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TOPIC HIGHLIGHT

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Inflammatory colonic carcinogenesis: A review on pathogenesis and immunosurveillance mechanisms in ulcerative colitis

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Abstract

Ulcerative colitis (UC) is characterized by repeated flare-ups of inflammation that can lead to oncogenic insults to the colonic epithelial. UC-associated carcinogenesis presents a different sequence of tumorigenic events compared to those that contribute to the development of sporadic colorectal cancer. In fact, in UC, the early events are represented by oxidative DNA damage and DNA methylation that can produce an inhibition of oncosuppressor genes, mutation of p53, aneuploidy, and microsatellite instability. Hypermethylation of tumor suppressor and DNA mismatch repair gene promoter regions is an epigenetic mechanism of gene silencing that contribute to tumorigenesis and may represent the first step in inflammatory carcinogenesis. Moreover, p*53* is frequently mutated in the early stages of UC-associated cancer. Aneuploidy is an independent risk factor for forthcoming carcinogenesis in UC. Epithelial cell-T-cell cross-talk mediated by CD80 is a key factor in controlling the progression from low to high grade dysplasia in UC-associated carcinogenesis.

Key words: Colorectal cancer; Ulcerative colitis; Carcinogenesis; Immune surveillance

Core tip: The ulcerative colitis (UC)-associated carcinogenesis presents a different sequence of tumorigenic events compared to those that contribute to the development of sporadic colorectal cancer. In fact, in UC, early events are represented by oxidative DNA damage and DNA methylation that can produce inhibition of oncosuppressor genes, mutation of p53, aneuploidy, and microsatellite instability. Epithelial cell-T-cell cross-talk mediated by CD80 is a key factor in controlling the progression from low to high grade dysplasia in UC-associated carcinogenesis.

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INTRODUCTION

Ulcerative colitis (UC) is historically known as a risk factor for developing intestinal cancers *via* mechanisms that remain incompletely understood. In a recent meta-analy-

sis of population-based cohorts, UC increases the risk of colorectal cancer (CRC) 2.4-fold. Male sex, UC diagnosis at young age, and extensive colitis also increase this risk[1]. In European collaborative studies, northern countries were observed to have more inflammatory bowel disease (IBD)-related intestinal cancers than southern ones[2]. The cumulative risk of colon cancer is approximately 8% 20 years after the initial UC diagnosis, rising to 18% at 30 years[3,4]. Adenocarcinoma of the colon develops from a dysplastic precursor lesion. In UC patients, pre-malignant histological changes are broadly referred to as dysplasia rather than adenoma, since the dysplasia is very often not polypoid[5]. Even though recent studies reported that at least 25% of UC patients may be diagnosed with low grade dysplasia in a 10 year follow-up period, some studies, such as the one by Lim *et al*[6] and Lynch *et al*[7] in 1993, suggested that low grade dysplasia will develop in all UC patients if they are followed for an adequate length of time. Nevertheless, very recent epidemiological data seems to make uncertain these classical pillars in IBD-associated cancer knowledge. In fact, very recent Dutch data pointed out that a high proportion of IBD-associated CRCs develop before the recommended start of surveillance[8,9]. Moreover, an authoritative Danish study concluded that a diagnosis of UC or CD no longer seems to increase patients' risk of CRC, although subgroups of patients with UC remain at an increased risk[10]. The decreasing risk for CRC from 1979 to 2008 might result from the improved therapies for IBD patients that have developed over that time[10].

In recent years, a causal link between chronic inflammation and gastrointestinal tract carcinogenesis has gained increasingly strong support[11,12]. In a recent Finnish study, the degree of inflammation and duration of disease were observed to cumulatively increase the risk for dysplasia and CRC in IBD patients[13]. A chronic inflammatory condition exposes IBD patients to a number of signals with potential tumorigenic effects. These signals include persistent activation of the nuclear factor-kappa B (NF-κB) and cyclooxygenase-2 (COX2) pathways, release of proinflammatory mediators such as tumor necrosis factor-alpha (TNFα) and interleukin-6 (IL-6), and augmented levels of reactive oxygen and nitrogen species. An inflammatory microenvironment can contribute to colonic tumorigenesis *via* 3 major processes: (1) increasing oxidative stress, which causes direct DNA damage that contributes to tumor initiation; (2) activating prosurvival and anti-apoptotic pathways in epithelial cells that contribute to tumor promotion; and (3) creating a microenvironment that promotes sustained growth, neoangiogenesis, migration, and invasion of tumor cells, thus supporting tumor local progression and distant metastasis[14]. Precancerous lesions and invasive carcinoma in UC differ from sporadic ones in terms of a younger age at onset and flat mucosa within large fields of genetic abnormalities, rather than as isolated and visible exophytic lesions[15-17]. However, many of the genetic abnormalities observed in sporadic adenoma and carcinoma, including alterations in adenomatous polyposis coli (*APC*), *p53*, *bcl-2*, and *K-ras* genes, microsatellite instability, and aneuploidy, are also observed in UC-related neoplasms, albeit with a different frequency and timing in many cases[18-26].

