Cancer Genetics

- "Cancer" is a collection of disorders that share the common feature of uncontrolled cell growth. This leads to a mass of cells termed a **neoplasm** (Greek, "new formation"), or **tumor.** The formation of tumors is called **tumorigenesis.**

- Several key events must occur if cells are to escape the usual constraints that prevent uncontrolled proliferation. Additional growth signals must be produced and processed, and cells must become resistant to signals that normally inhibit growth. Because these abnormal characteristics would typically trigger the process of programmed cell death **(apoptosis),** cells must somehow disable this process.

- The growing cell mass (tumor) requires nourishment, so a new blood supply must be obtained through **angiogenesis**. Additional inhibitory signals must be overcome for the tumor to achieve a **malignant** state, in which neoplasms invade nearby tissues and **metastasize** (spread) to more distant sites in the body.

- The capacity to invade and metastasize distinguishes malignant from **benign** neoplasms.

- Many of the basic biological features of **carcinogenesis** are now understood.

- Throughout our lives, many of our cells continue to grow and differentiate into a cell type appropriate for their role in the body. Alternatively, if the cell is abnormal or damaged, it may undergo apoptosis.

- Occasionally one of these cells fails to differentiate and begins to divide without restraint. The descendants of such cells can become the founders of neoplasms, capable of further transformation into invasive, metastatic cancer.

- We wish to understand in detail what has gone wrong in these cells, to detect them early, and ultimately to intervene in their development so as to eliminate them.

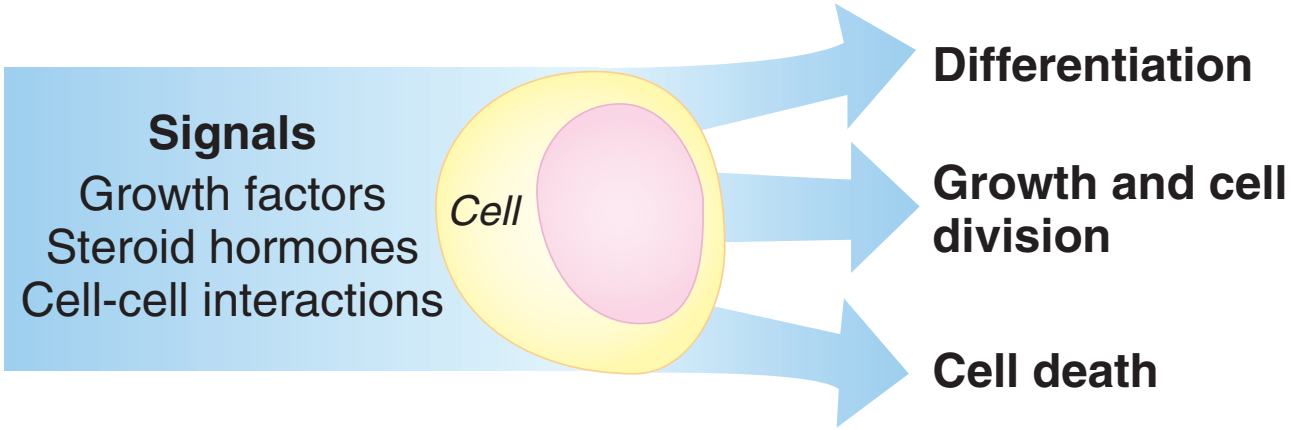

FIG 11-1 In response to environmental signals, a cell may continue to divide or it may differentiate or die (apoptosis).

CAUSES OF CANCER

Genetic Considerations

- Genetic alterations of cell regulatory systems are the primary basis of carcinogenesis.
- Most of the genetic events that cause cancer occur in somatic cells. The frequency of these events can be altered by exposure to mutagens, thus establishing a link to environmental **carcinogens**.
- These genetic events are not transmitted to future generations because they occur in somatic, rather than germline, cells. Even though they are *genetic* events, they are not *inherited.*
- It is also possible for cancer-predisposing mutations to occur in germline cells. This results in the transmission of cancer-causing alleles from one generation to the next, producing families that have a high incidence of specific cancers.
- Such "cancer families," although rare, demonstrate that inheritance of a damaged gene can cause cancer.

