Genetic variant of cyclooxygenase-2 in gastric cancer: More inflammation and susceptibility

Xuan-Ke Ji, Sailaja Vatsalya Madhurapantula, Gui He, Kun-Yan Wang, Chun-Hua Song, Jian-Ying Zhang, Kai-Juan Wang

Abstract

Gastric cancer accounts for the majority cancer-related deaths worldwide. Although various methods have considerably improved the screening, diagnosis, and treatment of gastric cancer, its incidence is still high in Asia, and the 5-year survival rate of advanced gastric cancer patients is only 10%-20%. Therefore, more effective drugs and better screening strategies are needed for reducing the incidence and mortality of gastric cancer. Cyclooxygenase-2 (COX-2) is considered to be the key inducible enzyme in prostaglandins (PGs) synthesis, which is involved in multiple pathways in the inflammatory response. For example, inflammatory cytokines stimulate innate immune responses via Toll-like receptors and nuclear factor-kappa B to induce COX-2/PGE2 pathway. In these processes, the production of an inflammatory microenvironment promotes the occurrence of gastric cancer. Epidemiological studies have also indicated that non-steroidal anti-inflammatory drugs can reduce the risk of malignant tumors of the digestive system by blocking the effect of COX-2. However, clinical use of COX-2 inhibitors to prevent or treat gastric cancer may be limited because of potential side effects, especially in the cardiovascular system. Given these side effects and low
INTRODUCTION

Gastric cancer is the fifth most commonly diagnosed cancer and the third leading cause of cancer-related deaths worldwide. The incidence of gastric cancer remains high in Eastern Asia despite its global decrease in the last few years[1,2]. Approximately 75% of patients with gastric cancer are diagnosed at advanced stage and the median survival is 7-10 mo[3]. Therefore, individualized prevention and early detection and treatment are of clinical significance in improving the survival time and reducing the mortality of gastric cancer.

Environmental factors including smoking, drinking, and Helicobacter pylori (H. pylori) infection and genetic alterations such as susceptible genetic variants and epigenetic alterations have been associated with gastric carcinogenesis[4,5]. Cyclooxygenase-2 (COX-2) has been extensively studied in carcinogenesis, and its participation in chronic inflammation and various infections (such as H. pylori infection and chronic viral hepatitis) significantly increases the risk of cancer[6,7]. In this review, we will summarize the association between whole COX-2 sequence variation and susceptibility to gastric cancer and synthesizing the new progress in understanding the role of COX-2 in gastric carcinogenesis.

Core Tip: Cyclooxygenase-2 (COX-2) is considered to be the key inducible enzyme in prostaglandins synthesis, and non-steroidal anti-inflammatory drugs can reduce the risk of malignant tumors of the digestive system by blocking the effect of COX-2. However, COX-2 inhibitors to prevent or treat gastric cancer may be limited because of their cardiovascular side effects. This review will be helpful for early screening and further research to find new approaches to gastric cancer treatment by summarizing the association between whole COX-2 sequence variation and susceptibility to gastric cancer and synthesizing the new progress in understanding the role of COX-2 in gastric carcinogenesis.

Key Words: Cyclooxygenase-2; Inflammation; Genetic variant; Gastric cancer; Prostaglandin E2
MOLECULAR CHARACTERISTICS OF COX-2

COX-2 is known as the key inducible enzyme in prostaglandins (PGs) synthesis, and the COX-2 gene is located at chromosome 1q25.2-25.3 and composed of 9 introns and 10 exons[8]. The 5' region of the COX-2 gene has binding sites for several activated transcriptional factors, such as nuclear factor-kappa B (NF-kB), stimulatory protein 1 (SP1), activator protein-2 (AP-2), and transforming growth factor. In order to explore the expression of COX-2 in normal tissues, the expression data of COX-2 were downloaded from the genotypic tissue expression (GTEx) database (https://xenabrowser.net/datapages/) and the distribution of COX-2 expression in different tissues was visualized by plotting an anatomical map with R-3.5.3 software. Detailed data are shown in Supplementary material 1. Previous studies have shown that COX-2 has negative expression in normal tissues and organs under physiological conditions, though it is constitutively expressed in the brain and kidney. We also found that COX-2 gene was rarely expressed in normal tissues (including the stomach), but distributed more in the colon and lungs, both in males and females (Figure 1). However, its expression is increased dramatically in response to certain inflammatory stimuli such as cytokines, oncogenes, and tumor inducers[9]. COX-2 have been shown to play crucial roles in tumorigenesis[10]. The COX-2/PGE2 pathway activates macrophage infiltration and further induces cytokine signaling to activate the transcription factors NF-xB and signal transducer and activator of transcription 3 (Stat3)[11,12], which can change the tumor microenvironment and affect the occurrence of cancer.

GENETIC VARIANTS OF COX-2 IN TUMORIGENESIS

COX-2 has been implicated in the etiology of cancer and its expression has been confirmed to be increased in gastric cancer. Genetic variants may lead to an increase in expression and change in the function of COX-2, which may affect the occurrence of cancer. Studies have suggested that COX-2 single nucleotide polymorphisms (SNPs) may affect the gastric tumorigenesis. However, these studies only focused on a few or particular region SNPs, and lacked an overall description of the whole sequence variation of COX-2. In this review, we summarize the SNPs in the whole COX-2 gene sequence, including exons, introns, and both the 5' and 3' untranslated regions (UTR). In addition, we also analyze the copy number variation (CNV) information of COX-2 in gastric cancer.
CNV of COX-2 in gastric cancer

The SNPs of COX-2 have been widely studied, but its CNV was rarely mentioned. We downloaded the copy number data of the COX-2 gene in gastric cancer from The Cancer Genome Atlas (TCGA) database (https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga), and then visualized the data with R-3.5.3 software (detailed data in Supplementary material 2). The genes displayed are all genes with CNV, but no CNV of the COX-2 gene was found.

