Activation of Peroxisome Proliferator-activated Receptor γ Suppresses Nuclear Factor κB-mediated Apoptosis Induced by Helicobacter pylori in Gastric Epithelial Cells*

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Helicobacter pylori colonization leads to epithelial cell hyperproliferation within inflamed mucosa, but levels of apoptosis vary, suggesting that imbalances between rates of cell production and loss may contribute to differences in gastric cancer risk among infected populations. Peroxisome proliferator-activated receptor γ (PPARγ) regulates inflammatory and growth responses of intestinal epithelial cells. We determined whether activation of PPARγ modified H. pylori-induced apoptosis in gastric epithelial cells. PPARγ was expressed and functionally active in gastric epithelial cell lines sensitive to H. pylori-induced apoptosis. PPARγ ligands 15d-PGJ2 and BRL-49653 significantly attenuated H. pylori-induced apoptosis, effects that could be reversed by co-treatment with a specific PPARγ antagonist. Cyclopenanone prostaglandins that do not bind and activate PPARγ had no effects on H. pylori-induced apoptosis. The ability of H. pylori to activate nuclear factor (NF)-κB and increase levels of the NF-κB target IL-8 was blocked by co-treatment with PPARγ antagonists, and direct inhibition of NF-κB also abolished H. pylori-stimulated apoptosis. These results suggest that activation of the PPARγ pathway attenuates the ability of H. pylori to induce NF-κB-mediated apoptosis in gastric epithelial cells. Because PPARγ regulates a multitude of host responses, activation of this receptor may contribute to varying levels of cellular turnover as well as the diverse pathologic outcomes associated with chronic H. pylori colonization.

Chronic gastritis induced by Helicobacter pylori significantly increases the risk for non-cardia gastric cancer (1, 2), and host responses that may affect the threshold for carcinogenesis include alteration of epithelial cell proliferation and apoptosis. Mucosal hyperproliferation has been reproducibly demonstrated in H. pylori-infected human (3–8) and rodent gastric tissue (9–11), and proliferation scores normalize following successful eradication in humans (3–6). However, maintenance of tissue integrity requires that enhanced cell production be accompanied by increased rates of cell loss; consequently, studies have also examined the effect of H. pylori on apoptosis. In contrast to hyperproliferation, H. pylori has been associated with increased (12–15), unchanged (16), or even decreased (17) levels of apoptosis in vivo, and within a particular population, substantial heterogeneity exists among apoptosis scores (12–15). These observations suggest that increases in proliferation that are not balanced by concordant increases in apoptosis over years of colonization may heighten the retention of mutated cells, ultimately enhancing the risk for gastric malignancy in certain populations. Differing levels of apoptosis may depend upon bacterial strain-specific factors, because carriage of isolates that possess the disease-associated gene cagA has been associated with enhanced proliferation but attenuated apoptosis in some (8, 18) but not all (19), studies. In vitro, however, H. pylori consistently stimulate apoptosis (15, 20–23), suggesting that mediators within inflamed mucosa modify the direct effect of this organism on epithelial cells and contribute to variability in levels of apoptosis observed in vivo.

One specific host pathway through which inflammatory mediators may influence H. pylori-induced apoptosis is the transcription factor peroxisome proliferator-activated receptor γ (PPARγ). PPARγ and the related isoforms PPARα and PPARδ constitute a family of nuclear hormone receptors with important roles in the regulation of fatty acid oxidation and glucose utilization (24, 25). PPARs form functional heterodimers with the retinoid X receptor family of nuclear receptors (26). It is now appreciated that PPARs are important in regulating pathways beyond energy homeostasis (27). For example, although PPARγ was originally identified as a transcription factor essential for adipocyte differentiation (27), there is now increasing evidence to indicate a role for this receptor in regulating other cell types including macrophages, lymphocytes, and epithelial cells. In colonic epithelial cells, activation of PPARγ inhibits intracellular signaling cascades, such as NF-κB, that regulate inflammation and apoptosis (28, 29). Thiazolidinediones (e.g. pioglitazone and rosiglitazone [BRL-49653]) are a family of synthetic compounds with anti-diabetic activity that represent an important class of high affinity, PPARγ-selective agonists (30). Putative endogenous PPARγ ligands include the.

