

Role of cyclooxygenase-2 in gastric cancer development and progression

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Abstract

Although the incidence of gastric cancer has been declining in recent decades, it remains a major public health issue as the second leading cause of cancer death worldwide. In China, gastric cancer is still the main cause of death in patients with malignant tumors. Most patients are diagnosed at an advanced stage and mortality is high. Cyclooxygenase-2 (COX-2) is a rate-limiting enzyme in prostanoid synthesis and plays an important role in the development and progression of gastric cancer. The expression of COX-2 in gastric cancer is upregulated and its molecular mechanisms have been investigated. *Helicobacter pylori* infection, tumor suppressor gene mutation and the activation of nuclear factor-kappa B may be responsible for the elevated expression of COX-2 in gastric cancer. The mechanisms of COX-2 in the development and progression of gastric cancer are probably through promoting the proliferation of gastric cancer cells, while inhibiting apoptosis, assisting angiogenesis and lymphatic metastasis, and participating in cancer invasion and immunosuppression. This review is intended to discuss, comment and summarize recent research progress on the role of COX-2 in gastric cancer development and progression, and elucidate the

molecular mechanisms which might be involved in the carcinogenesis.

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Key words: Cyclooxygenase-2; Gastric cancer; Prostaglandin; Carcinogenesis; Molecular mechanism

Core tip: Cyclooxygenase-2 (COX-2) plays an important role in gastric cancer development and progression. The present review aims to determine the molecular mechanism of COX-2 overexpression in gastric cancer and focus on the detailed information on COX-2 involved in carcinogenesis. By reviewing research progress, this may be helpful in clarifying the internal relationship of the afore-mentioned aspects.

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INTRODUCTION

Gastric cancer is one of the most common malignant tumors worldwide, and the morbidity and mortality associated with this disease are ranked second highest of all malignant neoplasms^[1-3]. In China, the incidence of gastric cancer has been declining in recent years^[4]. Since 75% of gastric cancer patients are diagnosed at an advanced stage and cannot be cured merely by surgery, chemotherapy combined with surgery is often the primary treatment. There are many factors that affect the prognosis of gastric cancer, and of these factors invasion and metastasis are leading causes of death. The role of cyclooxygenase-2 (COX-2) in gastric cancer development and progression

has been extensively studied. The expression of COX-2 is elevated in gastric cancer tissues, therefore, inhibition of COX-2 expression may prevent or reverse gastric carcinogenesis. This review focuses on the crucial role of COX-2 in gastric cancer development and progression. In addition, its mechanisms of action are illustrated.

COX

COX, also known as prostaglandin synthase, is the rate-limiting enzyme responsible for the conversion of arachidonic acid (AA) into the various prostaglandins (PGs), a family of lipid mediators that have widespread and diverse biological functions^[5]. This enzyme possesses both peroxidase activity in catalyzing prostaglandin G₂ (PGG₂) to prostaglandin H₂ (PGH₂) and COX catalytic activity in the conversion of PGG₂ from AA^[6]. Members of the PGs family including PGD₂, PGE₂, PGF₂, PGG₂, and PGH₂ are widely distributed in organic bodies and play different roles in metabolism^[7-11]. It is reported that PGE₂ was overexpressed in tumor tissues and was involved in carcinogenesis^[12-14].

COX, with a relative molecular mass of 71000, is a type of glycoprotein which is located on the surface of the nuclear membrane and microsomal membrane. Two COX isoforms have been found: COX-1 and COX-2. Although COX-1 and COX-2 share a high level of homology (65%), the activity and expression of these enzymes are different, and they can function independently within the same cell type^[15].

The *COX-1* gene, comprised of 11 exons and 10 introns, is a type of housekeeping gene, which is located at chromosome 9 q^{32-33.3}. The full length of the *COX-1* gene is about 22.5 kb, and no hogness box and promoter elements are found. In most tissues, COX-1 is composed of 599-600 amino acid residues and expressed constitutively and continuously^[16]. The basic functions of COX-1 are not only promoting the synthesis of PGs, but also maintaining the homeostasis of an organism such as regulating the clotting mechanism, stabilizing renal blood flow and protecting gastric mucosa^[17-19]. COX-1 is expressed negatively or weakly in tumor tissues and is not involved in carcinogenesis^[20].

