PO Box 2345, Beijing 100023, China
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2006 May 14; 12(18): 2884-2889
World Journal of Gastroenterology ISSN 1007-9327

REVIEW

Non-steroidal anti-inflammatory drugs in prevention of gastric cancer

Yun Dai, Wei-Hong Wang

Yun Dai, Wei-Hong Wang, Department of Gastroenterology, First Hospital, Peking University, Beijing 100034, China
Correspondence to: Wei-Hong Wang, MD, Department of Gastroenterology, First Hospital, Peking University, Beijing 100034, China. wh2581@sohu.com
Telephone: +86-10-66551122-2581 Fax: +86-10-66518105
Received: 2005-07-18 Accepted: 2005-12-05

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase 2 (COX-2) selective inhibitors, are potential agents for the chemoprevention of gastric cancer. Epidemiological and experimental studies have shown that NSAID use is associated with a reduced risk of gastric cancer although many questions remain unanswered such as the optimal dose and duration of treatment. The possible mechanisms for the suppressor effect of NSAIDs on carcinogenesis are the ability to induce apoptosis in epithelial cells and regulation of angiogenesis. Both COX-dependent and COX-independent pathways have a role in the biological activity of NSAIDs. Knowledge of how NSAIDs prevent neoplastic growth will greatly aid the design of better chemopreventive drugs and novel treatments for gastric cancer.

Key Words: Nonsteroidal anti-inflammatory drugs; Gastric cancer; Cyclooxygenase; Prevention; Intervention

Dai Y, Wang WH. Non-steroidal anti-inflammatory drugs in prevention of gastric cancer. *World J Gastroenterol* 2006; 12(18): 2884-2889

http://www.wjgnet.com/1007-9327/12/2884.asp

INTRODUCTION

Gastric cancer is a major cause of death in the world. However, the etiology of gastric cancer is not fully understood. Although early diagnosis and treatment of gastric cancer significantly improve prognosis[1,2], the 5-year survival rate is only 10%-15% in those with advanced disease[3]. Therefore, the primary prevention of gastric cancer is of particular importance. Several studies have shown that human gastric carcinoma expresses significantly higher levels of cyclooxygenase (COX)-2 than non-cancerous adjacent mucosa[4], suggesting that COX-2 plays a possible role in gastric carcinogenesis. Numerous observations and clinical studies have suggested that the use of NSAIDs is associated with reduced incidence of gastric cancer[5-8]. NSAIDs, particularly the highly selective COX-2 inhibitors, are promising chemopreventive agents[9-12].

Although the effects of NSAIDs on gastric cancer remain unclear, both COX-dependent and independent mechanisms may have roles in the biological activity of NSAIDs. In this review, we concentrate on the use of NSAIDs for gastric cancer prevention and the underlying mechanisms. Furthermore, we also suggest research opportunities on clinical application of NSAIDs for gastric cancer prevention.

NSAIDS AND GASTRIC CANCER

Epidemiological evidence

There are indications, although still limited and preliminary, of a protective effect of NSAIDs on gastric cancers. The risk of gastric cancer is reduced, though not significantly, in the Swedish[13] cohorts of patients with rheumatoid arthritis, with the relative risk (RR) of 0.63 (95%CI = 0.5 to 0.9) for NSAID users. In the American Cancer Society cohort, there is a significant reduction in the risk of death for gastric cancer in aspirin users (RR = 0.64, 95%CI = 0.51 to 0.80). In addition, a dose-dependent trend in risk reduction has been observed, with the RR of 0.73 (95%CI = 0.56 to 0.96) for occasional use (1-15times per month) and 0.49 (95%CI = 0.33 to 0.74) for use 16 or more times per month[5]. With regard to case-control studies, in an American study of cancers of the esophagus and stomach, based on 261 adenocarcinomas of the cardia, 368 noncardia and 695 population controls, current aspirin users have a lower risk for noncardia cancer (RR = 0.46, 95%CI = 0.31 to 0.68), but not for cardia cancer (RR = 0.80, 95%CI = 0.54 to 1.19) when compared to never users. However, there is no significant trend for the risk reduction of gastric cancer with the frequency and the duration of aspirin use[6]. A case-control study from Russia was conducted on 448 gastric cancer cases and 610 hospital controls. The use of aspirin is significantly associated with a risk reduction for the development of gastric cancer (RR = 0.49, 95%CI = 0.31 to 0.77), although the favorable effect seems to be limited for patients with noncardia cancer and *Helicobacter pylori* (*H pylori*) infection[7]. Another case-control study from Sweden, conducted on 567 cases

and 1165 hospital controls, reported that users of aspirin have a moderately reduced risk of gastric cancer compared to never users (RR = 0.7, 95% CI: 0.6 to 1.0), and gastric cancer risk falls with the increasing frequency of aspirin use. Moreover, the risk reduction is statistically significant not only for cardia but also for noncardia cancer, and is slightly more marked in patients with *H pylori* infection[8].

However, there are several limitations for the above observational studies. First, the small number of cases may result in inadequate statistical power[7,8,15]. Second, the choice of control subjects in case-control studies may distort the results because hospital-based controls can not represent population-based controls[16]. Third, different definition of drug exposure and different doses of drugs have been evaluated in these studies. Therefore, the optimal duration and dose of treatment could not be recommended from these studies.