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1 The abbreviations used are: PPARγ, peroxisome proliferator-activated receptor γ; cagA, cytotoxin-associated gene A; COX-2, cyclooxygenase-2; PG, prostaglandin; 15d-PGJ2, 15-deoxy-Δ12,14-prostaglandin J2; PDTC, pyrrolidine dithiocarbamate; BAY 11-7082, N-(3-(4-methylphenyl))-sulfonyl-2-propenenitrile; NF-κB, nuclear factor κB; ILK, IκB kinase; IL, interleukin; PCR, polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; PBS, phosphate-buffered saline; GST, glutathione S-transferase; PPBE, PPAR response element; IFN-γ, interferon-γ.
cyclopentanone prostaglandin 15-deoxy12,14,15 (15d-PGJ2), which is derived from PGD2, a metabolite of cyclooxygenases (COX) (31, 32).

Over-expression of COX-2 is a promoting event for colorectal cancer (33), and aberrant expression of COX-2 within H. pylori-colonized mucosa has also been implicated in gastric carcinogenesis. Levels of COX-2 are increased within gastric mucosa of infected but not uninfected persons, suggesting that prostaglandins are important mediators of the host response to H. pylori (34–37). COX-2 expression is further increased in H. pylori-induced pre-malignant (atrophic gastritis and intestinal metaplasia) and malignant (adenocarcinoma) lesions (38–40); the chronic use of aspirin or nonsteroidal medications that inhibit COX-2 decreases the risk for distal gastric cancer (41–43). The molecular mechanism by which COX-2 enhances gastric cancer risk may involve attenuation of apoptosis, since H. pylori-induced apoptosis is augmented in the presence of COX-2 inhibitors in vitro (44) and within gastric mucosa of COX-2-deficient mice (45). Collectively, these findings suggest that prostaglandin products generated by COX-2 may contribute to the heterogeneous levels of apoptosis found within H. pylori-colonized mucosa. Because H. pylori strains invariably induce gastritis and COX-2-generated ligands of PPARγ may contribute to apoptosis in vivo, the aims of this study were to determine whether PPARγ activation affects the ability of H. pylori to induce apoptosis and to identify the molecular pathways required for these events.

**EXPERIMENTAL PROCEDURES**

**Cell Culture, Plasmids, and Reagents—**AGS (ATCC CRL1739) and MKN28 (kindly provided by Dr. Robert Coffey, Vanderbilt University) human gastric epithelial cells were grown in RPMI 1640 (Life Technologies, Inc.), supplemented with 10% fetal bovine serum (FBS) (Sigma, St. Louis, MO) and 200 μg/ml gentamicin in an atmosphere of 5% CO2 at 37 °C. Experiments were performed in antibiotic-free media with 10% fetal bovine serum using 6- or 96-well polypropylene tissue culture plates (Nunc). Plasmid PPRE3-tk-luciferase was a gift from R. Evans (Salk Institute, San Diego, CA). GW9662 was provided by Timothy M. Willson (GlaxoSmithKline, Research Triangle Park, NC). 15d-PGJ2, BAY 11-7082, and phenylmethylsulfonyl fluoride (PMSF) (Calbiochem, San Diego, CA) were added, 1% Nonidet P-40, with leupeptin (10 μg/ml), to AGS and MKN28 cells (30). Commercially available ELISA (Becton Dickinson, Mountain View, CA) (46).

