

Immune remodeling in inflammatory bowel disease-associated colorectal cancer: Mechanisms and immunotherapeutic implications (Review)

TAO ZHANG^{1,2*}, ZHETAN REN^{3*}, LING WANG¹, RU MAN⁴, LIN WANG⁴, JING WANG²,
XIAOZHEN CHENG⁵, JIRUN PENG^{3,6} and YONGDUO YU⁷

¹The Second Clinical College, Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning 110847, P.R. China;

²Department of Anorectal Surgery, Second Affiliated Hospital, Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning 110034, P.R. China; ³Department of General Surgery, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038, P.R. China; ⁴School of Nursing, Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning 110847, P.R. China; ⁵Department of Anorectal Surgery, Shenzhen Traditional Chinese Medicine Hospital, Shenzhen, Guangdong 518033, P.R. China; ⁶Ninth School of Clinical Medicine, Peking University, Beijing 100038, P.R. China; ⁷Administrative Office, Second Affiliated Hospital, Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning 110034, P.R. China

Received May 7, 2026; Accepted July 17, 2026

DOI: 10.3892/ijmm.2026.6024

Abstract. Inflammatory bowel disease-associated colorectal cancer (IBD-CRC) arises in the setting of long-standing chronic intestinal inflammation, in which immune dysregulation cannot be readily attributed to the dominance of a single inhibitory pathway or to global immunosuppression. Persistent inflammatory signaling sustains a state of prolonged immune engagement, yet with constrained effector output, potentially compromising antitumor immune surveillance and limiting the clinical benefit of immunotherapy. The present review synthesizes the accumulated knowledge on the long-term immunological alterations induced by chronic inflammation, including the integration of immune signaling, shifts in activation thresholds, metabolic reprogramming, and functional polarization of immune cells. These changes are discussed in the context of both tumor initiation and tumor maintenance

to delineate the immunological evolution of IBD-CRC. The review further examines the relationship between inflammation-induced response constraints and the limited efficacy of immune checkpoint inhibitors, and summarizes the mechanistic barriers to immunotherapy in IBD-CRC. Collectively, these observations suggest that relieving inhibition through a single target may be insufficient to restore effective antitumor immunity. Finally, the potential value of natural plant-derived interventions characterized by multi-component, low-intensity, and long-term modulation is discussed, particularly with respect to reducing inflammatory burden and improving immune metabolic states, thereby providing a conceptual basis for the development of combination immunotherapeutic strategies.

Contents

1. Introduction
2. Immunological differences between sporadic CRC and IBD-CRC
3. Intestinal immunity in the context of inflammatory bowel disease
4. Molecular network of inflammatory-immune crosstalk
5. Immunodynamic evolution of IBD-CRC
6. Current status and future directions of immunotherapy in IBD-CRC
7. Summary and perspectives

Correspondence to: Professor Jirun Peng, Department of General Surgery, Beijing Shijitan Hospital, Capital Medical University, 10 Tieyi Road, Haidian, Beijing 100038, P.R. China
E-mail: pengjr@medmail.com.cn

Professor Yongduo Yu, Administrative Office, Second Affiliated Hospital, Liaoning University of Traditional Chinese Medicine, 32 Huanghe North Street, Huanggu, Shenyang, Liaoning 110034, P.R. China
E-mail: yuyongduo@163.com

*Contributed equally

Key words: inflammatory bowel disease, colorectal cancer, immune remodeling, chronic inflammation, tumor immunity, microbiome, immunotherapy

1. Introduction

Inflammatory bowel disease (IBD) is a group of disorders characterized by chronic, relapsing intestinal inflammation (1,2). During disease progression, persistent infiltration of immune

cells, continuous release of pro-inflammatory cytokines, and prolonged activation of mucosal immune responses are commonly observed (3-5). Colorectal cancer (CRC) arising in the setting of long-term inflammation exhibits distinct features in terms of tumor immune microenvironment composition, immune response patterns, and regulatory mechanisms compared with sporadic CRC (6). IBD-associated CRC (IBD-CRC) develops within a chronically inflamed intestinal mucosal environment, where antitumor immune responses are often insufficient and difficult to sustain (7,8).

In sporadic CRC, immune checkpoint inhibitors (ICIs) have demonstrated clear clinical benefits in patients with specific molecular subtypes (9). However, therapeutic strategies that enhance tumor immune responses by relieving immunosuppressive signaling have shown inconsistent efficacy in patients with IBD-CRC (10,11). Clinical studies indicate substantial variability in responses to immunotherapy among patients with IBD-CRC. In some cases, treatment may exacerbate intestinal inflammatory activity, and the risk of immune-related adverse events may also increase (12,13). These observations suggest that the limited efficacy of immunotherapy in IBD-CRC is not solely attributable to treatment-related toxicity and cannot be adequately explained by alterations in a single immune pathway.

Current studies on immune abnormalities in IBD-CRC have largely focused on molecular and cellular alterations, including persistent activation of inflammatory signaling pathways, expansion of immunosuppressive cell populations, and upregulation of immune checkpoint molecules (14-16). Chronic inflammation associated with IBD not only provides a permissive background for tumor development but also continuously influences the functional state of the immune system and reshapes its regulatory mechanisms through sustained inflammatory signaling (17). Under prolonged inflammatory stress, the immune system does not simply become suppressed or inactivated. Instead, its regulatory mechanisms tend to prioritize the control of inflammation and the maintenance of tissue tolerance, conditions that are not conducive to the generation of durable and effective antitumor immune responses (18,19).

To better understand the immunological characteristics of IBD-CRC, the present review first compares the major differences between sporadic CRC and IBD-CRC in terms of immune microenvironment and inflammatory background. On this basis, the functional state of the immune system under chronic inflammatory conditions is elucidated, the molecular and cellular interactions between inflammatory signaling and immune regulation are summarized, and their roles in the development and progression of IBD-CRC are examined. Furthermore, in light of the clinical performance of immunotherapy in IBD-CRC, potential reasons for the limited therapeutic efficacy are investigated, and the potential role of natural plant-derived bioactive compounds in combination immunotherapy are explored, with the aim of providing insights for future research.

2. Immunological differences between sporadic CRC and IBD-CRC

Although both sporadic CRC and IBD-CRC are histologically classified as malignant colorectal tumors, they differ markedly

in their underlying etiological background and immune regulatory environment. In sporadic CRC, immune abnormalities typically emerge after tumor initiation and are mainly characterized by a gradually established local immunosuppressive tumor microenvironment. This includes enhanced immune checkpoint signaling, impaired antigen presentation, and other mechanisms that enable tumor cells to evade immune surveillance (9,10).

By contrast, IBD-CRC develops in the context of long-standing chronic intestinal inflammation. In this setting, immune alterations often arise prior to tumor formation and are closely associated with mucosal barrier disruption, gut microbiota dysbiosis, and the persistent activation of inflammatory cytokine networks. Evidence suggests that these two types of CRC exhibit distinct features in terms of immune cell infiltration patterns, inflammatory signaling characteristics, and mechanisms of immune suppression (13,14). Such differences may influence both the process of tumorigenesis and the responsiveness to immunotherapy.

The key immunological differences between sporadic CRC and IBD-CRC, along with their primary sources of evidence, are summarized in Table I (9-14,20-22).

3. Intestinal immunity in the context of inflammatory bowel disease

IBD commonly arises in the context of persistent inflammatory stimulation and continuous immune involvement and can be viewed as a disease state that gradually develops and is maintained under such conditions. As the disease progresses, the intestinal immune system is frequently mobilized and repeatedly engaged in inflammatory responses (23). Recurrent inflammatory activity disrupts the integrity of the intestinal mucosal barrier and is accompanied by long-term alterations in the tissue microenvironment, gradually leading immune responses to adopt a relatively stable pattern distinct from that observed in healthy individuals (24,25). Under these conditions, the inflammatory state characteristic of IBD can be sustained, while the baseline conditions and initiation thresholds of various immune responses, including antitumor immunity, may also be altered.

From the perspective of innate immunity, intestinal immune components are chronically exposed to stimulatory signals derived from luminal contents and barrier disruption. When the mucosal barrier remains persistently damaged, microbe-associated molecular patterns and damage-associated molecular patterns frequently coexist, suggesting prolonged activation of pattern recognition receptor-related signaling pathways (26,27). In addition, alterations in the composition of the gut microbiota are considered an important factor linking chronic inflammation to tumorigenesis. In the context of IBD, the intestinal microbiota often exhibits reduced diversity and compositional imbalance. Certain pro-inflammatory microbial communities and their metabolites can continuously stimulate the intestinal mucosal immune system, thereby amplifying inflammatory responses and disrupting immune homeostasis (28). Microbial-derived signaling molecules can participate in immune regulation through pattern recognition receptor-associated pathways such as Toll-like receptors, thereby influencing mucosal barrier integrity and the functional

Table I. Key immunological differences between sporadic CRC and IBD-CRC.

Feature	Sporadic CRC	IBD-CRC	(Refs.)
Inflammatory background	Predominantly localized tumor-associated inflammation, which usually increases after tumor development	Long-standing chronic mucosal inflammation that precedes tumor initiation	(14)
Tumor development environment	Relatively confined tumor microenvironment	Mucosal barrier disruption and persistent inflammatory environment	(20)
Immune cell infiltration	Mainly characterized by tumor-driven immunosuppression, with gradually impaired effector T-cell function	Inflammation-driven persistent immune cell infiltration with more prominent innate immune activation	(9,10)
Immunosuppressive mechanisms	Upregulation of immune checkpoints and impaired antigen presentation	Sustained chronic inflammation, enhanced regulatory immune responses, and maintenance of checkpoint signaling	(10,11)
Microbiota and barrier factors	Generally play a secondary role	More pronounced mucosal barrier damage and microbiota dysbiosis	(21,22)
Response to immunotherapy	Certain molecular subtypes (such as MSI-H) show clear benefit from immune checkpoint inhibitors	More heterogeneous responses, with potential risk of exacerbating intestinal inflammation	(10,12,13)

CRC, colorectal cancer; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; MSI-H, microsatellite instability-high.

state of immune cells (29). Furthermore, interventions such as probiotics and prebiotics have been suggested to modulate gut microbial composition, improve the mucosal immune environment, and reduce inflammatory burden, potentially influencing the risk of IBD-CRC to some extent (30,31).

In addition to changes in microbial composition, alterations in microbiota-derived metabolites are also considered an important mechanism linking IBD with tumor development. The gut microbiota can produce a variety of metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, and tryptophan-derived metabolites. These molecules can participate in immune regulation by influencing immune cell metabolism, modulating inflammatory signaling pathways, and altering mucosal barrier function (32,33). Further research has shown that under IBD conditions, the levels of immunoregulatory metabolites such as SCFAs are often reduced, while certain pro-inflammatory metabolites may increase, thereby further amplifying inflammatory responses and disrupting mucosal immune homeostasis (34).

Compared with innate immune responses triggered by acute infection, immune reactions in the context of IBD generally exhibit a relatively lower intensity but tend to persist for a longer duration (35). Under these conditions, innate immune components, including neutrophils, macrophages, and dendritic cells, are continuously recruited into mucosal immune responses. These cells maintain heightened sensitivity to environmental stimuli and display a tendency toward rapid activation upon stimulation (36,37). Adaptive immunity is likewise situated within this altered immune environment. The persistent presence of antigenic stimulation, the influence of inflammation-related cytokines, and ongoing changes in the tissue microenvironment lead to frequent participation of

T and B lymphocytes in mucosal immune responses (38-40). Consequently, the activation threshold, frequency of engagement, and functional output of adaptive immune responses may be altered to some extent (41,42). Available evidence suggests that immune activity under these conditions tends to shift toward functions associated with mucosal defense and the limitation of inflammation, whereas immune responses directed toward specific antigens may be relatively attenuated (43).

Under prolonged inflammatory pressure, intrinsic regulatory mechanisms of the immune system impose certain constraints on immune responses, while tissue injury and functional impairment may occur repeatedly (44). During the progression of IBD, the immune system gradually establishes multiple feedback regulatory relationships, forming a relatively balanced state between defensive requirements and tissue tolerance (45-47). These regulatory processes coexist with chronic inflammation and become an integral component of the overall immune functional state (48). Accordingly, the objective of immune responses often shifts from the complete elimination of stimuli toward maintaining inflammatory activity within a tolerable range while minimizing tissue damage (49).

