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Marie Muller, Franck Hansmannel, Djesia Arnone, Myriam Choukour, Ndeye Coumba Ndiaye, Tunay Kokten, Rémi Houlgatte, Laurent Peyrin-Biroulet, Ndeye Coumba Ndiaye, Laurent Peyrin-biroulet

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Marie Muller¹ , Franck Hansmannel² , Djesia Arnone²,
 Myriam Choukour¹, Ndeye Coumba Ndiaye², Tunay Kokten²,
 Rémi Houlgatte² and Laurent Peyrin-Biroulet^{1,2}

Abstract

Patients with inflammatory bowel disease are at increased risk of colorectal cancer, which has worse prognosis than sporadic colorectal cancer. Until recently, understanding of pathogenesis in inflammatory bowel disease-associated colorectal cancer was restricted to the demonstration of chromosomal/microsatellite instabilities and aneuploidy. The advance of high-throughput sequencing technologies has highlighted the complexity of the pathobiology and revealed recurrently mutated genes involved in the RTK/RAS, PI3K, WNT, and TGF β pathways, leading to potentially new targetable mutations. Moreover, alterations of mitochondrial DNA and the dysregulation of non-coding sequences have also been described, as well as several epigenetic modifications. Although recent studies have brought new insights into pathobiology and raised the prospect of innovative therapeutic approaches, the understanding of colorectal carcinogenesis in inflammatory bowel disease and how it differs from sporadic colorectal cancer remains not fully elucidated. Further studies are required to better understand the pathogenesis and molecular alterations leading to human inflammatory bowel disease-associated colorectal cancer.

Keywords

Inflammatory bowel disease, colorectal cancer, inflammatory bowel disease-associated cancer, genomics, epigenetics, molecular pathways

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic and idiopathic disorders defined as inflammatory bowel diseases (IBDs).¹ In both diseases, patients have an increased risk of developing colorectal cancer (CRC).² IBD-associated CRC (IBD-CRC) is diagnosed at a younger age and has worse prognosis than sporadic CRC (S-CRC). For this reason, developing knowledge about the pathobiological mechanisms contributing to this disease is essential. Such an understanding may enable the initiation of targeted preventive strategies.

The molecular events in the initiation of oncogenesis in IBD and the progression to IBD-CRC in humans have been a subject of interest for decades. Until recently, knowledge in this field was restricted to the demonstration of chromosomal instability (CIN),

aneuploidy, microsatellite instability,³ and few genetic alterations. Among these altered genes, the most commonly described are *p53* tumor suppressor gene mutations and *p53* loss of heterozygosity (LOH),⁴ which are found in >80% of IBD-CRC patients.⁵ *p53* loss of function appears to be an early event in the initiation of IBD-CRC pathogenesis,⁶ whereas it is a late event in

¹Department of Gastroenterology, Nancy University Hospital, University of Lorraine, France

²Inserm U1256 "Nutrition – Genetics and exposure to environmental risks - NGERE", Nancy, France.

Corresponding author:

Laurent Peyrin-Biroulet, Université de Lorraine Faculté de Médecine, allée morvan, Vandoeuvre-les-Nancy, 54505, France
 Email: peyrinbiroulet@gmail.com

S-CRC. Other genetic alterations, such as in the *APC* tumor suppressor gene or *KRAS* oncogene,⁷ have been identified in IBD-CRC, but at a lower frequency than in S-CRC.

More recently, the genomic landscape of IBD-CRC has been explored by means of new high-throughput sequencing technologies.^{5,8,9} Extensive genomic analyses have revealed new recurrent genomic alterations.

Moreover, the emergence of new fields of research (such as epigenomics and the tumoral microenvironment) highlights the complex network of factors involved in IBD-CRC. The gut microbiota is also a subject of interest and intense research.

In this review, we describe current knowledge on the molecular alterations involved in human IBD-CRC oncogenesis.

Genetic alterations in DNA coding sequences

Somatic genetic alterations

The accumulation of molecular events and mutations in somatic cells, followed by their clonal expansion, have been studied for a role in IBD-CRC pathogenesis (Figure 1). This process gives rise to a widespread pre-neoplastic “field change” in colonic mucosa before any histological evidence of dysplasia.¹⁰

The main genetic alterations associated with IBD-CRC were first described in the early 1990s.⁶

Similar chromosomal alterations are found in S-CRC and IBD-CRC, yet there are differences in their frequency and timing of occurrence.

