TABLE 101e-1 COMMON ONCOGENES ALTERED IN HUMAN CANCERS

Oncogene	Function	Alteration in Cancer	Neoplasm
AKT1	Serine/threonine kinase	Amplification	Stomach
AKT2	Serine/threonine kinase	Amplification	Ovarian, breast, pancreatic
BRAF	Serine/threonine kinase	Point mutation	Melanoma, lung, colorectal
CDK4	Cyclin-dependent kinase	Point mutation, amplification	Breast, melanoma, myeloma, others
CTNNB1	Signal transduction	Point mutation	Colon, prostate, melanoma, skin, others
FOS	Transcription factor	Overexpression	Osteosarcomas
ERBB2	Receptor tyrosine kinase	Point mutation, amplification	Breast, ovary, stomach, neuroblastoma
JUN	Transcription factor	Overexpression	Lung
MET	Receptor tyrosine kinase	Point mutation, rearrangement	Osteocarcinoma, kidney, glioma
MYB	Transcription factor	Amplification	AML, CML, colorectal, melanoma
C-MYC	Transcription factor	Amplification	Breast, colon, gastric, lung
L-MYC	Transcription factor	Amplification	Lung, bladder
N-MYC	Transcription factor	Amplification	Neuroblastoma, lung
PIK3A	Phosphoinositol-3-kinase	Point Mutation	Multiple cancers
HRAS	GTPase	Point mutation	Colon, lung, pancreas
KRAS	GTPase	Point mutation	Melanoma, colorectal, AML
NRAS	GTPase	Point mutation	Various carcinomas, melanoma
REL	Transcription factor	Rearrangement, amplification	Lymphomas
WNT1	Growth factor	Amplification	Retinoblastoma

Abbreviations: AML, acute myeloid leukemia; CML, chronic myeloid leukemia.

through their ability to control cell division (cell birth) or cell death (apoptosis), although the mechanisms can be extremely complex. While tightly regulated in normal cells, oncogenes acquire mutations in cancer cells, and the mutations typically relieve this control and lead to increased activity of the gene products. This mutational event typically occurs in a single allele of the oncogene and acts in a dominant fashion. In contrast, the normal function of tumor-suppressor genes is usually to restrain cell growth, and this function is lost in cancer. Because of the diploid nature of mammalian cells, both alleles must be inactivated for a cell to completely lose the function of a tumor-suppressor gene, leading to a recessive mechanism at the cellular level. From these ideas and studies on the inherited form of retinoblastoma, Knudson and others formulated the *two-hit hypothesis*, which in its modern version states that both copies of a tumor-suppressor gene must be inactivated in cancer.

There is a subset of tumor-suppressor genes, the *caretaker genes*, that do not affect cell growth directly, but rather control the ability of the cell to maintain the integrity of its genome. Cells with a deficiency in these genes have an increased rate of mutations throughout their genomes, including in oncogenes and tumor-suppressor genes. This "mutator" phenotype was first hypothesized by Loeb to explain how the multiple mutational events required for tumorigenesis can occur in the lifetime of an individual. A mutator phenotype has now been observed in some forms of cancer, such as those associated with deficiencies in DNA mismatch repair. The great majority of cancers, however, do not harbor repair deficiencies, and their rate of mutation is similar to that observed in normal cells. Many of these cancers, however, appear to harbor a different kind of genetic instability, affecting the loss or gains of whole chromosomes or large parts thereof (as explained in more detail below).

ONCOGENES IN HUMAN CANCER

Work by Peyton Rous in the early 1900s revealed that a chicken sarcoma could be transmitted from animal to animal in cell-free extracts, suggesting that cancer could be induced by an agent acting positively to promote tumor formation. The agent responsible for the transmission of the cancer was a retrovirus (Rous sarcoma virus, RSV) and the oncogene responsible was identified 75 years later as *v-src*. Other oncogenes were also discovered through their presence in the genomes of retroviruses that are capable of causing cancers in chickens, mice, and rats. The cellular homologues of these viral genes are called protooncogenes and are often targets of mutation or aberrant regulation in human cancer. Whereas many oncogenes were discovered because of their presence in retroviruses, other oncogenes, particularly those involved in translocations characteristic of particular leukemias and lymphomas, were isolated through genomic approaches. Investigators cloned the sequences surrounding the chromosomal translocations observed cytogenetically and then deduced the nature of the genes that were the targets of these translocations (see below). Some of these were oncogenes known from retroviruses (like *ABL*, involved in chronic myeloid leukemia [CML]), whereas others were new (like *BCL2*, involved in B cell lymphoma). In the normal cellular environment, protooncogenes have crucial roles in cell proliferation and differentiation. **Table 101e-1** is a partial list of oncogenes known to be involved in human cancer.

The normal growth and differentiation of cells is controlled by growth factors that bind to receptors on the surface of the cell. The signals generated by the membrane receptors are transmitted inside the cells through signaling cascades involving kinases, G proteins, and other regulatory proteins. Ultimately, these signals affect the activity of transcription factors in the nucleus, which regulate the expression of genes crucial in cell proliferation, cell differentiation, and cell death. Oncogene products have been found to function at critical steps in these pathways **(Chap. 102e)**, and inappropriate activation of these pathways can lead to tumorigenesis.

MECHANISMS OF ONCOGENE ACTIVATION

POINT MUTATION

Point mutation is a common mechanism of oncogene activation. For example, mutations in one of the *RAS* genes (*HRAS*, *KRAS*, or *NRAS*) are present in up to 85% of pancreatic cancers and 45% of colon cancers but are less common in other cancer types, although they can occur at significant frequencies in leukemia, lung, and thyroid cancers. Remarkably—and in contrast to the diversity of mutations found in tumor-suppressor genes (see below)—most of the activated *RAS* genes contain point mutations in codons 12, 13, or 61 (these mutations reduce RAS GTPase activity, leading to constitutive activation of the mutant RAS protein). The restricted pattern of mutations observed in oncogenes compared to that of tumor-suppressor genes reflects the fact that gain-of-function mutations are less likely to occur than mutations that simply lead to loss of activity. Indeed, inactivation of a gene can in theory be accomplished through the introduction of a stop