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The Proinflammatory Effect of Prostaglandin E₂ in Experimental Inflammatory Bowel Disease Is Mediated through the IL-23→IL-17 Axis

Amir F. Sheibanie,* Jui-Hung Yen,*† Tanzilya Khayrullina,*† Frances Emig,* Ming Zhang,* Ronald Tuma,* and Doina Ganea2*

Although Crohn’s disease has been traditionally considered to be Th1-mediated, the newly identified Th17 cells emerged recently as crucial participants. Th1/Th17 differentiation is controlled primarily by the IL-12 family of cytokines secreted by activated dendritic cells (DCs) and macrophages. IL-23 and IL-12/IL-27 have opposite effects, supporting the Th17 and Th1 phenotypes, respectively. We found that PGE₂, a major lipid mediator released in inflammatory conditions, shifts the IL-12/IL-23 balance in DCs in favor of IL-23, and propose that high levels of PGE₂ exacerbate the inflammatory process in inflammatory bowel disease through the IL-23→IL-17 axis. We assessed the effects of PGE₂ on IL-12, IL-27, and IL-23 and found that PGE₂ promotes IL-23, inhibits IL-12 and IL-27 expression and release from stimulated DCs, and subsequently induces IL-17 production in activated T cells. The effects of PGE₂ are mediated through the EP2/EP4 receptors on DCs. In vivo, we assessed the effects of PGE analogs in an experimental model for inflammatory bowel disease and found that the exacerbation of clinical symptoms and histopathology correlated with an increase in IL-23 and IL-17, a decrease in IL-12p35 expression in colon and mesenteric lymph nodes, and a substantial increase in the number of infiltrating neutrophils and of CD4⁺ IL-17⁺ T cells in the colonic tissue. These studies suggest that high levels of PGE₂ exacerbate the inflammatory process through the preferential expression and release of DC-derived IL-23 and the subsequent support of the autoreactive/inflammatory Th17 phenotype. The Journal of Immunology, 2007, 178: 8138–8147.

Inflammatory bowel diseases (IBD), which include Crohn’s disease (CrD) and ulcerative colitis (UC), are chronic, relapsing disorders, characterized by inflammatory reactions to microbial Ags of the commensal flora (1, 2). Recent studies highlighted the importance of both adaptive and innate immunity in IBD pathogenesis (3–5).

CrD was traditionally considered a Th1-type disease (6–8). Recently however, the Th17 cells emerged as crucial mediators in autoimmune disorders, including IBD (9–15). CrD and UC patients, but not healthy individuals or patients with infectious or ischemic colitis, have increased IL-17 levels in serum and in the colonic mucosa (16–18). In animal models of colitis, the administration of anti-IL-17 Abs ameliorates intestinal inflammation (19). In addition, IL-17R-deficient mice are less susceptible to 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis, although they express higher levels of IFN-γ, a hallmark of the Th1 response (20).

Members of the IL-12 cytokine family, i.e., IL-12, IL-23, and IL-27, are important in Th1/Th17 differentiation (21–23). In contrast to IL-23, which stabilizes the Th17 phenotype (14, 19, 24–27), IL-12 and IL-27 promote Th1 responses (28–32) and suppress Th17 development and function (33–35). Therefore, the IL-12/IL-27 vs IL-23 balance has a direct effect on the ensuing numbers of Th1/Th17 effectors.

We reported previously that PGE₂ induces IL-23 and inhibits IL-12p70 release from dendritic cells (DC) (36). In this study, we propose that high levels of PGE₂ released locally in inflammatory/autoimmune conditions sustain inflammation by activating resident DC to express IL-23 and shifting the T cell response toward Th17. We addressed this hypothesis in vivo in the TNBS-induced colitis model which shares many characteristics with human CrD in terms of ulceration, inflammation, leukocyte infiltration, and transmural lesions (37).

Materials and Methods

Mice

B10.A and BALB/c mice (males, 6–8 wk old; 20–22 g; The Jackson Laboratory) were maintained in the Temple University Animal Facility under pathogen-free conditions. The animal protocols were approved by the Committee on Use and Care of Laboratory Animals at Temple University (249-A3).