The first genetic investigations in IBD-CRC revealed that CIN was a major feature in the initiation of CRC in IBD, being found in 80% of cases.¹¹ CIN is associated with the progressive accumulation of mutations in oncosuppressor genes and oncogenes.³ Aneuploidy is a consequence of CIN and occurs before dysplasia in mucosal colonic biopsy samples from patients with IBD.¹² Moreover, there is a statistically significant relationship between increased aneuploidy and histological progression to dysplasia/carcinoma in UC.⁶ This observation highlights the progressive genomic instability during neoplastic progression of IBD-CRC.

Another primary genetic alteration involved in IBD-CRC development is mutation of the *p53* tumor suppressor gene, suspected to typically occur before development of any dysplasia.¹³ *p53* has a pivotal influence on cell proliferation and prevents clonal expansion of mutant cells.¹⁴ There is also a strong correlation between histological progression from low grade dysplasia (LGD) to carcinoma and *p53* LOH.⁶ In tissue from UC-CRC, *p53* LOH was found in 6% of samples without dysplasia, in 33% with LGD, and in 85% with UC-CRC.⁶ *p53* LOH was only found in aneuploid cells, suggesting these events are early in IBD-CRC pathogenesis. By contrast, *p53* alteration is a late event in S-CRC oncogenesis.¹⁵

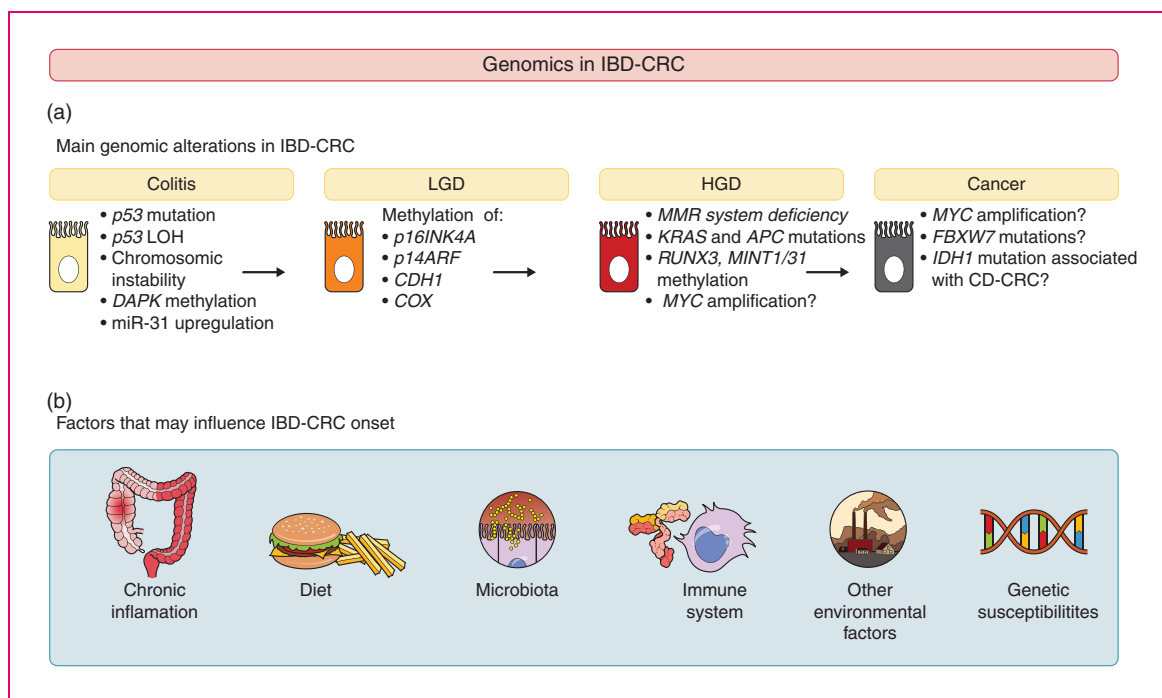


Figure 1. Update of the main genomic alterations described in IBD-CRC and their chronology of appearance in the colitis/cancer sequence.

Loss of function of adenomatous polyposis coli (*APC*), another tumor suppressor gene, is also an early event in IBD-CRC,⁷ but occurs much less frequently than in S-CRC (6% versus 74%).¹⁶ Such observations support the hypothesis that IBD-CRC does not emerge from the classical *APC* inactivated adenoma pathway, as seen in S-CRC.¹⁷ The role of *APC* in IBD-CRC carcinogenesis is not clearly understood.⁶

Oncogene alterations in IBD-CRC are less described than tumor suppressor gene alterations. Mutations in the *KRAS* oncogene, which are believed to occur early in IBD-CRC oncogenesis,^{6,7} are less frequent in IBD-CRC than in S-CRC (9% versus 50%).¹⁸

Oxidative stress contributes to oncogenesis by impairing the DNA mismatch repair (MMR) system,¹⁹ leading to an accumulation of replicative mistakes and a microsatellite instability (MSI) phenotype in colonic mucosa in 15% of patients with IBD-CRC,²⁰ a rate similar to S-CRC.

