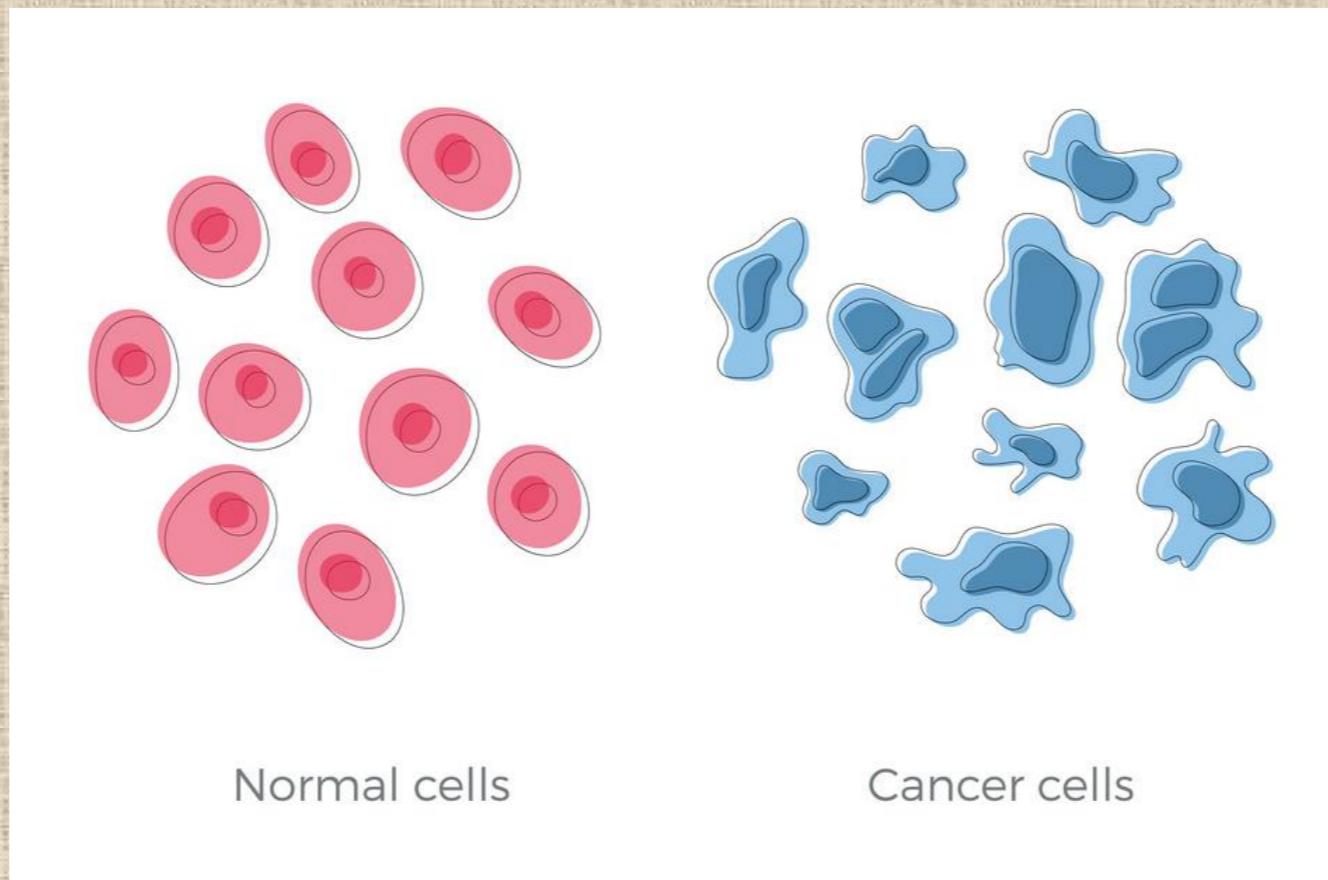


Biology of Cancer

Introduction



Cancer cells grow and divide at an abnormally rapid rate, are poorly differentiated, and have abnormal membranes, cytoskeletal proteins, and morphology. The abnormality in cells can be progressive with a slow transition from normal cells to benign tumors to malignant tumors.

In 2000 cancer biologists Robert Weinberg and Douglas Hanahan published an article entitled "The Hallmarks of Cancer." [Cell 2000;100(1):57-70] While they recognized that cancers occurred through a series of mutations in any of many genes. Despite this, they listed six essential alterations in cell physiology that characterized malignancy.

1. Self-sufficiency in growth signals: cancer cells acquire an autonomous drive to proliferate - pathological mitosis - by virtue of the activation of oncogenes such as ras or myc.
2. Insensitivity to growth-inhibitory (antigrowth) signals: cancer cells inactivate tumor suppressor genes, such as Rb, that normally inhibit growth.
3. Evasion of programmed cell death (apoptosis): cancer cells suppress and inactivate genes and pathways that normally enable cells to die.
4. Limitless replication potential: cancer cells activate specific gene pathways that render them immortal even after generations of growth.
5. Sustained angiogenesis: cancer cells acquire the capacity to draw out their own supply of blood and blood vessels - tumor angiogenesis.
6. Tissue invasion and metastasis: cancer cells acquire the capacity to migrate to other organs, invade other tissues, and colonize these organs, resulting in their spread throughout the body.

CANCERS

BY
BODY LOCATION/SYSTEM

Oral cavity
cancer



Gastrointestinal
cancer



Lymph node
cancer



Lung cancer



Stomach cancer



Liver cancer



Leukemia



Colon cancer



Bladder cancer



Prostate cancer



Oral cavity
cancer

Lymph node
cancer

Breast cancer

Thyroid cancer

Lung cancer

Stomach cancer

Liver cancer

Colon cancer

Leukemia

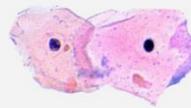
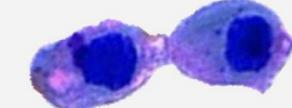
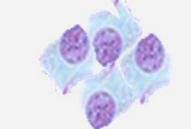
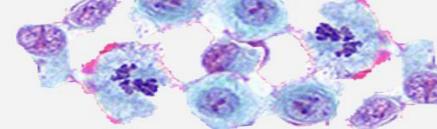
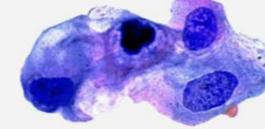
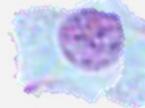
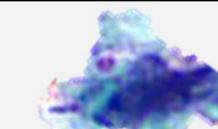
Bladder cancer

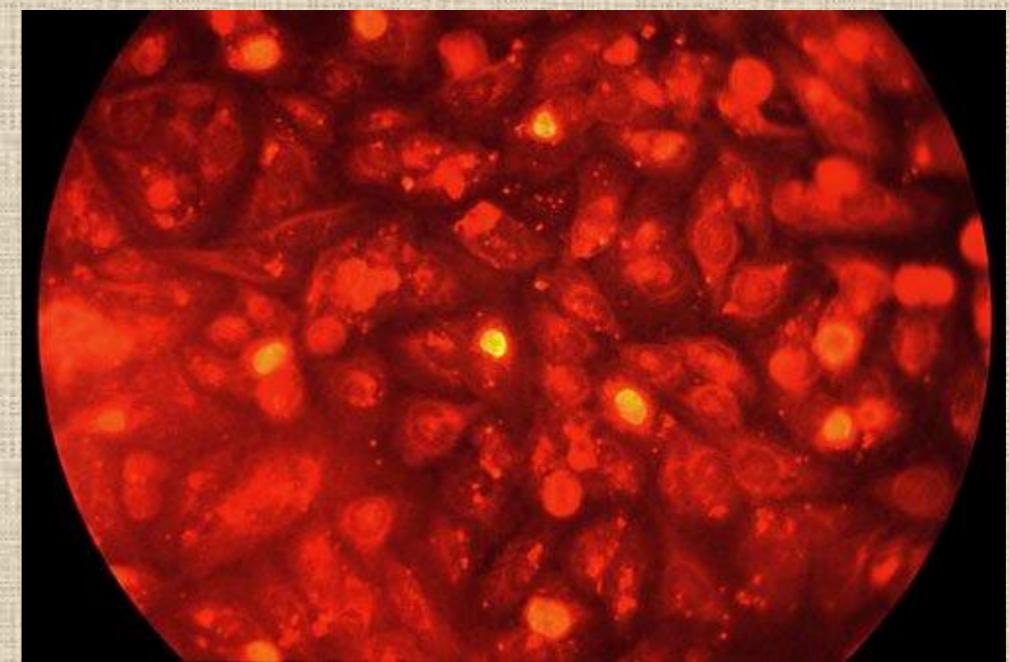
Uterine cancer

Ovarian cancer

Cervical cancer

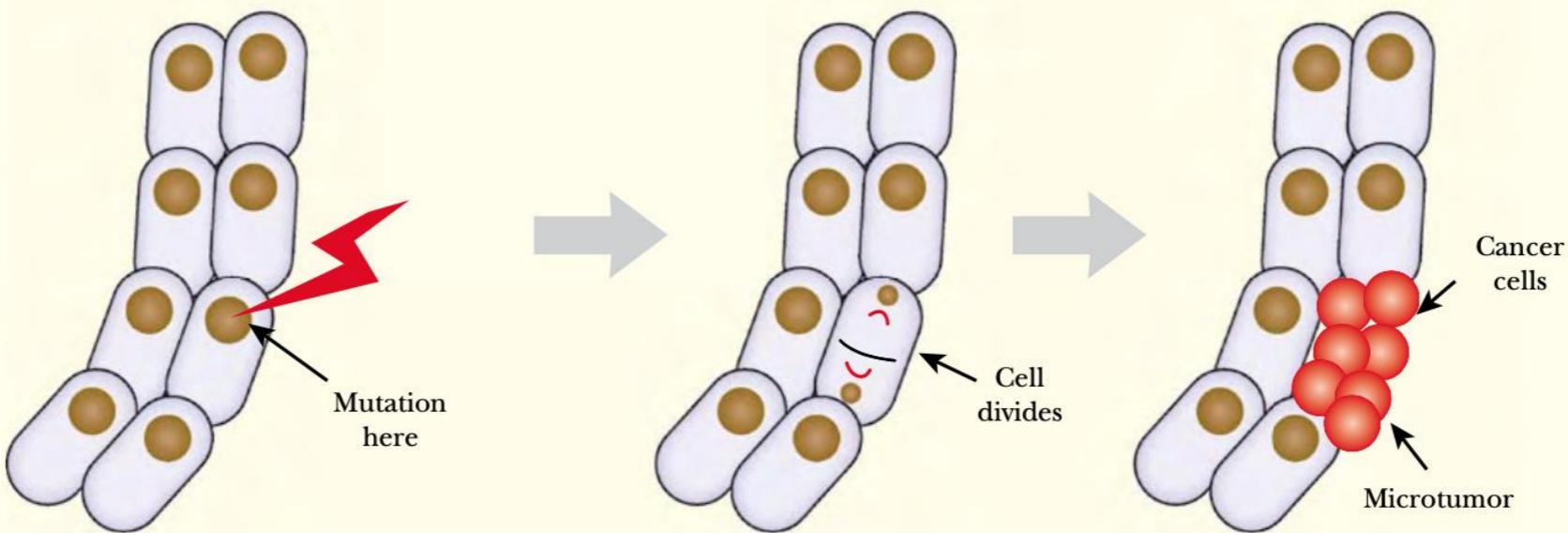
Introduction

Normal	Cancer	
		Large, variably shaped nuclei
		Many dividing cells; Disorganized arrangement
		Variation in size and shape
		Loss of normal features



