Advances in molecular mechanisms of inflammatory bowel disease-associated colorectal cancer (Review)

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Abstract. The link between inflammation and cancer is well documented and colonic inflammation caused by inflammatory bowel disease (IBD) is thought to be a high-risk factor for the development of colorectal cancer (CRC). The complex crosstalk between epithelial and inflammatory cells is thought to underlie the progression from inflammation to cancer. The present review collates and summarises recent advances in the understanding of the pathogenesis of IBD-associated CRC (IBD-CRC), including the oncogenic mechanisms of the main inflammatory signalling pathways and genetic alterations induced by oxidative stress during colonic inflammation, and discusses the crosstalk between the tumour microenvironment, intestinal flora and host immune factors during inflammatory oncogenesis in colitis-associated CRC. In addition, the therapeutic implications of anti-inflammatory therapy for IBD-CRC were discussed, intending to provide new insight into improve clinical practice.

Contents

1. Introduction

Chronic inflammation has been identified as the key contributing factor to the malignant state (1). Inflammation occurs when the organism responds to pathogens or to physical or chemical damage to eliminate the source of the damage and restore homeostasis (2). However, the complex crosstalk between cytokines, chemokines, growth factors and reactive oxygen species (ROS) produced by inflammatory cells and injured parenchymal cells during chronic inflammation may lead to carcinogenesis (3,4), which has been well demonstrated in inflammatory bowel disease-associated colorectal cancer (IBD-CRC).

IBD is a group of inflammatory disorders which manifest in the intestines, including Crohn's disease (CD) and ulcerative colitis (UC) (5). IBD is currently thought to be related to chronic inflammation caused by autoimmune factors and intestinal microbiota. The chronic inflammatory disease can feature extensive infiltration of inflammatory cells in a biopsy specimen of the intestinal mucosa and unconventional dysplasia can frequently be detected during endoscopy (6). The severity of colon inflammation is an independent risk factor for UC-associated CRC and increased inflammatory insults may contribute to higher rates of genomic instability and malignant

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Abbreviations: IBD, inflammatory bowel disease; CRC, colorectal cancer; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; ROS, reactive oxygen species; UC, ulcerative colitis; sCRC, sporadic CRC; CD, Crohn's disease; NF-κB, nuclear factor κB; TNF-α, tumour necrosis factor-α; IKK, IκB kinase; CAF, cancer-associated fibroblast; STAT3, signal transducer and activator of transcription 3; JAK, Janus kinase; S1P, sphingosine-1-phosphate; APC, adenomatosis polyposis coli protein; DSS, dextran sulfate sodium; MMP, matrix metalloproteinase; RNS, reactive nitrogen species; IL, interleukin; AOM, azoxymethane; RONS, reactive oxygen and nitrogen species; CIN, chromosomal instability; MSI, microsatellite stability; MMR, mismatch repair; DAPK, death-associated protein kinase; CMS, consensus molecular subtype; PIGR, polymeric immunoglobulin receptor; OSMR, cytokine oncostatin M; TAM, tumour-associated macrophage; LPS, lipopolysaccharide; TGF-β, transforming growth factor-β; Treg, T regulatory; MDSC, myeloid-derived suppressor cell; PMN-MDSC, polymorphonuclear MDSC; SCFA, short-chain fatty acid; GABA, γ-aminobutyric acid; FXR, farnesoid X receptor; PRR, pattern recognition receptor; TLR, Toll-like receptor; Ig, immunoglobulin; CAC, colitis-associated CRC; ETBF, enterotoxigenic *Bacteroides fragilis*; NSAID, non-steroidal anti-inflammatory drug; GPR, G protein-coupled receptor; COX, cyclooxygenase

Key words: inflammatory bowel disease, colorectal cancer, signalling pathway, oxidative stress, tumour microenvironment, intestinal microbiota, host immune factors

transformation in nonconventional dysplasia (7). Compared to sporadic CRC (sCRC), IBD-CRC follows a different clinicopathological, molecular and risk profile and can be considered a complication of chronic bowel inflammation (8).

The overall incidence of CRC in patients with IBD is thought to increase almost linearly with disease duration. The incidence of IBD-CRC is related to the disease course of IBD, so it is difficult to give an accurate numerical indication of the annual incidence of IBD-CRC. The cumulative probability of developing CRC in patients with UC is 2% at 10 years, 8% at 20 years and 18% at 30 years (9). A meta-analysis based on population-based cohort studies concluded that the pooled standardized incidence ratio of CRC in all patients with IBD in population-based studies was 1.7 [95% confidence interval (CI), 1.2-2.2]. Cumulative risks of CRC were 1, 2 and 5% after a disease duration of 10, 20 and >20 years, respectively (10). In part, this is attributed to the emergence of novel targeted agents targeting inflammatory pathways in colitis and a paradigm shift in management aimed at histological remission. The colonic inflammatory load in patients with IBD has been effectively reduced, leading to an improvement in their disease course and prognosis.

In the present review, the key relationships between chronic inflammation and IBD-CRC pathogenesis were explored. Specifically, the study delved into the oncogenic mechanisms of the primary inflammatory signalling pathways that arise during colonic inflammation and the genomic changes that result from oxidative stress. In addition, the interplay between the tumour microenvironment, gut microbiota and host immune factors in the development of inflammatory carcinogenesis in IBD-CRC was explored. Furthermore, the significance of anti-inflammatory therapy for IBD-CRC was discussed to provide ideas for clinical management.

2. Inflammatory mediators and signalling pathways in IBD-CRC

The main difference between IBD-CRC and sporadic CRC in terms of pathogenesis is thought to be in the damaging effects of oxidative stress resulting from the crosstalk between inflammatory signalling pathways and epithelial cells and various inflammatory cells, which in turn leads to the development of an inflammatory-multifocal dysplasia-cancer sequence. This section describes the inflammatory mediators and signalling pathways associated with IBD-CRC.

Nuclear factor κB (NF-κB). The transcription factor NF-κB is a significant regulator of epithelial cell integrity and intestinal immune homeostasis. Its upstream activation by various mechanisms, such as innate and adaptive immune responses and the release of pro-inflammatory cytokines [e.g. tumour necrosis factor (TNF)-α and interleukin (IL)-1β], causes NF-κB to translocate to the nucleus to promote the transcription of cell cycle genes (11), inhibits apoptosis and further increases the transcription of pro-inflammatory cytokines. Activation of NF-κB depends on the induction of NF-κB inhibitors by IκB kinase (IKK) (12) (Table I) (13-29).

The NF-κB signalling pathway is involved in inflammation-associated tumourigenesis and development and represents a critical molecular link between inflammation and cancer. Furthermore, the tumour-promoting role of NF-κB in different cells varies. IKKβ in intestinal epithelial cells inhibits apoptosis via the mitochondrial pathway, promoting inflammation-associated tumourigenesis (13). By contrast, IKKβ in myeloid cells mainly affects tumour multiplication and size by regulating pro-inflammatory mediators such as cyclooxygenase (COX)-2, matrix metalloproteinase (MMP)-9 and ROS (13). Cancer-associated fibroblasts (CAFs) regulate the production of pro-inflammatory and oncogenic mediators by activating NF-κB, which regulates tumour characteristics and the microenvironment, leading to tumour progression (14). This activity is similar to the function of IKKβ in myeloid cells. NF-κB can activate signal transducer and activator of transcription 3 (STAT3) by increasing IL-6 transcription, and STAT3 activation is essential for sustained NF-κB activation in tumour cells. NF-κB activation is also necessary for sustained NF-κB activation in tumour cells (30).

STAT3. Phosphorylation activation of STAT3, another essential transcription factor linking IBD and IBD-CRC, can provide transcriptional nodes for cancer cells to autonomously initiate transcription of tumour-promoting genes associated with proliferation and survival (31,32). Numerous STAT3-induced regulated genes reactivate the STAT3 pathway and maintain a stable feedback loop between tumour immune and stromal cells in the tumour microenvironment (Table II) (32-47).