The *COX-2* gene, located at chromosome 1q^{25.2-25.3}, is composed of 10 exons and 9 introns. With hogness box, CAAT/enhancer binding protein (C/EBP) and cAMP response elements in the 5'-terminal nucleotide sequence, the gene is approximately 8.3 kb in size^[21]. There are also some binding sites in the gene sequence such as the activator protein-2 (AP-2) binding site and the nuclear factor-kappa B (NF-κB) binding site^[22]. COX-2 is composed of 604 amino acid residues and is expressed negatively in normal tissues and organs under physiological conditions, except the constitutive expression in kidney and brain. It is inducible in response to certain stimuli such as growth factors and cytokines. COX-2 is involved in many pathological processes such as inflammation and carcinogenesis^[23,24]. It was reported that more than 15% of

malignant tumors are correlated with infection^[25]. Various inflammation networks have been confirmed to play crucial roles in the microenvironment of carcinogenesis^[26], and the most important network is the COX-2/PGE₂ pathway^[27]. In addition, it has been well established that COX-2 is up-regulated in a variety of cancers and promotes their growth^[28-30].

EXPRESSION OF COX-2 IN GASTRIC CANCER

The first report on the expression of COX-2 in gastric cancer was from Ristimäki *et al.*^[23]. Their study showed that human gastric adenocarcinoma tissues contained significantly higher levels of COX-2 mRNA when compared with paired gastric mucosal specimens devoid of cancer cells. Immunohistochemical staining detected COX-2 protein expression in the cytoplasm of gastric carcinoma cells, but not in the surrounding stroma. Ue-fuji confirmed the overexpression of COX-2 protein in human gastric adenocarcinomas by immunoblotting, and reported that overexpression of COX-2 protein was independent of the histologic type of gastric cancer^[31]. A study further confirmed the significant difference in COX-2 protein expression between normal tissues and gastric cancer tissues^[32]. Researchers found that the overexpression of COX-2 protein was not related to the clinicopathological characteristics of gastric cancer patients^[33], but related to tumor node metastasis clinical stage, depth of invasion and metastasis^[33,34]. A series of studies showed that COX-2 protein expression was associated with intestinal histological subtype, proximal location, tumor size and advanced clinical stage and lymph node involvement^[35-39]. Importantly, the expression of COX-2 protein and mRNA was already detected in noninvasive gastric dysplasia^[40,41]. Thus, it seems likely that COX-2 plays a role in early gastric carcinogenesis.

There are controversial results in the association between COX-2 and survival rate. Although COX-2 played a crucial role in gastric carcinogenesis and was relevant to the degree of tumor differentiation, the expression of COX-2 protein was not correlated with survival rate. In addition, it made little sense in predicting gastric cancer prognosis^[42]. In contrast, other research results suggested that COX-2 was an independent prognostic factor for gastric cancer as the 5-year survival rate of COX-2 protein positively expressed patients was lower than that of negatively expressed patients^[43]. In addition, early-stage gastric cancer patients with high expression of COX-2 protein were at a higher risk for cancer-related death than those with a low level of COX-2 expression^[35]. Another study^[44] assessed the correlation between tumor progression and epithelial mesenchymal transition using multivariate analysis, and showed that COX-2 protein overexpression was an independent prognostic factor for poor survival, due to angiogenesis, cancer invasion and metastasis. Recently, scientists also found that COX-2 protein and *p53* expression were independent prognostic

factors for poor survival, in addition to late-stage disease and non-curative surgery^[45]. Most of the findings illustrated above share the similar points, while the controversial points need to be further investigated to reach a consensus.

MECHANISM OF ELEVATED COX-2 EXPRESSION IN GASTRIC CANCER

Helicobacter pylori infection

Some studies suggested that *Helicobacter pylori* (*H. pylori*) infection was significantly related to COX-2 expression^[46-48]. *H. pylori* infection can lead to a local inflammatory response, phenotypic change of epithelial cells, promotion of cell proliferation and inhibition of cell apoptosis, and ultimately an increased risk of gastric cancer^[49].

