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Review

# Chronic inflammation in the development of colorectal cancer: pathological model and therapeutic targets

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**Abstract**

Colorectal cancer is very severe and a hard disease to treat because it is the second most deadly type of cancer in the world. The primary causes of mortality from colorectal cancer, which can be associated with a common and potentially fatal malignancy, are metastases to the liver and peritoneum. Colorectal cancer is fueled by chronic inflammation, which is caused by immune system molecules that launch a cascade of reactions that lead to the emergence of positive feedback to maintain the resulting inflammatory response. Pro-inflammatory cytokines, such as interleukins 1, 6, and 17 (IL-1, IL-6, IL-17), along with tumor necrosis factor-alpha (TNF-α), are released into tumor sites during immune cell infiltration by macrophages. These cytokines play a critical role in promoting tumor invasion, growth, and survival. To develop innovative approaches to immune response modulation against cancer, a thorough knowledge of these intricate molecular interactions is essential. These approaches may include both targeting cytokines and inflammatory factors, as well as transcription factors such as STAT3/6, (TNF)-α, which underlie the initiation of inflammation. This review will present current knowledge on the role of chronic inflammation in colorectal cancer development, present a model of chronic inflammation development, and propose therapeutic targets based on it. This work will allow researchers and physicians to take a new look at one of the aspects of colorectal cancer pathogenesis. The pathological model and potential therapeutic strategies described in this review can become the basis for finding new therapeutic targets and developing drugs for the treatment of colorectal cancer.

**Keywords:** Inflammation, Cancer, Colon, Cytokines, Lymphocytes, Mutations

## 1. Introduction

Colorectal cancer is a multifactorial disease. It is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide. The etiology of colorectal cancer remains unclear [1]. Although early diagnosis can significantly improve prognosis, patients with colorectal cancer often lack typical clinical manifestations or show only non-specific features at an early stage, resulting in a low rate of early diagnosis. Numerous treatment options are available depending on the tumor stage and patient characteristics. These include surgery, chemotherapy, radiotherapy, molecular targeted therapy, immunotherapy, and other programs [2].

The majority of occurrences of colon cancer are random, while around 5% are caused by a genetic mutation that was inherited, primarily as a result of Lynch syndrome. The progression from healthy intestinal epithelium to invasive cancer tissue often occurs over a number of years and is marked by the formation of genetic alterations, the development of adenomas, and then carcinoma (also known as the adenoma-carcinoma sequence) [3].

The third most frequent type of cancer is colorectal cancer. Colon cancer affects men slightly more than women (52% versus 48%). [4]. Although the rate of reduction has lately slowed, the incidence of this malignancy has been continuously decreasing. People under 50 are experiencing a higher percentage of newly diagnosed malignancies [5]. Rectal and colon cancers on the right side have also become more common [6].

The usual treatment for resectable colon cancer that is resectable is surgical excision. The position and development of the tumor determine the kind of resection, degree of lymphadenectomy, and particular procedures [7]. In certain cases of more advanced colon tumors, adjuvant chemotherapy is recommended [8]. Systemic treatment is used to treat patients with metastatic illness [9]. Colon cancer seldom uses radiation [10]. Patients who have progressive colon cancer may occasionally get palliative therapy through surgical techniques [11].

Rather than particular inherited genes, environmental

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variables account for the majority of occurrences of colon cancer [12]. Certain gut bacteria and infections, effects of environmental and nutritional mutagens, and persistent intestinal inflammation that occurs before tumor formation are risk factors [13], [14]. Since chronic inflammation is one of the pathological conditions of colorectal cancer, studies are needed to understand the development and progression of inflammation in CRC. Therefore, this review aimed to establish a model for the development of chronic inflammation in colorectal cancer and propose therapeutic targets based on it.

## 2. General pathogenesis of colorectal cancer

Genetic alterations occur during the shift from standard intestinal epithelium to the development of dysplasia, which eventually results in cancer [15]. Chromosome instability (CIN), mismatch repair mechanism (MMR), and CpG island methylator phenotype (CIMP) are the three primary genetic routes by which colon cancer can arise [16]. These paths greatly overlap but do not conflict with one another.

