



VIVEKANANDA COLLEGE THAKURPUKUR

KOLKATA-700063

NAAC ACCREDITED 'A' GRADE

TOPIC	: CANCER
COURSE TITLE	: CELL BIOLOGY
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NAME OF THE TEACHER	: DR. MALABIKA BHATTACHARJEE
NAME OF THE DEPARTMENT	: DEPARTMENT OF ZOOLOGY [UG & PG]

CANCER

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REFERENCE

1. CELL-COOPER
2. CELL-BRUCE ALBERTS
3. CELL-LEWIN
4. MOLECULAR CELL BIOLOGY-LODISCH
5. THE WORLD OF CELL-BECKER
6. MOLECULAR BIOLOGY OF CANCER
7. MOLECULAR BIOLOGY OF CANCER
8. CANCER CELL SIGNALLING

CELL CYCLCE, CELL DEATH & CANCER....

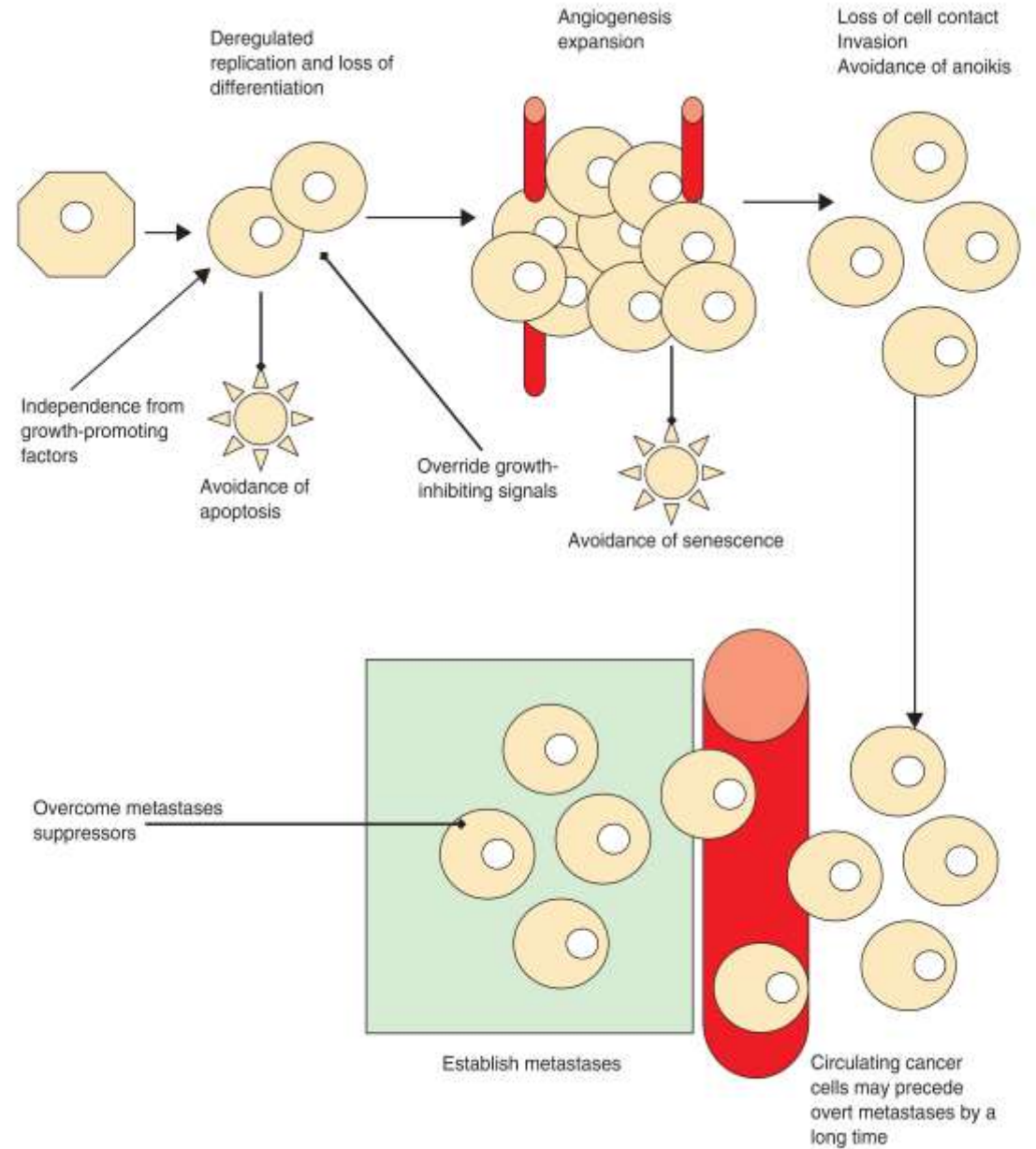
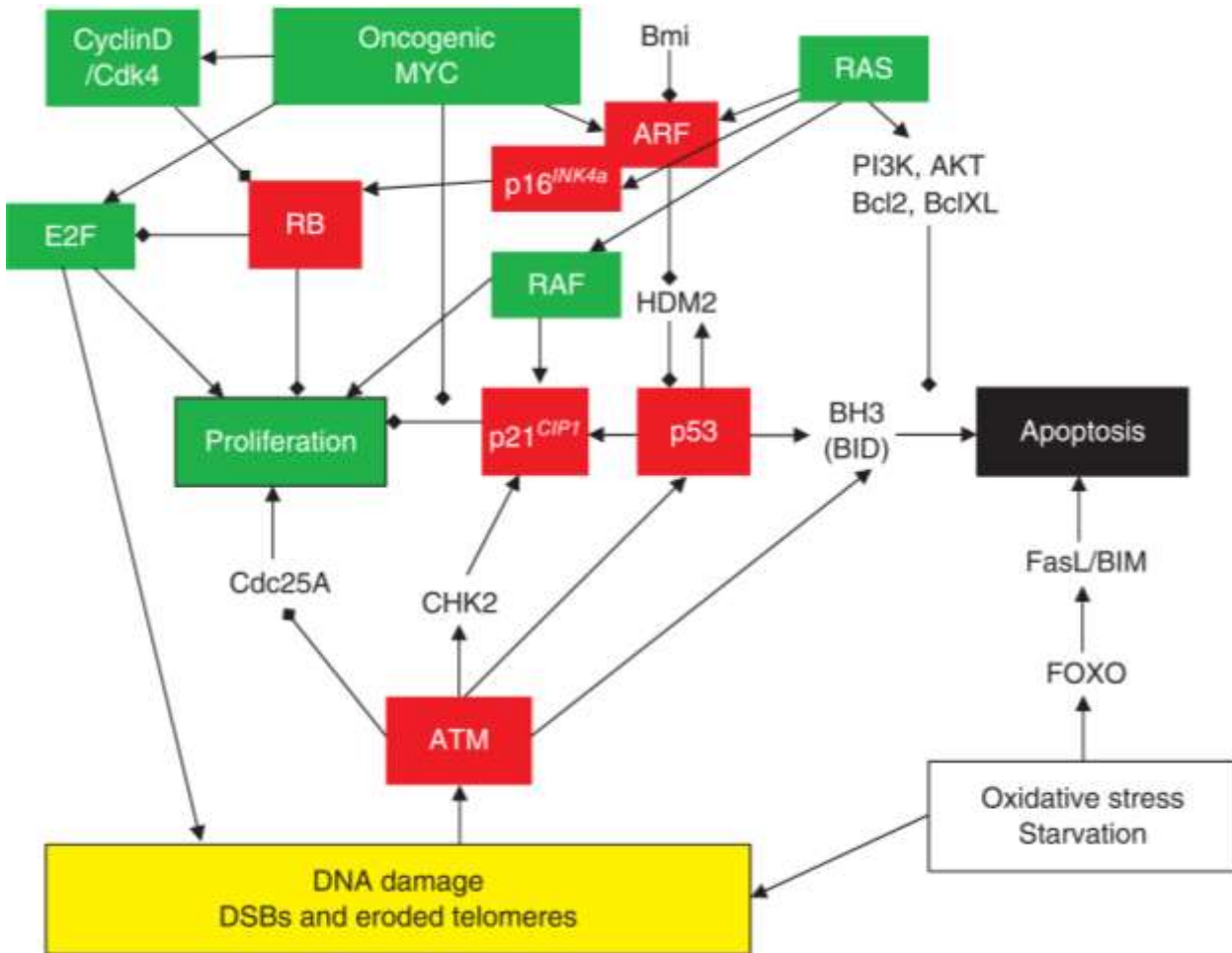


Figure 1.8 Processes contributing to cancer formation. The "hallmark" features of cancer are shown, appearing in a potential sequence. It should be noted that this does not imply that this is the actual sequence in which such features are acquired in any particular cancer.

THE ORIGIN OF THE WORD....CANCER

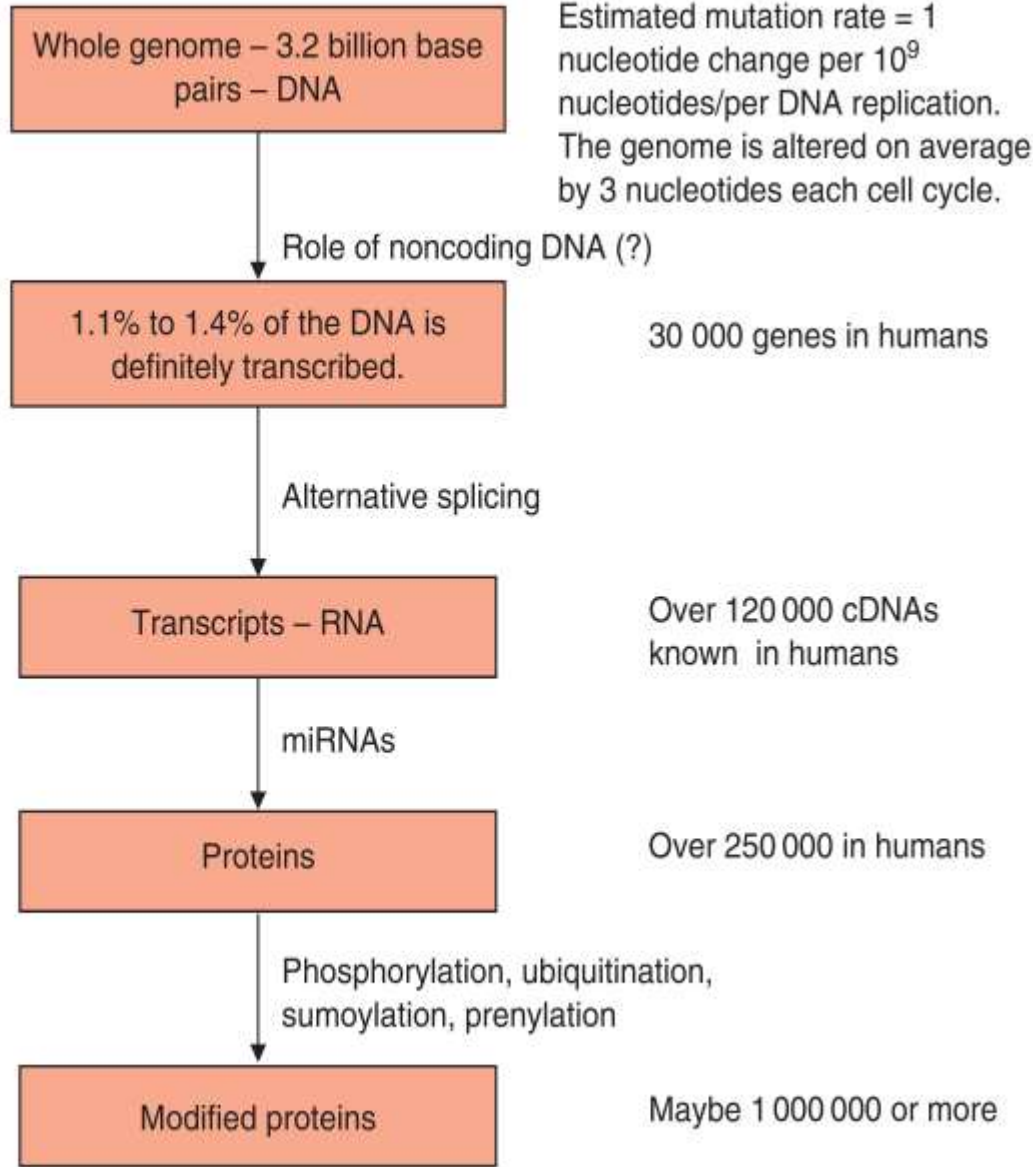
Nevertheless, many of the early written descriptions of cancer originate from the Classical Greek and Roman physicians Hippocrates and Galen, who laid the foundations for modern medicine by emphasizing that diseases were natural physical processes.

In fact, *we owe our names for cancer to Hippocrates, who first applied the terms karkinos and karkinoma (Ancient Greek for “crab”) to various diseases, including cancers of the breast, uterus, stomach, and skin.*

Cancer is the Latin equivalent. Interestingly, although Galen performed some early surgical interventions for cancer, he maintained that cancer was generally best left untreated, a view that appears to still find favor with some health economists.

However, Galen also believed that ***diseases resulted from imbalances*** in the four bodily “***humors***” (***blood, phlegm, yellow bile, and black bile***), which were also responsible for differing temperaments such as melancholy!

HUMAN GENOME AND MUTATION RATE....



18 000 or so genes in the nematode worm, which has only 1000 cells!

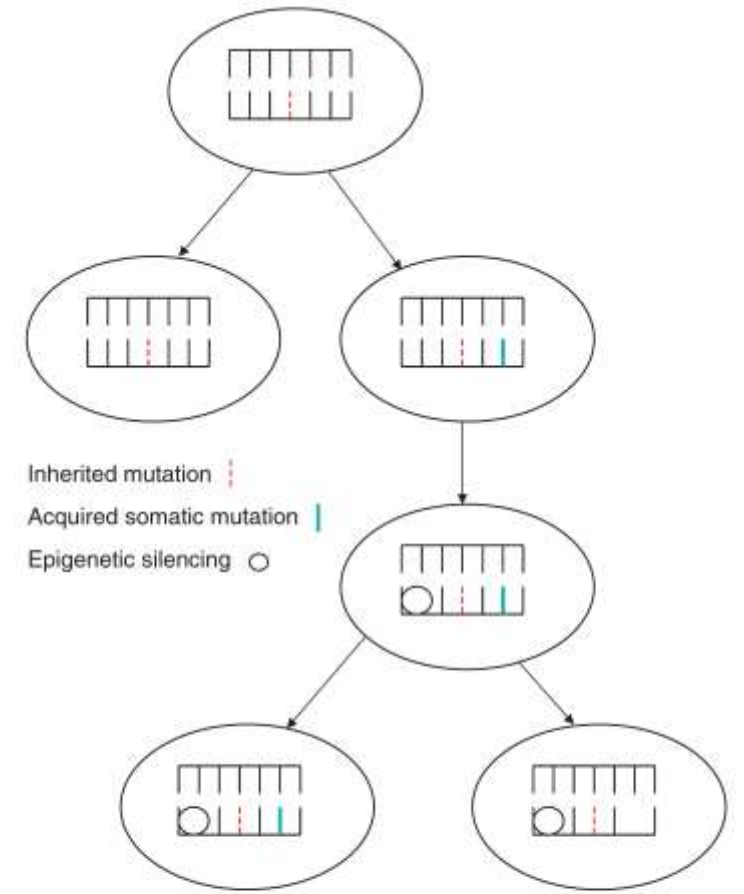


Figure 1.13 Tumorigenesis ultimately results from disordered gene expression. Tumor cells arise through aberrant expression of genes and the proteins they encode. This may result from mutations in the coding or noncoding regulatory regions of genes, which can be either inherited or acquired in somatic cells or even by major rearrangements of the chromosomes; epigenetic factors such as altered patterns of methylation and acetylation, which control the “accessibility” of genes for transcription. These events may in turn affect the stability and processing of RNA or proteins.

IMPORTANT DATES

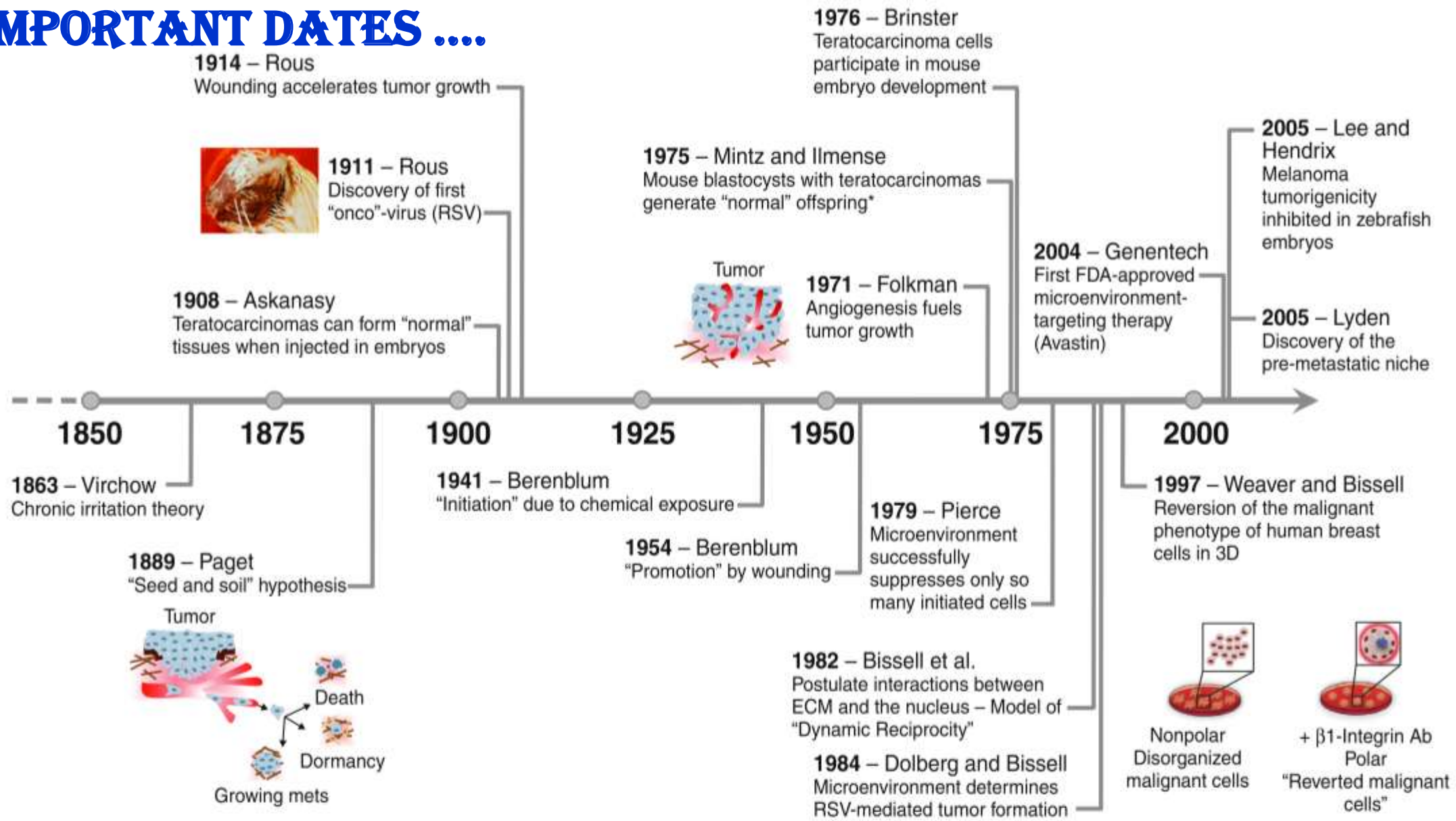


FIGURE 16-1 A HISTORICAL PERSPECTIVE ON THE ROLE OF THE MICROENVIRONMENT IN CANCER A timeline detailing landmark discoveries that showed the dominance of microenvironment over genotype. If space had permitted, a number of other important experiments could have been included, such as Emerman and Pitelka’s demonstration that normal mammary epithelial cells on floating collagen gels recapitulate their in vivo phenotype,¹⁴ Folkman’s demonstration that cell shape regulates DNA synthesis,¹⁵ and experiments demonstrating that reconstituted 3D BM gels act as a “blotter” to distinguish the normal from the malignant phenotype.^{16,17}

1. Oncogenesis may be due to:

- a. Spontaneous genetic changes, such as spontaneous gene or chromosome mutations.
- b. Exposure to mutagens or radiation.
- c. The action of genes introduced by tumor viruses.

Tumor Cells and the Onset of Cancer

1. The abnormal behavior of cancer cells begins when a single cell in a tissue undergoes a transformation that converts it from a normal cell to a cancer cell. Normally, the immune system recognizes and destroys transformed cells.
2. However, cells that evade destruction proliferate to form a tumor, a mass of abnormal cells.
3. If the abnormal cells remain at the originating site, the lump is called a **benign tumor**. Most do not cause serious problems and can be removed by surgery. Benign tumors do not spread – warts for example.
4. In a **malignant tumor**, the cells leave the original site to impair the functions of one or more organs and spread throughout the body . In addition to chromosomal and metabolic abnormalities, cancer cells often lose attachment to nearby cells, are carried by the blood and lymph system to other tissues, and start more tumors in a event called **metastasis**.
5. Cancers arise more readily in tissues that contain proliferating (stem) cells.

Figure 18.1

A mammogram showing a tumor.



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NORMAL VERSUS ABNORMAL

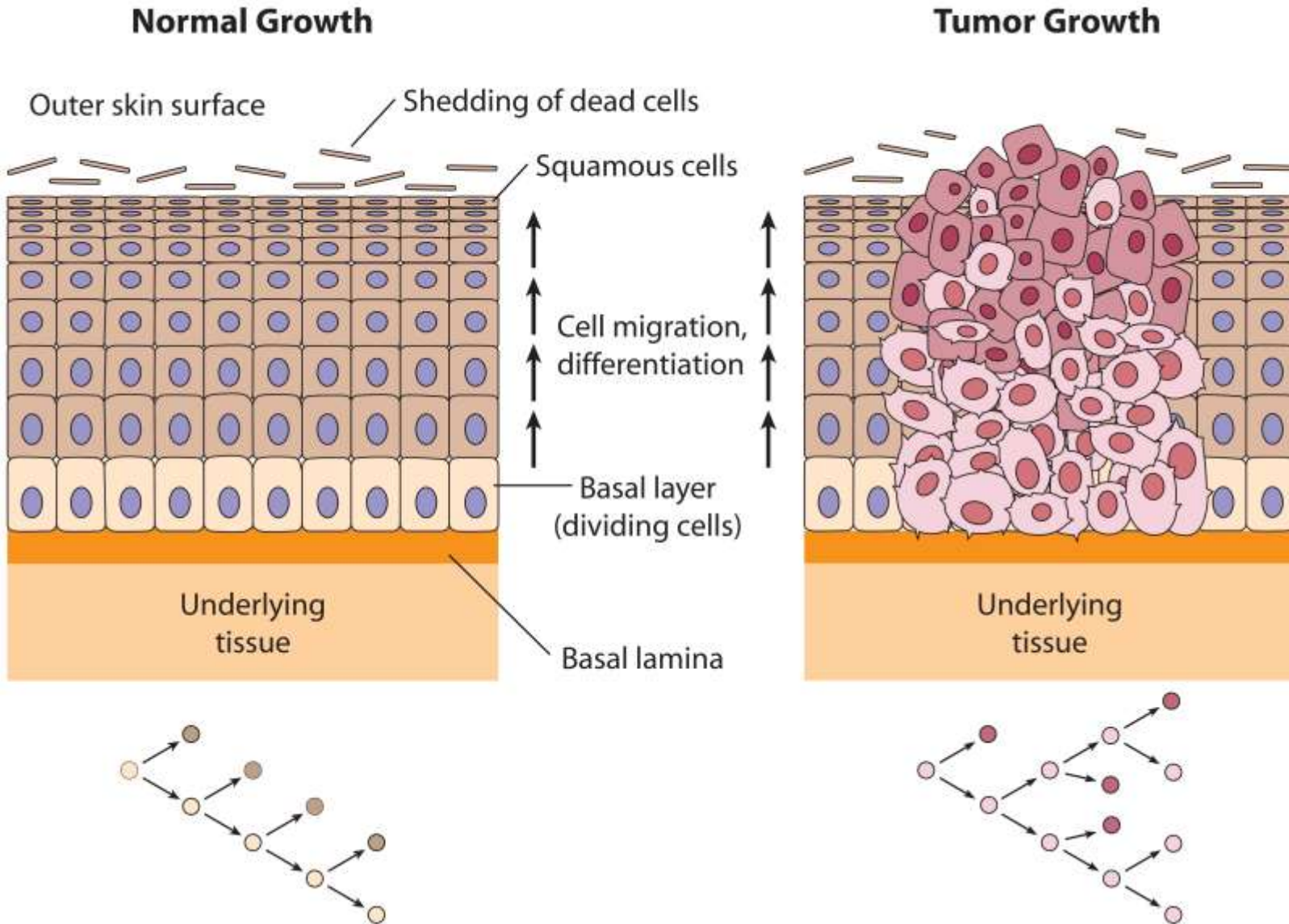


FIGURE 24-1 Comparison of Normal and Tumor Growth in the Epithelium of the Skin. (Top left) In normal skin, cell division in the basal layer gives rise to new cells that migrate toward the outer surface of the skin, changing shape and losing the capacity to divide. (Top right) In tumor growth, this orderly process is disrupted and some of the cells that migrate toward the outer surface retain the capacity to divide. In both diagrams, lighter color shading is used to identify cells that retain the capacity to divide. (Bottom) Schematic diagrams illustrating the fate of dividing cells. In normal skin, each cell division in the basal layer gives rise on average to one cell that retains the capacity to divide (lighter color shading) and one cell that differentiates, thereby losing the capacity to divide (darker color shading). As a result, no net accumulation of dividing cells occurs. In tumor growth, cell division is not appropriately balanced with cell death or differentiation, thereby leading to a progressive increase in the number of dividing cells.

BASIC TYPES: BENIGN & MALIGNANT

1. Carcinomas – arise from endoderm (gut) or ectoderm (skin, neural epithelium).

2. Sarcomas – arise from mesodermal tissues (muscle, blood, connective tissue).

3. Leukemias and lymphomas – arise from blood forming cell and from cells of the immune system

BASIC STEPS IN TUMOR FORMATION

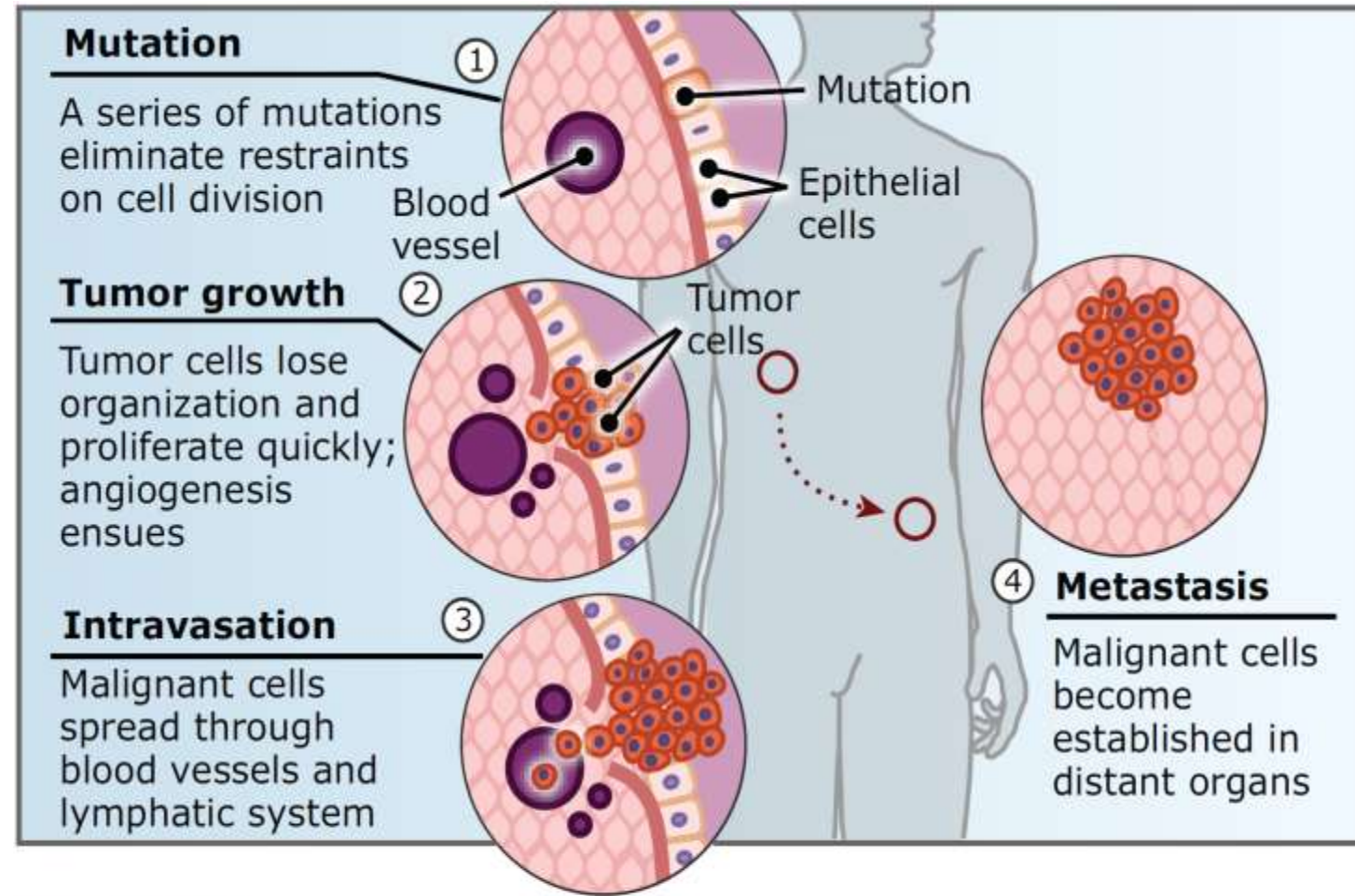
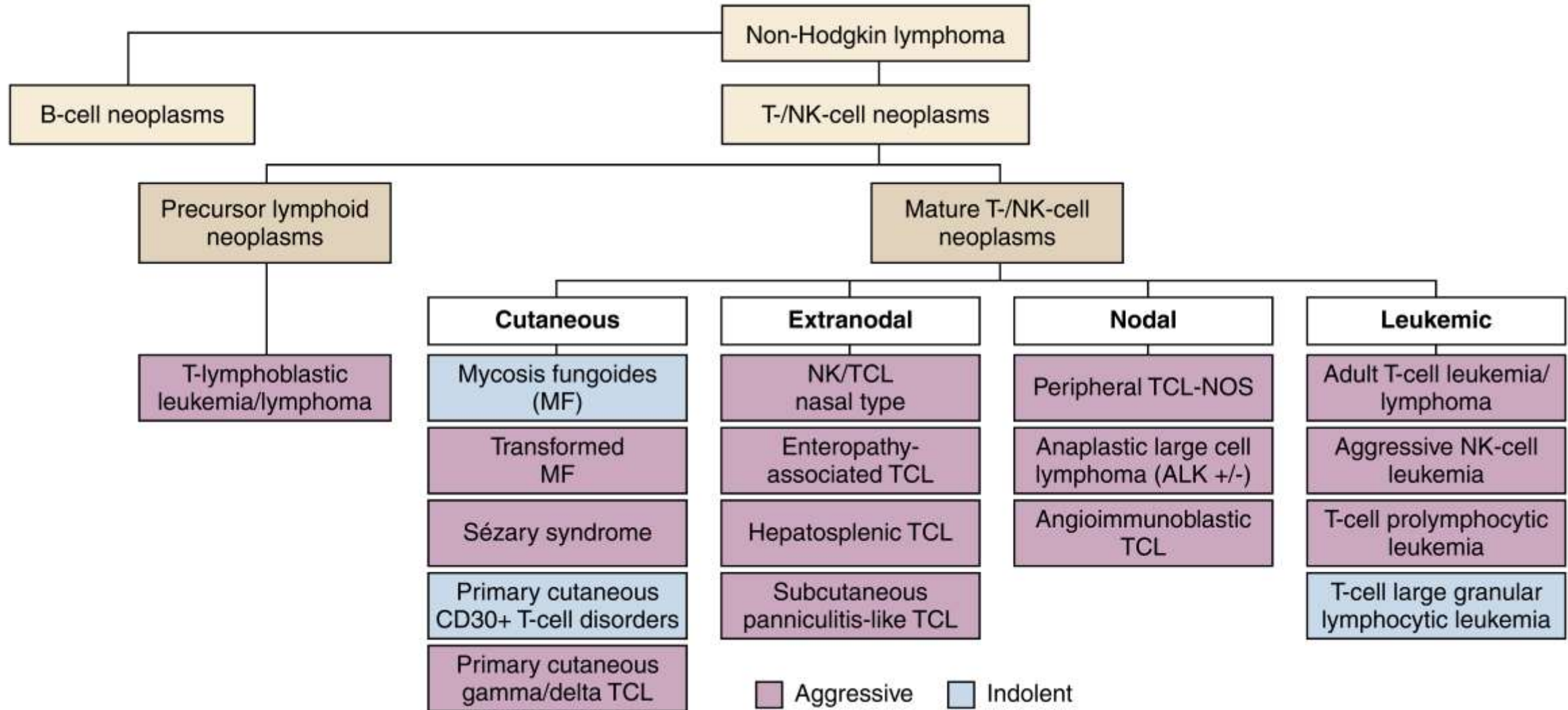


FIGURE 17.1 In general, cancer progresses from a local tumor to widespread metastasis. Here we show the basic steps that occur after an epithelial cell has been mutated.

