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Effect of Taxol and Taxotere on Gene Expression in Macrophages: Induction of the Prostaglandin H Synthase-2 Isoenzyme

Philip J. Moos,* D. T. Muskardin,† and F. A. Fitzpatrick*‡

Induction of genes encoding cytokines or other, unidentified proteins may contribute to the pharmacological effects of taxol. We hypothesized that prostaglandin H synthase-2 (PGHS-2) was one of the unidentified genes induced by taxol. Taxol alone or taxol plus IFN-γ increased PGE2 formation, PGHS-2 protein expression, and PGHS-2 mRNA expression in RAW 264.7 murine macrophages. The kinetics for mRNA induction, protein expression, and catalysis were self-consistent. A selective inhibitor of PGHS-2 blocked PGE2 formation by cells incubated with taxol; a selective inhibitor of PGHS-1 had no effect. A glucocorticoid blocked the induction of mRNA, the expression of PGHS-2 protein, and the formation of PGE2. Neither taxol alone nor taxol plus IFN-γ altered the expression of the PGHS-1 isoenzyme in RAW 264.7 cells. Taxotere, an analogue that stabilizes microtubules as potently as taxol, did not alter the expression of PGHS-2, implying that its induction in RAW 264.7 murine macrophages did not originate from microtubule stabilization. Taxol and taxotere each induced PGHS-2 expression in human monocytes suspended in 10% human serum. However, human monocytes suspended in 10% bovine serum responded only to LPS, not to taxol or taxotere, implying that they act independently of the LPS-mimetic process that is prominent in mice. Taxol induced PGHS-2 in human and murine macrophages via a p38 mitogen-associated protein kinase pathway. The inclusion of PGHS-2 among the early response genes induced in leukocytes may be relevant to the beneficial and adverse effects encountered during taxol administration. The Journal of Immunology, 1999, 162: 467–473.

T

axol (paclitaxel) and taxotere (docetaxel) are diterpenes that bind to tubulin and derange the equilibrium between microtubule assembly and disassembly (1, 2). Stabilization of microtubules by taxol impairs mitosis and exerts an antineoplastic effect in several common tumors (3, 4). Recent investigations suggest that taxol acts by additional mechanisms that are distinct from its effects on microtubules. Namely, taxol induces the expression of genes encoding TNF-α and certain cytokines that can activate immune surveillance and lymphocyte-mediated tumor destruction (5–15). Induction of these and other unidentified genes may contribute to the pharmacological and toxicological profile of taxol (3, 4, 15–17). We hypothesized that prostaglandin H synthase-2 isoenzyme (PGHS-2) (18, 19) would be one of these unidentified genes, and that increased formation of prostanoid mediators would influence the pharmacology of taxol. This hypothesis originates from four observations. First, taxol may share a signaling pathway with LPS (5–7, 20), and LPS induces PGHS-2 (21, 22). Second, taxol activates NF-κB, which can modulate the transcription of PGHS-2 (23, 24). Third, alterations in cellular eicosanoid formation are consistent with several toxic effects encountered during taxol administration (16, 17). Fourth, management of these toxic effects with corticoids is compatible with suppression of genes such as PGHS-2 (22, 25). Experiments using RAW 264.7 murine macrophages and human monocytes substantiate our hypothesis. However, in human monocytes taxol and taxotere both induced PGHS-2 expression via a pathway that does not involve the LPS-mimetic process that is prominent in murine cells (5–7, 20, 26).

Materials and Methods

Reagents

We used taxol and taxotere (Calbiochem (La Jolla, CA) or Pharmacia & Upjohn Co. (Fiscataway, NJ)); SB203580 (Upstate Biotechnology, Lake Placid, NY); PGF2α-acetylcholinesterase conjugate, NS398 (N-2-cyclohexyloxy-4-nitrophenyl)methanesulfonamide) (27), valeryl salicylic acid (28), and PGE2 (Cayman Chemical, Ann Arbor, MI); dexamethasone, acetylsalicyclic acid, N-(naphthyl)-ethylenediamine, sulfanilamide, and LPS Escherichia coli strain 0111:B4 (Sigma, St. Louis, MO); RAW 264.7 transformed murine macrophages (American Type Culture Collection, Manassas, VA); RPMI 1640, DMEM, endotoxin-free PBS (lots 11112588 and 11112466, HyClone, Logan, UT); and human serum (lot CS14C, Scantibodies Laboratory, Santee, CA); murine recombinant IFN-γ (Life Technologies, Grand Island, NY); arachidonic acid (NuChek Prep, Elyssian, MN); goat anti-rabbit horseradish peroxidase (HRP) conjugate, streptavidin-HRP conjugate, and biotinylated m.w. standards (Bio-Rad, Richmond, CA); and enhanced chemiluminescence reagents (Amersham, Arlington Heights, IL). We used rabbit polyclonal antiserum that recognizes the unique 18-amino acid insert of murine PGHS-2 (Dr. D. Jones, University of Utah), and rabbit polyclonal Ab against PGHS-1 that has no cross-reaction with PGHS-2 (Dr. D. DeWitt, Michigan State University). We used restriction enzymes (Life Technologies), pBlueScript II-SK+ (Stratagene, La Jolla, CA); MAXScript in vitro transcription kits, murine pTRI-GAPDH antisense template (Ambion, Austin, TX); Cytostar-T plates (Amersham); and T7 or T3 phage RNA polymerase for RNase protection assays. PBS is 100 mM phosphate buffer, pH 7.4, with 150 mM NaCl. TBS is 50 mM Tris buffer, pH 7.0, with 150 mM NaCl. Lysis buffer is 20 mM