Association between COX-2 SNPs and gastric cancer

The SNPs of COX-2 may have a functional effect on COX-2 transcription and cause COX-2 overexpression to change the response to various inflammatory stimuli. However, only a single locus of SNP can explain the occurrence of cancer very little, which is not enough to fully demonstrate the association between COX-2 SNPs and gastric cancer. We combined data from the TCGA (https://portal.gdc.cancer.gov/repository; downloaded data in Supplementary material 3) and Ensembl (http://grch37ensembl.org/Homo_sapiens/Tools/VcftoPed?db=core) using Haploview 4.2 software to screen SNPs. The criteria for screening SNPs were minor allele frequency ≥ 0.05 and pairwise r² < 0.8. All obtained SNPs are shown in Figure 2. At the same time, we retrieved the SNPs that have been studied. The results showed that 14 SNPs were associated with cancer in the whole sequence of COX-2, including 9 SNPs associated with gastric cancer (Table 1). At present, five COX-2 polymorphisms have been extensively studied, including rs5275 and rs689470T>C that are located in the 3' UTR, as well as rs689466G>A and rs20417G>C mutations that are located in the promoter region with multiple enhancers and transcriptional regulatory elements. SNPs in the COX-2 promoter region may change the activity of the promoter and C-reactive protein (CRP), which may be related to acute or chronic inflammation.

Although SNPs may have functional effects, there are still a large number of functional features of SNPs that have not been discovered, and their mechanism needs to be further studied. Meanwhile, risk estimates of previous studies have been inconsistent. Therefore, we made a summary and pooled analysis of the extracted data. The results showed that rs689466G>A, rs20417G>C, and rs3218625G>A in the promoter region confer a higher risk of gastric cancer [A vs G: odds ratio (OR) = 1.19, 95% confidence interval (CI): 1.10-1.29; C vs G: OR = 1.26, 95%CI: 1.12-1.41; and A vs G: OR = 1.62, 95% CI: 1.02-2.56]. Similarly, rs5275T>C and rs689470T>C in the 3'UTR were significantly associated with gastric cancer (C vs T: OR = 1.14, 95%CI: 1.01-1.29 and TC vs TT: OR = 7.49, 95%CI: 1.21-46.2). As to the rs2066826 G>A polymorphism, a significant association was detected in pancreatic cancer (A vs G: OR = 1.60, 95% CI: 1.06-2.40, P = 0.026). However, rs5279 T>C in the exon region and rs4648298A>G in the 3' UTR may reduce the risk of gastric and colorectal cancers (TC vs TT: OR = 0.24, 95%CI: 0.08-0.73 and G vs A: OR = 0.24; 95%CI: 0.10-0.56).

In our previous study of 296 gastric cancer patients and 319 control family members in the Chinese Han population, an increased risk was observed in individuals with the COX-2 rs689466AA genotype (OR = 2.03; 95%CI: 1.27-3.22), and the association decreased as the degree of relationship decreased[14]. Recently, we further performed genotyping in 660 gastric cancer cases form the First Affiliated Hospital of Zhengzhou University from 2013 to 2015 and 660 control individuals from a community-based cardiovascular diseases survey in the same time. Our results found that individuals with rs20417 CC genotype were more likely to develop gastric cancer (OR = 1.54, 95%CI: 1.08-2.19). Meanwhile, Zhang et al[15] found that rs689466 G>A enhanced the transcriptional activity and thus increased the expression of COX-2 by creating a cMYB binding site.

These results suggest that the SNPs of the COX-2 gene plays an important role in the carcinogenesis of gastric cancer, especially the variation in the promoter region which may have functional consequences. In addition, SNPs in the promoter region could enhance COX-2 gene transcription, affect the stability of mRNA, regulate the inflammatory response, and consequently lead to individual variation in susceptibility to gastric cancer[16,17]. Our study provides a basis for more thoroughly exploring the exact function of COX-2 in the occurrence of gastric cancer. Further functional studies will be considered and be elaborated in another study.

INFLAMMATORY MECHANISM OF COX-2 IN GASTRIC CANCER

COX-2 overexpression has been found in a variety of cancers, including gastric cancer [18,19]. A large number of studies have shown that many factors (such as H. pylori
### Table 1 Summary of single nucleotide polymorphisms in whole region of cyclooxygenase-2 and their association with risk of cancer

| SNP ID (rs number) | Chromosome location (GRCh38) | Cancer type | Model | Region | Effect | MAF | OR (95%CI) | P value | Ref.          |
|-------------------|-------------------------------|-------------|-------|--------|--------|-----|------------|---------|--------------|
| rs689465A>G       | 1:186681714                   | Gastric     | G/A   | Promoter | Significant interaction with *H. pylori* infection | 0.143 | 0.84 (0.57-1.24) | 0.381 | Zhang et al[55] |
| rs689466G>A       | 1:186681619                   | Gastric     | A/G   | Promoter | Increases transcriptional activity by creating a c-MYB binding site | 0.176 | 1.19 (1.10-1.29) | 0.002* | Li et al[14], Piranda et al[16], Zhang et al[55], Lopes et al[56], Liu et al[57], Shin et al[58], Guo et al[59], Zamudio et al[60], and Liao et al[61] |
| rs20417G>C        | 1:186681189                   | Gastric     | C/G   | Promoter | Reduces promoter activity by creating a binding site for NPM and P-NPM | 0.109 | 1.26 (1.12-1.41) | < 0.001* | Li et al[14], Piranda et al[16], Liu et al[17], Zhang et al[55], Shin et al[58], Sitarz et al[62], Saxena et al[63], Hou et al[64], Zhang et al[65], Campanhilo et al[66], He et al[67], and Di Marco et al[68] |
| rs3218625G>A      | 1:186674409                   | Gastric     | A/G   | Promoter | Enhances activity of COX-2 in vitro by causing the transition of Gly to Aly | < 0.001 | 1.62 (1.02-2.56) | 0.039* | Zhang et al[55] and Zhang et al[65] |
| rs5277G>C         | 1:186679065                   | Gastric     | GC/GG | Exon   | - | 0.108 | 0.42 (0.13-1.28) | 0.127 | Hussain et al[69] |
| rs5278T>C         | 1:186675337                   | Gastric     | TC/TT | Exon   | - | 0.021 | 2.27 (0.53-9.69) | 0.270 | Hussain et al[69] |
| rs5279T>C         | 1:186675946                   | Gastric     | TC/TT | Exon   | - | 0.015 | 0.24 (0.08-0.73) | 0.012* | Hussain et al[69] |
| rs2745557G>A      | 1:186680089                   | Pancreatic  | A/G   | Intron | - | 0.164 | 0.94 (0.64-1.39) | 0.764 | Özhan et al[70] |
| rs2066826G>A      | 1:186676795                   | Pancreatic  | A/G   | Intron | - | 0.188 | 1.60 (1.06-2.40) | 0.026* | Özhan et al[70] |
| rs4648262G>T      | 1:186679617                   | Pancreatic  | T/G   | Intron | - | 0.001 | 0.62 (0.22-1.73) | 0.364 | Özhan et al[70] |
| rs4648298A>G      | 1:186672550                   | Colorectal  | G/A   | 3′-UTR | Creates a longer and possibly more stable species of mRNA | 0.021 | 0.44 (0.22-0.75) | 0.003* | Gholami et al[71], Mosallaei et al[72], and Cox et al[73] |
| rs5275T>C         | 1:186673926                   | Gastric     | C/T   | 3′-UTR | Stabilizes mRNA of COX-2 by potential miRNA-binding sites | 0.351 | 1.14 (1.01-1.29) | 0.030* | Piranda et al[16], Li et al[74], and Furuya et al[75] |
| rs689470T>C       | 1:186671926                   | Gastric     | TC/TT | 3′-UTR | Degradation of the mRNA | 0.039 | 7.49 (1.21-46.20) | 0.030* | Hussain et al[69] and Hu et al[76] |
| rs2206593A>G      | 1:186673297                   | Breast      | G/A   | 3′-UTR | - | 0.060 | 0.92 (0.84-1.91) | 0.088 | Li et al[77] |

