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Inflammation in Colorectal Cancer: Understanding Its Dual Role and Therapeutic Implications

Anastasia V. Poznyakz[1*], Nikolay Konstantinovich Shakhpazyan[2], Yonghao Ma[3], Minghui Wu[3], Elizaveta Romanovna Korchagina[1], Alexander N. Orekhov[1]

[1]Institute for Atherosclerosis Research, Osennyaya 4-1-207, 121609 Moscow, Russia

Email ID: nshakhpazyan@gmail.com

[2]Institute of Human Morphology, Petrovsky Russian National Center of Surgery, 2 Abrikosovsky Lane, 119991 Moscow, Russia

Email ID: tehhy_85@mail.ru

[3]College of Veterinary Medicine, Nanjing Agricultural University, No. 1 Weigang, 210095 Nanjing, Jiangsu, China

*Correspondence: tehhy_85@mail.ru (AVP)

ABSTRACT

Colorectal cancer (CRC) continues to be a leading cause of cancer-related mortality, significantly influenced by both genetic and environmental factors. Although substantial progress has been made in early detection and treatment, sporadic cases account for over 70% of CRC diagnoses, with certain inherited syndromes further increasing risk. This review emphasizes the complex interplay between inflammation and CRC pathogenesis, examining three types of inflammation—chronic, tumor-elicited, and therapy-induced—and their roles in tumor initiation, promotion, and progression.

Chronic inflammation, particularly in conditions like inflammatory bowel disease, significantly increases the risk of cancer development and mutation accumulation. Additionally, inflammation induced by tumors contributes to immune evasion and fosters tumor growth through intricate intercellular interactions within the tumor microenvironment (TME). Therapy-induced inflammation can have dual effects, either suppressing or promoting recurrence.

Recent advancements in immunotherapy, especially the use of immune checkpoint inhibitors, have shown promising outcomes in specific CRC subtypes; however, challenges persist, particularly in proficient mismatch repair (pMMR) cases. Understanding the role of inflammation in various CRC contexts is crucial for developing targeted therapies and improving clinical outcomes. This comprehensive framework highlights the need for further research to dissect the complexities of inflammation in CRC, ultimately paving the way for more personalized treatment approaches.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer diagnosed in both men and women. Despite advancements in early detection and treatment, it remains the third leading cause of cancer-related deaths in the United States, with over 55,000 fatalities each year [1,2]. The onset of CRC is influenced by a combination of environmental and genetic factors, with more than 70% of cases being sporadic. Individuals with inherited CRC syndromes, such as familial adenomatous polyposis (FAP), Lynch syndrome, Peutz-Jegher's syndrome, Juvenile Polyposis syndrome, and MUTYH-associated polyposis (MAP), are at a markedly increased risk for developing CRC, along with potential cancers outside the gastrointestinal tract [3-5]. Additionally, inflammatory bowel disease (IBD), particularly ulcerative colitis, is linked to a heightened risk of colorectal cancer. The incidence of CRC, referred to as colitis-associated cancer (CAC), in IBD patients can be as much as 60% higher than that in the general population. Sporadic CRC cases can also present a notable inflammatory response known as tumor-induced inflammation [6-8].

Although sporadic CRC and CAC share certain genetic features, they differ in the timing of mutations within critical genes or pathways. For example, mutations in the Adenomatous Polyposis Coli (APC) tumor suppressor gene arise early in sporadic CRC, whereas they occur later in CAC progression; conversely, TP53 gene mutations show the opposite trend [9-11].

The influence of inflammation on tumorigenesis in CAC is recognized, but its effects on sporadic and hereditary CRC are more intricate. Emerging studies suggest that anti-inflammatory medications may help prevent or delay CRC onset in both hereditary and sporadic forms, indicating a potentially overarching role of inflammation in CRC progression [12-14]. The recent identification of four consensus molecular subtypes (CMSs) of CRC seeks to enhance the development of targeted and personalized treatment strategies. Two notable subtypes, CMS1 ("MSI immune," 14%) and CMS4 ("mesenchymal," 23%), are enriched with lymphoid and myeloid-specific genes, reflecting an "inflammatory" character in these sporadic CRC cases [15-17]. Importantly, patients with CMS1 exhibit poorer survival rates after relapse, while those with CMS4 have the lowest overall and relapse-free survival rates. These observations underscore the urgent need for a deeper understanding of inflammation's role in sporadic CRC [18,19].