**Immunofluorescence—**AGS cells were cultured on collagen-coated glass cover slides, and cells treated with H. pylori in the presence or absence of BRL-49653 were washed twice with ice-cold PBS, fixed in 1% paraformaldehyde in PBS for 10 min at 4 °C, and then permeabilized with methanol. Slides were dehydrated and mounted using Vectashield mounting medium (Vector Laboratories, Burlingame, CA). Immunofluorescence was observed using a fluorescence microscope, and for each sample, at least three fields were evaluated by the same observer unaware of experimental conditions. Results are expressed as the mean number of cells with nuclear localization of the NF-κB p65 subunit/total number of cells counted.

**iE6A Kinase (IKK) in Vitro Kinase Assays—**Cells were washed twice with ice-cold PBS and then solubilized in kinase buffer (20 mM Tris-HCl, pH 7.4, 20 mM MgCl2, 20 mM β-glycerophosphate, 20 mM p-nitrophenolphosphate 1 mM sodium orthovanadate, 1 mM EDTA, and 1% Nonidet P-40, with leupeptin (10 μg/ml), aprotinin (10 μg/ml), and phenylmethylsulfonyl fluoride (18 μg/ml)). In vitro GST-IκBα phosphorylation assays were performed by incubating cellular lysates (30 μg) in kinase buffer with 0.5 μg of GST-IκBα fusion protein (Santa Cruz) conjugated to glutathione-Sepharose 4B (Amersham Pharmacia Bio- tech) for 30 min at room temperature. The kinase reaction was stopped by a 1-min centrifugation at 4 °C followed by two washes in ice-cold PBS (49). GST-IκBα was recovered by solubilization in Laemmli sample buffer for detection of phosphorylation by Western blot analysis with anti-phospho-IκBα (Ser32) (Cell Signalling). Western blot analysis with anti-IκBα (Cell Signalling) was performed to verify equal protein loading.

**Statistics—**Two-tailed statistical tests were used to evaluate the data. Results are expressed as the mean ± S.D. The Mann-Whitney U test was used for statistical analyses of inter-group comparisons; p values < 0.05 were considered significant.

**RESULTS**

**PPARγ Is Expressed and Functionally Active in Gastric Epithelial Cell Lines Sensitive to H. pylori-induced Apoptosis—**Reverse transcription-PCR and Western blot analyses were performed to determine whether PPARγ is expressed in gastric epithelial cells. PPARγ-specific amplification products (Fig. 1A) and immunoreactive protein bands (Fig. 1B) were present in both AGS and MKN28 cells. To determine the functional activ-
Experimental Procedures.

Fig. 1. PPARγ is expressed and functionally active in gastric epithelial cells sensitive to H. pylori-induced apoptosis. A, RNA from AGS (lane 1) or MKN28 (lane 2) cells was subjected to reverse transcription-PCR using PPARγ-specific primers as described under “Experimental Procedures.” Amplification products of ~650 base pairs were present in both cell types as well as the positive (lane 3) but not the negative (no template, lane 4) control. MW, molecular weight standards. B, cellular lysates prepared from AGS (lane 1) and MKN28 (lane 2) cells were subjected to Western blot analysis with an anti-PPAR γ antibody as described under “Experimental Procedures.” Lane 3, positive control; lane 4, negative control. C, AGS cells were transiently transfected with the PPRE3-tk-luciferase reporter plasmid by lipid transfection as described under “Experimental Procedures.” Transfected cells were then exposed to the indicated ligand at 1, 5, 10, or 25 μM for 24 h. Cells were harvested, and the dual luciferase assay was performed. Data are represented as fold-activation of luciferase activity in which luciferase activity of ligand-treated samples was divided by luciferase activity of vehicle-treated cells and are the means of normalized relative light units from three independent experiments. Error bars, S.D. D, AGS and MKN28 cells were incubated in the absence or presence of H. pylori strain 60190 for 24–48 h, and DNA fragmentation was quantitated by ELISA. Data represent the mean ± S.D. of three independent experiments, and results are expressed as fold increases in nucleosomal release relative to uninfected control cells; a value of 1, therefore, represents base line. E, AGS cells were co-cultured with or without strain 60190 for 24–48 h, stained with propidium iodide, and visualized using fluorescence microscopy. Apoptotic cells are characterized by condensed chromatin and nuclear segmentation.

