Inhibition of Cyclooxygenase-2 Indirectly Potentiates Antitumor Effects of Photodynamic Therapy in Mice

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ABSTRACT

Purpose: The aim of the present study was to potentiate the antitumor effectiveness of photodynamic therapy (PDT). A cDNA microarray analysis was used to evaluate the gene expression pattern after Photofrin-mediated PDT to find more effective combination treatment with PDT and inhibitor(s) of the identified gene product(s) overexpressed in tumor cells.

Experimental Design: Atlas Mouse Stress Array was used to compare the expression profile of control and PDT-treated C-26 cells. The microarray results have been confirmed using Western blotting. Cytostatic/cytotoxic in vitro assay as well as in vivo tumor models were used to investigate the antitumor effectiveness of PDT in combination with cyclooxygenase (COX) 2 inhibitors.

Results: PDT induced the expression of 5 of 140 stress-related genes. One of these genes encodes for COX-2, an enzyme important in the tumor progression. Inhibition of COX-2 in vitro with NS-398, rofecoxib, or nimesulide, or before PDT with nimesulide did not influence the therapeutic efficacy of the treatment. Administration of a selective COX-2 inhibitor after PDT produced potentiated antitumor effects leading to complete responses in the majority of treated animals.

Conclusions: COX-2 inhibitors do not sensitize tumor cells to PDT-mediated killing. However, these drugs can be used to potentiate the antitumor effectiveness of this treatment regimen when administered after tumor illumination.

INTRODUCTION

PDT is an effective treatment modality used for the management of solid tumors (1). It is approved for use as a primary therapy for early stage disease, a palliation in advanced cancers, and as a surgical adjuvant in the treatment of lung, bladder, esophageal, and gastric cancers in many countries. Moreover, PDT is extensively investigated in clinical trials in the treatment of many other cancers including breast, colon, and bile duct cancers or brain tumors (1, 2).

PDT is a two-stage treatment. First, a photosensitizer is administered systemically and accumulates with some selectivity within the tumor. Then, a monochromatic and collimated beam of laser light is used to precisely illuminate the tumor (1). Therefore, PDT can be regarded as a dual specificity treatment. In the presence of oxygen the laser light activates the photosensitizer and initiates a complex photochemical reaction that generates cytotoxic intermediates (3). The damaging effects are specifically directed to the tumor and the nearest normal tissue. The antitumor effects of PDT result from direct killing of tumor cells as well as tumor vasculature (1, 4). Moreover, PDT-induced inflammatory and possibly adaptive immune responses can also contribute to the tumor destruction (5).

Many factors influence the effectiveness of PDT including the type of photosensitizer and, hence, the wavelength of laser light, the doses of the photosensitizer, and the fluence rate of the light (6). Additional critical parameters that influence the outcome of PDT include the origin of the tumor, its size, and oxygenation status (7). Heavily pigmented tumors, such as melanoma, or poorly vascularized tumors are resistant to PDT (8, 9). Accumulating evidence indicates that tumor cells can respond to photodynamic damage by either initiating a rescue response or by undergoing cell death by apoptosis or necrosis (10). Rescue responses to sublethal changes, which are particularly important in deeper layers of the tumor exposed to laser illumination, allow tumor cells to cope with the damage induced by the physicochemical stress. The surviving cells might be the cause of relapse rendering the treatment less effective. Therefore, elucidation of molecular changes in the treated cells, as well as identification of drugs that might interfere with rescue responses, becomes an important area of investigation. A sensitive and comprehensive approach to investigate the cellular

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2 The abbreviations used are: PDT, photodynamic therapy; COX, cyclooxygenase; HO, heme oxygenase; C-26, murine colon-26.
response of tumor cells to PDT should be provided by a gene expression analysis. Therefore, the aim of the present study was to analyze gene expression pattern after photodynamic treatment using a cDNA microarray technique and to exploit the results from the microarray studies to find more effective combination treatment with PDT and inhibitor(s) of the identified gene product(s) overexpressed in tumor cells.

**MATERIALS AND METHODS**

**Mice.** BALB/c mice, 8–12 weeks of age, were used in the experiments. Breeding pairs were obtained from the Institute of Oncology (Warsaw, Poland). All of the experiments with animals were performed in accordance with the guidelines approved by the Ethical Committee of the Medical University of Warsaw.

**Reagents.** Photofrin was a generous gift of QLT Phototherapeutics, Inc. (Vancouver, British Columbia, Canada). NS398 and nimesulide were purchased from Biomol Research Laboratories, Inc. (Plymouth Meeting, PA), and rofecoxib was obtained from Merck Research Laboratories (Rahway, NJ).