The 2000s have been characterized by significant evolution in genetic knowledge, exemplified by the completion of the Human Genome Project and the ENCODE project. These advances have been accompanied by the emergence of advanced DNA sequencing technologies, allowing low-cost genomic discoveries. Three studies have explored the genomic features of IBD-CRC through high-throughput sequencing.^{5,8,9}

In a first study,⁵ next-generation sequencing was used to investigate coding sequence alterations in 315 cancer-related genes in 47 IBD-CRC samples and compare them with S-CRC alterations reported in The Cancer Genome Atlas (TCGA). Approximately six genetic alterations per tumor were identified for IBD-CRC; among these, three genes were recurrently altered ($\geq 10\%$ of cases). *p53* was the most commonly altered gene, being altered in 89% of IBD-CRC tumors compared with 52% of S-CRC tumors in TCGA. *APC* was altered significantly less frequently in IBD-CRC than in S-CRC (21% versus 76%), and notably more frequently in CD-associated CRC (CD-CRC) than UC-CRC (39% versus 10%). *MYC* proto-oncogene amplification occurred in 26% of IBD-CRC samples versus 4% of S-CRC samples. Moreover, isocitrate dehydrogenase 1 (*IDH1*) mutations were significantly more frequent in IBD-CRC (11% of cases), whereas they are rare in S-CRC (affecting just 1%). *IDH1* alterations at the R132 hotspot were significantly more common in CD-CRC than UC-CRC. Potentially targetable mutations were found in 36% of IBD-CRC samples, and included mutations in the PIK3/mTOR and RTK/RAS/RAF pathways.

Whole-exome sequencing from paired CRC and non-neoplastic tissue samples from 31 well-characterized IBD patients has also been performed.⁸ Confirming earlier observations, *p53* was the most

commonly mutated gene (63% of cases) whereas both *APC* and *KRAS* were significantly less frequently mutated in IBD-CRC than what was observed in S-CRC from TCGA (*APC*: 13% versus 81%, *KRAS*: 20% versus 43%). Several recurrently mutated genes were identified in IBD-CRC involving RTK/RAS (*BRAF*), PI3K, WNT (*APC*, *CTNNB1*, *SOX9*), and TGF β (*SMAD 2/4*, *TGF β 2*) pathways. Other recurrent alterations involved the Rho GTPase network, cell communication/adhesion, cytokine signaling (IL16) and chromatin remodeling (*TRRAP*, *EP300*).⁸

More recently, 55 tumors from 48 IBD-CRC patients (35 tumors from 30 UC patients, 18 from 16 CD patients, two from patients with indeterminate colitis) were studied through a 50 gene hot-spot solid tumor panel.⁹ IBD-CRC tumor genomic profiles were compared with S-CRC TCGA data. Similar results were found to the previous genomic studies, including the presence of *IDH1* mutations in a subset of IBD-CRC (7% in IBD-CRC versus 1% in S-CRC from TCGA, with difference reaching statistical significance). Other genes were also altered in $>5\%$ of IBD-CRC but the difference with TCGA data did not reach statistical significance (*PIK3CA*, *SMAD4*, and *FBXW7*, which was only mutated in UC-CRC).

In summary, IBD-CRC exhibits differences in genetic alterations in comparison with S-CRC, suggesting that different molecular pathways contribute to the oncogenic processes (Table 1).

Table 1. Main genetic alterations in IBD-CRC compared with S-CRC.

Gene	Frequency of mutations in IBD-CRC	Frequency of mutations in S-CRC ^a	Statistical significance
<i>p53</i> ⁴	60–85%	58.25–82.48%	S*
<i>KRAS</i> ⁸	4–20%	41.65–43.5%	S*
<i>TGFBR2</i> ²⁰	17%	0.73–5%	NS
<i>SMAD4</i> ⁸	13%	13.5–19.71%	NS
<i>TRRAP</i> ⁸	13%	8.03–14.75%	NS
<i>SOX9</i> ⁸	10%	7.3–16%	NS
<i>PIK3CA</i> ⁸	10%	16–31%	NS
<i>SMAD2</i> ⁸	10%	5.11–6.5%	NS
<i>EP300</i> ⁸	10%	5.11–8.75%	NS
<i>IDH1</i> ⁵	11%	1.46–2%	S*
<i>FBXW7</i> ⁸	7%	19–20.44%	NS
<i>APC</i> ¹⁶	6%	77.25–88.32%	S*
<i>BRAF</i> ⁹	4%	4.38–15%	NS
<i>CTNNB1</i> ⁸	3%	5.11–8.75%	NS

^aData from The Cancer Genome Atlas Project (<https://portal.gdc.cancer.gov>).

