LECTURE PRESENTATIONS
For CAMPBELL BIOLOGY, NINTH EDITION
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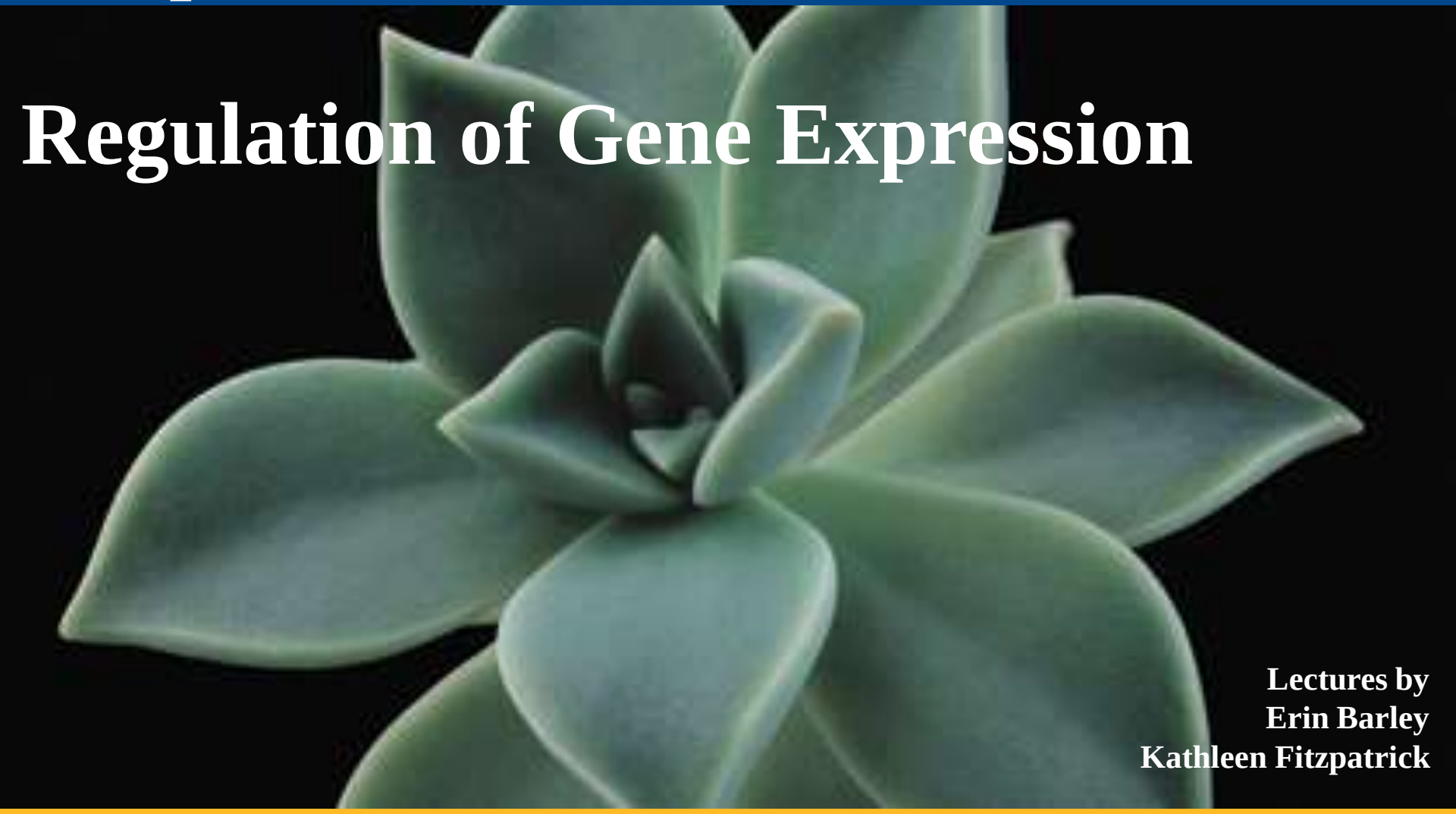
Chapter 18

Regulation of Gene Expression



Lectures by
Erin Barley
Kathleen Fitzpatrick

Overview: Conducting the Genetic Orchestra

- Prokaryotes and eukaryotes alter gene expression in response to their changing environment
- In multicellular eukaryotes, gene expression regulates development and is responsible for differences in cell types
- RNA molecules play many roles in regulating gene expression in eukaryotes

Concept 18.2: Eukaryotic gene expression is regulated at many stages

- All organisms must regulate which genes are expressed at any given time
- In multicellular organisms regulation of gene expression is essential for cell specialization

Differential Gene Expression

- Almost all the cells in an organism are genetically identical
- Differences between cell types result from **differential gene expression**, the expression of different genes by cells with the same genome
- Abnormalities in gene expression can lead to diseases including cancer
- Gene expression is regulated at many stages

Figure 18.6

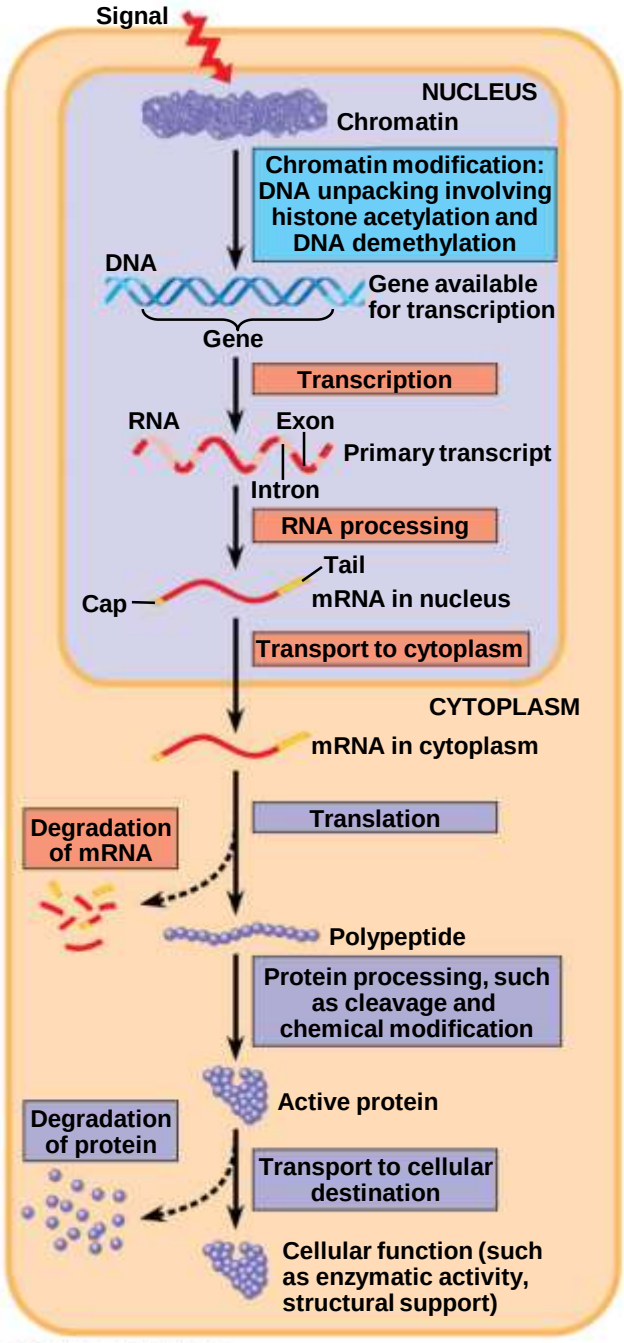


Figure 18.6a

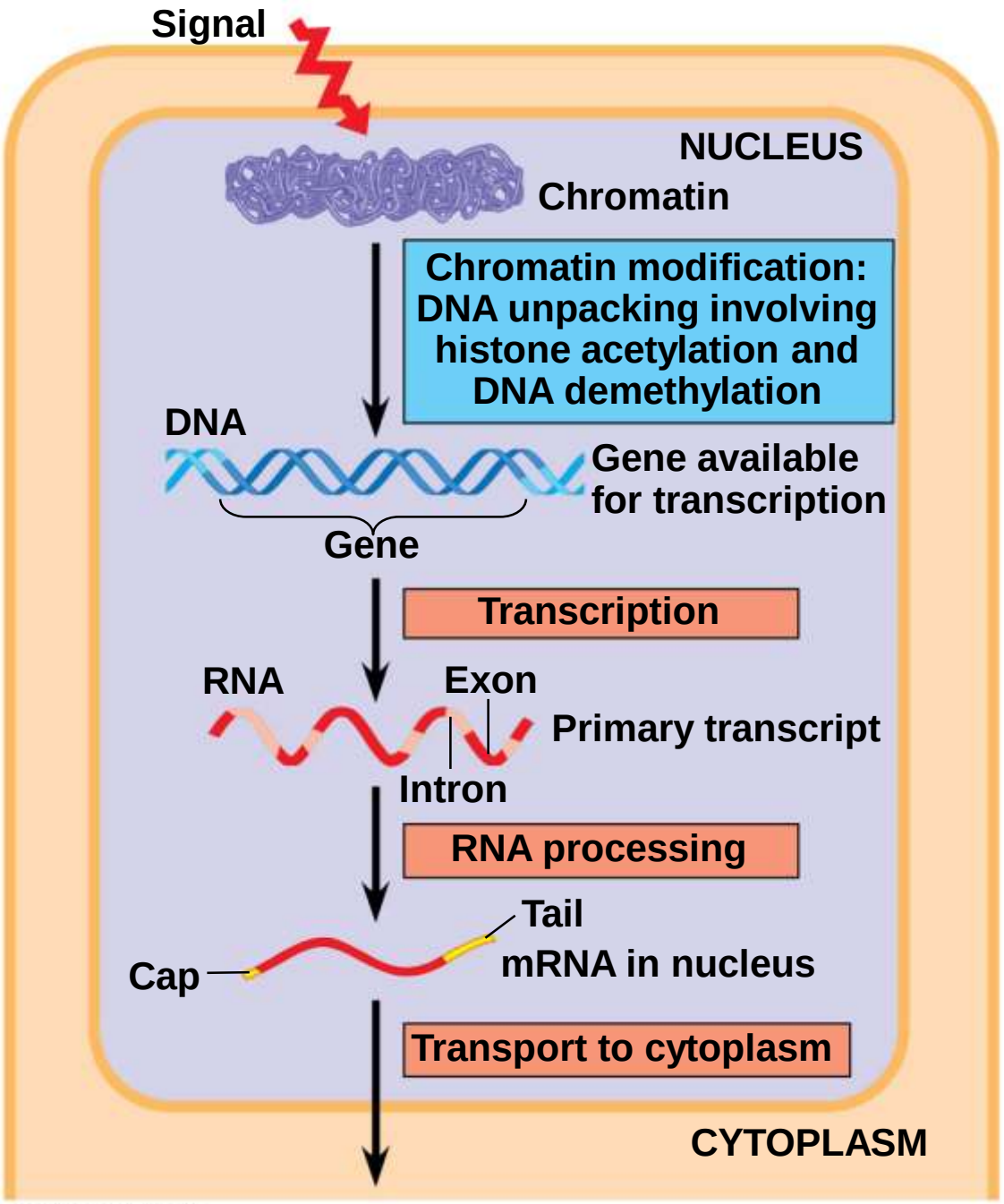
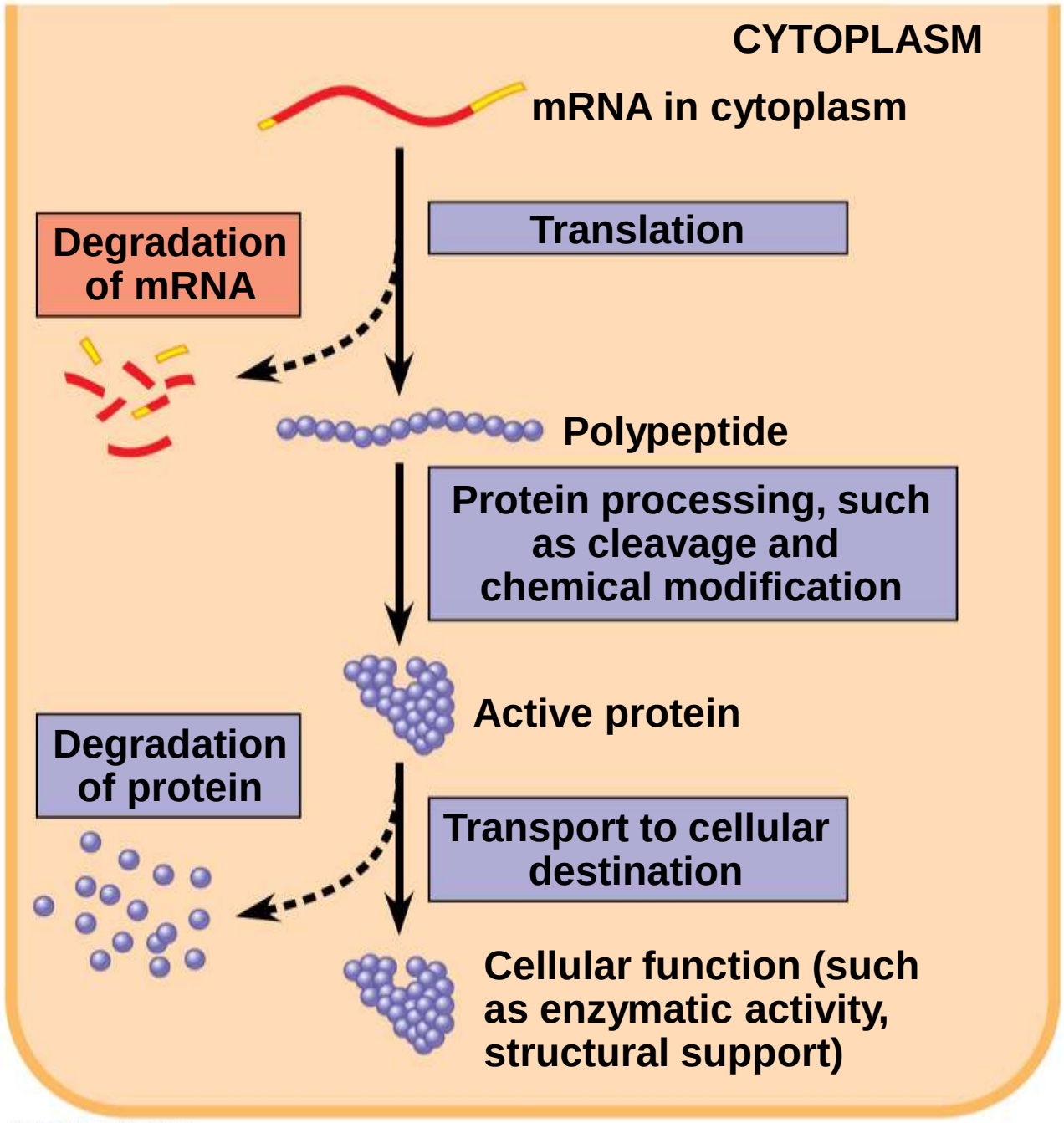


