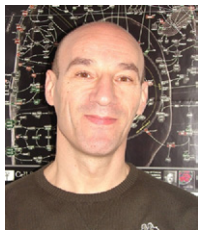
Inflammation and Colon Cancer

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The connection between inflammation and tumorigenesis is well-established and in the last decade has received a great deal of supporting evidence from genetic, pharmacological, and epidemiological data. Inflammatory bowel disease is an important risk factor for the development of colon cancer. Inflammation is also likely to be involved with other forms of sporadic as well as heritable colon cancer. The molecular mechanisms by which inflammation promotes cancer development are still being uncovered and could differ between colitis-associated and other forms of colorectal cancer. Recent work has elucidated the role of distinct immune cells, cytokines, and other immune mediators in virtually all steps of colon tumorigenesis, including initiation, promotion, progression, and metastasis. These mechanisms, as well as new approaches to prevention and therapy, are discussed in this review.

Keywords: Colon Cancer; Inflammation; Immunity; Cytokines.

More than 1 million new cases of colorectal cancer (CRC) are diagnosed worldwide each year.[1] CRC is the 3rd most common malignancy and 4th most common cause of cancer mortality worldwide.[1] CRC is also the 2nd most common cause of cancer deaths in the United States and other developed countries, despite important advances in detection, surgery and chemotherapy.[2,3] Only about 20% of CRC cases have a familial basis;[4] some are associated with well-defined syndromes, such as hereditary nonpolyposis colorectal cancer and familial adenomatous polyposis. However, the largest fraction of CRC cases has been linked to environmental causes rather than heritable genetic changes. Risk factors include environmental and food-borne mutagens, specific intestinal commensals and pathogens, and chronic intestinal inflammation, which precedes tumor development.

Colitis-associated cancer (CAC) is the CRC subtype that is associated with inflammatory bowel disease (IBD), is difficult to treat, and has high mortality.[5] More than 20% of IBD patients develop CAC within 30 years of disease onset, and >50% of these will die from CAC.[6] Although immune-mediated mechanisms link IBD and CAC,[7,8] there are similarities between CAC and other types of CRC that develop without any signs of overt inflammatory disease (Figure 1). Some of the essential stages of cancer development, including formation of aberrant crypt foci, polyps, adenomas, and carcinomas, are similar between noninflammatory CRC and CAC. However, some different pathogenic sequences have been proposed for CAC, including chronic inflammation and injury-dysplasia carcinoma, which arises without the formation of well-defined adenoma. Nonetheless, common genetic and signaling pathways, such as those involving Wnt, β-catenin, K-ras, p53, transforming growth factor (TGF)-β, and the DNA mismatch repair (MMR) proteins, are altered in sporadic CRC and CAC, although the timing of p53 and *adenomatous polyposis coli* (*APC*) inactivation and K-Ras activation can differ between CRC and CAC.[6,9] Importantly, development of both sporadic CRC and CAC is influenced by the intestinal microflora (at least, in animal models). Finally, even colorectal tumors that are not associated with clinically detectable IBD display robust inflammatory infiltration and increased

Abbreviations used in this paper: **AOM, azoxymethane; *APC*, *adenomatous polyposis coli*; CAC, colitis-associated cancer; COX2, cyclooxygenase 2; CRC, colorectal cancer; DC, dendritic cells; DSS, dextran sodium sulfate; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; IBD, inflammatory bowel disease; IEC, intestinal epithelial cells; IFN, interferon; IκB, inhibitor of κB; IKK, IκB kinase; IL, interleukin; MMR, mismatch DNA repair response; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NK, natural killer cells; PGE, prostaglandins; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TGF-β, transforming growth factor-β; TLR, toll-like receptors; TNF, tumor necrosis factor; Treg, T regulatory cells; VEGF, vascular endothelial growth factor.**

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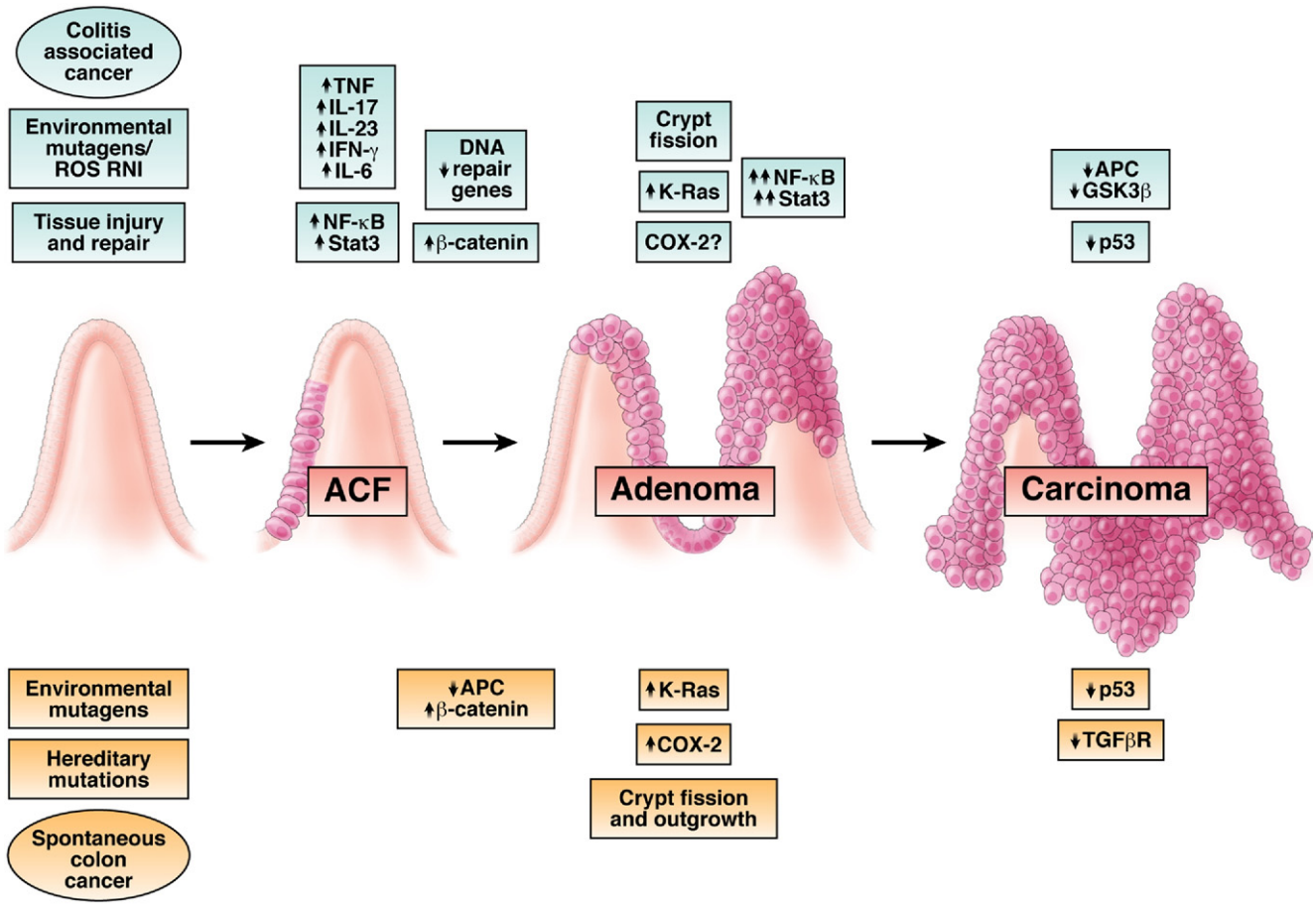

Figure 1. Mechanisms of colorectal cancer (CRC) and colitis-associated cancer (CAC) development.CRC is caused by accumulation of mutations in oncogenes and tumor suppressor genes; some of these lead to aberrant activation of β-catenin signaling. Mutations in *adenomatous polyposis coli (APC),* β-catenin, or other components of this pathway mediate the transition of single preneoplastic cells to aberrant crypt foci (ACF) and then to adenoma and colorectal carcinoma. Chronic inflammation, which leads to CAC, is characterized by production of proinflammatory cytokines that can induce mutations in oncogenes and tumor suppressor genes (*APC, p53, K-ras*) and genomic instability via various mechanisms. Persistent inflammation facilitates tumor promotion by activating proliferation and antiapoptotic properties of premalignant cells, as well as tumor progression and metastasis. There is considerable overlap in mechanisms of CRC and CAC pathogenesis. GSK-β, glycogen synthase kinase-β; RNI, reactive nitrogen intermediates; TGF, transforming growth factor.

expression of proinflammatory cytokines.[8,10–12] IBD patients with family history of CRC have >2-fold higher risk[13] for colon cancer development, suggesting overlap in mechanisms driving CRC and CAC. Moreover, a large fraction of CRC tumors and cell lines exhibit constitutive activation of transcription factors that are essential components of multiple inflammatory pathways, namely nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3)[14,15] (Table 1). It is therefore possible that immune cells and inflammatory cytokines act through similar yet distinct mechanisms in the pathogenesis of CAC and sporadic CRC. We discuss these mechanisms in this review.