**Tumor.** C-26, a poorly differentiated colon adenocarcinoma cell line, was obtained from Prof. Czestaw Radzikowski (Institute of Immunology and Experimental Medicine, Wroclaw, Poland). Cells were cultured in RPMI 1640 (Life Technologies, Inc., Paisley, United Kingdom) supplemented with 10% heat-inactivated FCS, antibiotics, 2-mercaptoethanol (50 μM), and L-glutamine (2 mM; all from Life Technologies, Inc.), hereafter referred to as culture medium.

**DNA Microarray Analysis.** C-26 cells were cultured with 10 μg/ml Photofrin for 24 h before illumination. After washing with PBS, the cells were illuminated with a 50-W sodium lamp (Philips) with a light filtered through a red filter to a final dose of 4.5 kJ/m². Two h later, total RNA was extracted from control and PDT-treated C-26 cells using a TRizol reagent (Clontech, Palo Alto, CA). cDNA probes were radiolabelled with [α-33P]dATP (Amersham-Pharmacia-Biotech, Freiburg, Germany), and cDNA was generated according to the Clontech protocol using the Moloney murine leukemia virus reverse transcriptase. The radiolabelled cDNA probes were purified from unincorporated nucleotides by gel filtration in Chroma Spin-200 columns (Clontech) and hybridized at 68°C to an Atlas Mouse Stress Array consisting of 140 known murine genes under tight transcriptional control as described by the manufacturer (Clontech). A complete list of genes, including GenBank and Swiss-Prot accession numbers, is provided. After four high stringency washes at 68°C, the membranes were exposed to a Phosphor Screen for 24 h and scanned with a Molecular Imagar FX phosphoimager (Bio-Rad, Hemel Hempstead, United Kingdom) at 50-μm resolution. Signals of paired control and PDT-treated cells were quantified using the TotalLab software.

**Western Blotting.** For Western blotting C-26 cells were cultured with 10 μg/ml Photofrin for 24 h before illumination. After washing with PBS, the cells were illuminated with a 50-W sodium lamp (Philips) with a light filtered through a red filter to a final dose of 4.5 kJ/m². After 1, 2, 4, 12, or 24 h of culture in the fresh medium the cells were washed with PBS and lysed with radiiodinontoprecipitation assay buffer (Tris base 50 mM, NaCl 150 mM, NP40 1%, sodium deoxycholate 0.25%, and EDTA 1 mM) with protease inhibitors mixture (Roche Diagnostics, Mannheim, Germany). Protein concentration was measured with the use of BCA protein assay (Pierce, Rockford, IL). Equal amounts of proteins were separated on 12% SDS-polyacrylamide gel, transferred onto polyvinylidene difluoride membranes, blocked with TBST [Tris buffered saline (pH 7.4) and 0.05% Tween 20] with 5% nonfat milk and 5% PBS. The following antibodies were used for the 6-h incubation: mouse monoclonal anti-β-tubulin at 1:2500 dilution (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and goat polyclonal anti-COX-2 at 1:2000 dilution (Santa Cruz Biotechnology). After extensive washing with TBST the membranes were incubated for 45 min in corresponding alkaline phosphatase-coupled secondary antibodies (Jackson Immuno Research Inc. West Grove, PA). The color reaction was developed using nitroblue tetrazolium and 5-bromo-4-chloro-3-indolyl phosphate (Sigma).

**Cytostatic/Cytotoxic Assay.** The cytostatic and/or cytotoxic effects of combination treatment were measured using a crystal violet staining. The C-26 cells were dispersed into a 96-well flat-bottomed microtiter plate (Nunc) at a concentration 5 × 10³ cells/100 μL/well and allowed to attach overnight. Then, the cells were treated for 24 h with the COX-2 inhibitors (nimesulide, rofecoxib, and NS-398) or control DMSO-containing medium and Photofrin (10 μg/ml final concentration). After a 24-h incubation, the medium in each well was replaced with a fresh no-phenol red RPMI 1640, and the cells in each well were exposed to a laser light delivered through a fiberoptic light delivery system. The illumination area was matching the size of the wells. Right after the illumination the medium was completely removed and replaced with fresh medium containing COX-2 inhibitors or a control medium. After another 24-h incubation the medium was removed, and the wells washed with PBS and stained with 0.5% crystal violet in 30% ethanol for 10 min at room temperature. The plates were washed four times with tap water. The cells were lysed in 1% SDS solution, and dye uptake was measured at 550 nm using an ELISA reader (SLT Labinstrument GmbH, Salzburg, Austria). The relative viability was calculated as follows: relative viability = [(experimental absorbance – background absorbance)/(untreated control absorbance – background absorbance)] × 100%.

