

REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

Oncogenes and Cancer

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N Engl J Med 2008;358:502-11.
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CANCER IS CAUSED BY ALTERATIONS IN ONCOGENES, TUMOR-SUPPRESSOR genes, and microRNA genes. These alterations are usually somatic events, although germ-line mutations can predispose a person to heritable or familial cancer. A single genetic change is rarely sufficient for the development of a malignant tumor. Most evidence points to a multistep process of sequential alterations in several, often many, oncogenes, tumor-suppressor genes, or microRNA genes in cancer cells.

Tumors often possess cytogenetically different clones that arise from the initial transformed cell through secondary or tertiary genetic alterations. This heterogeneity contributes to differences in clinical behavior and responses to treatment of tumors of the same diagnostic type. Apart from the initial clone and subclones, tumors can also contain progenitor cancer cells, all of which constitute a spectrum of cells with different genetic alterations and states of differentiation. These populations can differ in sensitivity to chemotherapy, radiotherapy, and other treatments, making clinical management difficult. For these reasons, the initiating steps in the development of cancer are of considerable clinical importance and are a priority in the development of rational cancer treatment.

An example of this concept is chronic myelogenous leukemia, which is initiated by a reciprocal t(9;22) chromosomal translocation that fuses the *ABL* proto-oncogene to the *BCR* gene.^{1,2} The fusion gene encodes an oncogenic *ABL* fusion protein with enhanced tyrosine kinase activity. All leukemic cells carry this chromosomal alteration, which is why inhibition of the excessive tyrosine kinase activity of the fusion protein by imatinib induces complete remission in most patients^{3,4}; when relapse occurs, the leukemic cells usually carry mutations in *ABL* that render them resistant to the drug.⁵

EVIDENCE OF SOMATIC GENETIC CHANGE

The first evidence that cancer arises from somatic genetic alterations came from studies of Burkitt's lymphoma, in which one of three different translocations juxtaposes an oncogene, *MYC*, on chromosome 8q24 to one of the loci for immunoglobulin genes. Chromosomes 14q, 22q, and 2p — the translocation partners — each carries enhancer elements in the immunoglobulin loci, thereby activating the juxtaposed *MYC* oncogene (see Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org).⁶⁻¹¹ Since every malignant lymphocyte carries the *MYC* translocation, deregulation of the *MYC* oncogene is probably the initiating event.

Second, transfection experiments have shown that mouse fibroblasts, when transfected in vitro with DNA from human cancer cells, acquire some of the properties of malignant cells (i.e., transformation). The transforming activity of the DNA was traced to a human homologue of the retroviral *RAS* oncogene. This oncogene bears mutations that activate the transforming property of the *RAS* oncogenic protein.^{12,13}

Third, the cloning and characterization of the chromosomal breakpoints that are characteristic of follicular lymphomas and some diffuse large B-cell lymphomas¹⁴ have shown a juxtaposition of the *BCL2* oncogene to enhancer elements in the immunoglobulin heavy-chain locus, resulting in deregulation of *BCL2*^{14,15} (see Fig. 2 in the Supplementary Appendix).

Fourth, in transgenic mice that carry an activated oncogene from a human tumor, cancers develop that resemble the human tumor.^{16,17} That these cancers appear only after a latent period suggests that alterations in other genes must occur before progression to frank neoplasia can occur — activation of a particular oncogene seems to be necessary but not sufficient for the development of overt cancer.

FUNCTIONAL PROPERTIES OF ONCOGENES

Historically, transformation events in cancer have been defined as initiation events (contributing to the early stages of neoplastic transition) or progression events (referring to subsequent transformative processes). **Oncogenes encode proteins that control cell proliferation, apoptosis, or both.** They can be activated by structural alterations resulting from mutation or gene fusion,¹⁸ by juxtaposition to enhancer elements,¹⁹ or by amplification. Translocations and mutations can occur as initiating events²⁰ or during tumor progression, whereas amplification usually occurs during progression. (Table 1 in the Supplementary Appendix lists oncogenes in tumors of different species, the methods used to identify them, their mechanisms of activation, and the functions of their encoded products; Table 2 in the Supplementary Appendix lists the molecularly characterized chromosomal rearrangements in human cancers.) **The products of oncogenes can be classified into six broad groups: transcription factors, chromatin remodelers, growth factors, growth factor receptors, signal transducers, and apoptosis regulators.**

PRODUCTS OF ONCOGENES

Transcription Factors

Transcription factors are often members of multigene families that share common structural domains. To act, many transcription factors require interaction with other proteins. In some tu-

mors, for example, the Fos transcription protein dimerizes with the Jun transcription factor to form the AP1 transcription factor, and this complex increases the expression of several genes that control cell division.^{21,22}