Development of CRC Compared with CAC

Development of CRC typically follows several consecutive steps, which were first described in a milestone study by Fearon and Vogelstein[16] (Figure 1). Although initiating mutations in normal epithelial or stem cells occur at random and at low rates, cells that contain activating mutations in Wnt or β-catenin are the most likely to form tumors. Mutations in *APC*, which has 15 exons and encodes a huge protein with molecular weight that is >300 kDa, are typically early events in the tumorigenic pathway. The APC protein is an inhibitor of β-catenin, sequestering it in the cytoplasm.[17–19] Wnt-dependent signaling results in the proteolytic degradation of APC, β-catenin activation and translocation to the nucleus.[17] Therefore, *APC* encodes a tumor suppressor; both alleles must be disrupted for transformation to occur.

Individuals with familial adenomatous polyposis carry a mutation in one *APC* allele; the 2nd allele is typically inactivated through loss of heterozygosity within the first 30 years of life, resulting in formation of multiple and aggressive tumors in the colon.[20] APC mutations are

Table 1. Main Features of Colitis-Associated Cancer and Colorectal Cancer

Up to 20% of IBD (UC) patients develop CAC within 30 years of disease onset.
High overall mortality rate (>50%).
NSAID use reduces the risk of CRC and therefore underlines the importance of inflammation in otherwise "non-inflammatory" CRC. Potential role for anticytokine therapy.
Can either develop through the classic adenoma to carcinoma sequence or through a sequence of chronic inflammation, injury, dysplasia, and colorectal carcinoma.
Common genetic and signaling pathways are altered in sporadic CRC and CAC, including those that involve β-catenin, p53, K-ras, and B-raf.
Colorectal tumors display robust inflammatory infiltration with multiple cell type infiltrates. These immune cells are important sources of protumorigenic inflammatory cytokines and chemokines. Most colorectal tumors and almost all colitis-associated tumors have constitutive activation of transcription factors, such as NF-κB and/or STAT3, which mediate the immune response and oncogenesis.
Growth and progression of colorectal tumors and colitis-associated tumors depend on the quality and quantity of intestinal microflora.

CAC, colitis-associated cancer; CRC, colorectal cancer; IBD, inflammatory bowel disease; NF-κB, nuclear factor-κB; NSAID, nonsteroidal anti-inflammatory drug; STAT3, signal transducer and activator of transcription 3; UC, ulcerative colitis.

required for the transition of preneoplastic cells to aberrant crypt foci and toward development of microadenoma and adenoma.[16,18] Inactivation of APC stops the migration and differentiation of premalignant cells and their subsequent shedding at the edge of the crypt.[21,22] Thus, cells with APC mutations, which would be otherwise shed into the intestinal lumen, have enough time to acquire the second and third mutations required for subsequent malignant conversion. Therefore, APC inactivation (or β-catenin activation) are essential for formation of adenomas—recent studies showed that APC inactivation must occur in intestinal stem cells, rather than epithelial cells.[21,23] Recent study suggests that loss of APC and activation of CtBP1 are needed for adenoma development, while subsequent KRAS activation and β-catenin nuclear localization promote CRC.[24] Although a very large gene such as *APC* can be easily inactivated by mutations, these are not the only mutations that lead to β-catenin activation. Mutations in glycogen synthase kinase-β, β-catenin itself, and other components of this pathway are found in 10% of colon tumors.[25] Interestingly, in *Helicobacter pylori*–induced gastric tumors, proinflammatory signaling by tumor necrosis factor (TNF)-α can induce β-catenin nuclear accumulation even without the presence of APC mutations.[26] Similarly, activation of the receptor EP2 by prostaglandin E2 (PGE_2), which is produced during acute and chronic inflammation, also increases β-catenin nuclear accumulation and transcriptional activity.[27] Other inflammatory signaling pathways converge at the point of glycogen synthase kinase-β and casein kinases 1 and 2, the protein kinases that control β-catenin activation.[28–31] To the same end, activation of NF-κB and Akt pathways by proinflammatory signaling promotes β-catenin activation.[32,33] Interestingly, conventionally raised, *Helicobacter*-infected, interleukin (IL)-10–deficient mice develop spontaneous inflammation and colon tumors,[34] but tumor cells do not contain APC or even p53 mutations, indicating a possible role for inflammation in APC-inactivation–independent activation of β-catenin signaling.[34,35] In a mouse model of CAC, mutations in exon 3 of the β-catenin gene are frequently detected, which result in nuclear localization of β-catenin.[7] There are, therefore, several different mechanisms of β-catenin activation, one of the key events in colorectal tumorigenesis.

Several additional pathways must be deregulated for early-stage adenomas to progress to carcinoma in situ and invasive metastatic carcinoma. This progression includes activation of the oncogenes *K-ras* and *B-Raf*, as well as inactivation of tumor suppressors, such as the TGF-β receptor (R)II (and other components of this signaling pathway), activin receptors, p53, and the proapoptotic protein Bax.[36–38] The adenoma to carcinoma transition also requires increased expression of cyclooxygenase 2 (COX2), the rate-limiting enzyme in prostaglandin biosynthesis.[39–41] "Gatekeeper" mutations in DNA integrity checkpoint genes also occur at this (or an earlier) point, resulting in microsatellite instability in 15% of colorectal tumors and/or chromosome instability in 80% of late-stage colorectal tumors.[38] Genetic instability results in the great variation in mutations detected in colorectal tumors and is responsible for their capacity to evolve, grow, progress, escape host control, and rapidly become resistant to therapy.

Immune System in Colon Cancer

Like other solid malignancies, colorectal and colitis-associated tumors are infiltrated by various types of immune cells. Cells of the innate immune system, such as neutrophils, mast cells, natural killer (NK) cells, dendritic cells (DC), and tumor-associated macrophages can be easily detected in these tumors (Table 2).[8] In addition, advanced tumors recruit specific myeloid subsets that represent phenotypically heterogeneous but a functionally similar population of $CD11b^+Gr1^+$ cells, called myeloid-derived suppressor cells.[42] These cells share some characteristic with monocytes, macrophages, neutrophils, and DC and help suppress antitumor immune responses and tumor angiogenesis.[42] Cells of the adaptive immune system are also recruited into colorectal and colitis-associated tumors, where they have either pro- or antitumorigenic roles. T cells, for instance, are required for inflammation, cancer development, and tumor progression, as well as for anticancer immunity.[43–45]

What is the contribution of tumor immunosurveillance vs tumor-promoting inflammation in CRC and CAC? In CAC, the immune system seems to have a mostly

Table 2. Tumor-Promoting Immune Cells and Cytokines in Colon Cancer

Cell type	Function or mechanism
T cells (CD4 and CD8)	Cytokine production (IL-6, IL-10, TNF, IL-21, IL-17, IL-22, IFN-γ, lymphotoxin, RANKL) Direct cytotoxicity or T-cell help
Treg cells	Cytokine production (IL-10, TGF-β) Immunosuppression Suppress inflammation
Macrophages, DC, MDSC, neutrophils	Cytokine production (IL-6, IL-1,VEGF, IL-23, TNF) Chemokine production MMP production Angiogenesis Immunosuppression (arginase)
NK cells	Cytokine production (IFN-γ, IL-22, IL-17) Direct cytotoxicity
B cells	Cytokine production? Antibody response?
Epithelial and tumor cells	IL-1, IL-6, TNF, EGF
Cytokine	**Mechanisms/pathways in cancer and immune cells**
TNF-α	Survival, activation, recruitment, growth. AP-1, MAPK and NF-κB activation
IL-6	Survival, growth, T-cell survival and differentiation, myeloid cell recruitment. STAT3, ERK, and Akt
IL-11	Survival, growth. STAT3, STAT1, ERK
IL-23	T-cell differentiation (Th17) and interference with Tregs, production of IL-17 and IL-22 by immune cells. No direct effect on cancer cells? STAT3.
IL-1α, IL-β	Survival, growth, cytokines, chemokines, T-cell activation and differentiation. NF-κB, MAPK
IL-22	Survival, mucosal integrity, chemokines. STAT3
IL-17A,F	Survival, chemokines, T-cell regulation, monocytes, and neutrophil recruitment. MAPK, NF-κB
EGF	Survival, proliferation. MAPK, STAT3
IL-10	Anti-inflammatory, Treg stimulation. Unknown effects on cancer cells. STAT3, MAPK