*P < 0.05. SNP: Single nucleotide polymorphism; NPM: Nuceophosmin; P-NPM: Phosphorylated NPM; OR: Odds ratio; CI: Confidence interval; COX-2: Cyclooxygenase-2.

Infection, NF-κB activation, K-ras expression, and the dysregulation of some trans-acting regulatory factors) can lead to overexpression of COX-2 and more inflammation in neoplasia[20-23].

**H. pylori infection and COX-2 expression**

It is generally accepted that *H. pylori* infection is an important risk factor for gastric cancer and *H. pylori* has been classified as a class I carcinogen. *H. pylori* infection may...
Figure 2  General location of cyclooxygenase-2 single nucleotide polymorphisms searched by bioinformatics (based on The Cancer Genome Atlas, NCBI, and UCSC).

trigger various inflammatory pathways to increase cancer risk. A study has shown that 24 h after *H. pylori* infection of the MKN 28 cell line, the level of COX-2 mRNA transcription and PGE2 expression increased 5-fold and 3-fold, respectively[24]. However, the exact molecular mechanisms underlying the increased expression of COX-2 in gastric cancer patients with *H. pylori* infection remains unclear.

A study found that *H. pylori* infection stimulates Toll-like receptors (TLRs), to activate innate immunity and the COX-2/PGE2 pathway, which induces "infection-associated inflammation" [such as CXCL1, 2, and 5, CCL3 and 4, interleukin (IL)-11, IL-23, and tumor necrosis factor alpha (TNF-α)], to generate an inflammatory microenvironment and further lead to gastric tumorigenesis[25,26]. Another study using AGS gastric cancer cells showed that *H. pylori* (patient isolate) promotes COX-2 transcription, which may be due to the activation of mitogen-activated protein kinase (MAPK) pathways (ERK1/2, p38, and JNK) and the activation of cAMP response element (CRE) and AP-1 on the COX-2 promoter by TLR2/TRL9[27]. Jüttner et al[28] found that the binding of upstream stimulatory factor 1/2 (USF1 and 2) to the CRE/Ebox site of the COX-2 promoter promotes the upregulation of COX-2 after *H. pylori* infection. Another study demonstrated that *H. pylori* infection may lead to the phosphorylation of p38 MAPK and its downstream activating transcription factor 2 (ATF-2), which affects the expression of COX-2[29]. Some studies have pointed out that the expression of COX-2 is induced by NF-κB, which is recognized and activated by c-Src or TLR2/TRL9 and MAPK kinase kinase 14 (MAP3K = NIK)[30]. In addition, *H. pylori* infection promoted the secretion of gastrin, which extended the half-life of COX-2 mRNA and increased the expression of COX-2[31]. Semple et al[32] reported that gastrin upregulates the expression of COX-2 by CCK-2R-mediated JAK2/Stat3 and subsequent PI3K/Akt activation in gastric cancer cell lines. Meanwhile, *H. pylori* infection may also activate NF-κB, which can induce COX-2 expression[33]. Moreover, another study showed that eradication of *H. pylori* infection significantly reduced COX-2 expression[34].
| Drug               | Cancer type | Effect(s)                                                                 | Mechanism                                                                 | Ref.          |
|--------------------|-------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------|
| Celecoxib         | Gastric     | Inhibits tumor growth                                                     | Increases CD206 and activates macrophages                                 | Thiel et al[40]|
| Aspirin            | Gastric     | Induces apoptosis; inhibits proliferation; inhibits angiogenesis          | Acetylates the active site of COX-2; inhibits PG synthesis; activates caspase-8/Bid and caspase-3 | Liu et al[57], and Niikura et al[78] |
| Oxadiazole 10c    | Colon       | Increases antitumor activity; increases sensitivity                       | Docked into the COX-2 bind site                                          | El-Husseiny et al[79] |
| Celecoxib and platinum | Gastric     | Prolong overall survival and progression-free survival                    | -                                                                         | Guo et al[80]|
| Celecoxib and rapamycin | Gastric     | Increase sensitivity                                                      | Inhibit PI3K/AKT pathway                                                  | Cao et al[81]|
| Celecoxib and FOLFOX4 | Gastric     | Inhibit angiogenesis                                                       | Down-regulate VEGF level                                                  | Teloczko-Iwaniuk et al[82] |
| Celecoxib and erlotinib | Colorectal  | Reduce angiogenesis; inhibit formation; inhibit expansion                 | Inhibit EGFR signaling                                                   | Roberts et al[83] |
| Celecoxib and Curcumin | Hepatocellular | Inhibit angiogenesis; inhibit proliferation; induce apoptosis             | Inhibit Akt/NF-κB/PG2/ROS pathway; inhibit COX-2/PG2 pathway             | Abdallah et al[84] |
| Sorafenib and meloxicam | Hepatocellular | Inhibit tumor cell growth; inhibit proliferation; enhance apoptosis       | Activate endoplasmic reticulum stress; enhance the cytotoxicity           | Zhong et al[85]|
| Ferrocene derivatives | Breast/cervical | Suppress tumor growth; increase antiproliferative activity; induce apoptosis | Increase the levels of cytotoxicity and reactive oxygen species; reduce the level of PG2 | Ren et al[86], and Farzaneh et al[87] |

COX-2: Cyclooxygenase-2; PGs: Prostaglandins; PI3K: Phosphatidylinositot 3 kinase; Akt (PKB): Protein kinase B; VEGF: Vascular endothelial growth factor; PG2: Prostaglandin E2; ROS (MDA): Reactive oxygen species measured as malondialdehyde.

