Two Opposing Effects of Non-steroidal Anti-inflammatory Drugs on the Expression of the Inducible Cyclooxygenase

MEDIATION THROUGH DIFFERENT SIGNALING PATHWAYS*

Ji H. Paik, Jeong H. Ju, Joo Y. Lee, Mary D. Boudreaux, and Daniel H. Hwang†

From the Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana 70808

The efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) is considered to be a result of their inhibitory effect on cyclooxygenase (COX) activity. Here, we report that flufenamic acid shows two opposing effects on COX-2 expression; it induces COX-2 expression in the colon cancer cell line (HT-29) and macrophage cell line (RAW 264.7); conversely, it inhibits tumor necrosis factor α (TNFα)- or lipopolysaccharide (LPS)-induced COX-2 expression. This inhibition correlates with the suppression of TNFα- or LPS-induced NFκB activation by flufenamic acid. The inhibitor of extracellular signal-regulated protein kinase, p38, or NFκB does not affect the NSAID-induced COX-2 expression. These results suggest that the NSAID-induced COX-2 expression is not mediated through activation of NFκB and mitogen-activated protein kinases. An activator of peroxisome proliferator-activated receptor γ, 15-deoxy-Δ12,14-prostaglandin J2, also induces COX-2 expression and inhibits TNFα-induced NFκB activation and COX-2 expression. Flufenamic acid and 15-deoxy-Δ12,14-prostaglandin J2 also inhibit LPS-induced expression of inducible form of nitric-oxide synthase and interleukin-1α in RAW 264.7 cells. Together, these results indicate that the NSAIDs inhibit mitogen-induced COX-2 expression while they induce COX-2 expression. Furthermore, the results suggest that the anti-inflammatory effects of flufenamic acid and some other NSAIDs are due to their inhibitory action on the mitogen-induced expression of COX-2 and downstream markers of inflammation in addition to their inhibitory effect on COX enzyme activity.

Many epidemiological studies have revealed that the use of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)³ can reduce the risk of colon cancer. Since the well-documented pharmacological action of aspirin and other NSAIDs is the inhibition of cyclooxygenase (COX, the rate-limiting enzyme in prostaglandin biosynthesis), it can be inferred that the beneficial effect of NSAIDs may be mediated through the inhibition of prostaglandin biosynthesis. However, experimental evidence to support this hypothesis has not been conclusively demonstrated. Several lines of experimental observations imply that the beneficial effects of NSAIDs may be mediated through both COX-dependent and COX-independent pathways.

Two isoforms of COX have been identified: constitutively expressed COX-1 (1–5) and mitogen-inducible COX-2 (6–11). Evidence supporting the hypothesis that the beneficial effect of NSAIDs in reducing the risk of colon cancer is mediated by the inhibition of COX activity includes the fact that cross-breeding of APC³⁷/³⁷ knockout mice with COX-2 knockout mice, or the administration of the COX-2 specific inhibitor to APC³⁷/³⁷ knockouts, resulted in a dramatic reduction in the numbers and size of the intestinal polyps (12). In addition, it has been demonstrated that the overexpression of COX-2 in intestinal epithelial cells leads to enhanced tumorigenic phenotypes, metastatic potential, and angiogenesis (13–15).

It has been shown that NSAIDs have pharmacological effects other than the inhibition of COX activity. Sodium salicylate and aspirin were shown to inhibit the transcription factor NFκB (16). NSAIDs can also activate peroxisome proliferator-activated receptors (PPAR) α and γ, and induce differentiation of pre-adipocytes to adipocytes (17). Results from recent studies by Meade et al. (18) demonstrated that various NSAIDs, as PPAR activators, induce the expression of COX-2 in epithelial cells. However, Xu et al. (19) showed that aspirin and sodium salicylate suppress COX-2 expression induced by IL-1 in endothelial cells. In addition, the activation of PPARα by Wy 14643 leads to the inhibition of IL-1-induced COX-2 expression in smooth muscle cells (20).

To clarify these seemingly opposing results, we studied the effects of NSAIDs on COX-2 expression in the presence or absence of a known inducer of COX-2 expression. COX-2 expression is induced by various mitogenic stimuli in different cell types (7, 9, 11, 22). The cis-acting NFκB element is present in the 5’-flanking regions of COX-2 genes of different species (23, 24). Results from our previous studies demonstrated that the activation of NFκB is required to induce the expression of COX-2 in the lipopolysaccharide (LPS)-stimulated macrophage cell line (25). The activation of mitogen-activated protein kinases (MAPKs, ERK-1 and -2, and p38) alone is not sufficient to induce the expression of COX-2, but the inhibition of ERK-1 and -2 or p38 results in partial suppression of COX-2 expression (26). Pro-inflammatory cytokines, such as TNFα and IL-1,
also activate NF-kB and MAPKs, and induce the expression of COX-2 in many cell types (26, 27).