Against the background of persistent alterations in both innate and adaptive immunity, accompanied by endogenous regulatory processes, inflammation and immune activity gradually enter a state of coexistence. Continuous inflammatory signaling intertwined with regulatory immune mechanisms may influence the actual efficiency of antitumor immune responses in terms of response intensity, resource allocation, and functional execution. To facilitate understanding of this long-term remodeling process, Fig. 1 provides a schematic overview of changes in immune signaling integration, resource

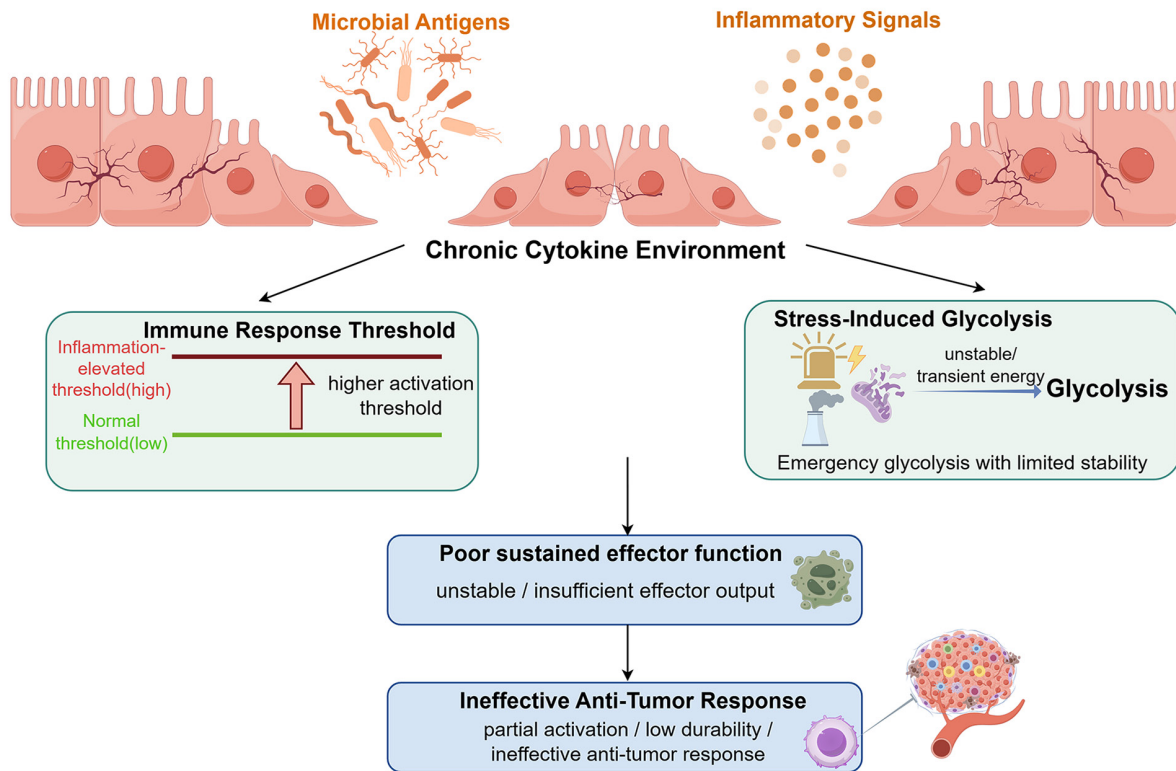


Figure 1. Chronic inflammation-shaped immune operational state and its impact on antitumor immunity in IBD. Under IBD conditions, persistent microbial antigens and inflammatory cytokine signals maintain the immune system in a chronically activated and inflammation-prioritized state. Continuous low-intensity inflammatory inputs progressively elevate immune response thresholds, alter immune resource allocation, and drive emergency glycolysis or unstable metabolic adaptation in immune cells. As a result, immune activity is preferentially directed toward inflammation control and tissue tolerance rather than durable antitumor immunity. Although immune cells remain engaged, this remodeled operational state limits the magnitude and persistence of antitumor responses and creates conditions permissive for IBD-CRC initiation and maintenance. IBD, inflammatory bowel disease; IBD-CRC, IBD-associated colorectal cancer.

allocation, and metabolic orientation of the immune system under conditions of chronic inflammation.

4. Molecular network of inflammatory-immune crosstalk

Chronic inflammatory signaling drives immune-state remodeling. During the long-term course of IBD, cytokines and related inflammatory signals are not transiently elevated. Instead, they persist and repeatedly accumulate, forming the basal signaling background of the chronic inflammatory microenvironment (50). These signals can regulate immune response thresholds, signaling integration, and immune resource allocation through pathways such as nuclear factor (NF)- κ B and signal transducer and activator of transcription (STAT)3. As a result, the immune system gradually adopts an inflammation-maintaining mode of operation (51).

Existing studies show that multiple pro-inflammatory and immunoregulatory factors remain persistently abnormal in the intestinal mucosa and peripheral circulation of patients with IBD. These include interleukin (IL)-6, tumor necrosis factor (TNF)- α , IL-1 β , IL-17, IL-23, interferon (IFN)- γ , IL-10, transforming growth factor (TGF)- β , granulocyte-macrophage colony-stimulating factor (GM-CSF), C-C motif chemokine ligand 2 (CCL2), and C-X-C motif chemokine ligand 8 (CXCL8) (Table II) (52-71). These factors are important for acute defense and tissue repair. However, in chronic inflammation, their long-term coexistence may promote a stable state in which pro-inflammatory, repair-related, and regulatory signals are intertwined.

Signaling axes such as IL-6/STAT3, TNF- α /NF- κ B, and IL-17/IL-23 can continuously influence immune cell differentiation, metabolic states, and effector output (72,73). This shifts the immune system toward inflammation control, mucosal repair, and tissue tolerance. Such a shift is unfavorable for antigen-specific recognition and sustained antitumor effector responses (74,75). In addition, external factors, including microbiota-derived metabolites, dietary composition, environmental exposures, and stress-related neuroendocrine signals, may also participate in immune remodeling in IBD-CRC by affecting inflammatory signaling, immunometabolism, and the mucosal microenvironment (69,70).

Current evidence is mainly derived from patient tissue analyses, serum profiling, and inflammation-associated animal models such as the azoxymethane/dextran sodium sulfate model. Although these systems differ in inflammatory duration, immune cell composition, and microenvironmental complexity, they generally support the idea that persistent inflammatory signaling continuously shapes the immune microenvironment associated with IBD-CRC (65,66).

Chronic inflammation-induced immune cell remodeling. Under persistent inflammatory stimulation, immune abnormalities in IBD are characterized less by a global reduction in immune cell numbers than by functional reprogramming and altered intercellular coordination (76,77). Impaired effector T-cell function, reduced antigen-presenting capacity, sustained activation of innate immunity, and enhanced regulatory immune

Table II. Key immune mediators in chronic inflammatory conditions and their systemic effects on immune regulation.

Factor	Primary immune effects	Impact on immune system operation	(Refs.)
IL-6	Sustains inflammatory responses and supports continuous expansion of effector T cells	Elevates baseline inflammatory signaling and reshapes immune response prioritization	(52,53)
TNF- α	Amplifies inflammatory responses and participates in tissue damage and repair	Chronically occupies immune signaling resources and maintains a high inflammatory load	(54,55)
IL-1 β	Promotes inflammatory cascades and enhances immune activation	Raises basal activation levels and reduces signal discrimination capacity	(56,57)
IL-17	Sustains chronic inflammation and promotes continuous recruitment of inflammatory cells	Drives inflammation-prioritized immune response programs	(58,59)
IL-23	Maintains Th17 cell stability and amplifies inflammatory circuits	Stabilizes pro-inflammatory immune axes and reduces immune state plasticity	(60,61)
IFN- γ	Enhances immune activation and antigen presentation capacity	Maintains immune system operation in a stress-adapted state under chronic inflammation	(62,63)
IL-10	Restricts inflammatory spread and maintains tissue tolerance	Elevates regulatory signaling baseline and constrains effector response amplification	(64,65)
TGF- β	Modulates immune responses and limits inflammatory expansion	Contributes to regulatory imbalance when coexisting with persistent pro-inflammatory signals	(66,67)
GM-CSF	Promotes recruitment and functional maintenance of myeloid cells	Alters immune cell composition and shapes an inflammation-biased immune ecosystem	(68,69)
CCL2, CXCL8	Mediate sustained immune cell migration and accumulation	Maintain high immune cell density and reinforce local inflammatory environments	(70,71)

In addition to the immune mediators summarized above, microbiota-derived metabolites, dietary factors, environmental exposures, and stress-related neuroendocrine signaling may also contribute to chronic immune dysregulation and immune remodeling in IBD-CRC. These factors are not individually listed because the present table focuses on representative immune mediators. IL, interleukin; TNF- α , tumor necrosis factor- α ; IFN- γ , interferon- γ ; TGF- β , transforming growth factor- β ; GM-CSF, granulocyte-macrophage colony-stimulating factor; CCL2, C-C motif chemokine ligand 2; CXCL8, C-X-C motif chemokine ligand 8; IBD-CRC, inflammatory bowel disease-associated colorectal cancer.

networks together establish the immune imbalance that underlies IBD-CRC (Fig. 2).

Within the adaptive immune compartment, persistent inflammatory signaling reshapes T-cell differentiation and compromises the maintenance of effector function. Continuous exposure to cytokines such as IL-6 and IL-1 β activates STAT3-associated transcriptional programs, promoting inflammatory T-cell phenotypes. Sustained TNF- α /NF- κ B signaling further maintains an aberrantly activated immune state (78-80). In parallel, hypoxia, nutrient competition, and metabolic stress within chronically inflamed tissues drive metabolic reprogramming of T cells. Increased dependence on glycolysis, mitochondrial dysfunction, and oxidative stress collectively impair long-term proliferation and cytotoxic activity (81-83).

In addition to T cells, antigen-presenting cells and innate immune cells also undergo functional remodeling. Under chronic inflammatory conditions, dendritic cells and macrophages gradually shift from transient activation toward inflammation-associated phenotypes, accompanied by reduced antigen processing and diminished capacity to initiate effective T-cell responses (84-86). In addition, neutrophils, monocyte-macrophage lineage cells, and subsets of innate lymphoid cells remain persistently engaged in inflammatory

amplification and exhibit lowered activation thresholds, fixed response patterns, and altered effector functions (87-89). Enhanced neutrophil extracellular trap formation and impaired natural killer-cell effector activity further suggest that innate immune cells remain highly active but become increasingly oriented toward sustaining inflammation rather than mediating efficient antitumor surveillance (90-92).

Chronic inflammation also promotes the establishment of regulatory immune networks. TGF- β - and IL-10-mediated signaling supports the maintenance of regulatory T cells (Tregs) and restricts sustained effector immune responses through metabolic competition, the release of immunosuppressive mediators, and remodeling of the local microenvironment (93,94). Consequently, immune abnormalities in IBD-CRC do not represent immune shutdown. Instead, they reflect a remodeled immune state that prioritizes inflammation control and tissue tolerance.

