COLORECTAL CANCER

Epidemiology

Colorectal cancer is the third most common cancer as well as the third most common cause of cancer-related death in the United States, with approximately 150,000 new cases diagnosed each year. Worldwide, it is a growing problem and is one of the most common cancers. There appears to be an increased association with high dietary fat, red meat consumption, low dietary fiber, obesity, and alcohol use. Conversely, increased physical activity and use of supplemental estrogen, folate vitamin, aspirin, and nonsteroidal anti-inflammatory drugs appear to be protective. A history of inflammatory bowel disease is a risk factor for colorectal cancer.

Pathology

Adenocarcinoma of the colon progresses from normal epithelium to frank cancer in a stepwise fashion, as illustrated in Figure 57-1. Most colon cancers arise in polyps. Typically, hamartomatous polyps are non-neoplastic, serrated, and hyperplastic; they have low neoplastic potential, whereas adenomatous polyps can progress to cancer. Sporadic colon cancers arise by one of three major molecular pathways:

1. The classic adenoma-carcinoma sequence, accounting for about 75% of all colon cancers, is initiated by a somatic mutation of the adenomatous polyposis coli *(APC)* gene. This leads to dysregulation of the *WNT* signaling pathway through release of β-catenin and subsequent upregulation of *MYC* and *CCND1 (Cyclin D1)*, two key cell proliferation genes, causing adenoma formation. As disease progresses, chromosomal instability and mutations in other genes, such as *KRAS*, *TP53*, and *SMAD2/4* accumulate, leading to eventual development of adenocarcinoma.
2. In the DNA mismatch repair pathway, mutations accumulate, leading to the formation of "microsatellites." This condition, termed *microsatellite instability*, is associated with 15% of all colon cancers. Increased methylation of tandem repeats of cytosine and guanine, called CpG islands, in the promoter region of various genes in this pathway (e.g., *MLH1*), promote carcinogenesis. *BRAF* mutations are commonly seen in association with this pathway.
3. Promoter methylation, in the absence of microsatellite instability, can also lead to colon cancer formation. These tumors also develop *KRAS*, but not *BRAF*, mutations. Such cases account for about 5% of all colon cancers.

Inherited abnormalities in many of the genes mentioned earlier lead to a genetic predisposition to colon cancer. Such syndromes are responsible for 3% to 5% of all colon cancers. They can be divided into syndromes associated with underlying polyps and those without polyps. Classic familial adenomatous polyposis (FAP) is caused by an autosomal dominant mutation in the *APC* gene. The colon is full of polyps—hundreds to thousands—that start forming during adolescence, leading to development of cancer in early adulthood. Patients with attenuated FAP have fewer polyps and later development of malignancy. *MYH*-associated polyposis is caused by an autosomal recessive mutation in the *MYH* gene, and the phenotype mimics that of attenuated FAP. Peutz-Jeghers syndrome, juvenile polyposis, and Cowden's syndrome are other uncommon conditions that are associated with an inherited predisposition to colorectal polyps leading to cancer.

The classic nonpolyposis syndrome is hereditary nonpolyposis colorectal cancer, also called Lynch syndrome. Germline recessive mutations in genes involved in the mismatch repair pathway (*MSH2, MSH3, MSH6, MLH1, MLH3, PMS1, PMS2*) lead to adenocarcinoma. These cases are indistinguishable from sporadic cases associated with defective mismatch repair except for the family history of colon and other associated cancers in the inherited syndrome.

Clinical Presentation

Hematochezia and altered bowel habits are the classic symptoms of colon cancer. Early cases are essentially asymptomatic and are typically identified by screening. Advanced cases can manifest with bowel obstruction or perforation, frank rectal bleeding, weight loss, abdominal pain, and ascites due to hepatic or peritoneal metastases. Cancers associated with the mismatch repair pathway have certain typical features: They are right-sided, occur

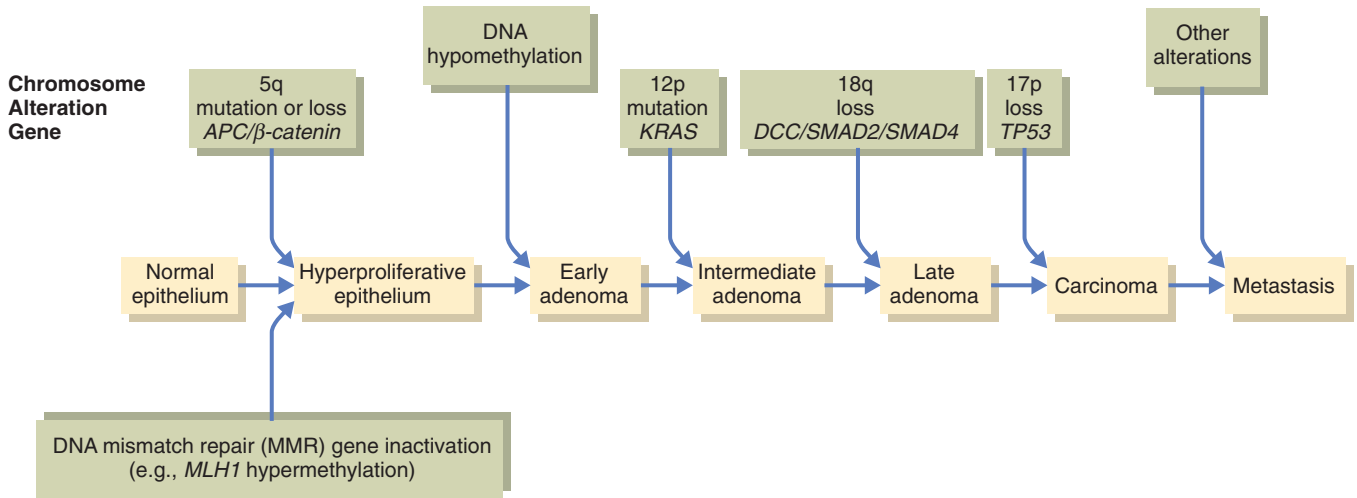

FIGURE 57-1 Model of colorectal carcinogenesis. Several genes are involved in the stepwise progression from normal colonic epithelium to adenocarcinoma.