**Helicobacter pylori Inhibits the G₁ to S Transition in AGS Gastric Epithelial Cells**

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**Abstract**

Infection with the bacterium *Helicobacter pylori* is associated epidemiologically with development of gastric cancer. To better understand the role of *H. pylori* in carcinogenesis, we examined the effects of *H. pylori* on cell cycle-related events in the AGS gastric cancer cell line. During coculture, wild-type, toxigenic, cagA-positive *H. pylori* induced both apoptosis and inhibition of cell cycle progression at G1-S in AGS cells. These effects were most apparent in AGS cells synchronized by serum-deprivation and then stimulated to progress through the cell cycle by refeeding. An isogenic cagA-negative mutant *H. pylori*, produced similar effects. In contrast to changes induced by 5-fluorouracil, the inhibition of cell cycle progression from G1 to S caused by *H. pylori* was not accompanied by sustained changes in p53 or p21Waf1, but was associated with reduced expression of p27kip1 and inhibition of transcriptional activation of the serum-response element of c-fos. Our results indicate that *H. pylori* inhibits cell cycle progression at G1-S and induces apoptosis, associated with reduced expression of p27kip1 in AGS gastric cancer cells. In vivo, similar effects as a result of *H. pylori* infection may lead to potentially deleterious compensatory hyperproliferation by nonneoplastic gastric epithelial cells.

**Introduction**

Chronic colonization of the human stomach by the Gram-negative bacterium *Helicobacter pylori* is associated with the development of cancer in the distal portion of the stomach (1). Because of this strong epidemiological association, *H. pylori* is classified as a definite carcinogen by the IARC (2). Support for *H. pylori* as a major cause of gastric cancer has come from two independent groups using the Mongolian gerbil. In this model, intragastric inoculation of *H. pylori* alone induced changes similar to those found in human infection, including chronic gastritis, intestinal metaplasia, and adenocarcinoma (3, 4). Despite these advances, the mechanisms by which *H. pylori* supports the development of gastric adenocarcinoma remain unclear. Current models have suggested that *H. pylori* is not directly mutagenic, but acts more indirectly (for example, through inflammatory mediators or decreasing gastric acid secretion), thus, favoring the formation of mutagenic substances (5–7). Alternatively, *H. pylori* may predispose to cancer by altering gastric epithelial cell turnover. Increased numbers of cells expressing markers of proliferation can be demonstrated in immunohistochemical studies of various *H. pylori*-associated precursor lesions of gastric cancer and even in early lesions, such as chronic superficial gastritis (8). Increased numbers of apoptotic epithelial cells have also been found in the gastric mucosa of infected individuals in vivo (5, 9, 10). Therefore, *H. pylori* infection seems to increase both apoptosis and proliferation, implying increased gastric epithelial cell turnover. Furthermore, strains of *H. pylori* carrying the cag pathogenicity island, which is associated with an increased risk for gastric cancer in Western countries (11), alter the balance between apoptosis and proliferation within the gastric mucosa (12).

Previous studies have shown that gastric epithelial cells undergo apoptosis when cultured in vitro together with *H. pylori* (13–16). To clarify further the interaction between *H. pylori* and the gastric epithelial cell cycle, we have examined in detail the effect of *H. pylori* on cell kinetics, apoptosis, and the expression of cell cycle-related proteins in the AGS gastric epithelial cell line. Our results indicate that *H. pylori* initially inhibits the G1 to S progression of the cell cycle in this gastric cancer cell line and that this cell cycle inhibition is associated with alterations in gene expression and, eventually, in apoptosis. Assuming similar changes occur in nontransformed gastric epithelial cells, our findings suggest that the hyperproliferative response to *H. pylori* observed in vivo is compensatory to an initial inhibitory effect of this bacterium on the cell cycle.