Overall, chronic inflammation drives extensive immune remodeling in IBD-CRC, resulting in a unique immune landscape characterized by persistent inflammatory signaling and continuous immune cell engagement. However, antigen recognition, metabolic support, and sustained effector responses required for effective antitumor immunity are progressively constrained. This state of sustained activation

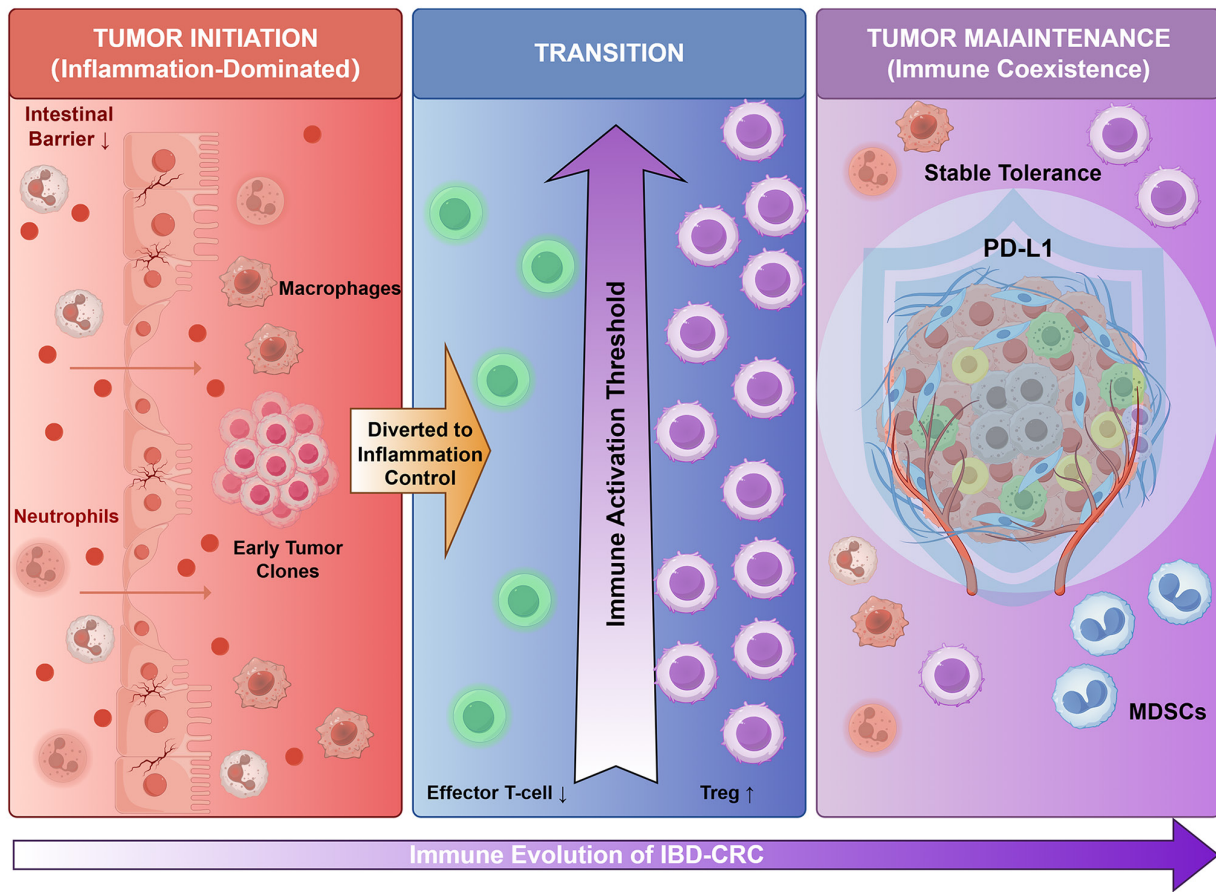


Figure 2. Mechanisms constraining antitumor T-cell function under chronic inflammatory conditions. This schematic illustrates how chronic inflammation constrains antitumor T-cell responses despite persistent immune-cell activation. The green T cell represents a relatively activated and metabolically competent phenotype that can still receive antigen-presenting signals from dendritic cells. The weak and discontinuous signal indicates suboptimal antigen presentation and insufficient costimulatory support in the chronically inflamed microenvironment. By contrast, the blue T cell represents a metabolically restricted, functionally impaired, or exhausted-like phenotype. This state may arise from prolonged inflammatory cytokine exposure, repeated low-quality antigenic stimulation, hypoxia, nutrient competition, mitochondrial stress, metabolic byproduct accumulation, and suppressive regulatory signals. Neutrophils and macrophages sustain the inflammatory background, whereas Tregs impose additional inhibitory constraints. Together, these pressures drive a shift from metabolically competent activation toward dysfunctional or exhausted-like T-cell states, thereby reducing the magnitude and durability of antitumor immunity. Tregs, regulatory T cells; DC, dendritic cell; APC, antigen-presenting cell.

but functionally restricted immunity provides a mechanistic basis for tumor immune evasion and the suboptimal efficacy of immunotherapy.

5. Immunodynamic evolution of IBD-CRC

Under the background of long-standing chronic inflammation, the development of IBD-CRC can be understood as a process in which the immune system, remaining in a persistently dysregulated state, gradually develops abnormalities across multiple functional levels. Long-term alterations in the gut microbiota and their metabolites are also considered important factors shaping the immune microenvironment of IBD-CRC. The overall immune evolutionary process of IBD-CRC is illustrated in Fig. 3. Previous research has suggested that the increased risk of CRC may be associated with long-term imbalance within the immune microenvironment (95).

However, this understanding is mainly derived from two types of research systems: One based on inflammation-driven animal models of colon cancer, and the other based on molecular analyses of tissue samples from patients with IBD. Because these two research approaches differ in terms of the

duration of inflammation, the composition of immune cell populations, and the complexity of the microenvironment, some uncertainty remains in the current understanding of the immune evolutionary process in IBD-CRC. From the perspective of temporal changes in immune functional states, the immune evolution of IBD-CRC can be broadly divided into two stages: The tumor initiation stage and the subsequent maintenance stage. Although these stages are mechanistically continuous, they exhibit certain differences in their immunological manifestations.

Early stages of CRC initiation. During the early stage of tumor initiation in IBD-CRC, the intestinal immune system may not yet have entered a clearly immunosuppressive state. Instead, it often remains in a relatively active condition within an immune environment dominated by chronic inflammation (96). A more prominent feature of this stage is that persistent inflammatory pressure alters the operating conditions of immune surveillance, making it difficult for the immune system to generate high-quality and sustainable elimination responses against newly emerging abnormal epithelial clones (97).

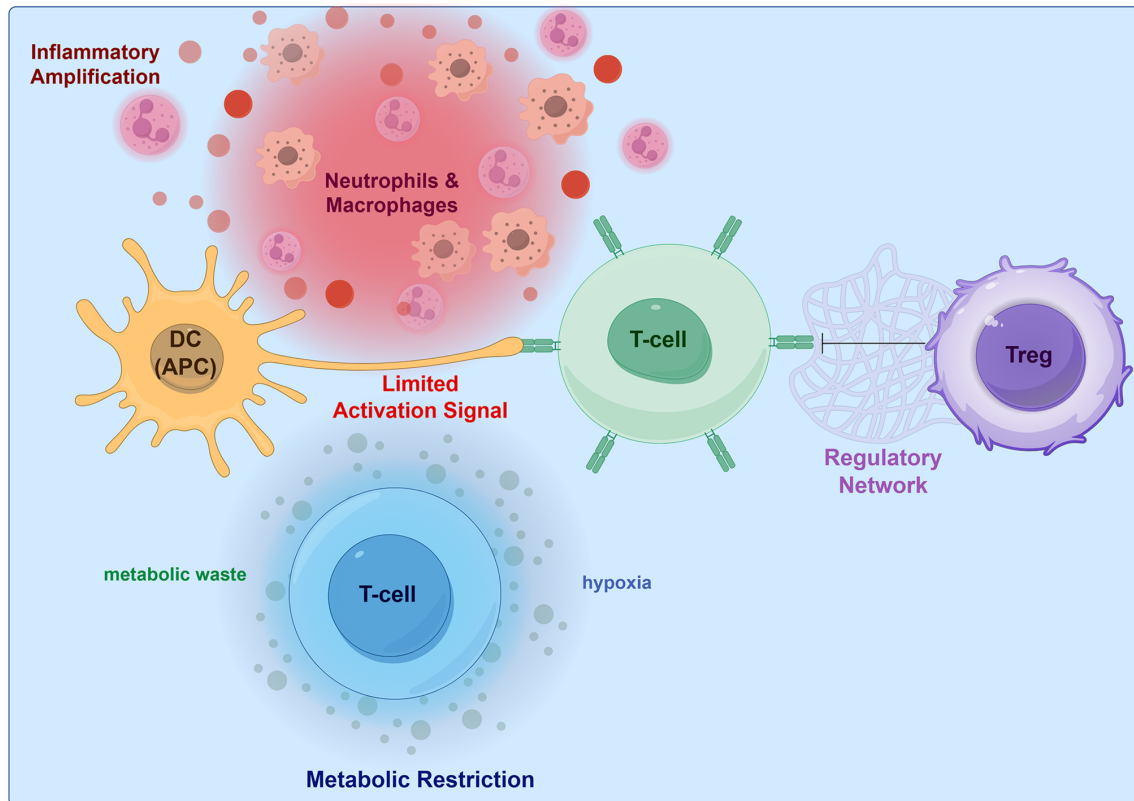


Figure 3. Immune evolutionary model of tumor initiation and maintenance in IBD-CRC. Under chronic inflammatory conditions associated with IBD, colorectal cancer development follows a stage-dependent immune evolutionary trajectory. During tumor initiation, intestinal barrier disruption and innate immune-dominated inflammation create a permissive environment for early tumor-clone survival. As inflammation persists, immune response thresholds increase, and immune resources are preferentially diverted toward inflammation control rather than antitumor surveillance. This leads to a transitional state characterized by reduced effector T-cell activity. Ultimately, expanded regulatory immune networks and sustained immune checkpoint signaling contribute to a stable immune coexistence phase, in which tumor persistence is maintained under chronic immune tolerance. IBD-CRC, inflammatory bowel disease-associated colorectal cancer; Treg, regulatory T cell; PD-L1, programmed death-ligand 1; MDSCs, myeloid-derived suppressor cells.

Disruption of the immune barrier and antigen influx. The intestinal barrier plays a crucial role in maintaining mucosal homeostasis and may also function as a link between inflammatory immunity and tumor immune surveillance. In the pathological context of IBD, recurrent inflammatory episodes can continuously damage the intestinal epithelium. Common manifestations include downregulation of tight junction proteins, thinning of the mucus layer, and imbalance in antimicrobial peptide secretion, all of which make the intestinal barrier more prone to increased permeability (98-100). Clinical research also suggests that, in patients with ulcerative colitis, the expression levels of tight junction-related molecules in the mucosa are associated with disease activity and mucosal healing status (101).

In addition to structural disruption, inflammatory cytokines may also participate in the dynamic regulation of tight junctions through multiple signaling pathways. Persistent activation of pathways such as STAT3, STAT6, and NF- κ B in epithelial cells can both sustain the inflammatory background and contribute to impaired epithelial polarity and abnormal proliferative signaling (102-104). Experimental animal research suggested that, in CRC models, epithelial barrier dysfunction often precedes the formation of tumor nodules. When tight junction-related genes or proteins are functionally impaired, the severity of colitis may increase, and tumor development is more readily observed (105).

Following increased barrier permeability, microorganisms and their metabolites can continuously cross the mucosal barrier, exposing the immune system to a sustained antigen load (106). Under such conditions, limited immune resources and effector responses are often preferentially allocated to controlling inflammation and clearing microbial stimuli. Functionally, this may compress the capacity of the immune system to recognize and expand responses against low-abundance, early tumor antigens, thereby allowing abnormal epithelial clones to acquire greater opportunities for survival and accumulation under ongoing immune pressure.

Immune evasion. During the initiation stage of IBD-CRC, immune evasion may not primarily arise from active immunosuppressive mechanisms induced by tumor cells. Instead, it may represent a passive consequence of the long-term impact of chronic inflammation on the immune system. Under persistent inflammatory stimulation, the differentiation lineage, migratory capacity, and expression patterns of costimulatory molecules in dendritic cells and macrophages may undergo significant alterations (107,108). Consequently, even when immune cell infiltration increases, it does not necessarily translate into the generation of high-quality antitumor immune responses.

Further studies suggest that the chronic inflammatory environment may alter the functional orientation of

antigen-presenting cells, making them more likely to induce transient and relatively low-intensity T-cell activation (109). While such activation may contribute to the maintenance of inflammatory responses, it may not effectively translate into robust antitumor immune activity. At the same time, immune metabolic imbalance can predispose immune cells to enter states of exhaustion or reduced responsiveness. Thus, even when infiltration levels remain elevated, the functional output of immune cells may remain primarily directed toward sustaining inflammation rather than establishing effective tumor immune clearance.

