

## WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

# *Helicobacter pylori* infection, gastrin and cyclooxygenase-2 in gastric carcinogenesis

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Author contributions: Shao Y and Sun WH designed and wrote the paper; Sun K, Xu W and Li XL analyzed the literature; Shen H and Sun WH checked and revised the manuscript.

Supported by The National Natural Science Foundation of China, No. 81072030 and No. 81372659; and a Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD)

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Received: November 27, 2013 Revised: March 12, 2014

Accepted: May 29, 2014

Published online: September 28, 2014

**Key words:** *Helicobacter pylori*; Gastrin; Cyclooxygenase-2; Gastric cancer

**Core tip:** *Helicobacter pylori* (*H. pylori*) is one of the most common pathogens, infecting approximately half of the world's population. It is well known that *H. pylori* infection has been associated with an elevated risk of developing gastric carcinoma. In this review, we present the latest clinical and experimental evidence showing the role of gastrin and cyclooxygenase-2 in *H. pylori*-infected patients and their possible association with gastric cancer risk.

Shao Y, Sun K, Xu W, Li XL, Shen H, Sun WH. *Helicobacter pylori* infection, gastrin and cyclooxygenase-2 in gastric carcinogenesis. *World J Gastroenterol* 2014; 20(36): 12860-12873 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i36/12860.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i36.12860>

## Abstract

Gastric cancer is one of the most frequent neoplasms and a main cause of death worldwide, especially in China and Japan. Numerous epidemiological, animal and experimental studies support a positive association between chronic *Helicobacter pylori* (*H. pylori*) infection and the development of gastric cancer. However, the exact mechanism whereby *H. pylori* causes gastric carcinogenesis remains unclear. It has been demonstrated that expression of cyclooxygenase-2 (COX-2) is elevated in gastric carcinomas and in their precursor lesions. In this review, we present the latest clinical and experimental evidence showing the role of gastrin and COX-2 in *H. pylori*-infected patients and their possible association with gastric cancer risk.

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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is one of the most common pathogens, infecting approximately half of the world's population. It is well known that *H. pylori* infection has been associated with an elevated risk of developing gastric carcinoma<sup>[1-4]</sup>, and this bacterium has been classified as a class I biological carcinogen by the World Health Organization<sup>[5]</sup>. However, the exact mechanism responsible for the development of gastric cancer in *H. pylori*-infected patients remains unclear.

Numerous studies suggested a positive association between hypergastrinemia (caused by *H. pylori* infection) and gastric cancer in humans and mice<sup>[6-11]</sup>. Hypergastrinemia and *H. pylori* infection synergistically promoted gastric carcinogenesis in transgenic mice that overexpress amidated gastrin (INS-GAS)<sup>[8-11]</sup>. The role of *H. pylori* in-

fection and hypergastrinemia in the development of gastric carcinogenesis has been a matter of scientific debate.

Cyclooxygenase (COX) is a key enzyme that catalyses the formation of prostaglandins (PGs) and other eicosanoids from arachidonic acid. Two isoforms of COX have been identified: constitutively expressed COX-1 and mitogen-inducible COX-2<sup>[12,13]</sup>. Increased expression of COX-2 has been linked to gastric carcinogenesis<sup>[14-17]</sup>. Furthermore, enhanced COX-2 expression in human stomach has been linked to *H. pylori* infection<sup>[6,17-22]</sup>. However, the molecular mechanisms underlying the aberrant expression of COX-2 in gastric cancer patients infected with *H. pylori* remain unclear. In this review, we present the latest clinical and experimental evidence showing the role of gastrin and COX-2 in *H. pylori*-infected patients and their possible association with gastric cancer risk.

## EVIDENCE FOR THE CARCINOGENICITY OF *H. PYLORI* FROM EPIDEMIOLOGICAL STUDIES

Infection with *H. pylori* and the resulting chronic inflammation are a major step in the initiation and development of gastric cancer. Early epidemiological studies linking *H. pylori* infection with gastric cancer include a plethora of case-control<sup>[23]</sup> and prospective cohort studies<sup>[24]</sup>, and the evidence is now available as pooled estimates from meta-analyses<sup>[25]</sup>. To clarify the association between gastric cancer and prior infection with *H. pylori*, three nested case-controlled studies were performed in 1991 and the results showed that the positive rate of *H. pylori* antibody was higher in the patients with gastric cancer than that in the control group<sup>[26-28]</sup>. A prospective study confirmed that gastric cancer developed in 2.9% of the *H. pylori*-infected group but none of the uninfected patients<sup>[29]</sup>.

In a review of 5 meta-analyses concerning the association of *H. pylori* seropositivity with gastric cancer, Eslick<sup>[25]</sup> reported a pooled estimate of the relative risk ranging from 1.92-2.56 (mean 2.28), and confidence interval ranging from 1.35-3.55. Despite some differences in the number, type, and design of the included studies, the strength of association from each of the meta-analyses was consistent in size and precision, supporting the validity of the pooled estimate and conclusions regarding the association. Six meta-analyses of cohort studies, case-controlled and nested case-controlled studies revealed a positive odds ratio between *H. pylori* seropositivity and gastric cancer<sup>[23,24,30-33]</sup>. All these meta-analyses showed that *H. pylori* infection is associated with approximately a two-fold increased risk of developing gastric cancer.

In addition, a multicentre epidemiological study was designed to look at the relation between the prevalence of *H. pylori* infection and the incidence of gastric cancer in 17 populations from 13 countries, chosen to reflect the global range of gastric cancer incidence. The results indicated an approximately six-fold increased risk of gastric cancer in populations with 100% *H. pylori* infection

compared with populations that have no infection<sup>[34]</sup>. The main carcinogenic effect of *H. pylori* is dependent on the presence of the cytotoxic associated gene A (cagA) and vacuolating cytotoxin A (vacA)<sup>[35,36]</sup>. A meta-analysis conducted by Huang *et al*<sup>[33]</sup> showed that the risk of gastric cancer was twice as high in people who were positive for antibodies against CagA in sera.

Nevertheless, a later meta-analysis conducted by Wang *et al*<sup>[37]</sup> showed a protective role for *H. pylori* infection in the prognosis of gastric cancer. Several studies have also examined the relationship between *H. pylori* infection and prognosis of patients with gastric cancer, providing evidence of a better prognosis in patients with *H. pylori* infection compared with patients without *H. pylori* infection<sup>[38-41]</sup>. The underlying mechanisms need to be further elucidated, which could provide new therapeutic approaches for gastric cancer.