This is a comprehensive overview of the available literature on pathogenesis and immunosurveillance mechanisms in inflammatory colonic carcinogenesis. A text word literature review was performed using PubMed and Medline databases. Although this was not a systematic review, the search terms used were as follows: colorectal AND cancer OR carcinoma AND UC OR IBD OR AND pathogenesis OR immune surveillance. The reference lists of identified articles were searched for further relevant publications. Two researchers (Scarpa M and Pozza A) independently selected the studies, which were limited to clinical studies published between January 1980 to July 2013 and in the English language. Unpublished data and data published in abstract form only were excluded, as these were unlikely to contain sufficient methodological information to allow valid conclusions to be made. Whenever discordance regarding study inclusion existed, the two researchers negotiated an agreement.

HOW IT STARTS: DNA DAMAGE AND GENOMIC INSTABILITY

Definition

Genomic instability includes microsatellite instability (MSI) associated with mutant phenotypes and chromosome instability (CIN) characterized by gross chromosomal abnormalities[27]. Three fundamental intracellular mechanisms are involved in the repairing of DNA damage: nucleotide excision repair (NER), base excision repair, and mismatch repair (MMR). Their alteration/inactivation can lead to MSI. On the other hand, CIN is typically associated with the progressive accumulation of mutations in oncosuppressor genes and oncogenes[16]. Defects in DNA MMR genes and CIN pathways are responsible for a variety of hereditary cancer predisposition syndromes, including hereditary non-polyposis colorectal carcinoma, Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia[27]. Furthermore, besides the many genetic contributors to CIN and MSI, there are also epigenetic factors that can be equally damaging to cell-cycle control. Hypermethylation of oncosuppressor and DNA MMR gene promoter regions is an epigenetic mechanism of gene silencing involved in colorectal carcinogenesis. Finally, telomere shortening has been demonstrated to increase genetic instability and tumor formation in mice models[27].

Role of genomic instability

In UC, colonocytes are subject to high levels of genetic damage. In fact, chronic inflammation of the colon can contribute to carcinogenesis by increasing oxidative stress which promotes DNA damage, thus contributing to tumor initiation. Oxidative DNA damage is more evident

