translocates to the nucleus, where it forms a complex with the DNA-binding factor TCF and activates the transcription of genes, including MYC and cyclin D1, that promote proliferation. The critical role of β-catenin in this pathway is demonstrated by the fact that many colon cancers without *APC* mutations harbor β-catenin mutations that allow them to avoid APC-dependent degradation, thereby having the same impact as loss of APC function. Additional mutations accumulate, including activating mutations in *KRAS* that promote growth and prevent apoptosis. The idea that mutation of *KRAS* is a late event in carcinoma development is supported by the observation that such mutations are present in fewer than 10% of adenomas less than 1 cm in diameter but are found in 50% of adenomas greater than 1 cm in diameter and in 50% of invasive adenocarcinomas. Neoplastic progression is also associated with mutations in other tumor suppressor genes such as those encoding SMAD2 and SMAD4, which are effectors of TGF-β signaling. Because TGF-β signaling normally inhibits the cell cycle, loss of these genes may allow unrestrained cell growth. The tumor suppressor gene *TP53* is mutated in 70% to 80% of colon cancers, but is uncommonly affected in adenomas, suggesting that *TP53* mutations also occur at later stages of tumor progression. Loss of function of *TP53* and other tumor suppressor genes is often caused by chromosomal deletions, supporting the idea that chromosomal instability is a hallmark of the APC/β-catenin pathway. Alternatively, tumor suppressor genes may be silenced by methylation of a CpG-rich zone, or CpG island, a 5′ region of some genes that frequently includes the promoter and transcriptional start site. Expression of telomerase also increases as lesions become more advanced.

- **In patients with DNA mismatch repair deficiency, mutations accumulate in microsatellite repeats, a condition referred to as microsatellite instability (MSI).** These are referred to as MSI high, or MSI-H, tumors. Some microsatellite sequences are located in the coding or promoter regions of genes involved in regulation of cell growth, such as those encoding the type II TGF-β receptor and the pro-apoptotic protein BAX (Fig. 17-50). Because TGF-β inhibits colonic epithelial cell proliferation, mutation of type II TGF-β receptor can contribute to uncontrolled cell growth, while loss of *BAX* may enhance the survival of genetically abnormal clones.
- **A subset of microsatellite unstable colon cancers without mutations in DNA mismatch repair enzymes demonstrate the CpG island hypermethylation phenotype (CIMP).** In these tumors, the *MLH1* promoter region is typically hypermethylated, thereby reducing MLH1 expression and repair function. Activating mutations in the oncogene *BRAF* are common in these cancers. In contrast, *KRAS* and *TP53* are not typically mutated. Thus, the combination of microsatellite instability, *BRAF* mutation, and methylation of specific targets, such as *MLH1*, is the signature of this pathway of carcinogenesis.
- **A small group of colon cancers display increased CpG island methylation in the absence of microsatellite instability.** Many of these tumors harbor *KRAS* mutations, but *TP53* and *BRAF* mutations are uncommon. In contrast, *TP53* mutations are common in colon cancers that do not display a CpG island methylator phenotype.

While morphology cannot reliably define the underlying molecular events that lead to carcinogenesis, certain correlations have been associated with mismatch repair deficiency and microsatellite instability. These molecular alterations are common in sessile serrated adenomas and cancers that arise from them. In addition, invasive carcinomas with microsatellite instability often have prominent mucinous differentiation and peritumoral lymphocytic infiltrates. These tumors, as well as those with a CpG island hypermethylation phenotype, are frequently located in the right colon. Tumors with microsatellite instability can be recognized by the absence of immunohistochemical staining for mismatch repair proteins or by molecular genetic analysis of microsatellite sequences. It is important to identify patients with HNPCC because of the implications for genetic counseling, the elevated risk of a second malignancy of the colon or other organs, and, in some settings, differences in prognosis and therapy.

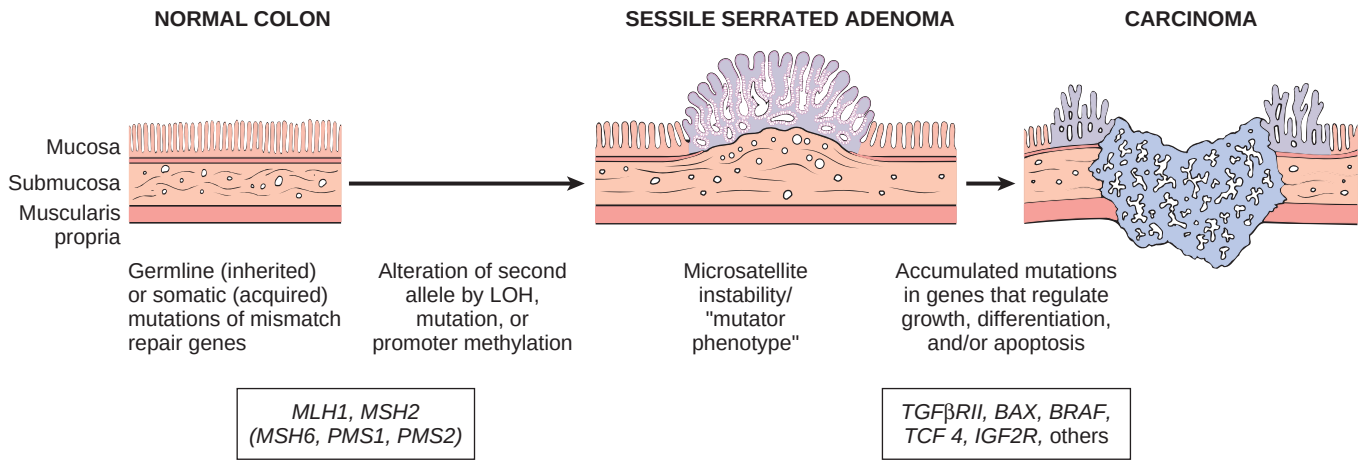

Figure 17-50 Morphologic and molecular changes in the mismatch repair pathway of colon carcinogenesis. Defects in mismatch repair genes result in microsatellite instability and permit accumulation of mutations in numerous genes. If these mutations affect genes involved in cell survival and proliferation, cancer may develop.