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Dispelling Stasis and Detoxification Method based on COX-2/PGE2 Pathway

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Abstract: ***Gastric cancer is a disease with high mortality rate among global cancers, and its survival rate is extremely low and treatment prognosis is extremely poor, which seriously impedes the development of the world economy. Pre-cancerous gastric lesion (PLGC) is the early stage of gastric cancer, so far modern medicine has no effective measures to prevent and reverse the development of PLGC to gastric cancer, the pathogenesis of PLGC is not yet clear, but the theory of inflammatory cancer transformation is now more popular. Therefore, the COX-2/PGE2 pathway can generate an inflammatory environment, promote cell proliferation, inhibit apoptosis, promote angiogenesis and other processes, so that PLGC gradually develops into gastric cancer. According to Chinese medicine, gastric cancer is mostly caused by stagnation of qi and blood stasis, and the internalisation of fire and toxicity, so the elimination of blood stasis and detoxification fits the pathogenesis of the disease, and Chinese medicine can play an anti-inflammatory role in the COX-2/PGE2 pathway by inhibiting cell proliferation, promoting apoptosis, and inhibiting the formation of capillaries, which can prevent PLGCs from progressing to gastric cancer, and thus preventing the development of gastric cancer. This article reviews the pathogenesis of PLGC by COX-2/PGE2 signalling pathway, and the progress of TCM drugs targeting PLGC based on COX-2/PGE2 pathway by dispelling stasis and detoxification, with the aim of providing more theoretical basis and prescription research for clinical practice.***

Keywords: Inflammation, Inflammatory cancer transformation, PLGC, COX-2/PGE2.

1. Introduction

Gastric cancer is one of the major malignant tumours threatening the life and health of the population. According to the data of World Health Organization (WHO), in 2020, there will be 479,000 new cases of gastric cancer and 374,000 deaths in China, accounting for 44.0% and 48.6% of the global incidence and deaths of gastric cancer respectively [1]. The incidence and mortality rate of gastric cancer in China will be 479,000 cases. The high incidence and mortality rates of gastric cancer in China are mainly due to diet, and the low rate of early detection [2]. The COX-2/PGE2 pathway is a common pathway induced by inflammation and a key factor in the physiology and pathogenesis of various cancers. Its activation often produces increased prostaglandin production, generating inflammation and inducing cancer, and its involvement and activation of various pathways, including NF-kb, wnt signalling, etc., ultimately induces the development of PLGC (gastric pre-cancerous lesions). In recent years, with the gradual improvement of people's living standards, the public has begun to pay attention to the role of traditional Chinese medicine (TCM) in the treatment of diseases, and this paper reviews the therapeutic efficacy of TCM on PLGC through the COX-2 / PGE2 pathway.

2. Research on Pathogenesis

2.1 Basic Structure and Function of the COX-2 / PGE2 Pathway.

Cyclooxygenase (COX) is an important enzyme that causes the conversion of arachidonic acid to prostaglandins, and it exists in three isoforms, COX-1, COX-2, and Cox-3 [3]. COX-1 is the structural type, which is expressed in physiological or pathological conditions, in normal arteries and AS lesions, and is located in tissues and organs such as blood vessels, stomach, etc., and mainly maintains normal physiological functions; COX-2 is the inducible pro-inflammatory type, which is expressed in organs such as the brain, pancreatic islet cells, ovaries, uterus, etc., or expressed in large quantities only when stimulated by a specific inflammatory condition [4]. Cox-3 is located in the mitochondria and has also been reported to be located in the nucleus, and its gene sequence is the most conserved among the cytochrome c oxidase subunits, and it may contribute to lymphoid-associated lesions [6].

2.2 Activation of the COX-2/PGE2 Pathway

The COX-2/PGE2 pathway plays a key role in tumourigenesis. Arachidonic acid is a 20-carbon chain endogenous polyunsaturated fatty acid substrate for COX-1 and COX-2 and is responsible for the activation of phospholipase A2 via several types of thrombin action, growth factors, calcium ion carriers, bradykinin or cytokines [7]. It is derived from membrane phospholipids through the action of the hydrolase phospholipase A2. These prostaglandins are collectively known as arachidonic acid-like, and thus it is considered a local hormone that regulates essential cellular physiological processes [8]. It is an important mediator of signal transduction pathways and is involved in cellular functions such as cell adhesion, growth and differentiation. COX-2/PGE2 expression is an essential step in the pathogenesis of cancer through two mechanisms; one prostaglandin-dependent and the other prostaglandin-independent. Arachidonic acid (AA) is converted from membrane phospholipids to the unstable endoperoxide PGG2.The cyclic endoperoxide PGG2 is immediately converted to the dimeric membrane enzyme prostaglandin H2 (PGH2) by reduced glutathione (GSH)-dependent peroxidase (PG-hydroperoxide) [9-12]. This unstable endoperoxide is then isomerised to form important biological mediators called prostaglandin biosynthesis (a subclass of eicosanoids) including prostaglandins, prostacyclins and thromboxanes (PGE2, PGF2α, PGD2, TxA2 and PGI2) [13] form precursors for the conversion of AA to PGG2 and further to PGH2.