Reagents

TNBS, LPS (Escherichia coli 055:B5), and indomethacin were obtained from Sigma-Aldrich. The myeloperoxidase assay kit was obtained from CytoStore. Recombinant murine (rm) GM-CSF was purchased from PeproTech. Capture and biotinylated anti-mouse IL-17, rmIL-17, and the
ELISA kit for murine IL-27p28 were obtained from R&D Systems. Capture and biotinylated anti-mouse IL-6, IL-10, IFN-γ, TNF, IL-10, IL-12p40, IL-12p70, FITC-conjugated anti-CD4, PE-conjugated anti-IL-17 Abs, anti-CD3, and anti-CD28 mAbs were purchased from BD Pharmingen. The ELISA kit for murine IL-23 and rmIL-23 standards were obtained from eBioscience. PGE2, misoprostol, and PGE2-OH were purchased from Cayman Chemical. The FD Rapid Multistain kit used for H&E staining was purchased from FD Neurotechnologies.

**Generation of bone marrow-derived DCs**

DC were generated in vitro from B10.A bone marrow as previously described (38). Purified CD11c+ DC were cultured with LPS (1 μg/ml), PGE2 (10−5 or 10−6 M), or both, for 3 h for RNA preparation and 12 h for ELISA.

**IL-17 production by activated T cells**

CD4+ T cells were purified from the spleen of B10.A mice using anti-CD4-coated magnetic beads. The CD4+ T cells (>97% by FACS) were cultured at a concentration of 2 × 105 cells/ml in 24-well plates (250 μl/well) precoated with anti-CD3 mAbs (2.5 μg/well), and 4 days later the amount of secreted IL-17 was determined by ELISA. The detection limit for the IL-17 ELISA is 15 pg/ml.

**The TNBS colitis model**

Colitis was induced in BALB/c males (20–22 g) anesthetized with isoflurane, by intracolonic administration of TNBS (3 mg in 50% ethanol). PGE2, misoprostol, and PGE1-OH were purchased from Cayman Chemical. The FD Rapid Multistain kit used for H&E staining was purchased from FD Neurotechnologies.

**Results**

We have shown previously that PGE2 induces IL-23 but not IL-12 release from immature DC and induces IL-12p70 production in LPS-stimulated DC (36). Because IL-12 (p40/p35) and IL-27 (p28/EBI3) induce Th1 responses, whereas IL-23 (p40/p19) is essential for the Th17 response, we determined the effects of PGE2 on p40, p35, p19, p28, and EBI3 expression in LPS-stimulated DC. In time-course experiments, we established that all subunits are expressed early, with maximum induction at 3 h (results not shown). Purified CD11c+ DC were treated with LPS with or without PGE2 and p40, p35, p19, p28, and EBI3 expression levels were determined 3 h later by RT-PCR. PGE2 inhibited p35, reduced p40, and increased p19 expression (Fig. 1A), shifting the IL-12/IL-23 balance in favor of IL-23. As for IL-27, the EBI3 subunit is constitutively expressed in DC and up-regulated by LPS, whereas the p28 subunit is induced following LPS stimulation (Fig. 1B). PGE2 does not affect EBI3 levels, but reduces p28 expression (Fig. 1B).

**Measurement of myeloperoxidase (MPO) activity**

A total of 50 mg/ml colon tissue was homogenized and the MPO activity was measured as described previously (40). MPO activity was expressed as units per gram of tissue.

**Cytokine determination by ELISA**

Supernatants collected from DC cultures and from mesenteric lymph nodes (MLN) harvested from mice with colitis and restimulated ex vivo (see below) were assayed for cytokines by ELISA. The detection limits are 15 pg/ml for IL-17, IL-6, IL-12p40, IL-4, IL-10, and IL-23, 30 pg/ml for IFN-γ and IL-12p70, 7.8 pg/ml for IL-27p28, and 5 pg/ml for TNF. For measurement of tissue cytokines, colonic tissue was processed as previously described (40) and cytokine content was determined by ELISA.

**Isolation and culture of MLN**

MLN were collected 36 h after TNBS administration. Single-cell suspensions (1 × 106 cells/ml) were resuspended with immobilized anti-CD3 mAb (2.5 μg/ml) and soluble anti-CD28 mAb (2 μg/ml). Supernatants collected 72 h later were assayed for cytokines by ELISA.

