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MINIREVIEWS

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

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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

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treatment efficacy, new therapeutic approaches and early screening strategies are urgently needed. Some studies have shown that genetic variation in *COX-2* also play an important role in carcinogenesis. However, the genetic variation analysis in these studies is incomplete and isolated, pointing out only a few single nucleotide polymorphisms (SNPs) and the risk of gastric cancer, and no comprehensive study covering the whole gene region has been carried out. In addition, copy number variation (CNV) is not mentioned. 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. Results suggest that *COX-2* does not increase its expression through the CNV and the SNPs in *COX-2* may serve as the potential marker to establish risk stratification in the general population. This review synthesizes emerging insights of COX-2 as a biomarker in multiple studies, summarizes the association between whole *COX-2* sequence variation and susceptibility to gastric cancer, and discusses the future prospect of therapeutic intervention, which will be helpful for early screening and further research to find new approaches to gastric cancer treatment.

Key Words: Cyclooxygenase-2; Inflammation; Genetic variant; Gastric cancer; Prostaglandin E2

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.

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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 Asian 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. We will also discuss the crucial role of *COX-2* in the occurrence of gastric cancer and its mechanisms.

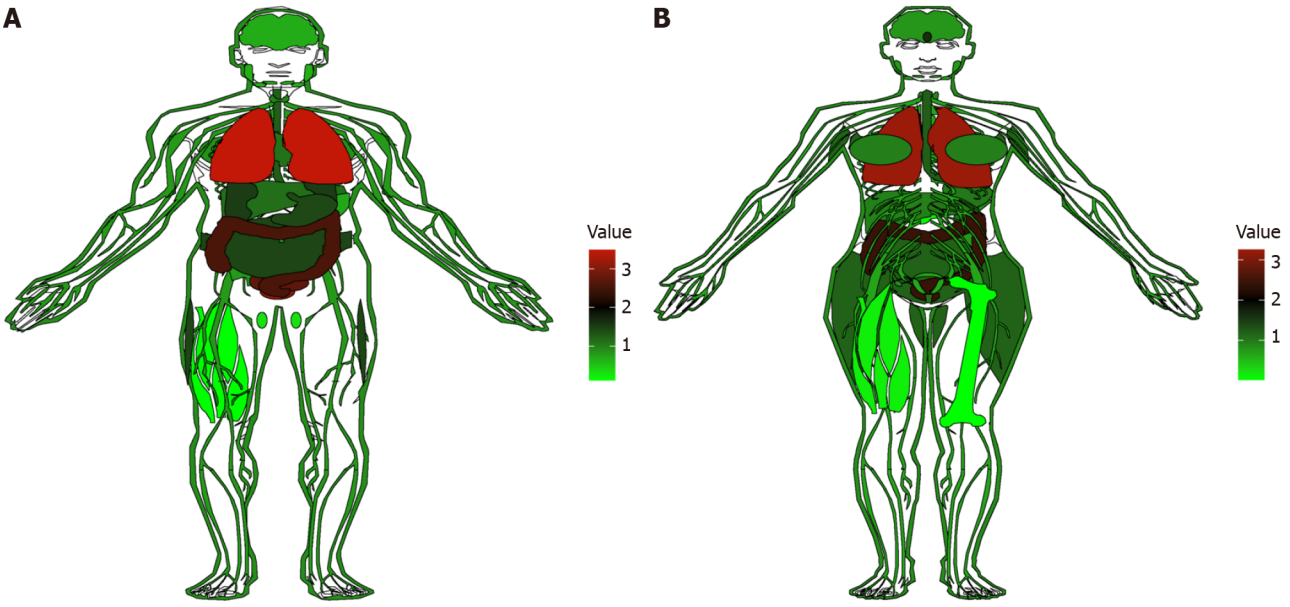

Figure 1 Visualization of cyclooxygenase-2 expression in normal tissues from the genotypic tissue expression database. The red parts indicate the organs with more cyclooxygenase-2 distribution, while the green parts indicate less distribution. A: Distribution of expression in males; B: Distribution of expression in females.

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-κB), 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-κB 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://grch37.ensembl.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 $r^2 < 0.8$. 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[13]. 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 conferred 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 GC 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 c-MYB 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[a]	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 Luo *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[a]	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], Campanholo *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[a]	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	1:186676537	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[a]	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[a]	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 (0.25-0.75)	0.003[a]	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[a]	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[a]	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]