## EVIDENCE FOR EFFICACY OF *H. PYLORI* ERADICATION THERAPY IN THE PREVENTION OF GASTRIC CANCER

In experimental research, gastric cancer was induced in Mongolian gerbils through *H. pylori* inoculation plus administration of low-dose chemical carcinogens, and *H. pylori* eradication suppressed the incidence of gastric cancer<sup>[42]</sup>. The animal experiment also suggested that eradication at an earlier period was effective in reducing gastric carcinogenesis compared with that at the middle or late period<sup>[43]</sup>. The strong association of *H. pylori* with gastric cancer has spurred a large number of randomized controlled trials to investigate the effects of *H. pylori* eradication on gastric carcinogenesis.

According to Correa's model, gastric cancer develops in a multistep process from chronic active gastritis, gastric glandular atrophy, intestinal metaplasia, dysplasia (currently distinguished into low-grade and high-grade intraepithelial neoplasia), and finally to gastric cancer<sup>[44]</sup>. In studies of precancerous gastric lesions, *H. pylori* eradication generally reduced the rate of progression<sup>[45]</sup>. To clarify the effects of *H. pylori* eradication on prevention of gastric cancer development in patients with chronic gastritis, Uemura *et al*<sup>[46]</sup> conducted a nonrandomized *H. pylori* eradication trial in cases whose gastric cancer was removed by endoscopic resection, and suggested that *H. pylori* eradication might improve neutrophil infiltration and intestinal metaplasia in the gastric mucosa and inhibit the development of new carcinomas. A multi-centre, open-label, randomized controlled trial demonstrated that patients in whom *H. pylori* had been successfully eradicated following their initial gastric cancer resection had a highly significantly reduced risk of developing a second gastric cancer (hazard ratio 0.35 at 3 years of follow-up)<sup>[47]</sup>.

However, a double-blind randomized study in China showed that gastric cancer still occurred after successful eradication of *H. pylori* and that *H. pylori* eradication did not lead to a significant decrease in the incidence of

gastric cancer<sup>[48]</sup>. Sub-analysis of previous papers showed that the preventive effect of *H. pylori* eradication for gastric cancer incidence was limited to patients without atrophy and metaplasia<sup>[48,49]</sup>. Randomized prospective studies demonstrated that eradication significantly reduced the presence of premalignant lesions, providing additional evidence that *H. pylori* had an effect on early stages of gastric carcinogenesis<sup>[45,48]</sup>. It is speculated that eradication of *H. pylori* significantly decreases the risk of gastric cancer in infected individuals without premalignant lesions. In meta-analysis, the relative risk of gastric cancer following *H. pylori* eradication was calculated to be 0.65 overall (95%CI: 0.43-0.98)<sup>[50]</sup>. Taken together, these studies support an unequivocal role for *H. pylori* in the development of gastric cancer and indicate that anti-*H. pylori* therapy may be an effective means of gastric cancer prevention.

## GASTRIN AND DNA METHYLATION POTENTIATE THE CARCINOGENIC EFFECTS OF *H. PYLORI* INFECTION

The role of *H. pylori* infection and hypergastrinemia in the development of gastric carcinogenesis has been a matter of scientific debate. A possible pathogenetic mechanism involves the persistent *H. pylori* colonization and inflammation of the gastric mucosa, particularly when the *H. pylori* strains express CagA which often results in the development of chronic atrophic gastritis and subsequently hypergastrinemia, through a reverse-feedback mechanism<sup>[51]</sup>. To clarify whether *H. pylori* CagA can induce gastrin expression, Zhou *et al.*<sup>[52]</sup> constructed a eukaryotic expression vector pCDNA3.1/*cagA* and a luciferase reporter vector pGL/gastrin promoter, and then co-transfected them into gastric cancer cells, and suggested that CagA could activate the gastrin promoter and up-regulate gastrin mRNA expression in AGS and SGC-7901 cells. It has been widely reported that the number of G cells and the release of gastrin increase during *H. pylori* infection in human subjects and various animal models<sup>[53-55]</sup>. As *H. pylori* infection inhibits acid secretion<sup>[56]</sup>, the observed hypergastrinemia might be in response to the hypochlorhydria. Indeed, direct inhibition of acid secretion by omeprazole is sufficient to stimulate gastrin gene expression *in vivo*<sup>[57]</sup>. Previous studies suggested that *H. pylori* colonizing the gastric antrum might create an alkaline pH sufficient to stimulate G cells through its production of urease and conversion of urea to ammonia<sup>[58]</sup>. However, this mechanism was subsequently disproven by studies showing that *H. pylori* products rather than the live organism can stimulate gastrin release from cultured G cells<sup>[59,60]</sup>. Furthermore, *H. pylori*-induced inflammatory cytokines stimulate antral G cells to release gastrin<sup>[61]</sup>.

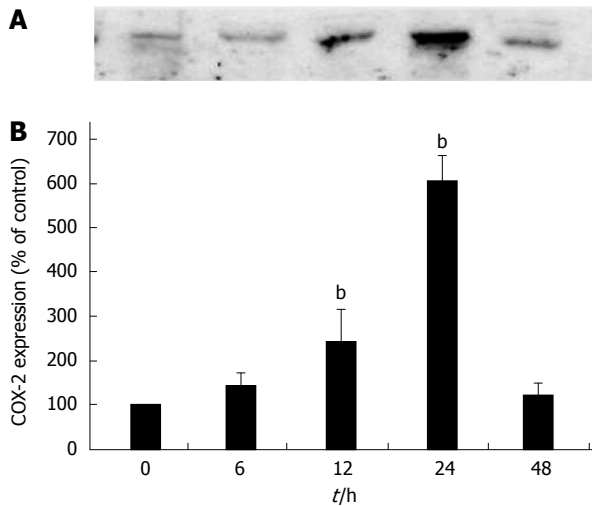
Several previous studies have shown that *H. pylori* can increase circulating gastrin levels in the blood<sup>[62-64]</sup>. *H. pylori* has been reported to induce G-cell hyperfunc-

tion in antral gastric tissue, which could contribute to the onset of hypergastrinemia<sup>[65]</sup>. Gibbons *et al.*<sup>[66]</sup> showed that patients infected with *H. pylori* had increased gastrin mRNA levels, whereas Sumii *et al.*<sup>[67]</sup> reported no change in gastrin mRNA expression. Buchan and coworkers reported that *H. pylori* increases basal levels of gastrin in primary G-cell cultures, but did not induce secretion, suggesting that *H. pylori* increased gastrin synthesis and possibly gene expression<sup>[68]</sup>. *H. pylori* also activates gastrin releasing peptide and regulates the gastrin modulator somatostatin to increase gastrin expression<sup>[53,69]</sup>. Taken together, it is unclear whether the hypergastrinemia that occurs in *H. pylori*-infected individuals is attributable to hypochlorhydria, suppression of somatostatin, chronic gastritis, gastric atrophy or the direct induction of gastrin gene expression by the bacterium itself.

