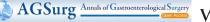REVIEW ARTICLE

Research Progress on the Relationship Between Inflammation and Colorectal Cancer

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Abstract

Colorectal cancer is one of the common malignant tumors. Relevant epidemiology and a large number of experimental studies have proved that chronic inflammation is highly correlated with the occurrence and development of colorectal cancer. And inflammatory bowel disease has been proven to be an independent risk factor for colorectal cancer. Various inflammatory cells participate in the establishment of the chronic inflammatory intestinal microenvironment required for the onset of colorectal cancer. The abnormal signal pathways mediated by various inflammatory factors and inflammatory mediators promote the occurrence of tumors, which are related to colorectal cancer and pathogenesis-related inflammation mechanisms. At the gene level, miRNAs can also affect the pathogenesis of colorectal cancer by regulating mesenchymal epithelial transformation. This article reviews the relationship between inflammation and colorectal cancer as well as the related inflammatory mechanisms.

KEYWORDS
colorectal cancer, cytokines, inflammation, intestinal microenvironment, MiRNAs

1　|　INTRODUCTION

Colorectal cancer (CRC), as one of the most prevalent types of cancer worldwide and the most common gastrointestinal malignant tumor, has become the third largest fatality rate of malignant tumor.[1-3] As people change their lifestyle in recent years, together with the environmental pollution influence factors, the incidence of CRC is on the rise in the world. CRC is easily misdiagnosed; those diagnosed in the early phase are less than 40% and for most of the patients at the time of definite diagnosis, the cancer has already metastasized.[4] Treatment with surgery is given priority, combined with radiotherapy and chemotherapy, but epidemiological data show that patients with CRC mortality are higher still.[5,6] In the middle of the nineteenth century, Virchow observed leukocyte infiltration in tumor tissues and first proposed the possible correlation between malignant tumors and inflammation.[7] With the deepening of such research, it has now been confirmed that chronic inflammation takes part in a tumor's start, proliferation, metastasis, aging, and apoptosis at various stages. Inflammation is also known as the seventh largest biological feature of malignant tumor.[7-10]

2　|　INFLAMMATION AND TUMORS

2.1　|　Tumors associated with chronic inflammation

The occurrence and development of tumors include many complex physiological and pathobiological behaviors, including the

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activation of oncogenes, the formation of tumor microenvironment promoted by chronic inflammation, and ultimately lead to cell proliferation and malignant transformation.[11] Inflammation is a series of defense responses of the body against pathogen infection and tissue damage, and through the interaction of various cytokines in the body's microenvironment, it regulates the balance of various physiological and pathological states of the body. In a normal body, the inflammatory response will end after infection and other inflammatory factors disappear. This inflammation is called "resolving inflammation", but if the tissue cannot be separated from the continuous external stimulation, the inflammatory response persists. This inflammation is called "nonresolving inflammation".[12] Uncontrollable inflammation plays an important role in inducing and promoting the formation and metastasis of malignant tumors.[13]

The occurrence of a variety of tumors can confirm the above view. For example, chronic gastritis with helicobacter pylori infection can induce gastric cancer,[14,15] inflammatory bowel disease is related to the incidence of CRC,[16–18] and hepatitis B virus infection can induce liver cancer.[19,20] Silicosis caused by asbestos fibers or silica dust is related to lung cancer.[21] Barrett's esophagitis is related to esophageal cancer.[22,23]

2.2 | Evidence of the relationship between inflammation and CRC

Inflammation is also closely related to the occurrence and development of CRC. The most representative one is the relationship between inflammatory bowel disease (IBD) and CRC.[24] IBD includes Crohn's disease (CD) and ulcerative colitis (UC). Studies have shown that IBD is an independent risk factor for CRC. And with the prolongation of the history of IBD, the incidence of CRC has increased significantly.[25] In the study of primary CRC, it was found that there are inflammatory cell infiltrations and high expressions of related inflammatory factors in cancer tissues. Inflammation is highly related to the occurrence and outcome of CRC.[26] In this review, we selected

several items to present an overall picture of the relationship between inflammation and CRC, as shown in Table 1.