Inflammation is a hallmark of cancer, arising from various sources, including infections and exposure to carcinogens such as tobacco, alcohol, and radiation, as well as aging and obesity. Its role in cancer is dualistic. On one hand, targeting cancer cells via cytotoxic T-lymphocytes (CTLs) or reducing general inflammation through regulatory T cells (T-regs) can produce anti-cancer effects [20-22]. These positive responses are typically associated with Th1 polarization and correlate with a reduced likelihood of CRC recurrence. Additionally, the inflammasome complex can induce cell death in response to foreign agents or DNA damage through various sensors and inflammatory pathways [23]. Conversely, non-specific, chronic inflammation—often driven by Th17-related cytokines—may promote cellular proliferation and facilitate mutations that contribute to cancer development, leading to poorer outcomes [24,25].

Key players in inflammation related to cancer include innate immune cells (such as neutrophils, macrophages, innate lymphoid cells, intraepithelial lymphocytes, myeloid-derived suppressor cells, and natural killer cells), adaptive immune cells (B and T lymphocytes), intestinal epithelial cells (including Paneth cells), and various stromal cells (like fibroblasts, endothelial cells/pericytes, mesenchymal cells, adipocytes, and neurons) [26-28]. Interactions among these cell types primarily involve a sophisticated network of cytokines, chemokines, and growth factors, with the specific effects of these molecules depending on the receptors present on the cells, which can either promote tumor destruction or support tumor growth [29-31].

THREE FORMS OF INFLAMMATION IN CRC

Inflammation's influence on CRC development can be categorized into three distinct phases: chronic inflammation preceding tumor formation, inflammation induced by the tumor itself, and inflammation resulting from therapeutic interventions. Each of these types is characterized by the activation of innate immune cells, which contribute to tumor progression and the establishment of an immunosuppressive tumor microenvironment (TME) [32-34].

Table 1. Inflammation Types and Their Roles in Colorectal Cancer (CRC)

Inflammation Type	Definition and Context	Mechanism of Action	Role in CRC
Chronic Inflammation	Persistent inflammation, often due to IBD or environmental factors	Drives mutation accumulation and induces DNA damage	Initiates tumor formation, increases cancer risk
Tumor-Elicited Inflammation	Inflammation induced by tumor presence in tissue	Alters immune cell recruitment and functionality	Supports tumor growth, facilitates immune evasion
Therapy-Induced Inflammation	Inflammation resulting from cancer treatments (chemo/radiotherapy)	Activates immune responses focused on tumor cell death	Can promote recurrence or enhance anti-tumor immunity
Microbiota-Induced Inflammation	Inflammation triggered by gut microbiota dysbiosis	Alters cytokine profiles that affect epithelial cells	Contributes to inflammation-related tumor progression

INFLAMMATION-ASSOCIATED TUMORIGENESIS

Chronic inflammation, fueled by infections, immune system dysfunction, or environmental factors such as tobacco smoke, air pollutants, and certain dietary habits, significantly increases the risk of cancer development. In the context of colorectal cancer (CRC), chronic inflammatory bowel disease (IBD) and gastrointestinal inflammation linked to a Western-style diet

are major risk factors [35,36]. Although only a small fraction of CRC cases (up to 5%) is associated with clear chronic inflammation, studies employing mouse models, particularly the azoxymethane/dextran sulfate sodium (AoM/DSS) model, have been instrumental in revealing mechanisms of cancer development that are also applicable to sporadic cancers [37-40].

The transformation of a normal cell into a tumor cell involves two critical steps. The first step, initiation, occurs when mutations or epigenetic modifications lead to the inactivation of tumor suppressor genes or the overactivation of oncogenes, providing cells with a growth and survival advantage [41,42]. The second step, tumor promotion, is characterized by the rapid proliferation and expansion of these mutated cells, ultimately resulting in the formation of a detectable tumor. Inflammation plays a vital role in both of these processes [43,44].