Chromosomal translocations often activate transcription-factor genes in lymphoid cancers²³ and sometimes do so in solid tumors (e.g., prostate cancer²⁴; see Table 2 in the Supplementary Appendix). In certain sarcomas, chromosomal translocations that result in fused proteins occur consistently; in Ewing's sarcoma, for example, the *EWS* gene is fused with one of a number of partner genes, resulting in aberrant transcriptional activity of the fused proteins (see Table 2 in the Supplementary Appendix). The *EWS* protein is an RNA-binding molecule with a domain that, when fused to a heterologous DNA-binding domain, can greatly stimulate gene transcription. Prostate carcinomas carry translocations of the *TMPR552* gene that fuse with and activate *ERG1* or *ETV1*. These genes are members of the ETS family of transcription regulators, which can activate or repress genes involved in cellular proliferation, differentiation, and apoptosis. The fusion of *TMPR552*, which has androgen-responsive promoter elements, with an ETS-related gene creates a fusion protein that increases proliferation and inhibits apoptosis of cells in the prostate gland, thereby facilitating their transformation into cancer cells.²⁴

Chromatin Remodelers

Modifications in the degree of compaction of chromatin play a critical role in the control of gene expression, replication, and repair and of chromosome segregation. Two kinds of enzymes remodel chromatin: ATP-dependent enzymes²⁵ that move the positions of nucleosomes, the repeating subunits of the histones in chromatin around which DNA winds, and enzymes that modify the N-terminal tails of histones.²⁶ The pattern of histone modification constitutes an epigenetic code that determines the interaction between nucleosomes and chromatin-associated proteins.²⁷ These interactions, in turn, determine the structure of chromatin and its transcriptional capacity.

In acute lymphocytic leukemia and acute myelogenous leukemia, the *ALL1* (also named *MLL*) gene can fuse with 1 of more than 50 genes. *ALL1* is part of a very large, stable multiprotein complex. Most of the proteins in the complex are

components of transcription complexes²⁸; others are involved in histone methylation and RNA processing. The entire complex remodels, acetylates, deacetylates, and methylates nucleosomes and free histones.²⁸ The fusion of ALL1 with 1 of more than 50 proteins results in the formation of the chimeric proteins that underlie acute lymphoblastic leukemia and acute myelogenous leukemia. ALL1 (MLL) fusion proteins deregulate homeobox genes (which encode transcription factors), the *EPHA7* gene (which encodes a receptor tyrosine kinase), and microRNA genes such as *miR191*.

Growth Factors

Constitutive activation of a growth factor gene can contribute to malignant transformation. Platelet-derived growth factor (PDGF) consists of α and β chains and is released from platelets during coagulation.²⁹ It can induce the proliferation of various cell types and stimulate fibroblasts to par-

ticipate in wound healing. The *sis* oncogene of simian sarcoma virus is structurally similar to the gene for the β chain of PDGF.²⁹ Overexpression of PDGF induces the in vitro transformation of fibroblasts containing PDGF receptors; it does not influence fibroblasts lacking these receptors. This autocrine loop entails overexpression of *PDGF- β* , the expression of the PDGF- β receptor, and unregulated cell growth. An antibody against PDGF- β , an antibody against its receptor, or small molecules that block the receptor inhibit growth of the transformed fibroblasts.

The WNT family of secreted glycoproteins inhibits phosphorylation of β -catenin, which is involved in cell-cell adhesion and the activation of several signal-transduction pathways³⁰ (Fig. 1). The APC protein controls the activity of β -catenin. In familial adenomatous polyposis, inactivating mutations of APC block the degradation of β -catenin by inhibiting its phosphorylation. As a result, free β -catenin in the cytoplasm