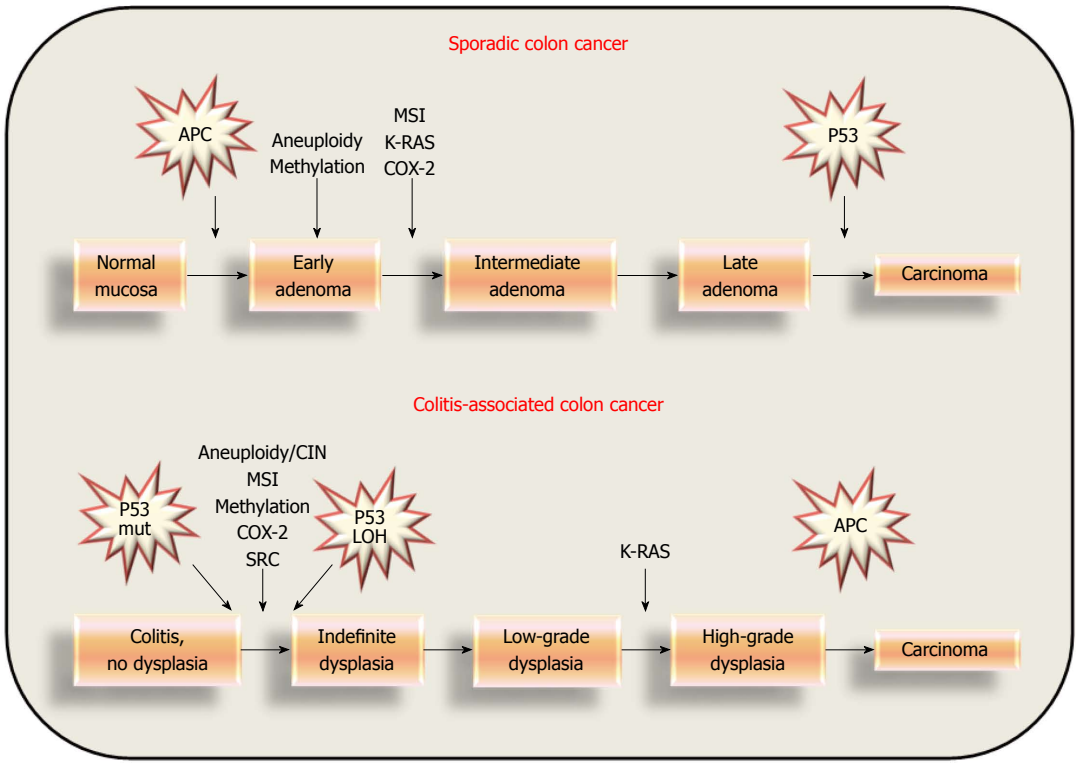

Figure 1 Timing of mutation occurrence in inflammatory and sporadic colorectal carcinogenesis. LOH: Loss of heterozygosis; MSI: Microsatellite instability; COX-2: Cyclooxygenase-2; APC: Antigen-presenting cell.

in patients with UC and dysplasia[28,29]. Furthermore, the severity of colitis inflammation has been associated with high levels of reactive oxygen species (ROS) and reduced defenses to oxidative stress. Both of these mechanisms might contribute to oxidative DNA damage[25,30-36]. ROS induce genetic damage either as base alterations, "abasic" sites, or as strand breaks, and each of these damage types could cause genomic instability. Therefore, an interesting hypothesis is that in a subgroup of UC patients who could be defined as "progressors", the mucosal epithelium is damaged by ROS, producing genomic instability and eventually carcinogenesis initiation and progression. This hypothesis is supported by the observation of chromosomal instability and MSI in the non-dysplastic mucosa of UC patients with dysplasia and cancer[25,37,38]. Genomic instability occurs with the same frequency (10%) throughout the whole neoplastic progression in UC. Therefore, genomic instability does not accumulate as the neoplasia progresses, but rather occurs very early and persists at a steady level. The constant presence of instability may be linked to the maximal tolerated degree of genetic damage and the dynamic rate of cell turnover in the inflamed colon.

Genomic instability rate in the colonic mucosa without dysplasia from patients with UC and dysplasia is significantly higher than that of UC patients who are completely dysplasia/cancer-free. On the other hand, in normal mucosa from patients with sporadic colon cancers and adenomas, genomic instability is not observed[39]. On the contrary, in patients with widespread UC, genomic instability precedes neoplastic transformation, and may be related to the extension of chronic inflammation. These observations suggest once again the peculiarity of the pathogenesis of UC CRC, and can in part explain the difference from sporadic cancers: in fact, UC neoplasia is frequently multifocal, widespread, and may occur in flat mucosa. The differences in UC-related and sporadic colorectal carcinogenesis is shown in Figure 1.

On the other hand, non-progressor patients may be exposed to a lower oxidative stress in their colon than progressors, or may present a lower susceptibility for genomic instability after oxidative stress because of better protective mechanisms. For example, glutathione and glutathione S-transferase levels vary among UC patients and may influence ROS levels[40]. Nevertheless, a small amount of heterogeneity was also observed in the non-progressor group: 20% of patients demonstrated increased genomic instability in the colon without any trace of dysplasia or cancer at the optimized combination of sensitivity and specificity. Curiously enough, the genomic instability rate approximates the percentage of patients with no dysplasia or cancer that one might expect to develop a cancer in the following 20 to 30 years[41]. Nevertheless, the question as to why some UC patients have a mutator phenotype, while others do not, still remains open[42].

Role of MSI

UC-related colonic carcinogenesis can also be associated with MSI. In fact, it was demonstrated that MSI can be

caused by ROS[43]. Microsatellites are short repetitive sequences (1- to 5-nucleotide) of DNA that are randomly distributed throughout the whole genome. The stability of these sequences is a good measure of the general integrity of the genome. MSI reflects a gain or loss of repeat units in a germline microsatellite allele, suggesting the clonal expansion that is typical of a cancer. A high rate of MSI in severe long standing UC is probably related to the genomic instability produced by repeated inflammatory insults. Therefore, the influence of inflammation should be considered when estimating MSI in UC[44]. Indeed, although the great number of molecular mechanisms involved in the increased risk of CRC in UC is still unclear, it appears to be related to MSI[25,45]. The prevailing hypothesis is that overproduction of free radicals saturates the ability of the cell to repair oxidative DNA damage prior to replication[25,46]. Another hypothesis is that prolonged and repeated oxidative insults directly inactivate DNA MMR genes[47]. One study reported half of UC mucosal samples with high MSI as having MLH1 hypermethylation[48]. However, differently from what is observed in hereditary non-polyposis colon cancer, other studies found little evidence for MMR defects as a cause of MSI in UC[49,50]. These data suggest the possibility that mechanisms other than MMR defects exist. Recently, adaptive increased activity of 3-methyladenine DNA glycosylase (AAG) and apurinic endonuclease (APE1) in areas of UC colon undergoing active inflammation was observed[51]. Interestingly, this imbalanced increase appeared to be associated with the MSI observed in UC. These data were consistent with a possible novel mechanism by which patients with chronic colonic inflammation acquire MSI. UC patients were demonstrated to have increased AAG and APE1 enzyme activity in epithelial areas of their colon with active inflammation, and those with MSI have the largest increase and imbalance in the levels of AAG and APE1 in inflamed areas of their colons. These observations showed that the adaptive imbalanced increase of these enzymes may have DNA-damaging effects and contribute to carcinogenesis in chronic colonic inflammation[51].