Alteration of immune activation thresholds. Within the long-standing pathological background of IBD, the conditions required for the immune system to respond to antigenic stimulation may gradually change, often manifesting as an increased requirement for signal strength and integration to initiate effective immune responses (110). This shift in immune response thresholds is thought to contribute to the gradual limitation of immune surveillance during the initiation stage of IBD-CRC. When antigenic signals are restricted in either intensity or presentation quality, T cells, even in the presence of persistent antigen exposure, may more readily enter activation states of limited magnitude and short duration, thereby failing to fully initiate downstream effector programs (111). This process is sometimes accompanied by epigenetic regulatory changes, suggesting that the sensitivity of immune cells to early tumor antigens may decline further.

Prolonged inflammatory stimulation may also alter the molecular expression profiles and cytokine secretion patterns of dendritic cells, making antigen presentation more likely to induce limited or transient T-cell activation. As a result, tumor-associated neoantigens may have greater difficulty triggering high-quality immune responses (112). Meanwhile, mitochondrial dysfunction and reduced efficiency of oxidative phosphorylation may compromise the capacity of immune cells to sustain the energy demands required for robust immune activation (113,114).

Tumor maintenance phase. After escaping early immune surveillance and completing tumor initiation, IBD-CRC gradually enters a tumor maintenance stage characterized primarily by long-term persistence. Compared with the immune evolutionary trajectories commonly observed during the progression of numerous solid tumors, IBD-CRC often exhibits several distinctive immunological features during this phase (115). Notably, chronic intestinal inflammation does not necessarily diminish after tumor formation; instead, it frequently persists as a long-standing background signal.

Dysregulation of immune resources. During the tumor maintenance stage, the immune abnormalities observed in IBD-CRC suggest that the overall functional state of the immune system may have undergone deeper alterations. Persistent inflammation occupies a substantial portion of immune system activity, directing immune functions toward inflammation control, barrier repair, and maintenance of tissue homeostasis (116). Consequently, even when tumor-associated antigens remain continuously present, antitumor immune responses may be difficult to sustain, allowing tumor progression to continue.

From a metabolic perspective, this shift is often reflected in altered patterns of energy allocation within immune cells. In an inflammation-dominant state, immune cells tend to support rapid, short-term response outputs, while providing insufficient metabolic support for energy-intensive, mitochondria-dependent long-term cytotoxic effects. Although effector T cells may appear phenotypically activated, they often fail to establish the metabolic conditions and functional configuration required for sustained tumor clearance (117,118). At the same time, the antigen-presenting system frequently remains under prolonged functional burden.

Immunosuppression and immune tolerance. During the tumor maintenance stage, immune suppression and tolerance may no longer primarily manifest as short-term regulatory responses directed against specific stimuli. Instead, they increasingly resemble a relatively stable immunological background state. In this process, regulatory T cells and immunosuppressive myeloid cell subsets, under the influence of persistent local signals, may impose long-term constraints on the intensity, duration, and functional upper limit of effector T-cell responses (107,109).

Of particular interest is the possibility that immune tolerance may gradually develop within effector T cells themselves and be maintained under certain conditions. Immune checkpoint pathways, including programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), can contribute to the establishment and maintenance of this tolerant state by limiting effector intensity and metabolic capacity, thereby preventing effector T cells from achieving high-level functional output (119,120). At both metabolic and epigenetic levels, this tolerant state may become increasingly stabilized. Thus, immune tolerance during the tumor maintenance stage may not simply represent a passive response to tumor presence; rather, it is more likely to develop gradually within the context of chronic inflammation and persist through the combined influence of multiple factors. As a result, antitumor immune responses remain at relatively low levels over extended periods, providing conditions that support the continued persistence of IBD-CRC (117).

Immune coexistence. Under the combined influence of immune resource redistribution and tolerance mechanisms, IBD-CRC may gradually enter a relatively stable state characterized by the long-term coexistence of inflammation and tumor growth. From a spatial perspective, inflammation-dominated regions may maintain relatively high immune activity to limit tissue damage, whereas tumor-associated areas are more likely to accumulate inhibitory signals and metabolic constraints. From a temporal perspective, immune signaling pathways, metabolic programs, and epigenetic states may gradually establish mutually reinforcing interactions, rendering this immune condition relatively stable and less responsive to short-term interventions. This functional partitioning of immune signaling and activity across space and time is often associated with phenomena such as immune cell functional exhaustion, sustained expression of immune checkpoint signals, and difficulty in enhancing anti-tumor responses (121,122).

The state of immune coexistence suggests that IBD-CRC may enter an abnormal yet relatively fixed condition in which

Table III. Current immunotherapeutic strategies for IBD-CRC and their mechanistic limitations.

Therapeutic category	Mechanism of action	Major limitations	(Refs.)
PD-1/PD-L1 inhibitors	Relieve PD-1/PD-L1-mediated T-cell inhibition and enhance effector T-cell activity	Highly heterogeneous efficacy; limited ability to lower antigen recognition thresholds; potential to induce or exacerbate IBD activity; risk of irAEs, including colitis exacerbation and mucosal injury	(128-130)
CTLA-4 inhibitors	Enhance initial T-cell priming and reduce regulatory T cell-mediated suppression	High risk of inflammation-related toxicity and irAEs; potential aggravation of intestinal inflammation or systemic inflammatory flares; limited efficacy in reversing established immune tolerance	(131-133)
Dual immune checkpoint blockade	Relieve inhibitory signals at multiple levels and increase the magnitude of immune activation	Markedly increased toxicity and risk of severe irAEs; potential for colitis exacerbation, mucosal injury, and systemic inflammatory flares; limited capacity to restore durable and effective antitumor immune execution	(134-136)

IBD-CRC, inflammatory bowel disease-associated colorectal cancer; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; irAEs, immune-related adverse events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4.

the immune system prioritizes inflammation control and the maintenance of tissue tolerance, while antitumor immune responses remain constrained at relatively low levels. This also implies that interventions aimed solely at relieving inhibitory signaling may not be sufficient to disrupt the established immune background. It is also noteworthy that, during this stage, IBD-CRC-associated tumor cells and their surrounding stromal components can continuously release pro-inflammatory mediators, growth factors, and metabolic products, further reinforcing local inflammatory signaling (123-125). As a result, inflammation and tumor growth may form a long-term relationship of mutual reinforcement, although not necessarily in a balanced manner, at the level of immune regulation.

6. Current status and future directions of immunotherapy in IBD-CRC

Current landscape and mechanistic limitations of immunotherapy in IBD-CRC. In recent years, immunotherapy, particularly ICIs, has achieved clear clinical progress in several solid tumors and has partly reshaped the treatment landscape of CRC. Previous studies have shown that ICIs can achieve relatively high response rates in tumors with deficient mismatch repair or high microsatellite instability. By contrast, among patients with IBD-CRC, only some patients achieve disease control, while a substantial proportion still show limited therapeutic benefit (126,127).

In addition, immunotherapy may be accompanied by aggravated intestinal inflammation and immune-related adverse events (irAEs). These include colitis exacerbation, mucosal injury, and systemic inflammatory reactions, which may affect the feasibility and safety of immunotherapy. The major classes of currently available ICIs, including PD-1/programmed death-ligand 1 (PD-L1) inhibitors, CTLA-4 inhibitors, and dual immune checkpoint blockade, as well as their mechanisms of action and limitations in IBD-CRC, are summarized in Table III (128-136).

Current evidence suggests that the limited efficacy of immunotherapy in IBD-CRC is not simply due to immune deficiency. It also cannot be fully explained by the dominance of a single inhibitory pathway. Instead, it may be more closely related to multi-layered immune imbalance shaped by long-term chronic inflammation. Current ICI strategies mainly exert antitumor effects by relieving inhibitory signals or enhancing immune activation. However, in IBD-CRC, the immune system may undergo persistent shifts in antigen recognition, immune response thresholds, resource allocation, metabolic support, and effector maintenance. These alterations may prevent antitumor immune responses from achieving optimal efficacy. Single-target immunotherapy primarily functions to relieve established inhibitory signaling, yet it rarely ameliorates inflammatory burden and metabolic restrictions simultaneously; this distinction is illustrated in Fig. 4.

It should also be noted that ICIs may induce or exacerbate intestinal inflammation. The risks of colitis relapse, intestinal perforation, and other severe complications may also increase. This clinical concern has limited the investigation and clinical application of ICIs in IBD-CRC to some extent (137,138). In addition to ICIs and their combination regimens, some studies have attempted to improve antitumor responses by modulating inflammation-related pathways or introducing other immunotherapeutic strategies (139,140). However, in the pathological context of IBD-CRC, these exploratory interventions often face difficulty in balancing inflammatory safety with durable antitumor immunity. Overall, the clinical application of immunotherapy in IBD-CRC remains cautious and exploratory.

Implications of multi-component natural plant interventions for immunological research in IBD-CRC. In IBD-CRC, immune abnormalities are shaped by the long-term combined effects of chronic inflammation, mucosal barrier damage, gut microbiota dysbiosis, immunometabolic stress, and regulatory immune networks. Therefore, single-target interventions may not be sufficient to simultaneously ensure inflammatory

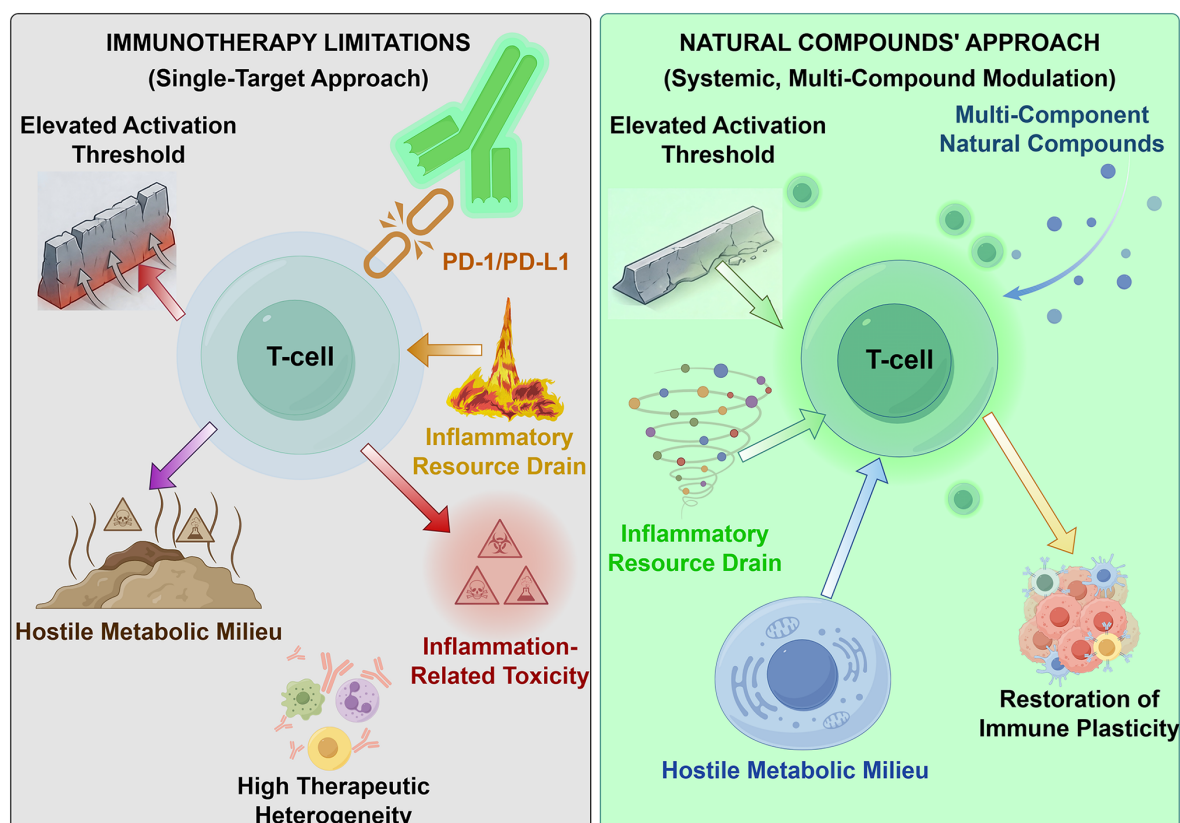


Figure 4. Conceptual comparison between single-target immunotherapy and multi-component immune modulation in IBD-CRC. Under chronic inflammatory conditions in IBD-CRC, the immune system operates under elevated activation thresholds, persistent diversion of immune resources toward inflammation control, and a metabolically constrained microenvironment. Single-target immunotherapeutic strategies, such as PD-1/PD-L1 blockade, may partially relieve inhibitory signaling but often fail to concurrently address inflammatory burden, metabolic restriction, and reduced immune plasticity, resulting in heterogeneous therapeutic responses and increased risk of inflammation-associated toxicity. By contrast, multi-component modulation exemplified by natural compounds emphasizes low-intensity, system-level regulation of inflammatory signaling, metabolic conditions, and immune regulatory networks. Rather than directly amplifying effector responses, this approach may help alleviate inflammation-driven resource consumption and improve immune system adaptability, thereby providing a conceptual framework to support the design of safer and more sustainable combinatorial immunotherapeutic strategies. IBD-CRC, inflammatory bowel disease-associated colorectal cancer; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1.

safety, maintain mucosal homeostasis, and restore antitumor immunity. In this disease context, natural plant-derived agents, characterized by multi-component composition, multi-target actions, and relatively mild long-term regulation, provide a perspective distinct from conventional single-target strategies for IBD-CRC immunotherapy research (141-143). The potential regulatory features of several representative natural plant-derived agents in inflammation- and tumor-related pathways are summarized in Table IV.

