Noscapine, a Benzylisoquinoline Alkaloid, Sensitizes Leukemic Cells to Chemotherapeutic Agents and Cytokines by Modulating the NF-κB Signaling Pathway

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Abstract

Noscapine, a benzylisoquinoline alkaloid derived from opium, was recently reported to exhibit activity against a variety of cancers through a poorly understood mechanism. Because the transcription factor NF-κB has been linked with inflammation, survival, proliferation, invasion, and angiogenesis in tumors, we hypothesized that noscapine mediates its effects by modulating the NF-κB activation pathway. We found that noscapine potentiates apoptosis induced by cytokines and chemotherapeutic agents in tumor cells. Noscapine alone suppressed proliferation of human leukemia and myeloma cells and downregulated the constitutive expression of cell survival proteins. Noscapine also abrogated the inducible expression of proteins involved in survival, proliferation, invasion, and angiogenesis, all of which are regulated by NF-κB. Noscapine suppressed both inducible and constitutive NF-κB activation in tumor cells through inhibition of IκB kinase, leading to inhibition of phosphorylation and degradation of IκBα. Noscapine also suppressed phosphorylation and nuclear translocation of p65, leading to inhibition of NF-κB reporter activity induced by various components of the NF-κB activation pathway. Activity of the NF-κB-containing cyclooxygenase-2 promoter was also inhibited by noscapine. Thus, noscapine inhibits the proliferation of leukemia cells and sensitizes them to tumor necrosis factor and chemotherapeutic agents by suppressing the NF-κB signaling pathway. Cancer Res; 70(8); 3259–68. ©2010 AACR.

Introduction

Noscapine (also called narcotine, nectodon, nospen, and anarcotine) is a benzylisoquinoline alkaloid derived from the opium poppy Papaver somniferum. This alkaloid lacks sedative activity and has been used as a cough suppressant for decades, with no evidence of toxicity or side effects (1). In 1998, noscapine was shown to have potent antitumor activity in vitro, including leukemia and lymphoma (3, 4), melanoma (5), ovarian cancer (6), gliomas (7), breast cancer (8), lung cancer (9), and colon cancer (10). This alkaloid also sensitizes human gliomas to taxol and radiation (11). Noscapine inhibits the growth of tumor cells with little toxicity to normal cells (12).

How noscapine exhibits its antitumor effects is not fully understood, but various mechanisms including its ability to inhibit microtubule assembly (2), suppress expression of hypoxia-inducible factor-1α (13), induce p21 and p53 (10), induce apoptosis-inducing factor (14), activate c-Jun NH2-terminal kinase (6), repress Bcl-2 (9), and activate p34 (cdc2) have been implicated. Like paclitaxel, noscapine is a microtubule-interacting agent, but it can efficiently inhibit the growth of both paclitaxel-sensitive and paclitaxel-resistant ovarian cancer cells (6), indicating that noscapine may mediate anticancer effects through other mechanisms. Because of the critical role of NF-κB in inflammation and tumor cell survival, proliferation, invasion, angiogenesis, radioresistance, and chemoresistance (15, 16), we hypothesized that noscapine mediates its effects through modulation of the NF-κB signaling pathway.

NF-κB is a transcription factor that consists of five proteins: c-Rel, RelA (p65), RelB, NF-κB1 (p50 and p105), and NF-κB2 (p52; ref. 17). Under resting conditions, NF-κB consists of a heterotrimer of p50, p65, and IκB subunit α (IκBα) residing in the cytoplasm (18). NF-κB is activated by a sequence involving the phosphorylation, ubiquitination, and degradation of IκBα, and the phosphorylation of p65, which in turn lead to the translocation of NF-κB to the nucleus, where it binds to specific response elements in the DNA (19). NF-κB regulates the expression of several genes whose products are involved in tumorigenesis, including antiapoptotic proteins (e.g., Bcl-2, Bcl-xL, cIAP, survivin, and TRAF1);
cylooxygenase-2 (COX-2); matrix metalloproteinase-9 (MMP-9); genes encoding adhesion molecules, chemokines, and inflammatory cytokines; and cell cycle regulatory genes (e.g., cyclin D1 and c-Myc; ref. 15). Because of the critical role of NF-κB in many cancers and leukemia in particular, we investigated the effects of noscapine on proliferation of leukemia cells, on apoptosis induced by tumor necrosis factor-α (TNF-α) and chemotherapeutic agents, on NF-κB-regulated gene products, and on the NF-κB activation pathway. We found that noscapine is a potent inhibitor of activation of IκB kinase (IKK), which is required for NF-κB activation. Noscapine suppressed the NF-κB pathway, inhibited various gene products, inhibited proliferation, and potentiated apoptosis in leukemia cells.