Role of mitochondrial DNA damage

In inflammatory conditions, ROS induce DNA damage[31], and since mitochondrial DNA (mtDNA) lacks histones and related protective systems, mutations accumulate there more than in nuclear DNA[52]. The human mitochondrial genome includes a 16.5-kb circular double-stranded DNA molecule encoding 13 polypeptides of the respiratory chain, 22 transfer RNAs, and 2 ribosomal RNAs necessary for protein synthesis. Since the correct expression of the complete mitochondrial genome is necessary for the maintenance of mitochondrial functions, including electron transport, even small changes in the mtDNA sequence can cause profound functional impairment that enhances generation of free radicals, which in turn increase the extent of DNA mutation. Free radicals can act as initiators and/or promoters that can cause DNA damage, and thus they can activate oncogenes and inactivate oncosuppressors[34,53]. Therefore, oxidative injury to mitochondria in a chronic inflammation situation may contribute to the early stages of carcinogenesis. Human cancers are characterized by mutations of mtDNA[54-56] and, curiously enough, accumulation of mtDNA mutations in cancerous tissue seems to be related to the grading of malignancy. An interesting hypothesis is that genetic instability in the process of carcinogenesis results in the high rate of mtDNA mutation in the colorectal mucosa of individuals with UC, and the increased instability of genes in mtDNA are consistent with the high incidence of CRC in individuals with UC.

Recently, Nishikawa *et al*[54,57] observed that the number of mtDNA mutations in the colonic mucosa in UC patients is significantly higher than that found in other types of malignancies. Moreover, the rate and the timing of genetic mutations underlying sporadic cancer (adenoma-carcinoma sequence) and UC-associated carcinogenesis seem to be different. Although the definite mechanism of these differences is still unknown, increased oxidative stress in the UC colon[58,59] appears to be a major cause of DNA damage[60]. Thus, the high mtDNA mutation rate in the colonic epithelial cells of UC patients is associated with mutation of nuclear DNA in long-lasting inflammation. The observation that the great majority of mtDNA mutations in UC patients were homoplasmic in nature suggests that these mutations had become dominant in their mucosa. Mitochondrial DNA with certain types of mutations are characterized by the generation of abnormal proteins and increased electron leakage from the electron transport chain, and therefore the amounts of endogenously produced free radicals may be increased in these cells. Finally, in tissues with chronic inflammation, the resulting increase in oxidative stress acts to enhance the mutation of either mtDNA or, probably, nuclear DNA, thereby promoting the early stage of tumorigenesis. Given its clonal nature and the large number of mtDNA copies, mutation of the mitochondrial genome in the colonic mucosa of UC patients is suggestive of genomic instability that enhances carcinogenesis. The high incidence of mtDNA mutation in the colonic mucosa of subjects with UC indicates that the DNA mutation rate is enhanced in their epithelial cells by the oxidative stress produced by chronic inflammation and, hence, malignant transformation can occur more easily than in normal subjects[57].

Role of epigenetic mutations

Finally, DNA hypermethylation may play a role in UC carcinogenesis. Altered genomic methylation is a well-recognized characteristic of tumor cells, and specific aberrant methylation events occur in the early steps of colorectal carcinogenesis, leading to profound modifications in gene expression[61]. In fact, the aberrant methylation of H-cadherin (CDH13) beginning at an early stage of colorectal tumorigenesis frequently silences the expression of this tumor suppressor gene in colorectal ad-

enomas and cancers[62]. Moreover, besides germ-line mutations associated with hereditary familial adenomatous polyposis and somatic mutations in sporadic colorectal tumors, hypermethylation provides an important mechanism for impairing APC function[63]. Furthermore, hypermethylation of the CpG island in the cellular DNA-repair protein O-6-methylguanine-DNA-methyltransferase (MGMT) gene[64] and in the MLH1 gene is associated with the reduced gene expression observed in the majority of sporadic primary CRCs with MSI[65]. Finally, in gastrointestinal cancer RUNX3 hypermethylation decreases transforming growth factor-β (TGF-β)/BMP signaling[66]. In our series, the methylation of these genes occurred in more than half of the patients (data not yet published). Garrity-Park *et al*[67] evaluated the methylation status of 10 genes [p16, p14, runt-related transcript factor-3 (RUNX3), COX-2, E-cadherin, methylated-in-tumor-1 (MINT1), MINT31, HPP1, estrogen receptor, and SLC5A8] in mucosal samples from UC-CRC tumors and non-neoplastic colonic tissue from both UC-CRC cases and UC controls. Methylated promoters of RUNX3, MINT1, and COX-2 resulted in potential biomarkers of the presence of CRC in patients with UC, and so these genes might also be used as biomarkers for colorectal dysplasia.

