Cyclooxygenase inhibitors block uterine tumorigenesis in *HMGA1a* transgenic mice and human xenografts

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Abstract

Uterine cancer is a common cause for cancer death in women and there is no effective therapy for metastatic disease. Thus, research is urgently needed to identify new therapeutic agents. We showed previously that all female *HMGA1a* transgenic mice develop malignant uterine tumors, indicating that *HMGA1a* causes uterine cancer *in vivo*. We also demonstrated that HMGA1a up-regulates *cyclooxygenase-2* (*COX-2*) during tumorigenesis in this model. Similarly, we found that *HMGA1a* and *COX-2* are overexpressed in human leiomyosarcomas, a highly malignant uterine cancer. Although epidemiologic studies indicate that individuals who take COX inhibitors have a lower incidence of some tumors, these inhibitors have not been evaluated in uterine cancer. Here, we show that *HMGA1a* mice on sulindac (a COX-1/COX-2 inhibitor) have significantly smaller uterine tumors than controls. To determine if COX inhibitors are active in human uterine cancers that overexpress *HMGA1a*, we treated cultured cells with sulindac sulfide or celecoxib (a specific COX-2 inhibitor). Both drugs block anchorage-independent growth in high-grade human uterine cancer cells that overexpress *HMGA1a* (MES-SA cells). In contrast, neither inhibitor blocked transformation in cells that do not overexpress *HMGA1a*. Moreover, xenograft tumors from MES-SA cells were significantly inhibited in mice on sulindac. More strikingly, no tumors formed in mice on celecoxib. These preclinical studies suggest that COX inhibitors could play a role in preventing tumor onset or progression in uterine cancers with dysregulation of the HMGA1a-COX-2 pathway. Importantly, these drugs have lower toxicity than chemotherapeutic agents used to treat advanced-stage uterine cancers. [Mol Cancer Ther 2008;7(7):2090–5]

Introduction

Despite recent advances in our understanding of the molecular abnormalities associated with uterine cancer, these discoveries have not been translated into better therapy for patients (1–3). Uterine cancer is the most common cancer of the female genital tract and the fourth most frequent cause for cancer death in women in the United States (1, 2). These cancers include carcinomas, sarcomas, and mixed epithelial-mesenchymal tumors. For all subtypes, the only available treatment is hysterectomy. There is no effective therapy once these tumors have spread outside the uterus; adjuvant therapy for metastatic disease does not enhance survival. Thus, further study is needed not only to identify chemotherapeutic agents to treat uterine cancer after it has developed but also to discover new strategies to prevent or delay disease progression. Preclinical studies of therapeutic interventions for uterine cancer recently became possible with the generation of *HMGA1a* transgenic mice, which develop malignant uterine tumors with complete penetrance (4). These tumors recapitulate salient histologic and molecular features found in human uterine sarcomas (4). At the molecular level, we showed that HMGA1a up-regulates *cyclooxygenase-2* (*COX-2*) during uterine tumorigenesis in this model (4). We also found that high-grade human leiomyosarcomas overexpress both *HMGA1a* and *COX-2*, similar to our transgenic mice (4). COX-2 is a key enzyme involved in prostaglandin formation, which leads to signal transduction, inflammation, and mitogenesis, depending on the cellular context (5). Although COX-2 has been well studied in human cancers of epithelial origin, such as gastrointestinal, breast, and prostate (5), there are no studies evaluating its functional role in uterine cancer. We therefore sought to determine if COX inhibitors could block uterine tumorigenesis using both our transgenic mice and human uterine cancer xenografts as model systems. Although additional studies are needed, our findings indicate that COX inhibitors could play a role in preventing the onset or progression of selected uterine cancers in humans.

Materials and Methods

Drugs

Celecoxib (800 ppm; LKT Laboratories) or sulindac (320 ppm; Sigma-Aldrich) were mixed with pelleted, purified rodent diet

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AIN-76A (Dyets). For *in vitro* studies, sulindac sulfide, sulindac sulfone (Sigma-Aldrich), and celecoxib were prepared in DMSO and added to medium. DMSO alone was used for controls.