Figure 18.6b



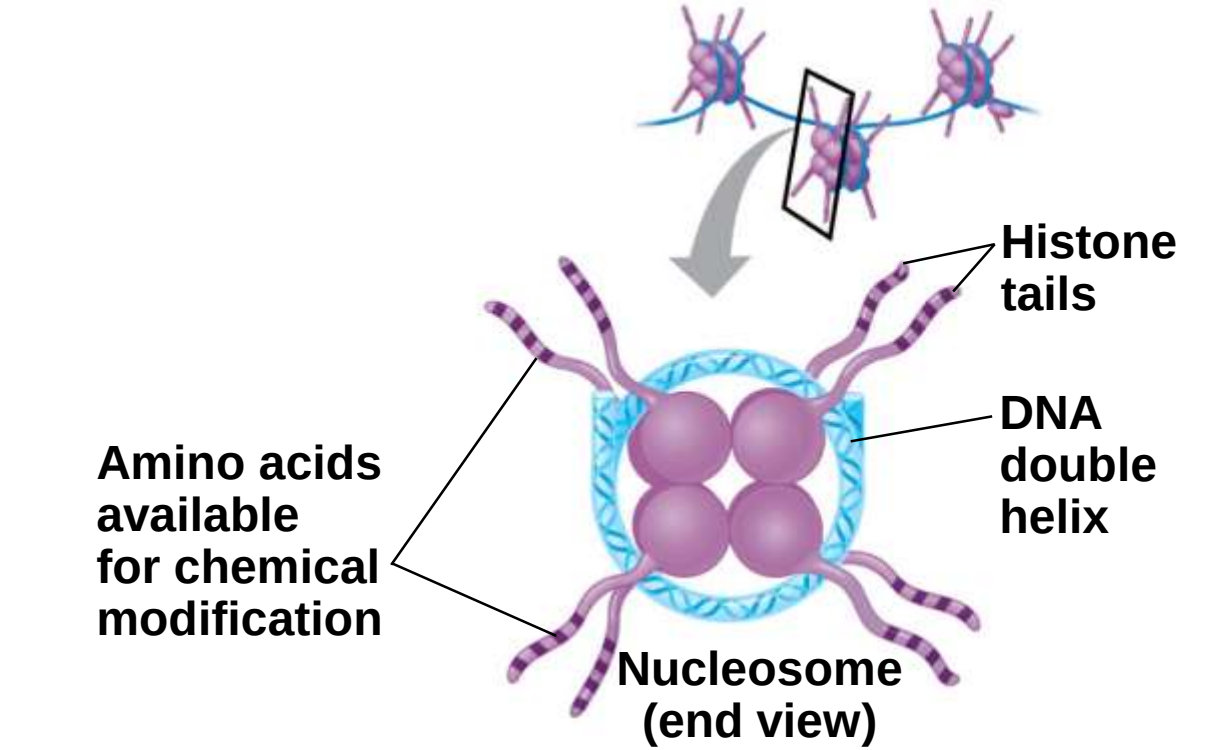
Regulation of Chromatin Structure

- Genes within highly packed heterochromatin are usually not expressed
- Chemical modifications to histones and DNA of chromatin influence both chromatin structure and gene expression

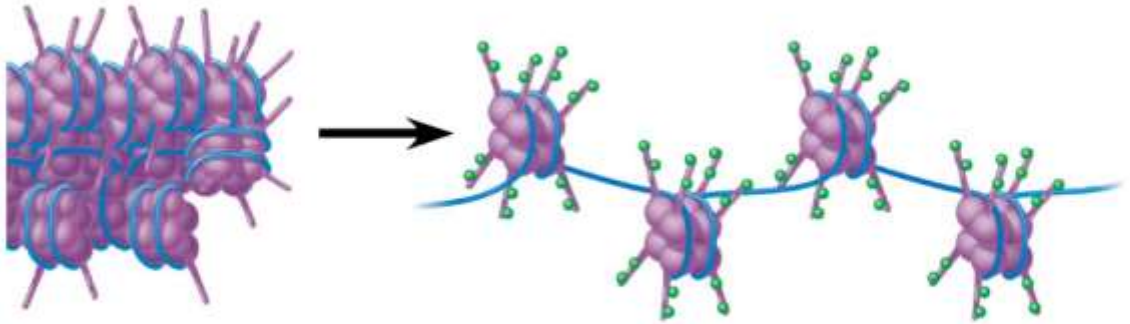
Histone Modifications

- In **histone acetylation**, acetyl groups are attached to positively charged lysines in histone tails
- This loosens chromatin structure, thereby promoting the initiation of transcription
- The addition of methyl groups (methylation) can condense chromatin; the addition of phosphate groups (phosphorylation) next to a methylated amino acid can loosen chromatin

Figure 18.7



(a) Histone tails protrude outward from a nucleosome



(b) Acetylation of histone tails promotes loose chromatin structure that permits transcription

- The *histone code hypothesis* proposes that specific combinations of modifications, as well as the order in which they occur, help determine chromatin configuration and influence transcription

DNA Methylation

- **DNA methylation**, the addition of methyl groups to certain bases in DNA, is associated with reduced transcription in some species
- DNA methylation can cause long-term inactivation of genes in cellular differentiation
- In genomic imprinting, methylation regulates expression of either the maternal or paternal alleles of certain genes at the start of development

Epigenetic Inheritance

- Although the chromatin modifications just discussed do not alter DNA sequence, they may be passed to future generations of cells
- The inheritance of traits transmitted by mechanisms not directly involving the nucleotide sequence is called **epigenetic inheritance**

Regulation of Transcription Initiation

- Chromatin-modifying enzymes provide initial control of gene expression by making a region of DNA either more or less able to bind the transcription machinery

Organization of a Typical Eukaryotic Gene

- Associated with most eukaryotic genes are multiple **control elements**, segments of noncoding DNA that serve as binding sites for transcription factors that help regulate transcription
- Control elements and the transcription factors they bind are critical to the precise regulation of gene expression in different cell types

Figure 18.8-1

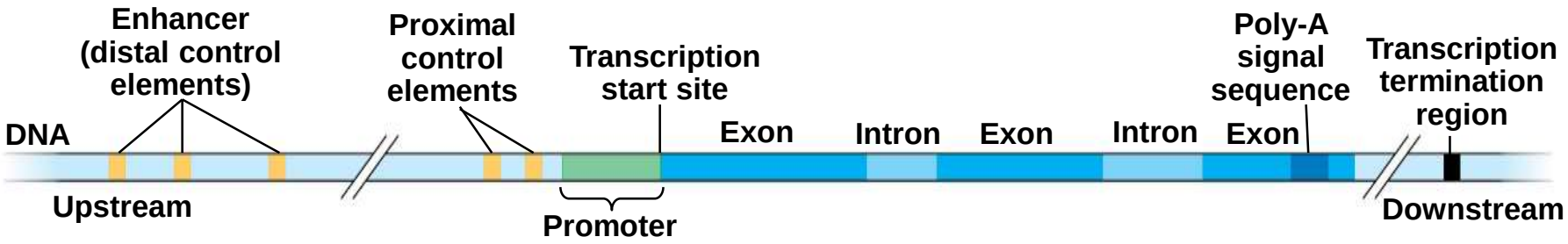


Figure 18.8-2

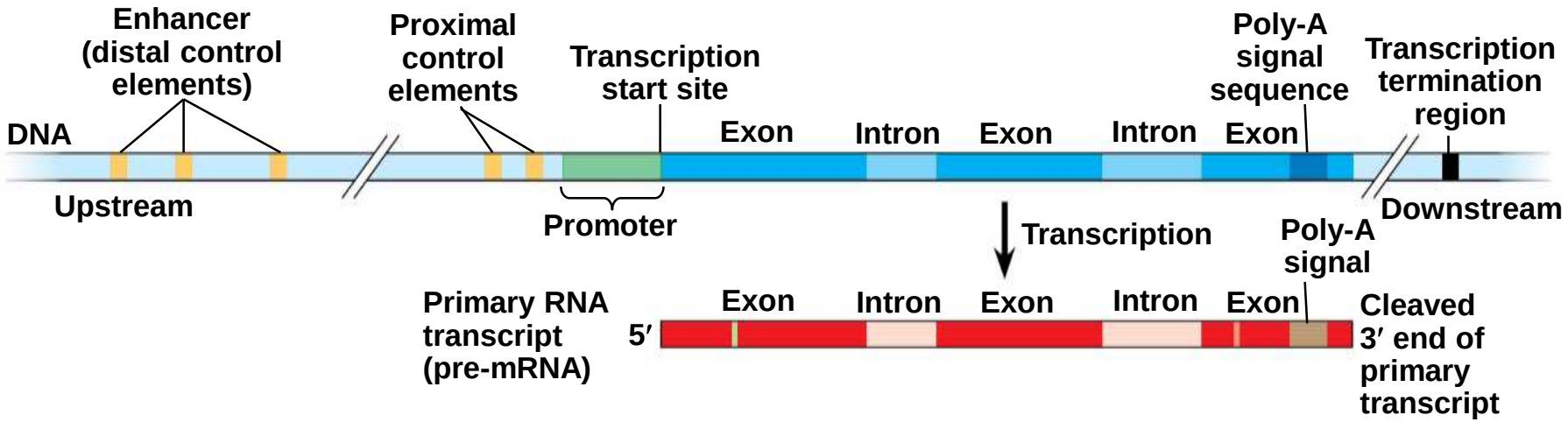
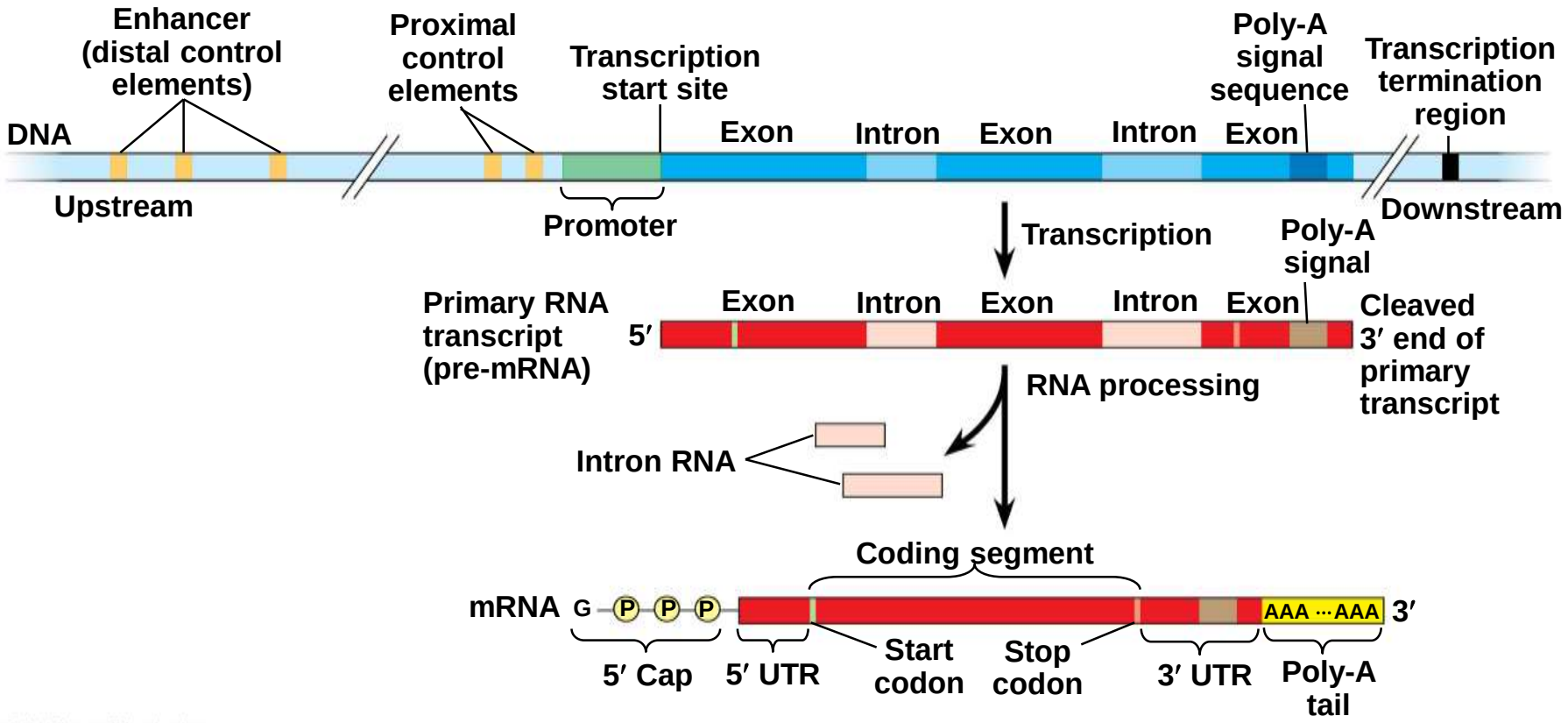


