Inflammatory Bowel Disease and Risk of Colorectal Cancer: An Overview From Pathophysiology to Pharmacological Prevention

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Increased risk of colorectal cancer (CRC) in inflammatory bowel disease (IBD) patients has been attributed to long-standing chronic inflammation, with the contribution of genetic alterations and environmental factors such as the microbiota. Moreover, accumulating data indicate that IBD-associated CRC (IBD-CRC) may initiate and develop through a pathway of tumorigenesis distinct from that of sporadic CRC. This mini-review summarizes the current knowledge of IBD-CRC, focusing on the main mechanisms underlying its pathogenesis, and on the important role of immunomodulators and biologics used to treat IBD patients in interfering with the inflammatory process involved in carcinogenesis.

Keywords: inflammatory bowel diseases, colorectal cancer, inflammation, epigenetics, microbiota, immunomodulators

INTRODUCTION

Inflammatory bowel disease (IBD), comprising ulcerative colitis (UC) and Crohn’s disease (CD), is a chronic relapsing inflammatory disorder associated with an increased risk of colorectal cancer (CRC) compared to the general population (Eaden et al., 2001; Baipai et al., 2019). Interestingly, incidence rates of IBD-associated CRC (IBD-CRC) decreased over the last decades (Castaño-Milla et al., 2014; Choi et al., 2015). Several risk factors have been described, such as disease duration and extension (Ekbom et al., 1990; Eaden et al., 2001), inflammation (Rutter et al., 2004) and primary sclerosing cholangitis (Soetikno et al., 2002). Despite the limited number of studies, younger age at onset and onset of IBD in childhood seem to be associated with an increased incidence of CRC (Jess et al., 2012; Olén et al., 2020). Unlike sporadic CRC (sCRC), in patients with IBD-CRC, long-standing chronic inflammation initiates and drives tumorigenesis and important elucidation of the multiple factors involved in the process of carcinogenesis are emerging (Ullman and Itzkowitz, 2011; Baker et al., 2018). The present mini-review summarizes the recent advances in the pathophysiology of IBD-CRC, including the role of the immunomodulators currently used in the treatment of IBD (Figure 1).

PATHOGENESIS OF CRC IN IBD PATIENTS: GENETIC AND EPIGENETIC BASES

CRC tumorigenesis needs a tumor-initiating event that modifies normal intestinal epithelial cells by spontaneous mutation, environmental mutagens or inflammation-induced genetic and epigenetic
alterations (Schmitt and Greten, 2021). Several lines of evidence suggest that IBD-CRC can result from a different mechanism of tumorigenesis in comparison to sCRC (Salk et al., 2009; Risques et al., 2011; Baker et al., 2019). The epithelial tumor tissue of IBD-CRC patients presents a lower frequency of somatic adenomatous polyposis coli (APC) and Kirsten rat sarcoma virus (KRAS) mutations, while tumor protein P53 (TP53) mutations and Myc proto-oncogene protein (MYC) amplifications are detected earlier during tumor progression in comparison to sCRC (Yaeger et al., 2016; Du et al., 2017; Chatila et al., 2020). Insights on germline alterations of IBD patients with CRC were provided for 25 patients with IBD-CRC, sequencing 39 genes potentially involved in predisposition to cancer (Biscaglia et al., 2021). Six patients (24%) presented pathogenic variants (International Agency for Research on Cancer, IARC class 4 or 5). Of these, four concerned the APC region, three the MLH1 gene, and the remaining ones the MSH2, MSH3, MUTYH, EPCAM, BRCA1, CHEK2, POLE, CDKN2A and PDGFRA genes. The onset of CRC was significantly earlier in patients carrying these variants than in patients with benign or unidentified variants.

DNA and RNA-sequencing and methylation analysis were performed in 2500 CRC cases, including 31 IBD-CRC (Rajamäki et al., 2021). As expected, somatic mutations in APC and KRAS were less frequent in IBD-CRC; a significant enrichment of somatic mutations at noncoding 5′UTR of TP53 in IBD-CRC, resulting in low TP53 expression, was found. Aberrant promoter methylation patterns were detected exclusively in IBD-CRC in two genes related to mucosal immunity, in particular hypermethylation of polymeric immunoglobulin receptor (PIGR) and hypomethylation and strong overexpression of oncostatin M receptor (OSMR). Interestingly, increased levels of the interleukin-6 (IL-6) family member OSM and its receptor have been already detected in patients with active IBD and their presence was associated with failure of anti-tumor necrosis factor α (TNF) therapy (West et al., 2017), suggesting a potential role of the OSMR signaling in the molecular mechanism of IBD-associated tumorigenesis.

