Chapter 18

Regulation of Gene Expression

PowerPoint® Lecture Presentations for

Biology

Eighth Edition

Neil Campbell and Jane Reece

Lectures by Chris Romero, updated by Erin Barley with contributions from Joan Sharp

Overview: Conducting the Genetic Orchestra

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

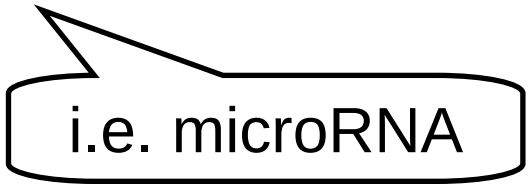
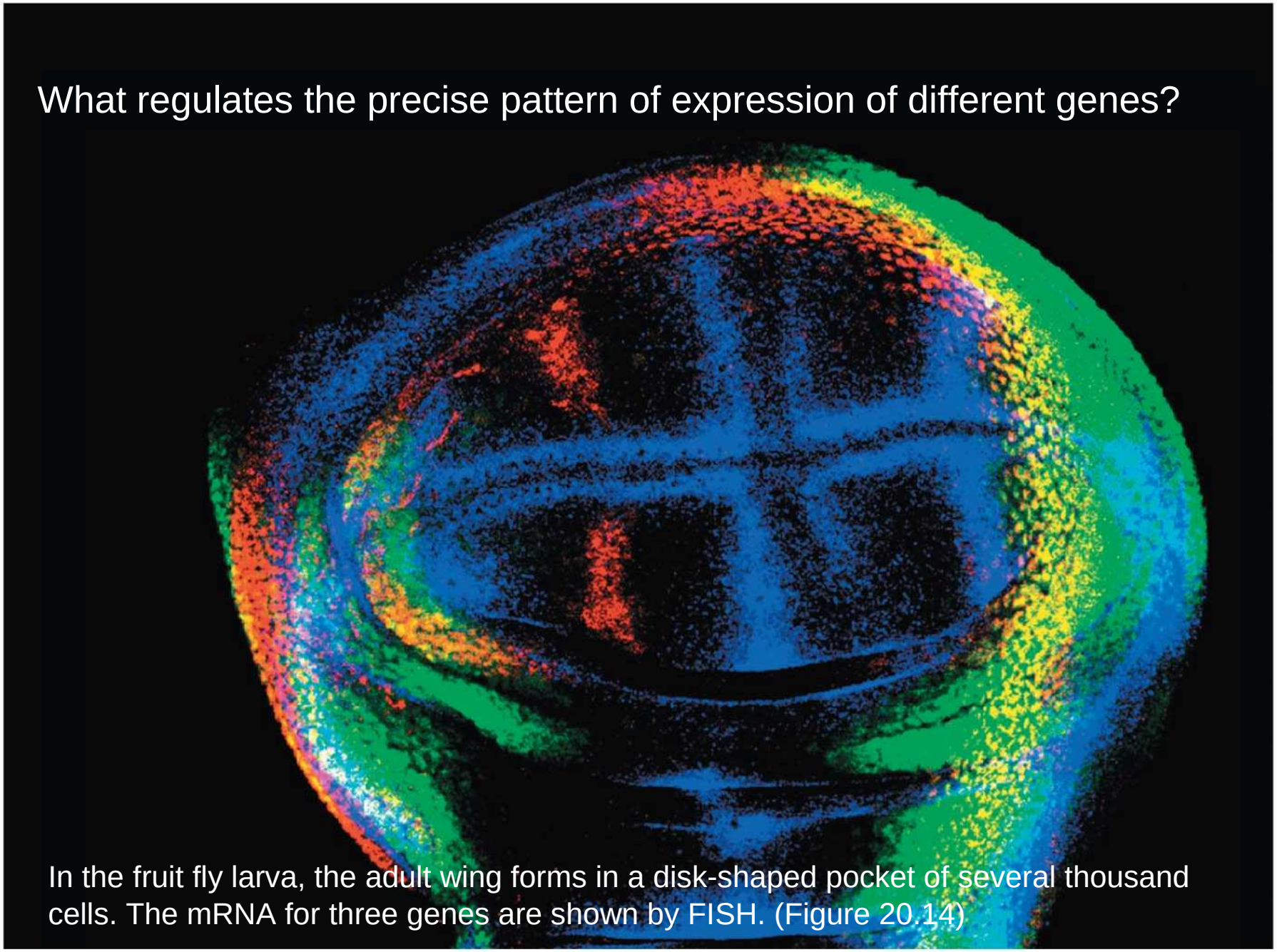
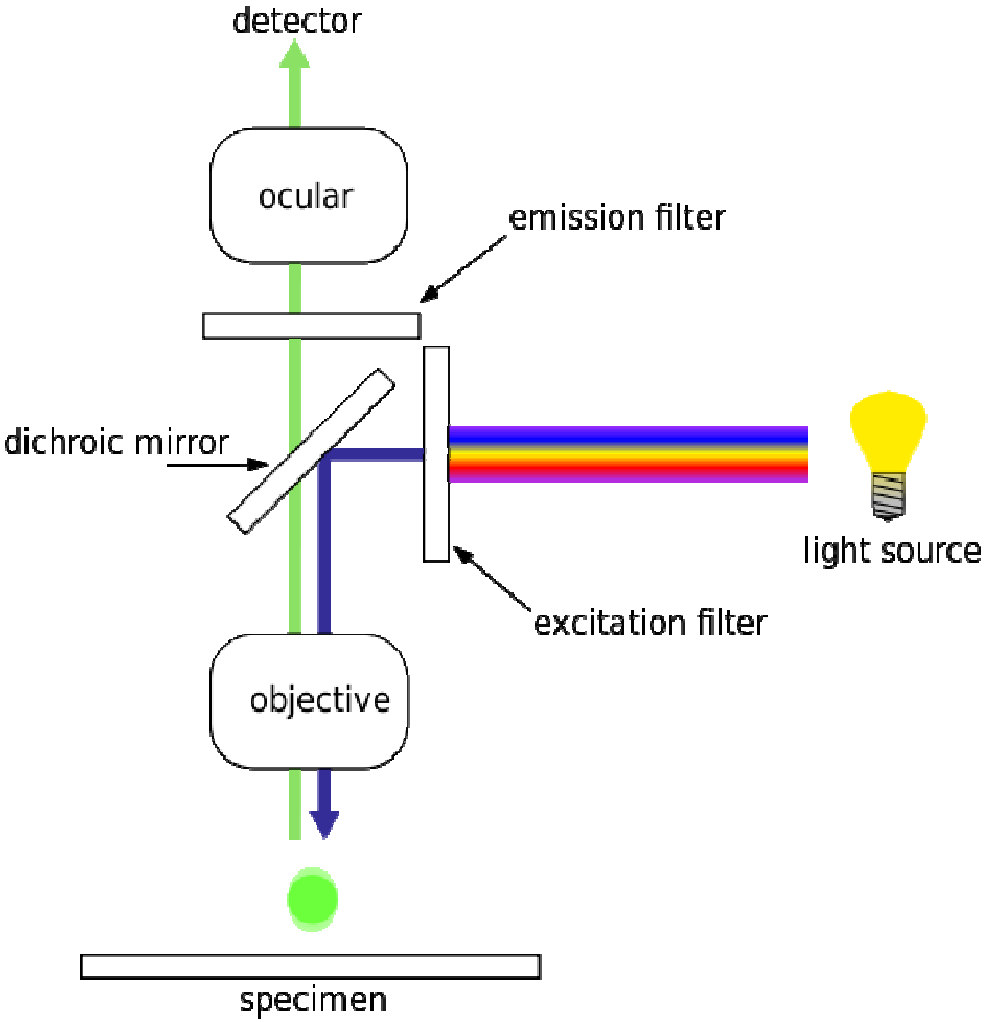
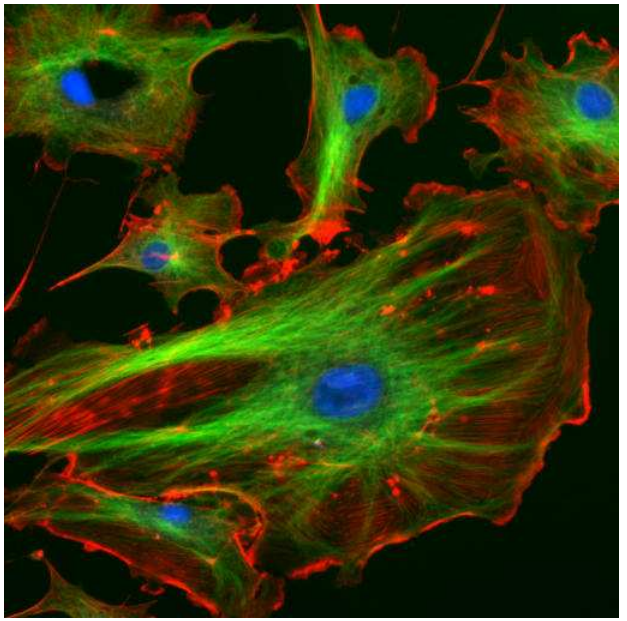