In intestinal epithelial cells, STAT3 can inhibit apoptosis by inducing the expression of B-cell lymphoma extra large protein, survivin and heat shock protein 70 and can promote cell proliferation by controlling the expression of G1/S and G2/M cell cycle regulators (32). In addition to activation in tumour cells, STAT3 signalling is essential for the differentiation of pro-inflammatory type 17 T-helper cells (Th17 cells), inhibition of dendritic cell maturation and maintenance of the immunosuppressive function in forkhead box P3 (Foxp3)+ T-regulatory (Treg) cells. Constitutive activation of STAT3 in various tumour-infiltrating immune cells, such as dendritic cells and macrophages, will lead to sustained secretion of pro-inflammatory cytokines and shift the local microenvironment towards an immunosuppressive direction (45,48).

IL-6 and IL-11 can activate STAT3 transcription via Janus kinase (JAK), affecting downstream inflammatory signalling (47). The NF-κB/IL-6/JAK/STAT3 cascade is an important regulatory pathway for the proliferation and survival of tumour-initiating intestinal epithelial cells (37). IL-6/soluble IL-6 receptor α produced by macrophages can induce IL-6 transduction signalling in epithelial cells, which has a vital role in the development of IBD-CRC (37). The activation of STAT3 by most signalling molecules is mainly transduced by the activation of STAT3 by IL-6.

Recent studies have shown that activating the STAT3 signalling axis by IL-11 production by cancer-associated fibroblasts and myeloid cells is more potent for gastrointestinal tumour progression than IL-6 (39). IL-11+ fibroblasts promote tumour progression by secreting IL-11 to activate colonic tumour epithelial cells and colonic fibroblasts (42). IL-11 activation of STAT in cancer-associated fibroblasts often indicates poor prognosis (35).

Table I. Mechanisms of action of NF-κB in IBD-CRC.

Related molecule	Main findings	(Refs.)
NF-κB	• Tumour suppression by deletion of IKKβ in intestinal epithelial cells is associated with increased apoptosis of epithelial cells during tumour promotion. • Removal of IKKβ from myeloid cells reduced the expression of pro-inflammatory cytokines that may act as tumour growth factors, without affecting apoptosis. • CAFs produce pro-inflammatory and tissue remodelling molecules via NF-κB transcription, regulating the production of pro-inflammatory and oncogenic mediators, which in turn regulate tumour properties and the microenvironment, leading to tumour progression.	(13,14)
β-catenin	Regulation of NF-κB activity by β-catenin via TNFRSF19 may contribute to colorectal tumorigenesis.	(15)
TNFR1	TNF-α/TNFR1-mediated signalling enhances the expression of chemokines KC/CXCL1 and MCP-1/CCL2, which regulate the infiltration of neutrophils and macrophages involved in the development and progression of colitis-associated cancers.	(16)
TNFR2	• TNFR2 signaling in intestinal epithelial cells may be directly involved in the development of IBD-CRC with persistent colitis. • The NF-κB pathway is activated in colonic epithelia from DSS-administered mice in association with upregulation of TNFR2 rather than TNFR1. • IL-6- and TNFα-induced TNFR2 expression in colon cancer cells is mediated primarily by STAT3, providing evidence that TNFR2 may contribute to the tumor-promoting roles of STAT3.	(17,18)
IFN	IFN gene stimulating factor may inhibit colorectal tumourigenesis by limiting the activation of NF-κB and STAT3 signalling pathways and further inhibiting increased levels of the pro-inflammatory cytokines IL-6 and KC.	(19)
RIPK3	RIPK3 deficiency can lead to uncontrolled activation of NF-κB, STAT3, AKT and Wnt-β-catenin signalling pathways, enhancing the ability of intestinal epithelial cells to proliferate aberrantly in a persistent inflammatory microenvironment and promoting CRC.	(20)
TLR4	• TLR4 in intestinal epithelial cells is required for the recruitment and activation of COX-2 expressing macrophages. • TLR4 activation appears to promote the development of colitis-associated cancer by mechanisms including enhanced COX-2 expression and increased EGFR signaling.	(21,22)
TLR9	• The protein expression level of TLR9 is gradually upregulated during the development of CRC. • The expression level of TLR9 was found to be positively correlated with that of NF-κB and Ki67. • TLR9 may play an important role in the development of IBD-CRC by regulating NF-κB signaling.	(23)
IL-17RD	The absence of IL-17RD had no effect on the proliferation of normal or tumourous intestinal epithelial cells, but there was elevated expression of pro-inflammatory tumourigenic cytokines (e.g. IL-17A and IL-6) and an increase in STAT3 tyrosine phosphorylation.	(24)
EGFR	TNF-α, IL-1β and IFN-γ pro-inflammatory cytokines mediated by EGFR signaling in macrophages have an important role in IBD-CRC.	(25)
Smad7	Low expression of IL17A caused by the Smad7 expression in tumor-infiltrating CD4 (+) T cells enabled the TNF-α-mediated killing of cancer cells both *in vitro* and *in vivo*, thus indicating that the Smad7-mediated plastic effect on the T-cell phenotype protects against CRC.	(26)
Claudin-1	• TNF-α is able to mediate Claudin-1, which has a regulatory role in the tumourigenic capacity of colon cancer cells. • Dysregulation of Claudin-1 expression plays a key role in inflammation-induced colon cancer growth and progression through regulation of ERK and Src signaling.	(27)

Table I. Continued.

Related molecule	Main findings	(Refs.)
Src kinase	Src kinase activation enhances the response of epithelial cells to TNF-α, leading to increased invasion through mechanisms that involve production of reactive oxygen intermediates.	(28)
Mutant P53 CRC	Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated.	(29)

NF-κB, nuclear factor κB; IKK, IκB kinase; CAF, cancer-associated fibroblast; TNF-α, tumour necrosis factor-α; TNFR2, TNF receptor-2; TNFRSF19, TNFR superfamily member 19; STAT3, signal transducer and activator of transcription 3; TLR, Toll-like receptor; COX, cyclo-oxygenase; CK, casein kinase; EGFR, epidermal growth factor receptor; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; IFN, interferon; MCP, monocyte chemoattracting protein; CXCL-1, C-X-C motif ligand 1; CCR5, C-C motif chemokine receptor 5; RIPK3, receptor interacting serine/threonine kinase 3; COX, cyclooxygenase.

Table II. Mechanisms of action of STAT3 in IBD-CRC.

Related molecule	Main findings	(Refs.)
STAT3	• STAT3 has the ability to mediate IL-6 and IL-11-dependent IEC survival and promote proliferation through G1 and G2/M cell cycle progression. • T cells within the local stroma of tumours are highly activated in myeloid STAT3 knockout IBD-CRC model mice. Myeloid cells may mediate immune evasion of tumours through STAT3 signaling. • STAT3 signaling in the tumour microenvironment induces an increase in IL-23 secretion by tumour-associated macrophages, while decreasing IL-12 secretion by dendritic cells and upregulating IL-10 secretion by Treg cells, thereby altering the balance of tumour immunity towards oncogenesis.	(32-34)
STAT3 mTORC1	Inflammation promotes the development of IBD-CRC via the STAT3 and mTORC1 pathways.	(35,36)
IL-6	• IL-6 mediated by the transcription factor STAT3 produced by intrinsic layer myeloid cells protects normal and premalignant epithelial cells from apoptosis. The NF-κB-IL-6-STAT3 cascade is an important regulator of the proliferation and survival of tumour-initiating IECs. • IL-6 trans-signalling in epithelial cells induced by macrophage-derivedIL-6/ soluble IL-6 receptor α has a crucial role in the development of IBD-CRC.	(37,38)
IL-11	• The IL-11/STAT3 signalling axis is a more potent driver of gastrointestinal tumour progression than IL-6. Colitis-induced IL11 activates STAT3 in colon crypt epithelial cells.	(39-41)
IL-6/IL-11	IL-6/IL-11 activates STAT3 in tumour-associated fibroblasts and is associated with poor prognosis.	(42)
RORγt	FoxP3+RORγt+ Tregs drive colitis-associated CRC growth by activating STAT3 in tumour cells and promoting uncontrolled expression of IL-6 in tumour-infiltrating dendritic cells	(43)
IL-21	IL-21 promotes an inflammatory environment in IBD-CRC through increased T-cell infiltration and increased expression of IL-6 and IL-17A.	(44)
S1P	• S1P is essential for the production of the multifunctional NF-κB-regulated cytokine IL-6, the sustained activation of the transcription factor STAT3 and the upregulation of the S1P receptor S1PR1, linking chronic inflammation and IBD-CRC. • STAT3-induced S1PR1 expression is crucial for persistent STAT3 activation in tumours.	(45,46)
Sphk1	Intestinal epithelial deletion of Sphk1 prevents colitis-associated cancer development by inhibition of epithelial STAT3 activation.	(47)

STAT3, signal transducer and activator of transcription 3; IL, interleukin; IEC, intestinal epithelial cell; IBD-CRC, inflammatory bowel disease associated colorectal cancer; NF-κB, nuclear factor κB; S1P, sphingosine-1-phosphate; Sphk1, sphingosine kinase; S1PR1, S1P receptor 1; Treg, T regulatory cell; FOXP3, forkhead box P3; ROR, RAR-related orphan receptor.

