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CANCER NOMENKLATURE AND SUSTAINED PROLIFERATIVE SIGNALING

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Abstract
Cancer is a leading cause of suffering and death in the developed world. It is now understood that cancer is a collection of more than 100 different diseases, each caused by a specific and often unique age-related accumulation of genetic and epigenetic alterations. Environment, heredity, and behavior interact to modify the risk of developing cancer and the response to treatment. Improvements in treatment strategies and supportive care, coupled with new, often individualized therapies based on advances of the basic pathophysiology of malignancy, have contributed to an increasing number of effective options for these diverse, often lethal disorders collectively called cancer.

Keywords: Cancer, rhabdomyosarcoma, guanine diphosphate (GDP), epidermal growth factor (EGF), guanine triphosphate (GTP).

Introduction

The National Cancer Institute (NCI) of the National Institutes of Health (NIH) defines cancer as "diseases in which abnormal cells divide without control and are able to invade other tissues". The term cancer comes from the Latin translation of the Greek word for crab, karkinoma, which the physician Hippocrates used to describe the appendage-like projections extending from tumors into adjacent tissue. The word tumor originally referred to any swelling that is caused by inflammation but is now generally reserved for describing a new growth, or neoplasm.

The careful evaluation of each cancer is important for many reasons. Different cancers will have different causes, different rates and patterns of progression, and different responses to treatment. The classification starts with knowing the tissue and organ of origin, the extent of distribution to other sites, and the microscopic appearance of the lesion. Increasingly, it also includes a detailed description of the critical genetic changes in the cancer.

Tumors can be benign or malignant (cancerous). Benign tumors are usually encapsulated with connective tissue and contain fairly well-differentiated cells and well-organized stroma. They retain recognizable normal tissue structure and do not invade beyond their capsule, nor do they spread to regional lymph nodes or distant locations. Mitotic cells are very rarely present during microscopic analysis. Benign tumors are generally named according to the tissues from which they arise with the suffix "-oma," which indicates a tumor or mass. For example, a benign tumor of the smooth muscle of the uterus is a leiomyoma, and a benign tumor of fat cells is a lipoma. Benign tumors can become extremely large and, depending on their location in the body, can cause

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morbidity or be life-threatening. For example, a benign meningioma at the base of the skull may cause symptoms by compressing adjacent normal brain tissue.

Some tumors initially described as benign can progress to cancer and then are referred to as malignant tumors, which are distinguished from benign tumors by more rapid growth rates and specific microscopic alterations, including loss of differentiation and absence of normal tissue organization. One of the microscopic hallmarks of cancer cells is anaplasia, the loss of cellular differentiation. Malignant cells are also pleomorphic, with marked variability of size and shape. They often have large darkly stained nuclei, and mitotic cells are common. Malignant tumors may have a substantial amount of stroma, but it is disorganized, with loss of normal tissue structure. Malignant tumors lack a capsule and grow to invade nearby blood vessels, lymphatics, and surrounding structures. The most important and most deadly characteristic of malignant tumors is their ability to spread far beyond the tissue of origin, a process known as metastasis. Unlike benign tumors, which are named related to the tissue of origin, cancers generally are named according to the cell type from which they originate. Cancers arising in epithelial tissue are called carcinomas, and if they arise from or form ductal or glandular structures are named adenocarcinomas. Hence a malignant tumor arising from breast glandular tissue is a mammary adenocarcinoma, whereas an example of a benign breast tumor is a fibroadenoma. Cancers arising from mesenchymal tissue (including connective tissue, muscle, and bone) usually have the suffix sarcoma. For example, malignant cancers of skeletal muscle are known as rhabdomyosarcomas. Cancers of lymphatic tissue are called lymphomas, whereas cancers of blood-forming cells are called leukemias. However, many cancers, such as Hodgkin disease and Ewing sarcoma, are named for historical reasons that do not follow this nomenclature convention.

The first and foremost hallmark of cancer is uncontrolled cellular proliferation. Normal cells generally only enter proliferative phases in response to growth factors that bind to specific receptors on the cell surface. The cytoplasmic components of the receptors are associated with signaling molecules that undergo activation and in turn activate intracellular signaling pathways leading to induction/activation of regulatory factors affecting DNA synthesis, entrance into the cell cycle, and changes in expression of other genes related to cell metabolism for optimal growth. One example is initiation of proliferation by epidermal growth factor (EGF). EGF binds and cross-links two EGF receptors on the cell surface. The cytoplasmic portions of the receptors are tyrosine kinases that attach phosphorus to tyrosine in neighboring proteins, including each other (autophosphorylation). Phosphorylation allows the receptor to attach to bridging protein, which links the EGF receptors to plasma membrane–associated inactive RAS. RAS is an acronym for “rat sarcoma,” where it was found originally. Inactive RAS is associated with guanine diphosphate (GDP). Association between the EGF receptor and inactive RAS modifies the binding of GDP, which is replaced with guanine triphosphate (GTP). GTP activates RAS, which is a GTPase that converts GTP to GDP, during which it can activate signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinosityl-3-kinase (PI3K) pathway. These signaling pathways phosphorylate other cytoplasmic proteins and affect activity and nuclear localization of transcription factors, such as myelocytomatosis viral oncogene homolog (MYC), that govern the transcription of cell cycle regulators, such as cyclins, and entrance into cellular proliferation. Proliferation can be discontinued through this pathway by decreased levels of growth

