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Review Article

Review Article

Inflammatory Bowel Disease-Associated Colorectal Cancer: Translational Risks from Mechanisms to Medicines

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Abstract

The cumulative impact of chronic inflammation in patients with inflammatory bowel diseases predisposes to the development of inflammatory bowel disease-associated colorectal cancer [IBD-CRC]. Inflammation can induce mutagenesis, and the relapsing–remitting nature of this inflammation, together with epithelial regeneration, may exert selective pressure accelerating carcinogenesis. The molecular pathogenesis of IBD-CRC, termed the 'inflammation–dysplasia–carcinoma' sequence, is well described. However, the immunopathogenesis of IBD-CRC is less well understood. The impact of novel immunosuppressive therapies, which aim to achieve deep remission, is mostly unknown. Therefore, this timely review summarizes the clinical context of IBD-CRC, outlines the molecular and immunological basis of disease pathogenesis, and considers the impact of novel biological therapies.

Key Words: Colitis-associated cancer; cancer; biologics

1. Introduction

Inflammatory bowel disease [IBD] describes chronic immune-mediated conditions characterized by relapsing–remitting inflammation of the gastrointestinal tract. Ulcerative colitis [UC] and Crohn's disease [CD] are the dominant phenotypes and prevalence is estimated to be as high as 1 in 125 [0.8%] in countries such as the UK.[1] While prevalence is rising throughout the world, the greatest acceleration is observed in newly industrialized countries: since 1990 Africa, Asia and South America have seen an annual percentage change of +11.1% (95% confidence interval [CI] 4.8, 17.8) for CD and +14.9% [95% CI 10.4, 19.6] for UC.[2] With an ageing population compound prevalence suggests that IBD-associated colorectal cancer [herein IBD-CRC] could become an emerging global issue.

Abbreviations: AOM, azoxymethane; APC, adenomatous polyposis coli; CARD9, caspase recruitment domain containing protein 9; CRC, colorectal cancer; CD, Crohn's disease; CIB, chronic inflammatory burden; DSS, dextran sulphate sodium; Fgl2, fibrinogen-like protein 2; FMT, faecal microbial transplantation; iNOS, inducible nitric oxide synthase; IBD, inflammatory bowel disease; IBD-CRC, inflammatory bowel disease-associated colorectal cancer; IFN, interferon; IL, interleukin; IR, incidence rates; IEC, intestinal epithelial cell; JAK, Janus Kinase; MIF, macrophage migration inhibitory factor; MAdCAM-1, mucosal addressin cell adhesion molecule-1; M-cell, microfold cell; MSI, microsatellite instability; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIK, NF-κB-inducing kinase signalling; Nucleotide-binding; NOD, Oligomerisation Domain; PSC, primary sclerosing cholangitis; S1P, Sphingosine-1-Phosphate; SGPL1, S1P lyase1; SIR, standardised incidence ratios; STAT, signal transducer and activator of transcription; SphK1, sphingosine-kinase 1; S-CRC, sporadic CRC; TNF, tumour necrosis factor; TLR, toll-like receptors; TNBS, trinitrobenzene sulfonic acid; UC, ulcerative colitis.

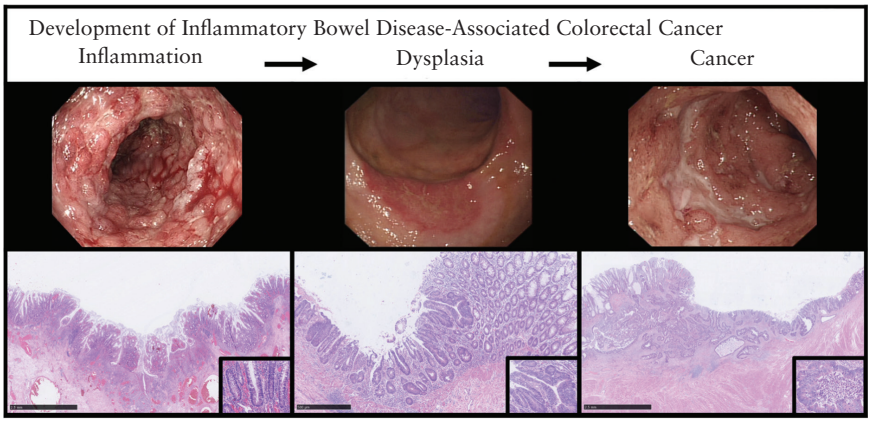

Figure 1. Clinical photographs and photomicrographs of IBD-CRC. Endoscopic images and histopathology photomicrographs illustrate the development of inflammatory bowel disease-associated colorectal cancer [IBD-CRC] through the 'inflammation–dysplasia–carcinoma' sequence. Histopathology photomicrographs provided by Lothian NRS Bioresource [M.J.A.] and colonoscopy images provided by Edinburgh IBD Unit [S.D.].

Over the past two decades, we have defined IBD-CRC through the inflammation–dysplasia–carcinoma sequence [Figure 1]. However, many fundamental questions remain, including elucidation of disease immunopathogenesis. The impact of potent immunosuppressive therapies in IBD, which aim to achieve 'deep remission', is mostly unknown and their subsequent effect on IBD-CRC is yet to be established. This timely review summarizes the epidemiological and clinical context of IBD-CRC, outlines molecular and immunological disease pathogenesis, and considers the impact of novel biological therapies.