Chronic inflammation promotes aberrant DNA methylation in IBD, which in turn may predispose to the development of cancer (Barnicle et al., 2017; Somineni et al., 2019). A progressive increase in the percentage of methylated genes in the WNT signaling pathway from normal colon samples (n = 24) to IBD (n = 25) to IBD-CRC (n = 16) was observed, indicating their potential involvement during cancer development (Dhir et al., 2008). In particular, methylation of APC1A, APC2, SFRP1, and SFRP2 genes characterized the progression from IBD to IBD-CRC, indicating their potential role as biomarkers for early detection.
detection of cancer in IBD patients. These results have recently been validated in an additional cohort of UC CRC (Beggs et al., 2019).

The methylation status of 10 candidate genes involved in tumor suppression, cell-cycle regulation, and aging, in UC-CRC tumors and non-neoplastic tissues from both UC-CRC and UC patients (n = 114 for each) was analyzed (Garrity-Park et al., 2010). Methylation of RUNX3, MINT1, and COX-2 genes in non-neoplastic tissue was significantly associated with UC-CRC, suggesting their role as potential indicators of carcinogenesis (Garrity-Park et al., 2010). An altered methylation status of RUNX3 in the non-neoplastic sections of UC-CRC was also observed by Scarpa and others (Scarpa et al., 2016).

Among the epigenetic factors, emerging data have implicated the altered expression of specific microRNAs in IBD-associated tumorigenesis: miR-18a, -19a, -21, -31, -155 and -214 were upregulated in IBD-CRC colon tissues compared to healthy controls while miR-124, -193a and -139 were downregulated (Bocchetti et al., 2021), however, further prospective studies on large cohort of patients are needed.

**INFLAMMATION AND TUMORIGENESIS IN IBD-CRC**

The innate and adaptive immune system cells play an important role in the onset of IBD-CRC. Crosstalk between these cell types occurs mainly through a network of cytokines that drive and maintain inflammation and contribute to tumorigenesis via oxidative stress, epithelial cell proliferation, and angiogenesis (Long et al., 2017). In Table 1 is reported a brief summary of the effects of different inflammation-related molecules in IBD-CRC.

Among these molecules, the macrophage migration inhibitory factor (MIF), a pleiotropic cytokine that drives cellular proliferation and regulates the migration and activation state of immune cells, seems to be relevant. The pathophysiological role of MIF in a wide range of inflammatory diseases, among which IBD, was already demonstrated (Nishihira and Mitsuyama, 2009). Increased MIF in macrophages in a CRC mouse model was demonstrated, and loss of MIF expression protects mice during tumor initiation (Pacheco-Fernández et al., 2019; Klemke et al., 2021). In cancer cells from CRC patients and in an acute colitis-CRC mouse model, a tumor-specific elevation of MIF expression was demonstrated (Klemke et al., 2021). The heat shock protein 90 (HSP90) chaperone machinery stabilizes and protects MIF from degradation and supports tumor progression via macrophage recruitment and angiogenesis.

In the context of inflammation and CRC, the most investigated pathways are the nuclear factor κ light-chain enhancer (NF-κB) and IL-6/signal transducer and activator of transcription 3 (STAT3) and STAT6 signaling pathways (Grivennikov and Karin, 2011).

NF-κB plays an important role in tumorigenic process by several mechanisms: promotes the production of reactive oxygen and nitrogen species which induce DNA damage, causes chromosomal instability and epigenetic changes (Grivennikov and Karin, 2011). Furthermore, by stimulating the production of inflammatory cytokines and growth factors, NF-κB enhances the proliferation of tumor progenitor cells, favoring tumor progression. This effect is also enhanced by the anti-apoptotic role of NF-κB; in fact in a IBD-CRC mouse model, it was demonstrated that NF-κB suppresses apoptosis through the induction of the anti-apoptotic protein B-cell lymphoma-extra large (Bcl-xl) (Greten et al., 2004). The NF-κB pathway results