Fig. 18-1



Fluorescent Microscope

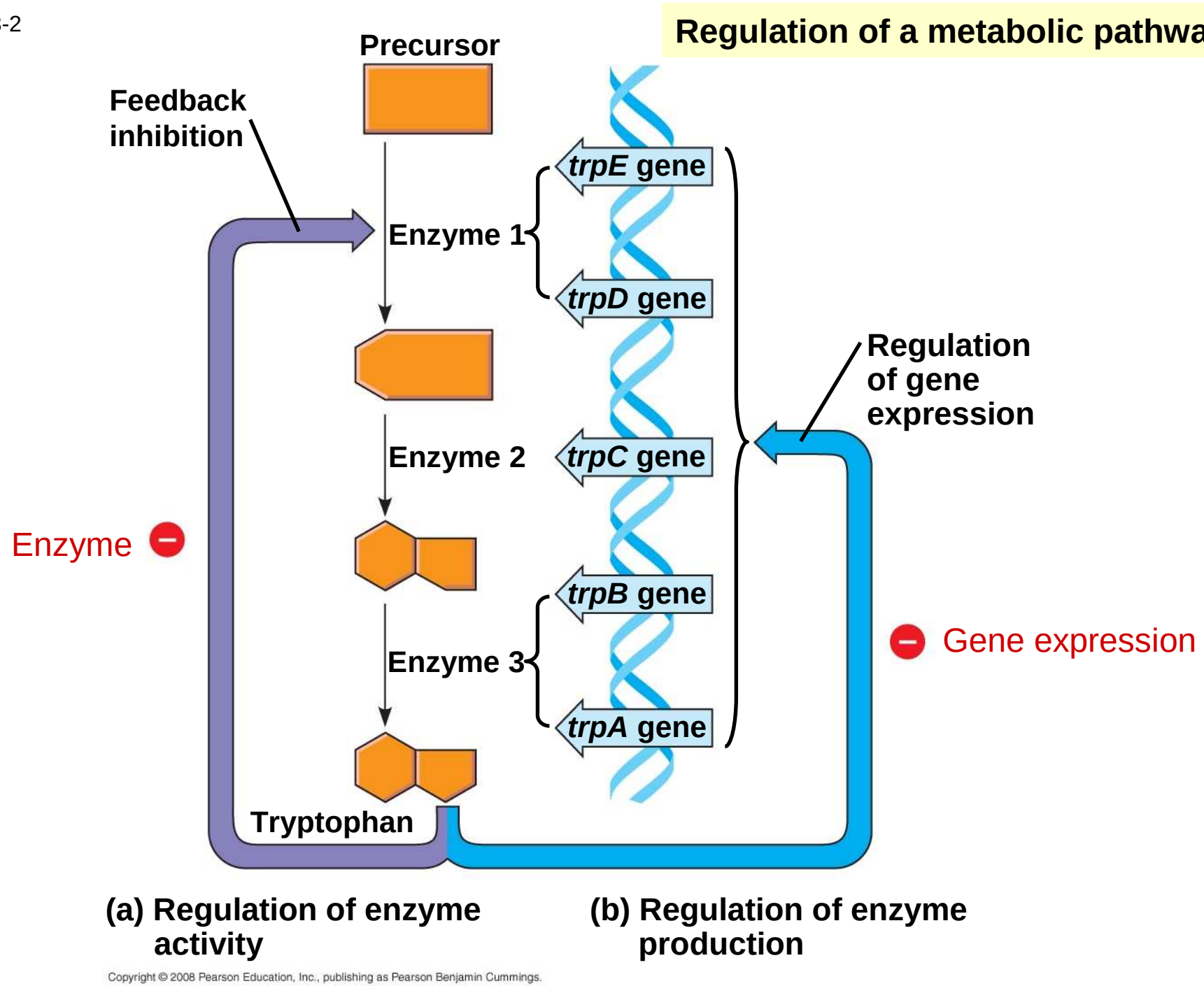




Concept 18.1: Bacteria often respond to environmental change by regulating transcription

- Natural selection has favored bacteria that produce *only the products needed* by that cell
- A cell can regulate the production of enzymes by feedback inhibition or by gene regulation
- Gene expression in bacteria is controlled by the operon model

Fig. 18-2



Operons: The Basic Concept 操縱子(?)

- A cluster of functionally related genes can be under coordinated control by a single on-off "switch"
- The regulatory "switch" is a segment of DNA called an **operator** usually positioned within the promoter
- An **operon** is the entire stretch of DNA that includes the operator, the promoter, and the genes that they control

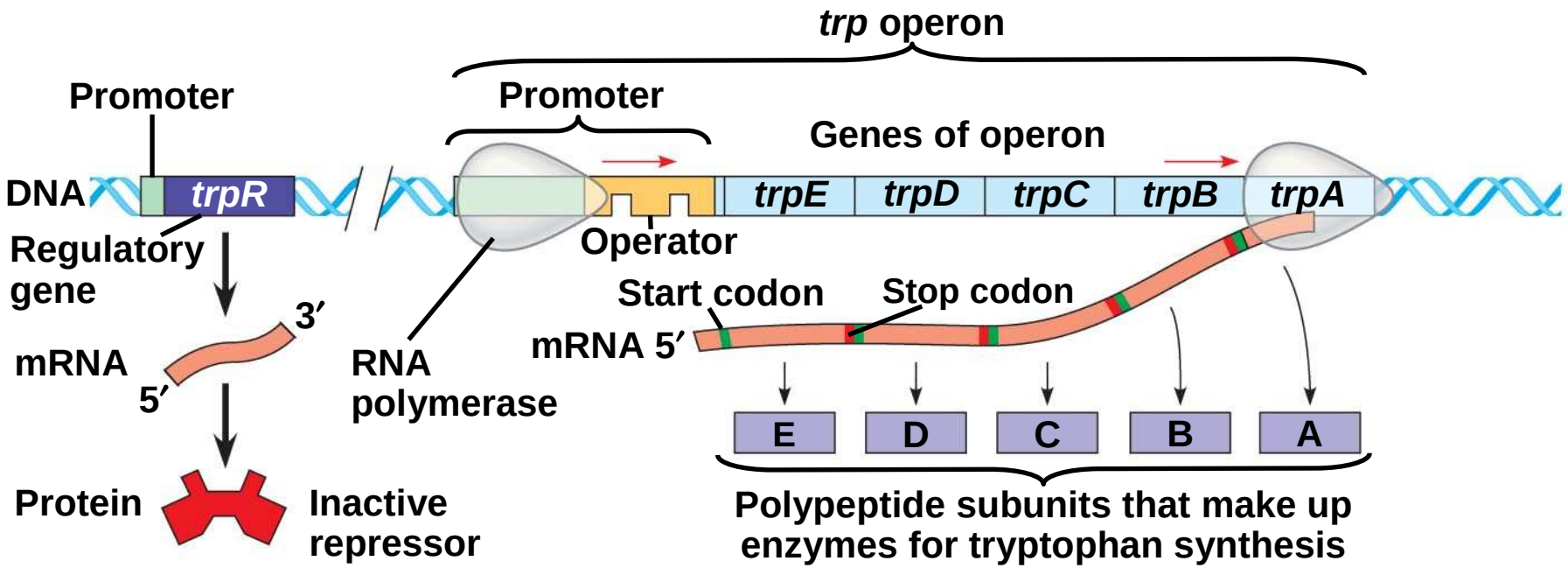
Repressor 抑壓子(?)

- The operon can be switched off by a protein **repressor**
- The repressor prevents gene transcription by binding to the operator and blocking RNA polymerase
- The repressor is the product of a separate **regulatory gene**

- The repressor can be in an active or inactive form, depending on the presence of other molecules
- A **corepressor** is a molecule that cooperates with a repressor protein to switch an operon off
- For example, *E. coli* can synthesize the amino acid tryptophan

Fig. 18-3a

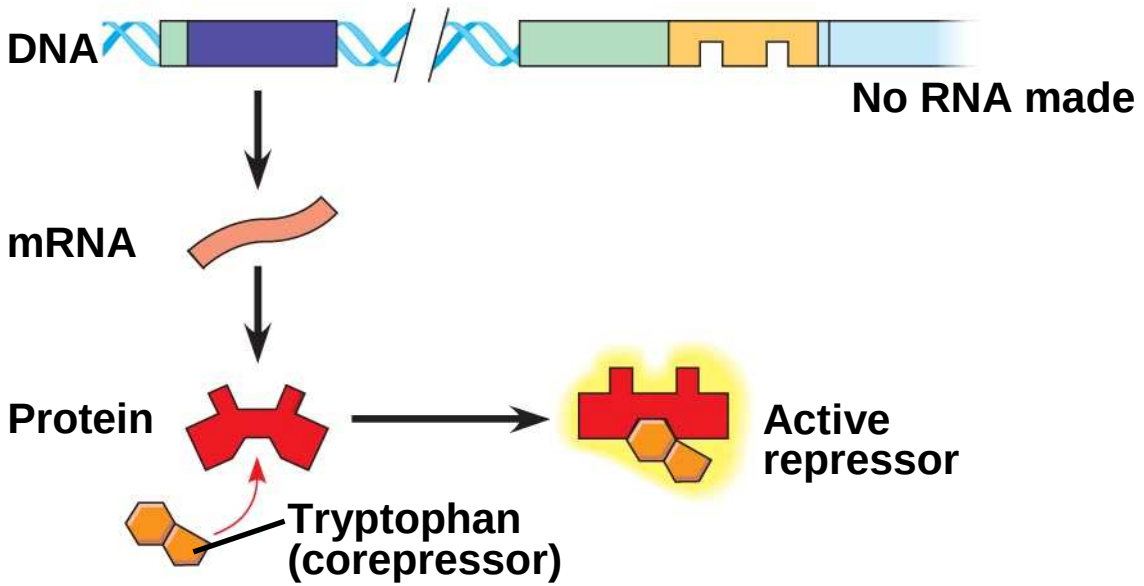
The *trp* operon in *E. coli*: regulated synthesis of repressible enzymes