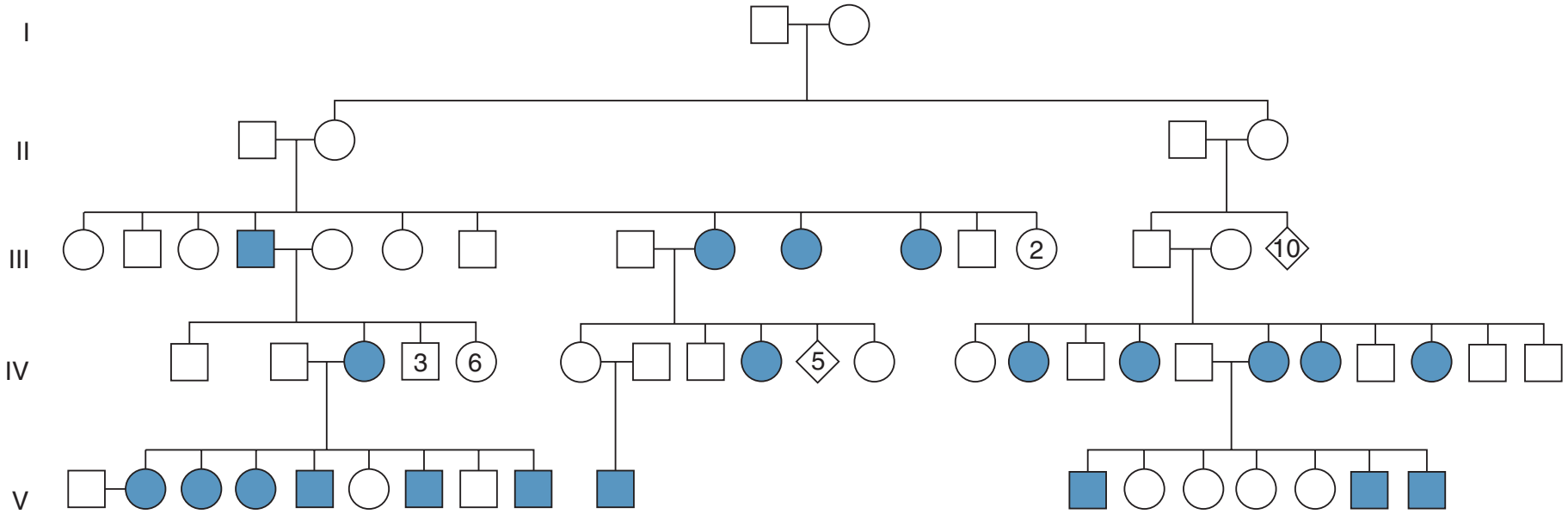

FIG 11-2 A familial colorectal cancer pedigree. *Darkened symbols* represent individuals with diagnosed colorectal cancer.

- The childhood cancer of the eye, retinoblastoma, is a good example. Those who inherit a mutant version of the retinoblastoma gene have approximately a 90% chance of developing one or more retinoblastoma tumors.

- Although the transmission of cancer as a single-gene disorder is relatively uncommon, there is good evidence for more frequent clustering of some cancer types in families.

- For many kinds of cancer, such as those of the breast and colon, the diagnosis of the cancer in a first-degree relative implies at least a twofold increase in one's risk of developing the cancer. It is very likely that the inheritance of altered forms of specific genes is at least partly responsible for this increased risk.

- The extent to which each of these mechanisms—inherited germline mutations versus mutations occurring in somatic cells—contributes to human cancer is an important question.
- If inherited predispositions are significant determinants of a person's risk of acquiring a specific form of cancer, it should be possible to identify those in whom the risk is elevated.

CAUSES OF CANCER

Environmental Considerations

- Tumor cells arise when certain changes, or mutations, occur in genes that are responsible for regulating the cell's growth. The frequency and consequences of these mutations can be altered by a large number of environmental factors.

- It is well documented, for example, that many chemicals that cause mutation in experimental animals also cause cancer and are thus carcinogens. Furthermore, other environmental agents can enhance the growth of genetically altered cells without directly causing new mutations. Thus, it is often the interaction of genes with the environment that determines carcinogenesis; both play key roles in this process.

- Two additional lines of argument support the idea that exposure to environmental agents can significantly alter a person's risk of cancer.

- The first is that a number of environmental agents with carcinogenic properties have been identified. For example, epidemiological studies and laboratory experiments have shown that cigarette smoke causes lung and other types of cancer.
- The second line of argument is based on epidemiological comparisons among populations with differing lifestyles.

- Examination of genetically similar populations under differing lifestyles provides an opportunity to evaluate the genetic and environmental components of cancer.

- Epidemiological studies among **migrant Japanese** populations have yielded important findings with respect to colon cancer. This type of cancer was, until recently, relatively rare in the Japanese population living in Japan, with a lifetime risk of 0.5%, but it is 10 times more common in the United States.

- Stomach cancer, is common in Japan but relatively rare in the United States.

- These statistics in themselves cannot distinguish environmental from genetic influences in the two populations. However, because large numbers of Japanese have immigrated, first to Hawaii and then to the U.S. mainland, we can observe what happens to the rates of stomach and colon cancer among the immigrants.
- It is important to note that many of the Japanese immigrants maintained a genetic identity, marrying largely among themselves.

- These observations strongly suggest an important role for environment or lifestyle in the etiology of colon cancer.
- In each case, diet is a likely culprit: a high-fat, low-fiber diet in the United States is thought to increase the risk of colon cancer, whereas techniques used to preserve and season the fish commonly eaten in Japan are thought to increase the risk of stomach cancer.

- It is also interesting that the incidence of colon cancer in Japan has increased dramatically during the past several decades, as the Japanese population has adopted a diet more similar to that of North America and Europe.

- Are we then to assume that genetic factors play no role in colon cancer? The fact remains that in the North American environment some people will get colon cancer but most will not. This distinction can result from differences within this environment (e.g., dietary variation) as well as differences in genetic predisposition: inherited genes that increase a person's probability of developing cancer.