Inflammation can initiate cancer by inducing DNA damage independently of external carcinogens, often associated with increased oxidative stress. This stress arises when immune cells such as macrophages and neutrophils release high levels of reactive oxygen and nitrogen species during inflammatory responses [45-47]. These reactive species can cause various types of DNA damage in intestinal epithelial cells (IECs), including single and double-strand breaks, nucleotide alterations, and the formation of abasic sites. Particularly, elevated levels of reactive oxygen species produced by myeloid cells can lead to widespread DNA mutations and can directly transform IECs, initiating cancer in the setting of chronic intestinal inflammation without the presence of carcinogenic agents [48,49]. Furthermore, inflammation compromises the epithelial barrier, potentially exposing intestinal stem cells to environmental mutagens or placing them in proximity to inflammatory cells that release genotoxic substances [50-52].

The disruption of the intestinal barrier allows both commensal and pathogenic microbes to invade, fostering interactions between IECs and microbiota components that may promote tumor growth. Chronic intestinal inflammation triggers excessive tissue regeneration, which stimulates the proliferation and clonal expansion of cells with initial tumorigenic alterations (tumor promotion) and the reprogramming of differentiated cells into stem-like cells to assist in tissue repair [53-56]. Intestinal stem cells have a greater capacity than non-stem cells to endure replication stress and DNA damage, and cells reverting to a more primitive state gain the ability to initiate tumors. Consequently, inflammation not only heightens the mutation rate but also increases the pool of cells capable of giving rise to tumors. Additionally, inflammation disrupts important cytokine receptor-mediated signaling pathways crucial for tumor initiation and promotion in CRC, including the activation of nuclear factor-κB (NF-κB) through signals from tumor necrosis factor (TNF) and interleukin-1 (IL-1) receptors, as well as the activation of the transcription factor STAT3 via gp130 in response to IL-6 and/or IL-11 [57-59]. Notably, IL-22, which also activates STAT3, promotes the transcription of genes involved in the DNA damage response, helping to mitigate the genotoxic effects of inflammation. In inflammatory-driven CRC, mutations that enhance TP53 functionality are detected early and are known to amplify TNF, NF-κB, and STAT3 signaling. Other mutations observed in inflammatory conditions, such as human ulcerative colitis—specifically in NFKBIZ, ZC3H12A, TRAF3IP2, and HNRNPF—are rarely found in CRC [60-62].

Beyond causing mutations through DNA damage, inflammation can also exert influence via epigenetic modifications, leading to the silencing of key tumor suppressor genes. Cytokines such as IL-1β, IL-6, and TNF regulate the activity of DNA methyltransferases DNMT1 and DNMT3, altering the methylation and expression of critical genes involved in CRC pathways like NOTCH and p53 signaling [63-65]. Recent studies indicate that NOTCH signaling can drive extensive metastasis in KRAS-driven CRC by recruiting neutrophils dependent on TGFβ, contributing to invasion and metastasis in a CMS4 tumor context [66-68].

Prostanoids, lipid compounds produced during chronic inflammation through cyclooxygenase 1 (COX1) and COX2 activity, play significant roles in all stages of colorectal cancer development. Prostaglandin E2 (PGE2), the most abundant prostanoid in CRC, promotes tumor initiation and growth by upregulating DNMT1 and DNMT3B, facilitating the expansion of cancer stem cells through NF-κB signaling activation [69-71]. Additionally, PGE2 enhances the differentiation of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs), influences macrophage polarization, and suppresses natural killer (NK) cell-mediated remodeling of the tumor microenvironment, thereby aiding immune evasion [72-75].

Further mechanisms through which inflammation may lead to the epigenetic suppression of cancer-associated pathways include the action of microRNAs and long non-coding RNAs (lncRNAs) targeting crucial pathways like WNT and Hippo that are significant in CRC development. These RNAs regulate essential signaling pathways implicated in CRC, including p53, NF-κB, and STAT3 signaling [76-78]. For example, the lncRNA H19 is upregulated in individuals with ulcerative

colitis and in animal models subjected to lipopolysaccharide-induced sepsis and DSS-induced colitis. In inflammatory contexts, IL-22 produced by various immune cells can trigger H19 production in IECs, promoting their proliferation. H19 acts as a competitive inhibitor of microRNAs that normally suppress growth, thereby accelerating colonic epithelium regeneration during DSS-induced colitis. Likewise, the increase in H19 lncRNA mediated by IL-22 may also enhance the proliferation of cancer cells during the progression of colitis-associated CRC [79-81].