(a) Tryptophan absent, repressor inactive, operon on

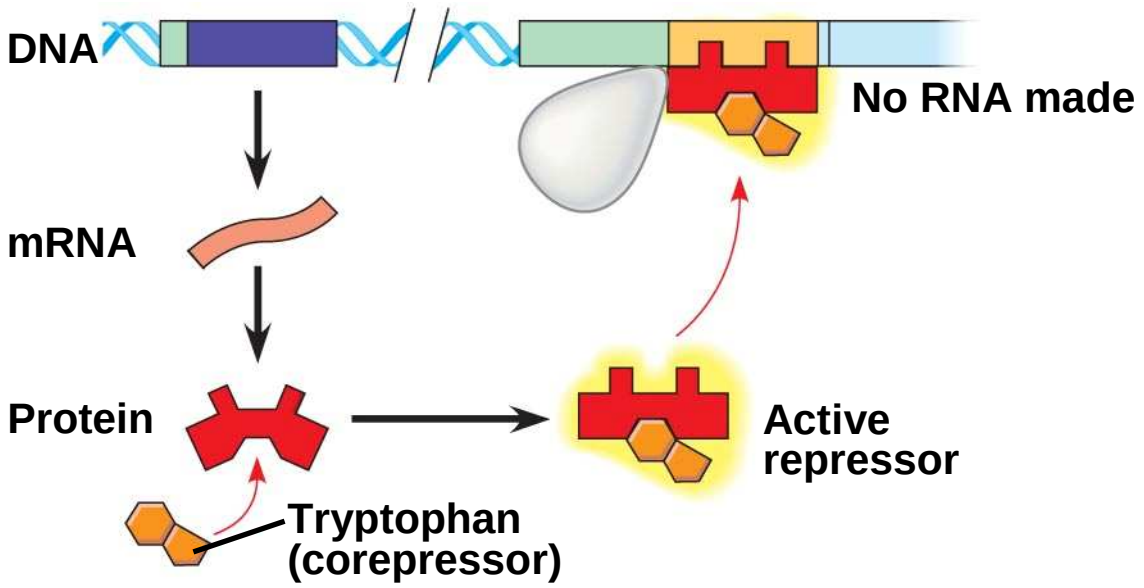
Fig. 18-3b-1

The *trp* operon in *E. coli*: regulated synthesis of repressible enzymes



Tryptophan present, repressor active

Fig. 18-3b-2



repressor active, operon off

Summary

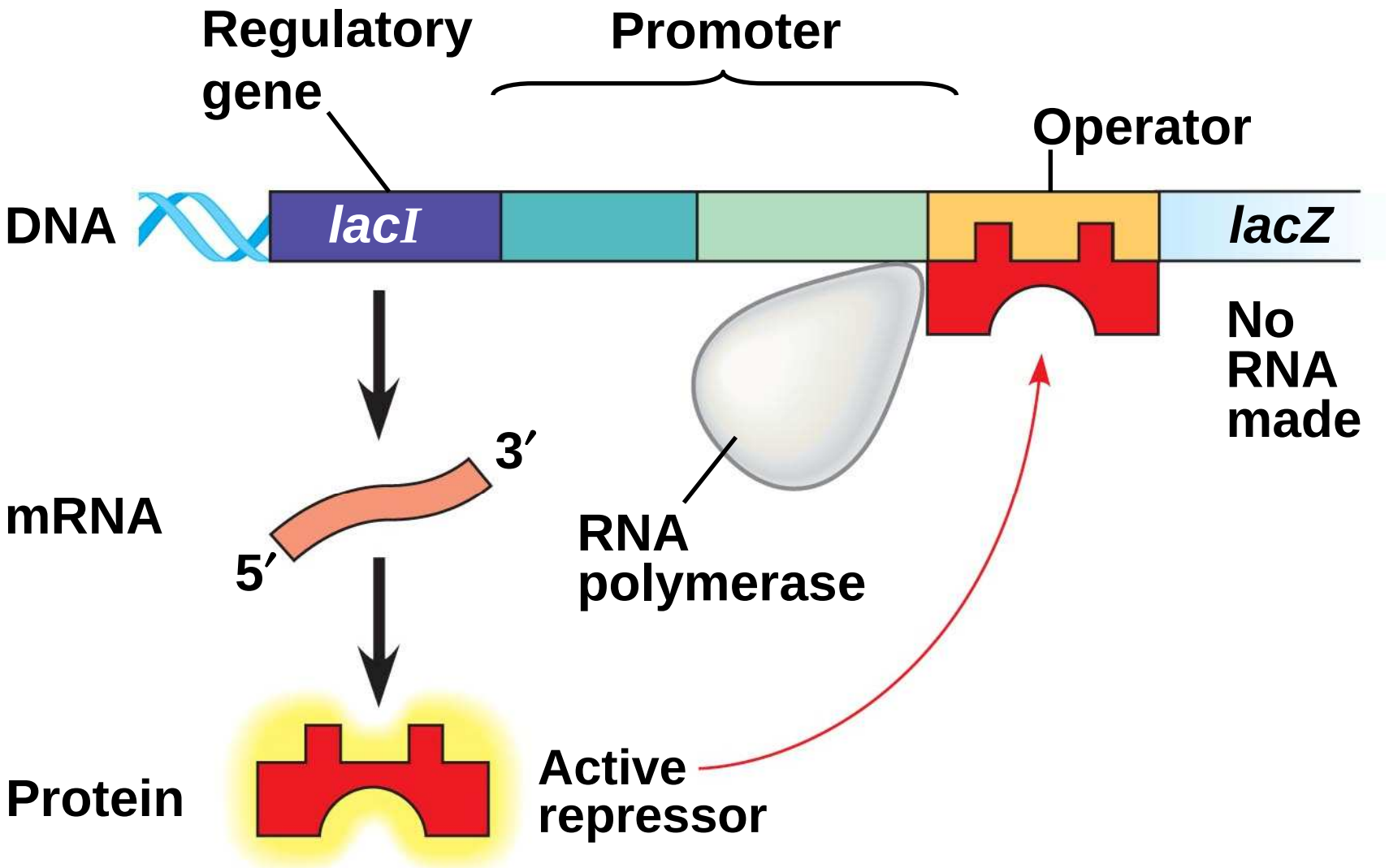
- By default（系統默認值）the *trp* operon is on and the genes for tryptophan synthesis are transcribed
- When tryptophan is present, it binds to the *trp* repressor protein, which turns the operon off
- The repressor is active only in the presence of its corepressor tryptophan; thus the *trp* operon is turned off (repressed) if tryptophan levels are high

Repressible and Inducible Operons: Two Types of Negative Gene Regulation

- A repressible operon is one that is usually on; binding of a repressor to the operator shuts off transcription
- The *trp* operon is a repressible operon
- An inducible operon is one that is usually off; a molecule called an inducer inactivates the repressor and turns on transcription

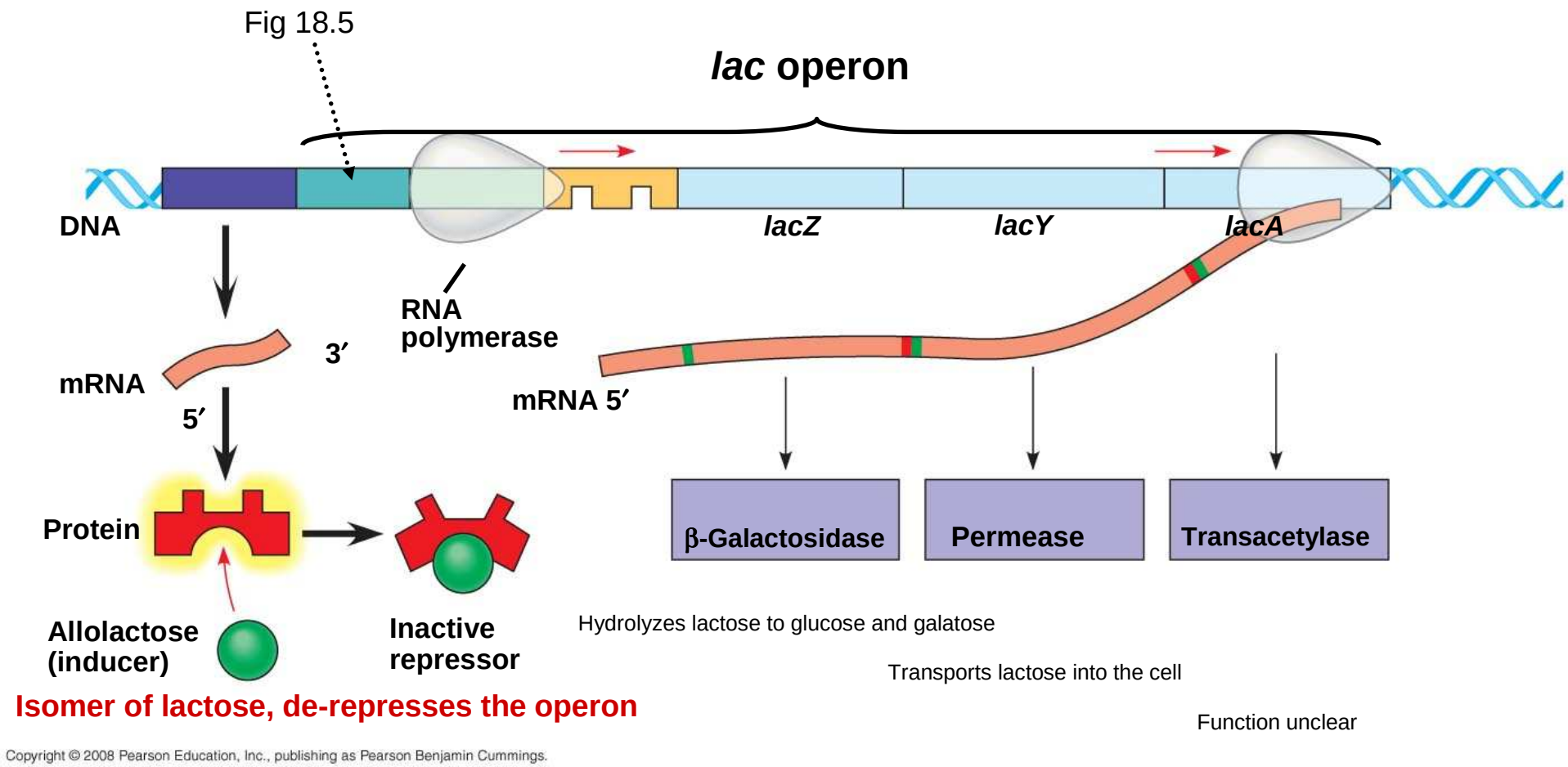
- The *lac* operon is an inducible operon and contains genes that code for enzymes used in the hydrolysis and metabolism of lactose
- By itself, the *lac* repressor is active and switches the *lac* operon off
- A molecule called an **inducer** inactivates the repressor to turn the *lac* operon on