Figure 18.8-3



The Roles of Transcription Factors

- To initiate transcription, eukaryotic RNA polymerase requires the assistance of proteins called transcription factors
- General transcription factors are essential for the transcription of all protein-coding genes
- In eukaryotes, high levels of transcription of particular genes depend on control elements interacting with specific transcription factors

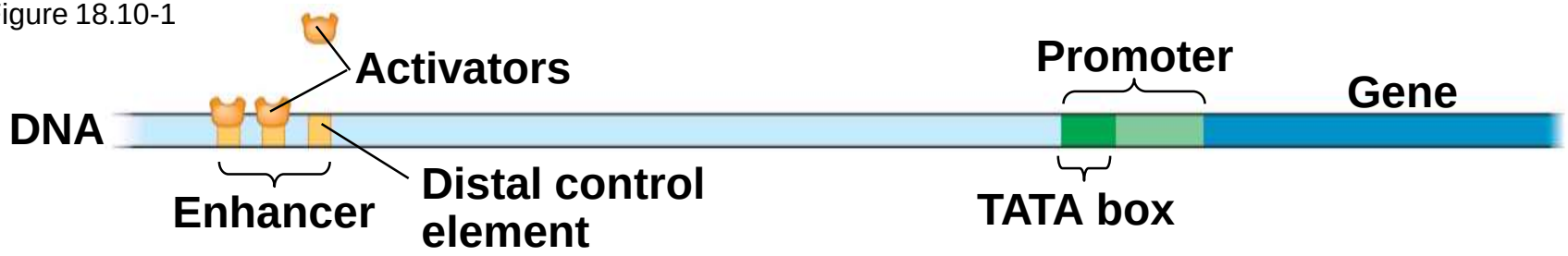
Enhancers and Specific Transcription Factors

- Proximal control elements are located close to the promoter
- Distal control elements, groupings of which are called **enhancers**, may be far away from a gene or even located in an intron

- An activator is a protein that binds to an enhancer and stimulates transcription of a gene
- Activators have two domains, one that binds DNA and a second that activates transcription
- Bound activators facilitate a sequence of protein-protein interactions that result in transcription of a given gene

- Some transcription factors function as repressors, inhibiting expression of a particular gene by a variety of methods
- Some activators and repressors act indirectly by influencing chromatin structure to promote or silence transcription

Figure 18.10-1



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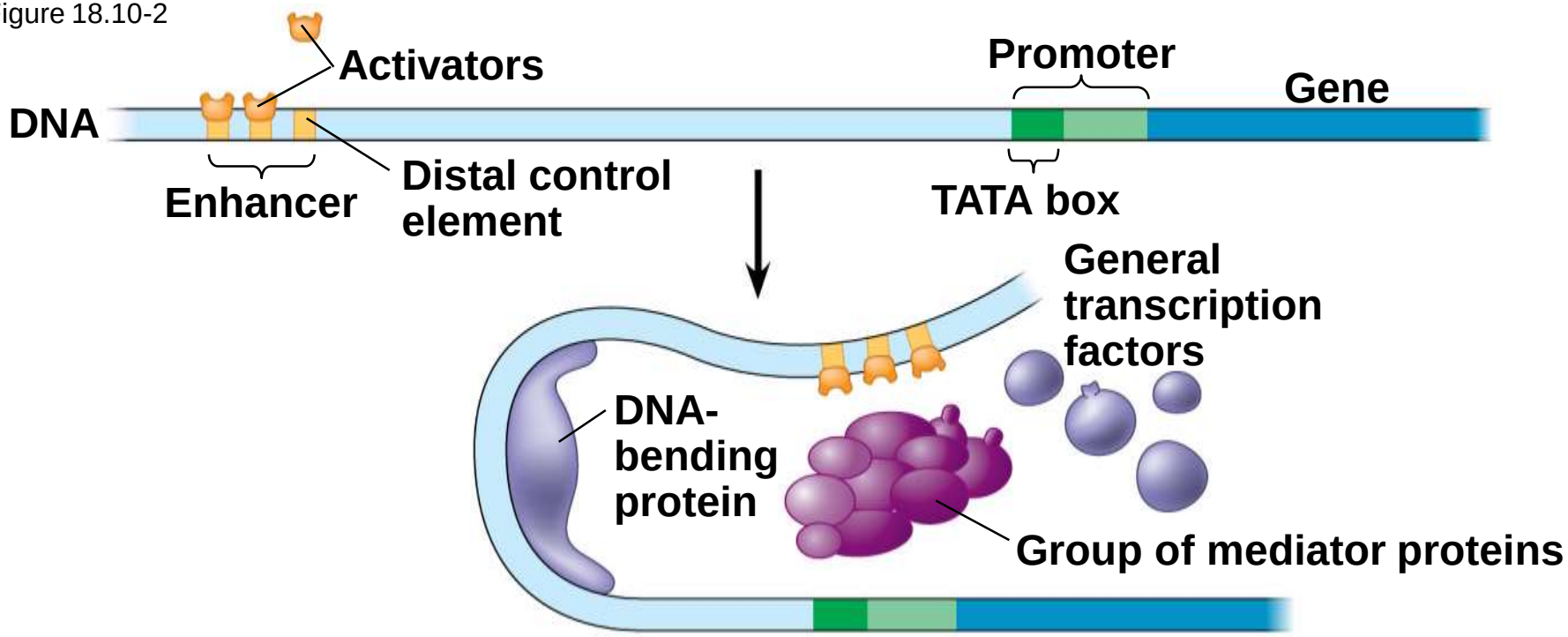

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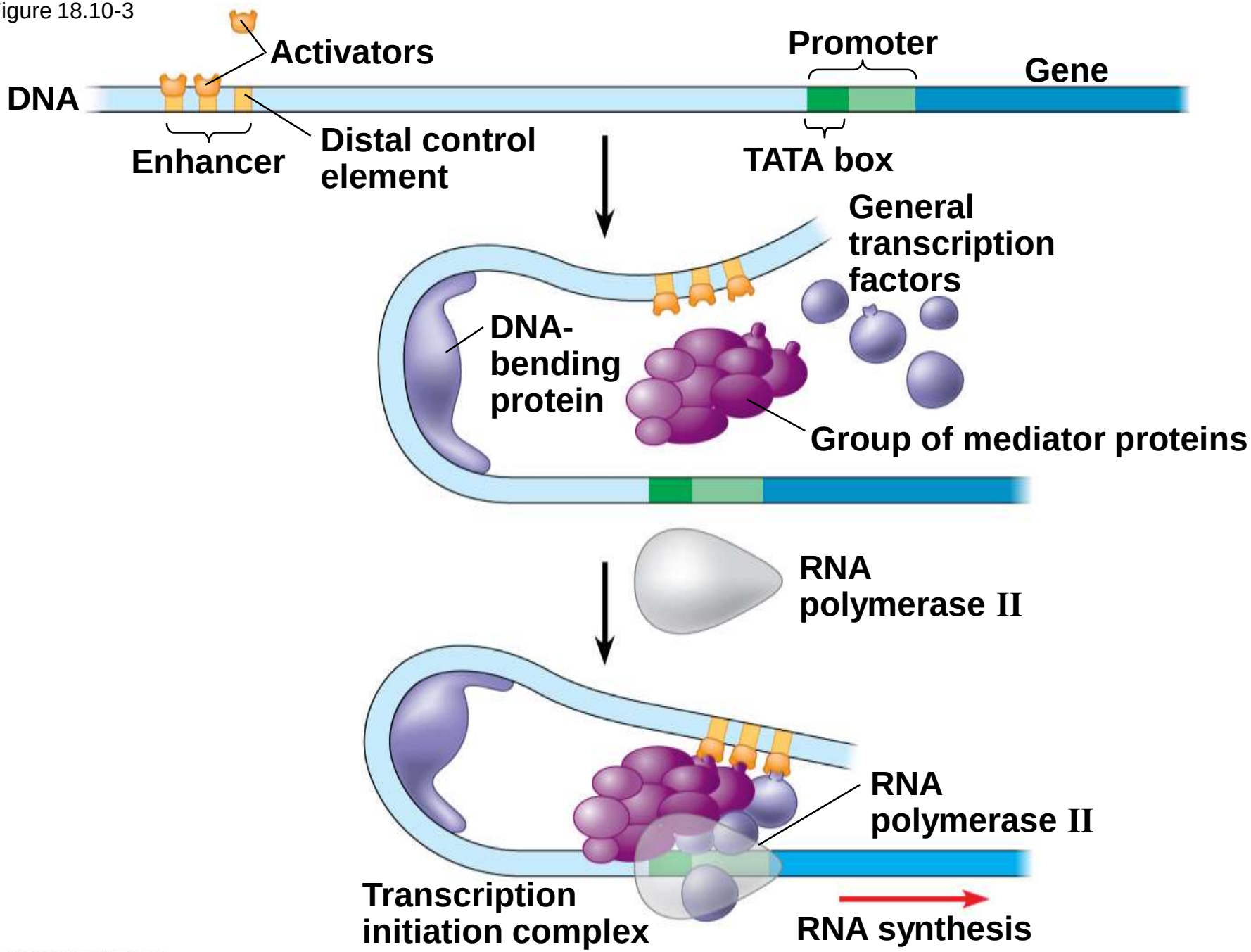


Combinatorial Control of Gene Activation

- A particular combination of control elements can activate transcription only when the appropriate activator proteins are present

