Identification of a Chemical Inhibitor of the Oncogenic Transcription Factor Forkhead Box M1

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Abstract

The oncogenic transcription factor forkhead box M1 (FoxM1) is overexpressed in a number of different carcinomas, whereas its expression is turned off in terminally differentiated cells. For this reason, FoxM1 is an attractive target for therapeutic intervention in cancer treatment. As a first step toward realizing this goal, in this study, using a high-throughput, cell-based assay system, we screened for and isolated the antibiotic thiazole compound Siomycin A as an inhibitor of FoxM1. Interestingly, we observed that Siomycin A was able to down-regulate the transcriptional activity as well as the protein and mRNA abundance of FoxM1. Consequently, we found that the downstream target genes of FoxM1, such as *Cdc25B, Survivin*, and *CENPB*, were repressed. Also, we observed that consistent with earlier reports of FoxM1 inhibition, Siomycin A was able to reduce anchorage-independent growth of cells in soft agar. Furthermore, we found that Siomycin A was able to induce apoptosis selectively in transformed but not normal cells of the same origin. Taken together, our data suggest that FoxM1 inhibitor Siomycin A could represent a useful starting point for the development of anticancer therapeutics. (Cancer Res 2006; 66(19): 9731-5)

Introduction

Mammalian transcription factor forkhead box M1 (FoxM1; previously known as HFH-11B, Trident, WIN, or MPP2) is induced during G_1 phase of the cell cycle and its expression continues through S phase and mitosis (1). FoxM1 is especially important for the execution of the mitotic program as seen by the failure of FoxM1-depleted cells to progress beyond the prophase stage of mitosis (2). This is consistent with the demonstration that FoxM1 transcriptionally up-regulates a number of target genes, including *cyclin B, survivin, Aurora B kinase, Cdc25b phosphatase*, and *Plk1*, all of which are implicated in mitosis (2, 3). Also, FoxM1 transcriptionally induces Skp2 and Cks1 (specificity subunits of Skp1-Cullin1-F-box ubiquitin ligase complex) leading to the degradation of cyclin-dependent kinase (CDK) inhibitors $p21^{WAF1}$ and $p27^{KIP1}$, thereby resulting in cell cycle progression (2). In line with its proproliferative nature, whereas FoxM1 is expressed in all dividing mammalian cells and tumor-derived cells, its expression is turned off in terminally differentiated cells (4–7).

FoxM1 is overexpressed significantly in primary breast tumors (8), basal cell carcinomas (9), hepatocellular carcinomas (10, 11), intrahepatic cholangiocarcinomas (12), non–small cell lung cancers (13), anaplastic astrocytomas, and glioblastomas (14). Also, increased levels of FoxM1 has been seen to accelerate prostate cancer development and progression in mouse models (15). Furthermore, a large-scale analysis of microarray results revealed that FoxM1 is one of the most common genes overexpressed in a majority of solid tumors (16). Together, these studies indicate that FoxM1 could be an attractive target for anticancer therapy. This notion is supported by a recent finding that depletion of FoxM1 by RNA interference in breast cancer cells leads to mitotic catastrophe (8). In a similar manner, knockdown of FoxM1 by small interfering RNAs (siRNA) in several prostate and lung cancer cell lines was shown to lead to a significant reduction in cell proliferation and anchorage-independent cell growth on soft agar (13, 15). Consistent with these observations, inhibition of FoxM1 transcriptional activity by a peptide containing amino acids 24 to 46 of $p19^{ARF}$ also reduced anchorage-independent cell growth (17).

In this study, using a cell-based assay system, we identified the antibiotic thiazole compound Siomycin A as a potent inhibitor of FoxM1 transcriptional activity. We also showed that this compound reduces FoxM1-induced cell growth on soft agar and kills transformed cells selectively, suggesting that it could be an attractive candidate for anticancer drug development.

