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REVIEW

Molecular Alterations of Colorectal Cancer with Inflammatory Bowel Disease

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Abstract Inflammatory bowel disease (IBD) is an important etiologic factor in the development of colorectal cancer (CRC). The risk of CRC begins to increase 8 or 10 years after the diagnosis of IBD. This type of cancer is called colitis-associated CRC (CA-CRC). The molecular pathogenesis of inflammatory epithelium might play a critical role in the development of CA-CRC. Genetic alterations detected in CA-CRC such as genetic mutations, microsatellite instability, and DNA hypermethylation are also recognized in sporadic CRC; however, there are differences in the timing and frequency of molecular events between CA-CRC and sporadic CRC. Interaction between gene–environmental factors, including inflammation, lifestyle, psychological stress, and prior appendectomy, might be associated with the etiopathology of IBD. The mucosal inflammatory mediators, such as oxidant stress, free radicals, and chemokines, may cause the genetic alterations. Understanding the molecular mechanisms of CA-CRC might be important to develop clinical efficacies for patients with IBD. This review discusses the molecular characteristics of CA-CRC, especially ulcerative colitis-associated CRC, including clinical features, signaling pathways, and interactions between genetic alterations and environment involved in inflammatory carcinogenesis.

Keywords Colorectal cancer · Ulcerative colitis · Crohn's disease · Genetic alterations · Dysplasia · Inflammatory bowel disease

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Introduction

Crohn and Rosenberg reported the first case of adenocarcinoma complicating ulcerative colitis (UC) in 1925 [1]. Since then, it has been recognized that the risk of developing colorectal cancer (CRC) is increased in patients with long-term inflammatory bowel disease (IBD) such as UC and Crohn's disease (CD) [2, 3]. Chronic inflammation plays a critical role in human carcinogenesis in some types of solid cancers [4, 5]. Colitis-associated colorectal cancer (CA-CRC) is also believed to occur by a progression from a non-neoplastic inflammatory epithelium to dysplasia to carcinoma [2]. Recent studies elucidate the molecular pathogenesis of CA-CRC, particularly in ulcerative colitis-associated CRC (UC-CRC) [6–8]. CA-CRC shows characteristic genetic changes including nucleotide mutation, chromosomal alteration, and hypermethylation in oncogenes and tumor suppressor genes. Reactive oxygen, nitrogen species, and cytokines involved in inflammatory mucosa might be associated with these genetic alterations as pathogenesis of CA-CRC. Analysis of the correlation between these molecular features and clinicopathologic features in CA-CRC might be useful to develop new biomarkers and drugs for patients with CA-CRC [9, 10]. In this paper, we present an overview of the molecular characteristics in CA-CRC, mainly in UC-CRC.

Clinical Features of Colitis-Associated CRC

An inflammatory environment is believed to play an important role for the pathogenesis of CRC in patients with chronic colitis [2]. UC-CRC accounts for about 1 % of all CRC [11]. The risk of CRC begins to increase 8 or 10 years after the diagnosis of UC [12–14]. UC-CRC patients more

frequently have multiple cancerous lesions and histologically show permeating pattern of spread including mucinous or signet ring cell carcinomas [15–17]. Risk factors for CRC with UC patients include young age at diagnosis [12, 18], longer duration [19], greater anatomic extent of colonic involvement [20], the degree of inflammation [21–23], family history of CRC [24, 25], and the presence of primary sclerosing cholangitis [26]. Especially, the extent of colitis is an independent risk factor for the development of CRC. UC patients with pancolitis are at highest risk, left-sided colitis carries a moderate risk, and patients with proctitis and protosigmoiditis are at similar risk of CRC without IBD [21–23]. In addition, smoking, pseudopolyps, persisting inflammation of the colon, and backwash ileitis are also risk factor for CRC [27, 28]. Also, the relative risk of CRC in patients with CD was two- to threefold, and that for small bowel carcinoma was ten- to 12-fold [29, 30], while some studies reported that few CD patients developed cancer of the small intestine [31, 32].