A recent systematic review with meta-analysis of nine observational studies evaluating the association between NSAID use and the risk of gastric cancer suggested that long-term use of aspirin or other NSAIDs is associated with a statistically significant, dose-dependent reduction in the risk of gastric cancer (OR = 0.78, 95%CI = 0.69 to 0.87). When the analysis is stratified by the site of gastric cancer, use of NSAIDs is associated with a statistically significant lower risk for noncardia gastric cancer (OR = 0.72, 95%CI = 0.58 to 0.89), but not for gastric cancer at the cardia. However, whether the minimum effective duration of NSAID use can reduce gastric cancer risk remains undetermined because of the relatively small number of studies, the use of different cut-off time points of treatment duration, and varying definitions of drug exposure[14]. More prospective studies are needed to clarify whether a duration effect exists in the relationship between NSAID use and gastric cancer risk.

Animal models and in vitro studies

The results obtained from animal models evaluating the effect of NSAIDs on gastric cancer have been conflicting. Two studies on animal models of carcinogens suggested that NSAIDs (aspirin and flurbiprofen) could enhance chemical-induced gastric carcinogenesis in rats[17,18], indicating that prostglandins (PGs) produced by the gastric mucosa protect against the action of carcinogens in this rodent model. In contrast, broad anticarcinogenic effects of NSAIDs have been demonstrated both *in vivo* using laboratory animals and *in vitro* using cancer cell lines. Chemically-induced gastric tumors can be reduced by aspirin[19], indomethacin[20], sulindac and ibuprofen[21] in mice. Sawaoka *et al*[22] have investigated the effects of NS-398, a selective COX-2 inhibitor, or indomethacin, a non-selective COX-2 inhibitor, on the growth of gastric cancer xenografts *in vivo*. Both drugs could reduce the tumor volume significantly in a dose-dependent manner. Fu *et al*[23] also found that sulindac and celecoxib obviously decrease the blood vessel quantity and tumor size of SGC7901 cancer xenografts. In a recent study Hu *et al*[24] showed that treatment with celecoxib could suppress MNNG-induced gastric cancer in rats. Indomethacin, sulindac and NS-398 significantly inhibit the proliferation and growth of human gastric cancer cell line MKN28 *in vitro*[25,26].

POSSIBLE MECHANISMS OF CANCER PREVENTION

The results described above provide convincing evidence that non-selective NSAIDs and selective COX-2 inhibitors can inhibit gastric cancer cell formation and growth. However, the molecular basis for the striking chemo-preventive effects has not been fully clarified. Several studies indicate that COX-2 expression is a relatively early event during carcinogenesis in the stomach[27-30]. The best known target of NSAIDs is COX, the rate limiting enzyme in the conversion of arachidonic acid to prostanoids. Thus, the chemo-preventive effects of NSAIDs on gastric cancer may be attributed to inhibition of COX and the resulting decrease in production of PGs[31-33]. However, there are several studies that conflict with this observation. For example, NSAID derivates that lack the ability to inhibit COX (sulindac sulfone) have been shown to inhibit gastrointestinal tumor growth *in vivo* and *in vitro*[34-37]. COX-1 and COX-2 null mouse embryofibroblast cells remain sensitive to the anti-proliferative and anti-neoplastic effects of NSAIDs[38]. Furthermore, the concentration of NSAIDs that inhibits the growth of cancer cells *in vitro* is 10-100 times higher than that required to inhibit COX activity, suggesting the existence of additional cellular targets.

Induction of apoptosis

A substantial body of evidence now supports the idea that the induction of programmed cell death (apoptosis) is one of the main ways by which NSAIDs prevent cancer in a COX-2 dependent manner or a COX-2 independent manner.

COX 2-dependent mechanisms

One of the primary pharmacological properties of the NSAIDs is their ability to inhibit the COX. Analysis of COX expression has shown that COX-2 is increased in gastric cancer, but not in normal mucosa[4,39-42]. These findings support the idea that COX-2 over-expression is important during gastric carcinogenesis. In addition, over-expression of COX-2 can increase production of PGE2, adhesion to the extra-cellular matrix, concentrations of BCL2, and reduce TGF-2 receptor expression and E-cadherin protein. All these changes, which suggest an increased tumorigenic potential, support the notion that COX-2 overexpression alters the biology of cells and plays a part in the transformation process[43,44]. The question of how COX-2 inhibition induces apoptosis has been hotly debated. Several studies have suggested that decreased COX-2 activity can reduce eicosanoids such as the PGs, and in turn affect cell proliferation and apoptosis[45]. So far, there is no definitive evidence that supports the existence of a signaling pathway through which PGs can directly affect apoptosis. However, specific observations provide some clues and warrant mention here. The peroxisome proliferator-activated receptors (PPARs), a family of ligand-activated transcription factors comprising a subset within the steroid receptor family of intracellular receptors, have been shown to modulate the apoptotic response of various cell types[46,47]. It is conceivable that certain COX-2

products may be physiological ligands for the PPARs. Thus, it is hypothesized that PPARs are downstream of COX-2 in gastric carcinogenesis and may play a part in NSAIDs-mediated antineoplastic effects[48-50].

Arachidonic acid may also provide a mechanism underlying COX-2-dependent NSAIDs-induced apoptosis. Arachidonic acid is produced by hydrolysis of phospholipids and triglycerides. The phospholipase A2 cleaves phospholipids and releases arachidonic acid into the cytosol. Once released, it serves as a precursor for PGs production and is a signaling molecule in its own right. Treatment with various NSAIDs results in inhibition of COX-2 and a dramatic increase in the concentration of arachidonic acid, the main substrate for COX-2[45,51]. This buildup of arachidonic acid stimulates the sphingomyelinase to convert sphingomyelin to ceramide, a potent inducer of apoptosis[52-55]. Other studies have shown that the cellular concentration of arachidonic acid is a general mechanism by which apoptosis is regulated[56-59]. It seems that arachidonic acid can alter mitochondrial permeability and cause cytochrome C release, leading to apoptosis[58,60].