Figure 18.11

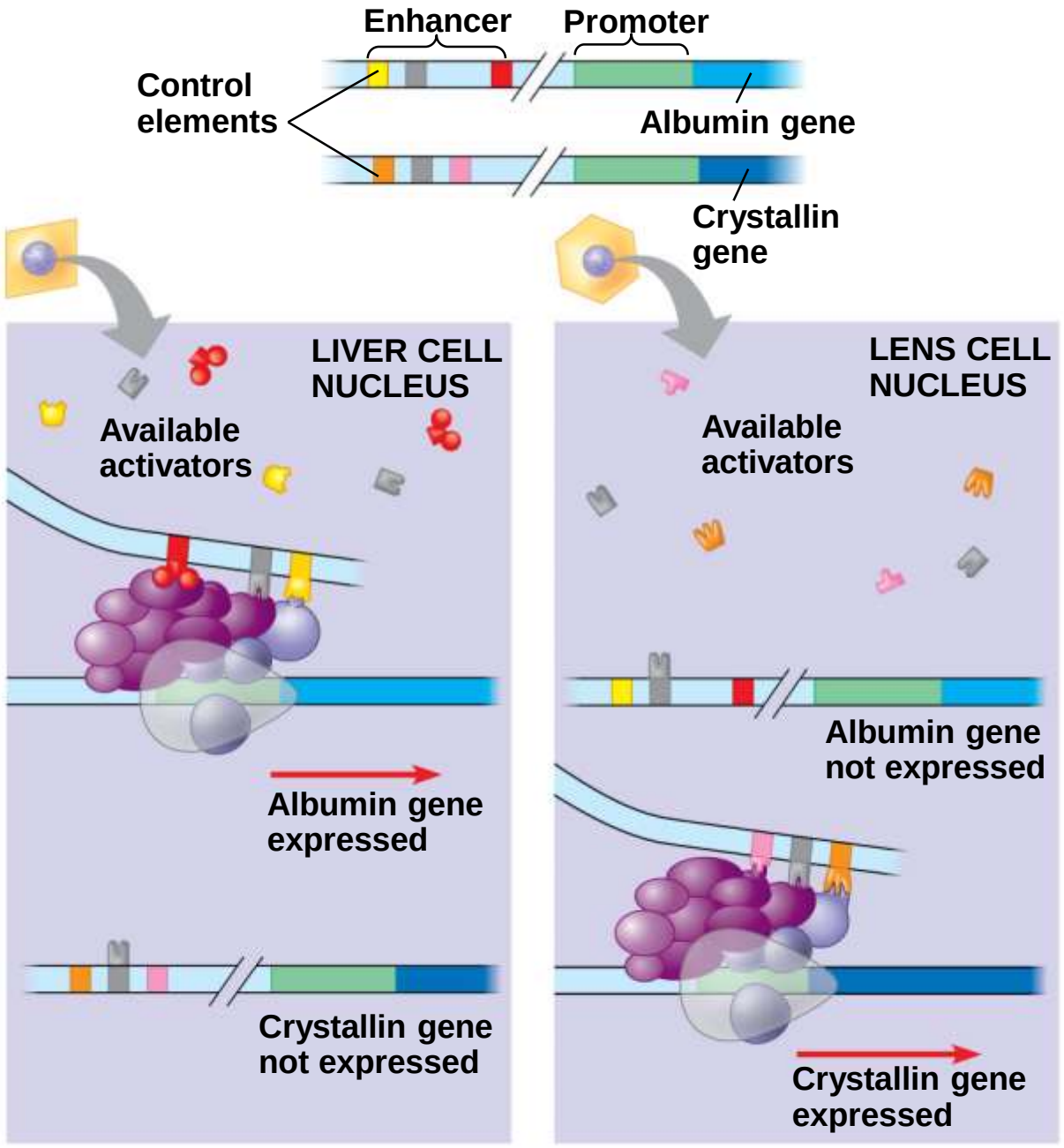
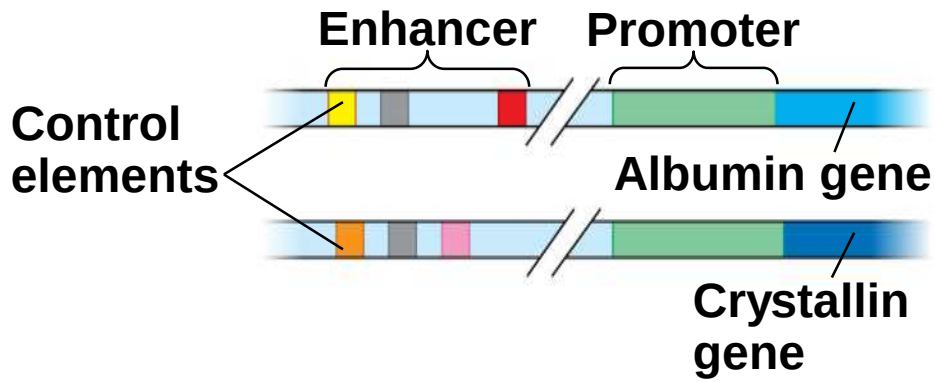
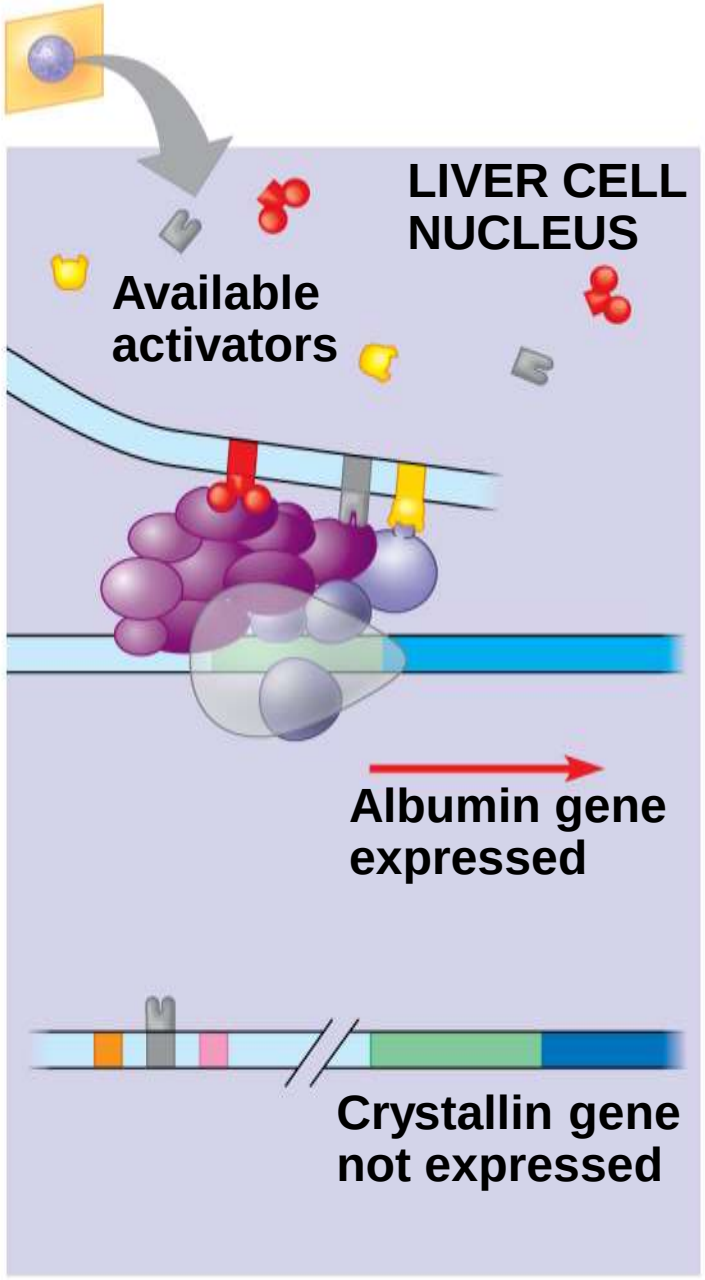


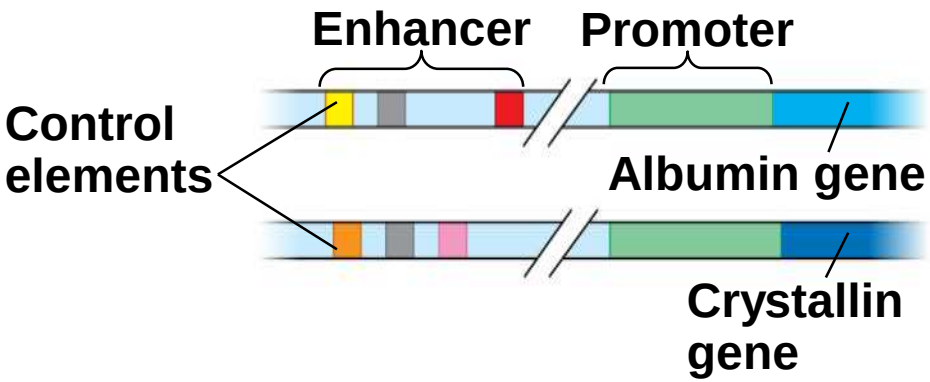
Figure 18.11a

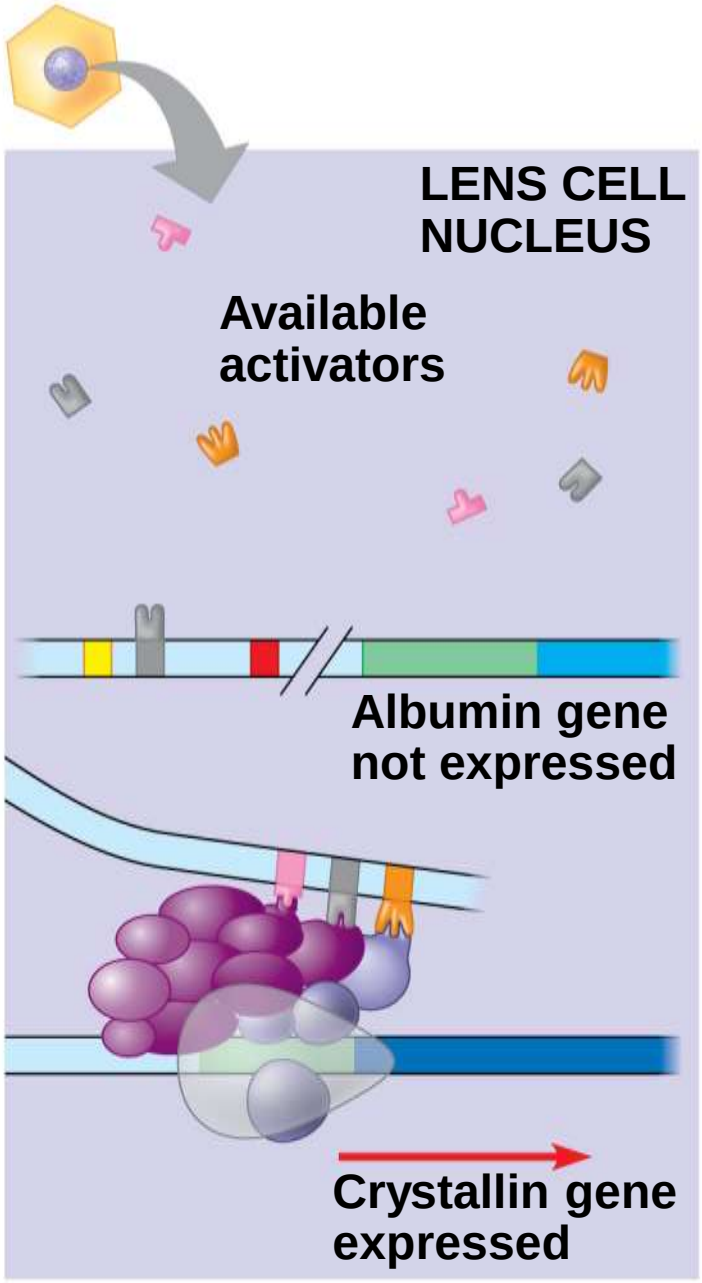




(a) Liver cell

Figure 18.11b





(b) Lens cell

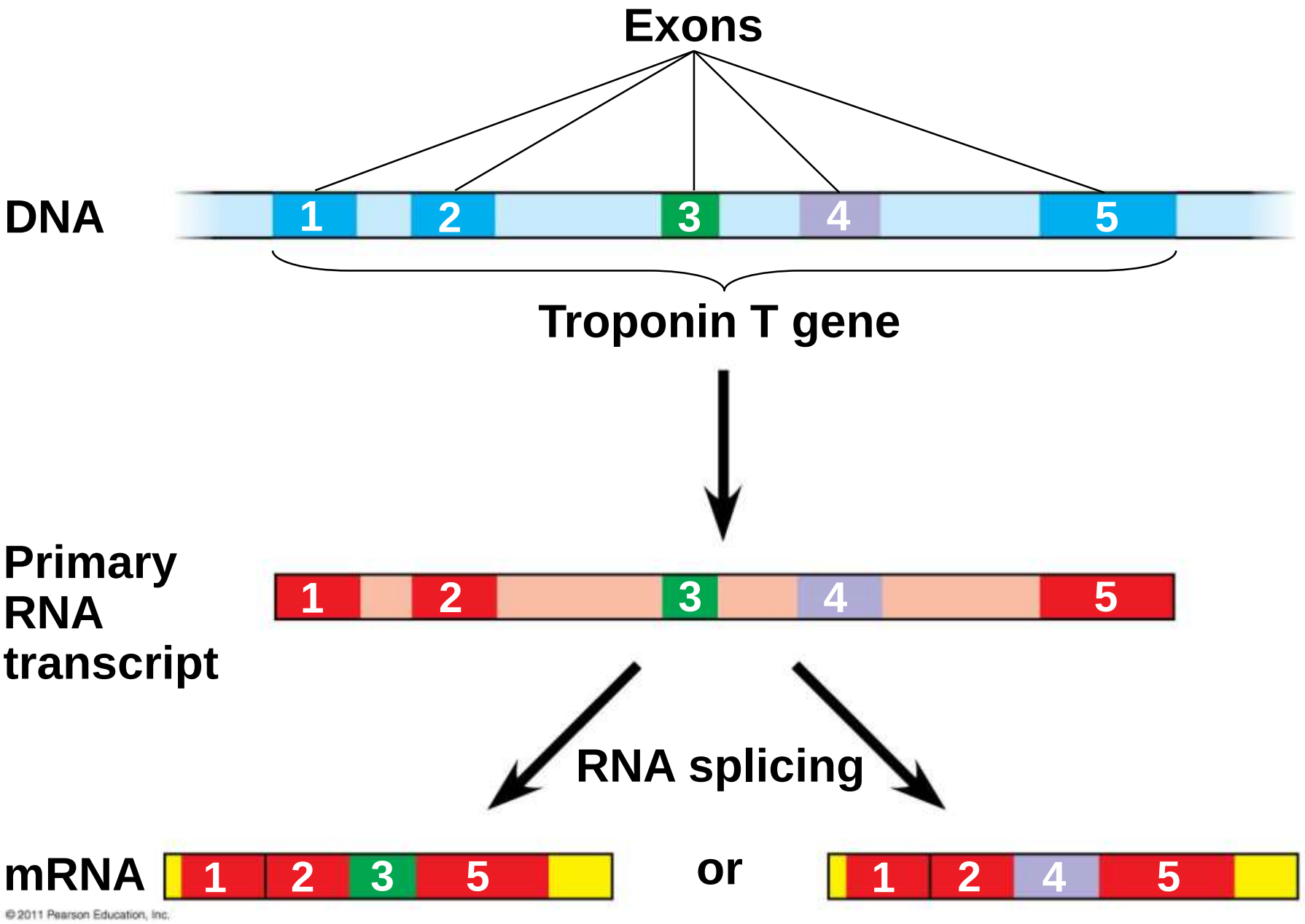
Mechanisms of Post-Transcriptional Regulation