**Histology**

Tissue samples were fixed and stained with H&E. Immunohistochemistry, the slides were incubated with 3% BSA for 30 min, washed, and incubated with PE-labeled anti-IL-17 (5 μg/ml) and FITC-labeled anti-CD4 (5 μg/ml) Abs. After incubation, the sections were covered with prolong anti-fade (Molecular Probes) and analyzed using a Nikon TE2000 epifluorescence microscope, equipped with a Hamamatsu camera. Red filters (range 575–615 nm) and green filters (range 500–550 nm) were used for PE and FITC staining, respectively.

**Statistical analysis**

All values are expressed as mean ± SD. Survival curves were analyzed by Kaplan-Meier log-rank test. Changes in body weight were compared by Kruskal-Wallis ANOVA. The in vitro data were analyzed by two-tailed Student’s test for unpaired samples and ANOVA for comparison of multiple groups. Macrophage and histologic scores between TNBS and TNBS plus misoprostol groups were analyzed with a two-sided Wilcoxon rank-sum test.
In this study, we tested the effect of supernatants collected from DC treated with PGE2 or various EP receptor agonists on IL-17 production. Direct addition of EP agonists to activated T cells did not result in IL-17 release. In contrast, supernatants harvested from DC treated with PGE2, misoprostol or butaprost, but not sulprostone, induced IL-17 release (Fig. 1D, lower panel). This indicates that EP2/EP4 receptors mediate the effect of PGE2 in inducing DC that promote IL-17 production in T cells.

**PGE2 agonists exacerbate TNBS colitis**

We hypothesized that PGE2 shifts locally the IL-12/IL27 vs IL-23 balance in favor of IL-23, leading to the preferential accumulation of Th17 cells. Based on the in vitro data, we chose two stable PGE analogs, misoprostol, a potent, nonselective agonist (EP4, EP3>EP1>EP2), and the EP4 agonist PGE4-OH (42) for the in vivo studies. Colitis was induced in BALB/c mice by a single intracolonic administration of TNBS in 50% ethanol. Misoprostol (60 μg/animal) was injected i.p. 1 and 12 h after TNBS administration. Control groups consisted of ethanol and ethanol plus misoprostol (no TNBS). One hundred percent of the animals survived in the control groups with no significant weight loss over the observation period (10 days) (Fig. 2A and B). In contrast, 40% of the mice in the TNBS group and 90% in the TNBS plus misoprostol group succumbed by day 3 (Fig. 2A). There was significant weight loss in the TNBS plus misoprostol-treated group as compared with the TNBS control (Fig. 2B). Misoprostol by itself does not affect survival or induce wasting (Fig. 2A). Similar to misoprostol, administration of PGE4-OH (30 μg/mouse) to mice...
treated with TNBS resulted in 80% mortality (Fig. 2). Lower doses of misoprostol (6 and 20 μg/mouse) and of PGE₁-OH (5 μg/mouse) had marginal effects.

Macroscopic analysis of colons obtained 36 h after TNBS administration indicated striking hyperemia, ulceration, and necrosis in mice treated with misoprostol (Fig. 2D, upper panel). The histology score was also higher in mice treated with misoprostol (Fig. 2D, lower panel). The analyses were performed at 36 h because most of the mice treated with misoprostol died 60 h after TNBS administration. In mice treated only with TNBS, 36 h represent an early time point (maximum effects are observed at 72 h), and therefore our macroscopic and histology scores for TNBS-treated mice are lower than those reported in the literature.

Misoprostol affects colonic p19, p35, and p40, and IL-17 expression

Colons from mice sacrificed 36 h after TNBS administration were processed for RT-PCR. TNBS induces increases in both IL-23 and IL-12 expression, i.e., up-regulation of p35, p40, and p19 (Fig. 2E). As expected, there is increased IFN-γ and IL-17 expression. In contrast, animals treated with TNBS plus misoprostol show impressive increases in p40 and p19, and a significant decrease in p35 expression (Fig. 2E). This confirms the shift in the IL-12/IL-23 balance.
balance observed in vitro in DC. As expected, the levels of colonic IL-17 expression in TNBS plus miso-treated mice were significantly higher compared with TNBS (Fig. 2, lower panel). These results suggest that the PGE₂ agonist induces the IL-23→IL-17 axis in colon, presumably through Th17 cells, in addition to the existing Th1-mediated IFN-γ response.