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**Table 1 | Cytokines and/or pro-inflammatory molecules in IBD-CRC.**

| Molecule | Function in IBD-CRC | Reference |
|----------|---------------------|-----------|
| TNF-α    | Activates oncogenic signaling pathways in epithelial cells, such as Wnt and NF-κB, that maintain a pro-inflammatory environment favoring tumor progression and angiogenesis. | Grivennikov and Karin, (2011) |
| IL-1β    | Induces tumor cell proliferation and leads to Wnt signaling pathway activation. | Hnatsyshyn et al. (2019) |
| IL-6     | Critical for long-standing inflammation, for the recruitment and activation of Th17 cells and the inhibition of the regulatory T cells functions. The ability of IL-6 to activate STAT3 in epithelial cells is critical for its pro-tumorigenic activity. | Grivennikov et al. (2009) |
| IL-8     | This chemokine was associated with increased metastatic and angiogenic potential in a mouse model of IBD-CRC. | Luo and Zhang, (2017) |
| IL-21    | In mouse intestinal epithelial cells, IL-21 increases the risk of IBD-CRC by enhancing the expression of induced cytokine deaminase gene which deaminates cytosine residues to cause cytosine-to-thymine transitions. | Araki et al. (2019) |
| IL-22    | Induces proliferation of enterocytes and dysplasia in a mouse model of IBD-CRC. IL-22 induces the nitric oxide synthase that leads to nitric oxide production within crypt epithelial cells driving DNA damage and carcinogenesis. | Wang et al. (2017) |
| COX-2    | Overexpression of COX-2 contributes to increased proliferation, angiogenesis and resistance to apoptosis favoring tumour initiation and progression. The release of proinflammatory cytokines induced and maintained COX-2 expression and leads to the transition from acute to chronic inflammation. The use of COX-2 inhibitors reduces IBD-CRC development in mice thanks to the inhibition of cell proliferation, the reduction of β-catenin activation, COX-2 activity and nitric oxide production. | Kohn et al. (2005); Hnatsyshyn et al. (2019) |
| Prostaglandins Prostaglandin E2/EP favors IBD-CRC development by switching the phenotype of macrophages and neutrophils to pro-tumor, increasing cellular migration through the up-regulation of vascular endothelial growth factor receptor-1 signaling and by activating NF-κB. | Mizuno et al. (2019) |
aberrantly activated in most of colitis-associated tumors and is involved in the expression of pro-inflammatory genes including COX-2, TNF-α and IL-6 (Gambhir et al., 2015).

The impaired regulation of NF-κB in tumor cells is also mediated by STAT3 which prompts the retention of NF-κB into the nucleus and hence amplifies its effect during the tumorigenic process and increases the interactions and communication between cancer cells and the microenvironment (Onizawa et al., 2009). The pro-oncogenic effects of STAT3 are mostly evident following inactivation of the negative regulators of IL-6 signaling, such as the suppressor of cytokine signaling 3 (SOCS3), that leads to an increased phosphorylation of protein kinase B (AKT), and NF-κB, initiating the disease process in patients that will progress towards IBD-CRC (Johnson et al., 2018). An increased IL-6/p-STAT3 signaling in dysplasia and colon cancer was demonstrated (Li et al., 2010). SOCS3 expression is reduced during progression from active UC to IBD-CRC and the altered methylation of SOCS3 may be involved in tumor progression increasing STAT3 signaling.

Another mechanism by which STAT3 promotes tumor progression is by favoring immune cell recruitment via the sphingosine-1-phosphate (SIP) signaling (Liang et al., 2013). SIP is formed by two related sphingosine kinases, SphK1 and SphK2, and it has already been demonstrated that SphK1 and intracellular SIP maintain a persistent activation of NF-κB and STAT3 pathways that lead to IBD-CRC development (Kawamori et al., 2009; Liang et al., 2013). Interestingly, in mice, the knockout of SphK2 increased SphK1 and S1PR1 expression, providing a pro-inflammatory environment through the secretion of IL-6 and favoring the infiltration of macrophages and T cells into tumor tissues.

Being the most abundant immune cells in tumor microenvironment, tumor-associated macrophages might be critical players in IBD-CRC progression. The role of Wnt5a, a member of the Wnt family, was already assessed in CRC: Wnt5a is a critical player in IBD-CRC progression to dysplasia, the regulatory T cells, monocytes and regulatory T-cells. During IBD and inflammation and proliferation processes leading to tumorigenesis, new accessible chromatin sites in these pro-inflammatory genes were generated, leading to their upregulated expression. Enhanced β-catenin binding to TCF-1 may alter the TCF-1–Foxp3-dependent regulation of these genes. In particular, pathway enrichment analysis revealed that co-binding of TCF-1 and Foxp3 increases the accessibility and transcription of genes involved in Th17 differentiation and T cell activation pathways such as IL-17, IFN-γ and TNF.