2. Patients with IBD are at Increased Risk for Developing CRC with a Poor Prognosis

A 2012 meta-analysis of population-based cohort studies [n = 10,385 patients] reported that patients with UC have an increased risk of developing CRC [standardised incidence ratios (SIR) 2.4, 95% CI 2.1, 2.7], especially if they are male, have extensive colitis and are young when diagnosed with UC.[3] A more recent study by Olén and colleagues [n = 96 447 UC and n = 949 207 control patients] reported that, while the incidence of UC-CRC may be decreasing in Scandinavian countries, patients with UC have a 1.7-fold increased risk for incident CRC compared with matched controls.[4]

For CD, Canavan and colleagues published a meta-analysis [n = 11 840 patients] that reported the relative risk for developing CRC in those with colonic disease is 4.5 [95% CI 1.3, 14.9], with a cumulative risk of 2.9% [95% CI 1.5, 5.3] 10 years after diagnosis.[5] A prospective cohort study from Hong Kong [n = 2621 patients] reported that patients with CD have an increased risk of anorectal cancer [SIR 4.11, 95% CI 1.84, 9.14].[6] A more recent study by Olén and colleagues [n = 47 035 CD and n = 463,187 matched reference individuals] also demonstrated increased CRC incidence in CD: hazard ratio [HR] 1.40 [95% CI 1.27, 1.53].[7]

There is also an increased IBD-CRC risk for paediatric patients; a 2018 review [n = 271 patients] concluded that, while rare, CRC is the most common fatal malignancy in paediatric IBD patients.[8]

IBD-CRC confers a poor prognosis. A large meta-analysis [n = 3472 patients] reported that patients with IBD-CRC have poorer overall survival compared to patients with sporadic[S]-CRC [HR 1.24 95% CI 1.19, 1.29].[9] These patients were more likely to have proximal tumours [odds ratio [OR] 2.52, 95% CI 1.35, 4.72) and poorer histopathological differentiation [OR 1.59, 95% CI 1.26, 1.99]. Olén and colleagues also reported patients with UC have a 1·6-fold increased risk of death from cancer, compared with S-CRC.[4] Similarly, patients with CD have increased mortality compared with matched controls [HR 1.42, 95% CI 1.16, 1.75], when adjusted for tumour stage.[7] Reported differences between IBD-CRC and S-CRC prognosis are probably due to differences in tumour biology [Table 1].[10]

3. IBD-CRC Develops from Dysplasia and Inflammation is a Critical Initiating Factor

With an increasing global prevalence of IBD, and patients living longer, it is important to consider the cumulative impact that multiple occurrences of acute and chronic inflammation have on the development of IBD-CRC. Clinicians strive to modulate natural disease progression at a very early stage, often using potent agents to achieve early mucosal healing. The 'top down' or 'treat to target' approach aims to reduce the risk of hospitalizations, future use of biologics and surgery. While lower colectomy rates are desirable, preservation of damaged colorectum, particularly in the setting of potent immunomodulation, is unknown and could result in an increased incidence of IBD-CRC. Understanding the molecular and immunological pathogenesis of IBD-CRC is therefore important for clinicians and scientists to develop new therapies that achieve deep remission and reduce IBD-CRC risk.

Our current understanding of S-CRC is defined through the sequential histological and genetic changes known as the adenoma–carcinoma sequence [Figure 2A]. In contrast, IBD-CRC develops through the 'inflammation–dysplasia–carcinoma' sequence [Figure 2B]. Here, low-grade dysplasia develops on a background of mucosa that has been genetically altered by chronic inflammation and is at increased risk of malignant progression. Inflammation can induce mutations and the relapsing–remitting nature of this inflammation with proliferative epithelial regeneration exerts selective pressure that accelerates evolution.[11] Increased reactive oxygen species production and lipid peroxidation and decreased antioxidant capacity with increased oxidative DNA damage in IBD are likely mechanisms that drive mutagenesis.[12,13]

Mutations that contribute to IBD-CRC pathogenesis are similar to those implicated in S-CRC; however, the order that mutations are accrued is often described as 'reversed'. Early loss of *TP53* function is a hallmark of IBD-CRC, with mutations observed in

Table 1. IBD-CRC is distinct from S-CRC. This table illustrates the key epidemiological, pathophysiological and clinical differences between sporadic [S-CRC] and inflammatory bowel disease-associated colorectal cancer [IBD-CRC]

	S-CRC	IBD-CRC
Epidemiology		
Disease burden	10% of global cancer diagnoses.[100]	IBD patients have a higher incidence of CRC, possibly >60%.[4,7,101]
Sex	Male preponderance.[100,102]	Male preponderance.[3]
Age	Older age of onset [>50 years old]; an increasing incidence in younger patients.[102]	Younger age of IBD onset.[3] Paediatric IBD-CRCs can develop.[8] Patients with IBD are living longer.[1]
Risk factors	Diet, smoking, obesity, family CRC history, *H. pylori*, alcohol [J-shaped association likely], colonic polyps and others.[103–106]	Extensive colitis, increased duration of disease, family history of S-CRC, PSC.[107–109]
Disease pathogenesis		
Pre-malignant lesion	Adenomatous polyps [polypoid/sessile].[110]	Flat dysplasia. Genetic aberrations seen [*TP53* mutations] in histologically normal mucosa.[11,14,17]
Molecular sequence	Mostly adenoma–carcinoma sequence [slow].[110]	Inflammation-dysplasia-carcinoma sequence [fast].[11]
Genetic aberrations	Chromosomal instability, microsatellite instability and CpG island methylator phenotype [CIMP] pathways [not mutually exclusive]. Early and more frequent *APC* mutations. Late and frequent *TP53* mutations.[14,15,111,112]	Mutation sequence is 'reversed': early *TP53* mutation, late and infrequent loss of *APC*, earlier MSI, later *KRAS* mutations.[14–16]
Contribution of inflammation and regeneration to the initiation of cancer	Promotes cancer progression.[113]	Drives mutagenesis and selects for mutagenic clones.[11–13]
Contribution of inflammation to the progression to cancer	Tumour-promoting inflammation is critical for most cancers, including colorectal cancer.[113]	Critical pathways signal through NF-κB and IL-6/STAT3.[26–32,35–40,42,46,114] Th17 cells and associated cytokines are generally pathogenic.[30,43,45,47–49,52,53,55,56,58,115]
Clinical features		
Endoscopic characteristics	Commonly raised/polypoidal lesions; some sessile.	Flat dysplasia. Synchronous and recurrent tumours.
Histological characteristics	Majority adenocarcinoma. Comparatively favourable differentiation; fewer contain mucinous/signet ring cell morphology.[116]	Majority adenocarcinoma. Mucinous/signet ring cell differentiation is more common.[10,116]
Mortality and prognosis	Prognosis is improving, especially if diagnosed early.[102]	Poor prognosis compared with S-CRC [2-fold].[117] Increase in recurrence [3-fold].[10] Poor prognosis associated with PSC, male sex, extensive colitis and early age of diagnosis.[4,7,9,10,107,108,118]