COX 2-independent mechanisms

Several recent observations cast doubt on the idea that COX is the sole target of NSAID action. The finding that some NSAIDs can inhibit proliferation and induce cell death in cells that do not express COX, suggests that other targets may play a part in NSAIDs-mediated apoptosis[61].

One potential mechanism involves the transcription factor NF-κB, which promotes cell survival and enhances proliferation. Several investigators have suggested that NSAIDs could promote apoptosis by inhibiting NF-κB signaling pathway[62-64]. The effect that seems to be due to its ability to inhibit the activity of IκB kinase β (IKKβ), an enzyme that activates the NF-κB pathway by phosphorylating the inhibitory subunit of NF-κB (IκB-α) and targeting it for destruction. Subsequently, genes required for cancer cell growth and survival may not be transcribed[65]. Furthermore, Yasui *et al*[66] reported that sulindac inhibits TNF-α-mediated NF-κB activation and greatly sensitizes human gastric cancer cell line MKN45 to TNF-α. The study data strongly suggest that combination therapy of TNF-alpha with sulindac may sensitize tumor cells to TNF-α and augment its proapoptotic potential. Moreover, Wong *et al*[67] showed that SC236, a selective COX-2 inhibitor, could inhibit NF-κB mediated gene transcription and binding activity in gastric cancer. This effect occurs through a mechanism independent of COX activity and PG synthesis. Furthermore, unlike aspirin, SC236 affects neither the phosphorylation, degradation, nor the expression of IκB-α, suggesting that the effects of SC236 are independent of IKK activity and IκB-α gene transcription. Instead, SC236 works directly through suppressing the nuclear translocation of RelA/p65. It is possible that SC236 directly targets proteins that facilitate the nuclear translocation of NF-κB[67].

The role of protein kinase C (PKC) and apoptosis-related oncogenes has also attracted more attention. Zhu *et al*[68] showed that both aspirin and indomethacin induce apoptosis in gastric cancer cells which may be mediated by up-regulation of *c-myc* proto-oncogene. PKC activation can abrogate the effects of NSAIDs by decreasing *c-myc* expression. Jiang *et al*[69] also showed that SC-236 induces apoptosis in AGS cells. SC-236 down-regulates the protein expression and kinase activity of PKC-β(1) in AGS cells, which provides an explanation for COX-independent apoptotic effects of selective COX-2 inhibitors in cultured gastric cancer cells. They also suggested that PKC-β(1) acts as a survival mediator in gastric cancer. Down-regulation of PKC-β(1) by SC-236 may provide new targets for future treatment of gastric cancer[69].

Furthermore, it was reported that the pro-apoptotic proteins Bax and Bak play a role in NSAIDs-induced gastric cancer cell apoptosis[70], suggesting that one of the major pathways mediating the anti-tumor response of aspirin and indomethacin in gastric cancer cells is through the up-regulation of Bax and Bak and activation of caspase-3.

Besides, Wu *et al*[71] demonstrated that SC-236 induces apoptosis in gastric cancer cells via the up-regulation of 15-lipoxygenase-1 (15-LOX-1), and increases endogenous 13-S-hydroxyoctadecadienoic acid (13-S-HODE), a novel target for chemoprevention effect of NSAIDs.

Regulation of angiogenesis

It is now clear that angiogenesis is critical for the progression of most human cancers[72]. Angiogenesis is a complex process controlled by a balance of angiogenic and angiostatic factors involved in multiple pathways that result in endothelial cell proliferation, differentiation, and organization into a functional network of vascular channels. Among the reported angiogenic factors, vascular endothelial growth factor (VEGF) is the most powerful endothelial cell specific mitogen that plays a key role in the complicated process of angiogenesis.

COX-2 has been shown to directly promote angiogenesis in several different experimental systems[73,74]. Masferrer *et al*[80] have examined more than 150 samples of different types of human cancers and found that COX-2 is present in the angiogenic vasculature in most of the tumors analyzed. Therefore, COX-2-derived PGs contribute to tumor growth by inducing newly formed blood vessels that sustain tumor cell viability and growth. Furthermore, xenografts of COX-2 over-expressing gastric cancer, when implanted into nude mice, express angiogenic factors in a COX-2-dependent manner, and both angiogenesis and tumor growth can be inhibited in these mice by administration of NSAIDs[23,78].

COX-2 expression has been shown to correlate with microvessel density (MVD), an accepted histologic marker of tumor angiogenesis in several different human malignancies, including gastric cancer[30]. Recent years, the relationships between COX-2 expression, VEGF expression, tumor angiogenesis, and outcome parameters in gastric cancer patients have been reported[75-77]: COX-2 expression significantly correlates with VEGF, and the colocalization of these proteins is most frequent at the advancing edge of cancer cells[75]. MVD is higher in COX-2 and VEGF positive cases than in COX-2 and VEGF negative cases[76]. Co-expression of COX-2 and VEGF, age, lymph node status, and serosal invasion are

independent prognostic factors for overall survival in gastric cancer patients[77].