DIVERSE CATEGORIES OF LYMPHOMA: A GLIMPSE

2NHL Neoplasm Grouping

2008 WHO Classification of Major Subtypes^{2,3}



SELECTIVE LYMPHOMA RELATIVE TO THEIR SITES OF ORIGIN

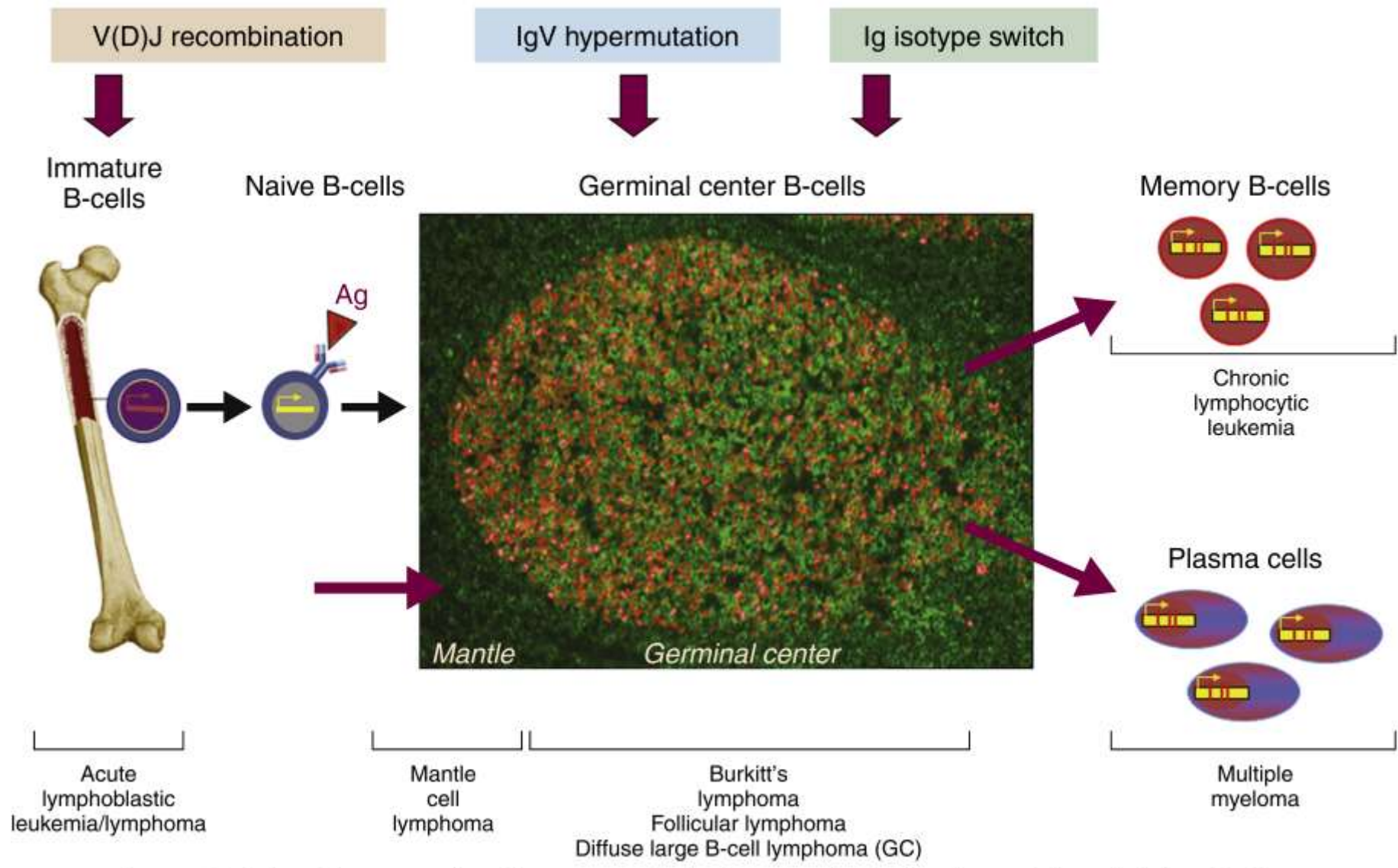


FIGURE 29-2 Schematic representation of the ontogeny of B-lymphocytes and select lymphoma relative to their sites of origin.

THE MULTISTEP NATURE OF CANCER

1. **Cancer induction may require accumulation of 6–7 independent mutations over several decades, typically involving:**
 - a. Conversion of proto-oncogenes to oncogenes.
 - b. Inactivation of tumor suppressor genes.
2. **An example is Vogelstein's model for a form of colorectal cancer, hereditary FAP**
 - a. **Mutation of both alleles** of a tumor suppressor gene on **chromosome 5, APC** (adenomatous polyposis coli), causes increased cell growth.
 - b. **Hypomethylation of the DNA** leads to a benign tumor (adenoma class I).
 - c. Mutation of the **chromosome 12 ras proto-oncogene** allows cells to form a larger benign tumor (adenoma class II).
 - d. **If both copies of DCC, a tumor suppressor gene on chromosome 18, are lost**, an even larger adenoma class III results.

Mutation of both *p53* alleles on chromosome 17 results in conversion to a carcinoma. Other gene losses result in the cancer metastasizing.

 - g. Other paths are possible, but in all cases deletions of APC and mutations of ras occur before deletions of DCC and *p53*.

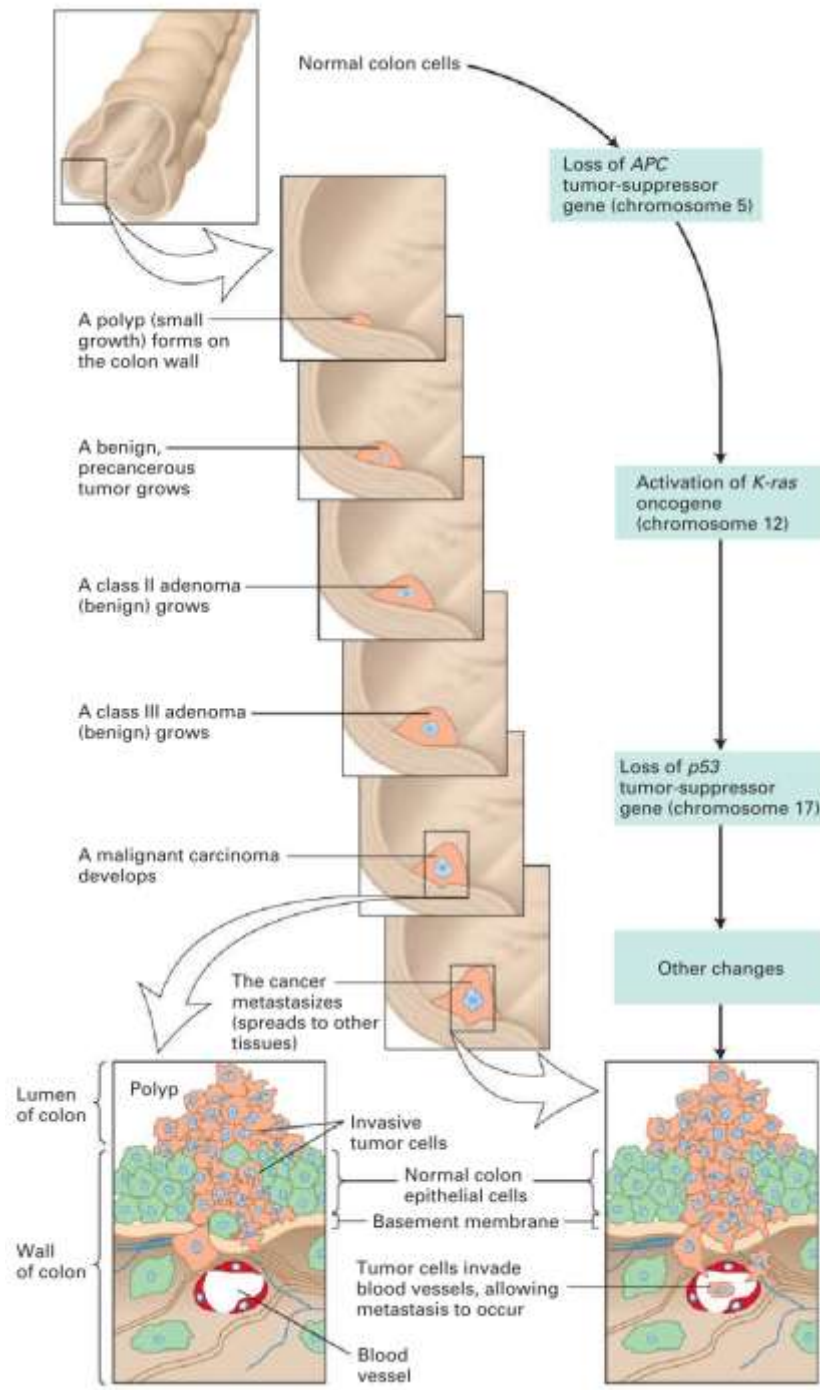
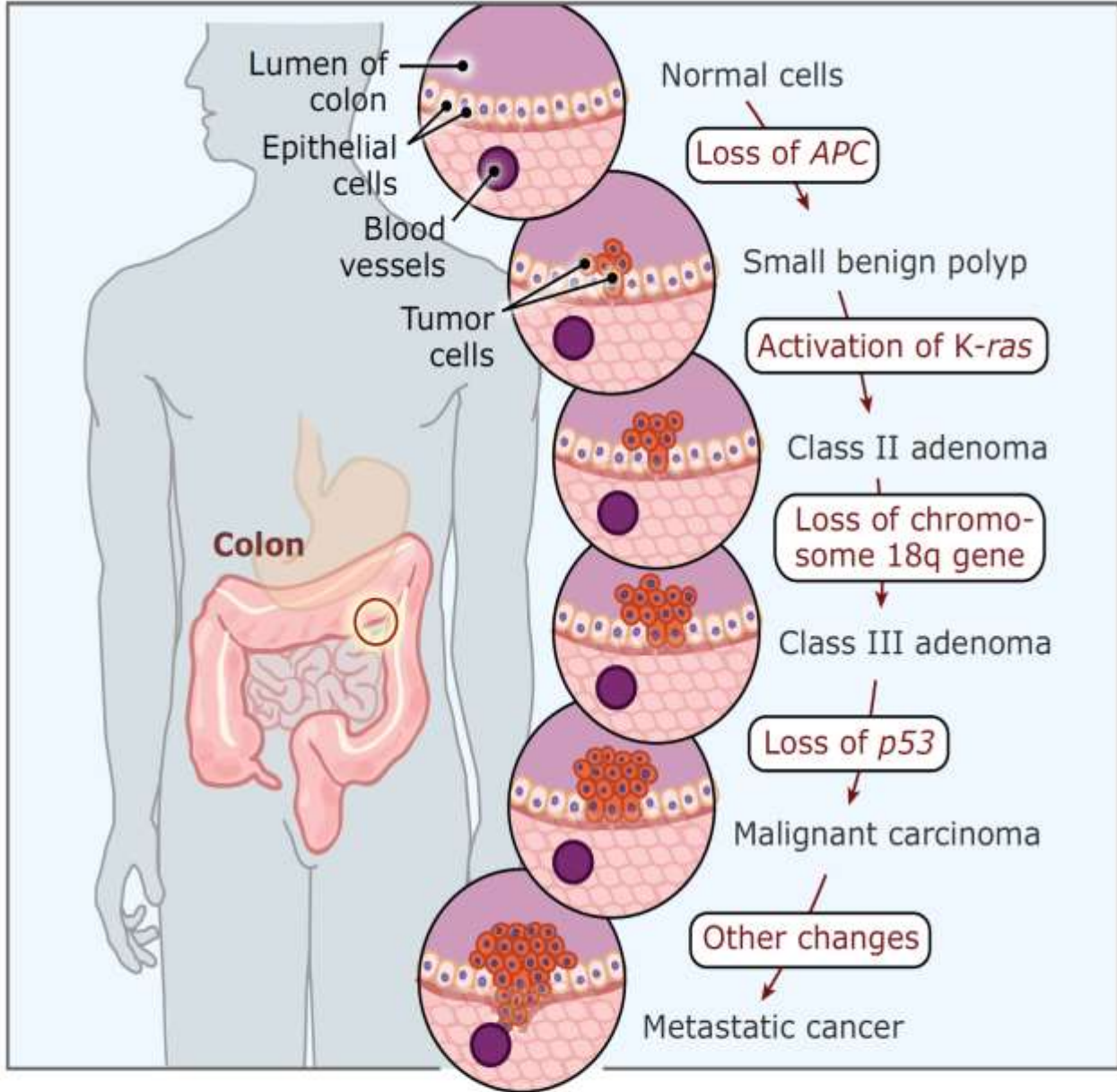
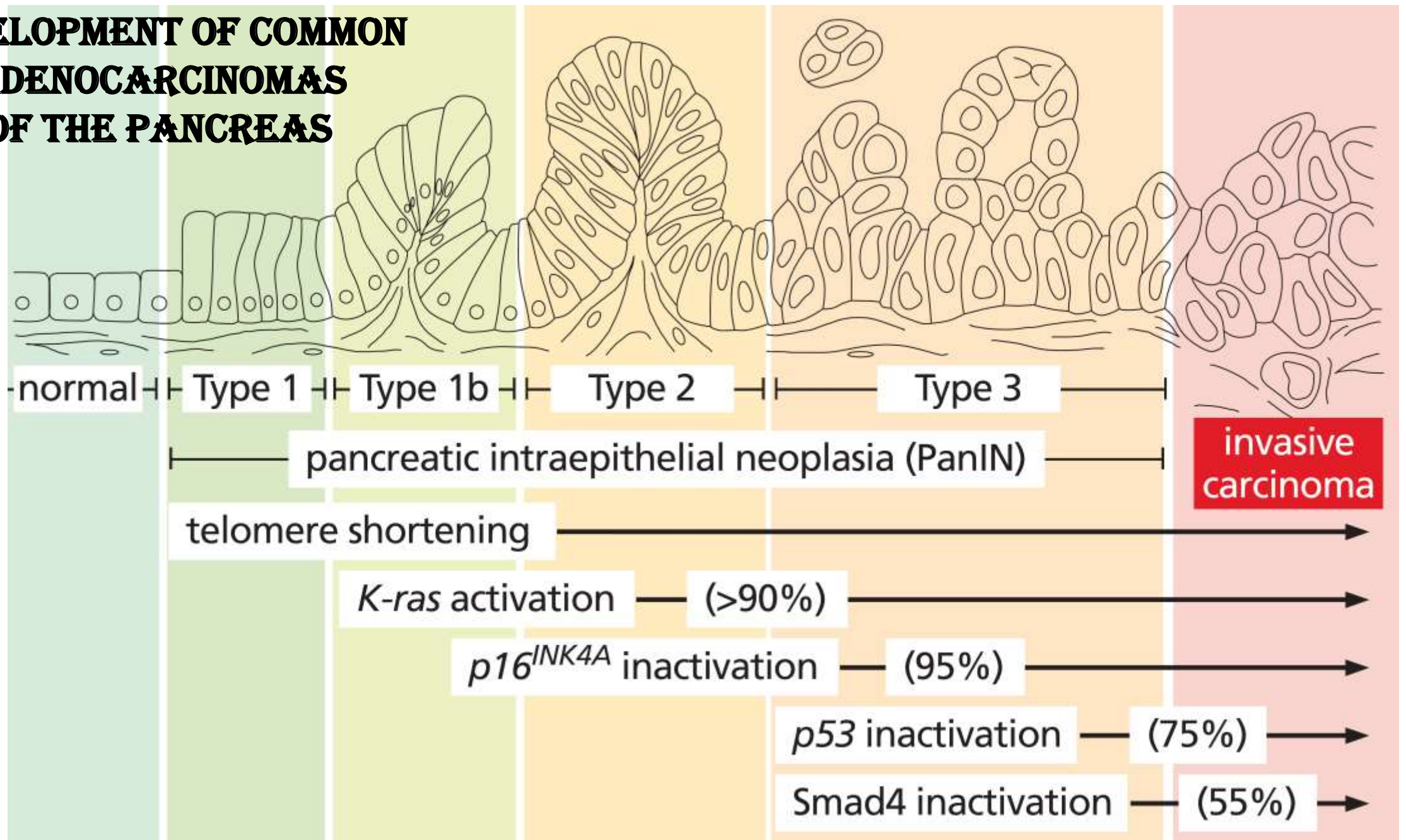


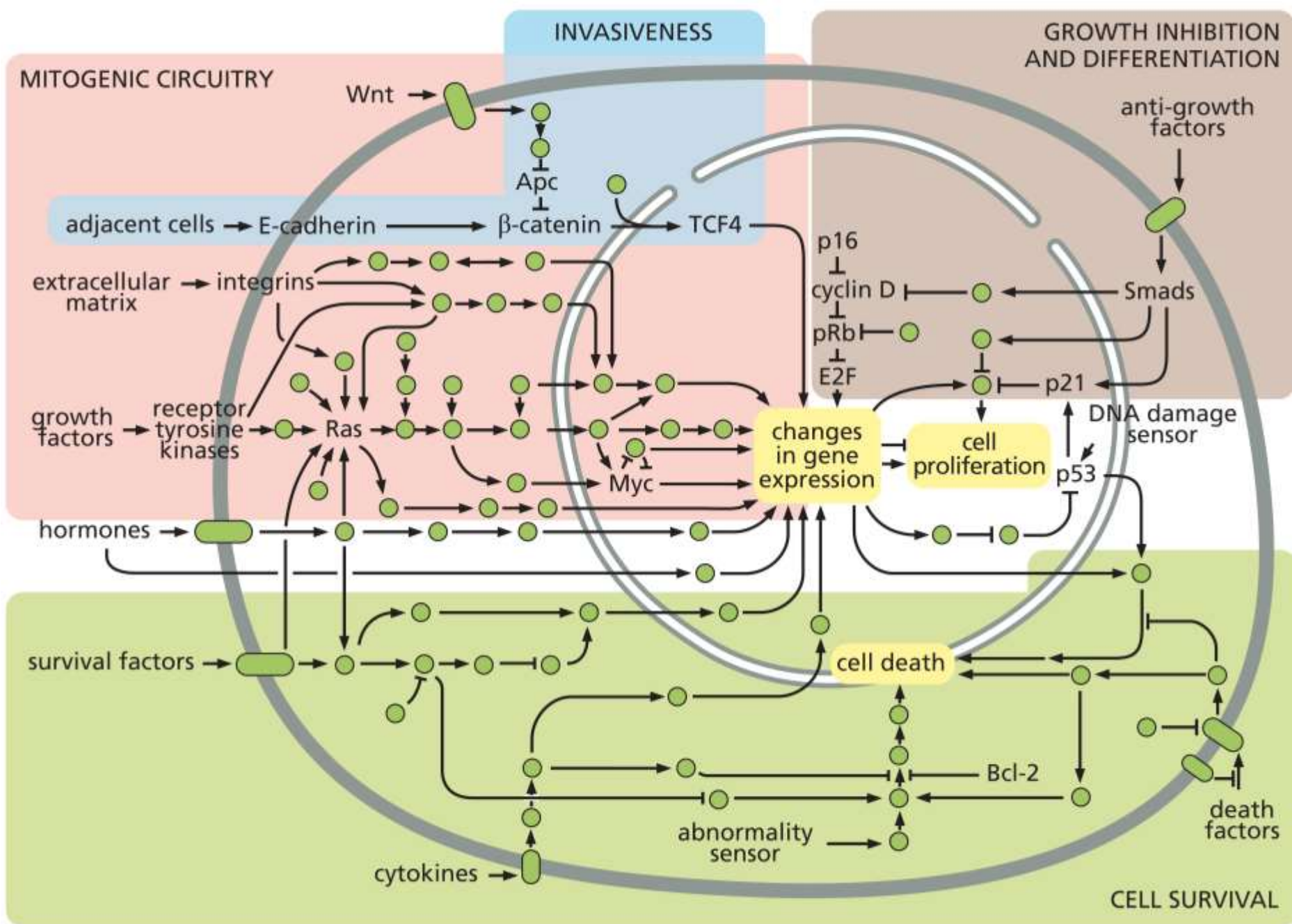
FIGURE 24-12 The development and metastasis of human colorectal cancer and its genetic basis. A mutation in the APC tumor-suppressor gene in a single epithelial cell causes the cell to divide (although surrounding epithelial cells do not), forming a mass of localized benign tumor cells, called a polyp. Subsequent mutations lead to expression of a constitutively active Ras protein and loss of the tumor-suppressor gene p53. These mutations, together with additional genetic changes yet to be identified, generate a malignant cell. The cancer continues to divide, and its progeny invade the basement membrane that surrounds the tissue, but do not penetrate the basement membrane of capillaries (bottom left). Some tumor cells spread in blood vessels that will distribute them to other sites in the body (bottom right). Additional mutations permit the tumor cells to exit from the blood vessels and proliferate at distant sites. See B. Vogelstein and K. Kinzler, 1993, *Trends Genet.*

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FIGURE 17.14 In colorectal cancer, mutations in the APC gene initiate the process, whereas additional mutations are associated with various stages of progression.

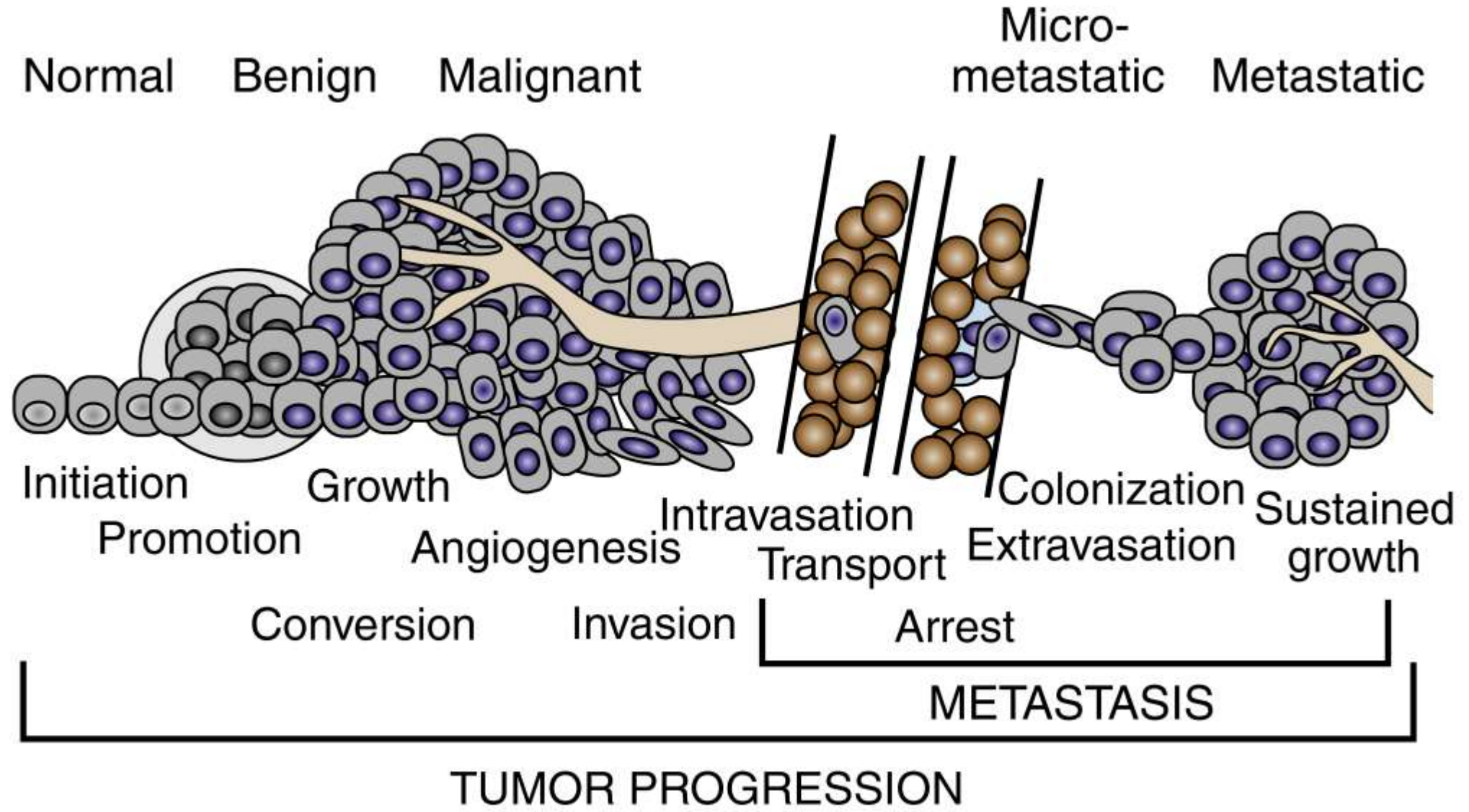
DEVELOPMENT OF COMMON ADENOCARCINOMAS OF THE PANCREAS





THE INTRACELLULAR SIGNALING CIRCUITRY AND COLLABORATION BETWEEN CANCER ASSOCIATED GENES

TUMOR PROGRESSION



STEPS OF METASTASIS

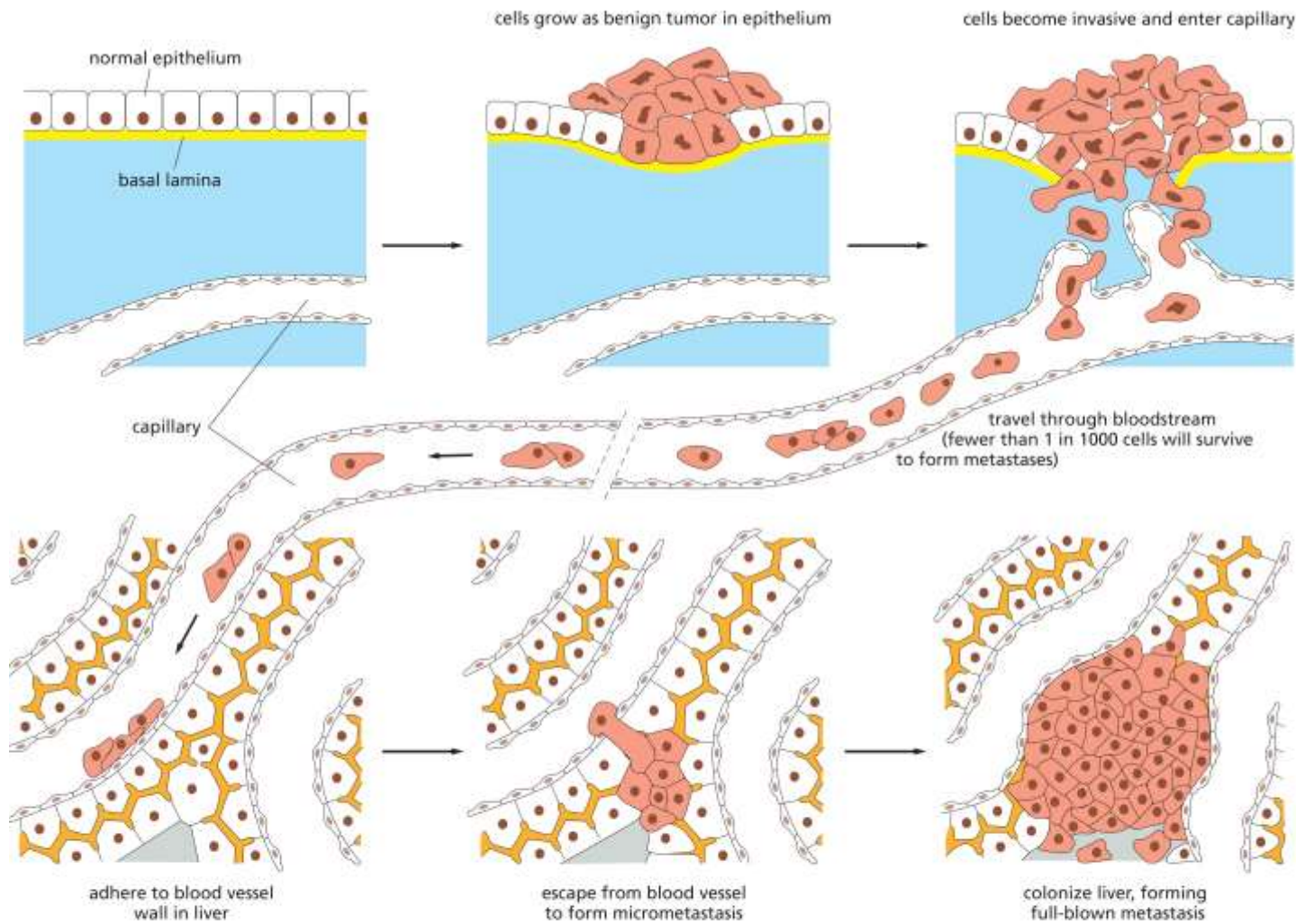


Figure 20-16 Steps in the process of metastasis. This example illustrates the spread of a tumor from an organ such as the bladder to the liver. Tumor cells may enter the bloodstream directly by crossing the wall of a blood vessel, as diagrammed here, or, more commonly perhaps, by crossing the wall of a lymphatic vessel that ultimately discharges its contents (lymph) into the bloodstream. Tumor cells that have entered a lymphatic vessel often become trapped in lymph nodes along the way, giving rise to lymph-node metastases.