Sphingosine kinase 1 (SphK1)/sphingosine-1-phosphate (S1P)/S1P receptor 1 (S1PR1) axis. The SphK1/S1P/S1PR1 axis lies between NF-κB and STAT3, and S1P is essential for the production of the multifunctional NF-κB-regulated cytokine IL-6 and for the sustained activation of the transcription factor STAT3 (44). Adenomatosis polyposis Coli protein (APC) is a common genetic mutation in early-stage colorectal cancer patients. Mucosal proliferation is reduced in APC Min/+ mice with Sphk1 deficiency in the intestinal epithelium, STAT3 activation is inhibited and gene expression of cyclin D1 and cMyc is decreased in tumour cells (46), suggesting that its role in colitis-associated CRC (CAC) development should not be underestimated. Recent studies indicate that S1P may influence CD8+ T-cell proliferation and survival in a cell-intrinsic manner through S1PR4 by expressing phosphoinositide-3-kinase adaptor protein 1 and leukotriene A4 hydrolase, two downstream gene products considered to be associated with T cell proliferation and/or survival, limiting CD8+ T-cell expansion and thus promoting tumour growth (49), although this has not been validated in IBD-CRC models.

Wnt/β-catenin signalling. Wnt/β-catenin signalling has been involved as a major player in cancer development and progression with its regulatory role in the inflammatory cascade as well as oxidative stress, both of which are crucial determinants of cancer (50). The Wnt/β-catenin signalling pathway regulates the inflammatory cascade response and oxidative stress, favouring tumour development and progression. Hyperactivation of the Wnt/β-catenin signalling pathway has been associated with the development of CRC. There is growing evidence that mutations in the critical regulators of the Wnt/β-catenin signalling pathway are associated with most CRCs (51).

β-catenin is a critical component of Wnt signalling. It is controlled by a destruction complex composed of axis inhibition protein, APC, casein kinase-1 and glycogen synthase kinase-3β (52). Being the core component of the Wnt/β-catenin signalling pathway, β-catenin has a paramount role in Wnt signal transduction (50) by translocating into the nucleus to coactivate, with transcription factor4, the transcription of downstream genes, including c-Myc and cyclin D1, giving rise to the pathogenic phenotype of CRC, such as proliferation, metastasis, chemoresistance and recurrence (53).

In most CRCs, the earliest event is APC gene deletion, leading to nuclear β-catenin accumulation (54). However, in IBD-CRC, APC gene mutations occur at a lower incidence of early progression. β-catenin accumulation in IBD-CRC may occur through an APC-independent pathway, resulting in cancer development. A transcriptome-based analysis of tumour subtypes showed that the typical epithelial tumour subtype associated with Wnt/β-catenin signalling was completely absent in IBD-CRCs (55).

While another clinical trial has shown that β-catenin expression is strongly connected with CAC (56), β-catenin levels increase progressively with the progression from dysplasia to carcinoma. Dysregulation of the Wnt signalling pathway may have an essential role in IBD-CRC, with 55% of dysplastic lesions and up to 100% of cancers expressing nuclear β-catenin (57). However, in contrast to the sCRC pathway, in which early loss of APC function leads to abnormal Wnt signalling, loss of APC function in IBD-CRC occurs later in <50% of cases (58). This may be attributed to the inflammation-driven upregulation of β-catenin in the early stages of IBD-CRC, which induces APC mutations independent of Wnt signalling (59).

Although there are currently conflicting reports on the role of β-catenin in IBD-associated CRC, when considering the role of the gut microbiota, it was found that the effect of specific microbiota in the gut on IBD-CRC stems, at least in part, from the activation of β-catenin signalling. For instance, *Fusobacterium nucleatum* regulates β-catenin signalling by binding its *F. nucleatum* adhesion protein A (FadA) adhesion factor to E-cadherin (60). *Bacteroides fragilis* secretes a zinc-dependent metalloprotease toxin that cleaves E-cadherin, leading to β-catenin nuclear translocation, increased c-Myc expression and cell proliferation (61). Further below, carcinogenesis driven by candidate pathogenic bacteria, this will be described in detail.

IL-23/Th-17 axis. The IL-23/Th-17 axis has a vital role in inflammation-associated tumour development. During chronic intestinal inflammation, the breakdown of the epithelial barrier leads to the activation of dendritic cells by microbial products, whose secreted IL-23 activates pro-inflammatory cytokines such as IL-17A and IL-17F by Th17 cells located in the lamina propria mediated by the IL-6/STAT3 pathway (62). These pro-inflammatory cytokines stimulate, through activation of the STAT3/NF-κB-dependent pathway, the production of additional pro-inflammatory cytokines, including IL-6 and TNF-α, further amplifying the inflammatory response (63,64). Observations in IL-17A-deficient dextran sulfate sodium (DSS)-induced mice revealed that the number of tumours and mean tumour size were significantly reduced in IL-17A-deficient mice compared to wild-type mice, suggesting that it has a vital role in the initiation of CAC development and may indirectly contribute to tumour progression (65). In addition, the IL-23/Th-17 axis can also promote excessive proliferation of IBD-CRC through mechanisms such as increased angiogenesis, upregulation of MMP-9 and reduced infiltration of CD8+ T cells, thus improving its tumourigenic capacity (66).

TNF-α. TNF-α participating in chronic inflammatory diseases is an inflammatory mediator associated with carcinogenesis that promotes the conversion of noncancer cells into tumour stem cells (67). TNF-α undergoes trimerisation upon binding to its receptor, activating downstream signalling pathways, including the NF-κB inflammatory pathway, the Fas pro-apoptotic pathway and the cellular inhibitor of apoptosis protein-1 anti-apoptotic pathway (68). Low-level, sustained TNF-α production induces a tumour phenotype (69). The tumour-promoting mechanism of TNF-α is based on the generation of ROS and reactive nitrogen species (RNS), which induce DNA damage and thus promote tumourigenesis (28). In the presence of TNF-α and IL-1, PI3K/AKT activates NF-κB signalling by phosphorylating IKK (70).

The TNF-α/TNF receptor axis, on the one hand, leads to massive local infiltration of macrophages and neutrophils through the release of chemokines, which in turn activates

inflammatory pathways such as NF-κB and controls inducible nitric oxide synthase (iNOS) production; on the other hand, TNF may also promote tumour angiogenesis by inducing infiltration of macrophages and neutrophils expressing COX-2.

Azoxymethane (AOM)/DSS-treated colitis mice exhibit increased TNF-α expression. In AOM/DSS mice deficient in the central TNF receptor, neutrophil and macrophage infiltration in the mucosa is reduced, mucosal damage is attenuated and tumour formation is inhibited (16). The increase in TNF-α induced by inflammation was mainly produced by infiltrating inflammatory cells and further activated the NF-κB signalling pathway in the inflammatory cells, causing widespread colonic inflammation, which induced carcinogenesis in this model.

3. Oxidative stress in CAC

Oxidative stress induced by chronic inflammation has a central role in IBD-CRC carcinogenesis, which may also be one of the critical differences in pathogenesis between IBD-CRC and sCRC.

