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REVIEW

Inflammatory bowel disease, colitis, and cancer: unmasking the chronic inflammation link

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Abstract

Background Chronic inflammation is a significant driver in the development of various diseases, including cancer. Colitis-associated colorectal cancer (CA-CRC) refers to the increased risk of colorectal cancer in individuals with chronic inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease.

Methods This narrative review examines the link between chronic inflammation and CA-CRC. A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science, focusing on studies published between 2000 and 2024. Studies were selected based on relevance to the role of inflammation in CA-CRC, specifically targeting molecular pathways and clinical implications. Both clinical and mechanistic studies were reviewed.

Conclusion Sustained inflammation in the colon fosters a pro-tumorigenic environment, leading to the initiation and progression of CA-CRC. Prevention strategies must focus on controlling chronic inflammation, optimizing IBD management, and implementing regular screenings. Emerging therapies targeting key inflammatory pathways and immune responses, along with microbiome modulation, hold promise for reducing CA-CRC risk. Understanding these molecular mechanisms provides a path toward personalized treatment and better outcomes for patients with IBD at risk of colorectal cancer.

Keywords Chronic inflammation · Colitis-associated colorectal cancer · Inflammatory bowel diseases · Pro-inflammatory mediators

Introduction

The well-established link between chronic inflammation and cancer development is particularly evident in colorectal cancer (CRC), which ranks as the second leading cause of cancer-related deaths in Western countries [1, 2]. Colitis-associated colorectal cancer (CA-CRC) is a significant contributor to morbidity and mortality among patients with inflammatory bowel disease (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD) [3]. Although only 1–2% of IBD patients develop CRC, CA-CRC accounts for approximately 15% of all IBD-related deaths [4]. As the global incidence of IBD continues to rise, there is an urgent

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need to better understand the mechanisms that link chronic inflammation to colorectal cancer development [5].

Chronic inflammation is recognized as a key driver in the progression of many diseases, including cancer. Within the colon, persistent inflammation plays a crucial role in the onset of CA-CRC. While patients with IBD can develop sporadic neoplasia, chronic inflammation remains the primary factor contributing to cancer risk [6]. Prolonged intestinal inflammation, coupled with the use of immunosuppressive therapies, increases the risk of cancer in IBD patients [7]. This sustained inflammatory state creates an environment where immune cells, inflammatory mediators, and the colonic epithelium interact, promoting a pro-tumorigenic microenvironment [8–10].

The mechanisms by which chronic inflammation fosters tumor development are multifaceted. Macrophages, neutrophils, and other inflammatory cells release pro-inflammatory cytokines, chemokines, and growth factors, establishing a microenvironment conducive to tumor proliferation, angiogenesis, and tissue remodeling [11]. In addition, chronic inflammation leads to increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which cause DNA damage and genomic instability, further driving cancer progression [12]. Prolonged inflammation also disrupts normal tissue repair processes, weakening the epithelial barrier and allowing harmful luminal factors, such as microbial components and toxins, to penetrate and exacerbate inflammation, further promoting tumorigenesis [13].

The complex relationship between IBD and CA-CRC presents significant clinical challenges in both prevention and management. Effective risk stratification, routine surveillance, and individualized treatment strategies are critical for improving long-term patient outcomes. Given the complexity of managing IBD patients at risk for CA-CRC, multidisciplinary care involving specialists from gastroenterology, oncology, and surgery is essential [14]. New advancements in surveillance techniques, combined with targeted therapies that address key inflammatory signaling pathways and immune responses, offer promising avenues for reducing CA-CRC risk in IBD patients [15].

Targeted therapies aimed at pro-inflammatory cytokines (such as IL-6and TNF-α) and pathways like NF-κB and STAT3 have shown potential in reducing inflammation and slowing cancer progression [16]. The use of advanced diagnostic tools, such as artificial intelligence-assisted colonoscopy [17, 18], may enhance the early detection of dysplasia, thereby improving survival outcomes for IBD patients at risk of CA-CRC. Additionally, it integrates lifestyle modifications and immunotherapy [19, 20]. Treatment strategies could further reduce CA-CRC incidence and improve prognosis.

Several recent reviews have explored the relationship between IBD and the increased risk of CA-CRC, focusing on various aspects of inflammation and cancer development. For example, some reviews highlight the role of chronic inflammation in fostering tumorigenesis, while others examine genetic and molecular differences between CA-CRC and sporadic colorectal cancer (S-CRC) [21–23]. Additionally, reviews have emphasized the importance of controlling inflammation through IBD therapies and the potential role of the microbiome [24] in promoting early tumor development.

However, these existing reviews often focus on isolated elements of the IBD-cancer connection, without fully integrating both the molecular mechanisms and the clinical implications. The novelty of our review lies in its comprehensive approach, which bridges the gap between molecular discoveries and clinical practice, providing a unified understanding of CA-CRC development and management. Our review delves into the molecular mechanisms driving inflammation and tumor progression while offering insights into clinical applications such as personalized medicine, advanced diagnostics, and emerging therapeutic strategies. By addressing both the pathophysiological and clinical dimensions, our work offers a more holistic view that is essential for advancing the prevention and treatment of CA-CRC, particularly in light of evolving technologies like artificial intelligence and multidisciplinary care. Figure 1 provides a comprehensive summary of the immune system's role in the progression from chronic inflammation to CA-CRC. It illustrates how chronic inflammatory conditions, such as Crohn's disease and ulcerative colitis, disrupt normal immune regulation. In the early stages of inflammation, innate immune cells, including macrophages and neutrophils, are activated in response to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). These cells release pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β, which trigger downstream signaling pathways such as NF-κB and STAT3, perpetuating inflammation. The figure further demonstrates how chronic activation of these pathways leads to DNA damage through the production of reactive ROS and nitrogen species (RNS), contributing to genetic instability and tumor initiation. Over time, epithelial barrier disruption allows luminal antigens to penetrate the tissue, amplifying the immune response and accelerating neoplastic transformation. Additionally, tumor-associated macrophages (TAMs) within the tumor microenvironment promote angiogenesis and cancer cell survival, driving tumor progression. Figure 1 ultimately shows how chronic immune activation and persistent inflammation synergize to create a pro-tumorigenic environment, highlighting

