Intestinal Inflammation and Cancer

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Patients with ulcerative colitis and Crohn's disease are at increased risk for developing colorectal cancer (CRC). Chronic inflammation is believed to promote carcinogenesis. The risk for colon cancer increases with the duration and anatomic extent of colitis and presence of other inflammatory disorders (such as primary sclerosing cholangitis), whereas it decreases when patients take drugs to reduce inflammation (such as mesalamine and steroids). The genetic features that lead to sporadic CRC—chromosome instability, microsatellite instability, and DNA hypermethylation—also occur in colitis-associated CRC. Unlike the normal colonic mucosa, cells of the inflamed colonic mucosa have these genetic alterations before there is any histologic evidence of dysplasia or cancer. The reasons for these differences are not known, but oxidative stress is likely to be involved. Reactive oxygen and nitrogen species produced by inflammatory cells can affect regulation of genes that encode factors that prevent carcinogenesis (such as p53, DNA mismatch repair proteins, and DNA base excision-repair proteins), transcription factors (such as nuclear factor–κB), or signaling proteins (such as cyclooxygenases). Administration of agents that cause colitis in healthy rodents or genetically engineered, cancer-prone mice accelerates development of colorectal tumors. Mice genetically prone to inflammatory bowel disease also develop CRC, especially in the presence of bacterial colonization. Individual components of the innate and adaptive immune response have also been implicated in carcinogenesis. These observations offer compelling support for the role of inflammation in colon carcinogenesis.

Keywords: IBD; Intestine; Neoplasia; Animal Model; Innate Immunity; Adaptive Immunity.

Patients with the inflammatory bowel diseases (IBD) ulcerative colitis (UC) or Crohn's colitis are at increased risk of developing colorectal cancer (CRC). This increase in risk is more likely to result from chronic inflammation of the gastrointestinal mucosa than from any clear-cut genetic predisposition. Most CRCs, in general, develop from a dysplastic precursor lesion. In sporadic CRC, the dysplastic precursor is usually the adenomatous polyp (adenoma), a discrete focus of neoplasia that is typically removed by endoscopic polypectomy. In contrast, patients with IBD develop dysplastic lesions that can be polypoid, flat, localized, or multifocal; these are markers of colon inflammation and increased risk for neoplasia, and often indicate the need for surgical removal of the entire colon and rectum. These differences in morphology and biological behaviors of lesions not only make it a challenge to screen for CRC among patients with IBD, but they raise the important question of how chronic inflammation contributes to development of CRC. The progression from adenoma to carcinoma that occurs during development of sporadic colorectal tumors appears to be an inflammation–dysplasia–carcinoma sequence in IBD-associated CRC. We review the clinical and molecular features of CRC in patients with IBD, referred to as colitis-associated colorectal cancer and then discuss how inflammation might contribute to colitis-associated colorectal cancer pathogenesis.

Clinical and Pathologic Features of Colitis-Associated Cancer

Several lines of evidence indicate that chronic inflammation is a key risk factor for CRC in patients with

Abbreviations used in this paper: APC, adenomatous polyposis coli; AOM, azoxymethane; CRC, colorectal cancer; DSS, dextran sodium sulfate; GPX, glutathione peroxidase; IL, interleukin; MSI, microsatellite instability; NF-κB, nuclear factor–κB; NOS, nitric oxide synthase; PRR, pattern recognition receptors; PSC, primary sclerosing cholangitis; RONS, reactive oxygen and nitrogen species; Stat, signal transducers and activators of transcription; Th, T-helper; TLR, Toll-like receptor; TNF, tumor necrosis factor; TNF-R, tumor necrosis factor receptor; Treg, regulatory T; UC, ulcerative colitis; UDCA, ursodeoxycholic acid.

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IBD.[1,2] The risk for developing CRC increases with longer duration of colitis. CRC is rarely encountered in patients who have had colitis for less than 7 years; thereafter the risk increases at a rate of approximately 0.5%–1.0% per year. The extent of colitis is another important risk factor; the more colonic surface that is involved with colitis, the greater the risk for colon cancer. However, patients who have inflammation that is limited to the rectum do not have a significant increase in cancer risk. The risk of CRC is much greater among the small subset of IBD patients who also have primary sclerosing cholangitis—an idiopathic condition characterized by chronic inflammation of the bile ducts—which also predisposes to biliary tract cancer. Some studies have reported that anti-inflammatory drugs, particularly mesalamine and possibly corticosteroids, reduce the chances of developing colorectal dysplasia and cancer among patients with IBD. Similar findings of reduced adenoma size and number have been reported for healthy individuals and patients with familial adenomatous polyposis who take nonsteroidal anti-inflammatory agents.