Thus, we investigated signaling pathways through which NSAIDs modulate the expression of COX-2 in a colon tumor cell line (HT-29) treated with TNF-α and a macrophage-like cell line (RAW 264.7) stimulated by LPS. If NSAIDs can modulate mitogen-induced expression of COX-2 in addition to inhibiting the enzyme activity of COX, this may represent a new mechanism of anti-inflammatory and anti-neoplastic actions of NSAIDs.

**EXPERIMENTAL PROCEDURES**

Reagents—Polyclonal antibodies for COX-1 and COX-2 were prepared and characterized as described previously (28, 29). Polyclonal antibodies for IκBα, IκBα, and IκBα-1 were purchased from Santa Cruz Biotechnology (Santa Cruz, CA) and polyclonal antibody for β-actin was from Sigma. Goat anti-mouse and donkey anti-rabbit immunoglobulin G (IgG) antibodies conjugated to horseradish peroxidase were purchased from Amersham Pharmacia Biotech. Enhanced chemiluminescence (ECL) Western blotting detection reagents were purchased from Amersham Pharmacia Biotech.

Polyvinylidene difluoride membrane was purchased from Millipore (Bedford, MA). PD98059, SB203580, and piroxicam were from Calbiochem (La Jolla, CA). NS-398 and flurbiprofen were purchased from Cayman Co. (Ann Arbor, MI). NS-398 was used at 10 μM concentrations above 200 μM. All other NSAIDs were purchased from Sigma. 

Purified COX-1 and COX-2 enzymes were purchased from Santa Cruz Biotechnology. Among various NSAIDs, Flufenamic Acid, and Sulindac Sulfide Inhibit TNFα-induced NF-kB Activation: This Inhibition Leads to the Suppression of COX-2 Expression—Among various NSAIDs tested, flufenamic acid and sulindac sulfide were the most potent inhibitors of TNFα-induced NF-kB activation determined by IκBα degradation in HT-29 cells (data not shown). Thus, we investigated these two NSAIDs in this report.

Pretreatment of HT-29 cells with flufenamic acid shows a biphasic effect on TNFα-induced COX-2 expression: enhancement at concentrations below 200 μM but inhibition at concentrations above 200 μM (Fig. 1A). However, flufenamic acid suppressed the TNFα-induced activation of NFκB in a dose-dependent fashion without showing the biphasic effect as demonstrated both by EMSA and NFκB reporter gene assay (Fig. 1, B and C). Flufenamic acid at concentrations up to 200 μM does not affect viability of HT-29 and RAW 264.7 cells as determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (data not shown). However, flufenamic acid induces cell death at concentrations above 200 μM. Thus, only adherent cells were harvested and analyzed by Western blot analysis for the cells treated with flufenamic acid at concentrations above 200 μM.

Similar to flufenamic acid, sulindac sulfide inhibits TNFα-induced COX-2 expression and this inhibition correlates with the suppression of TNFα-induced NFκB activation by sulindac sulfide (Fig. 2, A and B). In addition, TNFα-induced COX-2

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Dewitt, Michigan State University, East Lansing, MI) was used. After transfected with 2.5 μg of murine COX-2 gene promoter (nt-1,017/50 ng/ml, Sigma) or LPS in the serum-poor (0.25% FBS) medium. The luciferase activity was determined using the Lucerase Assay System (Promega, Madison, WI). The luciferase activity was normalized to the internal control plasmid HSP70-lacZ by measuring β-galactosidase activity.

**RESULTS**

NSAIDs, Flufenamic Acid, and Sulindac Sulfide Inhibit TNFα-induced NFκB Activation: This Inhibition Leads to the Suppression of COX-2 Expression—Among various NSAIDs tested, flufenamic acid and sulindac sulfide were the most potent inhibitors of TNFα-induced NFκB activation determined by IκBα degradation in HT-29 cells (data not shown). Thus, we investigated these two NSAIDs in this report.

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expression is suppressed by the inhibitor of NFκB (data not shown). These results suggest that the inhibition of TNFα-induced COX-2 expression by flufenamic acid or sulindac sulfide is at least in part due to its inhibitory effect on TNFα-induced NFκB activation.