[a]$P < 0.05$. 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

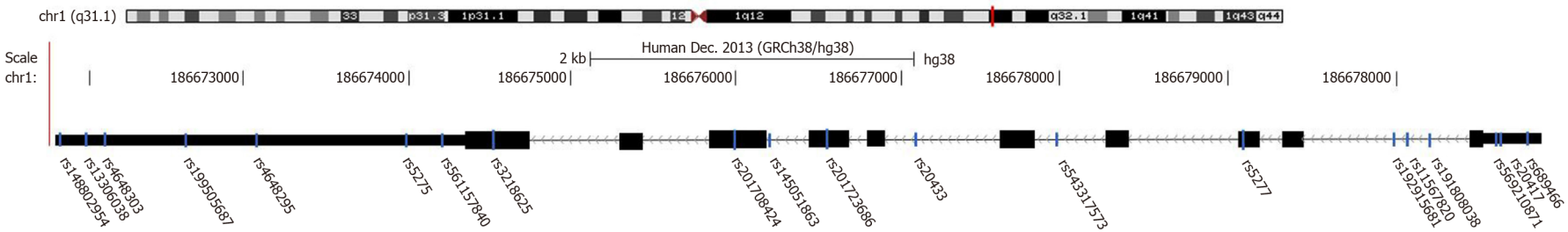

Figure 2 General location of cyclooxygenase-2 single nucleotide polymorphisms searched by bioinformatics (based on The Cancer Genome Atlas, NCBI, and UCSC).

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/TLR9 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].

Table 2 Application of cyclooxygenase-2 inhibitors in cancer

Drug	Cancer type	Effect(s)	Mechanism	Ref.
Celecoxib	Gastric	Inhibits tumor growth	Increases CD206 and activates macrophages	Thiel *et al*[46]
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	Tołoczko-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/PGE2/ROS pathway; inhibit COX-2/PGE2 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 PGE2	Ren *et al*[86], and Farzaneh *et al*[87]

COX-2: Cyclooxygenase-2; PGs: Prostaglandins; PI3K: Phosphatidylinositol 3 kinase; Akt (PKB): Protein kinase B; VEGF: Vascular endothelial growth factor; PGE2: 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-1b*, 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/PGE2 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).

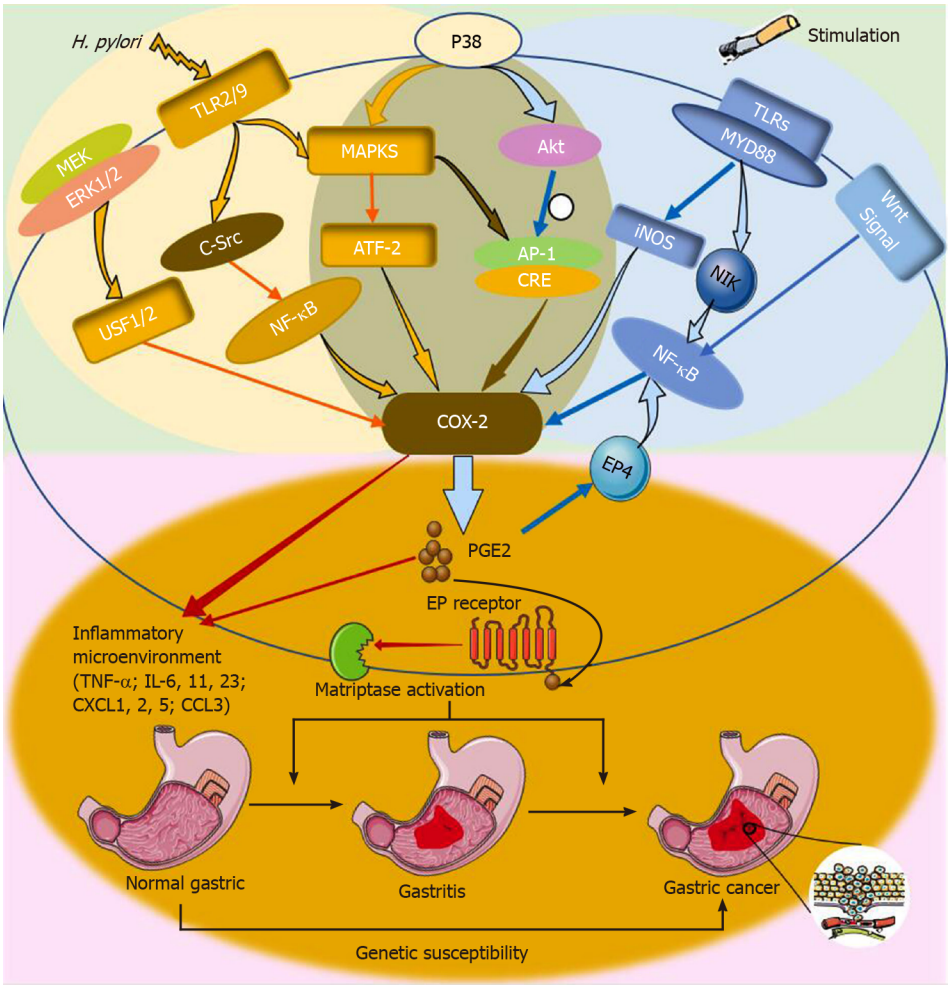

Figure 3 Schematic representation of interactions in regulation of cyclooxygenase-2 to generate an inflammatory microenvironment that has been described in the review. The active pathway of *Helicobacter pylori* infection is shown on the right. TLR: Toll-like receptor; NF-κB: Nuclear factor κB; PGE2: 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 *H. 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.

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