Asymptomatic patients with *H. pylori* colonisation have been shown to have elevated serum gastrin concentrations relative to a control population, despite similar gastric acid output<sup>[62]</sup>, while Levi *et al.*<sup>[70]</sup> demonstrated that following *H. pylori* eradication, there was a reduction in fasting serum gastrin concentration. It has also been demonstrated that following eradication of *H. pylori*, there was an increase in somatostatin mRNA and a concomitant decrease in gastrin mRNA in patients with duodenal ulcers<sup>[71]</sup>. This was associated with increased numbers of D-cells in the gastric corpus<sup>[71]</sup>, suggesting that the hypergastrinemia caused by *H. pylori* infection may result from a loss of somatostatin control over gastrin secretion.

Clinical and experimental evidence indicates that gastrin can potentiate the carcinogenic effects of *H. pylori* infection on the gastric mucosa<sup>[72]</sup>. Our prior studies suggested that the proliferation of MKN-45 cells, which were derived from a poorly differentiated gastric carcinoma and had been reported to express CCK2/gastrin receptor (CCK2R), decreased when treated with the CCK2R antagonists<sup>[73,74]</sup>. It also has been demonstrated that long-term treatment with CCK2R antagonist YF476 prevented the development of *H. pylori*-associated gastric cancer in INS-GAS mice<sup>[10,75]</sup>. Taken together, these results indicate that the gastrin signaling pathway provides a potential target for cancer chemoprevention.

On the other hand, aberrant DNA methylation in gastric biopsies from *H. pylori*-infected patients was found to be correlated with a greater gastric cancer risk<sup>[76,77]</sup>. Previous studies have reported that infection with *H. pylori* is associated with promoter methylation of various gastric cancer-associated genes<sup>[78,79]</sup> and eradication of the bacteria was able to reverse the process in patients with gastritis, but not in patients with intestinal metaplasia<sup>[80,81]</sup>. Recently, Niwa *et al.*<sup>[82]</sup> demonstrated that treatment with the DNA demethylation agent 5-aza-2'-deoxycytidine decreases the incidence of gastric cancers in an animal model of *H. pylori*-promoted gastric cancer. This study also showed that induction of aberrant methylation is an important mechanism for gastric carcinogenesis by *H. pylori* infection.

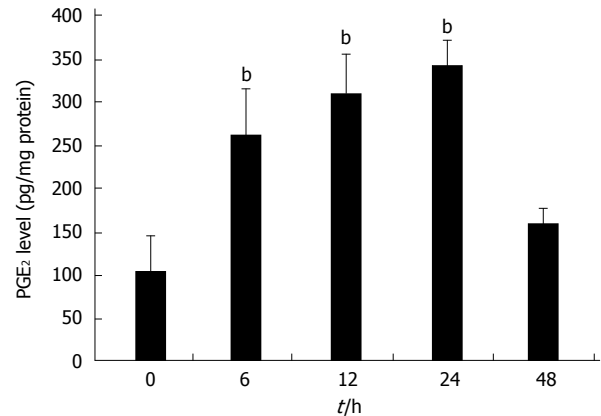


**Figure 1** Time course of *Helicobacter pylori* water extracts on cyclooxygenase-2 expression in rat gastric mucosa cells. Western blot analysis was performed on cell lysates (50  $\mu$ g) from rat gastric mucosa (RGM1) cells incubated for 0, 6, 12, 24 or 48 h with 10  $\mu$ g/mL *Helicobacter pylori* (*H. pylori*) water extracts. The top panel (A) shows representative of three separate experiments undertaken. The histogram at the bottom (B) represents the means  $\pm$  SD of densitometric values for the cyclooxygenase-2 (COX-2) bands obtained from three independent experiments. Data are expressed as the percentages of the densities of the control cells incubated with *H. pylori* water extracts for 0 h, and analyzed using ANOVA with Dunnett's multiple comparison test of the means. <sup>b</sup> $P < 0.01$  vs 0 h. Reproduced from Ref [90] with permission.

## COX-2 IN HUMAN GASTRIC CARCINOGENESIS

It is well known that *H. pylori* infection causes inflammation, and COX-2 is involved in inflammatory responses<sup>[21]</sup>. However, in *H. pylori* associated gastritis, COX-2 protein mainly localizes to the lamina propria<sup>[18,19,83,84]</sup>, with variable levels in the epithelium<sup>[18,84]</sup>; but in gastric cancer, COX-2 is most strongly expressed in the epithelium of malignant and dysplastic glands<sup>[18,85,86]</sup>. Romano *et al.*<sup>[87]</sup> reported that *H. pylori* up-regulates COX-2 mRNA expression and stimulates the release of PGE<sub>2</sub> in MKN 28 gastric mucosal cells *in vitro*; and this effect was independent of VacA, CagA, or urease-generated ammonia. However, other *in vitro* studies have demonstrated that *H. pylori* up-regulates COX-2 expression in human gastric cancer cells; and this effect is specifically related to VacA toxin<sup>[88,89]</sup>.

Our previous study using rat gastric epithelial cells treated with *H. pylori* water extract (only containing bacterial proteins but not bacterial cells) led to an increase in COX-2 expression (Figure 1) and PGE<sub>2</sub> levels (Figure 2) that peaked 24 h after treatment and declined at 48 h<sup>[90]</sup>. These results indicate that development of gastric carcinoma associated with *H. pylori* infection may depend on COX-2 expression. The expression of COX-2 results in the induction of the proinflammatory prostaglandin, PGE<sub>2</sub><sup>[91,92]</sup>. PGs play an important role in the growth and stimulation of the inflammation-associated gastric carcinogenesis<sup>[93,94]</sup>. In addition, *H. pylori*-induced chronic gastritis is associated with overexpression of COX-2 and



**Figure 2** Effect of *Helicobacter pylori* water extracts on PGE<sub>2</sub> synthesis in rat gastric mucosa cells. Rat gastric mucosa (RGM1) cells were incubated for 0, 6, 12, 24, or 48 h with 10  $\mu$ g/mL *Helicobacter pylori* water extracts. PGE<sub>2</sub> levels in the media of RGM1 cells were measured by enzyme-linked immunosorbent assay and expressed as pg/mg protein. Data are shown as mean  $\pm$  SD,  $n = 5$  per group, and analyzed using ANOVA with Dunnett's multiple comparison test of the means. <sup>b</sup> $P < 0.01$  vs the control or 0 h. Reproduced from Ref [90] with permission.