Flufenamic Acid in the Absence of Other COX-2 Inducers in the Medium Induces the Expression of COX-2 in HT-29 Cells: This Induction Was Not Inhibited by the Inhibitors of MAPKs or NFκB—Next, to determine whether enhancement of TNFα-induced COX-2 expression by flufenamic acid at concentrations below 200 μM (Fig. 1A) is due to COX-2 expression induced by flufenamic acid itself, cells were treated with flufenamic acid alone in the absence of other COX-2 inducers. Flufenamic acid alone induces COX-2 expression in a dose-dependent fashion (Fig. 3A). This induction was not inhibited by the pretreatment of cells with SB203580, a specific inhibitor of p38, or a mixture of inhibitors, PD98059 and TPCK, for MEK1 and NFκB, respectively (Fig. 3, B and C). Sulindac sulfide also induces COX-2 in the serum-poor medium and this induction was not inhibited by inhibitors of MAPKs or NFκB (Fig. 4, A−C). Flufenamic acid and other NSAIDs alone do not induce the degradation of IκBα (data not shown). Flufenamic acid and other NSAIDs do not affect COX-1 expression in HT-29 cells (data not shown). These results suggest that the expression of COX-2 induced by NSAIDs such as flufenamic acid or sulindac sulfide is not mediated through the activation of MAPKs and NFκB signaling pathway.

Results from recent studies demonstrated that some NSAIDs including flufenamic acid can bind and activate PPARγ and PPARα (17) and induce the expression of COX-2 in epithelial cells and fibroblasts (18, 32). Our immunoblot analyses demonstrated that PPARγ, but not PPARα, was detected in HT-29 cells (data not shown). Thus, we determined the effects of another known activator of PPARγ on COX-2 expression in
HT-29 cells. Results show that, similar to flufenamic acid, other known PPARγ activators troglitazone, indomethacin, and 15d-PGJ2 induce COX-2 expression (Fig. 5). In addition, pretreatment with 15d-PGJ2 results in the inhibition of TNFα-induced IκBα degradation and COX-2 expression (Fig. 6, A and B). However, indomethacin, although it induces COX-2 expression, does not inhibit TNFα-induced COX-2 expression (data not shown).

To determine whether NSAIDs bind PPARγ, HT-29 cells were transfected with the chimeric receptor expression construct, pcDNA3-hPPARγ/GAL4 and the reporter gene construct, pUAS(5x)-tk-luc as described elsewhere (33). Treatment of HT-29 cells with flufenamic acid, sulindac sulfide, or 15d-PGJ2 resulted in a significantly increased ligand binding activity to hPPARγ (Fig. 7A). The same pattern of results was shown in RAW 264.7 cells (Fig. 7B). These results imply that flufenamic acid- and sulindac sulfide-induced COX-2 expression is mediated through the activation of PPARγ both in HT-29 cells and RAW 264.7 cells.

Flufenamic Acid Induces COX-2 Expression and Also Inhibits the LPS-induced Activation of NFκB and COX-2 Expression in the Murine Macrophage-like Cell Line (RAW 264.7)—We next determined in a cell type other than HT-29 cells whether flufenamic acid induces COX-2 expression and also inhibits activation of NFκB and COX-2 expression induced by mitogenic stimulation. Pretreatment of RAW 264.7 cells with flufenamic acid leads to a dose-dependent inhibition of LPS-stimulated transcriptional activity of COX-2 promoter and NFκB reporter genes (Fig. 8, A and C, respectively).

Flufenamic acid, in the absence of other inducers of COX-2 expression, enhances transcriptional activity of COX-2 promoter-reporter gene in RAW 264.7 cells (Fig. 8B). However, flufenamic acid alone does not affect the basal promoter activity of NFκB (Fig. 8D), indicating that flufenamic-induced COX-2 expression is not mediated through the activation of NFκB. This result corroborates with the results, obtained by Western blot analyses of endogenous COX-2 protein in HT-29 cells (Fig. 3), demonstrating that the inhibitor of NFκB does not suppress flufenamic-induced COX-2 expression.

Flufenamic Acid and 15d-PGJ2 Inhibit the LPS-induced Expression of Other Pro-inflammatory Marker Gene Products Such as iNOS and IL-1α in RAW 264.7 Cells—Pretreatment of RAW 264.7 cells with flufenamic acid or 15d-PGJ2 leads to a dose-dependent inhibition of LPS-induced expression of iNOS and IL-1α as determined by Western blot analyses (Fig. 9, A and B). These results suggest that NSAIDs, which inhibit mitogen-induced activation of NFκB, can suppress the expression of many genes whose induction is mediated in part through activation of NFκB.