Abbreviations: APC [adenomatous polyposis coli]; IBD-CRC [inflammatory bowel disease-associated colorectal cancer]; IL-6 [interleukin-6]; KRAS [Kirsten rat sarcoma viral oncogene homologue]; MSI [microsatellite instability]; NF-κB [nuclear factor kappa-light-chain-enhancer of activated B cells]; PSC [primary sclerosing cholangitis]; qFIT [quantitative faecal immunohistochemical test]; S-CRC [sporadic colorectal cancer]; UC [ulcerative colitis]; STAT3 [signal transducer and activator of transcription 3].

diploid, non-dysplastic epithelial cells, and they precede *TP53* loss of heterozygosity.[14] In contrast, S-CRC *TP53* mutations occur late.[14] *KRAS* activating mutations are important alternative gatekeeper mutations that occur later and less frequently in IBD-CRC [~20% of cases].[15] Hypermethylation of the tumour suppressor gene *MLH1* also occurs earlier in IBD-CRC, and this contributes to microsatellite instability [MSI] in an important subset of cancers, similar in frequency to that observed in S-CRC.[16] Dysregulation of the Wnt signalling pathway plays an important role in IBD-CRC, with ~55% of dysplastic lesions and up to 100% of cancers expressing nuclear β-catenin.[17] However, unlike the S-CRC pathway, which has early loss of *APC* function leading to aberrant Wnt signalling, APC function is lost late in IBD-CRC and only occurs in <50% of cases.[15,18] This may be explained by inflammation-driven upregulation of β-catenin in IBD-CRC, which can induce *APC* mutation-independent Wnt signalling.[19]

Throughout the IBD colon, genetic and epigenetic abnormalities develop in histologically normal mucosa and can expand to form pre-malignant patches.[20] IBD patients have dysplastic lesions with increased chromosomal instability compared with sporadic adenomas.[21] Chronic inflammation is the underlying mechanism that leads to telomere shortening, and thus chromosomal instability,[22] in pre-malignant IBD mucosa.[23] This induces senescence, which acts as a tumour-suppressor mechanism to prevent progression past low-grade dysplasia. Mutant intestinal epithelial cells [IECs] eventually escape senescence and progress—this is associated with telomere lengthening and loss of *TP53* function.

The mutational landscape of cancer is diverse; our recent mutational analysis of 34 IBD-CRCs identified six distinct mutational signatures.[24] In S-CRC with MSI, patients have a better prognosis by at least 15%, probably due to a cumulative mutational burden with resulting anti-tumour immune cell responses.[25] In IBD-CRC, proximal