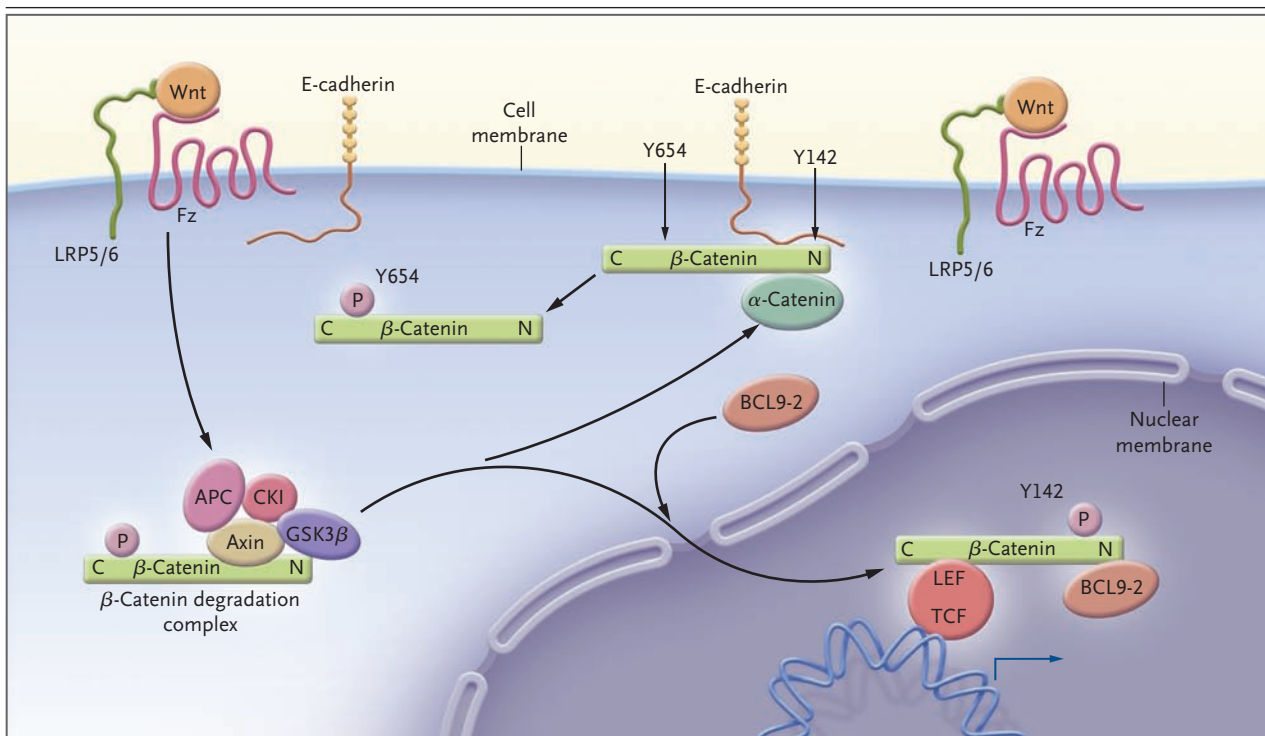


Figure 1. Dual Functions of β -Catenin in Cell Adhesion and Transcription.

β -Catenin is in a destructive cytoplasmic complex composed of activated protein C (APC), axin, glycogen synthase kinase 3 beta ($GSK3\beta$), and casein kinase (CKI). CK1 and $GSK3\beta$ induce serine-threonine phosphorylation of the N-terminal of β -catenin. Binding of Wnt ligands to the frizzled (F_z), LRP5, and LRP6 receptors inhibits the degradation of this complex and leads to nuclear accumulation of β -catenin. Phosphorylation (P) of tyrosine 142 of β -catenin leads it to interact with BCL9-2 and to migrate to the nucleus, where the β -catenin-BCL9-2 complex binds LEF and TCF to induce the expression of target genes. Phosphorylation of tyrosine Y654 of β -catenin results in the disassociation of E-cadherin and β -catenin, causing loss of cell-cell adhesion and increased cell motility.⁶⁻¹¹

translocates to the nucleus, where it activates genes involved in cell proliferation and invasion (Fig. 1).

Growth Factor Receptors

Growth factor receptors are altered in many cancers (Fig. 2).³¹ In many tumors, a deletion of the ligand-binding domain of epidermal growth factor receptor (EGFR), a transmembrane protein with tyrosine kinase activity, causes constitutive activation of the receptor in the absence of ligand binding.³² The activated receptor phosphorylates tyrosines in the intracellular domain of the receptor, providing interaction sites for cytoplasmic proteins containing the SRC homology domain and other binding domains. These interactions deregulate signaling in several pathways. Activating mutations occur in three other members of the EGFR family — ERBB2, ERBB3, and ERBB4 — and within the kinase domains of the HER2/neu and KIT signaling receptors. Such mutations occur in lung and breast cancer and gastrointestinal stromal tumors. Two classes of clinically active anti-EGFR agents have been developed: a monoclonal antibody against the extracellular domain of the receptor (cetuximab) and competitive inhibitors of the tyrosine kinase activity of the receptor (e.g., erlotinib and gefitinib).

Vascular endothelial growth factor (VEGF) regulates hypoxia-dependent control of gene transcription (Fig. 3). The activity of VEGF is mediated by three receptor tyrosine kinases: VEGFR1 (FLT1), VEGFR2 (FLK1-KDR), and VEGFR3 (FLT4). VEGF stimulates angiogenesis in a variety of cancers, and inhibitors of VEGF and of the VEGFRs have been developed. Bevacizumab is a monoclonal anti-VEGF antibody, and SU5412, a small molecule, binds the receptor tyrosine kinases of VEGFR1 and VEGFR2 as well as the kinases of the PDGF receptor and KIT. In addition to inhibiting the ABL kinase, imatinib also inhibits the PDGF and KIT receptor kinases. Gastrointestinal stromal tumors that carry activating mutations of *KIT*^{33,34} respond to imatinib or other inhibitors of these receptor kinases.