Table 2. Key Mechanisms Linking Inflammation and CRC Progression

Mechanism	Description	Cellular Players Involved	Impact on CRC
DNA Damage	Reactive oxygen and nitrogen species cause various DNA mutations	Macrophages, neutrophils	Initiates genetic changes leading to cancer transformation
Altered Cytokine Signaling	Pro-inflammatory cytokines (IL-1, TNF, IL-6) promote survival of cancer cells	T cells, B cells, macrophages	Enhances survival, drives tumor progression
Epigenetic Changes	Altered gene expression due to inflammatory cytokines	DNA methyltransferases, histone-modifying complexes	Silences tumor suppressors and activates oncogenes
Microbiota Interaction	Changes in gut microbiota create inflammatory responses	Gut microbiota, epithelial cells	Increases cancer risk through enhanced inflammation

TUMOR-ELICITED INFLAMMATION

While inflammation can significantly contribute to tumor development, most cancers do not initiate with overt inflammatory responses. However, sporadic tumors can induce inflammation and heavily rely on interactions within the tumor microenvironment (TME) to facilitate both local and distant tumor growth. Researchers have identified various mechanisms that modulate innate and adaptive immune responses as well as stromal cell activation during the progression of colorectal cancer (CRC) [82-85].

An early event in this process is the disruption of the intestinal barrier, often triggered by WNT pathway activation in intestinal epithelial cells (IECs), typically due to mutations in the APC gene. This disruption allows microbial products from the gut to activate myeloid cells that express IL-23, resulting in the release of IL-17A, which promotes early-stage CRC. IL-1, produced by monocytes, stromal cells, and tumor cells, plays a crucial role in inducing tumor-related inflammation, affecting various cell types [86-89]. In IECs, IL-1 signaling stimulates cancer development, NF-κB activation, and cell proliferation, independent of inflammation induced by the tumor. In T cells, IL-1 signaling enhances IL-23 expression, further fueling the inflammation that supports cancer growth. Notably, IL-1 signaling in myeloid cells is essential for regulating microbial infiltration in tumors, which helps prevent tumor-associated microbial imbalances and inflammation following the disruption of the epithelial barrier [90-93]. Furthermore, the loss of p53 function in later cancer stages compromises epithelial integrity, resulting in increased microbial activation of NF-κB and STAT3 pathways, thus promoting inflammation. The activation of oncogenes and the loss of tumor suppressor genes not only facilitate cancer cell survival and growth but also sustain tumor-induced inflammation by indirectly releasing pro-inflammatory cytokines, growth factors, and chemokines that attract immune inflammatory cells to the tumor [94-97].

As tumors grow and outstrip their blood supply, hypoxia and nutrient deprivation lead to necrotic cell death and the subsequent release of pro-inflammatory molecules such as HMGB1, IL-1, uric acid, and ATP. Tumor hypoxia can induce the expression of hypoxia-inducible factor 1α (HIF1α) in both tumor and TME cells and activate cancer-associated fibroblasts to secrete TGFβ, CXCL13, and other chemokines [98-100]. These substances attract various myeloid and lymphoid cells, including monocytes, macrophages, and B cells, as observed in prostate cancer. In TME environments characterized by high levels of TGFβ and hypoxic stress, there is an increase in regulatory T cell (Treg) formation and a suppression of effector T cell differentiation, impairing the immune system's ability to combat tumors in CRC [101-103].

Importantly, the cytokine composition within the colorectal TME not only initiates inflammation that supports tumors but also creates an immunosuppressive environment. For instance, cytokines released by tumors, such as TGFβ, diminish the antigen-presenting capabilities of dendritic cells (DCs), suppress T cell proliferation and cytotoxicity, promote Treg cell development, and reduce the efficiency of natural killer (NK) cells [104-106]. Elevated TGFβ levels in the TME further