DC, dendritic cells; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; IL, interleukin; MAPK, mitogen-activated protein kinase; MDSC, myeloid-derived suppressor cells; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; NK, natural killer; STAT3, signal transducer and activator of transcription 3; TGF, transforming growth factor; TNF, tumor necrosis factor; Treg, regulatory T cells; VEGF, vascular endothelial growth factor.

protumorigenic role. In sporadic CRC, there seems to be a well-defined balance between immunosurveillance (executed by $CD8^+$ T cells, NK cells, and $CD4^+$ T cells) and tumor-promoting inflammation (executed by innate immune cells, B cells, and various subtypes of T cells) (Figure 2). In CRC and CAC, immunosurveillance could mediate the early detection and elimination of transformed cells and aberrant crypt foci, and also keep small tumors at dormant state. Immunosurveillance may be also important during metastasis, when small numbers or single metastatic cells travel and can be attacked by antitumor immune cells that are not inhibited by factors in the tumor microenvironment. In many other stages of colorectal and colitis-associated tumorigenesis, inflammation counteracts and outcompetes antitumor immunity by direct immunosuppressive effects, as well as by regulation of tumor-cell survival, proliferation, angiogenesis, and other hallmarks of tumorigenesis. Lymphocyte infiltration into sporadic colorectal tumors is generally associated with good prognosis.[46–49] On the other hand, regulatory T (Treg) cells, which are abundant in the intestine, suppress inflammation and antitumor immune responses[43,50] are in fact antitumorigenic in gastrointestinal cancers.[43] In other types of cancer, T-cell infiltration has been associated with bad prognosis,[51] (references 51–242 can be found at www.gastrojournal.org) and some T-cell subsets have been reported to promote tumorigenesis in the colon.[52,53] One seemingly important difference between CRC (and especially CAC) and other epithelial cancers is that in the other types of cancer, infiltrating T cells have specificity for altered, tumor-specific, or self-antigens and can thereby destroy cancer cells. In case of CAC, many inflammatory T cells are actually specific for the commensal microflora and are therefore unable to kill cancer cells directly. So in CAC, even cytotoxic $CD8^+$ T cells can promote tumor growth through production of cytokines.[52] When therapeutic approaches based on interference with immune functions are considered, it is important that only tumor-promoting immune functions are inhibited and antitumor immunity is spared.

Inflammation in CRC and CAC Initiation

It is unlikely that inflammation initiates sporadic CRC because most intratumoral immune cells are recruited after the tumor is formed and so, in this case, chronic inflammation does not precede but follows tumor development. However, after a tumor forms, the localized inflammatory microenvironment can promote accumulation of additional mutations and epigenetic changes. Activated inflammatory cells produce reactive oxygen species (ROS) and reactive nitrogen intermediates that can induce DNA damage and mutation[54,55] (Figure 3). In IL-10 knockout mice, however, inactivation of inducible nitric oxide synthase, the enzyme that produces most reactive nitrogen intermediates during inflammation, decreases, rather than increases, adenoma formation. So, nitric oxide appears to protect mice against chronic inflammation and tumorigenesis.[56] In addition to the ROS produced by immune cells, which is unlikely to diffuse and induce mutations in adjacent epithelial cells, cytokines, and other factors, can stimulate ROS production within epithelial cells—this is more likely to induce mutations and epigenetic silencing of tumor suppressor genes. Nonetheless, the contribution of immune-

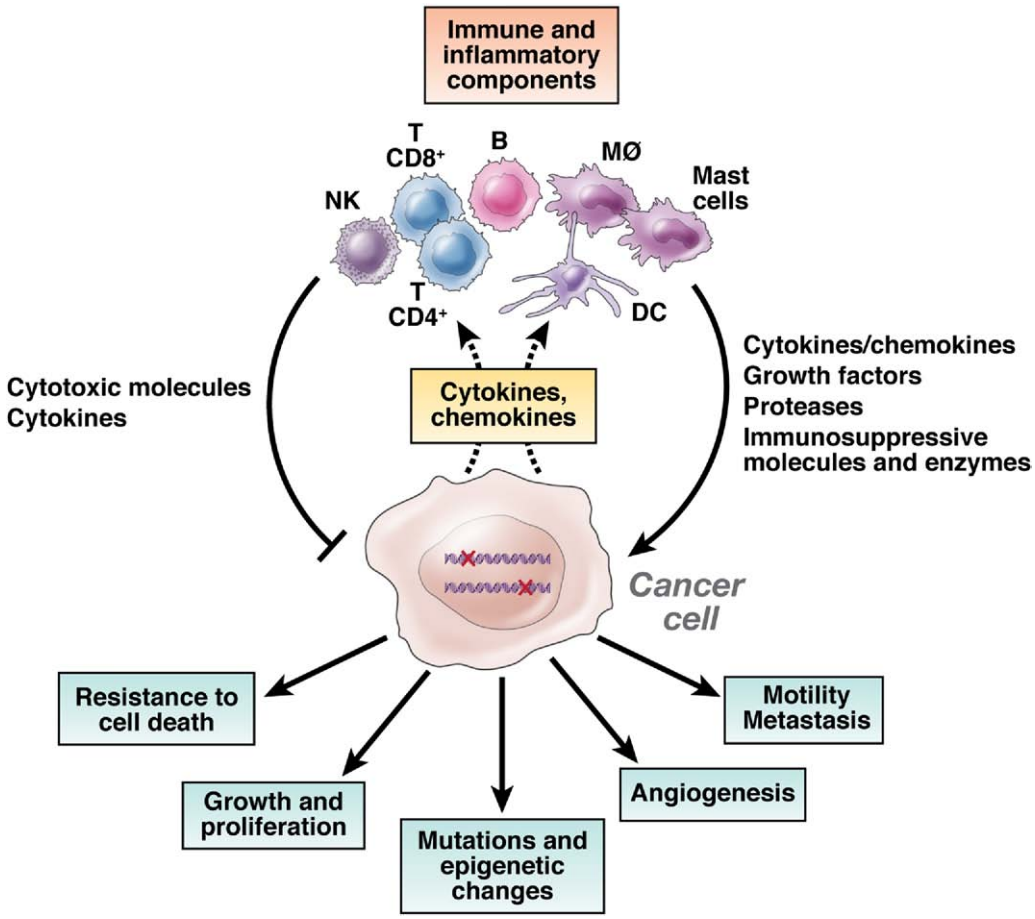

Figure 2. Immunosurveillance and inflammation in colorectal cancer (CRC) and colitis-associated (CAC). Imunosurveillance is typically mediated by cytotoxic and helper T lymphocytes as well as natural killer (NK) cells. Innate and adaptive immune cells also promote tumor development. Inflammation can promote colitis-induced tumorigenesis. In sporadic CRC, these 2 coexist in equilibrium;[45] in established tumors this balance may be skewed towards tumor-promoting inflammation. DC, dendritic cells; NK, natural killer cells.

mediated mechanisms, as opposed to dietary and environmental mutagens, to cancer-initiating mutations is not yet clear.[57]

Unlike CRC, chronic inflammation precedes colitis-associated tumor development. In CAC, chronic inflammation causes oxidative damage to DNA, leading to the p53 mutations observed in tumor cells and the inflamed, but nondysplastic epithelium.[58,59] In mice, chronic colonic inflammation triggered by administration of the irritant dextran sodium sulfate (DSS) induced DNA damage, resulting in a low incidence of colonic adenomas.[54] Adenoma numbers increased and adenomas appeared much earlier if the procarcinogen azoxymethane (AOM) was administered to mice before DSS.[60] Inflammation-induced mutagenesis can also cause inactivation or repression of MMR genes and ROS can directly oxidize and inactivate mismatch repair enzymes at protein level.[57,61] In *Gi*$\alpha 2^{-/-}$ mice, which develop spontaneous colonic inflammation and cancer, expression of MMR components (MLH1 and PMS2) is specifically lost in enterocytes through histone deacetylase– and DEC-1-mediated epigenetic repression of the *Mlh1* promoter.[62]