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3 Abbreviations used in this paper: PGHS prostaglandin H synthase; HRP, horseradish peroxidase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; TBS, Tris-buffered saline; NOS, nitric oxide synthase; NO, nitric oxide; MAPK, mitogen-associated protein kinase.
Tris HCl, pH 7.5, containing 16 mM 3-(3-cholamidopropyl)dimethylamino)-1-propane-sulfonate, 1 mM EDTA, 1 mM benzamide, 1 µg/ml leupeptin, and 10 µg/ml soybean trypsin inhibitor. Electrophoresis buffer is 20 mM Tris-HCl, pH 6.8. Sample buffer is 0.4% (w/v) SDS, 50% (v/v) glycerol, 0.24 M 2-ME, and bromophenol blue.

**Assays for cellular PGHS and NOS activity**

We maintained RAW 264.7 macrophages in DMEM medium supplemented with 10% FBS, 2 mM l-glutamine and penicillin/streptomycin. We isolated, washed, and resuspended cells in medium with 2% FBS (1 x 10⁶ cells/ml) with or without 10 U of murine IFN-γ/ml, and we incubated them at 37°C with 10 µM taxol or DMSO vehicle (0.1% (v/v) final concentration). We sampled medium (1.0 ml) for quantification of nitrite, an index of cellular NOS activity (29). We retained the cells for immunochemical analysis of PGHS-1 and PGHS-2 isoenzymes. We measured PGHS activity by providing cells with exogenous arachidonic acid, the substrate for PGHS, and measuring its conversion into PGE₂. Specifically, we incubated cells with taxol and IFN-γ, as described above. At 0, 1, 2, 4, 6, 12, and 24 h we removed the medium, added 30 µM arachidonic acid in PBS, and incubated the cells for 15 min at 37°C. We quantified PGE₂ formation (30) and expressed the results as nanograms of PGE₂ per 10⁶ cells per well. We used this protocol for all experiments on the time course, concentration response, and pharmacological modulation of PGHS. In the latter experiments we incubated 10⁶ cells/ml at 37°C with 2 µM dexamethasone for 1 h, then with 10 µM taxol or 0.1% (v/v) DMSO vehicle for 24 h, then with 30 µM arachidonic acid for 15 min. For experiments with the PGHS inhibitors, we incubated cells first with 10 µM taxol for 12 h at 37°C; then with 30 µM NS-398, acetyl salicylate, or valeryl salicylate for 30 min; then with 30 µM arachidonic acid for 15 min. We estimated the IC₅₀ for inhibition of PGE₂ formation by nonlinear regression analysis. In certain experiments we investigated taxotere, a taxol analogue with a r-buty! group at C3’ and a hydroxyl group at C10. We measured statistical significance by analysis of variance. Values represent the mean ± SE for six or more experiments.

**Immunohistochemical determination of PGHS-2**

We isolated RAW 264.7 cells (1 x 10⁶), homogenized them at 4°C in 300 µl of lysis buffer, centrifuged the lysates at 10,000 x g for 10 min at 4°C, and denatured 100-µl portions of the supernatant fractions with 25 µl of 5X electrophoresis buffer. We fractionated samples (20–25 µg of protein) by SDS-PAGE. We transferred proteins to nitrocellulose membranes for immunohistochemical hybridization. We washed the membranes with TBS containing 0.1% (v/v) fish gelatin, 0.1% (v/v) Tween-20, and 5% (w/v) nonfat dried milk to reduce nonspecific binding. We equilibrated the membranes for 1 h at 25°C with anti-PGHS-1 or anti-PGHS-2 Abs (1/1000, v/v). Then, we washed the membranes with 0.1% Tween-TBS and incubated them for 1 h at 25°C with goat anti-rabbit serum conjugated with HRP (1/5000) to detect the PGHS-Ab complex. After washing with TBS containing 0.1% (v/v) Triton X-100, 0.1% (v/v) Tween-20, and 0.5% (w/v) milk protein, we detected Ag:Ab complexes by enhanced chemiluminescence.