**DISCUSSION**

Our results demonstrate that NSAIDs have two opposing effects on COX-2 expression; NSAIDs inhibit cytokine-induced COX-2 expression, while NSAIDs alone can induce COX-2 ex-
expression. Results from promoter-reporter assays demonstrate that flufenamic acid inhibits LPS-induced COX-2 expression and NFκB activation in RAW 264.7 cells (Fig. 8, A and C), whereas it induces COX-2 expression in the absence of LPS (Fig. 8B). The concentrations of flufenamic acid required to inhibit LPS-induced COX-2 expression and to induce COX-2 expression are in a similar range. Thus, the magnitude of the inhibition of LPS-induced COX-2 expression by flufenamic acid might have been even greater if there was no simultaneous induction of COX-2. In HT-29 cells, enhancement of TNFα-induced COX-2 expression by flufenamic acid at 200 μM or lower is likely due to the fact that the additive induction of COX-2 expression by flufenamic acid is greater than its inhibitory effect on TNFα-induced COX-2 expression at these concentrations. However, the inhibitory effect of flufenamic acid on TNFα-induced COX-2 expression at higher concentrations may far exceed the additive induction of COX-2 expression by flufenamic acid. Flufenamic acid does not cause cell death at concentrations up to 200 μM; however, it induces cell death at concentrations above 200 μM. It has been well documented that activation of NFκB suppresses apoptotic signals in many cell types (36–39); conversely, inhibition of NFκB can induce apoptosis. Thus, it is likely that induction of apoptosis and inhibition of TNFα-induced COX-2 expression by flufenamic acid are mediated through a common signaling pathway, i.e. inhibition of NFκB.

Flufenamic acid does not have an opposing effect on NFκB activation. In both cell types, pretreatment with flufenamic acid leads to a dose-dependent inhibition of TNFα- or LPS-induced NFκB activation. Flufenamic acid alone does not cause NFκB activation.

Many NSAIDs bind and activate PPARα and some PPAR activators have been shown to inhibit NFκB activity (17, 20). TNFα-induced COX-2 expression in HT-29 cells was inhibited by flufenamic acid, sulindac sulfide, or 15d-PGJ2, all of which bind PPARα (Fig. 7). However, indomethacin, a known activator of PPARγ, does not inhibit TNFα-induced COX-2 expression and NFκB activation (data not shown). It was previously shown that, unlike sulindac sulfide, indomethacin does not inhibit 1α,25-dihydroxyvitamin D3 activation (40, 41). Recently, it was demonstrated that not all PPAR activators inhibit NFκB activation (21) and cytokine production in macrophages (42). Together, these results suggest that the inhibition of TNFα-induced COX-2 expression or

![Figure 7](http://www.jbc.org/)

**FIG. 7.** Ligand binding activity of various NSAIDs for PPARα in HT-29 and RAW 264.7 cells. A, HT-29 cells were transfected with the chimeric receptor expression construct, pcDNA3-hPPARα/GAL4 containing the ligand binding domain of hPPARα and the yeast GAL4 transcription factor DNA binding domain. Ligand binding activity was measured by co-transfecting the reporter gene construct, pUAS(5x)-tk-luc, which contains five copies of GAL4 response element. Transfected cells were treated with 100 μM of sulindac sulfide (Si), salicylic acid (Sa), acetaminophen (Ac), flufenamic acid (Flu), or 15d-PGJ2 (PGJ2). Vehicle (Veh). B, RAW 264.7 cells were transfected with the same plasmids as above. The transfected cells were treated with 50 μM sulindac sulfide, flufenamic acid, and 100 μM salicylic acid, acetaminophen, NS398, or 1 μM 15d-PGJ2. Luciferase activity was determined as described in Fig. 1. The panels are representative data from more than three different assays. Values are mean ± S.E. (n = 3).

