Most (but not all) of these neoplasms are aggressive lymphomas composed of mature B cells. Particularly illustrative is the rare X-linked recessive immunodeficiency disorder termed *XLP (X-linked lymphoproliferative syndrome)*, caused by mutations in the gene encoding an adapter protein, SAP, which participates in NK and T-cell signaling pathways. In affected boys, EBV infection does not take the usual self-limited form of infectious mononucleosis but instead evolves into a chronic or sometimes fatal form of infectious mononucleosis or, even worse, a lymphoma comprised of EBV-infected B cells.

Most cancers occur in persons who do not suffer from any overt immunodeficiency. It is evident, then, that tumor cells must develop mechanisms to escape or evade the immune system in immunocompetent hosts. Several such mechanisms may be operative (Fig. 7-40).

- **Selective outgrowth of antigen-negative variants**. During tumor progression, strongly immunogenic subclones may be eliminated, an example of immunoediting that has already been discussed.
- **Loss or reduced expression of MHC molecules**. Tumor cells may fail to express normal levels of HLA class I molecules, thereby escaping attack by cytotoxic T cells. Such cells, however, may trigger NK cells if the tumor cells express ligands for NK cell activating receptors.
- **Activation of immunoregulatory pathways**. An important emerging concept is that tumor cells actively inhibit tumor immunity by engaging normal pathways of immune regulation that serve as "checkpoints" in immune responses. Through a variety of mechanisms, tumor cells may downregulate the expression of costimulatory factors on antigen-presenting cells, such as dendritic cells; as a result, the antigen presenting cells fail to engage the stimulatory receptor CD28 and instead activate the inhibitory receptor CTLA-4 on effector T cells. This not only prevents sensitization but also may induce long-lived unresponsiveness in tumor-specific T cells. Tumor cells also may upregulate the expression of PD-L1 and PD-L2, cell surface proteins that activate the programmed death-1 (PD-1) receptor on effector T cells. PD-1, like CTLA-4, may inhibit T cell activation. Antibodies that block the inhibitory CTLA-4 or PD-1 receptors have produced promising results in clinical trials conducted in patients with advanced-stage solid tumors. Additional clinical trials are being planned using both PD-1 and CTLA-4 blocking antibodies in combination with each other and with conventional or targeted chemotherapy. The success of these agents has led to a new paradigm in cancer immunotherapy, sometimes called "checkpoint blockade". This is centered on the idea that treatments that remove the "brakes" imposed by tumors on host anti-tumor immune responses can be highly effective in treating cancer.
- **Secretion of immunosuppressive factors by cancer cells**. Tumors may secrete several products that inhibit the host immune response. TGF-β is secreted in large quantities by many tumors and is a potent immunosuppressant. Other tumors secrete galectins, sugar-rich lectin-like factors that skew T-cell responses so as to favor immunosuppression. Many other soluble factors produced by tumors are also suspected of inhibiting the host immune response, including interleukin-10, prostaglandin E2, certain metabolites derived from tryptophan, and VEGF, which can inhibit the diapedesis of T cells from the vasculature into the tumor bed.
- **Induction of regulatory T cells (Tregs)**. Some studies suggest that tumors produce factors that favor the development of immunosuppressive regulatory T cells, which could also contribute to "immunoevasion."

Thus, it seems that there is no dearth of mechanisms by which tumor cells can outwit the host immune system. Nevertheless, the aforementioned response of tumors to immunomodulatory agents, such as antibodies that block CTLA-4 and PD-1, has generated tremendous excitement around the potential of modern cancer immunotherapy. The major challenges now are to determine which immune evasion mechanisms are most important in human cancers (preferably using sensitive and specific biomarker tests that can be performed on each individual patient's cancer) and to develop a broader set of therapies that overcome these mechanisms and induce effective host immunity.

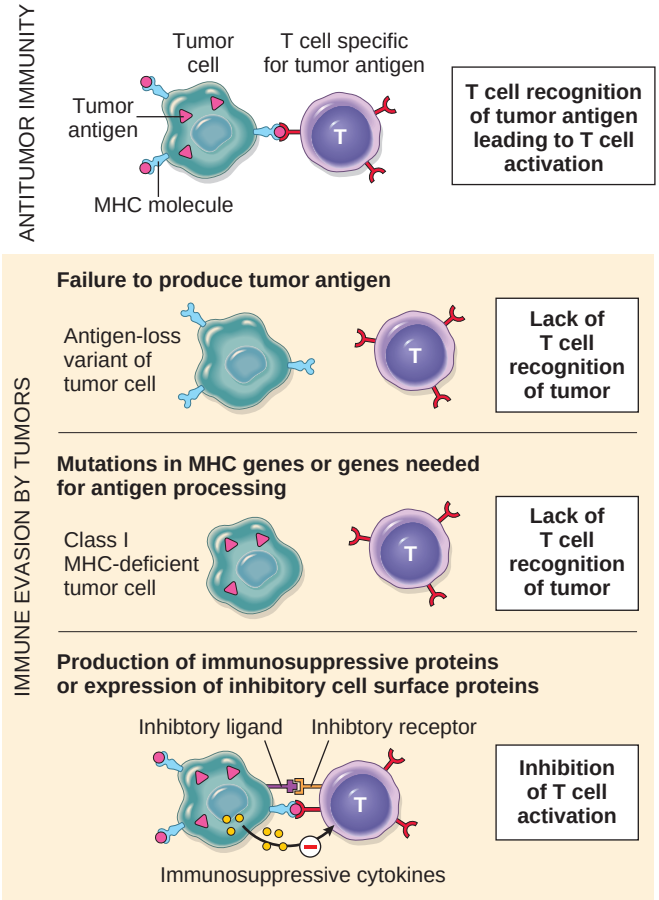

Figure 7-40 Mechanisms by which tumors evade the immune system. Tumors may evade immune responses by losing expression of antigens or major histocompatibility complex (MHC) molecules or by producing immunosuppressive cytokines or ligands such as PD-L1 for inhibitory receptors on T cells. (Reprinted from Abbas AK, Lichtman AH, Pillai S: Cellular and Molecular Immunology, 7th ed. Philadelphia, WB Saunders, 2012.)