H. pylori is classified as a class I carcinogen by the International Agency for Research on Cancer. Over-expression of COX-2 was detected in *H. pylori* positive gastritis compared with *H. pylori* negative gastritis^[50]. COX-2 over-expression was found in 50%-80% of gastric cancer patients. Another study showed that 24 h after *H. pylori* infection of epithelial cells in mice, the expression of COX-2 and PGE₂ were significantly elevated^[51]. An *in vitro* study also obtained similar results^[48]. After the co-culture of MKN 28 cell lines with *H. pylori* for 24 h, the COX-2 mRNA transcription level increased five-fold and the expression of PGE₂ increased three-fold, suggesting that synthesis of COX-2 and PGE₂ was one of the factors for *H. pylori* associated gastric cancer^[52].

The mechanism of COX-2 over-expression caused by *H. pylori* infection is not entirely clear. In an *in vitro* study, *H. pylori* induced the expression of COX-2 and inducible nitric oxide synthase by activating AP-1 of AGS cells^[53]. Cytokines from the *H. pylori* associated inflammatory response also promoted the upregulation of COX-2^[54]. In an *in vivo* study, *H. pylori* infection influenced the expression of 385 genes, and 160 of these genes were related to COX-2, including the inflammation genes (*Icam1*), the apoptosis genes (*Cln*), the proliferation genes (*Gdf3*, *Igf2*), the gastric physiology genes (*Galr-1*) and the epithelial barrier function genes (*Tjp1*, *Aqp5*). After treatment with NS398, a COX-2 inhibitor, the expression of 140 genes changed, which indicated that COX-2 was correlated with the occurrence of gastritis^[55]. Another study indicated that *H. pylori* could lead to the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and its downstream transcription factor ATF-2, and the expression of COX-2 could be inhibited by a p38 MAPK inhibitor. These results indicated that the p38/ATF-2 signal transduction pathway induced by *H. pylori* was the crucial mechanism involved in COX-2 expression^[56]. Infection with *H. pylori* stimulated the secretion of gastrin which promoted the expression of COX-2 and extended the half-life of COX-2 mRNA^[57]. In addition, the inhibitor of gastrin-releasing peptide decreased the expression of COX-2, which indicated that gastrin may be involved

in COX-2 expression induced by *H. pylori*^[58].

Suppressor gene mutation

An imbalance of oncogenes and suppressor genes is responsible for carcinogenesis. The mutation of a suppressor gene can lead to the occurrence of cancer. A study revealed that COX-2 expression in patients with *P53* mutation was higher than in those without *P53* mutation. This indicated that *P53* mutation might be related to COX-2 over-expression^[59]. The protein of wild-type *P53* could inhibit the formation of a complex composed of TATA box binding proteins and promoters located upstream of the gene sequences, and eventually inhibited the expression of COX-2. In contrast, the product of mutant type *P53* could elevate COX-2 expression by the Ras/Raf/MAPK signal pathway. Moreover, COX-2 could reversibly induce mutation of *P53*, and both were co-expressed in gastric cancer tissues^[60].

P16 is a tumor suppressor gene located at chromosome 9p²¹. It can inhibit the function of cyclinD1/CDK4 and CDK6 complex, and cause *p53*-independent G1 arrest through the phosphorylation of pRb^[61,62]. This gene is usually inactivated in human gastric cancers for different reasons. A study indicated that *p16* was found to harbor promoter methylation associated with the loss of protein expression in cancer cells, suggesting that *p16* inactivation due to promoter methylation may be important for gastric tumorigenesis^[63]. Other mechanisms such as mutation and homozygous deletion, are also responsible for the inactivation of *p16*, which lead to the development and progression of tumors^[64]. Researchers explored the expression of COX-2 protein and *p16* protein in gastric cancer mucosa, and found that COX-2 protein expression was negatively related to *p16* protein expression. There may be a relationship between the expression of COX-2 and *p16*. However, the mechanism involved needs to be clarified in further research^[65,66].