IBD-CRC: inflammatory bowel disease-associated colorectal cancer; S-CRC: sporadic colorectal cancer; S*: significant; NS: not significant.

Mitochondrial DNA (mtDNA)

The role of mitochondria in cancer is poorly understood. However, it is well-established that oxidative stress may increase mutations in mtDNA, which might correlate with precancerous status.²¹ In one study, mtDNA mutation rates were compared between seven UC-CRC patients, 19 UC patients without CRC and nine healthy controls.²² Patients with UC-CRC had a significantly higher number of mtDNA alterations than both healthy controls and UC patients without CRC,²² suggesting that the rate of mtDNA mutation is enhanced in mucosal cells by oxidative stress caused by chronic inflammation, leading to an accelerated oncogenic transformation.²²

In another study,²³ cytochrome C oxidase (COX) and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1 α) immunostainings were used to study mitochondria protein expression in nine UC patients with colonic high grade dysplasia (HGD) or CRC compared with nine UC controls. Significant COX expression loss was found in UC colonic dysplasia compared with UC controls. Surprisingly, COX and PGC1 α immunostaining intensity were significantly increased in UC-CRC, a finding supported by the increased mtDNA copy number in UC-CRC. Authors hypothesized that mitochondrial loss occurs before colonic dysplasia development in UC patients and cancer cells restore mitochondria numbers to support further proliferation.

Analyses of mtDNA could provide a new therapeutic target, and may be useful for the prediction of risk of carcinogenesis in IBD patients.

Genetic alterations in DNA non-coding sequences

Epigenetic alterations

Epigenetics refers to the heritable changes in gene expression and chromatin organization that are not due to alterations in the DNA sequence, and include DNA methylation, histone modification, RNA interference and the positioning of nucleosome. A number of studies have investigated the contribution of epigenetic mechanisms to IBD-CRC.

Promoter methylation and consequent silencing of several genes, particularly *p16^{INK4a}*, *p14^{ARF}*, and cadherin 1 (*CDH1*), is a common event. Promotor hypermethylations in *p16^{INK4a}* and *p14^{ARF}* are frequent and early events in IBD-CRC carcinogenesis, found in 100% and 50% of UC-CRC,^{24,25} respectively. Both genes play important parts in cell cycle inhibition.^{24,25} Methylation of the *CDH1* promoter was detected in 93% of IBD patients with colorectal dysplasia, versus

6% in IBD patients without dysplastic lesions.²⁶ This gene has an essential role in biological processes that are dysregulated in cancer, such as ordering of cell sorting, migration, and differentiation.

In IBD neoplasia, *hMLH1* promoter hypermethylation occurs as frequently as in S-CRC in the setting of CRC with microsatellite instability.²⁷ *hMLH1* hypermethylation and MSI are strongly associated with diminished expression of hMLH1 protein, a component of the DNA MMR machinery, suggesting that *hMLH1* hypermethylation causes defective DNA MMR in a subset of IBD neoplasms.²⁸

A progressive increase in methylation of WNT signaling pathway genes is observed during IBD-CRC pathogenesis.²⁹ This is in contrast with genetic mutations in this pathway, which occur late during colitis-associated tumorigenesis (i.e. *APC*).³⁰

Epigenetics modification also included suppressor of cytokine signaling 3 (*SOCS3*) methylation. Indeed, the number of (*SOCS3*)-positive epithelial cells were significantly reduced during UC-CRC progression from LGD to CRC in UC patients (9.1% in UC-CRC versus 33.3% in UC-LGD),³¹ and this observation was correlated with prominent expression of the DNA methyltransferase gene (*DMNT1*).³² *SOCS3* is a target gene of the IL6/STAT3 pathway that is known to regulate negative feedback of the JAK/STAT signaling cascade.³³ Methylation-specific polymerase chain reaction analysis showed that *SOCS3* silencing was due to its methylation. *SOCS3* methylation was detected in all investigated UC-CRC samples, whereas no *SOCS3* methylation was found in biopsy samples from healthy controls.³¹

Furthermore, the methylation status of 10 selected genes involved in tumor suppression, cell cycle regulation and aging was investigated in a large number of UC-CRC samples and compared with non-neoplastic tissue from both UC-CRC cases and UC controls.³⁴ The degree of methylation for *p16^{INK4a}*, runt-related transcription factor 3 (*RUNX3*), methylated in tumor gene 1 (*MINT1*), *MINT31*, and hyperplastic polyposis protein 1 (*HPPI*) was significantly higher in UC-CRC tumor compared with UC controls. Conversely, unmethylated cyclooxygenase 2 (*COX2*) was an indicator of CRC.