Furthermore, in UC-associated carcinogenesis, hypermethylation of the promoter of Death-Associated Protein Kinase (DAPK) was observed in long-standing UC patients[68]. DAPK is a pro-apoptotic protein implied in various apoptotic cascades. Kuester *et al*[68] observed that DAPK is overexpressed in inflamed colonic epithelium, suggesting a protective role of this molecule. Therefore, its inactivation mediated by promoter hypermethylation might be critical for the accumulation of epithelial cells with genomic damage in inflamed epithelium of UC, and might contribute to the initiation of the neoplastic process and development of UC-associated carcinoma. Increased expression of DNA methyltransferase (DNMT)-1 in non-neoplastic mucosa may either precede or be a relatively early event in UC-related carcinogenesis, and may be useful to predict the risk of colorectal neoplasia in UC[69]. In fact, in our series of UC patients DNMT1, DNMT3a, and DNMT3b, mRNA expression resulted in being significantly higher than in patients without an inflammatory condition (data not yet published).

Role of aneuploidy

Aneuploidy is an independent risk factor for tumorigenesis in UC. A less favorable prognosis in patients with UC-related CRC compared with those with sporadic CRC has been reported. UC-related neoplasms presented a significantly higher rate of aneuploidy than sporadic CRC. UC-related CRC and aneuploid sporadic CRC have a similarly lower than that of diploid sporadic CRC. Aneuploidy resulted in being the strongest independent prognostic marker for R0-resected CRC patients[70].

HOW IT GROWS: ONCOGENE INVOLVEMENT IN INFLAMMATORY COLONIC CARCINOGENESIS

UC-associated cancer vs sporadic cancer

Preneoplastic lesions and invasive cancers associated with UC usually develop as multiple and superficially extended lesions called DALMs (dysplasia-associated lesion or mass)[71-74]. DALMs are frequent in the most inflamed colonic areas. Thus, a chronic inflammation - dysplasia - carcinoma sequence has been suggested[75]. Comparisons of the molecular alteration profiles between sporadic and UC-associated CRCs have shown clear differences. The timing and frequency of the gene alterations in UC-related cancers appear to be unique. Mutations of *APC* and of *K-ras* genes are less frequent[76,77] in UC-related cancer than sporadic ones. LOH at the *APC* loci in UC was noted in dysplasia with associated carcinoma, but LOH of *APC* was not present either in cases of non-dysplastic epithelium or in high grade dysplasia alone. Conversely, LOH of APC is present in 20% of colonic adenomas[78,79]. In contrast, *p53* is frequently mutated at the early stages of UC-related carcinogenesis; 33%-67% in dysplasia and 83%-95% in UC-related cancer[20,80]. Moreover, loss of heterozygosity (LOH) of the *p53* gene and *src* activation occur in UC non-dysplastic epithelium, UC-associated dysplasia, and in UC-associated carcinoma, whereas there is an absence of LOH of *p53* in regions with negative, indefinite, or low grade dysplastic histology[81]. Mutations in the *ras* proto-oncogene are present in 40%-60% of sporadic colon cancers and are probably an early event; in contrast, these mutations are less frequently seen in UC-related cancer, and are probably a late event[22,82,83]. Finally, network analysis discovered that *Sp1* and *c-myc* proteins may play roles in UC in the early and late stages of carcinogenesis, respectively. Two over-expressed proteins in the non-dysplastic tissue of UC progressors, CPS1 and S100P, were further confirmed by IHC analysis[84]. Finally, telomerase and ILK activation occurs during the later stages of carcinoma progression, whereas upregulation of survivin, c-MYB, and Tcf-4 is a feature of the early stage development of neoplasia, and thus they might serve as early indicators for UC-associated colorectal carcinogenesis[85]. These distinctive molecular patterns seem to result from different aetiological factors and microenvironments that characterize the adenoma-carcinoma sequence or UC-associated carcinogenesis[75].

