



Figure 7-24 Hallmarks of cancer. (Adapted from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; 144:646.)

Warburg effect), which enables the synthesis of the macromolecules and organelles that are needed for rapid cell growth.

- **Evasion of apoptosis.** Tumors are resistant to programmed cell death.
- **Limitless replicative potential (immortality).** Tumors have unrestricted proliferative capacity, a stem cell-like property that permits tumor cells to avoid cellular senescence and mitotic catastrophe.
- **Sustained angiogenesis.** Tumor cells, like normal cells, are not able to grow without a vascular supply to bring nutrients and oxygen and remove waste products. Hence, tumors must induce angiogenesis.
- **Ability to invade and metastasize.** Tumor metastases are the cause of the vast majority of cancer deaths and arise from the interplay of processes that are intrinsic to tumor cells and signals that are initiated by the tissue environment.
- **Ability to evade the host immune response.** You will recall that the cells of the innate and adaptive immune system can recognize and eliminate cells displaying abnormal antigens (e.g., a mutated oncoprotein). Cancer cells exhibit a number of alterations that allow them to evade the host immune response.

The acquisition of the genetic and epigenetic alterations that confer these hallmarks may be accelerated by **genomic instability** and by **cancer-promoting inflammation**. These are considered enabling characteristics because they promote cellular transformation and subsequent tumor progression.

In the following sections, each of the hallmarks and enabling characteristics of cancer cells is discussed, focusing on the most important contributing genes and cellular pathways. The discussion of cancer pathophysiology ends with a review of the roles that epigenetic changes and noncoding RNAs play in the disease.

Self-Sufficiency in Growth Signals: Oncogenes

Genes that promote autonomous cell growth in cancer cells are called *oncogenes*, and their unmutated cellular counter-

parts are called *proto-oncogenes*. **Oncogenes are created by mutations in proto-oncogenes and encode proteins called oncoproteins that have the ability to promote cell growth in the absence of normal growth-promoting signals.** *Oncoproteins* resemble the normal products of proto-oncogenes but bear mutations that are often inactivate internal regulatory elements; consequently, their activity in cells does not depend on external signals. Cells expressing oncoproteins are thus freed from the normal checkpoints and controls that limit growth, and as a result proliferate excessively.

To aid in the understanding of the nature and functions of oncoproteins and their role in cancer, it is necessary to briefly describe how normal cells respond to growth factors. Under physiologic conditions growth factor signaling pathways can be resolved into the following steps:

- The binding of a growth factor to its specific receptor
- Transient and limited activation of the growth factor receptor, which, in turn, activates several cytoplasmic signal-transducing proteins
- Transmission of the transduced signal to the nucleus via additional cytoplasmic effector proteins and second messengers or by a cascade of signal transduction molecules
- Induction and activation of nuclear regulatory factors that initiate DNA transcription
- Expression of factors that promote entry and progression of the cell into the cell cycle, ultimately resulting in cell division
- In parallel, changes in the expression of other genes that support cell survival and metabolic alterations that are needed for optimal growth

Aberrations in multiple signaling pathways have been identified in various tumors; many components of these pathways act as oncoproteins when mutated (Table 7-5). Conversely, a number of tumor suppressors act by inhibiting one or more components of these pathways (discussed later). In Chapter 1, the major signaling pathways that regulate cellular behavior are laid out, including the receptor tyrosine kinase pathway, the G protein-coupled receptor pathway, the JAK/STAT pathway, the WNT pathway, the Notch pathway, the Hedgehog pathway, the TGF β /SMAD pathway, and the NF- κ B pathway. Abnormalities in all these pathways are implicated in the development and progression of various cancers. This chapter focuses on the receptor tyrosine kinase pathway, because it appears to be the most frequently mutated oncogenic pathway in human neoplasms. Oncogenic mutations involving other signaling pathways are also mentioned, because many exemplify certain key concepts underlying cancer phenotypes and some are the targets of effective therapies.

Traditionally, oncoproteins have been likened to accelerators that speed the replication of cells and their DNA; by contrast, tumor suppressors have been viewed as brakes that slow or arrest this process. This view has merit and we will follow it in our initial description of the activities of oncogenes and tumor suppressors. However, the proliferation of cells not only requires the replication of DNA, but also sufficient biosynthesis of membrane, protein, and various macromolecules and organelles to enable a “mother” cell to divide and produce two complete