Materials and Methods

Screening system. The development of U2OS clone C3 cell line with doxycyclin-inducible FoxM1-green fluorescent protein (GFP) fusion protein has been described before (17). This cell line was transfected with a plasmid expressing firefly luciferase under the control of 6× FoxM1 responsive promoter (17), along with pcDNA3.1 (Invitrogen, Carlsbad, CA) plasmid that expresses neomycin phosphotransferase. The resultant cells were selected in 800 μg/mL G418 (Invitrogen) and a single resistant clone that showed severalfold doxycycline-dependent induction in firefly luciferase activity was expanded. This clone was further transfected with pRL-CMV (Promega, Madison, WI) that expresses renilla luciferase along with pLPCX-puro (Clontech. Mountain View, CA) and the cells were selected in 2 μg/mL puromycin. This cell line, which expresses FoxM1-dependent firefly luciferase and constitutive renilla luciferase, was named as C3-Luc and used for the screening of compound libraries (Challenge set and Diversity set) from the National Cancer Institute (NCI).

Luciferase assays. For high-throughput screening, the C3-Luc cells were grown in 96-well plates and treated overnight with a combination of 1 μg/mL doxycycline and 10 μmol/L of compounds from the library. The next day, the firefly and renilla luciferase activities were measured with the Dual Glo system (E2940; Promega).

For the other luciferase assay experiments, the cells were treated as indicated in the figure legend and the luciferase activity was measured using the Dual Luciferase reporter assay system (E1910; Promega) according to the instructions from the manufacturer.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

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Real-time quantitative reverse transcription PCR. Cells treated with Siomycin A or DMSO (control) were harvested 24 hours later and RNA was extracted using the TRIzol reagent (Invitrogen). cDNA was prepared from this RNA using the Bio-Rad cDNA synthesis kit. The following sense (S) and antisense (AS) primer sequences and annealing temperatures (T_a) were used to amplify and measure the amount of human mRNA by real-time reverse transcription-PCR (RT-PCR): FoxM1-S, 5′-GGAGGAAATGCCACACTTAGCG-3′, and FoxM1-AS, 5′-TAGGACTTCTTGGGTCTTGGGGTG-3′ (T_a, 55.7°C); survivin-S, 5′-TCAAGGACCACCGCATCTCTA-3′, and survivin-AS, 5′-TGAAGCAGAAGAAACACTGGGC-3′ (T_a, 61°C); CENPB-S, 5′-ATTCAGACAGTGAGGAAGAGGACG-3′, and CENPB-AS, 5′-CATCAATGGGGAAGGAGGTCAG-3′ (T_a, 58°C); Cdc25B-S, 5′-CCCTTCCCTGTTTTCCTTTC-3′, and Cdc25B-AS, 5′-ACACACACTCCTGCCATAGG-3′ (T_a, 61.7°C). These real-time RT-PCR RNA levels were normalized to human cyclophilin mRNA levels, and these primers are as follows: cyclophilin-S, 5′-GCAGACAAGGTCCCAAAGACAG-3′, and cyclophilin-AS, 5′-CACCCTGACACATAAACCCTGG-3′ (T_a, 55.7°C).

Immunoblot analysis and immunoprecipitation. Immunoblotting was done as described (18–20) with antibodies specific for p21 (556431; BD PharMingen, San Diego, CA), survivin (Santa Cruz Biotechnology, Santa Cruz, CA), cleaved caspase-3 (Cell Signaling Technology, Danvers, MA), and β-actin (Sigma-Aldrich, St. Louis, MO) antibodies. Immunoblot for FoxM1 was done using the previously generated rabbit antisera (2), and phospho-FoxM1 was detected using the MPM2 monoclonal antibody (Upstate Biotechnology, Lake Placid, NY), which recognizes the phosphorylated protein sequence phosphoserine/phosphothreonine-proline.