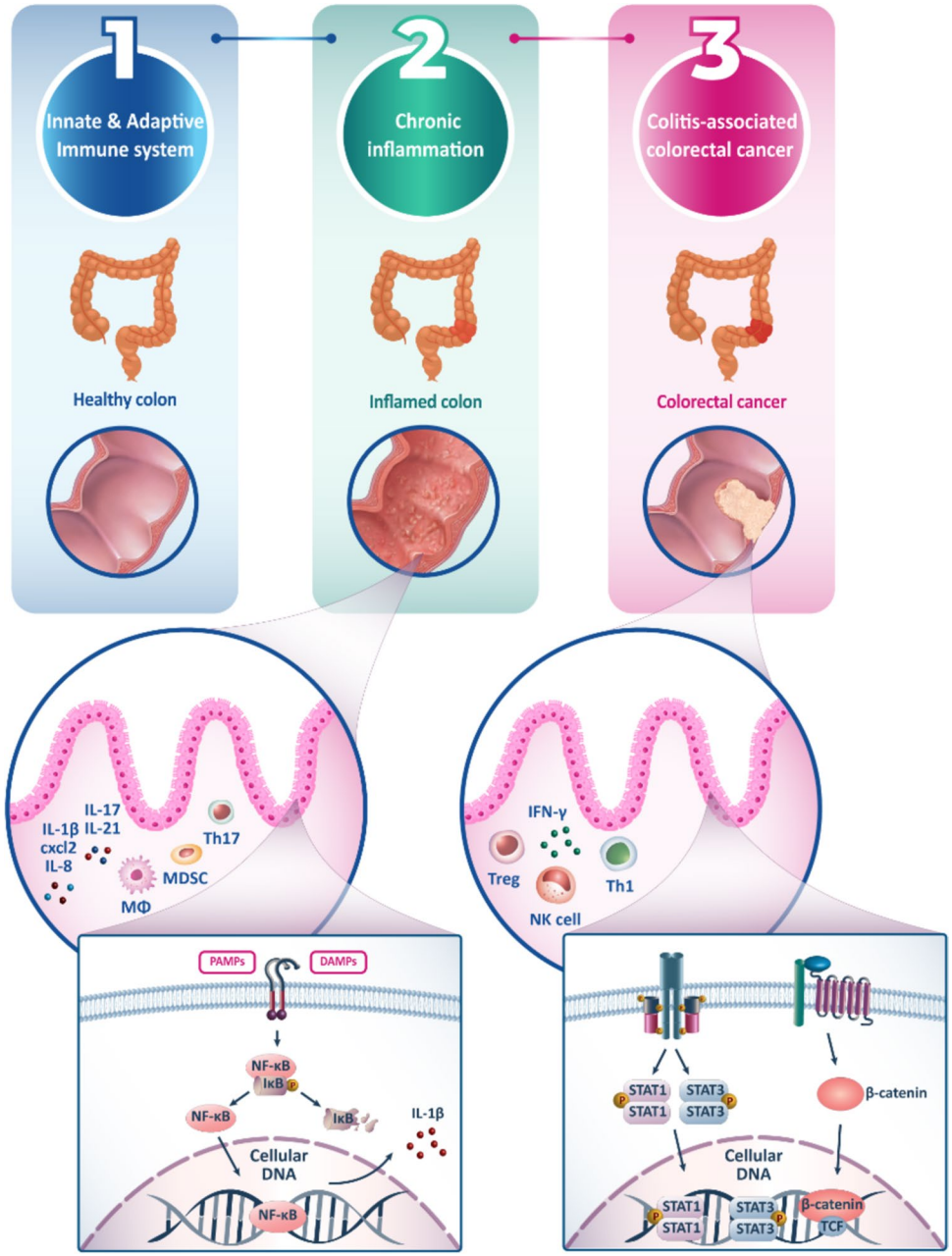


Fig. 1 Overview of the immune system's role in chronic inflammation and the progression to colitis-associated colorectal cancer (CA-CRC). The diagram shows the interaction between innate immune cells, inflammatory mediators, DNA damage, and epithelial barrier disruption. Chronic activation of pathways such as NF-κB and STAT3 leads to a pro-tumorigenic environment that fosters cancer cell survival, angiogenesis, and metastasis

key molecular pathways involved in the development of CA-CRC.

Methods

This narrative review explores the relationship between chronic inflammation and cancer, with a focus on CA-CRC. To ensure comprehensive coverage, literature searches were conducted using the following databases: PubMed, Scopus, Web of Science, and Google Scholar. The search was restricted to studies published between 2000 and 2023 and used keywords such as "colitis-associated colorectal cancer," "chronic inflammation and cancer," "inflammatory bowel disease (IBD) and cancer," "tumor microenvironment and inflammation," "signaling pathways in CA-CRC," and "colorectal cancer risk in IBD." Articles in English were included if they focused on the role of chronic inflammation in cancer development, specifically in CA-CRC. Both clinical and mechanistic studies, as well as reviews, were considered. Studies were excluded if they did not address the specific connection between chronic inflammation and colorectal cancer or focused exclusively on sporadic colorectal cancer. Additionally, articles without full-text availability were omitted.