CANCER GENES

Genetic Control of Cell Growth and Differentiation

- Cancers form when a clone of cells loses the normal controls over growth and differentiation. More than 100 cancer-causing genes that encode proteins participating in this regulation have now been identified.

- One component of cell regulation is mediated by external signals coming to the cell through **growth factors** (e.g., platelet-derived growth factor, epidermal growth factor, steroid hormones) produced in other cells.

- Each growth factor interacts with specific **growth factor receptors** located on the cell surface. Binding of a growth factor activates the receptor, triggering molecules that send messages to the cell's nucleus in the process of **signal transduction.**

- These signal transduction molecules include **protein kinases,** such as Src tyrosine kinase, mitogen-activated protein kinase (MAPK), and Jun kinase (JunK), which can alter the activity of target proteins by tagging them at a specific site with a phosphate molecule (phosphorylation).
- The ultimate stage of the signal transduction pathway is regulation of DNA transcription in the nucleus.

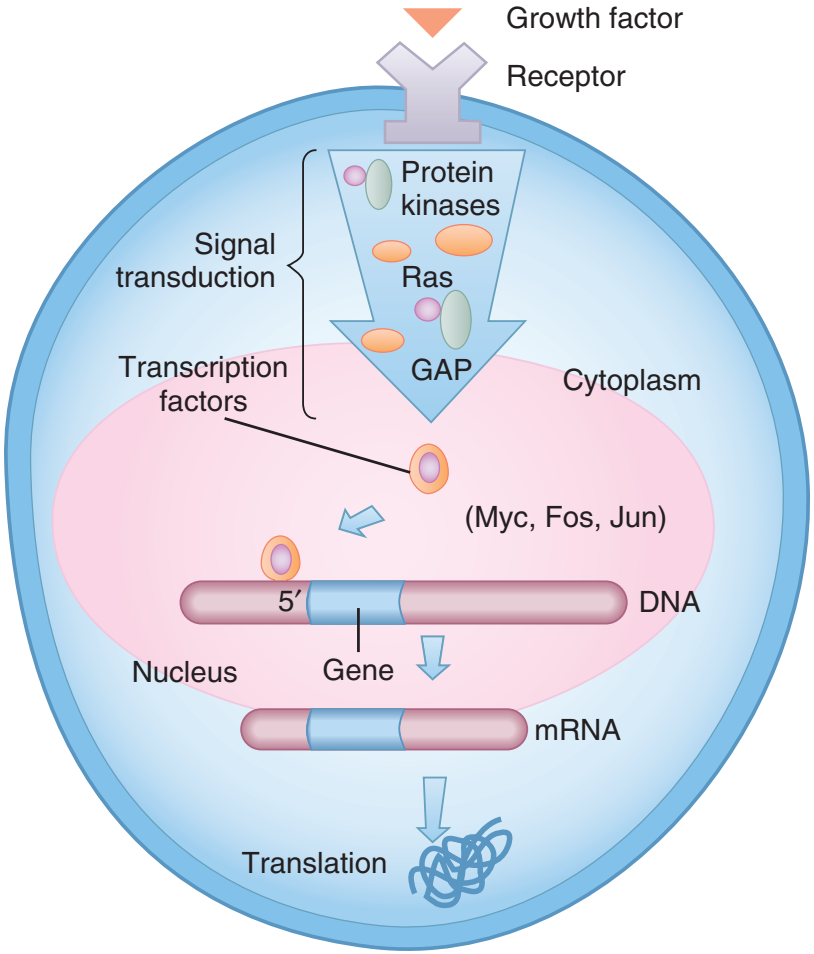

FIG 11-3 The major features of cellular regulation. External growth factors (proteins and steroid hormones such as epidermal growth factor) bind to membrane-spanning growth factor receptors on the cell surface, activating signal-transduction pathways in which genes such as *RAS* participate. Components of the signal-transduction pathway in turn interact with nuclear transcription factors, such as Myc and Fos, which can bind to regulatory regions in DNA. *mRNA,* Messenger RNA.

- After several rounds of cell division, cells normally receive signals that tell them to stop growing and to differentiate into specialized cells.

- A cancer cell can emerge from within a population of growing cells through the accumulation of mutations in these genes. Although such mutations occur only rarely, these cells can fail to respond to differentiation signals and continue to divide instead of undergoing their normal differentiation program.

- Cancers seem usually to result from a progressive series of events that incrementally increase the extent of deregulation within a cell lineage. Eventually, a cell emerges whose descendants multiply without appropriate restraints. Further changes give these cells the capacity to invade adjacent tissues and form metastases.

- Each of these changes involves mutations, and the requirement for more than one mutation has been characterized as the **multihit concept of carcinogenesis.** An example of this concept is given by colorectal cancer, in which **several genetic events** are required to complete the progression from a benign growth to a malignant neoplasm

The Inherited Cancer Gene versus the Somatically Altered Gene

- In 1971, Alfred Knudson's analysis of retinoblastoma, a disease already mentioned as a model of inherited cancer, led him to a hypothesis that opened a new window into the mechanism of carcinogenesis.