### 2.1. Chromosomal instability (CIN) pathway

The CIN route, which was formerly known as the traditional adenoma-carcinoma sequence, is distinguished by mutational gain, which causes an imbalance between tumor suppressor genes and oncogenes. The adenomatous polyposis coli (APC), Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS), and tumor protein p53 (TP53) alterations are often seen [17]. About 60% of colon tumors have APC mutations, which typically promote carcinogenesis [18]. β-catenin is bound by normal APC, which regulates the Wnt signaling pathway. This signaling process becomes aberrant due to APC mutations, which impair the control of cell division, apoptosis, and proliferation [19]. Mutations in KRAS and B-Raf Proto-Oncogene (BRAF) are also seen in CIN cancers, although they are not related to this pathway [20].

### 2.2. Mismatch repair mechanism (MMR)

DNA replication is a highly accurate process, and several mechanisms have evolved to avoid errors in this process. One of these is the mismatch repair (MMR) mechanism, which was originally discovered in prokaryotes. Nine different homologies have been described in humans [21]. Dysfunction of these mismatch repair proteins as a result of the inheritance of one mutated germline allele underlies Lynch syndrome [22]. The other allele may be inactivated by loss of heterozygosity (LOH), epigenetic silencing, or mutation [23]. Regions of short DNA segments repeated hundreds of thousands of times in the genome are called microsatellites. MMR-deficient cells are likely to accumulate DNA errors many times over [24]. The deficient mismatch protein system results in expansion or contraction of these microsatellites, a phenomenon called microsatellite instability [25].

Patients with Lynch syndrome have an earlier age of onset of invasive cancer, more common proximal or right-sided colon cancer, poorly differentiated histology, mucinous subtype, prominent lymphocytic infiltrate, but, surprisingly, the prognosis for stage II disease is better compared with mismatched colon cancer [26].

### 2.3. CpG island methylator phenotype (CIMP)

About 15% of colon tumors are associated with the CIMP pathway, which is defined by CpG island hypermethylation. KRAS and BRAF polymorphisms are commonly linked to CIMP-associated malignancies, which usually develop as serrated polyps as opposed to traditional adenomas [27].

A subset of sporadic colorectal tumors is characterized by microsatellite instability and mutant BRAF V600 [28]. The pathogenic hallmark is epigenetic silencing of mismatch repair proteins, mediated by CpG hypermethylation. This hypermethylation process occurs in the promoter region of genes encoding mismatch repair proteins, resulting in mismatch repair enzyme deficiency [29]. These tumors are termed CIMP+ tumors (CpG island methylator phenotype) [16]. Activating BRAF mutations, including BRAF V600, are an exclusive feature of these tumors [15]. This mutation is also more commonly associated with proximal or right colon cancers but portends a worse prognosis. The presence of CIMP has been studied as a biomarker of response to fluoropyrimidine-containing cytotoxic regimens such as FOLFOX or FOLFIRI, but its role remains controversial [30].

## 3. Model of chronic inflammation development in colorectal cancer

### 3.1. The occurrence of chronic inflammation in colorectal cancer

One of the organism's most basic and noticeable defense mechanisms is based on inflammation, which is a result of several chemical processes and cellular activity. The inflammatory response in the wounded area of the body triggers immunological reactions and cellular alterations that result in the healing of injured tissue and cell growth at the wounded part [31]. Chronic inflammation results in mutations that specifically aid in the development of cancer [32] if the underlying cause of the inflammation does not stop or if specific regulatory systems that should stop the process are in a state of malfunction.

Tumor cells in accelerated division, stroma, new blood vessels that feed tumor and different types of inflammatory cells that play an important role in carcinogenesis are all recognized components of the tumor microenvironment. A population of leukocytes, neutrophils, dendritic cells, macrophages, myeloid-derived suppressor cells, eosinophils, and natural killer cells may be present in the inflammatory neoplasm component. These cells are able to produce a variety of signaling agents, including cytokines and cytotoxic modulators such as reactive oxygen species and proteolytic enzymes [33].