The nature of chronic inflammation

Inflammatory mediators

Inflammation is the body's response to harm, aiming to defend against injuries and infections. While acute inflammation helps resolve tissue damage, unchecked or prolonged chronic inflammation leads to disease development, including cancer. In chronic inflammation, the immune system shifts from its protective function to a maladaptive state, characterized by abnormal tissue repair and immune suppression, creating a pro-tumorigenic microenvironment [25]. Inflammatory tumor microenvironments (TMEs) result from interactions between cancer cells and stromal/inflammatory cells. Chronic inflammation in the TME enhances cancer cell survival, proliferation, angiogenesis, metastasis, immune evasion, and treatment resistance. The continuous release of inflammatory mediators, including prostaglandins, chemokines, reactive oxygen species (ROS), and pro-inflammatory cytokines like IL-6 and TNF-α, plays a pivotal role in these processes [26, 27]. These mediators increase cancer cell genetic instability by causing DNA damage, disrupting DNA repair mechanisms, and promoting replication errors. Additionally, they activate key signaling pathways, such as IL-6/STAT3 and NF-κB, which enhance tumor growth and survival even in the presence of DNA damage [26, 27]. Neoplastic cells exploit these pathways for angiogenesis, survival, and metastasis [28–30].

DNA damage and genomic instability

Chronic inflammation results in the production of reactive molecules, such as ROS and reactive nitrogen species (RNS), which can cause significant DNA damage [26, 27]. Over time, this persistent DNA damage increases the likelihood of mutations and genomic instability, two key drivers of cancer progression [26, 27]. In conditions like Crohn's disease and ulcerative colitis, where chronic inflammation is ongoing, the risk of colorectal cancer is substantially higher than in the general population [30–32]. Inflammatory cells infiltrating the tumor microenvironment continuously release these reactive molecules, damaging the DNA of epithelial cells and promoting neoplastic transformation [33–36]. Chronic inflammation also interferes with the body's natural DNA repair mechanisms, further exacerbating genomic instability [32, 37]. This accumulation of mutations accelerates the transition from normal epithelial cells to cancerous ones.

Epithelial barrier disruption

In chronic inflammatory diseases such as Crohn's disease and ulcerative colitis, the intestinal epithelial barrier is often compromised. The disruption of tight junctions between epithelial cells increases intestinal permeability, allowing harmful luminal antigens, including bacteria, to penetrate the tissue. This further aggravates inflammation, leading to the persistent activation of immune responses [38–40]. The weakened epithelial barrier allows more immune cells to infiltrate the tissue, perpetuating tissue damage and promoting carcinogenesis [38–40]. This process creates a vicious cycle where inflammation leads to barrier disruption, which in turn fosters more inflammation, eventually promoting tumor development [32, 37]. This phenomenon is particularly relevant in the context of CA-CRC, where persistent epithelial barrier disruption is a hallmark of disease progression.

Key inflammatory pathways in CA-CRC

Multiple signaling pathways are activated by chronic inflammation, promoting tumor development. The IL-6/STAT3 and NF-κB pathways are central to this process, as they regulate immune responses, cell proliferation, and survival. The IL-6/STAT3 pathway, in particular, supports tumor growth by promoting angiogenesis and immune evasion [28–30], while NF-κB signaling drives the production of inflammatory cytokines that sustain tumor progression [33–36]. Additionally, tumor-associated macrophages (TAMs) within the TME release factors such as VEGF-A and IL-8, which promote angiogenesis and metastasis [1, 41, 42]. The activation of MAPK, JAK-STAT, Nrf-2, and Akt signaling pathways further contributes to cancer development by enhancing cell survival, resistance to apoptosis, and genetic instability [43]. Table 1 has been compiled summarizing the different approaches illustrating how chronic inflammation is involved in the development of CA-CRC. The mechanisms by which chronic inflammation bridges to CA-CRC are comprehensively outlined in this table, emphasizing the significant role of chronic inflammation in the pathogenesis of this disease.

Colitis-associated colorectal cancer (CA-CRC)

There is a well-established association between IBD and an increased risk of colorectal cancer (CRC) due to chronic inflammation that highlights significant concerns, with implications for CRC development [59].

Colitis-associated CRC (CA-CRC) stands distinct from spontaneous CRC (S-CRC), as they likely originate from differing molecular pathways, some of which are still under exploration [60, 61].

Patients with IBD face a greater risk of CRC, with risk factors being the degree and persistence of inflammation. CA-CRC often displays distinct histological features, such as a higher prevalence of signet ring and mucinous cells, compared to sporadic colorectal cancer (S-CRC). This difference

Table 1 Different approaches on how chronic inflammation bridges to colitis-associated colorectal cancer (CA-CRC); chronic inflammation plays a significant role in the development of CA-CRC

Aspect	Chronic inflammation's role in CA-CRC	References
Underlying inflammatory condition	CA-CRC is associated with long-term inflammation in the colon, often resulting from conditions like inflammatory bowel disease (IBD), particularly ulcerative colitis	[44]
Inflammatory mediators	Inflammatory cytokines, such as TNF-α, IL-6, and IL-23, are produced during chronic inflammation, leading to sustained immune activation and tissue damage	[45, 46]
DNA damage and genomic instability	Chronic inflammation can cause DNA damage and genomic instability in colonic cells, increasing the risk of genetic mutations and the development of cancerous cells	[47, 48]
Altered microenvironment	Inflammatory cells infiltrate the colon, releasing pro-inflammatory factors, growth factors, and chemokines, leading to an altered microenvironment that supports tumor growth	[11, 49, 50]
Activation of oncogenic pathways	Inflammatory signaling pathways, including NF-κB and STAT3, become activated, promoting cell survival, proliferation, and resistance to apoptosis, contributing to cancer development	[51, 52]
Angiogenesis	Chronic inflammation induces angiogenesis, promoting the formation of new blood vessels in the colon, which enhances nutrient supply to tumors and facilitates their growth	[53, 54]
Immune suppression	Prolonged inflammation can lead to immune suppression, impairing the immune system's ability to detect and eliminate cancer cells, allowing tumor progression	[55, 56]
Therapeutic implications	Targeting inflammatory pathways, using anti-inflammatory agents, and managing the underlying inflammatory condition are potential strategies to reduce the risk of CA-CRC development	[57, 58]