**Materials and Methods**

**Cell Lines and Culture Conditions.** AGS human gastric epithelial cells (#CRL-1739; American Type Culture Collection) were maintained in Ham’s F-12 medium with 10% FBS1 (Life Technologies, Inc.) in 180 ml of tissue culture flasks (Nunclon, Rochester, NY) at 37°C in 5% CO2. Cells were fed fresh medium with serum every 2–3 days and split when subconfluent. For experiments with synchronized cells, AGS cells were serum-deprived for 48 h. Attempts to use AGS cells synchronized by treatment with 50 μM lovastatin were unsuccessful because massive apoptosis was induced.

**H. pylori Strains and Culture Conditions.** Coculture experiments were performed, as described previously (13), using *H. pylori* strain 88–23, a cagA-positive and VacA-positive strain isolated from a patient with nonulcer dyspepsia, and its isogenic cagA-negative mutant (17). Bacteria were maintained on trypticase soy agar containing 5% sheep blood (TSAI, BBL, Becton Dickinson, Cockeysville, MD) incubated at 37°C in 5% CO2. Cells were fed fresh medium with serum every 2–3 days and split when subconfluent. For experiments with synchronized cells, AGS cells were serum-deprived for 48 h. Attempts to use AGS cells synchronized by treatment with 50 μM lovastatin were unsuccessful because massive apoptosis was induced.

**Effect of *H. pylori* on Growth of AGS Cells.** Exponentially growing AGS cells were seeded in triplicate in 6-well (3.5 cm in diameter) cell culture plates (Becton Dickinson) at a concentration of 1 × 10³/well and incubated at 37°C in 5% CO2 after the addition of fresh medium containing 10% FBS alone or fresh medium containing 10% FBS and *H. pylori* (epithelial:bacteria cell ratio = 1:200). Cells were collected by trypsinization at 0, 20, 30, and 48 h, and cell numbers were determined with a Coulter counter.

**Effect of *H. pylori* on Cell Cycle Distribution and Apoptosis.** AGS cells cocultured with *H. pylori* were analyzed in parallel with cells grown in the absence of organisms to determine effects on cell cycle distribution. Adherent

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and floating cells were collected together and fixed in 70% ethanol. Cell pellets were suspended in 400 μl of 0.2 mg/ml propidium iodide containing 0.6% NP40 (ICN Pharmaceuticals, Costa Mesa, CA) plus the same volume of 2 mg/ml RNase (Sigma Chemical Co., St. Louis, MO) and then incubated in the dark at room temperature for 30 min. Cell suspensions were filtered through a 60-μm mesh filter (Spectrum Medical Industries, Laguna Hills, CA). Data acquisition and analysis were performed on a FACScan instrument equipped with a FACStation (Becton Dickinson Immunocytometry Systems, San Jose, CA). Debris was eliminated from the analysis using a forward angle light scatter threshold. Cell doublets and other clumps were removed from the analysis by gating fluorescence pulse area (integral fluorescence). All fluorescence and laser light scatter measurements were made with linear signal-processing electronics. Data from 10,000–20,000 cells were collected for each data file. Cell cycle analysis was performed with Multicycle software (Phoenix Flow Systems, San Diego, CA). Apoptotic cells were considered to constitute the sub-G1 cell population. The induction of apoptosis was confirmed by examining the cells under fluorescent microscopy after double staining with propidium iodide and Annexin V-FITC according to the manufacturer’s instructions (Trevenig, Gaithersburg, MD), as described previously (13). AGS cells treated with 10 μM 5FU (Sigma Chemical Co.) were studied in parallel, as a positive control for apoptosis (13). All experiments were performed at least three times and gave similar results.