**Effect of misoprostol on cytokine production in colon**

Colons were processed for cytokine determination. We detected proinflammatory cytokines, i.e., IL-12p40, IFN-γ, IL-17, IL-6, TNF, and IL-1β, in the colons of TNBS-treated mice. Animals inoculated with TNBS and misoprostol showed increased levels of IL-17, IL-12p40, IL-1β, IL-6, and TNF, but not IFN-γ (Fig. 3A).

**Effect of misoprostol on IL-17, IFN-γ, and IL-4 production in MLN**

MLN cells were restimulated ex vivo with anti-CD3 and anti-CD28 mAb. Supernatants collected 72 h later were subjected to ELISAs for IL-17, IFN-γ, and IL-4. Cells from mice inoculated with TNBS plus miso released more IL-17 and less IFN-γ than...
cryosections were prepared (36 h) and stained with H&E. (A) Cells from mice inoculated with TNBS alone (Fig. 3). Misoprostol promotes transmural inflammatory cell infiltration whose major function is the attraction and activation of neutrophils. The colons of mice that received TNBS plus misoprostol exhibited intense necrosis and significantly higher levels of inflammation compared with the TNBS-treated mice (data not shown). Cross-sections of distal colons were stained with H&E. Colons from mice treated with ethanol or with ethanol plus misoprostol show no inflammatory infiltrates and have an intact anatomy of the colonic wall (Fig. 4A, A and B). In contrast, in colons of TNBS-treated mice we observed inflammatory infiltrates and slight tissue disruptions (Fig. 4C). The pathology is less severe than reported by others because the tissues were harvested 36 h after TNBS administration and not at the time of the maximum clinical score. In contrast, colons from mice given TNBS plus misoprostol showed transmural inflammation, marked increases in the thickness of the muscular layer, epithelial cell loss, pronounced depletion of mucin-producing goblet cells, patchy ulceration, disseminated fibrosis, and focal crypt loss (Fig. 4D).

**Misoprostol leads to a significant increase in the number of IL-17-producing CD4+ T cells in the intestinal mucosa**

Colon sections harvested 36 h post-TNBS treatment were stained with FITC-labeled anti-CD4 Abs (Fig. 4I, upper panels) and PE anti-IL-17 Abs (middle panels). Double-stained cells (CD4+IL-17+) are shown in the lower panels. There are no identifiable IL-17 producing CD4+ T cells in mice treated with ethanol plus misoprostol (Fig. 4I, A, D, and G). Thirty-six hours after TNBS administration, there are moderate numbers of CD4+ cells (Fig. 4IB), of IL-17-producing cells (Fig. 4IE), and of double-positive cells (Fig. 4IH). In contrast, following treatment with TNBS and misoprostol, there is a significant influx of CD4+ cells (Fig. 4IC), high numbers of IL-17-positive cells (Fig. 4IF), and high numbers of double-positive CD4+IL-17+ cells (Fig. 4III).

**Cyclooxygenase (Cox) inhibitors exacerbate TNBS-induced colitis without inducing significant increases in IL-17 and p19 expression**

We hypothesized that high levels of PGE2 generated locally in autoimmune/inflammatory conditions affect the IL-12/IL-23 balance in resident DC, promoting a preferential IL-17 T cell response. The data presented above show exacerbation of clinical colitis and increased p19/IL-23 and IL-17 levels upon administration of misoprostol in the TNBS model.

However, several reports indicate that Cox inhibitors, which block endogenous PG release, have a detrimental effect in patients with Crohn’s disease (43–47). Therefore, we sought to determine whether blockade of endogenous PG synthesis by using Cox inhibitors affects TNBS-induced colitis and whether this is associated with increased IL-23/IL-17 expression. Indomethacin (a nonselective Cox inhibitor) has been used previously to block PGE2 synthesis in various models, including TNBS-induced colitis (45, 48, 49). Mice were injected i.p. with indomethacin 30 min before TNBS administration, followed by indomethacin inoculations every 12 h on days 1 and 2. Control mice received only EtOH, or EtOH plus indomethacin (no TNBS). Similar to misoprostol, indomethacin exacerbated TNBS-colitis, with 80% of animals succumbing by day 3, and no survivor by day 7 (Fig. 5A). Macroscopic analysis of colons obtained 48 h after indomethacin administration showed hyperemia with prominent hemorrhagic areas (Fig. 5B).