may be attributed to the chronic inflammatory environment in CA-CRC, which alters the tumor microenvironment and promotes the accumulation of mucins and the development of these distinct cell types. Mucinous carcinomas and signet ring cells are associated with increased inflammation, altered epithelial repair mechanisms, and immune evasion strategies, contributing to a more aggressive tumor phenotype [62] in contrast to sporadic colorectal cancer (S-CRC), which occurs independently of chronic inflammatory conditions [63, 64].

The clinical presentation of CA-CRC often challenges the medical community. Its propensity to arise from non-polypoid dysplasia amidst regions of inflammation and scarring makes its identification problematic, often leading to missed diagnoses during routine checks [65, 66].

The correlation between inflammation degree, persistence, and CRC risk underscores the integral role of inflammation in CA-CRC development. In IBD patients, the efficacy of colonoscopy surveillance is less efficient than routine colorectal cancer screening protocols [67].

Despite rigorous surveillance, interval cancer rates in IBD can reach 32%. Furthermore, there is a notable chance of detecting unobserved CA-CRC in patients undergoing urgent pan proctocolectomy for dysplasia. This highlights the pressing need to discern CA-CRC's molecular underpinnings and its progression [68, 69].

Diving deeper into the molecular distinctions, the TP53 mutation is an early occurrence in CA-CRC, often detected even in pre-malignant phases [70]. This contrasts with its rare appearance in S-CRC adenoma precursors. Genomic instability, evident from chromosomal abnormalities in non-dysplastic colitis mucosa, seems pivotal in CA-CRC's initial stages. Other differences include CA-CRC's diminished incidence of APC and KRAS mutations compared to S-CRC. Whole exome sequencing (WES) for CA-CRC has further unveiled unique genes with single nucleotide polymorphisms (SNPs) distinct to CA-CRCs [71, 72]. Understanding CA-CRC's distinct developmental pathway is crucial for advancing both its prognosis and preventive measures. As researchers continue to identify and understand these variations, it will pave the way for innovative therapeutic targets, potentially revolutionizing treatment, and management strategies for CA-CRC [73, 74].

The innate and adaptive immune responses both play important roles in CA-CRC. The innate system provides immediate defense, while the adaptive system generates a memory-based response. Their interaction influences disease progression and treatment outcomes, as explored in the following discussion.

Innate immune responses in CA-CRC

In CA-CRC, the innate immune system is activated in response to harmful microorganisms and damage to the intestinal lining [75]. This response involves pattern recognition receptors (PRRs), which detect microbial components or tissue damage, triggering immune signaling pathways that contribute to chronic inflammation and tumor development. While innate immunity plays a crucial role in maintaining gut homeostasis and protecting the host from pathogens, persistent dysregulation can promote

carcinogenesis, particularly in the context of inflammatory bowel disease (IBD) [76, 77].

Pattern recognition receptors (PRRs) in CA-CRC

PRRs, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), are key players in the recognition of microbial components and damaged cells. In CA-CRC, chronic inflammation alters the gut microbiota, and PRRs detect these abnormalities, triggering inflammatory responses that contribute to tumor initiation and progression [78, 79].

PRR-mediated inflammation and cancer development In CA-CRC, PRRs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), leading to the activation of inflammatory signaling pathways such as NF-κB and MAPK, which promote the release of pro-inflammatory cytokines like TNF-α, IL-1, and IL-6 [80, 81]. These cytokines create a tumor-promoting microenvironment by sustaining chronic inflammation, enhancing cell proliferation, and supporting tumor growth [81, 82].

Impact on tissue repair and tumor progression While PRRs are essential for tissue repair and regeneration, their dysregulated activation in chronic inflammation disrupts the balance between tissue healing and tumorigenesis. In CA-CRC, excessive PRR activation can impair proper healing, increase susceptibility to further damage, and promote cancer development by fostering an environment where immune cells produce pro-tumorigenic factors [83].

Tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs)

Tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) play crucial roles in promoting tumor progression in CA-CRC. TAMs, typically polarized toward a pro-tumorigenic phenotype, are recruited to the tumor microenvironment (TME) by chemokines and growth factors like CCL2 and VEGF, where they facilitate tumor growth by producing angiogenic factors and matrix metalloproteinases (MMPs) [84, 85].

Similarly, MDSCs suppress anti-tumor immune responses by inhibiting T cell activity, enhancing immune suppression in the TME, and supporting cancer progression. Their accumulation in CA-CRC is driven by chronic inflammation and contributes to immune evasion mechanisms, making them a key target for potential therapeutic interventions [86–88].

Complement system in CA-CRC

The complement system, an integral component of the innate immune response, has a dual role in CA-CRC (Fig. 2). While originally intended to protect against pathogens, the complement system's pathological activation in the TME can promote tumor progression. In CA-CRC, activation of the lectin pathway is significantly enhanced, and complement components such as C5a and C1q have been implicated in promoting tumor cell proliferation, migration, and immune evasion (Table 2) [89–91].

Adaptive immune responses in CA-CRC

Adaptive immune responses are also critical in the progression of CA-CRC. T cells and B cells interact with tumor cells in the inflamed colon, influencing the tumor microenvironment and contributing to either tumor suppression or promotion, depending on the immune cell activity and cytokine environment [93, 94].