Cell Lines and *In vitro* Studies

Human uterine cancer cell lines MES-SA and SK-UT-1 obtained from the American Type Culture Collection were grown as recommended. MES-SA cells (6) are derived from a poorly differentiated uterine cancer that arose as a recurrent tumor 5 months after hysterectomy for a malignant mixed mullerian tumor (carcinosarcoma). SK-UT-1 cells are derived from the sarcomatous region of a grade 3 malignant mixed mullerian tumor. Both cell lines are designated as sarcoma cells (American Type Culture Collection). Cell proliferation was assessed using the CellTiter Cell Proliferation Assay (Promega). Anchorage-independent growth was assessed as described previously (4).

Mice

The construction of the transgenic mice was described previously (4, 7). Briefly, the cDNA encoding murine *HMGA1a* (previously *HMG-I*; ref. 8) was cloned into the vector pHSE3′ (9). This construct was cleaved with *Xho*I to release a DNA fragment containing the *HMGA1a* coding sequence flanked by the H-2K promoter and immunoglobulin μ intronic enhancer (7). The transgene was injected into fertilized eggs from B6C57/SJL females and maintained by mating hemizygous mice with wild-type B6C57 mice (7). This construct was shown previously to drive transgene expression in T and B lymphoid cells (7, 9). In addition, we showed that the transgene is also overexpressed in the uteri of all female mice (4). As reported previously, all mice develop lymphoid malignancies (7) and all females develop uterine tumors by 8 to 10 months (4). The females exhibit mild uterine enlargement and abnormal histopathologic findings at necropsy as early as 8 to 10 weeks with large sarcomas by 8 to 10 months (4). Mouse experiments were approved by the Animal Care and Use Committee according to NIH guidelines.

Chemoprevention Study

At age 8 weeks, *HMGA1a* transgenic mice (10 in each arm) were randomly assigned to one of three groups: control, sulindac, or celecoxib. Body weights were monitored weekly. Mice were sacrificed at either age 29 or 36 weeks (5 in each group). Data were analyzed by Student's t test. $P < 0.05$ was considered significant.

Uterine Xenograft Studies

Uterine cancer cells (5.0×10^6) were injected s.c. into nude mice as described (6, 8). Mice were fed celecoxib, sulindac, or control food starting 3 days before injections. Mice were sacrificed when tumors reached a maximum diameter of 1.5 cm (after 11-14 days) in the control group. Tumor volumes were estimated as length $\times$ width^2 / 2 (6). The proportion of mice with tumors in each group was compared by the exact test of the null hypothesis of equal proportions between two groups.

Histology

Histopathologic analysis was done as described (7, 8).

Gene Expression Analysis

RNA extraction, reverse transcription, and quantitative real-time PCR were done as described previously (4).

Results

Sulindac Inhibits Uterine Tumorigenesis in the *HMGA1a* Mice

We used our *HMGA1a* mice for the initial preclinical studies because they develop uterine cancer that recapitulates histologic and molecular features characteristic of human uterine sarcomas (4). To determine if COX inhibitors could prevent the development or progression of uterine cancer, the mice were fed a diet supplemented with either sulindac, a COX-1/COX-2 inhibitor (320 ppm, $n = 10$), celecoxib, a specific COX-2 inhibitor (800 ppm; $n = 10$), or control ($n = 10$), starting at age 8 weeks. The doses were based on published reports that showed antitumor efficacy in mice (10–12). There was no significant difference in food intake or weight gain in each treatment arm over the study period (Supplementary Fig. S1).[7]

At age 29 weeks (Fig. 1A), there were significantly smaller uterine tumors in the sulindac arm (1.01 ± 0.34 versus 2.17 ± 0.84 g; $P = 0.024$; $n = 5$). To control for differences in body weight, the tumor size was expressed as percentage of body weight (Fig. 1B), and the difference was even more significant (3.85 ± 1.09% versus 8.75 ± 3.05%; $P = 0.014$; $n = 5$). Histopathologic examination of the uterine tumors on sulindac showed a decrease in volume, edema, and hypercellularity of the endometrial stroma. The uterus in the treated mouse also lacks the polypoid proliferation that protrudes into the uterine cavity in the untreated mouse (Fig. 1C and D). The celecoxib arm did not show statistically significant differences compared with controls at age 29 weeks (Supplementary Fig. S2).[7]