Surveillance Colonoscopy

Surveillance colonoscopy is currently the most widely used method to detect dysplasia and cancer in patients with IBD [28, 33–37]. Current guidelines from the British Society of Gastroenterology (BSG) [36, 38–41], European Crohn's and Colitis Organization (ECCO) [42], and the American Gastroenterology Association (AGA) [43] recommend colonoscopic surveillance every 1–5 years at the beginning of 8–10 years after symptom onset for IBD-colitis patients. The main aim of surveillance programs is to detect early dysplastic alterations because cancer surveillance is based on the high-risk factors that identify patients who are likely to develop cancer. The recommended guidelines of colonoscopy are as follows [36, 39–41]: (a) Screening colonoscopy should be performed when the disease is in remission. (b) Initial surveillance colonoscopy should be performed in each patient beginning 8–10 years after symptom onset, partly to reassess disease extent. (c) Regular surveillance should begin on an annual or biannual basis beginning 8–10 years of disease for patients with left-sided or extensive colitis after symptom onset. (d) Two to four random biopsy specimens should be taken every 10 cm from the entire colon, with additional samples of suspicious areas. Particularly in UC, consideration should be given to taking 4-quadrant biopsies every 5 cm in the lower sigmoid and rectum, because the frequency of CRC is higher in this region. (e) If dysplasia (of any grade) is detected, the biopsies should be reviewed by a second gastrointestinal pathologist, and if confirmed, then colectomy is usually advisable. On the other hand, surveillance of small bowel cancer is not recommended, because of its low risk of small bowel cancer in CD [44].

Molecular Features

Genetic Alterations in Sporadic CRC

It is widely accepted that sporadic CRC result from the sequential accumulation of alterations in genes that regulate the growth of colonic epithelial cells [45, 46]. The multistep carcinogenesis concept resulted from correlative analyses between the neoplastic lesions of the colon (adenomas and carcinomas), and the genetic alterations found in association with each of the steps in the progression [47, 48]. These alterations include activating point mutations of K-*ras* [49, 50] and inactivation of specific tumor suppressor genes (TSGs), most notably the *adenomatous polyposis coli* (*APC*) gene on chromosome 5q21 [51], the *p53* gene on 17p13 [52], and one of several candidate TSGs on chromosome 18q, most likely *deleted in colon cancer* (*DCC*)or *deleted in pancreatic cancer-4* (*DPC4*) gene [53]. Mutational activation of K-*ras* has been found in more than 50 % of adenomas and CRCs [50, 54]. A typical mechanism for the inactivation of TSGs in colorectal neoplasms is the sequential inactivating mutation on one allele, followed by allelic loss, or loss of heterozygosity (LOH), of the other allele [52, 54]. Inactivation of the DNA mismatch repair (MMR) genes *hMSH2* on chromosome 2p or *hMLH1* on 3p leads to the mutator phenotype, which occurs in 10–15 % of CRCs [55, 56] by promoter hypermethylation.

Genetic Alterations in Ulcerative Colitis-Associated CRC and Dysplasia

Many of the molecular changes responsible for sporadic CRC development also play a critical role in the carcinogenesis of UC-CRC. There are similarities of the genetic pathway between sporadic colon cancer and colitis-associated CRC, including MSI, DNA methylation, and mutation and eventual LOH of *p53*. However, distinguishing features of UC-CRC are differences in the timing and frequency of these alterations (Fig. 1). Chromosomal abnormalities are found in non-dysplastic, dysplastic, and cancerous epithelia in the UC-CRC as follows.

K-ras

Most of the studies revealed a lower incidence of K-*ras* mutation in UC-CRC compared with that in sporadic CRC; K-*ras* mutation was detected in approximately 15 % of cases with inflamed mucosa ($n = 100$ [57]; $n = 212$ [58]; $n = 18$ [59]), and in 20–25 % of dysplasias ($n = 14$ [57]; $n = 61$ [58]; $n = 8$ [59]; $n = 13$ [60]) and of carcinomas ($n = 4$ [57]; $n = 5$ [58]; $n = 9$ [60]) in the