Studies in animals show that typically far fewer than one in every thousand malignant tumor cells that enter the bloodstream will colonize a new tissue so as to produce a detectable tumor at a new site.

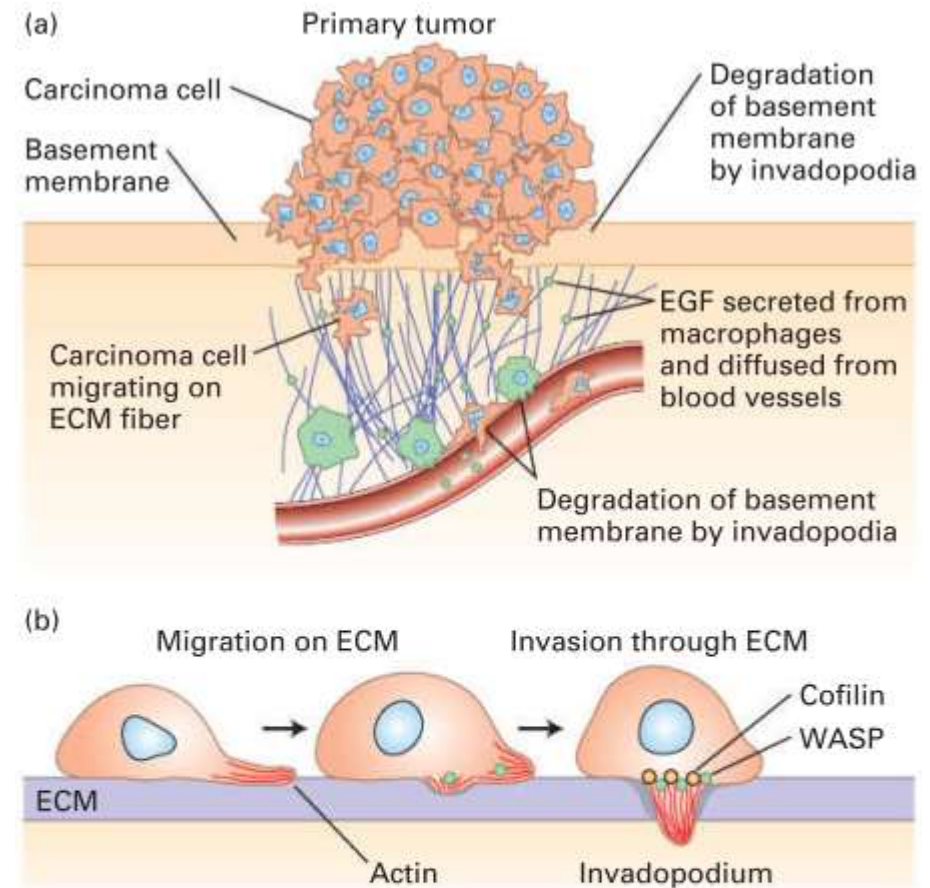
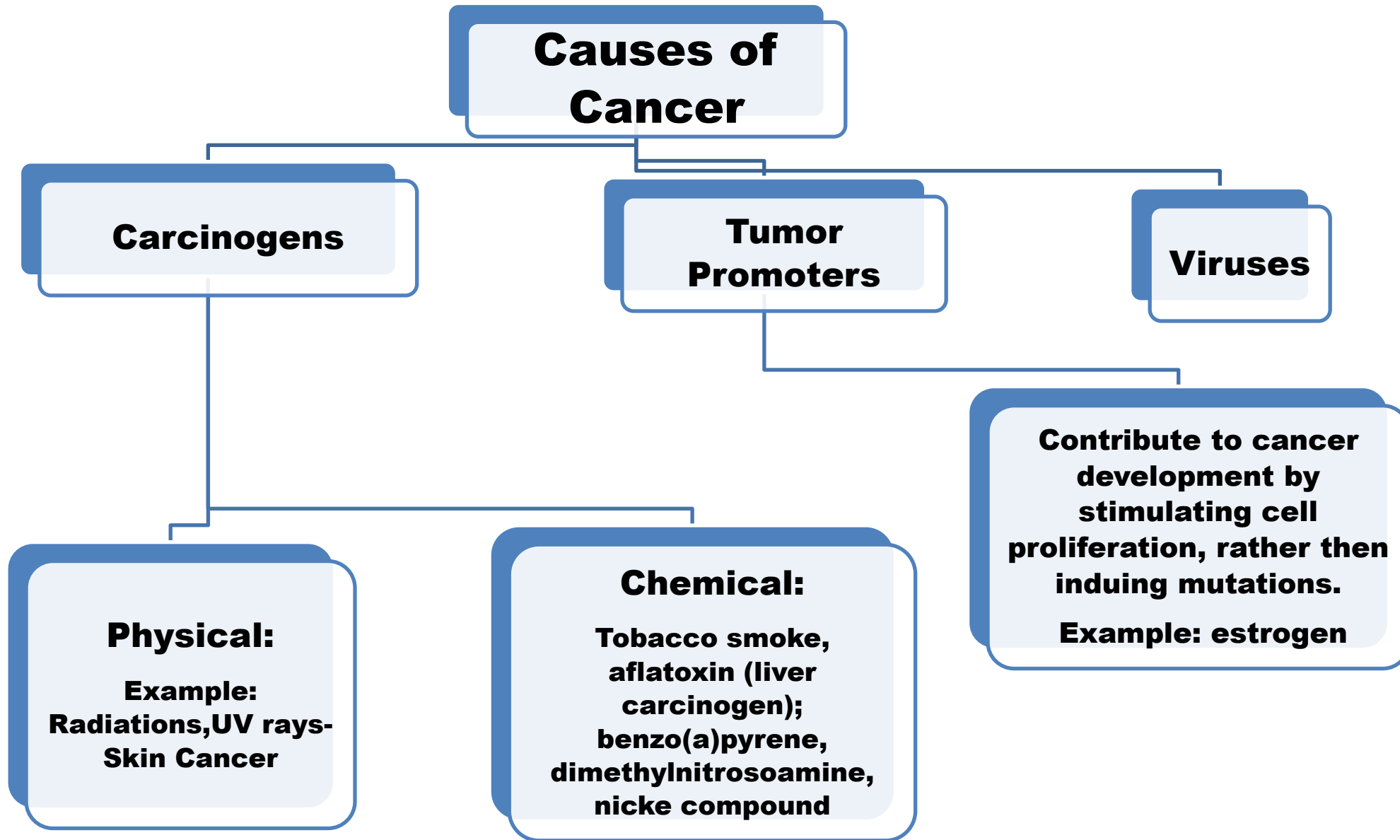
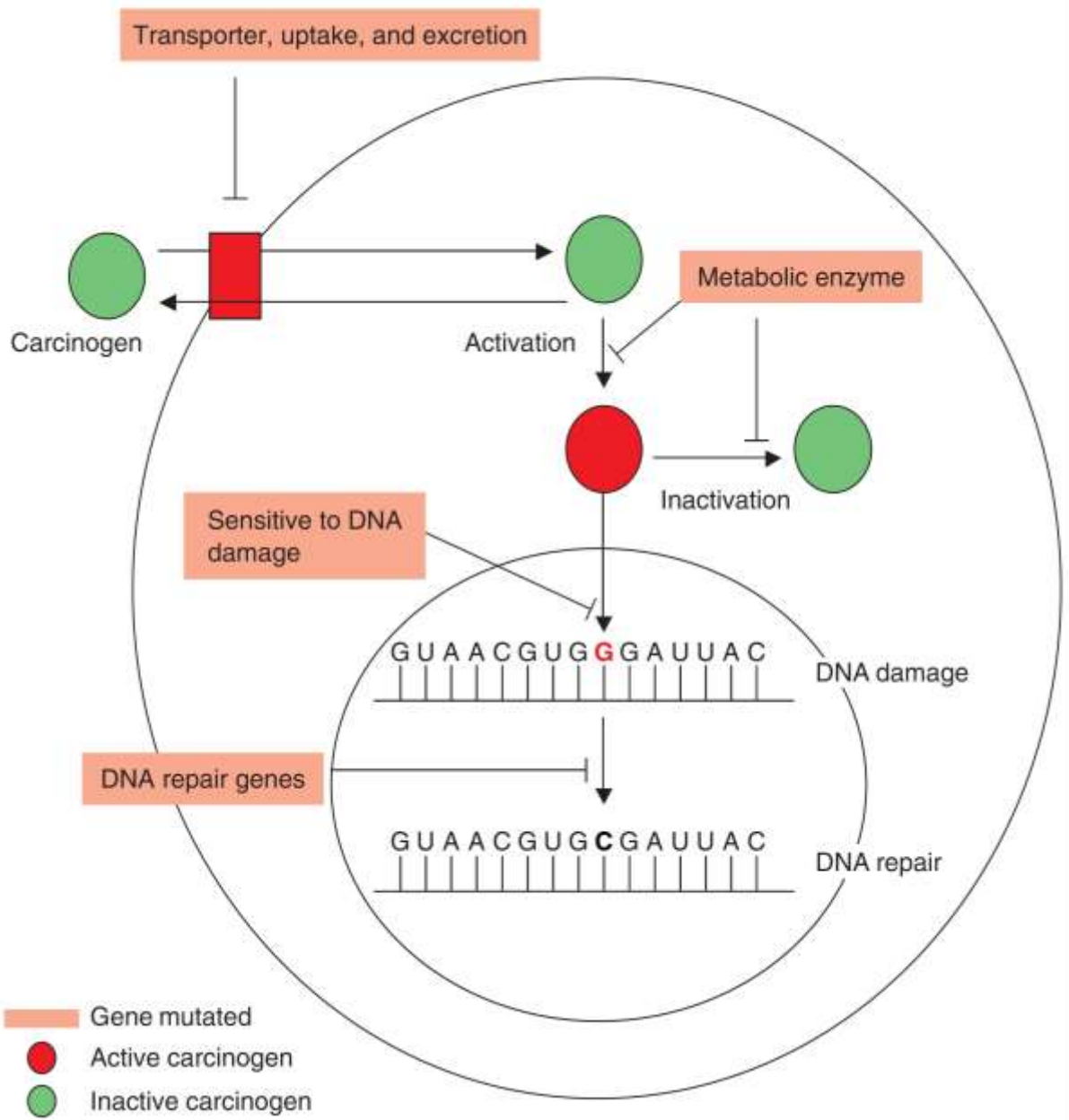
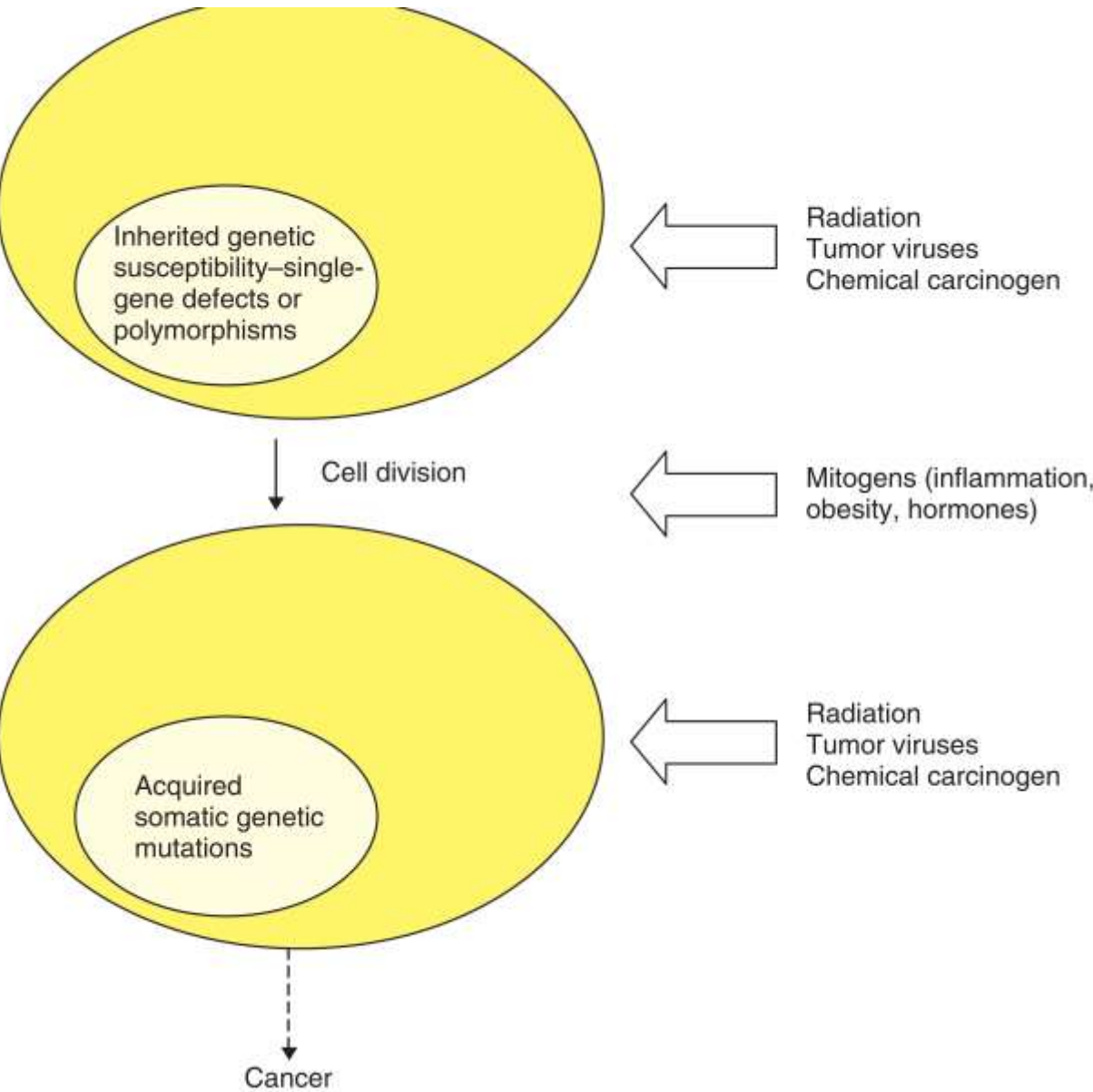


FIGURE 24-7 Metastasis. (a) First steps in metastasis, using breast carcinoma cells as an example. Cancer cells leave the main tumor and attack the basement membrane, using extracellular matrix (ECM) fibers to reach the blood vessels. The cancer cells can be attracted by signals such as epidermal growth factor (EGF), which can be secreted by macrophages. At the blood vessels they penetrate the layer of endothelial cells that forms the vessel walls and enter the bloodstream. (b) Carcinoma cells penetrate the extracellular matrix and blood vessel wall by extending "invadopodia," which produce matrix metalloproteases and other proteases to open up a path. [Adapted from H. Yamaguchi et al., 2005, *Curr. Opin. Cell Biol.* **17**:559.]

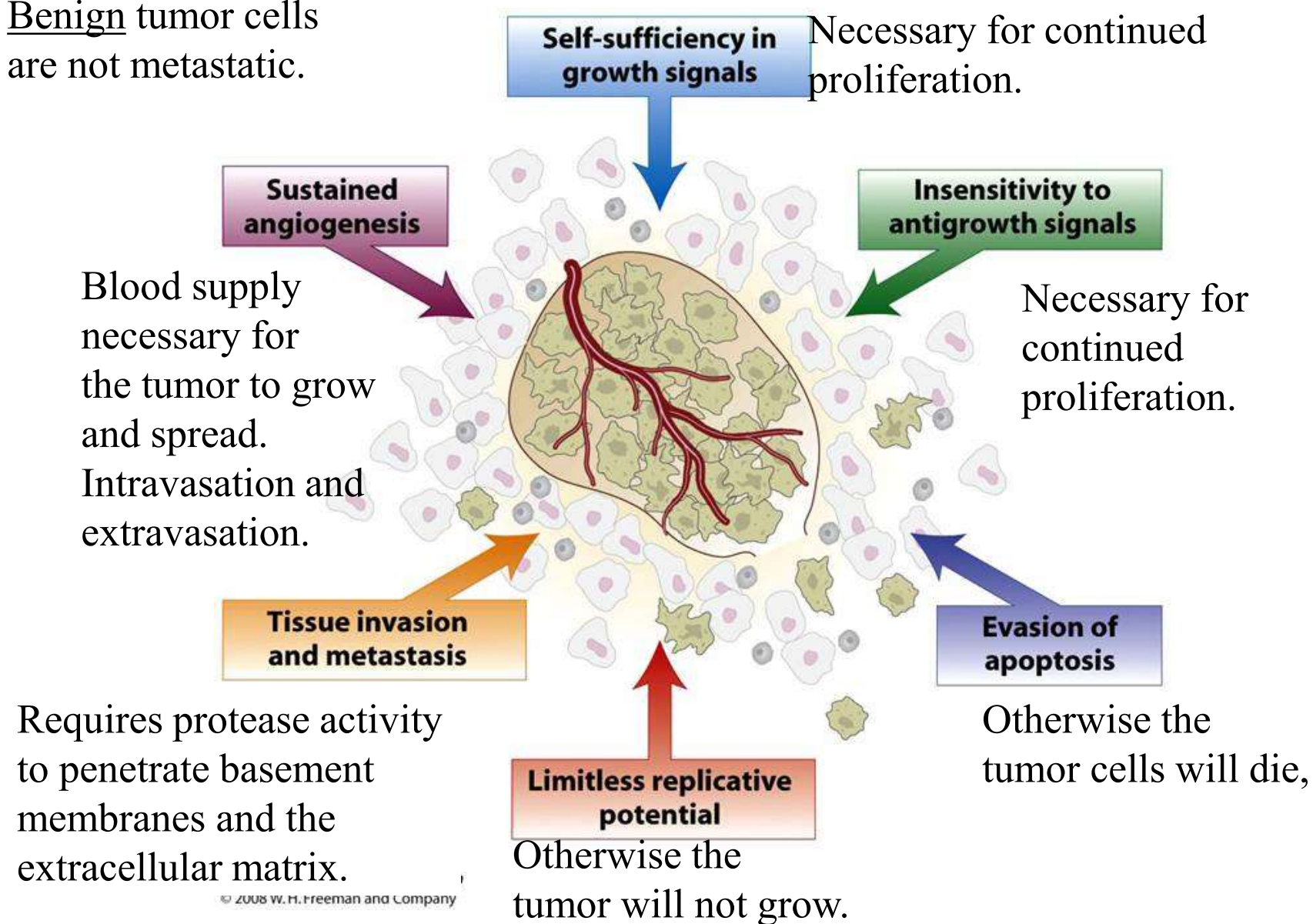


CAUSES.....CONTINUED



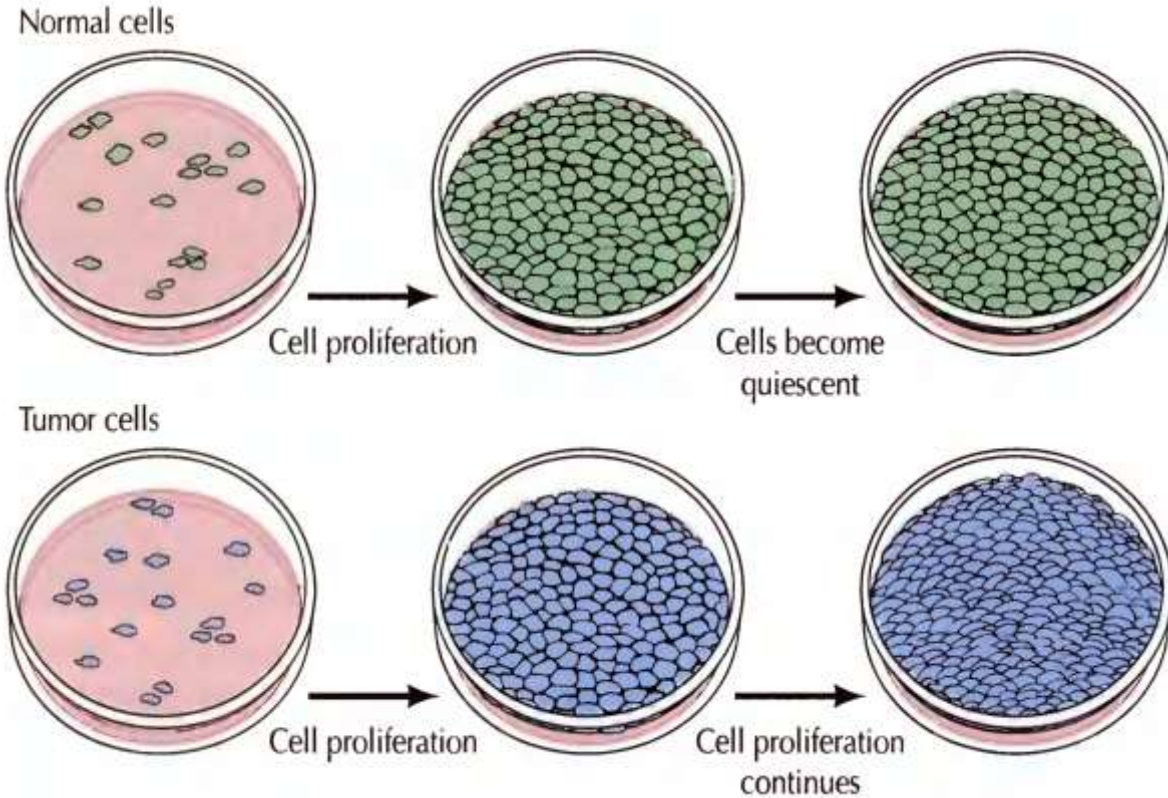
SIX CHARACTERISTICS OF METASTATIC (MALIGNANT) TUMOR CELLS

Benign tumor cells are not metastatic.



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CANCER CELL PROPERTY: DENSITY-INDEPENDENT GROWTH



Normal cells proliferate in culture until they reach a finite cell density at which point they become quiescent.

Tumor cells, however, continue to proliferate independent of cell density.

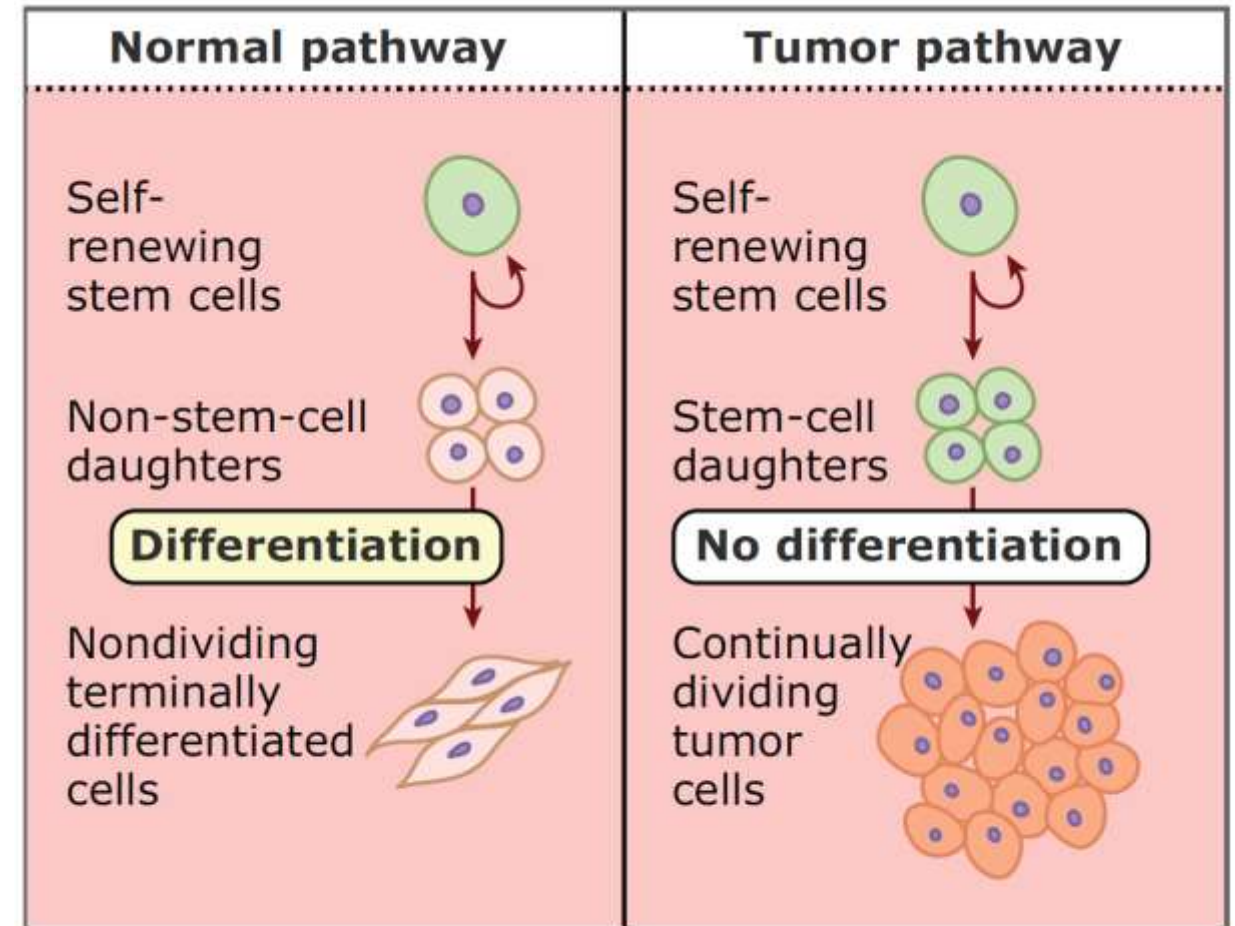
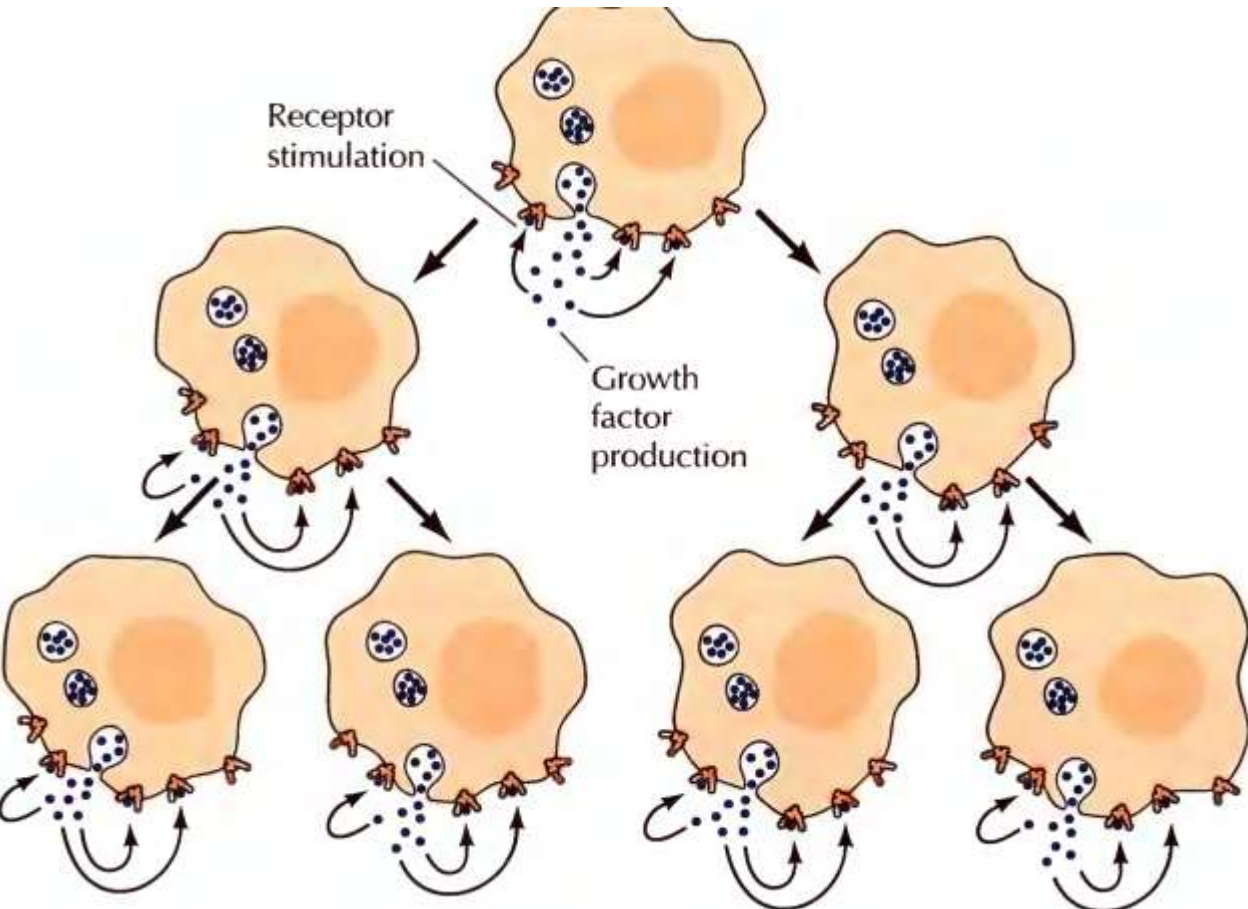
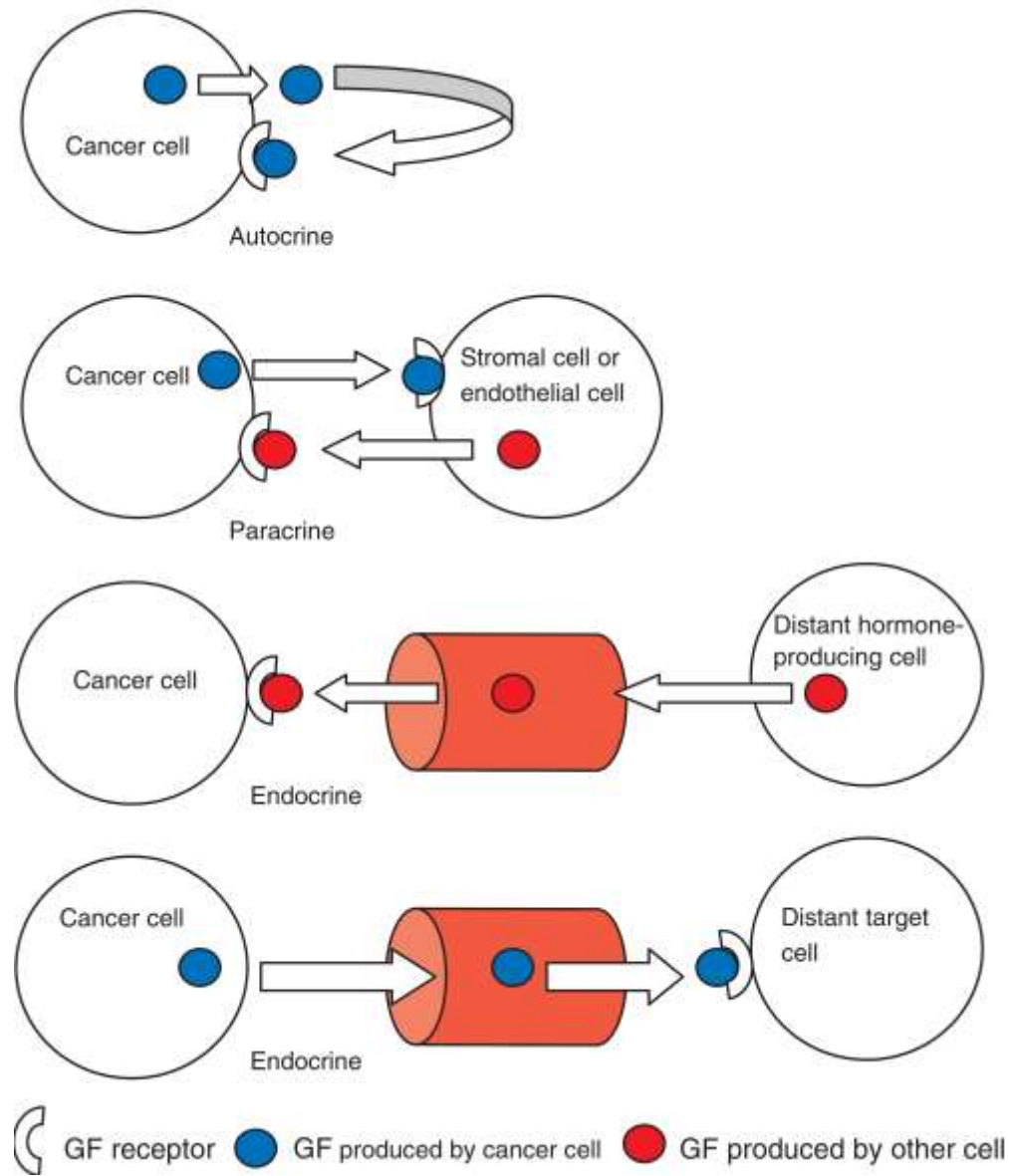


FIGURE 17.23 Differentiation is one way to limit the pool of dividing cells. Failure of cells to differentiate can lead to tumors.