Interestingly, COX-1, the other isozyme expressed in tumor vascular endothelia, participates in tumor angiogenesis, because an anti-sense oligonucleotide of COX-1 suppresses *in vitro* angiogenesis induced by COX-2-overexpressing cells. Non-specific COX inhibitors reduce the growth and angiogenesis in cancer xenografts by inhibiting COX-1 in vascular endothelial cells, even when the tumor does not express COX-2. These results demonstrate that COX inhibitors suppress angiogenesis and tumor growth by inhibiting expression of angiogenic factors and vascular endothelial cell migration[79].

COX-2 expression and H pylori infection

H pylori infection is also a strong risk factor for the development of gastric cancer via the pathway of atrophy, intestinal metaplasia and dysplasia in chronic infection. Infection with *H pylori* up-regulates mediators of the inflammatory response, leading to the production of inflammatory cytokines and PGs which themselves may suppress cell-mediated immune responses and promote angiogenesis. These factors may also have effects on cell growth and survival signaling pathways, resulting in induction of cell proliferation and inhibition of apoptosis[81].

H pylori up-regulates COX-2 mRNA expression and PGE_2 synthesis in gastric cancer cells[82], and both pre-malignant and malignant gastric lesions demonstrate high COX-2 expression levels[83]. Therefore, *H pylori*-induced gastric carcinogenesis may be associated with the elevated expression of COX-2 in gastric epithelium. It is possible that NSAIDs may inhibit the replication and proliferation of *H pylori*[84,85], neutralize the increased COX-2 expression and PG synthesis and reverse the increased apoptosis and proliferation of epithelial cells associated with *H pylori* infection[86,89], thereby reducing the risk of gastric cancer[90,91]. Experimental models of cell proliferation have also shown that, in hyperplastic gastritis in the murine model infected with *H pylori*, treatment with etodolac could significantly decrease PGE_2 production and the thickness of gastric pits in the infected groups[87].

Whether eradication of *H pylori* can prevent gastric cancer remains contradictory. COX-2 expression remains in gastric epithelium even after successful eradication of *H pylori*[88]. This may suggest that combined treatment of COX-2 inhibitors and *H pylori* infection may be more useful in eliminating *H pylori*-induced COX-2 expression than either anti-*H pylori* antibiotics or COX-2 inhibitors alone. This issue deserves further study.

CONCLUSIONS AND FUTURE DIRECTIONS

Combining the evidence from humans, animal models and cell culture systems can establish the targeted inhibition of COX-2 was a viable approach to gastric cancer prevention and/or treatment. However, despite these successes, many questions remain unanswered such as the optimal dose and duration of treatment. Selective COX-2 inhibitors, which have an advantage of minimizing the gastrointestinal side-effects, have received wide attention. An exciting area for future investigation is to investigate whether COX-2 inhibitors can be used in the treatment of patients who have preneoplastic gastric lesions or suffer from gastric cancer, and whether combination therapy with COX-2 inhibitors and the drugs targeting other oncogenic pathways can lead to improved clinical outcomes.

REFERENCES

1 **Popiela T,** Kulig J, Kolodziejczyk P, Sierzega M. Long-term results of surgery for early gastric cancer. *Br J Surg* 2002; **89:** 1035-1042
2 **Forman D,** Morris E, Eastwood A, Kleijnen J. Guidelines for treatment of upper gastrointestinal cancer. *Lancet* 2003; **361:** 80
3 **Maruyama M.** Treatment results of gastric cancer staged by the TNM classification. In: Maruyama M, Kimura K, editors. Review of clinical research in gastroenterology. Tokyo (Japan): Igaku-Shoin,1998: 112
4 **Ristimäki A,** Honkanen N, Jänkälä H, Sipponen P, Härkönen M. Expression of cyclooxygenase-2 in human gastric carcinoma. *Cancer Res* 1997; **57:** 1276-1280
5 **Thun MJ,** Namboodiri MM, Calle EE, Flanders WD, Heath CW Jr. Aspirin use and risk of fatal cancer. *Cancer Res* 1993; **53:** 1322-1327
6 **Farrow DC,** Vaughan TL, Hansten PD, Stanford JL, Risch HA, Gammon MD, Chow WH, Dubrow R, Ahsan H, Mayne ST, Schoenberg JB, West AB, Rotterdam H, Fraumeni JF Jr, Blot WJ. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1998; **7:** 97-102
7 **Zaridze D,** Borisova E, Maximovitch D, Chkhikvadze V. Aspirin protects against gastric cancer: results of a case-control study from Moscow, Russia. *Int J Cancer* 1999; **82:** 473-476
8 **Akre K,** Ekström AM, Signorello LB, Hansson LE, Nyrén O. Aspirin and risk for gastric cancer: a population-based case-control study in Sweden. *Br J Cancer* 2001; **84:** 965-968
9 **Husain SS,** Szabo IL, Tamawski AS. NSAID inhibition of GI cancer growth: clinical implications and molecular mechanisms of action. *Am J Gastroenterol* 2002; **97:** 542-553
10 **Baron JA,** Sandler RS. Nonsteroidal anti-inflammatory drugs and cancer prevention. *Annu Rev Med* 2000; **51:** 511-523
11 **Vainio H,** Morgan G. Non-steroidal anti-inflammatory drugs and chemoprevention of cancer. *Ann Chir Gynaecol* 2000; **89:** 173-176
12 **Jolly K,** Cheng KK, Langman MJ. NSAIDs and gastrointestinal cancer prevention. *Drugs* 2002; **62:** 945-956
13 **Gridley G,** McLaughlin JK, Ekbom A, Klareskog L, Adami HO, Hacker DG, Hoover R, Fraumeni JF Jr. Incidence of cancer among patients with rheumatoid arthritis. *J Natl Cancer Inst* 1993; **85:** 307-311
14 **Wang WH,** Huang JQ, Zheng GF, Lam SK, Karlberg J, Wong BC. Non-steroidal anti-inflammatory drug use and the risk of gastric cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2003; **95:** 1784-1791
15 **Schreinemachers DM,** Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiology* 1994; **5:** 138-146
16 **Wacholder S,** Silverman DT, McLaughlin JK, Mandel JS. Selection of controls in case-control studies. II. Types of controls. *Am J Epidemiol* 1992; **135:** 1029-1041
17 **Newberne PM,** Charnley G, Adams K, Cantor M, Suphakarn V, Roth D, Schrager TF. Gastric carcinogenesis: a model for the identification of risk factors. *Cancer Lett* 1987; **38:** 149-163
18 **Takahashi M,** Kokubo T, Furukawa F, Kurokawa Y, Hayashi Y. Effects of sodium chloride, saccharin, phenobarbital and aspirin on gastric carcinogenesis in rats after initiation with N-methyl-N'-nitro-N-nitrosoguanidine. *Gann* 1984; **75:** 494-501
19 **Bespalov VG,** Troian DN, Petrov AS, Aleksandrov VA. [The inhibition of esophageal tumor development by the use of the nonsteroidal and steroidal anti-inflammatory preparations indomethacin and dexamethasone]. *Farmakol Toksikol* 1989; **52:**