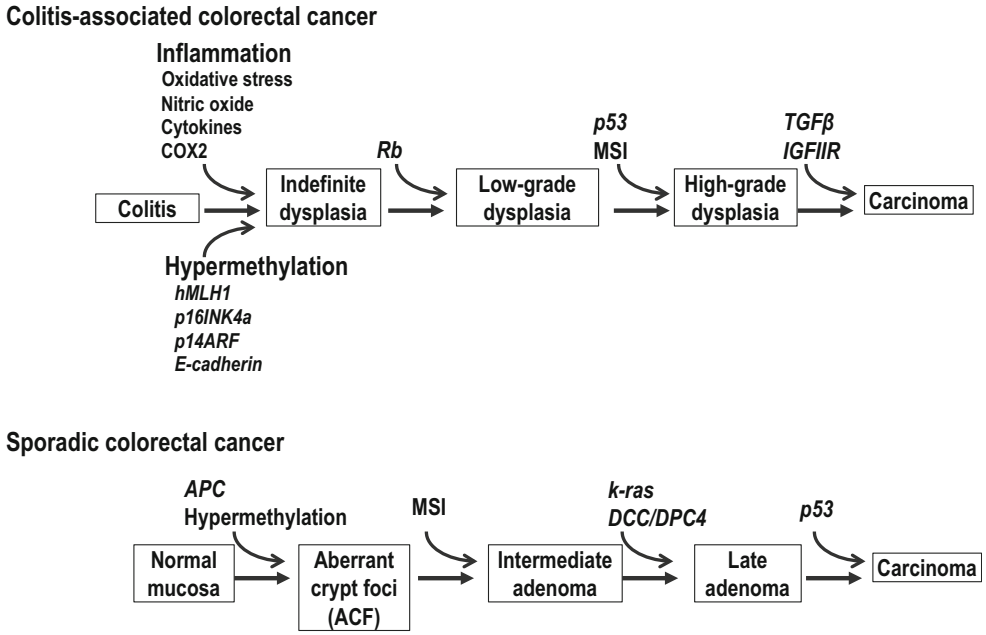

Fig. 1 Molecular alteration of colitis-associated colorectal cancer and sporadic colorectal cancer. Genetic events of MSI, DNA hypermethylation, and p53 are common in malignant degeneration of both colitis-associated colorectal cancer and sporadic colorectal cancer of the genetic pathway between sporadic colon cancer and colitis-associated colorectal cancer. In contrast, frequency and sequence of APC, K-*ras*, and DCC/DPC4 differ between the two types. *ROS* reactive oxygen species, *COX-2* cyclooxygenase-2, *Rb* retinoblastoma gene, *MSI* microsatellite instability, *TGF* transforming growth factor, *APC adenomatous polyposis coli*

IBD. The lower incidence of mutation indicated that K-*ras* does not seem to play a significant role in the development of UC-CRC. In contrast, mutational activation of K-*ras* has been reported to promote exophytic growth of intestinal neoplasms and may favor development of more differentiated intestinal type of intestinal cancer [50, 61]. UC-CRC is often raised only minimally above the level of the surrounding mucosa and grows in a more diffuse fashion than sporadic CRC [62]. Therefore, the infrequent mutational activation of K-*ras* might be associated with the macroscopic flat morphology and the histologic diffuse growth of UC-CRC.

Adenomatous Polyposis Coli (APC)

APC loss of function, considered to be an early event in sporadic CRC, is relatively less frequent and usually occurs as a late event in the colitis-associated dysplasia–carcinoma sequence [63–65]. Mutant APC proteins have been detected in around 3–13 % of UC-associated dysplasia- or carcinoma-bearing patients ($n = 8$ [63, 66]; $n = 30$ [63, 66]), while 26 % of sporadic cancers exhibited *APC* mutation ($n = 42$ [63, 66]). Nearly 30 % of dysplastic lesions and 50 % of cancers exhibited *APC* LOH ($n = 21$ [63, 66, 67]; $n = 6$ [68]). *APC* mutation may play a relatively unimportant role in the development of UC-associated dysplasia.

p53

The percentage of *p53* mutation-containing samples is increasing with the morphological progression to carcinoma. Up to 6 % of normal cases ($n = 14$); 9 % in the category "indefinite for dysplasia," 33 % with low-grade dysplasia ($n = 13$ [60]; $n = 22$ [68]), 63 % with high-grade dysplasia ($n = 12$ [69]), and 50–85 % of cases with cancer ($n = 18$ [70]; $n = 10$ [71]; $n = 9$ [60]) have been found to have a deletion of *p53*. *p53* LOH was also observed in nearly 70 % of CRC ($n = 8$ [68]; $n = 17$ [67]) and 45 % of dysplastic lesions ($n = 33$ [72]; $n = 19$ [68]). *p53* analysis might contribute to the accurate pathological diagnosis of UC-associated dysplasia [72]. Thus, the early appearance of *p53* alteration might make it a clinically useful marker in the screening for UC-associated dysplasia and in the assessment of cancer risk. In contrast to the reported gatekeeper properties of *p53* in sporadic CRC, which in colon adenoma is frequently altered to yield carcinoma [54], p53 might not contribute as a gatekeeper for cancer progression in UC-CRC.