For the immunoprecipitation experiment, FoxM1 antisera (2) was used along with protein A-Sepharose to pull down FoxM1 protein, which was resolved on an SDS-PAGE gel and transferred to polyvinylidene difluoride membrane. The total and phospho-FoxM1 levels were determined by using the antibodies described above.

Soft agar assay. The assay was done as described previously (21, 22). Briefly, C3-Luc cells were plated subconfluently in six-well plates in 0.7% agarose on a 1.4% agarose bed in the presence or absence of 10 μmol/L Siomycin A and 1 μg/mL doxycycline. Three times a week, the tissue-culture medium containing these agents was replaced. After 4 weeks, cell colonies that were larger than 1 mm in size were scored.

Apoptosis assay. Apoptosis was detected by 4′,6-diamidino-2-phenylindole (DAPI) staining. All treatments were done in triplicates in six-well plates and cells were stained with DAPI and visualized by fluorescent microscopy. Four random fields for each sample were photographed and at least 500 cells per field were counted to estimate apoptosis. The data are represented as mean ± SD.

Results and Discussion

Identification of Siomycin A as an inhibitor of FoxM1 transcriptional activity. To screen for inhibitors of FoxM1 transcriptional activity in a high-throughput fashion, we developed a U2OS cell line C3-Luc (described in Materials and Methods) that stably expresses doxycycline/tetracycline–inducible FoxM1-GFP, firefly luciferase under the control of multiple FoxM1 response elements, and a renilla luciferase under the control of a CMV promoter (Fig. 1*A*). We first verified that when doxycycline is added to the medium, FoxM1-GFP is highly induced, leading to several fold induction in firefly luciferase activity with minimal change in the renilla luciferase activity (data not shown). We then used this C3-Luc cell line to screen against compounds (Challenge Set and Diversity Set) obtained from NCI (Supplementary Table S1). We found that although the relative firefly luciferase activity was enhanced ~16-fold upon induction with doxycycline, addition of