Signal Transducers

Binding of receptor tyrosine kinases to the appropriate ligand causes reorganization of the receptors and autophosphorylation of tyrosines in the intracellular portion of the molecules³⁵ (Fig. 2). Autophosphorylation enhances the kinase ac-

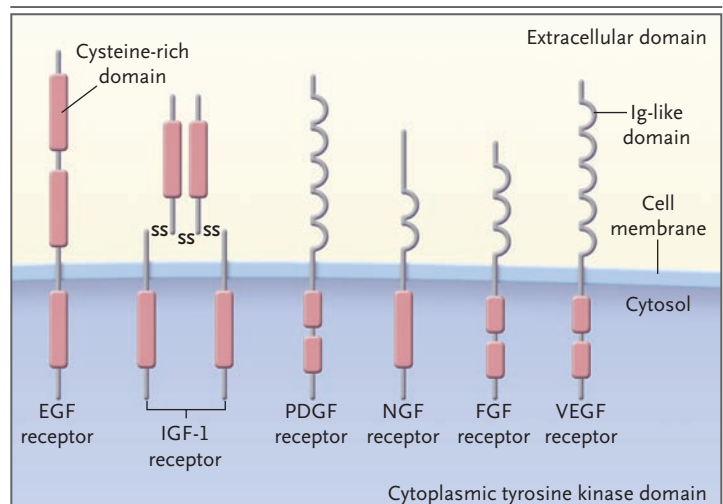


Figure 2. Examples of Receptor Tyrosine Kinases.

The epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) receptors have been found to be involved in a variety of human cancers. NGF denotes nerve growth factor, SS disulfide bonds, and VEGF vascular endothelial growth factor.

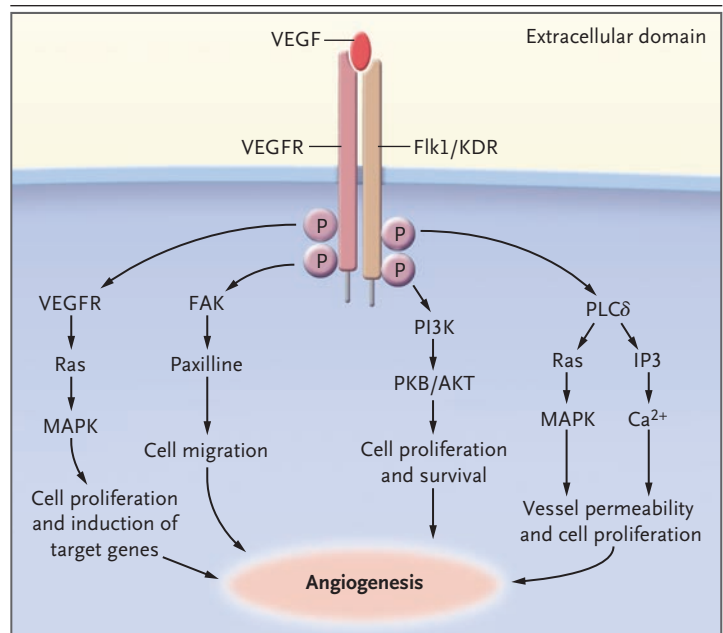
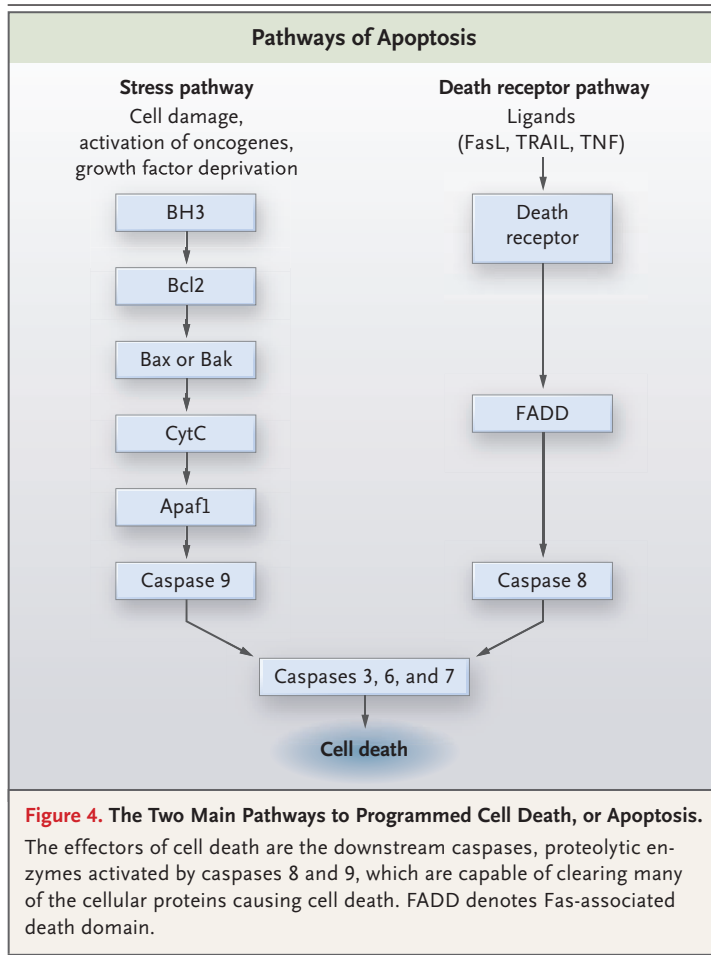


Figure 3. Role of VEGF-VEGFR Interaction in Angiogenesis.