Deleted in Colon Cancer (DCC) or Deleted in Pancreatic Cancer-4 (DPC4)

LOH of 18q, the site of the putative *deleted in colon cancer (DCC)*, was observed in 12 % of eight cancers and 33 % of

30 dysplasia lesions and was not detected in non-dysplastic, inflamed epithelia [73]. *Deleted in pancreatic cancer-4* (*DPC4*)/*SMAD2* at 18q was not detected in 10 case of UC-CRC [74]. LOH of 18q is relatively a rare event and may not be important in UC-associated carcinogenesis.

Retinoblastoma Gene (Rb)

Wild-type *retinoblastoma* gene (*Rb*) suppresses neoplastic phenotypes and is frequently mutated or lost in malignant tumor [75, 76]. *Rb* LOH was found in about 50 % of UC-associated carcinoma or dysplasia ($n = 27$ [67]).

Cyclin-Dependent Kinase Inhibitor p16 (p16INK4a)

The cyclin-dependent kinase inhibitor p16 is a component of the Rb tumor suppressor pathway [77, 78]. LOH studies of the *p16* locus at 9p showed a high rate of *p16* loss in 50 % of dysplasia ($n = 14$) [68], and hypermethylation of the *p16* promoter region is early occurring event during the process of neoplastic progression in UC as described below [79]. Alterations of *p16* may be important early markers of carcinogenic progression in UC patients.

Microsatellite Instability (MSI) and DNA Repair Genes

Inactivation of the DNA MMR system leads to widespread somatic mutations at microsatellite loci. MSI tumors have been found to display microsatellite alterations not only in introns but also in coding exons. Genetic targets of this type of genomic instability include the exons in *transforming growth factor β receptor type II* (*TGFβRII*), *insulin-like growth factor II receptor* (*IGFIIR*), *BAX, hMSH3*, and *hMSH6*, all of which contain mononucleotide repeats in coding sequences [80]. The frequency of MSI in UC-associated neoplasia varies from 2.4 to 50 %, mostly 30 % [81–86]. Fujiwara et al. [81] analyzed the MSI status in fifty-seven patients with UC and found that high-frequent MSI was found in four of 11 cancer cases (36 %); five of 15 dysplasia cases (33 %); five of 11 indefinite cases (45 %); and none of 20 normal cases (0 %). The relatively high frequency of MSI in non-dysplastic, inflamed epithelia, as compared with dysplasia, suggests that MSI may be associated with the pathogenesis of IBD. A frameshift mutation of *TGFβRII* was significantly correlated with worsening histologic glade. High-frequent MSI was significantly associated with *hMLH1* hypermethylation and loss of hMSH2 expression. The carcinogenesis process in UC-CRC was closely associated with the MSI pathway through *TGFβRII* mutation by a dysfunction of the MMR system [81, 82, 87]. In colorectal epithelial cells, TGFβ signal is involved mainly in the suppression of cell proliferation [88]. Microsatellite mutations of the *IGFIIR* gene have also been detected in UC-associated neoplasms with MSI [89]. Genetic or epigenetic alterations of mismatch repair proteins, including *MLH1* promoter hypermethylation and loss of MSH2 expression, may lead to high-frequent MSI in UC-associated lesions [81, 90]. MiR-155 overexpression being particularly associated to MSI in CA-CRC [91].