Death-associated protein kinase (*DAPK*), a tumor suppressor gene, also seems to undergo epigenetic modification during IBD-CRC oncogenesis.³⁵ *DAPK* silencing by promoter hypermethylation might be crucial for accumulation of DNA damage in UC mucosa, and therefore could contribute to initiation of the neoplastic process in UC-CRC.³⁵

These data (Table 2) indicate that epigenetic modifications in IBD may contribute to the oncogenic

Table 2. Main epigenetic alterations (methylation) in IBD-CRC compared with S-CRC.

Gene	Gene methylation rate in IBD-CRC	Significance between gene's promoter methylation and IBD-CRC	Gene methylation rate in S-CRC
<i>p16^{INK4a}</i> ²⁴	100%	S*	32–40%
<i>CDH1</i> ²⁶	93%	S*	87%
<i>HPP1</i> ³⁴	40–78.7%	S*	84%
<i>MINT31</i> ³⁴	59.4%	S*	11%
<i>MINT1</i> ³⁴	50.5%	S*	15%
<i>p14^{ARF}</i> ²⁵	50%	S*	33%
<i>hMLH1</i> ²⁷	9%	NS	5%
<i>RUNX3</i> ³⁴	44.6%	S*	23.5%
<i>DAPK</i> ³⁵	27.6%	S*	57.4%

IBD-CRC: inflammatory bowel disease-associated colorectal cancer; S-CRC: sporadic colorectal cancer; IBD-CRC: IBD associated colorectal cancer; S-CRC: sporadic colorectal cancer; S*: significant; NS: not significant.

transformation into CRC, and highlight the need for further research in this area.

microRNAs

microRNAs (miRs) have recently emerged as important factors in cancer biology. These small non-coding RNAs are involved in post-transcriptional regulation and have a role in carcinogenic processes through their control of key cellular functions (apoptosis, differentiation, cell cycle progression and immune functions).³⁶

The involvement of miRs and their dysregulation in IBD-CRC has recently been explored in two important works.^{37,38}

In the first published study,³⁷ 175 fresh-frozen colon tissue samples from 14 healthy controls, 35 IBD patients (inflamed and non-inflamed mucosa), 11 IBD-dysplasia, 37 IBD-CRC, and 15 S-CRC were collected and their miR expression determined by miR microarrays. The expression level of miR-31 was found to increase in the progression from inflamed IBD colonic tissue to IBD-dysplasia,³⁷ suggesting that miR-31 upregulation is an early event in colorectal neoplastic transformation in IBD patients. miR-31 expression levels were also threefold higher in IBD-CRC than in S-CRC.³⁷

In the second study,³⁸ the same experience was repeated, using miR microarrays to identify altered expression of miRs between IBD-CRC samples and IBD controls. Thirty differentially expressed miRs were identified between those two populations (18 upregulated and 12 downregulated in IBD-CRC). miR-224, which was overexpressed, exhibited the highest discriminatory power for distinguishing between IBD-CRC from IBD controls. miR-224 is assumed to dysregulate cell cycle control by targeting *p21*, a key cell cycle regulator.³⁸

Those recent results uncover new miRs signaling pathways, suggesting an etiologic role for miRs in the development of IBD-CRC.

Proinflammatory and protumoral molecular pathways

TLR4 (Toll-like receptor 4)/NFκB (nuclear factor-kappa B) signaling pathways

TLR4/NFκB overactivation and overexpression have been observed in several inflammatory diseases, including IBD, and are suspected to promote colitis and its associated CRC.³⁹ In humans, only two studies exploring the role of TLR4/NFκB signaling pathway in IBD-CRC have been published.^{40,41} Using a Western blot assay, it was demonstrated in 2007 that non-dysplastic colon samples from four patients with UC-associated CRC (UC-CRC) had low expression of TLR4 protein, whereas matched tumor protein samples from the same UC-CRC patients showed higher expression of TLR4.⁴⁰ Moreover, immunostaining analysis revealed a predominantly epithelial expression of TLR4.⁴⁰