**Determination of mRNA expression**

We deposited 2 x 10⁶ RAW 264.7 cells/200 µl in 96-well Cytosar-T (Amersham) plates and incubated them for 12 h with 10 µM taxol plus 10 U of IFN-γ/ml. We quantified PGHS-2 and NOS mRNA by a cell-based RNase protection assay (31). We synthesized 32P-labeled riboprobes for PGHS-2 and NO synthase with a MAXIscript in vitro transcription kit and T7 phage RNA polymerase. We synthesized a [33 P]GAPDH riboprobe.

**Isolation of human monocytes**

We isolated monocytes from human whole blood (32) and suspended 3–4 x 10⁶ monocytes/ml in RPMI 1640 medium supplemented with 10% (v/v) bovine or human serum. Cell suspensions contained >95% viable monocytes. We incubated 2 ml of these cell suspensions with 0–30 µM taxol or taxotere or with 10 ng/ml LPS for 12 h at 37°C and determined PGHS-2 protein expression by immunohistochemical analysis.

**Results**

Taxol, alone or with IFN-γ, increased PGHS activity by RAW 264.7 murine macrophages in a time-dependent manner. PGHS activity increased within 1 h, approached steady state within 6 h, and remained 10-fold greater than the corresponding control value for 24 h (Fig. 1A). Cells incubated with taxol plus IFN-γ produced approximately 50% more PGE₂ than cells incubated with taxol alone (Fig. 1A).

We measured NOS activity, reflected by nitrite formation, as a control response (8, 10, 26, 33). Taxol alone did not alter NO formation by RAW 264.7 cells, consistent with reports by others (8, 10, 26). Cells incubated for 24 h with 10 µM taxol produced 1.7 ± 0.3 µM nitrite; corresponding control cells produced 2.1 ± 0.2 µM nitrite. In contrast, taxol combined with IFN-γ increased NO formation in a time-dependent manner (Fig. 1B). NO formation increased slowly, beginning at 6 h, and it did not reach a steady state during the course of the experiment. Cells incubated for 24 h with taxol plus IFN-γ produced 12.6 ± 2.0 µM nitrite; corresponding control cells incubated with IFN-γ alone produced 2.2 ± 0.3 µM nitrite (p < 0.05). Fig. 1 indicates that changes in PGHS activity do not correlate directly with changes in NOS activity. For comparison, Table I shows NOS activity in RAW 264.7...
cells incubated with LPS with or without IFN-γ. LPS alone stimulated nitrite formation with an efficacy equal to that of taxol plus IFN-γ. LPS plus IFN-γ stimulated nitrite formation about two- to threefold more than taxol plus IFN-γ. These values are within the range reported with other murine macrophages systems (8, 10, 33).

Taxol, alone or with IFN-γ, caused a concentration-dependent increase in PGHS activity (Fig. 2A). Consistent with the results presented in Fig. 1, taxol alone did not increase NOS activity; taxol plus IFN-γ did increase NOS activity (Fig. 2B).

We used selective PGHS inhibitors to determine whether PGHS-1 or PGHS-2 catalyzed PGE2 formation in cells incubated with taxol. NS-398 and acetylsalicylic acid both inhibited PGHS activity in cells incubated for 12 h with 10 μM taxol (Fig. 3). NS-398, which selectively inhibits the PGHS-2 isoenzyme (27), potently reduced PGHS activity (IC50 = 5.0 nM). Acetylsalicylic acid, which inhibits both PGHS-1 and PGHS-2 indiscriminately, inhibited PGHS activity with 800-fold lower potency (IC50 = 4.3 μM). At concentrations ≤10−4 M, valeryl salicylic acid, which selectively inhibits the PGHS-1 isoenzyme (28), had no significant effect on PGHS activity. These data indicate that PGHS-2 catalyzed PGE2 formation in RAW 264.7 cells treated with taxol.