Several pathways are activated by the interaction of vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFR). FAK denotes focal adhesion kinase, Flk fetal liver kinase, IP3 inositol triphosphate, KDR kinase-insert domain-containing receptor, MAPK mitogen-activated protein kinase, PI3K phosphoinositol 3-kinase, PKB protein kinase B, and PLC phospholipase C.



tivity of the receptor or promotes the interaction of the receptor with domains of cytoplasmic proteins (e.g., the SRC homology 2 domain) that are effectors and regulators of intracellular signaling.³⁶ In humans, there are approximately 120 SRC homology 2 domains in 100 different proteins that mediate responses to signals initiated by phosphorylated tyrosines. Some of these proteins share domains with enzymatic activity, whereas others link activated receptors to downstream targets.

Many oncogenes encode members of signal-transduction pathways. They fall into two main groups: nonreceptor protein kinases and guanine-triphosphate-binding proteins.^{37,38} The nonreceptor protein kinases are of two types: tyrosine kinases (e.g., ABL, LCK, and SRC) and serine and threonine kinases (e.g., AKT, RAF1, MOS, and PIM1). Proteins involved in signal transduction become oncogenic if they bear activating mutations. An important example is PI3K and

some of its downstream targets, such as AKT and SGK, which are critical to tyrosine kinase signaling and can be mutated in cancer cells.

Apoptosis Regulators

The *BCL2* gene, which is involved in the initiation of almost all follicular lymphomas and some diffuse large B-cell lymphomas (see Fig. 2 in the Supplementary Appendix),^{14,15} encodes a cytoplasmic protein^{39,40} that localizes to mitochondria and increases cell survival by inhibiting apoptosis.⁴¹ *BCL2* is also important in chronic lymphocytic leukemia and lung cancer. The *BCL2* family members *BCL-XL* and *BCL2* inhibit apoptosis and are up-regulated in many cancers.

Two main pathways lead to apoptosis: the stress pathway and the death-receptor pathway (Fig. 4). The stress pathway is triggered by proteins that contain the *BCL2* homology 3 domain; this domain inactivates *BCL2* and *BCL-XL* (which normally inhibit apoptosis) and thereby activates the caspases that induce apoptosis (Fig. 4). Drugs that mimic the *BCL2* homology 3 domain and can bind to *BCL-XL* or *BCL2* (peptides or small organic molecules that bind in a groove of these proteins) are under development. This approach has attracted considerable attention because many tumors overexpress *BCL2* or related proteins. The death-receptor pathway is activated by the binding of Fas ligand, TRAIL, and tumor necrosis factor α , to their corresponding (death) receptors on the cell surface. Activation of death receptors activates caspases that cause cell death (Fig. 4).

ONCOGENE ACTIVATION

Activation of oncogenes by chromosomal rearrangements, mutations, and gene amplification confers a growth advantage or increased survival of cells carrying such alterations. All three mechanisms cause either an alteration in the oncogene structure or an increase in or deregulation of its expression.⁴²

Chromosomal Rearrangements

Chromosome inversions and translocations are common cytogenetic abnormalities in cancer cells. In hematopoietic cancers and solid tumors, the translocations and inversions increase or deregulate transcription of the oncogene. In prostate cancer, gene fusion occurs between a gene that carries a promoter that is very active in the target

cells, and another that carries the oncogenic activity (e.g., *ERGI*).²⁴ In cancers of B and T cells, the most common mechanism of activation by translocation resembles *MYC* deregulation, whereas in myeloid cancers and soft-tissue sarcomas, gene fusion is more common (see Table 2 in the Supplementary Appendix).

Mutations

When an oncogene is activated by mutation, the structure of the encoded protein is changed in a way that enhances its transforming activity. Many types of mutation occur in oncogenes.⁴³ Examples are the *RAS* oncogenes (*KRAS*, *HRAS*, and *NRAS*), which encode proteins with guanosine-nucleotide-binding activity and intrinsic guanosine triphosphatase activity. When mutated in codon 12, 13, or 61, the *RAS* genes encode a protein that remains in the active state and continuously transduces signals by linking tyrosine kinases to downstream serine and threonine kinases. These incessant signals induce continuous cell growth. Mutation of oncogenes in the *RAS* family has been associated with exposure to environmental carcinogens. Mutations of *KRAS* are common in carcinomas of the lung, colon, and pancreas,⁴³ whereas mutations of *NRAS* occur principally in acute myelogenous leukemia and the myelodysplastic syndrome.⁴⁴

Activating point mutations of the *BRAF* gene occur in 59% of melanomas, 18% of colorectal cancers, 14% of hepatocellular carcinomas, and 11% of gliomas.⁴⁵ Most of the *BRAF* mutations change the valine residue at position 599 to glutamic acid (V599E). This change occurs within the kinase domain of the *BRAF* protein, resulting in a constitutively active protein that uncontrollably stimulates the MAP kinase cascade, thereby deregulating genes involved in cell proliferation, differentiation, and survival.^{45,46} In melanoma, *BRAF* mutations can precede neoplastic transformation; several types of nevi carry *BRAF* mutations.