During the process of the host immune system combating intestinal pathogenic bacteria and dealing with pre-existing inflammation, various kinds of recruited inflammatory cells produce massive amounts of ROS and RNS, which are collectively known as reactive oxygen and nitrogen species (RONS). RONS can cause oxidative stress, leading to DNA damage in intestinal epithelial cells (71). Patients with IBD presenting with chronic intestinal inflammation have been found to have increased RONS production and lipid peroxidation and decreased antioxidant capacity with increased oxidative DNA damage, which are likely mechanisms that drive mutagenesis (72).

The accumulation of molecular events and mutations in somatic cells, followed by their clonal expansion, have been studied for their role in IBD-CRC pathogenesis. This process leads to extensive preneoplastic 'field changes' in the colonic mucosa before the development of histological evidence of dysplasia. In this section, the recently discovered impact of inflammation-induced oxidative stress on IBD-CRC and the commonly found molecular oncogenic pathways of IBD-CRC will be discussed.

Genomic instability caused by oxidative stress. During acute inflammation, RONS from activated immune cells can promote tissue repair and regeneration in addition to their pathogen-killing effects. However, recurrent histological damage and RONS repair processes also induce permanent DNA damage (including single- and double-strand breaks, nucleotide modifications and abrogation sites) and genomic instability in proliferating intestinal epithelial cells (4).

Apart from oxygen free radicals produced by inflammatory cells, extracellular free radicals from intestinal bacteria significantly increase DNA damage in co-clonal epithelial cells, possibly associated with CRC-associated chromosomal instability (CIN) (73).

Furthermore, it has been shown that there is a positive feedback relationship between inflammation and genomic instability (74). Inflammation is attributed to mutations that damage DNA through the production of RONS, exacerbating the inflammation in turn. Despite being influenced by complex signalling networks and DNA repair mechanisms, it usually leads to carcinogenesis under long-term chronic inflammatory conditions (75,76).

The accumulation of ROS and RNS has been observed in inflammatory tissues of patients with active UC and CD (75). If RONS disrupt proto-oncogenes in the intestinal epithelium, it may cause alterations in the genetics and epigenetics of heritable intestinal epithelial cells.

The primary genetic alterations in IBD-CRC differ in frequency and timing from those in sCRC, which are thought to be closely related to genomic damage induced by oxidative stress. Metagenomic studies have found that proto-oncogene p53 mutations and loss of heterozygosity occur early in IBD-CRC (77). P53 loss of function appears to be an early event in initiating IBD-CRC pathogenesis (78). P53 critically impacts cell proliferation and prevents clonal expansion of mutant cells. Besides being found in >80% of patients with IBD-CRC (79), p53 mutations have been found in inflamed mucosa of 50% of patients with UC without cancer (80,81). *In vitro* studies have shown that the acquisition of mutant p53 (mutp53) function is manifested in DSS-induced colitis mice by the rapid emergence of flattened developmentally abnormal lesions that can progress to invasive carcinomas, accompanied by the accumulation of mutant p53 and enhanced activation of NF-κB. This change is similar to the developmental pattern of human IBD-CRC and may explain the early appearance of p53 mutations in human IBD-CRC (30).

Loss of function of the oncogene APC and the proto-oncogene KRAS also occur as early events in IBD-CRC but with a much lower prevalence than in sCRC (82). APC encodes an essential member of the β-catenin disruption complex. This complex critically attenuates the nuclear localisation of β-catenin and its binding to the TCF family of transcription factors, promoting Wnt signalling. Amplification of MYC proto-oncogene occurred in 26% of IBD-CRC samples compared to 26% of sCRC samples. In addition, isocitrate dehydrogenase 1 mutations were significantly more common in IBD-CRC and rare in sCRC.

Carcinogenic pathways of IBD-associated CRC. Inflammation is instrumental in promoting gene mutations and genomic instability (74). Inflammation-driven genetic alterations, along with changes at the epigenetic level, may have an essential role in the tumourigenesis of CRC, particularly in IBD-CRC (83). Similar to sCRC, the major oncogenic molecular pathways in IBD-CRC include CIN, microsatellite instability (MSI) and CpG island methylator phenotype.

CIN. CIN is usually triggered by mutations in oncogenes followed by a series of duplications that ultimately lead to an altered chromosome number (aneuploidy) and chromosomal structural abnormalities (somatic copy number alterations, deletions, insertions and amplifications) (84) and possible loss of oncogene heterozygosity and chromosomal rearrangements. CIN is considered a significant feature of the pathogenesis of CAC and is found in 80% of cases (74,76). CIN is associated with a progressive accumulation of mutations in pro-oncogenes and tumour suppressor gene. Aneuploidy is a consequence of CIN and occurs before dysplasia in colonic mucosal biopsy samples from patients with IBD (85).

Furthermore, there was a statistically significant relationship between increased aneuploidy and histological progression of dysplasia/carcinoma in UC (78). This observation highlights the progressive genomic instability during IBD-CRC tumour progression.

MSI and hypermethylation pathway. MSI is thought to be a genomic microsatellite hypermutation phenotype due to faulty operation of the DNA mismatch repair (MMR) mechanism. Following the inactivation of MMR genes, mutations continually accumulate in the cancer genome as there is a lack of ability to repair post-DNA replicative base substitutions or slippage mistakes at microsatellite sequences. With defective MMR, there has been a significant increase in mutated genes that have not been able to be correctly repaired and this ability to increase mutation frequency is thought to shorten the typical time frame for adenoma-to-carcinoma formation from 1-2 decades to 1-2 years (86).

Damage to the DNA MMR system induced by oxidative stress would lead to the accumulation of MSI phenotypes in the colonic mucosa of patients with IBD-CRC. The MSI phenotype can be observed in ~15% of patients with IBD-CRC, a rate similar to that of sCRC (87). In patients with IBD-CRC, high MSI is closely associated with hMLH1 hypermethylation and hMSH2 expression deficiency, two mismatch repair genes (88). In IBD-CRC, proximal tumours with high mutation rates correlate with MSI and have a higher predicted neo-epitope load (89). Such tumours tend to have increased immunogenicity and may respond better to immunotherapy.

The CpG island methylation phenotype itself overlaps with MSI pathogenesis. Distinguished from MSI, the hypermethylation pathway is characterised by the CpG island methylator phenotype, resulting in the epigenetic silencing of several genes, particularly tumour suppressor genes. Several studies have explored the hypermethylation pathways in patients with IBD-CRC. For instance, promoter hypermethylation of $p16^{INK4a}$ and $p14^{ARF}$, which are expected early events in IBD-CRC carcinogenesis, was found in 100 and 50% of UC-CRC, respectively, and these two genes have a crucial role in cell cycle inhibition (90). In addition, CDH1 promoter methylation was detected in 93% of patients with IBD with colonic dysplasia, compared with 6% of patients with IBD without dysplastic lesions (91). This gene is involved in biological processes that are dysregulated in cancer, such as the sequence of cell sorting, migration and differentiation. Death-associated protein kinase (DAPK), a tumour suppressor gene, also appears to undergo epigenetic modifications during IBD-CRC carcinogenesis. A study using surgical resection specimens from patients with UC for DAPK epigenetic analysis concluded that DAPK silencing induced by promoter hypermethylation may lead to the accumulation of mucosal DNA damage in UC and, therefore, may contribute to the development of UC-associated CRC (92).

Epithelial consensus molecular subtypes of IBD-CRC. A transcriptome-based analysis of tumour subtypes showed that the typical epithelial tumour subtype associated with Wnt signalling was absent in IBD-CRCs; instead, a mesenchymal stroma-rich subtype predominated (55). IBD-CRCs exhibit a switch from the epithelial consensus molecular subtype (CMS)2 to the more mesenchymal CMS4 phenotype [epithelial-mesenchymal transition (EMT)]. Dysregulation of Wnt signalling activates transforming growth factor (TGF)-β and results in an 'immuno-inflammatory' inhibitory microenvironment enriched with CD4+ cells. EMT involves loss of tumour cell polarity and cell-cell adhesion to enhance cell migratory and invasive properties (93).

