Targeting FoxM1 Effectively Retards p53-Null Lymphoma and Sarcoma

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Abstract
The forkhead box transcription factor FOXM1 is considered to be a promising target for cancer therapy. However, the significance of FOXM1 in tumors harboring mutation in p53, which is very common, is unclear. In this study, we investigated the efficacy of FOXM1 targeting in spontaneous p53-null tumors using genetic ablation as well as using a peptide inhibitor of FOXM1. We show that conditional deletion of FOXM1 inhibits growth of the p53-null thymic lymphoma and sarcoma cells. In addition, deletion of FOXM1 induces apoptotic cell death of the p53-null tumors, accompanied by reduced expression of the FOXM1 target genes survivin and Bmi1. An ARF-derived peptide that inhibits the activity of FOXM1, by targeting it to the nucleolus, also induces apoptosis in the p53-null sarcoma and lymphoma, leading to a strong inhibition of their metastatic colonization. Together, our observations suggest that FOXM1 is critical for survival and growth of the p53-null lymphoma and sarcoma and provide proof-of-principle that FOXM1 is an effective therapeutic target for sarcoma and lymphoma carrying loss of function mutation in p53. Mol Cancer Ther; 12(5); 759–67. ©2013 AACR.

Introduction
The tumor suppressor p53, encoded by the TP53 gene, is a short-lived transcription factor involved in a wide range of cellular processes that are critical for tumor suppression (1–3). Although p53 is expressed at a low level in normal cells, it serves as a protective barrier against development of many types of cancers mainly through preventing proliferation of the incipient cancer cells, induction of apoptosis, as well as through its role in the maintenance of genome integrity (3). Mice deficient in p53 develop spontaneous tumors including thymic lymphoma and sarcoma (3, 4). The essential role of p53 as a tumor suppressor is further manifested by the fact that the p53 gene is mutated in approximately half of the human cancers (1). Given the high prevalence of p53 inactivation in human cancers, it is important to validate therapeutic strategies targeting cancer cells with loss of p53 function.

The forkhead box transcriptional factor FOXM1 is aberrantly overexpressed in many types of human malignancies including liver, prostate, breast, colon, neural tissue, and others (5–8). FOXM1 facilitates development of cancers in several ways. First, it transcriptionally activates genes involved in cell proliferation and promotes progression through G1–S and G2–M phases of the cell cycle (9, 10). It stimulates expression of DNA repair genes, ensuring the chromosome stability (11, 12). In addition, FoxM1 has been implicated in alleviating oxidative stress in tumor cells by activating reactive oxygen species (ROS) scavenger proteins (13) and mediating resistance (14, 15). A recent study in a mouse hepatocellular carcinoma (HCC) model showed that FOXM1 also functions as a potent activator of tumor metastasis through promoting the epithelial-to-mesenchymal transition, increased motility of the tumor cells, and establishment of the premetastatic niches in the distal target organ (16, 17). Two recent studies in neuroblastoma and embryonic carcinoma cells indicated a role of FOXM1 in the maintenance of the undifferentiated state of the tumor cells by activating pluripotency-associated genes (8, 18).

Given the multifaceted functions of FOXM1 in tumor progression, targeting FOXM1 represents a rational and promising anti-cancer therapeutic strategy. This is further supported by the fact that FOXM1 is a proliferative-specific transcriptional factor whose expression is unique to the proliferating cells (19, 20). Several strategies have been developed to target FoxM1 in cancer cells. On the basis of the fact that FoxM1 is an inhibitory target of mouse ARF tumor suppressor, a cell-penetrating ARF26–44 peptide, which consists of 9 N-terminal D-arginine (D-Arg) residues and amino acid residues 26–44 of the mouse ARF protein was synthesized (6). The ARF26–44 peptide, which inhibits...
FOXM1 by sequestering it to the nucleolus, is effective in diminishing tumor size in HCCs by reducing tumor cell proliferation and inducing apoptosis (21). That ARF peptide also effectively prevents pulmonary metastasis of HCC cells (16). In addition, thiazole antibiotics have been shown to downregulate FOXM1 and induce apoptosis in various cancer cells (22, 23).