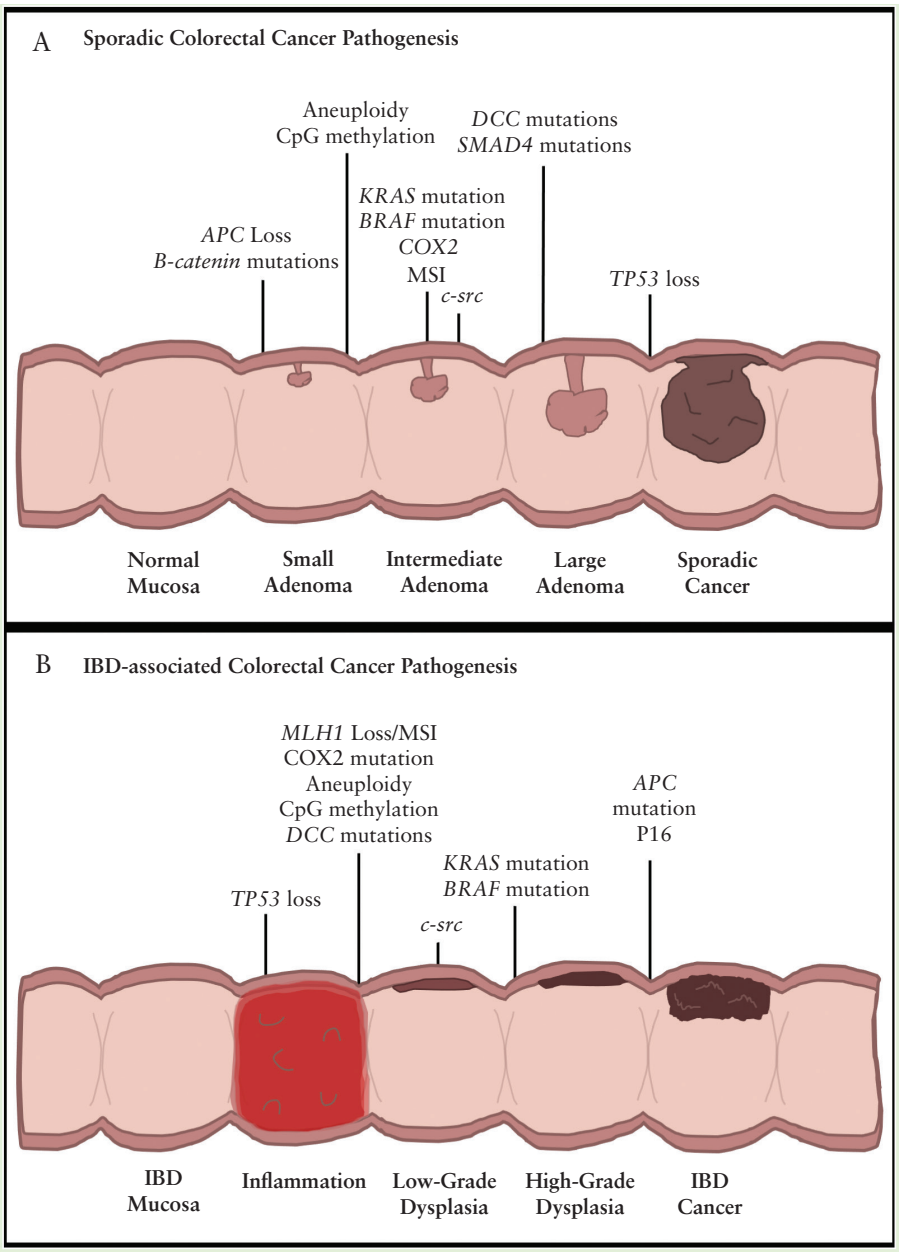

Figure 2. Contemporary model for the molecular pathogenesis of [A] sporadic and [B] IBD-associated colorectal cancer. Sporadic colorectal cancer [S-CRC] develops through the 'adenoma–dysplasia–carcinoma sequence' whereas inflammatory bowel disease-associated colorectal cancer develops through the 'inflammation–dysplasia–carcinoma' sequence. The figure illustrates genetic mutations that can contribute to cancer development.

tumours have high mutational rates, are associated with MSI [especially loss of *MLH1* and defects in DNA *POLE* proofreading function], and have a higher predicted neo-epitope load,[24] suggesting increased immunogenicity. It is unknown if or how chronic inflammation in IBD influences the development of IBD-CRC mutational signatures or molecular phenotypes.

4. Dysregulation of Critical Immune-Mediated Pathways in IBD-CRC

4.1. NF-κB and IL-6/STAT3 signalling pathways promote IBD-CRC

The two most comprehensively studied pro-inflammatory and pro-tumour pathways in IBD-CRC are the nuclear factor kappa-light-chain-enhancer of activated B cells [NF-κB] and interleukin [IL]-6/signal transducer and activator of transcription [STAT]3 signalling pathways. These pathways are well established[26–28] [Figure 3].

In summary, inhibition of the canonical NF-κB pathway abrogates tumorigenesis in the azoxymethane [AOM]/dextran sulphate sodium [DSS] mouse model by two main mechanisms: [1] IKKβ deletion in myeloid cells reduces both intestinal inflammation and tumour size through decreased production of pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, KC, MIP-2, tumour necrosis factor [TNF]-α, COX-2 and ICAM), and [2] IKKβ deletion in IECs reduces tumour incidence and is associated with apoptosis; however, it does not reduce inflammation.[29] Non-canonical NF-κB signalling, mediated by NF-κB-inducing kinase signalling [NIK], contributes to intestinal homeostasis through maintenance and differentiation