In IBD-associated CRC, polymeric immunoglobulin receptor (PIGR) and cytokine oncostatin M (OSMR), which are involved in mucosal immunity, are dysregulated by epigenetic modifications. Low expression of PIGR may promote epithelial barrier dysfunction and persistent inflammation. Increased OSMR signalling may then favour the establishment of mesenchymal CRC subtype in patients with IBD (77). A previous single-cell analysis showed the presence of an activated mesenchymal cell population in the mesenchyme surrounding the colonic crypts of patients with IBD. This subpopulation expresses TNF superfamily member 14, fibroblastic reticulocyte-associated genes, IL-33 and lysyl oxidase. In addition, it induces factors that impair epithelial proliferation and maturation and contribute to oxidative stress and disease severity *in vivo* (94). Whether this process may contribute to the cancerous process requires further exploration.

4. Inflammatory/tumour microenvironment

Various cells in the inflammatory microenvironment (e.g., epithelial cells, immune cells and stromal cells) communicate with each other through direct contact or through secreted cytokines and chemokines, coordinating the ongoing inflammatory response by autocrine and paracrine ways. The transformation process of the inflammatory microenvironment to the immunosuppressive tumour microenvironment has now been documented. Various immune mediators and the abundance and activation status of immune cells in the local microenvironment determine the anti-tumour response and pro-tumour effects of inflammation (95). The tumour microenvironment formed by infiltrating immune cells, stromal cells and tumour cells is essential for maintaining signalling proliferation, resisting cell death and inducing angiogenesis (Fig. 1).

Myeloid cells promoting immunosuppression. In the inflammatory microenvironment, myeloid cells are the central cells that suppress the inflammatory response. However, myeloid cells are hidden in their original anti-inflammatory function in most established tumours under the influence of existing tumour cells. Local infiltration of myeloid cells by the tumour makes it difficult to contain tumour growth and drives the tumour microenvironment further toward immunosuppression under the influence of local immune mediators (96) (Fig. 2).

Tumour-associated macrophages (TAMs). Inflammation-promoting macrophages are a central and potent component of innate immunity. During colon inflammation, intestinal epithelial cells stimulated by lipopolysaccharide (LPS) release chemokines (e.g., C-X-C motif chemokine ligand-2 and C-C motif chemokine ligand 2) and recruit large numbers of monocytes and neutrophils (38). Massive macrophages infiltrate the intestinal lamina propria, triggering polarisation towards M1 or M2 in response to continuous exposure to inflammatory microenvironmental signals (97,98). Bacterial products and Th1 cytokines induce macrophage polarisation towards

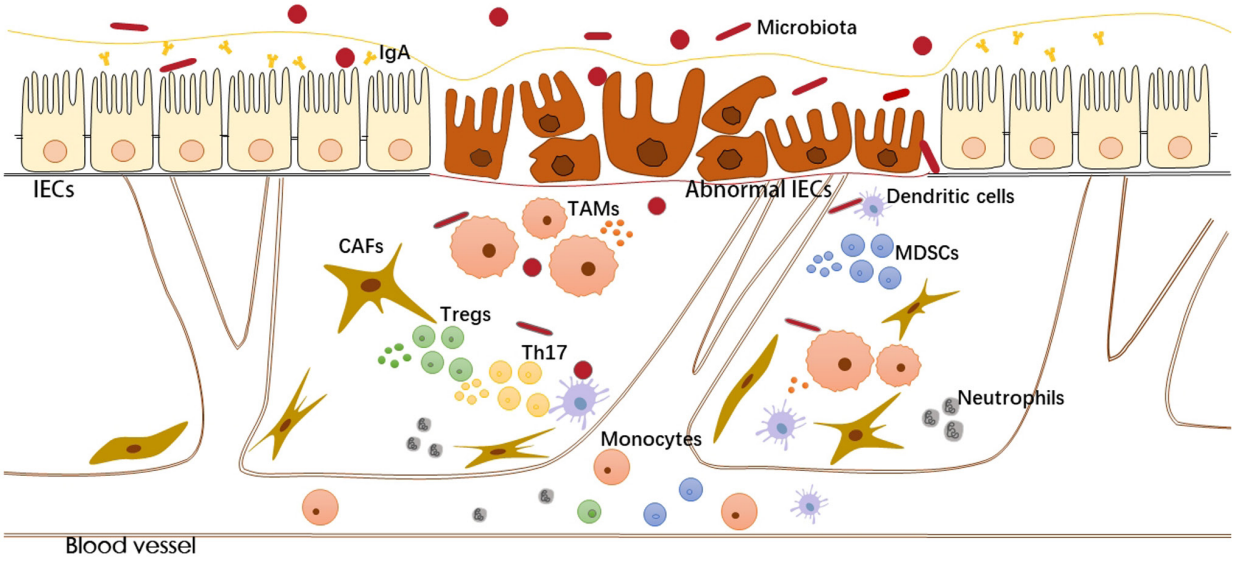

Figure 1. Tumour microenvironment with local infiltration of colitis-associated colorectal cancer. Inflammatory factors and chemokines secreted by intestinal epithelial cells after damage to the intestinal barrier attract a large number of inflammatory cells. Under the influence of crosstalk between inflammatory cells, the local environment evolves towards immunosuppression. IEC, intestinal epithelial cell; CAF, cancer-associated fibroblast; TAM, tumour-associated macrophage; MDSC, myeloid-derived suppressor cell; Treg, T-regulatory cell; Th17, type 17 T-helper cell.

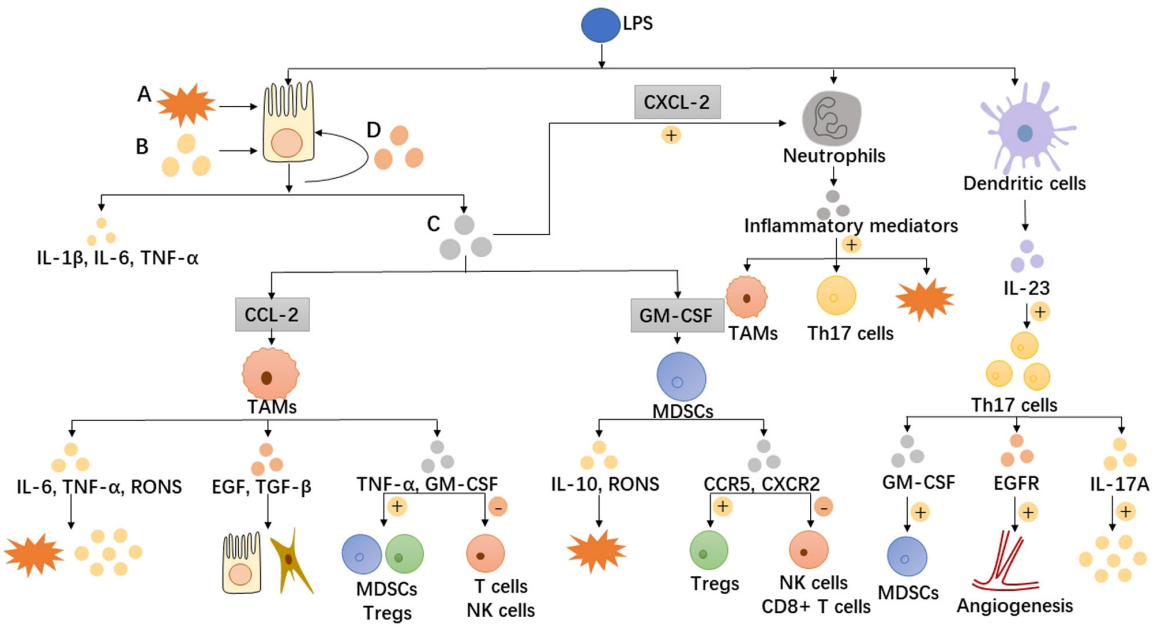

Figure 2. Disruption of the intestinal mucosal barrier provides an opportunity for bacterial products (e.g. LPS) to enter the lamina propria and continuously stimulate recruited immune cells by chemokines, leading to continuous activation of inflammatory signalling pathways and the production of large amounts of inflammatory mediators. Potential mechanisms include the following: i) Inflammatory factors, such as IL-6, IL-10 and TNF-α, produced by a large number of infiltrating macrophages, MDSCs and other inflammatory cells crosstalk via paracrine and autocrine signals, activating the inflammatory pathways of various cells in the tumour microenvironment and causing inflammation to induce uncontrollable development. ii) Cells with immunosuppressive properties (e.g. MDSCs and Tregs) inhibit cytotoxic CD8+ T-cells and NK cells either directly or in an indirect manner through the secretion of chemokines, promoting the establishment of an immunosuppressive microenvironment. iii) Damage to intestinal epithelial cells by RONS produced by inflammatory cells further contributes to the progression of inflammation and malignancy. iv) The secretion of various growth factors drives angiogenesis, provides nutrition for tumour cell growth and induces mesenchymal cell function and differentiation. A, oxidative stress; B, pro-inflammatory cytokines; C, pro-inflammatory chemokines; and D, growth factors. LPS, lipopolysaccharide; IL, interleukin; TNF-α, tumour necrosis factor-α; GM-CSF, granulocyte-macrophage colony-stimulating factor; TAMs, tumour-associated macrophages; RONS, reactive oxygen and nitrogen species; TGF-β, transforming growth factor-β; epidermal growth factor, EGF; Tregs, T regulatory cells; NK, natural killer; CXCL-2, C-X-C motif ligand 2; CCR5, C-C motif chemokine receptor 5; EGFR, epidermal growth factor receptor; MDSC, myeloid-derived suppressor cell.