3 | INFLAMMATORY MICROENVIRONMENT AND CRC

3.1 | Inflammatory markers participate in the establishment of the intestinal microenvironment of CRC

Inflammation is associated with the progression of most malignant tumors, including CRC, and the inflammatory response markers reflect the degree of the host's inflammatory response to the tumor.[27] Studies have found that inflammatory response markers are indicators of good predictive value in the prognostic evaluation of CRC,[8,28,29] and they also have good predictive value in the prognostic evaluation of metastatic CRC as well.[30,31] Inflammatory response markers mainly include serum albumin, C-reactive protein (CRP), plasma fibrinogen, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR).[32–35]

3.1.1 | CRP

Among these inflammatory response markers, CRP is a sensitive and most widely used marker reflecting the degree of systemic inflammation, and it has a good predictive effect on the prognosis of patients with tumors that can or cannot be surgically resected.[36,37] Meanwhile, it can also be used as a good indicator to predict anastomotic leakage following CRC surgery; for colorectal surgery, the patients' CRP increases significantly on the first day after surgery, and then gradually decrease; the postoperative CRP level of patients with anastomotic leakage is significantly higher than that of patients with successful anastomotic healing; on the third or fourth day after surgery, the CRP level can be used as an early indicator to predict anastomotic leakage.[38,39] The study results of Scepanovic

TABLE 1 Inflammation and colorectal cancer

Items	Contents		
Inflammatory Markers	C-Reactive Protein (CRP)	Neutrophil to Lymphocyte Ratio (NLR)	Tumor-Associated Macrophages (TAMs)
Transcription Factors	Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)	Signal Transducer and Activator of Transcription 3 (STAT3)	Reactive Oxygen Species (ROS) & Reactive Nitrogen Species (RNS)
Cytokines	Tumor Necrosis Factors-α (TNF-α)	Interleukin Family (IL Family)	Cyclooxygenase-2 (COX-2) & Nonsteroidal Antiinflammatory Drugs (NSAIDs)
Gene Level	micro RiboNucleic Acids (miRNAs)		

et al[40] showed that the sensitivity of CRP >135 mg/L in predicting abdominal surgery anastomotic leakage is 73% and the specificity is 73% on the third postoperative day. Almeida et al's[41] study shows that on the fifth postoperative day the sensitivity of CRP >140 mg/L in predicting anastomotic leakage after colorectal surgery was 78%, and the specificity was 86%.

3.1.2 | NLR

There exist neutrophil infiltrations in tissues in the inflammatory phase, which can produce cell growth factors and related proteases to promote the transformation of normal cells into tumor cells.[42] Tumor-infiltrating lymphocytes (TILs) are considered to be an important part of inducing the body to produce an antitumor immune response; they are a special type of lymphocyte that can kill tumor cells and reduce tumor metastasis. The number and function of TILs can reflect the level of the body's antitumor response.[43]

Elevated neutrophil levels and decreased lymphocyte levels are one of the specific signs of systemic inflammation, the significant role of NLR as a systemic inflammatory response indicator in the prognostic evaluation of CRC is recognized; NLR can effectively predict local recurrence, complication rate, distant metastasis rate, disease-free survival rate, and overall survival rate after CRC surgery.[42,44]

Neutrophils are an important part of inflammatory cell infiltration—they can protect the body and eliminate pathogens when the body is infected by microorganisms, and are also widely present in the tumor microenvironment.[45] It has been found that neutrophils can be induced by related factors in the tumor microenvironment to undergo phenotypic and functional remodeling and in the early stage of inflammation, mature neutrophils in the bone marrow are rapidly activated, and the number in the blood increases rapidly. In addition, due to the action of bacteria and various toxins, specific immune activation and nonspecific damages make lymphocytes apoptosis and the number of lymphocytes in the blood decrease; during the process of inflammation, the increase in NLR can be used as a marker of inflammation.[46]

Therefore, the NLR can reflect the immune status of the body, as well as the tumor microenvironment composed of inflammatory factors and the inflammatory system. It has been shown that the NLR value is closely related to the prognosis of malignant tumors.[47] Guthrie et al[48] found that a low NLR value indicates a better prognosis for patients with CRC. Masatsune et al[49] mentioned that if patients with CRC still have a high NLR value after surgery, it indicates that the patient is in a state of easy recurrence. Woo et al[50] proved that NLR is related to the infiltration depth of CRC, tumor node metastasis (TNM) stage, and other clinical features.