67-70
20 **Tanaka T,** Kojima T, Yoshimi N, Sugie S, Mori H. Inhibitory effect of the non-steroidal anti-inflammatory drug, indomethacin on the naturally occurring carcinogen, 1-hydroxyanthraquinone in male ACI/N rats. *Carcinogenesis* 1991; **12:** 1949-1952
21 **Jalbert G,** Castonguay A. Effects of NSAIDs on NNK-induced pulmonary and gastric tumorigenesis in A/J mice. *Cancer Lett* 1992; **66:** 21-28
22 **Sawaoka H,** Kawano S, Tsuji S, Tsujii M, Gunawan ES, Takei Y, Nagano K, Hori M. Cyclooxygenase-2 inhibitors suppress the growth of gastric cancer xenografts via induction of apoptosis in nude mice. *Am J Physiol* 1998; **274:** G1061-G1067
23 **Fu SL,** Wu YL, Zhang YP, Qiao MM, Chen Y. Anti-cancer effects of COX-2 inhibitors and their correlation with angiogenesis and invasion in gastric cancer. *World J Gastroenterol* 2004; **10:** 1971-1974
24 **Hu PJ,** Yu J, Zeng ZR, Leung WK, Lin HL, Tang BD, Bai AH, Sung JJ. Chemoprevention of gastric cancer by celecoxib in rats. *Gut* 2004; **53:** 195-200
25 **Husain SS,** Szabo IL, Pai R, Soreghan B, Jones MK, Tarnawski AS. MAPK (ERK2) kinase--a key target for NSAIDs-induced inhibition of gastric cancer cell proliferation and growth. *Life Sci* 2001; **69:** 3045-3054
26 **Wu YL,** Sun B, Zhang XJ, Wang SN, He HY, Qiao MM, Zhong J, Xu JY. Growth inhibition and apoptosis induction of Sulindac on Human gastric cancer cells. *World J Gastroenterol* 2001; **7:** 796-800
27 **Yamagata R,** Shimoyama T, Fukuda S, Yoshimura T, Tanaka M, Munakata A. Cyclooxygenase-2 expression is increased in early intestinal-type gastric cancer and gastric mucosa with intestinal metaplasia. *Eur J Gastroenterol Hepatol* 2002; **14:** 359-363
28 **van Rees BP,** Saukkonen K, Ristimäki A, Polkowski W, Tytgat GN, Drillenburg P, Offerhaus GJ. Cyclooxygenase-2 expression during carcinogenesis in the human stomach. *J Pathol* 2002; **196:** 171-179
29 **Ohno R,** Yoshinaga K, Fujita T, Hasegawa K, Iseki H, Tsunozaki H, Ichikawa W, Nihei Z, Sugihara K. Depth of invasion parallels increased cyclooxygenase-2 levels in patients with gastric carcinoma. *Cancer* 2001; **91:** 1876-1881
30 **Honjo S,** Kase S, Osaki M, Ardyanto TD, Kaibara N, Ito H. Cyclooxygenase-2 expression in human gastric tubular adenomas and carcinomas; correlation with intratumoral microvessel density and apoptotic index. *Anticancer Res* 2004; **24:** 1439-1444
31 **Prescott SM,** White RL. Self-promotion? Intimate connections between APC and prostaglandin H synthase-2. *Cell* 1996; **87:** 783-786
32 **Chen CN,** Sung CT, Lin MT, Lee PH, Chang KJ. Clinicopathologic association of cyclooxygenase 1 and cyclooxygenase 2 expression in gastric adenocarcinoma. *Ann Surg* 2001; **233:** 183-188
33 **Oshima M,** Dinchuk JE, Kargman SL, Oshima H, Hancock B, Kwong E, Trzaskos JM, Evans JF, Taketo MM. Suppression of intestinal polyposis in Apc delta716 knockout mice by inhibition of cyclooxygenase 2 (COX-2). *Cell* 1996; **87:** 803-809
34 **Piazza GA,** Rahm AL, Krutzsch M, Sperl G, Paranka NS, Gross PH, Brendel K, Burt RW, Alberts DS, Pamukcu R. Antineoplastic drugs sulindac sulfide and sulfone inhibit cell growth by inducing apoptosis. *Cancer Res* 1995; **55:** 3110-3116
35 **Piazza GA,** Alberts DS, Hixson LJ, Paranka NS, Li H, Finn T, Bogert C, Guillen JM, Brendel K, Gross PH, Sperl G, Ritchie J, Burt RW, Ellsworth L, Ahnen DJ, Pamukcu R. Sulindac sulfone inhibits azoxymethane-induced colon carcinogenesis in rats without reducing prostaglandin levels. *Cancer Res* 1997; **57:** 2909-2915
36 **Reddy BS,** Kawamori T, Lubet RA, Steele VE, Kelloff GJ, Rao CV. Chemopreventive efficacy of sulindac sulfone against colon cancer depends on time of administration during carcinogenic process. *Cancer Res* 1999; **59:** 3387-3391
37 **Mahmoud NN,** Boolbol SK, Dannenberg AJ, Mestre JR, Bilinski RT, Martucci C, Newmark HL, Chadburn A, Bertagnolli MM. The sulfide metabolite of sulindac prevents tumors and restores enterocyte apoptosis in a murine model of familial adenomatous polyposis. *Carcinogenesis* 1998; **19:** 87-91