In this study, we show that FOXM1 is critical for survival and growth of p53−/− tumor cells both in vitro and in vivo. The ARF36–44 peptide, which inhibits the activity of FOXM1, induces apoptosis in p53-null tumors. These observations validate the therapeutic strategy of targeting FOXM1 in tumors with p53 loss of function.

Materials and Methods

Animals

The CreERT2 strain (strain 01XAB) was obtained from Tyler Jacks’ laboratory (Massachusetts Institute of Technology). Foxm1b fl/fl strain was generated as previously described (24). The C57Bl/6 p53−/− strain was obtained from the Jackson Laboratories. The triple transgenic CreERT2, Foxm1b fl/fl, p53−/− mice were generated by mating the 3 individual strains. Nu/nu nude mice were obtained from Charles River Laboratories. ICR SCID mice were obtained from Taconic Farms.

Establishment of p53-null thymic lymphoma and sarcoma cell lines

Thymic lymphoma tissue was isolated from the thymus of mice and sarcoma was isolated from a tumor encompassing the rear leg of the mouse. Tumors were excised, minced, and enzymatically dissociated with 0.25% trypsin. They were then washed and replaced with fresh media. Thymic lymphoma cells grew in suspension and sarcoma cells were adherent and were maintained in Dulbecco’s Modified Eagle’s Media (DMEM) supplemented with 10% FBS, L-glutamine, and maintained in Dulbecco’s Modified Eagle’s Media in suspension and sarcoma cells were adherent and were replaced with fresh media. Thymic lymphoma cells grew or papain (10 mg/mL). Cells were then washed and maintained in Dulbecco’s Modified Eagle’s Media (DMEM) supplemented with 10% FBS, L-glutamine, and freshly added protease inhibitor cocktail (Roche). Protein lysates were prepared in NP-40 lysis buffer consisting of 1% NP-40, 5% glycerol, 20 mmol/L β-glycerophosphate, 2 mmol/L NaF, 5 mmol/L EDTA, 5 mmol/L EGTA, and freshly added protease inhibitor cocktail (Roche).

Cell viability assay

Cells were counted and seeded at a density of 2 × 10^3 cells per well in triplicate in 48-well plate (Corning). The growth of the cell was monitored by measuring the luminescent signal using the CellTiter-Glo Kit (Promega) every other day following manufacturer’s protocol.

Soft agar assays and foci formation assay

For soft agar assay, cells were counted and plated in 6-well plates in 0.35% agarose on a 0.7% agarose bed in triplicate for 2 weeks. For foci formation assay, 1,000 cells were plated in 6-well plates for 2 weeks. In both assays, colonies were stained with crystal violet and counted after 3 weeks. Pictures were taken under dissecting microscope.

Allograft assay and intravenous tail vein injection

Cells were counted and suspended in cold PBS. For allograft model, 1 × 10^6 cells were injected subcutaneously into rear flank of the nude mice. After palpable tumor formation, mice were randomized into 2 groups. Either corn oil or tamoxifen (1 mg/per injection) were injected into the nude mice intraperitoneally every other day.

Tumor sizes were measured with a caliper and calculated by length × height × width × 0.5. For tail vein injection, cells were stably transduced with pFU-L2G luciferase construct obtained from Dr. Sanjiv Sam Gambhir of Stanford University (Stanford, CA) and optimized by Dr. Huiping Liu (25). This construct enables the expression of both the bioluminescence and GFP. eGFP-positive cells were sorted by Beckman Coulter MoFlo. A total of 3 × 10^6 cells were suspended in cold PBS and injected through tail vein. Live animal imaging was done on the IVIS Spectrum Optical Imaging Machine (Caliper Life Sciences).

Peptide treatment

Both wild-type ARF26–44 (rrrrrrrrKFVRSRPRTASCALAFVN) and mutant ARF37–44 (rrrrrrrSCALAFVN) peptides were synthesized by Genemed Synthesis Inc. The N-terminus of each peptide was modified with 9 D-Arg(r) residues. The peptides were also blocked with amidation at the C-terminus and acetylation at the N-terminus. For sarcoma cells, mice were treated with 5 mg/kg body weight of peptide every other day 10 times. For lymphoma cells, mice were treated with 2.5 mg/kg body weight of peptide every other day for 10 times.