CANCER CELL PROPERTY: AUTOCRINE GROWTH STIMULATION



A cell produces a growth factor to which it also responds, resulting in continuous stimulation of cell proliferation.



CANCER CELL PROPERTY: AUTOCRINE GROWTH STIMULATION

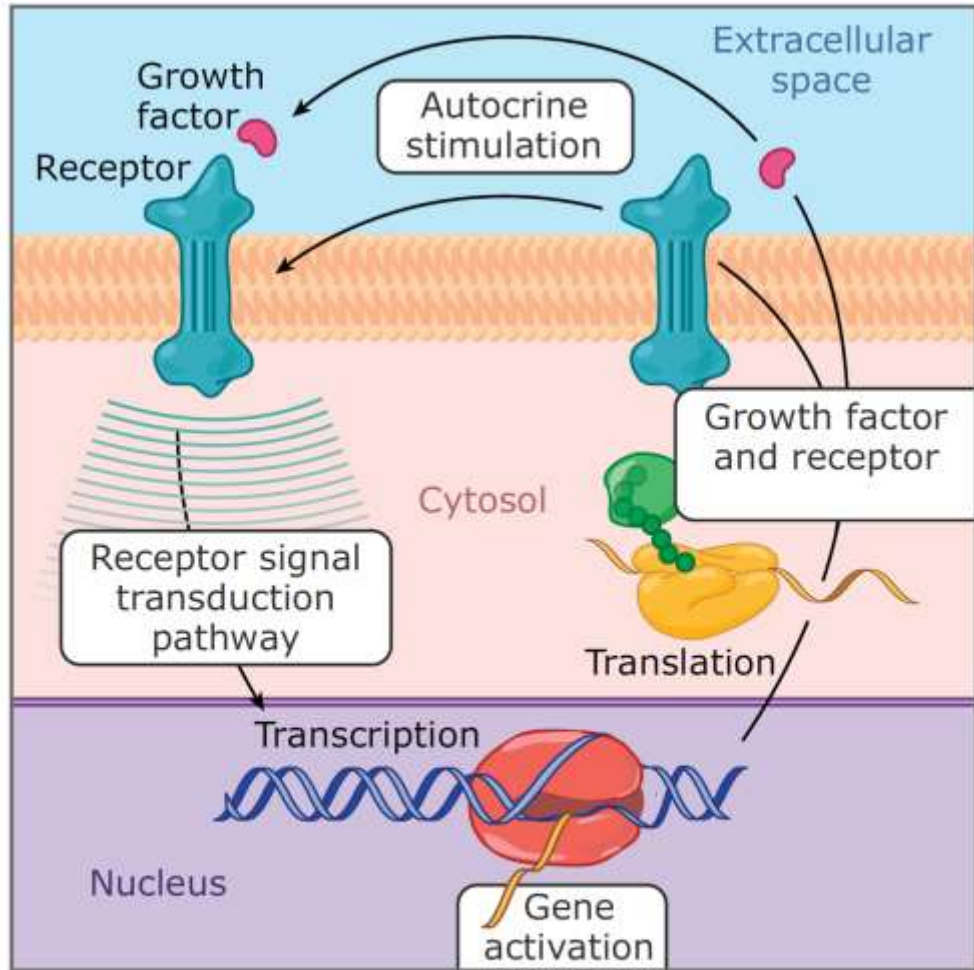


FIGURE 17.19 When a cell produces a growth factor that stimulates its own growth, an autocrine loop is set up that is self-perpetuating.

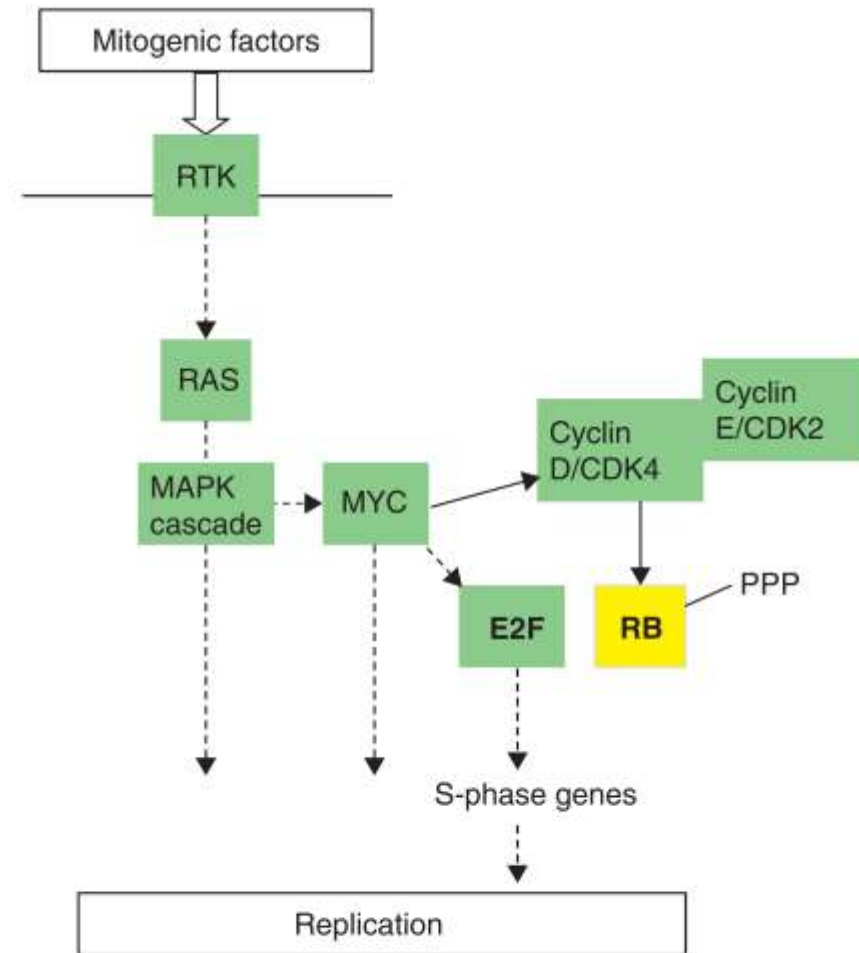


Figure 5.4 Main signaling pathways for mitogens. Mitogenic factors largely, but not exclusively, act via RTK to activate in particular the MAPK/ERK cascade.

CANCER CELL PROPERTY: CONSTITUTIVE SIGNALLING

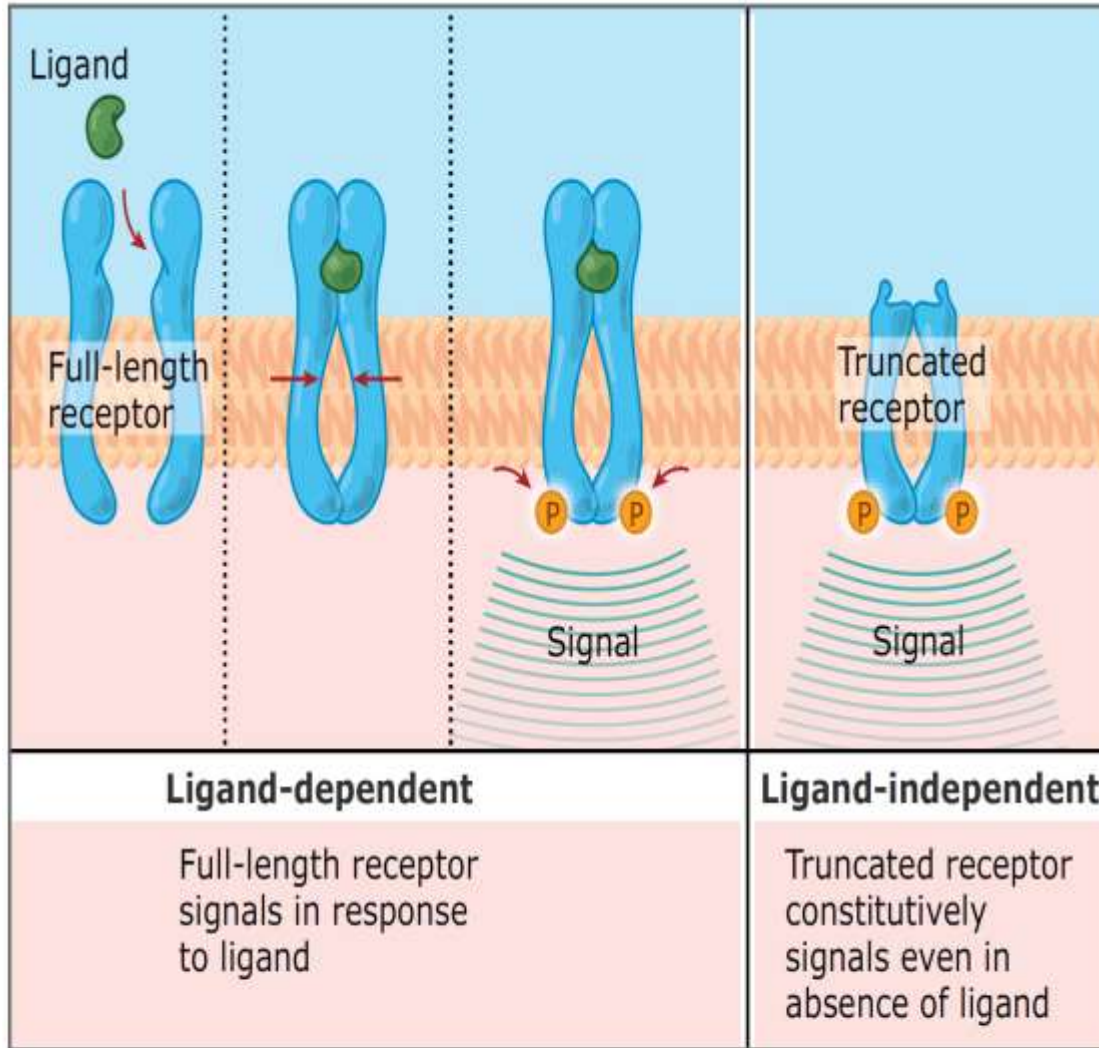


FIGURE 17.20 In some cases, removal of the ligand-binding domain of a receptor causes constitutive signaling because ligand binding is no longer required for receptor dimerization.

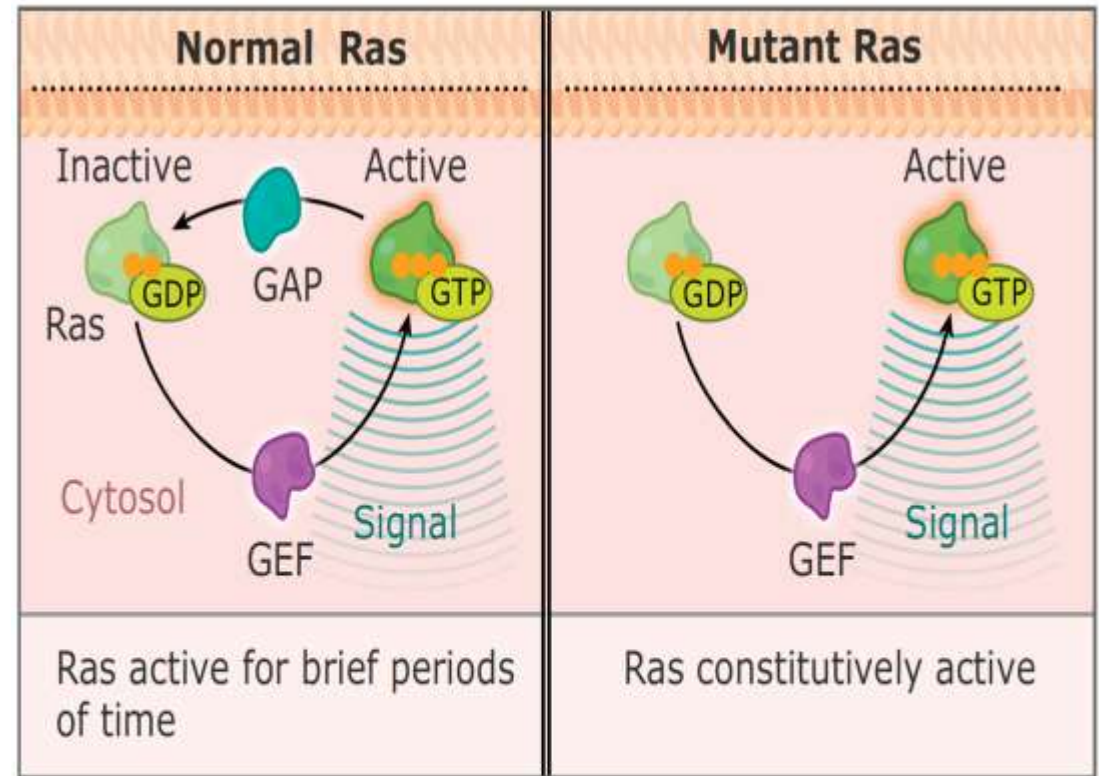


FIGURE 17.21 Some mutant Ras proteins are stuck in a guanosine triphosphate-bound conformation and constitutively activate downstream signal transduction pathways.

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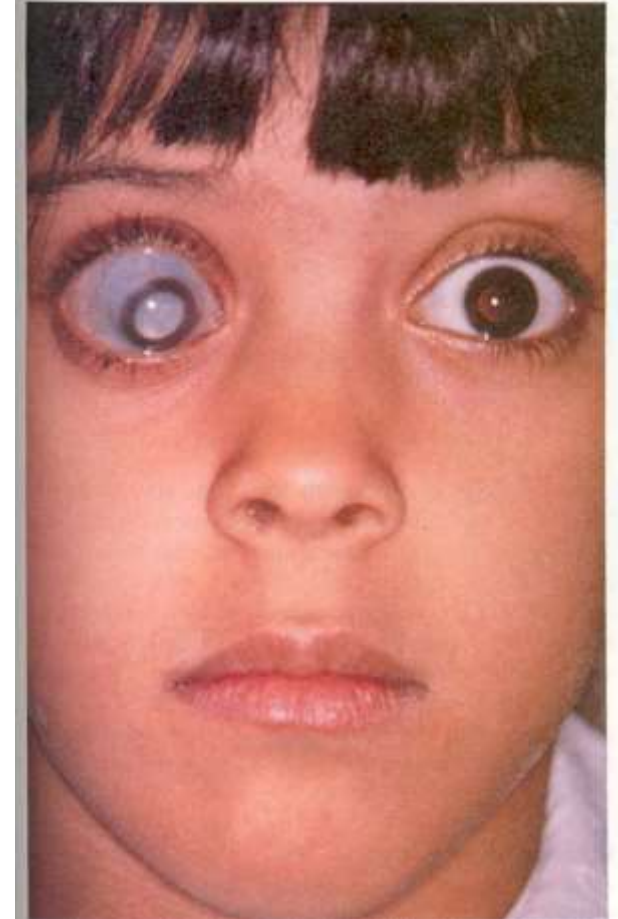
ACCEPTED MODEL FOR CANCER

THE TWO-HIT MUTATION MODEL FOR CANCER

1. Cancers can be caused by viruses, but most result from mutations in cellular genes. Usually these mutations have accumulated over time, and research has identified the genes involved.
2. **The incidence of cancer falls into two categories:**
 - a. **Sporadic cancers**, the more frequent type, do not appear to have an hereditary cause.
 - b. **Familial (hereditary) cancers** run in families. Retinoblastoma provides an example .
 - i. Retinoblastoma is the most common eye tumor in children birth to 4 years. Early treatment (usually gamma radiation) is over 90% effective.
 - ii. Retinoblastoma has two forms:
 - (1) **Sporadic retinoblastoma** (60%) develops in children with no family history of retinoblastoma, and occurs in one eye (unilateral tumor).
 - (2) **Hereditary retinoblastoma** (40%) patients typically develop multiple tumors involving both eyes (bilateral tumors).
 - (a) Onset is usually earlier in the hereditary form.
 - (b) Siblings and offspring often develop the same type of tumor.
 - (c) Pedigrees of affected families are consistent with a single gene responsible for retinoblastoma.

Figure 18.3

An eye tumor in a patient with retinoblastoma.

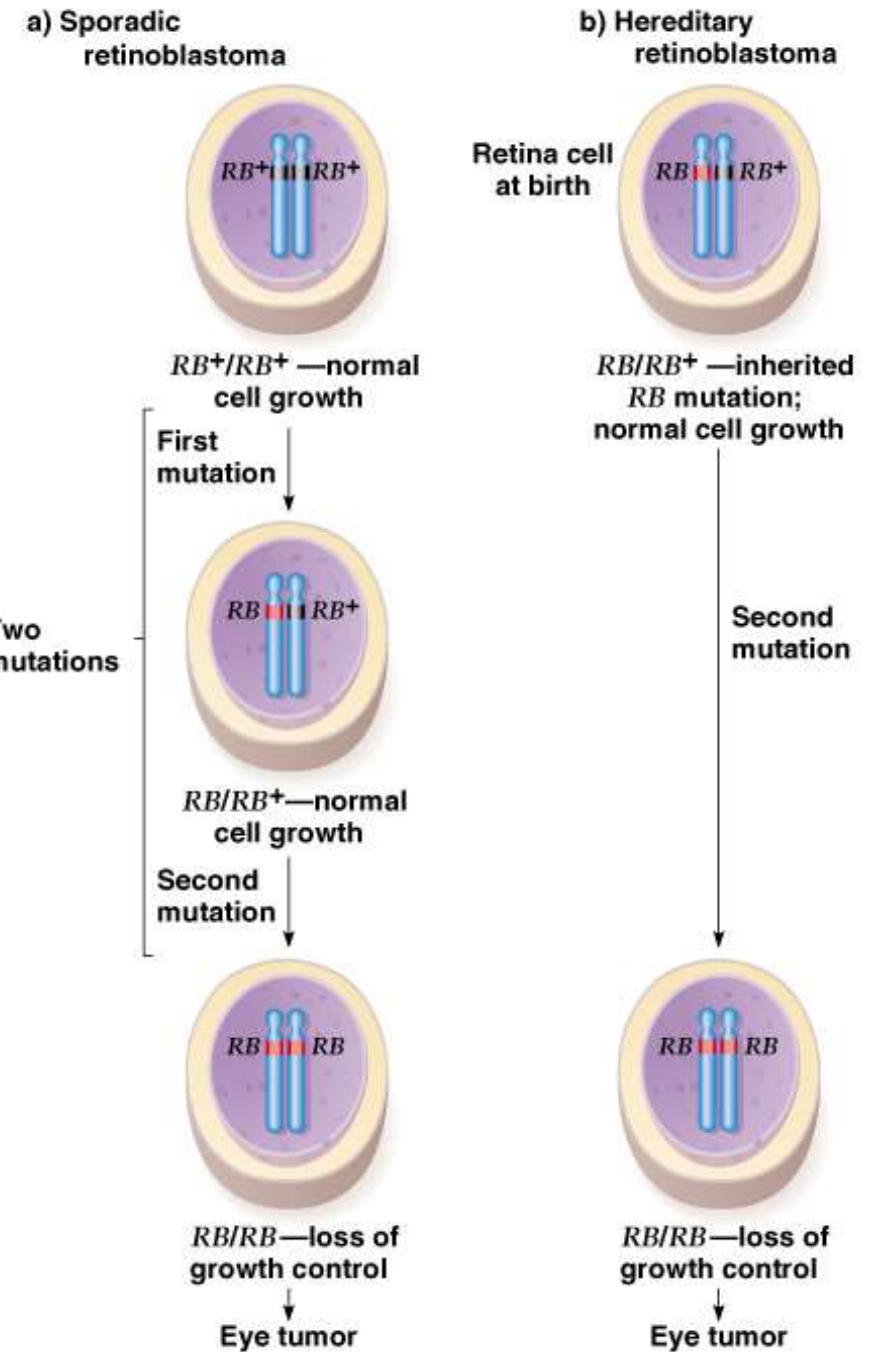


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KNUDSON : TWO-HIT MUTATION MODEL FOR CANCER

3. Knudson (1971) proposed the 2-hit mutational model, that two mutations were required for development of retinoblastoma (Figure 18.4).
 - a. In sporadic retinoblastoma, the child starts with two wild-type alleles (RB^+/RB^+)
 - i. Both alleles must mutate to produce the disease genotype (RB/RB).
 - ii. The probability of both mutations occurring in the same cell is low, so only one tumor forms.
 - b. In hereditary retinoblastoma, the child starts out heterozygous (RB/RB^+).
 - i. Only one mutation is needed for tumor formation (RB/RB).
 - ii. Mutations resulting in loss of heterozygosity (LOH) are likely in rapidly dividing cells, and multiple tumors occur.
4. In Knudson's model:
 - a. Retinoblastoma alleles are recessive, because only homozygotes (RB/RB) develop tumors.
 - b. However, in pedigree analysis, the disease appears to be dominant. This is because
 - i. Heterozygous individuals (RB/RB^+) are predisposed to the cancer, since only one mutation is required for the neoplasm. Families with one allele already mutated will have a significant incidence of the disease.
 - ii. Homozygous dominant individuals (RB^+/RB^+) develop the cancer only if both alleles in the same cell are mutated. Therefore, most children in the general population do not develop the disease.
5. This hypothesis is supported by later studies of the chromosomes of retinoblastoma patients which:
 - a. Mapped the gene to 13q14.1-q14.2 (long arm of chromosome 13).
 - b. Showed that the gene encodes a growth inhibitory factor (tumor suppressor).
6. Retinoblastoma is rare among cancers because a single gene is critical for its development. In most cases, cancers result from a series of mutations in different genes for growth and division.

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KNUDSON : TWO-HIT MUTATION MODEL FOR CANCER

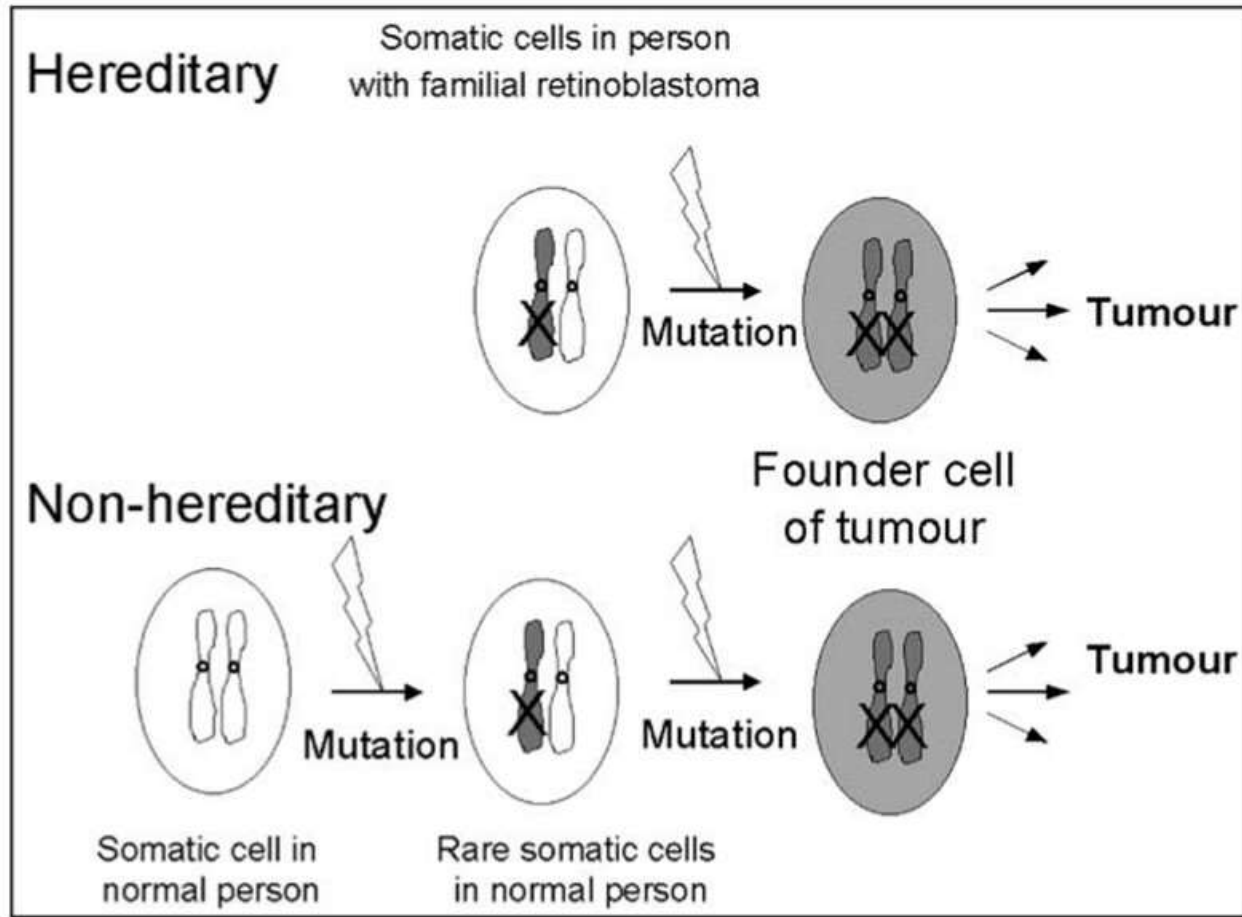
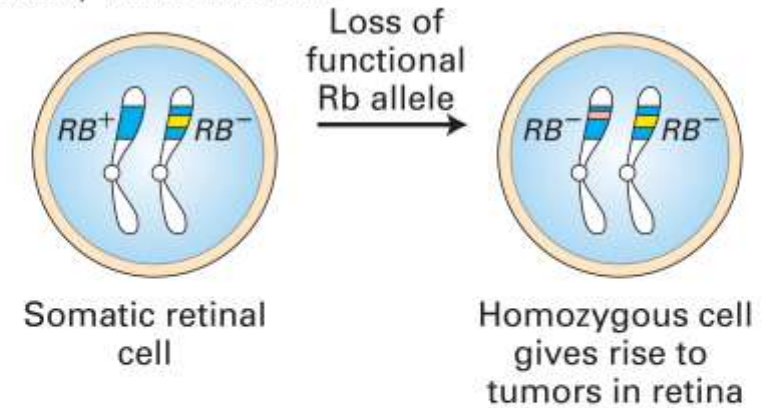


Figure 7.3 Knudson's two-hit hypothesis: tumour formation in both hereditary and non-hereditary retinoblastoma. A one-hit clone is a precursor to the tumour in non-hereditary retinoblastomas, whereas all cells are one-hit clones in hereditary retinoblastoma.