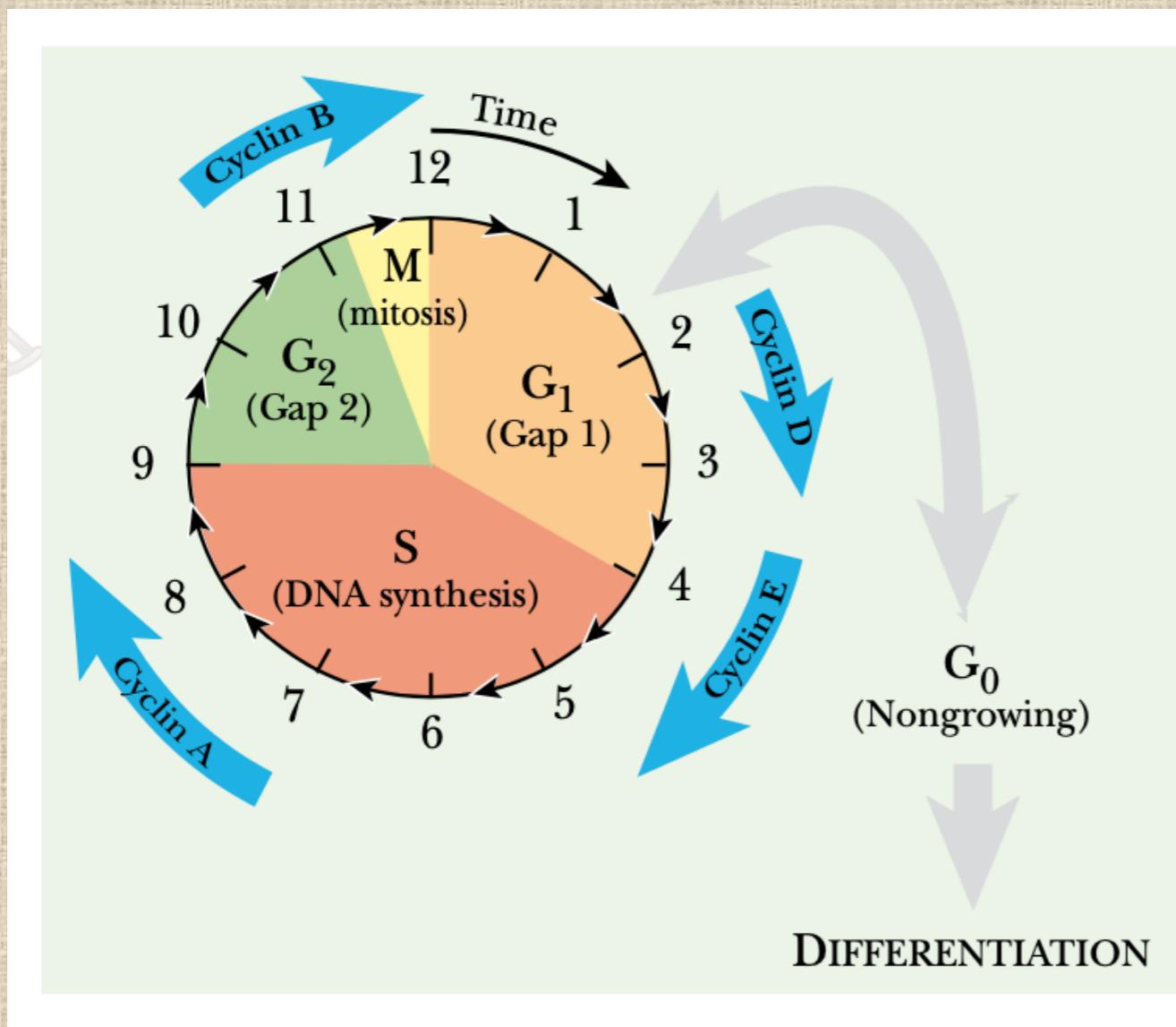
HeLa cell, a cancerous cell belonging to a strain continuously cultured since its isolation in 1951 from a patient suffering from cervical carcinoma. The designation HeLa is derived from the name of the patient, Henrietta Lack. HeLa cells were the first human cell line to be established and have been widely used in laboratory studies, especially in research on viruses, cancer and human genetics.

B) CANCER



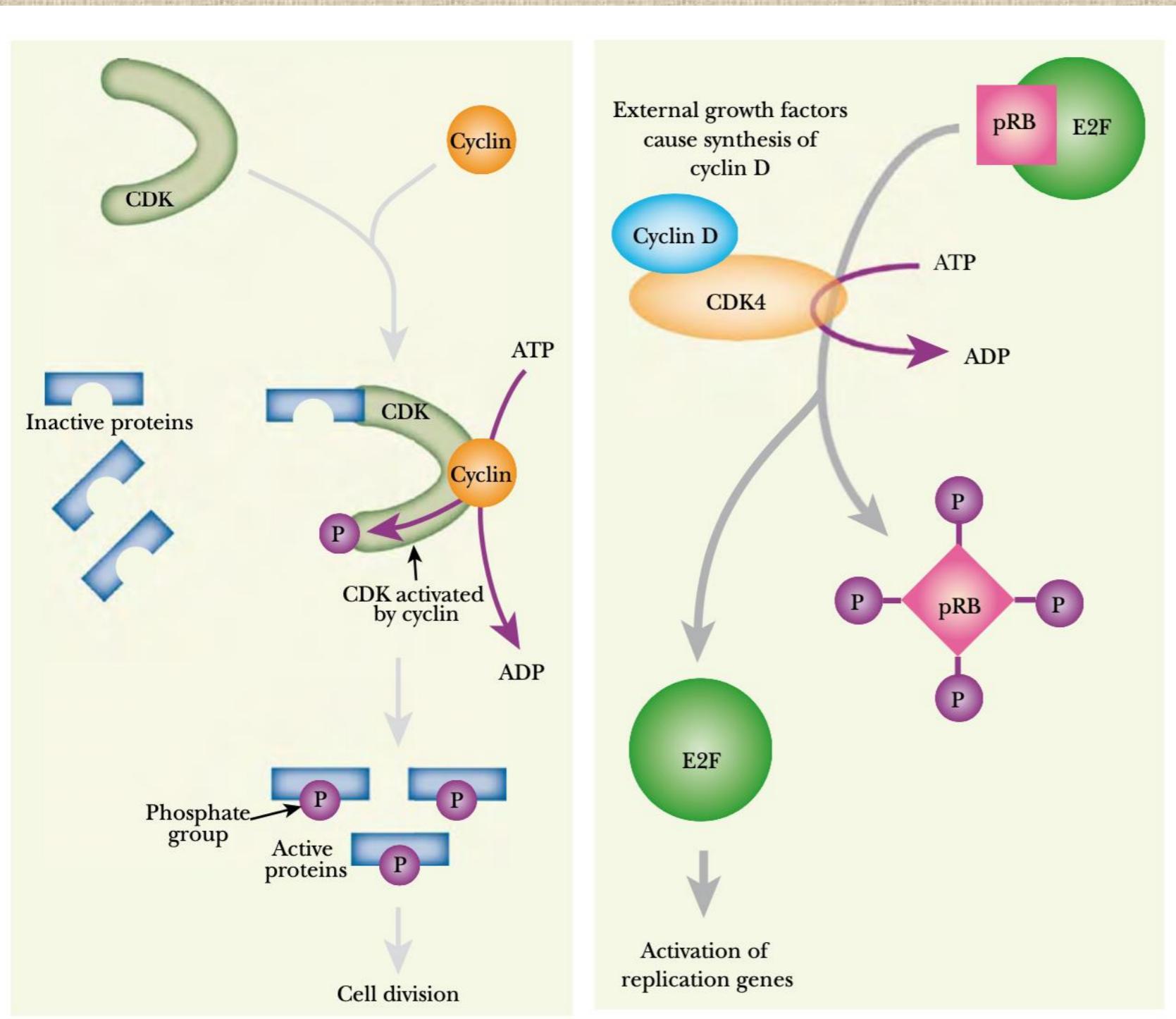
Cancer Is Caused by Somatic Mutations

Cancer occurs when a somatic cell mutates because of errors during DNA replication or exposure to a carcinogen. The mutation allows division in a cell that should no longer divide. The mutant cells keep dividing to form a microtumor.



Eukaryotic Cell Cycle: division versus differentiation

The cell cycle normally consists of the four stages G₁, S, G₂, and M. However, if the conditions are right, rather than going from G₁ into the S phase, the cell may differentiate and enter G₀. If the cell does not differentiate, a signal is received from cyclin D and E, and the cell enters S phase and replicates its DNA. After about 5 hours another signal from cyclin A triggers the cell to enter G₂. After cyclin B becomes active, the cell enters mitosis and divides.

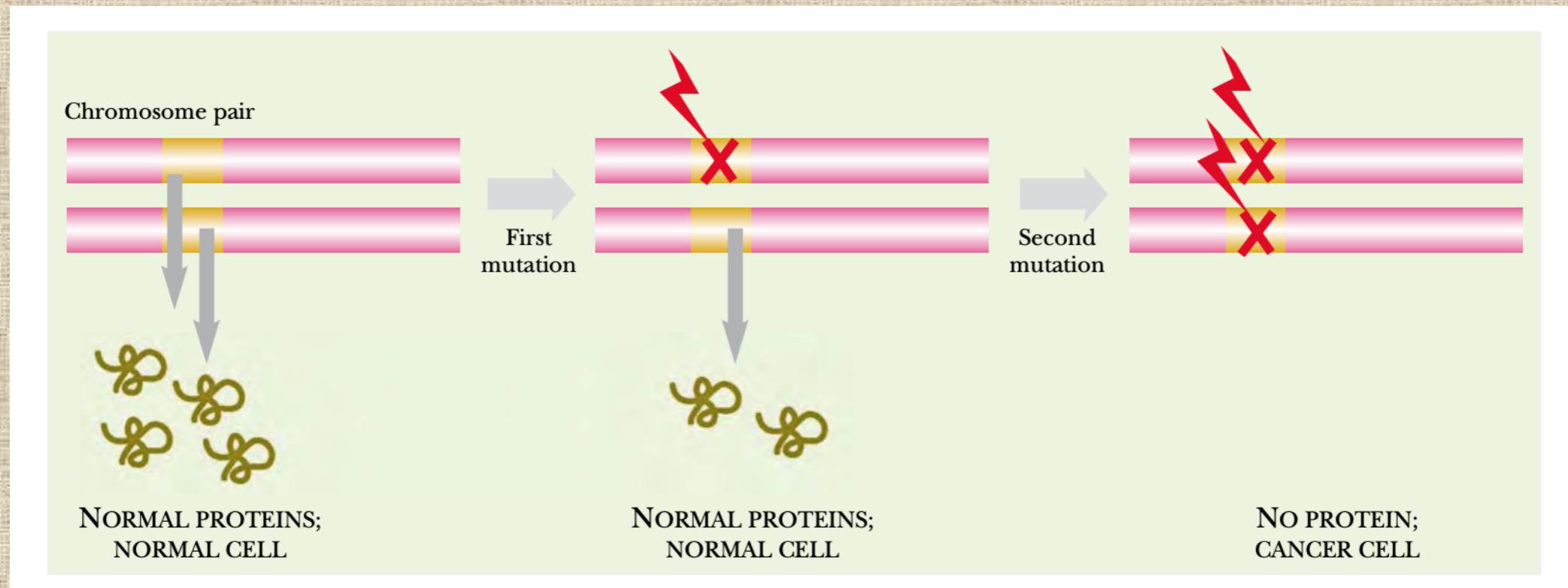


Control of G₁ to S Transition by pRB and E2F

At the end of G₁, cyclin D must be activated to initiate transition into S phase. This requires binding of cyclin D to its partner, CDK4. Once they are together, ATP is hydrolyzed and a phosphate is transferred to the cyclinD/CDK4 complex. This phosphate is then transferred to pRB, which releases E2F to transcribe genes needed to initiate DNA replication.

