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Cyclooxygenase-2-Mediated Prostaglandin E₂ Production in Mesenteric Lymph Nodes and in Cultured Macrophages and Dendritic Cells after Infection with Salmonella¹

Christal C. Bowman and Kenneth L. Bost²

Although numerous studies have demonstrated the ability of intestinal epithelial cells to produce PGs after infection with wild-type strains of Salmonella, few studies have focused on Salmonella-induced prostanoids in mucosal lymphoid tissues. This is surprising in view of the profound effects PGs can have on the host response. To begin to address PG production at mucosal sites, mice were orally inoculated with Salmonella, and at varying times postinfection cyclooxygenase-2 (COX-2) mRNA expression and PGE₂ synthesis were investigated. COX-2 mRNA expression was highly inducible in the mesenteric lymph nodes, whereas COX-1 mRNA levels were constitutive. PGE₂ production also increased significantly in the mesenteric lymph nodes following exposure to viable Salmonella, but not after exposure to killed bacteria. This increased PGE₂ response could be blocked by treatment of mice with the selective COX-2 inhibitor, celecoxib. Treatment of mice with celecoxib during salmonellosis resulted in increased viable bacteria in the mesenteric lymph nodes by day 3 postinfection. However, celecoxib treatment prolonged the survival of lethally infected animals. In vitro studies demonstrated Salmonella-induced up-regulation of COX-2 mRNA expression and PGE₂ secretion by both macrophages and dendritic cells, which could also be blocked in the presence of celecoxib. Interestingly, exposure of these cultured APCs to viable Salmonella was a much greater stimulus for induction of PGE₂ synthesis than exposure to Salmonella-derived LPS. The present study demonstrates induction of PGE₂ synthesis in mesenteric lymph nodes, macrophages, and dendritic cells after infection with wild-type Salmonella. The Journal of Immunology, 2004, 172: 2469–2475.

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3 Abbreviations used in this paper: COX-2, cyclooxygenase-2; TFA, trifluoroacetic acid.
this possibility, we demonstrate in this study that pathogenic *Salmonella* is a potent inducer of PGE\(_2\) secretion in cultured macrophages and dendritic cells and in these cells present in the mesenteric lymph nodes after infection. However, the role for *Salmonella*-induced PG production in vivo seems complex. Oral administration of celecoxib, a COX-2 inhibitor, resulted in increased bacterial burdens early during salmonellosis, but treatment with celecoxib also increased the survival of mice given a lethal infection. In light of the divergent roles that PGs seemed to play in modulating immune responses (10, 11), these unexpected results may not be altogether surprising.

Materials and Methods

**Infection of BALB/c mice with Salmonella typhimurium**

 Overnight cultures of *S. typhimurium* 12023 were subcultured in Luria broth and grown to an OD of 1.0 at 600 nm. Bacteria were centrifuged, washed twice, and resuspended in sterile saline. For UV killing, 1 ml of resuspended *Salmonella* was exposed to germicidal UV light for 20 min to reduce the viability of the culture to \(<1\) CFU/\(\mu\)l bacteria. Cultures were diluted to 2 \(\times\) 10\(^8\) bacteria/ml, and 10\(^8\) CFU in 0.5 ml of saline were administered to 6- to 8-wk-old female BALB/c mice intragastrically with a blunt-tip feeding needle (Popper & Sons, New Hyde Park, NY). At the indicated times postinfection, mice were euthanized, and mesenteric lymph nodes were taken for mRNA analyses, protein analyses, or bactericidal assays. Select groups of mice received treatment with the selective COX-2 inhibitor, celecoxib (Pharmacia Biotech, Peapack, NJ), given orally at a dose of 10 mg/kg as a suspension in sterile saline 4 h before infection and every 24 h postinfection until mice were euthanized.