In colorectal cancer (CRC), signaling pathways such as: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducer and activator of transcription 3 (STAT3) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) are essential for the cascade launch leading to the occurrence of chronic inflammation [34]. A transcription factor NF-κB controls immune cell growth and activity as well as the synthesis of adhesion molecules and proinflammatory cytokines [35], [36]. NF-κB activation raises the vulnerability to cancer in people with colorectal and inflammatory bowel disease (IBD) via upregulating phosphoinositide-3-kinase regulatory subunit 3 (PIK3R3) in colon epithelial cells [37]. Additionally, the NF-κB pathway is activated by the contact

between intestinal epithelial cells and microbiome, which promotes carcinogenesis [38]. It has been shown that with obesity, altered microflora contributes to increased inflammation in the intestines, which subsequently leads to carcinogenesis [39]. Moreover, NF-κB is crucial for macrophage function, and changes in its activation may impact the onset of colitis and malignancies linked to colitis [40]. In the context of IBD, our findings emphasize the critical role that NF-κB plays in the inflammatory process of the pathogenesis of colorectal cancer [41]. Neutrophils also play a role in the development of chronic inflammation in colorectal cancer. Thus, elevated levels of cir-nDNA, NETosis products that are highly immunogenic molecules, were found in patients' plasma with colorectal cancer [42].

Phosphoinositide kinase PI3K is engaged in several cell signaling pathways, one of which involves activating serine/threonine protein kinase B (AKT), an essential regulator of various cellular activities, including metabolism, survival, and proliferation [43]. Inflammation is exacerbated by PI3K/AKT activation, which raises the cytokine TNF-α production [44]. Since this signal pathway inhibits apoptotic mechanisms in epithelial cells, it causes alterations in the cells located around the tumor related to survival and division [45]. AKT increases the expression of anti-apoptotic regulator proteins, including B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra large (Bcl-xL) and downregulates a number of pro-apoptotic regulator proteins like caspase-9 and Bad. In order to ensure that the tumor receives enough blood supply, AKT encourages the synthesis of vascular endothelial growth factor (VEGF), which in turn increases angiogenesis [46]. The PI3K/AKT pathway in immune cells has the ability to regulate the activity of different leukocytes [47]; in particular, this initiation is necessary for regulatory T cells (Tregs) to proliferate and perform their suppressive role, which aids tumors in evading the antitumor immune reaction [48].

In response to the increased level of IL-6 and IL-22, another important regulatory factor, STAT3, is initiated, which enhances cell viability and the advancement of colorectal cancer [49]. In a study in a mouse model of CRC, IL-6 was found to induce increased expression of VEGFR2, which promoted increased tumor cell proliferation via STAT3 signaling [50]. Apart from its upregulation in tumor cells, STAT3 activation is necessary for the development of Th17 cells, prevention of dendritic cell maturation, and preservation of Foxp3+ Treg cells' immunosuppressive properties. IL-17 is a cytokine produced by Th-17 lymphocytes and is an important regulator of angiogenesis in CRC by activating PGE1, PGE2, and VEGF [51]. In addition, IL-17 promotes increased expression of anti-apoptotic proteins: Bcl-2 and Bcl-x [52]. Long STAT3 activation would cause proinflammatory cytokine production to continue and would change the local tumor microenvironment to be immunosuppressive in nature in a variety of tumor-infiltrating immune cells, including macrophages and dendritic cells [53].

### 3.2. Development and establishment of chronic inflammation in colorectal cancer

Prolonged inflammation results in impaired mitochondrial activity and reduced ATP synthesis, which in turn generates excessive reactive oxygen species (ROS) and nitrogen. Significantly, prolonged exposure to highly reactive nitrogen and oxygen molecules produced by inflammatory tumor cells causes damage to the epigenome, inhibits the processes of cellular DNA repair, accumulates DNA alterations (such as point mutations, gene deletions, or rearrangements), and eventually increases the unchecked growth of tumor cells that have transformed [54].