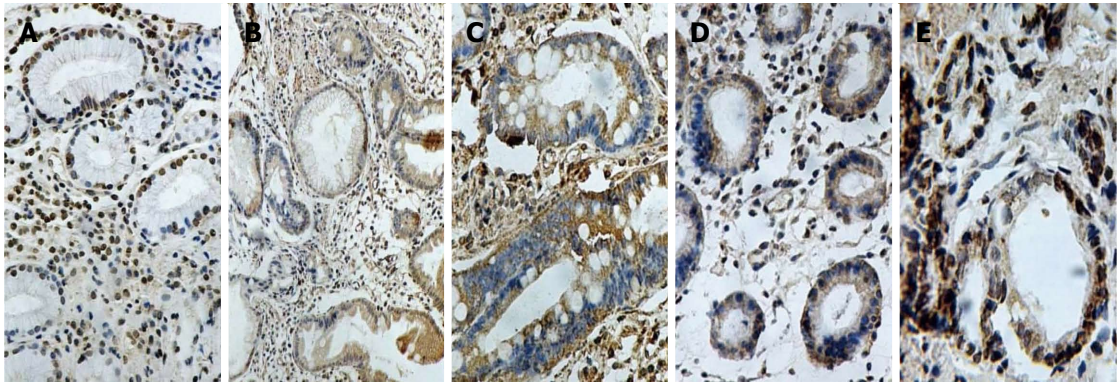
increased production of eicosanoids, especially PGE<sub>2</sub><sup>[95]</sup>. Noteworthy, successful eradication of *H. pylori* infection leads to a significant reduction in COX-2 expression<sup>[96]</sup>.

COX-2 is upregulated in the gastric mucosa of *H. pylori*-infected patients<sup>[19,21,83,84,97]</sup>. *In vivo* studies show that COX-2 is further upregulated in *H. pylori*-mediated gastric adenocarcinoma<sup>[18,85,98]</sup>. Overexpression of COX-2 has been observed not only in *H. pylori*-positive gastritis, but also in pre-cancerous lesions such as atrophic gastritis and intestinal metaplasia, and in gastric cancer, suggesting a role of COX-2 in early gastric carcinogenesis<sup>[19,21,98]</sup>. Recent studies showed that COX-2 expression significantly decreases following *H. pylori* eradication in patients with atrophic gastritis<sup>[22,99]</sup>. Several previous studies showed that the expression of COX-2 was even high in the early stage of gastric carcinogenesis (pre-cancerous lesions) and gradually increased with the aggravation of gastric mucosal lesions<sup>[100,101]</sup>. Our previous study also showed that COX-2 was expressed in human gastric cancer and its precursor lesions as detected by immunohistochemistry<sup>[21]</sup> (Figure 3). From chronic superficial gastritis to gastric glandular atrophy, intestinal metaplasia, dysplasia and finally to gastric cancer, expression of COX-2 showed an ascending tendency<sup>[21]</sup> (Table 1). These results collectively suggest that COX-2 expression induced by *H. pylori* infection is a relatively early event during carcinogenesis in the stomach. In addition, COX-2 overexpression enhances the possibility of invasion and metastasis and correlates with poor prognosis in human gastric carcinoma<sup>[102-104]</sup> (Table 2).

## MECHANISMS OF COX-2 UPREGULATION IN *H. PYLORI*-ASSOCIATED GASTRIC CANCER

Gastrin has been shown to mediate the induction of





**Figure 3** Immunostaining for cyclooxygenase-2 in the gastric mucosa with chronic superficial gastritis (A), gastric glandular atrophy (B), intestinal metaplasia (C), dysplasia (D) and gastric cancer (E). Chronic superficial gastritis shows strong expression in foveolar and glandular epithelium and weak expression in mononuclear inflammatory cells, myofibroblasts, and endothelial cells in the lamina propria; gastric glandular atrophy shows strong expression in the atrophic glands of the gastric mucosa; intestinal metaplasia shows strong expression in intestinal epithelium and goblet cells; and gastric cancer shows strong expression in cancer cells. Reproduced from Ref [21].

**Table 1** Expression of cyclooxygenase-2 in gastric mucosa with various lesions *n* (%)

Pathological diagnosis	COX-2 expression
Chronic superficial gastritis	30 (10.0)
Gastric glandular atrophy	28 (35.7) <sup>a</sup>
Intestinal metaplasia	45 (37.8) <sup>b</sup>
Dysplasia	12 (41.7) <sup>a</sup>
Gastric cancer	23 (69.5) <sup>bc</sup>

<sup>a</sup>*P* < 0.05, <sup>b</sup>*P* < 0.01 *vs* chronic superficial gastritis; <sup>c</sup>*P* < 0.05 *vs* gastric glandular atrophy. Data adapted from Sun *et al* [21]. COX-2: Cyclooxygenase-2.

COX-2 in gastrointestinal cells<sup>[105,106]</sup>, indicating that there is a direct mechanistic link between gastrin and inflammation (Figure 4). Chronic atrophic gastritis caused by *H. pylori* activates synthesis of growth factors, cytokines, and gastrin leading to elevated COX-2 expression<sup>[107]</sup>. Recent studies have demonstrated that hypergastrinemia induced by *H. pylori* infection is often associated with increased COX-2 expression in chronic atrophic gastritis and gastric cancer<sup>[6,96]</sup>. Some studies have shown that COX-2 is co-expressed with gastrin in gastric ulcers and gastric cancer<sup>[6,55]</sup>. On the other hand, an *in vitro* study indicates that gastrin stimulates COX-2 gene and protein expression in human gastric cancer cells<sup>[108]</sup>. Our recent study demonstrated that gastrin up-regulates COX-2 expression in gastric cancer cell lines and this occurs through CCK-2R-mediated JAK2/STAT3 and subsequent PI3K/Akt activation<sup>[74]</sup> (Figure 5). Additionally, Subramaniam *et al*<sup>[109]</sup> reported that gastrin induced COX-2 expression in human gastric cancer cell line AGS stably expressing CCK2R. Gastrin not only increased the stability of COX-2 mRNA in a p38-dependent manner but also enhanced COX-2 gene transcription through the activator protein-1 (AP-1) transcription factor<sup>[109]</sup>.