38 **Zhang X,** Morham SG, Langenbach R, Young DA. Malignant transformation and antineoplastic actions of nonsteroidal antiinflammatory drugs (NSAIDs) on cyclooxygenase-null embryo fibroblasts. *J Exp Med* 1999; **190:** 451-459
39 **Lim HY,** Joo HJ, Choi JH, Yi JW, Yang MS, Cho DY, Kim HS, Nam DK, Lee KB, Kim HC. Increased expression of cyclooxygenase-2 protein in human gastric carcinoma. *Clin Cancer Res* 2000; **6:** 519-525
40 **Soydan AS,** Gaffen JD, Weech PK, Tremblay NM, Kargman S, O'Neill G, Bennett A, Tavares IA. Cytosolic phospholipase A2, cyclo-oxygenases and arachidonate in human stomach tumours. *Eur J Cancer* 1997; **33:** 1508-1512
41 **Walker MM.** Cyclooxygenase-2 expression in early gastric cancer, intestinal metaplasia and Helicobacter pylori infection. *Eur J Gastroenterol Hepatol* 2002; **14:** 347-349
42 **Ratnasinghe D,** Tangrea JA, Roth MJ, Dawsey SM, Anver M, Kasprzak BA, Hu N, Wang QH, Taylor PR. Expression of cyclooxygenase-2 in human adenocarcinomas of the gastric cardia and corpus. *Oncol Rep* 1999; **6:** 965-968
43 **Chan TA.** Nonsteroidal anti-inflammatory drugs, apoptosis, and colon-cancer chemoprevention. *Lancet Oncol* 2002; **3:** 166-174
44 **Scartozzi M,** Galizia E, Freddari F, Berardi R, Cellerino R, Cascinu S. Molecular biology of sporadic gastric cancer: prognostic indicators and novel therapeutic approaches. *Cancer Treat Rev* 2004; **30:** 451-459
45 **Sjödahl R.** Nonsteroidal anti-inflammatory drugs and the gastrointestinal tract. Extent, mode, and dose dependence of anticancer effects. *Am J Med* 2001; **110:** 66S-69S
46 **Roberts RA,** James NH, Woodyatt NJ, Macdonald N, Tugwood JD. Evidence for the suppression of apoptosis by the peroxisome proliferator activated receptor alpha (PPAR alpha). *Carcinogenesis* 1998; **19:** 43-48
47 **Tsubouchi Y,** Sano H, Kawahito Y, Mukai S, Yamada R, Kohno M, Inoue K, Hla T, Kondo M. Inhibition of human lung cancer cell growth by the peroxisome proliferator-activated receptor-gamma agonists through induction of apoptosis. *Biochem Biophys Res Commun* 2000; **270:** 400-405
48 **Konturek PC,** Konturek SJ, Bielanski W, Kania J, Zuchowicz M, Hartwich A, Rehfeld JF, Hahn EG. Influence of COX-2 inhibition by rofecoxib on serum and tumor progastrin and gastrin levels and expression of PPARgamma and apoptosis-related proteins in gastric cancer patients. *Dig Dis Sci* 2003; **48:** 2005-2017
49 **Leung WK,** Bai AH, Chan VY, Yu J, Chan MW, To KF, Wu JR, Chan KK, Fu YG, Chan FK, Sung JJ. Effect of peroxisome proliferator activated receptor gamma ligands on growth and gene expression profiles of gastric cancer cells. *Gut* 2004; **53:** 331-338
50 **Lehmann JM,** Lenhard JM, Oliver BB, Ringold GM, Kliewer SA. Peroxisome proliferator-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *J Biol Chem* 1997; **272:** 3406-3410
51 **Chan TA,** Morin PJ, Vogelstein B, Kinzler KW. Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis. *Proc Natl Acad Sci U S A* 1998; **95:** 681-686
52 **Jayadev S,** Hayter HL, Andrieu N, Gamard CJ, Liu B, Balu R, Hayakawa M, Ito F, Hannun YA. Phospholipase A2 is necessary for tumor necrosis factor alpha-induced ceramide generation in L929 cells. *J Biol Chem* 1997; **272:** 17196-17203
53 **Hannun YA.** Functions of ceramide in coordinating cellular responses to stress. *Science* 1996; **274:** 1855-1859
54 **Kolesnick RN**, Haimovitz-Friedman A, Fuks Z. The sphingomyelin signal transduction pathway mediates apoptosis for tumor necrosis factor, Fas, and ionizing radiation. *Biochem Cell Biol* 1994; **72:** 471-474
55 **Masamune A,** Shimosegawa T, Masamune O, Mukaida N, Koizumi M, Toyota T. Helicobacter pylori-dependent ceramide production may mediate increased interleukin 8 expression in human gastric cancer cell lines. *Gastroenterology*