Aberrant Methylation

It is well recognized that hypermethylation of CpG islands in the gene promoter regions is associated with silencing of the genes in various tumors. The density of CpG methylation increased from morphologically normal epithelia to dysplasia and carcinoma in UC [92]. The methylation of CpG islands can contribute to genomic instability and appears to be exist in the mucosa of patients with IBD carcinogenesis [81, 92]. Hypermethylation may be due to the elevated rate of cell turnover and oxidative stress characteristic of long-standing UC [92]. Promoter hypermethylation and possible silencing of the *p16INK4a* gene occurred in 70 % of UC-CRC and 40 % of dysplasia lesions in UC colectomy specimens ($n = 89$) [79], whereas it was 12.7 % of negative for dysplasia, which suggested that hypermethylation of the *p16INK4a* promoter region is a frequent and early occurring event during the process of neoplastic progression in UC. Methylation of *p16* exon 1 was also found in the regions of normal mucosa in UC patients with dysplasia [92]. Hypermethylation of *p14ARF*, encoding a modulator of p53 protein levels via MDM-2, was also detected in 19 of 38 (50 %) UC-CRC, four of 12 (33 %) dysplasia lesions, and three of the 5 (60 %) non-cancerous, but only three of 40 (3.7 %) non-dysplastic lesions. Promoter hypermethylation leads to the loss of alternate reading frame product of the *CDKN2A* locus (*p14ARF*) [93]. Methylation of *p14ARF* is a relatively common early event in UC-associated carcinogenesis [94]. Hypermethylation is a frequent mechanism of *MLH1* silencing in the subset of UC-associated dysplasias and carcinomas with high-level MSI as described above. *E-cadherin* promoter methylation was detected in about half of UC-CRC, while there was no difference between the UC-CRC and sporadic CRC [95]. Methylation of these genes offers potential as a biomarker for the early detection of cancer or dysplasia in UC. On the other hand, Issa et al. reported that DNA methylation alterations are uncommon in UC-CRC [96]. It will be necessary to clarify the significance of aberrant methylation in the pathogenesis of UC-CRC.

Crohn's Disease-Associated CRC

Mutations in *CARD15/NOD2* gene that activate nuclear factor NF-kB might be associated with the pathogenic mechanism of Crohn's disease [97, 98]. Associations have

also been found between Crohn's disease and SNP in the Toll-like receptor 4 [99] or interleukin 23 receptor (IL-23R) [100]. In contrast, few studies in the pathogenesis of Crohn's disease-associated CRC are available [101]. K-*ras* and *p53* alterations occur early during inflammatory tumor development, while *APC*, *DCC*, and *TGFβRII* mutations are rare in CD-associated CRC [31, 102].

Dysplasia in UC

Dysplasia arising on the grounds of UC may precede the development of carcinoma [62]. Classification of polypoid mucosa of UC is important with respect to clinical treatment for dysplasia. The dysplasia found in IBD is categorized as follows: low-grade dysplasia (LGD), high-grade dysplasia (HGD), dysplasia-associated lesion or mass (DALM), adenoma-like mass (ALM), and adenoma-like DALM. UC with HGD usually leads to a total colectomy because of the high incidence of adenocarcinoma [41, 103, 104]. When HGD in flat mucosa was the initial discovery, surgery or polypectomy is done [41]. In contrast, the management of LGD is controversial [105]. There is evidence that an unrecognized synchronous CRC may already be present in up to 20 % of individuals who undergo colectomy for LGD [8, 103]. In contrast, some studies have shown that patients with LGD have a lower rate of CRC than previously thought [106]. Dysplasia found in DALM is believed to be the origin CRC [107, 108]. DALM has been reported to be associated with CRC in up to 46 % of CD specimens and 62.1 % of UC specimens, supporting the requirement for surgical resection [109, 110]. In contrast, ALM, a lesion found in an area without inflammation, is tend to be treated by standard polypectomy. A strong correlation between p53 mutations and the histologic progression from LGD to invasive carcinoma in patients with IBD has been shown [111]. DALM or areas without any macroscopically visible mucosal alteration are considered to be the origin CRC [107, 108]. Mutations of *p53* occur more frequently in DALM. *Rb* LOH was detected in 25 % of UC patients with DALM, or dysplasia [67]. The guidelines for surveillance colonoscopy also state that particular attention should be paid to DALM [37], because the occurrence of DALM is frequently associated with synchronic or metachronic CRC. Therefore, patients with DALM are recommended to undergo prophylactic proctocolectomy with ileoanal pouch. Recently, raised dysplastic lesions or DALMs with the appearance of sporadic adenomas have been termed adenoma-like DALM. UC-associated non-adenoma-like DALMs have a different molecular genotype than UC-related adenoma-like DALMs and non-CRC sporadic adenomas [112]. Serrated adenomas are polypoid lesions present in the colon that are characterized by saw-toothed or serrated crypts with dysplasia, and the serrated neoplasia pathway was recently proposed in CRC [61]. Bossard et al. [113] found that serrated lesions, such as hyperplastic polyps and sessile serrated polyps/adenomas, accounted for approximately 7 % of premalignant lesions in the inflamed mucosa in patients with IBD. The serrated lesions contained BRAF mutations. It has been reported that LOH of *APC*, chromosome 3 (chromosome 3p), *p53* locus, and K-*ras* mutations were present in 0 % (0/11), 20 % (2/10), 0 % (0/11), and 37 % (4/11) of sporadic hyperplastic polyps [61]. In contrast, Odze et al. [114] reported that LOH of *APC*, chromosome 3p, *p53*, and K-*ras* mutations were present in 21, 40, 27, and 19 % of UC-associated hyperplastic polyps. UC-associated hyperplastic polyps are more likely to have an LOH event on at APC *and p53* locus, compared with sporadic hyperplastic polyps. Hyperplastic polyps are generally regarded as non-neoplastic lesions; however, UC-associated hyperplastic may evolve through a different genetic pathway than sporadic hyperplastic polyps.