Mechanistically, the potential advantage of natural plant-derived components lies primarily in their integrated regulation of the 'immune response background,' rather than direct targeting of a single terminal inhibitory pathway. Representative natural bioactive compounds, such as curcumin, resveratrol, berberine, and ginsenosides, may affect inflammation- and tumor-related pathways, including NF- κ B, STAT3, AMP-activated protein kinase (AMPK), Wnt/ β -catenin, phosphoinositide 3-kinase PI3K-protein kinase B (AKT), and mitogen-activated protein kinase (MAPK) (144-161). Through these pathways, they may regulate inflammatory signaling intensity, immunometabolic states, epithelial barrier function, and immune cell differentiation. These interventions are more likely to act on the long-term operating conditions of the immune system. They may reduce the persistent occupation of

immune resources by chronic inflammation and improve the tissue environment required for antitumor immune responses.

The low-intensity and long-term regulatory properties of natural plant-derived interventions may also be particularly relevant to the clinical context of IBD-CRC. Patients with IBD-CRC usually have a previous or ongoing background of intestinal inflammation. Strong immune activation may increase the risk of colitis exacerbation, mucosal injury, or immune-related adverse events. Therefore, the value of natural plant-derived agents should not be simply interpreted as standalone antitumor therapy. Instead, they may be better understood as a 'background-modulating strategy' before or during combination immunotherapy. Their potential effects include reducing chronic inflammatory burden, improving immunometabolic states, stabilizing the mucosal barrier, and regulating gut microbiota and their metabolites. These effects may enhance the plasticity of the immune system and support antitumor treatment responses (162-164).

In addition, some herbal formulas or extracts may better meet the need for multi-level regulation than single compounds. For example, tonic formulas or plant extracts may simultaneously affect inflammatory signaling, immunometabolism, barrier repair, and the tumor microenvironment. Current evidence is still mainly derived from animal experiments, cell-based

Table IV. Representative natural compounds with immunomodulatory and tumor-related regulatory properties relevant to IBD-CRC.

Category	Natural compound	Source	Immunomodulatory/anti-inflammatory features	Antitumor-related effects	(Refs.)
Monomeric compound	Curcumin	Turmeric	Modulates inflammation-tumor related signaling pathways such as NF- κ B and STAT3; influences Th17/Treg immune balance	Regulates NF- κ B and STAT3 mediated inflammation-tumor signaling axes	(144-146)
Monomeric compound	Resveratrol	Grapes	Antioxidant activity; regulates mitochondrial function and immune metabolic states	Modulates tumor-related pathways including Wnt/ β -catenin and AMPK signaling	(147-149)
Monomeric compound	Berberine	<i>Coptis chinensis</i>	Improves intestinal barrier function; modulates gut microbiota and mucosal immune responses	Regulates tumor progression-related pathways such as Wnt/ β -catenin and AMPK	(150-152)
Monomeric compound	Ginsenosides	Ginseng	Influences dendritic cell function and T-cell differentiation	Regulates tumor cell survival and stress signaling pathways including PI3K-AKT and MAPK	(153-156)
Herbal formula	Danggui Buxue Decoction	<i>Angelica sinensis</i> and <i>Astragalus membranaceus</i>	Regulates immunometabolism and inflammatory responses; improves inflammation-related immune imbalance	May modulate the immune microenvironment and inflammation-tumor transition in IBD-CRC	(157,158)
Herbal extract	Huaier extract	Huaier fungus	Regulates inflammatory signaling and immune responses	Suppresses colitis-associated tumorigenesis	(159)
Herbal extract	Astragaloside IV	<i>Astragalus membranaceus</i>	Modulates mucosal immune responses and inflammation-related signaling pathways	May inhibit the transition from colitis to colorectal cancer	(160,161)

IBD-CRC, inflammatory bowel disease-associated colorectal cancer NF- κ B, nuclear factor- κ B; STAT3, signal transducer and activator of transcription 3; Th17, T helper 17; Treg, regulatory T cell; AMPK, AMP-activated protein kinase; PI3K-AKT, phosphoinositide 3-kinase/protein kinase B; MAPK, mitogen-activated protein kinase.

studies, and indirect mechanistic inference. It is therefore insufficient to support these interventions as standard therapies for IBD-CRC. Nevertheless, their potential roles in reducing inflammatory background, improving immune tolerance, and supporting immunotherapy deserve further investigation. Future studies should clarify the active material basis, dose-response relationships, safety boundaries, and optimal timing and patient selection for combining natural plant-derived interventions with immune checkpoint inhibitors or other therapeutic strategies.

7. Summary and perspectives

IBD-CRC can be conceptualized as a tumor entity that emerges progressively following alterations in immune status under the sustained influence of long-standing chronic intestinal

inflammation. Its immune abnormalities are not necessarily dominated by a single inhibitory pathway, nor do they invariably reflect a global loss of immune function. Rather, they more commonly manifest as a state in which immune responses remain persistently engaged but are constrained in their effector capacity. Current immunotherapeutic approaches largely exert their effects by releasing inhibitory signals or enhancing immune activation; however, within the context of IBD-CRC, the clinical benefit of such strategies is often limited and accompanied by uncertain risks of exacerbating inflammation and inducing immune-related toxicities.

Multi-component immunomodulatory strategies derived from natural plants therefore warrant consideration, with their potential value lying primarily in a lower toxicity burden and their capacity to exert gradual influences on immune states

shaped by chronic inflammation. Although existing evidence is insufficient to support these approaches as standalone antitumor therapies, the insights they offer, particularly with respect to mitigating treatment-related adverse effects and improving the sustainability of immune interventions, may nevertheless inform the development of combination immunotherapeutic strategies for IBD-CRC.

Acknowledgements

Not applicable.

Funding

This work was supported by the Liaoning University of Traditional Chinese Medicine Interdisciplinary Team Construction Project for Traditional Chinese Medicine Science and Technology Innovation (grant no. 2025-Dxkjc-06-02), and the Science and Technology Plan Joint Project of Liaoning Province (grant no. 2025JH2/101800405).

Availability of data and materials

Not applicable.

Authors' contributions

TZ, ZR, LingW, RM, LinW, JW, XC, JP and YY contributed to the conception and design of the work and drafting of the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Liu X, Dong Y, Wang C and Guo Z: Application of chitosan as nano carrier in the treatment of inflammatory bowel disease. *Int J Biol Macromol* 278 (Pt 4): 134899, 2024.
- Nagayama M, Gogokhia L and Longman RS: Precision microbiota therapy for IBD: premise and promise. *Gut Microbes* 17: 2489067, 2025.
- Li M, Liu N, Zhu J, Wu Y, Niu L, Liu Y, Chen L, Bai B, Miao Y, Yang Y and Chen Q: Engineered probiotics with sustained release of interleukin-2 for the treatment of inflammatory bowel disease after oral delivery. *Biomaterials* 309: 122584, 2024.
- Monteleone G, Calisi C, Salvatori S and Marafini I: Fundamental and emerging insights into innate and adaptive immunity in inflammatory bowel diseases. *Front Immunol* 16: 1665530, 2025.
- Park JD, Lee SR, Dhennezel C, Taylor N, Dame A, Kadoki M, Pishchany G, Graham DB, Xavier RJ and Seyedsayamdost MR: Elucidating the role of *Campylobacter concisus*-derived indole metabolites in gut inflammation and immune modulation. *Proc Natl Acad Sci USA* 122: e2514071122, 2025.
- Hisamatsu T, Miyoshi J, Oguri N, Morikubo H, Saito D, Hayashi A, Omori T and Matsuura M: Inflammation-associated carcinogenesis in inflammatory bowel disease: Clinical features and molecular mechanisms. *Cells* 14: 567, 2025.
- Muñiz Pedrego DA, Sears CL and Melia JMP: Colorectal cancer in inflammatory bowel disease: A review of the role of gut microbiota and bacterial biofilms in disease pathogenesis. *J Crohns Colitis* 18: 1713-1725, 2024.
- Zhang H, Shi Y, Lin C, He C, Wang S, Li Q, Sun Y and Li M: Overcoming cancer risk in inflammatory bowel disease: New insights into preventive strategies and pathogenesis mechanisms including interactions of immune cells, cancer signaling pathways, and gut microbiota. *Front Immunol* 14: 1338918, 2024.
- Sharma S, Singh N, Turk AA, Wan I, Guttikonda A, Dong JL, Zhang X and Opyrchal M: Molecular insights into clinical trials for immune checkpoint inhibitors in colorectal cancer: Unravelling challenges and future directions. *World J Gastroenterol* 30: 1815-1835, 2024.
- Kennel KB and Greten FR: The immune microenvironment of colorectal cancer. *Nat Rev Cancer* 25: 945-964, 2025.
- Capuzzo M, Picone C, Sabbatino F, Santorsola M, Caraglia F, Iervolino D, Sirica R, Gualillo O, Di Mauro G, Castiello R, *et al*: Genetic, epidemiological, clinical, and therapeutic trajectories in colon and rectal cancers. *Cancers (Basel)* 17: 3438, 2025.
- Wang Q, Guo F, Zhang Q, Hu T, Jin Y, Yang Y and Ma Y: Organoids in gastrointestinal diseases: From bench to clinic. *MedComm* (2020) 5: e574, 2024.
- Qiu W, Akanyibah FA, Xia Y, Ocansey DKW, Mao F and Liang Y: Emerging role of small RNAs in inflammatory bowel disease and associated colorectal cancer (Review). *Int J Mol Med* 55: 33, 2025.
- Nardone OM, Zammarchi I, Santacroce G, Ghosh S and Iacucci M: Inflammation-Driven colorectal cancer associated with colitis: From pathogenesis to changing therapy. *Cancers (Basel)* 15: 2389, 2023.
- Triantaphyllopoulos KA, Ragia ND, Panagiotopoulou ME and Sourlingas TG: Integrating inflammatory and epigenetic signatures in IBD-Associated colorectal carcinogenesis: Models, mechanisms, and clinical implications. *Int J Mol Sci* 26: 9498, 2025.
- Li WJ, Dong GH, Bi Y, Han YY, Sun LL, Wang T, Lin ZH and Ren XS: The cGAS-STING pathway in colorectal cancer: bridging innate immunity and therapeutic strategies. *J Exp Clin Cancer Res* 44: 286, 2025.
- Shahgoli VK, Noorolyai S, Ahmadpour Youshanlui M, Saeidi H, Nasiri H, Mansoori B, Holmskov U and Baradaran B: Inflammatory bowel disease, colitis, and cancer: Unmasking the chronic inflammation link. *Int J Colorectal Dis* 39: 173, 2024.
- Li M, Jiang H, Hu P and Shi J: Nanocatalytic anti-tumor immune regulation. *Angew Chem Int Ed Engl* 63: e202316606, 2024.
- Wu X, Li Y, Wen M, Xie Y, Zeng K, Liu YN, Chen W and Zhao Y: Nanocatalysts for modulating antitumor immunity: Fabrication, mechanisms and applications. *Chem Soc Rev* 53: 2643-2692, 2024.
- Zhou RW, Harpaz N, Itzkowitz SH and Parsons RE: Molecular mechanisms in colitis-associated colorectal cancer. *Oncogenesis* 12: 48, 2023.
- Quaglio AEV, Grillo TG, De Oliveira ECS, Di Stasi LC and Sasaki LY: Gut microbiota, inflammatory bowel disease and colorectal cancer. *World J Gastroenterol* 28: 4053-4060, 2022.
- Yuan L, Wang Y, Li N, Yang X, Sun X, Tian H and Zhang Y: Mechanism of action and therapeutic implications of Nrf2/HO-1 in inflammatory bowel disease. *Antioxidants (Basel)* 13: 1012, 2024.
- Horn V and Sonnenberg GF: Group 3 innate lymphoid cells in intestinal health and disease. *Nat Rev Gastroenterol Hepatol* 21: 428-443, 2024.
- Zhou X, Wu Y, Zhu Z, Lu C, Zhang C, Zeng L, Xie F, Zhang L and Zhou F: Mucosal immune response in biology, disease prevention and treatment. *Signal Transduct Target Ther* 10: 7, 2025.
- Balakrishnan R, Kang SI, Lee JY, Rho YK, Kim BK and Choi DK: Gut microbiota-immune system interactions in health and neurodegenerative diseases: Insights into molecular mechanisms and therapeutic applications. *Aging Dis* 16: 3421-3452, 2024.
- Santana PT, de Lima IS, Silva E Souza KCD, Barbosa PHS and de Souza HSP: Persistent activation of the P2X7 receptor underlies chronic inflammation and carcinogenic changes in the intestine. *Int J Mol Sci* 25: 10874, 2024.