Epigenetic silencing (via DNA and histone methylation or microRNA-based silencing) reduces the expression of proteins that maintain fidelity during DNA replication or act as tumor suppressors, promoting CAC and CRC development.[4,38,61,63–66] Both alleles for such genes should be inactivated to achieve a protumorigenic advantage, and it is tempting to speculate that epigenetic silencing is an easier and quicker way to inactivate a tumor suppressor, because silencing can affect 2 alleles simultaneously, whereas genetic inactivation of a tumor suppressor gene requires 2 independent and rare mutational events (Figure 3). For example, APC, Bax, and INK4a can be silenced by the mechanisms mentioned previously, as well as MLH and other component of MMR response.[61,67,68] Several microRNAs regulate the stability of gene transcripts critical for colon cancer development, including TGFβRII, TCF4, MSH1,2, APC, K-Ras , Smad4, and PTEN.[64] DNA methyl transferases, Dnmt1 and Dnmt3, activity and expression can be induced during inflammation and those enzymes may mediate silencing of numerous target genes in mouse and human colon cancers.[69] Inactivation of DNA methyl transferases using hypomor-

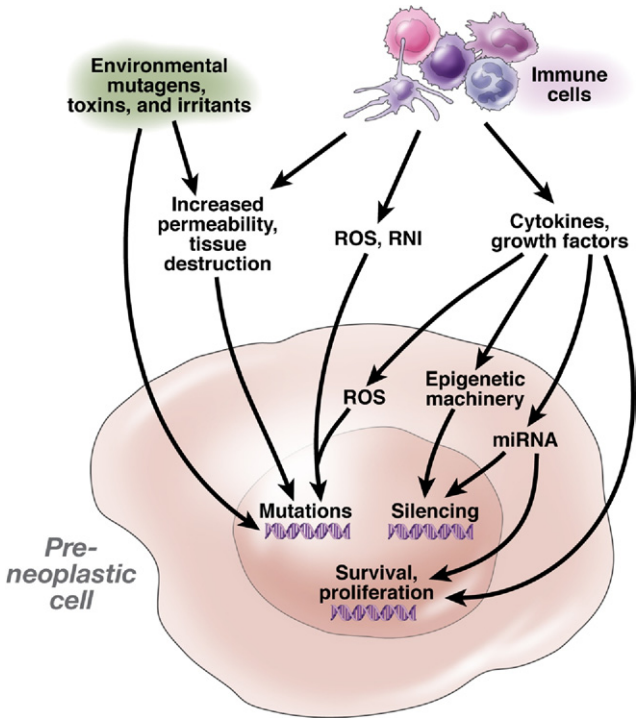

Figure 3. Initiation of sporadic colorectal cancer (CRC) and colitis associated cancer (CAC). Environmental mutagens initiate mutations in epithelial cells in sporadic colon cancer whereas reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI), produced by inflammatory cells, can cause DNA damage that in addition to other mutagens can initiate CAC. Cytokines from inflammatory cells can increase intracellular ROS and RNI in pre-malignant cells, resulting in epigenetic changes that silence tumor suppressors and promote tumor initiation. miRNA, microRNA; ROS, reactive oxygen species; RNI, reactive oxygen intermediates.

phic alleles in the sporadic model of CRC (the *Apc*^{min} mice) results not only in decreased tumor progression but also in almost complete suppression of tumor formation.[70] Furthermore, inflammatory signals can induce epigenetic switch responsible for cell transformation. For example, NF-κB regulated microRNA Let-7 influences IL-6 and STAT3 signaling in cancer cells,[71] but it remains to be determined whether such process is pivotal for CAC pathogenesis. Taken together, inflammation-driven genetic alterations and epigenetic changes are important aspects of tumor initiation in CRC and especially in CAC.

Inflammation in Promotion of CRC and CAC

Tumor promotion is a process of tumor growth from a single premalignant cell into a fully developed tumor. Initial and continuous tumor growth both depend on a balance between cell death and cell proliferation. Cytokines and chemokines can serve as tumor growth and survival factors and can promote tumor growth by promoting angiogenesis and suppressing immune-mediated tumor elimination[15,72,73] (Table 2). Other factors in the intestine, such as intestinal microbiota and dietary compounds, can influence colon cancer development, particularly by their ability to regulate cytokine- transcription factor proinflammatory signaling networks.

Role of the Intestinal Microbiota in Cancer Development

If the microbiota is involved in cancer development, the colon must be its major site of action—the human intestine contains >500 different types of microorganisms and the colon contains >10^{13} bacterial cells.[74] Studies have shown that CAC development depends qualitatively and quantitatively on the intestinal microflora.[75,76] The intestinal microflora has important homeostatic immune and metabolic functions, affects the proliferation and survival of epithelial cells, and provides protection against pathogens.[77] Almost 99% of gastrointestinal bacteria are anaerobic; 60% belong to *Firmicutes* class (mainly composed of *Clostridium spp*) and >20% belong to the *Bacteroides* class. The intestinal microbiota metabolizes nonabsorbed carbohydrates; dead epithelial cells; and mucus, and produces metabolites that influence epithelial cell function; energy balance; and immune responses..[78–80] The microflora produces short-chain fatty acids that regulate the inflammatory response in IBD[81] and vitamins, and metabolizes bile acids.[82] Moreover, bacteria are important for metabolic activation of different carcinogens and mutagens, including AOM, environmental polyamines, phenols, and alkylating agents.[60] The absence of intestinal bacteria in germ-free mice decreases the frequency of oncogenic mutations and tumor formation in the AOM + DSS model of CAC and the *Apc*^{min} model of CRC.[83] Gastrointestinal bacteria are also required to trigger production of IL-10 (tolerogenic) and IL-17 (proinflammatory), which might promote development of sporadic CRC or especially CAC.[84,85]

There are several ways by which disrupting homeostasis of the intestinal microflora could promote cancer. Microbial pathogens can cause intestinal inflammation through activation of pattern recognition receptors or by endocytosis, adherence, and secretion of toxins or invasion.[86] Intestinal inflammation can result from an aberrant ratio of protective (tolerogenic) to aggressive (proinflammatory, damage-inducing, protumorigenic) microflora. Changes in the number, diversity, and stability of commensal bacteria (dysbiosis), particularly the *Clostridia* group, can alter normal physiological processes and lead to disease, including CRC[87]; the quantity and quality of gastrointestinal microbiota also affects CAC development.[76] The enterotoxigenic *Bacteroides fragilis* can promote colon tumorigenesis, if it is capable of inducing tissue damage and colitis, with subsequent STAT3 activation and IL-17 production.[53] It is possible that only bacteria that induce a combination of tissue injury and inflammation appear to promote cancer, whereas inflammation without continuous cycles of injury and repair is insufficient for tumor induction. Other pathogens or conditional commensals also contribute to tumorigenesis.

Table 3. Microbes Linked to Colorectal Cancer, Colitis-Associated Cancer, and Inflammatory Bowel Disease

Microbe	Mechanism of pathology
CRC	
Bacteroides fragilis, enterotoxigenic	Activation of STAT3 in the colon, triggers injury and IL-17 production[53]
Bacteroides vulgates	MyD88 dependent signaling, possibly NF-κB activation[76]
Bifidobacterium longum	Increased bacterial presence[75,231]
Clostridium butyricium	
Mitsuokella multiacida	
Escherichia coli, invasive	Intracellular colonization[232,233]
Enterococcus faecalis	ROS production and DNA damage[88]
Germ-free condition	Resistance to colon cancer[79]
Streptococcus bovis	Production of IL-8, aberrant crypt formation, increased proliferation[234,235]
Inflammatory bowel disease	
Bacteroides fragilis	Stimulate IL-17 production[236]
Bacteroides thetaiotaomicron	Glycosylation changes (defective adhesion and migration)[237]
Clostridium difficile	Increased bacterial presence and translocation[238]
Clostridium leptum and *C coccoides*	Altered diversity of microbiota with a potential shift to pro-inflammatory/pro-tumorigenic[87,239]
Escherichia coli, invasive	Colonization of IEC, production of IL-8, IFN-γ, TNF-α, and carcinoembryonic antigen-related cell adhesion molecule 6 mediated adhesion[233,240,241]

CRC, colorectal cancer; IFN, interferon; IL, interleukin; NF-κB, nuclear factor-κB; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor.

These can activate the immune system to produce either ROS, as in case of *Enterococcus faecalis*, or prosurvival and proangiogenic cytokines (ie, IL-6, IL-8, IL-17), as in case of *Streptococcus bovis*, *B fragilis,* and other bacteria.[88] In *Il10*$^{-/-}$ mice, infection with different *Helicobacter spp* results in CAC development, whereas eradication of bacteria with antibiotics ameliorated IBD and prevented CAC.[89] Many bacterial species were found to be enriched in colorectal tumor samples and in tissue adjacent to tumors (Table 3).