Fig. 18-4a



(a) Lactose absent, repressor active, operon off

Fig. 18-4b



(b) Lactose present, repressor inactive, operon on

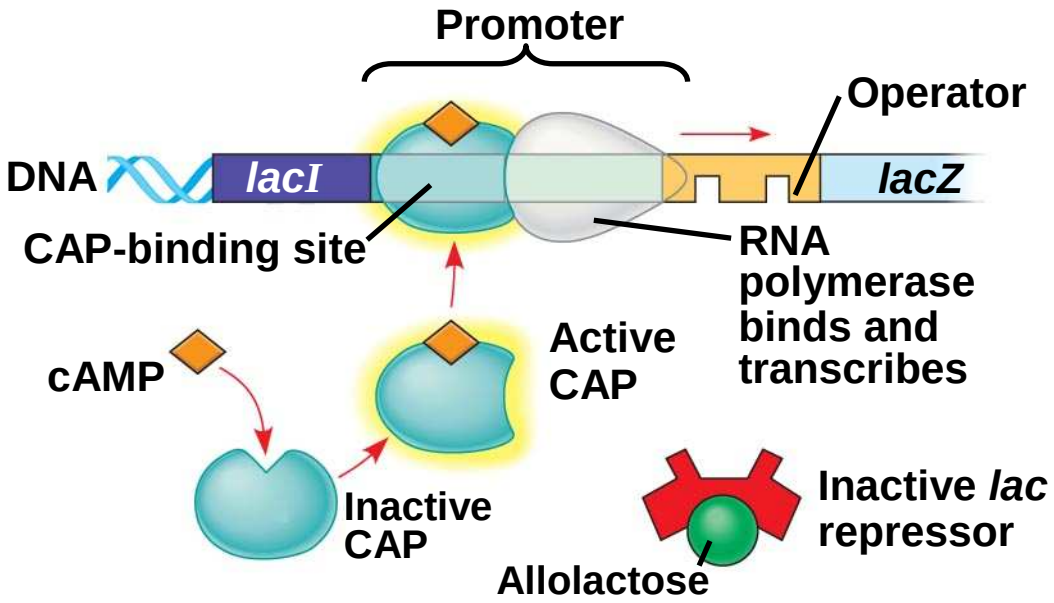
- Inducible enzymes usually function in catabolic pathways（催化、分解）; their synthesis is induced by a chemical signal
- Repressible enzymes usually function in anabolic pathways（合成代謝）; their synthesis is repressed by high levels of the end product
- Regulation of the *trp* and *lac* operons involves negative control of genes because operons are switched off by the active form of the repressor

Positive Gene Regulation

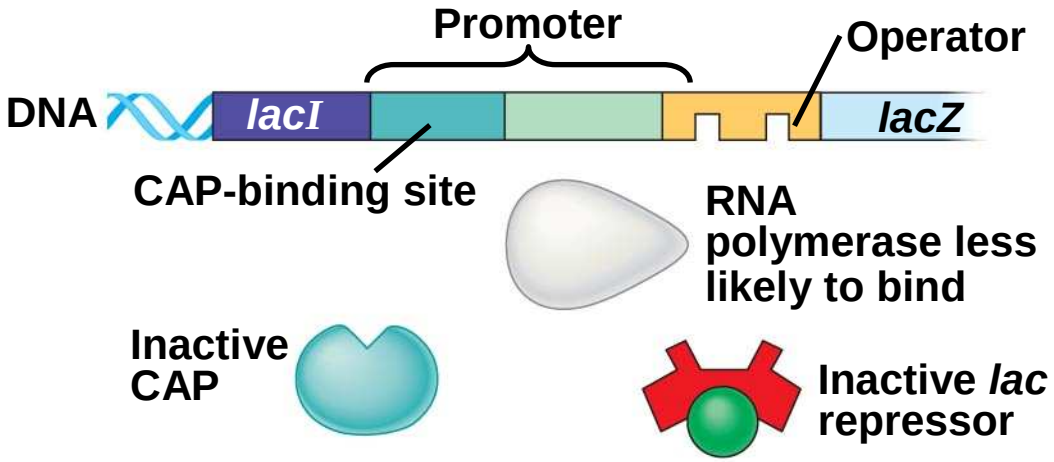
- Some operons are also subject to positive control through a stimulatory protein, such as catabolite activator protein (CAP), an **activator** of transcription
- When glucose (a preferred food source of *E. coli*) is scarce, CAP is activated by binding with **cyclic AMP**
- Activated CAP attaches to the promoter of the *lac* operon and increases the affinity of RNA polymerase, thus accelerating transcription

- When glucose levels increase, CAP detaches from the *lac* operon, and transcription returns to a normal rate
- CAP helps regulate other operons that encode enzymes used in catabolic pathways

Fig. 18-5



(a) Lactose present, glucose scarce (cAMP level high): abundant *lac* mRNA synthesized



(b) Lactose present, glucose present (cAMP level low): little *lac* mRNA synthesized

Concept 18.2: Eukaryotic gene expression can be regulated at any stage

- All organisms must regulate which genes are expressed at any given time
- In multicellular organisms 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
- Errors in gene expression can lead to diseases including cancer
- Gene expression is regulated at many stages