Immunohistochemical analysis substantiated that taxol, alone or with IFN-γ, increased the expression of PGHS-2 in a time-dependent manner (Fig. 4A). PGHS-2 protein increased within 1–2 h and approached steady state by 6–12 h, consistent with the time course for cellular PGE2 formation. Neither the DMSO vehicle nor IFN-γ altered PGHS-2 expression, consistent with their lack of effect on cellular PGE2 formation (Fig. 4B). Dexamethasone, a glucocorticoid, blocked the expression of PGHS-2 protein in RAW 264.7 cells incubated for 12 h with taxol (Fig. 4C). Dexamethasone also blocked PGHS-2 expression at other times and in cells incubated with taxol plus IFN-γ (data not shown). Consistent with these results, dexamethasone inhibited PGE2 formation by RAW 264.7 cells incubated for 12 h with taxol or with taxol plus IFN-γ (Fig. 5A). Dexamethasone also inhibited NO formation by cells incubated with taxol plus IFN-γ (Fig. 5B). Taxol, alone or with IFN-γ, did not alter the expression of the PGHS-1 isoenzyme in these cells.

RNase protection assays substantiated that taxol, alone or with IFN-γ, induced PGHS-2 mRNA rapidly (Fig. 6, A and B). PGHS-2 mRNA expression increased in ≤1 h and remained 2- to 6-fold above the initial expression level for 12 h. Consistent with the results shown in Figs. 4 and 5, dexamethasone inhibited transcription of PGHS-2 mRNA (Fig. 6, A and B). Consistent with the data shown in Figs. 1, 2, and 5, taxol plus IFN-γ induced NOS mRNA, but taxol alone did not (Fig. 6C). NOS mRNA increased at 2 h and remained 10- to 20-fold above the initial expression level for 12 h.

In contrast to taxol, taxotere did not increase either PGHS activity or PGHS-2 expression in RAW 264.7 murine macrophages (Fig. 7).

### Table I. Effect of LPS and IFN-γ on NOS activity in RAW cells

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<tr>
<td>6</td>
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</tr>
<tr>
<td>12</td>
<td>3.9 ± 0.8</td>
<td>15.1 ± 1.3</td>
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<tr>
<td>24</td>
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NOS activity corresponds to nitrite in the culture medium. Values = mean ± SE (n = 5).

### FIGURE 2. Concentration-dependent effect of taxol on PGHS activity in RAW 264.7 macrophages. A, PGHS activity in RAW 264.7 cells incubated for 12 h with 0–10 μM taxol (○) or 0–10 μM taxol plus 10 U of IFN-γ/ml (●). PGHS activity corresponds to nanograms of PGE2 formed per 1 × 10⁶ cells/well when cells were incubated with 30 μM arachidonic acid for 15 min at 37°C. B, Concentration dependence of cellular NO formation in the same experiments. NO formation corresponds to micromolar concentrations of nitrite in the medium.

### FIGURE 3. Selective inhibition of PGHS-2 isoenzyme activity in RAW 264.7 macrophages. PGHS activity in RAW 264.7 cells incubated at 37°C for 12 h with 10 μM taxol; then for 30 min with NS398 (●), acetylsalicylic acid (▲), or valeryl salicylic acid (○); then for 15 min with 30 μM arachidonic acid. PGHS activity corresponds to PGE2 formation by 1 × 10⁶ cells/well.
PGHS-2 expression in human monocytes incubated with taxol depends on the composition of the culture medium (Fig. 8). Neither taxol nor taxotere induced PGHS-2 in monocytes suspended in 10% (v/v) FBS; however, LPS used as a control did induce PGHS-2 (Fig. 8B). Thus, human monocytes did not act via a putative LPS signaling pathway that is prominent in murine leukocytes (5–7, 20, 34, 35). In contrast, both taxol and taxotere induced PGHS-2 in human monocytes suspended in 10% (v/v) human serum (Fig. 8A). SB203580, an inhibitor of p38 MAPK, blocked PGHS-2 induction by LPS and taxol in RAW 264.7 cells and human monocytes (Fig. 8, A and C), consistent with an established role for p38 MAPK signaling in PGHS-2 expression (36).

Discussion

Taxol induces PGHS-2 expression in RAW 264.7 murine macrophages and increases their capacity for PG biosynthesis. PGHS-2 joins a group of taxol-inducible early genes that now includes TNF-α, NOS, and the cytokines IL-1β, IL-6, and IL-8 (5–14). Induction of PGHS-2 differs from induction of some of these other genes in at least two respects. First, RAW 264.7 cells, like other murine macrophages (8, 26), required a combination of IFN-γ plus taxol for induction of NOS. However, taxol alone was sufficient for the induction of PGHS-2. This dissociation between PGHS-2 and NOS expression indicates that cellular PGHS activity did not rise because of an interaction of NO with PGHS (37) or an increase in the activation state of RAW 264.7 macrophages, reflected by NOS activity. Second, taxol induced PGHS-2 expression and TNF-α expression simultaneously and independently. This contrasts with the induction of NOS, which occurs secondary to TNF-α induction (26).