Noteworthy, COX-2 is overexpressed not only in *H. pylori* positive gastritis and gastric cancer, but also in precancerous lesions such as intestinal metaplasia and atrophic gastritis, suggesting that COX-2 plays a key role in the early gastric carcinogenesis[35,36]. These may be associated with individual genetic susceptibility, especially inflammatory genes, such as COX-2, IL-1β, and TNF-α gene polymorphisms in our previous reports[14,37].

**Inflammatory pathway of COX-2**

COX-2 is regulated by multiple pathways in gastric cancer cell lines. The pathway of COX-2/PG2 has been shown to play crucial roles in tumorigenesis by triggering the production of an inflammatory microenvironment[10,38,39]. However, the exact tumor-promoting mechanism of PGE2 remains unclear. It has been reported that TLR signaling through the adaptor molecule MyD88 induces the COX-2/PGE2 pathway to promote the occurrence of gastritis and gastric cancer[26]. Meanwhile, the expression of COX-2 was significantly reduced when NF-κB signal was blocked by chondroitin sulfate[40]. Some inflammatory cytokines, such as IL-6, IL-8, and TNF-α, can activate NF-κB to induce overexpression of COX-2[41].

It has also been reported that the expression of K-ras and the activation of matrix metalloproteinase-2 (MMP-2) and MMP-9 are significantly related to the increased expression of COX-2[42]. They may jointly promote the occurrence of gastric cancer, but the mechanism is not clear.

Recent studies suggest that the cooperation of the COX-2/PGE2 pathways and TLR/MyD88 signaling through NF-κB activation is crucial in tumorigenesis[26]. Some genetic studies have shown that the activation of carcinogenic Wnt is related to the occurrence of gastric tumors induced by COX-2[10,38]. In the TCGA database, the Wnt signal and the NF-κ B and COX-2 inflammatory pathways were observed to be activated simultaneously in intestinal gastric cancer[26]. The adenomatous polyposis coli (APC) regulates the expression of COX-2 through a β-catenin-independent mechanism[43]. Inducible nitric oxide synthase (iNOS) can increase the activity of COX-2 to upregulate the production of PGs[44].

These results suggest that COX-2 promotes the occurrence of cancer through induction of various inflammatory pathway signaling and generation of an inflammatory microenvironment (Figure 3).
Figure 3 Schematic representation of interactions in regulation of cyclooxygenase-2 to generate an inflammatory microenvironment that has been described in the review. The active pathway of Helicobacter pylori infection is shown on the right. TLR: Toll-like receptor; NF-κB: Nuclear factor κB; PGE2: Prostaglandin E2; EP4: Prostaglandin E receptor subtype 4; C-Src: Cellular src; Akt: Protein kinase B; AP-1: Activator protein 1; MEK1: MAP kinase kinase 1; USF: Upstream stimulatory factor; NIK: Mitogen-activated protein kinase kinase kinase 14; Inos: Inducible nitric oxide synthase; MAPK: Mitogen-activated protein kinase; ATF-2: Activating transcription factor 2; TNF-α: tumor necrosis factor-α; IL: Interleukin; CXCL: Chemokine (CXC motif) ligand; CCL: Chemokine (C-C motif) ligand; COX-2: Cyclooxygenase-2.

ROLE OF COX-2 IN CANCER PREVENTIONS AND THERAPEUTICS

Epidemiological studies have indicated that the application of COX-2 inhibitors can reduce the inflammatory response and suppresses gastrointestinal cancerization. It may be an effective and crucial target to treat patients with atrophic gastritis and reduce the risk of Helicobacter pylori-related gastric cancer[22,45]. The use of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin can reduce the risk of malignant tumors of the digestive system by blocking the effect of COX-2[46].

NSAIDs can reduce the number and size of colorectal carcinomas in patients with familial adenomatous polyposis. Celecoxib, an selective COX-2 inhibitor, and NSAID can also reduce the occurrence of digestive system cancers, such as inhibiting the proliferation of gastric, esophageal, and colorectal cancer cells[47,48]. It is estimated that long-term use of NSAIDs can reduce the incidence of colon cancer by 40%-50% [49]. However, studies have shown that the use of NSAIDs is not an effective chemoprophylaxis for all cancer patients, as aspirin has no effect on the incidence of colorectal adenoma or cancer in patients with Lynch syndrome[50]. Therefore, the combined use of COX-2 inhibitors and the development of new inhibitors have gradually emerged and have better antitumor activity. More detailed results are shown in Table 2. Moreover, clinical use of COX-2 inhibitors to prevent or treat gastric cancer may be limited because of potential side effects, especially in the cardiovascular system, such as elevated blood pressure and myocardial infarction[51,52]. Recently, a systematic review of 329 studies suggested that in addition to COX-2-selective inhibitors, NSAIDs also increase the risk of cardiovascular morbidity[53]. These side effects and low
treatment efficacy hinder the application of NSAIDs and COX-2 selective inhibitors as chemopreventive drugs to prevent cancer. At the same time, a study indicated that the combined regulation of the inflammatory microenvironment by inhibiting the COX-2/PGE2 and TLR/MyD88 pathways may be an effective strategy to prevent or treat the development and malignant progression of gastrointestinal cancer, especially those with p53 gain-of-function mutations[54]. Therefore, targeting the COX-2/PGE2 pathway combined with TLR/MyD88 signal pathway may inhibit the inflammatory microenvironment and the stemness of gastric tumor cells, which may be an effective strategy for the prevention and treatment of gastric cancer and needs further clinical evaluation[26]. In addition, as the information of genetic susceptibility and COX-2 SNPs may have the potential to establish risk stratified markers in the general population, it is helpful for early screening and treatment of precancerous lesions in high-risk population groups to reduce the incidence of gastric cancer and avoid unnecessary treatment.

CONCLUSION

It has been established that the expression of COX-2 in gastric cancer cells is induced by various pathways including *H. pylori* infection and COX-2 overexpression results in the generation of an inflammatory microenvironment to promote the occurrence of gastric carcinomas. The polymorphisms including rs689466G>A, rs20417G>C, rs3218625G>A, rs5275T>C, and rs689470T>C in COX-2 confer individuals a higher susceptibility to gastric cancer. NSAIDs can reduce the risk of digestive system malignant tumors. In addition, the combined regulation of the COX-2/PGE2 and TLR/MyD88 signaling pathways may be an effective strategy to prevent or treat the occurrence and development of gastrointestinal tumors. However, these treatments may increase the incidence of cardiovascular diseases. The above results encourage further functional research to find more accurate individualized prevention strategies and better therapies for gastric cancer.