However, although both indomethacin- and misoprostol-treated mice developed severe TNBS colitis, the cytokine profile turned out to be quite different in the two groups. In contrast to misoprostol, which induces high expression of both p19 and IL-17, indomethacin did not increase IL-17 above TNBS levels in lymph node cells, and resulted in relatively low expression of both p19 and IL-17 in colon (Fig. 5C). These results suggest that high levels of PGE2/misoprostol exacerbate colitis through an inflammatory process involving the IL-23→IL-17 axis, whereas Cox inhibitors which prevent both constitutive and inflammatory endogenous PG synthesis exacerbate colitis through mechanisms unrelated to IL-23/IL-17-induced inflammation.
Discussion

The newly identified CD4\(^+\) Th17 cells emerged recently as central players in inflammatory/autoimmune conditions such as rheumatoid arthritis, experimental autoimmune encephalomyelitis, and IBDs (19, 20, 33, 50–53). Although Th17 differentiation depends primarily on TGF\(\beta\) and IL-6, IL-23 is essential for the Th17 expansion and survival (24, 25, 27). In contrast to IL-23, the two other members of the IL-12 family, IL-12p70 and IL-27, suppress the development of Th17 effectors (33, 35, 54). We showed previously that PGE\(_2\) induces IL-23, but not IL-12p70, secretion from DC and inhibits IL-12p70 release from LPS-stimulated DC (36). Based on these results, we hypothesized that PGE\(_2\) plays a proinflammatory role in inflammatory/autoimmune diseases through the DC-derived IL-23→Th17 axis. In the present study, we show that PGE\(_2\) promotes IL-23 and inhibits IL-12/IL-27 expression in LPS-stimulated DC and that PGE\(_2\) analogs exacerbate clinical symptoms/histopathology in the TNBS colitis model. In agreement with the proposed effect of PGE\(_2\), we found that administration of PGE\(_2\) analogs results in an increase in IL-23 and IL-17 and a decrease in IL-12p35 expression in colon and MLN and a substantial increase in the number of colonic CD4\(^+\)IL-17\(^+\) T cells.

Although CrD was previously considered a Th1-type disease (6–8), there is convincing new evidence that IL-17 plays a central role in this disease.
role in CrD. CrD patients have increased levels of IL-17 in serum and intestinal mucosa (16–18), and treatment with anti-p40 Abs, leading to IL-17 decrease, is beneficial (17). In colitis models, IL-17 was identified in colon and administration of anti-IL-17 Abs suppressed intestinal inflammation (19). TNBS-induced colitis is an established IBD model based on similarities with human CrD (37). Although TNBS colitis is considered a Th1-type disease, the fact that mice expressing high levels of IFN-γ but lacking IL-17R are less susceptible to disease indicates that IL-17, and not IFN-γ, plays the central role (20).

We found that PGE2 inhibits IL-12/IL-27 and promotes IL-23 expression in DC, and that in vivo administration of PGE analogs results in higher expression of IL-23 and IL-17, and in the accumulation of Th17 cells in the inflamed intestine. This is in agreement with the recently established role of the IL-12 cytokine family in CD4+ T cell differentiation. IL-12 and IL-27 are strong promoters of Th1 differentiation (28–32), and directly suppress Th17 development (33–35), possibly through the induction of Tbet which prevents and destabilizes the Th17 phenotype (55, 56). In contrast, IL-23 is required to stabilize the Th17 phenotype (14, 19, 24–27).

Although the role of IL-23 in IBD has been questioned recently (57), an overwhelming number of clinical and experimental observations support IL-23→Th17 involvement in IBD. Increases in p19 expression were reported in intestinal mucosal biopsies from CrD and UC patients, but not in non-IBD colitis patients (58, 59), and a nonsynonymous variant of the IL-23R has been reported as one of the three markers associated with childhood onset of IBD (the other two markers being located in the NOD2/CARD15 gene) (60). In a model of spontaneous colitis, p19-deficient mice were shown to be disease resistant, and IL-23 administration together with transfer of CD4+CD45RBhigh T cells into Rag-1-deficient mice significantly accelerated disease onset (19). Increased p19 expression was localized to lamina propria CD11c+ F4/80+ CD68− cells (61), pointing to DC as the major IL-23 source. In addition, in models of bacterially induced colitis, IL-23 was shown to play a key role in both innate and T cell-mediated intestinal inflammation (62, 63).