Fig. 18-6a

細胞核内

Stages in gene expression that can be regulated in eukaryotic cells

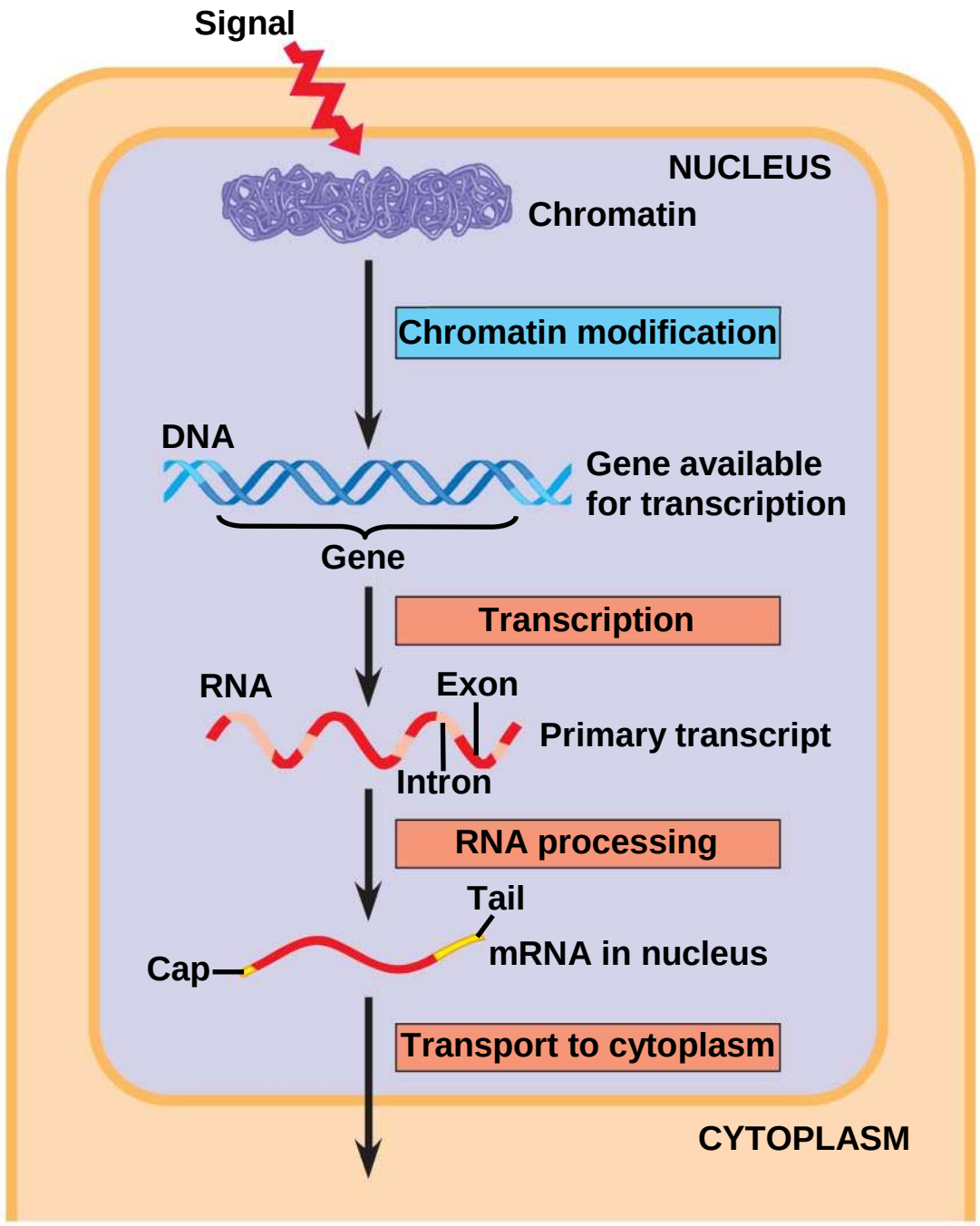
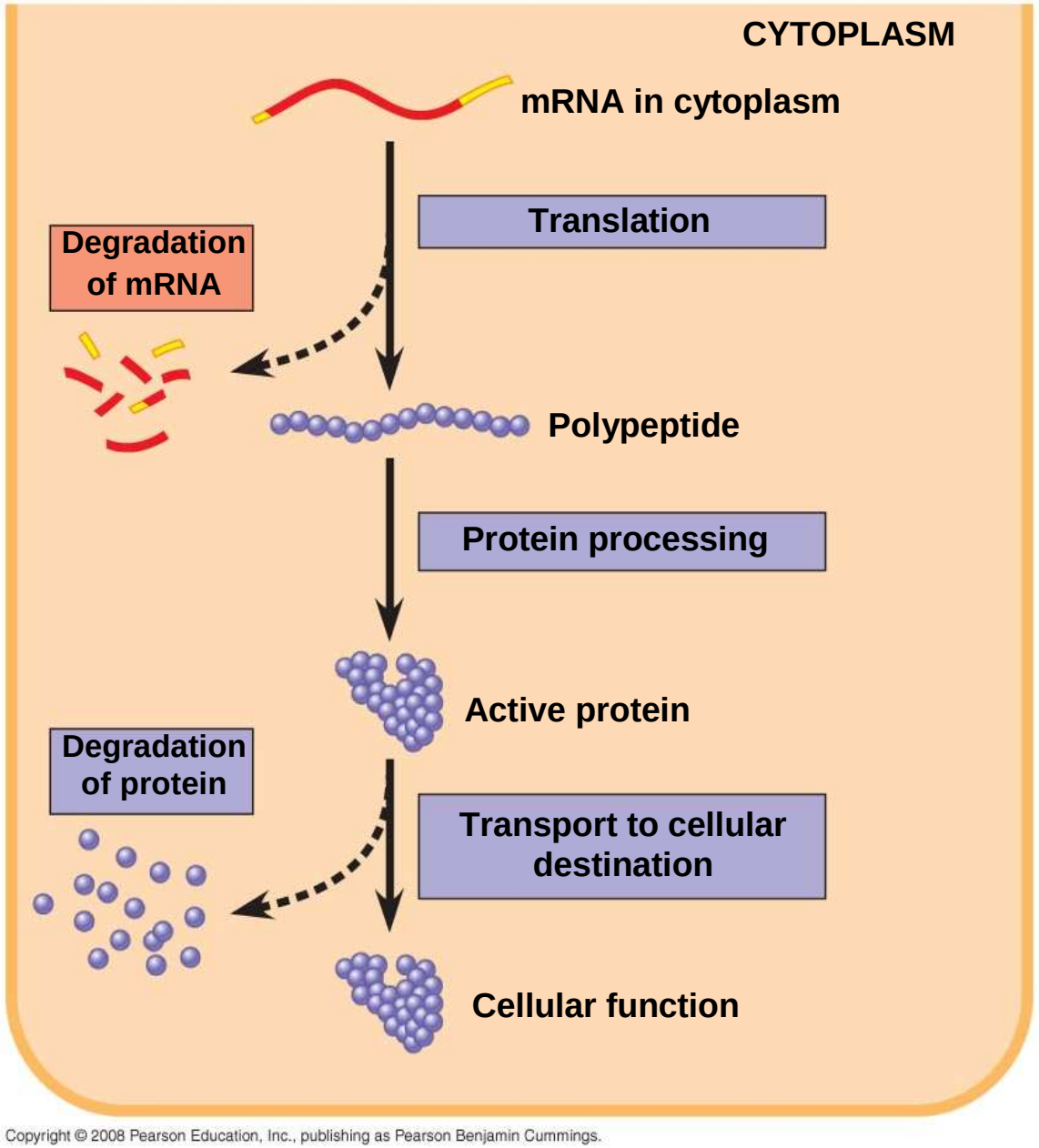


Fig. 18-6b

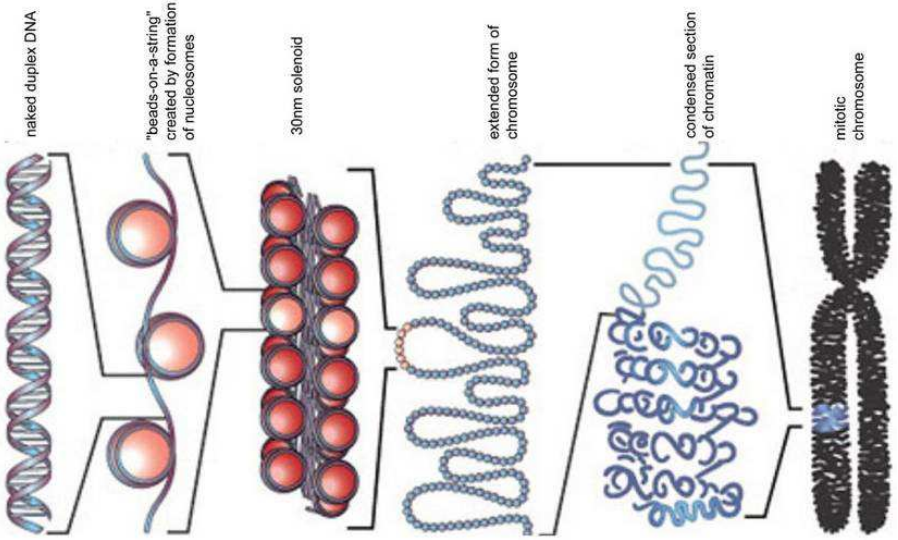
細胞質内

Stages in gene expression that can be regulated in eukaryotic cells



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



核染色質的堆疊與結構會影響基因表現

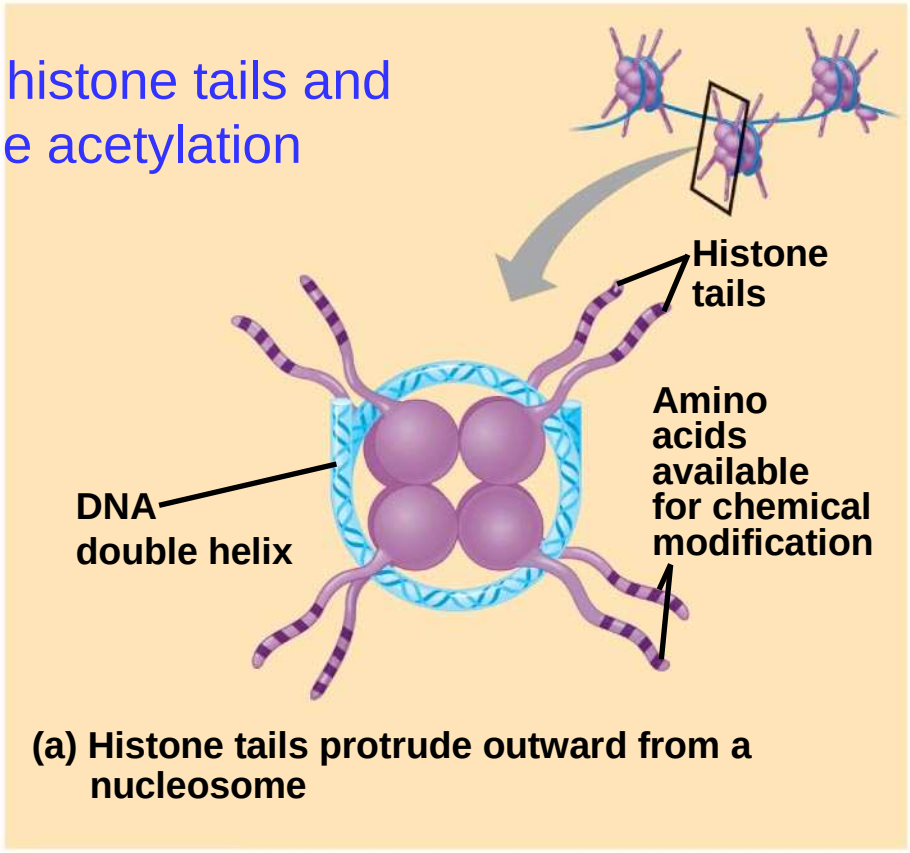
Histone Modifications

- In **histone acetylation**, acetyl groups are attached to positively charged lysines in histone tails. This process 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

PLAY Animation: DNA Packing

Fig. 18-7

A simple model of histone tails and the effect of histone acetylation



- The histone code hypothesis proposes that specific combinations of modifications 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 **control elements**, segments of noncoding DNA that help regulate transcription by binding certain proteins
- Control elements (it is DNA) and the proteins they bind are critical to the precise regulation of gene expression in different cell types