More recently, TLR4/NFκB signaling was investigated in 35 Algerian patients with UC and nine with UC-CRC.⁴¹ Transcriptomic analysis demonstrated that mRNA levels of TLR4 were significantly increased in colonic mucosa of UC-CRC patients compared with UC patients.⁴¹ Circulating levels of tumor necrosis factor (TNF) and nitric oxide were increased in UC-CRC versus UC patients, with statistical significance for plasma TNF levels (374.7 pg/ml versus 291.5 pg/ml).⁴¹ This result was supported by significantly higher TNF mRNA levels in colonic mucosa of patients with UC-CRC compared with active UC patients.⁴¹ Additionally, immunofluorescent staining analyses indicated that NFκB and IκB kinase protein expression

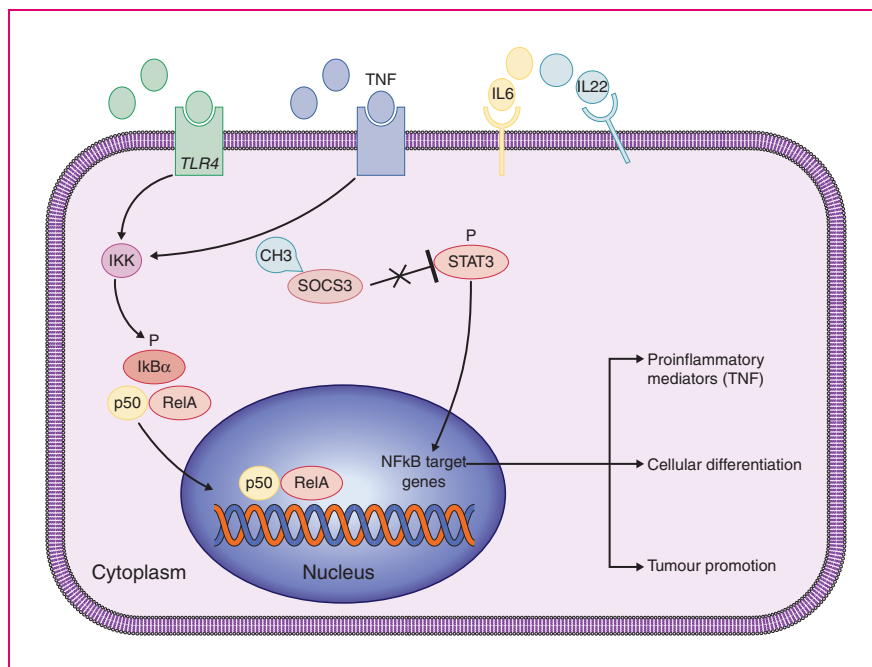


Figure 2. TLR4/NFκB and STAT3 pathways in IBD-CRC.

was highly increased in colonic mucosa of UC-CRC in comparison with UC controls.⁴¹

These results suggest that increased epithelial TLR4 expression occurs during the initiation of UC-CRC and might have a role in the transition from inflammation to neoplasia *via* the TLR4/NFκB pathway. Thus, proteins of the NFκB pathway could be useful therapeutic targets in IBD-CRC patients (Figure 2).

STAT3 (signal transducer and activator of transcription 3) pathway

STAT3 pathway activation has been observed in many human carcinomas, including CRC.⁴² This signaling pathway promotes survival, cell proliferation and may also promote NFκB activity. Several inflammatory cytokines that activate STAT3 have been associated with IBD, including interleukin (IL) 6⁴³ and IL22 (Figures 2 and 3).⁴⁴

Three studies have explored STAT3 signaling in human IBD-related colorectal carcinogenesis;^{31,45,46} two investigated the IL6/STAT3 axis,^{31,45} whereas another studied IL22/STAT3 signaling.⁴⁶

In a first study, authors used immunohistochemical scoring to determine IL6/STAT3 expression in colon biopsy specimens from patients with UC-CRC at different phases of the oncogenic process:³¹ nine UC patients with LGD, seven UC patients with HGD and 11 patients with UC-CRC.³¹ Patients with UC-CRC had significantly increased expression of IL6 (72.7% in UC dysplasia and/or UC-CRC versus

0% in healthy controls) and p-STAT3 (54.5% versus 11.1%) in colonic epithelial cells.³¹

