are sufficiently specific that they can serve as markers that aid in tumor diagnosis and clinical management. The two most thoroughly characterized oncofetal antigens are carcinoembryonic antigen (CEA) and α-fetoprotein (AFP). These are discussed in the section on "Tumor Markers."

- **Altered cell surface glycolipids and glycoproteins.** Most human and experimental tumors express higher than normal levels and/or abnormal forms of surface glycoproteins and glycolipids, which may be diagnostic markers and targets for therapy. These altered molecules include gangliosides, blood group antigens, and mucins. Mucins are high-molecular-weight glycoproteins containing numerous O-linked carbohydrate side chains on a core polypeptide. Tumors often have dysregulated expression of the enzymes that synthesize these carbohydrate side chains, which leads to the appearance of tumor-specific epitopes on the carbohydrate side chains or on the abnormally exposed polypeptide core. Several mucins have been the focus of diagnostic and therapeutic studies, including CA-125 and CA-19-9, expressed on ovarian carcinomas, and MUC-1, expressed on both ovarian and breast carcinomas. Unlike many mucins, MUC-1 is an integral membrane protein that is normally expressed only on the apical surface of breast ductal epithelium, a site that is relatively sequestered from the immune system. In ductal carcinomas of the breast, however, the molecule is expressed in an unpolarized fashion and contains new, tumor-specific carbohydrate and peptide epitopes detectable by mouse monoclonal antibodies. The peptide epitopes induce both antibody and T-cell responses in cancer patients and are therefore considered candidates for tumor vaccines in patients with breast cancer and possibly ovarian cancer as well.
- **Cell type–specific differentiation antigens.** Tumors express molecules that are normally present on the cells of origin. These antigens are called *differentiation antigens* because they are specific for particular lineages or differentiation stages of various cell types. Such differentiation antigens are typically normal self-antigens, and therefore they do not induce immune responses in tumor-bearing hosts. Their importance is as potential targets for immunotherapy and for identifying the tissue of origin of tumors. There are now several examples of monoclonal antibodies that recognize cell type specific antigens that are highly effective anti-tumor agents. Antibodies against CD20, a transmembrane protein that is expressed on the surface of all normal mature B cells, have broad cytocidal activity against mature B-cell lymphomas and leukemias and are widely used in the treatment of these tumors. These antibodies are believed to induce cell killing through several mechanisms, including opsonization and phagocytosis of tumor cells, antibody-dependent cell-mediated cytotoxicity and complement fixation. Anti-CD20 antibodies also kill normal B cells, but because hematopoietic stem cells are spared, normal B cells reemerge following treatment.

  Monoclonal antibodies may also be covalently coupled to drugs, toxins, or radiochemicals; in this instance, the antibody serves as guided missile that delivers a therapeutic warhead to cancers expressing particular surface antigens. This strategy has now produced effective treatments for several cancers. For example, CD30 is a member of the TNF receptor family of transmembrane proteins that is expressed by particular T cell lymphomas and most Hodgkin lymphomas. Antibodies against CD30 linked to a cytotoxic drug have recently produced remarkable responses in patients with CD30-positive lymphomas that have failed conventional therapies. Other antibodies of this type, such as toxin-conjugated antibodies specific for HER2, are now being evaluated. Finally, bispecific antibodies engineered to have two different antigen recognition surfaces, one that binds tumor antigens and a second that binds to the CD3 signaling molecule on T cells, have produced some promising results in clinical trials.

Antitumor Effector Mechanisms

Cell-mediated immunity is the dominant antitumor mechanism in vivo. Although sera from cancer patients may contain antibodies that recognize tumors, there is limited evidence that they play a protective role under physiologic conditions. The cellular effectors that mediate immunity are described in Chapter 6.

- **Cytotoxic T lymphocytes**. The antitumor effect of cytotoxic T cells reacting against tumor antigens is well established in experimentally induced tumors. In humans, CD8+ CTLs have a clear protective role against virus-associated neoplasms (e.g., EBV- and HPV-induced tumors), and several studies have shown that the number of tumor-infiltrating CD8+ T cells and the presence of a "gene signature" associated with CD8+ CTLs correlates with a better prognosis in a variety of cancers, not only those caused by oncogenic viruses.
- **Natural killer cells.** NK cells are lymphocytes that are capable of destroying tumor cells without prior sensitization and thus may provide the first line of defense against tumor cells. After activation with IL-2 and IL-15, NK cells can lyse a wide range of human tumors, including many that seem to be nonimmunogenic for T cells. While the importance of NK cells in host response against spontenous tumors is still not well established, cytokines that activate NK cells are being used for immunotherapy.
- **Macrophages**. Activated macrophages exhibit cytotoxicity against tumor cells in vitro. T cells, NK cells, and macrophages may collaborate in antitumor reactivity, because interferon-γ, a cytokine secreted by T cells and NK cells, is a potent activator of macrophages. Activated macrophages may kill tumors by mechanisms similar to those used to kill microbes (e.g., production of reactive oxygen species; Chapter 2).

Immune Surveillance and Escape

Given the many potential antitumor mechanisms, is there any evidence that they operate in vivo to prevent emergence of neoplasms? One strong argument for the existence of immune surveillance is the increased frequency of cancers in the setting of immunodeficiency. Persons with congenital immunodeficiencies develop cancers at about 200 times the rate in immunocompetent individuals. Immunosuppressed transplant recipients and persons with AIDS also have an increased incidence of malignancies.