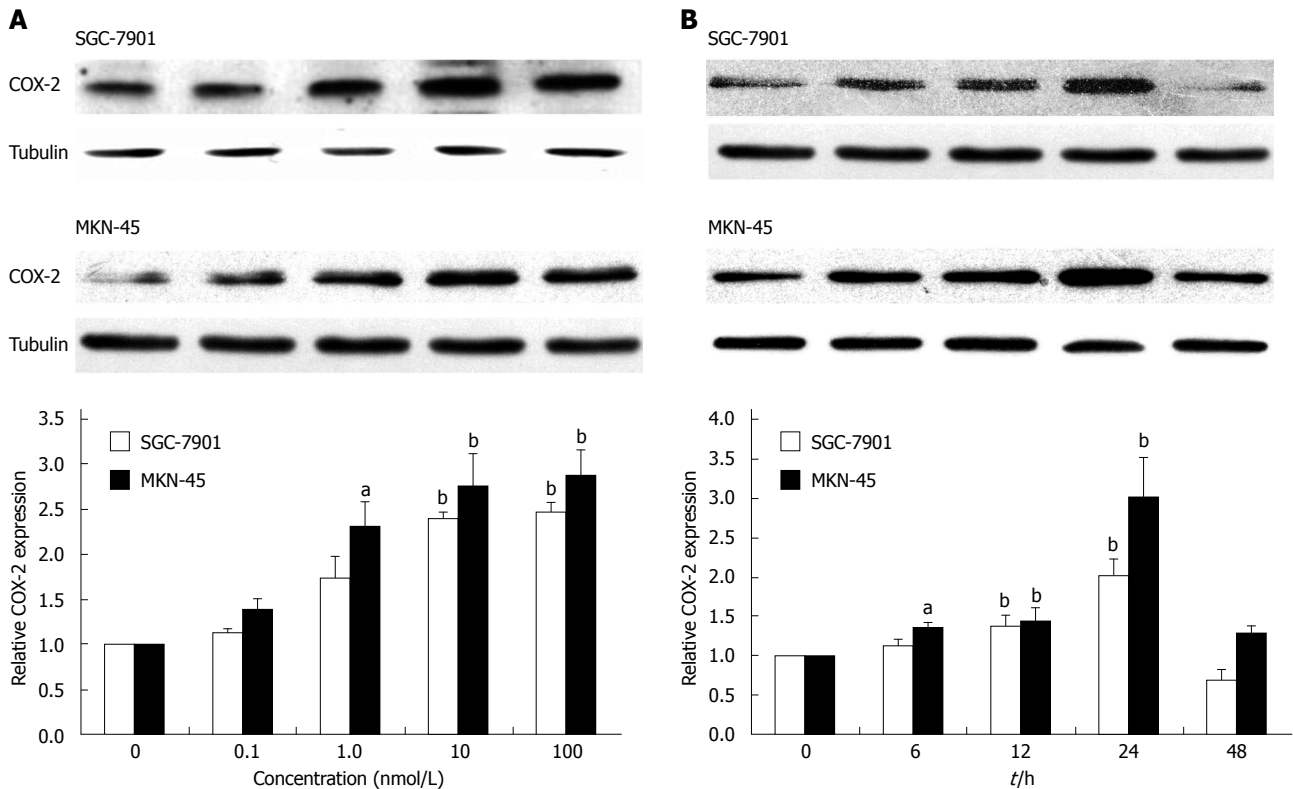
In another study using AGS gastric cancer cells, *H. pylori* promoted COX-2 transcription through TLR2/TRL9 that activated the MAPK pathways (ERK1/2, p38, JNK) and resulted in the activation of CRE and AP-1 in the

**Table 2** Correlation of clinicopathological parameters with cyclooxygenase-2 expression in gastric cancer

Clinicopathological parameter	<i>n</i>	COX-2 expression					<i>P</i> value
		0	1	2	3	Rate	
Age (yr)							
< 60	35	7	9	9	10	80.0%	0.526 <sup>1</sup>
≥ 60	61	12	15	26	8	80.3%	0.969 <sup>2</sup>
Gender							
Male	67	10	17	27	13	85.1%	0.156 <sup>1</sup>
Female	29	9	7	8	5	69.0%	0.069 <sup>2</sup>
Tumor site							
Cardia	30	9	7	9	5	70.0%	0.427 <sup>1</sup>
Corpus	26	5	6	9	6	80.8%	0.191 <sup>2</sup>
Antrum	40	5	11	17	7	87.5%	
Stages							
I + II	38	14	9	10	5	63.2%	0.004 <sup>1</sup>
III + IV	58	5	15	25	13	91.4%	0.001 <sup>2</sup>
Histological type							
Tubular	54	12	13	20	9	77.8%	0.107 <sup>1</sup>
Papillary	30	6	9	9	6	80.0%	0.633 <sup>2</sup>
Mucinous	6	1	2	3	0	83.3%	
Signet ring cell	6	0	0	3	3	100.0%	
Histological grading							
Well and moderately	65	11	17	26	11	83.1%	0.735 <sup>1</sup>
Poorly	31	8	7	9	7	74.2%	0.307 <sup>2</sup>
Lymph node metastasis							
Present	58	7	13	26	12	87.9%	0.018 <sup>1</sup>
Absent	38	12	11	9	6	68.4%	0.019 <sup>2</sup>

<sup>1</sup>Result from grade comparisons of cyclooxygenase-2 (COX-2) expression among the patients with different clinicopathological characteristics using Wilcoxon test or Kruskal-Wallis non-parametric test; <sup>2</sup>Result from percentage comparisons of COX-2 expression among the patients with different clinicopathological characteristics using  $\chi^2$ -test. Data adapted from Sun *et al*<sup>[104]</sup>. Specimens with a grade of > 1 were regarded as positive expression, whereas grades 2 and 3 were defined as overexpression.

COX-2 promoter<sup>[110]</sup>. In MKN-45 gastric cancer cells the p38MAPK/ATF-2 pathway was necessary for increased COX-2 expression after *H. pylori* infection<sup>[111]</sup>. Thus, *H. pylori* clearly induces COX-2, but the mechanism seems to be dependent on the *H. pylori* strain properties and the



**Figure 4** Mature amidated gastrin (G17) induces cyclooxygenase-2 expression in gastric cancer cells. Western blot analysis was performed on cell lysates (30 µg) from SGC-7901 and MKN-45 cells cultured for 24 h with increasing concentrations of G17 (A), or with G17 at 10 nmol/L for the indicated time points (B). The top panels show a representative immunoblot of six separate experiments undertaken. The histograms at the bottom represent the relative expression of cyclooxygenase-2 (COX-2) proteins compared with tubulin. Data represent the mean  $\pm$  SD of six independent experiments. <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$  vs 0 nmol/L or 0 h. Reproduced from Ref [74] with permission.