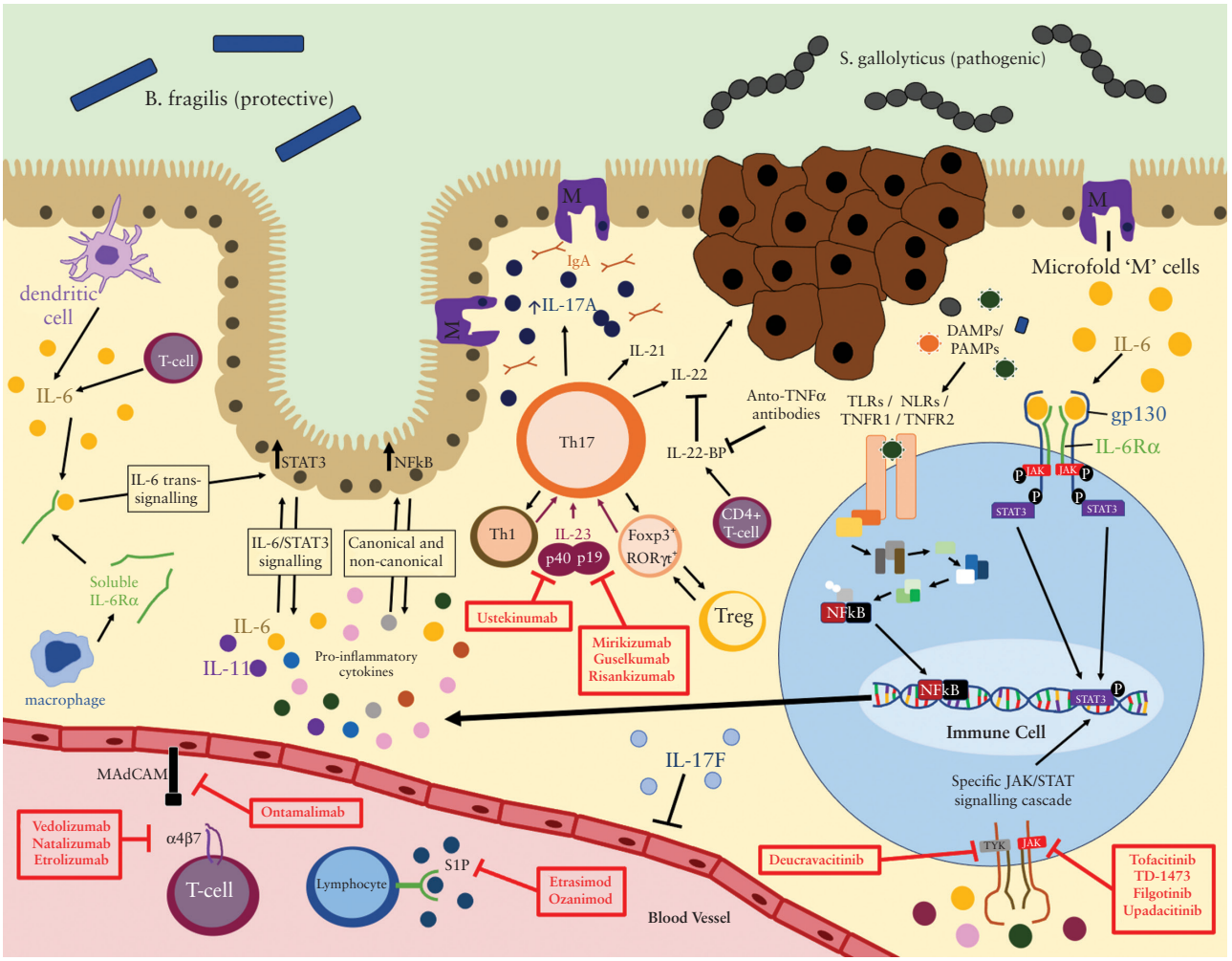

Figure 3. Immunopathogenesis of inflammatory bowel disease-associated colorectal cancer [IBD-CRC]—a perfect storm? There is dysregulation of critical immune-mediated pathways in IBD-CRC, such as NFκB and IL-6/STAT3 signalling, and Th17 cell responses. The impact of novel therapeutic immunomodulators requires careful consideration.

of microfold [M]-cells [specialized epithelial cells of mucosal-associated lymphoid tissue], and local and systemic IL-17A and IgA production.[30] Mice with intact NIK are protected against colitis; however, constitutively activated NIK signalling worsens colitis and is associated with increased IL-17A production and ectopic colonic M-cells.[30] NF-κB signalling can also be driven by genetic aberrations: mutant p53 augments and prolongs the response of IECs to low levels of inflammatory cytokines, resulting in chronic NF-κB activation, which promotes persistent tissue damage and inflammation.[31] Mutant p53 mice exposed to DSS are prone to colitis-associated cancer: the gain-of-function mutation is associated with flat dysplastic lesions that progress to cancer, similar to those seen in IBD-CRC.[31]

TNF-α is the quintessential pro-inflammatory cytokine and can bind to either of its receptors [TNFR1 or TNFR2] and induce inflammation through either canonical or non-canonical NF-κB signalling pathways. There are data suggesting TNF-αα can enhance Wnt signalling through NF-κB actvation[32] and promote mucosal regenerative healing through colonic epithelial stem and progenitor cell populations.[33] A protective role for TNF is perhaps controversial. Nonetheless, this is important to consider in IBD-CRC as IEC p53 stabilization post-immune activation is dependent on TNFR1/2 and inducible nitric oxide synthase [iNOS].[34] TNF-α-induced iNOS activates a p53-dependent pathway of IEC apoptosis, and this may hypothetically be prevented in patients receiving anti-TNF treatment. This could mean that without p53 wild-type function, such as during early IBD-CRC, damaged IECs evade apoptosis and thus have selective advantage.[34]

NF-κB signalling in immune and epithelial cells upregulates IL-6 and constitutively activates STAT3 in human tumours, maintaining NF-κB signalling.[35] Thus, IL-6/STAT-3 and NF-κB signalling are not mutually exclusive. IL-6/STAT3-deficient mice treated with AOM/DSS have a reduced tumour burden compared with wild-type mice.[36,37] This is because IL-6, produced mainly by bone marrow-derived myeloid cells, such as macrophages and dendritic cells [along with some T-cells], increases IEC proliferation and resistance to apoptosis through the STAT3-dependent pathway.[36,37] Furthermore, STAT3 acts as a critical mediator for stimulating cell survival [*bcl-x*, *survivin*, *Hspa1a*] and proliferation [cdk4/cyclinD1, cdc2/cyclinB1, cMyc, RegIIIb/PAP], through G1 and G2/M phases of the cell cycle to promote carcinogenesis.[37]

Increased IL-6 expression in UC is also associated with reduced nuclear expression of *MSH3*, and this increases with duration of disease, as well as when dysplasia then cancer develops; expression in

UC-CRC is higher than in S-CRC.[38] This suggests a link between IL-6 signalling and MSI in IBD-CRC. Trans-IL-6 signalling, in which IL-6 binds to soluble IL-6R and dimerizes with gp130 on cells that do not express IL-6R, is also important; macrophage-derived IL-6/soluble IL-6Rα is particularly important.[39,40]

STAT3 signalling can also be induced by other cytokines, such as IL-11, which may be more potent.[41] STAT3 is important to Th17 cell function as FAM64A, a multifunctional protein involved in cell cycle progression, drives the IL-6/STAT signalling pathway and induces Th17 differentiation in AOM/DSS-induced murine colitis.[42]

4.2. Th17 cells and associated cytokines promote IBD-CRC

Patients with IBD have increased numbers of Th17 cells and associated cytokines [IL-17, IL-21 and IL-22] in their intestinal mucosa and peripheral blood, compared with healthy controls.[43] It is important to differentiate IL-17A [which promotes inflammation and tumorigenesis] from IL-17F [which is protective against IBD-CRC, possibly by inhibiting angiogenesis].[44,45] IL-6/STAT3 signalling is also involved in the induction of T-cell RORγt expression, which is a key transcription factor of Th17 cells.[46] However, Th17 cells demonstrate functional plasticity and can convert into interferon [IFN]-γ producing Th1 cells or regulatory T-cells.[47]

IL-23 is produced by many antigen presenting cells and plays an important role in maintaining the Th17 cell phenotype.[48] In IBD-CRC, data suggest Baft-dependent IL-23$^+$IL-6$^+$CD4$^+$Th17 cells, rather than RORγt-dependent Th17 cells, mediate downstream effects of IL-23.[49] IL-23 and IL-12 are part of the IL-12 family of cytokines, both share the p40 subunit, and they heterodimerize with p19 or p35, respectively.[50,51] p47phox is a protein of NADPH oxidase that regulates induction of the TLR9-induced IL-12/Th1 axis. In AOM/DSS-treated mice, IL-12p35$^{-/-}$ mice have reduced colitis but increased susceptibility to CRC, whereas p47phox$^{-/-}$ mice have worsened colitis but reduced tumour growth.[52] Therefore, tilting the IL-23/IL-12 balance toward IL-12 might reduce tumorigenesis in IBD-CRC. However, this is not viable as this would probably worsen IBD symptoms.[52]