ROLE OF MICROBIOTA IN THE PATHOGENESIS OF IBD-CRC

Although the exact mechanism of inflammation-associated carcinogenesis is still not completely known, the contribution of the gut microbiota, especially of some pathogenic bacterial species, seems to be relevant. There is a general consensus on the relationship between the gut microbiota and the immune system: microbes, through pathogen-associated molecular patterns (PAMPs), are capable to communicate with pattern recognition receptors (PRRs) in the innate immune system, such as Toll-like receptors (TLRs), retinoic acid-inducible gene I-like receptors (RLRs) and nucleotide-binding oligomerization domain-receptors (NLRs), and to trigger the immune response (Mogensen, 2009; Lu et al., 2018). Interestingly, the expression of TLR4 is strongly upregulated in colonic tissues of BALB/c mice treated with azoxymethane/dextran sodium sulphate (AOM/DSS) to induce IBD-CRC, and blocking TLR4 signaling slows the development of the tumor (Pastille et al., 2021). In addition, downregulation of the TLR2 gene inhibits the proliferation of IBD-CRC. In particular, knocking out the TLR2 gene in mice treated with 1,2-dimethylhydrazine-dextran sodium sulphate, reduced the shortening of colorectal length, the number and volume of tumors, the pathological score and tumor severity. Furthermore, knocking down the TLR2 gene in the colorectal cancer cell lines HCT116 and HT29 inhibited their proliferation (Meng et al., 2020). It is noteworthy that also the deficient stimulation of other PRRs, such as NOD2, leads to a higher risk of IBD-CRC: in particular, NOD2<sup>−/−</sup> mice, treated with AOM to induce IBD-CRC, presented an increase in the number and size of tumors (Couturier-Maillard et al., 2013).

Moreover, upon stimulation with PAMPs, the NF-κB pathway and Wnt signaling, mentioned before for their role in the inflammation and proliferation processes leading to tumorigenesis, can be activated (Santaolalla et al., 2013; Peng et al., 2020).
Growing evidence confirms the association between IBD and the alteration of the composition of gut microbiota, sometimes referred to as dysbiosis (Kang and Martin, 2017). Overgrowth of specific bacterial species at the expense of commensals is related not only to IBD but also to the development of CRC (Kang and Martin, 2017; Fan et al., 2021).

Nevertheless, to the author’s knowledge, only one study investigated the gut microbiota composition in IBD-CRC patients (Richard et al., 2018), examining the gut microbiota from colonic mucosa of 10 healthy subjects (HS), 10 patients suffering from sCRC and seven patients affected by IBD-CRC. The bacterial microbiota of IBD-CRC patients had a reduced diversity compared to HS and a composition different from that of sCRC patients. In particular, when compared to HS, IBD-CRC patients have a decreased abundance in Firmicutes and Bacteroidetes and an increase in Proteobacteria; instead, the bacterial microbiota of both IBD and IBD-CRC patients are in sCRC, was evidenced; indeed, the Streptococcus genus was found to be more abundant in the IBD-CRC microbiota compared to the healthy adjacent mucosa (Richard et al., 2018). Streptococcus species, representative of the bacterial population of the mucosa and of the lumen of IBD patients, are associated with tumorigenesis (Biarc et al., 2004; Santoru et al., 2017; Zhang et al., 2018; Lo Presti et al., 2019). For instance, S. galolyticus allows the tumor progression in C57BL/6 mice with AOM/DSS-induced CRC through the recruitment of tumor-infiltrating myeloid cells which can inhibit competence of T cells and increase proinflammatory cytokines (Zhang et al., 2018). Moreover, 12 proteins isolated from S. bovis are able to trigger the release of chemokines and prostaglandins in both human epithelial colonic Caco-2 cells and in rat colonic mucosa, and to promote pre-neoplastic lesions in AOM-treated rats (Biarc et al., 2004).

Investigating the gut microbiota in the AOM-DSS mouse model of IBD-CRC, similarly to what was encountered for IBD-CRC patients the microbial community was drastically altered by chronic colitis: in particular, in addition to Lactobacillus hamster, Bacteroides uniformis and Bacteroides ovatus, also Streptococcus latticeae, belonging to Streptococcus genus mentioned above for its pathogenic role, increases (LiC et al., 2014).

**CHEMOPREVENTIVE EFFECTS OF THERAPIES FOR IBD**

Since several observations support the important role of inflammation in the development of IBD-CRC, the use of anti-inflammatory and immunosuppressant drugs in IBD can reasonably reduce inflammation in the gut and consequently the risk of inflammation-related cancers.