Gene Amplification

An example of gene amplification, which usually occurs during tumor progression, is the amplification of the dihydrofolate reductase gene (*DHFR*) in methotrexate-resistant acute lymphoblastic leukemia.⁴⁷ Amplification of *DHFR* is accompanied by cytogenetic alterations that mirror amplification of oncogenes.^{48,49} The amplified DNA seg-

ment usually involves several hundred kilobases and can contain many genes. Members of four different oncogene families are often amplified: *MYC*, cyclin D1 (or *CCND1*), *EGFR*, and *RAS*. *MYC* is amplified in small-cell lung cancer, breast cancer, esophageal cancer, cervical cancer, ovarian cancer, and head and neck cancer, whereas amplification of *NMYC* correlates with an advanced tumor stage.⁵⁰ The t(11;14) translocation juxtaposes *CCND1* and immunoglobulin enhancer elements and is characteristic of mantle-cell lymphoma.¹⁴ *CCND1* amplification also occurs in breast, esophageal, hepatocellular, and head and neck cancer. *EGFR* (*ERBB1*) is amplified in glioblastoma and head and neck cancer. Amplification of *ERBB2* (also called *HER2/neu*) in breast cancer correlates with a poor prognosis.⁵¹ A monoclonal antibody against the product of this oncogene (trastuzumab) is effective in breast cancers that overexpress *HER2/neu*. Table 3 in the Supplementary Appendix lists oncogenes that are amplified in different types of cancer.

ONCOGENES IN CANCER INITIATION AND PROGRESSION

When chronic myelogenous leukemia converts to acute leukemia, the malignant clone acquires an additional t(9;22) translocation, an isochromosome 17, or trisomy of chromosome 8. When follicular lymphoma becomes aggressive, the lymphoma cells often bear a t(8;14) translocation in addition to the original t(14;18) translocation. These findings support the hypothesis that most hematopoietic tumors and soft-tissue sarcomas are initiated by the activation of an oncogene, followed by alterations in tumor-suppressor genes and other oncogenes. In contrast, most carcinomas are initiated by the loss of function of a tumor-suppressor gene, followed by alterations in oncogenes and additional tumor-suppressor genes.^{52,53} This multistep process in human cancer has also been found in mouse models carrying activated oncogenes or inactivated tumor-suppressor genes, in which the duration and aggressiveness of the disease can be changed by introducing into the mouse genome the same sequential genetic alterations observed in human tumors. Methylation of CpG islands located in the promoter regions of a number of tumor-suppressor genes has also been considered an important epigenetic step in the process of carcinogenesis. This topic will be covered later in this series.

Table 1. Cancer Therapies That Target Oncogenic Proteins.*

Anticancer Drug	Target	Disease
Monoclonal antibodies		
Trastuzumab (Herceptin, Genentech)	ERBB2	Breast cancer
Cetuximab (Erbix, ImClone)	EGFR	Colorectal cancer
Bevacizumab (Avastin, Genentech)	VEGF	Colorectal cancer, non–small-cell lung cancer
Small molecules		
Imatinib (Gleevec, Novartis)	ABL, PDGFR, KIT	Chronic myelogenous leukemia, gastrointestinal stromal tumors, chordoma
Gefitinib (Iressa, AstraZeneca)	EGFR	Non–small-cell lung cancer
Erlotinib (Tarceva, Genentech)	EGFR	Non–small-cell lung cancer
Sorafenib (Nexavar, Bayer/Onyx)	VEGFR, PDGFR, FLT3	Renal-cell carcinoma
Sunitinib (Sutent, Pfizer)	VEGFR, PDGFR, FLT3	Gastrointestinal stromal tumors, renal-cell carcinoma

* EGFR denotes epidermal growth factor receptor, FLT3 FMS-like tyrosine kinase 3, PDGFR platelet-derived growth factor receptor, and VEGF vascular endothelial growth factor.

ONCOGENES AS THERAPEUTIC TARGETS

Oncogenic proteins in cancer cells can be targeted by small molecules and, when the oncogenic protein is expressed on the cell surface, by monoclonal antibodies. Table 1 contains a summary of the targets and drugs (small molecules and monoclonal antibodies) being used in the treatment of a variety of human cancers.

Imatinib targets the initial step of the multi-step process in chronic myelogenous leukemia.⁵⁴ The same drug can affect the KIT and PDGFR receptor kinases.^{55,56} Of particular interest are inhibitors of the BCL2 family, which can induce the apoptotic death of cancer cells. In acute promyelocytic leukemia, which is initiated by a t(15;17) chromosome translocation that fuses the PML gene to RAR α (a nuclear receptor for retinoic acids^{57–59}; see Table 2 in the Supplementary Appendix), retinoic acid can induce terminal differentiation and death of APL cells. This modality is called differentiation therapy.