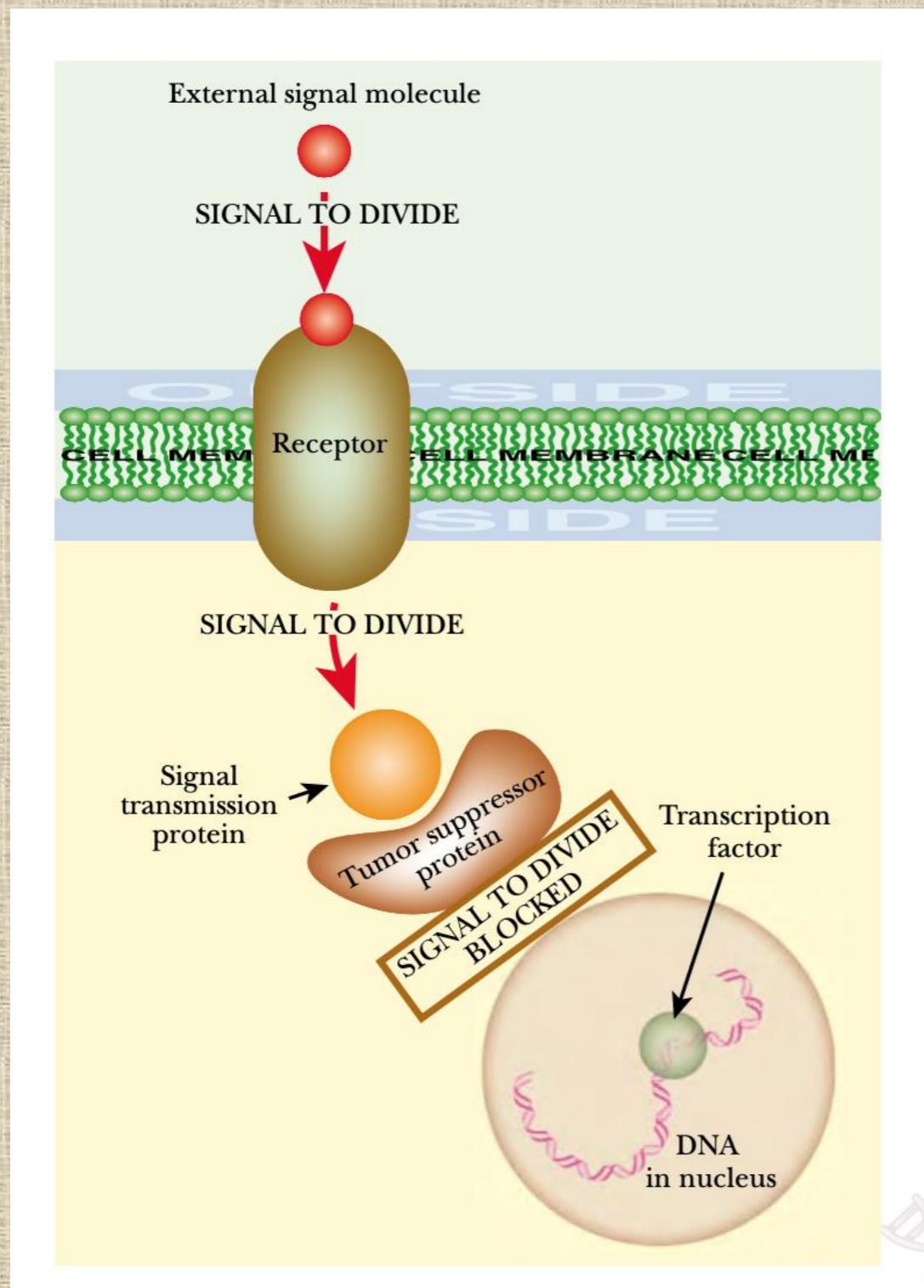
Cyclins Operate via Cyclin-Dependent Kinases

Before each cell can enter a new phase of the cell cycle, the cyclin must complex with a cyclin-dependent kinase (CDK). Addition of a phosphate from ATP activates the cyclin/CDK complex. The active complex then transfers the phosphate to other proteins that execute cell division.



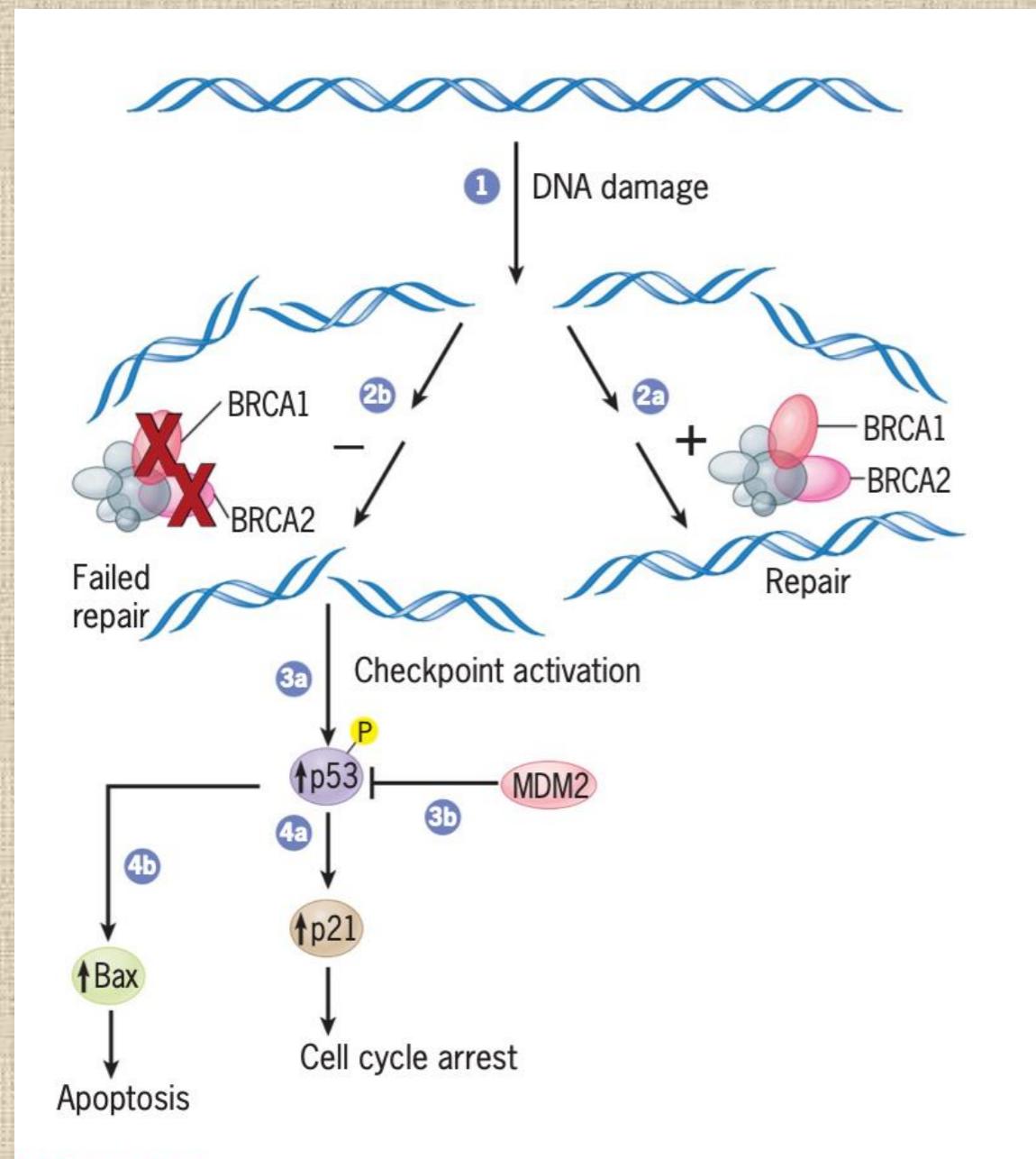
Mutations in Tumor-Suppressor Genes Are Recessive

In a normal situation, two wild-type anti-oncogenes are present. Two mutation events must occur to completely inactivate the anti-oncogene.



External Signal for Cell Division

Because growth-promoting signals often circulate in the blood, most cells in the body will be exposed to the growth cue. Only some cells divide, because proteins encoded by anti-oncogenes block transmission of the external stimulus. Anti-oncogene proteins may bind to signal transmission proteins and prevent them from activating transcription factors.



DNA damage initiates activity of a number of proteins encoded by both tumor-suppressor genes and proto-oncogenes.

In this simplified figure, DNA damage is seen to cause double-strand breaks in the DNA (step 1) that are repaired by a proposed multiprotein complex that includes BRCA1 and BRCA2 (step 2a). Mutations in either of the genes that encode these proteins can block the repair process (step 2b). If DNA damage is not repaired, a checkpoint is activated that leads to a rise in the level of p53 activity (step 3a). The p53 protein is normally inhibited by interaction with the protein MDM2 (step 3b). p53 is a transcription factor that activates expression of either (1) the *p21* gene (step 4a), whose product (p21) causes cell cycle arrest, or (2) the *BAX* gene (step 4b), whose product (Bax) causes apoptosis. p53 activation can also promote cellular senescence, but the pathway is unclear.