pro-inflammatory, cytotoxic and antigen-presenting M1, whereas Th2 cytokines polarise macrophages towards immunomodulatory, pro-angiogenic M2 (99).

TAMs are the most abundant myeloid cell population infiltrating solid tumours, predominantly displaying an M2 phenotype as crucial for promoting tumour inflammation

and mediating immunosuppression (100). TAMs have been found to have poor antigen-presenting capacity and limited anti-tumour responses. Reduced killing capacity of TAMs has been associated with reduced iNOS expression (101).

The tumour-promoting effects of TAMs are multifaceted. TAMs infiltrated in the TME, on the one hand, promote the formation of the inflammatory microenvironment through a large amount of released inflammatory mediators (e.g., IL-6, TNF-α and RONS) (102); on the other hand, they further provide proliferation signals through the supply of mitogenic growth mediators [e.g., epidermal growth factor (EGF) and TGF-β] to maintain the uncontrolled proliferation of epithelial and mesenchymal cells (103). In addition, TAMs have recruitment effects on immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs) and Tregs and inhibitory effects on T cells and natural killer (NK) cells, resulting in the suppression of immune activity in the local microenvironment (104,105). In the early stages of IBD-CRC, monocyte-like macrophages are recruited into the local microenvironment and promote the expansion of Th17 cells by producing IL-1β, which further exacerbates dysbiosis and inflammation, leading to a vicious cycle and contributing to tumourigenesis (102).

MDSCs. Similar to TAMs, MDSCs [including monocytic MDSCs and polymorphonuclear MDSCs (PMN-MDSCs)] are also premature myeloid cells. Although they overlap with monocytes and granulocytic myeloid cells, they represent two cell populations with distinct immune phenotypes. MDSCs can suppress both adaptive and innate immunity. Infiltration of MDSCs may promote tumourigenesis on the one hand through activation of the STAT3 and NF-κB pathways (106), and on the other hand, may influence the function of other cells through chemokines. MDSCs, which express C-X-C motif chemokine receptor 2, can directly inhibit cytocidal cytotoxicity of NK cells and CD8+ T cells (107,108), accelerating tumour growth (109). Furthermore, C-C motif chemokine receptor 5-expressing MDSCs can also induce local aggregation of Tregs in tumours (110), promoting immunosuppression. Mouse models with breast cancer have additionally shown that MDSCs can affect tumour immunity by increasing IL-10 production and inhibiting macrophage secretion of IL-12 (111).

T cells that promote immunosuppression. Tumour-infiltrating T cells have been associated with improved clinical prognosis and survival of patients with CRC (112,113). Tumour-killing type 1 T-helper cells, CD4+ T cells and CD8+ T cells have anti-tumour effects. However, these types of cells are regulated by other immunosuppressive cells in the tumour microenvironment, which, to a certain extent, maintains the local inflammatory state and leads to an immunosuppressive state in the local microenvironment.

Th17 cells. The IL-23/Th17 signalling pathway has an important role in inflammation-associated tumours. IL-23 produced by inflammatory dendritic cells infiltrated in the tumour microenvironment induces the polarisation of Th17 cells. Tumour-infiltrating γδT17 cells further activate downstream inflammatory signals by secreting inflammatory factors such as IL-17A. In addition, IL-8, TNF-α and granulocyte-macrophage colony-stimulating factor secreted by Th17 cells chemotactically attract immunosuppressive PMN-MDSC and maintain immunosuppressive activity (114-116).

Treg cells. Treg cells modulate adaptive immunity, suppressing inflammation in chronic inflammatory diseases. Treg cells promote the clearance of pathogenic bacteria by establishing a protective immune response during intestinal infections (117,118). However, the cytotoxic effects of Treg cells on antitumourigenic CD8+ T cells have suggested that these cells are immunosuppressive in the tumour environment (119), and different subpopulations of Treg cells exhibit other immune properties in an environmentally dependent manner.

Massive infiltration of RAR-related orphan receptor (ROR)γt+Foxp3+ cells has been observed in the intestinal lamina propria of UC and colon cancer (120), a subpopulation of Foxp3+ Treg cells induced in a chronic inflammatory environment. This subpopulation of Tregs can exhibit certain features of Th17 cells, such as secretion of IL-17A, which has been shown to have a pathogenic role in the pathogenesis of infiltrative CRC (121). In addition, this group of cells promotes the production of inflammatory cytokines, such as IL-17A, IL-1, IFN-γ and TNF-α, by colitis cells (120), which supports local inflammatory responses and oxidative stress insults.

Treg cells can perform an immunosuppressive function by inhibiting the anti-tumour response of CD4+ T cells and CD8+ T cells, contributing to the formation of an immunosuppressive tumour microenvironment (122). The co-expressed transcription factors Foxp3 and RORγt on Treg cells can drive IBD-CRC growth by activating STAT3 in tumour cells and promoting uncontrolled expression of IL-6 in tumour-infiltrating dendritic cells (38).

Mesenchymal cells that promote immunosuppression. Mesenchymal stromal cells in tumours, also known as CAFs, are a significant component of the tumour stroma, which secrete growth factors and inflammatory ligands. In the tumour microenvironment, CAFs with distinct phenotypes are activated by bacterial products (e.g., LPS) and cytokines (e.g., TNF-α) (123) to promote tumour progression through the expression of a wide range of growth and inflammatory factors [e.g., IL-8, vascular endothelial growth factor (VEGF) and fibroblast growth factor 2] (124-127), resulting in a sustained inflammatory environment. Factors from diverse cellular and tumour sources shape the phenotype of heterogeneous CAFs (128). Similar to the polarisation of TAMs, CAFs show a high degree of plasticity. The function of CAFs has been shown to impact the development of the tumour microenvironment substantially and has been found to have partial anti-tumour activity. Studies on the role of fibroblasts in the IBD-CRC model are summarised in Table III (14,39,42,123-130).

5. Gut microbiota and host immune factors

Human gut microbiota is a complex community of 100 trillion microorganisms, including various types of bacteria, fungi, protists and viruses, which is considered a 'microbial organ'. The intestinal immune system of the host interacts with the microbiota and produces a variety of metabolites or components. These metabolites maintain the normal metabolism, proliferation and differentiation of epithelial cells and have essential physiological functions such as protective activities

Table III. Functions of fibroblasts in the IBD-CRC model in response to different signals.