The chemopreventive effect of 5-aminosalicylic acid (5-ASA) in IBD patients has been widely studied even though the results remain conflicting (Terdiman et al., 2007; Bernstein et al., 2011; Carrat et al., 2017). A systematic literature search including 164 studies and meta-analyses to identify all prognostic factors for advanced CRC in patients with IBD (Wijnands et al., 2021),
showed that patients who received 5-ASA had a lower risk of advanced CRC. In a systematic review, a protective role of 5-ASA against CRC in UC patients in clinical-based studies but not in population-based studies was shown (Qiu et al., 2017). In IBD patients, 5-ASA at a dosage ≥1.2 g/day showed higher protective effects against CRC than at dosages <1.2 g/day. Interestingly, a recent observational study provided molecular evidence of changes in genes related to the carcinogenesis pathways such as CDC25A, CXCL10, IL8, NF-κB, and Ki-67 in colonic biopsies of 62 UC patients during long-term 5-ASA maintenance therapy; these changes may contribute to the chemopreventive effects observed in UC patients (Bajpai et al., 2019).

One of the most recent systematic review and meta-analysis, including 11 cohort and 16 case-control studies and involving 95,397 patients, highlighted that the use of thiopurines, azathioprine and mercaptopurine, was associated with a reduced risk of CRC; this chemopreventive effect was confirmed in patients with long disease duration (Beaugerie et al., 2013) but not in those with extensive colitis or primary sclerosing cholangitis (Zhu et al., 2018). Studies conducted on CESAME (19,486 patients) and ENEIDA (831 patients) cohorts confirmed that the risk for CRC is lower among IBD patients receiving thiopurine therapy (Bajpai et al., 2013; Gordillo et al., 2015). In a well-established murine model, the thiopurine thioguanine inhibits colitis-associated cancer by decreasing β-catenin activation/nuclear translocation, providing important evidence in support of the potential therapeutic utility of this class of drugs (Sheng et al., 2021).

The impact of biological drugs on IBD-CRC development has yet to be confirmed and long-term follow-up studies will be extremely important. Considering the role of TNFα in the initiation and progression of IBD-CRC (Popivanova et al., 2008; Wilson, 2008) the use of anti-TNFα agents may be useful in preventing CRC in patients with IBD (Biancone et al., 2009). A large-scale database study showing the inverse association of CRC with anti-TNFα therapy in the IBD population (225,090 CD and 188,420 UC) was recently published (Alkhayyat et al., 2021). In this study, patients with IBD who received any of the anti-TNFα agents and those who received combined treatment (anti-TNFs plus immunomodulators) had a lower risk of developing CRC. The relationship between anti-TNFα and CRC in IBD is also supported by the results obtained in animal models treated with infiximab in which CRC carcinogenesis associated with chronic colitis was reduced (Kim et al., 2010).

**CONCLUSION**

In summary, this mini-review summarizes the recent advances in the knowledge of the pathophysiology of IBD-CRC, a complex disease associated with multifactorial causes. Inflammatory pathways seem to be the major drivers of tumorigenesis in IBD patients even if the mechanisms that link inflammation and carcinogenesis remain not well characterized in patients. In this context, development of therapies targeting specific proinflammatory cytokines involved in tumorigenesis can provide a novel approach to prevent tumor initiation or progression. Further studies with large numbers of subjects are needed to address the existing gaps in the knowledge of the role of epigenetics in the process of carcinogenesis and to validate the predictive power and clinical value of the data collected so far. The identification of predictive and prognostic epigenetic markers could favor an early detection of IBD patients with increased risk of CRC. These analyses could also consider purified cellular populations, in particular epithelial cells.

Since the mucosal associated microbiota of IBD-CRC patients is characterized by the overgrowth of bacterial species playing a role in the pathogenesis of IBD-CRC, it could be assumed that increasing the levels of beneficial bacteria with probiotics could enhance the levels of the anti-inflammatory bacterial products SCFAs, restore the equilibrium and possibly ameliorate IBD-CRC condition. In addition, IBD-CRC may be at least partially prevented through mucosal healing of intestinal lesions, and the power of the potential anti-tumor effects of IBD drugs should be evaluated by rigorous prospective studies in the near future.

**AUTHOR CONTRIBUTIONS**

ML, DC and MF: Conceptualization and drafting of the initial manuscript. GD and GS: writing review and editing.

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