Role of apoptosis related genes

Recently, van der Woude *et al*[86] observed that *Bcl-xl* was not expressed in chronic UC, but was clearly present in UC-related cancer tumor cells. Furthermore, they found interesting differences in the expression of *Fas* and *Bcl-xl* between UC-related cancer and sporadic carcinoma. *Fas*

Table 1 Altered genes in ulcerative colitis-associated carcinogenesis

Gene	Function	Ref.
Mutation/overexpression		
Apc	Wnt signaling pathway inhibition	23,80,81,88,89
Bcl-xl	Apoptosis suppression	90
Ptgs2	Inflammation promotion and apoptosis inhibition	26
iNos	Apoptosis inhibition through NO production	90
Kras	Cell survival promotion and apoptosis suppression	22,80,81,84-86
Tp53	Cell-cycle regulation	20,82,83,87
Tnfrsf6	Apoptosis promotion	90
Smad3	Wnt signaling pathway component	121
Aberrant methylation		
p16	Cell-cycle regulation	71
Mlh1	DNA mismatch repair	69
Runx3	Transcription factor	71
Dapk	Induction of cell death	72

expression was strong in most UC-related dysplasia and tumor cells, whereas it was weak in sporadic carcinoma tumor cells. Moreover, *Bcl-xl* expression was important in chronic UC tumor cells, but was only weak in sporadic colon cancer cells[86]. However, the different expression patterns of proapoptotic and anti-apoptotic proteins did not result in actual differences in apoptosis[85]. Activated *caspase 3* staining, used as a marker of apoptosis, was weakly represented in both chronic UC-associated colon cancer and sporadic colon cancer, and may be the result of the decreased apoptosis rate in the presence of increased cell proliferation[86].

The inflammation process leads to the activation of the transcription factor NF-κB, which stimulates the expression of many genes promoting cell survival, including anti-apoptotic genes[12,85,87]. NF-κB regulation of inducible nitric oxide synthase (iNOS) and COX-2 in the gastritis-metaplasia-gastric cancer sequence and in the metaplasia-dysplasia-adenocarcinoma sequence in Barrett's esophagus have been extensively assessed[88]. Nitric oxide, produced by iNOS, was demonstrated to inhibit apoptosis by downregulating caspase activity[89]. In a paper by Watson *et al*[90], increased expression of iNOS in UC-associated dysplasia was described, whereas iNOS expression was absent in UC-associated carcinoma.

COX-2 is an inducible cyclooxygenase whose production is stimulated by IL-1, TNF, and many other inflammatory mediators[90,91]. COX-2 was demonstrated to play a role in the reparative process after mucosal injury in the gastrointestinal tract[90,91]. Multiple studies reported COX-2 overexpression (either protein or mRNA levels) in colonic adenomas and carcinomas, suggesting that this enzyme is definitely involved in sporadic colorectal carcinogenesis[92-94]. In a study by Agoff *et al*[26], COX-2 expression was examined at protein and mRNA levels on several mucosal samples in total colectomy specimens from UC patients who had developed dysplasia or carcinoma, which they showed that COX-2 overexpression in UC-related neoplasms occurs at the early stages, beginning in mucosa that is only diploid and still negative for dysplasia, and in mucosa that is not yet inflamed. Moreover, they showed that COX-2 protein overexpression detected by immunohistochemistry in mucosal samples occurs early on in UC-related neoplastic progression.

Two potential mechanisms may be involved in the relationship between COX-2 overexpression and neoplastic progression in UC: one related to malondialdehyde levels, and one related to the up-regulation of bcl-2[84]. The first hypothesis suggests that increased COX-2 activity, in part related to the normal physiological response to injury and inflammation, may induce DNA damage through increased production of malondialdehyde, a mutagenic by-product of COX-mediated prostaglandin synthesis and lipid peroxidation[40,95]. This malondialdehyde production would be in addition to that produced by the constitutive activity of COX-1, which is thought to be important in sporadic colorectal neoplasia[90]. In support of this hypothesis, elevated levels of malondialdehyde have been observed both in sporadic colon cancer and in IBD[96-99]. After tumor initiation, COX-2 may promote its progression by increasing expression of bcl-2[100,101]. In fact, bcl-2 mediates the resistance to apoptosis, and bcl-2 up-regulation was also observed in UC-associated neoplasia. Moreover, overexpression of bcl-2 is reversible by both nonspecific COX inhibitors[101] and by highly selective COX-2 inhibitors[102]. Genes involved in UC-related carcinogenesis are shown in Table 1.