Roles for Pattern Recognition Receptors in Colon Cancer

Pattern recognition receptors such as Toll-like receptors (TLR) and Nod-like receptors (NLR) are activated during tumorigenesis by components of bacteria and viruses, products of tissue damage, and necrosis, stress, or other signals.[90–92] However, the overall contribution of pattern recognition receptors to epithelial cells compared with immune or inflammatory cells is not clear; analyses of cell-type specific knockout mice are required. TLRs and receptors for IL-1 family cytokines (IL-1 and IL-18) are required for intestinal homeostasis in health and disease; loss of their major adaptor protein MyD88 exacerbates chemically induced colitis,[93] but may inhibit commensal flora-induced chronic colitis.[94] It remains to be determined whether deficiency in MyD88 reduces colon cancer incidence and growth uniformly in spontaneous- and inflammation-associated cancers.[95] TLRs are differentially expressed along the human gastrointestinal tract and most are present on intestinal epithelial cells, in addition to resident innate immune cells.[96] Mice that lack either TLR4 or its MyD88 adaptor exhibit decreased epithelial cell proliferation in response to chemical-induced injury.[93,97] Germ-free mice also have decreased intestinal cell proliferation, indicating that TLR4 is activated by flora-derived agonists.[98] Furthermore, TLR4- and MyD88-deficient mice have increased epithelial cell apoptosis after DSS-induced injury.[97] Genetic studies suggest that polymorphisms in the genes encoding TLRs are associated with increased risk for CRC.[90,99]

NF-κB and Colorectal Cancers

Most tumor-promoting cytokines are activated via NF-κB transcription factors or (along with other inflammatory stimuli) activate NF-κB signaling in premalignant cells and immune/inflammatory cells.[72] NF-κB is likely to have a prominent role in colorectal and colitis-associated tumorigenesis. Aberrant NF-κB activation was detected in >50% of colorectal and colitis-associated tumors and mouse studies have established a role for NF-κB in CAC development.[100,101] The protumorigenic role of NF-κB can be achieved via classical or alternative activation route.[7,102] NF-κB activation can support tumorigenesis by increasing cell proliferation and angiogenesis, inhibiting cell death, and promoting cell invasion and metastasis.[103] The antiapoptotic activity of NF-κB is mediated via its activation of *Bcl2*, *Bcl-xL*, and *cFLIP*, along with other genes.[103,104] Cancer cells with activated NF-κB are resistant to chemotherapeutics and ionizing radiation; inhibition of NF-κB activity greatly increases cell sensitivity to these agents.[105]

The transcription factor NF-κB is a dimer; each combination of subunits is likely to be involved in regulation of different genes.[106] There are 5 subunit family members: p105/p50, p100/p52, RelA (p65), c-Rel, and RelB. These are held inactive in the cytoplasm as precursors or by their specific inhibitors, the inhibitor of κB (IκB) proteins. Classic mechanisms of NF-κB activation occur in CAC and CRC and include signaling by pattern recognition receptors and by tumor-promoting cytokines, such as TNF, IL-1, and IL-17.[72] These signal transduction pathways activate the IκB kinase (IKK) complex, comprising 1 regulatory (IKKγ/NEMO) and 2 catalytic (IKKα and IKKβ) subunits. Activated IKKβ phosphorylates the IκBs, targeting them for ubiquitination and subsequent degradation in proteasome, which liberates NF-κB (mainly p50/p65) to migrate to nucleus and regulate

gene transcription. The alternative pathway includes an IKKα homodimer and p52/RelB transcription factors.[106] In CRC and CAC, this pathway could be activated by cytokines such as RANKL and lymphotoxin-β. Prolonged NF-κB nuclear retention may be in some cases mediated by active STAT3,[107] which is constitutively active in >50% of colorectal tumors. No activating mutations in NF-κB or STAT3 have been detected in colorectal or colitis-associated tumors, indicating that these transcription factors are activated in paracrine or autocrine manners or upon activation of upstream components of their signaling pathways.

IBD is associated with persistent NF-κB activation in myeloid and epithelial cells of the colonic mucosa.[108–110] Inhibition of RelA expression in mice with antisense oligonucleotides alleviates many IBD symptoms.[111] In chronic, T-cell driven colitis, NF-κB activation is believed to be essential in myeloid but not in epithelial cells, because inactivation of IKKβ in myeloid cells decreased intestinal inflammation in IL-10-deficient mice.[112] However, in intestinal injury-dependent acute colitis, induced by DSS activation, NF-κB activation in intestinal epithelial cells has a protective role.[7,112] Most of the drugs that are commonly used to treat acute IBD and control remission, including sulfasalazine, mesalamine, glucocorticoids, and methotraxate, inhibit NF-κB or IKK kinases.[113,114] Conditional ablation of IKKβ in enterocytes decreased tumor incidence by 80% without affecting tumor size,[7] indicating that NF-κB activation is involved in early stages of tumor promotion, rather than progression or growth.[101] Analysis of early pathogenic events in the AOM + DSS mouse model of colitis showed that apoptosis is increased among IKKβ-deficient enterocytes, including premalignant cells, which probably resulted from defective activation of Bcl-xL.[7] Therefore, it is expected that hyperactivation of NF-κB in epithelial cells will result in increased tumor incidence.

By contrast, deletion of IKKβ in inflammatory cells (eg, DC, macrophages, neutrophils) decreased tumor incidence only by 50%, but resulted in a substantial reduction in tumor size.[7] Indeed, detailed analysis revealed that, whereas IKKβ did not affect the proliferation of enterocytes, ablation of IKKβ in myeloid cells inhibited inflammation-induced enterocyte proliferation and inflammation-stimulated growth of colitis-associated tumors. These seminal findings indicated that activation of NF-κB in myeloid cells (especially lamina propria macrophages and DC) results in the production of cytokines that acted as growth factors for premalignant enterocytes.[101] Some of these cytokines included TNF-α, IL-6, IL-1β, and IL-11;[7,115–117] the role of other NF-κB-dependent cytokines awaits experimental evaluation. Expression of TNF-α and IL-6, which was detected in serum samples from patients, was associated with increased risk for colorectal adenoma.[118]

Cytokine Signaling and Tumor Promotion

Most, but not all, tumor-promoting cytokines activate receptors on intestinal epithelial cells that activate oncogenic transcription factors and other oncogenic signaling pathways, such as extracellular signal-regulated kinase or Akt/mammalian target of rapamycin (mTOR). Transcription factors NF-κB and STAT3 are particularly important in the development of CAC and CRC.[7,116,119,120] (Figure 4). Although the initial evidence for cytokine-regulated tumor promotion came from the studies in the mouse model of CAC,[7,115] the same mechanisms might be applied to sporadic CRC. Cytokines that promote colorectal and colitis-associated tumor development include TNF, IL-6, and IL-1;[121,122] while many others were found to be upregulated in these tumor types. By contrast, cytokines such as IL-10[34] and TGF-β inhibit colorectal tumorigenesis.[115,123]

Most tumor-promoting cytokines are produced by lamina propria macrophages and DC during early states of CAC development[116] or by T cells during late-stage tumor progression[115] (Table 2). In colitis-associated tumors, the activated protease ADAM17 was found to mediate shedding of the membrane-bound IL-6 receptor.[115,124] The resulting, soluble IL-6 receptor activates STAT3 in gp130-expressing cells via trans-signaling, regardless of their IL-6 receptor expression levels.[115] In the *Apc*^{min} mice, which develop colorectal tumors, IL-6 was found to stimulate proliferation of premalignant enterocytes, as it does in models of CAC and in colon cancer cells.[115,116,125,126] Additionally, IL-6 is a potent stimulator of colon cancer cell proliferation and tumor growth.[126] IL-6 has a dual role on colitis—it mediates a pathogenic immune response, hence its inactivation completely blocks colitis in several animal models and in patients.[127–129] IL-6 also has a distinct, tissue-protective role in the gastrointestinal mucosa and tissue regeneration after injury requires IL-6.[116,130,131] Interestingly, interference with ADAM17 functions leads to severe colitis in DSS model, partially because of the loss of IL-6 receptor trans-signaling, which is important for epithelial regeneration,[116,132,133] but mostly because of the defective shedding of the cytokines of epidermal growth factor (EGF) family, such as TGF-α, EGF, and epiregulin,[132] important for activation of STAT3 and other prosurvival pathways in intestinal epithelial cells (IEC).

