
Xia LM (L Xia et al. 2012)	liver cancer	hepatectomy	136	immunstaining
Sun HC (HC Sun et al. 2011)	liver cancer	hepatectomy	151	immunstaining
Sun HC (H Sun et al. 2011)	liver cancer	liver transplantation	99	immunstaining
Wang RT (R Wang et al. 2013)	gallbladder cancer	surgical resection	92	immunstaining
Okada K (K Okada et al. 2013)	gastric cancer	surgery, chemotherapy	77	immunstaining
Li X (X Li et al. 2013)	gastric cancer	gastrectomy	103	immunstaining
Li Q (Q Li et al. 2009)	gastric cancer	gastrectomy	86	immunstaining
Li DW (D Li et al. 2013)	colon cancer	colectomy	185	immunstaining
Chu XY (XY Chu et al. 2012)	colon cancer	colectomy	112	immunstaining
He SY (SY He et al. 2012)	cervical cancer	hysterectomy	102	immunstaining
Bektas N (N Bektas et al. 2008)	breast cancer	surgical resection	204	immunstaining
Priller M (M Priller et al. 2011)	medulloblastoma	surgical resection	43	immunstaining

models], and they reported an estimate of precision, such as a standard error or 95%CI. We also included articles that failed to report precision directly but from which we could reconstruct an estimate of precision using P values and other study data (Parmar et al., 1998).

We could see that FoxM1 could be a stable prognostic marker in different types of cancer patients who underwent surgical resection or chemotherapy, including renal cancer, pancreatic cancer, nerve sheath tumor, lung cancer, laryngeal cancer, liver cancer, gallbladder cancer, gastric cancer, colon cancer, cervical cancer, breast cancer and medulloblastoma. Figure 1 displayed a plot of HRs and the associated 95%CIs for overall survival (OS) (A) and tumor-free survival (TFS) (B) from each study. Higher FoxM1 expression was associated with a decrease in OS and TFS in different kinds of cancer, with a pooled HR for OS across all studies of 2.02 (95%CI, 1.77-2.30), with significant evidence of heterogeneity (I^2=63%, p<0.001), and with a pooled HR for TFS across all studies of 1.71 (95%CI, 1.42-2.05), with no obvious heterogeneity (I^2=0%, p=0.466), indicating the relationship of FoxM1 with poor overall and tumor-free survival.

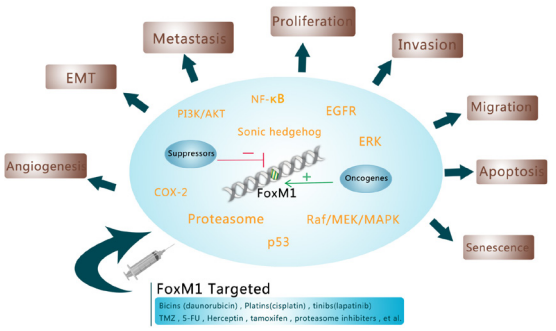

Figure 2. Drugs Targeting FoxM1 Signaling and Its Interaction with Other key signaling pathways in Tumorigenesis, Highlighting the Application of FoxM1 Targeted Drugs in Clinic in the Near Future

Possbible mechanisms

As a promising prognostic marker of cancer, great efforts have been put to explore the underlying mechanisms of FoxM1 in tumorigenesis, such as the cell cycle progression, apoptosis, senescence, angiogenesis, proliferation, invasion and migration (Koo et al., 2012). We have previously discovered that the knockdown of FoxM1 by siRNA interference would decrease cell proliferation, induce cell cycle arrest, and inhibit cell

Table 3. Drugs Targeting FoxM1 or Assoicated with FoxM1-Related Durg Resistance, in Different Cancer Cell-Lines