27. Pradeu T, Thomma BPHJ, Girardin SE and Lemaitre B: The conceptual foundations of innate immunity: Taking stock 30 years later. *Immunity* 57: 613-631, 2024.
28. Haneishi Y, Furuya Y, Hasegawa M, Picarelli A, Rossi M and Miyamoto J: Inflammatory bowel diseases and gut microbiota. *Int J Mol Sci* 24: 3817, 2023.
29. Iyer K, Erkert L and Becker C: Know your neighbors: Microbial recognition at the intestinal barrier and its implications for gut homeostasis and inflammatory bowel disease. *Front Cell Dev Biol* 11: 1228283, 2023.
30. Fan X, Wang X, Chao Y and Xu E: Probiotic and prebiotic mechanisms in IBD-associated colorectal carcinogenesis: Recent advances. *Front Nutr* 12: 1693875, 2026.
31. Chen L, Zhang L, Hua H, Liu L, Mao Y and Wang R: Interactions between toll-like receptors signaling pathway and gut microbiota in host homeostasis. *Immun Inflamm Dis* 12: e1356, 2024.
32. Hu C, Xu B, Wang X, Wan WH, Lu J, Kong D, Jin Y, You W, Sun H, Mu X, *et al*: Gut microbiota-derived short-chain fatty acids regulate group 3 innate lymphoid cells in HCC. *Hepatology* 77: 48-64, 2023.
33. Luo M, Zhao F, Cheng H, Su M and Wang Y: Macrophage polarization: An important role in inflammatory diseases. *Front Immunol* 15: 1352946, 2024.
34. Ma Z, Wang Z, Cao J, Dong Y and Chen Y: Regulatory roles of intestinal CD4⁺ T cells in inflammation and their modulation by the intestinal microbiota. *Gut Microbes* 17: 2560019, 2025.
35. Dulfer EA, Joosten LAB and Netea MG: Enduring echoes: Post-infectious long-term changes in innate immunity. *Eur J Intern Med* 123: 15-22, 2024.
36. Wang R, Lan C, Benlagha K, Camara NOS, Miller H, Kubo M, Heegaard S, Lee P, Yang L, Forsman H, *et al*: The interaction of innate immune and adaptive immune system. *MedComm* (2020) 5: e714, 2024.
37. Yang B, Wu J, Hou X, Bai T and Liu S: Memory in misfire: The gut microbiome-trained immunity circuit in inflammatory bowel diseases. *Int J Mol Sci* 26: 9663, 2025.
38. Wang L, Liang Y, Zhao C, Ma P, Zeng S, Ju D, Zhao M, Yu M and Shi Y: Regulatory T cells in homeostasis and disease: Molecular mechanisms and therapeutic potential. *Signal Transduct Target Ther* 10: 345, 2025.
39. Zou D, Li XC and Chen W: Beyond T-cell subsets: Stemness and adaptation redefining immunity and immunotherapy. *Cell Mol Immunol* 22: 957-974, 2025.
40. Zhang Z, Hong W, Zhang Y, Li X, Que H and Wei X: Mucosal immunity and vaccination strategies: Current insights and future perspectives. *Mol Biomed* 6: 57, 2025.
41. Jugder BE, Park E, Du L, Jawale C, Popov N, Guo Z, Bednar KJ and Ort T: Tissue-specific roles of regulatory T cells: Mechanisms of suppression and beyond along with emerging therapeutic insights in autoimmune indications. *Front Immunol* 16: 1650451, 2025.
42. Xie C, Yang J, Gul A, Li Y, Zhang R, Yalikun M, Lv X, Lin Y, Luo Q and Gao H: Immunologic aspects of asthma: From molecular mechanisms to disease pathophysiology and clinical translation. *Front Immunol* 15: 1478624, 2024.
43. Medzhitov R: The spectrum of inflammatory responses. *Science* 374: 1070-1075, 2021.
44. Kern C, Bonventre JV, Justin AW, Kashani K, Reynolds E, Siew K, Davis B, Karakoy H, Grzesiak N and Bailey DM: Necrosis as a fundamental driver of loss of resilience and biological decline: What if we could intervene?. *Oncogene* 44: 1893-1904, 2025.
45. Kou R, Guo Y, Qin Z, Xu X, Liu Y, Wei W, Chen Y, Jian Z and Lan B: Systemic dysregulation of the gut microenvironment plays a pivotal role in the onset and progression of inflammatory bowel disease. *Front Immunol* 16: 1661386, 2025.
46. Li H, Zhang Y, Du S, Shen J, Liu X and Jing J: 'Remodeling the intestinal immune microenvironment': Immune regulation and tissue regeneration by mesenchymal stem/stromal cells in the repair microenvironment of inflammatory bowel disease. *Front Immunol* 16: 1543702, 2025.
47. Li P, Wang Y, Dong Y and Zhang X: Unveiling the gut-liver axis: The behind-the-scenes 'manipulator' of human immune function. *Front Immunol* 16: 1638197, 2025.
48. Arneth B: Molecular mechanisms of immune regulation: A review. *Cells* 14: 283, 2025.
49. Franceschi C, Olivieri F, Moskalev A, Ivanchenko M and Santoro A: Toward precision interventions and metrics of inflammation. *Nat Aging* 5: 1441-1454, 2025.
50. Ma H, Liu M, Fu R, Feng J, Ren H, Cao J and Shi M: Phase separation in innate immune response and inflammation-related diseases. *Front Immunol* 14: 1086192, 2023.
51. Ozcan A, Vicanolo T, Angeli V, Rinkevich Y and Hidalgo A: Structural immunity: Immune cells as architects of tissue barriers. *Nat Rev Immunol* 26: 314-325, 2026.
52. Speake C, Habib T, Lambert K, Hundhausen C, Lord S, Dufort MJ, Skinner SO, Hu A, Kinsman M, Jones BE, *et al*: IL-6-targeted therapies to block the cytokine or its receptor drive distinct alterations in T cell function. *JCI Insight* 7: e159436, 2022.
53. Rose-John S, Jenkins BJ, Garbers C, Moll JM and Scheller J: Targeting IL-6 trans-signalling: Past, present and future prospects. *Nat Rev Immunol* 23: 666-681, 2023.
54. Song Y, Liang F, Tian W, Rayhill E, Ye L and Tian X: Optimizing therapeutic outcomes: Preconditioning strategies for MSC-derived extracellular vesicles. *Front Pharmacol* 16: 1509418, 2025.
55. Kumar M, Murugesan S, Ibrahim N, Elawad M and Al Khodor S: Predictive biomarkers for anti-TNF alpha therapy in IBD patients. *J Transl Med* 22: 284, 2024.
56. Huang J, Kuang W and Zhou Z: IL-1 signaling pathway, an important target for inflammation surrounding in myocardial infarction. *Inflammopharmacology* 32: 2235-2252, 2024.
57. Garlanda C, Di Ceglie I and Jaillon S: IL-1 family cytokines in inflammation and immunity. *Cell Mol Immunol* 22: 1345-1362, 2025.
58. Zhang J and Shen M: The role of IL-17 in systemic autoimmune-inflammatory diseases: Mechanisms and therapeutic perspectives. *Clin Rev Allergy Immunol* 68: 27, 2025.
59. Lee SY, Moon J, Lee AR, Moon YM, Choi JW, Lee CR, Jeon SB, Sohn HS, Youn J, Shin D, *et al*: mtSTAT3 suppresses rheumatoid arthritis by regulating Th17 and synovial fibroblast inflammatory cell death with IL-17-mediated autophagy dysfunction. *Exp Mol Med* 57: 221-234, 2025.
60. García-Domínguez M: The role of IL-23 in the development of inflammatory diseases. *Biology* (Basel) 14: 347, 2025.
61. Tang Z, Shi J, Xu S, Liu S, Yin W, Xiang Y, Li J, He Z, Yao X, Li Z, *et al*: Single-cell multiomics reveals macrophage-derived IL-23 and CXCL9/10 drive pathogenic IFN γ +IL17+ T cells in immunotherapy-related colitis. *J Immunother Cancer* 13: e011959, 2025.
62. Gao T, Yuan S, Liang S, Huang X, Liu J, Gu P, Fu S, Zhang N and Liu Y: In situ hydrogel modulates cDC1-Based antigen presentation and cancer stemness to enhance cancer vaccine efficiency. *Adv Sci (Weinh)* 11: e2305832, 2024.
63. Merchak AR, Wachamo S, Brown LC, Thakur A, Moreau B, Brown RM, Rivet-Noor CR, Raghavan T and Gaultier A: Lactobacillus from the Altered Schaedler Flora maintain IFN γ homeostasis to promote behavioral stress resilience. *Brain Behav Immun* 115: 458-469, 2024.
64. Zhang Q, Liao J, Liu Z, Song S, Tian L and Wang Y: The immune tolerance role of Bregs in inhibiting human inflammatory diseases, with a focus on diabetes mellitus. *Front Immunol* 16: 1565158, 2025.
65. Zheng H, Xu B, Fan Y, Tuekprakhon A, Stamataki Z and Wang F: The role of immune regulation in HBV infection and hepatocellular carcinogenesis. *Front Immunol* 16: 1506526, 2025.
66. Cecerska-Heryć E, Jerzyk A, Goszka M, Polikowska A, Rachwalska J, Serwin N, Wojciuk B and Dołęgowska B: TGF- β signaling in cancer: Mechanisms of progression and therapeutic targets. *Int J Mol Sci* 26: 7326, 2025.
67. Yin X, Zhang W, Wang G, Liu Y, Dai B and Yue L: The 'double-edged sword' effect of cytokines in cancer: Coexisting opportunities and challenges. *Front Immunol* 16: 1701405, 2025.
68. Guerrero P, Bono C, Sobén M, Guiu A, Cheng QJ, Gil ML and Yáñez A: GM-CSF receptor expression determines opposing innate memory phenotypes at different stages of myelopoiesis. *Blood* 143: 2763-2777, 2024.
69. Ma T, Zhang T, Peng C, Liu K, Xiong Y, Chen K, Peng N, Wei Z, Kuang J and Ou L: Immune cells: The key mediator between the gut microbiota and osteoporosis. *Front Immunol* 16: 1680021, 2025.
70. Wang C, Wang J, Zhu Z, Hu J and Lin Y: Spotlight on pro-inflammatory chemokines: Regulators of cellular communication in cognitive impairment. *Front Immunol* 15: 1421076, 2024.
71. Papayannakos CJ, Israr M, DeVoti JA, Lam F, Arazi A, Frank DK, Kamdar DP, Pereira LM, Seetharamu N, Steinberg BM and Bonagura VR: Oropharyngeal carcinomas induce circulating monocytes to express a TAM-like pro-tumor expression profile that suppresses T-cell proliferation. *Front Immunol* 16: 1539780, 2025.
72. Pohl S, Akamp T, Smeda M, Uderhardt S, Besold D, Krastl G, Galler KM, Buchalla W and Widbiller M: Understanding dental pulp inflammation: From signaling to structure. *Front Immunol* 15: 1474466, 2024.