Fig. 18-8-1

A eukaryotic gene and its transcript

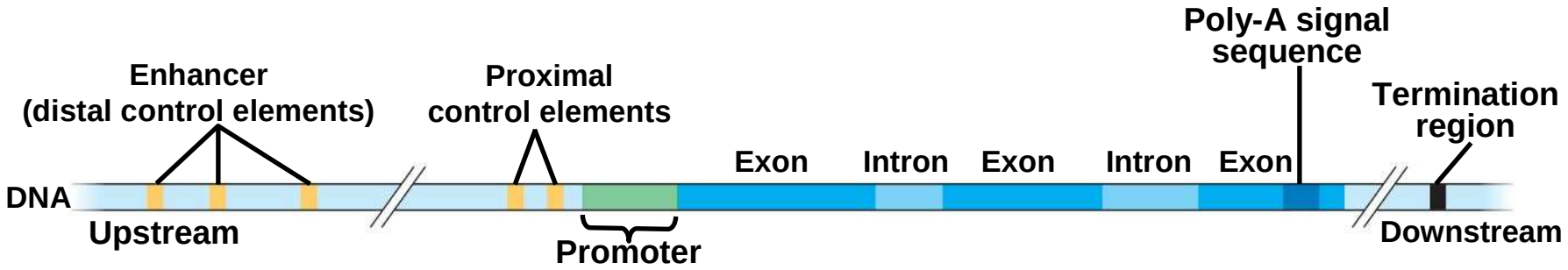


Fig. 18-8-2

A eukaryotic gene and its transcript

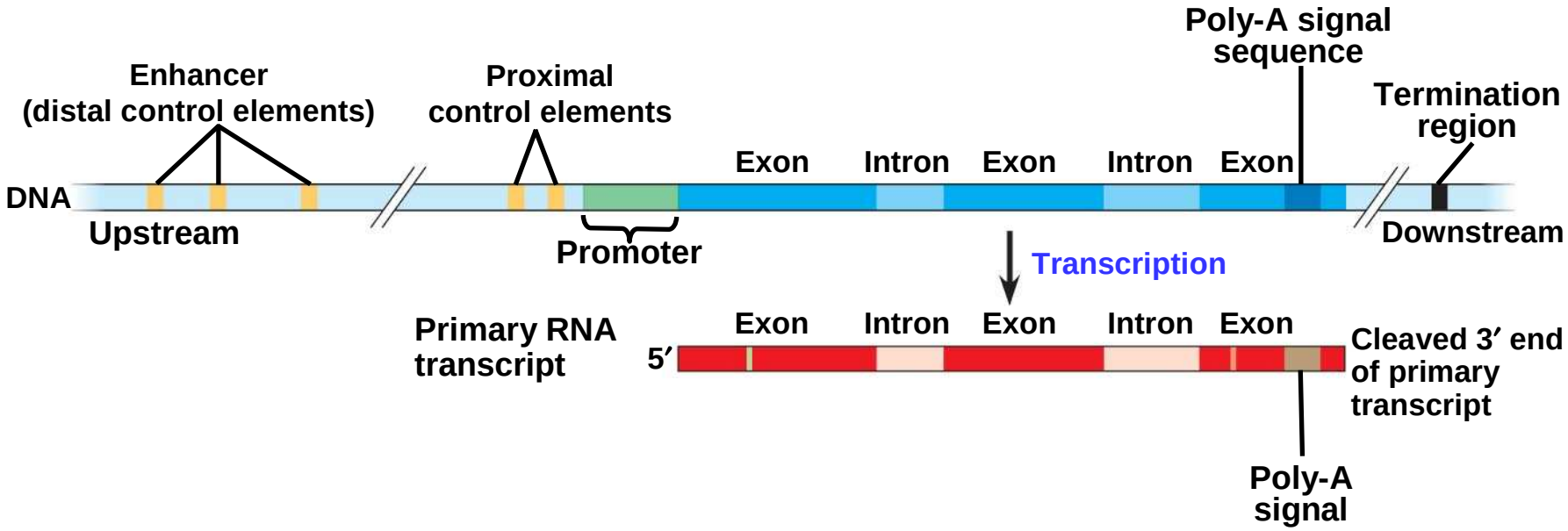
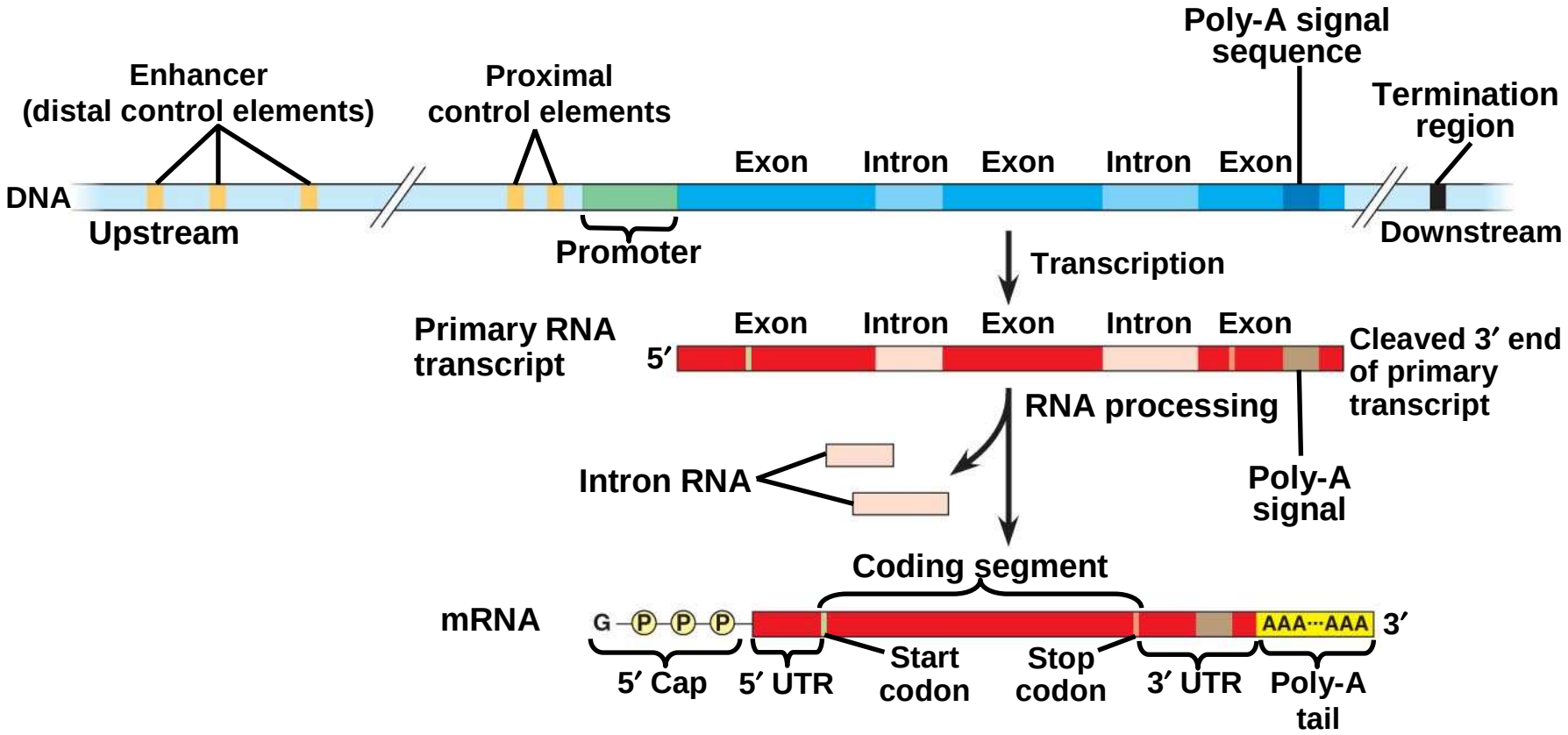


Fig. 18-8-3

A eukaryotic gene and its transcript



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**, groups 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
- Bound activators cause mediator proteins to interact with proteins at the promoter