Materials and Methods

Reagents. A 50 mmol/L solution of (S,R)-noscapine (Sigma-Aldrich) was prepared in 100% DMSO, stored at −20°C, and then diluted as needed in cell culture medium. Bacteria-derived recombinant human TNF-α was kindly provided by Genentech. Penicillin, streptomycin, 5% newborn calf serum (FBS), and 37°C. Cells were stained with 25 μmol/L noscapine for 12 h and then treated with 1 nmol/L TNF for 16 h at 37°C. Cells were stained with the live/dead reagent (5 μmol/L ethidium homodimer and 5 μmol/L calcein-AM) and incubated at 37°C for 30 min. Cells were analyzed under a fluorescence microscope (Labophot-2, Nikon).

Annexin V assay. To detect apoptosis, we used Annexin V antibody conjugated to FITC. In brief, 1 × 10⁶ cells were pretreated with 25 μmol/L noscapine for 12 h, treated with 1 nmol/L TNF for 24 h, and subjected to Annexin V staining. Cells were washed, stained with FITC-conjugated antibody to Annexin V, and analyzed with a flow cytometer (FACScalibur, BD Biosciences).

Terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling assay. We assayed cytotoxicity by the terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) method using an in situ cell death detection reagent (Roche Pharmaceuticals). In brief, 1 × 10⁶ cells were pretreated with 25 μmol/L noscapine for 12 h and with 1 nmol/L TNF for 24 h at 37°C. Thereafter, cells were incubated with reaction mixture for 60 min at 37°C. Stained cells were quantified by flow cytometry (FACScalibur).

Results

The aim of this study was to investigate the effect of noscapine (Fig. 1A) on the NF-κB signaling pathway, NF-κB–regulated gene products, and NF-κB–mediated cellular responses such as survival, proliferation, chemosensitization, invasion, and angiogenesis in leukemia cells. The concentration of noscapine we used, and the duration of exposure, had minimal effect on cell viability as determined by the trypan blue dye exclusion test (data not shown), suggesting that the effects of noscapine on the NF-κB signaling pathway are not due to its cytotoxic effects. To examine the effect of noscapine on the NF-κB activation pathway, we used TNF because the pathway activated by this agent is relatively well investigated. For most studies, we used human leukemia and myeloma cells.

Noscapine potentiates apoptosis induced by TNF and chemotherapeutic agents. Inflammatory cytokines, such as TNF, and chemotherapeutic agents have been shown to activate NF-κB. Because NF-κB activation has been shown to
Figure 1. Noscapine potentiates apoptosis induced by TNF and chemotherapeutic agents. A, chemical structure of noscapine. B, noscapine (Nos) potentiates cytotoxicity induced by TNF and chemotherapeutic agents. KBM-5 cells were pretreated with 25 μmol/L noscapine for 12 h and then incubated with 1 nmol/L TNF, 10 μg/mL thalidomide, 5 nmol/L paclitaxel, and 20 nmol/L bortezomib for 24 h. Cell viability was then analyzed by MTT assay. C, left, noscapine potentiates TNF-induced apoptosis. KBM-5 or U266 cells (1 × 10^6) were pretreated with 25 μmol/L noscapine for 12 h and then incubated with 1 nmol/L TNF for 24 h. Cells were stained with live/dead assay reagent for 30 min and then analyzed under a fluorescence microscope. Right, cells were pretreated with 25 μmol/L noscapine for 12 h and then incubated with 1 nmol/L TNF for 16 h. Cells were incubated with FITC-conjugated antibody to Annexin V, or with TUNEL assay reagent, and then analyzed by flow cytometry for early apoptotic effects. D, left, noscapine enhances TNF-induced caspase activation. Cells were pretreated with 25 μmol/L noscapine for 12 h and then incubated with 1 nmol/L TNF for 16 h. Whole-cell extracts were prepared and analyzed by Western blotting using the indicated antibodies. Right, cells were incubated with 1 nmol/L TNF, alone or with 25 μmol/L noscapine, for the indicated times. PARP cleavage was determined by Western blot analysis.
suppress the apoptosis induced by various chemotherapeutic agents (22–24), we examined the effect of noscapine on apoptosis induced by TNF and chemotherapeutic drugs. As determined by the MTT assay, noscapine significantly potentiated the cytotoxic effects of TNF, thalidomide, paclitaxel, and bortezomib in human leukemia KBM-5 cell lines (Fig. 1B). We also determined the dose of noscapine required to inhibit cell growth by 50% (IC50) either alone or in combination with chemotherapeutic agents. We found that the IC50 of noscapine for KBM-5 cells decreased from 84.4 μmol/L when used alone to 53.6, 18.9, 15.2, and 16.5 μmol/L when combined with TNF (1 nmol/L), thalidomide (10 μg/mL), paclitaxel (5 nmol/L), and bortezomib (16.5 μmol/L), respectively. Similarly, for U266 cells, the IC50 was 155, 72, 47.5, 64.5, and 62.8 μmol/L when used alone or in combination with TNF, thalidomide, paclitaxel, or bortezomib, respectively.