Statistical analysis

Statistical significance was calculated by the Student t test (2-tailed) with GraphPad Prism software, Microsoft Excel, and R. Statistically significant changes are indicated with asterisks (*, P < 0.05; **, P < 0.01).

Results

p53-null thymic lymphoma and sarcoma cells are addicted to FoxM1 for survival

FoxM1 is a p53-regulated gene (26, 27). Our database analyses indicated that FoxM1-mRNA is upregulated in cancers harboring mutations in p53 (Supplementary Fig. S1; refs. 28–31). In this study, we analyzed the role of FoxM1 in p53 loss-of-function tumors. To investigate this, we generated a strain of triple transgenic mice harboring...
CreERT2, Foxm1 fl/fl, and p53−/− alleles by crossing the 3 individual strains. Mice developed a spectrum of spontaneous tumors, as expected from the p53-null background (4). The presence of CreERT2 allele in the triple transgenic strain permits Cre recombinase expression upon 4-OH tamoxifen treatment to excise flox-flanked Foxm1 alleles, thus silencing FoxM1 expression. However, our attempts to study the effects of Foxm1 deletion on endogenous lymphomas/sarcomas were inconclusive mainly because the lymphomas/sarcomas developed at different times in the cohorts of mice used in the study. Also, as the Foxm1 alleles are deleted in most cell types in this system, it would be difficult to avoid the effects of Foxm1 deletion in the other cell types on the lymphoma/sarcoma development and progression. Therefore, we decided to isolate lymphoma/sarcoma cells from the triple transgenic and analyze them in host mice. Two thymic lymphoma (L1 and L2) and a sarcoma (S) triple transgenic cell lines were generated from the endogenous tumors. In addition, a control thymic lymphoma line (C) isolated from Foxm1 fl/fl p53−/− tumor was established in parallel. We tested the deletion efficiency of FoxM1 by immunoblot and confirmed that FoxM1 expression was significantly reduced in triple transgenic lines L1, L2, and S but not in control line C upon treatments with 4-OH tamoxifen (Fig. 1A–D). A sarcoma line stably transduced with FoxM1 expression was constructed (S: FoxM1) and treated with 800 nmol/L of 4OH-tamoxifen (Tam). Cell viability was measured by proportional luminescence signal generated by CellTiter-Glo assay.

Figure 1. FoxM1 is critical for the survival and tumorigenicity of p53-null thymic lymphoma and sarcoma. A–C, CreERT2, Foxm1 fl/fl, and p53−/− thymic lymphoma (L1 and L2) and Foxm1 fl/fl and p53−/− thymic lymphoma (C) were treated with ethanol as vehicle or 800 nmol/L of 4OH-tamoxifen (Tam). D, CreERT2, Foxm1 fl/fl, and p53−/− sarcoma (S) was treated with ethanol as vehicle or 800 nmol/L of 4OH-tamoxifen (Tam). Sarcoma line stably transduced with FoxM1 expression was constructed (S: FoxM1) and treated with 800 nmol/L of 4OH-tamoxifen (Tam). Cell viability was measured by proportional luminescence signal generated by CellTiter-Glo assay.

To examine the effect of FoxM1 ablation, growth curves were plotted following 4-OH tamoxifen treatment. FoxM1 deletion led to a profound decrease in the cell viability starting from early time point in all 3 of the triple transgenic lines L1, L2, and S (Fig. 1A–D). A sarcoma line stably transduced with exogenous FoxM1 expression was generated. Treatments with 4-OH tamoxifen did not diminish the exogenous FoxM1 expression (Fig. 1D). We also tested the tumorigenic properties of the sarcoma cells by conducting soft agar assay. FoxM1 deletion significantly reduced the ability of cells to grow under anchorage-independent conditions (Supplementary Fig. S2A). After FoxM1 deletion, cells
formed about 60% less colonies on the soft agar plate compared with the control. In addition, cells without FoxM1 also formed about 50% less colonies on the adherent plate (Supplementary Fig. S2B). These results indicate that FoxM1 function is important for the survival and tumorigenicity of tumor cells with p53 loss of function.