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(a) Hereditary retinoblastoma



(b) Sporadic retinoblastoma

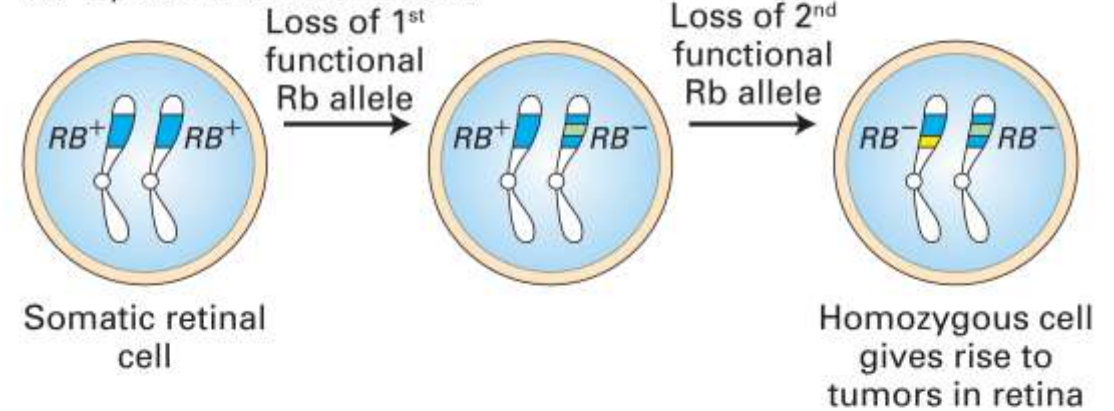
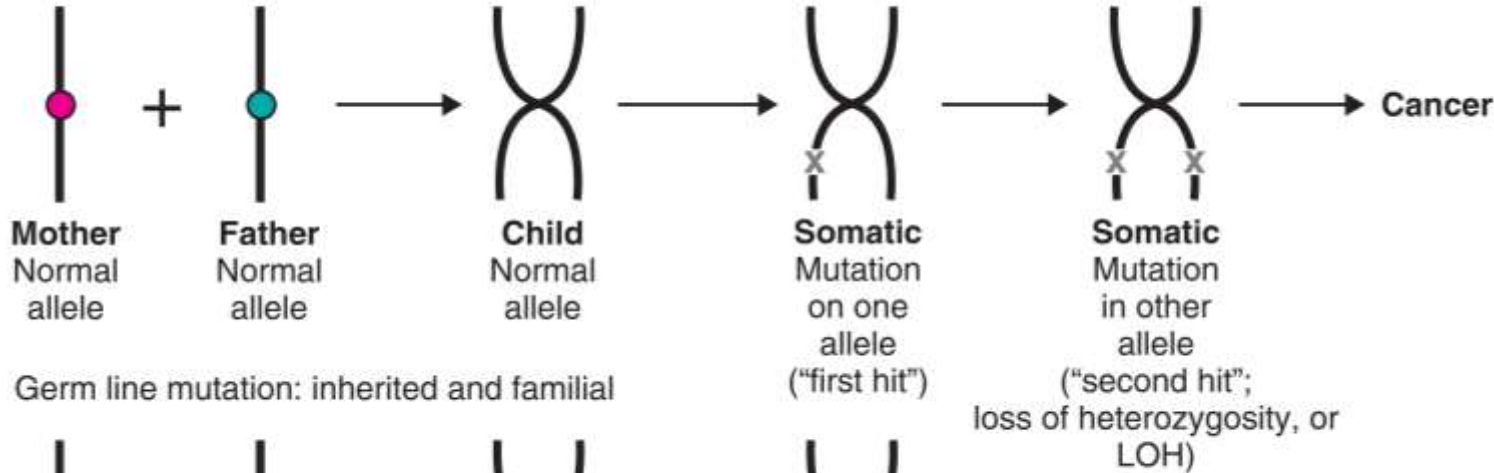


FIGURE 24-17 Role of spontaneous somatic mutation in retinoblastoma. This disease is marked by retinal tumors that arise from cells carrying two mutant RB^- alleles. (a) In hereditary (familial) retinoblastoma, a child inherits a normal RB^+ allele from one parent and a mutant RB^- allele from the other parent. When the second normal allele is lost in a heterozygous somatic retinal cell, a cell is generated that lacks any Rb gene function. (b) In sporadic retinoblastoma, a child inherits two normal RB^+ alleles. Two separate Rb loss events must occur in a particular retinal cell to produce a cell lacking all Rb function.

HEREDITARY AND SPORADIC RETINOBLASTOMA

Somatic mutation: nonhereditary and sporadic



Germ line mutation: inherited and familial

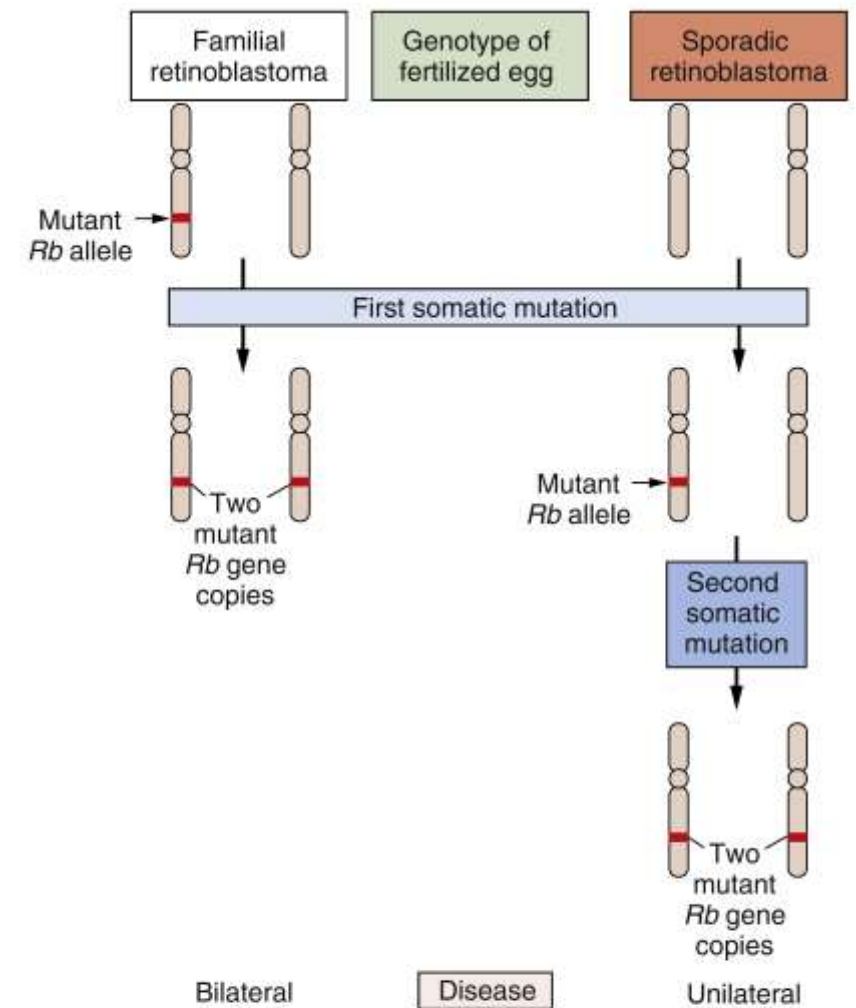
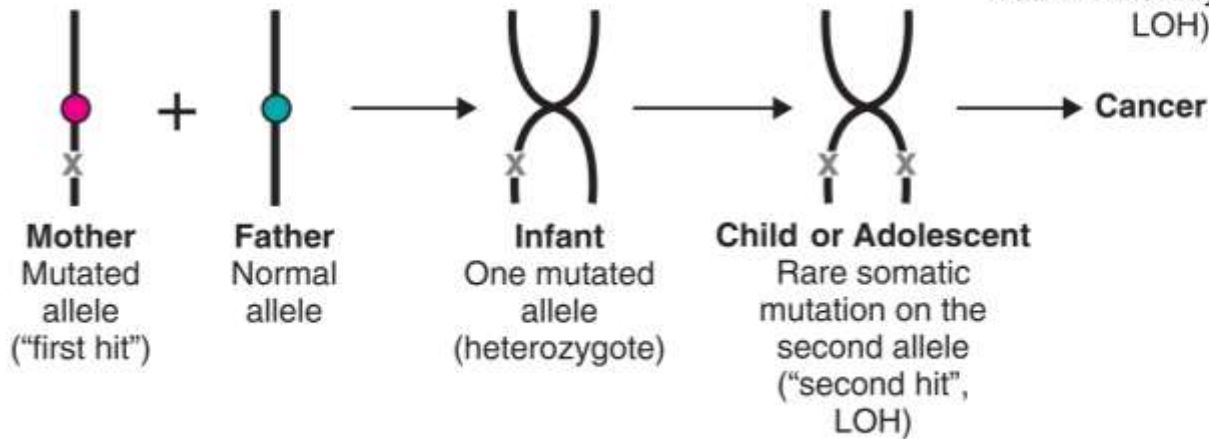


FIGURE 1-5 GENETICS OF RETINOBLASTOMA DEVELOPMENT The development of retinoblastomas requires the successive inactivation of two copies of the chromosomal *RB* gene. In the case of familial retinoblastomas, one of the two copies of this gene is already mutated in one or another gamete and is transmitted to the offspring, who is therefore heterozygous at this locus in all cells of the body; subsequent loss, through somatic alterations, of the surviving wild-type gene copy leaves a retinal cell with no functional copies of this gene, enabling tumor formation to begin. In sporadic retinoblastomas, the conceptus is genetically wild type; however, two successive somatic mutations occurring in a lineage of retinal precursor cells leaves some of these cells, once again, without functional *RB* gene copies, and as before permits retinoblastoma tumorigenesis to begin.

GENES AND CANCER

	Normal Function of Genes	Examples of Gene Products	Effect of Mutation	Genetic Properties of Mutant Gene	Origin of Mutations
Proto-oncogenes	Promote cell survival or proliferation	Anti-apoptotic proteins, components of signaling and signal transduction pathways that result in proliferation, transcription factors	Gain-of-function mutations allow unregulated cell proliferation and survival	Mutations are genetically dominant	Arise by point mutation, chromosomal translocation, amplification
Tumor-suppressor genes	Inhibit cell survival or proliferation	Apoptosis-promoting proteins, inhibitors of cell cycle progression, checkpoint pathway proteins that assess DNA/chromosomal damage, components of signaling pathways that restrain cell proliferation	Loss-of-function mutations allow unregulated cell proliferation and survival	Mutations are genetically recessive	Arise by deletion, point mutation, methylation
Genome maintenance genes	Repair or prevent DNA damage	DNA-repair enzymes	Loss-of-function mutations allow mutations to accumulate	Mutations are genetically recessive	Arise by deletion, point mutation, methylation

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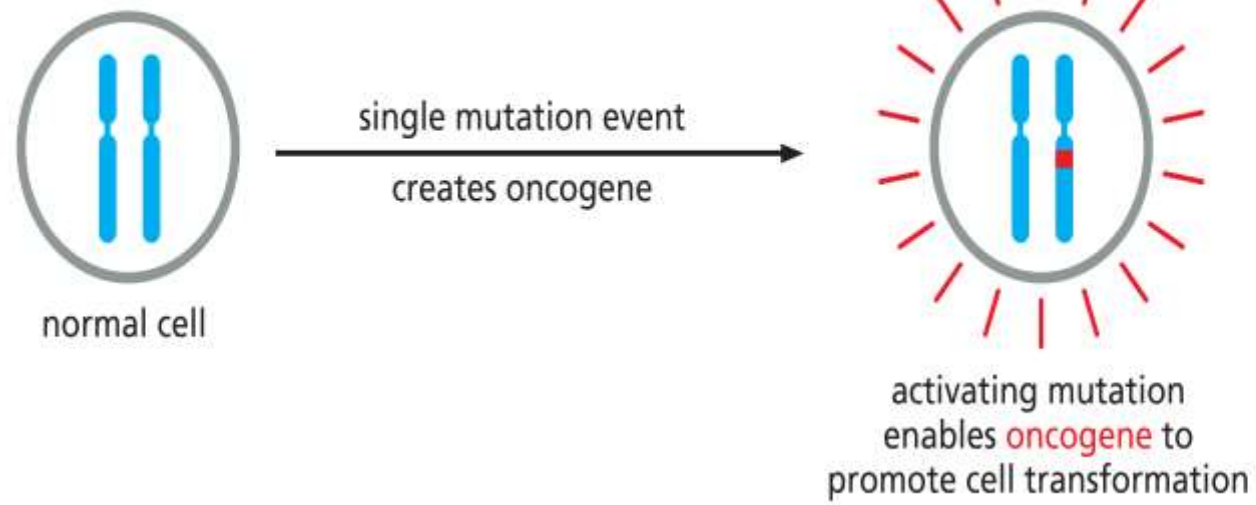
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ONCOGENES AND TSG

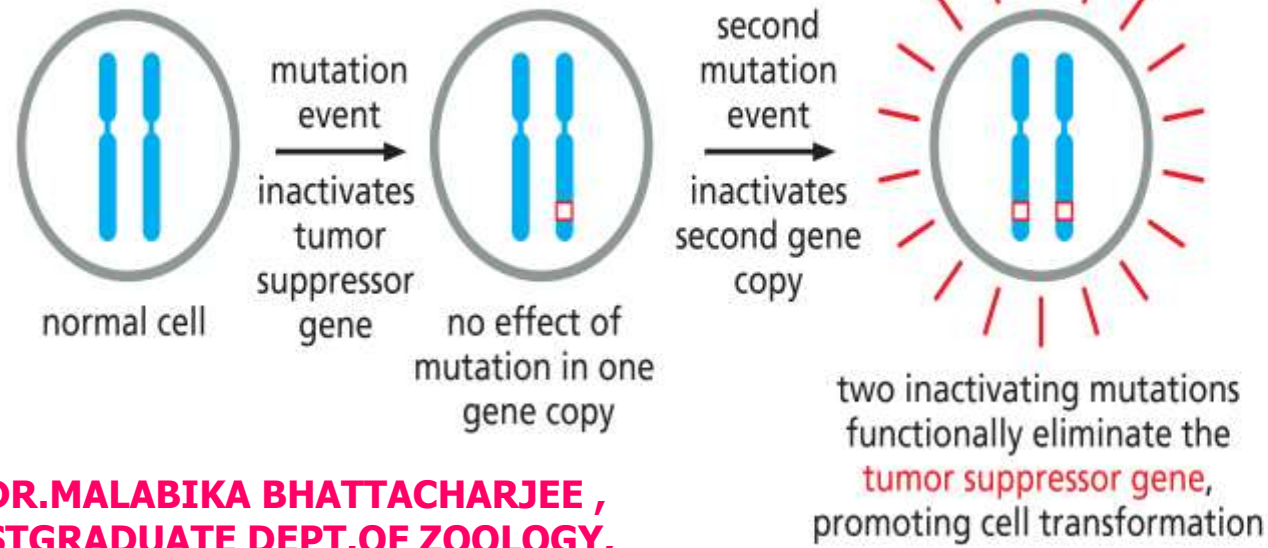
1. When a cell is exposed to a mutagen, genes that serve as either positive or negative regulators of cell growth and proliferation may be damaged. The two types of regulatory genes normally work in opposing fashions to ensure a well-balanced control system.

2. The positive regulators that act to promote normal cell growth and division are termed **proto-oncogenes**; after mutation, these genes become activated into **oncogenes**. The **negative regulators** that normally serve to constrain proliferation are termed **tumor suppressors**; these genes become involved in carcinogenesis when they are inactivated by mutations, depriving the cells of their growth-suppressing powers.

(A) overactivity mutation (gain of function)



(B) underactivity mutation (loss of function)



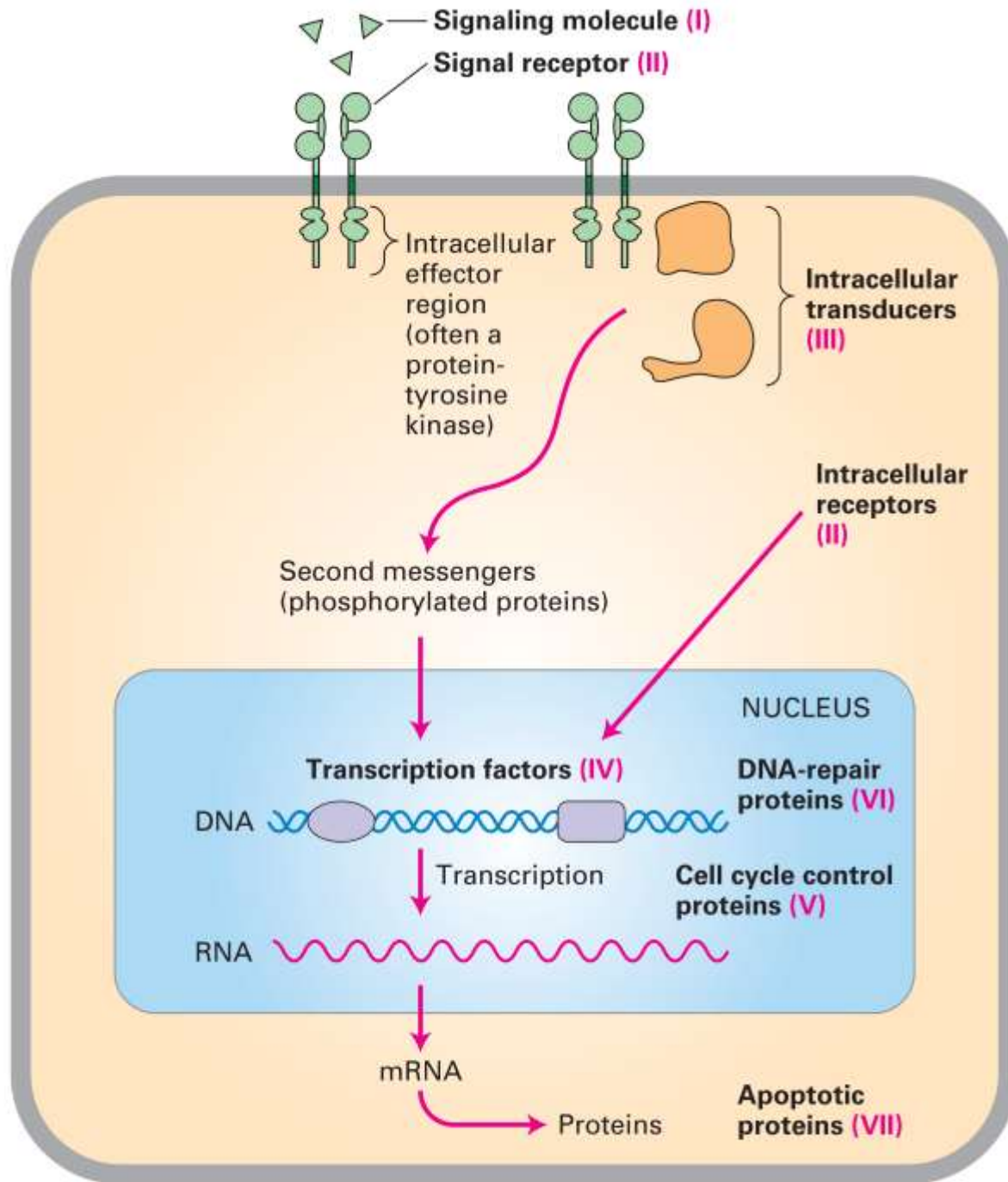
ONCOGENES & TSG

EXAMPLES

TABLE 20-1 Some Genetic Abnormalities Detected in Colorectal Cancer Cells

Gene	Class	Pathway affected	Human colon cancers (%)
<i>K-Ras</i>	Oncogene	Receptor tyrosine kinase signaling	40
<i>β-Catenin</i> ¹	Oncogene	Wnt signaling	5–10
<i>Apc</i> ¹	Tumor suppressor	Wnt signaling	>80
<i>p53</i>	Tumor suppressor	Response to stress and DNA damage	60
<i>TGFβ receptor II</i> ²	Tumor suppressor	TGFβ signaling	10
<i>Smad4</i> ²	Tumor suppressor	TGFβ signaling	30
<i>MLH1</i> and other DNA mismatch repair genes (often silenced by DNA methylation)	Tumor suppressor (genetic stability)	DNA mismatch repair	15

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ONCOGENES & TSG: 7 SISTERS

FIGURE 24-15 Cancer can result from the expression of mutant forms of seven types of proteins. Mutations changing the structure or expression of proteins that normally promote cell growth generally give rise to dominantly acting oncogenes. Many, but not all, extracellular signaling molecules (I), signal receptors (II), signal-transducing proteins (III), and transcription factors (IV) are in this category. Cell cycle control proteins (V), which function to restrain cell proliferation, and DNA-repair proteins (VI) are encoded by tumor-suppressor genes. Mutations in these genes act recessively, greatly increasing the probability that the mutant cells will become tumor cells or that mutations will occur in other gene classes. Apoptotic proteins (VII) include tumor suppressors that promote apoptosis and oncoproteins that promote cell survival.

ONCOGENES AND VIRUSES

1. Tumor viruses induce infected cells to proliferate and produce a tumor. There are two types, based on the viral genome:

a. RNA tumor viruses transform cells by introducing viral oncogenes. (An oncogene is any gene that stimulates unregulated proliferation.)

b. DNA tumor viruses do not carry oncogenes, and use other mechanisms to transform the cell.

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1. **RNA tumor viruses are all retroviruses, and their oncogenes are altered forms of normal host genes.** Examples include:

- Rous sarcoma virus.**
- Feline leukemia virus.**
- Mouse mammary tumor virus.**
- Human immunodeficiency virus (HIV-1, cause of AIDS).**

2. Structurally, retroviruses have:

- Two copies of the 7-10 kb ssRNA genome.**
- A protein core (often icosahedral).**
- An envelope derived from host membrane and bearing viral glycoproteins used to enter a host cell.**

3. The retroviral life cycle was first characterized (1910) for a “filterable agent” from a chicken tumor, later named the Rous sarcoma virus (RSV). RSV’s genome organization is known

ONCOGENES & VIRUSES EXAMPLES

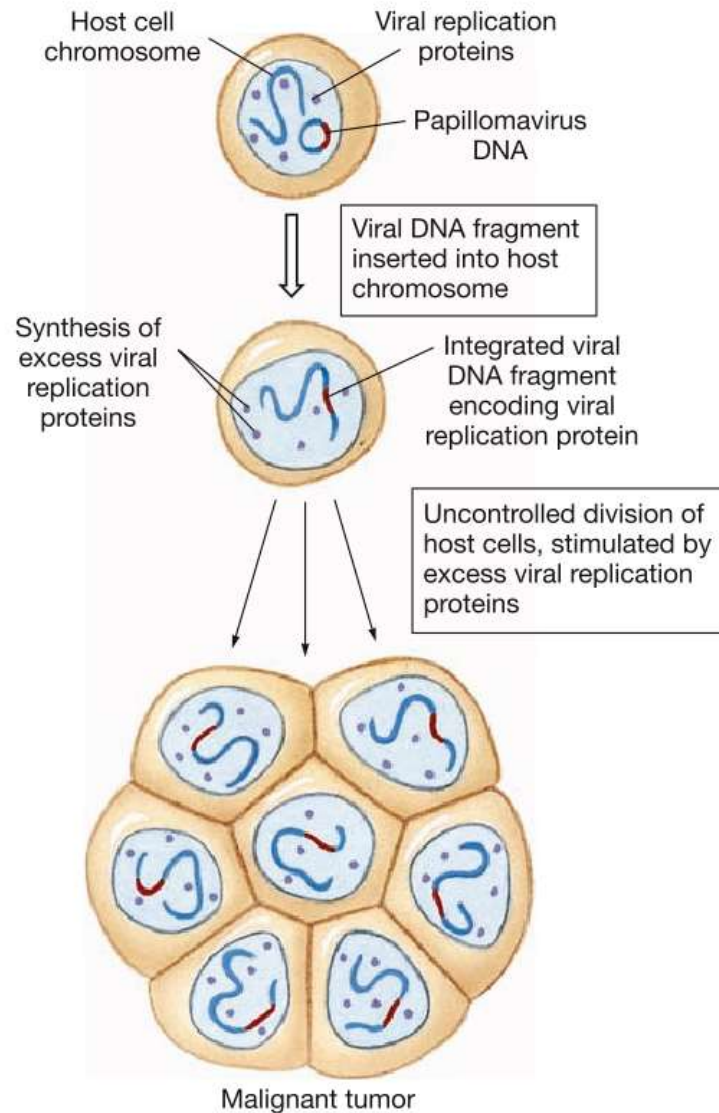


FIGURE 10.28 Malignant tumor formation. This particular tumor is caused by a papillomavirus (DNA tumor virus). Integration of the provirus causes synthesis of viral replication proteins that promote host cell divisions, leading to cancer.

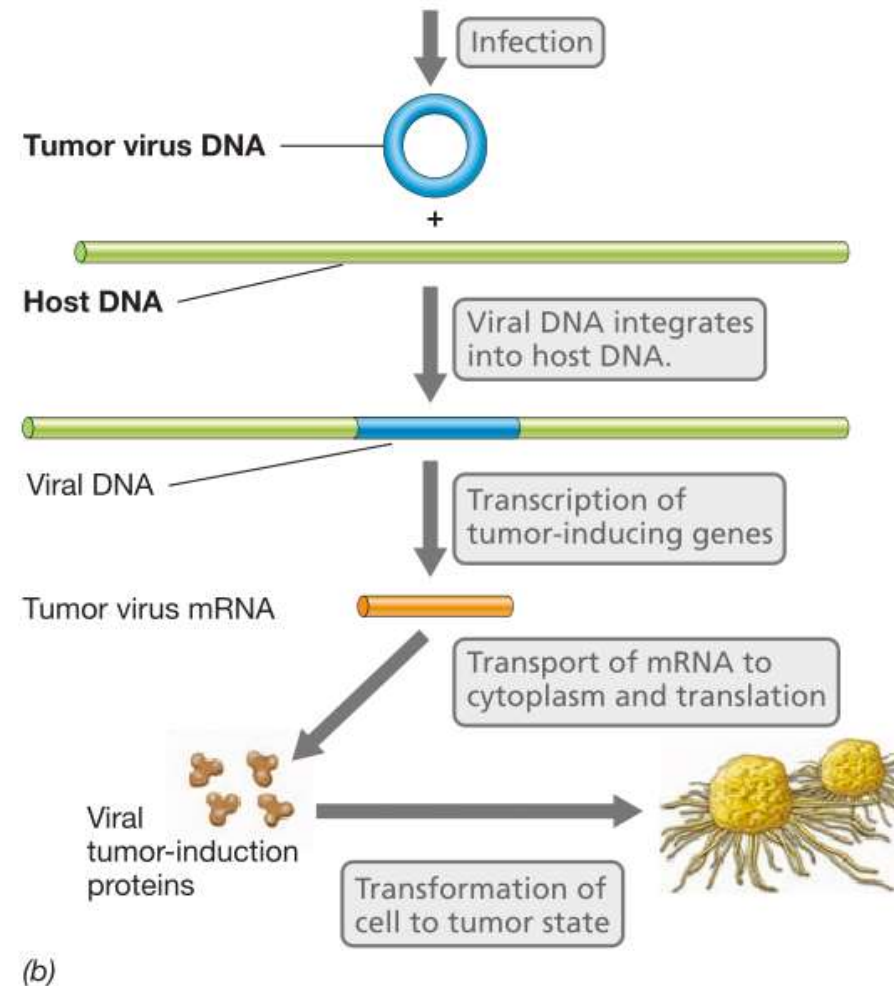


Figure 9.13 Polyomaviruses and tumor induction. (a) Transmission electron micrograph of relaxed (nonsupercoiled) circular DNA from a tumor virus. The contour length of each circle is about 1.5 μm . (b) Events in cell transformation by a polyomavirus such as SV40. Viral DNA becomes incorporated into the host genome. From there, viral genes encoding cell transformation events are transcribed and transported to the cytoplasm for translation.

ONCOGENES & VIRUSES : RETROVIRUS GENOME

Stylized drawing of a retrovirus

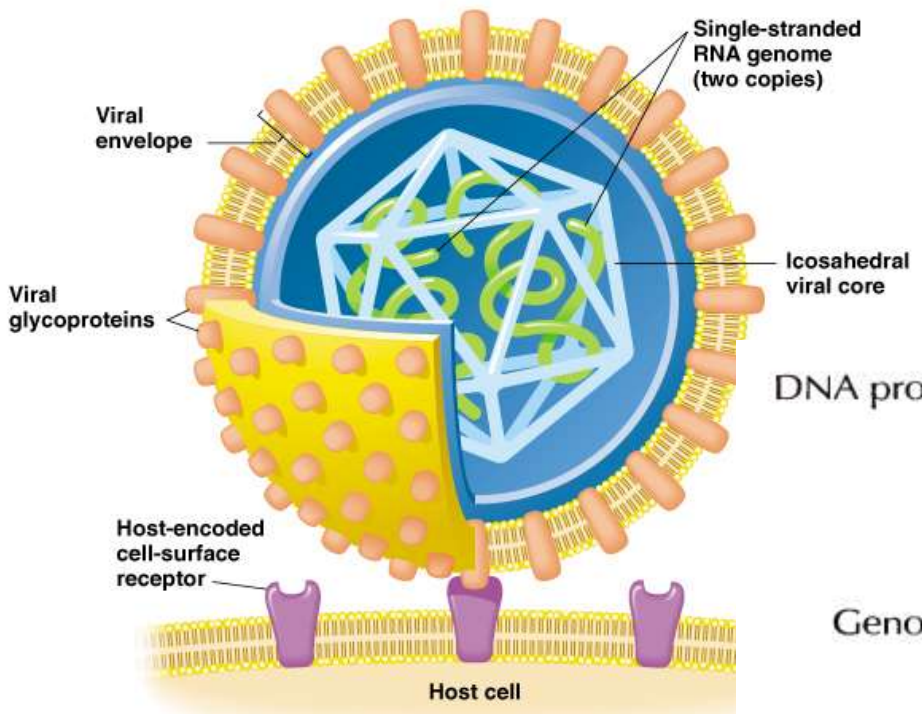
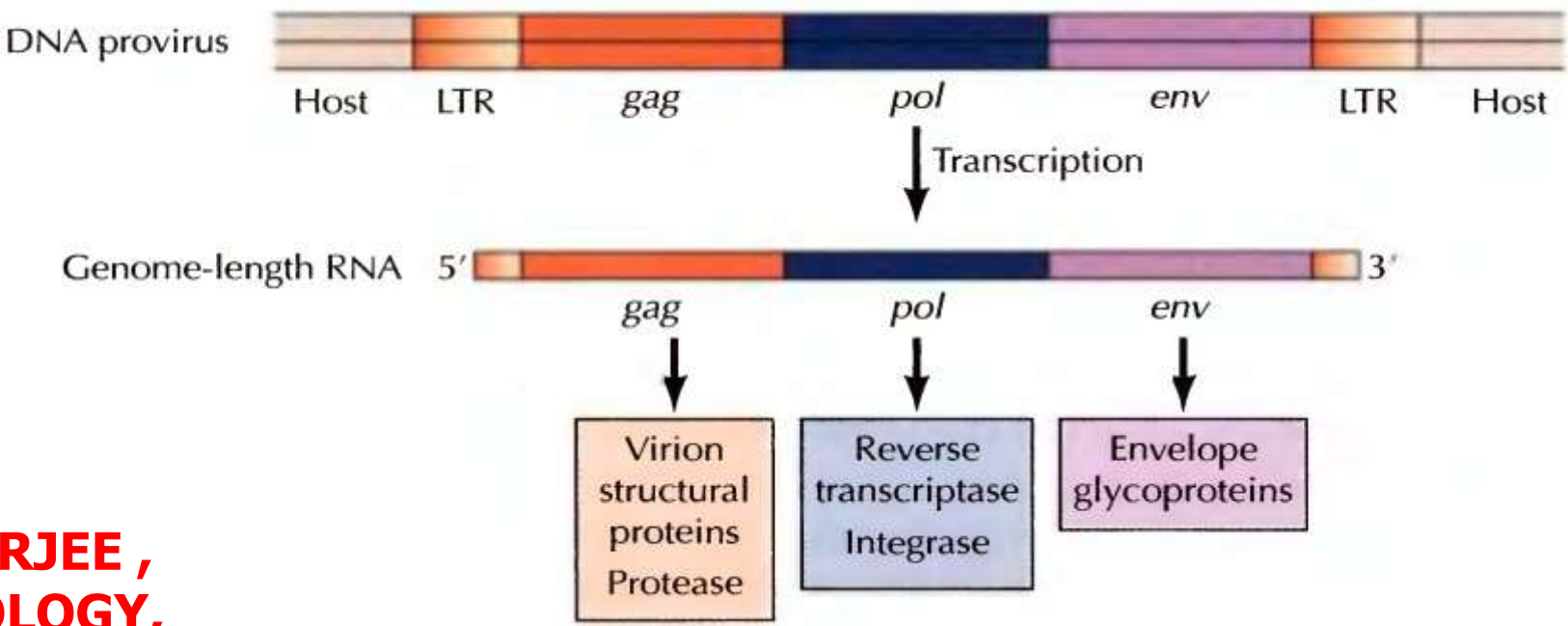


FIGURE 18.16 A typical retrovirus genome The DNA provirus, integrated into cellular DNA, is transcribed to yield genome-length RNA. This primary transcript serves as the genomic RNA for progeny virus particles and as mRNA for the *gag* and *pol* genes. In addition, the full-length RNA is spliced to yield mRNA for *env*. The *gag* gene encodes the viral protease and structural proteins of the virus particle, *pol* encodes reverse transcriptase and integrase, and *env* encodes envelope glycoproteins.