T cells and immunological memory in CA-CRC

Cytotoxic CD8 + T cells play a crucial role in recognizing and eliminating tumor cells. However, in CA-CRC, tumor cells can evade immune surveillance by upregulating immune checkpoint ligands, such as PD-L1, which inhibit T cell activity [95, 96]. This mechanism allows tumors to escape immune destruction. Targeting immune checkpoints, such as PD-1 and CTLA-4, with immune checkpoint inhibitors has shown promise in restoring T cell-mediated antitumor responses in CA-CRC patients [97].

Moreover, memory T cells play a significant role in preventing tumor recurrence by providing rapid and robust responses upon re-encountering tumor antigens, helping to control tumor growth over the long term [98].

B cells and antibody-mediated responses

B cells produce tumor-specific antibodies that play an important role in anti-tumor immunity. These antibodies facilitate the destruction of tumor cells via mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [92]. The presence of tumor-infiltrating B cells and the production of these antibodies are associated with improved prognosis in CA-CRC (Fig. 3) [92].

Molecular pathways involved in inflammation-induced *cancer*

The development of CA-CRC is driven by multiple, interconnected inflammatory pathways, each contributing to the

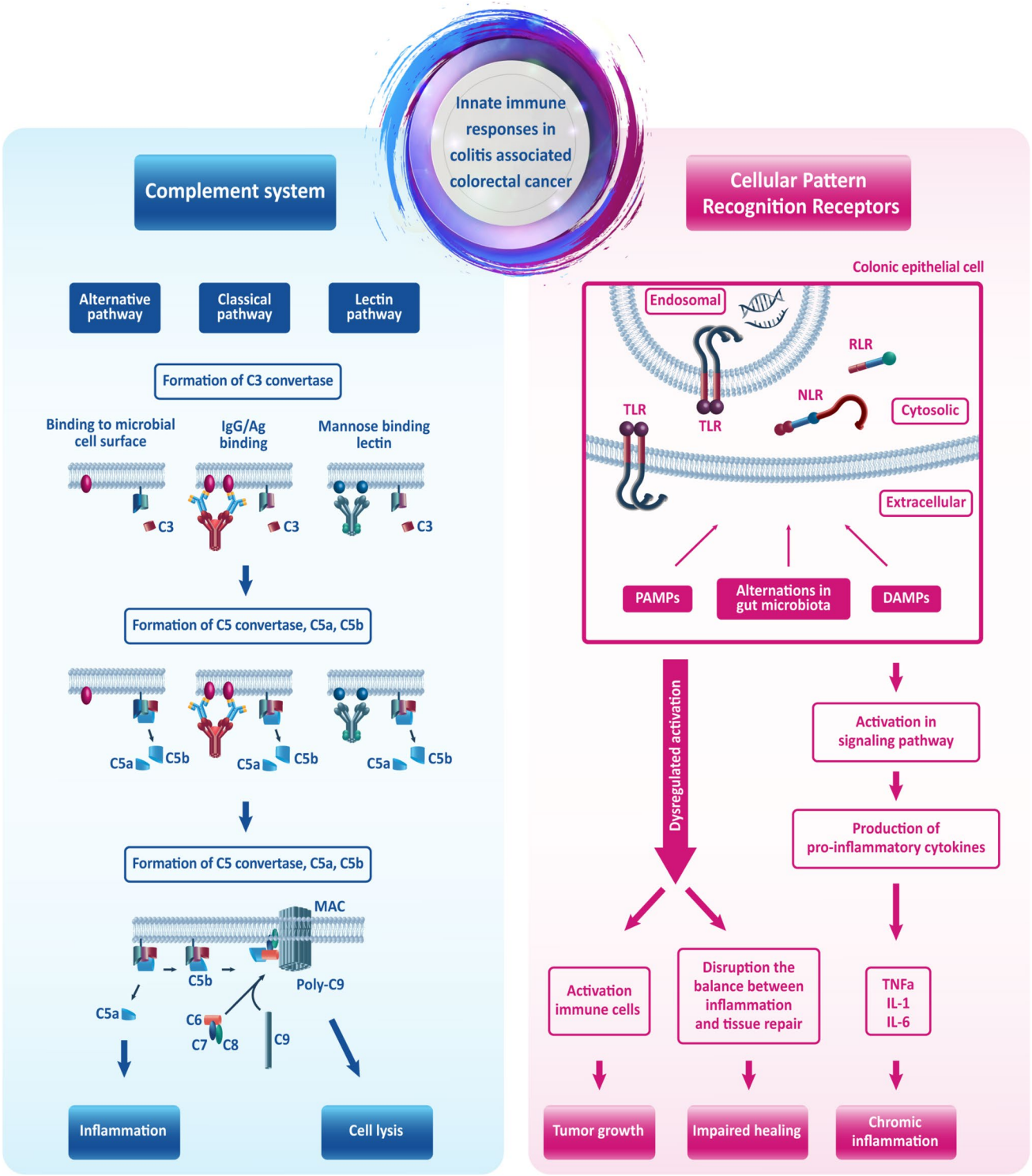


Fig. 2 Diagram illustrating the innate immune response mechanisms relevant to colorectal cancer. The left section highlights the complement system. Different complement activation pathways are involved in various cancers, with the lectin pathway significantly enhanced in colorectal cancer (CRC). Pathological activation of the complement cascade in the TME enhances tumorigenesis by controlling inflammation, epithelial-mesenchymal transition (EMT), tumor cell proliferation, stromal cell immunity, invasiveness, and migration. The right section showcases cellular pattern recognition receptors, highlighting their importance in recognizing and responding to specific molecular patterns

Table 2 Summary of clinical trials focusing on targeting MDSCs in colorectal cancer (CRC) patients [92]

Drug	Target	Intervention	Tumor	ClinicalTrials.gov identifier
DS-8273a	TRAIL-R2	Nivolumab	CRC	NCT02076451
Pexidartinib	CSF1R	Durvalumab	CRC	NCT02777710
Nivolumab	STAT3	BBI608	CRC	NCT03647839
Pembrolizumab	CCR5	Maraviroc	CRC	NCT03274804
Durvalumab	CSF-1R	Pexidartinib	CRC	NCT02777710
Bevacizumab	RAR/RXR	Vitamin D3	CRC	NCT04094688

initiation and progression of cancer through distinct, yet overlapping, molecular mechanisms. A better understanding of how these pathways interact can provide insights into potential therapeutic targets, many of which are already being explored (Table 3).

