tumors—properties that permit the relapse of patients following initial treatment success, which creates a pressing need for alternative agents that could be used as later lines of therapy. In fact, drug resistance is still a major problem in oncology and affects old therapies, new targeted drugs, and personalized cancer treatments.

2 TUMORIGENESIS AND ONCOGENES: PHARMACOGENOMICS

Tumorigenesis is a multistep process whose steps reflect genetic alterations including small-scale changes in DNA sequences, such as point mutations; larger scale chromosomal aberrations, such as translocations, deletions, and amplifications; and changes that affect the chromatin structure and are associated with dysfunctional epigenetic control, such as aberrant methylation of DNA or acetylation of histones.[4] Any of these genetic alterations confers one or another type of growth advantage that drives the progressive transformation of normal cells into highly malignant cancer cells. Hanahan and Weinberg reported six hallmarks or biological capabilities acquired during the multistep development of human tumors: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis.[5] Later conceptual progress added new hallmarks to this list: evading immune destruction, deregulating cellular energetics (reprogramming of energy metabolism), genomic instability and mutation, and tumor-promoted inflammation (Figure 1.1).

Furthermore, cancer is not only a cell disease but also a tissular disease in which the normal relationships between epithelial cells and their underlying stromal cells are altered.[6] In fact, tumors contain recruited cells that contribute to the acquisition of the previously mentioned hallmark traits by creating an adequate tumor microenvironment.[7]

Although cancer is not a contagious disease, infectious agents such as viruses can contribute to its origin. Most oncogenes were identified by using retroviruses, and the first evidence of the tumorigenic potential of some genes derived from studies on malignant diseases caused by them. The term *oncogene* was introduced in the mid-1960s to denote special parts of the genetic material of certain viruses

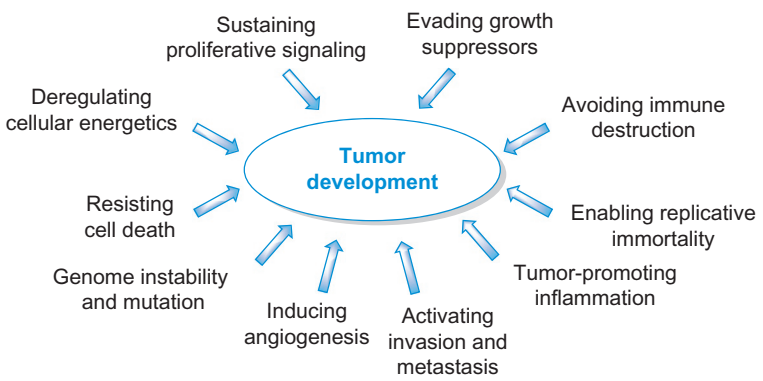

FIGURE 1.1

The tumorigenesis process.