Role of inflammatory cytokines

The importance of IL6/p-STAT3 in patients with inflammation-induced CRC has recently been demonstrated[103]. In fact, IL-6 is a critical tumor promoter during early CAC tumorigenesis. In addition to enhancing proliferation of tumor-initiating cells, IL-6 produced by lamina propria myeloid cells protects normal and premalignant intestinal epithelial cells from apoptosis. By binding to its gp130-associated receptor, IL-6 activates three separate signaling pathways, namely Shp2-Ras-ERK, JAK1/2-Stat3, and PI3K-Akt-mTOR[104] and, according to their results, Grivennikov concluded that among these, Stat3 is a critical IL-6 effector in colitis-associated cancer induction[103]. In fact, Stat3 has the capacity to mediate IL-6- and IL-11-dependent IEC survival and to promote proliferation through G1 and G2/M cell-cycle progression as the common tumor cell-autonomous mechanism that bridges chronic inflammation to tumor promotion[105]. Moreover, IL-6 signaling also seems to affect tumor growth during later stages of CAC[106]. IL-6 signaling during that stage increases TNF-α production, and its interference with TNF-α signaling inhibits tumor growth and reduces IL-6 production. Such cross-regulation was also observed in the case of IL1 and IL-6; IL-1 can induce IL-6 production in colon cancer cell lines[107]. The role for suppressor cytokines is more controversial. In fact, TGF-β signaling in colonic myeloid cells is significantly involved in the development of colitis-associated

cancer[108]. In fact, Suppressor of Cytokine Signaling 3 (SOCS3) seems to be involved in UC pathogenesis, and its absence seems critical for CRC progression[109]. Oncogenic Smad3 signaling, altered by chronic inflammatory conditions and eventual somatic mutations, promotes UC-associated neoplastic progression through the up-regulation of growth-related proteins[110].

HOW WE DEFEND OURSELVES: IMMUNE SURVEILLANCE IN INFLAMMATORY COLONIC CARCINOGENESIS

The inconsistencies between the high frequency of colonic dysplasia and the much lower incidence of invasive cancer suggests the presence of mechanisms of surveillance that may prevent malignant progression of neoplasms in the colon in most cases. Observations that proctocolectomy specimens with preoperative UC and dysplasia showed cancer or dysplasia only in 64% cases[111] and, that 64% of UC patients with low grade dysplasia (LGD) had indefinite or no dysplasia after 4-year follow-up[16], suggest the presence of an efficient immune surveillance mechanism based on T-lymphocytes activation, ensuring the elimination of developing tumor cells.

Tumor cell escape from immunosurveillance enables unrestrained neoplastic cell growth and metastatic diffusion. The immune escape is thought to be facilitated both by active defense of tumor cells and by defects in function of the immune system[112,113]. Both CD4 and CD8 T lymphocytes are responsible for anti-tumor immunity[114,115]. The effective activation of naive T lymphocytes implies the engagement of the T cell receptor (TCR) with the major histocompatibility complex (MHC)-antigen-complex in the presence of co-stimulation molecules that promote an effective interaction of APC and T cells[116-118]. The presentation of MHC-antigen-complex without co-stimulatory signals leads to T-cell energy[119]. These co-stimulatory signals are provided by the interaction of CD80 or CD86 on APC surface, with their receptors expressed by T-cells[120,121]. CD80 or CD86 binding to CD28 induces tyrosine phosphorylation of several substrates and enhances T cell activation promoted by the MHC-TCR interaction[122]. An increase in CD4/CD8 ratio was observed in sentinel lymph nodes draining dysplastic epithelium compared to normal mucosa. The increase in CD4(+) T cells in relation to CD8(+) T cells correlated with the degree of dysplasia reflected by a significant increase in the ratio against low-grade dysplasia compared to indefinite dysplastic lesions. The T-cell response was specific to antigens from dysplastic epithelial lining, as seen in proliferation assays. This observation suggests an important surveillance role for the immune system against premalignant intestinal lesions in patients with long-standing UC[123]. The products of oncogenes or oncosuppressor mutated proteins can act as potentially immunogenic proteins, and are expressed by CRC cells without any rejection by the immune system. Moreover, antigen presenting cells infiltrating colorectal carcinoma express MHC molecules, but do not express CD80 or CD86[124]. *In vitro*, the observation of CD80 and CD86 expression by human carcinoma cells lines up well with the regulation by IFN that was attributed to the early stage of carcinogenesis when they were selected[125]. In fact, the role of co-stimulatory molecules in the immune response to tumor initiation and progression has already been suggested by Antonia *et al*[126], who showed in 1995 that surface CD80 expression can be induced by an oncogenic insult, and its downregulation at a later stage in the carcinogenesis process may lead to their escape from immunosurveillance mechanisms. In previous work by our group, we showed that there is significant and specific CD80 overexpression in the colon mucosa of patients with UC and dysplasia that is downregulated at later stages in carcinogenesis. On the other hand, in the non-inflammatory carcinogenesis pathway, CD80 is significantly less expressed[127,128]. Our more recent data show that the proportion of epithelial cells acting as antigen presenting cells peaks in the dysplastic colonic mucosa of UC patients, and that the activation of CD8+ T cells can be mediated by epithelial cells through a CD80-dependent mechanism. Moreover, in a murine model of inflammatory colonic carcinogenesis, we demonstrated that CD80 inhibition significantly increased the high grade dysplasia rate and extension, whereas enhancing CD80 signaling with anti-CTLA4 antibody significantly decreased these lesions (data not yet published). These data suggest that, in UC-associated carcinogenesis, the progression from dysplasia to invasive cancer is controlled not by a mere immunoediting process, such as that observed in sporadic invasive cancer by Galon *et al*[129], but a truly effective immunosurveillance mechanism mediated by CD80 expression on epithelial cells (data not yet published). Immune surveillance mechanisms in UC-related carcinogenesis are shown in Figure 2.