IL-6/STAT3 pathway

The IL-6/STAT3 pathway plays a central role in the progression of CA-CRC by promoting chronic inflammation, tumor cell survival, and immune evasion. Pro-inflammatory cytokine IL-6 activates STAT3, leading to increased expression of genes involved in cell proliferation (cyclin D1, c-Myc), survival (Bcl-2, Survivin), and angiogenesis (VEGF). Notably, the activation of STAT3 also triggers an immunosuppressive tumor microenvironment by upregulating molecules like IL-10 and PD-L1, allowing the tumor to evade immune surveillance [99, 111–113].

NF-κB pathway

The NF-κB pathway is one of the primary drivers of inflammation in CA-CRC. Activation of NF-κB by pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and microbial compounds leads to the expression of genes that promote cell survival and proliferation. NF-κB also upregulates COX-2, which contributes to chronic inflammation and tumor growth by increasing the production of prostaglandins. The sustained activation of NF-κB creates a feedback loop, where inflammation and tumorigenesis reinforce one another [51, 52, 114–116].

COX-2 pathway

The COX-2 pathway mediates inflammation through the production of prostaglandins, particularly PGE2, which has strong pro-tumorigenic effects in CA-CRC. COX-2 expression is upregulated by pro-inflammatory cytokines like TNF-α and IL-1β, leading to increased levels of PGE2, which promotes cell proliferation, angiogenesis, and resistance to apoptosis. Targeting COX-2 with inhibitors such as celecoxib has shown potential in reducing inflammation and slowing tumor progression in CA-CRC [95, 96, 117, 118].

Wnt pathway

The Wnt/β-catenin pathway plays a crucial role in maintaining intestinal homeostasis, and its dysregulation is frequently observed in CA-CRC. Inflammation-driven activation of Wnt ligands leads to the accumulation of β-catenin, which translocates to the nucleus and drives the expression of genes involved in cell proliferation and stemness. The Wnt pathway also contributes to the maintenance of cancer stem cells, which are associated with tumor initiation, metastasis, and resistance to therapy [119–123].

TGF-β pathway

The TGF-β pathway plays dual roles in CA-CRC, acting as both a tumor suppressor and promoter depending on the stage of cancer progression. Early in cancer development, TGF-β inhibits cell proliferation and induces apoptosis. However, as the disease progresses, chronic inflammation disrupts TGF-β signaling, allowing for uncontrolled cell growth, angiogenesis, and immune evasion. TGF-β also plays a key role in creating an immunosuppressive environment by promoting Treg cell development, which allows tumors to evade immune detection [124–126].

PI3K/Akt pathway

The PI3K/Akt pathway is critical in promoting cell survival and proliferation in CA-CRC. Dysregulation of this pathway, often through mutations in the PIK3CA gene, results in increased Akt activation, which promotes tumor cell growth and inhibits apoptosis. The PI3K/Akt pathway also enhances angiogenesis by upregulating VEGF, and it facilitates tumor invasion and metastasis through the regulation of MMPs (matrix metalloproteinases) [127–129].

MAPK pathway

The MAPK pathway, specifically the ERK and p38 branches, plays a vital role in cell proliferation and inflammation in CA-CRC. Activation of ERK1/2 leads to the expression of genes that promote tumor cell survival, migration, and inflammation. Meanwhile, the JNK and p38 pathways regulate the production of pro-inflammatory cytokines like TNF-α and IL-6, which further fuel tumor progression [130–132].