**Protein Extraction and Western Blotting.** Cells were collected with a rubber policeman, washed twice in ice-cold PBS, and resuspended in lysis buffer containing 50 mM HEPES, 150 mM NaCl, 2.5 mM EGTA, 1.0 mM EDTA, 1.0 mM DTT, 0.1% Tween 20, 10% glycerol, 10 mM β-glycerophosphate, 1.0 mM sodium fluoride, and 0.1 mM sodium orthovanadate (adjusted to pH 7.5), plus the protease inhibitors leupeptin (10 mg/ml), aprotonin (10 mg/ml), and 1.0 mM phenylmethylsulfonyl fluoride, which were added just before use. The suspended cells were left on ice for 10 min before sonication on ice, twice for 10 s with a Sonifer Cell Disrupter (Ultrasonics Inc., Plainview, NY), and then centrifuged at 14,000 rpm for 10 min at 4°C to yield soluble cell lysates. Protein concentrations were determined using the Bio-Rad Protein Assay (Bio-Rad Laboratories, Richmond, CA), and lysates were stored at −80°C for further analysis. For Western blotting, 50–100 μg of a total cell lysate were subjected to SDS-PAGE. The proteins were then transferred, using transfer buffer (50 mmol/liter Tris, 190 mmol/liter glycine, and 10% methanol), to Immobilon-P membranes (Millipore, Bedford, MA) at 60V for 3 h. The membranes were incubated with blocking buffer (50 mmol/liter Tris, 200 mmol/liter NaCl, 0.2% Tween 20, and 3% BSA) overnight at 4°C and incubated with a 1:5000 dilution of the indicated antibody for 60 min. The primary antibodies used were mouse monoclonal antibodies to pRB (clone G3-245), PCNA (clone PC10; Pharmingen, San Diego, CA) and p53 (Ab 1801; Santa Cruz Biotechnology, Santa Cruz, CA), and rabbit polyclonal antibodies to cyclins A, D1, and E (Upstate Biotechnology, Lake Placid, NY), p21waf1 (sc-397-G) and p27kip1 (sc-528-G, Santa Cruz) and actin (Sigma Chemical Co.). After washing three times with washing buffer (blocking buffer without 3% BSA) for 10 min each, horseradish peroxidase-linked antirabbit donkey serum (1:3000) or antirabbit serum (1:4000; Amersham Corp., Arlington Heights, IL) were added for 1 h. The membranes were washed again, and immune detection was performed using the enhanced chemiluminescence Western blotting detection system (Amersham Corp., Arlington Heights, IL). Actin immunoblotting was performed to verify that equal amounts of protein had been loaded in each lane.

**SRE Luciferase Reporter Assay.** To determine whether *H. pylori* induced changes in signal transduction pathways that are associated with mitogenesis, transient transfection reporter assays were done using a SRE-luciferase construct. AGS cells were grown in Ham’s F-12 medium containing 10% FBS and plated at 2.0 × 104/well (3.5 cm in diameter) in 6-well plates, in triplicate, 24 h before transfection. To normalize the transfection efficiency, the SRE-luciferase plasmid (provided by Dr. Ron Prywes, Columbia University, New York, NY) was cotransfected with a CMV-β-galactosidase plasmid (Stratagene, La Jolla, CA) at a ratio of 2:1, using lipofectin (Life Technologies, Inc.). Six hours after transfection, cells were fed with fresh medium and incubated overnight. The cells were then serum-starved for 48 h before the addition of *H. pylori* at final AGS-bacterial cell ratios of 1:200, 1:1,000, and 1:10,000. After 3 h, the cells were washed twice with cold PBS and lysed by addition of 500 μl of reporter lysis buffer (Promega) for 15 min at room temperature. Lysates were clarified by centrifugation at 14,000 × g for 2 min, and the supernatant fraction was collected. Each lysate (30 μl) was used for luciferase assays, as described (18). β-galactosidase activity was determined using the β-galactosidase Enzyme Assay System (Promega), according to the manufacturer’s instructions. The luciferase level in each sample was normalized by the corresponding value for β-galactosidase activity.