Most of the effects of IL-6 in cancer cells are mediated by STAT3, a transcription factor that is activated by many growth factors and cytokines, including IL-11; IL-22; hepatocyte growth factor; and EGF receptor ligands, such as TGF-α and EGF, as well as oncogenic tyrosine kinases such as c-Met or Src.[15,116,117] Cytokine-driven STAT3 activation protects the gastrointestinal epithelium and stimulates its regeneration.[116,117,134] Therefore, IL-6 and STAT3 are attractive therapeutic targets for CAC, because their inhibition blocks proliferation of

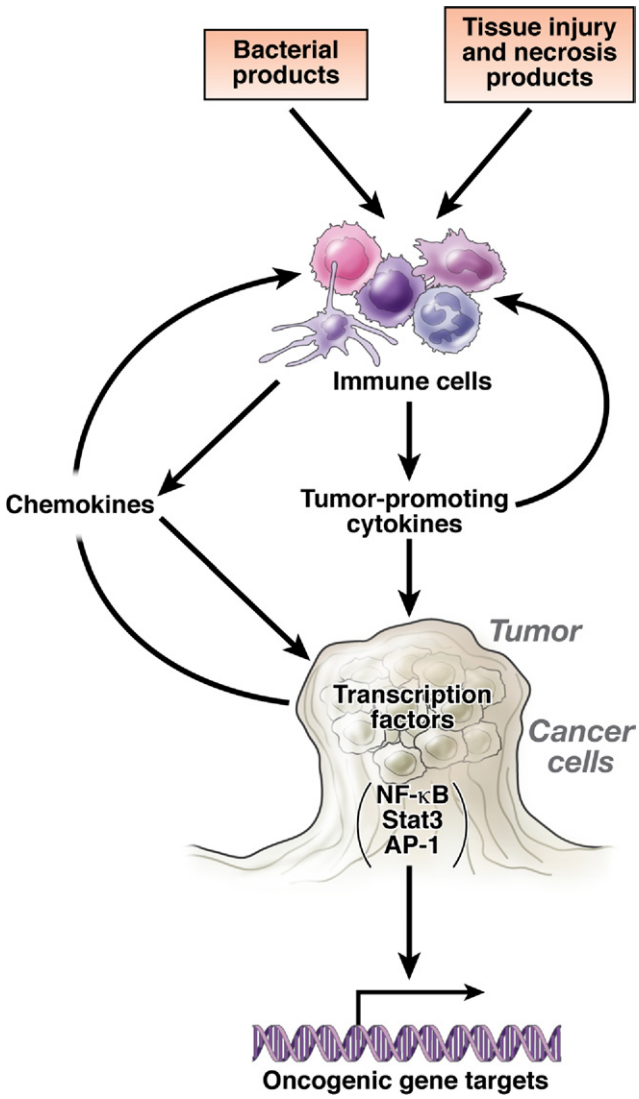

Figure 4. Cytokines and transcription factors involved in tumor promotion. Tissue injury, commensal and pathogenic microbiota, and necrotic products stimulate cytokine production by immune cells in the tumor microenvironment. This process depends on nuclear factor-κB (NF-κB) activation in immune cells, whereas signal transducer and activator of transcription 3 (STAT3) has anti- and pro-inflammatory roles in immune cells. Cytokines and growth factors in the tumor microenvironment activate transcription factors such as NF-κB, STAT3, and AP-1, which regulate genes that control numerous processes such as cell proliferation, tumor growth, resistance to cell death, angiogenesis, and tumor progression and invasion. Activation of NF-κB, STAT3, and AP-1 induces positive signaling loops that increase production of chemokines and cytokines and recruit and activate inflammatory cells in the tumor microenvironment. NF-κB, nuclear factor-κB; Stat3, signal transducer and activator of transcription 3; AP-1, activator protein-1.

premalignant cells as confirmed by selective STAT3 ablation from IEC.[116,117] In CAC, STAT3 may be also activated by IL-11, which has a similar role to IL-6, in gastric cancer.[135] Activation of STAT3 induces expression of antiapoptotic genes, such as *Bcl2* or *Bcl-xL*, proliferative genes like *Cyclin D1* or *c-Myc*, and vascular endothelial growth factor (*VEGF*), which encodes a proangiogenic factor.[136,137] Activated STAT3 can also induce prolonged activation of NF-κB—an important feature of pathogenesis, because both these transcription factors activate genes required for every aspect of cancer development.[107,119] IL-6 also promotes Th17 cell differentiation,[138] which can promote and sustain IBD,[139] and regulates the survival of other proinflammatory T cells, such as Th1 cells, while inhibiting the function of Treg cells.[128,140] A pivotal trial of an antagonistic IL-6 receptor antibody led to clinical improvement of patients with IBD, validating this signaling pathway as a therapeutic target.[141]

TNF is produced during the initial inflammatory response; it initiates and propagates many reactions, such as production of other cytokines, chemokines, and endothelial adhesion molecules. TNF also increases vascular permeability, leading to recruitment of activated leukocytes to the site of infection or injury.[142,143] These properties make TNF a promoter of inflammation, angiogenesis, and tumor dissemination; it should therefore be considered a tumor-promoting factor.[144,145] TNF also activates the transcription factors AP-1 and NF-κB in many tumor types.[122,145] TNF levels increase in patients with Crohn's disease or ulcerative colitis, or those with other forms of IBD,[146] so various TNF antagonists are used to treat patients with IBD.

TNF expression increases during colon tumorigenesis and ablation of TNFR1-reduced tumor induction in a mouse model of CAC.[122] Moreover, interference with TNF signaling with a soluble decoy receptor decreased tumorigenicity and tumor growth.[122] Inactivation of transcription factor T-bet in DCs led to spontaneous intestinal inflammation and CAC, and this process was largely dependent on TNF.[147] Prospective studies with these drugs have shown reduced incidence of CAC and amelioration of IBD in patients; additional studies will reveal whether inhibition of TNF can decrease tumor growth and progression in patients with CAC or CRC. Another cytokine produced during the initial stage of the inflammatory response is IL-1, which is upregulated in patients with CAC[148] and mediates the tumorigenesis of various gastrointestinal cancers, including gastric cancer[149] and CAC.[150,151]

TGF-β is cytokine with paradoxical role in cancer development. It is displaying antitumorigenic effects by inhibiting proliferation, stimulating apoptosis, and by suppressing protumorigenic cytokine expression.[152] Mutation in TGF-β pathway within epithelial cells predisposes to or facilitate colonic tumor development and growth.[153,154] Proper TGF-β signaling in T cells is also required for prevention of gastrointestinal malignancies[155] and inactivation of TGF-βRII or Smad4 in T cells results in increased tumorigenicity in colitis-associated and spontaneous cancers.[115,155] On the other hand, during malignant progression, TGF-β promotes epithelial-

mesenchymal transition (EMT) and suppresses antitumor activity of immune cells[156] to facilitate metastasis.

IL-23 is another cytokine that is upregulated in various types of cancer, including colon cancer[157]; specific polymorphisms in the gene encoding its receptor were associated with Crohn's disease and ulcerative colitis.[158,159] Not surprisingly, IL-23 expression is also increased in IBD and normally is limited to the gastrointestinal tract.[11,160] The mechanisms and importance of IL-23 action in sporadic CRC and CAC are not clear, but could involve the effects of IL-23 on the differentiation and propagation of Th17 cells. Other possible mechanisms include the effects of IL-23 on monocytes, memory T cells, and Tregs. The Th17-produced cytokine IL-22 belongs to the IL-10 family and protects against experimental colitis.[161,162] Another cytokine, IL-21, might have an important role in the pathogenesis of colitis, by regulating the Treg and Th17 balance and also influencing the integrity of the mucosal barrier[163] (Table 2). IL-13 might be required for intestinal fibrosis and is clearly involved in the Th2-skewed form of ulcerative colitis, which predisposes patients to CAC.[164] With the exception of IL-23, it is not clear yet whether these cytokines are involved in colorectal tumorigenesis.

Prostaglandin Synthesis, Inflammation, and Colorectal Tumorigenesis

COX2 is an inducible mediator of prostaglandin synthesis and an important factor in colorectal tumorigenesis.[41] COX2 expression is upregulated in the colorectal tumors and in experimental models of CAC.[165,166] Selective inhibitors (such as celecoxib) and nonspecific inhibitors (aspirin) of COX reduce CRC incidence.[40,165,166] The protumorigenic effects of COX2 are mediated by its major end product, PGE_2; and human colorectal tumors have increased levels of PGE_2.[167–170] These mediators of inflammation are important components of colorectal malignancies, or at least of sporadic CRC.[171] In treating patients with IBD or CAC, the situation is more complex because COX2 inhibitors can exacerbate colitis and intestinal injury.