3.1.3 | TAMs

Tumor-associated macrophages (TAMs) are also involved in the occurrence of tumors. TAMs can differentiate into different types under different conditions, including antitumor M1 macrophages and tumor-promoting M2 macrophages.[51] In most malignant tumors, TAMs tend to the expression of M2, through the secretion of corresponding growth factors such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), platelet derived growth factor (PDGF), and more chemokines are involved in the escape of tumor cells.[52] TAMs in the stroma can also participate in matrix remodeling and promote tumor infiltration. In CRC, Schafer et al[53] found that STAMs can enhance the migration of intestinal epithelial cells and promote their antiapoptotic ability, indicating that TAMs play an important role in the pathogenesis of inflammation-related CRC. Kang et al[54] studied pathological specimens of CRC and found that the number of TAMs in the tumor is significantly related to the TNM stage and the presence or absence of distant metastasis. Other studies have found that TAM in CRC is not a simple M1 or M2 type, and sometimes it can exist at the same time.

3.2 | The role of transcription factors and inflammatory mediators in the formation of CRC

Recent studies have shown that in the occurrence and invasion of CRC, in addition to the infiltration of inflammatory cells, the activation of tumor signal pathways mediated by various inflammatory factors and inflammatory mediators is more involved. Many abnormal signal pathways are involved in the occurrence of CRC.[55–58]

3.2.1 | NF-κB

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) belongs to the family of transcription factor proteins and plays a regulatory role in the process of inflammation. It has also been proven to play a role in the occurrence of inflammation-related tumors.[59] NF-κB can regulate the transcription of genes related to proliferation and apoptosis and induce the expression of a variety of inflammatory factors, such as TRAIL, P53, Bcl-2, and CyclinD1, which are all target gene products of NF-κB.[60,61] A variety of experiments have proven that the NF-κB signaling pathway promotes the onset of CRC. Clinical data[62] have shown that more than 50% of CRC tissues are found in the activation of NF-κB. It is found in mouse experimental models that reducing the level of NF-κB in intestinal epithelial cells can significantly inhibit tumor growth.[63] NF-κB is also related to the therapeutic effect of CRC. The abnormal activation of NF-κB mediates the drug resistance of tumor cells through the antiapoptotic pathway.[64] A study[65] has found that spirulina protein and selective COX-2 inhibitors are combined with nonsteroidal antiinflammatory drugs for CRC cells, and the results show that the above-mentioned drugs have the effect of promoting apoptosis by activating P53 protein and inhibiting NF-κB activation; in this process, the cyclin/

CDK complex is inhibited to activate the expression of P53, and together with the level of NF-κB decreases.

3.2.2 | STAT3

Signal transducer and activator of transcription 3 (STAT3) belongs to the STAT family and is an important member of transcription activators. It exists in the cytoplasm and can be activated by extracellular signals such as epidermal growth factor (EGF), interleukin (IL)-6, and other cytokines.[66] In colitis-related CRC, a large number of cytokines such as IL-6 and IL-11 continuously activate STAT3 to promote cell proliferation and malignant transformation.[67] It has now been confirmed that STAT3 is an independent risk factor for poor prognosis of CRC.[68,69] The IL-6/STAT3 signaling pathway disorder plays an important role in the occurrence and metastasis of CRC. And the regulation of this pathway can inhibit the occurrence of colitis-related colon cancer.[70,71]

3.2.3 | ROS and RNS

The oxidative stress response often occurs in chronic inflammation. Under the stimulation of chronic inflammation, inflammatory cells produce large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), causing DNA strand breaks and base mutations. Meanwhile, it is accompanied by a high mutation of P53 and eventually leads to the occurrence of CRC.[72] Nitric oxide (NO), one of the RNSs, produced during inflammation can cause pathological changes as the dose increases and participate in the growth of tumor cells.[73]