73. Paparozzi V, Hooshmandabbasi R, Ravoni A, Ma Y, Manni L, Koh TJ, Maake C, Guarnieri T, Lai D, Zablotskii V and Nardini C: Anti-inflammatory effects of physical stimuli: The central role of networks in shaping the future of pharmacological research. *Br J Pharmacol* 183: 2177-2196, 2026.
74. Liu Z, Lei M and Bai Y: Chronic stress mediates inflammatory cytokines alterations and its role in tumorigenesis. *J Inflamm Res* 18: 1067-1090, 2025.
75. Fioranelli M, Rocchia MG, Flavin D and Cota L: Regulation of inflammatory reaction in health and disease. *Int J Mol Sci* 22: 5277, 2021.
76. Yang M, Wu S, Zhang J, Lu L, Deng D, Xia Q, Lovell JF, Shi X and Jin H: Immunotherapies for aging and age-related diseases: Advances, pitfalls, and prospects. *Research (Wash D C)* 8: 0866, 2025.
77. Wang X, Fan D, Yang Y, Gimble RC and Zhou S: Integrative multi-omics approaches to explore immune cell functions: Challenges and opportunities. *iScience* 26: 106359, 2023.
78. Wen C, Lan Q, Wang Y, Ni Y, Wong AST and Liu D: Interferon signaling pathways in health and disease. *Mol Biomed* 6: 135, 2025.
79. Fu Y, Wang B, Alu A, Hong W, Lei H, He X, Shi H, Cheng P and Yang X: Immunosenescence: Signaling pathways, diseases and therapeutic targets. *Signal Transduct Target Ther* 10: 250, 2025.
80. Zhong L, Wang YH, Kahlfuss S, Jishage M, McDermott M, Yang J, Tao AY, Hu K, Noyer L, Raphael D, *et al*: STIM1-mediated NFAT signaling synergizes with STAT1 to control T-bet expression and TH1 differentiation. *Nat Immunol* 26: 484-496, 2025.
81. Riffelmacher T and Kronenberg M: Metabolic control of innate-like T cells. *Nat Rev Immunol* 26: 67-82, 2026.
82. Chen X, Lin P, Lu Y, Zheng J, Lin Y, Zhou Z, Cui L and Zhao X: Mitochondrial regulation of CD8⁺ T cells: Mechanisms and therapeutic modulation. *Adv Sci (Weinh)* 12: e03095, 2025.
83. Norton EG, Chapman NM and Chi H: Mitochondria and lysosomes in T cell immunometabolism. *Trends Immunol* 46: 635-651, 2025.
84. Kulakova K, Lawal TR, McCarthy E and Floudas A: The contribution of macrophage plasticity to inflammatory arthritis and their potential as therapeutic targets. *Cells* 13: 1586, 2024.
85. Lang F, Li Y, Yao R and Jiang M: Osteopontin in chronic inflammatory diseases: Mechanisms, biomarker potential, and therapeutic strategies. *Biology (Basel)* 14: 428, 2025.
86. Shi Y, Zhang H and Miao C: Metabolic reprogram and T cell differentiation in inflammation: Current evidence and future perspectives. *Cell Death Discov* 11: 123, 2025.
87. Ummarino A, Calà N and Allavena P: Extrinsic and cell-intrinsic stress in the immune tumor micro-environment. *Int J Mol Sci* 25: 12403, 2024.
88. Saxena Y, Routh S and Mukhopadhyaya A: Immunoporosis: Role of innate immune cells in osteoporosis. *Front Immunol* 12: 687037, 2021.
89. Mussbacher M, Derler M, Basílio J and Schmid JA: NF- κ B in monocytes and macrophages - an inflammatory master regulator in multitalented immune cells. *Front Immunol* 14: 1134661, 2023.
90. Malengier-Devlies B, Metzemaekers M, Wouters C, Proost P and Matthys P: Neutrophil homeostasis and emergency granulopoiesis: The example of systemic juvenile idiopathic arthritis. *Front Immunol* 12: 766620, 2021.
91. Zhou Y, Cheng L, Liu L and Li X: NK cells are never alone: Crosstalk and communication in tumour microenvironments. *Mol Cancer* 22: 34, 2023.
92. Li S, Zhang Y, Tong H, Sun H, Liao H, Li Q and Ma X: Metabolic regulation of immunity in the tumor microenvironment. *Cell Rep* 44: 116463, 2025.
93. Kennedy-Batalla R, Acevedo D, Luo Y, Esteve-Solé A, Vlasea A, Correa-Rocha R, Seoane-Reula ME and Alsina L: Treg in inborn errors of immunity: Gaps, knowns and future perspectives. *Front Immunol* 14: 1278759, 2024.
94. Braileanu GT: Use of regulatory cells for achieving functional tolerance of pig heart xenotransplants in humans: A literature review. *Front Immunol* 16: 1648926, 2025.
95. Zhou P, Zhang W, Liao Y, Zhai Z, Lu S, Jiang S, Hu W and Gong W: Colorectal cancer: The immune microenvironment and the gut microbiota - new perspectives, challenges, and opportunities. *Int J Surg* 111: 5363-5386, 2025.
96. Deng Y, Jia X, Liu L, He Q and Liu L: The role of intestinal macrophage polarization in colitis-associated colon cancer. *Front Immunol* 16: 1537631, 2025.
97. Li L, Xu T and Qi X: Balanced regulation of ROS production and inflammasome activation in preventing early development of colorectal cancer. *Immunol Rev* 329: e13417, 2025.
98. Luo D, Luo G, Xu H, Li K, Li Z and Zhang C: Inorganic dietary nanoparticles in intestinal barrier function of inflammatory bowel disease: Allies or adversaries?. *Front Immunol* 16: 1563504, 2025.
99. Yang J, Huang Q, Long J and Li J: Microbiota and inflammatory bowel disease: The dual effect mechanism of polysaccharide therapy. *Front Immunol* 16: 1666866, 2025.
100. Zhang Y, Xun L, Qiao R, Jin S, Zhang B, Luo M, Wan P, Zuo Z, Song Z and Qi J: Advances in research on the role of high carbohydrate diet in the process of inflammatory bowel disease (IBD). *Front Immunol* 15: 1478374, 2024.
101. Nishioka K, Ogino H, Ihara E, Chinen T, Kimura Y, Esaki M, Bai X, Minoda Y, Tanaka Y, Wada M, *et al*: Importance of rectal over colon status in ulcerative colitis remission: the role of microinflammation and mucosal barrier dysfunction in relapse. *J Gastroenterol* 60: 416-429, 2025.
102. Xie Y, Liu F, Wu Y, Zhu Y, Jiang Y, Wu Q, Dong Z and Liu K: Inflammation in cancer: Therapeutic opportunities from new insights. *Mol Cancer* 24: 51, 2025.
103. Guo Q, Jin Y, Chen X, Ye X, Shen X, Lin M, Zeng C, Zhou T and Zhang J: NF- κ B in biology and targeted therapy: New insights and translational implications. *Signal Transduct Target Ther* 9: 53, 2024.
104. Wang L, Hu Y, Song B, Xiong Y, Wang J and Chen D: Targeting JAK/STAT signaling pathways in treatment of inflammatory bowel disease. *Inflamm Res* 70: 753-764, 2021.
105. Zolotova N, Kirillova M, Dzhaliolova D, Tsvetkov I, Fokichev N and Makarova O: Microplastics' impact on the development of AOM/DSS-Induced colitis-associated colorectal cancer in mice. *Int J Mol Sci* 26: 11511, 2025.
106. Ullah H, Arbab S, Tian Y, Chen Y, Liu CQ, Li Q and Li K: Crosstalk between gut microbiota and host immune system and its response to traumatic injury. *Front Immunol* 15: 1413485, 2024.
107. Zhang Y, Ji S, Miao G, Du S, Wang H, Yang X, Li A, Lu Y, Wang X and Zhao X: The current role of dendritic cells in the progression and treatment of colorectal cancer. *Cancer Biol Med* 21: 769-783, 2024.
108. Huang HK, Liu SP, Deng X, Zhao RL, Feng Y and Wu JS: Crosstalk between macrophages and diverse immune cells accelerates the development of acute lung injury. *Life Sci* 380: 123925, 2025.
109. Ning J, Wang Y and Tao Z: The complex role of immune cells in antigen presentation and regulation of T-cell responses in hepatocellular carcinoma: Progress, challenges, and future directions. *Front Immunol* 15: 1483834, 2024.
110. Gonzalez-Garcia P, Moares N, Serrano-García I, Fernandez-Cisnal R, Luna-Espejo R, Ocaña-Cuesta J, Yi-He W, Muñoz-Miranda JP, Gabucio A, Fernandez-Ponce CM and Garcia-Cozar F: Discordant CAR-T cell signaling: Implications of divergence from physiological T cell activation. *J Transl Med* 23: 834, 2025.
111. Even Z, Meli AP, Tyagi A, Vidyarthi A, Briggs N, de Kouchkovsky DA, Kong Y, Wang Y, Waizman DA, Rice TA, *et al*: The amalgam of naive CD4⁺ T cell transcriptional states is reconfigured by helminth infection to dampen the amplitude of the immune response. *Immunity* 57: 1893-1907.e6, 2024.
112. Vesin B, Fert I, Noirat A, Authié P, Ciret S, Blanc C, Vitrenko Y, Charneau P, Majlessi L and Anna F: Optimized lentiviral backbone induces robust and diverse T cell immunity against neoantigens to counteract tumor heterogeneity. *NPJ Vaccines* 10: 143, 2025.
113. Li M, Liang S, Chang L, Lu B, Cheng J, Yang T, Wu Y, Lyu Y, He X and Yue C: Targeting mitochondrial dysfunction to intervene in liver cancer. *Cancer Biol Med* 22: 1181-1209, 2025.
114. Uccella S and Hayakawa Y: Immunological aspects of cancer cell metabolism. *Int J Mol Sci* 25: 5288, 2024.
115. Karim A, Garg R, Saikia B, Tiwari A, Sahu S, Malhotra M, Minz RW, Rawat A, Singh S and Suri D: Unraveling the unphosphorylated STAT3-unphosphorylated NF- κ B pathway in loss of function STAT3 Hyper IgE syndrome. *Front Immunol* 15: 1332817, 2024.
116. Cen C, Li J, Zhou P, Fisher D, Hien NTT, Musabaev E, Pronyuk K and Zhao L: The effects of cynaroside on lipid metabolism and lipid-related diseases: A mechanistic overview. *Front Pharmacol* 16: 1648614, 2025.
117. Pan X, Wang J, Zhang L, Li G and Huang B: Metabolic plasticity of T cell fate decision. *Chin Med J (Engl)* 137: 762-775, 2024.
118. Frlic T and Pavlin M: Metabolic reprogramming of CAR T cells: A new frontier in cancer immunotherapy. *Front Immunol* 16: 1688995, 2025.