NF-κB

NF-κB is a protein which has the ability to combine with the nucleotide sequence in the promoter region and enhancer region of some genes, and consequently activate or enhance the transcription of these genes. NF-κB is usually distributed in the cytoplasm in the inactive form under physiological conditions. It is then activated and enters the nucleus in response to outside stimuli. The NF-κB signal pathway is involved in many processes such as the inflammatory response, cell proliferation, apoptosis and carcinogenesis. Some inflammatory cytokines, such as tumor necrosis factor (TNF)-α, can activate NF-κB, and this activated transcription factor can induce over-expression of inflammatory factors including COX-2 and TNF-α itself, forming the inflammatory network in the tumor microenvironment^[67]. The COX-2 promoter region contains several elements, with the presence of two NF-κB consensus sites^[68]. COX-2 expression decreased significantly when NF-κB was blocked by chondroitin sulfate^[69,70]. Expression of COX-2 and NF-κB increased

simultaneously during the process from chronic atrophic gastritis, dysplasia to gastric cancer. The co-expression of COX-2 and NF- κ B played an important role in the angiogenesis of stomach tissues. In addition, NF- κ B up-regulated the expression of vascular endothelial growth factor (VEGF), which is an important promoter of angiogenesis^[71].

MECHANISM OF COX-2 IN GASTRIC CARCINOGENESIS

Cell proliferation and apoptosis

Accumulating evidence indicates that inflammation plays an important role in the development of cancers^[72,73]. TNF- α , which is a mediator of PGE₂, plays a crucial role in mediating the inflammatory process through activation of NF- κ B. It has been found that stromal NF- κ B can enhance proliferation of epithelial cells by inducing cytokines, chemokines, and growth factors, such as IL-6, IL-1 β , macrophage inflammatory protein-2 and TNF- α , while epithelial NF- κ B can suppress apoptosis by inducing anti-apoptotic proteins, such as GADD45 β , A1/Bfl1, and cIAP1^[74,75]. As a product of AA catalyzed by COX-2, PGE₂ is involved in gene mutation and cancer cell proliferation^[76]. Protein encoded by COX-2 genes is a type of oncogenic protein, which could promote the high expression of PGE₂. PGE₂ can stimulate the growth of blood vessels, inhibit local immune function and regulate a variety of signal transduction pathways which ultimately influence the proliferation of cells and the growth of tumors^[77]. It has also been confirmed that over-expression of COX-2 promoted cell proliferation by weakening the anti-proliferative effect of transforming growth factor- β (TGF- β)^[78].

An *in vitro* study showed that cell proliferation was suppressed when gastric cells were treated with COX-2 small interfering RNA (siRNA)^[79]. In MKN-45 cells, inhibition of COX-2 with NS-398 led to reduced proliferation and induction of apoptosis, connected with downregulation of *Bcl-2* (an anti-apoptotic gene) and upregulation of *Bax* (an apoptotic gene)^[80]. COX-2 was a regulatory factor in the *Bcl-2* upstream sequences, which upregulated the expression of *Mcl-1*, a member of the *Bcl-2* family, through the phosphatidylinositol 3-kinase (PI3K) signal pathway, and eventually inhibited the apoptosis of cancer cells^[81]. Some studies confirmed that COX-2 could inhibit the apoptosis of cancer cells by inducing the mutation of *P53*^[82]. Other researchers indicated that COX-2 weakened the apoptotic signal mediated by *Fas* protein. After adding the COX-2 inhibitor, they detected the elevated expression of caspase, a key enzyme of death receptor signaling and apoptotic signaling pathways^[83].