**Tumor Treatment and Monitoring.** For in vivo experiments exponentially growing C-26 cells were harvested, resuspended in PBS at a concentration of 2 × 10⁶/20 μL of PBS, and injected into the footpad of the right hind limb of experimental mice. Tumor cell viability measured by trypan blue exclusion was 98%. Tumor bearing mice were treated with nimesulide i.p. at a dose of 50 mg/kg dissolved in DMSO and suspended in PBS. Mice in the control group received DMSO dissolved in PBS in the same regimen as nimesulide-treated mice. Nimesulide was administrated in two different schedules. One involved administration of nimesulide before PDT on days 4–7 after inoculation of tumor cells (the last dose of COX-2 inhibitor was administrated immediately before illumination of tumors). In the 3 Internet address: http://www.clontech.com/atlas/genelists/index.shtml.
second schedule nimesulide was administered immediately after light exposure, at 4, 24, and 48 h after light exposure, and every other day until the day 22 of the experiment. PDT was performed as described (11). Photofrin was administered i.p. at a dose of 10 mg/kg 24 h before illumination with 630 nm light (day 6 after inoculation with tumor cells). Control mice received 5% dextrose. The light source was a He-Ne ion laser (Laser-Project 2000, Warsaw, Poland). The light was delivered on day 7 after inoculation with tumor cells using a fiberoptic light delivery system. The power density at the illumination area, which encompassed the tumor and 1–1.5 mm of the surrounding skin, was ~80 mW/cm² (40 mW laser output). The total light dose delivered to the tumors was 120 J/cm². During the light treatment mice were anesthetized with ketamine (87 mg/kg) and xylazine (13 mg/kg), and restrained in a specially designed holder. Local tumor growth was determined as described (12) by the formula: tumor volume (mm³) = (longer diameter) × (shorter diameter)². Relative tumor volume was calculated as follows: relative tumor volume = [(tumor volume)/(initial tumor volume)] × 100%.

RESULTS

PDT induces oxidative stress in tumor cells. Therefore, radioactively labeled cDNA of PDT-treated and untreated control tumor cells were hybridized to Atlas Mouse Stress Array and processed as described in “Materials and Methods.” This analysis revealed that only 5 of 140 genes were at least 2-fold overexpressed in PDT-treated as compared with control tumor cells. These included HO-1, aldehyde dehydrogenase, RhoB, cytochrome P450, and COX-2. The most interesting of these genes was COX-2 because of the role played by this enzyme and the ready availability of specific inhibitors. A time course cDNA microarray analysis revealed that COX-2 expression was already increased at 1 h and slightly diminished at 4 h after PDT (data not shown). There was no induction of COX-1 gene. To confirm the findings by microarray analysis, the expression level of COX-2 was additionally examined using Western immunoblot analysis. In agreement with microarray studies, we observed a time-dependent induction of COX-2 expression that peaked 2 h after PDT (Fig. 1). At 4 h after PDT there was a drop in the COX-2 expression followed by an increase during 24 h after PDT.

To investigate whether COX-2 is up-regulated in tumor cells as an adaptive response conferring increased resistance to PDT, we incubated C-26 cells with various doses of selective COX-2 inhibitors. Quite unexpectedly, neither rofecoxib, NS-398, nor nimesulide were capable of sensitizing tumor cells to PDT-induced damage (Fig. 2). Therefore, these studies are in apparent contrast with the observations by Ferrario et al. (13), who showed that a COX-2 inhibitor potentiates the antitumor effects of PDT in mice. COX-2 inhibitors demonstrate pleiotropic antitumor effects that include induction of apoptosis and inhibition of angiogenesis. Because NS-398 used by Ferrario et al. (13) was used chronically for 20 days after PDT it seems possible that the potentiating effects were indirect and resulted from independent antitumor effects of NS-398. To verify this hypothesis we performed in vivo experiments with C-26-bearing mice treated with PDT and two different COX-2 inhibitor schedules (Fig. 3). One group of mice was treated with nimesulide before PDT, and another group received chronic nimesulide until day 22 of the experiment. Photodynamic treatment resulted in a statistically significant retardation of tumor growth (P < 0.05 on days 15–21 as compared with controls; Student’s t test) and prolonged the survival of mice (P < 0.05 as compared with controls; log-rank test). Administration of nimesulide before PDT did not influence the effectiveness of this treatment regimen. However, when given chronically after illumination of tumors it significantly (P < 0.05 on days 13–23 as compared with all other groups; Student’s t test) potentiated antitumor effects of PDT. Additionally, the combination treatment resulted in complete cures in 6 of 8 mice (P < 0.05 as compared with all other groups; log-rank test).