Related molecule	Main findings	(Refs.)
NF-κB	CAFs produce pro-inflammatory and tissue remodelling molecules via NF-κB transcription, regulating the production of pro-inflammatory and oncogenic mediators,which in turn regulate tumour properties and the microenvironment leading to tumour progression.	(14)
IL-11	Tumour cells induce IL-11+ fibroblasts; a feed-forward loop between colon tumour epithelial cells and IL-11+ fibroblasts via secretion of IL-11 may contribute to tumour development.	(39)
IL-6/IL-11	IL-6/IL-11 activates STAT3 in tumour-associated fibroblasts and is associated with poor prognosis.	(42)
FGF-1 and FGF-3	CAFs promote tumour growth and angiogenesis by secreting FGF-1 and FGF-3, which promote the production of MMP-7 and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase in tumour cells.	(128)
Tpl2	Tpl2 expressed by IMF suppresses epithelial tumorigenesis by inhibiting the HGF/c-Met pathway.	(123)
EREG	CAFs can stimulate the activation of ERK in tumour cells through the production of EREG, which directly promotes the proliferation of tumour cells.	(124)
CCL3-CCR5	CCL3-CCR5 in the tumour microenvironment mediates CAF accumulation and promotes CAF proliferation and heparin-binding epidermal growth factor-like growth factor expression.	(125)
Tenascin-C	• In the early stages of IBD-CRC, tenascin-C produced by IMFs affects tumour development via integrin αvβ3-mediated angiogenesis.of IBD-CRC via • Tenascin-C-derived peptide TNIIIA2 may contribute to the formation activation of stromal fibroblasts based on β1-integrin activation.	(126,127)
IMP1	The tumour suppressor role of stromal IMP1 and its ability to modulate protumorigenic factors suggest that the status of IMP1 is important for the initiation and growth of epithelial tumours.	(129)
PGE	Locally infiltrating CAF and neutrophils express EP2, which synergises with TNF-α to amplify activation of the NF-κB inflammatory cascade response and amplify recruitment to neutrophils through autocrine amplification of CXCL1, resulting in the formation of the tumour microenvironment.	(130)

CAF, cancer-associated fibroblast; NF-κB, nuclear factor κB; IL, interleukin; STAT3, signal transducer and activator of transcription 3; FGF, fibroblast growth factor; Tpl2, tumor progression locus 2; IMF, intestinal myofibroblasts; EREG, epiregulin; HGF, hepatocyte growth factor; CCL3, C-C chemokine ligand; CXCL1, C-X-C motif ligand 1; CCR5, CC chemokine receptor 5; IBD-CRC, inflammatory bowel disease associated colorectal cancer; IMP1, insulin-like growth factor II mRNA-binding protein 1; PGE, prostaglandin; EP2, PGE receptor 2; TNF-α, tumour necrosis factor-α; MMP, matrix metalloproteinase.

against pathogens and immune system regulation (131,132). It has also been shown that gut microbiota is involved in the brain-gut axis of brain-gut communication, thereby affecting the mental and neurological functions of the host (133).

However, dysbiosis disrupts the mucosal barrier, leading to prolonged inflammation and cancer. Current research on the impact of the gut microbiota on the progression of IBD towards CRC has advanced. This section describes the intricate physiological role of the gut microbiota in maintaining host health and the latest information on the function of gut dysbiosis in colorectal carcinogenesis and progression (134).

Physiological role of the gut microbiota. The gut microbiota and its metabolites have a multifaceted role in inhibiting inflammation, maintaining the mucosal barrier and modulating immunity during interactions with the host. The gut microbiota can produce a wide range of metabolites using exogenous undigested dietary substrates (e.g., dietary fibre) and endogenous compounds [e.g., bile acid (BA) metabolites] to provide energy and nutrients to the host. Certain bacterial species, such as Bifidobacteria, are involved in the biosynthesis of various components such as vitamin K and B (135).

Several bacteria, such as Firmicutes, Bacteroidetes and certain anaerobic gut microorganisms, can provide short-chain fatty acids (SCFAs) with biologically active components through the fermentation of dietary fibre (136). SCFAs produced in the gut are rapidly absorbed by host epithelial cells. They are a significant source of energy for colonic epithelial cells and have systemic immunomodulatory and anti-inflammatory effects (136). The most abundant SCFAs

in the colon are acetate, propionate and butyrate (13,15,16), which promote the proliferation of beneficial bacteria, stimulate Treg cells and macrophages to reduce the production of inflammatory mediators and increase the oxygen consumption of colonic epithelial cells, resulting in the enhancement of immunomodulation and intestinal barrier function (137). Butyrate has been found to enhance intestinal barrier function by activating AMPK, Akt and other signalling pathways to promote tight junction assembly in a dose-dependent manner (138). Furthermore, during colitis, butyrate induces T cell-independent immunoglobulin A (IgA) secretion in the colon through activation of free fatty acid receptor 3 [also known as G protein-coupled receptor (GPR)41] and carboxylic acid receptor 2 (also known as GPR109A), as well as inhibition of histone deacetylase, which restores the epithelial barrier function under inflammatory conditions (139).

In addition to producing substances that regulate energy metabolism in colonic epithelial cells, the gut microbiota can synthesise several neurochemicals that can affect both the central nervous and peripheral gut systems. For instance, γ-aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the brain and numerous neuropsychiatric disorders have been linked to GABA dysfunction, which is also thought to be connected to the brain-gut axis connection.

The gut microbiota has also reportedly been involved in synthesising substances such as BA, cholesterol and conjugated fatty acids and branched-chain amino acids (140). Bile salts escaping during enterohepatic circulation become substrates for gut microbial metabolism. Bacteria, including Clostridium, Bifidobacterium, Bacteroides, Listeria and Lactobacillus, are involved in deconjugating bile acids, which is vital for the gut microbiota to mediate immune regulation. On the one hand, bile acids can produce direct antimicrobial effects by disrupting bacterial biomembrane. On the other hand, the bile acid receptors farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 can be activated by bile acid derivatives, which are essential for the regulation of intestinal inflammation and tumourigenesis. For example, activated FXR signalling suppresses CRC progression by antagonising the Wnt/β-catenin pathway and inhibiting cytokine signalling 3 gene transcription.

Another significance of the gut microbiota for the host is its fundamental role in the differentiation of the host's immune system. Symbiotic bacteria in the gut are able to not only competitively inhibit pathogenic pathogens in the gut, but also indirectly defend against pathogens by activating the immune response. For instance, LPS and flagellin derived from the gut microbiota enhance the expression of antimicrobial peptide and RegIIIγ from epithelial cells by stimulating Toll-like receptor (TLR)4+ stromal cells and TLR5+ CD103+ dendritic cells (141). The gut microbial metabolite butyrate modulates T-cell differentiation and proliferation. It enhances Treg cell function and induces their differentiation (142), inhibits IL-17 levels as well as Th17 cells in peripheral blood and colon tissues of rats with 2,4,6-trinitrobenzenesulfonic acid-induced colitis (143), and suppresses the proliferation of CD4+ and CD8+ T cells in a dose-dependent manner (144).

Host recognition of microbial metabolites relies on pattern recognition receptors (PRRs), essential for initiating the innate immune response (145). One of the most well-studied PRRs is the TLR, a transmembrane protein expressed in intestinal epithelial cells and innate immune cells. TLRs have an essential role in activating the innate immune mechanism and maintaining the integrity of the intestinal epithelial barrier by recognising highly conserved structural molecules expressed by microbial pathogens (146). TLR4 pre-expression is upregulated in intestinal epithelial cells during UC development and is further increased in CAC, suggesting an essential role in the transition from inflammation to cancer (147,148).

The gut microbiota controls the levels of antimicrobial peptides and immunoglobulin IgA by regulating the differentiation of intestinal lymphoid tissues and the number of lymphocytes, which then handles the development and maturation of the immune system.

Carcinogenesis driven by candidate pathogenic bacteria. Dysregulation of the interaction between the host and its microbiota leads to a loss of host immune tolerance (149), which induces immune responses. This aberrant immune response is thought to link inflammation to cancer (136). For instance, an increased abundance of pathogenic bacteria that can cling to the intestinal epithelium correlates with increased intestinal permeability. Alterations in the diversity and composition of the gut microbiota would lead to the induction of intestinal inflammation by regulating the expression of inflammatory genes (150).

In patients with IBD with an impaired mucus layer of the gastrointestinal tract, the luminal microbiota can penetrate the epithelial cells, causing proliferative and inflammatory processes (151). The microbiota activates the host's innate and adaptive immune response by producing metabolites that act as antigens, which cause inflammation and promote tumour growth. Mucous membranes under the influence of inflammatory damage are more susceptible to bacterial, particularly pathogenic, stimulation, which causes the submucosa to be exposed to more antigens, which leads to a vicious, positive feedback loop of mucosal damage (152).