3.3 | Cytokines and CRC

3.3.1 | TNF-α

Tumor necrosis factor-α (TNF-α) can induce tumor cell apoptosis under normal circumstances, but under pathological conditions it acts as an inflammatory factor to promote tumor development.[74,75] TNF-α can induce the expression of genes involved in tumor invasion and metastasis by activating NF-κB, including adhesion molecules, matrix metallopeptidase 9 (MMP9), cyclooxygenase-2 (COX-2), and vascular endothelial growth factor (VEGF).[75,76] In addition, TNF-α can also trigger the activation of the epithelial–mesenchymal transition (EMT).[77] These characteristics can promote the formation and metastasis of CRC neovascularization. Clinical studies have shown that high levels of TNF-α expression are found in the bodies of a large number of CRC patients, and TNF-α levels can be seen to decrease after the removal of the primary tumor, which may be due to the surgical removal of the primary tumor, thereby reducing the stimulation of the immune system and reducing the production of TNF-α by lymphocytes.[78] These studies prove the high correlation

between TNF-α and CRC.[79] In animal models, mice deficient in TNF receptors also have a significantly reduced incidence of CRC.[80]

3.3.2 | IL family

IL-6 and IL-10 are important cytokines related to the occurrence of CRC, and participate in the occurrence of CRC through various mechanisms. IL-6 stimulates the proliferation of CRC cells mainly by activating the STAT3 transcription factor, and also promotes tumor angiogenesis and tumor cell growth and invasion by regulating the immune cell function.[81,82] Compared with the normal control group, IL-6 is highly expressed in CRC, and the level of IL-6 in the peripheral blood of CRC patients is highly correlated with its clinical stage and disease progression.[83] In addition to being produced in large quantities by T cells, IL-10 can also be produced by T regulatory cells (Tregs). Both in normal colorectum and CRC, it is an important immune factor with a dual effect of immune suppression and immune stimulation; excessive local secretion of IL-10 will produce an immunosuppressive microenvironment around the tumor, while systemic IL-10 increase inhibits the body's antitumor immune killing effect.[84] IL-10 in the tumor microenvironment can also enhance the activation of STAT3, thereby affecting the immune status of the body.[85] Studies have found that in mouse experimental models, the increased IL-10 can promote the occurrence and development of CRC.[86,87]

3.3.3 | Other cytokines and CRC

COX-2 is mostly not expressed or underexpressed under normal physiological conditions, but when there is an inflammatory stimulus it is activated through various pathways such as protein kinase A (PKA), and then rapidly synthesized and expressed.[88] Prostaglandin E2 (PGE2), produced by COX-2, has been shown to be highly correlated with the occurrence and development of CRC.[89,90] After PGE2 binds to the EP2 receptor, it activates the related signaling pathways, thereby regulating inflammation and promoting tumorigenesis. The content of PGE2 in CRC tissue is closely related to the growth of tumor cells,[91] and the selective inhibition to PGE2 can inhibit CRC and regulate mucosal immunity.[92] Another study[93] found that in the bodies of patients with liver metastases from CRC, the PGE2 value was significantly higher than that of the control group, suggesting that PGE2 may be involved in tumor metastasis and spread.

A large number of epidemiological and clinical studies have shown that the clinical application of nonsteroidal antiinflammatory drugs (NSAIDs) can reduce the incidence of CRC.[94,95] NSAIDs such as aspirin can inhibit the formation of COX-2, reduce the synthesis of PGE2, and have a certain effect on the treatment of CRC.[96] Flossmann and Rothwell[97] found through clinical studies that long-term oral aspirin can reduce the incidence risk of CRC. All of the above indicate that COX-2/PGE2 is closely related to the occurrence and development of CRC, and also provide new ideas for the treatment of COX-2/PGE2 as the target.

4 | MiRNAS AFFECT THE OCCURRENCE AND DEVELOPMENT OF CRC BY REGULATING EPITHELIAL-MESENCHYMAL TRANSITION

MicroRNAs (miRNAs) are a type of noncoding single-stranded small RNAs that participate in the regulation of various physiological and pathological processes in the body.[98] MiRNAs mainly exert biological functions by combining with the 3'non-coding region of specific target genes, thereby reducing the expression of target genes, or by inhibiting their translation, participating in the regulation of cell proliferation and differentiation, tumor metastasis and invasion, and other processes.[99] It has been pointed out in the literature that compared with normal tissues, CRC tissues have different miRNAs expression levels.[100] MiRNAs have a duality in the pathogenesis of CRC. On the one hand, they can act as an oncogene or tumor suppressor gene. On the other hand, they can play an important role in promoting the occurrence of CRC by regulating the EMT.[101] The EMT process can stimulate the production of inflammatory factors by cancer cells,[102] and the evidence of its relationship with inflammation in CRC has been fixed.[103] EMT mainly refers to the biological process in which epithelial cells lose their epithelial properties and turn into mesenchymal cells. Its main features are the reorganization of the cell skeleton and the loss of intercellular adhesion. Among them, the expression of E-cadherin, which can enhance intercellular adhesion, is reduced, and it is converted to the main vimentin of the mesenchymal cell skeleton. The adhesion between cells is decreased, the connection is loose, and it is easier to invade and metastasize.[104,105] Studies have shown that in patients with CRC, the expression of E-cadherin is reduced, and the tumor is more prone to invasion and metastasis.[106]