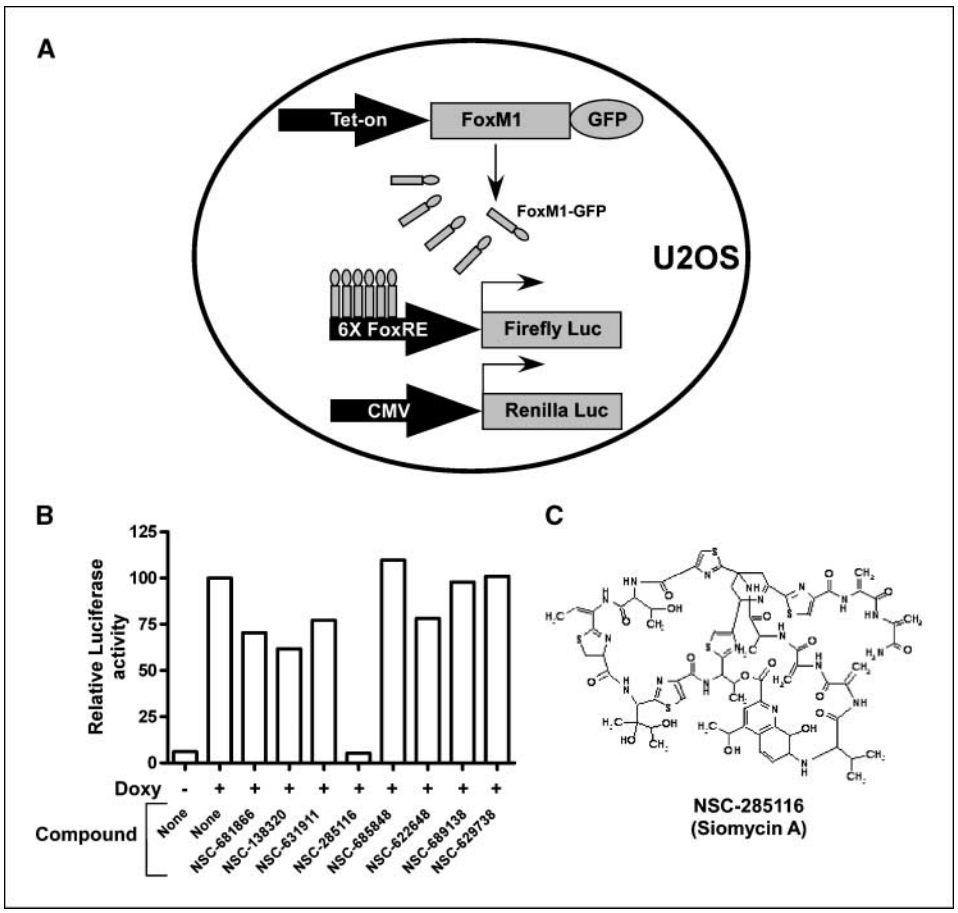

Figure 1. Identification of an inhibitor of FoxM1 transcriptional activity. *A*, the C3-Luc cell line was derived from U2OS cells as described in Materials and Methods. These cells were used for screening against the library of compounds from the NCI. *B*, part of the screening data containing the positive hit (NSC-285116; Siomycin A). Compounds were tested at a final concentration of 10 μmol/L. *C*, chemical structure of the antibiotic thiazole compound Siomycin A.

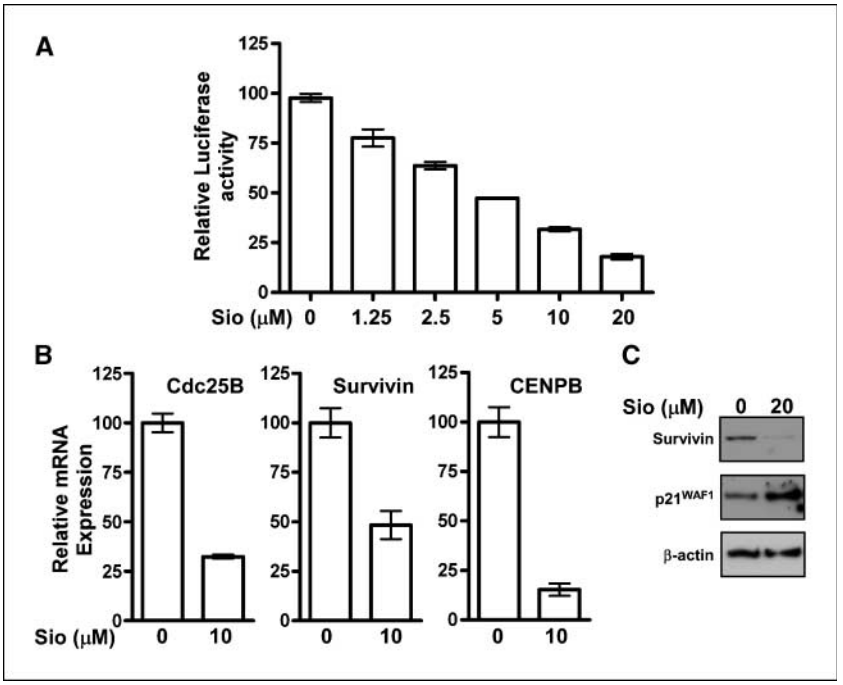

Figure 2. Siomycin A inhibits endogenous FoxM1 transcriptional activity. *A,* C3-Luc cells without doxycycline induction were treated with increasing dose of Siomycin A and luciferase activity was determined as described in Materials and Methods. *B,* C3-Luc cells treated either with DMSO (control) or Siomycin A (*Sio*) were harvested 24 hours later and the RNA was subjected to real-time RT-PCR for quantitation of mRNA levels of FoxM1 target genes *Cdc25B, survivin*, and *CENPB. C,* C3-Luc cells treated as indicated were harvested 24 hours later and used for immunoblot analysis to determine the levels of survivin and $p21^{WAF1}$. β-Actin protein levels were used as loading control.