Despite evidence implicating chronic inflammation in CRC pathogenesis, few studies have directly investigated whether level of inflammation correlates with CRC risk in patients with IBD. Disease activity, measured according to the frequency of symptomatic exacerbations, did not correlate with incidence of CRC.[3,4] However, it might be more accurate to estimate the degree of active inflammation based on endoscopic and/or histologic criteria. A retrospective case-control study performed at an IBD center associated greater degrees of active inflammation, determined by histologic analysis, with incidence of CRC.[5] In that study, patients with cancer or dysplasia were matched with 2 dysplasia-free individuals (controls) of the same sex and with similar duration and extent of disease. Severity of inflammation, based on histological analysis, was a significant variable for colorectal neoplasia incidence, after other variables were controlled for in a multivariable model; each unit of inflammation, on a 5-point scale, increased the risk for dysplasia or cancer 4.7-fold. However, inflammation measured by endoscopy, which was significant in a univariate analysis, was not a significant determinant of cancer risk in the multivariable model. Importantly, limiting the analysis to cases with cancer (thereby eliminating dysplasia cases from the analysis) confirmed the association between histological inflammation and cancer. Although this case-control study included a new scale for histologic inflammation, and the authors did not account for changes in inflammatory status over time (mean scores were used), the degree of inflammation by histology was established as an independent risk factor for CRC. These findings were confirmed by a retrospective study that used a well-established system for measuring inflammation, and included only patients who were under surveillance and were found to be free of dysplasia.[6] That study employed a 4-point scale to classify histological inflammation (see Figure 1), finding that each unit increase in inflammation score conferred a 3.8-fold increase in risk for high-grade dysplasia or CRC over time.

CRC can arise in areas of microscopic colitis that are proximal to areas of gross colitis, supporting the concept that histologic, rather than colonoscopic, evidence of inflammation is a better determinant of cancer risk.[7] Patients with the most severe inflammation often undergo colectomy at early stages of disease because they have not responded to medical therapy. Because such patients are no longer at risk for colon cancer, this may give the false impression that severe colitis is not associated with increased CRC risk. Patients in whom active inflammation settles down enough to avoid early-stage colectomy are those who remain at risk for developing CRC. So despite evidence that active inflammation, measured histologically, is a risk factor for CRC, most patients with IBD who develop CRC have quiescent chronic inflammation.

Anti-inflammatory Medications

If chronic inflammation is the main cause of CRC in patients with IBD, then suppressing inflammation should lower the risk for colitis-associated cancer. However, studies have not established that the anti-inflammatory agents most commonly used to treat IBD have chemopreventive effects against cancer (reviewed in reference 1). The chemopreventive effects of mesalamine compounds (eg, sulfasalazine and mesalamine) have been investigated in mainly post-hoc, secondary analyses, and produced conflicting results. In a systematic review, Velayos et al concluded that mesalamine has chemopreventive effects against CRC and dysplasia (odds ratio = 0.51), but this study used heterogeneous definitions of mesalamine exposure and compared studies of different designs (case-control, retrospective cohort, secondary analyses).[8] Other studies that investigated the effects of inflammation on formation of dysplasia and CRC did not observe independent, chemopreventive effects of mesalamine-based agents.[5,9] So it is not clear if mesalamine-based therapies prevent colon dysplasia and CRC.

The anticancer effects of mesalamine that have been reported might have been mediated by its ability to scavenge molecules that cause oxidative damage to the mucosa. For example, mesalamine prevents degradation of glyceraldehyde-3-phosphate dehydrogenase after exposure to hypochlorite, the strongest oxidant produced by neutrophils.[10] Other medications used to treat IBD, such as methylprednisolone, 6-mercaptopurine, or metronidazaole, do not have mesalamine's ability to scavenge for reactive oxygen and nitrogen species (RONS).[10] Rectal administration of mesalamine to patients without IBD induced apoptosis selectively in tumor cells, but not in surrounding normal epithelial cells.[11] Mesalamine can also inhibit activation of β-catenin in colonic epithelial