Drug	Malignancy	Cell-lines	Drug	Malignancy	Cell-lines
Thiostrepton	breast cancer	MCF-7, MB-231	troglitazone	liver cancer	HepG2
ovarian cancer	OVCA433	pioglitazone	liver cancer	HepG2	
colorectal cancer	HCT-15, HCT-116	rosiglitazone	liver cancer	HepG2	
thyroid cancer	TPC-1	BI2536	esophageal cancer	OE33	
osteosarcoma	U2OS	casticin	liver cancer	HepG2	
pancreatic cancer	PaCa-2	5-fluorouracil	breast cancer	MCF-7	
Daunorubicin	breast cancer	MCF-7	olaparib	liver cancer	HepG2
liver cancer	HepG2	TMPP	leukemia	U937, YRK2	
osteosarcoma	U2OS	natura-α	prostate cancer	LNCaP	
colorectal cancer	HCT-116	DIM	breast cancer	MB-231, MB-468, SKBR3, MCF-7	
Doxorubicin	breast cancer	MCF-7, MB-231	Ursolic acid	breast cancer	MCF-7
colorectal cancer	HCT-116	DFOG	ovarian cancer	SKOV3, CoC1	
liver cancer	Hep3B		gastric cancer	AGS, SGC-7901	
pancreatic cancer	PaCa-2	genistein	pancreatic cancer	BxPC-3, HPAC, PaCa-2, PANC28	
Epirubicin	breast cancer	MCF-7, MB-453		prostate cancer	PC-3, LNCaP, C4-2B
osteosarcoma	U2OS		ovarian cancer	SKOV3, CoC1	
Cisplatin	breast cancer	MCF-7		gastric cancer	AGS, SGC-7901
lung cancer	A549	ICI182780	breast cancer	MCF-7, ZR-75-1	
Oxaliplatin	liver cancer	HepG2, SMMC7721	docetaxel	prostate cancer	LNCaP, PC-3, C4-2B
Tamoxifen	breast cancer	MCF-7, ZR-75-1		breast cancer	MCF-7, SKBR3, MB-231, MB-468
Herceptin	breast cancer	SKBR3, BT474, MB-453	mithramycin	liver cancer	HepG2
Gefitinib	breast cancer	BT474, SKBR3	Siomycin A	colorectal cancer	SW480, SW620
lung cancer	NCI-H292, SPC-A-1		osteosarcoma	U2OS	
Lapatinib	breast cancer	SKBR3, BT474	nutlin-3	osteosarcoma	U2OS
Imatinib	CML	K562		colorectal cancer	HCT-116
Vemurafenib	melanoma	A375, 501mel	MG132	pancreatic cancer	Paca-2
Bortezomib	osteosarcoma	U2OS		breast cancer	MB-231
pancreatic cancer	Paca-2			colorectal cancer	HCT-116
breast cancer	MB-231				
colorectal cancer	HCT-116				

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

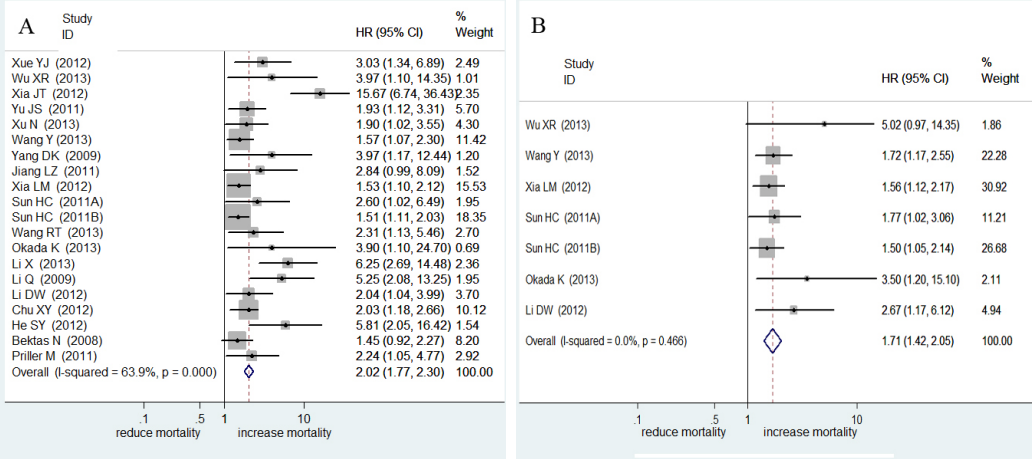

Figure 1. Forest Plots Representing Hazard Ratios of Prognosis in Cancer Patients Associated with FoxM1 expression. A) pool analysis of FoxM1 expression on overall survival in different tumors; B) Pool Analysis of FoxM1 expression on tumor free survival in different tumors

invasion in HCC cell lines (Wu et al., 2010). In addition, we successfully enhanced the oxaliplatin-induced senescence in hepatocellular carcinoma by the negative regulation of FoxM1 via P53 (Qu et al., 2013). Similarly, as the small molecule inhibition was thought to be the most promising method of inhibiting FoxM1, large numbers of studies have successfully applied the siRNA method to verify the anti-tumor effect of targeting FoxM1 in different kinds of cancer. However, deeper mechanisms of how the FoxM1 tumorigenesis worked are still needed to be illucidated.