IL-22 is a pleiotropic cytokine, part of the IL-10 family, that is produced by mature Th17 cells through IL-23-mediated STAT3 activation.[47] In Rag2$^{-/-}$ mice with *Helicobacter*-associated colitis, IL-22 induces iNOS within IECs, which induces DNA damage and dysplasia.[53] Patients with IBD have increased CD4$^+$ T-cells that produce high levels of IL-22 binding protein [IL-22BP]: IL-22BP is a soluble IL-22 receptor, without a transmembrane/intracellular domain, that binds to and neutralizes IL-22. The anti-inflammatory effects of TNF-α antibodies have been associated with reduced levels of IL-22BP.[54] IL-22BP is highly expressed in dendritic cells and during NLRP3 or NLRP6 inflammasome activation, such as in IBD; inflammasome activation can lead to IL-18-dependent IL-22BP downregulation. IL-22BP$^{-/-}$ mice also show strongly accelerated tumour growth.[55] Pleiotropic effects are likely because IL-22 is initially protective in inflammation, but induces tumorigenesis if uncontrolled during restitution of inflammation.[55] Therefore, dysregulation of the IL-22/IL-22BP axis may play a pivotal role in IBD-CRC development, perhaps in the context of anti-TNF therapy.

IL-21 is a multifunctional cytokine produced mainly by T-cell subsets such as follicular helper T-cells and Th17 cells. Some studies suggest IL-21-deficient mice are protected from DSS and trinitrobenzene sulfonic acid [TNBS]-induced colitis and this is likely because they are unable to upregulate Th17 responses.[56] However, other studies have suggested that IL-21 signalling, through IL-21R, is protective in DSS-treated mice due to downregulation of Th1 and upregulation of Th2, Th17 and Treg responses.[57] Studies have reported a reduced tumour burden in AOM/DSS-treated IL-21$^{-/-}$ mice,[58] and the underlying mechanism may be due to a reduced number of infiltrating T-cells, reduced STAT3 signalling and thus reduced IL-17A and IL-6.[58]

4.3. Recent advances in the immunopathogenesis of IBD-CRC

There remains a paucity of data characterizing the immune cell landscape in human IBD-CRC. From the studies that exist, IBD-CRC has a lower number of immune cells expressing CD3, CD8, Foxp3 or PD-L1;[59] increased CD3$^+$ and CD8$^+$ lymphocytes are associated with improved prognosis.[59] There is a need to comprehensively characterize the cells and cytokines that define the inflammation–dysplasia–carcinoma sequence.

The role of macrophages in IBD-CRC is poorly defined. Macrophages and mast cells infiltrate the colonic submucosa in a stage-dependent manner in the progression from inflammation to dysplasia to cancer.[60] Macrophage migration inhibitory factor [MIF] mediates macrophage and T-cell recruitment and MIF$^{-/-}$ mice treated with AOM/DSS have an increased tumour burden, associated with lower levels of macrophages.[61] Fibrinogen-like protein 2 [Fgl2] may be important for macrophage recruitment with/without polarization as Fgl2 loss induces M1-polarized and suppresses M2-polarized macrophages; Fgl2 may therefore reduce inflammation and IBD-CRC.[62] In contrast, TGFβ promotes macrophage recruitment through expression of CCR2 in the tumour microenvironment, and myeloid-cell TGFβ2 expression worsens AOM/DSS-induced tumorigenesis. Conditional TGFβ2 knock-out mice have reduced IL-6 and TNF-α expression, and increased numbers of Foxp3$^+$ T-regulatory cells [Tregs] in the early stages of carcinogenesis.[62] This suggests a pathogenic role of TGFβ signalling via macrophages in IBD-CRC. This hypothesis is strengthened by a study that reported conjugated linoleic acid ameliorated DSS-induced murine colitis through a macrophage PPARγ receptor-dependent pathway, whereas PPARγ activation induced TGFβ production by macrophages and T-cells that increased tumourigenesis in AOM/DSS-induced colitis.[63]

A novel subset of Foxp3$^+$RORγt$^+$ T-cells have been described and were thought to represent an intermediate stage during differentiation between immunosuppressive Tregs and proinflammatory Th17 cells. However, these cells can also be stable and functional [regulatory] in the intestine. Patients with IBD have increased expression of this unique T-cell subset, associated with IBD-dysplasia.[64–66] A recent study using AOM/DSS-treated mice reported that Foxp3$^+$RORγt$^+$ T-cells reduce the expression of FoxO3 in tumour infiltrating dendritic cells—FoxO3 is a transcription factor that controls the production of IL-6 by antigen presenting cells. This results in aberrant IL-6 signalling that upregulates STAT3 and induces proliferation of dysplastic cells.[66]

Barcode sequence analysis using 16S [MiSeq for bacteria] and ITS2 [pyrosequencing for fungi] reported a difference in bacterial, but not fungal, microbiome populations in IBD-CRC patients compared with both healthy controls and S-CRC.[67] Compared with S-CRC, IBD-CRC patients have increased abundance of the family Enterobacteriaceae family and genus *Sphingomonas* and reduced abundance of the genera *Fusobacterium* and *Ruminococcus*.[67] The mechanistic, clinical and therapeutic consequences of microbial dysbiosis in IBD-CRC are poorly understood. Some bacteria, such as *Bacteroides fragilis*, are protective[68,69] whereas others such as *Streptococcus gallolyticus* are pathogenic.[70] Faecal microbial transplantation [FMT] is being trialled as a therapy for IBD, with variable

success. Transplantation of carcinogenic bacteria may occur during FMT; robust screening and appropriate follow-up is needed to minimize FMT-associated IBD-CRC.[71]

Antimicrobial peptides, such as cathelicidin/LL-37, are essential for maintaining intestinal homeostasis. It is unsurprising that AOM/DSS-treated cathelicidin-related antimicrobial peptide knockout mice have an increased tumour burden.[72] This field is in its infancy and further work is required to determine whether bacteria and/or defence peptides play a significant role in the development of IBD-CRC.