The Interactions Between Environmental Component and Molecular Alterations in the Inflammatory Bowel Disease

IBD and cancer are complex disease processes driven by multiple interacting genes in concert with environmental influences [115]. A gene–environment interaction might contribute to the progressive process of cancer with genetic and epigenetic dysfunction in multiple systems including DNA repair and immune functions [116]. The etiopathology of IBD might be also associated with the gene × environment interactions [117–119]. Some of environmental factors, including inflammation, lifestyle, psychological stress, and prior appendectomy, have been suggested to be associated with IBD [120, 121]. Mucosal inflammatory mediators such as oxidative stress, nitric oxide, cytokines, receptors on the epithelial cells, COX-2, and luminal microbiota might be mainly responsible for the molecular alterations in the development of CA-CRC.

Inflammation

Oxidative Stress

One of major mechanisms, which link inflammation to proneoplastic genetic alterations, is oxidative stress [122–124]. IBD has been considered to be an "oxyradical overload" disease, in which chronic inflammation increases the risk of cancer [125]. Oxidative stress is mainly produced by inflammatory immune cells such as macrophages and granulocytes and includes the generation of various reactive oxygen and nitrogen species such as reactive oxygen species (ROS) and nitric oxide synthase (NOS) that pose a constant mutational challenge for the

intestinal epithelium [126]. This results in DNA breaks, DNA adducts, and damage to cellular lipids and proteins [126]. Oxidative stress secondary to chronic inflammation also plays a pivotal role in IBD-associated colorectal carcinogenesis [124, 125, 127]. ROS, reactive nitrogen free radicals, releases a cascade of inflammatory mediators such as inflammatory cytokines including interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNFα), and interferon-γ (IFN-γ) [8, 128, 129]. These cytokines bind DNA, RNA, proteins, or lipid [130], supposed to cause gene alterations, genetic instability, and aberrant methylation. Telomere damage [131, 132] in UC has been linked with the development of dysplasia [133, 134]. Lipid peroxidation occurs when ROS and NOS interact with cell membranes, causing DNA adducts leading to transition mutations [135] and frequently involving the p53 TSG [136]. In addition, these free radicals inhibit DNA repair proteins and are believed to be initiators of MSI [137]. The oxidative stress also increases the mutation of mitochondrial DNA and possibly correlates with the pathogenesis of UC-CRC [138]. The therapeutic effects of 5-aminosalicylic acid (5-ASA) have been attributed to antioxidant, iron-chelating, and radical scavenging effects [28, 139–144].

Nitric Oxide (NO)

Serum nitrite levels, a measure of NOS activity, are increased in active UC and CD patients and correlate with their disease activity [145–147]. NOS is induced in the inflamed human colonic epithelium and is associated with the formation of peroxynitrite and the nitration of cellular proteins [148]. High activity of the inducible NOS contributes to early onset IBD, which may contribute to colon carcinogenesis [149]. It has been suggested that ursodesoxycholic acid acts antioxidative and thereby reduces mutational stress by NOS [150, 151], and NO level suggested to be a useful biomarker of treatment response in IBD [152].