Cyclooxygenase-2 is a key enzyme in prostaglandin-like production associated with inflammation, which promotes tumour growth, cell proliferation, angiogenesis, tumour tissue invasion and increases the likelihood of metastasis through inflammatory responses [14][15]. The E-series prostaglandin receptors named EP1, EP2, EP3 and EP4 are repeatedly co-expressed in the same cell types and used differently. Stimulation of EP2 and EP4 receptors in prostaglandin E2 involves epidermal growth factor receptor (EGFR) used for trans-activation to promote tumourigenesis, which enhances cell proliferation, angiogenesis, suppresses the immune system, stimulates cell growth and apoptosis [16].

2.3 COX-2 / PGE2 Pathway-mediated Inflammatory Cancer Transformation Process in Gastric Cancer:

Since the discovery of Rudolf Virchow in the 19th century that suggested a possible link between cancer and inflammation, there has been a gradual focus on the relationship between inflammation and cancer. Several key components are required for the onset of cellular neoplastic transformation, including upregulation of growth factor production, insensitivity to growth inhibitors (tumour suppressors), evasion of apoptosis, limited replicative potential, sustained angiogenesis, tissue invasion and metastasis [19]. A common view is that chronic inflammation and associated intermediates may enhance the process of tumourigenesis by affecting cancer cells or cells in the tumour microenvironment [20]. It has been shown that K19-Wnt1/C2mE mice (Gan mice) develop gastric adenocarcinoma at 20 weeks of age when the oncogenic Wnt pathway is activated in addition to COX-2 and mPGES-1 [21]. Thus, the COX-2/PGE2 pathway plays an important role in the "inflammatory-cancer transition" in PLGC, i.e., gastric precancerous lesions, as it can be activated by the nuclear factor κB (NF-kB) pathway to generate an inflammatory environment, and it can also synergise with the wnt pathway to lead to tumourigenesis.

2.4 Function of the COX-2/PGE2 Pathway

Overexpression of the COX-2/PGE2 pathway promotes the generation of an inflammatory environment, cellular proliferation, and promotes angiogenesis.

2.5 Generating an Inflammatory Environment

COX-2 is an important regulatory pathway in the generation of an inflammatory environment Its production of prostaglandins is an important regulatory molecule in inflammation that promotes an inflammatory environment with tumour production and its spread through inflammation. Inflammation is a series of responses by the body to external stimuli, and in the digestive system, HP infection is an important infectious factor. Numerous studies have shown that many factors (e.g. H. pylori infection, NF-κB activation, K-ras expression, and dysregulation of certain trans-acting regulators) can lead to overexpression of COX-2/PGE2 and more inflammation and tumour formation [22]. One of the potential molecular mechanisms of COX-2 upregulation after infection with H. pylori (P12 wild type) was revealed in AGS and MKN-28 gastric cancer cells. The transcription factors USF1, USF2 and CREB were found to bind to the CRE/Ebox site of the COX-2 promoter and these transcription factors were induced by the MEK/ERK1/2 cascade [23]. Notably, COX-2 is overexpressed not only in H. pylori-positive gastritis and gastric cancer, but also in precancerous lesions such as intestinal epithelial hyperplasia and atrophic gastritis, suggesting that COX-2 plays a key role in early gastric carcinogenesis [24][25]. Some inflammatory cytokines such as IL-6, IL-8 and TNF-α can activate NF-κB to induce COX-2 overexpression [26]. Epidemiological studies have shown that the application of COX-2 inhibitors can reduce the inflammatory response and inhibit gastrointestinal carcinogenesis. The use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, can reduce the risk of digestive malignancies by blocking the action of COX-2 [27]. Thus targeting Cox-2 plays an important role in the blocking effect on the inflammatory milieu and preventing its transition from inflammation to cancer.