By triggering the nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP3) inflammasome and proinflammatory cytokines, ROS increase inflammation [55]. Particularly, it has been discovered that mitochondrial ROS function as signaling molecules that cause the generation of mediators increasing inflammation, specifically such cytokines as IL-1, IL-6, and TNF-α, which in turn activate STAT3 and NF-κB [56], the function of which was previously discussed. It has been discovered that TNFα causes DNA damage and ROS production, which in turn triggers carcinogenesis [57]. Remarkably, ROS are also crucial for controlling the NLRP3 inflammasome, a member of the NOD-like receptor family that triggers the inflammatory response [58].

### 3.3. Consequences of chronic inflammation in colorectal cancer

The effects of chronic inflammation in CRC extend throughout the body, from primary tumors to metastases, liver, bone marrow, intestine, skeletal muscle, and other organs. Recent studies have shown that even before metastatic disease, chronic inflammatory response promotes tumor progression by altering the interactions between neoplastic and non-neoplastic cells [59].

Acute phase protein synthesis as a reaction to inflammation is one of the better-understood hepatic processes in immunoregulation. Acute phase proteins are identified by their plasma concentration, which either rises in the case of positive acute phase proteins during inflammation or falls in the case of negative acute phase proteins [60]. Acute phase proteins can be classified as either positive or negative, with positive examples being ceruloplasmin, C-Reactive Protein (CRP), haptoglobin, and hepcidin, and negative examples including albumin, transferrin, transthyretin, and alpha-fetoprotein [61]. One of the main elements influencing the altered hepatic protein synthesis during the acute stage of inflammation has been shown to be IL-6. Circulating IL-6 levels spike in response to infection, spreading inflammatory signals throughout the organism [62]. One cytokine that stands out as having the highest rise in colorectal cancer patients when compared to healthy controls is IL-6, which also shows an increase in metastatic disease when compared to non-metastatic disease [63].

IL-6 also appears to be one of the major factors contributing to the alteration of liver metabolism in the conditions of pathological inflammatory reaction. It was shown that IL-6 led to systemic metabolic alterations in a mouse model of colorectal cancer (CRC), including a reduction of liver ketogenesis and significant hepatic glucocorticoid production. Consequently, anticancer immunotherapy failed as a result of the suppression of intratumoral immunity. One possible route by which immunosuppression in tumor tissue—often seen in individuals with advanced cancer—is linked to modifications in liver function and metabolic disturbances is the liver's IL-6-ketogenesis-glucocorticoid signal way [64].

Anemia is prevalent in CRC patients; in cases with curable illness, its frequency ranges from 30% to 40% [65].

A fraction of patients has microcytic anemia due to iron deficiency, which can be explained by the intraluminal bleeding that occurs commonly from colonic malignancies. Chronic inflammation, however, also seems to have a significant role in low hemoglobin levels and, specifically, normocytic anemia in CRC patients [66]. Anemia and chronic inflammation are linked by several interacting pathways. Firstly, iron availability to erythroid cells and iron absorption from the small intestine are restricted by hepcidin, an acute-phase protein generated in the liver [67]. Foremost, erythroid progenitor cell growth is directly inhibited by proinflammatory cytokines [68]. Moreover, reduced erythropoiesis results from proinflammatory cytokines' suppression of the kidneys' erythropoietin production. Reduced oxygen availability in cancer patients with anemia may be linked to systemic metabolic alterations, such as modifications in perfusion and hepatic lipid concentrations, which have been linked to hypoxia in animal studies [69]. These may also be connected with the principal anemia-related symptoms of fatigue, weakness, or dyspnea.

The multifaceted roles of chronic inflammation development in colorectal cancer are presented in Figure 1.

## 4. Therapeutic targets for chronic inflammation in colorectal cancer

### 4.1. Impact on the IL signaling pathway

It is difficult to find a viable treatment target for colorectal cancer (CRC) because of the intricate relationships between cytokines in various molecular networks. Targeting cytokine signaling, however, has been demonstrated in recent research to enhance chemo-inhibitory responses in colorectal cancer. For instance, in IL-17A-deficient mice models of familial polyposis, IL-17A showed two different effects. It lessened tumor invasion and the quantity of polyps [65]. In a CRC animal model, IL-22 suppression significantly lowered tumor burden and dysplasia while reducing intestinal inflammation to a certain degree [70].