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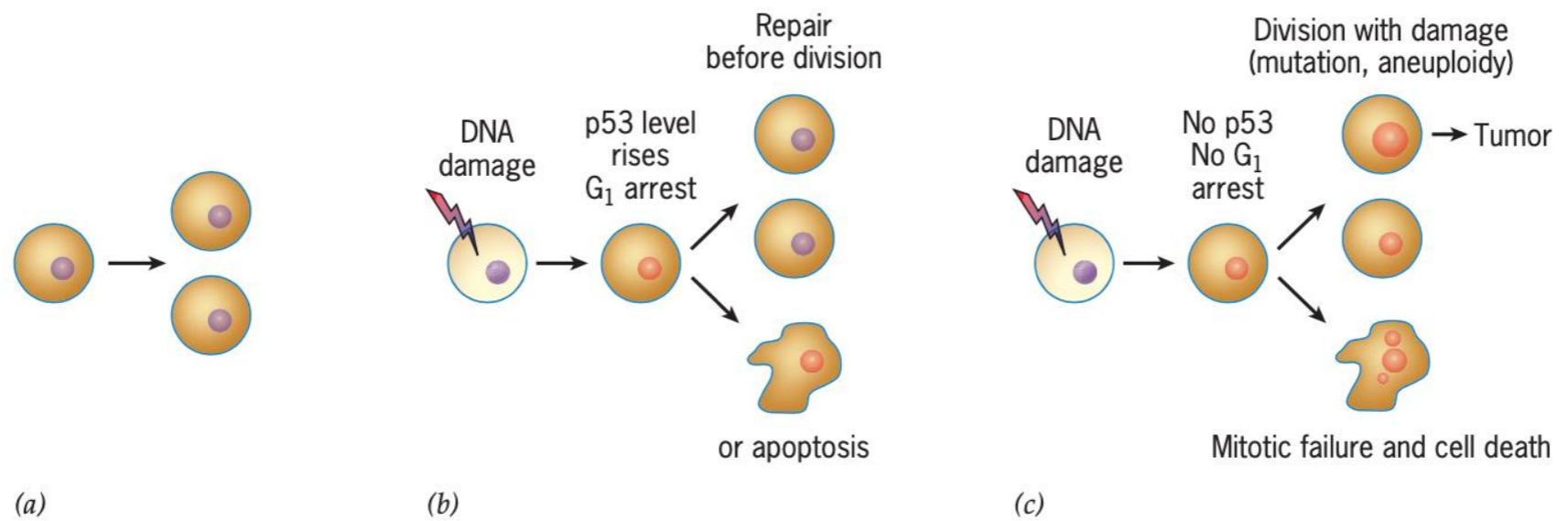
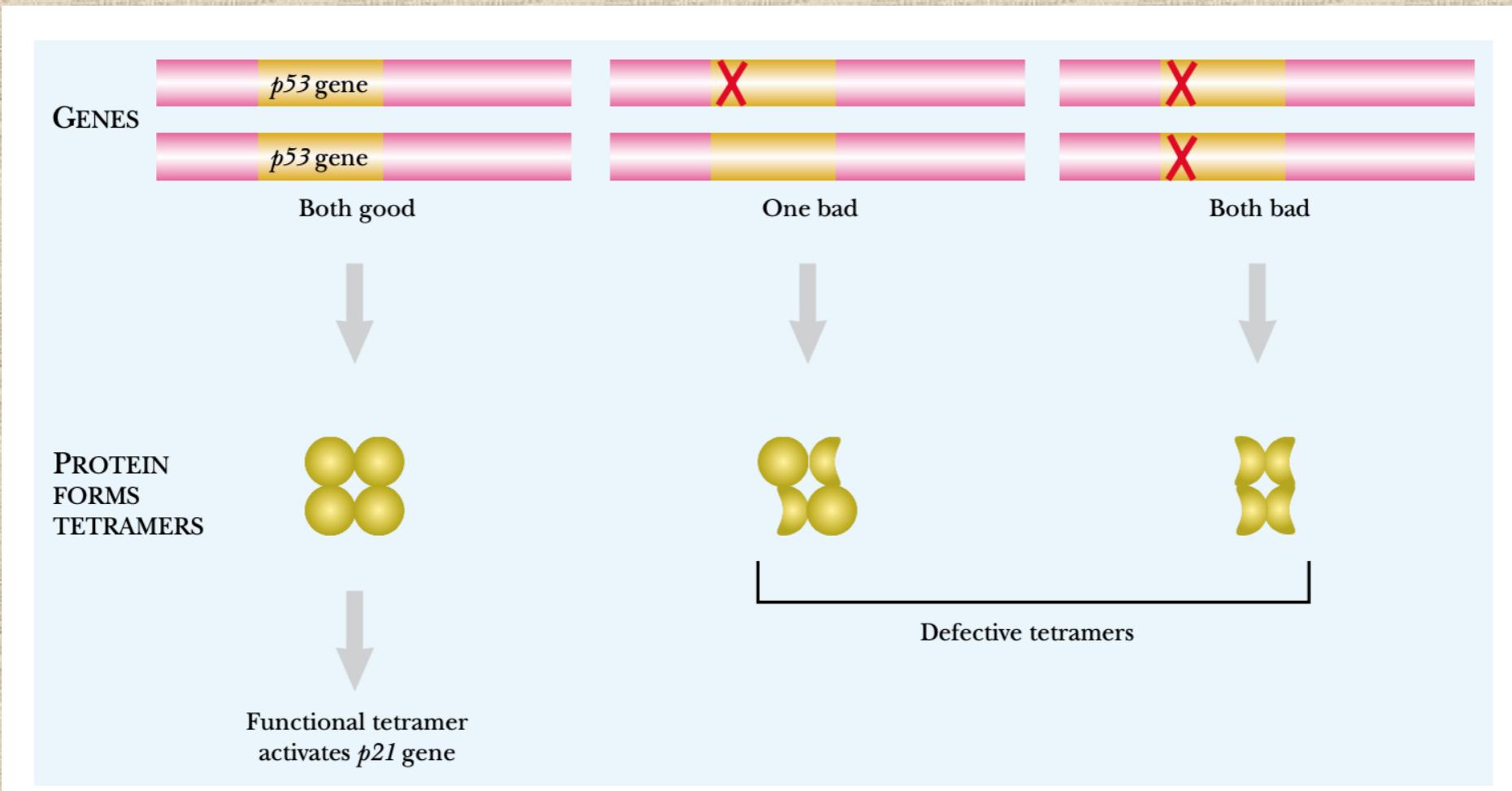


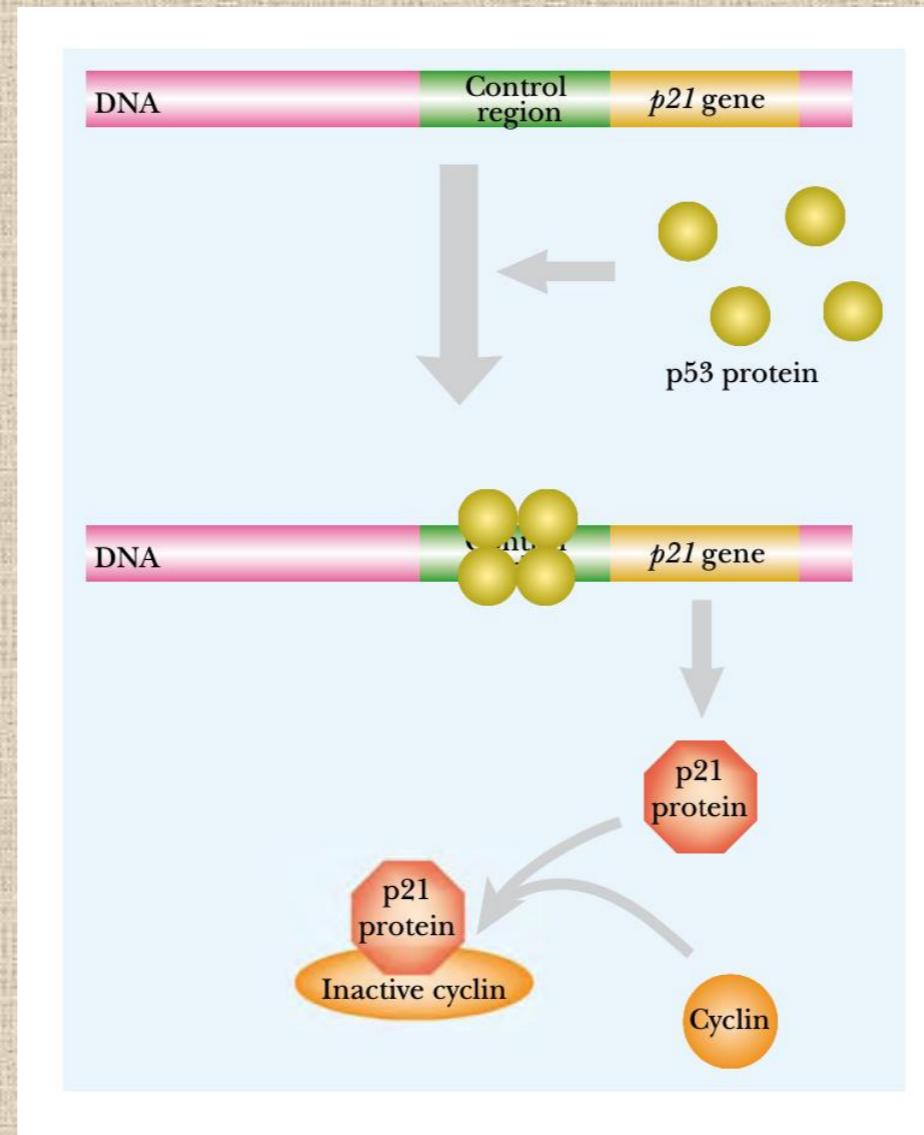
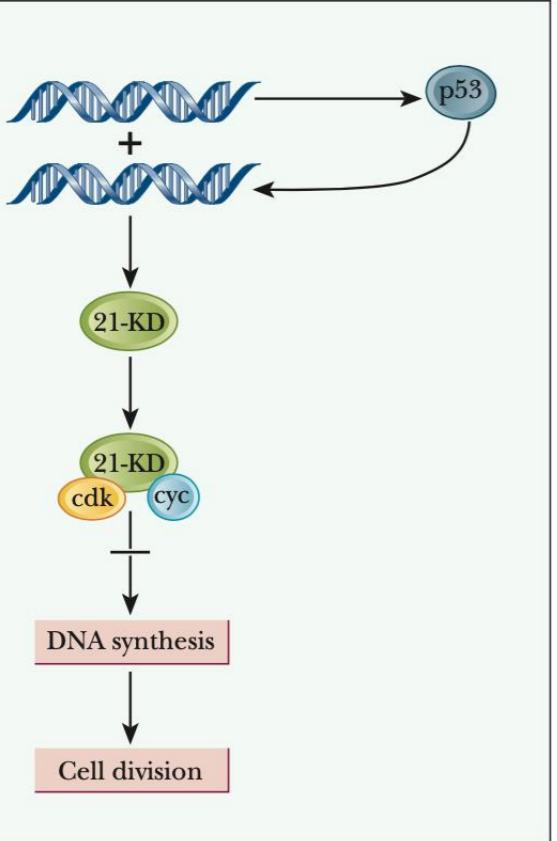
FIGURE 16.14 A model for the function of p53. (a) Cell division does not normally require the involvement of p53. (b) If, however, the DNA of a cell becomes damaged as the result of exposure to mutagens, the level of p53 rises and acts either to arrest the progression of the cell through G₁ or to direct the cell toward apoptosis. (c) If both copies of the TP53 gene are inactivated, the cell loses the ability to arrest the cell cycle or commit the cell to apoptosis following DNA damage. As a result, the cell either dies from mitotic failure or continues to proliferate with genetic abnormalities that may lead to the formation of a malignant growth.