To determine whether noscapine potentiates apoptosis, we used the live/dead assay, which examines intracellular esterase activity and plasma membrane integrity. Noscapine enhanced TNF-induced apoptosis in KBM-5 human chronic myeloid leukemia cells (Fig. 1C, left, top) and U266 human multiple myeloma cells (Fig. 1C, left, bottom). We also used Annexin V staining to examine apoptosis by membrane phosphatidylesterase exposure and found that noscapine potentiated TNF-induced early apoptosis from 5% to 33% (Fig. 1C, right, top). Similarly, when we examined apoptosis by DNA strand breaks using the TUNEL method, we found that noscapine enhanced apoptosis from 6% to 38% (Fig. 1C, right, bottom).

**Noscapine potentiates TNF-induced caspase activation and PARP cleavage.** TNF binds to TNFR1, which then sequentially recruits TNF receptor (TNFR)–associated death domain (TRADD) and TNFR-associated factor 2 (TRAF2), leading to activation of NF-κB and recruitment of Fas-associated death domain, which ultimately leads to activation of caspases (23). We investigated whether noscapine affects TNF-induced activation of caspase-8 (also called FLICE) and caspase-3. TNF alone had a minimal effect on activation of caspase-8 or caspase-3, whereas treatment with noscapine potentiated the activation, as indicated by the presence of cleaved caspases (Fig. 1D, left). We also used the PARP cleavage assay to detect TNF-induced apoptosis. Again, noscapine potentiated the effect of TNF-induced PARP cleavage, although noscapine alone...
Noscapine represses inducible NF-κB–dependent cell proliferation proteins. Various gene products, including cyclin D1 and COX-2, are induced by TNF and have been linked with proliferation of tumor cells (19). Cyclin D1 regulates the cell cycle transition from G1 to S phase and is overexpressed in a variety of tumors (25). COX-2 is an enzyme that catalyzes the production of prostaglandin E2 and has been linked to proliferation and metastasis of tumor cells (26). We examined whether noscapine modulates the expression of proliferative gene products induced by TNF. TNF induced the expression of cyclin D1 and COX-2 in a time-dependent manner, whereas noscapine significantly inhibited their expression (Fig. 3B). These results suggest a molecular mechanism on how noscapine suppresses tumor cell proliferation.

Noscapine suppresses TNF-induced, NF-κB–dependent proteins involved in invasion and angiogenesis. Invasion and angiogenesis are critical for tumor metastasis and are induced by TNF. ICAM-1, MMP-9, and VEGF have been implicated in invasion and angiogenesis (27–29). We therefore examined whether noscapine can suppress the expression of these proteins. TNF treatment induced the expression of VEGF, MMP-9, and ICAM-1 in a time-dependent manner, whereas noscapine inhibited their expression (Fig. 3C). These results suggest a potential mechanism on how this alkaloid suppresses invasion and angiogenesis.

Noscapine inhibits TNF-induced NF-κB activation. Because all of the gene products mentioned above are regulated by NF-κB, we examined whether noscapine modulates the activation of NF-κB. EMSA revealed that noscapine alone had no effect on NF-κB activation; however, noscapine inhibited TNF-mediated NF-κB activation in a dose-dependent manner (Fig. 4A). The suppression of NF-κB activation by noscapine was also time dependent (Fig. 4B).