CONCLUSION

Patients with UC undergo repeated episodes of colonic inflammation that are associated with various tumorigenic events, and the sequence of these events is different from that which contributes to the development of sporadic CRC. In fact, in UC, early events are represented by DNA methylation that produces inhibition of oncosuppressor genes, mutation of p53, aneuploidy, and MSI. Hypermethylation of tumor suppressor and DNA MMR gene promoter regions is an epigenetic mechanism of gene silencing that can be involved in tumorigenesis and may also represent the first step in inflammatory carcinogenesis. Moreover, p*53* is frequently mutated in the early stages of UC-associated carcinogenesis. Aneuploidy is an independent risk factor for forthcoming carcinogenesis in UC. Epithelial cell-T-cell cross-talk mediated by CD80 is a key factor in controlling the progression from LGD to HGD in UC-associated carcinogenesis.

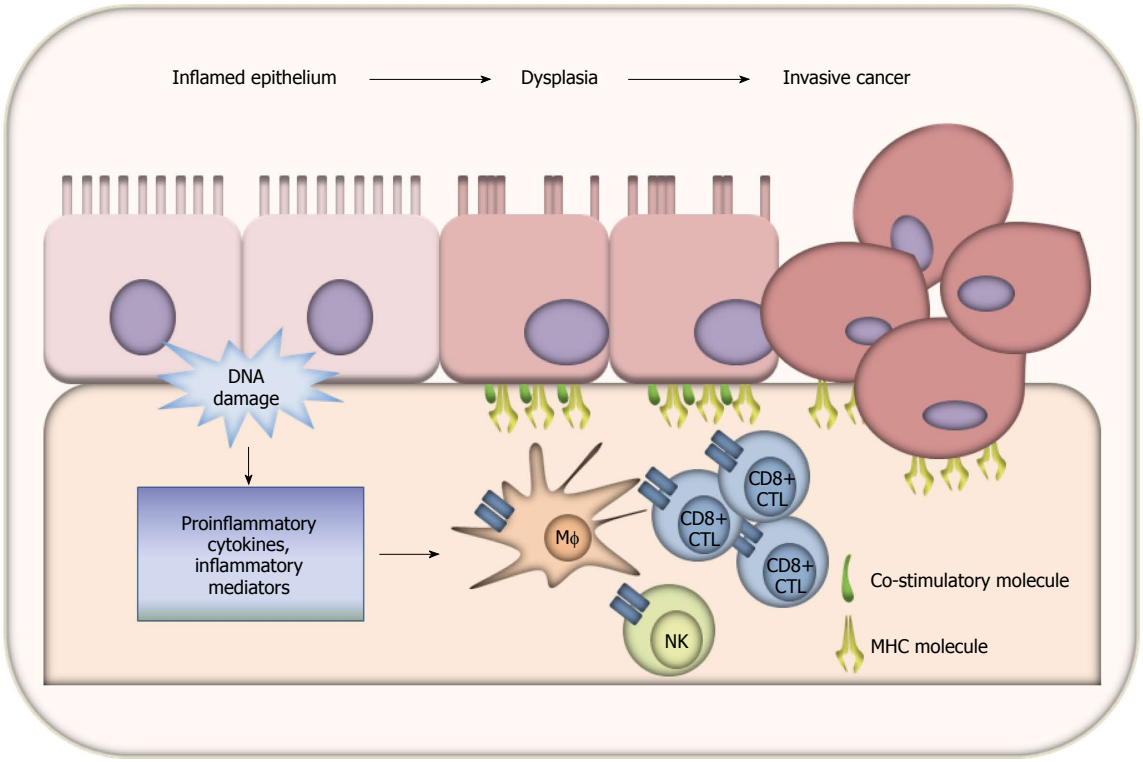

Figure 2 Mucosal microenvironment providing immune surveillance against carcinogenesis in ulcerative colitis. MHC: Major histocompatibility complex; NK: Natural killer; CTL: Cytotoxic T lymphocyte.

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