At 36 weeks, tumors were slightly smaller in both sulindac arm (2.50 ± 1.96 g or 9.05 ± 6.53%; $n = 5$) and celecoxib arm (2.47 ± 1.82 g or 8.63 ± 6.13%; $n = 5$) compared with controls (3.42 ± 2.24 g or 12.65 ± 8.54%), although the differences were not statistically significant (Supplementary Fig. S2).[7] At this later time point (36 weeks), it is possible that the oncogenic influence from the potent *HMGA1a* transgene allows tumor cells to escape the inhibitory effects of the drugs. Of note, the inhibitors had no effect on the lymphoid malignancies at the time points studied. Examination of tumor burden by splenic weights, histopathologic examination, and fluorescence-activated cell sorting showed no difference in the leukemic tumor burdens (data not shown).

To determine if sulindac has a direct effect on *HMGA1a* expression levels in the tumors, we assessed *HMGA1a* mRNA levels in the uterine tumor tissue at necropsy in the mice in the sulindac or control arms. By quantitative real-time PCR, we found no difference in the levels of *HMGA1a* mRNA in all groups tested at 29 or 36 weeks, indicating

[7] Supplementary material for this article is available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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that sulindac did not directly influence the expression of the transgene (Supplementary Fig. S3).[7]

Sulindac Sulfide and Celecoxib Block Anchorage-Independent Cell Growth in Human Uterine Cancer Cells *In vitro*

Because sulindac was effective in blocking tumor growth in our *HMGA1a* mouse model for uterine cancer, we next sought to determine if COX inhibitors interfere with transformation *in vitro* in high-grade human uterine cancer cells with high levels of *HMGA1a* expression. To this end, we assessed anchorage-independent cell growth in MES-SA cells, which have high levels of *HMGA1a* (4), and SK-UT-1 cells, which have low levels of *HMGA1a* (see Supplementary Fig. S4[7] for comparison of *HMGA1a* expression). Because sulindac is a prodrug that is metabolized to its active forms (sulindac sulfide and sulindac sulfone) *in vivo*, we used the active metabolites for these studies. Sulindac sulfide is a nonsteroidal anti-inflammatory compound with COX-1/COX-2 inhibitory effects; sulindac sulfone does not possess COX inhibitory activity (13). Drug concentrations that can be achieved in the plasma of patients on standard doses of sulindac or celecoxib were incubated with uterine cancer cells (14–16). Strikingly, we found that anchorage-independent cell growth was significantly inhibited by sulindac sulfide (50 μmol/L; $P = 0.03$) or celecoxib (10 μmol/L; $P = 0.03$) in the MES-SA cells (Fig. 2A). In contrast, sulindac sulfone (50 μmol/L) had no effect on foci formation (Fig. 2A). Moreover, cellular proliferation was not affected by any of these compounds (Fig. 2B), indicating that the concentrations were not toxic but rather inhibit foci formation through a transformation-specific mechanism. In contrast to the MES-SA cells, the COX inhibitors had no effect on foci formation in the SK-UT-1 cells (Fig. 2C and D). Taken together, these results indicate that the COX-2 inhibitors are effective *in vitro* in blocking anchorage-independent cell growth in high-grade uterine cancer cells that overexpress *HMGA1a*.

Sulindac and Celecoxib Block Tumorigenesis in Human Uterine Cancer Xenografts Overexpressing *HMGA1a*

Next, we sought to determine if the COX inhibitors could block tumorigenesis in the human uterine cancer cells that express high levels of *HMGA1a in vivo*. To this end, we injected MES-SA human uterine cancer cells s.c. into nude mice fed control diet or diet supplemented with sulindac or celecoxib. Large s.c. tumors formed in all (6 of 6) nude mice on control food after only 14 days (Table 1; Fig. 3A). As expected, the MES-SA xenograft tumors overexpressed *HMGA1a* (Fig. 3B). Tumor volumes ranged from 62.5 to 2025 mm^3 (mean volume, 561 ± 735 mm^3). In contrast, sulindac significantly inhibited tumor formation ($P = 0.02$). Only one small tumor (100 mm^3) formed in the six nude mice treated with sulindac. Moreover, mice treated with