- In the inherited form of retinoblastoma, an affected individual often has an affected parent, and there is a 50% chance of genetic transmission to each of the offspring.
- In the sporadic (noninherited) form, neither parent is affected, nor is there additional risk to other progeny.
- A key feature distinguishing the two forms is that inherited retinoblastoma is usually bilateral (affecting both eyes), whereas sporadic retinoblastoma usually involves only a single tumor and therefore affects only one eye (unilateral).

- Knudson reasoned that at least two mutations may be required to create a retinoblastoma. One of the mutations would alter the retinoblastoma gene; if this happened in the germline, it would be present in all cells of a child who received the mutant allele. The second mutation would be an additional, unspecified genetic event occurring in an already-altered cell.

- The hypothesis of a second event was required to explain why only a tiny fraction of the retinoblasts of a person who has inherited a mutant retinoblastoma gene actually give rise to tumors. Knudson's hypothesis is known as the **two-hit model of carcinogenesis.**

- Familial retinoblastoma would thus be caused by the inheritance of one of the genetic “hits” as a **constitutional** mutation (i.e., a mutation present in all cells of the body). Persons who inherited one hit would require only one additional mutational event in a single retinoblast for that cell to seed a tumor clone.

- In **sporadic** cases,, both mutations would have to occur somatically in the developing fetus (Fig. 11-4). This is a highly improbable combination of rare events, even considering the several million cells of the target tissue.

- The child who developed a retinoblastoma by this two-hit somatic route would be unlikely to develop more than one tumor. The child inheriting a mutant retinoblastoma gene, however, would need only a single, additional genetic hit in a retinoblast for a tumor clone to develop.

- Knudson argued that such an event was likely to occur in several of the retinoblasts of each carrier of the inherited mutant gene, thus explaining the bilaterality of inherited retinoblastoma.