In fact, CRC growth and progression are regulated by early loss of epithelial barrier caused by tumor-induced inflammasome activation or β-catenin activation. As a result, it may be possible to use IL-17/IL-23 expression as a therapeutic target to treat CRC [71]. Similarly, the expression of IL-6 and IL-6R is crucial to the pathophysiology of colorectal cancer. In colorectal cancer (CRC), IL-6 has a role in immune cell recruitment, proinflammatory cytokine production, and Th17 and Treg cell regulation [72].

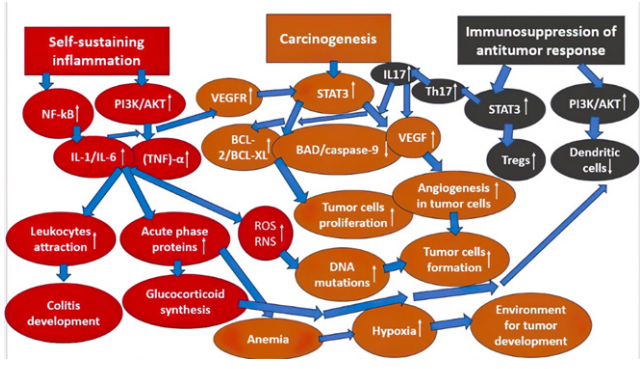


**Fig. 1.** The multifaceted roles of chronic inflammation development in colorectal cancer.

### 4.2. Effect on the NF-κB signaling pathway

The transcription factor NF-κB is a key regulator of inflammatory responses in IBD [73]. Because it regulates epithelial integrity and the communication between the intestinal microbiota and the mucosal system, NF-κB is critical for preserving intestinal homeostasis [74]. It has been documented that in individuals with ulcerative colitis, Crohn's disease, and non-specific colitis, NF-κB is stimulated in macrophages and epithelial cells of the inflamed mucosa. Fungal, microbial, and viral byproducts, as well as a variety of proinflammatory cytokines that stimulate the IκB kinase (IKK) complex, cause classical activation of the NF-κB pathway [73]. It has been reported that in a mouse model of colitis-associated cancer, deletion of IKKβ in intestinal cells significantly reduced tumor incidence without impacting tumor size but did not reduce inflammation. On the other hand, IKKβ deletion in myeloid cells led to a considerable reduction in tumor growth, suggesting that IKKβ can be selectively inactivated or pharmacologically inhibited in different cell types to successfully treat cancer [74].

Another work using a mouse model demonstrated that severe colitis, breakdown of epithelial integrity, and bacterial translocation were caused by targeted suppression of NF-κB by conditional ablation of the key modulator of NF-κB (NEMO) in intestinal epithelial cells. Furthermore, research revealed that NEMO deficiency made intestinal epithelial cells more susceptible to tumor necrosis factor (TNF)-induced apoptosis. This suggests that TNF signaling that is active causes inflammation in the colon and damages the integrity of the epithelial barrier, which ultimately results in the death of NF-κB-deficient intestinal epithelial cells [75].

Because it plays a crucial role in regulating inflammatory responses, TNF-α is another powerful cytokine that has been linked to a number of chronic inflammatory disorders, including IBD [74]. TNF receptor 2 (TNFR2) signaling has been linked to the development of colorectal cancer (CRC) in preclinical studies, indicating that TNFR2 activation plays a key role in the breakdown of the epithelial barrier, NF-κB-dependent tumor cell viability, and the production of proinflammatory cytokines [75]. In a separate preclinical study, it was demonstrated that administering azoxymethane and dextran sodium sulfate to wild-type mice induced TNF-α expression and leukocyte invasion in the colon's lamina propria and submucosa, leading to the development of many colonic tumors [76]. Furthermore, research demonstrated that administering a TNF-α antagonist and transplanting bone marrow defective in TNF receptor p55 (TNF-Rp55) to wild-type mice decreased mucosal damage and colonic expansion by neutrophils and macrophages [74].