- Transcription alone does not account for gene expression
- Regulatory mechanisms can operate at various stages after transcription
- Such mechanisms allow a cell to fine-tune gene expression rapidly in response to environmental changes

RNA Processing

- In **alternative RNA splicing**, different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns

Figure 18.13



mRNA Degradation

- The life span of mRNA molecules in the cytoplasm is a key to determining protein synthesis
- Eukaryotic mRNA is more long lived than prokaryotic mRNA
- Nucleotide sequences that influence the lifespan of mRNA in eukaryotes reside in the untranslated region (UTR) at the 3′ end of the molecule

Initiation of Translation

- The initiation of translation of selected mRNAs can be blocked by regulatory proteins that bind to sequences or structures of the mRNA
- Alternatively, translation of all mRNAs in a cell may be regulated simultaneously
- For example, translation initiation factors are simultaneously activated in an egg following fertilization

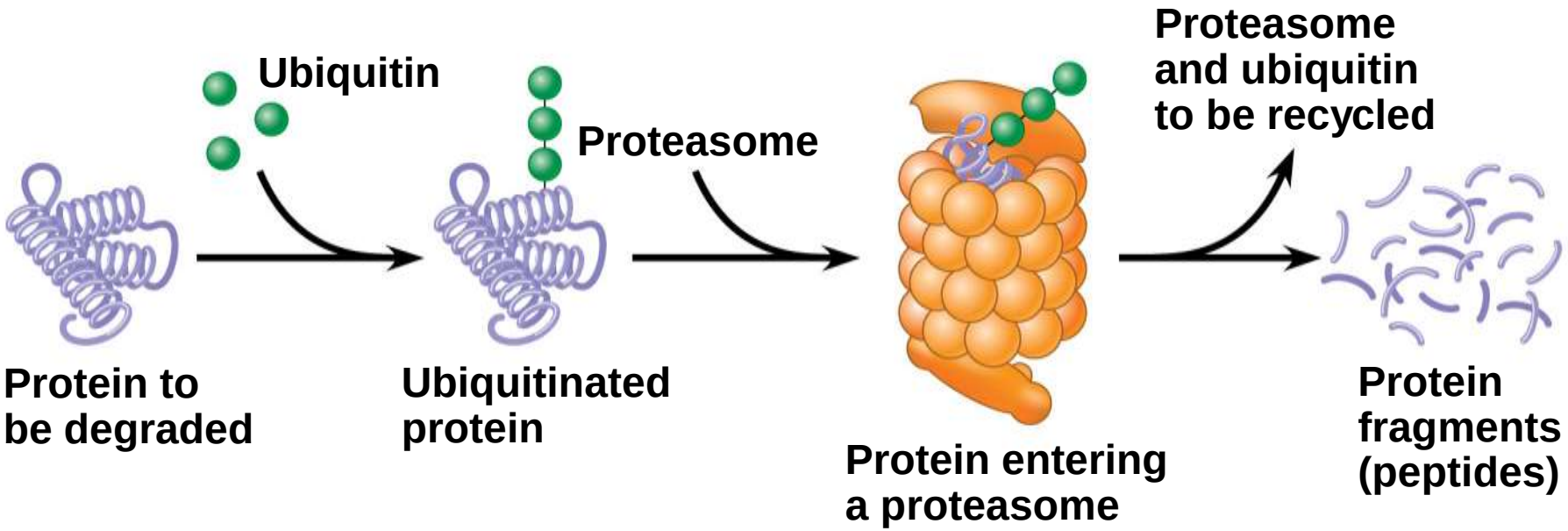
Protein Processing and Degradation

- After translation, various types of protein processing, including cleavage and the addition of chemical groups, are subject to control
- **Proteasomes** are giant protein complexes that bind protein molecules and degrade them

Animation: Protein Processing

Right-click slide / select “Play”

Figure 18.14



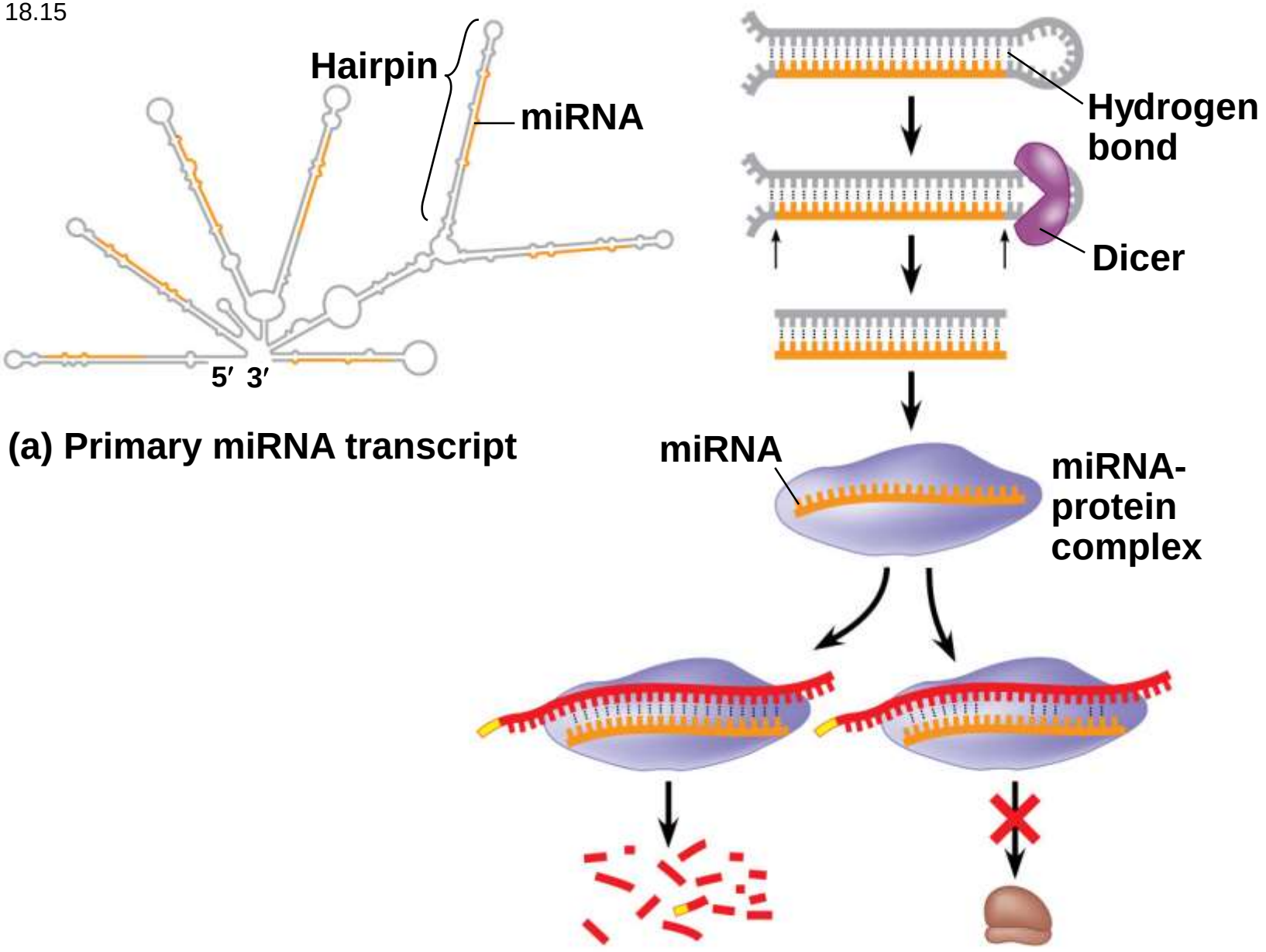
Concept 18.3: Noncoding RNAs play multiple roles in controlling gene expression

- Only a small fraction of DNA codes for proteins, and a very small fraction of the non-protein-coding DNA consists of genes for RNA such as rRNA and tRNA
- A significant amount of the genome may be transcribed into noncoding RNAs (ncRNAs)
- Noncoding RNAs regulate gene expression at two points: mRNA translation and chromatin configuration

Effects on mRNAs by MicroRNAs and Small Interfering RNAs

- **MicroRNAs** (**miRNAs**) are small single-stranded RNA molecules that can bind to mRNA
- These can degrade mRNA or block its translation

Figure 18.15



- The phenomenon of inhibition of gene expression by RNA molecules is called **RNA interference (RNAi)**
- RNAi is caused by **small interfering RNAs (siRNAs)**
- siRNAs and miRNAs are similar but form from different RNA precursors

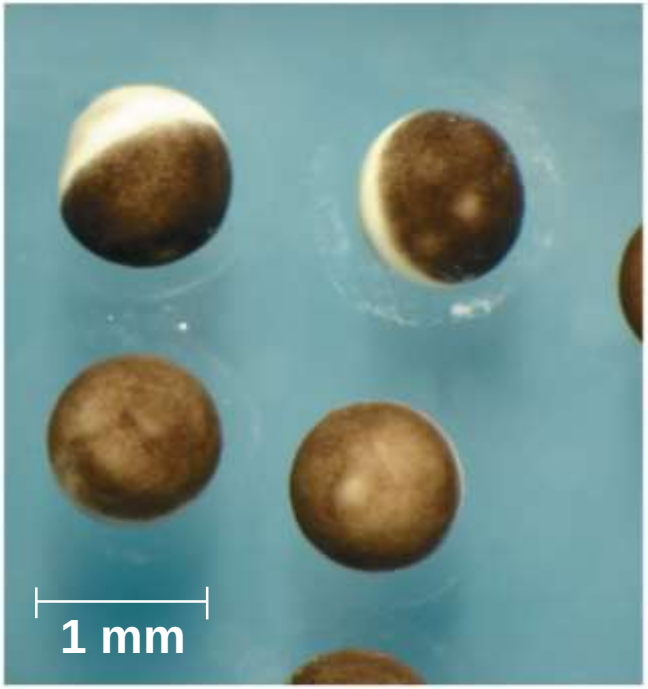
Concept 18.4: A program of differential gene expression leads to the different cell types in a multicellular organism

- During embryonic development, a fertilized egg gives rise to many different cell types
- Cell types are organized successively into tissues, organs, organ systems, and the whole organism
- Gene expression orchestrates the developmental programs of animals

A Genetic Program for Embryonic Development

- The transformation from zygote to adult results from cell division, cell differentiation, and morphogenesis

Figure 18.16



(a) Fertilized eggs of a frog

(b) Newly hatched tadpole

- **Cell differentiation** is the process by which cells become specialized in structure and function
- The physical processes that give an organism its shape constitute **morphogenesis**
- Differential gene expression results from genes being regulated differently in each cell type
- Materials in the egg can set up gene regulation that is carried out as cells divide

Cytoplasmic Determinants and Inductive Signals

- An egg's cytoplasm contains RNA, proteins, and other substances that are distributed unevenly in the unfertilized egg
- **Cytoplasmic determinants** are maternal substances in the egg that influence early development
- As the zygote divides by mitosis, cells contain different cytoplasmic determinants, which lead to different gene expression