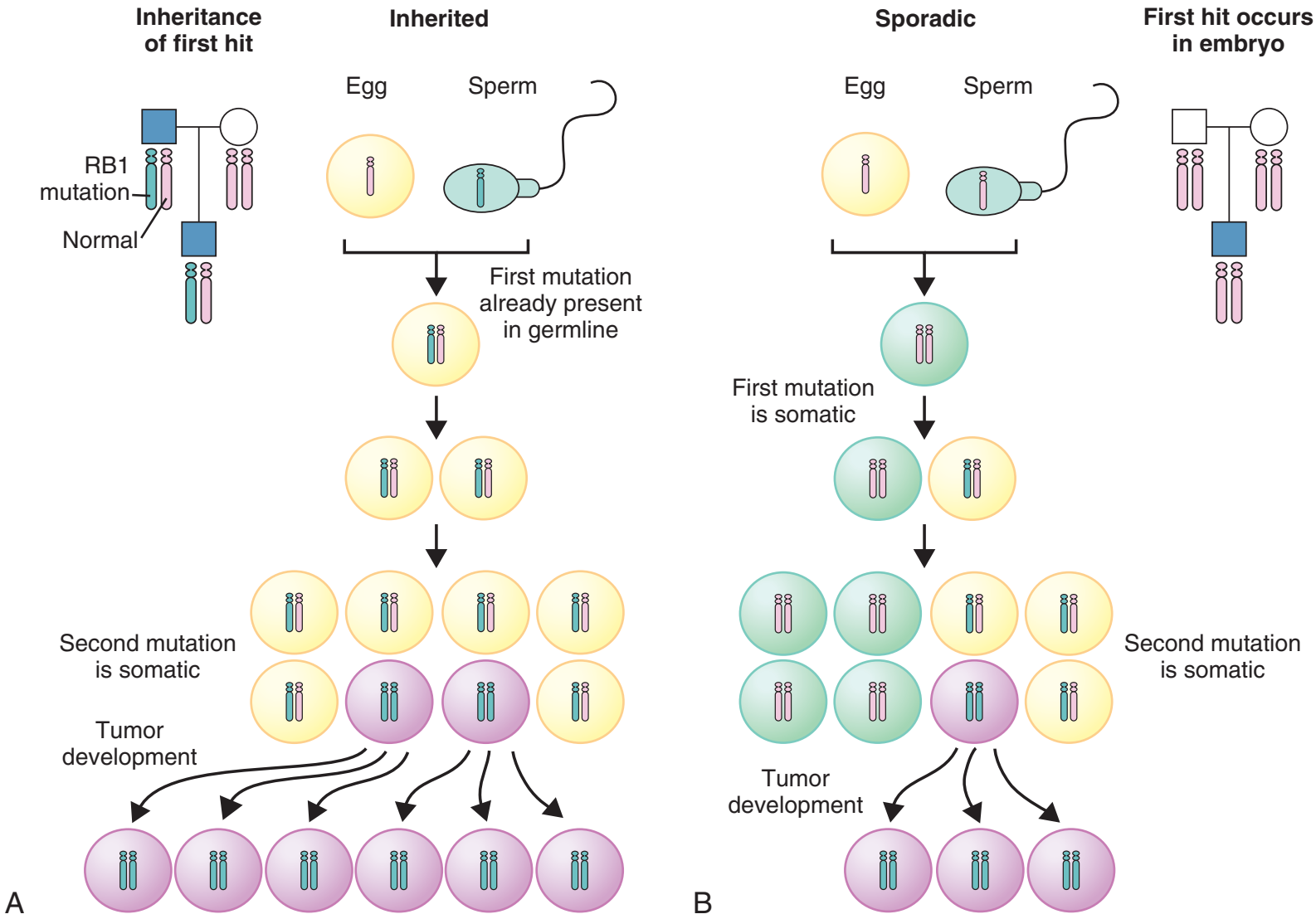

FIG 11-4 **A,** Persons inheriting an *RB1* mutation are heterozygous for the mutation in all cells of their body. The second hit occurs during embryonic development and typically affects more than one retinoblast, resulting in multiple tumors. **B,** In somatic retinoblastoma, both copies of the *RB1* gene must be disabled in the same retinoblast to cause tumor formation. Each process leads to homozygosity for the mutant *RB1* allele and thus to tumor development.

- If the first event in the two-hit model can be an inherited mutation, what is the nature of the second hit? Extensive molecular analysis of the region of chromosome 13 that contains the retinoblastoma-causing gene, *RB1,* showed that the second hit, like the first one, is a loss-of-function mutation.

- Several mechanisms, including point mutation, deletion, and hypermethylation of the *RB1* promoter region (associated with decreased transcription), can produce this effect.

- The second hit, which occurs in the fetus during the period in which retinoblasts are rapidly dividing and proliferating, has removed the remaining normal allele of this gene. This implies that a cell with one mutant *RB1* allele and one normal *RB1* allele cannot form a tumor. Thus, the product of the normal gene, even when present only in a single copy, prevents tumor formation.

- An important corollary of this two-hit hypothesis is that the genes in which inherited mutations cause familial cancer syndromes may be the same as those that generate common cancers by somatic mutation.
- *By understanding the nature of the mutant alleles inherited in rare cancer families, therefore, we will come to understand more about the somatic pathway to common cancer as well.*

- Indeed, somatic loss-of-function mutations of both copies of the *RB1* gene are seen frequently in many types of tumors, including small-cell lung carcinoma, breast carcinoma, glioblastoma (a brain tumor), and osteosarcoma.

MAJOR CLASSES OF CANCER GENES

Tumor Suppressor Genes

- The *RB1* gene was the first identified example of a **tumor suppressor gene,** a class of genes that control cell division and thus help to prevent tumors (Table 11-1).

- A perplexing feature of tumor suppressor genes is that inherited mutations are *dominant* alleles at the level of the individual (i.e., heterozygotes usually develop the disease), but they are *recessive* alleles at the level of the cell (heterozygous cells do not form tumors).
- This apparent contradiction is resolved by realizing that in individuals who have inherited the first hit, a second hit that occurs in any one cell will cause a tumor. Because there are several million target retinoblasts in the developing fetus, heterozygous persons form, on the average, several retinoblasts homozygous for an *RB1* mutation. Each of these can lead to a retinoblastoma.

- Thus, it is the strong predisposition to tumor formation (i.e., the first hit) that is inherited as an autosomal dominant trait. The incomplete penetrance of the retinoblastoma mutation (90%) is explained by the fact that some people who inherit the disease-causing mutation do not experience a second hit in any of their surviving retinoblasts.

TABLE 11-1 Examples of Tumor Suppressor Genes and DNA Repair Genes and Their Roles in Inherited Cancer

GENE (RELATED GENES IN PARENTHESES)	FUNCTION OF GENE PRODUCT	DISEASE CAUSED BY GERMLINE MUTATIONS
Tumor Suppressor Genes		
RB1(p107, p130)	Cell cycle brake; binds to E2F transcription factor complex	Retinoblastoma; osteosarcoma
APC	Interacts with β-catenin in Wnt signaling pathway	Familial adenomatous polyposis
SMAD4	Transmits signals from TGFβ	Juvenile polyposis
NF1	Down-regulates RAS protein	Neurofibromatosis type 1
NF2	Cytoskeletal protein regulation	Neurofibromatosis type 2
TP53	Transcription factor; induces cell cycle arrest or apoptosis	Li–Fraumeni syndrome
VHL	Regulates multiple proteins, including p53 and NFκB	Von Hippel–Lindau disease (renal cysts and cancer)
WT1	Zinc finger transcription factor; binds to epidermal growth factor gene	Wilms tumor
CDKN2A (p14, p16)	CDK4 inhibitor	Familial melanoma
PTEN	Phosphatase that regulates PI3K signaling pathway	Cowden syndrome (breast and thyroid cancer)
CHEK2	Phosphorylates p53 and BRCA1	Li–Fraumeni syndrome
PTCH	Sonic hedgehog receptor	Gorlin syndrome (basal cell carcinoma, medulloblastoma)
CDH1	E-cadherin; regulates cell–cell adhesion	Gastric carcinoma
DPC4	Transduces transforming growth factor-β signals	Juvenile polyposis
TSC2	Down-regulates mTOR (mammalian target of rapamycin)	Tuberous sclerosis
DNA Repair Genes		
MLH1	DNA mismatch repair	HNPCC
MSH2	DNA mismatch repair	HNPCC
BRCA1	Interacts with BRCA2/RAD51 DNA repair protein complex	Familial breast and ovarian cancer
BRCA2	Interacts with RAD51 DNA repair protein	Familial breast and ovarian cancer
ATM	Protein kinase; phosphorylates BRCA1 in response to DNA damage	Ataxia telangiectasia; conflicting evidence for direct involvement in breast cancer
XPA	Nucleotide excision repair	Xeroderma pigmentosum

- A general property of tumor suppressors is that they normally block the uncontrolled cellular proliferation that can lead to cancer. Often, this is done by participating in pathways that regulate the cell cycle.