facilitate immune evasion by hindering T cell infiltration; blocking TGFβ signaling has been shown to enhance immune cell access to MSS-like CRC tumors, significantly improving responses to immune checkpoint inhibitors and leading to the elimination of established metastases. In human serrated CRC tumors, lower levels of atypical protein kinase Cs (PKCς and PKCλ/ι) are associated with reduced immune surveillance [107-110]. Notably, in these tumors, the combined blockade of TGFβ and checkpoint inhibitors significantly decreases tumor size and aggression. Tumor cells can also evade T cell detection by suppressing STAT3-dependent mitophagy in IECs, which is crucial for antigen processing. Additionally, the recruitment of B cells to the TME may suppress immune responses. When exposed to cytokines such as TGFβ, IL-21, IL-33, and IL-10 within the TME, B cells undergo class switching from IgM to IgA. IgA mainly regulates the microbiota, which generally opposes tumor progression; additionally, IgA+ plasma cells exhibit anti-inflammatory and immunosuppressive properties [111-114]. For example, chronic liver inflammation leads to an accumulation of IgA+ plasma cells expressing PDL1 and IL-10, which directly inhibit cytotoxic CD8+ T cells and compromise anti-tumor immunity. An increase in IgA-secreting B cells has also been noted in CRC patients, although direct studies examining the role of B cells and/or IgA in CRC remain to be conducted [115-118].

THERAPY-INDUCED INFLAMMATION

Therapy-induced inflammation, arising from treatments such as radiotherapy and chemotherapy, plays a significant role in the progression of colorectal cancer (CRC). Although these therapies are designed to eliminate tumor cells and alter the tumor microenvironment (TME) to stimulate healing responses, they also inadvertently trigger inflammation. This inflammation, while not an intended outcome, is a crucial factor in determining treatment effectiveness and the risk of cancer recurrence [119,120]. It can exert dual effects on tumor growth, either suppressing or promoting it, depending on the context. Dying tumor cells release damage-associated molecular patterns (DAMPs) such as ATP, double-stranded DNA, calreticulin, and HMGB1, which can attract and activate antigen-presenting cells, potentially enhancing the immune system's ability to recognize and eliminate cancer cells through tumor neoantigens [121-123].

However, both research and clinical evidence suggest that the aftermath of tumor cell death can also stimulate tumor growth and impair the immune response against cancer. For instance, IL-1α, released by dying cells, can promote cancerous transformation, angiogenesis, and metastasis. It also encourages fibroblasts to adopt an inflammatory role that supports tumor development [124-126]. Moreover, treatments like radiotherapy and chemotherapy may suppress the immune response; radiation can increase regulatory T cells in skin tumors, while the chemotherapy agent oxaliplatin can recruit immunosuppressive cells to prostate cancer tissue. Additionally, the death of tumor cells induced by therapy can lead to the release of various growth factors and cytokines from TME cells, including WNT, epidermal growth factor, TNF, IL-17, and IL-6. These factors can enhance the survival of residual cancer cells and contribute to therapy resistance [127-129].

A specific form of inflammation resulting from therapeutic intervention is the intentional activation of the immune system through checkpoint blockade, which is a central strategy in contemporary immunotherapies. Immune checkpoint inhibitors targeting PDL1 and CTLA4 have shown partial effectiveness in treating patients with metastatic mismatch repair-deficient (MMR-deficient) or microsatellite instability-high (MSI-H) CRC [130-132]. However, not all MSI tumors respond positively to immunotherapy; some may develop resistance due to mutations that disrupt essential genes involved in HLA class I-restricted antigen presentation. Interestingly, MMR-proficient or microsatellite stable (MSS) CRC, which constitutes the majority of metastatic cases, demonstrates a lower response to immune checkpoint inhibitors. This observation contrasts with the prognostic value of the immunoscore for CRC patients, regardless of their microsatellite status [132-134]. Several factors may contribute to this discrepancy in MMR-proficient/MSS CRC, including reduced expression of HLA class I and II molecules, an increased presence of myeloid-derived suppressor cells (MDSCs), lower levels of inhibitory receptors like PD1, and a shift in macrophage and cancer-associated fibroblast populations towards creating an immunosuppressive environment. Understanding the precise mechanisms underlying these observations remains a significant challenge in the field [135-138].

IMMUNOTHERAPY — THE ONLY WAY?