119. Wang X, He J, Ding G, Tang Y and Wang Q: Overcoming resistance to PD-1 and CTLA-4 blockade mechanisms and therapeutic strategies. *Front Immunol* 16: 1688699, 2025.
120. Huang L, Li H, Zhang C, Chen Q, Liu Z, Zhang J, Luo P and Wei T: Unlocking the potential of T-cell metabolism reprogramming: Advancing single-cell approaches for precision immunotherapy in tumour immunity. *Clin Transl Med* 14: e1620, 2024.
121. Qi GX, Zhao RX, Gao C, Ma ZY, Wang S and Xu J: Recent advances and challenges in colorectal cancer: From molecular research to treatment. *World J Gastroenterol* 31: 106964, 2025.
122. Gupta T, Antanaviciute A, Hyun-Jung Lee C, Ottakandathil Babu R, Aulicino A, Christoforidou Z, Siejka-Zielinska P, O'Brien-Ball C, Chen H, Fawcner-Corbett D, *et al*: Tracking in situ checkpoint inhibitor-bound target T cells in patients with checkpoint-induced colitis. *Cancer Cell* 42: 797-814.e15, 2024.
123. Ballerini P, Contursi A, Bruno A, Mucci M, Tacconelli S and Patrignani P: Inflammation and cancer: From the development of personalized indicators to novel therapeutic strategies. *Front Pharmacol* 13: 838079, 2022.
124. De Visser KE and Joyce JA: The evolving tumor microenvironment: From cancer initiation to metastatic outgrowth. *Cancer Cell* 41: 374-403, 2023.
125. Chen X and Song E: The theory of tumor ecosystem. *Cancer Commun (Lond)* 42: 587-608, 2022.
126. Fanizza J, Bencardino S, Allocca M, Furfaro F, Zilli A, Parigi TL, Fiorino G, Peyrin-Biroulet L, Danese S and D'Amico F: Inflammatory bowel disease and colorectal cancer. *Cancers (Basel)* 16: 2943, 2024.
127. Tong Y and Lou X: Interplay between bile acids, gut microbiota, and the tumor immune microenvironment: Mechanistic insights and therapeutic strategies. *Front Immunol* 16: 1638352, 2025.
128. Li Y, Sharma A and Schmidt-Wolf IGH: Evolving insights into the improvement of adoptive T-cell immunotherapy through PD-1/PD-L1 blockade in the clinical spectrum of lung cancer. *Mol Cancer* 23: 80, 2024.
129. Chen X, Sun S, Li S, Yu S, Chen J, Chen X, Shi X and Liang Z: Quantitative spatial profiling of PD-1/PD-L1 and TIGIT/CD155 interaction indicates poor survival outcome and resistance to adjuvant chemotherapy in pancreatic adenocarcinoma. *Eur J Cancer* 232: 116159, 2026.
130. Dong Y, Liu JJ, Zhou Y, Kang W, Li S, Cheung AHK, Hu Y, Liao R, Wong N, Wong CC, *et al*: VSTM2A reverses immunosuppression in colorectal cancer by antagonizing the PD-L1/PD-1 interaction. *Mol Ther* 32: 4045-4057, 2024.
131. Iglesias M, Brennan DC, Larsen CP and Raimondi G: Targeting inflammation and immune activation to improve CTLA4-Ig-based modulation of transplant rejection. *Front Immunol* 13: 926648, 2022.
132. Wang SJ, Dougan SK and Dougan M: Immune mechanisms of toxicity from checkpoint inhibitors. *Trends Cancer* 9: 543-553, 2023.
133. Earland N, Zhang W, Usmani A, Nene A, Bacchiocchi A, Chen DY, Sznol M, Halaban R, Chaudhuri AA and Newman AM: CD4 T cells and toxicity from immune checkpoint blockade. *Immunol Rev* 318: 96-109, 2023.
134. Yuan X, Chen C, Pang Y, Wang X, Yang T, Long A, Liang N, Yang Y and Li C: Multimodal therapeutic strategies against gastric cancer: From conventional treatments to tumor microenvironment targeting. *Front Immunol* 16: 1623588, 2025.
135. Erman A, Ignjatović M, Lesković K, Miceska S, Lamprecht Tratar U, Bošnjak M, Kloboves Prevodnik V, Čemažar M, Kandolf Sekulović L, Avguštin G, *et al*: The prognostic and predictive value of human gastrointestinal microbiome and exosomal mRNA Expression of PD-L1 and IFN γ for immune checkpoint inhibitors response in metastatic melanoma patients: PROTOCOL TRIAL. *Biomedicines* 11: 2016, 2023.
136. Mertowski S, Mertowska P, Czosnek M, Smarz-Widelska I, Żaska W and Grynalska E: Checkpoint imbalance in primary glomerulopathies: comparative insights into IgA nephropathy and membranoproliferative glomerulonephritis. *Cells* 14: 1551, 2025.
137. Tang L, Wang J, Lin N, Zhou Y, He W, Liu J and Ma X: Immune checkpoint inhibitor-associated colitis: From mechanism to management. *Front Immunol* 12: 800879, 2021.
138. Xu S, Chen L, Liu K, Tao H, Ji Z, Wu J, Zhao Y, Zhou Q, Li L, Zhu H, *et al*: Preexisting ulcerative colitis increases the risk of immune-related colitis and predicts divergent survival outcomes in gastrointestinal cancer patients treated with immune checkpoint inhibitors. *Front Immunol* 16: 1627680, 2025.
139. Karagiannis GS, Kato Y and Entenberg D: Editorial: Exploring macrophage roles in cancer progression and therapeutic targeting. *Front Immunol* 16: 1612588, 2025.
140. Hsieh ML, Nishizaki D, Adashek JJ, Kato S and Kurzrock R: Toll-like receptor 3: A double-edged sword. *Biomark Res* 13: 32, 2025.
141. Liu X, Zhang W, Miao X and Hu Y: Natural metabolites used in traditional Chinese medicine for cardiovascular diseases: Pharmacological mechanisms, evidence, and future directions. *Front Pharmacol* 16: 1656751, 2025.
142. Meng W, Chao W, Kaiwei Z, Sijia M, Jiajia S and Shijie X: Bioactive compounds from Chinese herbal plants for neurological health: Mechanisms, pathways, and functional food applications. *Front Nutr* 12: 1537363, 2025.
143. Ma XT, Lou BY, Liu J and Liu B: Traditional Chinese medicines alleviate experimental chronic cerebral hypoperfusion injury through multi-components and multi-target mechanisms. *Front Pharmacol* 16: 1698436, 2025.
144. Zeng L, Yang T, Yang K, Yu G, Li J, Xiang W and Chen H: Curcumin and curcuma longa extract in the treatment of 10 types of autoimmune diseases: A systematic review and meta-analysis of 31 randomized controlled trials. *Front Immunol* 13: 896476, 2022.
145. Zafar A, Lahori D, Namit AF, Paxton Z, Ratna N, Thornton D and Ramana KV: Curcumin in inflammatory complications: Therapeutic applications and clinical evidence. *Int J Mol Sci* 26: 9366, 2025.
146. Afshari H, Noori S and Zarghi A: Curcumin potentiates the anti-inflammatory effects of Tehranolide by modulating the STAT3/NF-kappaB signaling pathway in breast and ovarian cancer cell lines. *Inflammopharmacology* 31: 2541-2555, 2023.
147. Cheng K, Jia P, Ji S, Song Z, Zhang H, Zhang L and Wang T: Improvement of the hepatic lipid status in intrauterine growth retarded pigs by resveratrol is related to the inhibition of mitochondrial dysfunction, oxidative stress and inflammation. *Food Funct* 12: 278-290, 2021.
148. Alesci A, Nicosia N, Fumia A, Giorgianni F, Santini A and Cicero N: Resveratrol and immune cells: A link to improve human health. *Molecules* 27: 424, 2022.
149. Wu SX, Xiong RG, Huang SY, Zhou DD, Saimaiti A, Zhao CN, Shang A, Zhang YJ, Gan RY and Li HB: Effects and mechanisms of resveratrol for prevention and management of cancers: An updated review. *Crit Rev Food Sci Nutr* 63: 12422-12440, 2023.
150. Yang F, Gao R, Luo X, Liu R and Xiong D: Berberine influences multiple diseases by modifying gut microbiota. *Front Nutr* 10: 1187718, 2023.
151. Du M, Liu X, Ji X, Wang Y, Liu X, Zhao C, Jin E, Gu Y, Wang H and Zhang F: Berberine alleviates enterotoxigenic Escherichia coli-induced intestinal mucosal barrier function damage in a piglet model by modulation of the intestinal microbiome. *Front Nutr* 11: 1494348, 2025.
152. Huang C, Sun Y, Liao SR, Chen ZX, Lin HF and Shen WZ: Suppression of berberine and probiotics (in vitro and in vivo) on the growth of colon cancer with modulation of gut microbiota and butyrate production. *Front Microbiol* 13: 869931, 2022.
153. Fekete T and Pázmándi K: Phytochemicals as modulators of dendritic cell functions: Implications for tolerogenic cell-based therapy. *Front Immunol* 16: 1653803, 2025.
154. Choi S, Yoo SA, Ji KY, Jung DH, Lee S, Lee KG, Kim KM, Lee JY, Jung MA, Pyun BJ, *et al*: Asthma alleviation by ginsenoside Rb1 via promotion of Treg proliferation and inflammatory T cell inhibition. *Allergy* 80: 1647-1668, 2025.
155. Qu L, Liu Y, Deng J, Ma X and Fan D: Ginsenoside Rk3 is a novel PI3K/AKT-targeting therapeutics agent that regulates autophagy and apoptosis in hepatocellular carcinoma. *J Pharm Anal* 13: 463-482, 2023.
156. Yao W and Guan Y: Ginsenosides in cancer: A focus on the regulation of cell metabolism. *Biomed Pharmacother* 156: 113756, 2022.
157. Zhang Y, Kang Q, He L, Chan KI, Gu H, Xue W, Zhong Z and Tan W: Exploring the immunometabolic potential of Danggui Buxue Decoction for the treatment of IBD-related colorectal cancer. *Chin Med* 19: 117, 2024.
158. Wang N, Li HZ, Pan TZ, Wen WB, Li YL, Wan QQ, Jin YT, Bian YH and Cui HT: Mechanisms and treatment of inflammation-cancer transformation in colon from perspective of cold and heat in complexity in integrative medicine. *Zhongguo Zhong Yao Za Zhi* 50: 2605-2618, 2025 (In Chinese).

159. Zou YF, Rong YM, Chen ZX, Shen ZH, Chen X, Tan YX, Weng JR, Huang XM and Lin XT: Effects of huaier extract on ameliorating colitis-associated colorectal tumorigenesis in mice. *Onco Targets Ther* 13: 8691-8704, 2020.
160. Wei X, Leng X, Liang J, Liu J, Chi L, Deng H and Sun D: Pharmacological potential of natural medicine Astragali Radix in treating intestinal diseases. *Biomed Pharmacother* 180: 117580, 2024.
161. Ran J, Ai Y, Ni J, Zhang Y, Chen J, Wang T, Ma J, Zheng J, Li R, Ma X, *et al*: A promising drug to prevent the transition from colitis to colorectal cancer. *Am J Chin Med* 53: 1065-1091, 2025.
162. Gasmi A, Shanaida M, Oleshchuk O, Semenova Y, Mujawdiya PK, Ivankiv Y, Pokryshko O, Noor S, Piscopo S, Adamiv S and Björklund G: Natural ingredients to improve immunity. *Pharmaceuticals (Basel)* 16: 528, 2023.
163. Song Z, Bu S, Sang S, Li J, Zhang X, Song X and Ran Y: The active components of traditional Chinese medicines regulate the multi-target signaling pathways of metabolic dysfunction-associated fatty liver disease. *Drug Des Devel Ther* 19: 2693-2715, 2025.
164. Wang XH, Xu DQ, Chen YY, Yue SJ, Fu RJ, Huang L and Tang YP: Traditional Chinese Medicine: A promising strategy to regulate inflammation, intestinal disorders and impaired immune function due to sepsis. *Front Pharmacol* 13: 952938, 2022.



Copyright © 2026 Zhang et al. This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.