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Cancer Biology

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INTRODUCTION

Cancer is a complex genetic disease that is defined by the transition of a normal cell, governed by processes that control its replication and behavior, into a cancer cell that is typified by unrestrained proliferation and dissemination, leading ultimately to a state of disease and/or death. The underlying landscape of cancer genetics is now fully defined for many cancers, aided by the evolving technologies in gene sequencing. Many therapeutic advances of the last decade have successfully focused on targets identified by the study of genetic mutations. Whereas genetic changes, usually acquired by cells over time, are at the ontologic core of cancer, many other patient factors affect its formation and the course of disease, including concurrent disease of the target organ, the immunologic response, and the underlying metabolic state. This chapter reviews the essential elements of cancer biology and key underlying genetic alterations driving this biology.

HALLMARKS OF CANCER

Cancer has many effects on the human body. This heterogeneity of clinical behaviors results from the various organs and tissues affected and the different ways in which cancers can alter normal physiologic function, and it is mirrored in the appearance of different cancers at the microscopic and genetic levels. Even among cancers originating from the same organ or cell type, there is wide diversity of behaviors. More than 100 types of cancer have been identified, and they are separated into categories based on the organ and tissue from which they arose and the histologic appearance. However, with further investigations into genetic subtypes of tumors, we may come to appreciate thousands of different diseases in years to come.

Despite the clinical, histologic, and genetic diversity of cancers, they tend to share common abilities and traits. Hanahan and Weinberg first defined the acquired capabilities that are essential for tumor growth in 2000 and then updated their conceptual framework for understanding cancer through the addition of "emerging hallmarks" and "enabling characteristics" (Table 53-1).

TABLE 53-1 THE CANCER PHENOTYPE

HALLMARKS OF CANCER	EMERGING HALLMARKS
Self-sufficiency in growth signals	Immune evasion
Insensitivity to anti-growth signals	Metabolic dysregulation
Evasion of apoptosis	**ENABLING CHARACTERISTICS**
Limitless replicative potential	Genomic instability
Induction of angiogenesis	Inflammation
Tissue invasion and metastasis	

Normal cellular division is controlled both by the restriction of growth and division signals to times of tissue injury and repair and by the presence of inhibitors of cell division and growth. In contrast, tumor cells universally are *self-sufficient in growth signals* and *insensitive to anti-growth signals*. *Resistance to apoptosis* (programmed cell death) also allows cancers to bypass another evolutionarily conserved mechanism that restrains cell survival. In addition, normal cells undergo only a set number of divisions, limiting their growth potential. Tumor cells, in contrast, are immortalized and have *limitless replicative potential*. Beyond factors inherent in the tumor cells themselves are two capabilities in the environment. *Angiogenesis*, or the establishment of a blood supply, provides tumors with the oxygen and nutrients needed to grow beyond a size of 1 to 2 mm. *Invasion and metastasis* allow tumor cells to escape their primary sites and establish colonies at new sites. Metastatic disease is the cause of death in more than 90% of cancer patients.

Recent research has redirected attention to areas of cancer biology that are important for cancer prevention and treatment. Emerging hallmarks include the *distinct metabolic requirements* of cancer cells, with a growing number of metabolic genes (e.g., *IDH1/2, FH,* and *SDHB*) identified as mutated in cancers. Also recognized as essential is the tumor's capacity to *evade the body's immune response*, which is reflected in the clinical efficacy of drugs targeting the immune-modulating molecule PD1.

Enabling characteristics of cancer include *genomic instability*, which is important for the development of cancers as well for the resistance to treatments that can emerge during systemic therapy. Tumor-promoting inflammation probably accounts for the stepwise progression of tumors and may sustain cancers by providing an inflammatory environment.

In many instances, identification of these hallmark cancer traits has led to novel therapeutic approaches. Examples include drugs that target growth-stimulating proteins and pathways by means of inhibitors developed against epidermal growth factor receptor (EGFR) in lung and colon cancer, HER2/neu (ERBB2) in breast cancer, and RAF and MEK in melanoma. Similarly, drugs that block angiogenesis (e.g., vascular endothelial growth factor [VEGF]) are now used in cancer therapy.

THE GENETICS OF CANCER

Cancers falls along a spectrum, ranging from minor genetic derangements in some malignancies (e.g., *BCR-ABL* translocation in chronic myelogenous leukemia [CML]) to a genetically complex, multistep process in others (e.g., in colon, pancreas, and breast cancer). A cell that is undergoing malignant transformation acquires a growth or survival advantage relative to normal