PLAY Animation: Initiation of Transcription

Fig. 18-9-1

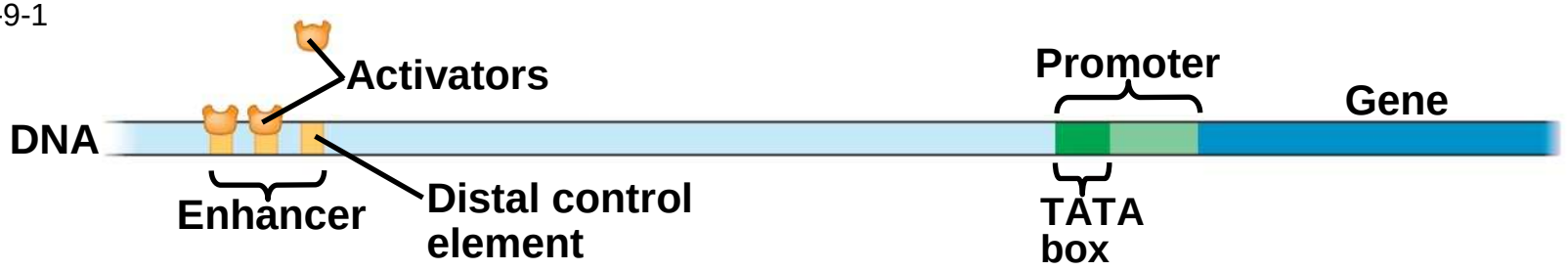


Fig. 18-9-2

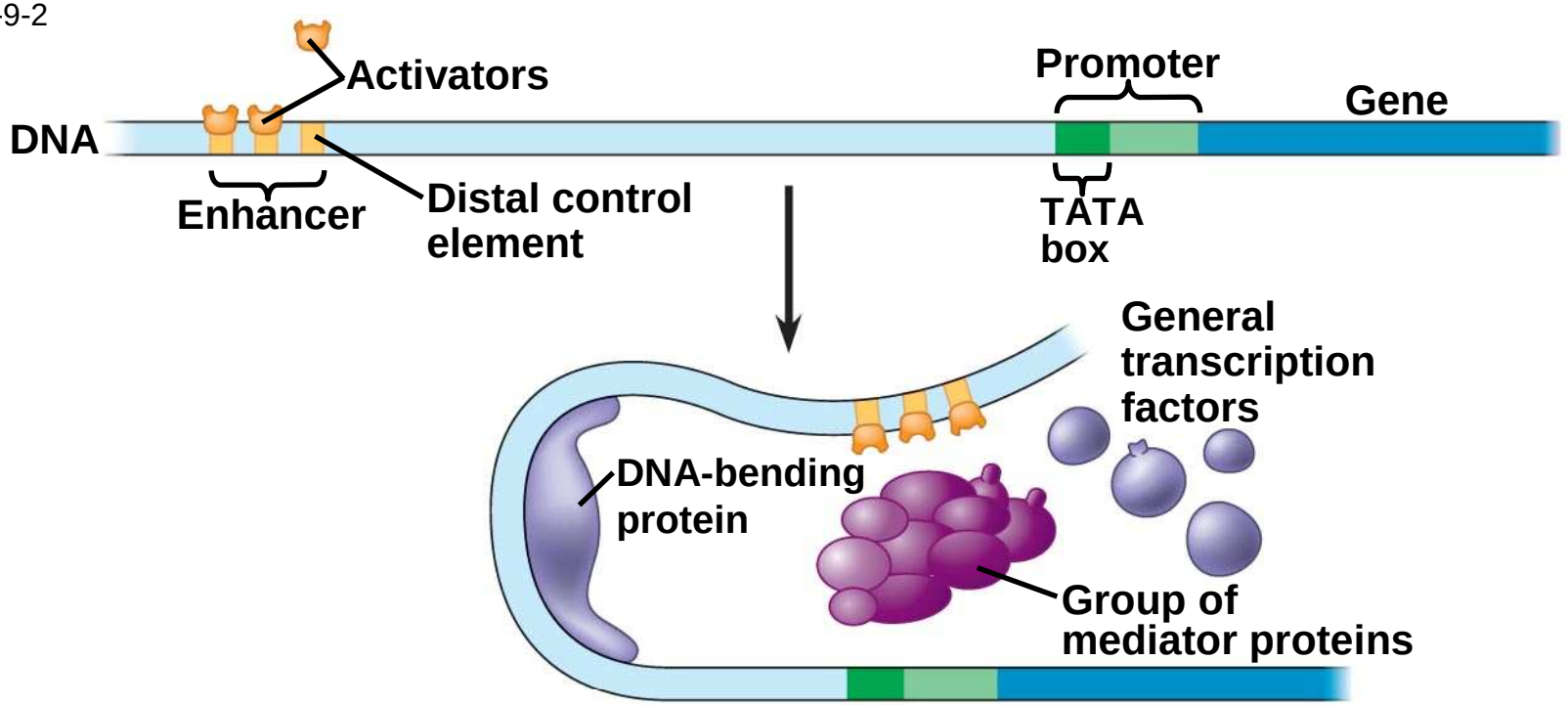
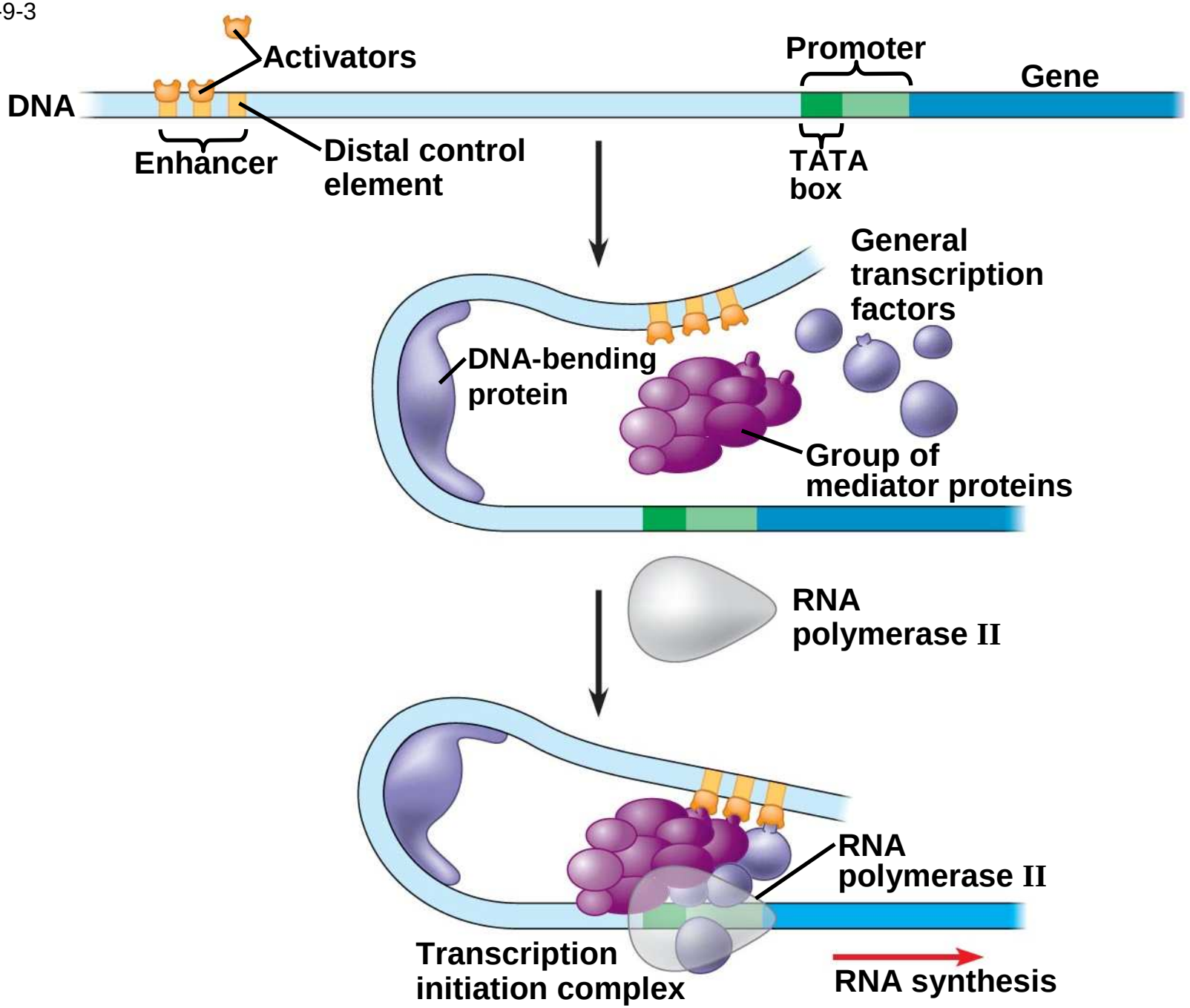