Taxotere stabilized microtubules but it did not alter PGHS-2 expression or activity in RAW 264.7 cells. This distinction between taxotere and taxol also occurs for the induction of NOS (10), TNF-α (9, 10, 20), IL-8 (12), and other genes (38) in murine macrophages. Thus, taxol induces genes in murine macrophages by a mechanism that is independent of microtubule stabilization. Originally, investigators proposed that this mechanism was an LPS receptor, CD14-dependent process (5–7, 20, 39). Second, taxol induces PGHS-2 in human monocytes under conditions supporting responses to LPS. Thus, this hypothesis may not apply to human cells, or it may apply to human and murine macrophages in species-specific ways, as pointed out by Manthey and Vogel (39). Second, taxol induces TNF-α and IL-1β (34) and IL-6 (35) in cells that lack the CD14 component of the LPS-receptor complex. This appears to exclude membrane-associated CD14 as part of the signaling pathway; however, soluble CD14 might be able to substitute for membrane-bound CD14 in some circumstances. Third, the reported effects of
rhodohacter sphaeroides diprophosphoryl lipid A (RsDPA) and a related LPS receptor antagonist on taxol-mediated gene induction (20) seem inconclusive without experiments explicitly showing that these LPS antagonists blocked the interaction of taxol and LPS at a common element involved in their signaling pathway. It is notable that taxol itself and several taxol analogues do not act as antagonists of LPS signaling in human or murine macrophages (13).

Investigations on explicit molecular processes provide better insight into taxane-mediated signaling and gene induction, and they may help to clarify the differences between murine and human responses to taxol. Taxol modulates three important kinase families in murine macrophages: 1) protein kinase C (26), 2) the 42- to 44-kDa extracellular receptor kinases (7, 41), and 3) p38 MAPK, as shown above and previously (42). In combination, often initiated by protein kinase C (43, 44), these three kinases govern membrane to nuclear signaling and induction of PGHS-2 (18), NOS (26, 45), and TNF-α (45). Human monocytes have a full, functional array of these kinases, implying that any differences between taxol-mediated gene induction in murine and human cells are not attributable to these signaling processes. Consequently, the distinct responses of murine macrophages and human monocytes to taxol must depend on differences in a molecular process upstream from kinase activation. Interestingly, serum appears to influence the responsiveness of human monocytes to taxol. Namely, human serum, but not bovine serum, supports the induction of PGHS-2 by taxol in human monocytes. Human serum also supports the induction of certain other genes, such as IL-1β (14); however, human serum does not support taxol-mediated induction of IL-8 (14) or TNF-α (13) in human monocytes. Thus, under some conditions taxol can apparently interact with a receptor on human monocytes, other than microtubules (1). This receptor is coupled to the p38 MAPK signaling pathway in both murine macrophages and human monocytes. Constituents of serum may influence the apparent dissociation constant (Kd) for the equilibrium between taxol and this receptor in human and murine monocytes. Although taxol may not induce TNF-α or IL-8 in human monocytes (13, 14), it can induce IL-8 in other human cell lines (11, 14). Thus, modulation of gene expression remains an attractive hypothesis to account for some pharmacological traits of taxol. For instance, hypersensitivity reactions halted the earliest clinical trials with taxol (16, 17). Precedents suggested that cremaphor, the vehicle used in the formulation, caused this phenomenon. However, this is unproven, and recent data suggest that taxol contributes directly to anaphylaxis (46). Increased eicosanoid formation could be part of this contribution. Corticoids, which are routinely administered to manage these hypersensitivity reactions, would be effective in part by suppressing PGHS-2 induction (22, 25). Selective PGHS-2 inhibitors, typified by NS-398 (27), might be an alternative to corticoids as prophylaxis against hypersensitivity reactions. Selective PGHS-2 inhibitors should diminish any adverse effects due to prostanoids without impairing the formation of cytokines and their accompanying antitumor effects. If increased formation of prostanoids contributes to other adverse effects of taxol, such as edema and pulmonary infiltration (16, 17, 47), PGHS-2 inhibitors might be suitable for their management. Finally, induction of PGHS-2 and
other genes may help to explain the effects of taxol in rodent models of neo-proliferative disorders such as T cell-dependent auto-immune arthritis (48).

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References


