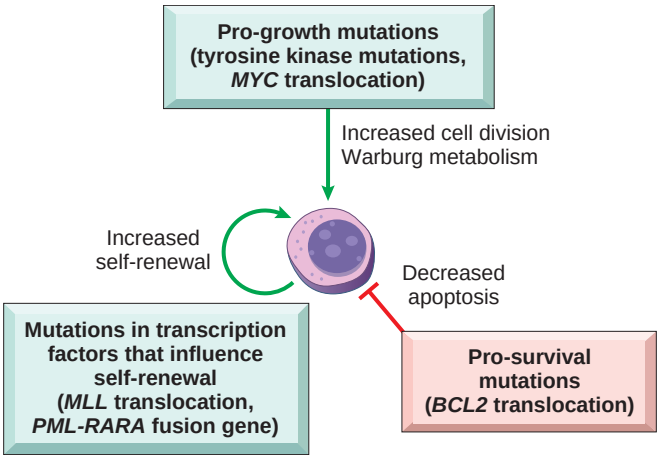

Figure 13-4 Pathogenesis of white cell malignancies. Various tumors harbor mutations that principally effect maturation or enhance self-renewal, drive growth, or prevent apoptosis. Exemplary examples of each type of mutation are listed; details are provided later under specific tumor types.

giving such cells stem-cell–like properties. These types of mutations often collaborate with mutations that produce a constitutively active tyrosine kinase; oncogenic tyrosine kinases activate RAS and its two downstream signaling arms, the PI3K/AKT and MAPK pathways (Chapter 7), and thereby drive cell growth and Warburg metabolism.

- Finally, mutations that inhibit apoptosis are prevalent in certain hematologic malignancies.

- **Proto-oncogenes are often activated in lymphoid cells by errors that occur during antigen receptor gene rearrangement and diversification.** Among lymphoid cells, potentially oncogenic mutations occur most frequently in germinal center B cells during attempted antibody diversification. After antigen stimulation, B cells enter germinal centers and upregulate the expression of activation-induced cytosine deaminase (AID), a specialized DNA-modifying enzyme that is essential for two types of immunoglobulin (Ig) gene modifications: *class switching*, an intragenic recombination event in which the IgM heavy-chain constant gene segment is replaced with a different constant segment (e.g., IgG_3), leading to a switch in the class (isotype) of antibody produced; and *somatic hypermutation*, which creates point mutations within Ig genes that may increase antibody affinity for antigen (Chapter 6). Certain proto-oncogenes, such as *MYC*, are activated in germinal center B-cell lymphomas by translocations to the transcriptionally active Ig locus. Remarkably, AID expression is sufficient to induce *MYC/Ig* translocations in normal germinal center B cells, apparently because AID creates lesions in DNA that lead to chromosomal breaks. Other proto-oncogenes, such as *BCL6*, a transcription factor that has an important role in many B cell malignancies, are frequently activated in germinal center B-cell lymphomas by point mutations that also seem to stem from "mistargeted" DNA breaks induced by AID. A different type of regulated genomic instability is unique to precursor B and T cells, which express a V(D)J recombinase that cuts DNA at specific sites within the Ig and T-cell receptor loci, respectively. This process is essential for the assembly of productive antigen receptor genes, but sometimes goes awry, leading to the joining of portions of other genes to antigen receptor gene regulatory elements. Particularly in tumors of precursor T cells, proto-oncogenes are often deregulated by their involvement in such aberrant recombination events.

Inherited Genetic Factors. As discussed in Chapter 7, individuals with genetic diseases that promote genomic instability, such as Bloom syndrome, Fanconi anemia, and ataxia telangiectasia, are at increased risk of acute leukemia. In addition, both Down syndrome (trisomy 21) and type I neurofibromatosis are associated with an increased incidence of childhood leukemia.

Viruses. Three lymphotropic viruses—human T-cell leukemia virus-1 (HTLV-1), Epstein-Barr virus (EBV), and Kaposi sarcoma herpesvirus/human herpesvirus-8 (KSHV/HHV-8)—have been implicated as causative agents in particular lymphomas. The possible mechanisms of transformation by viruses are discussed in Chapter 7. HTLV-1 is associated with adult T-cell leukemia/lymphoma. EBV is found in a subset of Burkitt lymphoma, 30% to 40% of Hodgkin lymphoma (HL), many B-cell lymphomas arising in the setting of T-cell immunodeficiency, and rare NK-cell lymphomas. In addition to Kaposi sarcoma (Chapter 11), KSHV is associated with an unusual B-cell lymphoma that presents as a malignant effusion, often in the pleural cavity.

Chronic Inflammation. Several agents that cause localized chronic inflammation predispose to lymphoid neoplasia, which almost always arises within the inflamed tissue. Examples include the associations between *H. pylori* infection and gastric B-cell lymphomas (Chapter 17), gluten-sensitive enteropathy and intestinal T-cell lymphomas, and even breast implants, which are associated with an unusual subtype of T cell lymphoma. This can be contrasted with HIV infection, which is associated with an increased risk of B-cell lymphomas that may arise within virtually any organ. Early in the course, T-cell dysregulation by HIV infection causes a systemic hyperplasia of germinal center B cells that is associated with an increased incidence of germinal center B-cell lymphomas. In advanced infection (acquired immunodeficiency syndrome), severe T-cell immunodeficiency further elevates the risk for B-cell lymphomas, particularly those associated with EBV and KSHV/HHV-8. These relationships are discussed in more detail in Chapter 6.

Iatrogenic Factors. Ironically, radiation therapy and certain forms of chemotherapy used to treat cancer increase the risk of subsequent myeloid and lymphoid neoplasms. This association stems from the mutagenic effects of ionizing radiation and chemotherapeutic drugs on hematolymphoid progenitor cells.

Smoking. The incidence of acute myeloid leukemia is increased 1.3- to 2-fold in smokers, presumably because of exposure to carcinogens, such as benzene, in tobacco smoke.