ACKNOWLEDGEMENTS

The authors express their gratitude to Dr. Liu M and Dr. Zhang X for giving excellent advice for modification.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca Cancer J Clin* 2018; 68: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
2. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, Gavin A, Visser O, Bray F. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer* 2018; 103: 356-387 [PMID: 30100160 DOI: 10.1016/j.ejca.2018.07.005]
3. Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *J Clin Oncol* 2006; 24: 2903-2909 [PMID: 16762930 DOI: 10.1200/jco.2005.05.0245]
4. Duan F, Song C, Zhang J, Wang P, Ye H, Dai L, Wang K. Evaluation of the Epidemiologic Efficacy of Eradicating Helicobacter pylori on Development of Gastric Cancer. *Epidemiol Rev* 2019; 41: 97-108 [PMID: 31497856 DOI: 10.1093/epirev/mxz006]
5. Jin G, Lv J, Yang M, Wang M, Zhu M, Wang T, Yan C, Yu C, Ding Y, Li G, Ren C, Ni J, Zhang R, Guo Y, Bian Z, Zheng Y, Zhang N, Jiang Y, Chen J, Wang Y, Xu D, Zheng H, Yang L, Chen Y, Walters R, Millwood Y, Dai J, Ma H, Chen K, Chen Z, Hu Z, Wei Q, Shen H, Li L. Genetic risk, incident gastric cancer, and healthy lifestyle: a meta-analysis of genome-wide association studies and prospective cohort study. *Lancet Oncol* 2020; 21: 1378-1386 [PMID: 33002439 DOI: 10.1016/S1470-2045(20)30460-5]
6. Clemente M, Sánchez-Archidona AR, Sardón D, Diez L, Martin-Ruiz A, Caceres S, Sassi F, Dolores Pérez-Alenza M, Illera JC, Dunner S, Peña L. Different role of COX-2 and angiogenesis in canine inflammatory and non-inflammatory mammary cancer. *Vet J* 2013; 197: 427-432 [PMID: 23489848 DOI: 10.1016/j.tvjl.2013.02.009]
7. Liu D, He Q, Liu C. Correlations among Helicobacter pylori infection and the expression of cyclooxygenase-2 and vascular endothelial growth factor in gastric mucosa with intestinal metaplasia or dysplasia. *J Gastroenterol Hepatol* 2010; 25: 795-799 [PMID: 20492336 DOI: ]
Ji XK et al. Role of cyclooxygenase-2 in gastric cancer

10.1111/j.1440-1746.2009.06168.x]

8 Hamy AS, Tury S, Wang X, Gao J, Pierga JY, Giacchetti S, Brain E, Pistilli B, Marty M, Esopié M, Benchimol G, Laas E, Laié M, Asselan B, Aouchiche B, Edelman M, Reyal F. Celecoxib With Neoadjuvant Chemotherapy for Breast Cancer Might Worsen Outcomes Differentially by COX-2 Expression and ER Status: Exploratory Analysis of the REMAGUS02 Trial. J Clin Oncol 2019; 37: 224-235 [PMID: 30702971 DOI: 10.1200/JCO.2018.03.0863]

9 Zhou TJ, Zhang SL, He CY, Zhuang QY, Han PY, Jiang SW, Yao H, Huang YJ, Ling WH, Lin YC, Lin ZN. Downregulation of mitochondrial cyclooxygenase-2 inhibits the stemness of nasopharyngeal carcinoma by decreasing the activity of dynamin-related protein 1. Theranostics 2017; 7: 1389-1406 [PMID: 28435473 DOI: 10.7150/thno.17647]

10 Oshima H, Matsunaga A, Fujimura T, Tsukamoto T, Takeko MM, Oshima M. Carcinogenesis in mouse stomach by simultaneous activation of the Wnt signaling and prostaglandin E2 pathway. Gastroenterology 2006; 131: 1086-1095 [PMID: 17030179 DOI: 10.1053/gastro.2006.07.014]

11 Grivennikov S, Karin E, Terzic J, Mucida D, Yu GY, Vallabhappurapu S, Scheller J, Rose-John S, Cheroutre H, Eckmann L, Karin M. IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. Cancer Cell 2009; 15: 103-112 [PMID: 19185845 DOI: 10.1016/j.ccr.2009.01.001]

12 Bollrath J, Phesse TJ, von Burstin VA, Putoczki T, Bennecke M, Bateman T, Nebelsiek T, Lundgren-May T, Canli O, Schiwatalla S, Matthews V, Schmid RM, Kirchner T, Arkan MC, Ernst M, Grendt FR. gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. Cancer Cell 2009; 15: 91-102 [PMID: 19185844 DOI: 10.1016/j.ccr.2009.01.002]

13 Papafili A, Hill MR, Brull DJ, McNulty R, Marshall RP, Humphries SE, Laurent GJ. Common promoter variant in cyclooxygenase-2 represses gene expression: evidence of role in acute-phase inflammatory response. Arterioscler Thromb Vasc Biol 2002; 22: 1631-1636 [PMID: 12377741 DOI: 10.1161/01.ATV.0000030430.80207.e5]

14 Li Y, Dai L, Zhang J, Wang P, Chai Y, Ye H, Wang K. Cyclooxygenase-2 polymorphisms and the risk of gastric cancer in various degrees of relationship in the Chinese Han population. Oncol Lett 2012; 3: 107-112 [PMID: 22740864 DOI: 10.3892/ol.2011.426]

15 Zhang X, Xiao X, Tan W, Ning B, Liu Z, Hong Y, Song W, Guo Y, Zhang X, Shen Y, Qiang B, Kadlubar FF, Lin D. Identification of functional genetic variants in cyclooxygenase-2 and their association with risk of esophageal cancer. Gastroenterology 2005; 129: 565-576 [PMID: 16083713 DOI: 10.1053/j.gastro.2005.05.003]

16 PirandA DN, Abreu RBV, Freitas-Alves DR, de Carvalho MA, Vianna-Jorge R. Modulation of the prostaglandin-endoperoxide synthase 2 gene expression by variant haplotypes: influence of the 3'-untranslated region. Braz J Med Biol Res 2017; 51: e6546 [PMID: 29221250 DOI: 10.1590/1414-431X20176546]