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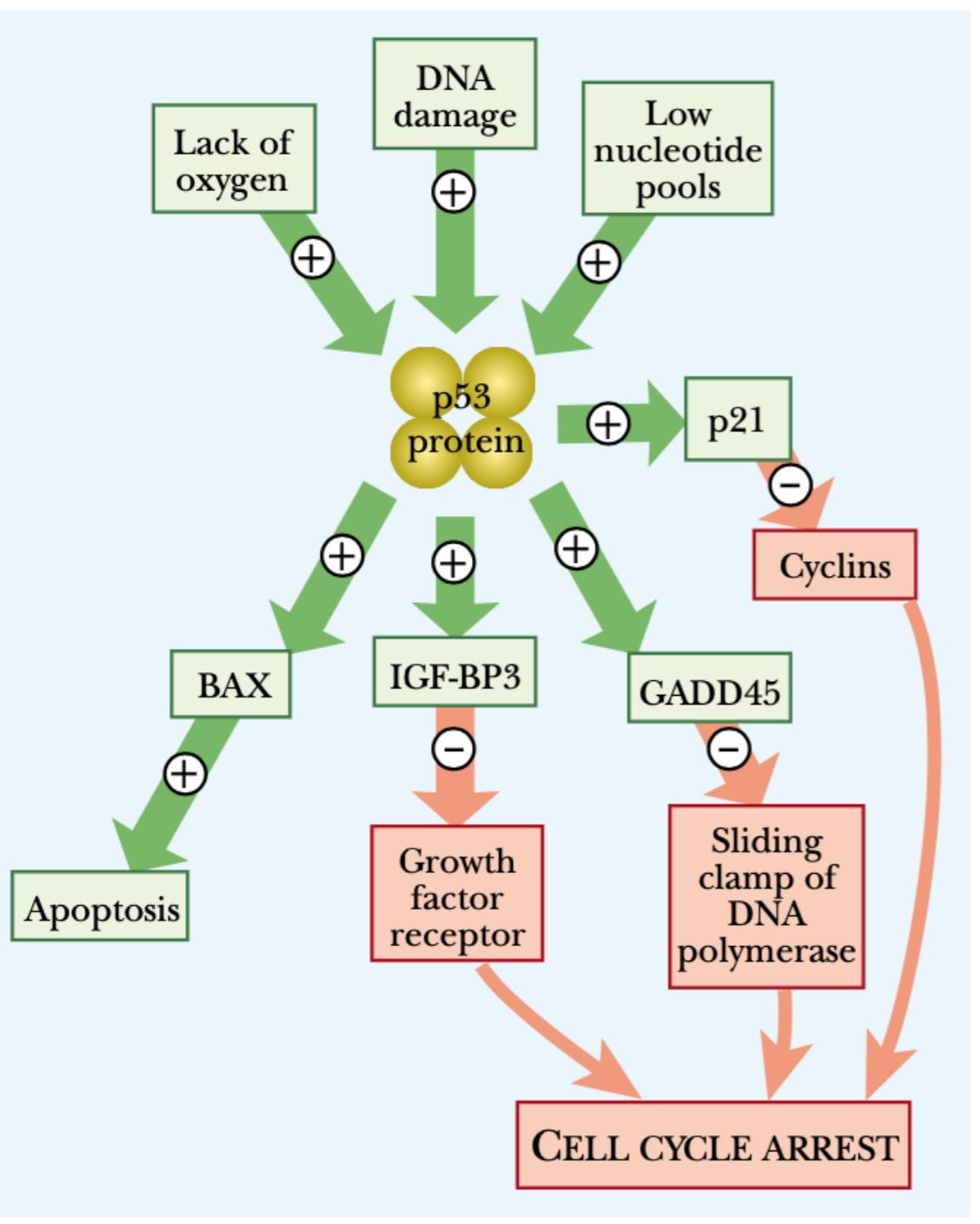
Mixed Tetramers of p53 Protein

Mutations in the *p53* gene are detrimental whether one or both copies are mutated. *p53* protein works as a tetramer, so even if only one of the alleles has a mutation, most of the tetramers are defective. *p53* only functions correctly if all four subunits of the tetramer are normal.

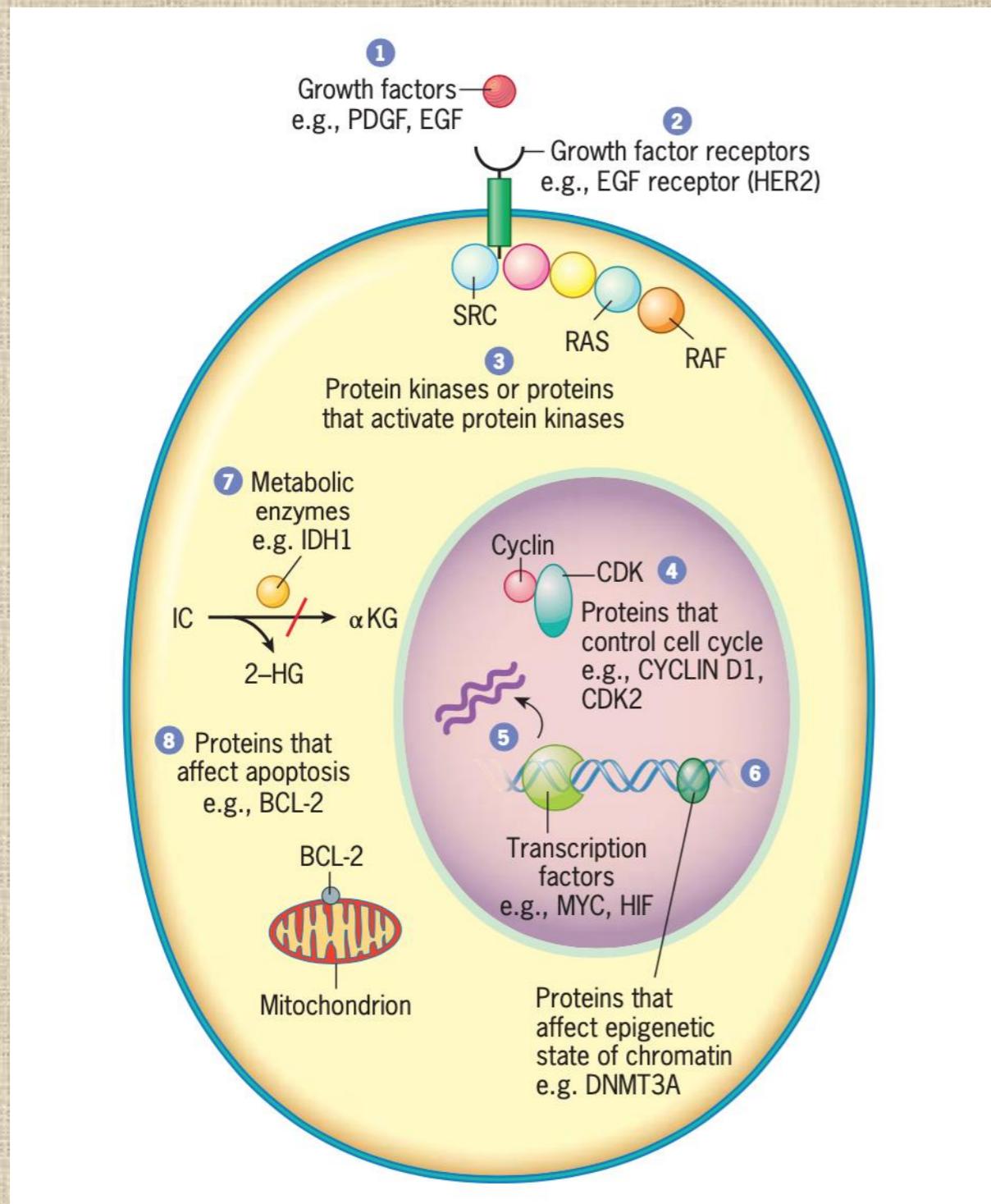


p53 and p21 Block the Cell Cycle

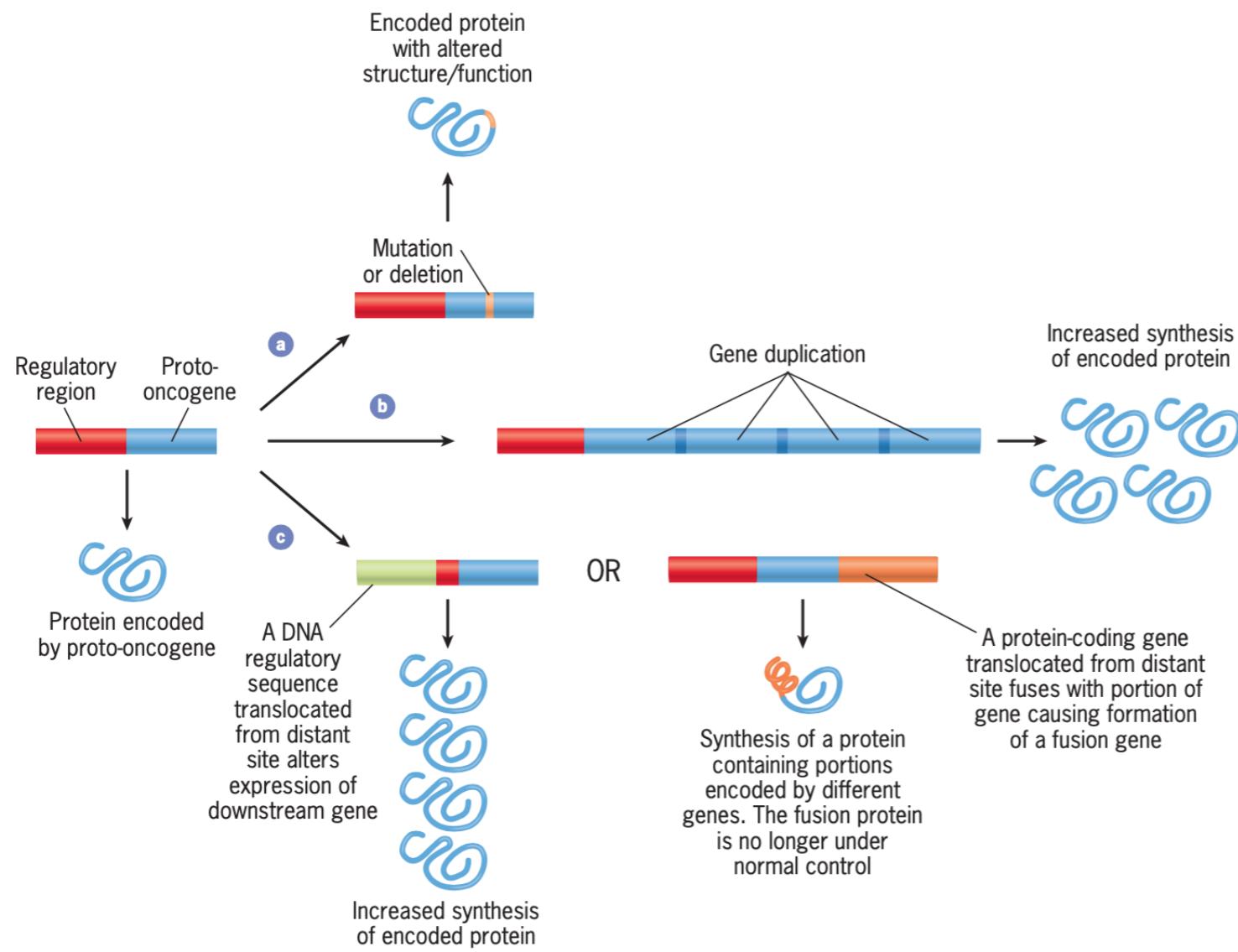
When a cell senses DNA damage, the p53 protein forms active tetramers that bind to the control region of the *p21* gene. p53 stimulates the transcription and translation of p21 protein. The p21 protein then binds to and inactivates the cyclins, preventing progression of the cell cycle.



Central Role of p53 Three possible cues activate p53 protein: lack of oxygen, DNA damage, and low nucleotide pools. Activated p53 affects many different targets. If there is severe damage, p53 activates Bax protein and programmed cell death. Otherwise, p53 activates cell cycle arrest by turning on p21, which in turn blocks the cyclins. Active p53 can also block synthesis by DNA polymerase through the action of GADD45. Active p53 also binds to growth factor receptors to block any further growth signals.



A schematic diagram summarizing the types of proteins encoded by proto-oncogenes. These include growth factors (1), receptors for growth factors (2), protein kinases and the proteins that activate them (3), proteins that regulate the cell cycle (4), transcription factors (5), proteins that modify chromatin (6), metabolic enzymes (7), and proteins that inhibit apoptosis (8). Proteins involved in mitosis, tissue invasion, and metastasis are not included.