**Isolation of CD11b\(^+\)/CD11c\(^-\) cells from the mesenteric lymph nodes of infected mice**

 Groups of mice were intragastrically inoculated with 10\(^8\) *Salmonella*, and at 3 days postinfection the mesenteric lymph nodes were removed from euthanized mice. Tissue fragments were minced in RPMI 1640 (Life Technologies, Gaithersburg, MD) containing 0.5 mg/ml collagenase IV (Sigma-Aldrich, St. Louis, MO) and 30 \(\mu\)g/ml DNase I (Sigma-Aldrich) at 37°C. Tissues were then passed through a 100-μm screen to dissociate cells and were washed in RPMI 1640 containing 2% FCS. Cells were incubated with a mixture of microbeads conjugated with anti-mouse CD11b and anti-mouse CD11c (Milenyi Biotec, Auburn, CA) for 30 min at 6°C. Cells were then passed over an LS separation column placed in a VarioMACS magnet (Miltenyi Biotec). Cells that passed through the column were used to isolate CD11b\(^+\)/CD11c\(^-\) populations. Cells retained on the column were collected and designated the CD11b\(^+\)/CD11c\(^-\) population. Total RNA was isolated from each cell population and subjected to RT-PCR analyses as described below.

**Semi-quantitative RT-PCR to detect mRNA expression after *Salmonella* infection**

 To detect the presence of mRNA encoding COX-1, COX-2, and G3PDH, RT-PCR analyses were performed using methods previously described (26, 27). Briefly, total RNA was extracted using TRIzol (Life Technologies), and the RNA was then reverse transcribed using Superscript II reverse transcriptase (Life Technologies). cDNA was amplified by PCR using the following reverse and negative strand primers: COX-1, 27 cycles, 5′-ACTGCTTGGAGATTTGGT-3′ and 5′-AGAGCGCAGGTGAT ACGTT-3′; COX-2, 25 cycles, 5′-TCAGCCAGGACGAAATCCCTTG-3′ and 5′-TAGTCCTCTATGA GTATGAGTC-3′; and G3PDH, 26 cycles, 5′-CCTACCCATCTTCCAGGGACGGCAGG-3′ and 5′-CAC AGGCTTCGGTTGCGATTG-3′. Amplified products were electrophoresed on ethidium bromide-stained gels and visualized by UV illumination.

**Quantification of PGE\(_2\) from the mesenteric lymph nodes and quantification of PGE\(_2\) by ELISA**

 Groups of BALB/c mice were treated orally with saline (−) or 10 mg/kg celecoxib (+) 4 h before infection with 10\(^8\) viable *Salmonella*. Celecoxib was given every 24 h thereafter, and mesenteric lymph nodes were removed from euthanized animals on day 3 postinfection. Tissue samples were snap-frozen and homogenized in 100 μl of 0.5% Triton-X containing indomethacin (Sigma-Aldrich). An equal volume of 1% trifluoroacetic acid (TFA) was added, and tissue homogenates were centrifuged at 13,000 \(\times\) g to remove solid debris. Supernatants were applied to 1-ml Bakerbond spe Octadeyl (C\(_{18}\)) columns (J. T. Baker, Phillipsburg, NJ), washed with 1% TFA, and eluted with acetoni/ter/1% TFA (60/40) before evaporation in a Centrivap concentrator (Labconco, Kansas City, MO). Samples were then suspended in assay buffer for analysis using the Prostaglandin E\(_2\) Direct Bioassay Kit (Amersham Pharmacia Biotech, Piscataway, NJ) and instructions supplied by the manufacturer.

To compare PGE\(_2\) levels to total protein in mesenteric lymph node homogenates, protein concentrations were determined using Bradford dye reagent concentrate (Bio-Rad, Hercules, CA) and BSA (Sigma-Aldrich) to generate a standard curve.

**Determination of bacterial burden in *Salmonella*-infected mice**

Groups of mice were intragastrically intubated with medium, UV-killed *Salmonella*, or 10\(^8\) viable *Salmonella*, and at 3 days postinfection mice were euthanized. Mesenteric lymph nodes were removed, weighed, and homogenized in 200 μl of sterile 0.5% Triton X (Sigma-Aldrich). Serial dilutions of tissue homogenates were plated onto MacConkey agar plates (Difco, Detroit, MI), and colony counts were performed after overnight growth.

**Isolation of peritoneal and bone marrow-derived macrophages**

Peritoneal macrophages were isolated as previously described (28, 29). Briefly, BALB/c mice were injected i.p. with 250 μl of IFA (Sigma-Aldrich). Four days later, the mice were euthanized, and peritoneal cavities were lavaged with RPMI 1640 (Life Technologies, Grand Island, NY) containing 5% FCS. Peritoneal cells were washed twice and then allowed to adhere to 12-well tissue culture plates (Costar, Cambridge, MA) for 45 min in RPMI 1640 containing 10% FCS before washing to remove nonadherent cells.