Immunotherapy, particularly through the use of immune checkpoint inhibitors (ICIs), has revolutionized cancer treatment. Although response rates to ICIs typically do not exceed 20%, patients who do respond often enjoy enduring benefits. The effectiveness of ICIs relies on several key factors, including the tumor's mutational burden—which results in a higher number of tumor-specific neoantigens—the presence of tumor-infiltrating lymphocytes, and the expression levels of regulatory checkpoint receptors [139-142]. ICIs function by inhibiting certain receptors on T cells, such as cytotoxic T

lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), thereby enhancing the immune system's ability to combat cancer.

T cells identify foreign antigens through interactions between their T cell receptors (TCR) and peptide fragments presented by major histocompatibility complex (MHC-I) molecules on tumor cells. Tumors with high mutational burdens are believed to produce a wider array of neoantigens that can be presented by MHC-I, leading to T cell activation and subsequent tumor destruction [143-145]. However, these T cells can become functionally impaired over time due to continuous exposure to antigens or interactions between PD-1 on T cells and PD-L1 on immune or tumor cells, or CTLA-4 and CD80/CD86 on dendritic cells, which play crucial roles in antigen presentation. Blocking these interactions has been shown to revive exhausted T cells, potentially resulting in tumor regression. The notably higher response rates observed in non-small cell lung cancer (NSCLC) and melanoma have been attributed to the elevated mutational loads typically found in these tumors [146-148].

For tumors that exhibit low levels of inflammation and T cell infiltration—possibly due to limitations in the initial immune response or a deficit of high-affinity T cells—strategies like vaccination or targeted therapies such as adoptive T cell therapy (ACT) may prove beneficial. These approaches are particularly effective for targeting specific mutated antigens and can be advantageous when used in conjunction with ICIs [149-151].

Cancer vaccines aim to stimulate an immune response by directly engaging the immune system. They achieve this by delivering antigens to dendritic cells and antigen-presenting cells (DC-APC), which subsequently activate both CD4+ and CD8+ T cells, leading to the elimination of tumor cells. These vaccines can focus on either tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) [152-154]. TAAs are present in both healthy and cancerous cells; however, T cells targeting these antigens may be eliminated due to immune tolerance mechanisms. In contrast, TSAs are unique to tumor cells and can effectively elicit an immune response by activating T cells. One significant challenge with TSA-based vaccines is the need for a personalized approach that tailors the vaccine to target the unique neoantigens present in an individual’s tumor [155-157].

Adoptive T cell therapy (ACT) provides a targeted treatment strategy that has shown promise, particularly when the neoantigen burden is low or undisclosed. For example, CD8 T cells that target specific mutations in genes such as KRAS or TP53 have been identified. Additionally, recently discovered circulating PD-1+ lymphocytes that can recognize neoantigens in human gastrointestinal cancers further highlight the potential of ACT in cancer therapy [158-160].

IMMUNOTHERAPY FOR CRC — IS IT WORTH A SHOT?

Initially, immune checkpoint inhibitors (ICIs) were not considered a viable treatment option for colorectal cancer (CRC). An early phase II trial assessing the efficacy of tremelimumab, a CTLA-4 monoclonal antibody, in CRC patients who had not responded to prior therapies showed no improvement after treatment. Furthermore, two phase I trials testing anti-PD-1 and anti-PD-L1 antibodies in previously treated CRC patients also failed to demonstrate positive responses [161-163]. The absence of information regarding the mismatch repair (MMR) and microsatellite instability (MSI) status of patients in these studies made interpreting the results challenging.

However, a subsequent phase I clinical trial with the anti-PD-1 antibody MDX-1106 in patients with various treatment-resistant cancers, including CRC, yielded a durable complete response in a CRC patient. This observation led to the hypothesis that CRC tumors characterized by high mutational loads due to MMR deficiencies might be more responsive to ICI therapy [164-166]. It was further established that patients with dMMR-MSI-H tumors exhibited a 40% objective response rate to pembrolizumab, while those with pMMR-MSI-L tumors had a 0% response rate. Additionally, dMMR-MSI-H patients demonstrated a remarkable 78% rate of immune-related progression-free survival. These findings suggested that MMR/MSI status could serve as a valuable predictor of a patient's potential response to pembrolizumab treatment [167-169].