Activation of a proto-oncogene to an oncogene. Activation can be accomplished in several ways as indicated in this figure. In pathway a, a mutation in the gene alters the structure and function of the encoded protein. In pathway b, gene amplification results in overexpression of the gene. In pathway c, a rearrangement of the DNA brings a new DNA segment into the vicinity or up against the gene, altering either its expression or the structure of the encoded protein.

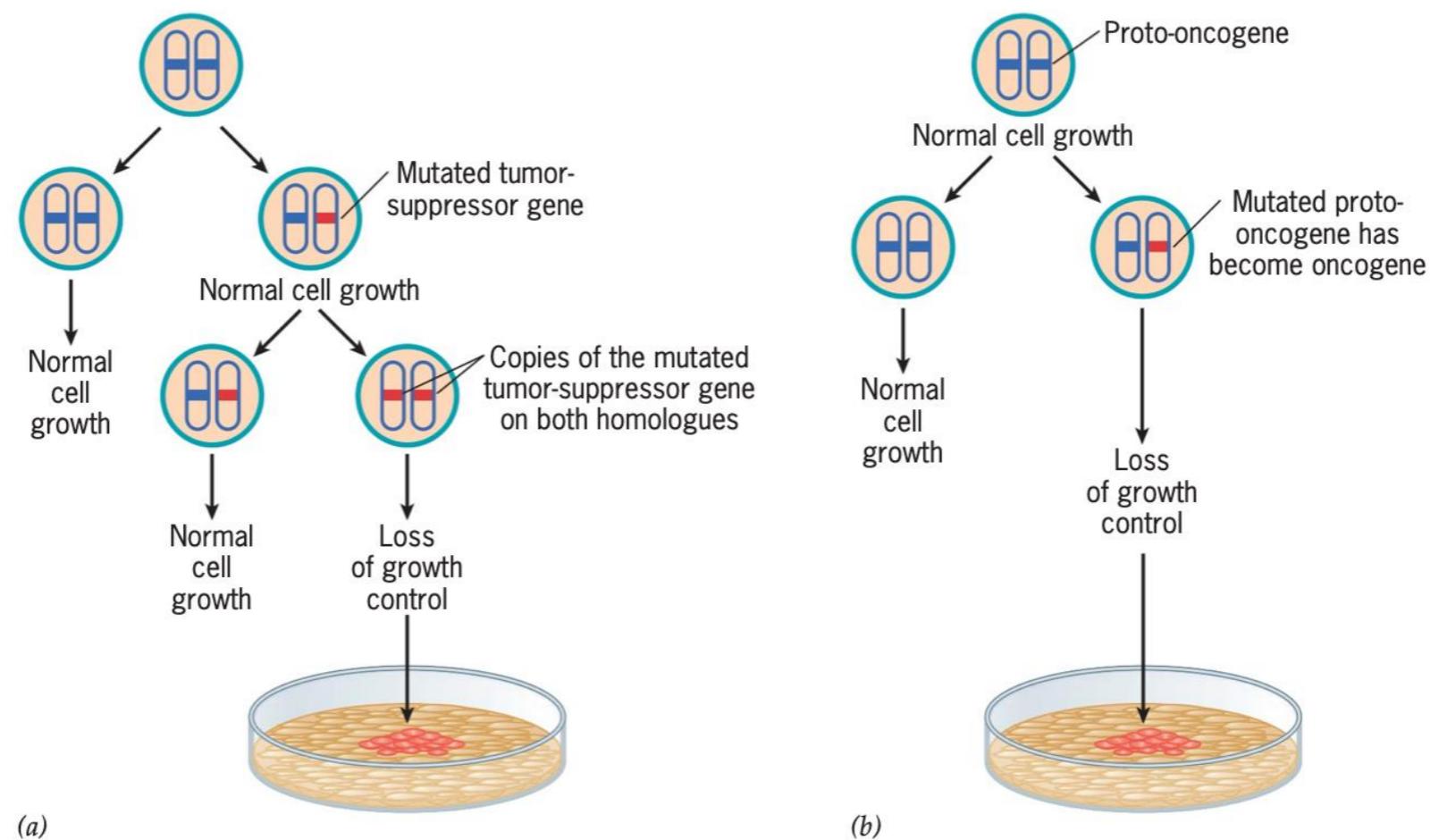


FIGURE 16.9 Contrasting effects of mutations in tumor-suppressor genes (a) and oncogenes (b). Whereas a mutation in one of the two copies (alleles) of an oncogene may be sufficient to cause a cell to lose growth control, both copies of a tumor-suppressor gene must be knocked out to induce the same effect. As discussed shortly, oncogenes arise from proto-oncogenes as the result of gain-of-function mutations, that is, mutations that cause the gene product to exhibit new functions that lead to malignancy. Tumor-suppressor genes, in contrast, suffer loss-of-function mutations and/or epigenetic inactivation that render them unable to restrain cell growth.

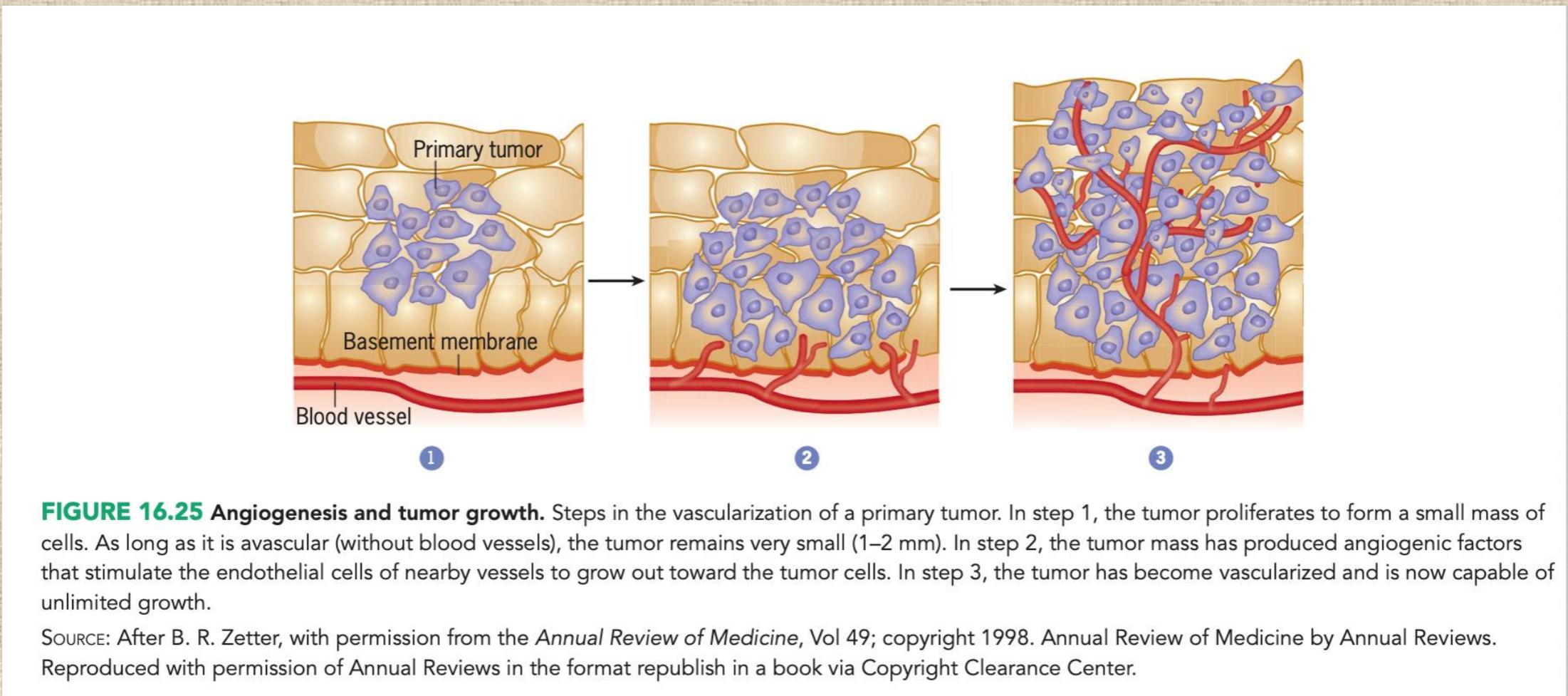


FIGURE 16.25 Angiogenesis and tumor growth. Steps in the vascularization of a primary tumor. In step 1, the tumor proliferates to form a small mass of cells. As long as it is avascular (without blood vessels), the tumor remains very small (1–2 mm). In step 2, the tumor mass has produced angiogenic factors that stimulate the endothelial cells of nearby vessels to grow out toward the tumor cells. In step 3, the tumor has become vascularized and is now capable of unlimited growth.

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TABLE 16.1 Tumor-Suppressor Genes

Gene	Primary tumor	Proposed function	Inherited syndrome
<i>APC</i>	Colorectal	Binds β -catenin acting as transcription factor	Familial adenomatous polyposis
<i>BRCA1</i>	Breast	DNA repair	Familial breast cancer
<i>MSH2, MLH1</i>	Colorectal	Mismatch repair	HNPPCC
<i>E-Cadherin</i>	Breast, colon, etc.	Cell adhesion molecule	Familial gastric cancer
<i>INK4a</i>	Melanoma, pancreatic	p16: Cdk inhibitor ARF: stabilizes p53	Familial melanoma
<i>NF1</i>	Neurofibromas	Activates GTPase of Ras	Neurofibromatosis type 1
<i>NF2</i>	Meningiomas	Links membrane to cytoskeleton	Neurofibromatosis type 2
<i>TP53</i>	Sarcomas, lymphomas, etc.	Transcription factor (cell cycle and apoptosis)	Li-Fraumeni syndrome
<i>PTEN</i>	Breast, thyroid	PIP ₃ phosphatase	Cowden disease
<i>RB</i>	Retinal	Binds E2F (cell cycle transcription regulation)	Retinoblastoma
<i>VHL</i>	Kidney	Protein ubiquitination and degradation	von Hippel-Lindau syndrome
<i>WT1</i>	Wilms tumor of kidney	Transcription factor	Wilms tumor