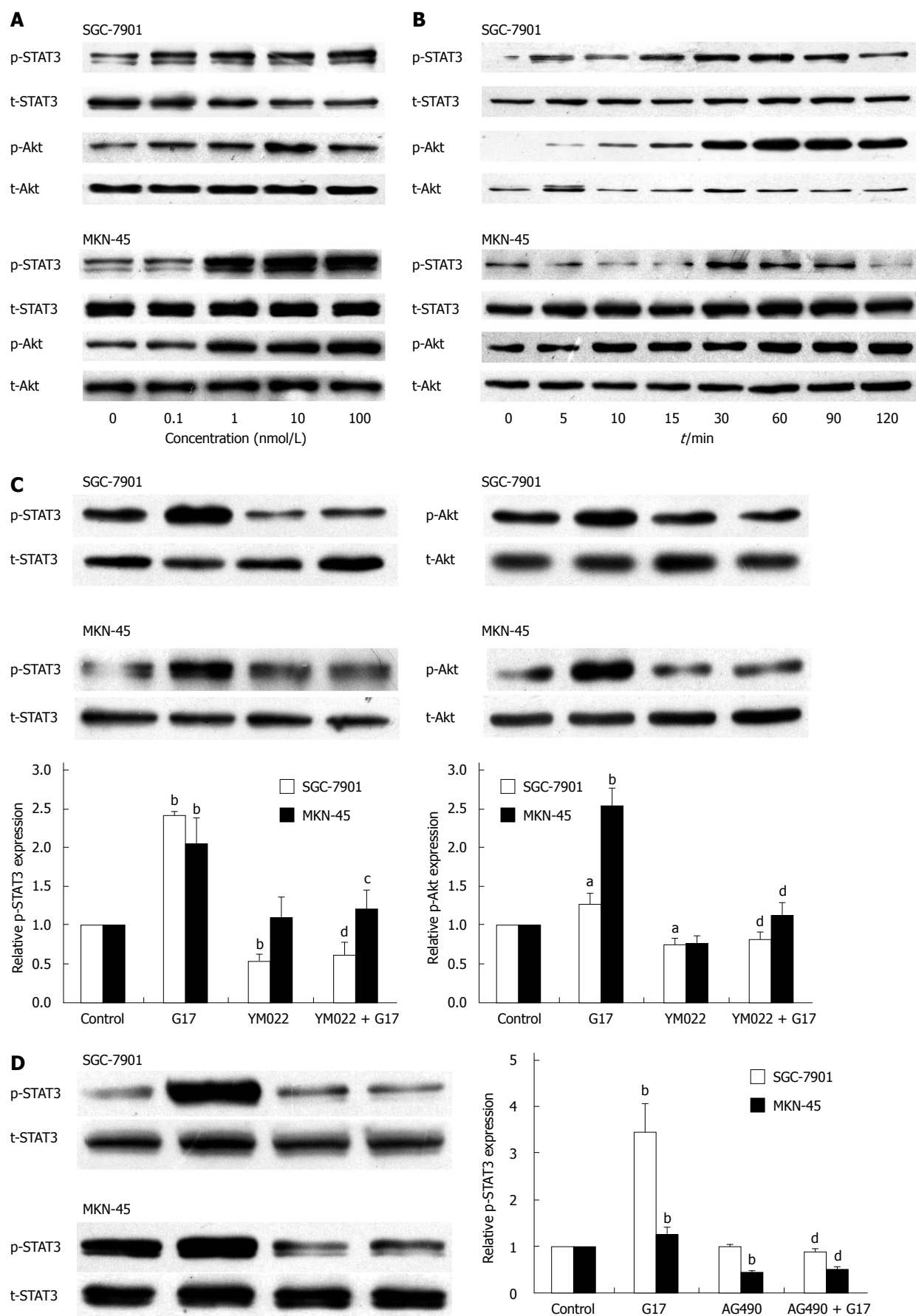
recipient cells.

In recent years dysregulated microRNAs (miRNAs) have also been found in gastric cancer, and they are linked to many processes, such as cell proliferation, apoptosis, and invasion<sup>[112]</sup>. Recently, we characterize miR-101 (miR-101) expression and its role in COX-2 expression regulation, and the results showed that miR-101 levels in gastric cancer tissues were significantly lower than those in the matched normal tissue<sup>[14]</sup>. We also found an inverse correlation between miR-101 and COX-2 expression in both gastric cancer specimens and cell lines. Significant decreases in COX-2 mRNA and protein levels were observed in the pre-miR-101 infected gastric cancer cells. These results collectively indicate that miR-101 may function as a tumor suppressor in gastric cancer, with COX-2 as a direct target<sup>[14]</sup>. When miR-101 was overexpressed in gastric cancer cell lines, the mRNA level of COX-2 was decreased in BGC-823, SGC-7901, MKN-45, and AGS cells<sup>[14,113]</sup>. In addition, miR-101 is downregulated in gastric mucosa infected with *H. pylori*<sup>[114]</sup>. These results provide new insights into miR-101 involvement in the pathogenesis of *H. pylori*-associated gastric cancer, with COX-2 as a direct target.