- For example, the protein encoded by RB1 (pRb) is active when it is unphosphorylated but is down-regulated when it is phosphorylated by cyclin-dependent kinases (CDKs) just before the S phase of the cell cycle.
- In its active, hypophosphorylated state, pRb binds to members of the E2F transcription complex, inactivating them (Fig. 11-5). E2F activity is required for the cell's progression into S phase, so its inactivation by pRb halts the cell cycle.

- A loss-of-function mutation in *RB1,* a deletion of the gene, or hypermethylation of its 5′ region can lead to its permanent inactivation. Without this brake on the cell cycle, the cell can proceed through numerous uncontrolled divisions.

- Loss-of-function mutations of other inhibitory factors can also lead to an unregulated cell cycle. A number of tumor suppressor genes encode **CDK inhibitors** (see Fig. 11-5), which inactivate CDKs and thus prevent them from phosphorylating target proteins such as pRb.

- Tumor suppressors can also control cell proliferation through their effects on transcription or on cell–cell interactions. Again, mutations in these genes can lead to unrestricted cell division and ultimately to cancer.

- Because of the pivotal role of tumor suppressors in preventing tumor formation, their study is of considerable medical significance. By understanding how cancer is naturally suppressed by the body, we can ultimately develop more effective medical therapies for tumor prevention and treatment.

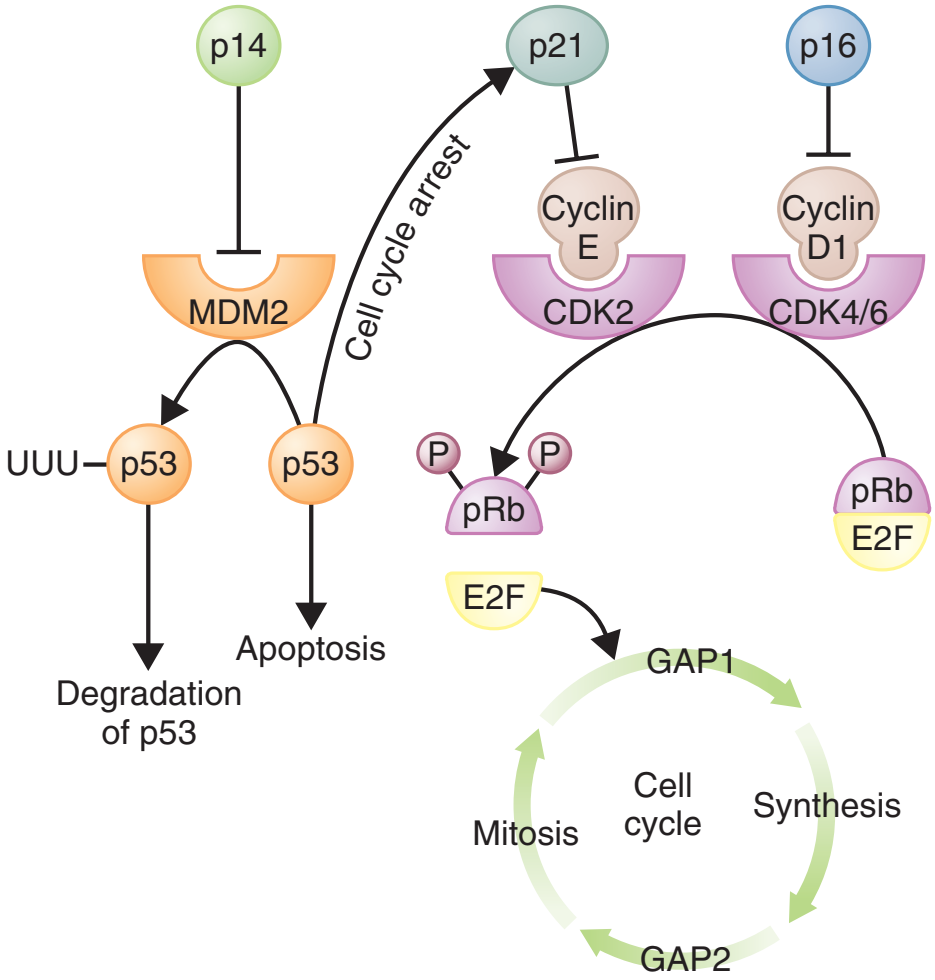

FIG 11-5 Regulation of the cell cycle is accomplished by a complex series of interactions among activators and repressors of the cycle. pRb acts as a master brake on the cell cycle by binding the E2F transcription complex, halting the cycle before S phase begins. The cyclin D–CDK4 complex inactivates pRb by phosphorylating it, thereby releasing the E2F complex and allowing the cell to progress through S phase. CDK inhibitors such as p16 and p21 inactivate CDKs, thus acting as another brake on the cycle. p53, acting through p21, can either halt the cell cycle or induce apoptosis in response to DNA damage. *CDK,* Cyclin-dependent kinase.