For isolation of bone marrow-derived macrophages, femurs were flushed with RPMI 1640 containing 2% FCS to collect total bone marrow cells. Spicules and bone matrix were allowed to settle and were removed. Total bone marrow cells were washed once, resuspended in LADMAC-conditioned medium, and plated in tissue culture plates. To produce LADMAC-conditioned medium, the LADMAC cell line (CRL-2420; American Type Culture Collection, Manassas, VA) was grown to confluence in 75-cm\(^2\) flasks for 5 days, followed by harvesting and filtering these culture supernatants. DMEM-10 supplemented with 10% FCS and 20% LADMAC supernatant was used as conditioned medium to foster the growth and differentiation of bone marrow macrophages. Conditioned medium, prepared in a similar manner, has been used to support the growth of bone marrow-derived macrophages because the LADMAC cell line is a source of M-CSF (30, 31). Bone marrow cells were fed with LADMAC-conditioned medium every 2 days. After 5 days in culture, nonadherent bone marrow cells were removed from culture wells by washing with RPMI 1640. Adherent bone marrow cells were then placed in tissue culture plates in RPMI 1640/10% FCS without antibiotics and exposed to medium, UV-killed *Salmonella*, or viable wild-type *Salmonella* as described below.

**FACS analyses were performed to determine the purity of isolated macrophages.** Cells were stained with PE-conjugated anti-mouse CD11b (clone M1/70; BD Biosciences, San Diego, CA) using techniques previously described (2). Immunofluorescence analyses were performed using a FACSCalibur (BD Biosciences, San Jose, CA) analyzing 10,000 cells/stain. Macrophages were determined to be \(>98\%\) positive for the expression of CD11b.

**Isolation of bone marrow-derived myeloid dendritic cells**

Bone marrow-derived myeloid dendritic cells were isolated as previously described (32). Briefly, femurs were flushed with RPMI 1640 containing 2% FCS to collect total bone marrow cells. Spicules and bone matrix were allowed to settle and were removed. Total bone marrow cells were washed once and resuspended in RPMI 1640 containing 12% FCS and 1000 U/ml GM-CSF (BD Biosciences). Cells were fed every 2 days by adding 50% fresh medium. After 7 days in culture, nonadherent cells were removed, washed, aliquoted into tissue culture plates in RPMI 1640/10% FCS without antibiotics, and exposed to medium, UV-killed *Salmonella*, or viable wild-type *Salmonella* as described below.

In some experiments, after 7 days in culture nonadherent cells were removed and washed, and CD11c\(^+\) and CD11c\(^-\) cells were isolated by MACS as previously described (33). Briefly, cells were incubated with microbeads conjugated with anti-mouse CD11c (Milenyi Biotec) for 30 min at 6°C. Cells were then passed over an LS separation column placed in a VarioMACS magnet (Milenyi Biotec). Cells that passed through the column were collected and designated the CD11c\(^+\) population. Cells retained on the column were collected and designated the CD11c\(^-\) population. These cell populations were then aliquoted into tissue culture plates in
the expression of CD11c, whereas MACS-purified dendritic cells were determined to be 95% positive for the expression of CD11c. Bulk cultures of dendritic cells were stained with PE-conjugated anti-mouse CD11c (clone HL3; BD Biosciences, San Diego, CA) using techniques previously described (2). Immunofluorescence analyses were performed using a FACScalibur (BD Biosciences) and analyzing 10,000 cells/stain. Bulk cultures of dendritic cells were determined to be >70% positive for the expression of CD11c, whereas MACS-purified CD11c+ cells were >95% positive for the expression of CD11c.

COX mRNA expression and quantification of PGE2 present in culture supernatants of Salmonella-infected macrophages and dendritic cells

Mouse macrophages or dendritic cells were isolated as described above and cultured in RPMI 1640/10% FCS without antibiotics. These cells were briefly exposed to UV-killed or live Salmonella at ratios of 3:1 or 10:1 cells to bacteria. After 45 min, extracellular bacteria were removed by washing the cells and by the addition of gentamicin-containing medium. In addition, some cultures were treated with 1 μM celecoxib for 20 min before the addition of bacteria. Also, some cultures were exposed to Salmonella-derived LPS (Sigma-Aldrich) at the indicated concentration. RNA or culture supernatants were isolated from these cultures at the indicated times postinfection for RT-PCR or ELISA, respectively. RT-PCR was performed as described above. Levels of PGE2 were measured by enzyme immunoassay without extraction before assay according to instructions from the manufacturer (Amersham Pharmacia Biotech) as described above.