MICRORNA GENES

MicroRNA genes, unlike other genes involved in cancer, do not encode proteins. Instead, the products of these genes consist of a single RNA strand of about 21 to 23 nucleotides; their function is to regulate gene expression. A microRNA molecule can anneal to a messenger RNA (mRNA) containing a nucleotide sequence that complements the sequence of the microRNA (Fig. 5). In this way, the microRNA blocks protein translation or

causes degradation of the mRNA. Examples of the role microRNA plays in cancer pathophysiology involve *miR-15a* and *miR-16-1*, which are deleted or down-regulated in most indolent cases of chronic lymphocytic leukemia, suggesting an early event in the pathogenesis of this disease.⁵⁹

Mapping of numerous microRNA genes has shown that many occur in chromosomal regions that undergo rearrangements, deletions, and amplifications in cancer cells.⁶⁰ The regions of the genome that are consistently involved in chromosomal rearrangements in cancer cells but that lack oncogenes or tumor-suppressor genes appear to harbor microRNA genes.

Expression profiling of microRNA genes has revealed signatures associated with tumor classification, diagnosis, staging, and progression, as well as prognosis and response to treatment.^{61–63} For example, microRNA expression profiling can distinguish between indolent and aggressive forms of chronic lymphocytic leukemia,⁶² and expression of a small panel of microRNA genes correlates with prognosis in stage 1 lung cancer.⁶³ Some microRNA genes that are deregulated in chronic lymphocytic leukemia have germ-line or somatic mutations in a microRNA precursor that affect the processing of short single-stranded microRNA molecules.⁶² MicroRNA genes can be up-regulated or down-regulated in cancer cells.⁶⁴ The up-regulated genes function as oncogenes by down-regulating tumor-suppressor genes, whereas the down-regulated genes function as tumor-