### 4.3. Impact on KRAS signaling pathway

One of the most significant oncogenes in colon cancer, KRAS, is also becoming known as a possible therapeutic target for KPP management. Numerous studies have documented the important function of KRAS signaling pathway in inflammation and oncogenesis [77]. The characteristics of endothelial cells, cancer-associated fibroblasts, and the extracellular matrix composition are all modulated by KRAS-mutated cancer cells [78]. Patients with KRAS mutations have variable expression of IL-17, IL-22, and IL-23 throughout the development of CRC, and this ex-

pression is linked to the progression of the disease. Tissues with KRAS + CRC have elevated levels of IL-17 and IL-23 mRNA and protein. On the other hand, KRAS-CRC tissues had greater IL-22 levels [77].

IFN-γ levels in CRC tissues (KRAS + or KRAS -) are comparatively lower than those in healthy tissues. Moreover, administration of the KRAS inhibitor manumycin A results in an increase in apoptosis and a suppression in cell viability. The findings indicate that KRAS signaling is necessary for cytokine production and that KRAS mutations are strongly linked to inflammation that promotes tumor growth pointing to a biological connection between inflammation and carcinogenesis as well as a promising therapeutic target for KRAS [78].

### 4.4. Impact on STAT6 signaling pathway

It is unknown how certain STAT6 inhibitors are used in CRC preclinical and clinical research. On the other hand, STAT6 inhibition decreases tumor cell proliferation, survival, adhesion, invasion, and metastasis in experimental cancer cell models and lines, indicating that STAT6 inhibition might be a useful target for colon cancer treatment [79].

In CRC-bearing mice, use of the STAT6-specific inhibitor AS1517499 decreased tumor development and disease markers [79]. Colonic tumor burden and tissue damage were lowered in vivo by STAT6 suppression, which was in line with a decrease in intestinal STAT6 phosphorylation. The tumor growth and early liver metastasis were reduced by AS1517499 in an orthotopic 4T1 breast cancer mouse model [80]. The administration of AS1517499 to primary epithelial cells from individuals with prostate cancer also decreased the development of IL-4-induced colonies.

Reduced STAT6 expression is linked to the upregulation of miR-135b and miRNA/miR-361. Propofol, a popular intravenous anesthetic, has been shown to reduce inflammation linked to tumors and to generate microRNAs that downregulate the expression of STAT6 [81]. Propofol therapies of CRC SW480 and RKO cell lines have been demonstrated to decrease cell proliferation and migration and raise the expression levels of STAT6-targeting microRNAs, miR-135b and miR-361, indicating that propofol modulates the IL-13/STAT6 signaling pathway [82]. However, further research is needed to determine propofol's in vivo effects. The research was reported on a preclinical model in which STAT6 expression in lung epithelial cells is precisely downregulated using small interfering RNA (siRNA). The study suggests that intranasal delivery of STAT6 siRNA decreased allergic airway inflammation, suggesting that STAT6 may be targeted to particular tissues. Therefore, more research is required to determine if inhibiting STAT6 signaling in the colonic epithelium is a potential. Since the use of STAT6 inhibitors inhibits IL-4R type I and type II, it is important to ascertain the detrimental effects on regular immunological processes [83].

## 5. Discussion

Tumorigenesis is a multifaceted process that involves the unchecked growth of aberrant cells that define cancer. It is impacted by hereditary, physical, and epigenetic variables. Chronic inflammation is an important "player" in cancer pathogenesis. In addition to promoting tumor growth, this long-term immune reaction also modifies the tumor microenvironment in a number of ways [84]. It is mediated by a variety of cells and chemicals, including macrophages, lymphocytes, and proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β. Chronic inflammation may increase an individual's risk of developing cancer by encouraging the formation of gene disorders and the selection of more aggressive cellular variations, in addition to activating molecular pathways [85].