Densitometric and statistical analyses

Densitometric analysis of ethidium bromide-stained agarose gel images was performed using Scion Image (Scion, Frederick, MD). Survival curves were compared using the log-rank test (GraphPad, San Diego, CA). Statistical analyses were performed using unpaired t tests. Results were determined to be statistically significant at p < 0.05.

Results

COX mRNA expression and production of PGE2 in mesenteric lymph nodes of Salmonella-infected mice

PG production by intestinal epithelial cells is a well-documented response to pathogenic Salmonella; however, no studies have focused on the inducibility of prostanoids in mucosal lymphoid tissues after infection. To address this possibility, groups of female BALB/c mice were orally inoculated with medium or with viable or UV-killed Salmonella. Animals were euthanized on days 0, 1, 2, or 3 postinfection, and the mesenteric lymph nodes were excised to detect the levels of COX mRNA expression or to quantify the levels of PGE2. COX-2 mRNA levels were detectable 2 days after exposure to viable Salmonella and were considerably elevated by day 3 postinfection (Fig. 1A). This was in contrast to mice inoculated with medium or UV-killed Salmonella, whose level of COX-2 mRNA expression was not detectable by this RT-PCR procedure. Analysis of COX-1 mRNA expression demonstrated a constitutive expression of this mRNA species that was relatively unchanged by inoculation with live or UV-killed organisms (Fig. 1B). Furthermore, differences in inducible COX-2 mRNA expression between infected mice and mice treated with medium or UV-killed Salmonella could not be attributed to significant differences in input RNA or efficiencies of RT between samples as indicated by amplification of the housekeeping gene, G3PDH (Fig. 1A) or COX-1 (Fig. 1B) from the same cDNA samples.

To demonstrate the phenotype of cells within the mesenteric lymph nodes that expressed COX-2 mRNA, CD11b+/CD11c+ and CD11b+CD11c+ cell populations were isolated by MACS 3 days after infection with Salmonella. RT-PCR analyses demonstrated that COX-2 mRNA was exclusively expressed in the CD11b+/CD11c+ cell population (Fig. 1C), indicating that macrophages and/or dendritic cells were responsible for leukocyte-derived COX-2 expression after infection.

To determine whether increased COX-2 mRNA expression translated into increased COX activity, the levels of tissue-associated PGE2 were determined. Homogenates of mesenteric lymph nodes from mice infected with Salmonella showed significantly higher levels of PGE2 per milligram of protein than did mice treated with medium (Fig. 1D). This increase was completely blocked by treatment of mice with the COX-2-selective inhibitor, celecoxib, indicating that the induction of PGE2 synthesis was due to the activity of this enzyme (Fig. 1D).

Effect of treatment with the COX-2 inhibitor, celecoxib, on salmonellosis

The induction of COX-2 after Salmonella infection (Fig. 1) suggested that this COX might affect the host response to this mucosal pathogen. To address this possibility, groups of mice were infected with Salmonella while being treated daily with saline or celecoxib. At 3 days postinfection, mice were euthanized, and viable bacteria...
present in the mesenteric lymph nodes were quantified by colony counting. Surprisingly, mice treated with the COX-2 inhibitor consistently had increased viable bacteria in this mucosal lymphoid organ (Fig. 2A), suggesting a beneficial effect of local prostanooid production on the early host response against Salmonella.

To further investigate the importance of COX-2 expression during salmonellosis, groups of mice were treated daily with celecoxib or saline, and the survival of these infected mice was determined. Median survival for saline treated mice was 8 days, whereas that of the celecoxib-treated group was 11 days (Fig. 2B), and a comparison of survival curves indicated these differences to be highly significant ($p = 0.009$). Therefore inhibiting COX-2 activity during the course of developing salmonellosis resulted in increased survival, suggesting that Salmonella-induced prostanooid production was detrimental to the host.