DISCUSSION

PDT is a promising treatment of various malignant and nonmalignant disorders. In the United States only Photofrin-PDT has been approved by the FDA for treatment of early and late endobronchial non-small cell lung cancer in patients for whom surgery and radiotherapy are not indicated, and for palliative treatment of advanced esophageal cancer (1, 2). Approval is pending for early stage esophageal cancer in conjunction with Barrett’s esophagus. At least five other photosensitizers are in various stages of clinical trials. Despite these developments...
Another, unbiased approach to find more effective combination therapies aimed at potentiating the antitumor effectiveness of PDT is to identify critical gene products induced in tumor cells capable of conferring survival advantage in the setting of oxidative stress. To this end we have undertaken cDNA microarray analysis of tumor cells exposed to PDT.

Two previous studies have used cDNA microarray technique to analyze the gene expression pattern in tumor cells after PDT. Verwanger et al. (19) used 5-aminolevulinic acid as a photosensitizer, and hybridized cDNA from control and PDT-treated tumor cells to the UniGene-set bacterial colony filters representing 16,000 different expressed sequence tags. Wang et al. (20) and we in the present study have used microarrays that contained more restricted sets of genes involved in the stress response of human and murine cells, respectively. With the exception of HO-1, all of these studies revealed nonoverlapping sets of genes induced by PDT. However, it should be emphasized that these studies used different cell lines, different photosensitizers, or different regimens of PDT. We have also performed a microarray analysis using a human pancreatic PaCa2 cells and Atlas Human Stress Array (data not shown). Although this array did not contain sequences for COX-2 we observed a marked induction of a gene encoding HO-1. Interestingly, we did not detect induction of heat shock protein 27 as did Wang et al. (20). This apparent discrepancy can be explained by the fact that we used cDNA from cells exposed to a single PDT as opposed to Wang et al. (20), who compared the expression profile of control cells and cells resistant to PDT obtained after a series of illuminations.

It was observed previously that biologically active COX-2 but not COX-1 can be induced in tumors growing in mice and treated with Photofrin-PDT (13). Because of the many roles in tumor progression and the ready availability of specific inhibitors we have focused our additional studies on the role of COX-2 as a potential enzyme capable of protecting tumor cells from PDT-induced damage. COX-2 inhibitors are effective in potentiating the antitumor activity of chemo- and radiotherapy (21–23). The mechanisms of their antitumor effects include induction of apoptosis as well as inhibition of angiogenesis (24–26). COX-2 inhibitors, including nimesulide, decrease secretion of angiogenic growth factors by tumor cells (27, 28). In the present study we observed that COX-2 inhibitors did not influence the antitumor effectiveness of PDT in vitro nor in the sensitization model in mice. Therefore, it is possible that the effects of these drugs may include interference with the reconstruction of blood vessels damaged by PDT.

Tumor destruction after PDT results from direct cytotoxic effects toward tumor cells, vascular damage, and induction of inflammatory reaction (1, 6). The relative contribution of all of these factors is difficult to establish; however, it seems that all of them are necessary for the successful outcome of the treatment. Tumor cell clonogenicity at various times after PDT revealed that direct photodynamic tumor cell kill is far short of the 6–8 log reduction required for tumor cure (29). PDT leads to a vascular damage that results from vessel constriction, increased vascular permeability, platelet activation, and the formation of thrombi and induction of leukocyte adhesion and diapedesis (6). Destruction of both tumor and normal microvasculature is responsible for optimal antitumor effects. Shielding

relapses do occur after PDT, and strategies to improve the therapeutic efficacy of this procedure are being intensively searched for.

The critical parameters that might limit the therapeutic effectiveness of PDT include inhomogeneous distribution of photosensitizer, photobleaching, tumor hypoxia, and vascularization status. Some of these problems have been to some extent overcome by procedures that involve fractionated light delivery (14), hyperbaric oxygen treatment (15), administration of erythropoietin (16), or stimulation of the inflammatory response (17, 18).
of normal tissues surrounding the tumor greatly decreases tumor curability by PDT (30). Vessel constriction and platelet aggregation occur within minutes after initiation of light treatment (4). Fractionated photosensitizer dosing that optimizes for both vascular and tumor compartment damage was superior to single dosage in controlling tumor growth (31). All of these data indicate that vascular damage contributes to long-term tumor control and that strategies that additionally target vasculature should result in potentiated antitumor effectiveness of PDT. Indeed, as shown by Ferrario et al. (32), antiangiogenic treatment after PDT resulted in stronger antitumor effects of PDT.

Because COX-2 inhibitors potentiate the antitumor effects of PDT indirectly, possibly through inhibition of angiogenesis, the combined modality should not cause enhanced skin photosensitivity, which is a major concern with Photofrin. Another major problem of PDT, especially in the treatment of esophageal lesions, is pain, which can be severe and last for days (2). Because COX-2 inhibitors are effective in attenuating acute and chronic pain (33, 34) it is possible that their use in combination with PDT might improve both antitumor effectiveness and patient quality of life.

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