17 Liu H, Pan K, Zhang X, Zhang Y, Zhang L, Ma J, Dong C, Shen L, Li J, Deng D, Lin D, You W. Genetic variants in cyclooxygenase-2: Expression and risk of gastric cancer and its precursors in a Chinese population. Gastroenterology 2006; 130: 1975-1984 [PMID: 16762620 DOI: 10.1053/j.gastro.2006.03.021]

18 Wu WK, Sung JJ, Yu L, Li ZJ, Chu KM, Cho CH. Constitutive hypophosphorylation of extracellular signal-regulated kinases-1/2 and down-regulation of c-Jun in human gastric adenocarcinoma. Biochem Biophys Res Commun 2008; 373: 330-334 [PMID: 18570890 DOI: 10.1016/j.bbrc.2008.06.025]

19 Brodie AM, Lu Q, Long BJ, Fulton A, Chen T, Macpherson N, DeJong PC, Blankenstain MA, Nortier JW, Sree PH, van de Ven J, van Gorp JM, Elbers JR, Schipper ME, Blijham GH, Thijssen JH. Aromatase and COX-2 expression in human breast cancers. J Steroid Biochem Mol Biol 2001; 79: 41-47 [PMID: 11850206 DOI: 10.1006/jsbm.2000.0311-5]

20 Dai M, Hu S, Liu CF, Jiang L, Yu W, Li ZL, Guo W, Tang R, Dong CY, Wu TH, Deng WG. BPTF cooperates with p50 NF-kB to promote COX-2 expression and tumor cell growth in lung cancer. Am J Transl Res 2019; 11: 7398-7409 [PMID: 31934287]

21 Cheng J, Fan XM. Role of cyclooxygenase-2 in gastric cancer development and progression. World J Gastroenterol 2013; 19: 7361-7368 [PMID: 24259966 DOI: 10.3748/wjg.v19.i42.7361]

22 Ren J, Liu J, Sui X. Correlation of COX-2 and MMP-13 expressions with gastric cancer and their effects on prognosis. J BUON 2019; 24: 187-193 [PMID: 30941909]

23 Clemente SM, Martinez-Costa OH, Monsalve M, Samihan-Arias AK. Targeting Lipid Peroxidation for Cancer Treatment. Molecules 2020; 25 [PMID: 33167334 DOI: 10.3390/molecules25215144]

24 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 [PMID: 11380326 DOI: 10.1046/j.1365-2036.2001.00965.x]

25 Wang K, Karin M. Tumor-Elicited Inflammation and Colorectal Cancer. Adv Cancer Res 2015; 128: 173-196 [PMID: 26216633 DOI: 10.1016/bs.acr.2015.04.014]

26 Echizen K, Hirose O, Maeda Y, Oshima M. Inflammation in gastric cancer: Interplay of the COX-2/prostaglandin E2 and Toll-like receptor/MyD88 pathways. Cancer Sci 2016; 107: 391-397 [PMID: 27079437 DOI: 10.1111/cas.12901]

27 Chang YJ, Wu MS, Lin JT, Sheu BS, Muta T, Inoue H, Chen CC. Induction of cyclooxygenase-2 overexpression in human gastric epithelial cells by Helicobacter pylori involves TLR2/TLR9 and c-Src-dependent nuclear factor-kappaB activation. Mol Pharmacol 2004; 66: 1465-1477 [PMID: 15456896 DOI: 10.1124/mol.104.005199]
Jüttner S, Cramer T, Wessler S, Walduck A, Gao F, Schmitz F, Wunder C, Weber M, Fischer SM, Schmidt WE, Wiedenmann B, Meyer TF, Naumann M, Höcker M. Helicobacter pylori stimulates host cyclooxygenase-2 gene transcription: critical importance of MEK/ERK-dependent activation of USF1/-2 and CREB transcription factors. Cell Microbiol 2003; 5: 821-834 [PMID: 14531897 DOI: 10.1046/j.1462-5822.2003.00324.x]

Li Q, Liu N, Shen B, Zhou L, Wang Y, Sun J, Fan Z, Liu RH. Helicobacter pylori enhances cyclooxygenase-2 expression via p38MAPK/ATF-2 signaling pathway in MKN45 cells. Cancer Lett 2009; 278: 97-103 [PMID: 19201083 DOI: 10.1016/j.canlet.2008.12.032]

Chang YJ, Wu MS, Lin JT, Chen CC. Helicobacter pylori-Induced invasion and angiogenesis of gastric cancer is mediated by cyclooxygenase-2 induction through TLR2/TLR9 and promoter regulation. J Immunol 2005; 175: 8242-8252 [PMID: 16339564 DOI: 10.4049/jimmunol.175.12.8242]

Subramaniam D, Ramalingam S, May R, Dieckgraefe BK, Berg DE, Pothoulakis C, Houchen CW, Wang TC, Antan S. Gastrin-mediated interleukin-8 and cyclooxygenase-2 gene expression: differential transcriptional and posttranscriptional mechanisms. Gastroenterology 2008; 134: 1070-1082 [PMID: 18395088 DOI: 10.1053/j.gastro.2008.01.040]

Semple G, Ryder H, Rooker DP, Batt AR, Kendrick DA, Szeli M, Olta M, Satoh M, Nishida A, Akuzawa S, Miyata K. (3R)-N-(1-tert-butylcarboxymethyl)-2,3-dihydro-2-oxo-5-(2-pyridyl)-1H-1,4-benzodiazepin-3-yl-N'-(3-(methylamino)phenyl)urea [YF476]: a potent and orally active gastric CCK-B antagonist. J Med Chem 1997; 40: 331-341 [PMID: 9022799 DOI: 10.1021/jm960669-1]

Konturek PC, Konturek SJ, Brzozowski T. Helicobacter pylori infection in gastric carcinogenesis. J Physiol Pharmacol 2009; 60: 3-21 [PMID: 19826177]

Konturek PC, Rembiasz K, Konturek SJ, Stachura J, Bielsanski W, Galuschka K, Karcz D, Hahn EG. Gene expression of ornithine decarboxylase, cyclooxygenase-2, and gastrin in atrophic gastric mucosa infected with Helicobacter pylori before and after eradication therapy. Dig Dis Sci 2003; 48: 36-46 [PMID: 12645788 DOI: 10.1023/a:1021774029089]

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: 12860-12873 [PMID: 25278683 DOI: 10.3748/wjg.v20.i36.12860]