Studies have shown that some miRNAs can regulate EMT to participate in the pathogenesis of CRC by regulating the expression of E-cadherin, vimentin, etc., and it has a dual nature. The miR-200 family can enhance the transcription and translation of E-cadherin by binding to the 3'non-coding regions of E-cadherin transcription inhibitors, Zinc finger E-box-binding homeobox 1 (ZEB1) and Zinc finger E-box-binding homeobox 2 (ZEB2), thereby inhibiting tumor invasion.[107] When ZEB1 is expressed in CRC, it can also increase the expression of miR-200, reverse the EMT process, and inhibit tumor cell proliferation and migration.[108] This shows that miR-200 and ZEB1 regulate each other to form a negative feedback mechanism to regulate EMT and affect the progression of CRC. Researchers have also described the role of the miR-200 family in different cancers and have described the role of miRNAs in CRC.[109] The miR-200 family members are transactivated by p53, via the inhibition or overexpression of the miRNAs, and affects p53-regulated EMT by altering ZEB1 and ZEB2 expression, which means p53-regulated miRNAs are critical mediators of p53-regulated EMT.[110] Stephen's group[111] performed a systematic review, regarding the function of the miR-200 family and EMT in CRC both in vitro and in human studies, and concluded that the miR-200 family played a central role in the EMT process and had potential for both prognostic and therapeutic

management of CRC. Hu et al[112] found that miR-363-3p was closely related to the pathological stage of CRC and lymph node metastasis, and the expression loss in the group with lymph node metastasis, and in vitro experiments, found that high expression of miR-363-3p could reverse the EMT process. Sun et al[113] confirmed that the expression of miR-610 decreased in CRC tissues. When miR-610 was increased, the expression of E-cadherin decreased, indicating that miR-610 could inhibit the occurrence of CRC by affecting the expression of EMT-related proteins. Zhang et al[114] showed that the expression of miR-187 was missing or decreased in CRC tissues compared with the control group. High expression of miR-187 could regulate the expression of the target genes SOX4, NT5E, and PTK6, leading to abnormal downstream signaling pathways and inhibiting the EMT process of CRC cells.

MiR-21 has the function of proto-oncogene and has been confirmed to be highly expressed in most tumors including CRC, and affects the proliferation and invasion of cancer cells. Kang et al[115] found that the expression of miR-21 in CRC tissue was significantly increased through case analysis, and miR-21 may negatively regulate E-cadherin by increasing the expression of metastasis-associated protein 1 (MTA1); the elevated miR-21 was an independent risk factor for recurrence in CRC patients. Wang's[116] group was convinced that miR-21 promoted TGF-β-induced EMT in CRC; they found that miR-21 was upregulated and promoted TGF-β-induced EMT in CRC cells, suggesting that TGF-β-induced EMT of CRC via transactivation of miR-21. Huang et al[117] collected clinical cases of CRC and found that the TNM stage and depth of invasion in the high expression group of miR-19a were significantly higher than those in the low expression group, and in vitro experiments suggested that upregulating miR-19a could promote the process of TNF-α-induced EMT, and the ability to cause cancer cell invasion was enhanced.

5 | CONCLUSION

CRC is a tumor closely related to inflammation. In the process of the occurrence, metastasis, and deterioration of CRC, inflammatory cells, inflammatory mediators, and various cytokines all play important roles. With the deepening of research on the relationship between inflammation and CRC, the understanding of CRC and other immune-related tumors has become more and more profound. We also hope that through research on the inflammatory indicators and pathogenesis of CRC, the probability of inflammatory bowel disease turning into intestinal cancers can be reduced, so as to improve the diagnosis and treatment of CRC.

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