**Results**

**Growth Characteristics and Synchronization of AGS Cells.** AGS cells were synchronized by serum deprivation. Cell cycle analysis indicated the distribution of serum-fed, exponentially dividing, 50% confluent AGS cell cultures were 47% in G0-G1, 26% in S, and 27% in G2-M. In contrast, serum deprivation for 48 h increased the percentage of cells in G0-G1 to 60% and decreased cells in S (22%) and G2-M (20%), consistent with cell cycle inhibition from G1 to S phase (Fig. 1, time 0). Serum-refeeding of serum-starved AGS cells induced a marked increase in the proportion of cells in S within 12 h and a reciprocal decrease in the G1 fraction, reflecting progression through the cell cycle (Fig. 1). Exponentially growing cells that had not been serum-starved showed little change in cell cycle distribution after serum refeeding. Cell cycle distributions for high density cultures at 100% confluence were similar to those for the exponentially growing cells at 50% confluence (data not shown), indicating that AGS cells do not exhibit significant contact inhibition of cell proliferation.

Our attempts to study AGS cells synchronized with lovastatin, which commonly causes reversible arrest of cells in G1 (19), were limited because treatment with 50 μM lovastatin resulted in massive apoptosis of AGS cells (55% at 24 h).

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**Fig. 1.** Cell cycle distribution of AGS cells at different times after the addition of fresh medium with 10% FBS. Cells were serum-deprived for 48 h (time = 0 h) and then were refed with either fresh medium containing 10% FBS alone (S-R, □) or with fresh medium containing 10% FBS and wild-type *H. pylori* at a bacterial to epithelial cell ratio of 200:1 (S-R+HP, □).

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Expression of Cell Cycle Control Proteins in Serum-starved and Refed AGS Cells. Western blotting of cell cycle control proteins confirmed that refeeding stimulated the serum-deprived AGS cells to progress through the cell cycle (Fig. 2A). The cellular levels of cyclins D, E, and A proteins increased at 12–24 h after refeeding, reflecting progression of the cells from G1 to the S phase. The increase in cyclins D, E, and A was accompanied by hyperphosphorylation and inactivation of pRb, thus, enabling the cells to pass through the G1-S checkpoint. Expression of the cyclin-dependent kinase inhibitors p21cip1 and p27kip1 both increased at 6–24 h after serum-refeeding. Similar, although less marked, changes in cell cycle control proteins were observed in exponentially dividing cultures (data not shown).

Effect of H. pylori on AGS Growth and Cell Cycle Kinetics. Addition of H. pylori to AGS cells at a bacterial:epithelial cell ratio of 200:1 was associated with significant growth inhibition, first evident at 48 h (data not shown). To examine the mechanism responsible for the growth inhibition by H. pylori, the cell cycle distribution of AGS cells was evaluated by flow cytometry. Addition of H. pylori at the same time as refeeding serum to serum-deprived AGS cells inhibited the refeeding-associated decrease in cells in the G1 and G2-M fractions and abolished the increase in the S phase fraction observed in cells refed serum alone (Fig. 1). Thus, H. pylori inhibited cell cycle progression from G1 to S phases. Similar effects were observed after the addition of 5FU to serum-deprived and refed cells (data not shown). Inhibition by H. pylori of progression from G1 to S phase was also observed in exponentially growing (nonserum-deprived) AGS cells and in cells at 100% confluence, although in both these conditions changes were less marked than in the serum-deprived and refed cells. Changes observed were the same whether coculture was performed with the wild-type H. pylori strain or its cagA-negative mutant.

Expression of Cell Cycle-related Proteins. Compared with cells refed serum alone, the addition of serum plus H. pylori to serum-deprived cells caused increased expression of cyclin D, which began at 12 h and peaked at 24 h (Fig. 2B). The addition of H. pylori was also associated with decreased expression of PCNA and cyclin A. In H. pylori-treated cells, expression of p21cip1 was decreased initially (at 6 h), followed by slightly increased expression at 12 h, when compared with serum-refed controls. The expression of p27kip1 was decreased at all time points after the addition of H. pylori. The expression of p53, cyclin E, and pRb was not altered by the addition of H. pylori. Similar patterns of cell-cycle protein expression were observed for cells infected with wild-type or cagA- strains of H. pylori. In contrast to changes induced by H. pylori, treatment with 5FU, which also inhibited cell cycle progression and induced massive apoptosis (72% at 48 h), was associated with a marked and sustained increase in both p21cip1 and p53 (data not shown).