Previous studies demonstrated that FoxM1 is a key regulator for G1/S, G2/M transition, and M phase progression. FoxM1's participation in tumorigenesis is largely due to its role in cell cycle progression and proliferation. The impact of FoxM1 on the expression of cell division genes are significant for cancer development and progression. It also cooperates with other cell cycle regulators and oncogenes to promote proliferation signals in cancer cells. For example, the activated RAS increases the expression of FoxM1, which is critical for RAS-induced transformation. Consistent with that, expression and transcriptional activity of FoxM1 are also regulated by the tumor suppressor genes, such as p53.

Several significant pathways were reported to be involved in the overexpression of FoxM1, such as PI3K/AKT pathway, NF-κB pathway, EGFR pathway, Raf/MEK/MAPK pathway, ERK pathway, Sonic hedgehog pathway, COX-2 pathway, and proteasome pathway (Wang et al., 2010). With respect to PI3K/AKT pathway for example, the PI3K inhibitors LY294002 and Wortmanin, could eliminate the expression of FoxM1 in osteosarcoma and prostate cancer via PI3K/AKT pathway (Wang et al., 2010). As in NF-κB pathway, inhibition of NF-κB by IκBα repressor in the MEFs could abrogate both the IKKβ-mediated induction of NF-κB targets and repression of the FoxM1 targets (Penzo et al., 2009). In EGFR pathway, a significant correlation was found in breast cancer, that FoxM1 expression was correlated with HER2, one of the most important members of EGFR family. HER2 regulates the FoxM1 expression at both mRNA and protein levels (Francis et al., 2009). Ma et al. found that Raf/MEK/MAPK is necessary for the nuclear translocation of FoxM1. The activation of the Raf/MEK/MAPK pathway enhances the transactivation of FoxM1 on the cyclin B1 promoter, while blocking the MAPK pathway could diminish FoxM1 transcription, indicating the cross-talks between Raf/MEK/MAPK and FoxM1 in human malignancies (Major et al., 2004). As in ERK pathway, FoxM1 degrades of the DUSP1 through transcriptional activation of CKS1 and SKP2, thus sustaining ERK activity in human HCC (Calvisi et al., 2009). In Sonic hedgehog pathway, FoxM1 was found at the downstream of Gli1 and Sonic hedgehog pathway, that FoxM1 expression was closely correlated with the Sonic hedge expression, suggesting the cross-talks between FoxM1 and Sonic hedgehog pathway via Gli1 in basal cell carcinoma, lung cancer and colorectal cancer (Douard et al., 2006; Gialmanidis et al., 2009). Some studies also reported that FoxM1 could regulate the COX2 expression directly or indirectly, indicating the involvement in the COX2 pathway (Wang et al., 2008). Recently, Gartel et al. (2009) reported that FoxM1 might be a general target of proteasome inhibitors such as MG115, MG132 and lactacystin, suggesting the important roles of FoxM1 in the proteasome pathway (Bhat et al., 2009).

Besides the various pathways discussed above, there were also close relationship between FoxM1 and lots of significant molecules involved in carcinogenesis, such as estrogen receptor, MMP, ROS, VEGF, c-Myc, Hif-1, and so on (Wang et al., 2010). Therefore, we conclude that FoxM1 plays important roles in the pathogenesis and progression of cancer by crosstalking with multiple cell signaling pathways and key molecules involved in carcinogenesis, revealing its potential application in the anticancer treatment.

Anticancer Drugs Targeting Foxm1 and Drug Resistance

Cancer can be defined as a disease in which a group of abnormal cells grow uncontrollably by disregarding the normal rules of cell division (Topcul and Cetin, 2014).

Conventional chemotherapy is used to treat cancer patients by stoping cancer cells from multiplying and spreading. However, although chemotherapy drugs are particularly toxic to cancer cells, they also damage healthy cells (Ray-Coquard et al., 2001). These side effects sometimes prevent patients from taking enough doses to inhibit cancer. Thus, specific targeted cancer therapies have been developed to avoid the unspecific toxicity, reducing the risk of damaging healthy tissue.