Figure 18.17

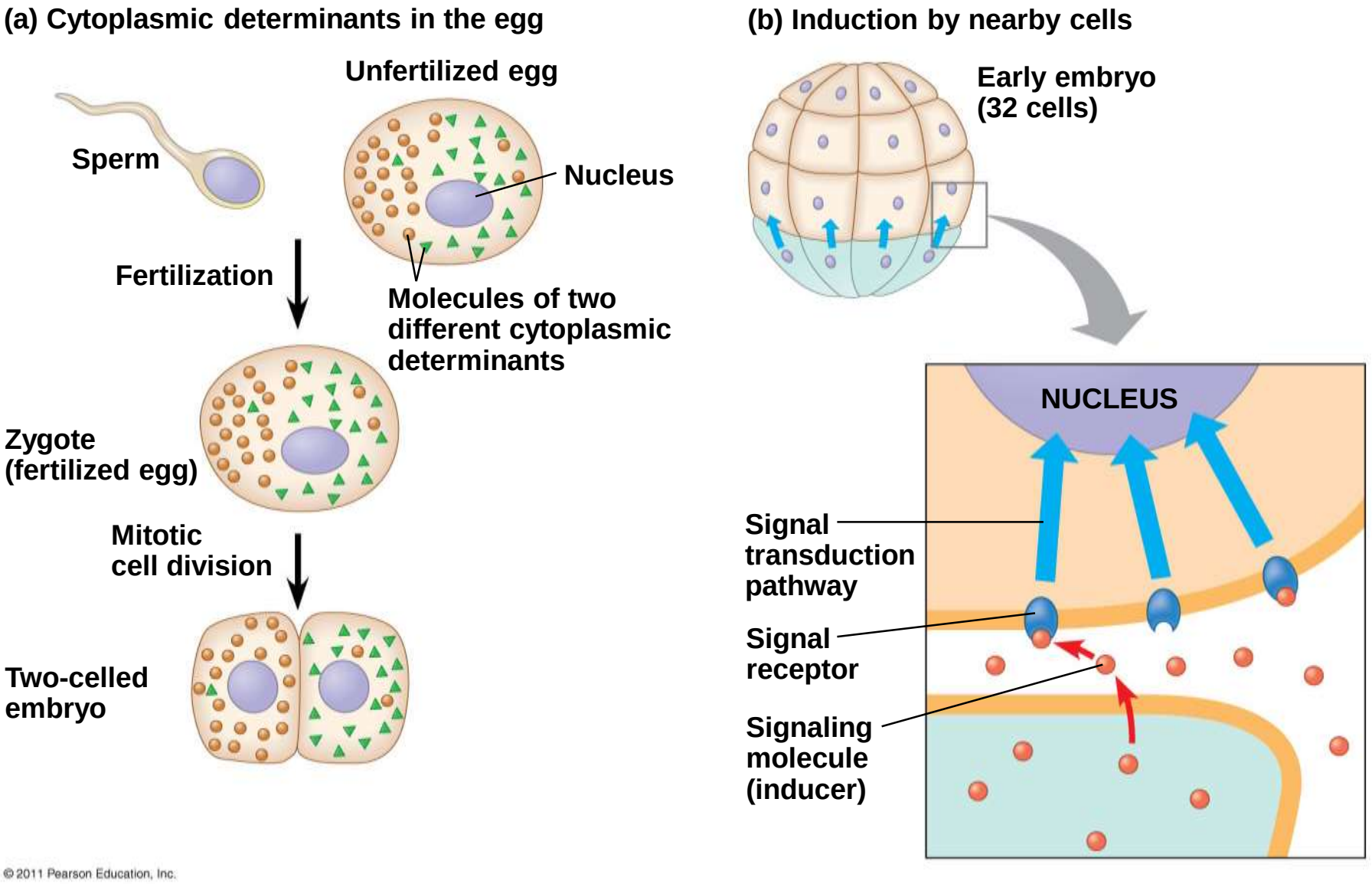
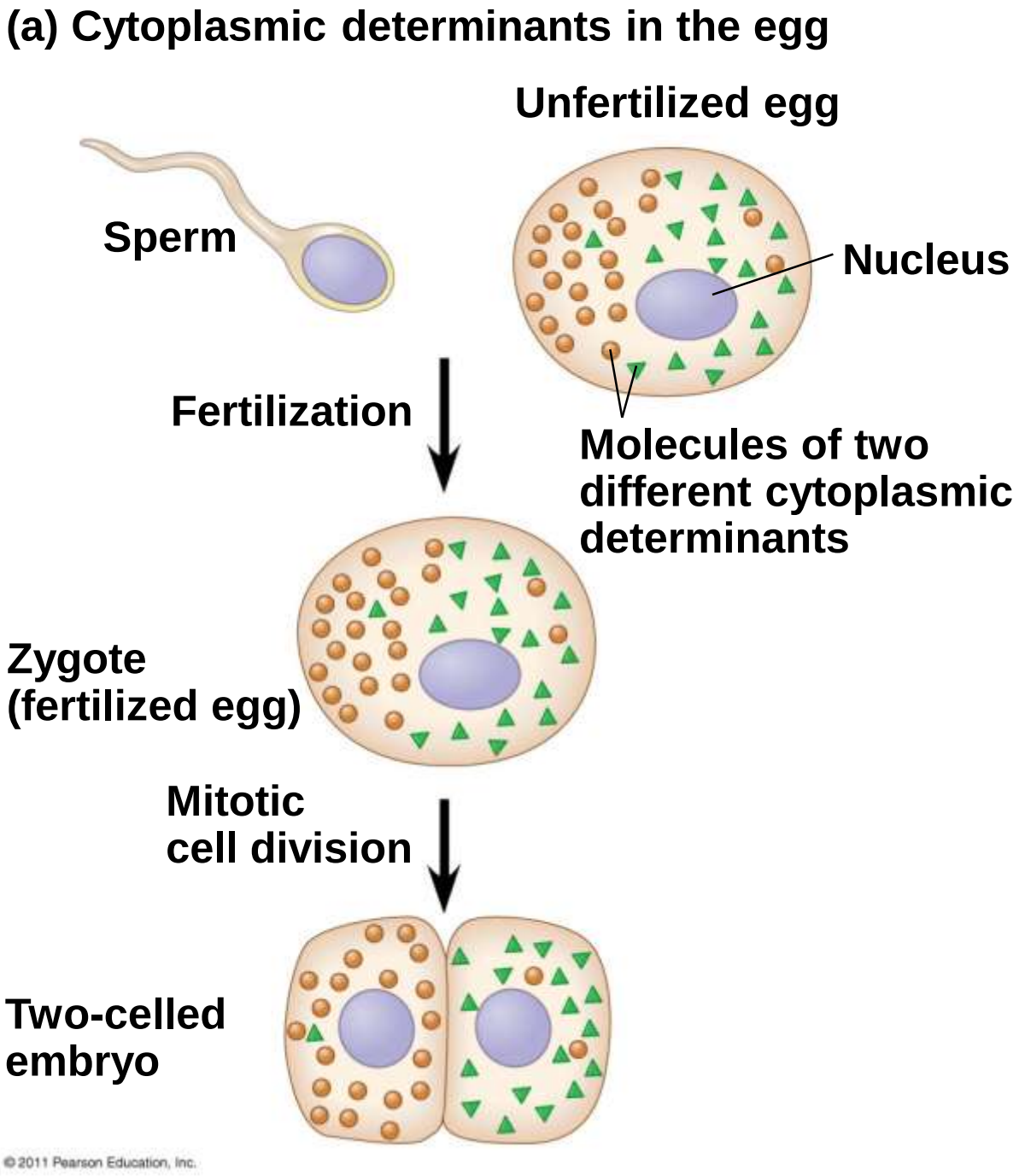
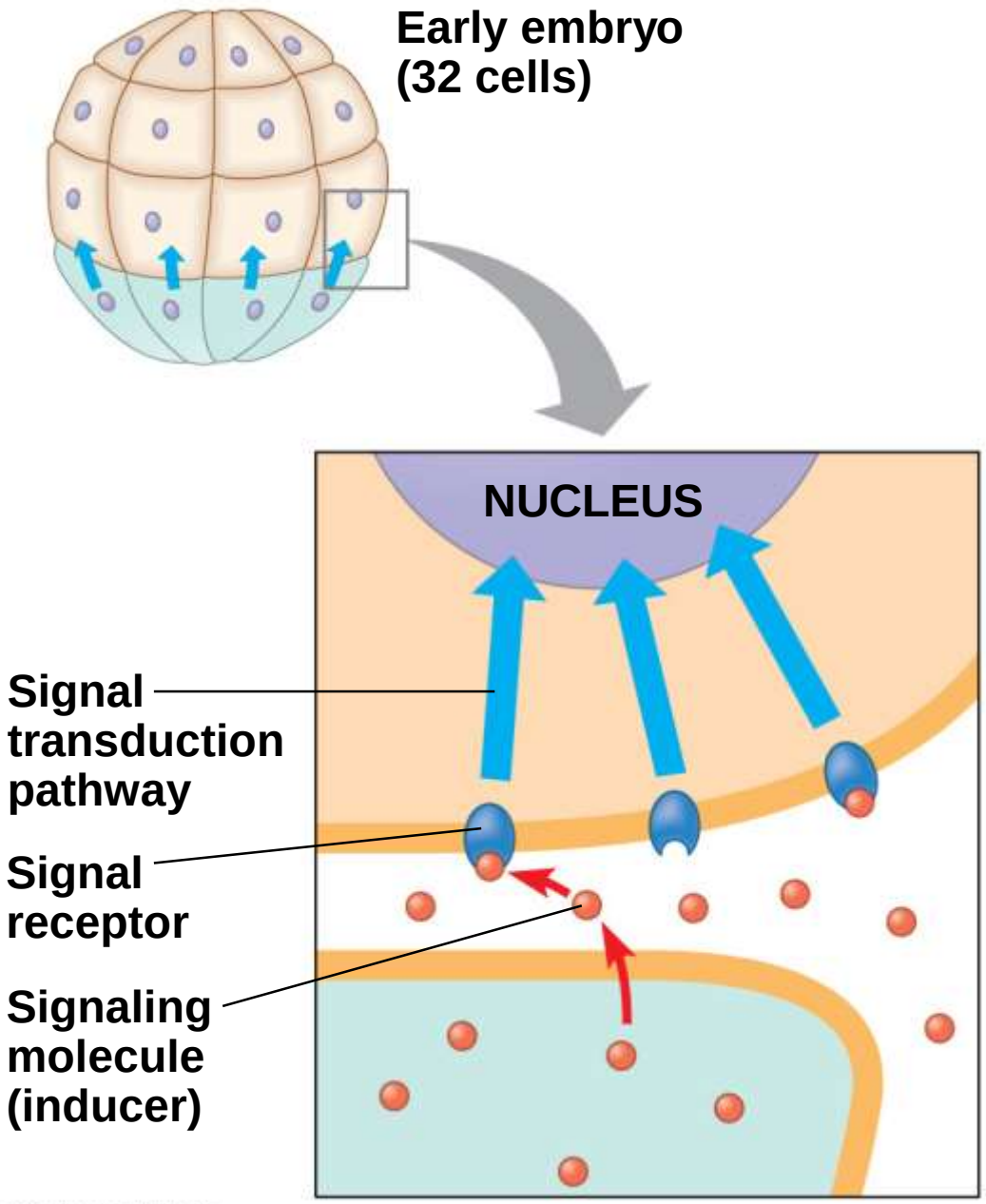


Figure 18.17a



- The other important source of developmental information is the environment around the cell, especially signals from nearby embryonic cells
- In the process called **induction**, signal molecules from embryonic cells cause transcriptional changes in nearby target cells
- Thus, interactions between cells induce differentiation of specialized cell types

Figure 18.17b



Concept 18.5: Cancer results from genetic changes that affect cell cycle control

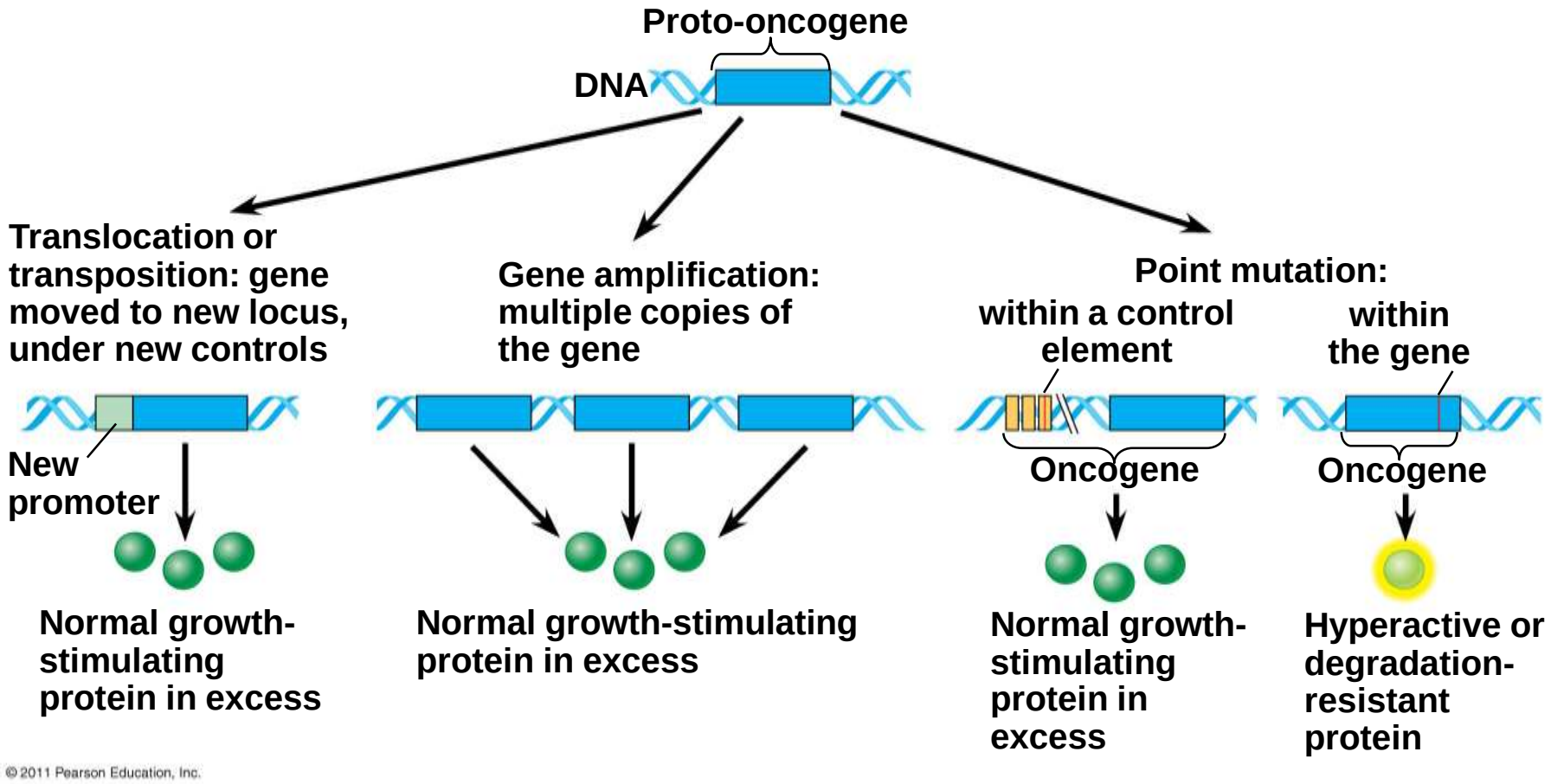
- The gene regulation systems that go wrong during cancer are the very same systems involved in embryonic development