Zhong and colleagues recently reviewed conflicting data on caspase recruitment domain-containing protein 9 [CARD9], an adaptor protein that can mediate inflammation.[73] The pro-tumour role for CARD9 may be through IL-1β-mediated STAT3 activation; however, whether CARD9 contributes to inflammasome-mediated cytokine production and whether intestinal fungi promote or prevent IBD-CRC are undetermined.[73]

The immunomodulatory role of the appendix has also recently attracted interest, as appendicectomy has been shown to induce clinical improvement in UC.[74] However, appendicectomy is also associated with an increased risk of developing IBD-dysplasia and IBD-CRC.[75] While trials are ongoing,[76] mechanistic data elucidating the impact of appendicectomy on the gut microbiota and immune cell responses are currently lacking.

5. Immunosuppression can be a Double-Edged Sword in IBD-CRC

The pro- or anti-tumour effects of 5-aminosalicylate, traditional immunomodulators [e.g. thiopurine] and anti-TNF therapy in IBD have been extensively discussed elsewhere.[77–79] IBD Cancer and Serious Infection in Europe [I-CARE] is an ongoing prospective, longitudinal, observational, multicentre [n = 16 countries] cohort study that aims to determine the risk of developing cancer or serious infections in IBD patients receiving immunosuppressive and biological therapies [NCT02377258]. Newly identified signalling pathways that can be manipulated to ameliorate inflammation may have unintended carcinogenic effects. This section explores the potential pro- or anti-tumour effects of the latest targeted IBD biological and small molecule therapies.

5.1. Therapeutic manipulation of the IL-12/IL-23 axis

Ustekinumab is a humanized monoclonal antibody that binds to the p40 subunit that comprises both IL-12 and IL-23.[80] The impact of p40 neutralization on IBD-CRC development is mostly unknown; however, the impact of neutralizing IL-12 and IL-23 activity can be considered separately. IL-12 induces anti-tumour immunity [involving IFN-γ, $CD4^+$ and $CD8^+$ T-cells][81] whereas IL-23 can promote carcinogenesis involving IL-17-associated pathways.[52] Teng and colleagues investigated the impact of IL-23 and IL-12 on methylcholanthrene-induced p53 mutant cancers in murine models and reported that IL-23p19 inhibition reduced the malignant potential of colonic lesions whereas IL-12/23p40 inhibition enhanced tumour outgrowth.[82] Therefore, neutralizing p40 may have some theoretical or potential pro-tumour effects in humans. A randomized control trial involving 961 patients with moderate-to-severe UC reported one case of colonic and one case of rectal cancer in patients receiving ustekinumab [n = 825] over 52 weeks, compared with zero CRC in patients receiving placebo [n = 319].[83] An observational cohort study has started recruiting patients to assess the long-term safety of ustekinumab compared with other biologics in CD; the primary outcome is incidence of malignancy with a time frame of up to 12 years [NCT04372108].

Targeted anti-IL-23 therapies are thus being explored for IBD as, theoretically, targeted IL-23 blockade therapy may ameliorate inflammation and reduce the risk of IBD-CRC.[84] Anti-IL-23 therapies against the p19 subunit are being trialled for CD patients compared with ustekinumab, including risankizumab [NCT04524611], mirikizumab [NCT03926130] and guselkumab [NCT03466411]. All trials have relatively short follow-up periods, which limits their usefulness for inferring overall IBD-CRC risk.

5.2. Therapies targeting leukocyte trafficking

α4β7 is an integrin [a transmembrane protein that facilitates cell adhesion] expressed on lymphocytes and is associated with increased responsiveness to pro-inflammatory cytokines IL-6, IL-7 and IL-21.[85] α4β7 allows peripheral lymphocytes to bind with mucosal addressin cell adhesion molecule-1 [MAdCAM-1] on intestinal endothelial cells, which allows lymphocytes to undergo diapedesis into the lamina propria.

Vedolizumab is the first humanized, gut-selective antibody used to treat IBD that blocks α4β7 integrin-expressing lymphocytes from trafficking from the systemic circulation into the lamina propria.[86] Data generally support no increased risk of malignancy in patients receiving vedolizumab: a retrospective analysis of 1087 patients reported only one case of IBD-CRC.[87] However, median follow-up in this study was only 302 days, which is too short to determine the true risk of malignancy.[87] These findings are supported by other data, such as a study that reports four CRC cases in a population of >2800 patients, which translates to 0.1/100 person years, and is no different to the background IBD risk [2.1/1000 person years, 95% CI 1.3, 3.2].[88] A recent retrospective cohort study reported no increased risk of new or recurrent cancer among patients with IBD and a history of cancer who were treated with vedolizumab or anti-TNF therapy, compared with patients who did not receive immunosuppression [follow-up median 6.2 person years].[89] Caution may be warranted, especially in patients with concurrent primary sclerosing cholangitis [PSC]. A retrospective observational cohort study [median follow-up of 19 months] reported that, of 75 patients with IBD and PSC treated with vedolizumab, nine developed digestive neoplasia [seven of which were colorectal cancers].[90] While there are no published data for similar therapies, there is an ongoing large interventional trial investigating etrolizumab in UC [9 years follow-up] that may reveal data regarding IBD-CRC risk [NCT02118584].