H. pylori-induced Apoptosis Is Attenuated by Co-treatment with PPARγ Ligands—To determine whether activation of PPARγ altered H. pylori-induced apoptosis, we pretreated cells with increasing concentrations of either 15d-PGJ2, BRL-49653, PGA1, or vehicle alone prior to the addition of H. pylori and quantified apoptosis by ELISA. H. pylori alone significantly increased apoptosis (p < 0.001 versus vehicle-treated cells, Fig. 2A). Treatment with 15d-PGJ2 or BRL-49653 alone did not significantly increase AGS cell apoptosis (data not shown). However, pre-incubation with either 15d-PGJ2 or BRL-49653 significantly (p ≤ 0.03 for each) inhibited H. pylori-induced apoptosis in a dose-dependent manner, and this reduction was not found following exposure to PGA1 (Fig. 2A). To more completely confirm the role of PPARγ activation, we attempted to reverse these events by using the PPARγ antagonist GW9662 (50). Pre-incubation with GW9662 partially reversed the suppressive effects of 15d-PGJ2 and BRL-49653 (Fig. 2B), providing further evidence that specific activation of PPARγ inhibits the ability of H. pylori to stimulate apoptosis in AGS cells.

Attenuation of H. pylori-induced Apoptosis by PPARγ Activation Is Not Strain-specific—Apoptosis levels within inflamed tissue have been shown to vary depending upon H. pylori strain characteristics (i.e. cagA) (8, 18). To determine whether attenuation of apoptosis by PPARγ activation was affected by strain variation, we measured AGS cell apoptosis during co-culture with a panel of cagA+ or cagA− isolates in the absence or presence of BRL-49653. Apoptosis was induced by all strains, although absolute levels varied between different isolates (Fig. 3). Specifically, cagA+ strains induced higher levels of nucleo-
somal release than cagA⁻ strains, which is consistent with previous reports (23). However, BRL-49653 decreased H. pylori-induced apoptosis in all samples, albeit to varying degrees, indicating that the ability of PPARγ to attenuate apoptosis is likely not related to the presence of cagA in the infecting isolate.

**PPARγ Agonists Inhibit NF-κB Activation by H. pylori**—NF-κB is a transcription factor for which activation is tightly controlled by inhibitory IκB proteins. NF-κB can induce (51, 52) or inhibit (53–55) apoptosis depending upon the specific cell type, and H. pylori activates NF-κB in gastric epithelial cells (56–58). Because PPARγ ligands suppress NF-κB activation in intestinal cells (28, 29), we determined whether inhibition of H. pylori-induced apoptosis by PPARγ activation in gastric cells occurs via a NF-κB-dependent mechanism. We first examined the kinetics of NF-κB activation by co-culturing strain 60190 with AGS cells and quantitating NF-κB nuclear translocation by immunostaining and fluorescence microscopy. H. pylori induces nuclear translocation of p50/p65 NF-κB heterodimers (56). Therefore, we used an antibody that recognizes the IκB binding region of the p65 subunit. Nuclear translocation of p65 occurred quickly (30 min) following treatment with phorbol 12-myristate 13-acetate (data not shown), indicating that all of the components required for NF-κB activation were functional in AGS cells. H. pylori also significantly (p ≤ 0.001 for each time point) increased nuclear translocation of NF-κB, and the percentage of H. pylori-infected cells with nuclear positivity for p65 peaked at 4 h and then decreased by 6 h (Fig. 4A). These results confirm the findings from previous investigations (56, 57) and demonstrate that H. pylori activates NF-κB in AGS cells.