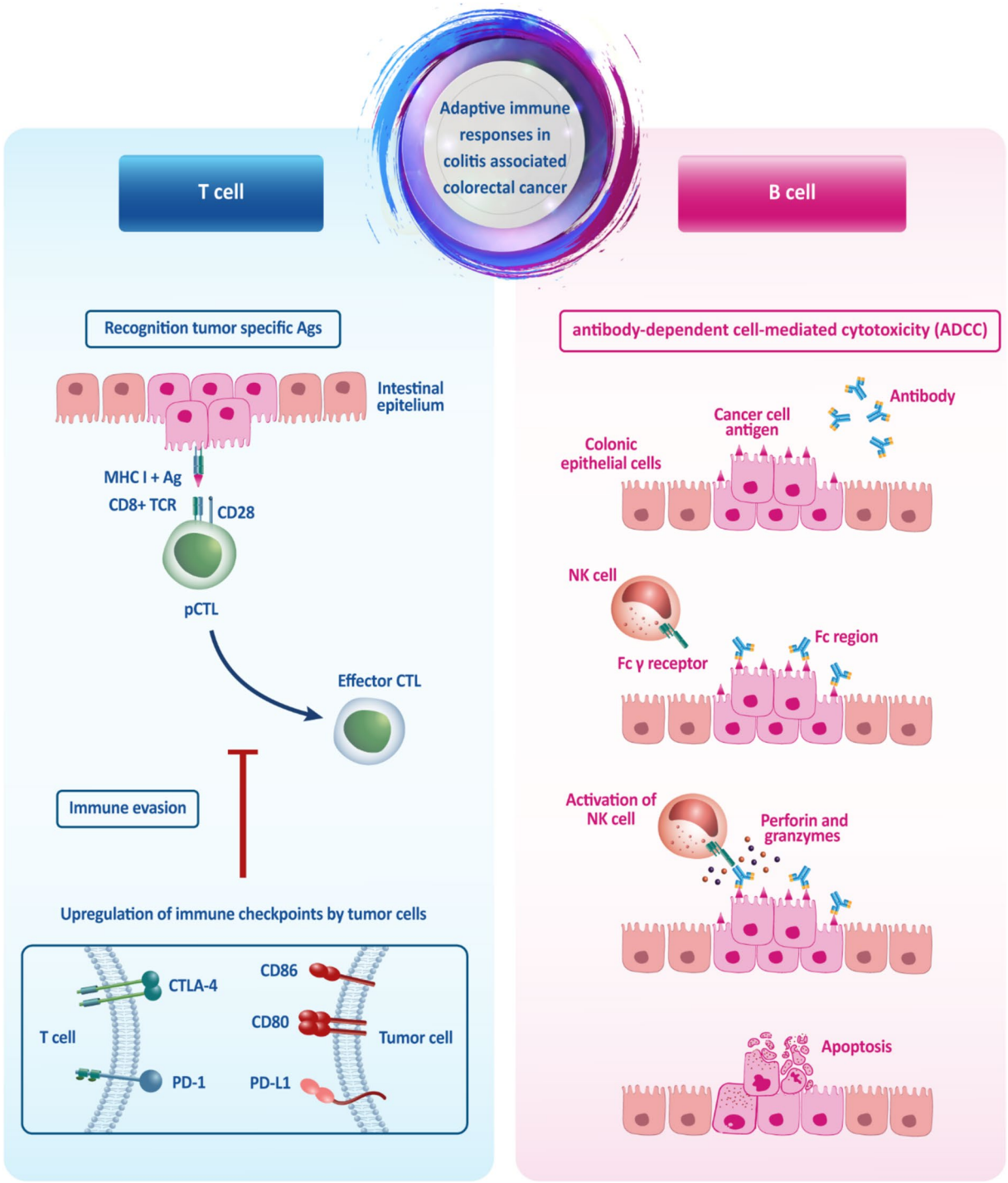


Fig. 3 Diagram illustrating the adaptive immune responses in colitis-associated colorectal cancer (CA-CRC). The image depicts the intricate network of components and interactions relevant to cancer progression, including T cell recognition of tumor-specific antigens, B cell involvement in antibody-dependent cell-mediated cytotoxicity, and the role of intestinal and colonic epithelial cells. It also highlights the interplay between major histocompatibility complex class I (MHCI), CD8 + T cell receptor (TCR), CD28 signaling, natural killer (NK) cells, immune evasion strategies, and immune checkpoint molecules (CD86, CTLA-4, CD80, PD-1, PD-L1)

Table 3 The major inflammatory pathways involved in colitis-associated colorectal cancer and their inhibitor drugs

Inflammatory pathway	Target molecules	Inhibitor drugs	References
IL-6/STAT3 pathway	IL-6, STAT3	Tocilizumab, siltuximab, ruxolitinib	[99]
NF-kB pathway	NF-kB, TNF-α	Infliximab, adalimumab, certolizumab	[100, 101]
COX-2 pathway	COX-2, PGE2	Celecoxib	[102, 103]
Wnt pathway	β-Catenin, APC	Wnt inhibitors (e.g., PRI-724, LGK-974)	[104]
TGF-β pathway	TGF-β, SMAD	Galunisertib, LY2157299	[105, 106]
PI3K/Akt pathway	PI3K, Akt	PI3K inhibitors (e.g., GDC-0941, BKM120)	[107, 108]
MAPK pathway	MEK, ERK	MEK inhibitors (e.g., trametinib, selumetinib)	[109, 110]

The gene therapy approaches in colitis-associated colorectal *cancer*

Gene therapy is a therapeutic approach that involves inserting, modifying, or replacing genetic material within an individual's cells in order to treat or prevent disease. There are also related approaches, such as gene editing. Gene therapy and gene editing come in a variety of flavors and approaches. Everything depends on understanding how genes function and how changes in genes can affect our health [133, 134]. Gene therapies are bringing new treatment options to multiple fields of medicine. Gene therapy in various forms has produced clinical benefits in patients with blindness, neuromuscular disease, hemophilia, immunodeficiencies, and cancer. Three essential tools for human gene therapy include adeno-associated virus (AAV), lentiviral vectors, and gene editing technologies. AAV and lentiviral vectors are the basis of several recently approved gene therapies. Gene editing technologies are in their translational and clinical infancy but are expected to play an increasing role in the field [135].

Genetic therapies that are currently approved by the FDA are available for people who have Leber congenital amaurosis, a rare inherited condition that leads to blindness. CAR T cell therapy is FDA approved for people who have blood cancers, such as acute lymphoblastic leukemia (ALL) external link and diffuse large B-cell lymphoma [136]. Gene therapy is an emerging field in the treatment of colorectal cancer, with ongoing research and clinical trials [137, 138]. Different gene therapy approaches and their target genes with delivery methods are summarized in Table 4.

The microbiome in CA-CRC

The gut microbiota, which refers to the complex community of microorganisms residing in the gastrointestinal tract, plays a significant role in various aspects of human health, including the development and progression of CA-CRC. Here is a closer look at the role of the gut microbiota.