The onset and progression of CRC do not depend on the species prevalent but on the entire metabolic functional pathway of the microbiota. Metagenomic studies have observed altered diversity and abundance of the gut microbiota in patients with IBD and CRC. In a recent survey of patients with CAC, Richard *et al* (153) reported that the CAC group had a significantly altered gut microbiota and reduced α-diversity compared to a healthy population and patients with sporadic tumours. Fusobacterium and Ruminococcus genera appeared to be significantly reduced in patients with IBD-CRC compared to those with sCRC (154). Indeed, evidence suggests that patients with CAC may experience changes in the composition of their gut microbiota at different stages. Specifically, CAC can show a significant increase in Akkermansia, Fusobacterium, Peptostreptococcus, Streptococcus and Ruminococcus at advanced stages, while Granulicatella and Lactobacillus were reduced (155).

Some of these genera have been shown to contribute to colorectal carcinogenesis through direct oncogenic effects or by participating in or promoting chronic inflammation-mediated epithelial cell damage (136). Gut microbes differentially affect DNA damage, DNA methylation, chromatin structure and non-coding RNA expression in CRCs. Several genes and

pathways altered by gut microbes have been implicated in the development of CRC, particularly those involved in cell proliferation and Wnt signalling.

Fusarium nucleatum is associated with developing cancers of the oral cavity and gastrointestinal tract. FadA inhibits the tumour suppressor activity of E-cadherin by binding to E-cadherin in epithelial and malignant cells, leading to increased levels of β-catenin-regulated transcription. This process leads to the expression of inflammatory molecules, such as NF-κB, IL-6, IL-8 and IL-18 and activation of TLR2/TLR4 (156). It has also been shown that *F. nucleatum* accelerates DNA methylation of cancer-specific genes in UC patients and inhibits cytotoxicity of NK cells through the expression of Fap2 protein, a lectin expressed by *F. nucleatum* (157).

Enterotoxigenic *Bacteroides fragilis* (ETBF) is positively associated with active IBD and CRC. Activation of Wnt/β-linker protein and NF-κB signalling by secretion of *B. fragilis* toxin cleaves E-calmodulin. This cleavage increases the permeability of the intestinal barrier and the signal transduction of E-cadherin and β-catenin in intestinal epithelial cells, giving the organism the potential for co-clonal oncogenic transformation (61). Furthermore, ETBF induces the STAT3 pathway and the Th17 cancer pathway by driving the local infiltration of Tregs, which promotes the pre-expression of inflammatory factors (e.g., IL-17, IL-8) and establishes an immunosuppressive tumour microenvironment, contributing to the development of IBD-CRC (158-161).

The polyketide genotoxin colistin, produced by *E. coli* via polyketide synthase (Pks), can cause DNA damage upon contact with epithelial cells and acts synergistically with host inflammation to create a tumour-promoting microenvironment (162). Colonic inflammation has been further shown to promote the genotoxic effects of Pks+ *E. coli* and facilitate *E. coli* colonisation of the mucosa, leading to an increase in colistin-induced DNA damage to colonic epithelial cells, which allows this bacterial strain to exert its oncogenic activity (162).

In the stool flora of patients with CRC, *Enterococcus faecalis* is significantly more abundant than in healthy individuals. The possible pathogenic role of *E. faecalis* in CRC is multifaceted. On the one hand, *E. faecalis* activates macrophage MMP-9, which disrupts the integrity of the intestinal monolayer and induces an inflammatory response in the intestine. On the other hand, ROS and extracellular superoxide produced by *E. faecalis* lead to genomic instability, causing damage to colonic DNA and inducing mutations that can lead to cancer (163).

It has been suggested that genotoxic indoleamine derived from *Morganella morganii* may affect multiple aspects of host biology, including direct DNA damage activity, triggering or exacerbating inflammatory processes, and cancer in abiotic mice (164). Bacteria produce genotoxicity that can increase species' competitive ability to grow in an inflammatory microenvironment, affecting microbiota composition. Dysbiotic microbiota will further contribute to the vicious cycle of inflammation and DNA damage in patients with IBD and ultimately lead to tumourigenesis.

The current consensus is that dysbiosis is present in both IBD and CRC and that dysbiosis may lead to disruption of the mucosal barrier and persistence of inflammation and cancer. It is thought that dysbiosis leads to an increase in bacteria such as E. coli and ETBF, which leads to a breakdown of the intestinal mucosal barrier, allowing more bacteria to move from the lumen of the bowel to the inside of the tissue. This condition leads to chronic tissue inflammation and the release of inflammatory and pro-cancer mediators increases the risk of developing CRC. This positive feedback loop of dysbiosis may underlie the inflammation-abnormal proliferation-cancer sequence. Further studies are required to elucidate the impact of host factors and pathogenic microbial interactions in patients with IBD-CRC.

6. Implications of anti-inflammatory therapy for IBD-CRC

The primary treatment for CRC includes surgical resection and chemotherapy. Furthermore, radiotherapy is used before or after surgery. In the case of metastatic CRC, targeted therapies such as anti-EGF receptor antibodies and anti-VEGF receptor antibodies are employed (165). For CRC, which evolves from IBD, anti-inflammatory therapy may be an effective treatment modality to delay tumour progression.

Chronic inflammation and oxidative stress are common pathological processes that accompany and contribute to cancer. Numerous epidemiological studies have shown that anti-inflammatory therapies can be used to target the chronic inflammatory microenvironment of tumours, contributing to therapeutic recovery from established cancers. It has been demonstrated that non-steroidal anti-inflammatory drugs (NSAIDs) can slow tumour growth by acting on chronic inflammation and oxidative stress. NSAIDs are peroxisome proliferator-activated receptor γ (PPARγ) agonists and, therefore, downregulate the aberrant Wnt/β-catenin pathway in cancer, which may have a positive effect on both cancer prevention and tumour treatment (166).

Acetyl salicylic acid (aspirin) is the most widely consumed NSAID, which also exhibits anticancer properties (167). Studies on four CRC cell lines (i.e., HCT116, SW948, LoVo and SW480) have shown that aspirin inhibits the transcription of genes regulated by the β-catenin-TCF complex, including Cyclin D1 (168). Aspirin-mediated phosphorylation of GSK-3β and β-catenin resulted in attenuating its downstream inflammatory signalling. In addition, aspirin regulates both β-catenin and COX-2 in colon cancer cells (169), exerting anti-cancer effects.

The mechanism of action of mesalazine can also be used to treat and prevent CRC. This is because mesalazine has a comprehensive effect on the pathways that lead to cancer development and progression (i.e., the Wnt/β-catenin pathway and PPARγ), as well as affecting the cell cycle or inhibiting the proliferation of cancer stem cells, which are the primary cause of CRC recurrence. Mesalazine also inhibits the COX and lipoxygenase pathways, thereby inhibiting the release of prostaglandin E2 and leukotrienes, which are closely related to inflammation (170). The ability of 5-aminosalicylic acid (5-ASA) to inhibit peroxynitrite-mediated DNA strand breaks, scavenge peroxynitrite and affect peroxynitrite-mediated formation of free radicals is partly responsible for the anti-inflammatory and anti-cancer effects of 5-ASA (171).

7. Conclusions

The pathogenesis of IBD-CRC has not yet been clearly described. To the best of our knowledge, this is the first review

of the pathogenesis of IBD-CRC that includes molecular mechanisms, oxidative stress, immune mechanisms and gut microbiota studies. The review is novel in that it provides a comprehensive summary of recent advances in the field. Anti-inflammatory therapies may be an effective treatment as the number of treatments available increases, and further research is needed before the efficacy of these therapies for IBD-CRC can be demonstrated. For instance, in terms of disease pathogenesis, further exploration of the tumour microenvironment and histological studies on patients with IBD-CRC may be worthwhile; in terms of treatment, more targeted therapies and development of novel drugs for IBD-CRC and metastatic tumours may improve the prognosis for these patients.

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Authors' contributions

ZW, YC, HBS, YQL and TYT drafted the manuscript. ZW, YC and HBS organized the structure of the manuscript. Funding acquisition for this study was performed by TYT and YQL. All authors read and approved the final version of the 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.

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