The NF-κB and JAK/STAT signaling pathways play crucial roles in leukocyte polarization and the regulation of antitumor immune responses in colorectal cancer. Specifically, activation of the NF-κB pathway promotes M1 macrophage polarization, which is associated with proinflammatory and antitumor functions. Conversely, inhibition of the NF-κB pathway facilitates M2 macrophage polarization, linked to immunosuppressive and tumor-promoting activities. These pathways are therefore central to modulating macrophage behavior and the overall immune surveillance against tumors in colorectal cancer [86]. Conversely, the JAK/STAT pathway controls Foxp3+ Treg cell cellular functions as well as T cell development [87].

Important study issues include the role of inflammation in cancer outcome prediction and the possible practical application of anti-inflammatory treatments in colorectal cancer. Chronic inflammation has been linked to the onset and spread of several cancers, including colorectal cancer. A tumor microenvironment that fosters cell growth, local expansion, and distant metastasis development is produced by this persistent systemic inflammation [88]. The inflammatory status of the tumor microenvironment in colorectal cancer can be used in the diagnosis of disease progression, survival, and response to therapy, as demonstrated in studies [89-91].

This inflammation involves several molecular pathways, one of which is the triggering of the nuclear factor kappa B (NF-κB) signaling pathway. This review illustrated the critical function of NF-κB stimulation as well as its relationship to colorectal cancer dysregulation. Thus, using anti-inflammatory drugs to target NF-κB activity could be a viable strategy for colon cancer treatment. Aspirin and celecoxib are two examples of non-steroidal anti-inflammatory medications (NSAIDs) that have shown anticancer effects in preclinical and clinical trials. These medications have the ability to block the NF-κB pathway, which reduces cell division, induces apoptosis, and suppresses the growth of tumor angiogenesis. NSAIDs that have been studied for possible application in the therapy of colorectal cancer include aspirin and sulindac. It has been demonstrated that sulindac lowers the risk of colorectal adenomatous polyps, which are the antecedents of colorectal cancer. Additionally, studies have demonstrated that aspirin helps prevent colorectal cancer, particularly in those with a family history of the condition [82].

In conclusion, a polypharmacological approach to modulating the complex signaling of inflammation and cancer appears to be the most promising option. Given the systemic and multifactorial nature of inflammation, targeting multiple proteins involved in inflammation and cancer pathogenesis is considered more effective than focusing on a single gene, protein, or signaling pathway. Thus, combination therapy based on potentially effective NF-kB and STAT3 inhibitors will contribute to both the resolution of the self-sustaining inflammatory response as a result of a decrease in the synthesis of IL-1/IL-6 and (TNF)-α, as

well as directly to tumorigenesis as a result of a decrease in the production of factors such as VEGF, BCL-2/BCL-XL. Potential clinical implications of such therapy would include both a reduced risk of developing inflammatory complications such as colitis and a reduction in the progression of tumor growth itself.

## 6. Conclusions

Research conducted over the past few decades has shown that chronic inflammation has a broad impact on CRC progression, including support of primary tumor invasion, proliferation, angiogenesis, and metastasis, as well as suppression of antitumor immunity. A better understanding of the signaling pathways involved in the development of chronic inflammation and promoting tumor progression and metastasis will provide a better understanding of the mechanistic details of disease aggressiveness and will facilitate the development of new therapeutic agents for the treatment of colorectal cancer. This review presented a model of chronic inflammation development in colorectal cancer and possible therapeutic targets based on it. This model is based on the initiation and interaction of signaling pathways: NF-kB, PI3K/AKT and STAT3, which form a single pathological network that includes such aspects as chronic inflammation that can develop into colitis; tumorigenesis based on the maturation and proliferation of tumor cells, as well as angiogenesis and antitumor immune response. Therapeutic effects on such targets as mediators of these signaling pathways (for example, cytokines IL-6/IL-17) or transcription factors initiating these signals (directly NF-kB) potentially contribute to a decrease in the progression of colorectal cancer.

## Author Contributions

AB and AO designed the review plan. NS, OM, and EK performed the data analyses. All authors wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflict of Interest

The authors declare no conflict of interest.

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