Noscapine-induced inhibition of NF-κB activation is not cell type specific. Because distinct signal transduction pathways can mediate NF-κB induction in different cell types (30), we examined the effect of noscapine on TNF-induced
NF-κB activation in human embryonic kidney A293 cells and human lung adenocarcinoma H1299 cells. Noscapine inhibited TNF-induced NF-κB activation in both cell types (Fig. 4C).

**Noscapine inhibits constitutive NF-κB activation in tumor cells.** We next tested the effect of noscapine on NF-κB activation in U266 human multiple myeloma and DU145 human prostate cancer cells, which express constitutively active NF-κB (31, 32). Treatment with various concentrations of noscapine suppressed constitutive NF-κB activation in both cell types (Fig. 4D).

**Noscapine inhibits constitutive IκBα phosphorylation and degradation.** The translocation of NF-κB to the nucleus is preceded by the phosphorylation, ubiquitination, and proteolytic degradation of IκBα (33). To determine whether inhibition of TNF-induced NF-κB activation by noscapine is caused by inhibition of IκBα degradation, we pretreated cells with noscapine and then exposed them to TNF for various time periods. EMSA showed that NF-κB was activated with increasing TNF incubation times, and noscapine pretreatment markedly decreased this activation (Fig. 5A). Western blot analysis showed that TNF induced IκBα degradation in control cells within 5 minutes, reaching maximum degradation at 15 to 30 minutes, but TNF could not induce IκBα degradation in noscapine-pretreated cells (Fig. 5B, left, top). These results indicate that noscapine inhibits both TNF-induced NF-κB activation and IκBα degradation.

We next determined whether noscapine affects the TNF-induced IκBα phosphorylation needed for IκBα degradation. TNF induced IκBα phosphorylation in control cells within 5 minutes, but noscapine-pretreated cells inhibited the phosphorylation of IκBα (Fig. 5B, left, second panel from top). Phosphorylated IκBα rapidly undergoes degradation. To stabilize phosphorylated IκBα, we used N-acetyl-leucyl-leucyl-norleucinal (ALLN), which suppresses degradation of IκBα by the 26S proteasome. Western blot analysis using an antibody to the serine-phosphorylated form of IκBα showed that TNF induced IκBα phosphorylation, whereas noscapine suppressed it (Fig. 5B, right).

**Noscapine inhibits TNF-induced activation of IKK.** Because IKK is needed for the phosphorylation of IκBα, we tested the effect of noscapine on TNF-induced IKK activation. Noscapine suppressed TNF-induced activation of IKK (Fig. 5C, left, top). Neither TNF nor noscapine had any effect on the expression of IKKα or IKKβ proteins (Fig. 5C, left, bottom two panels).
We next examined whether noscapine suppresses IKK activity directly by binding to the IKK protein. An immune complex kinase assay of whole-cell extracts from untreated and TNF-treated cells showed that noscapine did not directly affect the activity of IKK, suggesting that noscapine does not directly inhibit IKK but rather modulates the activation of IKK induced by TNF (Fig. 5D, right).

Noscapine inhibits nuclear translocation of p65. Suppression of IκBα degradation is known to inhibit the translocation of p65 to the nucleus. We examined whether noscapine inhibits nuclear translocation of p65 induced by TNF. TNF induced the nuclear translocation of p65 in as little as 5 minutes of incubation, whereas noscapine suppressed p65 translocation (Fig. 5D, top).

