KEY CONCEPTS

Evasion of Immune Surveillance

- Tumor cells can be recognized by the immune system as non-self and destroyed.
- Antitumor activity is mediated by predominantly cell-mediated mechanisms. Tumor antigens are presented on the cell surface by MHC class I molecules and are recognized by CD8+ CTLs.
- The different classes of tumor antigens include products of mutated proto-oncogenes, tumor suppressor genes, overexpressed or aberrantly expressed proteins, tumor antigens produced by oncogenic viruses, oncofetal antigens, altered glycolipids and glycoproteins, and cell type-specific differentiation antigens.
- Immunosuppressed patients have an increased risk for development of cancer, particularly types caused by oncogenic DNA viruses.
- In immunocompetent patients, tumors may avoid the immune system by several mechanisms, including selective outgrowth of antigen-negative variants, loss or reduced expression of histocompatibility antigens, and immunosuppression mediated by expression of certain factors (e.g., TGF-β, PD-1 ligand, galectins) by the tumor cells.
- Antibodies that overcome these mechanisms of immune evasion are showing promise in clinical trials conducted in patients with advanced cancer.

Genomic Instability

Genetic aberrations that increase mutation rates are very common in cancers and expedite the acquisition of driver mutations that are required for transformation and subsequent tumor progression. Although humans literally swim in environmental agents that are mutagenic (e.g., chemicals, radiation, sunlight), cancers are relatively rare outcomes of these encounters. This state of affairs results from the ability of normal cells to repair DNA damage, the death of cells with irreparable damage (see "Evasion of Apoptosis" earlier), and other mechanisms, such as oncogene-induced senescence and immune surveillance.

We have previously discussed is the role of the *TP53* tumor suppressor gene in protecting the genome from potentially oncogenic damage, both by arresting cell division to provide time for repair of DNA damage caused by environmental mutagens and by initiating apoptosis in irreparably damaged cells. The importance of DNA repair in maintaining the integrity of the genome is further highlighted by several inherited disorders in which genes that encode proteins involved in DNA repair are defective. Individuals born with such inherited defects in DNA-repair proteins are at a greatly increased risk of developing cancer. Moreover, defects in repair mechanisms are present in certain kinds of sporadic human cancers. Mutations in DNA-repair genes themselves are not oncogenic, but their abnormalities greatly enhance the occurrence of mutations in other genes during the process of normal cell division. Typically, genomic instability occurs when both copies of the DNA repair gene are lost; however, some work has suggested that haploinsufficiency of at least a subset of these genes may also promote cancer. As explained below, defects in three types of DNA-repair systems—mismatch repair, nucleotide excision repair, and recombination repair—contribute to different types of cancers.

Hereditary Nonpolyposis Colon Cancer Syndrome. Hereditary nonpolyposis colon cancer (HNPCC) syndrome is an autosomal dominant disorder characterized by familial carcinomas of the colon affecting predominantly the cecum and proximal colon (Chapter 17). It results from defects in a family of genes encoding a group of proteins that work together to carry out *DNA mismatch repair.* When a strand of DNA is being replicated, these proteins act as "spell checkers." For example, if there is an erroneous pairing of G with T rather than the normal A with T, the mismatch-repair factors correct the defect. Individuals with HNPCC syndrome inherit one abnormal copy of a mismatch repair gene. Trouble arises when cells acquire loss-of-function mutations, presumably at random, in their normal alleles. With "proofreading" function lost, errors gradually accumulate throughout the genome, and some of these errors may by chance activate proto-oncogenes or inactivate tumor suppressor genes. With time, a cancer may result. Thus, DNA-repair genes behave like tumor suppressor genes in their mode of inheritance, but in contrast to tumor suppressor genes (and oncogenes), they affect cell growth only indirectly—by allowing mutations in other genes during the process of normal cell division.

One of the hallmarks of patients with mismatch-repair defects is *microsatellite instability.* Microsatellites are tandem repeats of one to six nucleotides found throughout the genome. In normal people the length of these microsatellites remains constant. However, in people with HNPCC, these satellites are unstable and increase or decrease in length in tumor cells, creating alleles not found in normal cells of the same patient.

Of the various DNA mismatch-repair genes, at least four are involved in the pathogenesis of HNPCC. Germline mutations in the *MSH2* and *MLH1* genes each account for approximately 30% of cases. The remaining cases have mutations in other mismatch repair genes. Although HNPCC accounts only for 2% to 4% of all colonic cancers, microsatellite instability can be detected in about 15% of sporadic colon cancers. The cancer genes that are mutated in HNPCC tumors have not yet been fully characterized but include the genes encoding TGF-β receptor II, the TCF component of the β-catenin pathway, *BAX*, and other oncogenes and tumor suppressor genes.

Xeroderma Pigmentosum. Individuals with another inherited disorder of DNA repair, xeroderma pigmentosum, are at increased risk for the development of cancers of the skin particularly following exposure to the UV light contained in sun rays. UV radiation causes cross-linking of pyrimidine residues, preventing normal DNA replication. Such DNA damage is repaired by the nucleotide excision repair system. Several proteins are involved in *nucleotide excision repair*, and an inherited loss of any one can give rise to xeroderma pigmentosum.

Diseases with Defects in DNA Repair by Homologous Recombination. Several rare autosomal recessive cancer syndromes have been described that are characterized by hypersensitivity to certain kinds of DNA-damaging agents, such as ionizing radiation (*Bloom syndrome* and