Oncogenes

- **Oncogenes** (i.e., "cancer genes") are a second category of genes that can cause cancer. Most oncogenes originate from **proto-oncogenes,** which are genes involved in the four basic regulators of normal cell growth mentioned previously (growth factors, growth factor receptors, signal transduction molecules, and nuclear transcription factors).

- When a mutation occurs in a proto-oncogene, it can become an oncogene, a gene whose excessively active product can lead to unregulated cell growth and differentiation. When a cell proceeds from regulated to unregulated growth, the cell is said to have been **transformed.**

- Unlike tumor suppressor genes, oncogenes are usually dominant at the cellular level: only a single copy of a mutated oncogene is required to contribute to the multistep process of tumor progression.

- Whereas tumor suppressors are typically disabled by deletions or loss-of-function mutations, oncogenes are typically activated by gain-of-function mutations, gene amplification (i.e., increased numbers of the gene through trisomy or other mechanisms), hypomethylation of the oncogene's 5' region (which increases transcription), or chromosome rearrangements that upregulate the oncogene (e.g., the Philadelphia chromosome translocation)

- Most tumor suppressor genes are known to exhibit germline mutations that can cause inherited cancer syndromes (e.g., retinoblastoma, Li–Fraumeni syndrome). In contrast, although oncogenes are commonly found in sporadic tumors, germline oncogene mutations that cause inherited cancer syndromes are uncommon.

- Three approaches that have been used to identify specific oncogenes: retroviral definition, transfection experiments, and mapping in tumors.

- **Retroviruses,** a type of RNA virus that is capable of using reverse transcriptase to transcribe its RNA into DNA. In this way, the RNA genome of the retrovirus is converted to DNA, which can be inserted into a chromosome of a host cell.

- Some retroviruses carry altered versions of growth-promoting genes into cells. These growth-promoting genes are **oncogenes**, which were first identified through the study of retroviruses that cause cancer in chickens. When the retrovirus invades a new cell, it can transfer the oncogene into the genome of the new host, thus transforming the cell and initiating cancer.

TABLE 11-2 Comparison of Key Features of Tumor Suppressor Genes and Oncogenes

FEATURE	TUMOR SUPPRESSOR GENES	ONCOGENES
Function of normal version	Regulates cell growth and proliferation; some can induce apoptosis	Promotes cell growth and proliferation
Mutation (at cell level)	Recessive (both copies of gene inactivated)	Dominant (only one copy of gene mutated)
Effect of mutation	Loss of function	Gain of function
Germline mutations resulting in inherited cancer syndromes	Seen in most tumor suppressor genes	Seen in only a few oncogenes

- A number of gene products that affect cell growth or differentiation have been identified through the study of oncogenes carried by transforming retroviruses.

- For example, retrovirus studies **identified** the gene encoding the receptor molecule for epidermal growth factor (EGF), through the *ERBB* oncogene.
- These studies also **identified** the *RAS* (*ra*t *s*arcoma) oncogenes, which are altered in at least 25% of human cancers.
- Transforming retroviruses have also identified the nuclear transcription factor genes, *MYC, JUN,* and *FOS,* as other molecular components capable of initiating cell transformation.
- Table 11-3 provides some examples of proto-oncogenes.

TABLE 11-3 Examples of Oncogenes and Their Roles in Cancer*

ONCOGENE	FUNCTION	ASSOCIATED TUMOR
Growth Factor Genes		
HST	Fibroblast growth factor	Stomach carcinoma
SIS	β subunit of platelet-derived growth factor	Glioma (brain tumor)
KS3	Fibroblast growth factor	Kaposi sarcoma
Growth Factor Receptor Genes		
RET†	Receptor tyrosine kinase	Multiple endocrine neoplasia; thyroid carcinoma
ERBB	Epidermal growth factor receptor	Glioblastoma (brain tumor); breast carcinoma
ERBA	Thyroid hormone receptor	Acute promyelocytic leukemia
NEU (ERBB2)	Receptor protein kinase	Neuroblastoma; breast carcinoma
MET†	Receptor tyrosine kinase	Hereditary papillary renal carcinoma; hepatocellular carcinoma
KIT†	Receptor tyrosine kinase	Gastrointestinal stromal tumor syndrome
Signal Transduction Genes		
HRAS	GTPase	Carcinoma of colon, lung, pancreas
KRAS	GTPase	Melanoma, thyroid carcinoma, acute monocytic leukemia, colorectal carcinoma
NRAS	GTPase	Melanoma
BRAF	Serine/threonine kinase	Malignant melanoma; colon cancer
ABL	Protein kinase	Chronic myelogenous leukemia; acute lymphocytic leukemia
CDK4†	Cyclin-dependent kinase	Malignant melanoma
Transcription Factor Genes		
NMYC	DNA-binding protein	Neuroblastoma; lung carcinoma
MYB	DNA-binding protein	Malignant melanoma; lymphoma; leukemia
FOS	Interacts with *JUN* oncogene to regulate transcription	Osteosarcoma

*For additional examples, see Croce CM. Oncogenes and cancer. *N Engl J Med* 2008;358(5):502-511 and Garraway and Lander. Lessons from the cancer genome. *Cell* 2013;153:17-37.