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ONCOGENES & VIRUSES :

RETROVIRUS GENOME & PROTO-ONCOGENE PRODUCTS

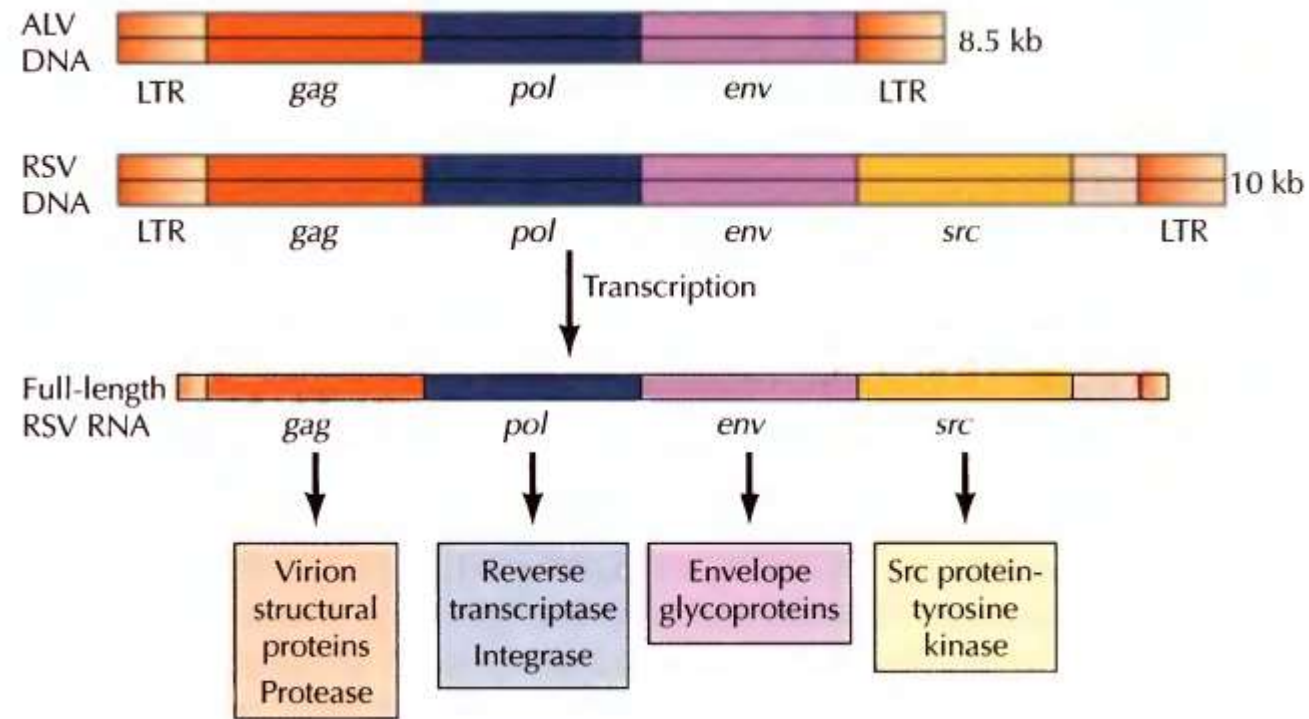


FIGURE 18.18 The RSV genome

RSV contains an additional gene, *src*, that is not present in ALV and encodes the Src protein-tyrosine kinase.

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Table 20.2 Classes of Proto-Oncogene Products

Growth factors

<i>sis</i>	PDGF B-chain growth factor
<i>int-2</i>	FGF-related growth factor

Receptor and nonreceptor protein-tyrosine and protein-serine/threonine kinases

<i>src</i>	Membrane-associated nonreceptor protein-tyrosine kinase
<i>fgr</i>	Membrane-associated nonreceptor protein-tyrosine kinase
<i>fps/fes</i>	Nonreceptor protein-tyrosine kinase
<i>kit</i>	Truncated stem cell receptor protein-tyrosine kinase
<i>pim-1</i>	Cytoplasmic protein-serine kinase
<i>mos</i>	Cytoplasmic protein-serine kinase (cytostatic factor)

Receptors lacking protein kinase activity

<i>mas</i>	Angiotensin receptor
------------	----------------------

Membrane-associated G proteins activated by surface receptor

H- <i>ras</i>	Membrane-associated GTP-binding/GTPase
K- <i>ras</i>	Membrane-associated GTP-binding/GTPase
<i>gsp</i>	Mutant-activated form of G α

Cytoplasmic regulators

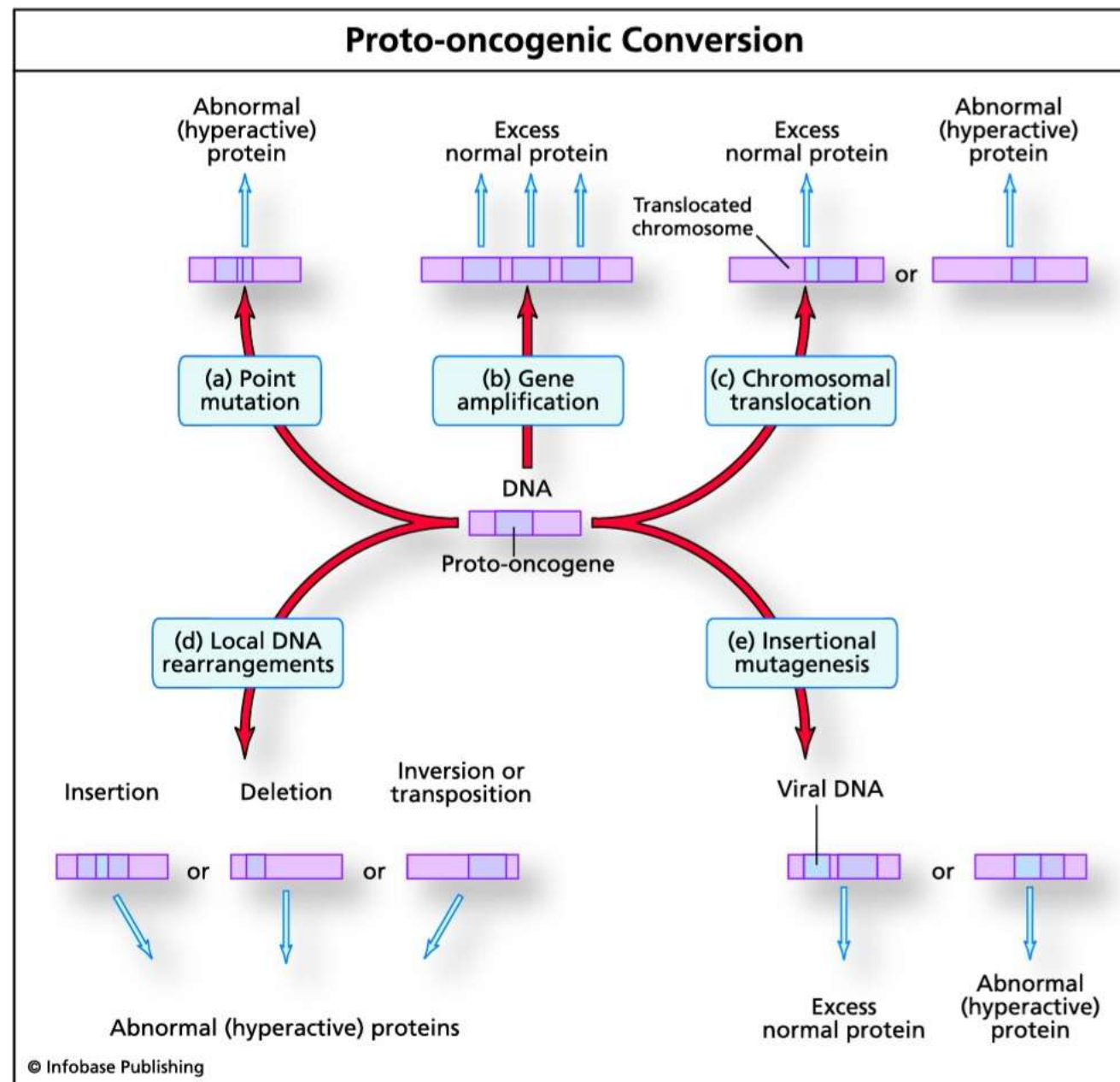
<i>crk</i>	SH-2/3 protein that binds to (and regulates?) phosphotyrosine-containing proteins
------------	---

Nuclear transcription factors (gene regulators)

<i>myc</i>	Sequence-specific DNA-binding protein
<i>fos</i>	Combines with <i>c-jun</i> product to form AP-1 transcription factor
<i>jun</i>	Sequence-specific DNA-binding protein; part of AP-1
<i>erbA</i>	Dominant negative mutant thyroxine (T3) receptor
<i>ski</i>	Transcription factor?

PROTO-ONCOGENES TO ONCOGENES

1. Conversion of proto-oncogenes to oncogenes relaxes cell control, allowing unregulated proliferation. Examples:
 - a. Point mutations in the coding or controlling sequences can either change the gene product or alter its expression. The ras genes are an example:
 - i. A point mutation produces a mutant protein that can cause cancer in many different types of cells.
 - ii. G proteins lose regulation, and constitutive growth signals are transmitted to the cell.
 - b. Deletions of coding or controlling sequences can change the amount of activity of growth stimulatory proteins, allowing proliferation. The myc gene is an example:
 - i. The myc gene product is a transcription factor that activates genes involved in cell division.
 - ii. Deletions can remove upstream sequences, allowing expression from an alternative promoter and changing the amount or activity of the protein product.
 - c. Gene amplification, caused by random overreplication of regions of genomic DNA, has been found in tumor cells. Multiple copies of ras in mouse adrenocortical tumors are an example.



PROTO-ONCOGENES TO ONCOGENES

: HUMAN CANCER

ONCOGENES IN HUMAN CANCER

POINT MUTATION:
GGC **GTC** :
 Here glycine (GGC) is changed to valine (GTC).
 In the process rasH proto-oncogene converted to oncogene

CHROMOSOME TRANSLOCATION:
 8 → 14
 translocation occurs. Cmyc translocated to Immunoglobulin heavy chain locus (Ig H)

GENE AMPLIFICATION:
 Amplified copies of N-myc gene results in development fo neuroblastoma.

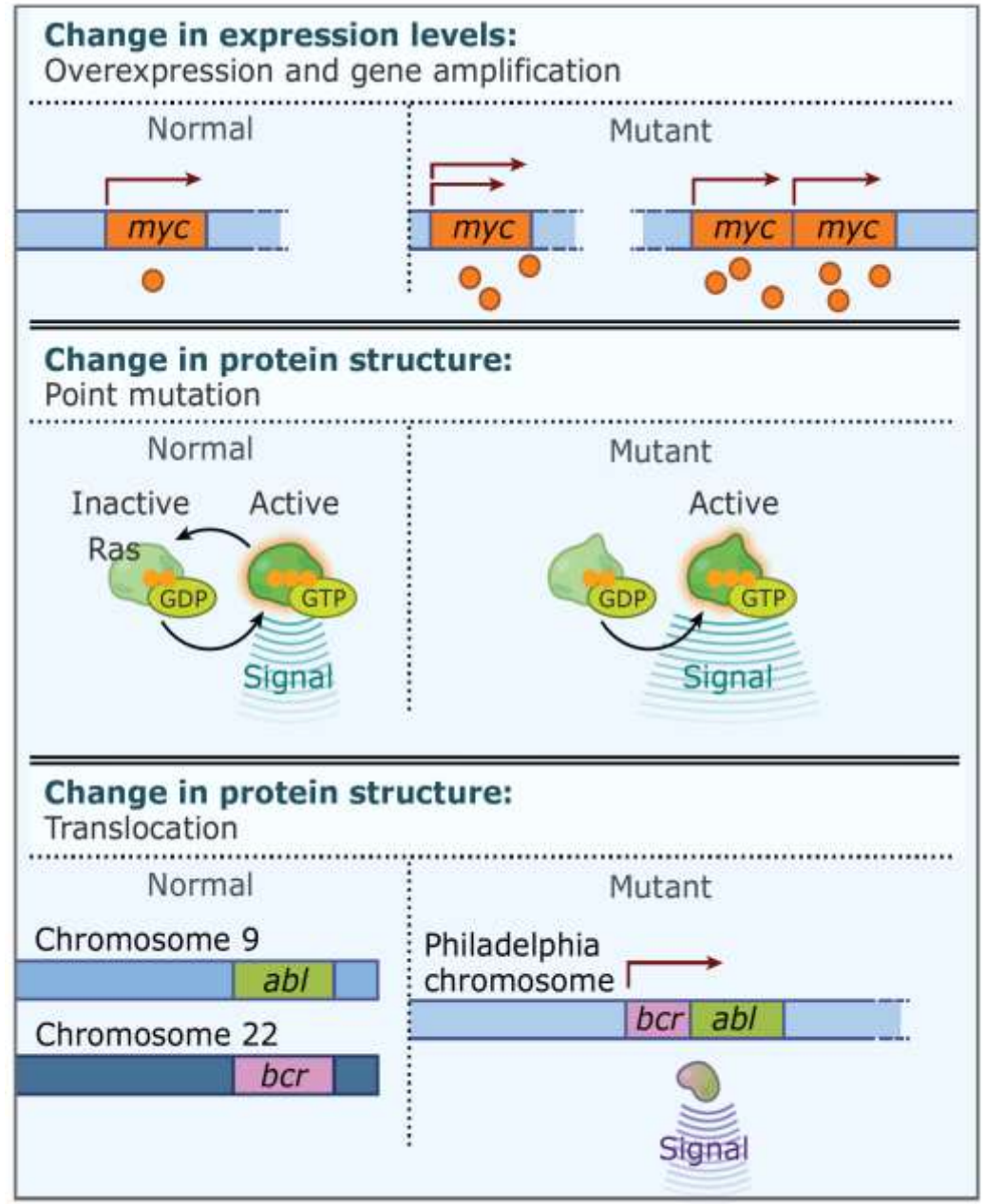


FIGURE 17.12 Oncogenes can be activated by both quantitative and qualitative changes.

PROTO-ONCOGENES TO ONCOGENES : RAS

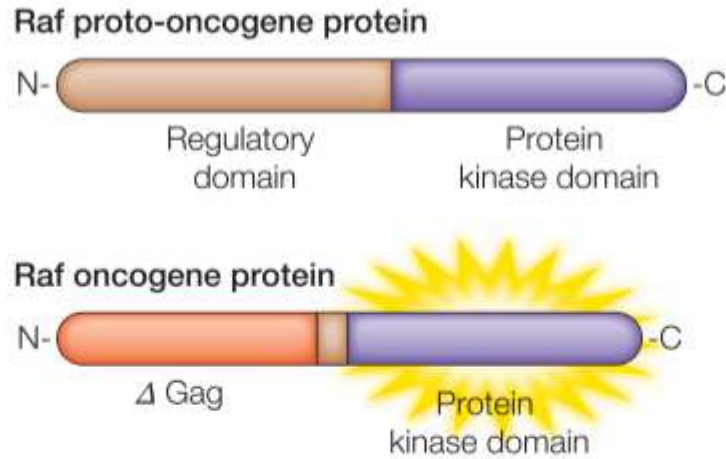


Figure 20.10 The Raf oncogene protein The Raf proto-oncogene protein consists of an amino-terminal regulatory domain and a carboxy-terminal protein kinase domain. In the viral Raf oncogene protein, the regulatory domain has been deleted and replaced by partially deleted viral Gag sequences (Δ Gag). As a result, the Raf kinase domain becomes constitutively active, causing cell transformation.

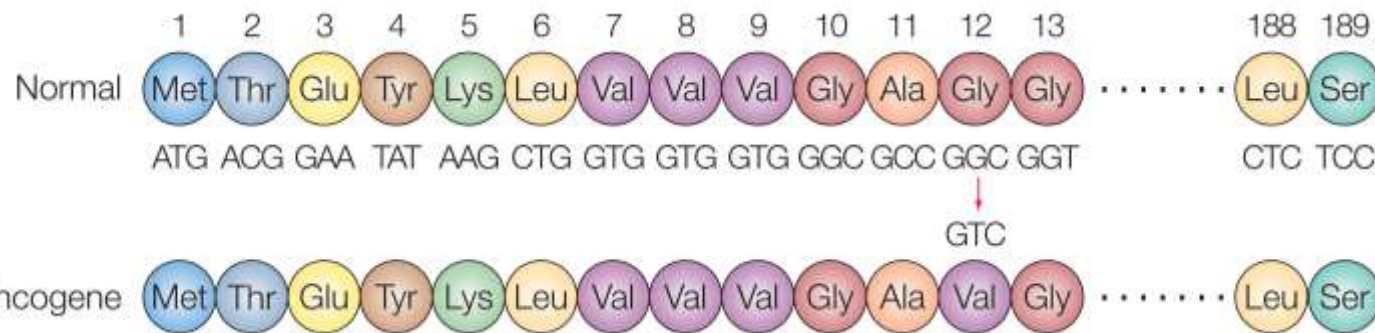
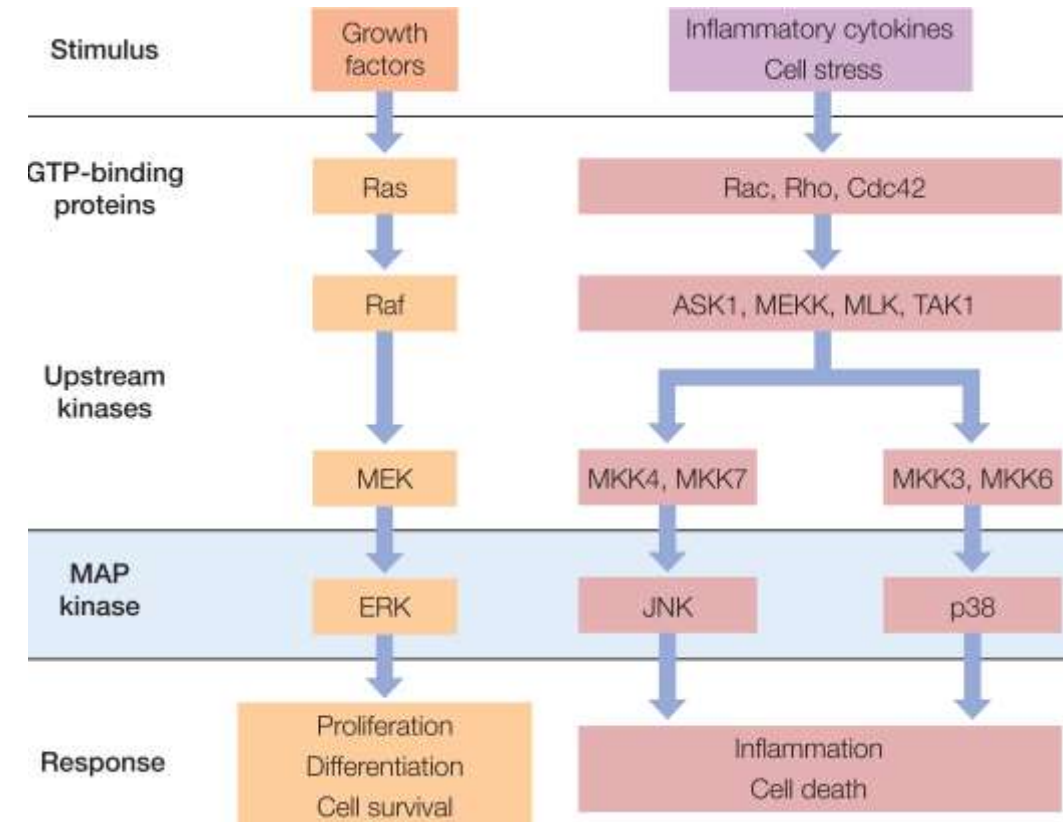


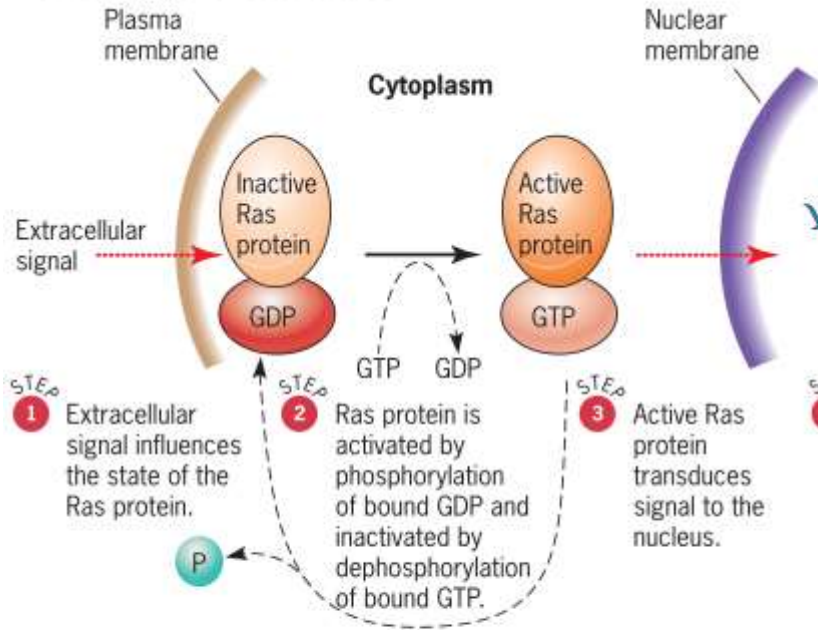
Figure 20.12 Point mutations in *ras* oncogenes A single nucleotide change, which alters codon 12 from GGC (Gly) to GTC (Val), is responsible for the transforming activity of the *rasH* oncogene detected in bladder carcinoma DNA.

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PROTO-ONCOGENES TO ONCOGENES :

RAS

Normal Ras protein is regulated



(a)

Mutant Ras protein is unregulated

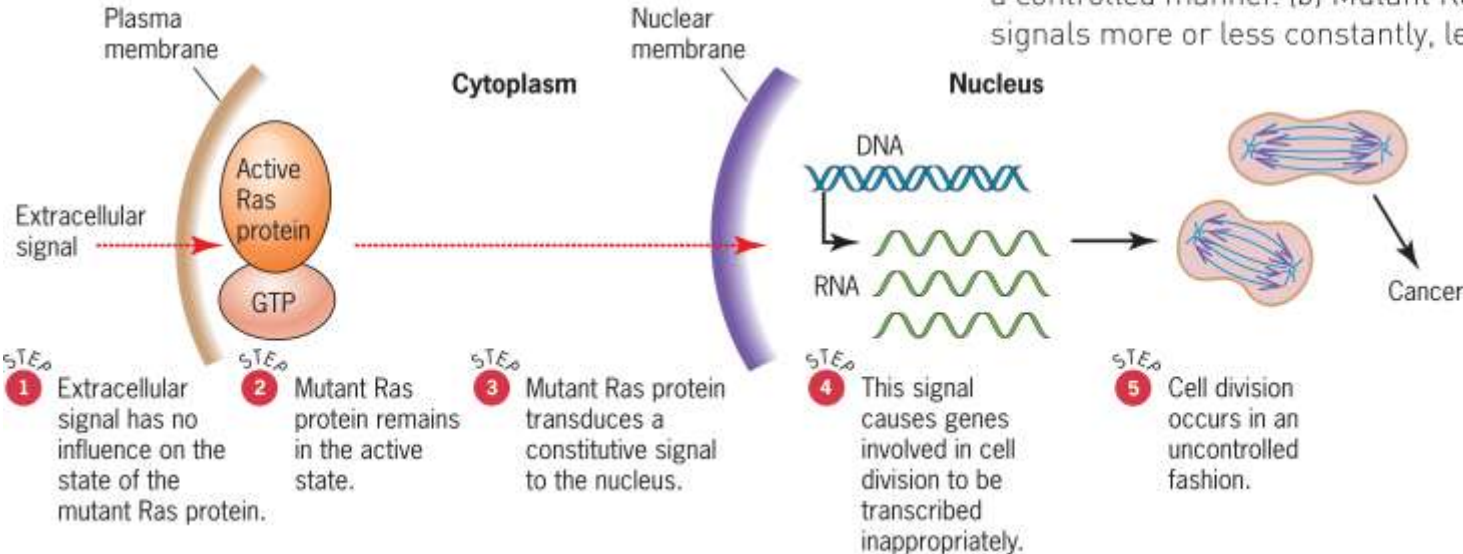


FIGURE 21.4 Ras protein signaling and cancer. (a) The normal protein product of the *ras* gene alternates between inactive and active states, depending on whether it is bound to GDP or GTP. Extracellular signals such as growth factors stimulate the conversion of inactive Ras to active Ras. Through active Ras, these signals are transmitted to other proteins and eventually to the nucleus, where they induce the expression of genes involved in cell division. Because this signaling is intermittent and regulated, cell division occurs in a controlled manner. (b) Mutant Ras proteins exist mainly in the active state. These proteins transmit their signals more or less constantly, leading to uncontrolled cell division, the hallmark of cancer.

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PROTO-ONCOGENES TO ONCOGENES : CHROMOSOMAL TRANSLOCATION

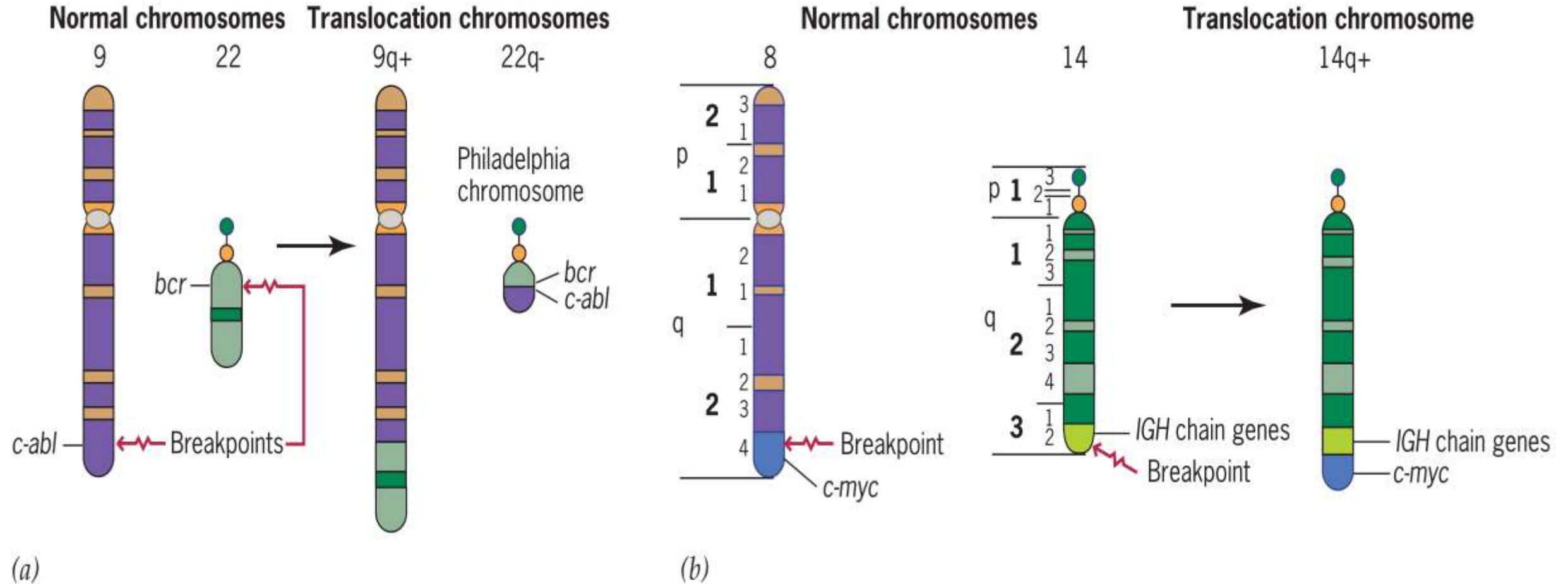
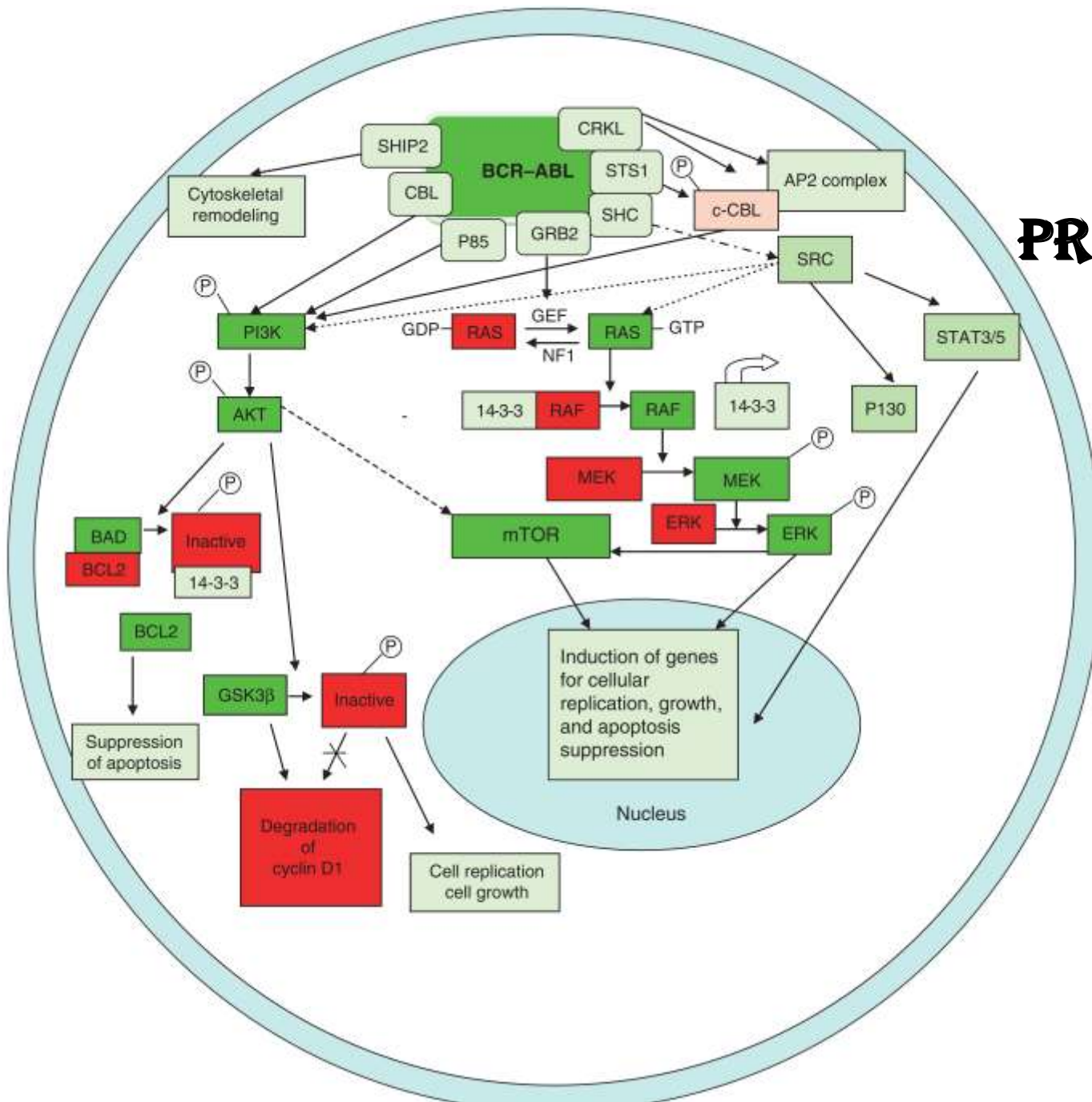


FIGURE 21.5 Translocations implicated in human cancers. (a) The reciprocal translocation involved in the Philadelphia chromosome that is associated with chronic myelogenous leukemia. (b) A reciprocal translocation involved in Burkitt's lymphoma. Only the translocation chromosome (14q+) that carries both the *c-myc* oncogene and the immunoglobulin heavy chain genes (*IGH*) is shown.