**FoxM1 ablation diminishes expression of survivin and Bmi1 in p53-null tumors accompanied by apoptosis**

Several studies have suggested targeting FoxM1 could serve as a therapeutic strategy toward treatment of cancer (21, 32, 33). To validate this strategy in tumors harboring p53 loss of function, we used a nude mice allograft model. One million thymic lymphoma (L1) or sarcoma (S) triple transgenic cells were injected subcutaneously into nude mice. About 1 week after injection, when the tumors became palpable, we randomized animals into 2 treatment groups and started to administer either tamoxifen or vehicle for 2 weeks. For both p53-null tumor lines, the tumors in the vehicle-treated control group grew significantly faster than of the tumors treated with tamoxifen (Fig. 2A and B). FoxM1 expression was examined by conducting immunohistochemical (IHC) staining. FoxM1 expression was largely reduced following 2 weeks of tamoxifen treatment, whereas abundant FoxM1 staining was detected in the vehicle treated group, consistent with FoxM1 overexpression in tumor cells (Supplementary Fig. S3A–S3D).

To investigate the basis for delayed tumor growth, we assayed for apoptosis of the tumor cells using terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) staining. In both lymphoma- and sarcoma-derived tumor sections, we observed an increased number of apoptotic cells following FoxM1 depletion, evidenced by increased number of TUNEL-positive cells (Fig. 2C and D; Supplementary Fig. S3E–S3L). We also assayed for cleaved caspase-3 and cleaved PARP, 2 apoptosis markers. Significant increases in the number of cleaved caspase-3- and cleaved PARP–positive cells were detected in FoxM1-depleted cells (Supplemental Fig. S3M and S3N). These observations suggested that the inhibition of the p53−/− tumors following loss of FoxM1 resulted from enhanced apoptosis of the tumor cells.

The increased apoptosis upon FoxM1 depletion was somewhat surprising because the p53−/− tumor cells are generally resistant to apoptosis (34). Survivin, which belongs to the inhibitor of apoptosis protein family, is a known transcriptional target of FoxM1 that plays important roles in both cell-cycle regulation and inhibition of apoptosis (9, 35). Previously, it was shown that reduced survivin levels contributed to apoptosis of HCC cells (21). Consistent with this finding, we observed that expression of survivin, which is abundant in control groups for both p53-null lymphoma and sarcoma, was downregulated following depletion of FoxM1 (Figs. 3A–D and 4). Bmi1, another FoxM1-induced gene (8, 36), has been shown also to protect tumor cells from apoptotic stimuli (37). Therefore, we assayed for the expression of Bmi1 in the tumor sections. We observed that the expression of Bmi1 was largely diminished in FoxM1-ablated tumors (Figs. 3E–H and 4). These observations suggest important roles of
Bmi1 and survivin in the survival of the p53/C0/ lymphoma and sarcoma. In Fig. 4, the doublet for Bmi1 is not obvious in the sarcoma samples because a higher percentage resolving gel was used. It is noteworthy that although the reduction of survivin and Bmi1 was evident, it was not complete possibly due to the presence of other signaling pathways that control expression of these 2 proteins. In that regard, NF-kB/STAT3 and ERK/AMPK/p38MARK signaling pathways were shown to activate the expression of survivin (38, 39). In addition, the expression of Bmi1 is regulated by microRNAs (40).

ARF-derived peptide inhibitor of FoxM1 induces apoptosis in p53-null tumor cells

A peptide (ARF26–44) derived from the mouse tumor suppressor ARF has been described that inhibits the activity of FoxM1 by relocalizing it to the nucleolus (6, 21). A cell-penetrating form of the peptide efficiently targets FoxM1 in liver tumors. In the DEN/PB-induced mouse hepatocellular carcinoma model, the ARF peptide is able to inhibit HCC progression by inducing apoptosis (21). The ARF peptide–induced apoptosis was observed mainly in the FoxM1-expressing cells (21). In addition, it has been shown to block the metastatic growth of the HCC cells (16). To see whether the ARF peptide is able to inhibit the p53-null tumors, we first examined the effect of the peptide, in vitro. A mutant peptide (ARF37–44), which lacks the interacting domain with FoxM1, was used as a control. One day after treatment, the wild-type ARF peptide–treated p53-null thymic lymphoma cell lines L1 and L2 underwent apoptosis. The number of viable cells was much less following treatment with wild-type ARF peptide than cells treated with the mutant peptide or PBS (Fig. 5A). The induction of apoptosis by the wild-type peptide was shown by TUNEL staining (Fig. 6A). A similar effect was observed in p53-null sarcoma cells (Figs. 5A and 6A). However, compared with the sarcoma lines, the p53/C0/ lymphoma cells are more sensitive to the ARF peptide, where 5 μmol/L of peptide was able to cause significant apoptosis (Fig. 6A). Cell growth and foci formation assay, as well as cleaved caspase-3 staining, were conducted to confirm the finding (Supplementary Fig. 5A). Treatments with the ARF peptide strongly inhibited expression of several FoxM1-induced genes, including survivin, Bmi1, EZH2, stathmin, and MMP9 (Fig. 6B). The ARF peptide had only a marginal effect on expression of Bax and GADD45, which are not direct targets of FoxM1.