1999; **116:** 1330-1341
56 **Wong BC,** Wang WP, Cho CH, Fan XM, Lin MC, Kung HF, Lam SK. 12-Lipoxygenase inhibition induced apoptosis in human gastric cancer cells. *Carcinogenesis* 2001; **22:** 1349-1354
57 **Cao Y,** Pearman AT, Zimmerman GA, McIntyre TM, Prescott SM. Intracellular unesterified arachidonic acid signals apoptosis. *Proc Natl Acad Sci U S A* 2000; **97:** 11280-11285
58 **Scorrano L,** Penzo D, Petronilli V, Pagano F, Bernardi P. Arachidonic acid causes cell death through the mitochondrial permeability transition. Implications for tumor necrosis factor-alpha aopototic signaling. *J Biol Chem* 2001; **276:** 12035-12040
59 **Fonteh AN,** LaPorte T, Swan D, McAlexander MA. A decrease in remodeling accounts for the accumulation of arachidonic acid in murine mast cells undergoing apoptosis. *J Biol Chem* 2001; **276:** 1439-1449
60 **Fan XM,** Tu SP, Lam SK, Wang WP, Wu J, Wong WM, Yuen MF, Lin MC, Kung HF, Wong BC. Five-lipoxygenase-activating protein inhibitor MK-886 induces apoptosis in gastric cancer through upregulation of p27kip1 and bax. *J Gastroenterol Hepatol* 2004; **19:** 31-37
61 **Jiang XH,** Wong BC. Cyclooxygenase-2 inhibition and gastric cancer. *Curr Pharm Des* 2003; **9:** 2281-2288
62 **Lim JW,** Kim H, Kim KH. Expression of Ku70 and Ku80 mediated by NF-kappa B and cyclooxygenase-2 is related to proliferation of human gastric cancer cells. *J Biol Chem* 2002; **277:** 46093-46100
63 **Yamamoto Y,** Yin MJ, Lin KM, Gaynor RB. Sulindac inhibits activation of the NF-kappaB pathway. *J Biol Chem* 1999; **274:** 27307-27314
64 **Lim JW,** Kim H, Kim KH. Nuclear factor-kappaB regulates cyclooxygenase-2 expression and cell proliferation in human gastric cancer cells. *Lab Invest* 2001; **81:** 349-360
65 **Yin MJ,** Yamamoto Y, Gaynor RB. The anti-inflammatory agents aspirin and salicylate inhibit the activity of I(kappa)B kinase-beta. *Nature* 1998; **396:** 77-80
66 **Yasui H,** Adachi M, Imai K. Combination of tumor necrosis factor-alpha with sulindac augments its apoptotic potential and suppresses tumor growth of human carcinoma cells in nude mice. *Cancer* 2003; **97:** 1412-1420
67 **Wong BC,** Jiang Xh, Fan XM, Lin MC, Jiang SH, Lam SK, Kung HF. Suppression of RelA/p65 nuclear translocation independent of IkappaB-alpha degradation by cyclooxygenase-2 inhibitor in gastric cancer. *Oncogene* 2003; **22:** 1189-1197
68 **Zhu GH,** Wong BC, Eggo MC, Ching CK, Yuen ST, Chan EY, Lai KC, Lam SK. Non-steroidal anti-inflammatory drug-induced apoptosis in gastric cancer cells is blocked by protein kinase C activation through inhibition of c-myc. *Br J Cancer* 1999; **79:** 393-400
69 **Jiang XH,** Lam SK, Lin MC, Jiang SH, Kung HF, Slosberg ED, Soh JW, Weinstein IB, Wong BC. Novel target for induction of apoptosis by cyclo-oxygenase-2 inhibitor SC-236 through a protein kinase C-beta(1)-dependent pathway. *Oncogene* 2002; **21:** 6113-6122
70 **Zhou XM,** Wong BC, Fan XM, Zhang HB, Lin MC, Kung HF, Fan DM, Lam SK. Non-steroidal anti-inflammatory drugs induce apoptosis in gastric cancer cells through up-regulation of bax and bak. *Carcinogenesis* 2001; **22:** 1393-1397
71 **Wu J,** Xia HH, Tu SP, Fan DM, Lin MC, Kung HF, Lam SK, Wong BC. 15-Lipoxygenase-1 mediates cyclooxygenase-2 inhibitor-induced apoptosis in gastric cancer. *Carcinogenesis* 2003; **24:** 243-247
72 **Folkman J.** Role of angiogenesis in tumor growth and metastasis. *Semin Oncol* 2002; **29:** 15-18
73 **Dermond O,** Rüegg C. Inhibition of tumor angiogenesis by non-steroidal anti-inflammatory drugs: emerging mechanisms and therapeutic perspectives. *Drug Resist Updat* 2001; **4:** 314-321
74 **Fosslien E.** Review: molecular pathology of cyclooxygenase-2 in cancer-induced angiogenesis. *Ann Clin Lab Sci* 2001; **31:** 325-348