We next examined whether activation of PPARγ attenuates H. pylori induction of NF-κB. Incubation with BRL-49653 alone had no discernible effect compared with control AGS cells, and as predicted, strain 60190 significantly (p < 0.001) increased p65 nuclear translocation at 4 h (Fig. 4, B and C). In contrast, pre-incubation with BRL-49653 prior to the addition of H. pylori dramatically reduced the number of cells containing nuclear p65 (80–90% reduction versus H. pylori alone, p < 0.001, Fig. 4, B and C). These results were confirmed by immunoblot analysis using a phosphorylation state-specific antibody for IκB. Immunoreactive bands for phosphorylated IκB were observed shortly (15 min) following H. pylori co-culture (Fig. 4D); however, H. pylori-stimulated IκB phosphorylation was abrogated by BRL-49653 (Fig. 4D).

In response to H. pylori signaling, activated IKKα and IKKβ directly phosphorylate IκB in gastric epithelial cells, leading to IκB degradation and NF-κB transactivation (58). Activation of PPARγ inhibits H. pylori-stimulated IκB phosphorylation (Fig. 4D). Therefore, we assessed IKK kinase activity toward IκB. H. pylori-induced IKK kinase activity was inhibited by BRL-49653 (Fig. 4E), consistent with the PPARγ-dependent suppression of IκB phosphorylation (Fig. 4D).

To determine whether inhibition of NF-κB activation by PPARγ agonists has functional consequences, we quantitated the release of a known downstream target of NF-κB, IL-8. H. pylori alone potently stimulated IL-8; however, BRL-49653 attenuated this effect (Fig. 4F), results that mirrored its ability to inhibit H. pylori-stimulated NF-κB nuclear migration and IκB phosphorylation (Fig. 4, B–E). These findings indicate that in AGS cells, activation of PPARγ inhibits NF-κB signaling through prevention of IκB phosphorylation and degradation, which leads to a corresponding reduction of NF-κB-dependent inflammatory mediators.

**Inhibition of NF-κB Suppresses H. pylori-induced Apoptosis**—Having established that PPARγ activation attenuates induction of NF-κB by H. pylori, we next asked whether H.
**DISCUSSION**

Alteration of epithelial cell proliferation and apoptosis is a manifestation of *H. pylori*-induced gastritis. However, the precise mechanisms underlying these effects remain incompletely clarified. In isolated cell culture systems, *H. pylori* directly stimulates apoptosis (15, 20–23); for example, urease can induce apoptosis by binding to major histocompatibility complex class II molecules expressed on the surfaces of gastric epithelial cells (60). In vivo, however, levels of apoptosis are considerably more variable (12–15), suggesting that apoptosis within gastric tissue is regulated by host inflammatory mediators.

The immune response elicited by *H. pylori* in humans and *Helicobacter felis* in mice is Th1-predominant (61–63). *H. pylori* infection of mice deficient in interferon-γ (IFN-γ), a Th1 lymphocyte-derived cytokine, leads to decreased levels of gas-

*pylori*-induced apoptosis was mediated by NF-κB. PDTC is a compound that inhibits NF-κB activation in AGS cells, thereby preventing NF-κB-mediated transcriptional activation (56). BAY 11-7082 is an agent that selectively inhibits tumor necrosis factor-α-induced phosphorylation of IκBα (59). We therefore used these inhibitors to demonstrate a link between NF-κB activation and induction of apoptosis in *H. pylori*-infected cells. PDTC or BAY 11-7082 alone had no significant effect on apoptosis (Fig. 5). In contrast, pretreatment with these compounds markedly inhibited *H. pylori*-induced apoptosis (>95% inhibition by 100 μmol/liter PDTC or 10 μmol/liter BAY 11-7082; p < 0.001 versus *H. pylori* alone, Fig. 5). These findings indicate that *H. pylori* stimulates apoptosis in AGS cells via NF-κB-dependent cascades. Thus, inhibition of NF-κB is likely the predominant mechanism through which PPARγ activation attenuates *H. pylori*-induced programmed cell death.
Stimulate apoptosis.