Cytokines

The chronic inflammatory changes in IBD are associated with increased levels of inflammatory cytokines from immune cells. It is now becoming clear that cytokines and growth factors released during inflammation may influence the carcinogenesis process [153]. IL-6 and IL-23, which play significant roles in the induction and maintenance of gut inflammation in IBD, have been recently shown to influence the development and growth of CA-CRC [153–157]. Also, cytokines activate receptors on intestinal epithelial cells that activate oncogenic transcription factors such as nuclear factor-kappaB (NF-κB) and Stat3 in the development of UC-CRC [156, 158]. TNFα increased gene mutations, gene amplification, micronuclei formation, and chromosomal instability [159], and a close relationship between the polymorphism of TNFα-308 G>A and the gene instability in UC-CRC [160]. NF-κB regulates the expression of various cytokines, modulates the inflammatory processes in IBD [161], and controls apoptosis, cell cycle progression and proliferation, and cell differentiation [162, 163]. NFκB is activated not only in sites of inflammation, but also in many solid tumors [164]. 5-ASA, the NFκB pathway inhibitor, is the first line agent for anti-inflammatory therapy [142, 144]. Toll-like receptors (TLR) play an important role in the interaction between the intestinal microflora and the mucosal immune defense via NFκB activation [165]. The potential association between TLR4 and chitinase 3-like 1 signaling has been reported, which seems to contribute to the proliferation, migration, and neoplastic progression of colonic epithelial cells under inflammatory conditions [166, 167].

Cyclooxygenase-2 (COX-2)

COX-2 is only induced by inflammation. COX-2 is triggered by inflammatory stimuli such as IL-1, IFN-γ, and TNFα and develops neoplastic changes [168–170]. Overexpression of COX-2 in epithelial, mesenchymal, and inflammatory cells results in the production of prostaglandins (PGs). PGE2 induced by COX-2 transactivates PPARδ through β-catenin and P13K/Akt signaling, which promotes cell survival and tumor growth [171]. PPARδ acts as a focal point of crosstalk between the PGs and Wnt/β-catenin pathways, which results in a shift from cell death to cell survival and consequently increased tumor growth [171]. Wnt/β-catenin signalings with downstream events including c-Myc and Cyclin-D1 represent the connection between IBD and increased risk of developing CRC [172]. Selective COX-2 inhibitor and PGE2 receptor inhibitor exert the cancer chemopreventive effects through the suppression of cell proliferation [173, 174].

Luminal Microbiota

Many studies have found a link between alterations in the commensal bacteria of the gut, termed the microbiota, and the pathogeneses of IBD [120, 175, 176]. Diet, such as Western diet and vegetarianism, and genetic factors might influence the changes in the microbiota composition [177]. The intestinal microbiota makes a significant contribution to the development of not only colitis, but also neoplasia by production of toxic and genotoxic bacterial [125]. Mice colonized with enterotoxigenic *B. Fragilis* exhibit colonic Th17 inflammatory infiltrates that are involved in induction of colon tumors by activating Stat3 [178]. Dysbiosis of gut microflora may also cause alterations in the immune response and increase risk of cancer [179, 180]. Ghadimi et al. [181] described that the commensal bacteria inhibited

the production of the IBD-causing cytokines, IL-17 and IL-23, thereby reducing histone acetylation and enhanced DNA methylation, suggesting that an imbalanced intestinal microbiota might be associated with the increased risk of CRC development in IBD. The microbiota might regulate the expression of heat shock protein (Hsp) that is associated with the immune system by folding, refolding, translocation, and degradation of intracellular proteins under normal and stress conditions. Studies conducted on patients affected by IBD showed a decrease in Hsp60, Hsp10, and Hsp70 in epithelium and lamina propria after a combined therapy of 5ASA [182].

Lifestyle Factors

The epigenetic changes are influenced by lifestyle factors, such as diet, smoking, and physical inactivity [183]. These factors might drive changes in gene expression and increase cancer risk. Poullis et al. [184] found a significant positive relationship between risk factors for CRC and increasing age, obesity, and physical inactivity, and an inverse relationship with fiber intake and vegetable consumption. Huxley et al. reported that the risk of CRC based on 103 cohort studies was significantly associated with alcohol, smoking, diabetes, obesity and high meat intakes, and physical activity.

