ataxia-telangiectasia), or DNA cross-linking agents, such as many chemotherapeutic drugs (*Fanconi anemia*). The phenotype of these diseases is complex and includes, in addition to predisposition to cancer, features such as neural symptoms (ataxia-telangiectasia), bone marrow aplasia (Fanconi anemia), and developmental defects (Bloom syndrome).

- As mentioned earlier, the gene mutated in ataxia-telangiectasia, *ATM*, is important in recognizing and responding to DNA damage caused by ionizing radiation. Persons with Bloom syndrome have a predisposition to a very broad spectrum of tumors. The defective gene encodes a helicase that participates in DNA repair by homologous recombination.
- There are 13 genes that make up the Fanconi anemia complex; mutation of any one of these genes can result in the phenotype. Interestingly, *BRCA2*, which is mutated in some individuals with familial breast cancer, is also mutated in a subset of persons with Fanconi anemia.
- Mutations in two genes, *BRCA1* and *BRCA2*, account for 25% of cases of familial breast cancer. In addition to breast cancer, women with *BRCA1* mutations have a substantially higher risk of epithelial ovarian cancers, and men have a slightly higher risk of prostate cancer. Likewise, mutations in the *BRCA2* gene increase the risk of breast cancer in both men and women as well as cancer of the ovary, prostate, pancreas, bile ducts, stomach, melanocytes, and B lymphocytes. Although their functions have not been elucidated fully, cells that lack these genes develop chromosomal breaks and severe aneuploidy. It appears that the Fanconi anemia proteins and the BRCA proteins form a DNA-damage response network whose purpose is to repair certain types of DNA damage using the homologous recombination repair pathway. Defects in this pathway leads to the activation of the salvage nonhomologous end joining pathway, formation of dicentric chromosomes, bridge-fusion-breakage cycles, and massive aneuploidy. Although linkage of *BRCA1* and *BRCA2* to familial breast cancers is established, these genes are rarely inactivated in sporadic cases of breast cancer. In this regard, *BRCA1* and *BRCA2* are different from other tumor suppressor genes, such as *APC* and *p53*, which are inactivated in both familial and sporadic cancers.

Cancers Resulting from Mutations Induced by Regulated Genomic Instability: Lymphoid Neoplasms. A special type of DNA damage plays a central role in the pathogenesis of tumors of B and T lymphocytes. As described in Chapter 6, adaptive immunity relies on the ability of B and T cells to diversify their antigen receptor genes. Early B and T cells both express a pair of gene products, RAG1 and RAG2, that carry out V(D)J segment recombination, permitting the asembly of functional antigen receptor genes. In addition, after encountering antigen mature B cells express a specialized enzyme called antigen-induced cytosine deaminase (AID), which catalyzes both immunoglobulin gene class switch recombination and somatic hypermutation. Errors during antigen receptor gene assembly and diversification are responsible for many of the mutations that cause lymphoid neoplasms (Chapter 13).

KEY CONCEPTS

Genomic Instability as Enabler of Malignancy

- Persons with inherited mutations of genes involved in DNA repair systems are at greatly increased risk for the development of cancer.
- Patients with HNPCC syndrome have defects in the mismatch repair system, leading to development of carcinomas of the colon. These patients' genomes show microsatellite instability, characterized by changes in length of short repeats throughout the genome.
- Patients with xeroderma pigmentosum have a defect in the nucleotide excision repair pathway and are at increased risk for the development of cancers of the skin exposed to UV light, because of an inability to repair pyrimidine dimers.
- Syndromes involving defects in the homologous recombination DNA repair system constitute a group of disorders—Bloom syndrome, ataxia-telangiectasia, and Fanconi anemia—that are characterized by hypersensitivity to DNA-damaging agents, such as ionizing radiation. *BRCA1* and *BRCA2*, which are mutated in familial breast cancers, are involved in DNA repair.
- Mutations incurred in lymphoid cells due to expression of gene products that induce genomic instability (RAG1, RAG2, AID) are important causes of lymphoid neoplasms.

Cancer-Enabling Inflammation

Infiltrating cancers provoke a chronic inflammatory reaction, leading some to liken them to "wounds that do not heal." In patients with advanced cancers, this inflammatory reaction can be so extensive as to cause systemic signs and symptoms, such as anemia (due to inflammation-induced sequestration of iron and downregulation of erythropoietin production, Chapter 14), fatigue, and cachexia (described later). However, studies carried out on cancers in animal models suggest that inflammatory cells also modify the local tumor microenvironment to enable many of the hallmarks of cancer. These effects may stem from direct interactions between inflammatory cells and tumor cells, or through indirect effects of inflammatory cells on other resident stromal cells, particularly cancer-associated fibroblasts and endothelial cells. Proposed cancer-enabling effects of inflammatory cells and resident stromal cells include the following:

- **Release of factors that promote proliferation**. Infiltrating leukocytes and activated stromal cells have been shown to secrete a wide variety of growth factors, such as EGF, and proteases that can liberate growth factors from the extracellular matrix (ECM).
- **Removal of growth suppressors**. As mentioned, the growth of epithelial cells is suppressed by cell-cell and cell-ECM interactions. Proteases released by inflammatory cells can degrade the adhesion molecules that mediate these interactions, removing a barrier to growth.
- **Enhanced resistance to cell death**. Recall that detachment of epithelial cells from basement membranes and from cell-cell interactions can lead to a particular form of cell death called *anoikis*. It is suspected that tumor-associated macrophages may prevent anoikis by