Figure 5. Noscapine inhibits TNF-dependent IκBα phosphorylation, IκBα degradation, p65 phosphorylation, and p65 nuclear translocation. A, noscapine inhibits TNF-induced activation of NF-κB. KBM-5 cells were incubated with 50 μmol/L noscapine for 12 h, treated with 0.1 nmol/L TNF for the indicated times, and analyzed for NF-κB activation by EMSA. B, left, effect of noscapine on TNF-induced IκBα degradation and phosphorylation. Cells were incubated with 50 μmol/L noscapine for 12 h and treated with 0.1 nmol/L TNF for the indicated times. Cytoplasmic extracts were prepared, fractionated on SDS-PAGE, and electrotransferred to nitrocellulose membrane. Western blot analysis was performed using the indicated antibody. Anti-β-actin antibody was used as a loading control. Right, effect of noscapine on phosphorylation of IκBα induced by TNF. Cells were preincubated with 50 μmol/L noscapine for 12 h, incubated with 50 μg/mL ALLN for 30 min, and treated with 0.1 nmol/L TNF for 10 min. Cytoplasmic extracts were fractionated and then subjected to Western blot analysis using antibody to phosphorylated IκBα. The same membrane was reblotted with antibody to IκBα. C, left, noscapine inhibits TNF-induced IκBα kinase activity. Whole-cell extracts were immunoprecipitated with antibody against IKKa and analyzed by an immune complex kinase assay. To examine the effect of noscapine on expression of IKK protein, whole-cell extracts were fractionated on SDS-PAGE and examined by Western blot analysis using antibodies to IKKa and IKKβ. Right, direct effect of noscapine on IKK activity induced by TNF. Whole-cell extracts were prepared from KBM-5 cells treated with 1 nmol/L TNF and immunoprecipitated with antibody to IKKa. The immune complex kinase assay was performed with the indicated concentrations of noscapine. D, effect of noscapine on TNF-induced p65 nuclear translocation and phosphorylation. Cells were incubated with 50 μmol/L noscapine for 12 h and treated with 0.1 nmol/L TNF for the indicated times. Nuclear extracts were prepared and performed for Western blot analysis using the indicated antibody. Anti-PARP was used as a loading control for nuclear extract.
The phosphorylation of p65 is required for the transcriptional activity of NF-κB. We assessed whether noscapine affects TNF-induced phosphorylation of p65. In the nuclear fraction of TNF-treated cells, there was a time-dependent increase in the phosphorylation of p65 at Ser536; this phosphorylation was suppressed by noscapine (Fig. 5D, middle).

**Noscapine represses TNF-induced, NF-κB–dependent reporter gene expression.** We investigated whether noscapine modulates NF-κB–dependent reporter gene transcription. TNF produced an 8-fold increase in NF-κB–dependent expression of secretory alkaline phosphatase (SEAP) activity over vector control (Fig. 6A). When the cells were pretreated with various concentration of noscapine, TNF-induced NF-κB–dependent expression of SEAP was inhibited in a dose-dependent manner (Fig. 6A). These results show that noscapine inhibits NF-κB–dependent reporter gene expression induced by TNF.

We next determined where noscapine acts in the TNF-induced NF-κB activation pathway that is sequentially linked through TNFR1, TRADD, TRAF2, NF-κB–inducing kinase (NIK; refs. 34, 35), transforming growth factor-β–activated kinase 1 (TAK1)/TAK1-binding protein (TAB1; ref. 36), and IKK recruitment. Transfection of cells with plasmids expressing TNFR1, TRADD, TRAF2, NIK, TAK1/TAB1, IKKβ, or p65 induced NF-κB–dependent reporter gene expression; noscapine suppressed reporter gene expression induced by all plasmids except p65 (Fig. 6B), indicating that noscapine acts at a site upstream to p65.

**Noscapine inhibits TNF-induced COX-2 promoter activity.** TNF induces COX-2, which has NF-κB binding sites in its promoter (37). Because downregulation of NF-κB by noscapine suppressed the expression of NF-κB–regulated gene products, including COX-2, we examined the effect of noscapine on TNF-induced COX-2 promoter activity using a COX-2 promoter-luciferase reporter plasmid. TNF induced COX-2 promoter activity, whereas noscapine suppressed this activity in a dose-dependent manner (Fig. 6C). This result suggests that noscapine inhibits NF-κB–regulated gene expression by suppressing NF-κB binding to the COX-2 promoter.

**Discussion.**

The aim of this study was to investigate the mechanism by which noscapine mediates antitumor effects. Because NF-κB has been linked to survival, proliferation, chemoresistance, invasion, and angiogenesis, we investigated the effects of noscapine on the NF-κB signaling cascade. We found that noscapine inhibited the proliferation of various tumor cell lines; potentiating the apoptosis induced by chemotherapeutic agents; suppressed the expression of antiapoptotic gene products that are regulated by NF-κB; and inhibited NF-κB activation through inhibition of IKK activation, IκBα phosphorylation, IκBα degradation, and p65 phosphorylation. Thus, we have identified NF-κB as a novel target for the action of noscapine.

