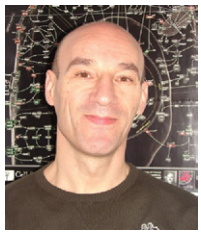
Inflammation and Colon Cancer

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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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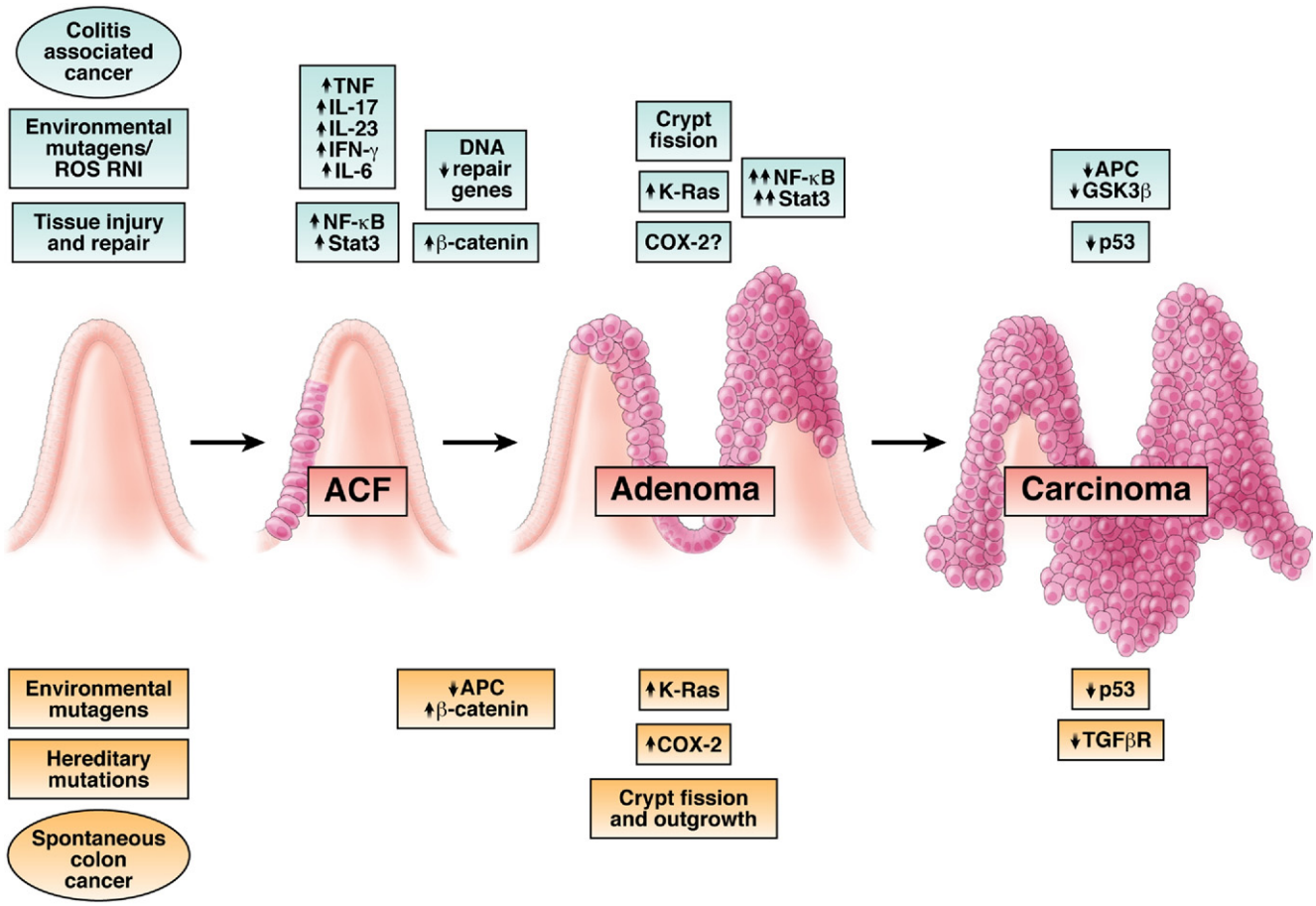

Figure 1. Mechanisms of colorectal cancer (CRC) and colitis-associated cancer (CAC) development.CRC is caused by accumulation of mutations in oncogenes and tumor suppressor genes; some of these lead to aberrant activation of β-catenin signaling. Mutations in *adenomatous polyposis coli (APC),* β-catenin, 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