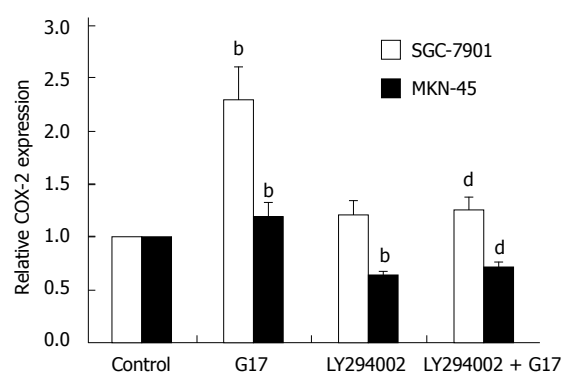
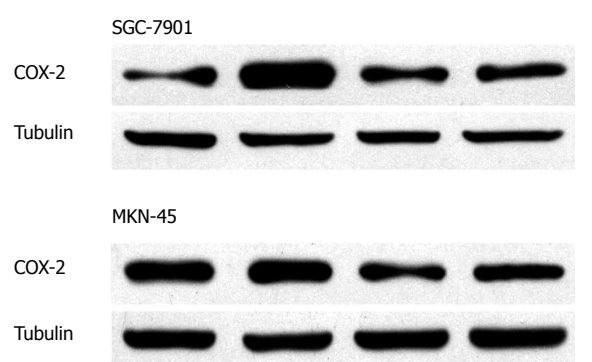
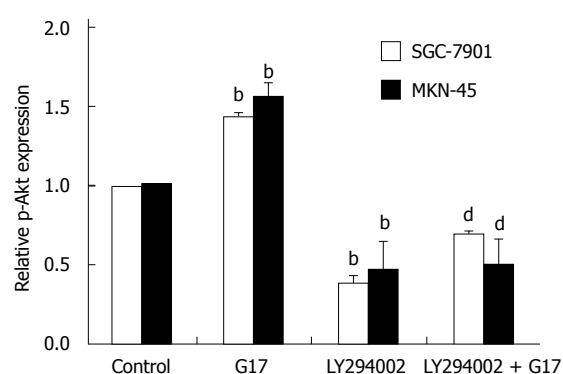
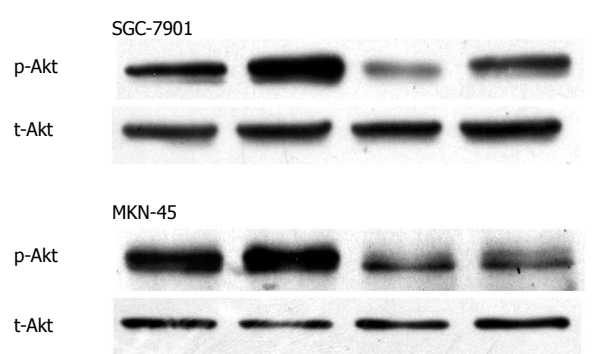
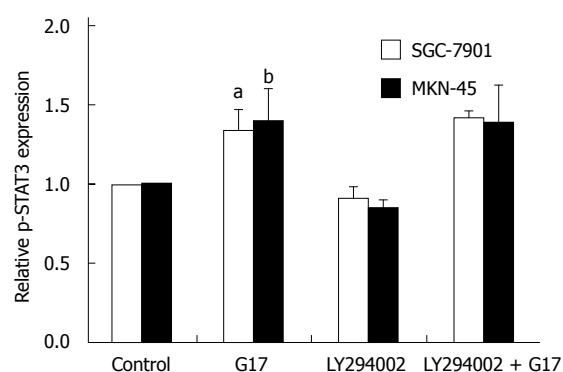
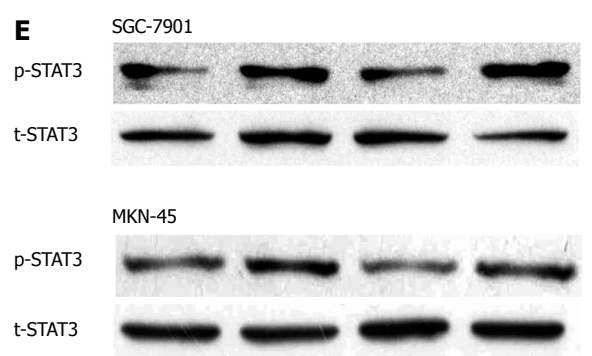
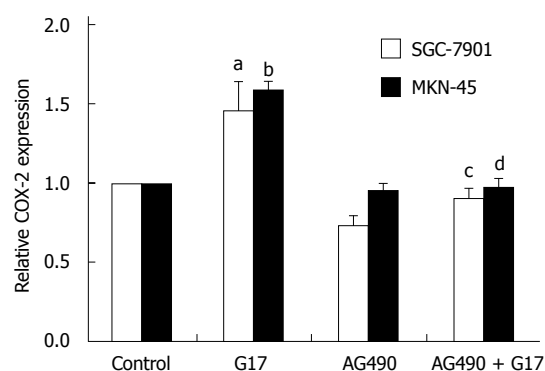
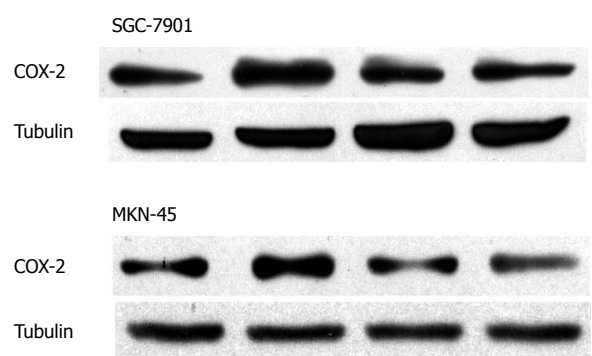
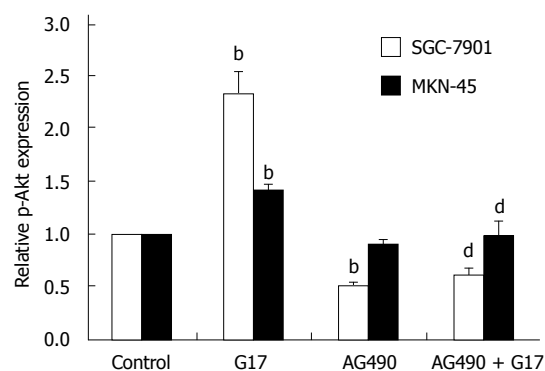
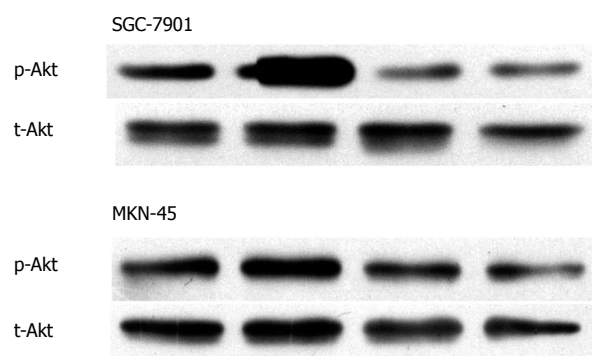
## NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN THE PREVENTION OF GASTRIC CANCER

A lower risk of gastric cancer has been associated with non-steroidal anti-inflammatory drugs (NSAIDs) in a dose-dependent manner<sup>[115]</sup>. There is also evidence from animal studies showing a reduced gastric cancer incidence under suppression of COX-2 using specific COX-2 inhibitors<sup>[116,117]</sup>. Considering the association between COX-2/PGE<sub>2</sub> pathway and *H. pylori*-associated gastric carcinogenesis, NSAIDs have been proposed as candidates for chemoprevention of gastric cancer. COX-2 selective inhibitors such as etodolac and celecoxib may have chemopreventive effects<sup>[118,119]</sup> not only suppressing inflammation, but also causing regression of early-stage tumors<sup>[120,121]</sup>. Therefore, there is a possibility that COX-2 inhibitors could be useful drugs for regression of remaining precancerous lesion and prevention of gastric cancer occurrence after *H. pylori* eradication.