The role of IL-12 and IL-23 were addressed recently in a colitis model based strictly on innate immune responses (5). In this model, IL-23 p19 secreted from intestinal DC acted locally, resulting in intestinal inflammation, whereas IL-12 acted systemically inducing serum proinflammatory cytokines and wasting disease. In our hands, exacerbation of TNBS colitis induced by PGE2 analogs correlates with increased IL-23 and reduced IL-12 expression, with a significant accumulation of Th17 cells, and with the up-regulation of proinflammatory cytokines in the inflamed intestinal tissue. This is in agreement with the proposed local effect of IL-23→IL-17 leading to intestinal inflammation.

PGE2, released at high levels during inflammation, plays mostly a proinflammatory role in vivo. In IBD, however, PGE2 appears to have a dual effect. On one hand, as demonstrated by our data, high levels of PGE2 analogs exacerbate clinical colitis, presumably through the induction of the IL-23→IL-17 proinflammatory axis. On the other hand, constitutive PGE2 production in the intestine appears to have a protective effect on the integrity of the epithelial intestinal wall, presumably through the enhancement of epithelium survival and regeneration (45, 64, 65). This is evident primarily in models of colitis where the central event is damage to the epithelial layer, such as dextran sodium sulfate-induced colitis, and in experimental models using Cox1/2- or EP4-deficient mice, where PGE2 synthesis or signaling of constitutive PGE2 through the EP4 receptor are prevented (65–67). In agreement with previously reported deleterious effect of nonsteroidal anti-inflammatory drugs or Cox inhibitors in IBD, we found that use of the nonselective Cox inhibitor indomethacin had as drastic an effect on TNBS colitis as the administration of high doses of misoprostol or PGE2-OH. There is however a significant mechanistic difference, with indomethacin having marginal effects on IL-23/IL-17 expression compared with misoprostol. This suggests that indomethacin, and possibly other nonsteroidal anti-inflammatory drugs and Cox inhibitors, act by preventing the beneficial effect of PGE2 and possibly other PG on the repair of the intestinal epithelial cell wall.

Based on our results, we hypothesize that although endogenous low levels of PGE2 are required for intestinal epithelial cell survival and regeneration, high PGE2 levels released locally in inflammatory conditions, such as in established colitis, contribute to the perpetuation of inflammation, exacerbating the disease process through the preferential induction of DC and possibly macrophage-derived IL-23 and subsequent expansion and survival of pathogenic autoimmune Th17 cells. We propose that high levels of PGE2 play a proinflammatory role in IBD by switching the cytokine profile of lamina propria DC (LPDC) (Fig. 6). In their abnormal response to commensal gut flora, LPDC express and release Tbet and IL-27. Th17 induction is mediated by IL-12p70 and IL-27. Th17 are also induced by IL-23, IL-6, and IL-1β strongly supports Th17 differentiation and function. IL-17 released from Th17 cells attracts and activates neutrophils, acts on various cells inducing cytokine/chemokine expression and metalloproteinase (MMP) release, and further promotes PGE2 release from myofibroblasts.
to the stabilization of the Th17 phenotype. In addition to activated T cells, IL-23 also acts on macrophages and DC expressing IL-23R. This leads to the release of IL-1β and IL-6, required for Th17 differentiation and stabilization. Therefore, in the presence of PGE2, there is preferential production of IL-17 from Th17 effectors, leading to neutrophil accumulation, and activation of fibroblasts, epithelial cells, macrophages to release proinflammatory cytokines and chemokines, as well as metalloproteinases (70). In addition, IL-17 synergizes with LPS to induce COX2 expression in colonic subepithelial myofibroblasts (71), maintaining a proinflammatory circuit. In conclusion, our model proposes that high levels of PGE2 act as endogenous regulators of the IL-12/IL-27 vs proinflammatory cytokines and chemokines, as well as metalloproteinases.

In addition, IL-17-driven DCs release IL-23 and IL-27, promoting the IL-23-→IL-17 axis, and resulting in locally amplified and sustained inflammation. The fact that high doses of exogenous PGE2 analogs exacerbate clinical colitis in the TNBS model might be relevant to the use of misoprostol to prevent ulcers in patients who take arthritis medication. The side effects listed for misoprostol include a variety of gastrointestinal tract problems, which could very well develop from the unwanted proinflammatory effect mediated by the IL-23→IL-17 axis.

Disclosures

The authors have no financial conflict of interest.

References
