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Review

Targeting FOXM1 in cancer

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ABSTRACT

Oncogenic transcription factor FOXM1 is overexpressed in the majority of human cancers. In addition, FOXM1 has been implicated in cell migration, invasion, angiogenesis and metastasis. The important role of FOXM1 in cancer affirms its significance for therapeutic intervention. Current data suggest that targeting FOXM1 in mono- or combination therapy may have promising therapeutic benefits for the treatment of cancer. However, challenges with the delivery of anti-FOXM1 siRNA to tumors and the absence of small molecules, which specifically inhibit FOXM1, are delaying the development of FOXM1 inhibitors as feasible anticancer drugs. In this review, we describe and summarize the efforts that have been made to target FOXM1 in cancer and the consequences of FOXM1 suppression in human cancer cells.

Contents

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1. Introduction

Forkhead Box M1 (FOXM1) is a member of the Forkhead family of transcription factors, which are identified by an evolutionarily conserved Forkhead/winged-helix DNA-binding domain [1–4]. FOXM1, is also known in the literature as Trident (mouse) [5], WIN or INS-1 (rat) [2], FKHL-16 [1], MPP-2 (partial human cDNA) [6] or HFH-11 (human) [3]. The FOXM1 protein exists in three different isoforms. Among them the FOXM1b and FOXM1c splice variants are transcriptionally active while FOXM1a is transcriptionally inactive [2–4]. For clarity, we refer to the alternative transcripts as FOXM1 in this review.

Initially, FOXM1 was described as an exclusively proliferation-specific mammalian transcription factor [4,7]. FOXM1 is expressed in proliferating cells, but its expression is excluded from quiescent and terminally differentiated cells [2,3,5]. Both FOXM1 mRNA and protein levels increase at the entry to the S-phase of the cell cycle and remain elevated during the G2 and M-phases [5]. As cells advance through the cell cycle, the transcriptional activity of FOXM1, which depends on its phosphorylation level, also increases and peaks at the G2/M transition. FOXM1 is hyperphosphorylated and transcriptionally fully active by the G2/M-phase as a result of sequential phosphorylation by multiple protein kinases at specific stages of the cell cycle [4,8–10].

However, FOXM1 is not only expressed in dividing cells, but it also controls cell cycle progression. For example, during G1/S transition it activates the transcription of Cdc25A [11], JNK1 [12], members of the Skp-cullin-F-box (SCF) ubiquitin ligase complex, Skp2 and Cks1 [13], thus promoting the Skp2-dependent proteasomal degradation of the Cdk inhibitors $p21^{Cip1}$ and $p27^{Kip1}$. At the G2/M transition and through mitosis FOXM1 is required for the expression of Cdc25B [13,14], cyclin B1 [15,16], Aurora B kinase [13], Polo-like kinase-1 (Plk-1) [16], centromere protein A, B [13] and F [16] (CENP-A, B, F) and survivin [13] to allow mitotic progression, proper assembly of the mitotic spindles, accurate chromosome segregation and cytokinesis [13,16–18].

Since FOXM1 has such an important role in cell proliferation and cell cycle progression, it is not surprising that increased expression of FOXM1 was detected in numerous cancer cell lines and human cancers. One of the early studies found FOXM1 upregulation in basal cell carcinoma (BCC) compared to normal skin samples [19]. A comparative microarray analysis conducted back in 2004 identified FOXM1 as one of the most commonly overexpressed genes in solid tumors of the prostate, lung, bladder, ovary, colon, liver, breast, kidney, stomach and pancreas [20]. In subsequent years, aberrant expression of FOXM1 has been found in a variety of other cancers including cervical cancer [21], malignant mesothelioma [22], glioblastoma multiforme (GBM) [23,24], malignant peripheral nerve sheath tumors (MPNST) [25], medulloblastoma [26], head and neck squamous cell carcinoma (HNSCC) [27], oral cavity squamous cell carcinoma (OCSCC) [28], oropharyngeal squamous cell carcinoma (OPSCC) [29], papillary thyroid carcinoma (PTC) [30], esophageal squamous cell carcinoma (ESCC) [31], laryngeal squamous cell carcinoma (LSCC) [32], nasopharyngeal carcinoma (NPC) [33] meningioma [34] and acute myeloid leukemia (AML) [35]. Also, using the PARADIGM model in order to identify aberrant pathways that affect the development and progression of ovarian cancer, it has been shown that the FOXM1 pathway is significantly activated in ovarian tumors [36]. A large-scale comparative meta-analysis of cancer microarray datasets identified FOXM1 among the genes that are highly expressed in undifferentiated cancer relative to well-differentiated cancer [37]. In general, FOXM1 overexpression in tumors is linked to late tumor stage, high proliferation rate [21,23,31,32] and poor prognosis [23,25,26,32,38–42], suggesting that FOXM1 could serve as a prognostic marker for cancer patients [25,26,38,41–43]. For example, elevated expression of FOXM1 was already detected in ductal carcinoma *in situ* (DCIS), a pre-invasive and curable stage of invasive ductal carcinoma (IDC). Thus, FOXM1 could be an early molecular marker for breast cancer and could be used for early diagnosis to improve prognosis of breast cancer [44].