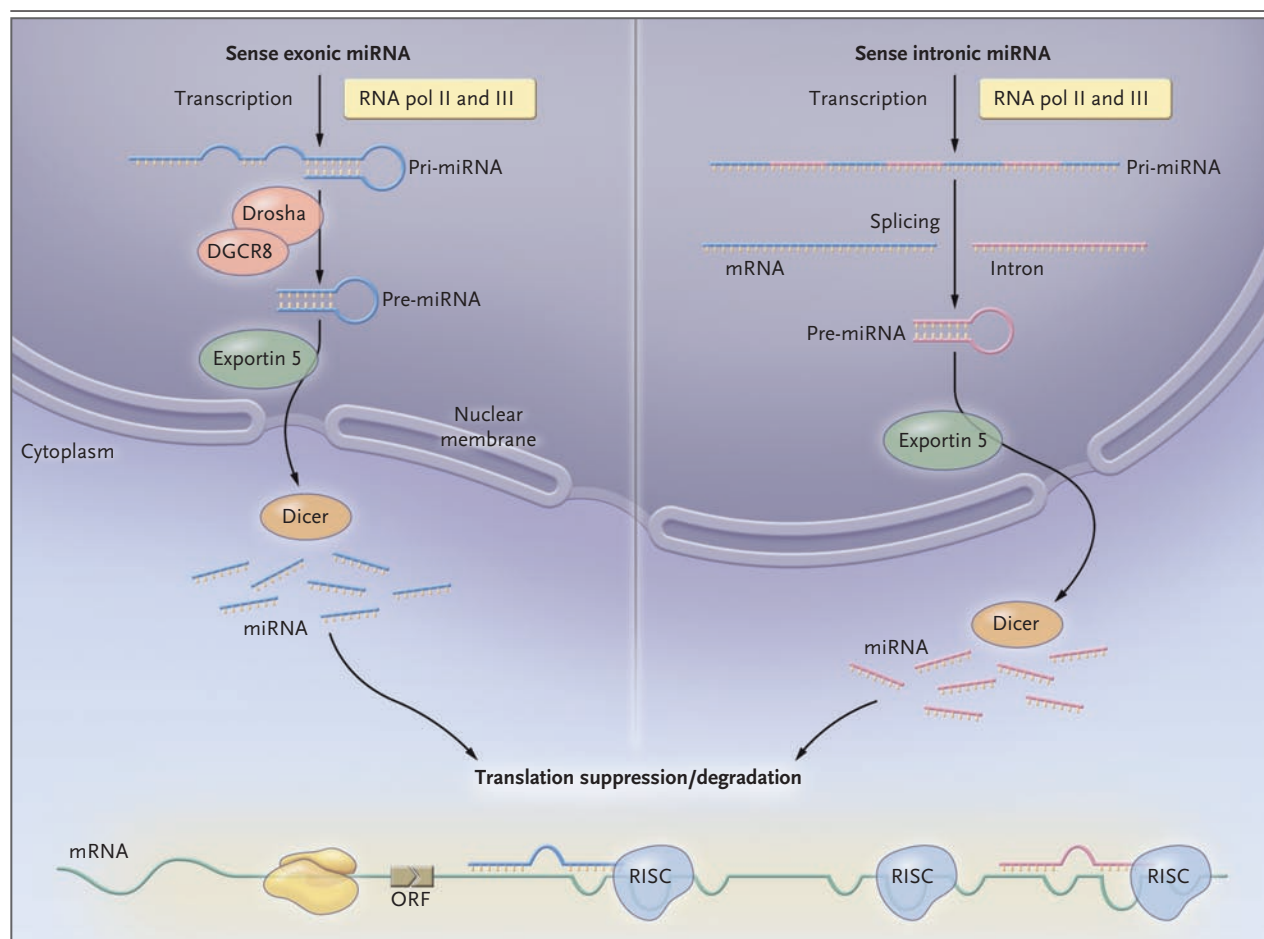


Figure 5. Mechanisms Involved in the Expression of Mature Exonic and Intronic MicroRNAs.

MicroRNA (miRNA) is transcribed mostly by RNA polymerase (pol) II and less frequently by RNA pol III. The primary transcript (pri-microRNA) can be quite large. During the process of splicing, pri-microRNA is processed in the nucleus by an enzymatic complex that includes Drosha and DGCR8, which leads to the formation of a smaller (70-to-100 nucleotide), second hairpin precursor named pre-microRNA. This second precursor binds exportin-5 in the nucleus and is transported to the cytoplasm, where it is cleaved by Dicer into mature microRNA. This mature microRNA, for the most part, binds to the 3' untranslated region of messenger RNA (mRNA) and, depending on the degree of complementarity with the target RNA, can lead to the degradation or blockage of translation mRNA. Recent studies suggest that translation blockage is accompanied by some degradation.

suppressor genes by down-regulating oncogenes. The function of microRNA genes depends on their targets in a specific tissue. A microRNA gene can be a tumor suppressor if in a given cell type its critical target is an oncogene, and it can be an oncogene if in a different cell type its target is a tumor-suppressor gene.

Up-regulation of microRNA genes can be due to amplification, deregulation of a transcription factor, or demethylation of CpG islands in the promoter regions of the gene. For example, the ALL1 (MLL) fusion proteins of acute lymphoblastic leukemia or acute myeloblastic leukemia carrying chromosome 11q23 translocations target the

Drosha nuclease complex to specific microRNA genes, including *miR191*, thereby enhancing the processing of their microRNA precursors.⁶⁵ The *miR191* gene is also up-regulated in numerous types of solid cancers,⁶⁴ suggesting that it is the downstream target of signal-translocation pathways involved in cancer.⁶⁵ MicroRNA genes functioning as tumor suppressors can be down-regulated because of deletions, epigenetic silencing, or loss of the expression of one or more transcription factors.

The *miR155* gene is overexpressed in diffuse large B-cell lymphoma,⁶⁶ the aggressive form of chronic lymphocytic leukemia,⁶² and in breast,

lung, and colon cancers. In transgenic mice carrying this gene under control of the E μ enhancer of immunoglobulin genes,⁶⁷ overexpression of *miR155* causes acute lymphoblastic leukemia or high-grade lymphoma, indicating that deregulation of a single microRNA gene can cause malignant transformation.⁶⁷ Since it takes several months for the tumors in these mice to become aggressive, it is likely that additional genetic alterations are needed for the development of frank neoplasia.

Members of the LET7 microRNA family, which are deleted or underexpressed in lung cancer, target *RAS*⁶⁸; loss of *LET7* results in overexpression of *RAS*.⁶⁸ *MIR15a* and *miR-16-1*, the microRNAs that are deleted or down-regulated in chronic lymphocytic leukemia, cause overexpression of *BCL2*, which protects cells from apoptosis (Fig. 4).⁶⁹ The expression of a set of 21 microRNAs is altered in at least three types of solid tumors.⁶⁴ One of these 21 genes, *miR21*, is of particular interest because it inhibits expression of the tumor suppressor *PTEN*.⁷⁰ *PTEN* encodes a phosphatase involved in the PI3K kinase signaling pathway and is deleted, mutated, or silenced in advanced breast, lung, gastric, and prostate cancers.⁷⁰

SUMMARY

The identification of oncogenes involved in the initiation and progression of tumors has generated targets for the development of new anticancer drugs. Several new drugs, small molecules, and monoclonal antibodies directly affecting oncogene products have been developed, and more will follow. Considerable progress has been made in producing small molecules capable of inhibiting the enzymatic activity of ABL, KIT, EGFR, and ERBB2. For cases in which the oncogene products are not enzymes, it has been much more difficult to develop new agents.

The advantage of targeted therapy is the dependency of cancer cells on the oncogene product for growth and survival. Thus, cancer cells are more sensitive to the treatment than are normal cells. All targets, however, are not equivalent. It is possible to foresee the development of multiple drugs that have multiple targets involved in the development of cancer. The discovery of the involvement of microRNAs in the initiation and progression of human cancer may provide additional targets for anticancer treatments.

No potential conflict of interest relevant to this article was reported.

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