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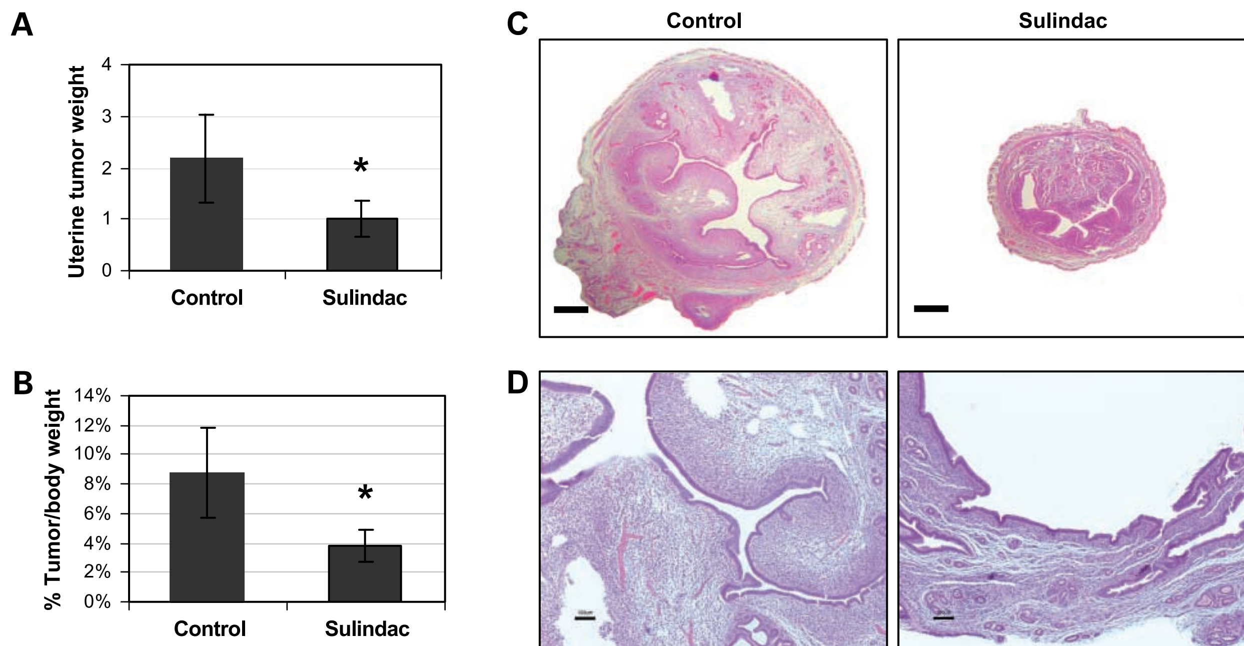

Figure 1. Sulindac inhibits uterine tumorigenesis in the *HMGA1a* mice. **A,** at 29 wk, uterine tumors from the transgenic mice treated with sulindac were significantly smaller that those of control mice. *Columns,* mean uterine weight (g) from five mice in each group; *bars,* SD. *, $P = 0.024$. **B,** uterine tumor weight was divided by the total body weight. Again, tumors in mice treated with sulindac were significantly smaller. *, $P = 0.014$. **C,** transverse section through the uterine horn from a representative *HMGA1a* transgenic mouse treated with sulindac compared with an untreated mouse. Bar, 500 μm. The uterine horn of the untreated mouse is expanded and filled by an intracavitary stromal proliferation. In the treated mouse, the horn and intracavitary lesion are markedly reduced in size. **D,** higher magnification of the uterine tumors from a *HMGA1a* mouse treated with sulindac compared with control (bar, 100 μm) shows a polypoid hypercellular and edematous stromal proliferation with intimately associated glandular epithelium in the untreated mouse. In the treated mouse, the lesion is reduced to an attenuated endometrium lacking the polypoid proliferation.