SRE Activity. It is known that the addition of serum or other mitogens to serum-starved cells induces the expression of the immediate early response gene c-fos through activation of mitogen-activated protein kinase leading, to transactivation of the SRE promoter element (20). Because H. pylori inhibited the progression of AGS cells from G1 to S after refeeding serum-deprived cells, we used an SRE-luciferase reporter to examine SRE activity in AGS cells treated with H. pylori. Refeeding serum induced a 3-fold increase in the activity of the luciferase construct (Fig. 3). This induction of luciferase activity by serum was markedly inhibited by H. pylori, both the wild-type and the isogenic cagA-negative mutant, at bacterial to epithelial cell ratios of 1,000:1 and 10,000:1 (Fig. 3).

Spontaneous and H. pylori-associated Apoptosis in Exponentially Dividing and Serum-starved Cells. Spontaneous apoptosis occurred in 2–5% of either exponentially growing or serum-deprived AGS cells, as assessed by subdiploid DNA-peak analysis on flow cytometry. After adding serum to serum-deprived AGS cells, the percentage of cells in the sub-G1 (apoptotic) fraction increased about 2-fold at 6–12 h, then returned to baseline levels at 48 h. This early (6–12 h) peak of apoptosis was much less marked in exponentially dividing, continuously fed AGS cells.

The addition of H. pylori together with serum induced a 2–5 fold increase in the percentage of cells in the sub-G1 population in both serum-deprived and exponentially dividing cells (Fig. 4). This effect peaked at 12 h in the serum-deprived and refed AGS cells and at 24 h in the exponentially dividing cells. No significant differences were observed between the extent and time course of apoptosis after infection by wild-type H. pylori or its isogenic cagA-negative mutant.

The amount of apoptosis induced by 10 μM 5FU was much greater than with H. pylori (about 75% of cells displayed a sub G1 peak) and peaked later than apoptosis induced by H. pylori (at 48–72 h; data not shown). The early (6 h) peak of apoptosis was partially reduced and delayed by concurrent addition of H. pylori with serum refeeding, suggesting that cell cycle progression may be necessary for refeeding-induced apoptosis.
Discussion

The major finding of the present study is that exposure of gastric epithelial cells to *H. pylori* causes inhibition of the G1 to S progression of the cell cycle and alters expression of specific cell cycle-related proteins. It seems likely, therefore, that these effects and the associated induction of apoptosis are responsible for the growth inhibition of gastric epithelial cells caused by *H. pylori* and observed in the current and previous studies (14).

The demonstration of these effects was facilitated by using cultures partially synchronized in G1/S by serum deprivation and stimulated to progress through G1 to S by the readdition of serum. Using this protocol, it was possible to observe *H. pylori*-induced changes in the expression of specific cell cycle-associated proteins. Exposure of AGS cells to *H. pylori* was associated with reductions in the expression of the PCNA and cyclin A proteins, which were consistent with inhibition of cell cycle progression and entry into S phase. Paradoxically, coculture with *H. pylori* was associated with decreased levels of the p27kip-1 protein, which binds to and inhibits several cyclins and cyclin-dependent kinases, especially cyclin E and cdk2 and, therefore, can inhibit the G1 to S transition. It was also surprising to find that *H. pylori* increased the expression of cyclin D, because this would also be expected to enhance rather than inhibit progression through G1. Thus, it seems that *H. pylori* does not simply act as a brake at the G1 to S transition, but instead disrupts the normal regulation of components of the cell cycle. These effects might also result in the enhancement of apoptosis seen in the *H. pylori*-treated cells (Fig. 4). All of the effects of *H. pylori* were also seen in exponentially dividing cells, but were less marked than in the serum-deprived and refed cells. Therefore, these effects may be dependent, at least in part, on the growth characteristics of the target cells.