Recently, the role of sphingosine kinase 1 (SPHK1) and sphingosine-1-phosphate (S1P) on IL6/STAT3 signaling in UC-CRC patients has been investigated.⁴⁵ S1P is a bioactive lipid mediator generated by SPHK1, with both molecules acting as upstream mediators of IL6 and STAT3 signaling.⁴⁷ Using immunohistochemistry, IL6, p-STAT3, and p-SPHK1 expression levels in S-CRC were measured in comparison with UC-CRC.⁴⁵ Although there was no difference in IL6 and p-STAT3 expression between the two populations, p-SPHK1 levels were significantly higher in UC-CRC (9/10 tumors) than in S-CRC (3/10 tumors).⁴⁵ Thus, upregulated SPHK1 in UC-CRC may lead to S1P increased expression and activation of IL6/STAT3 signaling *via* the S1P receptor (S1PR1).⁴⁵ Consequently, a persistent IL6/STAT3/S1PR1 amplification loop is created that is critical to the development of UC-CRC (Figure 3).

The IL22/STAT3 axis was investigated in colon biopsies from 74 UC patients and 10 patients with UC colonic dysplasia.⁴⁶ Immunohistochemical analysis showed that significantly more IL22-positive cells and p-STAT3 cells were observed in UC-dysplasia than in UC controls.

Chronic inflammation associated with IBD substantially due to reactive oxygen and nitrogen species over-synthesis contributed to the onset of IBD-CRC. Indeed, it induces a series of responses that prolong inflammation, such as matrix metalloproteinase and

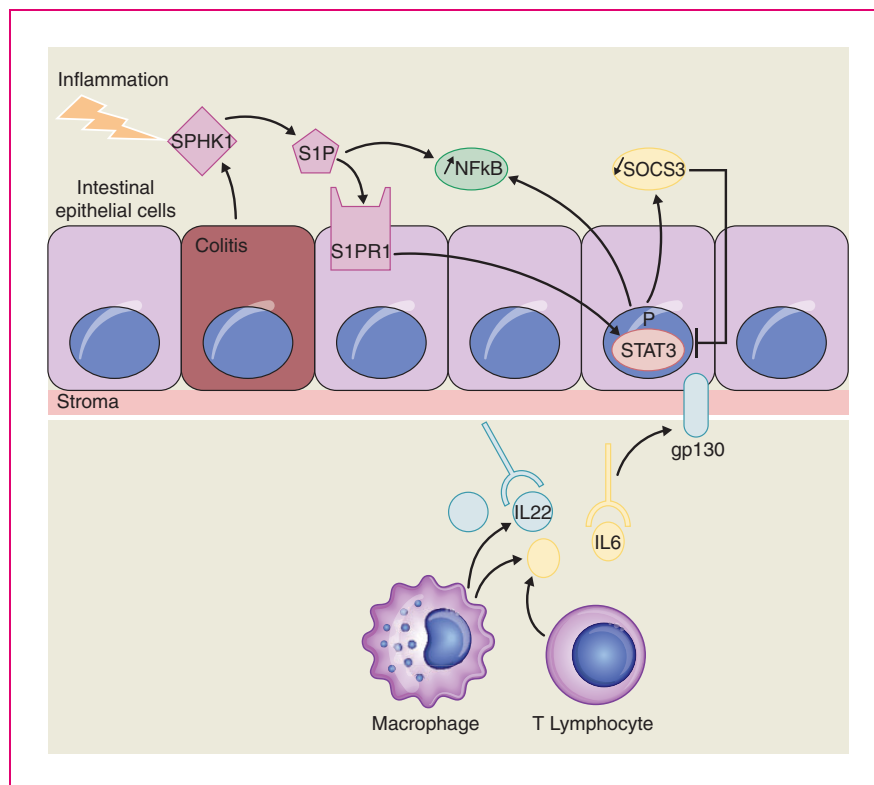


Figure 3. STAT3 pathway and IL6/STAT3/S1PR1 amplification loop in IBD-CRC.

TLR4/NFκB, resulting in DNA damages and the activation of procarcinogenic genes and silencing of tumor suppressor pathways.⁴⁸ Therefore, regulation of those proinflammatory and protumoral pathways may be important to control the progression of IBD into IBD-CRC.

STAT3 signaling is a complex network implicated in IBD-CRC pathogenesis. Overall, targeting the STAT3 pathway may offer different therapeutic options (STAT3 targeting drugs and inhibitors of IL6/IL22 and S1P/SPHK1) to prevent the progression of colitis into cancer.