Anistic insights into these programmed cell death. Our results have provided potential mechanisms that a COX-2 generated ligand of PPARγ/H9253 H. pylori polymorphisms of the human interleukin-1 receptor antagonist GW9662, we were able to substantially reverse the decrease in H. pylori-induced apoptosis seen with BRL-49653 treatment alone. Collectively, these results suggest that a majority of the anti-apoptotic response induced by PPARγ ligands in H. pylori-infected cells was due to specific modulation of PPARγ, a finding consistent with a recent report that provided direct genetic evidence of an anti-inflammatory role for PPARγ in colonic mucosa (29).

Contact between H. pylori and gastric epithelial cells results in brisk activation of NF-κB (56–58), and this is dependent upon activation of NF-κB-inducing kinase via activation of tumor necrosis factor receptor-associated receptors 2 and 6 (58). Activated NF-κB-inducing kinase then phosphorylates and activates IKKα and IKKβ, which in turn phosphorylate IκBα, leading to its proteosome-mediated degradation, with subsequent release and nuclear translocation of NF-κB. Stimulation and activation of NF-κB does not require protein synthesis, and therefore this system is particularly utilized in immune, inflammatory, and acute phase responses where rapid activation of defense genes following exposure to pathogens can be critical for the survival of an organism. Activation of NF-κB can also regulate cellular growth responses including apoptosis. Although NF-κB has been shown to inhibit tumor necrosis factor-α stimulated apoptosis (53–55), expression of IκB and subsequent apoptosis in T lymphocytes is dependent upon activation of NF-κB and AP-1 (52). NF-κB activation has also been demonstrated to enhance apoptosis in human embryonic kidney cells (51). Consequently, cell lineage characteristics in conjunction with additional intracellular mediators may ultimately dictate the apoptotic cellular response to stimuli that activate NF-κB.

The ability of PPARγ agonists to suppress H. pylori-induced apoptosis does not correlate with cagA genotype. cagA is the terminal open reading frame of an ~40-kilobase locus containing 31 genes (the cag pathogenicity island) (74, 75). Several cag island genes possess homology to components of a type IV bacterial secretion system (74, 75), which, in other prokaryotic species, functions as a conduit for the export of proteins across the bacterial membrane. CagA is translocated into and phosphorylated within host cells following H. pylori:epithelial cell contact (76–78). Carriage of cagA− strains significantly enhances the risk for severe gastritis, atrophic gastritis, and distal gastric cancer compared with that incurred by cagA+ strains (46, 79–83). Although cagA per se is not required for H. pylori induction of COX-2 and prostaglandin release by gastric

![Graph](https://example.com/graph.png)
epithelial cells, these events are dependent upon adjacent genes within the cag island (84). These findings raise the hypothesis that strains containing a functional cag island augment PPARγ activation by inducing higher levels of COX-2-generated prostaglandins in vitro, which may be responsible for reduced levels of apoptosis found in association with these strains in certain human populations (8, 18). However, other levels of control are likely to be important in regulating these pathways. For example, PPARγ ligands can reduce phorbol 12-myristate 13-acetate-dependent transcriptional activation of COX-2 in vitro by suppressing AP-1 activity (85), suggesting that PPARγ may regulate its own expression by decreasing eicosanoid production. Activation of PPARγ in MKN45 gastric epithelial cells also represses expression of the tyrosine kinase c-Met, which may alter additional signaling pathways that regulate cell growth and death (86).

In conclusion, we have demonstrated that PPARγ ligands suppress H. pylori-induced apoptosis in vitro, an effect likely dependent on the ability of PPARγ to inhibit H. pylori-mediated increases in NF-κB activity. Because PPARγ regulates a multitude of host responses such as inflammation, cell growth, and cell death, selective activation of this receptor may not only contribute to varying levels of cellular turnover within inflamed tissue but also to the diverse pathologic outcomes (gastritic atlas, peptic ulcer disease, distal gastric cancer) associated with chronic H. pylori colonization.

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