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factors in the environment or inactivation of signaling pathway components. The genes that encode components of receptor-mediated pathways designed to regulate normal cellular proliferation are collectively called proto-oncogenes. Cancerous cells characteristically express mutated or overexpressed proto-oncogenes, which are called oncogenes. Oncogenes are independent of normal regulatory mechanisms; thus the cell is driven into a state of unregulated expression of proliferation signals and uncontrolled cell growth. Oncogenes can affect any portion of the growth factor pathways, such as described for EGF. For instance, most growth factors originate from neighboring cells, but some cancers acquire the ability to secrete growth factors that stimulate their own growth, a process known as autocrine stimulation. As described later in this chapter, noncancerous stromal cells within a tumor are frequently modified to benefit the cancer. In some instances, stromal cells produce excessive growth factors that drive the proliferation of cancer cells. Other cancers increase the expression of growth factor receptors; for example, in breast cancer, production of the human epidermal growth factor receptor 2 (HER2), also known as the epidermal growth factor receptor gene (ERBB2), is up-regulated and is hyperresponsive to low levels of EGF. Some breast and lung cancers are treated by inhibitors of HER2 and other EGF receptors that block this pathway.

Oncogenes may lead to constant activation of the signal cascade from the cell surface receptor to the nucleus. Up to a third of all cancers have an activating mutation in the RAS gene resulting in a continuous cell growth signal even when growth factors are missing. Other mutations in the EGF receptor pathway include excessive proliferation signaling by hyperactivation of the PI3 kinase. Several types of genetic events can activate oncogenes. A point mutation that is frequently observed in lung cancer results in continuous activation of the EGF receptor tyrosine kinase. A point mutation in the RAS gene converts it from a regulated proto-oncogene to an unregulated oncogene. Activating point mutations in RAS are found in many cancers, especially pancreatic and colorectal cancer. Specialized tests, such as direct DNA sequencing, can detect such point mutations in clinical samples. Translocations can activate oncogenes by one of two distinct mechanisms. First, a translocation can cause excess and inappropriate production of a proliferation factor. One of the best examples is the t(8;14) translocation found in many Burkitt lymphomas; t(8;14) designates a chromosome that has a piece of chromosome 8 fused to a piece of chromosome 14. Burkitt lymphoma is an aggressive cancer of B lymphocytes. The MYC proto-oncogene found on chromosome 8 is normally activated at low levels in proliferating lymphocytes and is inactivated in mature lymphocytes. If the t(8;14) translocation occurs, the MYC gene is aberrantly placed under the control of a B-cell immunoglobulin gene (IG) present on chromosome 14. The IG gene is very active in maturing B lymphocytes. The t(8;14) translocation alters the control of MYC; its normal low level expression is switched to high levels, as directed by an IG gene promoter. Hyperproduction of MYC protein drives proliferation and blocks differentiation. Second, chromosome translocations can lead to production of novel proteins with growth-promoting properties. In chronic myeloid leukemia (CML) a specific chromosome translocation is almost always present. This translocation, t(9;22), was first identified in association with CML in Philadelphia in 1960 and is often referred to as the Philadelphia chromosome. Translocation fuses two chromosomes in the middle of two different genes: BCR (break point cluster region gene) on chromosome 9 and ABL (Abelson gene) on chromosome 22. The result is production of

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a BCR-ABL fusion protein containing the first half of BCR and the second half of ABL (a nonreceptor tyrosine kinase). BCR-ABL is an unregulated protein tyrosine kinase that promotes growth of myeloid cells. Imatinib, a drug that specifically targets this tyrosine kinase, represents the first successful chemotherapy targeted against the product of a specific oncogenic mutation. Imatinib and related tyrosine kinase inhibitors (TKIs) are highly effective in the treatment of CML and, because of their specificity, lack the toxic side effects noted with nonspecific anticancer drugs. However, imatinib is not effective in cancers that do not have the t(9;22) translocation or related mutations. In modern personalized cancer therapy, knowledge of the specific genetic alteration can dictate the optimal drugs for the individual.

Oncogenes also may be activated by gene amplification. Gene amplification results in increased expression of an oncogene, or in some cases drug resistance genes. The N-MYC oncogene, a member of the MYC family, is amplified in 25% of childhood neuroblastomas and confers a poor prognosis. The HER2 gene (ERBB2) is amplified in 20% of breast cancers.

All in all, a highly complementary hallmark capability for sustaining proliferative signaling in cancer cells is the ability to evade growth suppression. Several tumor suppressive protein-coding genes that operate in diverse ways to inhibit cellular growth and proliferation had been discovered.

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