Protumorigenic mechanisms of COX2 include inhibition of apoptosis, by increasing expression of Bcl2 via the mitogen-activated protein kinase or phosphoinositide 3-kinase-AKT signaling pathways.[27,172,173] PGE_2 also activates β-catenin-dependent signaling, which promotes survival and proliferation. COX2 can also stimulate tumor angiogenesis by inducing production of VEGF and basic fibroblast growth factor,[174] and increase tumor dissemination by altering the adhesive properties of cells and increasing matrix metalloproteinase activity.[175] Lastly, in myeloid cells, PGE_2 signaling reduces expression of antitumorigenic IL-12 and increases expression of protumorigenic IL-23.[176]

Inflammation in Invasion and Metastasis

The role of immune cells and their products in metastasis of colorectal and colitis-induced tumors has not been examined in details because of the lack of suitable mouse models. Indeed, tumors from classical models (APC^{Min} and AOM + DSS) rarely metastasize and, therefore, many models for colon cancer metastasis included transplantation of cell lines orthotopically or under the skin, as well as intrasplenic or intravenous injection to further assess metastatic colonization of target organs. Nevertheless, immune and inflammatory cells are present in advanced and metastasizing tumors, especially at the leading edge of the tumor, where invasion takes place[49,177] (Figure 5). The inflammatory microenvironment can influence several key stages of metastasis.[178] The first step is represented by EMT, in which cancer cells acquire fibroblastoid characteristics that increase their motility and allow them to invade epithelial linings/basal membranes and reach efferent blood vessels or lymphatics.[179] This process is largely regulated by TGF-β (unless TGF-β proximal signaling has been inactivated by mutations at earlier stage of tumorigenesis) and is characterized by loss of E-cadherin expression by malignant epithelial cell.[179,180]

Overexpression of Fzd7, a ligand for Wnt receptors, increases the motility and metastatic capabilities of colon cancer cells, even if β-catenin in these cells has been activated.[181] EMT can be facilitated by activation of NF-κB and/or STAT3 signaling.[121,182] In addition to TGF-β, EMT can be regulated by several proinflammatory cytokines, including IL-1; TNF-α; hypoxia-inducible factor-1α; and IL-6,[121,183–185] these activate transcription factors that regulate EMT, such as ZEB1; ZEB2; Twist; Kiss; and Snail.[184,186,187] Activated Snail represses E-cadherin transcription in epithelial cells. TNF-α signaling stabilizes Snail by preventing its degradation—this is one of the mechanisms by which TNF promotes metastasis of colon cancer cells.[184]

It remains to be determined whether other cytokines that share similarities with TNF-α in signaling pathways are also capable of inducing EMT and Snail expression. TNF-α promoted survival, attachment, and proliferation of metastatic colon cancer cells in a mouse model of lung metastasis.[188] These effects depended on activation of NF-κB by inflammatory cells (for TNF-α production) and cancer cells (for TNF-α action). Interestingly, when NF-κB was inhibited in cancer cells, TRAIL, another member of the TNF superfamily, induced regression of established metastases and killed metastatic seeds through an extrinsic apoptotic pathway. Therefore, some cytokines produced by immune system have antitumorigenic effects and act on single metastatic cells or small, secondary metastatic outgrowth.[189] STAT3 and NF-κB also significantly increase the mobility of premetastatic cells, facilitating their migration and invasion. This effect on motility is mediated not

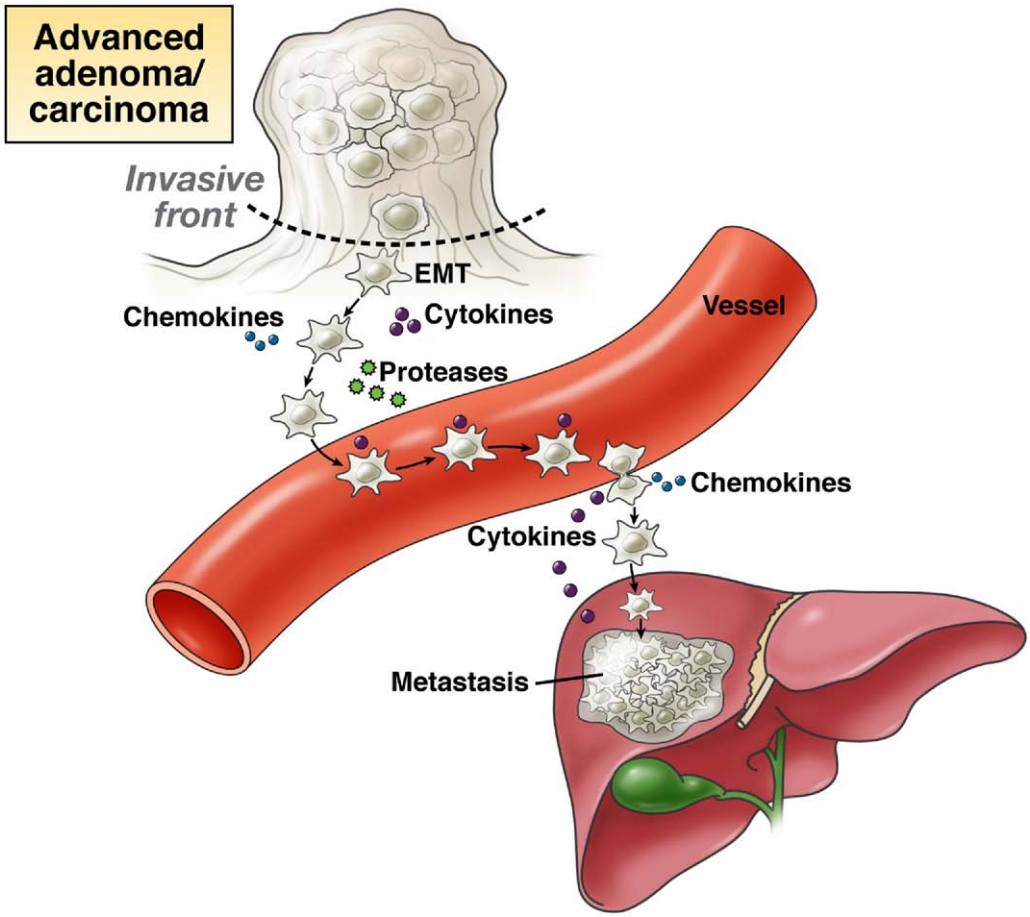

Figure 5. Role of inflammation in angiogenesis and metastasis cytokines, chemokines and proteases (MMP) produced by inflammatory cells influence the processes of angiogenesis and metastasis. They alter the migratory properties and behavior of cancer cells, degrade the ECM, and increase the tumor's blood supply and access to vasculature. Immune cells also create chemokine gradients that guide the migration of metastatic cells through the tissue to distant organs, and facilitate other aspects of metastasis. EMT, epithelial-mesenchymal transition; MMP, matrix metalloproteinase.

only by their effect on the transcription of EMT regulators, but also by the ability of STAT3 and NF-κB to regulate the cytoskeleton.

Disruption of TGF-β signaling in cancer cells also upregulates the SDF1 (CXCL12)-CXCR4 and CXCL5-CXCR2 chemokine:chemokine-receptor pairs and rapidly recruits MDSC, which promote metastasis and dampen antitumor immune responses.[190] Advanced-stage colorectal tumors upregulate CXCR4 and CXCL12; their overexpression correlates with poor prognosis.[191] CXCR4 signaling regulates metastasis at least by 2 different mechanisms: direct chemotactic attraction of migrating or invading metastatic seeds and stimulation of tumor neoangiogenesis. Chemokines can directly stimulate the migration of malignant cells toward blood vessels, whereas cytokines such as TNF can increase vascular permeability and facilitate intra- and extravasation of metastatic seeds. For example, CXCR3 chemokine axis is pivotal for metastasis into lymph nodes.[192] In contrast to CXCR4, which is constitutively expressed, CXCR3 is not expressed by normal IEC, but is dramatically upregulated during malignization.[192] Chemokines that activate CXCR3 during metastasis, including CXCL9, CXCL 10, CXCL 11, and CCL21, are upregulated by signaling of oncogenic proteins such as Ras[193]; chemokine expression can also be stimulated by proinflammatory cytokines, such as TNF-α, IL-17, or even interferon (IFN)-γ.[192,194,195] Chemokines not only regulate the migration of invading cells toward the bloods vessels, but some, like CXCR4, CCR4, CCR7, CCR9, and CCR10, also control migration of metastatic cells to distant organs.[196] Proinflammatory cytokines, such as IL-6 and IL-11, control the expression of Trefoil factor family 3 (Tff3)[130] and might thereby promote metastasis of colorectal tumors. Trefoil factor family is required not only for normal homeostasis and proliferation of IEC, but also for aggressive metastatic behavior of colon cancer cells, demonstrated in vitro.[197]