There is increasing evidence suggesting that the microbiota plays a critical role in the development and progression of colorectal cancer [154]. Studies have shown that specific bacterial species, such as *Fusobacterium nucleatum* and *Bacteroides fragilis*, are more abundant in the gut microbiota of individuals with colorectal cancer than in healthy individuals. These bacteria can promote cancer growth by inducing inflammation, producing toxic metabolites, and interacting with cancer cells [155, 156]. On the other hand, some bacterial species, such as *Faecalibacterium prausnitzii* and *Bifidobacterium* spp., have been shown to have anti-cancer properties by producing short-chain fatty acids and other compounds that have anti-inflammatory and anti-tumor effects [157, 158].

Overall, the microbiota's impact on colorectal cancer is complex and not fully understood, but there is growing evidence suggesting that targeting the microbiota could be a promising strategy for preventing or treating colorectal cancer.

Clinical implications

Clinical implications for diagnosis and surveillance

Enhanced screening in high-risk populations Based on the findings related to chronic inflammation and its role

Table 4 Different gene therapy approaches and their target genes with delivery methods

Gene therapy approach	Target gene	Method of delivery	References
Suicide gene therapy	HSV-TK, CD/5-FC	Adenovirus vector, lentivirus vector	[139–142]
Gene silencing therapy	TGF-β, IL-6	siRNA, shRNA	[143–146]
Immunogene therapy	IL-10, TGF-β, IFN-γ	Adenovirus vector, lentivirus vector	[147–149]
Gene replacement therapy	APC, p53, PTEN	Adenovirus vector, lentivirus vector	[150, 151]
Tumor suppressor gene therapy	TP53, PTEN	Adenovirus vector, lentivirus vector	[152, 153]

in promoting CA-CRC, one key clinical implication is the need for improved diagnostic and surveillance strategies in patients with IBD. Chronic inflammation significantly raises the risk of colorectal cancer, particularly in patients with Crohn's disease and ulcerative colitis [159]. Therefore, regular colonoscopic surveillance and the use of biomarkers to detect early signs of dysplasia or neoplastic changes are critical in this population.

Personalized risk assessment As the field effect of inflammation extends the risk beyond localized areas of dysplasia, comprehensive risk assessment tools could be developed to better stratify patients for personalized surveillance. Integrating these findings into clinical practice would allow physicians to categorize IBD patients not just based on disease activity, but also on the molecular and inflammatory markers that indicate an increased cancer risk**.**

Therapeutic implications

Targeted therapies for inflammation-driven cancer The identification of key inflammatory pathways, such as IL-6/STAT3, NF-κB, and MAPK, provides a basis for developing targeted therapies aimed at modulating these signaling pathways. Drugs that inhibit these inflammatory mediators could not only reduce cancer risk in IBD patients but also serve as adjunctive treatments in established CA-CRC. Clinical trials exploring inhibitors like STAT3 blockers or NF-κB inhibitors may lead to novel therapeutic options that directly target the inflammatory mechanisms driving tumor progression.

Surgical decision-making and conservative approaches Clinical guidelines have traditionally recommended extended colectomy for patients with high-grade dysplasia (HGD) or cancer, based on the concept of the "field effect" of inflammation in CA-CRC. This field effect suggests that chronic inflammation extends beyond the tumor site, increasing the risk of dysplasia or cancer in other regions of the colon. However, recent clinical data have begun to challenge this approach. Studies now suggest that more conservative, segmental resections may be sufficient in some cases, reducing the need for extensive surgeries without compromising patient outcomes [160, 161]. With a better understanding of the field effect and the pathways leading to tumor progression, clinicians may be more inclined to adopt segmental resections or less invasive approaches in selected patients. This would reduce the physical and emotional burden of extensive surgery while maintaining effective cancer control. Personalized surgery strategies, combined with close monitoring, could improve patient quality of life and outcomes.

Conclusion

In summary, chronic inflammation plays a pivotal role in the development of CA-CRC through mechanisms involving DNA damage, disrupted epithelial barriers, and the activation of pro-tumorigenic signaling pathways. Inflammatory mediators such as IL-6, TNF-α, and IL-1β are central to these processes, perpetuating a tumor-promoting environment in patients with IBD. Despite the progress made in understanding the molecular links between chronic inflammation and cancer, further research is required to translate these insights into effective therapeutic strategies.

Future research directions

Future research in the treatment of colitis-associated colorectal cancer (CA-CRC) should prioritize targeting critical inflammatory pathways, such as IL-6/STAT3 and NF-κB, as these play key roles in tumor development. The exploration of novel inhibitors for these pathways could help reduce the pro-tumorigenic effects of chronic inflammation while preserving the normal function of the immune system. Additionally, identifying biomarkers that reliably predict the transition from chronic inflammation to cancer in patients with inflammatory bowel disease (IBD) will be crucial. These biomarkers, particularly molecular signatures of inflammation-related carcinogenesis, could enable earlier diagnoses and provide a foundation for more personalized treatment strategies. Moreover, as the tumor microenvironment in CA-CRC is heavily influenced by immune cells, research into immune-modulating therapies, such as immune checkpoint inhibitors, holds promise for enhancing the immune system's ability to recognize and destroy cancer cells. Further, the development of anti-inflammatory agents that specifically target chronic inflammatory pathways could significantly impact the prevention or delay of CA-CRC in high-risk IBD patients. In parallel, microbiome-based therapies, such as probiotics or fecal microbiota transplants (FMT), represent a novel approach to restoring a healthy gut environment, reducing inflammation, and mitigating cancer risk. Ultimately, the future of CA-CRC treatment will depend on a deeper understanding of the molecular drivers of inflammation and cancer, with continued research into targeted therapies, biomarker development, and immune modulation playing critical roles in advancing prevention and treatment strategies. In conclusion, while current therapeutic strategies have improved outcomes for patients with CA-CRC, the future of treatment lies in a deeper understanding of the molecular drivers of inflammation

and cancer. Continued research into targeted therapies, biomarker development, and immune modulation will be critical in advancing both the prevention and treatment of inflammation-driven cancers.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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