angiogenesis inhibitors in cancer patients; of even greater potential benefit are therapies that overcome another hallmark of cancer cells—the ability to evade the host immune response (discussed next).

KEY CONCEPTS

Invasion and Metastasis

- Ability to invade tissues, a hallmark of malignancy, occurs in four steps: loosening of cell-cell contacts, degradation of ECM, attachment to novel ECM components, and migration of tumor cells.
- Cell-cell contacts are lost by the inactivation of E-cadherin through a variety of pathways.
- Basement membranes and interstitial matrix degradation is mediated by proteolytic enzymes secreted by tumor cells and stromal cells, such as matrix metalloproteases and cathepsins.
- Proteolytic enzymes also release growth factors sequestered in the ECM and generate chemotactic and angiogenic fragments from cleavage of ECM glycoproteins.
- The metastatic site of many tumors can be predicted by the location of the primary tumor. Many tumors arrest in the first capillary bed they encounter (lung and liver, most commonly).
- Some tumors show organ tropism, probably due to expression of adhesion or chemokine receptors whose ligands are expressed by endothelial cells the metastatic site.
- Genes that promote epithelial-mesenchymal transitions, like *TWIST* and *SNAIL*, may be important metastasis genes in epithelial tumors

Evasion of Host Defense

Long one of the "holy grails" of oncology, the promise of therapies that enable the host immune system to recognize and destroy cancer cells is finally coming to fruition, largely due to a clearer understanding of the ways by which cancer cells evade the host response. Paul Ehrlich first conceived the idea that tumor cells can be recognized as "foreign" and eliminated by the immune system. Subsequently, Lewis Thomas and Macfarlane Burnet formalized this concept by coining the term *immune surveillance,* which implies that a normal function of the immune system is to constantly "scan" the body for emerging malignant cells and destroy them. This idea has been supported by many observations—the presence of lymphocytic infiltrates around tumors and reactive changes in lymph nodes draining sites of cancer; experimental results, mostly with transplanted tumors; the increased incidence of some cancers in immunodeficient people and mice; the direct demonstration of tumor-specific T cells and antibodies in patients; and most recently and most directly, the response of advanced cancers to therapeutic agents that act by stimulating latent host T-cell responses (described later).

The fact that cancers occur in immunocompetent individuals indicates that immune surveillance is imperfect; however, that some tumors escape such policing does not preclude the possibility that many others were aborted. Assuming that the immune system is capable of recognizing and eliminating nascent cancers, it follows that the tumors that do grow out must be composed of cells that are either invisible to the host immune system or that release factors that actively suppress host immunity. The term *cancer immunoediting* has been used to describe the ability of the immune system to shape and mold the immunogenic properties of tumor cells in a fashion that ultimately leads to the darwinian selection of subclones that are best able to avoid immune elimination. In support of this idea, in the past several years it has become evident that tumors produce a number of factors that promote immune tolerance and immune suppression, and that therapeutic agents that neutralize these factors can lead to tumor regression, even in patients with advanced cancers. These encouraging clinical responses constitute strong evidence that evasion of host immunity is indeed a hallmark of many, if not all, human cancers.

The following section explores some of the important questions about tumor immunity: What is the nature of tumor antigens? What host effector systems recognize tumor cells? How do tumors evade these host mechanisms? And, how can immune reactions against tumors be exploited therapeutically?

Tumor Antigens

Antigens found in tumors that elicit an immune response have been demonstrated in many experimentally induced tumors and in some human cancers. Tumor antigens can be classified according to their molecular structure and source.

The main classes of tumor antigen are as follows (Fig. 7-39):

- **Products of mutated genes.** Neoplastic transformation, as discussed, results from genetic alterations in proto-oncogenes and tumor suppressor genes; these mutated genes encode variant proteins that have never been seen by the immune system and are thus recognized as non-self. Additionally, because of genetic instability, cancers often harbor a high burden of mutations throughout their genomes. Most of these acquired mutations are likely to be "passengers," mutations that are neutral in terms of cancer cell fitness and thus unrelated to the transformed phenotype. However, by chance, some of these passenger mutations may fall in the coding sequences of genes and give rise to protein variants that serve as tumor antigens. The products of altered proto-oncogenes, tumor suppressor genes, and "passenger" genes are translated in the cytoplasm of tumor cells, and like any cytoplasmic protein, they may enter the class I MHC antigen-processing pathway and be recognized by CD8+ T cells. In addition, these proteins may enter the class II antigen-processing pathway in antigen-presenting cells that have phagocytosed dead tumor cells, and thus be recognized by CD4+ T cells also. Some cancer patients have circulating CD4+ and CD8+ T cells that can respond to peptides derived from mutated oncoproteins such as RAS, p53, and BCR-ABL. In animals, immunization with mutated RAS or p53 proteins induces CTLs and rejection responses against tumors expressing these mutated proteins. However, the tumor-specific neoantigens that are recognized by CTLs in patients with cancer are for the most part currently unknown.