Siomycin A (NSC-285116) efficiently reduced the value to basal levels (Fig. 1*B*). Siomycin A is a well-known antibiotic and its structure is shown in Fig. 1*C*. It belongs to the thiazole group and this class of antibiotics exerts their antibacterial effect by interacting with the 23S rRNA (23).

Next, we wanted to investigate if Siomycin A can inhibit the transcriptional activity of endogenous FoxM1. To this end, we treated the C3-Luc cells (without doxycycline induction) with increasing concentration of Siomycin A and found a dose-dependent decrease in the firefly luciferase activity conferred by the FoxM1-responsive promoter (Fig. 2*A*; Supplementary Table S2). In addition, using quantitative real-time RT-PCR, we found that the mRNA levels of the transcriptional targets of FoxM1 were inhibited in C3-Luc cells upon treatment with Siomycin A (Fig. 2*B*). Whereas Cdc25B was reduced to ~32% of its basal value, Survivin and CENPB were reduced to ~48% and ~15%, respectively, compared with their initial levels after Siomycin A treatment (Fig. 2*B*). Also, protein levels of survivin were dramatically reduced in the presence of Siomycin A (Fig. 2*C*). Because FoxM1 transcriptionally induces Skp2 and Cks1, which degrade $p21^{WAF1}$ protein (2), an inhibitor of FoxM1 should increase $p21^{WAF1}$ protein levels. Accordingly, immunoblotting for $p21^{WAF1}$ revealed an increase in its protein levels after treatment with Siomycin A (Fig. 2*C*). Taken together, these data suggest that Siomycin A is capable of inhibiting both exogenous and endogenous FoxM1 transcriptional activity (Figs. 1 and 2).

Mechanism of FoxM1 inhibition by Siomycin A. Previously, it has been shown that CDK1/2-dependent phosphorylation of FoxM1 on Thr^{596}, resulting in p300/CBP recruitment, is essential for the transcriptional activity of FoxM1 (22). Based on this observation, we hypothesized that Siomycin A may inhibit FoxM1 transcriptional activity by blocking this phosphorylation event. To test this hypothesis, we treated C3-Luc cells with DMSO (control) or 100 μmol/L Siomycin A for 8 hours and immunoprecipitated FoxM1 from the lysates. We then analyzed these samples for phospho-FoxM1 levels by immunoblotting with MPM2, a monoclonal antibody that recognizes phosphorylated CDK1 and CDK2 sites. We found that Siomycin A treatment led to a decrease in phospho-FoxM1, whereas the total FoxM1 levels were only marginally reduced (Fig. 3*A*). We also found that prolonged treatment of C3-Luc cells for 24 hours with Siomycin A significantly decreased FoxM1 protein and mRNA levels (Fig. 3*B* and *C*; Supplementary Fig. S1). These data imply that Siomycin A antagonizes FoxM1 function by at least two distinct mechanisms—one by blocking its phosphorylation, thereby leading to its reduced transactivation ability, and the other by down-regulating its mRNA and protein levels.

Anticancer properties of FoxM1 inhibitor Siomycin A. In a previous study, it has been shown that inhibiting FoxM1 using a $p19^{ARF}$–derived peptide leads to a decrease in anchorage-independent growth of U2OS cells on soft agar (17). To test if Siomycin A could recapitulate this effect, we did a clonogenic assay, wherein we grew the C3-Luc cells with or without FoxM1 induction and Siomycin treatment for 4 weeks. We found that although induction of FoxM1 led to a ~2-fold increase in the number of colonies, addition of Siomycin A dramatically reduced the anchorage-independent growth to less than basal untreated value (Fig. 4*A* and *B*). This result suggests that Siomycin A may act as an effective inhibitor of FoxM1-based cellular transformation.