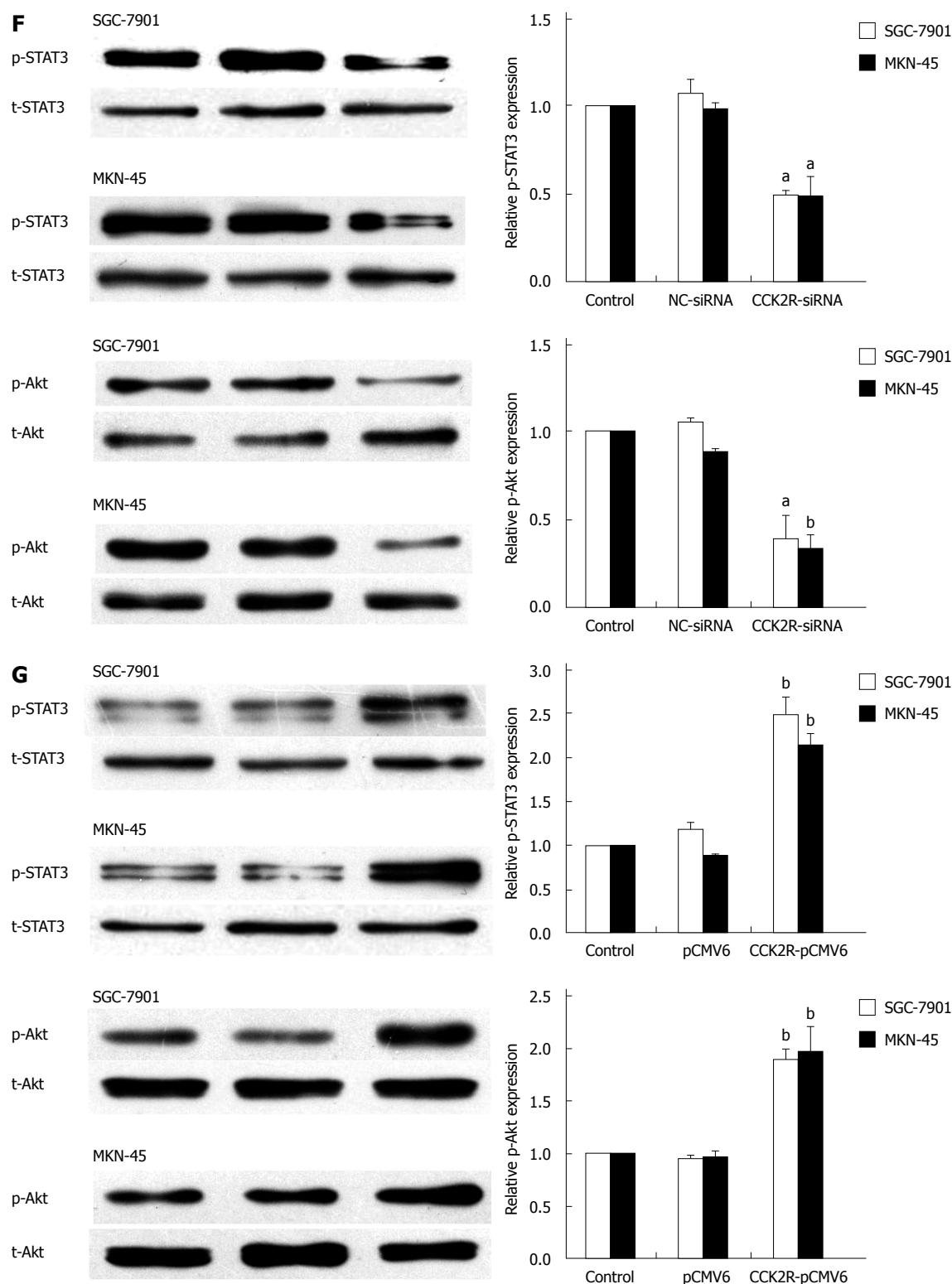
The chemopreventive effect of NSAIDs on the development of gastric cancer among *H. pylori* infected











**Figure 5** Mature amidated gastrin (G17) induces STAT3 and Akt phosphorylation in gastric cancer cells. SGC-7901 and MKN-45 cells were treated for 30 min with increasing concentrations of G17 (A), or with G17 (10 nmol/L) for the indicated time points (B), as well as pre-treated as indicated with 10 nmol/L CCK2R antagonist YM022 (C) or 40  $\mu$ mol/L JAK2 inhibitor AG490 (D) or 25  $\mu$ mol/L PI3K inhibitor LY294002 (E) for 1 h and then incubated with G17 (10 nmol/L) for 30 min to evaluate STAT3 and Akt phosphorylation or for 6 h to evaluate cyclooxygenase-2 (COX-2) expression. SGC-7901 and MKN-45 cells were transfected with either CCK2R-siRNA (F) or CCK2R-pCMV6 (G), followed by G17 (10 nmol/L) treatment for 30 min. Protein extracts were prepared and analyzed for total and phosphorylated forms of STAT3 or Akt by Western blot analysis using corresponding antibodies. The top panels show a representative immunoblot of six separate experiments undertaken. The histograms at the bottom represent the relative expression of phospho-STAT3 (p-STAT3) or phospho-Akt (p-Akt) or COX-2 compared with total STAT3 (t-STAT3) or total Akt (t-Akt) or tubulin, respectively. All data represent the mean  $\pm$  SD of six independent experiments. <sup>a</sup> $P$  < 0.05, <sup>b</sup> $P$  < 0.01 vs control or NC-siRNA or pCMV6; <sup>c</sup> $P$  < 0.05, <sup>d</sup> $P$  < 0.01 vs G17. Reproduced from Ref [74] with permission.

individuals has not been conclusively shown in human clinical trials<sup>[122,123]</sup>. In patients who underwent *H. pylori* eradication therapy, chronic use of celecoxib was associated with a higher regression rate of gastric precancerous intestinal metaplasia<sup>[122]</sup>. However, in patients who had received *H. pylori* eradication therapy, treatment with another selective COX-2 inhibitor, rofecoxib, for 2 years did not reduce intestinal metaplasia<sup>[123]</sup>. Considering that cancer chemoprevention by NSAIDs is modulated by both COX-2-dependent and -independent pathways<sup>[124]</sup>, NSAIDs may have variable efficacy in their abilities to prevent gastric cancer.

## CONCLUSION

*H. pylori* infection is considered a major risk factor for the development of gastric cancer. Hypergastrinemia associated with *H. pylori* infection induces COX-2 expression, which appears to be related to the carcinogenesis and progression of gastric cancer.

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P- Reviewer: Ding SG, Tong Q S- Editor: Gou SX

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ISSN 1007-9327