**COX mRNA expression and PGE$_2$ secretion by cultured macrophages and dendritic cells in response to Salmonella**

The results presented in Fig. 1C demonstrated that CD11b$^+$/CD11c$^-$ cells (i.e., macrophages or dendritic cells) within the mesenteric lymph nodes up-regulated COX-2 mRNA expression after infection. As there have been no comprehensive studies to define COX expression and prostanoid secretion in response to viable Salmonella, we investigated the response of primary cultures of mouse macrophages and dendritic cells. Bone marrow-derived macrophages demonstrated inducible COX-2 mRNA expression after exposure to viable or UV-killed Salmonella, whereas COX-1 mRNA expression was not induced (Fig. 3A). COX activity also increased after exposure of macrophages to Salmonella, as indicated by significant increases in PGE$_2$ secretion as early as 2 h postinfection (Fig. 3B). In fact, viable Salmonella induced significantly higher levels of PGE$_2$ secretion than did UV-killed bacteria, and this increase was dose dependent (Fig. 3B).

By 24 h postinfection of cultured bone marrow-derived or peritoneal macrophages, levels of PGE$_2$ continued to increase in the culture supernatants (Fig. 4). Importantly, this induced PGE$_2$ production could be completely blocked by the addition of celecoxib, indicating its synthesis by COX-2. Although exposure of macrophages for 8 h to UV-killed bacteria induced little PGE$_2$ secretion (Fig. 3B), an exposure of 24 h resulted in elevated levels of this prostanooid (Fig. 4). Of particular interest was the observation that Salmonella-derived LPS was not as potent a stimulus for PGE$_2$ production as was viable or killed Salmonella (Fig. 4). Taken together, these studies clearly demonstrate the rapid induction of high levels of COX-2-derived PGE$_2$ secretion after exposure of cultured macrophages to viable Salmonella.
Supernatants. Levels of PGE2 were measured by enzyme immunoassay and cells were washed to remove any extracellular bacteria with gentamicin-10:1 (10) bacteria to dendritic cell, as indicated. After exposure for 45 min, cells were washed to remove any extracellular bacteria with gentamicin-containing medium and cultured for the indicated period of time before isolating total RNA or culture supernatants for analyses. A, RT-PCR was performed to detect the presence of COX-2, COX-1, and G3PDH mRNAs. Results are presented as amplified products electrophoresed on ethidium bromide-stained agarose gels. B, Levels of PGE2 were measured by enzyme immunoassay and are reported as the mean ± SD of triplicate determinations. These studies were performed three times with similar results.

Similar studies were performed to demonstrate the ability of cultured dendritic cells to respond to Salmonella by inducing PG secretion. Bone marrow-derived dendritic cells demonstrated inducible COX-2 mRNA expression after exposure to viable or UV-killed Salmonella, whereas COX-1 mRNA expression was not induced (Fig. 5A). COX activity also increased after exposure of dendritic cells to Salmonella, as indicated by significant increases in PGE2 secretion as early as 2 h postinfection (Fig. 5B). By 24 h postinfection, both viable and UV-killed Salmonella induced increasing levels of PGE2 (Fig. 6). Importantly, this induced PGE2 production could be completely blocked by the addition of celecoxib, indicating its synthesis by COX-2. Once again, Salmonella-derived LPS was not as potent a stimulus for PGE2 production as was viable or killed Salmonella (Fig. 4).

To demonstrate that highly purified CD11c+ cells could respond to viable Salmonella, MACS was used to isolate this population of cells from GM-CSF-expanded bone marrow-derived dendritic cell cultures. After isolation, CD11c+ dendritic cells were cultured in medium or exposed to viable Salmonella for 24 h. RT-PCR analyses demonstrated an induction in COX-2 mRNA expression (Fig. 7A) and increased PGE2 secretion (Fig. 7B) in this CD11c+ cell population. Taken together, these studies clearly demonstrate the rapid induction of high levels of COX-2-derived PGE2 secretion after exposure of cultured dendritic cells to viable or UV-killed Salmonella.

Discussion
The studies presented in this article demonstrate a considerable potential for macrophages (Figs. 3 and 4) and dendritic cells (Figs. 5–7) to respond to Salmonella infection by increasing COX-2 mRNA expression, followed by PGE2 secretion. The fact that this response also occurs in the mesenteric lymph nodes (Fig. 1) demonstrates the presence of increased PGs at mucosal sites after infection and suggests that these mediators are present to influence the developing host response.