Nardone G, Rocco A, Vaira D, Staibano S, Budillon A, Tatangelo F, Sciulli MG, Perna F, Salvatore G, Di Benedetto M, De Rosa G, Patrignani P. Expression of COX-2, mPGE-synthase1, MDR-1 (P-gp), and Bcl-xL: a molecular pathway of H pylori-related gastric carcinogenesis. Cancer Sci 2009; 100: 1032-1041 [PMID: 19540665 DOI: 10.1111/j.1349-7006.2009.01258.x]

Oshima H, Oshima M. The inflammatory network in the gastrointestinal tumor microenvironment: lessons from model systems. J Gastroenterol 2012; 47: 97-106 [PMID: 22212104 DOI: 10.1007/s00347-011-0523-6]

Dicken BJ, Graham K, Hamilton SM, Andrews S, Lai R, Listgarten J, Jiangri GS, Saunders LD, Damaraju S, Cass C. Lymphovascular invasion is associated with poor survival in gastric cancer: an application of gene-expression and tissue array techniques. Ann Surg 2006; 243: 64-73 [PMID: 16371738 DOI: 10.1097/01.sla.0000194087.96582.3e]

Wu WK, Sung JI, Lee CW, Yu J, Cho CH. Cyclooxygenase-2 in tumorigenesis of gastrointestinal cancers: an update on the molecular mechanisms. Cancer Lett 2010; 295: 7-16 [PMID: 20381235 DOI: 10.1016/j.canlet.2010.03.015]

Kim SF, Huri DA, Snyder SH. Inducible nitric oxide synthase binds, S-nitrosylates, and activates cyclooxygenase-2. Science 2005; 310: 1966-1970 [PMID: 16373578 DOI: 10.1126/science.1119407]

Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. Br J Cancer 2009; 100: 551-557 [PMID: 19156150 DOI: 10.1038/sj.bjc.6604880]
clinical study. J Cancer Res Clin Oncol 2015; 141: 1221-1235 [PMID: 25257419 DOI: 10.1007/s00432-014-1892-z]

48 Thompson PA, Ashbeck EL, Roe DJ, Fales L, Buckmeier J, Wang F, Bhattacharyya A, Hsu CH, Chow SH, Ahnjen DJ, Boland CR, Heigh RI, Fay DE, Hamilton SR, Jacobs ET, Martinez EM, Alberts DS, Lance P. Celecoxib for the Prevention of Colorectal Adenomas: Results of a Suspended Randomized Controlled Trial. J Natl Cancer Inst 2016; 108 [PMID: 27530636 DOI: 10.1093/jnci/djv151]

49 Peak RM Jr. Prevention of colorectal cancer through the use of COX-2 selective inhibitors. Cancer Chemother Pharmacol 2004; 54 Suppl 1: S50-S56 [PMID: 15309515 DOI: 10.1007/s00280-004-0887-x]

50 Burn J, Bishop DT, Mecklin JP, Macrae F, Möslin G, Olschwang S, Bisgaard ML, Ramesar R, Eccles D, Maher ER, Bertario L, Jarvinen HJ, Lindblom A, Evans DG, Lubinski J, Morrison PJ, Ho JW, Vasan HF, Side L, Thomas HJ, Scott RJ, Dunlop M, Barker G, Elliott F, Jass JR, Fodder R, Lynch HT, Mathers JC; CAPP2 Investigators. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. N Engl J Med 2008; 359: 2567-2578 [PMID: 19073976 DOI: 10.1056/NEJMoa0801297]

51 Antman EM. Evaluating the Cardiovascular Safety of Nonsteroidal Anti-Inflammatory Drugs. Circulation 2017; 135: 2062-2072 [PMID: 2853319 DOI: 10.1161/CIRCULATIONAHA.117.027288]

52 Fanelli A, Ghisi D, Aprile PL, Lapi F. Cardiovascular and cerebrovascular risk with nonsteroidal anti-inflammatory drugs and cycloxygenase 2 inhibitors: latest evidence and clinical implications. Ther Adv Drug Saf 2017; 8: 173-182 [PMID: 28607667 DOI: 10.1177/2042098616690485]

53 Szeto CC, Sugano K, Wang JG, Fujimoto K, Whittle S, Modi GK, Chen CH, Park JB, Tam LS, Vareesangthip K, Tsoi KKF, Chan FKL. Non-steroidal anti-inflammatory drug (NSAID) therapy in patients with hypertension, cardiovascular, renal or gastrointestinal comorbidities: joint APAGE/APLAR/APSDE/APSH/APSN/PoA recommendations. Gut 2020; 69: 617-629 [PMID: 31937550 DOI: 10.1136/gutjnl-2019-139300]

54 Echizen K, Oshima H, Nakayama M, Oshima M. The inflammatory microenvironment that promotes gastrointestinal cancer development and invasion. Adv Biol Regul 2018; 6: 39-45 [PMID: 29428221 DOI: 10.1016/j.bior.2018.02.001]

55 Zhang X, Zhong R, Zhang Z, Yuan J, Liu L, Wang Y, Kadlubar F, Seng F, Miao X. Interaction of cyclooxygenase-2 promoter polymorphisms with Helicobacter pylori infection and risk of gastric cancer. Mol Carcinog 2011; 50: 876-883 [PMID: 21538574 DOI: 10.1002/mc.20784]

56 Lopes C, Pereira C, Farinha M, Medeiros R, Dinis-Ribeiro M. Genetic Variations in Prostaglandin E2 Pathway Identified as Susceptibility Biomarkers for Gastric Cancer in an Intermediate Risk European Country. Int J Mol Sci 2021; 22 [PMID: 33440718 DOI: 10.3390/ijms2205484]

57 Liu Y, Sun H, Hu M, Zhang Y, Chen S, Tighe S, Zhu Y. The Role of Cyclooxygenase-2 in Colorectal Carcinogenesis. Curr Colorectal Cancer 2017; 16: 165-172 [PMID: 27810226 DOI: 10.1016/j.ccc.2016.09.012]

58 Shin WG, Kim HJ, Cho SJ, Kim HS, Kim KH, Jang MK, Lee JH, Kim HY. The COX-2-1195AA Genotype Is Associated with Diffuse-Type Gastric Cancer in Korea. Gut Liver 2012; 6: 321-327 [PMID: 22844559 DOI: 10.5009/gnl.2012.6.3.321]