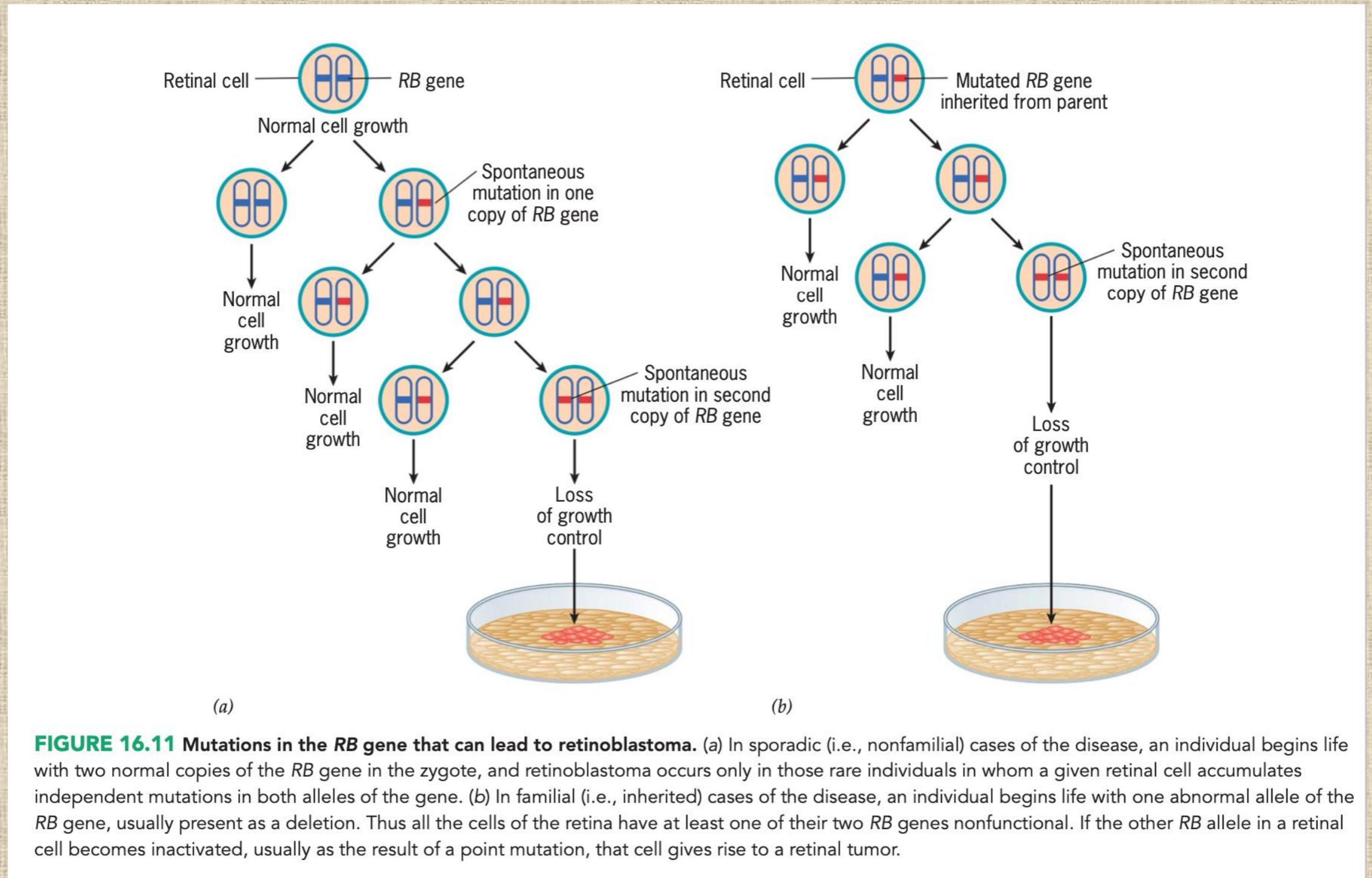
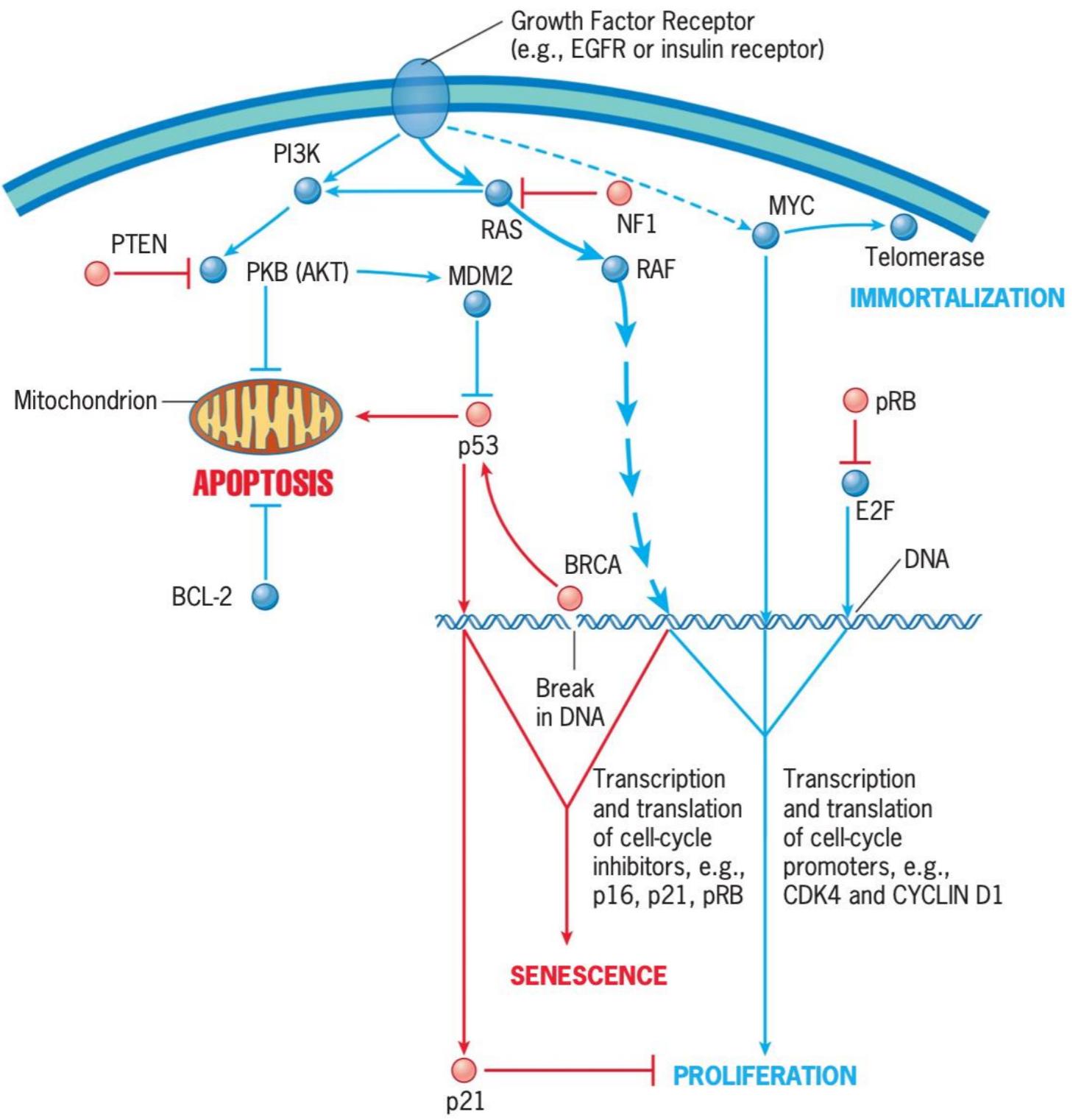
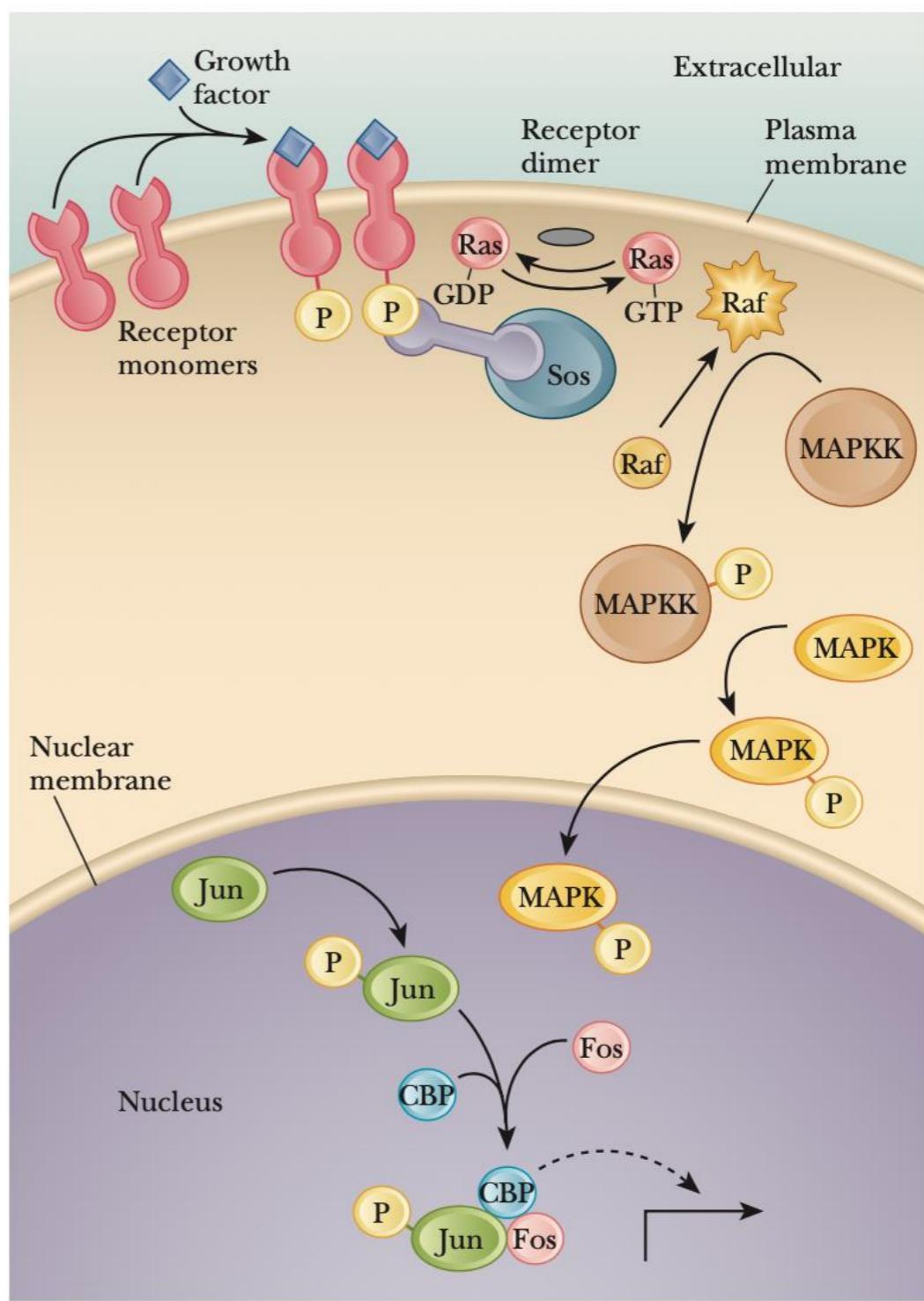


FIGURE 16.11 Mutations in the *RB* gene that can lead to retinoblastoma. (a) In sporadic (i.e., nonfamilial) cases of the disease, an individual begins life with two normal copies of the *RB* gene in the zygote, and retinoblastoma occurs only in those rare individuals in whom a given retinal cell accumulates independent mutations in both alleles of the gene. (b) In familial (i.e., inherited) cases of the disease, an individual begins life with one abnormal allele of the *RB* gene, usually present as a deletion. Thus all the cells of the retina have at least one of their two *RB* genes nonfunctional. If the other *RB* allele in a retinal cell becomes inactivated, usually as the result of a point mutation, that cell gives rise to a retinal tumor.