To further test the anticancer properties of Siomycin A and to see if it has any specificity toward transformed cells, we used a wild-type and SV40-transformed variant of MRC-5 human fetal lung fibroblasts. Forty-eight hours after treatment with Siomycin A, while the SV40-transformed cells underwent dose-dependent apoptosis, the untransformed normal cells did not exhibit significant cell death (Fig. 4*C* and *D*). This is further supported by our observation that transformed but not normal cells showed cleavage of caspase-3 upon Siomycin A treatment (Fig. 4*E*). We also investigated the effect of Siomycin A on survivin levels in these cells. Consistent with our previous report (24), we found elevated levels of survivin in the untreated transformed cells relative to normal MRC-5 fibroblasts. Because survivin is a downstream target of FoxM1 (2), Siomycin A was able to effectively repress survivin

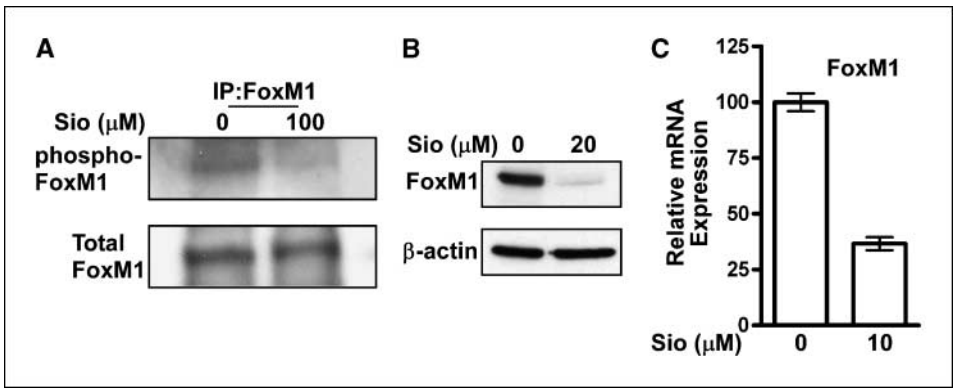

Figure 3. Mechanisms of FoxM1 inhibition by Siomycin A. *A,* C3-Luc cells treated as indicated were harvested after 8 hours and cell lysates were used for immunoprecipitation of FoxM1 protein. These samples were resolved on an SDS-PAGE gel and immunoblotted to determine total and phospho-FoxM1 levels. *B,* C3-Luc cells treated with Siomycin A or DMSO were harvested 24 hours later and the lysates were used to determine FoxM1 protein levels by immunoblotting. *C,* RNA from C3-Luc cells treated with Siomycin A or DMSO for 24 hours was used to determine levels of FoxM1 mRNA using real-time quantitative RT-PCR.

levels after treatment in both normal and transformed cells (Fig. 4*E*). Although survivin is down-regulated in both cell types, it is interesting to note that apoptosis selectively occurs in the transformed cells. It is possible that in line with the oncogene addiction hypothesis (25), the transformed cells are more dependent on survivin, depletion of which leads to a more drastic outcome than in the normal cells.

In summary, in this study, we have isolated Siomycin A as a potent inhibitor of FoxM1 action. In addition, Siomycin A inhibits anchorage-independent growth and induces apoptosis in transformed, but not in normal, cells. These anticancer properties of Siomycin A are consistent with an earlier report where it was identified in a screen for proapoptotic compounds using a human breast cancer MDA-MB-231 cell line in an ELISA assay that specifically recognizes caspase-cleaved cytokeratin 18 (26). Furthermore, another study indicated that Siomycin A induced endoplasmic reticulum stress and lysosomal membrane permeabilization followed by cell death in HCT116 colon cancer cells (27). Although p53 was induced due to Siomycin A treatment in these cells, apoptosis was found to be p53 independent. Interestingly, Siomycin A is a part of the NCI Challenge set, in which the compounds exhibit unusual patterns of cell sensitivity and resistance, but through currently unknown mechanism (28). Our data is consistent with the hypothesis that negative regulation of FoxM1 function and expression by Siomycin A at least partly contributes to the anticancer and proapoptotic activity of this antibiotic.