Interestingly, FOXM1 has also been implicated in such diverse cellular processes as cell migration, invasion, angiogenesis, metastasis, oxidative stress, inflammation, vascular permeability and surfactant homeostasis [45,46]. Over the years it became apparent that FOXM1 drives tumorigenesis not only by increasing proliferation but by affecting several features of cancer development and progression including evasion of the action of tumor suppressors, increasing the resistance of cancer cells to apoptosis, inducing replicative immortaliy, contributing to genomic instability and metabolism. In addition, FOXM1 can promote tumorigenesis in human keratinocytes by expanding the stem/progenitor compartment [47]. Without doubt, the significant and diverse role of FOXM1 in oncogenesis justifies its importance for therapeutic intervention. In this review, we will summarize and discuss the progress that has been made in targeting FOXM1 in cancer.

2. Targeting FOM1 by RNA interference

FOXM1 deletion studies reinforced its role as a critical regulator of cell proliferation and cell cycle progression. Whole body ablation of FOXM1 is embryonic lethal as a result of developmental abnormalities in the liver, the lung and the heart [48–51]. Cell proliferation was diminished in the liver [48] and the lung [49] of FOXM1 knockout mouse embryos. Also, FOXM1-deficient cells displayed polyploidy [13,48,50], suggesting that FOXM1 is important for avoiding DNA rereplication [48,50] and for maintaining genomic stability [16,17]. Moreover, hepatocyte-specific deletion of FOXM1 during liver regeneration significantly reduced DNA replication and inhibited mitosis in regenerating hepatocytes. Reduced hepatocyte proliferation correlated with elevated nuclear level of p21 and diminished expression of Cdc25B [14]. Also, FOXM1-depleted cells were unable to perform faithful chromosome segregation and cytokinesis, thus leading to incomplete mitosis [13,16–18]. All these data are in support of the fact that FOXM1 is not only expressed in proliferating cells, but it plays a key role in normal cell proliferation and cell cycle progression.

Depletion studies also uncovered multiple facets of FOXM1 in oncogenesis. Ablation of FOXM1 by RNA interference (RNAi) decreased proliferation of prostate [52], colon [53], breast [17], lung [54], pancreatic [55], cervical cancer cells [21], osteosarcoma [13], leukemia [35] and nasopharyngeal carcinoma (NPC) cells [33]. $FOXM1^{-/-}$ MEFs senesced prematurely [13] and knockdown of FOXM1 led to an increase in cellular senescence of gastric cancer cells [56] and mAKT1-expressing osteosarcoma cells [57]. Deletion of FOXM1 reduced migration, invasion or angiogenic potential of pancreatic [55], gastric [40], breast [58], colon cancer cells [59], glioma [60,61] and osteosarcoma cells [12] *in vitro*. In addition, RNAi-mediated knockdown of FOXM1 decreased anchorage-independent growth on soft agar in prostate [52], colon [53], gastric [56], breast [58], lung, [54], cervical [21], pancreatic cancer cells [62], glioma [23], osteosarcoma [12], neuroblastoma [63], and NPC [33] cells. FOXM1 ablation caused spontaneous differentiation in neuroblastoma cells, suggesting that FOXM1 is important for maintaining an undifferentiated state, thus promoting tumorigenesis [63] (Table 1).

FOXM1 knockdown in glioma [23,61], neuroblastoma [63] cells, gastric [40] and pancreatic cancer cells [62] compromised tumor growth in xenograft mouse models. Our group described the feasibility of FOXM1 suppression by anti-FOXM1 siRNA in established xenograft breast tumors [64]. Upon direct intratumoral