We found that noscapine inhibits the proliferation of various tumor cell lines, including T-cell leukemia, chronic myeloid leukemia, lymphoma, multiple myeloma, prostate cancer, and squamous cell carcinoma. These results agree with previous reports that this alkaloid inhibits the growth of leukemia and lymphoma (3, 4), melanoma (5), ovarian cancer (6), gliomas (7), breast cancer (8), lung cancer (9), and colon cancer (10). We found that the inhibition of cell proliferation by noscapine is...
associated with downregulation of constitutive NF-κB activation and inhibition of expression of survivin, cIAP-1, cFLIP, XIAP, Bcl-xl, TRAF1, Bcl-2, and Mcl-1. Our results agree with a report that noscapine suppresses Bcl-2 expression (9).

Besides antiapoptotic proteins, noscapine also down-regulates the expression of proteins linked to cell proliferation (cyclin D1), inflammation (COX-2), invasion (MMP-9), adhesion (ICAM-1), and angiogenesis (VEGF). These observations imply that noscapine has anti-inflammatory, antiangiogenic, and antimetastatic activities. In hypoxic human glioma cells, noscapine has been shown to inhibit the secretion of VEGF (13).

We also found that noscapine suppresses TNF-induced NF-κB activation. The suppression of NF-κB activation was accompanied by inhibition of IκB phosphorylation and degradation, as a result of inhibition of IKK activation. Numerous kinases have been implicated in the activation of IKK, including TAK1, which plays a major role in TNF-induced IKK activation. We found that noscapine inhibits TAK1-induced NF-κB reporter activity. Thus, TAK1 may be a direct target of noscapine in the NF-κB pathway. We found that noscapine also abrogated nuclear translocation and phosphorylation of p65, which has been linked to IKK (39). The inhibition of p65 phosphorylation by noscapine may therefore result from its inhibition of IKK.

Noscapine has been reported to suppress the transcription factor hypoxia-inducible factor 1 in human gliomas (13). We now find that noscapine also inhibits the NF-κB pathway. Although noscapine binds tubulin and suppresses microtubule assembly, like paclitaxel, noscapine also suppresses growth of paclitaxel-resistant cells, suggesting a difference in the mechanisms of action of the two compounds. Whereas noscapine inhibits NF-κB activation, paclitaxel has been shown to activate NF-κB. Our results indicate for the first time that unlike most other inhibitors of microtubule assembly (40), noscapine exhibits anti-inflammatory activities.

Whether all these activities are interconnected, however, is not certain. It is also not clear whether metabolites of noscapine, such as meconine, cortarnine, and hydrocotamine (41), are involved in additional activities. Vinblastine-resistant human T-lymphoblastoid cells have been shown to undergo apoptosis when exposed to noscapine analogues (4). Because NF-κB activation has been closely linked to drug resistance, this noscapine-induced sensitization of tumor cells to chemotherapeutic agents may be mediated through downregulation of NF-κB, as described above. This may also explain how noscapine overcomes resistance to paclitaxel. Unlike paclitaxel, noscapine is highly water soluble, well tolerated, and highly bioavailable (10). Noscapine alone has been shown to suppress the growth of a variety of tumors in rodent models (5, 8, 9, 42).

Preclinical pharmacokinetics and bioavailability of noscapine have been examined (43). The pharmacokinetics of oral noscapine in 20 healthy volunteers given 100, 200, and 300 mg tablets of noscapine or 200 mg as a solution indicated the terminal half-life of noscapine as 4.5 h, which was independent of formulation or dose (44). A phase I/II clinical trial with noscapine for non–Hodgkin’s lymphoma and for multiple myeloma are in progress (http://www.clinicaltrials.gov).

Overall, our results suggest that noscapine, a component of opioids, mediates antiproliferative, proapoptotic, anti-invasive, antiangiogenic, and chemosensitive effects through the suppression of NF-κB and NF-κB-regulated gene products. Our study suggests a novel function and a potential use in cancer treatment for this ancient drug.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Pierrette Lo for proofreading the manuscript and providing valuable comments.

Grant Support

Clayton Foundation for Research (B.B. Aggarwal), NIH core grant CA16672, NIH program project grant CA124767-01A2, and Center for Targeted Therapy at M.D. Anderson Cancer Center. B.B. Aggarwal is the Ransom Horne, Jr., Professor of Cancer Research.

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Received 11/18/2009; revised 01/19/2010; accepted 02/09/2010; published OnlineFirst 03/30/2010.

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Cancer Res 2010;70:3259-3268. Published OnlineFirst March 30, 2010.

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