PROTO-ONCOGENES TO ONCOGENES : BCR-ABL

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PROTO-ONCOGENES TO ONCOGENES : CHROMOSOMAL TRANSLOCATION

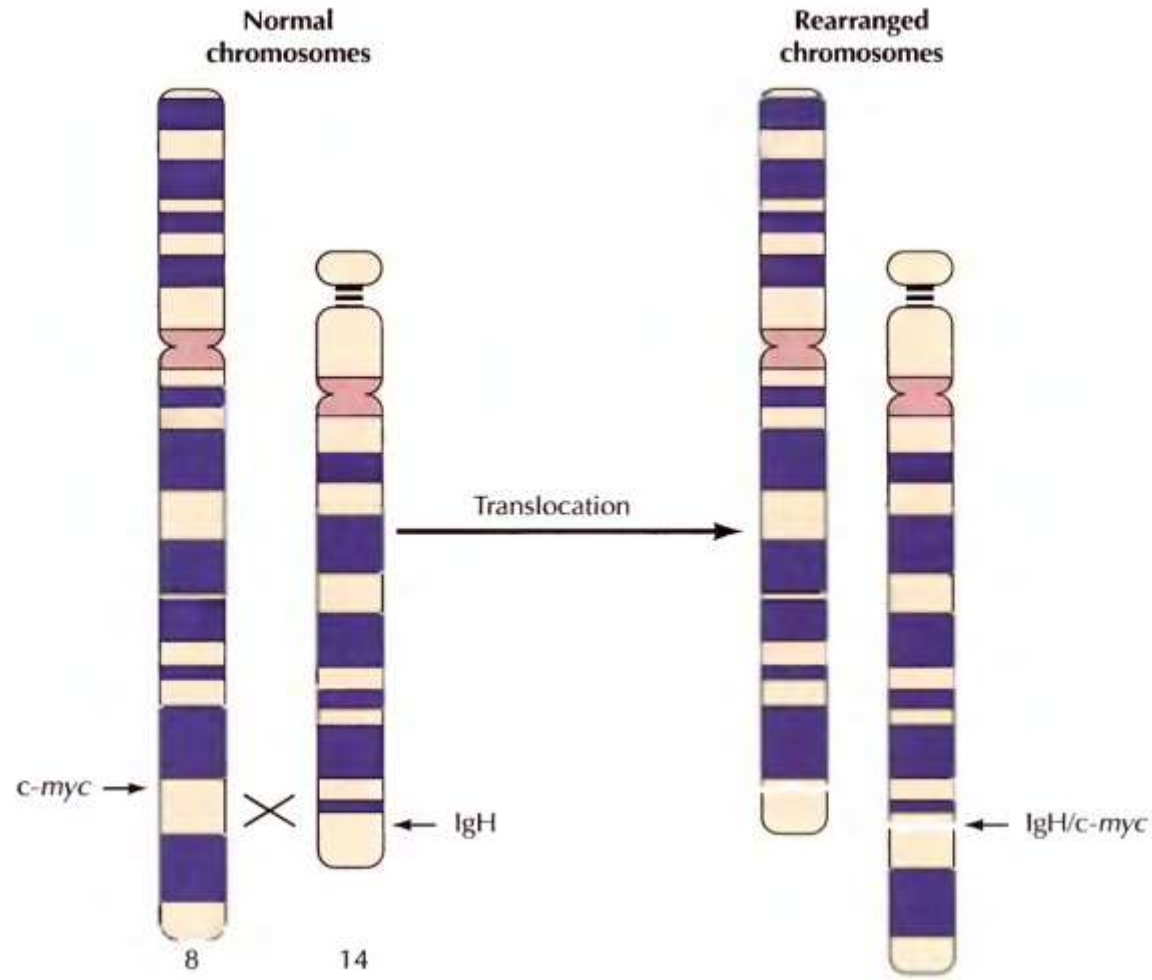


FIGURE 18.23 Translocation of *c-myc* The *c-myc* proto-oncogene is translocated from chromosome 8 to the immunoglobulin heavy-chain locus (*IgH*) on chromosome 14 in Burkitt's lymphomas, resulting in abnormal *c-myc* expression.

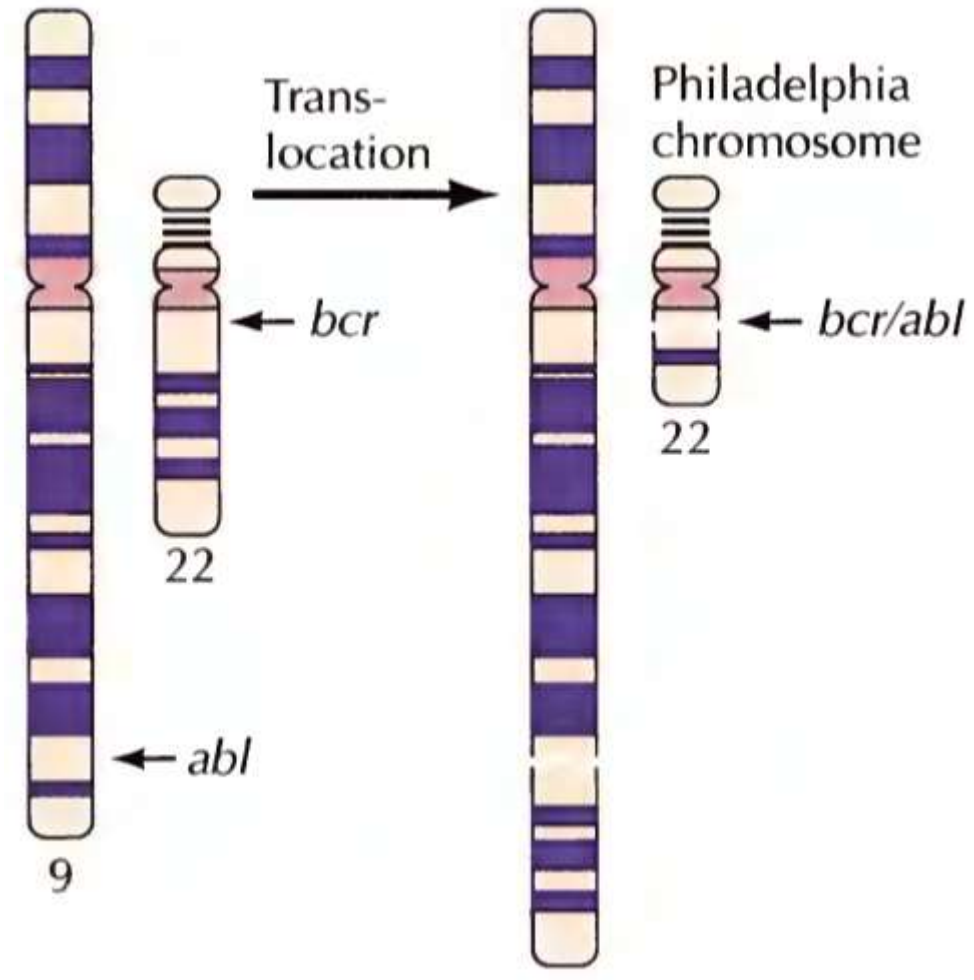


FIGURE 18.24 Translocation of *abl* The *abl* oncogene is translocated from chromosome 9 to chromosome 22, forming the Philadelphia chromosome in chronic myeloid leukemias. The *abl*

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CANCER INDUCTION BY RETROVIRUSES

1. One human, and many animal cancers, are caused by retroviruses. Two mechanisms can account for viral-induced cell proliferation independent of cell cycle control signals:
 - a. A v-onc carried by an integrated retrovirus may be transcribed from a viral promoter.
 - b. Proviral DNA may integrate near a proto-oncogene, and be transcribed from promoter and enhancer sequences in the viral LTR (insertional mutagenesis).

DNA TUMOR VIRUSES

1. Oncogenic DNA viruses do not carry oncogenes, but may transform cells using viral gene products.

Examples include:

- a. Papovaviruses.
- b. Hepatitis B viruses.
- c. Herpes viruses.
- d. Adenoviruses.
- e. Pox viruses.

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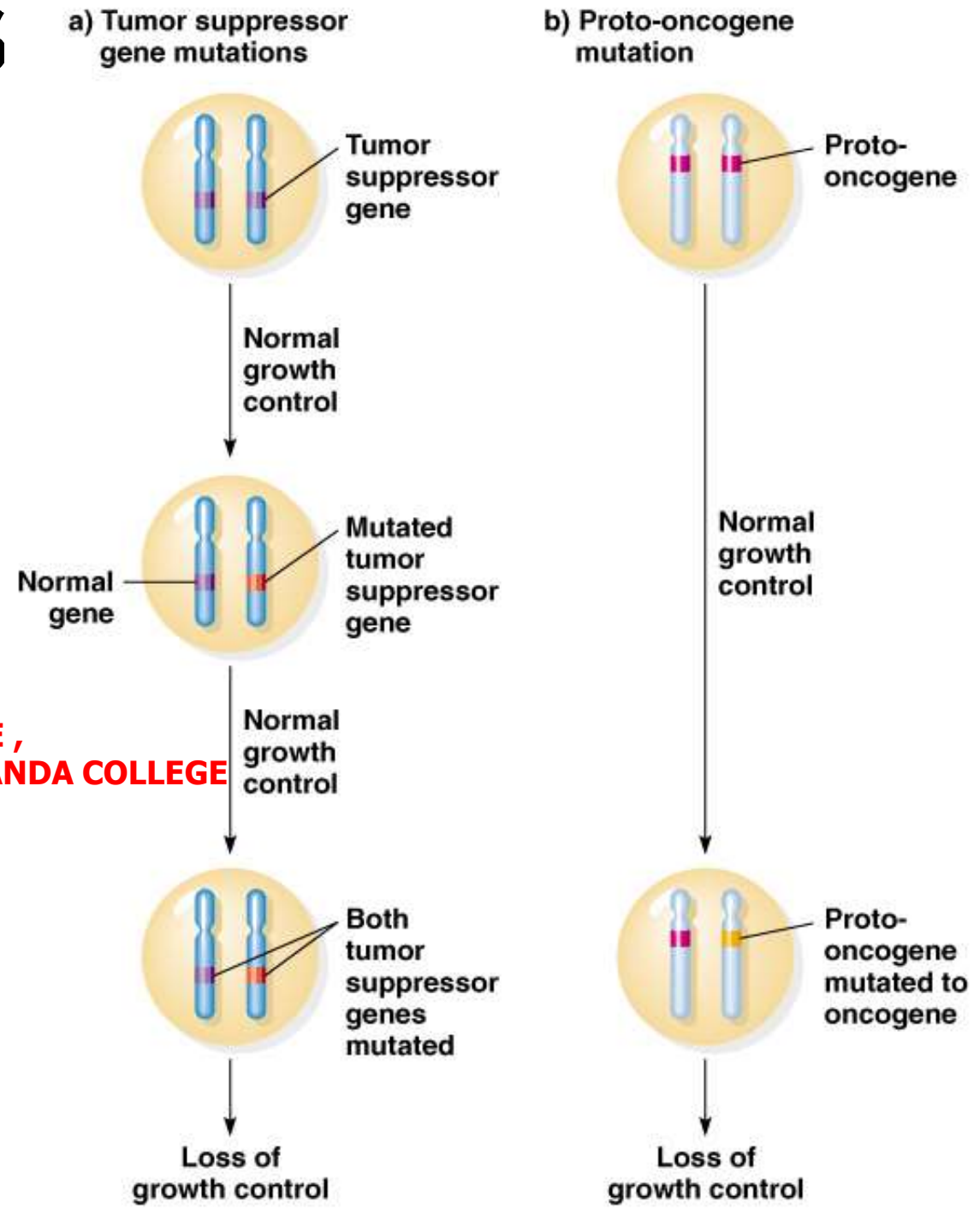
2. DNA viruses induce production of cellular DNA replication enzymes, which are used in viral replication. Rarely, viral DNA integrates into the host genome instead, and may produce protein(s) that stimulate the cell to proliferate. An example:
 - a. The papovavirus group includes many different papillomaviruses, some of which cause:
 - i. Human warts.
 - ii. **Human cervical cancer (HPV-16, HPV-18)**, due to action of the E6 and E7 viral genes, which influence cell growth and division.

TUMOR SUPPRESSOR GENES

1. Harris (1960s) showed that fusion of cancer cells and normal cells did not always result in a tumor, indicating the existence of tumor suppressor genes.
2. In certain cancers, both homologous chromosomes show deletion of specific regions, the sites of tumor suppressor genes that inhibit cell growth and division. Human examples include:
 - a. Breast cancer.
 - b. Colon cancer.
 - c. Lung cancer.

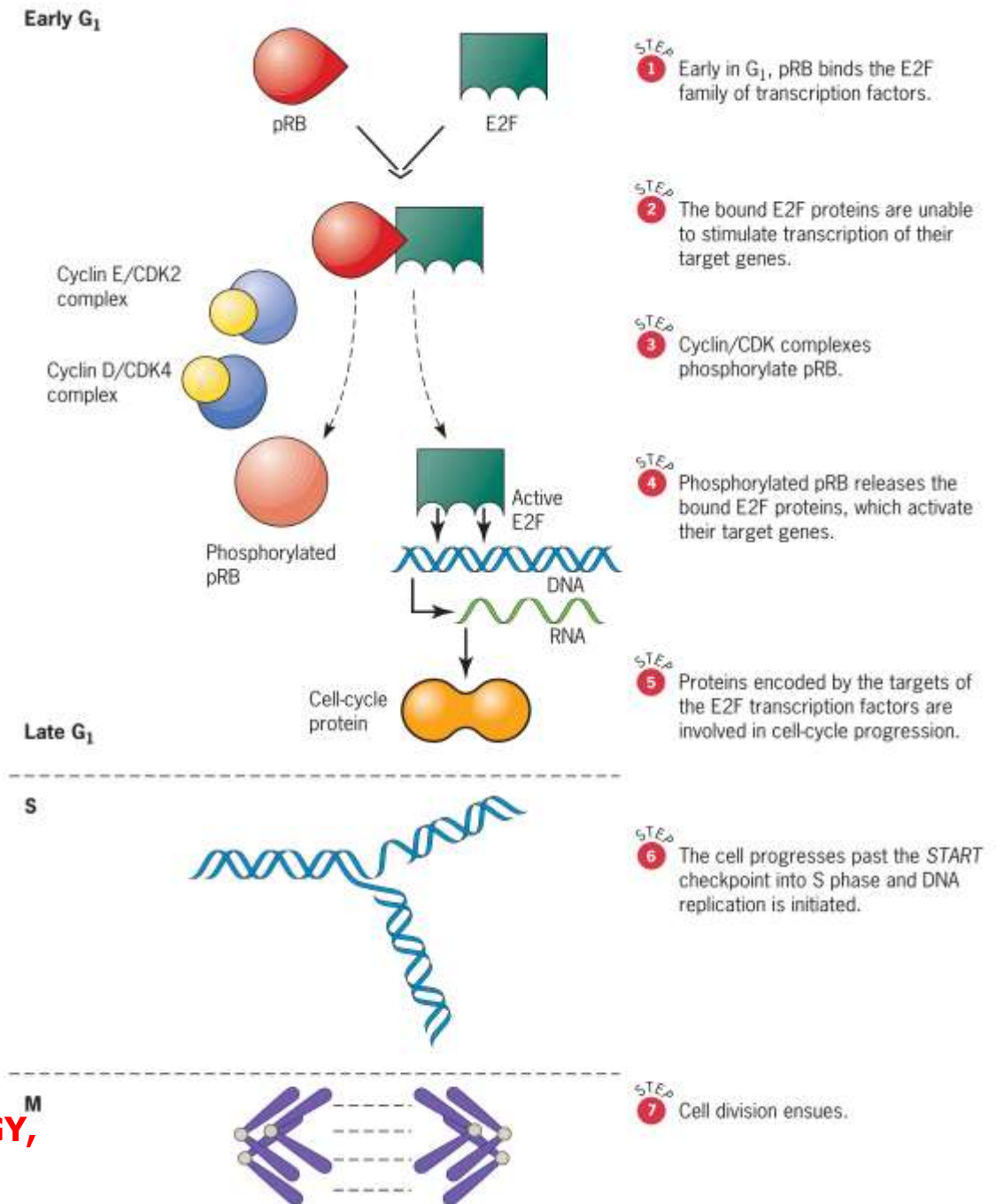
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3. **Action of tumor suppressors is the opposite of proto-oncogenes.**
4. **Both tumor suppressor genes must be lost for unregulated growth to occur (they are recessive), while only one mutation is needed to change a proto-oncogene to an oncogene (it is dominant)**



TSG: RB

1. The human RB tumor suppressor gene has been mapped (13q14.1-q14.2) and sequenced.
 - a. Its 180 kb of DNA encodes a 4.7 kb mRNA that produces a 928-amino-acid nuclear phosphoprotein, pRB.
 - b. pRB is expressed in every tissue type examined, regulating cell cycle and all major cellular processes.
 - c. Tumor cells have point mutations or deletions in the gene, leading to loss of pRB function.
 - d. Karyotype analysis detects about 5% of RB mutants, and the remainder are difficult to detect even with molecular techniques.
 - e. In hereditary retinoblastoma, both alleles are often identical, possibly due to:
 - i. Mitotic recombination.
 - ii. Chromosomal nondisjunction.
 - iii. Gene conversion.
2. The cell cycle transition from G₁ to S is regulated by pRB, committing the cell to the rest of the cycle.
 - a. In a normal G₁ cell, pRB binds two transcription factors, E2F and DP1 .
 - b. As long as pRB stays bound to the factors, the cell remains in G₁ or enters G₀.
 - c. At the signal to progress through the cell cycle, cyclin/cyclin-dependent kinase (Cdk) phosphorylates pRB so that it is unable to bind E2F.
 - d. Free E2F now binds and activates transcription of genes required for entry into S phase.
 - e. After the cell completes mitosis, pRB is dephosphorylated.



TSG: p53

1. Most cancers result from mutations in several genes. A gene mutated in about 1/2 of human cancers is p53, encoding a 53 kDa tumor suppressor protein (chromosomal location 17p13.1).

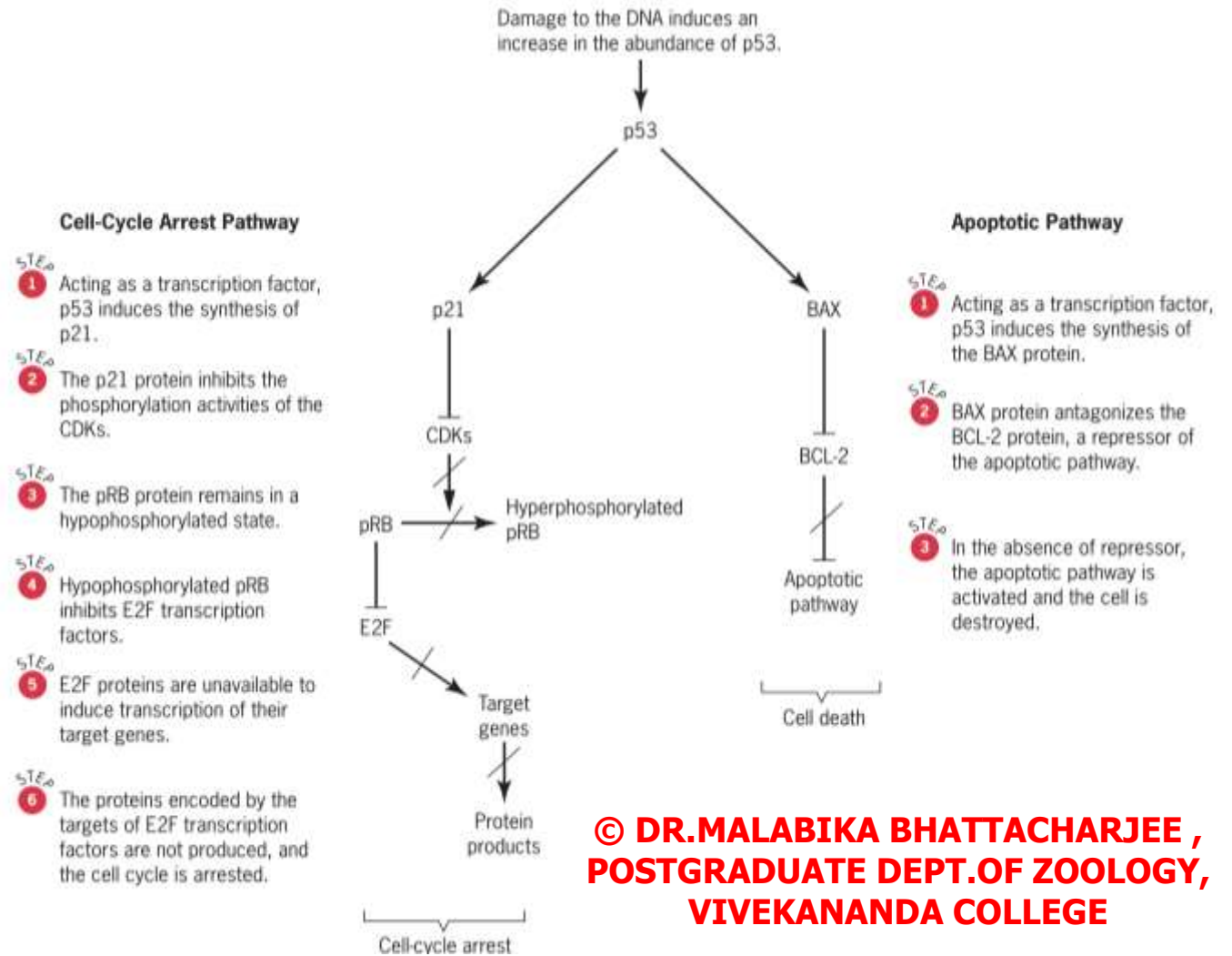
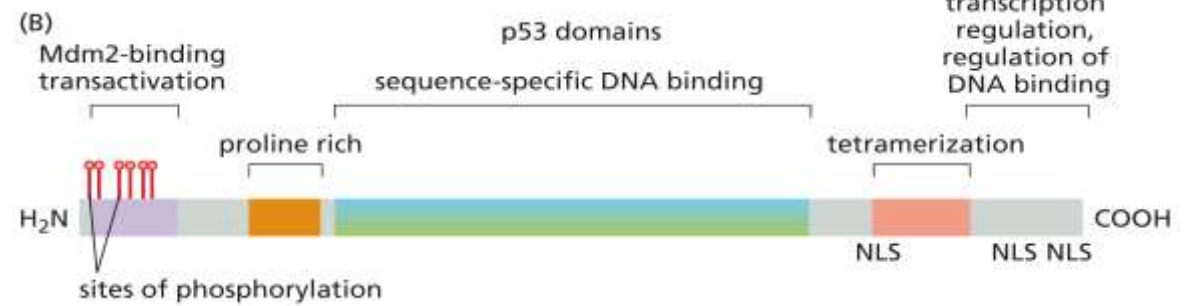
- Inheritance of 1 mutant p53 allele results in Li-Fraumeni syndrome, in which a rare form of cancer develops in a number of tissues.
- Tumors arise when the second p53 allele is mutated, so the trait is inherited as an autosomal dominant.

2. The p53 tumor suppressor protein (393 amino acids) is involved in many processes, including:

- Transcription.
- Cell cycle control.
- DNA repair.
- Apoptosis (programmed cell death).

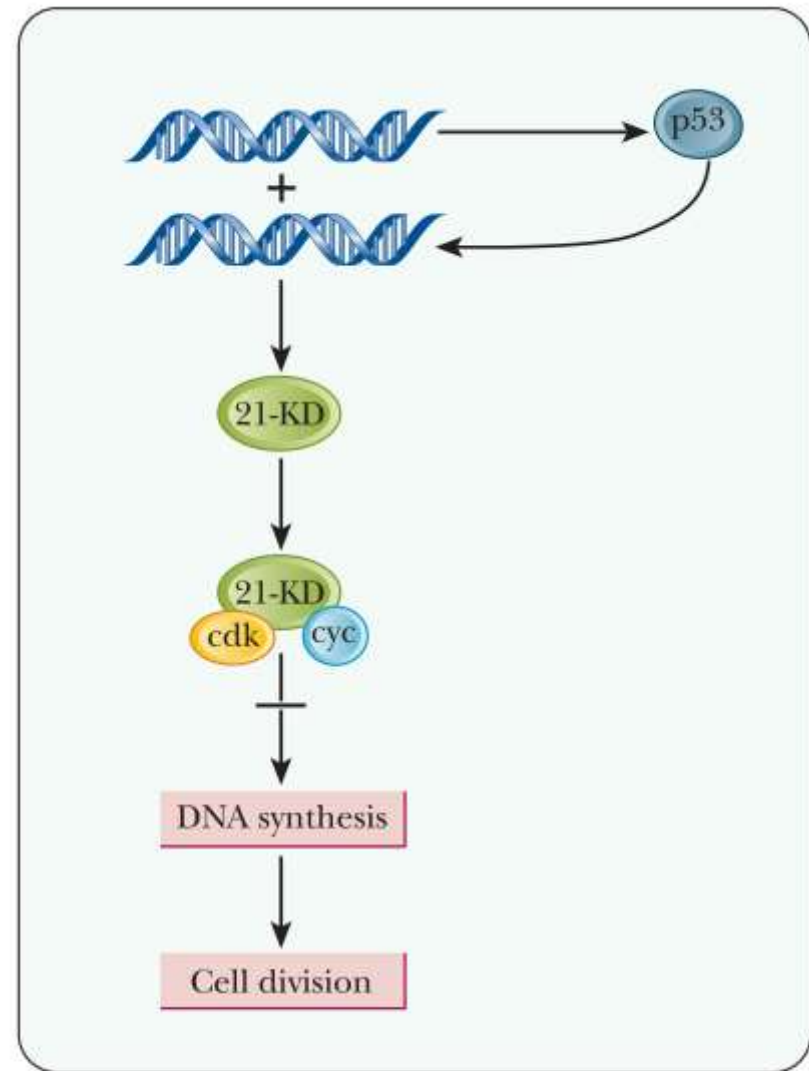
3. Wild-type p53 protein binds to several genes, including WAF1, which encodes p21.

- When p21 is activated by p53, it causes cells to arrest in G₁ by binding to a cyclin/cyclin-dependent kinase (Cdk) complex.
- Kinase activity is blocked, so genes for moving from G₁ to S are not activated.