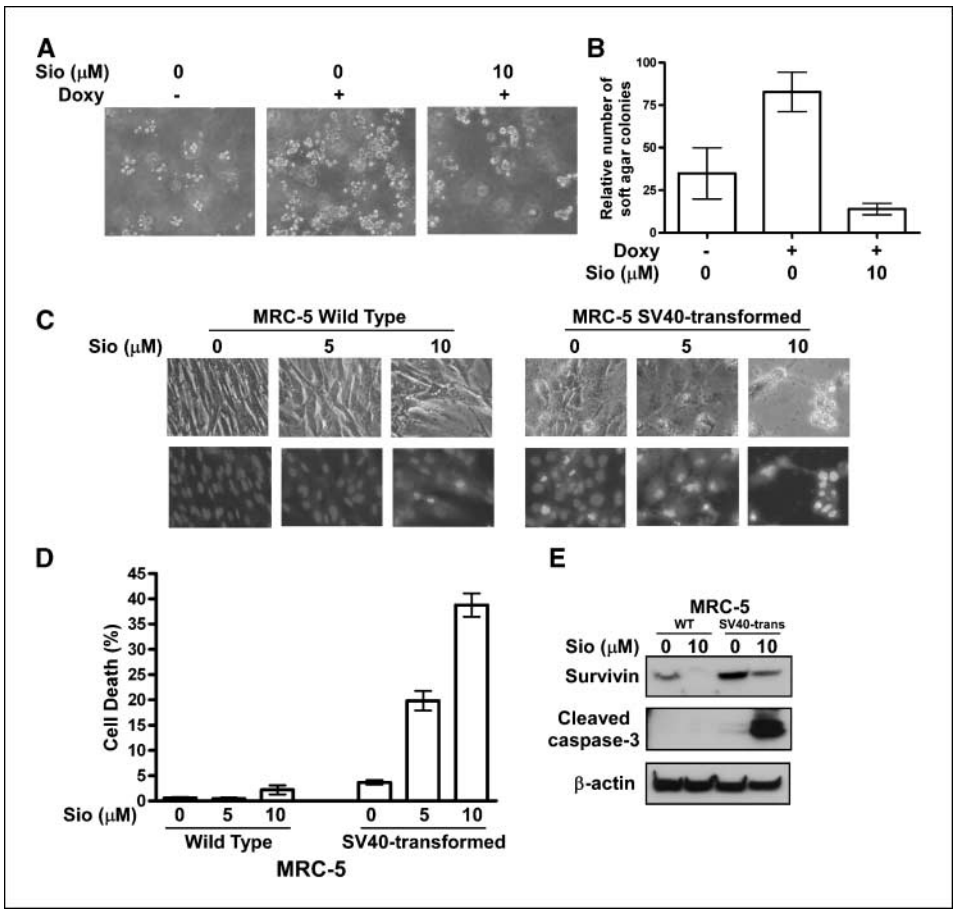

Figure 4. Anticancer properties of Siomycin A. *A,* representative photographs from soft agar experiment as described in Materials and Methods. *B,* number of colonies in the soft agar. *C,* wild-type and SV40-transformed MRC-5 human fetal lung fibroblasts were treated with indicated concentrations of Siomycin A for 48 hours. Photographs from phase contrast microscopy (*top*) and fluorescent microscopy after DAPI staining (*bottom*) are shown. *D,* apoptotic nuclei from normal and SV40-transformed MRC-5 fibroblasts treated with indicated concentrations of Siomycin A for 24 hours were scored after DAPI staining. *Columns,* mean percentage cell death ($n = 3$); *bars,* SD. *E,* wild-type and SV40-transformed MRC-5 fibroblasts were treated with Siomycin A as indicated for 48 hours, and the cell lysates were used for immunoblotting and probed for levels of survivin and cleaved caspase-3.

Acknowledgments

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