Types of Genes Associated with Cancer

- Cancer can be caused by mutations to genes that regulate cell growth and division
- Tumor viruses can cause cancer in animals including humans

- **Oncogenes** are cancer-causing genes
- **Proto-oncogenes** are the corresponding normal cellular genes that are responsible for normal cell growth and division
- Conversion of a proto-oncogene to an oncogene can lead to abnormal stimulation of the cell cycle

Figure 18.23



- Proto-oncogenes can be converted to oncogenes by
  - Movement of DNA within the genome: if it ends up near an active promoter, transcription may increase
  - Amplification of a proto-oncogene: increases the number of copies of the gene
  - Point mutations in the proto-oncogene or its control elements: cause an increase in gene expression

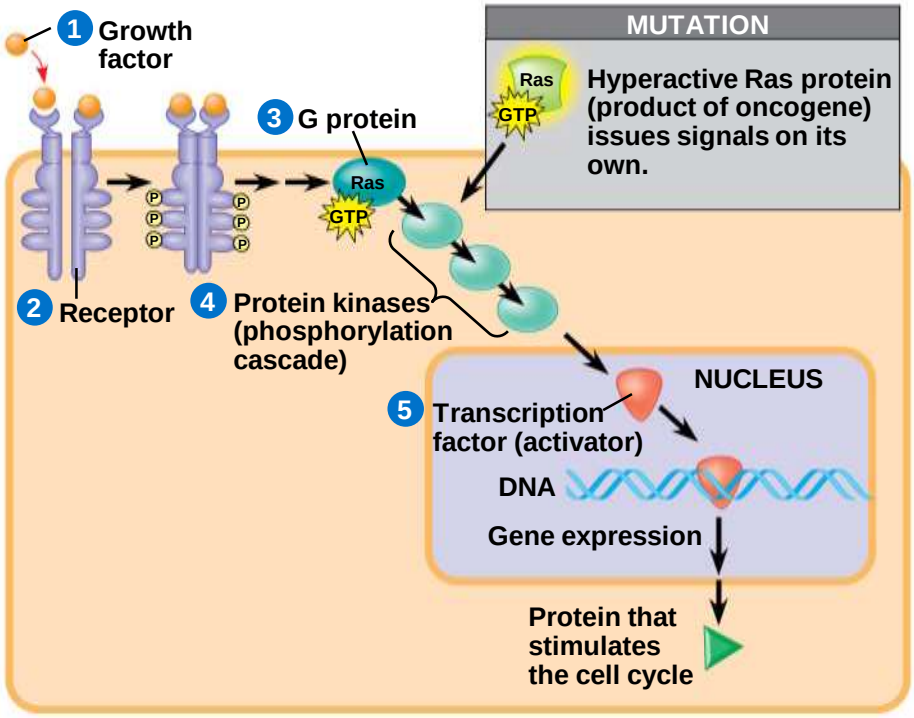
Tumor-Suppressor Genes

- **Tumor-suppressor genes** help prevent uncontrolled cell growth
- Mutations that decrease protein products of tumor-suppressor genes may contribute to cancer onset
- Tumor-suppressor proteins
  - Repair damaged DNA
  - Control cell adhesion
  - Inhibit the cell cycle in the cell-signaling pathway

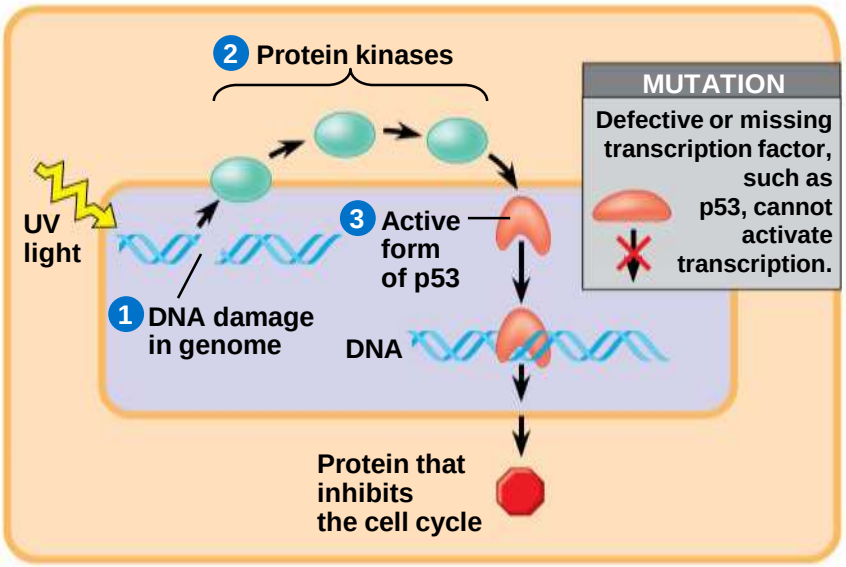
Interference with Normal Cell-Signaling Pathways

- Mutations in the *ras* proto-oncogene and *p53* tumor-suppressor gene are common in human cancers
- Mutations in the ***ras* gene** can lead to production of a hyperactive Ras protein and increased cell division