2.6 Promoting Angiogenesis

Angiogenesis, the formation of new capillaries, is essential not only for the growth and metastasis of solid tumours but also for wound and ulcer healing. Without angiogenesis, the delivery of oxygen and nutrients from the blood to the healing site cannot be restored. Angiogenesis and suppression of cell-mediated immunity are central to the development and progression of malignant disease. Studies suggest that COX may play a very important role in regulating angiogenesis associated with tumour cells. NSAIDs drugs, such as aspirin, have anti-angiogenic and immunomodulatory effects. COX-2 promotes tumour angiogenesis through various mechanisms. The key mechanisms appear to involve increased expression of the pro-angiogenic growth factor VEGF; production of the arachidonic acid-like products thromboxane (TX) A2, PGE2 and PGI2, which directly stimulate endothelial cell migration and growth factor-induced angiogenesis [28]. In MKN-28 cells, the EGFR-MAPK signalling pathway was involved in the up-regulation of VEGF after application of PGE2 [29]. Microarray analysis was used to identify COX-2-regulated angiogenesis-related molecules, which were confirmed by RT-PCR and Western blotting. VEGF, Flt-1, Flk-1/KDR, angiopoietin-1, tie-2, MMP2 and osteoblasts were found to be downregulated in response to COX-2 inhibition [30]. This shows that the use of Cox-2 inhibitors can effectively inhibit the angiogenesis of tumours and exert significant control over the growth and metastasis of solid tumours.

2.6 Promotion of cell Proliferation and Inhibition of Apoptosis

Cell proliferation is an important part of tumour formation and an important condition for the formation of PLGC. The key to tumour formation is cell proliferation and for the inhibition of apoptosis. In MKN-45 cells, inhibition of COX-2 with NS-398 led to a reduction in proliferation and induction of apoptosis, which was associated with downregulation of Bcl-2 and upregulation of Bax. Furthermore, in clinical gastric cancer tissue samples, COX-2 was associated with apoptotic and proliferative markers [31]. COX-2 signalling has been found to be involved in immunosuppression in gastric cancer, where regulatory T (Treg) cells (CD4+CD25+Foxp3+) suppress effector T cells (CD4+CD25-) [32]. Foxp3 expression correlates with COX-2

expression in Treg cells, and importantly, COX inhibitors and PGE2 receptor (EP2 and EP4) antagonists (AH6809 and AH23848) reverse the suppression of effector T-cell responses [33-36]. Gastric tumourigenesis was significantly attenuated in H. pylori and N-methyl-N-nitrosourea-treated mice and apoptosis was increased in these tumours when the (relatively) selective COX-2 inhibitor nimesulide was administered chronically [37]. So COX-2 can inhibit effector T cells by inhibiting oncogenes, promoting the development of proto-oncogenes, and thereby achieving cellular value.