FoxM1, which has attracted much attention as a potential target for the prevention and therapeutic intervention in human cancers, was widely evaluated in the clinical study in this respect. Many anticancer drugs targeting or inhibiting FoxM1, directly or indirectly, were thus developed, including Bicins (daunorubicin), Platins (cisplatin), Tinibs (lapatinib), TMZ, 5-FU, herceptin, tamoxifen, proteasome inhibitors, and so on, which highlighted the potential clinical application of FoxM1 study in the near future (Table 3) (Wierstra, 2013a; 2013b). Most of these drugs repress the FoxM1 promoter directly, inhibiting FoxM1 expression in a dose-dependent manner. For example recently, a high through-put screen identified a thiazole compound Siomycin A as potential FoxM1 inhibitors (Radhakrishnan et al., 2006). Subsequent studies revealed that cancer cells treated by Siomycin A would have a decrease in FoxM1 transcriptional activity, leading to a reduction in FoxM1 target genes such as Cdc25B, Survivin and CENPB (Radhakrishnan et al., 2006). What's more, recently, close relationship between miRNA and FoxM1 were demonstrated. Zhang et al. (2012) reported that miR-370 significantly targeted FoxM1 in acute myeloid leukemia, revealing another possible way of inhibiting FoxM1expression in clinic in the near future (Zhang et al., 2012).

One major challenge in targeted cancer therapy is drug resistance, since long-term drug treatment ultimately selects the worst tumor cells to survive and proliferate. Therefore, it is in urgent need to figure out strategies to overcome this resistance, perhaps via regulating some important molecules involved in drug resistance. Thus, the implication of FoxM1 in tumorigenesis makes it an attractive target for alleviating drug resistance.

Series studies have therefore focused on the roles of FoxM1 in regulating drug resistance in chemotherapy. In breast cancer for instance, which is the most widely used tumor type for drug resistance, FoxM1 is down-regulated in the sensitive cells but is maintained or induced in the resistant cells (Kwok et al., 2010). In these drugs, cisplatin, a very potent agent forming the platinum-adducts on genomic DNA, resulted in DNA damage and cell death. In MCF-7 cell line, cisplatin treatment activates DNA repair in the resistant MCF-7-CISR, but not in MCF-7 cells. The expression of active FoxM1 in cisplatin sensitive MCF-7 cells also confers resistance, whereas silencing of FoxM1 can resensitise the cells to drugs (Kwok et al., 2010). Similar studies were conducted in a series of different human malignancies, and specific drugs targeting FoxM1 or assoicated with FoxM1-related drug resistance were summarised and listed in Table 3. In general, these drugs caused significant apoptosis in cancer cells, while depletion of FoxM1 augmented the drug-induced apoptosis, as represented by caspase-3, caspase-8, and so on. Such data strongly implied that FoxM1 can promote resistance through enhancing DNA damage repair. Therefore targeting FoxM1 is promising in circumventing acquired drug resistance.

Highlights and Perspectives

In general, FoxM1 is involved in several cellular processes crucial to tumorigenesis. Preliminary clinical studies have indicated the predictive roles of FoxM1 on the prognosis of cancer patients. Multivariate analysis revealed that higher expression level of FoxM1 were correlated with the poorer prognosis of patients in a series of malignancies. The unique role of FoxM1 in the tumorigenesis of certain tissues offers exciting prospects for cancer-tissue-specific therapeutic initiatives (Myatt and Lam, 2007). The tissue-specific role of FoxM1 raises the possibility that anti-FoxM1 therapeutic strategies may have lower toxicity in normal tissues that display compensatory mechanisms compared with malignant cells.

FoxM1-targeted drugs are able to induce apoptosis and cell death as single agent in a broad spectrum of tumor cell lines and *in vivo* xenograft models. They were also shown of the ability to overcome drug resistance and to synergize with a number of conventional therapies. Although pre-clinical studies of FoxM1 have shown the highlights in the future clinical study, additional investigations are still anticipated to dig into the tumorigenesis role of FoxM1 in various malignancies, and the possibility of FoxM1 to work best as a component of combination therapy. Furthermore, in-depth *in vivo* animal experiments, and novel clinical trials are also needed to fully appreciate the effects of FoxM1 targeting therapies.

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