Although Salmonella-induced PG production by macrophages and dendritic cells is clear, the role that production of these mediators has in the host response against this pathogen is less certain. Treatment of mice with the COX-2 inhibitor, celecoxib, resulted in an increased bacterial burden in the mesenteric lymph nodes on day 3 after oral inoculation of mice with Salmonella (Fig. 2A). This result suggested that the presence of PGs early in the host response was beneficial and may be linked to proinflammatory effects of PGs during acute responses (11). However, prolonged treatment with celecoxib resulted in prolonged survival of mice exposed to a lethal dose of Salmonella (Fig. 2B). One possible explanation for this result may be the ability of COX-2-induced prostanooid production to contribute to the detrimental consequences of the host response to bacterial sepsis. In support of this possibility, a recent study demonstrated the increased survival of COX-2-deficient mice after a challenge with Escherichia coli LPS (34). This study suggested that the presence of PGs was harmful.
Together, these published studies and the results presented in this study suggest a dual role for Salmonella-induced PG production during the course of infection. Theoretically, contributions that PGs make toward the acute inflammatory response may be beneficial, whereas continued production of PGs during the course of salmonellosis may contribute to the detrimental host response to sepsis.

Unfortunately, this theory is likely to be somewhat simplistic when trying to understand the importance of induced COX activity during bacterial infections. A recent study provides insight into the importance of PG secretion at mucosal sites during bacterial pathogenesis (35). In this study it was found that inhibition of COX-1 and COX-2 using nonsteroidal anti-inflammatory drugs dramatically exacerbated the development of colitis in IL-10−/− mice. Although the authors speculated about the numerous mechanisms that might help to explain their findings, it is possible that the presence of PGs helped to limit this Th1-driven autoimmune response. Therefore, these in vitro studies use high levels of LPS for extended periods and relatively high concentrations of LPS can induce PG secretion after extended exposure to viable Salmonella. Similarly, the studies presented in this article begin to explore in vivo the importance of PGs present when these same macrophages were exposed to UV-killed primary macrophage cultures. Similar results have been found for these in vitro studies use high levels of LPS for extended periods and relatively high concentrations of LPS can induce PG secretion after extended exposure to viable Salmonella.

There are numerous in vitro studies suggesting that the presence of PGs can limit the development or magnitude of Th1 responses. For example, these mediators can be potent antagonists of IL-12 production (13–15) and of IL-12R expression (16). Furthermore, recent studies have suggested that particular PGs can regulate maturation of dendritic cells (36, 37) as well as their migration (38, 39). If such PG-mediated effects occur in lymphoid tissues during Salmonella infection, such mechanisms would probably have significant consequences for developing Th1 responses.

The possibility that bacterially induced PG production might limit the development of Th1 responses would be especially problematic for a protective host response against Salmonella. Using animal models, it is clear that deletion or antagonism of IL-12 (7) or IFN-γ (40, 41) increases susceptibility to salmonellosis. Furthermore, patients with genetic defects in IL-12R (4) or IFN-γR (8) signaling often present with a clinical picture of recurrent Salmonella infections. Taken together, these studies and clinical observations clearly demonstrate the importance of an intact Th1 response for host defense against this intracellular pathogen of macrophages (1) and dendritic cells (2). Thus, one result of Salmonella-induced PG secretion may be to limit the development of a Th1 response, thereby limiting the development of a protective host response.

Stimulated macrophages have traditionally been considered the most potent PG producers of all the leukocytes (20). Induction of COX-2 is responsible for most of the eicosanoids secreted by macrophages (42), although these cells can also constitutively express COX-1. In the current study we found that viable Salmonella induces macrophages to secrete substantial levels of PGE2 within a few hours after exposure (Fig. 3B). Such a response was not observed when these same macrophages were exposed to UV-killed bacteria (Fig. 3B) or Salmonella-derived LPS (Fig. 4). Although it is clear that LPS can induce PG secretion by macrophages, often these in vitro studies use high levels of LPS for extended periods of time (43) or investigate only macrophage cell lines (44, 45), not primary macrophage cultures. Similar results have been found for LPS-induced PG secretion by dendritic cells. Relatively high concentrations of LPS can induce PG secretion after extended exposure in vitro in IL-10−/− mice. However, it is clear from the studies presented in this study that the response of macrophages and dendritic cells to viable Salmonella results in more rapid and higher levels of PGE2 secretion than those observed with LPS alone.

Taken together, the studies presented in this article begin to suggest a complex role for PGs induced during the course of salmonellosis in modulating immunity. The kinetics and magnitude of PG release relative to the location of the invading pathogen along with the predominant PG species and the local cytokine milieu that accompany invasion are likely to be important considerations for defining the ultimate effect that prostanooids will have on the protective immune response.

References