![Figure 8](http://www.jbc.org/)

**FIG. 8.** Flufenamic acid induces COX-2 expression but it inhibits LPS-induced COX-2 expression and NFκB transactivation in RAW 264.7 cells. Cells were transfected with luciferase-reporter plasmid under the transcriptional control of COX-2 promoter (A and B), or NFκB response element (C and D). Transfected cells were treated with flufenamic acid (Flu) and LPS (25 ng/ml for panel A, and 1 μg/ml for panel C) or flufenamic acid alone for 24 h. Panels are representative data from more than three different analyses. Values are mean ± S.E. (n = 3). * indicates significantly different from the LPS alone (A and C) and the vehicle control (B) (p < 0.05).
due to their inhibitory effect on COX activity. However, the therapeutic benefit of NSAIDs is observed at plasma concentrations substantially higher than those required to inhibit COX (34). Emerging evidence now suggests that NSAIDs can also exert their anti-inflammatory and possible anti-tumor effects through COX-independent pathways (35). Our results demonstrating that NSAIDs inhibit TNFα-induced activation of NFκB signaling pathways suggest that NSAIDs can inhibit the cellular responses to pro-inflammatory cytokines by inhibiting the downstream signaling pathways derived from the activation of cytokine receptors. Furthermore, flufenamic acid inhibits not only COX-2 expression (Fig. 8) but also the expression of other inflammatory marker gene products such as iNOS and IL-1α induced by LPS in RAW 264.7 cells (Fig. 9). These results suggest that NSAIDs inhibit not only downstream signaling pathways derived from the activation of pro-inflammatory cytokine receptors, but also the expression of pro-inflammatory marker gene products in response to inflammatory stimuli.

Macrophages, important components of stromal cells in tumor tissues, can release cytokines, which in turn stimulate tumor cells and other stromal cells to induce the expression of COX-2. Our results suggest that NSAIDs can inhibit both the production of cytokines by macrophages, and the induction of COX-2 by tumor cells in response to the cytokines. These effects may represent an additional mechanism by which NSAIDs exert their anti-inflammatory and possible anti-neoplastic effects.

In summary, our results presented here suggest that the pharmacological effects of NSAIDs are mediated not only through the inhibition of COX activity but also the modulation of the expression of COX-2 and other pro-inflammatory marker gene products.