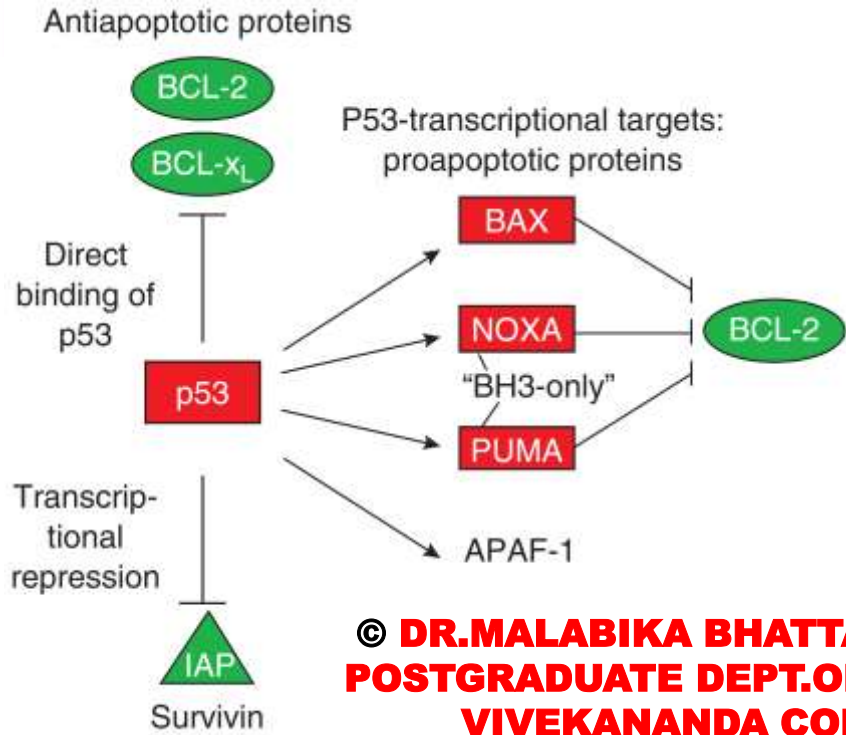
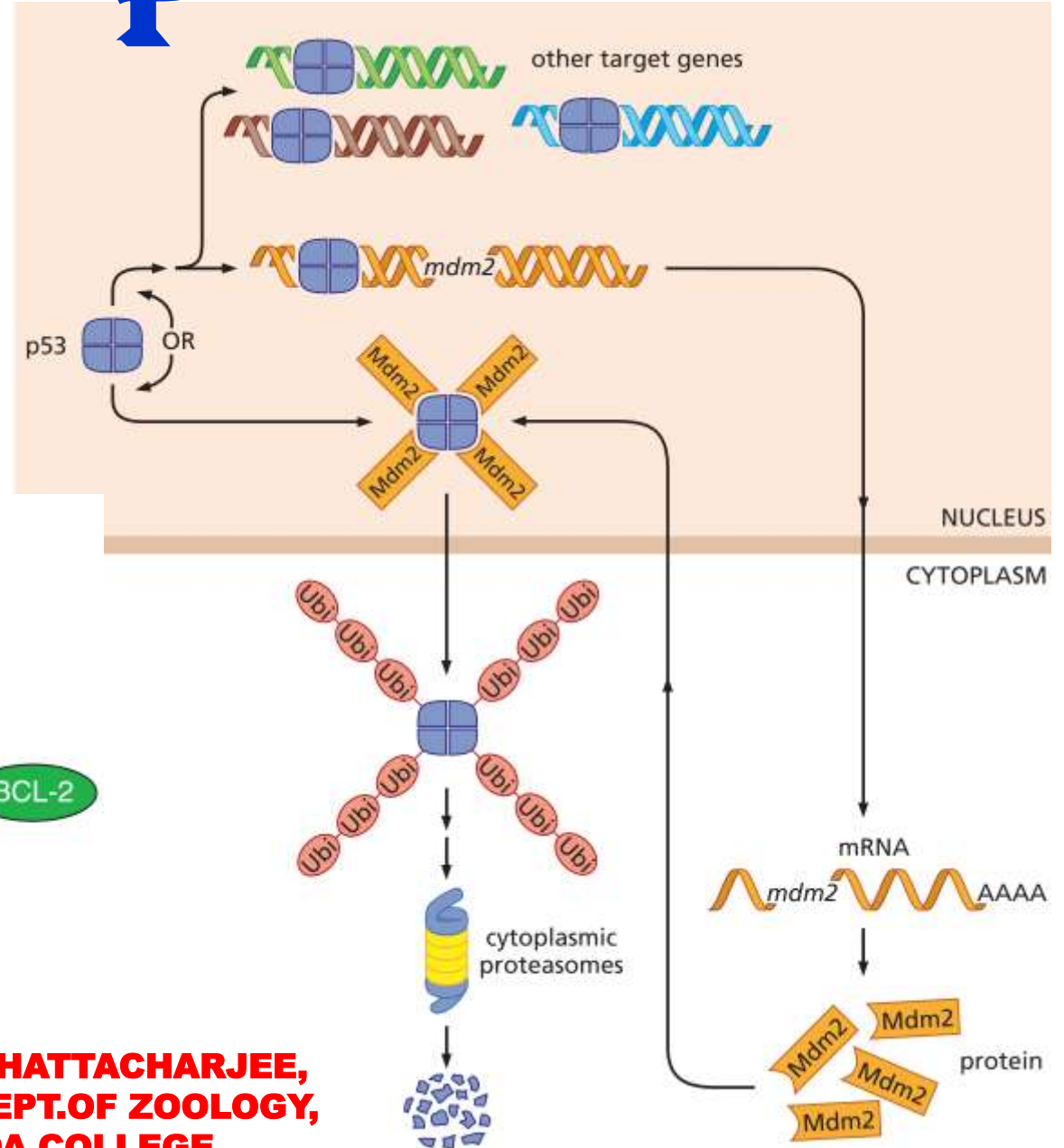
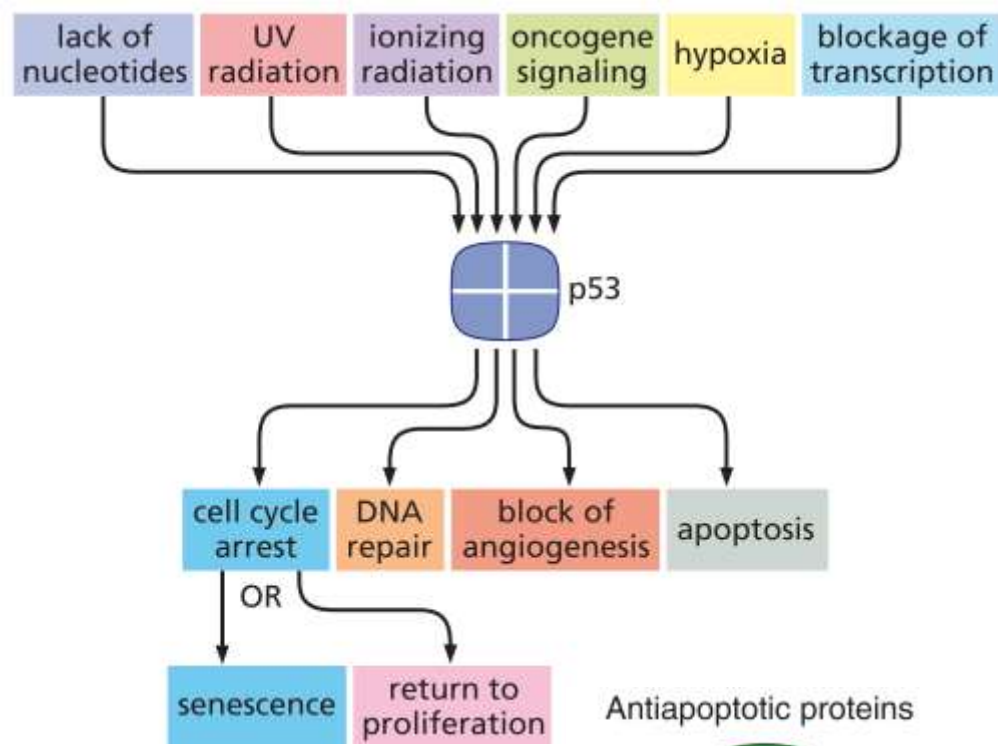
TSG: p53

4. **Damage to cellular DNA (e.g., by irradiation) causes *p53* to initiate the cascade of events leading to G_1 arrest (Figure 18.14).**
 - a. DNA damage leads to stabilization of *p53* in an unknown way.
 - b. The cell has time to repair the DNA damage, before allowing the cell cycle to resume.
 - c. If damage is too severe, the cell cycle does not resume, and apoptosis occurs. Induction of apoptosis is a function of *p53*.
5. **If both *p53* alleles are inactivated, WAF1 cannot be activated and p21 will not be available to block Cdk activity.**
 - a. The cell is unable to arrest in G_1 , and the cell cycle proceeds to S, regardless of DNA damage.
 - b. Apoptosis does not occur without *p53*.
 - c. Cell division produces cells with unrepaired genetic damage, allowing mutations to accumulate, and raising the risk of cancer.
6. **At least 17 cellular and viral proteins interact with *p53*. Virus proteins typically inactivate *p53*, allowing products needed for replication to be expressed.**
7. **Transgenic mice with deletions of both *p53* alleles (knockout mice) are fully viable.**
 - a. This indicates that *p53* is not essential for growth, cell division or differentiation.
 - b. The *p53*²/*p53*² knockout mice have one major phenotype, a very high frequency of cancers (100% by the tenth month).



■ **FIGURE 14.26** Action of *p53*. The *p53* protein turns on the production of a 21-kDa protein. This protein binds to complexes of cyclin-dependent kinases (CDKs) and cyclins. The result of binding is inhibition of DNA synthesis and cell growth. (Adapted from Science, Figure 1, Vol. 262, 1993, p. 1644, by K. Sutliff, © 1993 by the AAAS.)

TSG: p53



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TSG: p53

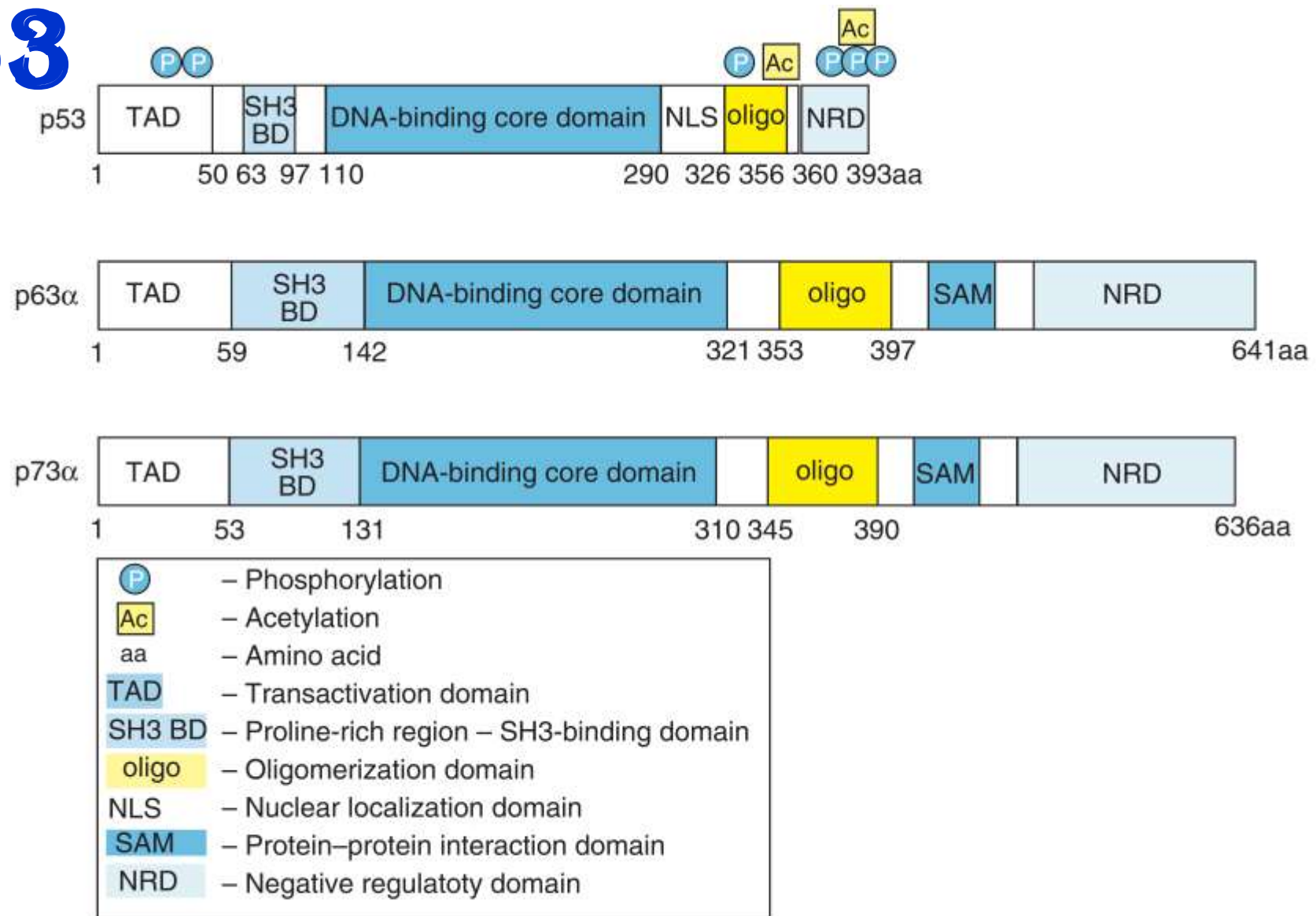


Figure 7.7 Schematic of the linear structure of the p53 family of proteins: p53, p63, and p73. Note that all three proteins share common domains but contain negative regulatory domains (NRD) of different lengths.

TSG: BRCA1 & BRCA2

1. Breast cancer is a very common type of cancer. About 5% of breast cancers are hereditary, and like retinoblastoma, the hereditary form often has earlier onset and is bilateral.
2. Several genes appear to be involved in familial breast cancer, with two (BRCA1 and BRCA2) thought to be tumor suppressor genes.
 - a. Mutations in BRCA1 (located at 17q21) are also involved in ovarian cancer. The gene is expressed in many tissues to produce a 190-kDa protein with a role in a number of functions, including:
 - i. Homologous recombination.
 - ii. Cellular responses to DNA damage.
 - iii. Transcription of mRNA (the BRCA1 protein is part of RNA polymerase II).
 - b. The BRCA2 gene (13q12-q13) is not involved with ovarian cancer.
 - i. The large BRCA2 protein has some similarity to BRCA1.
 - ii. BRCA2 is part of a complex playing a role in timely progression of cells through mitosis.

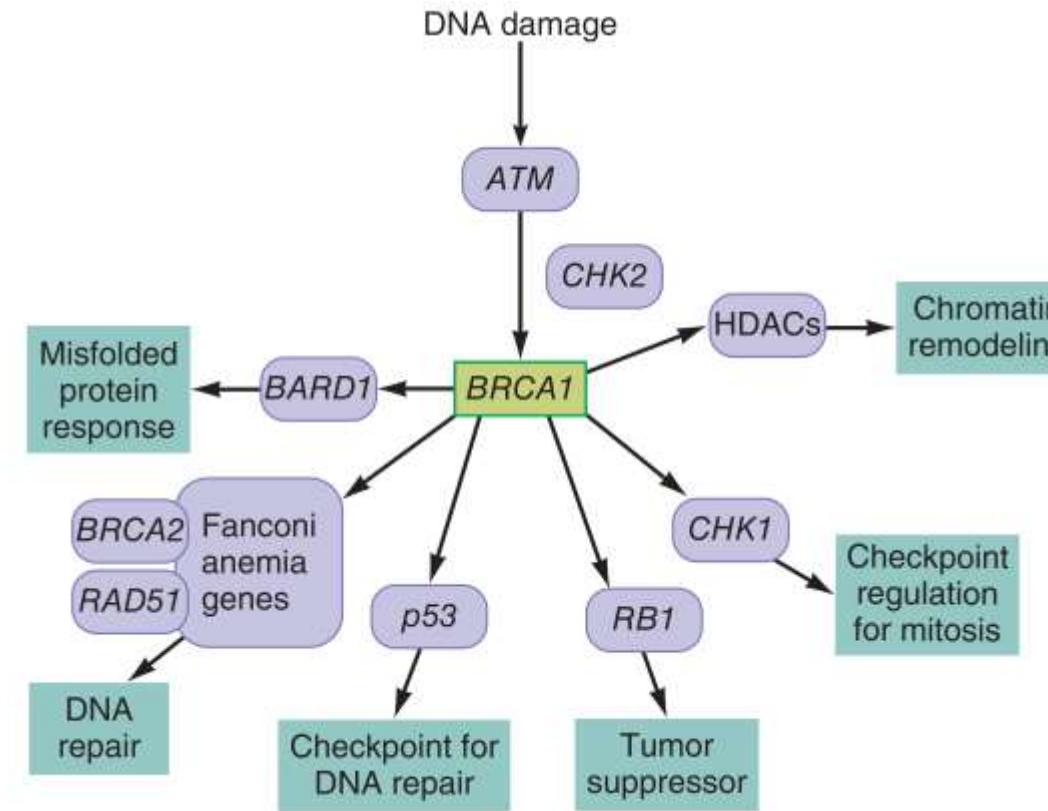


Figure 18.17 The *BRCA1* gene controls many cellular defense mechanisms. *BRCA1* functions as a genetic crossroads in handling DNA damage. Inheriting a *BRCA1* mutation increases susceptibility to several cancers (breast, ovary, cervix, uterine tube, uterus, peritoneum, pancreas, and prostate gland). Mutations in any of the genes with which it interacts increases cancer susceptibility too. (Italicized abbreviations indicate genes. HDACs are histone deacetylases.)

TSG: BRCA1 & BRCA2

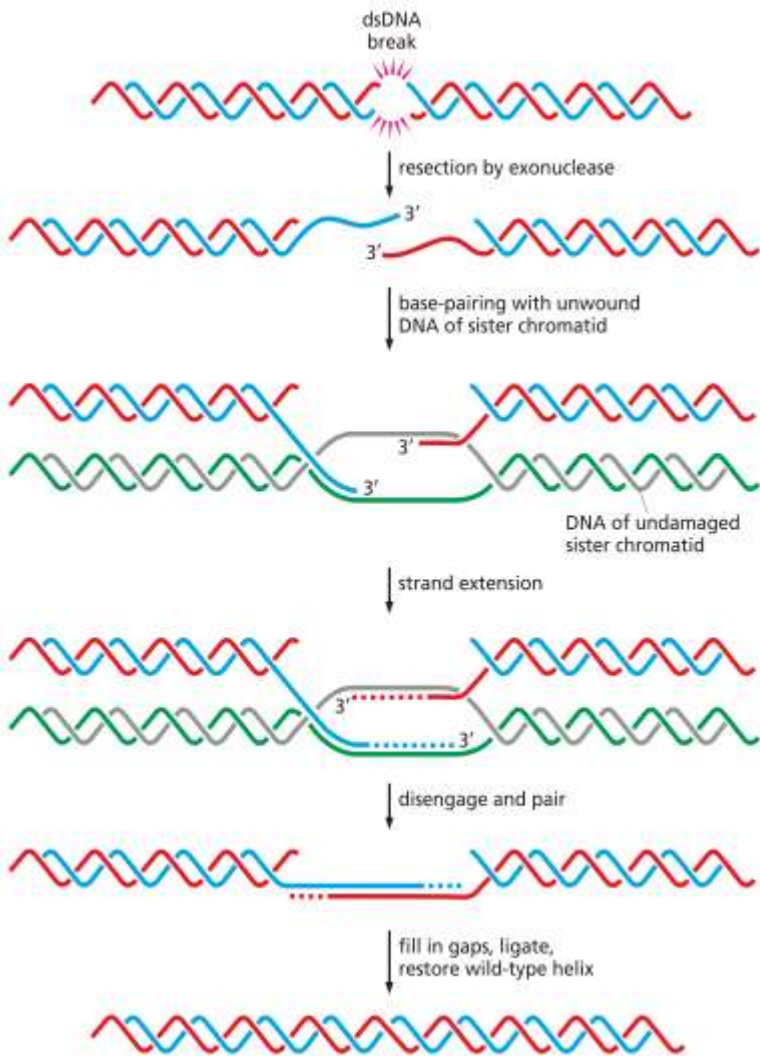


Figure 12.31 Homology-directed repair The repair of dsDNA breaks during the late S phase and G₂ phase of the cell cycle often depends on the ability of the repair apparatus to consult the sequences in the undamaged sister chromatid that was formed, together with the damaged chromatid, during the most recent S phase. Such homology-directed repair (HR) begins (top) with the resection (removal) by an exonuclease of one of the two DNA strands at each of the ends formed by a dsDNA break. Each of the resulting ssDNA strands (blue, red) then invades the undamaged sister chromatid, whose double helix (green, gray) has been unwound by the repair apparatus in order to accommodate the pairing of the invading ssDNA strands with complementary sequences in the undamaged sister chromatid. The ssDNA strands from the damaged chromatid are then elongated in a 5'-to-3' direction by a DNA polymerase, using the strands of the sister chromatid's DNA as templates. Thereafter, the extended ssDNA strands are released from the sister chromatid and caused to pair with one another, allowing further elongation by a DNA polymerase and a ligase, which together reconstruct a double helix possessing wild-type DNA sequences. Included among the DNA repair proteins known or thought to facilitate these complex steps of HR are RAD51, BRCA1, and BRCA2.

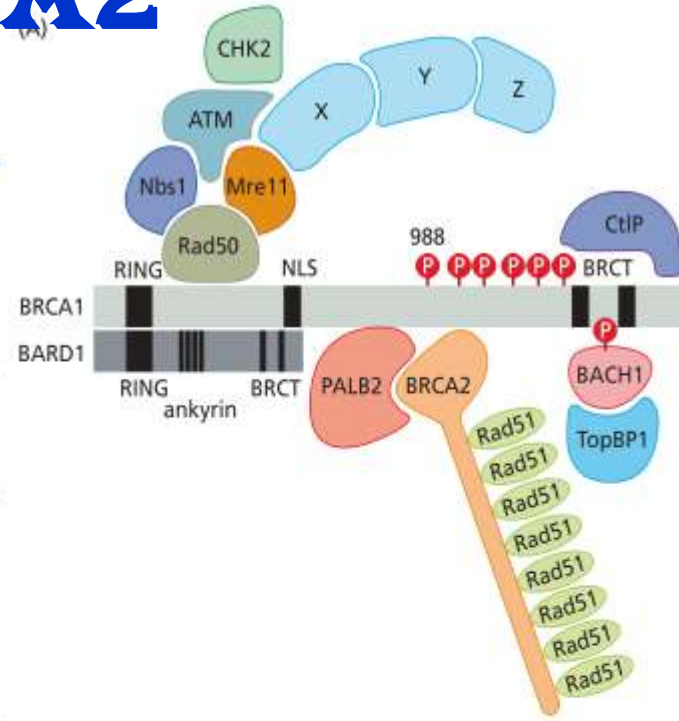
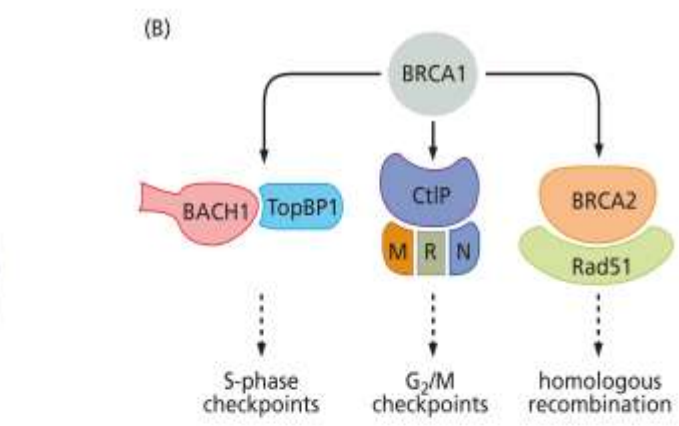


Figure 12.33 BRCA1, BRCA2, and their partners (A) The BRCA1 and BRCA2 proteins act, at least in part, as scaffolds to assemble a cohort of other DNA repair proteins into large physical complexes. Once assembled, these multiprotein complexes aid in the repair of dsDNA breaks, usually via homology-directed repair (HR). For example, one exon of the *BRCA2* gene encodes eight copies of a "BRC domain" (not shown); these aid in the recruitment of multiple RAD51 molecules, which form filaments and coat ssDNA strands as part of the HR process illustrated in Figure 12.31. The MRN complex, composed of MRE11, Rad50, and Nbs1, appears able to recognize the end created by a dsDNA break and to activate ATM kinase function in response. BRCA1 acts in different situations and locales (see panel B) as a scaffold for a variety of alternative partners, not all of which are concomitantly bound to BRCA1; for this reason, this image depicts a single complex that never



exists in a living cell. Moreover, this image does not capture the full complexity of BRCA1-associated proteins. For example, in the hydroxyurea-induced nuclear spots containing stalled replication forks (see Figure 12.29A), additional proteins have been discovered beyond those depicted, including MDC1, RPA32, γ-H2AX, RNF8, RNF168, 53BP1, FANCD2, and FANCI. (B) The loss of different partners of BRCA1 specifically affects different checkpoint controls in the cell cycle, in addition to compromising the processes of homologous recombination and homology-directed repair (HR). This illustrates the central role that BRCA1 plays as a scaffolding for a diverse array of proteins mediating a variety of processes involving DNA function. The checkpoint controls ensure that a cell halts before either S or M phase of the cell cycle if its genome carries significant unrepaired lesions, such as DSBs (see Figure 8.4). (A and B, courtesy of R.A. Greenberg and D.M. Livingston.)

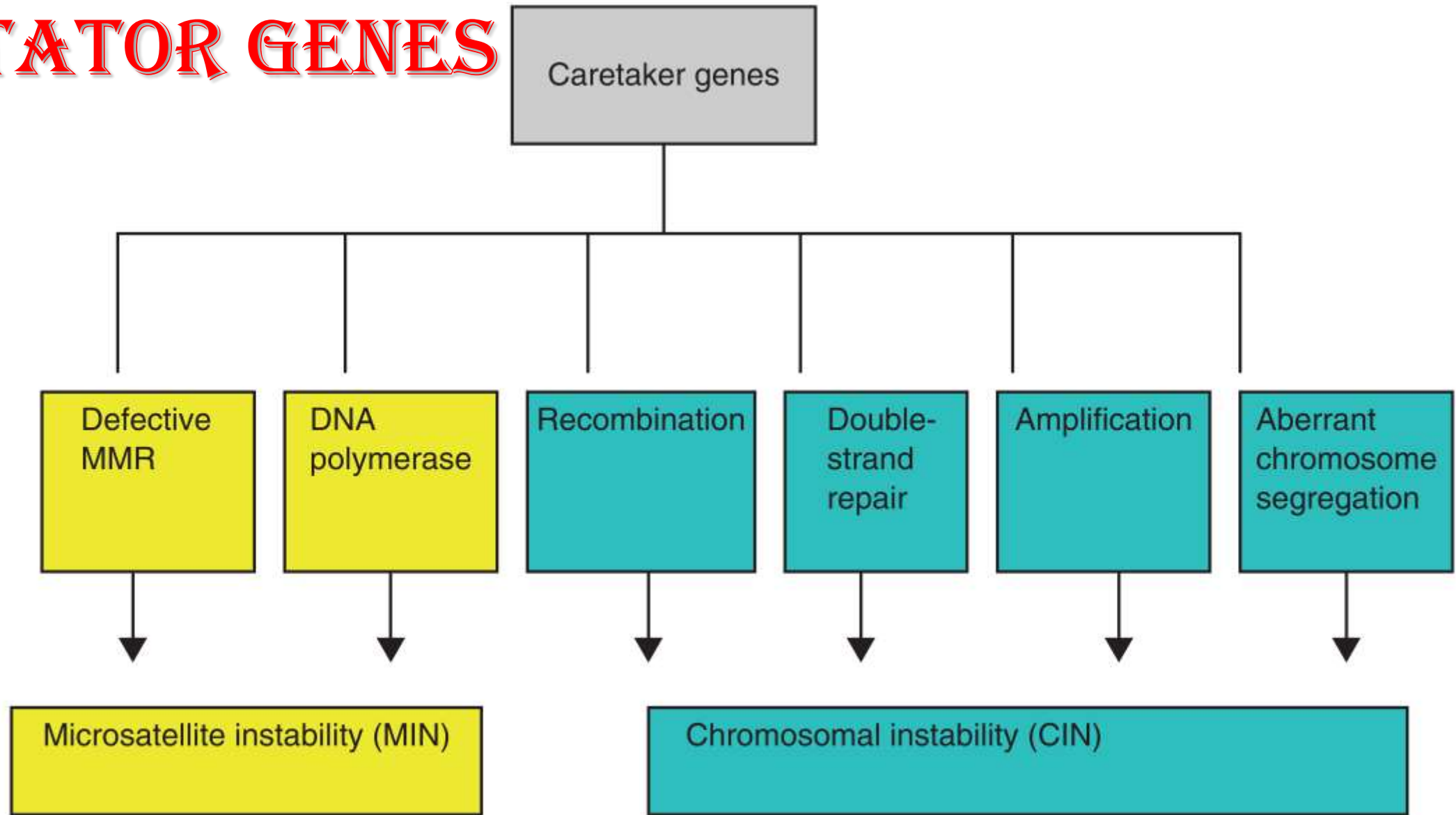
MUTATOR GENES

1. A gene that increases the spontaneous mutation rate when it is mutated is a mutator gene.
Wild-type mutator gene products are involved in DNA replication and repair, so mutations make the cell error-prone.

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2. **An example is hereditary nonpolyposis colon cancer (HNPCC).**
 - a. HNPCC results from an autosomal dominant allele that causes early onset of colorectal cancer in which no adenomas (polyps) form.
 - b. In humans, a mutation in any one of four genes (hMSH2, hMLH1, hPMS1 and hPMS2) gives hereditary predisposition to HNPCC.
 - c. A mutation in the single normal allele for any of these genes results in cancer, so its inheritance follows a dominant pattern.
 - d. All four genes have homologs in yeast and E. coli that are involved in DNA repair, and 1 of the human genes (hMSH2) has been shown to be active in E. coli through complementation.
 - e. DNA-based blood tests are available for all four genes, allowing carriers to be detected.

MUTATOR GENES



Potential causes of the "mutator" phenotype. Mutations in multiple pathways can result in the mutator phenotype in cancer cells.

Disease	DNA-Repair System Affected	Sensitivity	Cancer Susceptibility	Symptoms
PREVENTION OF POINT MUTATIONS, INSERTIONS, AND DELETIONS				
Hereditary nonpolyposis colorectal cancer	DNA mismatch repair	UV irradiation, chemical mutagens	Colon, ovary	Early development of tumors
Xeroderma pigmentosum	Nucleotide excision repair	UV irradiation, point mutations	Skin carcinomas, melanomas	Skin and eye photosensitivity, keratoses
REPAIR OF DOUBLE-STRAND BREAKS				
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Bloom's syndrome	Repair of double-strand breaks by homologous recombination	Mild alkylating agents	Carcinomas, leukemias, lymphomas	Photosensitivity, facial telangiectases, chromosome alterations
Fanconi anemia	Repair of double-strand breaks by homologous recombination	DNA cross-linking agents, reactive oxidant chemicals	Acute myeloid leukemia, squamous-cell carcinomas	Developmental abnormalities including infertility and deformities of the skeleton; anemia
Hereditary breast cancer, BRCA1 and BRCA2 deficiency	Repair of double-strand breaks by homologous recombination		Breast and ovarian cancer	Breast and ovarian cancer

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