Preliminary data suggest MAdCAM antibodies are efficacious in IBD, especially UC.[91] No studies have assessed the impact of MAdCAM antibodies on IBD-CRC development; however, MAdCAM-1 expression is reduced in colonic adenocarcinomas.[92] This could suggest that blocking MAdCAM may be advantageous for tumour development, warranting further investigation. There is an ongoing safety extension study investigating ontamalimab [MAdCAM-1 inhibitor] for the treatment of moderate to severe IBD [NCT03283085].

5.3. Small molecule therapies

Compared with monoclonal antibodies, small molecules are attractive as they have no inherent immunogenicity [they are synthetic drugs rather than proteins], can be administered orally and have relatively stable and predictable pharmacokinetics. Small molecules include janus kinase [JAK] inhibitors, tyrosine kinase inhibitors and sphingosine-1-phosphate [S1P] receptor antagonists.

Cytokines principally impact immune cell function by signalling through JAK/STAT pathways. As previously discussed, targeting these pathways could theoretically improve colitis and reduce the risk of IBD-CRC. With JAK inhibitors, the extent of signal inhibition is related to the target of the small molecule [i.e. pan vs selective JAK inhibition]. Most data relate to tofacitinib: data from 1157 patients who received tofacitinib [a JAK3-specific inhibitor, with lesser activity against JAK1/JAK2] reported that 11 patients developed malignancy [excluding non-melanoma skin cancer], one of which was colorectal adenocarcinoma—the risk of malignancy was not significant [incidence rates (IR) 0.7, 95% CI 0.3, 1.2].[93] However, we must be cautious as these data are only over 4.4 years. Another study reported that 2/1124 patients receiving tofacitinib developed CRC [IR 0.08, 95% CI 0.01, 0.27], with evaluation up to 6.8 years; however, one cancer possibly developed prior to tofacitinib therapy.[94] Data from other JAK inhibitors are on the horizon for IBD, such as TD-1473 [NCT03920254], filgotinib [NCT02914600, NCT02914535] and upadacitinib [NCT03345823, NCT02782663, NCT03006068]. Tyrosine kinase inhibitors may also be therapeutic in IBD, and deucravacitinib [BMS-986165] is an allosteric inhibitor of tyrosine kinase 2 under investigation for CD [NCT03599622] and UC [NCT03934216, NCT04613518]. Long-term follow-up studies using these patient cohorts will be important to determine IBD-CRC risk.

Sphingolipids are ubiquitous bioactive molecules that form part of the cell membrane and play a role in a multitude of cell functions such as migration, proliferation and apoptosis. S1P is the final product derived from sphingolipids and can activate STAT3 and NF-κB. STAT3-induced S1P receptor expression is important for persistent STAT3 activation [creating a positive feedback loop in immune and tumour cells] during carcinogenesis.[95] S1P also has immunoregulatory activity as T-cells require S1P signalling to egress from the thymus and from peripheral lymphoid organs.[96] A protumour role for S1P, and its regulatory enzyme sphingosine-kinase 1 [SphK1], has therefore been hypothesized. In a small [n = 20 patients] translational study, biopsies from curative surgical resections reported higher expression of phosphorylated SphK1 in IBD-CRC compared with S-CRC, which suggests the S1P pathway is especially important for IBD-related malignancy.[97] Given the outlined mechanism of action, inhibiting S1P may reduce both IBD and IBD-CRC. Carcinogenesis may be triggered by S1P lyase1 [SGPL1], which is responsible for the irreversible degradation of S1P. In an AOM/DSS model that utilized isogenic bone marrow transplantation of inducible SGPL1 knockout mice, immune-cell SGPL1 knockout was associated with colitis and pathological crypt remodelling with extracellular S1P signalling, which caused delayed tumour formation. However, tissue-SGPL1 knockout reduced immune activity and induced immediate tumorigenesis which was associated with an IL-12 to IL-23 shift.[98] This suggests that understanding the difference between tissue vs immune cell S1P lyase activity is important for optimizing S1P blockade therapy to treat IBD and reduce IBD-CRC risk. There are ongoing safety and efficacy trials for the S1P receptor modulators, such as etrasimod [NCT03950232] and ozanimod [NCT0253112].

6. Conclusions

Patients with IBD have an increased risk for developing CRC. The inflammation–dysplasia–carcinoma sequence of IBD-CRC is distinct from the sporadic normal–adenoma–adenocarcinoma sequence and confers a poorer prognosis. While key inflammatory pathways have been described, the immune cell landscape of IBD-CRC remains poorly characterized, although new data suggest Th17 cells and macrophages play important roles.

The selection pressure exerted by efficacious therapeutic agents is unknown and, although the overall inflammatory burden is lessened, the potential disruption to immune cancer surveillance is yet to be fully appreciated. Indeed, it will be some time before we see the full effect of these therapies on the incidence of IBD-CRC. More sensitive tools to detect early dysplasia are needed, and may include non-invasive stool testing for DNA methylation markers and improved computer-aided identification of dysplasia during surveillance procedures.[99]

In the clinic, preventing the burden of inflammation is probably the most important factor for minimizing IBD-CRC. With the growing therapeutic arsenal, caution is warranted that immunosuppression can be a double-edged sword, and it will be some time before we see the full effect of these therapies on the incidence of IBD-CRC.

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Conflicts of Interest

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Author Contributions

S.D., M.J.A. and R.J.P. contributed to review conceptualization and design. R.J.P. wrote the first draft of the manuscript and drafted Figures and Tables. M.J.A. and A.M.D.C. provided histopathology photomicrographs [via Lothian NRS Bioresource] and S.D. provided endoscopy images [via Edinburgh IBD Unit]. R.J.P., M.J.A., A.M.D.C. and S.D. performed literature searches, reviewed articles for inclusion, and reviewed, edited and approved the final manuscript [including Figures and Tables]. Medical Writer or Editor – none.

Data Availability

No new data were generated or analysed in support of this research.

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