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REFERENCES

1. DeWitt, D. L., and Smith, W. L. (1988) Proc. Natl. Acad. Sci. U. S. A. 85, 1412–1416
2. Merlie, J. P., Fagan, D., Mudd, J., and Needleman, P. (1988) J. Biol. Chem. 263, 3550–3553
3. Yokoyama, C., Takai, T., and Tanabe, T. (1988) FEBS Lett. 231, 347–351
4. DeWitt, D. L., el-Harith, E. A., Kraemer, S. A., Andrews, M. J., Yao, E. F., Armstrong, R. L., and, Smith, W. L. (1990) J. Biol. Chem. 265, 5192–5198
5. Yokoyama, C., and Tanabe, T. (1989) Biochem. Biophys. Res. Commun. 163, 888–894
6. Xie, W. L., Chipman, J. G., Robertson, D. L., Erikson, R. L., and Simmons, D. L. (1991) Proc. Natl. Acad. Sci. U. S. A. 88, 2692–2696
7. Kujubu, D. A., Fletcher, B. S., Varnum, B. C., Lim, R. W., and Herschman, H. R. (1991) J. Biol. Chem. 266, 12866–12872
8. O’Flannion, M. K., Sadowski, H. B., Winn, V., and Young, D. A. (1991) J. Biol. Chem. 266, 22361–22367
9. Hla, T., and Neilson, R. (1992) Proc. Natl. Acad. Sci. U. S. A. 89, 7384–7388
10. Jones, D. A., Cortlan, D. P., McIntyre, T. M., Zimmerman, G. A., and Prescott, S. M. (1993) J. Biol. Chem. 268, 9049–9054
11. Feng, L., Sun, W., Xia, Y., Tang, W. W., Channugam, P., Soyoola, E., Wilson, C. B., and Huang, D. (1995) Arch. Biochem. Biophys. 307, 361–368
12. Oshima, M., Dinchuk, J. E., Kargman, S. L., Oshima, H., Hancock, B., Kwong, E., Trzaskos, J. M., Evans, J. F., and Taketo, M. M. (1996) Cell 87, 803–809
13. Tsuchi, M., and DuBois, R. N. (1993) Cell 72, 403–407
14. Tsuchi, M., Kawano, S., and DuBois, R. N. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 3336–3340
15. Tsuchi, M., Kawano, S., Tsuchi, S., Sawawaka, H., Hori, M., and DuBois, R. N. (1998) Cell 94, 705–716
16. Kopp, E., and Ghosh, S. (1994) Science 265, 956–959
17. Lehmann, J. M., Lenhard, J. M., Oliver, B. V., Ringold, G. M., and Kileweer, C. A. (1997) J. Biol. Chem. 272, 3496–3410
18. Meade, E. A., McIntyre, T. M., Zimmerman, G. A., and Prescott, S. M. (1999) J. Biol. Chem. 274, 8328–8334
19. Xu, X. M., Santos-Garcia, L., Chen, X. M., Matijevic-Aleksic, N., Du, M., and Wu, K. K. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 5292–5297
20. Staels, B., Koening, W., Habib, A., Merval, R., Lebret, M., Torra, I. P., Delerive, P., Fadel, A., Chinetti, G., Fruchart, J. C., Najib, J., Maclouf, J., and Tedgui, A. (1998) Nature 393, 790–793
21. Rossi, A., Kapaht, P., Napolit, G., Takahashi, T., Chen, Y., Karin, M., and Santoro, M. G. (2000) Nature 403, 103–108
22. Feng, L., Xia, Y., Garcia, G. E., Huang, D., and Wilson, C. B. (1995) J. Clin.
1. Invest. 95, 1669–1675
2. Fletcher, B. S., Kujubu, D. A., Perrin, D. M., and Herschman, H. R. (1992) J. Biol. Chem. 267, 4338–4344
3. Yamamoto, K., Arakawa, T., Ueda, N., and Yamamoto, S. (1995) J. Biol. Chem. 270, 31315–31320
4. Hwang, D., Jang, B. C., Yu, G., and Boudreau, M. (1997) Biochem. Pharmacol. 54, 87–96
5. Schwenger, P., Alpert, D., Skolnik, E. Y., and Vilcek, J. (1998) Mol. Cell. Biol. 18, 78–84
6. Schwenger, P., Bellotta, P., Vietor, I., Basilico, C., Skolnik, E. Y., and Vilcek, J. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 2869–2873
7. Lee, S. H., Soyoola, E., Chanmugam, P., Hart, S., Sun, W., Zhong, H., Liou, S., Simmons, D., and Hwang, D. (1992) J. Biol. Chem. 267, 25934–25938
8. Hwang, D., Scollard, D., Byrne, J., and Levine, E. (1998) J. Natl. Cancer Inst. 90, 455–460
9. Chanmugam, P., Feng, L., Liou, S., Jang, B. C., Boudreau, M., Yu, G., Lee, J. H., Kwon, H. J., Beppu, T., Yoshida, M., Xia, Y., Wilson, C. B., and Hwang, D. (1995) J. Biol. Chem. 270, 5418–5426
10. Lassen, M. K. (1970) Nature 227, 680–685
11. Lu, X., Xie, W., Reed, D., Bradshaw, W. S., and Simmons, D. L. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 7961–7965
12. Berger, J., Leibowitz, M. D., Doehber, T. W., Elbrecht, A., Zhang, B., Zhou, G., Biswas, C., Cullinan, C., Hayes, N. S., Li, Y., Tanen, M., Ventre, J., Wu, M. S., Berger, G. D., Mosely, R., Marquis, R., Santini, C., Sahoo, S. P., Tolman, R. L., Smith, R. G., and Moller, D. E. (1999) J. Biol. Chem. 274, 6718–6725
13. McEvoy, G. K. (ed) (1997) AHFS 97 Drug Information, American Society of Health-Systems Pharmacists, Bethesda, MD
14. Jiang, C., Ting, A. T., and Seed, B. (1998) Nature 391, 82–86
15. Ferreira, V., Sidenius, N., Tarantini, N., Hubert, P., Chatenoud, L., Basi, F., and Körner, M. (1999) J. Immunol. 162, 6442–6450
16. Schneider, A., Martin-Villaiba, A., Weih, F., Vogel, J., Wirth, T., and Schwaninger, M. (1999) Nat. Med. 5, 554–559
17. Mayo, M. W., Wang, C., Cugswell, P. C., Rogers-Graham, K. S., Lowe, S. W., Der, C. J., and Baldwin, A. S., Jr. (1997) Science 278, 1812–1815
18. Liu, Z., Hsu, H., Goeddel, D. V., and Karin, M. (1996) Cell 87, 565–576
19. Yin, M. J., Yamamoto, Y., and Gaynor, R. B. (1999) J. Biol. Chem. 274, 27307–27314
20. Grassi, M., Pizzi, M., Memo, M., and Spano, P. (1996) Science 274, 1383–1385
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