Inhibition of cell cycle progression from G1 to S phases and induction of apoptosis also occurred when AGS cells were exposed to 5FU. With 5FU, these effects were associated with increased levels of both p21cip1 and p53 proteins. However, *H. pylori* did not cause a sustained increase in either of these proteins, suggesting that inhibition of cell cycle progression caused by *H. pylori* is mediated through an alternative p53- and p21cip1-independent mechanism.

We also tested the hypothesis that *H. pylori* might inhibit growth and cell cycle progression by inhibiting signaling pathways that mediate the transactivation of the SRE in the c-fos promoter. *H. pylori* did inhibit the serum stimulation of an SRE-luciferase construct in AGS cells, but this required a concentration of bacteria 5-fold greater than that required for growth inhibition. This may be due to the high copy number of the luciferase reporter construct transfected into the AGS cells. Alternatively, *H. pylori* may exert its effects on the cell cycle by inhibition of pathways downstream from c-fos. Studies are in progress to examine specific signaling pathways and transcription factors in greater detail.

As mentioned above, although *H. pylori* inhibited cell cycle progression, the treated AGS cells displayed a decrease in the cell cycle inhibitor p27kip1 (Fig. 2B). We have seen a similar reduction in the level of this protein in AGS cells chronically exposed to *H. pylori*. The significance of this effect is not known, but it is of interest that gastric cancers often display a decrease in this protein (21) and that this decreased level of p27kip1 in gastric and a variety of other types of cancer is associated with a poor prognosis (22).

A region of the *H. pylori* genome, designated the *cag* pathogenicity island, has been implicated in epidemiological studies of human gastric cancer and premalignant changes and altered gastric cell turnover (11, 12). Since in the present study, ablation of the *cagA* gene within the *cag* pathogenicity island did not alter any of the cell cycle effects, it seems that other genes within this island, but not *cagA* itself, may be responsible for these epidemiological observations. It will be of interest to use other mutants of *H. pylori* and the methods described in this study to identify these genes. In general, there have been relatively few studies examining the effects of bacteria on the cell cycle of mammalian epithelial cells. The inhibition of the cell cycle at G1-S by *H. pylori* observed in the present study contrasts with the G2 phase cell cycle block induced by toxins secreted by *Escherichia coli* (23), *Campylobacter jejuni* (24), and HIV (25). Thus, microorganisms seem to have evolved a number of different mechanisms to inhibit the mammalian cell cycle, thus, contributing to their specific pathogenic effects.

One limitation of our study, and virtually all studies that coculture *H. pylori* with gastric epithelial cells, is that the target cells examined are derived from gastric cancers. However, differences in response among gastric cancer cell lines may be instructive. We have found that cells of another gastric epithelial cell line, Kato-III, are relatively resistant to induction by *H. pylori* of both apoptosis and changes in the cell cycle. This may be related to the fact that, unlike AGS cells, Kato-III cells have mutated p53 and, thus, an altered apoptotic response to external stimuli (26), apparently including *H. pylori*. It is

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important to emphasize that whereas in the current cell culture studies, H. pylori caused inhibition of the cell cycle and the induction of apoptosis in the intact gastric mucosa, these short-term effects of H. pylori may be accompanied by compensatory changes unattainable in cell culture. Thus, in vivo, chronic colonization of the gastric mucosa by H. pylori seems to stimulate a compensatory hyperproliferative response, as evidenced by increased expression of S phase markers seen in several immunohistochemical studies (8).

The mechanisms by which H. pylori interacts with epithelial cells to induce apoptosis are not known (27). There is evidence both for increased expression of the proapoptotic Bcl-2 family member, Bak (13), and involvement of the Fas-Fas ligand pathways (16). However, increased expression of the proapoptotic Bcl-2 family member, Bak response, as evidenced by increased expression of S phase markers (14, 15) and decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study. The decreased expression of p27 kip1 seen in the current study.

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