Microbiota in IBD-CRC

It is established that gut microbiota plays a crucial role on the resistance against invading pathogens.⁴⁹ Dysbiosis of gut microbiota, defined as a shift in the balance between commensal and pathogenic microorganisms leading to a decrease in gut microbial diversity,⁵⁰ is often found in IBD.⁵¹ Resident microbes can promote carcinogenesis by inducing inflammation, increasing cell proliferation, and producing metabolites (such as butyrate),⁵² which might affect DNA integrity and immune regulation.⁵³

The *Enterobacteriaceae* family,⁵⁴ especially adherent-invasive *E. coli* and *Sphingomonas*,⁵⁵ have been

associated with the ileal mucosa of patients with IBD-CRC. Conversely, a decrease of *Fusobacterium* and *Ruminococcus* genus were observed in IBD-CRC versus S-CRC.⁵⁵ However, to our knowledge, there is still no evidence of significant microbiota changes between IBD-CRC and S-CRC.⁵¹

Microbiota changes might also generate epimutations,⁵⁶ which are currently a subject of intense research. Further investigations are needed to confirm the implication of microbiota in IBD-CRC and to determine its role in this oncogenic process.

Discussion

Although IBD-CRC represents <1% of all CRC cases, patients with IBD are among the highest risk groups for developing CRC. Moreover, IBD-CRC typically has an earlier occurrence and a worse prognosis than S-CRC.² Therefore, it is important to identify molecular mechanisms involved in IBD-CRC carcinogenesis to prevent IBD-CRC and to develop targeted therapies for patients. Such an understanding might also help to better understand the role played by inflammation in colonic cancer more generally.

IBD-CRC is a complex disease associated with multifactorial causes. It is now well established that chronic inflammation associated with IBD contributes to the

onset of IBD-CRC *via* increased expression of genes involved in cell cycle regulation and cancer-relevant signaling pathways.⁵⁷ Therefore, studying somatic genomic events in IBD-CRC is of major interest in understanding the molecular mechanisms responsible for the initiation and the progression of IBD-CRC. However, despite the major advances in genetics made these last ten years, very few genomic discoveries have been made about IBD-CRC. In this review, we reported all the studies about genetic and molecular alterations described in human IBD-CRC.

Three studies have investigated the genetic alterations in IBD-CRC using high-throughput sequencing technologies,^{5,8,9} the results of which support the theory that most IBD-CRCs arise through different pathways than S-CRC. They have also expanded existing knowledge of the molecular alterations in IBD-CRC, especially the identification of potentially targetable mutations and some relevant recurrent alterations (*MYC* amplification, *IDH1*, *FBXW7*), even though most of these findings did not reach statistical significance.

However, there are important limitations for these studies, mainly due to restricted genomic analysis (such as the hot-spot panel), retrospective designs and small sample sizes. Most of the published articles were conducted in UC patients, yet it could be hypothesized that the molecular alterations are similar in CD patients because they are at the same risk of CRC as UC patients of similar disease duration and extension. Moreover, limited data regarding epigenomics and microarrays analysis are available. Overall, there is no evidence of distinct genomic signatures in IBD-CRC and S-CRC.

The gut microbiota is of growing interest in IBD-CRC. Nowadays, IBD has become a global disease with accelerating incidence in newly industrialized countries, whose societies have become more westernized, and this might lead to an increased incidence of IBD-CRC in the near future. Because gut microbiota modifications are directly linked to environmental factors (especially diet), its role in IBD-CRC carcinogenesis should be considered an important component to better understand IBD-CRC development and to explore new therapeutic strategies such as fecal microbiota transplantation to prevent CRC initiation.

The tumoral microenvironment is a complex network and an emerging research field. The role of the tumor microenvironment in IBD-CRC has never been studied in humans but warrants further attention as it may provide new insights into malignant transformation, tumor progression, and combination therapy strategies for IBD-CRC.

Even though further investigations are required to understand the role of these factors in IBD-CRC

oncogenesis, this comprehensive review highlights the major molecular and somatic genomic alterations found in IBD-CRC. The described alterations in IBD-CRC would deserve further attention and should be considered as potential biomarkers to prevent CRC in patients suffering from IBD or as potentially new molecular targets for personalized medicine in IBD-CRC.

In conclusion, IBD-CRC is a complex disease. Although recent studies have brought new insights into IBD-CRC pathobiology and revealed potentially targetable molecular alterations, the understanding of colorectal carcinogenesis in IBD, which differs from S-CRC, remains not fully elucidated. Further studies are required to better understand the molecular alterations leading to human IBD-CRC and to propose precision medicine for these patients, including personalized endoscopic surveillance programs.

Declaration of conflicting interests


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ORCID iDs

Marie Muller  <https://orcid.org/0000-0001-6412-932X>

Franck Hansmannel  <https://orcid.org/0000-0003-1661-2362>

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