ARF peptide effectively reduces the colonization of p53-null tumor cells in vivo

To test the therapeutic effect of the ARF peptide on p53-null tumors in vivo, p53-null lymphoma/sarcoma cells were introduced into the circulation of SCID mice through intravenous injection. Both p53-null sarcoma and lymphoma cells were stably transduced with lentivirus carrying luciferase expression before injection. Shortly after injection, comparable fluorescence was detectable in the lung by injecting luciferin using Xenogen IVIS spectrum imaging machine (Fig. 7A and C). Mice were randomized into 3 groups and treated with PBS, mutant peptide, or the wild-type ARF peptide for 10 injections every other day starting from day 0 by intraperitoneal injection. Ten days after tumor inoculation, p53-null
sarcoma cells were found to colonize the lung (Fig. 7A and B). After 20 days following the initial inoculation, compared with the PBS- and the mutant peptide–treated mice, the amount of luciferase signal from the wild-type ARF peptide–treated mice was significantly reduced. The mice were sacrificed, and lung sections were analyzed for tumor colonies. A reduced number of tumor colonies that were larger than 100 \( \times \) 100 \( \mu \text{m} \) \(^2\) were detected in the lungs of the wild-type ARF peptide–treated mice (Fig. 7B). Moreover, survivin and Bmi1 expression was inhibited in the colonized tumors from mice treated with the wild-type ARF peptide compared with those treated with the mutant peptide (Fig. 7D).

The murine thymic lymphoma cells tended to colonize the kidney, liver, and spleen (41). For the p53-null thymic lymphoma cells, we observed metastatic growth in kidney. Around 20 days after inoculation, PBS and the mutant ARF peptide–treated mice displayed strong luciferase signals from the colonized lymphoma cells in the lower back region. On the other hand, the wild-type ARF peptide–treated mice emitted very little fluorescence, indicating an inhibition of colonized tumors (Fig. 7C).

When the mice were sacrificed, large tumor masses were found in the kidney by microscopic examination in the PBS and in the mutant peptide–treated mice. Atypical pale coloration and enlargement of the kidney were observed in the mice, and the mice carried a large tumor mass that encompassed the 2 kidneys, the connective tissues and the spinal cords. On the other hand, kidneys from the wild-type peptide–treated mice still retained the original size and structure with only a small white mass started to build up on the surface of the kidney (Supplementary Fig. S5A and S5B). These results clearly indicated that the wild-type ARF peptide was able to efficiently block the renal metastasis of the p53-null thymic lymphoma.

Figure 5. Cellular response of p53-null tumor cells following ARF\(\text{26-44}\) peptide treatment. A, phase-contrast picture of CreERT2, Foxm1\(\text{fl/fl}\), and p53\(\text{+/+}\) thymic lymphoma and sarcoma cells treated with PBS, ARF\(\text{37-44}\) peptide (Mut), or ARF\(\text{26-44}\) peptide (WT) at 24 hours. B, Western blotting of protein lysates extracted from thymic lymphoma cells treated with PBS (P), ARF\(\text{26-44}\) peptide (W), or ARF\(\text{37-44}\) peptide (M). \(\alpha\)-Tubulin was used as a loading control. The band intensities were quantified by ImageJ program, and the relative intensities after adjusting for loading control (intensity of the tubulin bands) are shown below each panel.