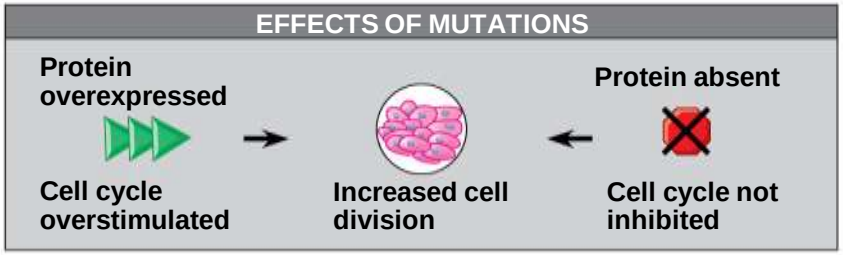
Figure 18.24



(a) Cell cycle–stimulating pathway

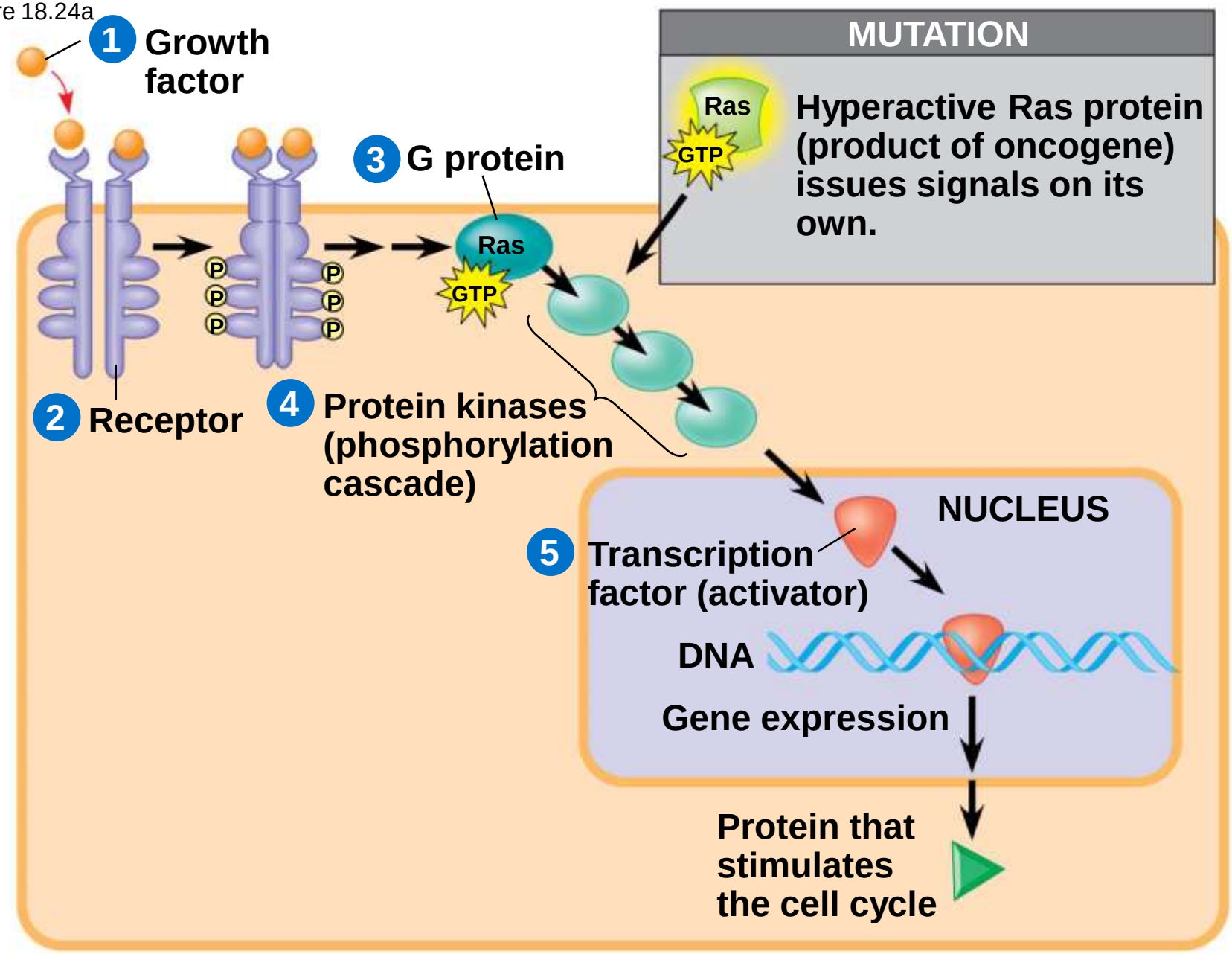


(b) Cell cycle–inhibiting pathway



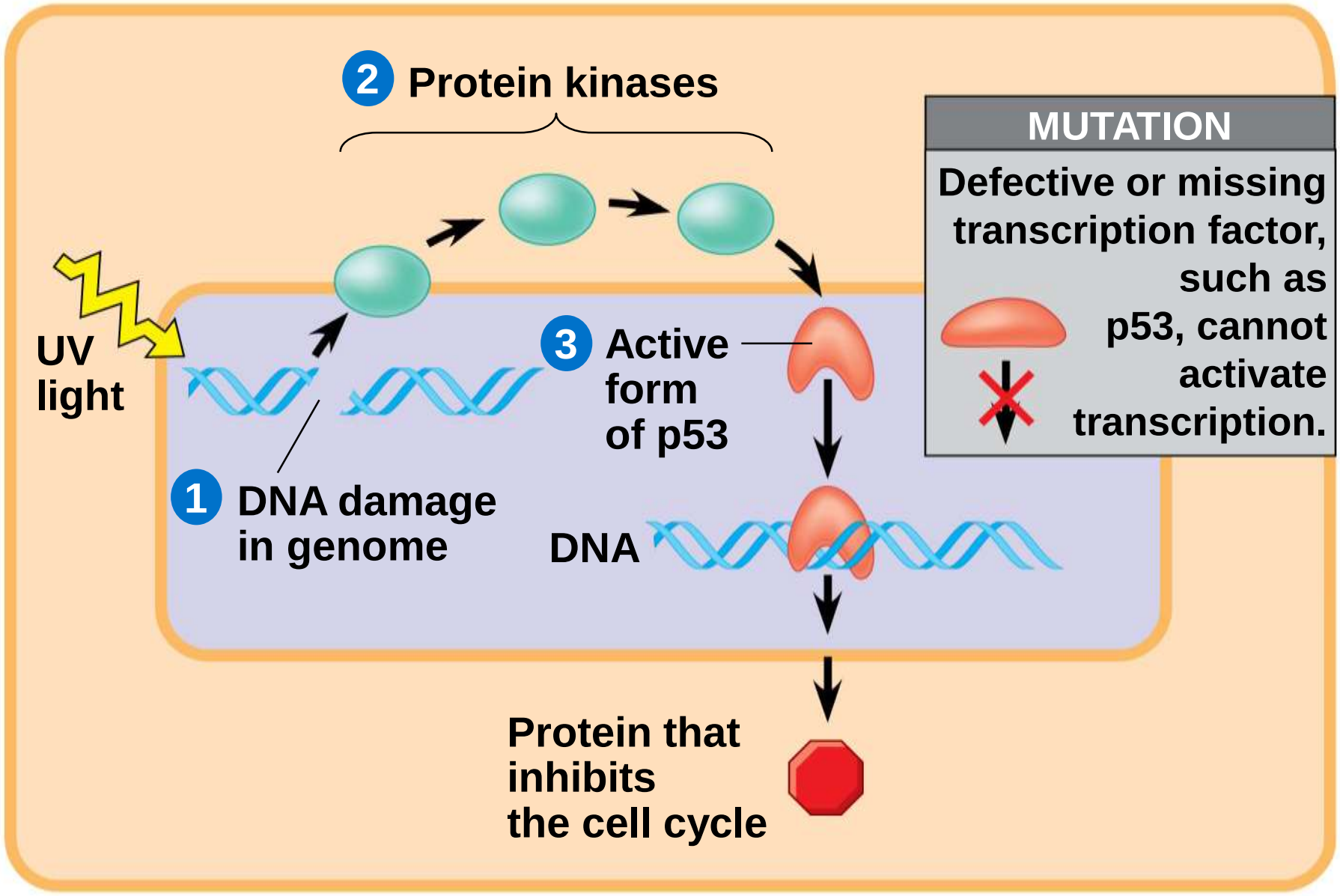
(c) Effects of mutations

Figure 18.24a



(a) Cell cycle–stimulating pathway

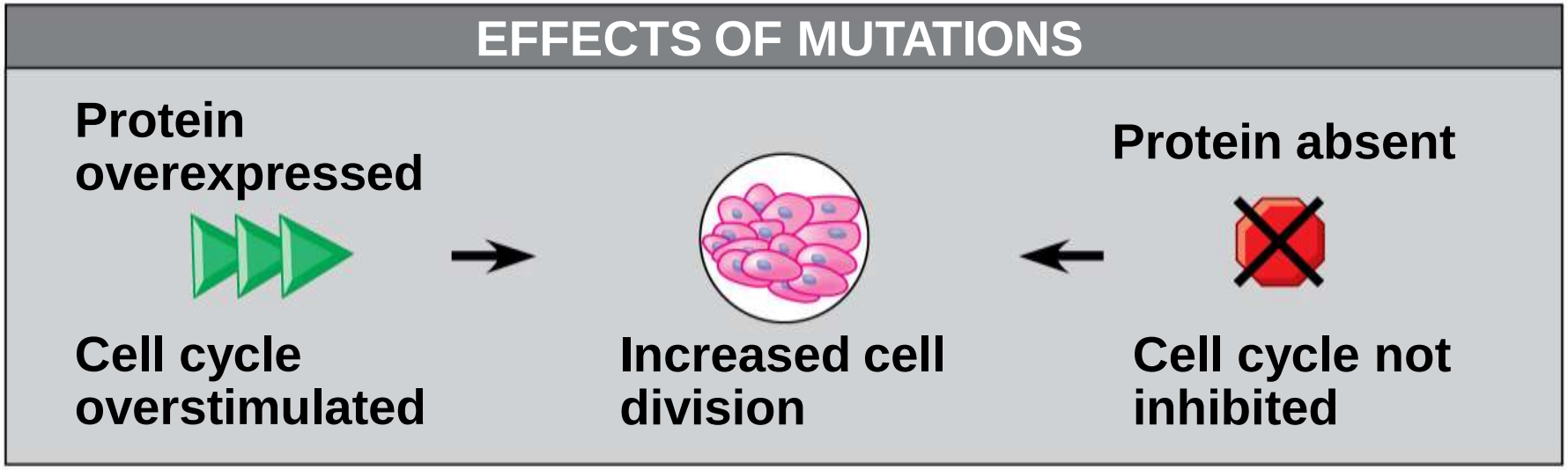
Figure 18.24b



(b) Cell cycle–inhibiting pathway

- Suppression of the cell cycle can be important in the case of damage to a cell's DNA; *p53* prevents a cell from passing on mutations due to DNA damage
- Mutations in the ***p53* gene** prevent suppression of the cell cycle

Figure 18.24c



(c) Effects of mutations

The Multistep Model of Cancer Development

- Multiple mutations are generally needed for full-fledged cancer; thus the incidence increases with age
- At the DNA level, a cancerous cell is usually characterized by at least one active oncogene and the mutation of several tumor-suppressor genes

Figure 18.25

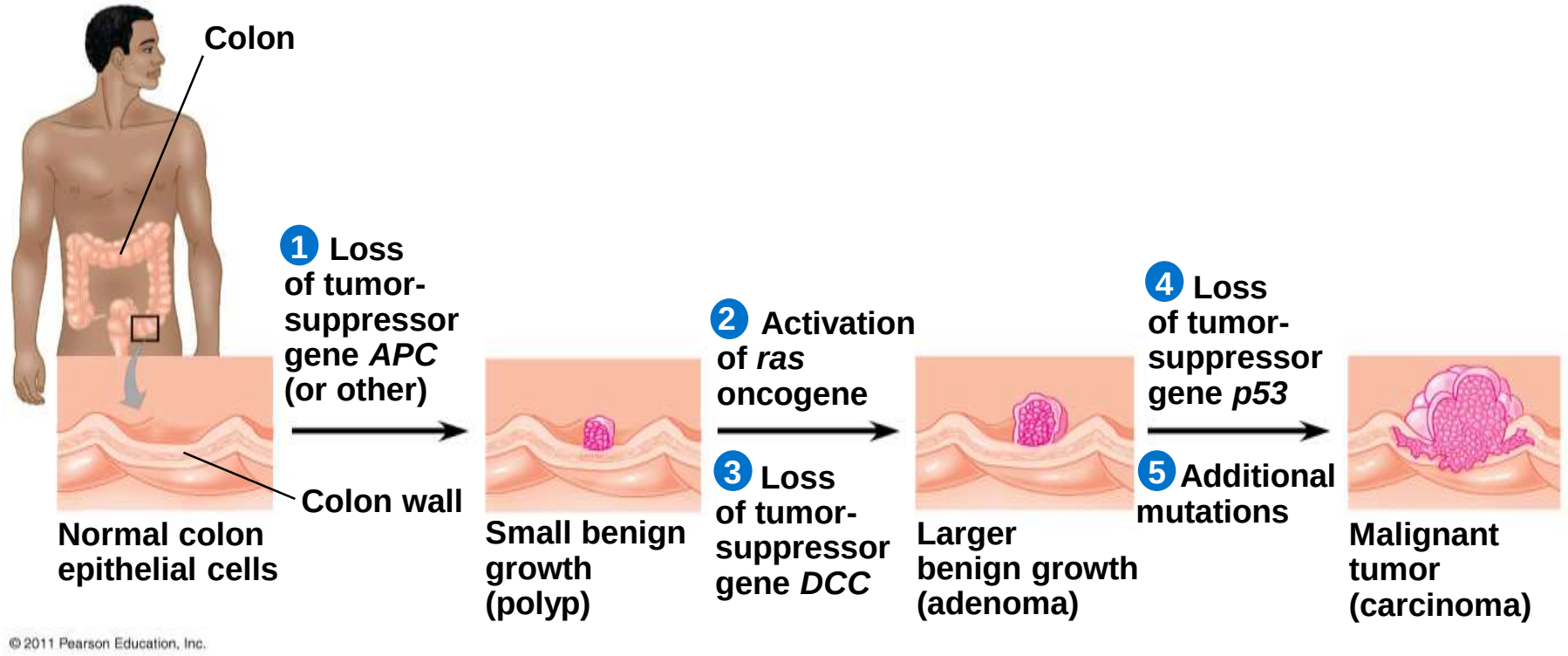
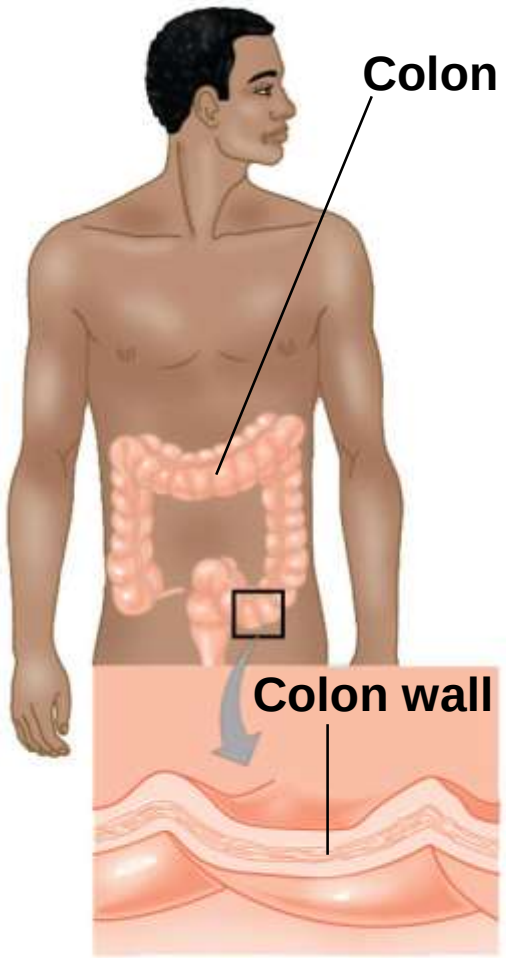


Figure 18.25a



Normal colon epithelial cells

Figure 18.25b

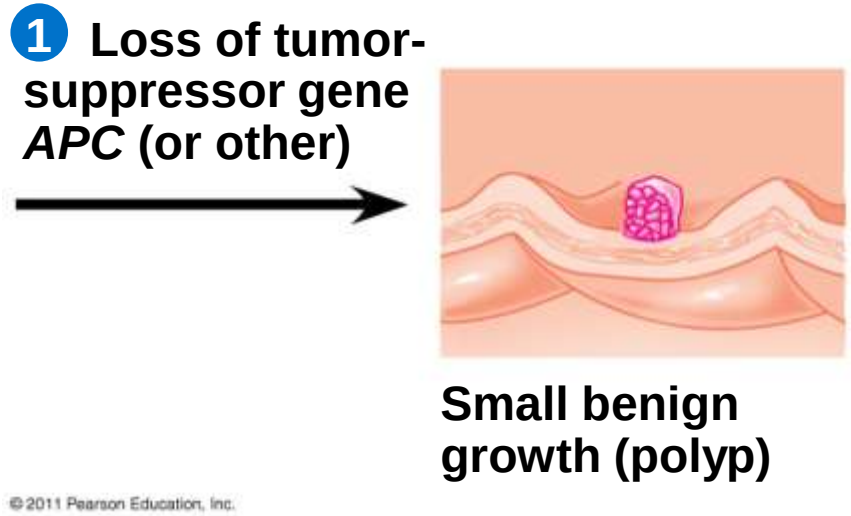


Figure 18.25c

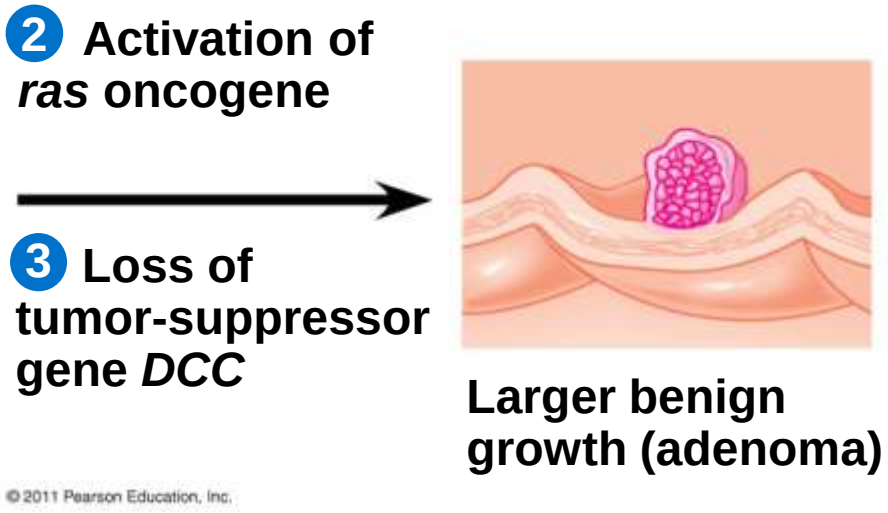
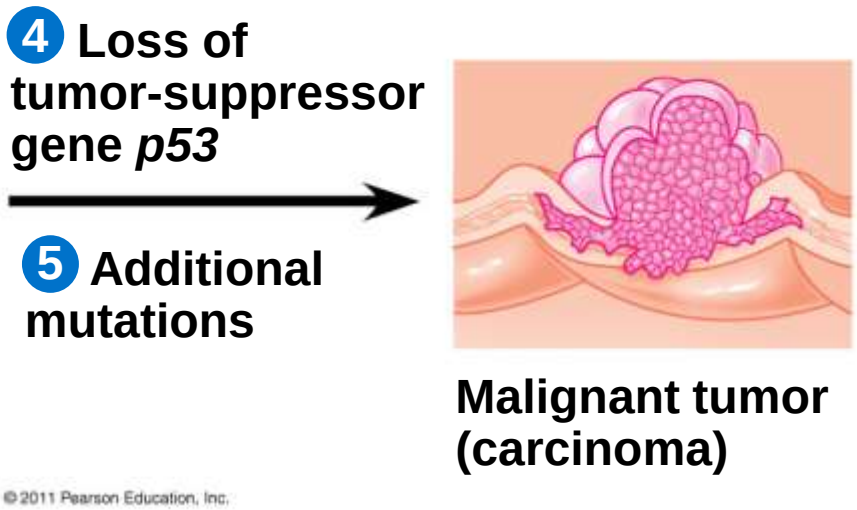


Figure 18.25d



Inherited Predisposition and Other Factors Contributing to Cancer

- Individuals can inherit oncogenes or mutant alleles of tumor-suppressor genes
- Inherited mutations in the tumor-suppressor gene *adenomatous polyposis coli* are common in individuals with colorectal cancer
- Mutations in the *BRCA1* or *BRCA2* gene are found in at least half of inherited breast cancers, and tests using DNA sequencing can detect these mutations