†*CDK4, KIT, MET,* and *RET* are proto-oncogenes in which germline mutations can give rise to inherited cancer syndromes.

- Oncogenes have also been identified in experiments in which material from human tumor cells was transferred to nontumor cells **(transfection),** causing transformation of the recipients.

- A classic experiment began with the transfer of DNA from a human bladder-cancer cell line into mouse cells. A few recipient cells became fully transformed. Cloning and examination of the human-specific DNA sequences present in the transformed mouse cells revealed that the transforming gene was a mutant allele of the same *RAS* oncogene previously identified by retroviral studies. Thus, the same oncogene that could be transferred by retroviruses also occurs naturally, as a proto-oncogene, in the human genome.

- Characterization of the protein product of mutant forms of *RAS* has revealed an important mechanism for the regulation of signal transduction. The RAS protein normally cycles between an *active* form bound to **guanosine triphosphate (GTP)** and an *inactive* form bound to **guanosine diphosphate (GDP).**
- The biochemical consequence of *RAS* mutations is a RAS protein that is unable to shift from the active GTP form, which stimulates growth, to the inactive GDP form. The mutant RAS protein cannot extinguish its growth signal, contributing to excessive cell division.

- A third approach for identifying oncogenes derives from the common observation of chromosomal rearrangements, such as translocations, in some types of tumor cells.

- A well-known example is the Philadelphia chromosome, in which a translocation between chromosomes 9 and 22 places the *ABL* proto-oncogene next to the *BCR* gene, which enhances tyrosine kinase activity and produces chronic myelogenous leukemia.

- Another translocation, t(15;17) (q22;q11.2-12), is seen in acute promyelocytic leukemia (APL) and fuses two genes together: the retinoic acid receptor alpha *(RARA)* gene on chromosome 17 and the promyelocytic leukemia *(PML)* gene on chromosome 15.

- The fusion product (PML-RARα) interferes with the ability of the normal RARα protein to induce terminal differentiation of myeloid cells. The fusion product also impairs the function of the PML protein, which acts as a tumor suppressor by helping to initiate apoptosis in damaged cells.

- The identification of oncogenes has greatly increased our understanding of some of the underlying causes of cancer. In addition, oncogenes provide important targets for cancer therapy because of their key role in carcinogenesis.

- For example, the *ERBB2* oncogene, mentioned earlier and also known as *HER2/NEU,* is amplified in approximately 20% to 30% of invasive breast carcinomas. Its amplification in breast tumor cells, which can be identified by fluorescent in situ hybridization (FISH) or array comparative genomic hybridization (CGH), is associated with aggressive cancer.
- The protein product of *HER2/NEU* is a growth factor receptor located on the surfaces of breast cancer cells. Identification of the oncogene and its product contributed to the development of drugs, such as trastuzumab, that bind to the amplified gene product, effectively down-regulating it and helping to treat this form of breast cancer.

- Similar drugs have been developed to counter the effects of the upregulated *ABL* oncogene in chronic myelogenous leukemia, an upregulated epidermal growth factor receptor gene in non–small-cell lung cancer, and several others.

DNA Repair Genes, Chromosome Integrity, and Tumorigenesis

- Tumor cells typically are characterized by widespread mutations, chromosome breaks, and aneuploidy. This condition, termed **genomic instability,** contributes to tumorigenesis because mutations and chromosome defects can activate oncogenes or deactivate tumor suppressor genes.

- Genomic instability can occur because of defects in the proteins required for accurate cell division or in proteins responsible for DNA repair. It is also associated with hypomethylation of DNA, a common feature of many tumors.

- These defects are in turn the result of mutations. Sometimes, these mutations are inherited, resulting in relatively rare inherited cancer syndromes (see Table 11-1). More often, they arise in somatic cells and contribute to common, noninherited cancers.

- There are a number of ways various types of genomic instability can give rise to cancer. Some breast cancers are caused by defective repair of double-stranded breaks that occur in DNA (e.g., from radiation exposure). This can result from mutations in genes such as *BRCA1, BRCA2,* or *ATM.*

- An inherited form of colon cancer, can result from faulty DNA **mismatch repair** (so named because single-base mutations can lead to a DNA molecule in which base pairs are not complementary to each other: a mismatch).

- Xeroderma pigmentosum, an inherited condition that is characterized in part by multiple skin tumors, is the result of impaired nucleotide excision repair.

- Defects in proteins responsible for chromosome separation during mitosis (e.g., spindle fibers) can give rise to the multiple aneuploidies typically seen in tumor cells. **Aneuploidy** can contribute to tumorigenesis by creating extra copies of onco- genes or by deleting tumor suppressor genes.