An overview of several of the signaling pathways involved in tumorigenesis. Tumor suppressors and tumor suppression are shown in red, whereas onco- genes and tumor stimulation are shown in blue. Arrows indicate activation, perpendicular lines indicate inhibition. Among the proteins depicted in this figure are transcription factors (p53, MYC, and E2F), a transcriptional coactivator or corepressor (pRB), a lipid kinase (PI3K) and lipid phosphatase (PTEN), a cytoplasmic tyrosine kinase (RAF) and its activator (RAS), a GTPase activating protein for RAS (NF1), a protein kinase that promotes cell survival (PKB/AKT), a protein that senses DNA breaks (BRCA), subunits of a cyclin-dependent kinase (CYCLIN D1 and CDK4), a Cdk inhibitor (p21), an antiapoptotic protein (BCL-2), a ubiquitin ligase (MDM2), an enzyme that elongates DNA (telomerase), and a protein that binds growth factors (e.g., EGFR). The arrows and lines do not necessarily represent direct activation or inhibition. For example, PTEN inhibits PKB through removal of a phosphate from PIP₃ and EGFR activates RAS via GRB2 and SOS. The dashed line indicates indirect action by activation of expression of the MYC gene. **Iwasa and Marshall 2016**

FIGURE 14.25 MAP kinase signal transduction. Signal transduction starts when a growth factor (blue) binds to a receptor monomer (red) on the cell membrane. The receptor is a tyrosine kinase, which then phosphorylates its partner receptor. The phosphorylated receptor is then recognized by GRB2 (light purple), which binds to the Ras exchanger Sos (blue). Sos is activated to exchange GDP for GTP on Ras (pink), activating it. Ras moves Raf (tan) to the cell membrane, where it becomes active. Raf phosphorylates MAP kinase kinase, which then phosphorylates MAP kinase (yellow). MAP kinase (MAPK) enters the nucleus and phosphorylates Jun (light green). Phosphorylated Jun binds to Fos and CBP and transcription is activated. (Reprinted by permission from Molecular Biology, by R. F. Weaver, 2nd ed., p. 375, McGraw-Hill.)



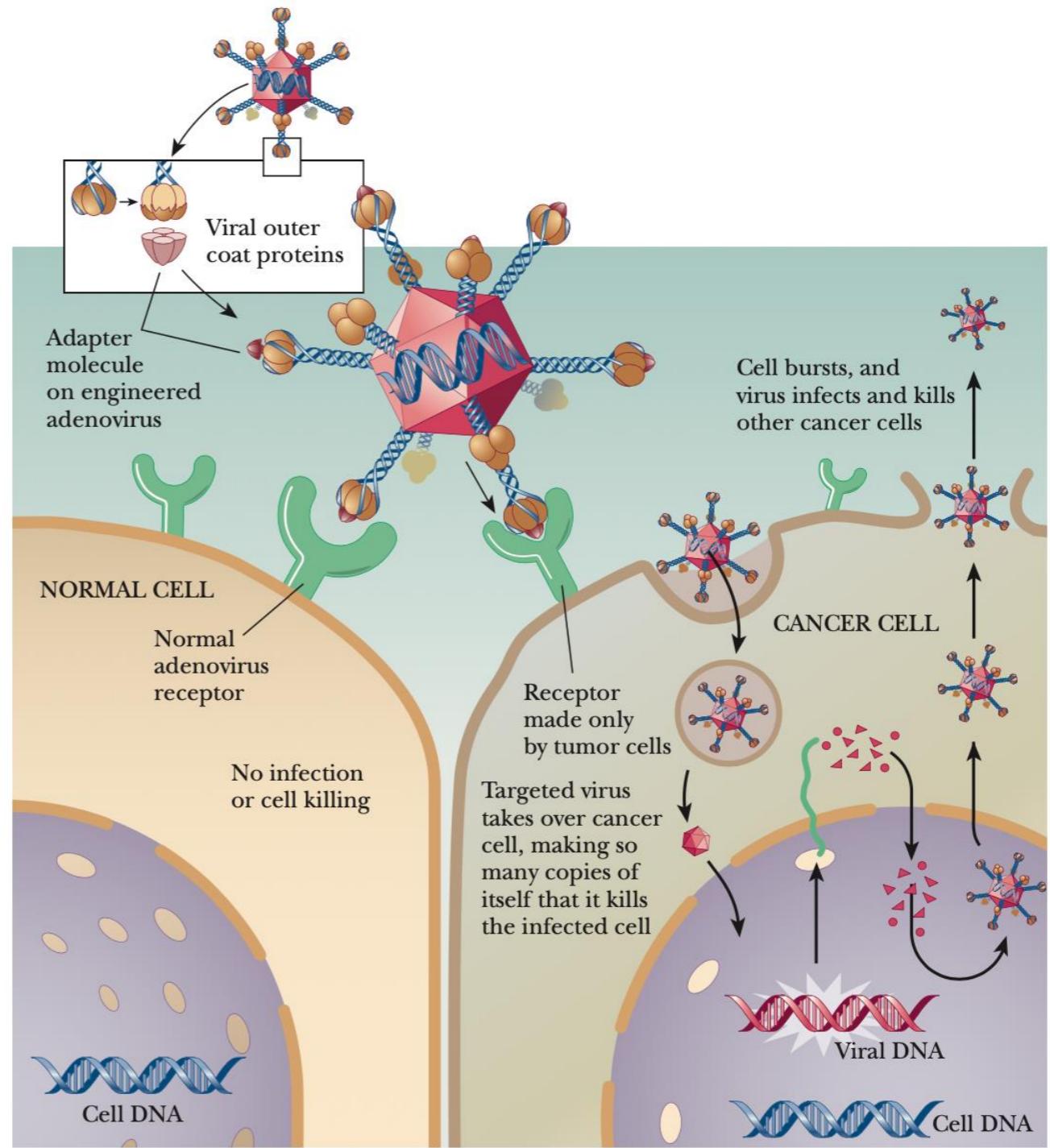


FIGURE 14.28 Transductional targeting in virotherapy. Viruses, such as adenovirus, are used to infect and destroy cancer cells selectively. Spikes on the adenovirus are mutated so that they recognize unique receptors on cancer cells. The virus selectively infects and lyses the cancer cells. (© 2003 Terese Winslow.)

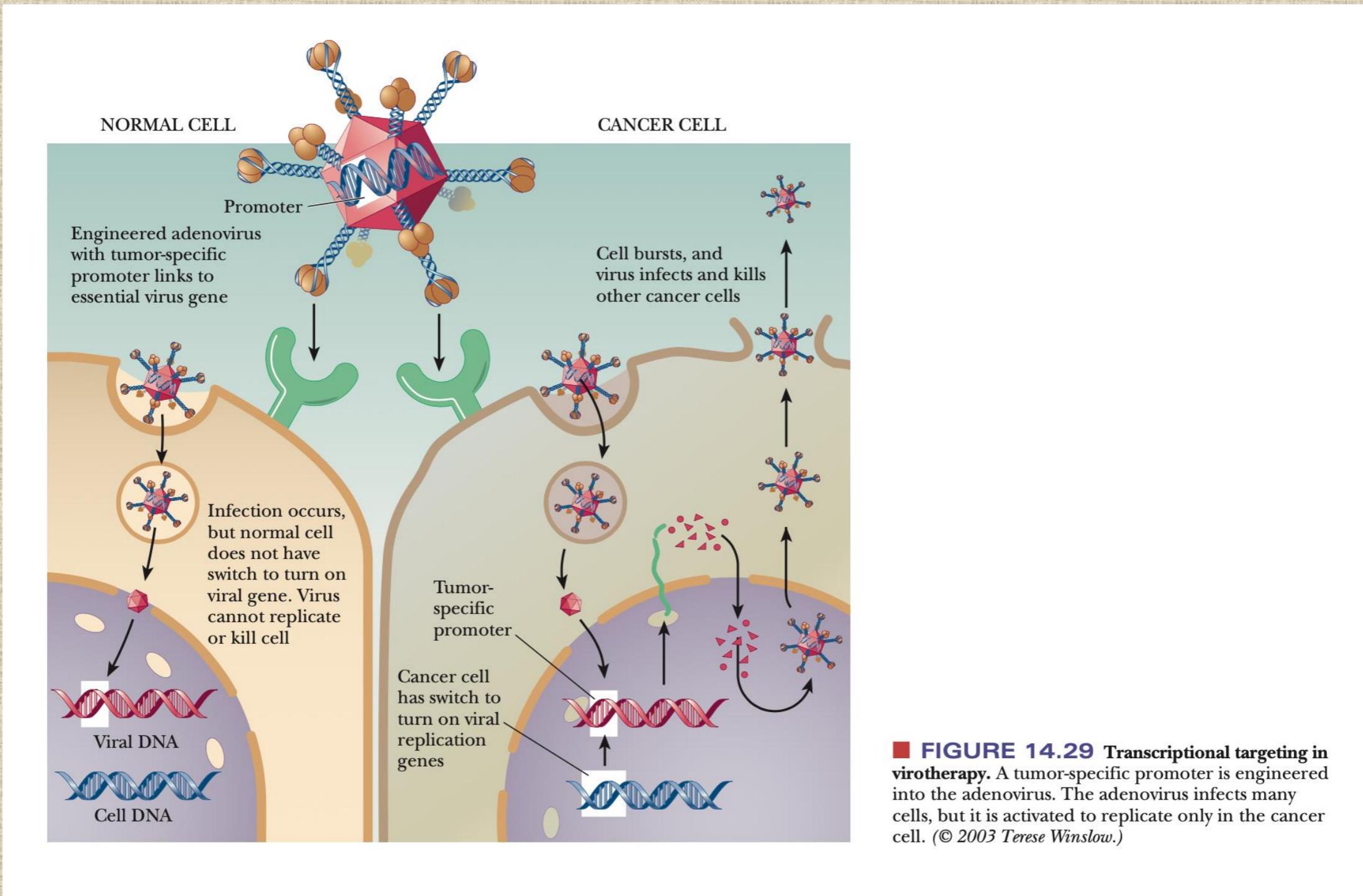


FIGURE 14.29 Transcriptional targeting in virotherapy. A tumor-specific promoter is engineered into the adenovirus. The adenovirus infects many cells, but it is activated to replicate only in the cancer cell. (© 2003 Terese Winslow.)

Table 14.2**A Representative List of Proto-Oncogenes Implicated in Human Tumors**

Proto-Oncogene	Neoplasm(s)
<i>abl</i>	Chronic myelogenous leukemia
<i>erbB-1</i>	Squamous cell carcinoma; astrocytoma
<i>erbB-2 (neu)</i>	Adenocarcinoma of breast, ovary, and stomach
<i>myc</i>	Burkitt's lymphoma carcinoma of lung, breast, and cervix
<i>H-ras</i>	Carcinoma of colon, lung, and pancreas; melanoma
<i>N-ras</i>	Carcinoma of genitourinary tract and thyroid; melanoma
<i>ros</i>	Astrocytoma
<i>src</i>	Carcinoma of colon
<i>jun</i>	Several
<i>fos</i>	

Adapted from Bishop, J. M. 1991, Molecular themes in oncogenesis, *Cell* **64**: 235–248.

The anticancer strategies includes

- (1) Antibodies or immune cells to attack tumor cells,
- (2) Inhibit the activity of cancer-promoting proteins, and
- (3) Prevent the growth of blood vessels that nourish the tumor.

Summary

- All potentially fatal cancers have several things in common, such as having cells that are immortal, that divide despite “stop growth” signals from nearby cells, that stimulate blood-vessel formation near to themselves, and that spread to other parts of the body.
- The development of cancer requires multiple breakdowns in normal metabolism. Most cancers have been linked to specific genes called oncogenes or to tumor-suppressor genes.
- When these genes are mutated, the cell loses the ability to control its replication.
- There are many classical ways to fight cancer, such as radiation therapy and chemotherapy. Both of these are very hard on healthy cells and, therefore, on the patient.
- Novel techniques using viruses are now being tried to target cancer cells more directly, and some of these are showing tremendous promise.