Figure 6. ARF\(\text{26-44}\) peptide activates apoptotic response in the p53-null tumor cells. A, TUNEL and 4',6-diamidino-2-phenylindole (DAPI) staining of CreERT2, Foxm1\(\text{fl/fl}\), and p53\(^{1−}\) thymic lymphoma and sarcoma cells treated with PBS, ARF\(\text{37-44}\) peptide (Mut), or ARF\(\text{26-44}\) peptide (WT). B, quantification of percentage of TUNEL-positive cells per field.
Discussion

The results presented here are significant in several ways. First, we show that p53-null lymphoma and sarcoma are addicted to FOXM1 for their survival, which might also be significant for other p53 loss-of-function tumors. Moreover, we show that the ARF-derived peptide inhibitor of FOXM1 effectively inhibits colonization and growth of the p53-null lymphoma and sarcoma, which will have strong implications with regard to a new therapeutic application of the ARF peptide against lymphomas and sarcomas.

Loss of function of p53 confers resistance to apoptosis because p53 stimulates expression of several proapoptotic genes including Puma, Noxa, Bax, Bad, DR4, DR5, Apaf1, caspase-6, and others (42). p53 also represses expression of anti-apoptotic genes such as survivin (43). The pro-apoptotic function of p53 is critical for elimination of cells harboring irreparable levels of DNA damage. It is noteworthy that p53 also stimulates several DNA repair genes (44). In the absence of p53, reduced DNA repair and apoptosis leads to the accumulation of mutant cells, which contributes to tumor development. For example, p53-null mice, used in this study, spontaneously develop lymphomas and sarcomas (4). p53 also stimulates expression of the cell-cycle inhibitor p21 (45) and represses FOXM1 (26, 27), contributing to cell-cycle arrest following DNA damage. Therefore, it is not surprising that p53 mutation also leads to aggressive progression of already developed tumor cells because of increased survival and proliferation. Increased expression of FOXM1 in the p53-mutant tumors is expected to drive aggressive progression because of its role in cell proliferation and inhibition of apoptosis. FOXM1 has been shown to inhibit apoptosis by activating the expression of survivin, which is inhibited by p53.

FOXM1 is an important target for cancer therapy. It is expressed mainly in the proliferating cells and in tumors (19, 46). On the basis of available evidence, it appears that FoxM1 is dispensable for survival or function of the normal cells in a tissue. For example, deletion of FoxM1 in the adult mouse liver has not visible effect for at least 1 year (6). But, it blocks development of HCC. Moreover, conditional deletion of FoxM1 after HCC development causes inhibition of tumor progression (21). Moreover, a peptide inhibitor derived from the tumor suppressor ARF, the ARF peptide used in this study, was shown to inhibit liver tumors, through increased apoptosis, without affecting the neighboring normal cells in the tumor-bearing liver (21). Therefore, selective inhibition of FOXM1 would be effective in cancer treatment. Our observations with p53-null lymphoma and sarcoma are significant in that regard because more than 50% of tumors harbor p53 mutations.

The observations that p53-null lymphoma and sarcoma cells depend upon FOXM1 and are highly sensitive to inhibition of FOXM1 suggest that the p53-null tumors are also candidates for therapeutic strategies that target FOXM1. Cre-recombinase–mediated deletion of FoxM1 inhibited tumor growth, at least partly, by inducing apoptosis. Deletion of FoxM1 caused a reduction in the expression of survivin, an anti-apoptotic protein. Moreover, there was a strong reduction of Bmi1, which was
shown to support survival of tumor cells (47). It is therefore likely that these FOXM1 target genes are involved in the survival of the p53-null lymphoma and sarcoma. Moreover, a cell-penetrating form of the ARF peptide, which inhibits FOXM1, also induced apoptosis and inhibited colonization of the p53-null lymphoma and sarcoma cells. The lymphoma cells were more sensitive to the peptide. It is possible that the entry of the peptide is more efficient in the less adherent lymphoma cells, raising the possibility that the ARF peptide would be highly effective against the tumor cells in circulation. Consistent with that, there was a drastic inhibition of the lymphoma colonization to the kidney, a major site of colonization for the T-lymphoma cells (41). These observations indicate the possibility of a new application of the ARF peptide in targeting the tumor cells in the circulation.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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