59 Guo CC, Wei N, Liang SH, Wang BL, Sha SM, Wu KC. Population-specific genome-wide mapping of expression quantitative trait loci in the colon of Han Chinese. J Dig Dis 2016; 17: 600-609 [PMID: 27534592 DOI: 10.1111/1751-2980.12399]

60 Zamudio R, Pereira L, Rocha CD, Berg DE, Muniz-Queiroz T, Sant Anna HP, Cabrera L, Combe JM, Herrera P, Jahuira MH, Leão FB, Lyon F, Rodrigues MR, Rodrigues-Soares F, Thompson PA, Sanchez-Escobar L, De Leng WW, Polak M, Morsink FM, Bakker O, Maciejewski R, Offerhaus GJ, Fanelli A, Echizen K, Ashbeck EL, Roe DJ, Fales L, Buckmeier J, Wang F, Bhattacharyya A, Hsu CH, Chow SH, Ahnjen DJ, Boland CR, Heigh RI, Fay DE, Hamilton SR, Jacobs ET, Martinez EM, Alberts DS, Lance P. Celecoxib for the Prevention of Colorectal Adenomas: Results of a Suspended Randomized Controlled Trial. J Natl Cancer Inst 2016; 108 [PMID: 27530636 DOI: 10.1093/jnci/djv151]

61 Luo MX, Long BB, Li F, Zhang C, Pan MT, Huang YQ, Chen B. Roles of Cyclooxygenase-2 gene -765G>C (rs20417) and -1195G>A (rs689466) polymorphisms in gastric cancer: A systematic review and meta-analysis. Gene 2019; 685: 125-135 [PMID: 30391440 DOI: 10.1016/j.gene.2018.10.077]

62 Sitarz R, Leguit RJ, de Leng WW, Polak M, Morsink FM, Bakker O, Maciejewski R, Offerhaus GJ, Milne AN. The COX-2 promoter polymorphism -765 G>C is associated with early-onset, conventional and stump gastric cancers. Mod Pathol 2008; 21: 685-690 [PMID: 18311113 DOI: 10.1038/modpathol.2008.36]

63 Saxena A, Prasad KN, Ghoshal UC, Bhagat MR, Krishnani N, Huisain N. Polymorphism of -765G>C COX-2 is a risk factor for gastric adenocarcinoma and peptic ulcer disease in addition to H pylori infection: a study from northern India. World J Gastroenterol 2008; 14: 1498-1503 [PMID: 18330937 DOI: 10.3748/wjg.14.1498]

64 Hou L, Grolli P, Zhu ZZ, Lisowska J, Yeager M, Zatonski W, Zhu G, Baccarelli A, Chanock SJ, Fraumeni JF Jr, Chow WH. COX1 and COX2 polymorphisms and gastric cancer risk in a Polish population. Anticancer Res 2007; 27: 4243-4247 [PMID: 18214026]

65 Zhang XM, Zhong R, Liu L, Wang Y, Yuan JX, Wang P, Sun C, Zhang Z, Song WG, Miao XP. Smoking and COX-2 functional polymorphisms interact to increase the risk of gastric cardia adenocarcinoma in Chinese population. PLoS One 2011; 6: e21894 [PMID: 21779349 DOI: 10.1371/journal.pone.0021894]
Zhong J, Dong X, Wang F, Wei H, Wang X, Xu Z, Liu F, Li J. Meloxicam inhibition of the Cbl-b-regulated PI3K/Akt pathway. *Cancer Res* 2015; 75: 3639-3649 [PMID: 25949619]

Li Q, Wang J, Liu M, Wang Y, Chen Z, Ye Y, Guan Q, Zhou Y. A comprehensive evaluation of clinical efficacy and safety of celecoxib in combination with chemotherapy in metastatic or advanced colorectal cancer patients: A phase III, randomized, double-blind, placebo-controlled trial. *Eur J Med Chem* 2017; 133: 104-113 [PMID: 28573530]

Cao Y, Qu J, Li C, Yang D, Hou K, Zheng H, Liu Y, Qu X. Celecoxib sensitizes gastric cancer to rapamycin via inhibition of the Cbl-b-regulated PI3K/Akt pathway. *Tumour Biol* 2015; 36: 5607-5615 [PMID: 25701378]

Tocelozi-Iwaniuk N, Dzieniawska-Kota D, Nowaszkiewicz K, Mityk W, Celecoxib in Cancer Therapy and Prevention - Review. *Curr Drug Targets* 2019; 20: 302-315 [PMID: 30073924] DOI: 10.2174/13894501196661809213121737

Roberts RB, Min L, Washington MK, Olsen SJ, Settle SH, Coffey RJ, Threadgill DW. Importance of epidermal growth factor receptor signaling in establishment of adenomas and maintenance of carcinomas during intestinal tumorigenesis. *Proc Natl Acad Sci USA* 2002; 99: 1521-1526 [PMID: 11818587] DOI: 10.1073/pnas.023795099

Abdallah FM, Helmy MW, Katary MA, Ghoneim AI. Synergistic antiproliferative effects of curcumin and celecoxib in hepatocellular carcinoma HepG2 cells. *Naunyn Schmiedebergs Arch Pharmacol* 2018; 391: 1399-1410 [PMID: 30155693] DOI: 10.1007/s00210-018-1557-6

Zhong J, Xia P, Dong X, Wang F, Wei H, Wang X, Xu Z, Liu F, Li T, Wang Y, Li J. Meloxicam...
combined with sorafenib synergistically inhibits tumor growth of human hepatocellular carcinoma cells via ER stress-related apoptosis. *Oncof Rep* 2015; 34: 2142-2150 [PMID: 26252057 DOI: 10.3892/or.2015.4181]

86 Ren SZ, Wang ZC, Zhu D, Zhu XH, Shen FQ, Wu SY, Chen JJ, Xu C, Zhu HL. Design, synthesis and biological evaluation of novel ferrocene-pyrazole derivatives containing nitric oxide donors as COX-2 inhibitors for cancer therapy. *Eur J Med Chem* 2018; 157: 909-924 [PMID: 30149323 DOI: 10.1016/j.ejmech.2018.08.048]

87 Farzaneh S, Zeinalzadeh E, Daraei B, Shahhosseini S, Zarghi A. New Ferrocene Compounds as Selective Cyclooxygenase (COX-2) Inhibitors: Design, Synthesis, Cytotoxicity and Enzyme-inhibitory Activity. *Anticancer Agents Med Chem* 2018; 18: 295-301 [PMID: 28971779 DOI: 10.2174/1871520617666171003145533]