Numerous clinical trials are investigating the use of ICIs in combination with various treatments for CRC. This extensive research has led the U.S. Food and Drug Administration (FDA) to approve pembrolizumab and nivolumab for patients with dMMR and MSI-H CRC. Pembrolizumab was the first to receive approval, marking the FDA's initial endorsement based on a tumor's genetic biomarker [170-172]. Following the results of the CheckMate-142 study, which reported a 31% objective response rate and a 73% one-year overall survival rate in treatment-resistant dMMR-MSI-H CRC patients, nivolumab also gained approval. This study further explored the efficacy of combining nivolumab with ipilimumab in the

same patient population, resulting in a 55% objective response rate and an 85% one-year overall survival rate, which ultimately led to FDA approval for this ICI combination in treatment-resistant dMMR-MSI-H CRC [173-175].

Given that the effectiveness of immunotherapy is often linked to the mutational burden, and considering that dMMR-MSI-H patients exhibit high mutation rates, vaccines targeting unique neoantigens may prove especially advantageous for these patients. Research using a mouse model with dMMR induced by MLH1 knockout demonstrated that vaccination extended overall survival and reduced tumor size, suggesting that vaccination could be an effective treatment strategy for dMMR in such models [176-178].

Moreover, human clinical trials of therapeutic cancer vaccines have shown promising results, which vary based on MSI status. A critical question that remains is whether the combination of ICIs with vaccines will provide greater efficacy than ICIs alone in dMMR-MSI-H CRC, or whether this strategy could elicit a response in proficient MMR (pMMR)-MSI-L CRC, which typically does not respond to ICIs by themselves [179,180].

ICI-RESISTANCE IN PMMR-MSI-L CRC

While immune checkpoint inhibitors (ICIs) have shown effectiveness in treating dMMR-MSI-H colorectal cancer (CRC), they are ineffective for pMMR-MSI-L CRC. This lack of response is thought to stem from a diminished antitumor immune response, as immune cells struggle to recognize these tumors due to their low mutation rates. This phenomenon has been observed in animal studies, where mice with MSI-H CRC exhibited more significant tumor reduction and T cell infiltration following anti-PD-1 therapy compared to those with MSI-L or intermediate MSI CRC [181-183].

Interestingly, despite the poor response to ICIs in MSI-L tumors, a greater presence of T cells within these tumors has been associated with improved disease-free survival. This finding suggests that certain MSI-L tumors may still be recognizable by T cells, prompting questions about whether these tumors utilize alternative mechanisms to evade immune detection. It may be possible to identify patients with higher T cell infiltration who could potentially benefit from ICI therapy [184-186].

A phase 3 study evaluated the combination of cobimetinib, an MEK inhibitor, with atezolizumab, an anti-PD-L1 monoclonal antibody, in patients with metastatic CRC. Inhibition of MEK resulted in increased infiltration of CD8+ T cells into the tumor, and in mouse models, this combination showed potential for enhancing tumor shrinkage [187]. However, despite these promising preclinical findings, the phase 3 trial did not reveal improved response rates or survival outcomes. The results indicated that combining MEK inhibitors with anti-PD-(L)1 therapy is ineffective in tumors characterized by low immune scores, such as pMMR-MSI-L CRC [188,189].

CONCLUSION

In summary, the intricate relationship between inflammation and colorectal cancer (CRC) is essential for understanding its development and progression. Chronic inflammation, whether originating from inherited conditions, inflammatory bowel disease, or environmental factors, plays a significant role in tumor initiation and the accumulation of mutations. Additionally, inflammation caused by tumors and that induced by therapies further complicate the clinical landscape by manipulating the tumor microenvironment, promoting immune evasion, and undermining treatment efficacy.

Recent insights into the varied roles of inflammatory mediators underscore the potential for new therapeutic interventions targeting these pathways. While immunotherapy, particularly immune checkpoint inhibitors, offers a promising treatment strategy, the complexities associated with CRC subtypes—especially in proficient mismatch repair cases—necessitate ongoing research to refine these approaches. Recognizing that inflammation can either promote or inhibit tumor growth calls for a more nuanced treatment strategy that considers patient-specific factors in therapeutic decision-making.

Ultimately, a better understanding of the inflammatory processes involved in CRC has the potential to transform treatment paradigms, paving the way for personalized medicine that addresses not only cancer cells but also the underlying inflammatory mechanisms. Continued investigation into these dynamics will be crucial for improving patient outcomes and lessening the impact of this widespread disease.

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