Inflammatory signals regulate the production and activity of proteases that degrade the extracellular matrix and facilitate invasion and extravasation of cancer cells.[187,198] Human colorectal tumors overexpress MMP 1, 2, 3, 7, 9, and 13.[199] Proinflammatory cytokines can in-

crease the expression of various MMPs, providing an independent stimulus for increased cell migration.[15,199] These cytokines include, but are not limited to, TNF-α and TGF-β. MMP are produced by stromal, cancer, and immune cells;[200–202] their production by nonimmune cells can be affected by inflammatory signals from immune cells in the tumor microenvironment. In addition, TNF family cytokines regulate the expression of MMP inhibitors such as TIMP3 or maspin.[203,204]

Anticancer and Anti-Inflammatory Agents

Although much has been learned about the molecular connection between inflammation and colon cancer, this knowledge has not been completely translated to the clinic. It is unlikely that anti-inflammatory drugs will be tremendously effective as monotherapies for patients with CRC, but they might be used with chemo- or radiotherapy. Anti-inflammatory agents might be used, alone or with other strategies, to prevent CAC. Therapy for CRC includes surgical resection, radiation, and chemotherapy with cytocidal chemicals and biologic agents. Traditional chemotherapeutic drugs, such as 5-flourouracil, fluoropyrimidine, and oxaliplatin are genotoxic agents that damage DNA or inhibit its synthesis, whereas biologic agents target various signaling pathways. Importantly, chemotherapeutic and biologic agents induce inflammatory responses or interfere with some of its aspects. Increased expression of VEGF and its receptor are associated with poor prognosis[205] and VEGF inhibition blocks tumor angiogenesis.[206] Interference with the EGF receptor signaling, which is aberrantly activated in approximately 80% of colon cancers,[207] reduces survival and growth of cancer cells. Cetuximab and panitumumab bind to the EGF receptor and block its activation, inhibiting tumor growth and inducing tumor cell apoptosis when used in combination with classical chemotherapeutic agents.[208]

Nonsteroidal anti-inflammatory drugs such as sulindac, which inhibits COX1, COX2,[209] and NF-κB activity, prevent and are used to treat CRC.[40,210] Other nonsteroidal anti-inflammatory drugs, such as aspirin, reduce CRC risk in a dose- and time-dependent manner, and are mostly considered to be chemopreventive agents.[211] One study showed a beneficial effect of aspirin use in patients who already have CRC.[212] Aspirin inhibits COX1 and COX2, although COX2 is the isoform whose increased activity is associated with CRC pathogenesis, whereas constitutively expressed COX1 might be required for homeostatic functions.[213] Specific COX2 inhibitors, such as celecoxib and rofecoxib, reduced CRC risk and slowed progression of colorectal adenomatous polyps to carcinomas.[166,214] However, prolonged use of rofecoxib (and to a lesser extent celecoxib) increased risk for cardiovascular complications.[215] Furthermore, COX2 inhibitors had detrimental effects in patients with chronic colitis, exacerbating mucosal damage repair requires PGE.[216] Highly selective inhibitors of PGE_2 signaling, such as ONO-8711 receptor antagonists, are expected to reduce the cardiovascular risks associated with COX inhibition but still prevent CRC.[217]

Table 4. Anticytokine Reagents that Prevent Intestinal Inflammation

Reagent	Target	Condition
Adalimumab[a]	TNF	CD, UC
Certolizumab pegol[a]		CD
CNI-1493		CD
Golimumab		CD, UC
Infliximab[a]		
C326	IL-6	CD
Tocilizumab		CD
ABT-874	IL-12/23	CD
STA 5326		CD
Ustekinumab		CD
Basiliximab	IL-2 receptor	UC
Daclizumab		UC
AIN457	IL-17	CD
HuZAF	IFN-γ	CD, UC
Rituximab	CD20	CD

NOTE. Data compiled from Waldner and Neurath,[52] Rutgeerts et al,[242] and www.clinicaltrials.gov.
CD, Crohn's disease; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; UC, ulcerative colitis.
[a]Compounds approved for clinical use.

Inhibitors of proinflammatory cytokines might also be developed to block inflammation and treat patients with CRC or CAC (Table 4). Reagents that inhibit cytokines such as IL-6, TNF, IL-1, IL-17, or IL-23 might be used to treat CRC and CAC, but have not been yet tested in clinical trials; these types of trials should be performed soon because some of these reagents have been shown to be effective in patients with IBD and their side effects are known (Table 4). Inhibitors of TNF and IL-1, such as infliximab, etanercept, or anakinra, are already used to treat patients with autoimmune disorders. Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, is in phase II trials and has beneficial effects in patients with Crohn disease.[141] Two monoclonal antibodies (ABT-874 and CNTO-1275) against the p40 subunit of IL-12 and IL-23[218] and an antibody against IFN-γ (fontolizumab)[219] are being tested in patients with IBD.

Blocking adhesion molecules on the immune cells can prevent their recruitment to the sites of injury, inflammation, or tumorigenesis and block an excessive inflammatory response. Natalizumab is humanized antibody against the α_4 integrin subunit; it was shown to be effective in treating patients with Crohn disease and is approved for clinical use.[220] Anti-$\alpha_4\beta_7$ (vedolizumab) is being tested in clinical trials for IBD,[221] but not colon cancer. A monoclonal antibody against CD3 (visilizumab), which prevents T-cell activation, had promising preliminary results in patients with active Crohn disease.[222] Studies are needed to determine whether these

drugs are effective in treating IBD and preventing CAC. However, they have potential to inhibit antitumor immune responses, especially at the early stages of tumor formation, when it is small enough to be eliminated by the host immune system. Some anticytokine and anti-inflammatory agents (such as anti-TNF, anti-IL-6, or anti-IL-23) appear to be more promising than others (eg, anti-CD3, anti-IFN-γ, anti-IL-12) for treatment of IBD, CAC, and CRC; it is important to determine which agents block IBD and tumor-promoting inflammation without reducing antitumor immunity.

Dietary Compounds that Influence CRC and CAC

Risk factors for CRC include obesity, lack of exercise, alcohol and tobacco consumption, and dietary factors, such the Western diet (large amounts of red meat and fat, low amounts of vegetables, fruit, and fiber).[223] Several other compounds have been found to reduce CRC risk, including carbohydrates (inulin and oligofructose), unsaturated n-3 fatty acids, vitamins, minerals (calcium and selenium), and phytochemicals (resveratrol, curcumin).[224] Although the molecular mechanisms of these compounds are unknown and probably numerous, there is evidence that they reduce inflammation and decrease the activity of oncogenic signaling pathways. For example, vitamin D reduces the amount of activated β-catenin and can therefore reduce expression of c-Myc in certain cell lines.[225,226] Butyrate, a derivate of inulin and oligofructose that is produced by certain colonic bacteria, seem to modulate TGF-β, COX2, and IFN-γ signaling by unknown mechanisms.[227,228] The anti-inflammatory effects of unsaturated, n-3 fatty acids are well-documented and could result from inhibition of JNK activation by saturated fatty acids (R. Holzer and M. Karin, unpublished). Curcumin, resveratrol, and green tea polyphenols have a wide range of antitumor activities, affecting inflammation by reducing activation of NF-κB.[229] However, their beneficial activities might arise from their antioxidant properties.[230]

Conclusions and Perspectives

Inflammation affects every facet of tumor development and might also affect the efficacy of cancer therapies. Anti-inflammatory drugs can reduce CRC risk and clinical trials should indicate the therapeutic efficacy of anti-inflammatory biologics, such as anti-TNF, anti-IL-6, anti-IL-1, and inhibitors of NF-κB and STAT3. Importantly, anti-inflammatory drugs target myeloid and lymphoid cells, which do not carry oncogenic mutations and, therefore, do not undergo rapid evolution and selection. This is a highly attractive feature of anti-inflammation therapies—they might avoid the rapid development of resistance that occurs to drugs that target cancer cells. Anti-inflammatory reagents that can be used to prevent and treat CRC and CAC might be combined with conventional therapies, such as chemo- or radiotherapy, to increase their efficacy.

Supplementary Material

Note: The first 50 references associated with this article are available below in print. The remaining references accompanying this article are available online only with the electronic version of the article. Visit the online version of Gastroenterology at www.gastrojournal.org, and at doi:10.1053/j.gastro.2010.01.058.

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Conflicts of interest

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