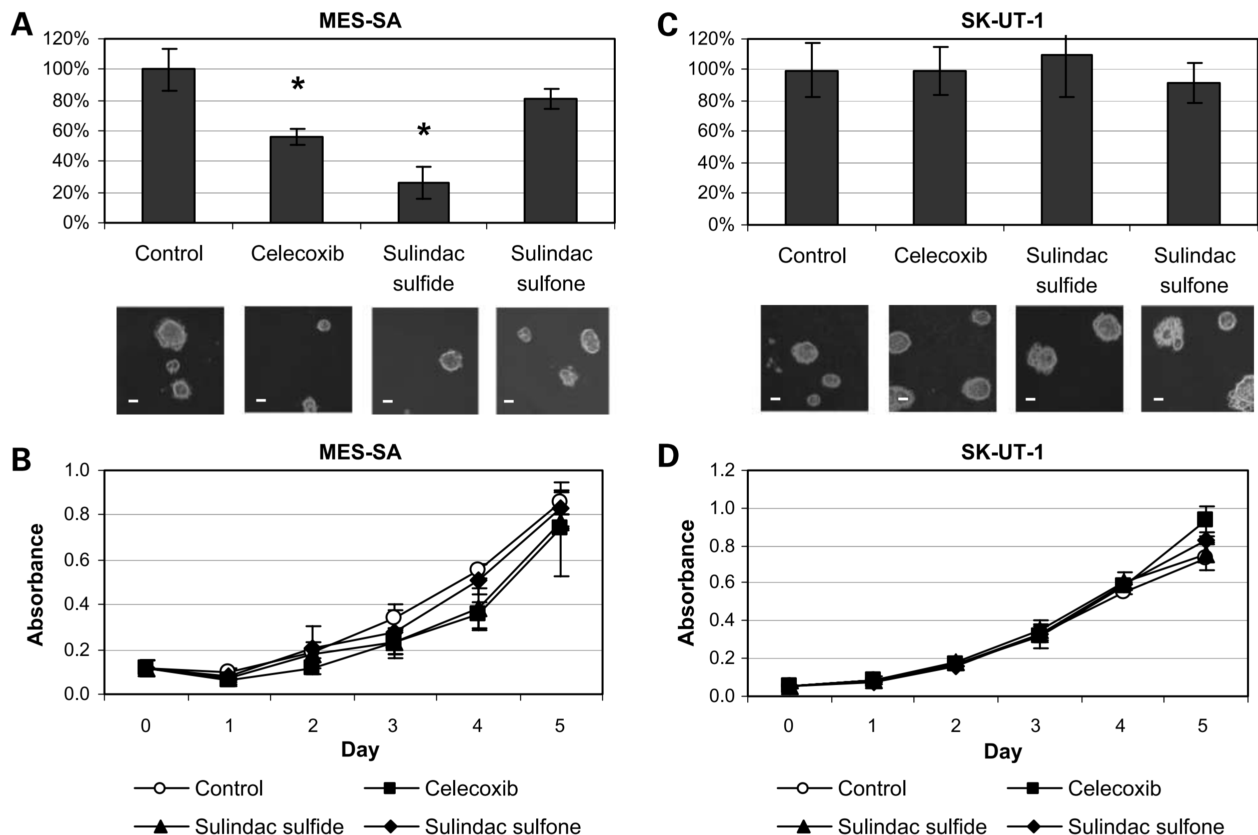

Figure 2. Sulindac sulfide or celecoxib block anchorage-independent cell growth in human uterine cancer cells overexpressing *HMGA1a*. **A,** MES-SA uterine cancer cells form fewer foci on methylcellulose in the presence of celecoxib (10 μmol/L) and sulindac sulfide (50 μmol/L) compared with vehicle control. **B,** cellular proliferation of MES-SA cells is not affected by the sulindac metabolites or celecoxib. **C,** in SK-UT-1 uterine cancer cells, foci formation is not affected by sulindac metabolites or celecoxib. **D,** cellular proliferation is also not affected by sulindac metabolites or celecoxib in the SK-UT-1 cells. Mean ± SD of at least two experiments done in triplicate. *, $P < 0.05$.