75 **Tatsuguchi A,** Matsui K, Shinji Y, Gudis K, Tsukui T, Kishida T, Fukuda Y, Sugisaki Y, Tokunaga A, Tajiri T, Sakamoto C. Cyclooxygenase-2 expression correlates with angiogenesis and apoptosis in gastric cancer tissue. *Hum Pathol* 2004; **35:** 488-495
76 **Joo YE,** Rew JS, Seo YH, Choi SK, Kim YJ, Park CS, Kim SJ. Cyclooxygenase-2 overexpression correlates with vascular endothelial growth factor expression and tumor angiogenesis in gastric cancer. *J Clin Gastroenterol* 2003; **37:** 28-33
77 **Uefuji K,** Ichikura T, Mochizuki H. Cyclooxygenase-2 expression is related to prostaglandin biosynthesis and angiogenesis in human gastric cancer. *Clin Cancer Res* 2000; **6:** 135-138
78 **Sawaoka H,** Tsuji S, Tsujii M, Gunawan ES, Sasaki Y, Kawano S, Hori M. Cyclooxygenase inhibitors suppress angiogenesis and reduce tumor growth in vivo. *Lab Invest* 1999; **79:** 1469-1477
79 **Tsuji S,** Tsujii M, Kawano S, Hori M. Cyclooxygenase-2 upregulation as a perigenetic change in carcinogenesis. *J Exp Clin Cancer Res* 2001; **20:** 117-129
80 **Masferrer JL,** Leahy KM, Koki AT, Zweifel BS, Settle SL, Woerner BM, Edwards DA, Flickinger AG, Moore RJ, Seibert K. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. *Cancer Res* 2000; **60:** 1306-1311
81 **O'Byrne KJ,** Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. *Br J Cancer* 2001; **85:** 473-483
82 **Romano M,** Ricci V, Memoli A, Tuccillo C, Di Popolo A, Sommi P, Acquaviva AM, Del Vecchio Blanco C, Bruni CB, Zarrilli R. Helicobacter pylori up-regulates cyclooxygenase-2 mRNA expression and prostaglandin E2 synthesis in MKN 28 gastric mucosal cells in vitro. *J Biol Chem* 1998; **273:** 28560-28563
83 **Sung JJ,** Leung WK, Go MY, To KF, Cheng AS, Ng EK, Chan FK. Cyclooxygenase-2 expression in Helicobacter pylori-associated premalignant and malignant gastric lesions. *Am J Pathol* 2000; **157:** 729-735
84 **Shirin H,** Moss SF, Stark B, Weinstein IB, Holt PR, Sordillo EM. Inhibition of Helicobacter pylori growth by sulindac. *Gastroenterology* 2000; **119:** A4931
85 **Wang WH,** Wong WM, Dailidiene D, Berg DE, Gu Q, Lai KC, Lam SK, Wong BC. Aspirin inhibits the growth of Helicobacter pylori and enhances its susceptibility to antimicrobial agents. *Gut* 2003; **52:** 490-495
86 **Takahashi M,** Katayama Y, Takada H, Kuwayama H, Terano A. The effect of NSAIDs and a COX-2 specific inhibitor on Helicobacter pylori-induced PGE2 and HGF in human gastric fibroblasts. *Aliment Pharmacol Ther* 2000; **14** Suppl 1: 44-49
87 **Xiao F,** Furuta T, Takashima M, Shirai N, Hanai H. Involvement of cyclooxygenase-2 in hyperplastic gastritis induced by Helicobacter pylori infection in C57BL/6 mice. *Aliment Pharmacol Ther* 2001; **15:** 875-886
88 **McCarthy CJ,** Crofford LJ, Greenson J, Scheiman JM. Cyclooxygenase-2 expression in gastric antral mucosa before and after eradication of Helicobacter pylori infection. *Am J Gastroenterol* 1999; **94:** 1218-1223
89 **Kim TI,** Lee YC, Lee KH, Han JH, Chon CY, Moon YM, Kang JK, Park IS. Effects of nonsteroidal anti-inflammatory drugs on Helicobacter pylori-infected gastric mucosae of mice: apoptosis, cell proliferation, and inflammatory activity. *Infect Immun* 2001; **69:** 5056-5063
90 **Nam KT,** Hahm KB, Oh SY, Yeo M, Han SU, Ahn B, Kim YB, Kang JS, Jang DD, Yang KH, Kim DY. The selective cyclooxygenase-2 inhibitor nimesulide prevents Helicobacter pylori-associated gastric cancer development in a mouse model. *Clin Cancer Res* 2004; **10:** 8105-8113
91 **Wambura C,** Aoyama N, Shirasaka D, Sakai T, Ikemura T, Sakashita M, Maekawa S, Kuroda K, Inoue T, Ebara S, Miyamoto M, Kasuga M. Effect of Helicobacter pylori-induced cyclooxygenase-2 on gastric epithelial cell kinetics: implication for gastric carcinogenesis. *Helicobacter* 2002; **7:** 129-138

S- Editor Wang J **L- Editor** Wang XL **E- Editor** Bi L