3. The Use of the Method of removing Stagnation and Detoxification in PLGCs

PLGC has no specific Chinese medical name, but PLGC generally refers to chronic atrophic gastritis with intestinal and atypical hyperplasia, according to its main manifestations of gastric and epigastric pain, plagiarism, fullness, etc., can be included in the Chinese medicine "plagiarism" "gastric and epigastric pain" category, "Stomach distension". According to Lao Shaoxian, it belongs to the evidence of the symptoms of this deficiency, with the deficiency of spleen and stomach qi and yin as the root, stagnation of qi and blood stasis, heat and toxicity in the stomach as the symptoms, and qi obstruction as the root of the disease. According to Gui Beihai, the key to the pathogenesis of chronic atrophic gastritis and PLGC is a deficiency of the spleen and kidneys, with stagnation of qi and blood stasis and heat-toxicity as the symptoms [38]. The method of eliminating blood stasis and removing toxins, i.e., promoting blood circulation to eliminate blood stasis, cooling blood and removing toxins, was used to treat PLGC. Dai Minglong et al. found that the efficacy of the formula of resolving blood stasis and removing toxins and clearing the channels was obvious in the treatment of patients with gastric stasis and toxicity type of gastric precancerous lesions, which could reduce inflammatory reactions, down-regulate the expression of COX-2 and up-regulate the expression of PGI and G-17 [39]. Gao Dong et al. found that Fuxian anti-iso soup its can clear heat and detoxify, strengthen the spleen and open the stomach. It can effectively improve the rate of improvement of endoscopic signs, reduce the pathological sign score, and also regulate the expression of P16, bcl-2, cox-2, survivin protein in gastric mucosa, which is worthy of promotion [40]. Liu Jindi et al. found that Xin Gastric Granules can promote gastric mucosal epithelial cell apoptosis and antiproliferation by down-regulating the expression of NF-κB and COX-2 genes and proteins in gastric tissues of PLGC rat model [41]. Yin Jing et al. found that Xinguang granules could promote apoptosis and anti-cell proliferation of gastric mucosal epithelial cells by down-regulating the expression of NF-κB and COX-2 genes and proteins in the gastric tissues of PLGC rat model [42]. Zheng Huanfan et al. found that atrophic gastric granules were able to reduce the expression of COX-2 in peripheral blood and gastric mucosal tissues and enhance the barrier capacity of gastric mucosa, thus exerting its therapeutic and preventive effects on CAG [43]. Tian Fang et al. found that the combination of the Compound Turbidifier Detoxification Soup and DCF chemotherapy programme can significantly reduce the expression levels of VEGF and COX-2 in the serum of patients with middle and advanced gastric cancer, and improve the quality of life of the patients, which is worthy of promotion in the clinic [44]. Song Keke et al. found that the traditional Chinese medicine Fugong Decoction could reduce the expression of COX-2, VEGF and its mRNA in the gastric tissues of rats with precancerous gastric lesions; and there was a certain quantitative relationship with the expression of VEGF [46]. Liu Qiquan et al. found that the treatment of gastric precancerous lesions with Xiao Gui Shao (小归芍), a formula for removing turbidity and detoxifying toxins, was effective in relieving patients' clinical symptoms and reversing precancerous lesions [47]. Bai Haiyan et al. found that Guilian Gastric Kang formula could improve the symptoms of patients with chronic atrophic gastritis with precancerous lesions and reverse the precancerous lesions [48]. Haiyan Bai et al. Zhao Weihan et al. found that Ginseng qi plankton-eliminating granules significantly improved gastric mucosal lesions in CAG rats, and the therapeutic mechanism may be related to the down-regulation of COX-2 and Bcl-2 protein expression. [Its therapeutic mechanism may be related to the down-regulation of COX-2 and Bcl-2 protein expression.] Therefore, the treatment of PLGC based on the COX-2/PGE2 pathway by activating blood circulation, dispelling blood stasis, cooling blood and detoxifying toxins has a significant improvement in the treatment of PLGC.

4. Discussion

Pre-cancerous lesions of the stomach belong to the category of "stomach pain" in traditional Chinese medicine, and its pathogenesis is mostly caused by stagnation of qi and blood stasis, blockage of blood and collaterals, and heat and stagnation of blood, and its treatment should be to activate blood circulation to eliminate blood stasis and cool blood to detoxify the toxin, so the method of eliminating blood stasis and detoxifying the toxin is close to the key of the disease mechanism. The COX-2/PGE2 pathway regulates several cellular activities in the human body including generating inflammatory environments, promoting cell proliferation and inhibiting apoptosis, and promoting angiogenesis, It promotes cell proliferation and inhibits apoptosis, and promotes angiogenesis, etc. It has a very important role in the human body. Moreover, the COX-2/PGE2 pathway can be a targeted signalling pathway for diagnosis and treatment of diseases due to its involvement in multiple pathways that jointly regulate PLGC production. Studies have shown that Chinese medicine has obvious effects on regulating the COX-2/PGE2 pathway, but it is often not convincing to the public due to its complex composition and lack of explanation of side effects. In some studies, the sample size was too small and the study sites were limited, which did not represent the efficacy of the drug for a wide range of patients. In addition, the use of gastroscopy in some studies was not operated by the same person, often resulting in bias, and did not use the technique of targeted biopsy, often resulting in errors in the degree of improvement of lesions, and after the completion of treatment, there was no follow-up, but only in the treatment, which questioned the therapeutic effect of the drug and its side effects. In some studies, the gastric mucosa of experimental rats was observed visually and not compared with the blank group, which did not determine the degree of improvement of the drug on the stomach, and no pathological evaluation was done, and only molecular level studies were available. Therefore, Chinese medicine for COX-2 / PGE2 pathway often because of its multi-component, multi-targeting, etc., more to be more disciplines, technology analysis, such as

network pharmacology, etc., and secondly, for the clinical observation of the study should pay more attention to its treatment process, and post-treatment follow-up process, to clarify the toxicity and side effects. In addition, most of the clinical observational studies have been the drug is effective in the treatment of disease, there is no contrary results or side effects of the study, the public is not convinced of the research drug, looking forward to future research on side effects and so on. With the development of gastroscopy technology, the degree of improvement of the lesion should be used to determine the degree of biopsy, and for the same person to ensure the accuracy of the operation. It is hoped that the mechanism of Chinese medicine on the cyclooxygenase family will be further improved in the future, and that Chinese medicine will be widely used in PLGC on the basis of clinician's diagnosis and treatment, so that the cause of Chinese medicine will be further developed.

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