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celecoxib developed no tumors (0 of 6; $P < 0.0001$). These findings show that sulindac, which inhibits both COX-1 and COX-2, or celecoxib, a specific COX-2 inhibitor, both block tumorigenesis in our high *HMGA1a*-expressing MES-SA uterine xenograft model (Table 1; Fig. 3). Interestingly, neither inhibitor was effective on SK-UT-1 cells (Supplementary Table S1).[7] *HMGA1a* expression in the SK-UT-1 xenografts was low (Fig. 3B), like we observed in the *in vitro* cell cultures (Supplementary Fig. S4).[7] Taken together, these experiments indicate that sulindac and celecoxib are effective in blocking tumorigenesis in uterine xenografts from high-grade uterine cancer cells that overexpress *HMGA1a*.

Table 1. Effect of sulindac or celecoxib on xenograft tumor formation in nude mice injected with MES-SA (high HMGA1a) human uterine cancer cells

Cell line	Treatment	Tumor, *n* (%)	Tumor volume (mm^3)					
			1	2	3	4	5	6
MES-SA	Control	6/6 (100)	125	270	384	62.5	500	2,025
	Sulindac	1/6 (17)*	100	—	—	—	—	—
	Celecoxib	0/6 (0)†	—	—	—	—	—	—

*$P = 0.02$.
†$P < 0.0001$.

Discussion

Because uterine cancer is common and often fatal, novel strategies to treat or prevent tumor progression in these malignancies will benefit women's health worldwide (1, 2). Although uterine sarcomas comprise only ~5% of all uterine cancers, they are more aggressive and have a worse prognosis than other uterine cancers (3). Leiomyosarcomas constitute ~30% of uterine sarcomas and have a 5-year survival of <20% for tumors that extend beyond the corpus uteri. Malignant mixed mullerian tumors (or carcinosarcomas) represent another high-grade uterine cancer composed of both malignant mesenchymal (sarcomatous) and epithelial (carcinomatous) components. Malignant mixed mullerian tumors represent ~5% of all uterine cancers and have a 5-year survival of 40% to 50% for all stages (2, 3). The ability to perform preclinical trials