Angiogenesis and lymphatic metastasis

The growth and metastasis of tumors depend on the formation of new blood vessels. PGE₂ and PGF₂ can promote vessel formation directly or indirectly^[84]. Research

has found that COX-2 over-expression was associated with increased PGE₂ biosynthesis and angiogenesis in gastric cancer^[85]. Furthermore, COX-2 can induce cells to produce VEGF and TGF- β , which could promote endothelial cell migration and tubular morphogenesis. In addition, VEGF was an independent prognostic factor for gastric cancer prognosis^[86]. After being transfected with COX-2 siRNA, the expression of VEGF was down-regulated and the growth of gastric cancer cells was significantly inhibited^[22]. Other studies indicated that COX-2 upregulated the expression of *Bcl-2* and *Akt*, which can inhibit the apoptosis of endothelial cells and promote vessel formation^[87,88].

VEGF-C has been identified as a new member of the VEGF family and is considered a specific lymphangiogenic factor. It can promote the formation and dilation of lymphatic vessels, enhance the permeability of lymphatic vessels and facilitate lymphatic metastasis. A recent study confirmed a positive correlation between the expression of COX-2 and VEGF-C in gastric cancer patients, and both were related to gastric cancer prognosis^[89].

Invasion and metastasis

Invasion is the premise of cancer metastasis which involves a variety of cytokines. Adhesion molecule is a type of cell surface glycoprotein that mediates cell adhesion. E-cadherin adhesion which inhibits the separation of cancer cells from tissue can prevent cancer cell invasion. COX-2 can lower the activity of E-cadherin, thus the invasiveness of cancer cells is enhanced for further metastasis. The activity of E-cadherin was enhanced after inhibition of COX-2^[90]. It has been confirmed that the over-expression of matrix metalloproteinase (MMP) accelerated the decomposition of collagen in local tissues, which was beneficial to the spread of cancer cells. A correlation between COX-2 and MMP upregulation was also found^[91]. COX-2 inhibitors reduce the expression of MMP^[92]. CD44, which acts as the membrane receptor of hyaluronic acid and is expressed in cancer stem-like cells, played an important role in cancer metastasis. A large number of CD44(+) gastric glands was found in human adenocarcinomas and adjacent metaplasias, but not in normal gastric epithelium. In addition, CD44(+) tumor cell expansion is triggered by the cooperative actions of PGE₂ and Wnt in gastric tumorigenesis^[93]. Studies also confirmed that PGE₂ could upregulate the expression of CD44^[94], while COX-2 inhibitor could inhibit CD44 expression^[95]. A study demonstrated that CD44v, a variant form of CD44, could protect tumor cells from oxidative stress in a mouse gastric cancer model, thus it plays an important role in tumor development^[96]. Other possible mechanisms include the upregulation of urokinase-type plasminogen activator (uPA) in promoting the metastasis of cancer cells^[97] and more potential pathways need to be further clarified.

Immunosuppression

It has been found that COX-2 was involved in the im-

munosuppression in gastric cancer, where effector T cells were suppressed by regulatory T cells. In Treg cells, expression of COX-2 was correlated with that of forkhead box p3. By using a COX-2 inhibitor, the immunosuppression of effector T cells was reversed^[98]. The possible mechanisms involved may be as follows: PGE₂ disabled the function of dendritic cells in the tumor microenvironment and the cells could not present the tumor antigen effectively, and eventually the T cells did not recognize or kill the cancer cells^[99]. In addition, PGE₂ may also reduce the immunosurveillance of the immune system on mutant cells by inhibiting the expression of human leucocyte antigen I and II, and by reducing the production of lymphokine. The immunosurveillance effect could be enhanced by using a COX-2 inhibitor and stimulating the activity of natural killer cells^[100].

CONCLUSION

The COX-2/PGE₂ pathway involved in the inflammatory response plays a critical role in the microenvironment of gastric tumorigenesis. Expression of COX-2 is elevated in gastric cancer and its over-expression is associated with *H. pylori* infection, mutation of suppressor genes and NF- κ B. Over-expressed COX-2 participates in gastric carcinogenesis by promoting cell proliferation, inhibiting cell apoptosis, inducing vessel formation, and enhancing metastasis and immunosuppression. Although progress has been made in exploring the mechanism of gastric cancer development, some issues remain to be explored in further studies. As research continues, interventions in gastric cancer using COX-2 as a target might eventually become a specific treatment of choice.

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