Dietary

Amre et al. [185] hypothesized that interactions between dietary substrates (fats, vegetables, and fruits) and DNA variants in the xenobiotic metabolizing enzymes would modify risk of IBD. Slattery et al. suggest that diet may be involved in disease pathways represented by p53 loss [186], Ki-ras mutations [187], and MSI [188]. Some studies suggest that vitamin D is associated with IBD [189, 190]. Vegetable consumption has long been hypothesized to be protective against CRC. Hutter et al. [191] reported that vegetable consumption is closely associated with CRC by a gene–environment interaction across studies. A meta-analysis reported that vegetable consumption of fruit and vegetable intake showed a significant inverse association with CRC risk [192]. Chen et al. reported that high intake of red and processed meat is associated with significant increased risk of CRC [193]. In contrast, several studies have failed to find a relationship [194, 195]. The ability of fruits and vegetables confers clearly that the ROS might be responsible for the mechanism [196]. Slattery et al. [197] suggest that alcohol contributes to rectal cancer risk.

Smoking

Smoking habit is an important environmental factor in UC [176, 198, 199]. Wang et al. examined the predictive value of combining the 133 UC risk loci with genetic interactions using genome-wide association studies and identified interactions between genes (HLA-DQA1, CALM3, TRIB1, and IL-2/IL-21) and smoking in the discovery cohort [119], while the exact mechanisms by which smoking influences the development of IBD are unknown. Slattery et al. suggest that smoking statistically significantly contributes to MSI in colon tumors [200] and that significant interactions were observed between MLH1 polymorphisms and smoking [201].

Psychological Stress

Psychosocial stress increases the likelihood of developing IBD and multiple types of malignant neoplasms [202]. Peters et al. suggested that chronic psychosocial stress increases the risk of inflammation-related CRC using azoxymethane/dextran sodium sulfate CRC mouse model, and colonic liver receptor homolog-1, COX-2, tumor necrosis factor, forkhead box P3 mRNA as well as colonic ß-catenin were also increased in CSC [203]. Acute psychologic stress induces systemic and mucosal proinflammatory responses, which could contribute to exacerbations of UC [204]. The effects of stress on inflammation in IBD are likely to be mediated through changes in hypothalamic–pituitary–adrenal function, alterations in bacterial-mucosal floral interactions, activation of mucosal mast cells, and peripheral release of corticotrophin releasing factor [202]. Soderholm et al. [205] reported that chronic psychological stress can be an initiating factor in intestinal inflammation by impairing mucosal defenses against luminal bacteria and highlight the importance of mast cells in this process. In contrast, Timmer et al. [206] reported that there was no evidence for efficacy of psychological therapy in adult patients with IBD in general.

Appendectomy

Prior appendectomy for appendicitis has been linked to a lower risk of UC [207], particularly among children experiencing appendicitis before 20 years of age [208, 209], while the effect of appendectomy on UC disease course remains inconclusive [210]. The appendix may act as a reservoir of enteric bacteria and may be involved in antigen sampling that regulates the immunologic response to host microflora [209]. Andersson et al. [211] suggest that appendicitis is mediated by T-helper 1 cells, which may explain the inverse associations between appendicitis and UC.

Future Perspectives

To clarify the pathogenesis of CRC in IBD, the resolution of complex gene–environmental interactions might be important.

New Biomarkers

Biomarkers for early detection of CRC in IBD are desired. Analysis of the correlation between these genetic features and clinicopathologic features might be useful to determine new biomarkers that can help in the early detection and predictive values of CRC in patients with IBD. The combination of the endoscopic and molecular screening approaches may be useful tools for the surveillance of patients with IBD.

Chemoprevention

The inflammatory stresses, such as ROS and some free radicals, have been considered to cause genetic damages to UC epithelium. The control of long-term inflammation and mucosal damage over time might be a potentially important strategy for reducing CRC risk in UC patients. Development of a new anti-inflammatory reagent might be useful to prevent and treat UC-CRC. Further clinical studies would be needed to develop useful drugs and validate potential modalities for the prevention of UC-associated carcinogenesis.

Crohn's Disease

Genetic alteration of CRC with CD remains unclear in comparison with that of UC. Further studies are needed to evaluate similarities and differences in genetic alterations of UC-CRC and CD-associated neoplasia.

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Conflict of interest None.

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