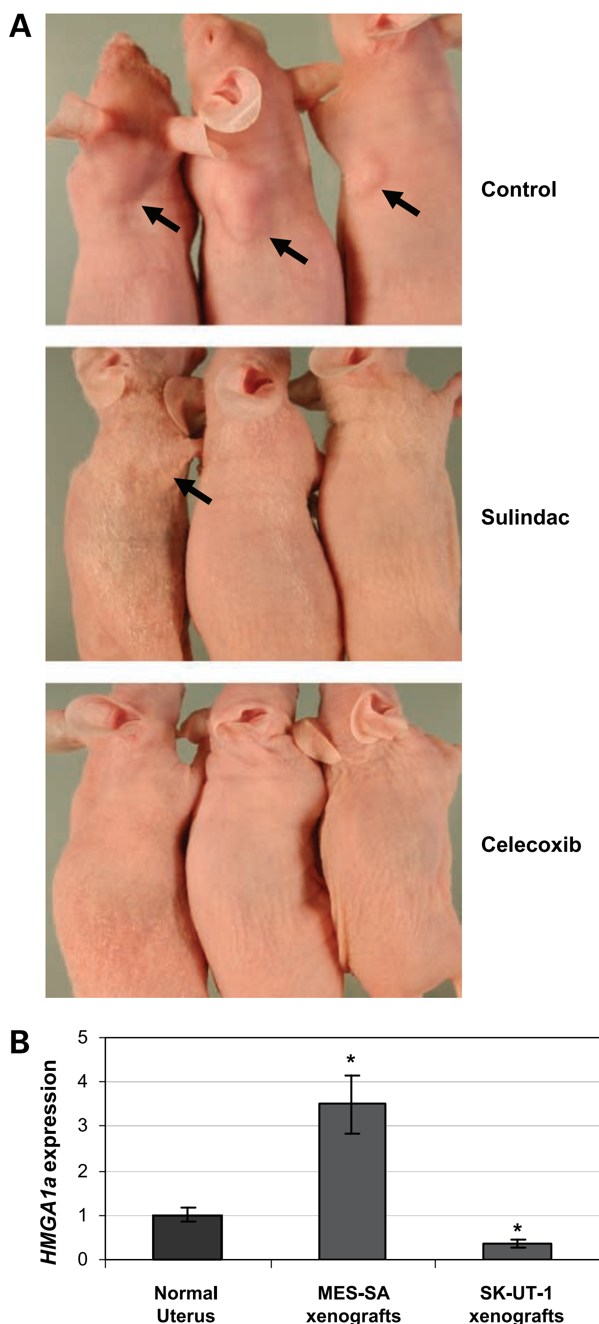

Figure 3. Sulindac and celecoxib block tumorigenesis in human uterine cancer xenografts overexpressing *HMGA1a*. **A,** representative nude mice treated with control food or food supplemented with sulindac or celecoxib. **B,** MES-SA xenografts overexpress *HMGA1a* mRNA compared with normal human uterus or SK-UT-1 xenografts. *Columns,* mean of at least two experiments done in triplicate; *bars,* SD. *, $P < 0.05$.

relevant to these types of aggressive uterine cancer was recently advanced by the development of the *HMGA1a* mice, which develop malignant uterine tumors with complete penetrance by 8 to 10 months of age (4). These mice express *HMGA1a* in the uterus at levels 5- to 15-fold above those observed in normal uteri and up-regulate *COX-2* during uterine tumorigenesis (4). Similarly, our previous study showed that human leiomyosarcomas overexpress *HMGA1a* by 5- to 20-fold above normal uterine tissue and *COX-2* is also up-regulated in these tumors (4). Other mouse models for uterine sarcomas have relied on exposure to carcinogenic agents (17) or overexpression of a viral oncogene (18). Our model is unique because the initiating genetic lesion (overexpression of the *HMGA1a* oncogene) occurs in diverse, high-grade human uterine cancers (4). Using this model, we showed that sulindac blocks uterine tumor growth. Moreover, we showed that both sulindac and celecoxib were effective in blocking transformation in human uterine cancer cells with high levels of *HMGA1a* both *in vitro* and *in vivo.* Our results suggest that uterine cancers characterized by up-regulation of *HMGA1a* will respond to COX inhibitors.

Previous studies have shown that COX inhibitors have pleiotropic antitumor effects, although these investigations have focused primarily on tumors of epithelial origin. Most work in this area has been directed at gastrointestinal tumors with both *in vitro* and *in vivo* studies showing antitumor efficacy with COX inhibitors (5, 12). More recently, epidemiologic studies have shown that individuals who take aspirin, which blocks both COX-1 and COX-2 function, have lower incidences of diverse tumors. Similarly, celecoxib has been shown to have antitumor effects in patients with lung and other cancers (5, 12). Enthusiasm for COX-2 inhibitors has been dampened, however, by the recent reports of cardiovascular toxicity in rare cases. Nonetheless, a recent clinical trial with lung cancer showed benefit in selected patients on celecoxib and no cardiovascular toxicity (19). Thus, the current challenge is to identify selected patients who could benefit from COX-2 inhibitors and to develop next generation agents that lack toxicity. Because uterine cancers that extend beyond the uterus have a dismal prognosis, these patients could benefit from COX inhibitors. The mechanism of action of COX inhibitors is not completely understood, although studies indicate that several pathways may be affected, including angiogenesis, invasion, and inhibition of apoptosis (5). Our *in vitro* and *in vivo* studies showed that sulindac and celecoxib were efficacious in blocking transformation in uterine cancer cells that overexpress *HMGA1a*, suggesting that *HMGA1a* could serve as a marker to identify uterine cancers that may respond to COX inhibitors. The inhibition of anchorage-independent cell growth by celecoxib and sulindac sulfide, and not sulindac sulfone, is consistent with a COX-2-dependent mechanism of action in our *in vitro* studies.

In summary, we show that our *HMGA1a* mouse model is a useful tool for preclinical therapeutic studies. Furthermore, our studies suggest that COX-2 inhibitors could play a role in preventing tumor development or progression in women with high-grade uterine cancers that up-regulate *HMGA1a*. Importantly, COX-2 inhibitors have lower toxicity than the chemotherapeutic agents currently used

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to treat advanced-stage uterine cancers. Moreover, these tumors are typically unresponsive to therapy. Thus, future studies are warranted to investigate the role of COX inhibitors in uterine cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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