Fig. 18-9-3



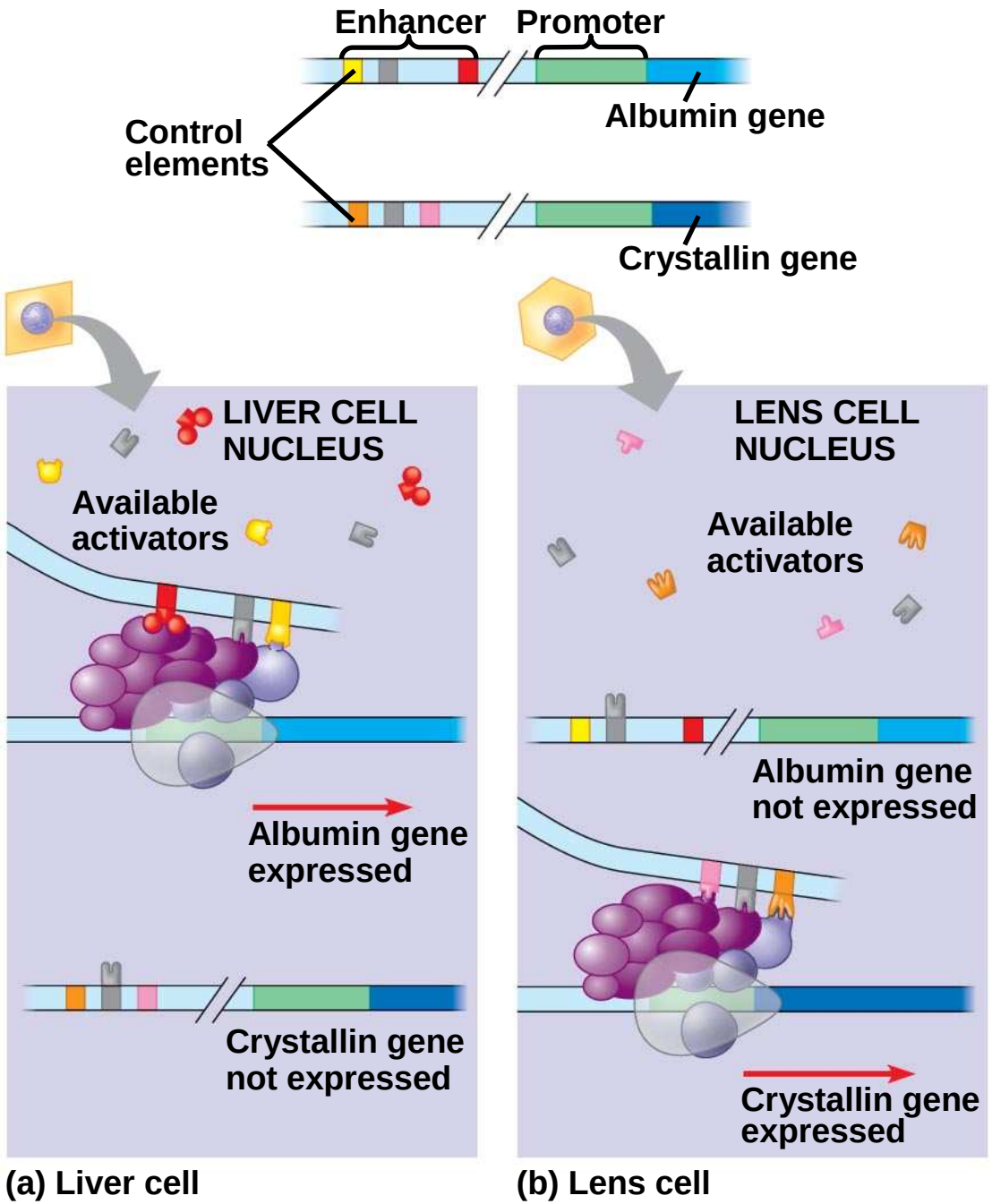
- Some transcription factors function as repressors, inhibiting expression of a particular gene
- Some activators and repressors act indirectly by influencing chromatin structure to promote or silence transcription

Combinatorial Control of Gene Activation

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

Fig. 18-10

Cell type–specific transcription



Coordinately Controlled Genes in Eukaryotes

- Unlike the genes of a prokaryotic operon, each of the coordinately controlled eukaryotic genes has a promoter and control elements
- These genes can be scattered over different chromosomes, but each has the same combination of control elements
- Copies of the activators recognize specific control elements and promote simultaneous transcription of the genes

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

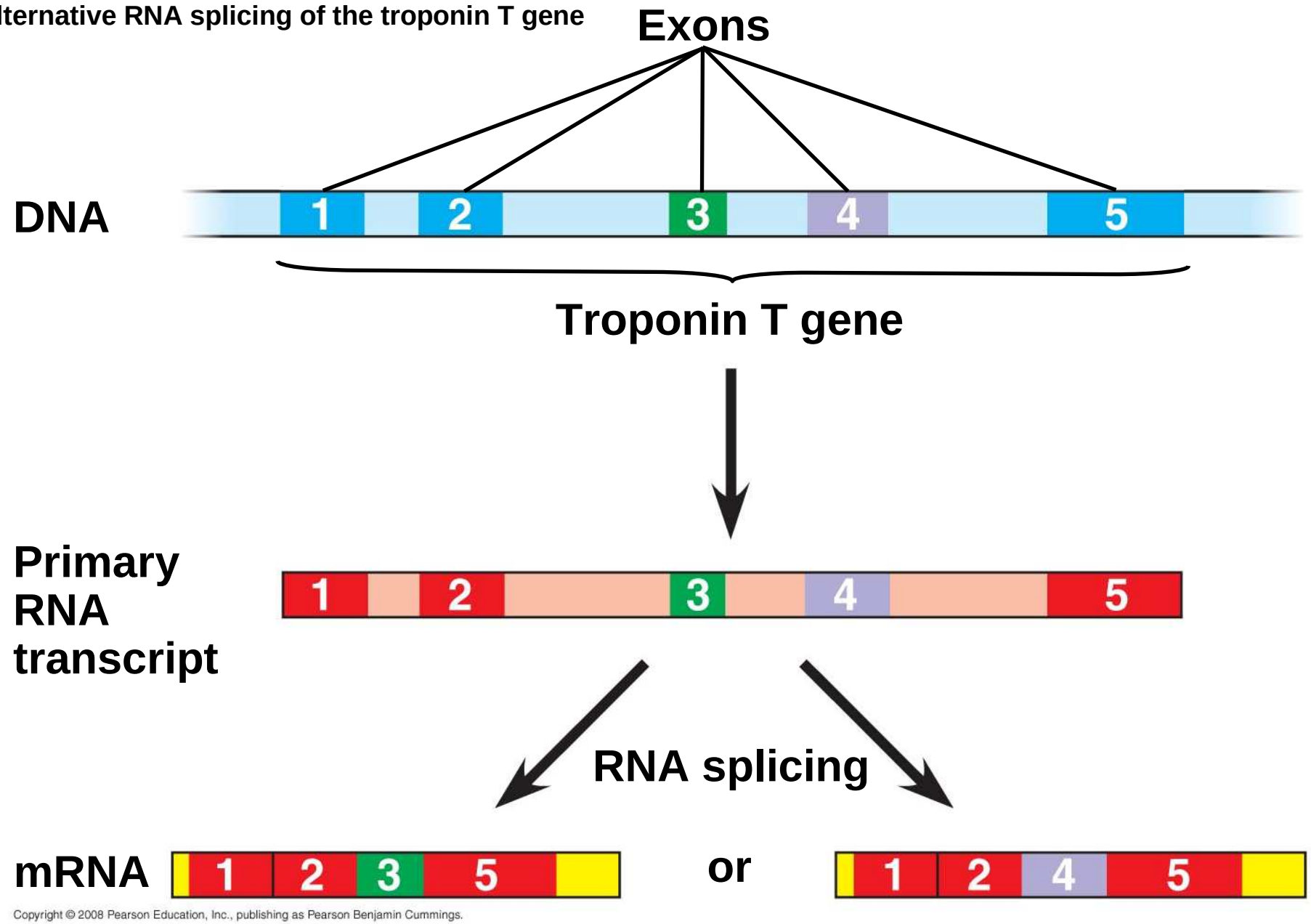
- In **alternative RNA splicing**, different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns

In fruit fly, less than ~13,700 genes can generate more than 38,000 proteins from alternatively spliced exons.

PLAY Animation: RNA Processing

Fig. 18-11

Alternative RNA splicing of the troponin T gene



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
- The mRNA life span is determined in part by sequences in the leader and trailer regions

PLAY Animation: mRNA Degradation

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

PLAY Animation: Blocking Translation

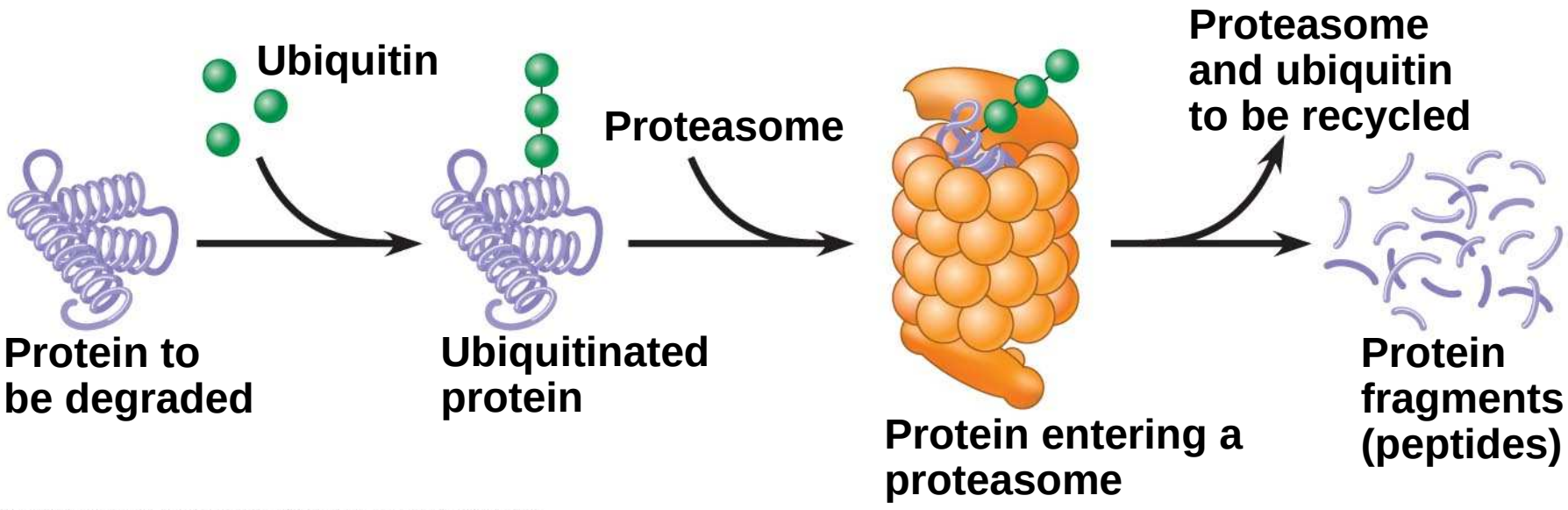
Protein Processing and Degradation

- 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

PLAY Animation: Protein Processing

PLAY Animation: Protein Degradation

Fig. 18-12



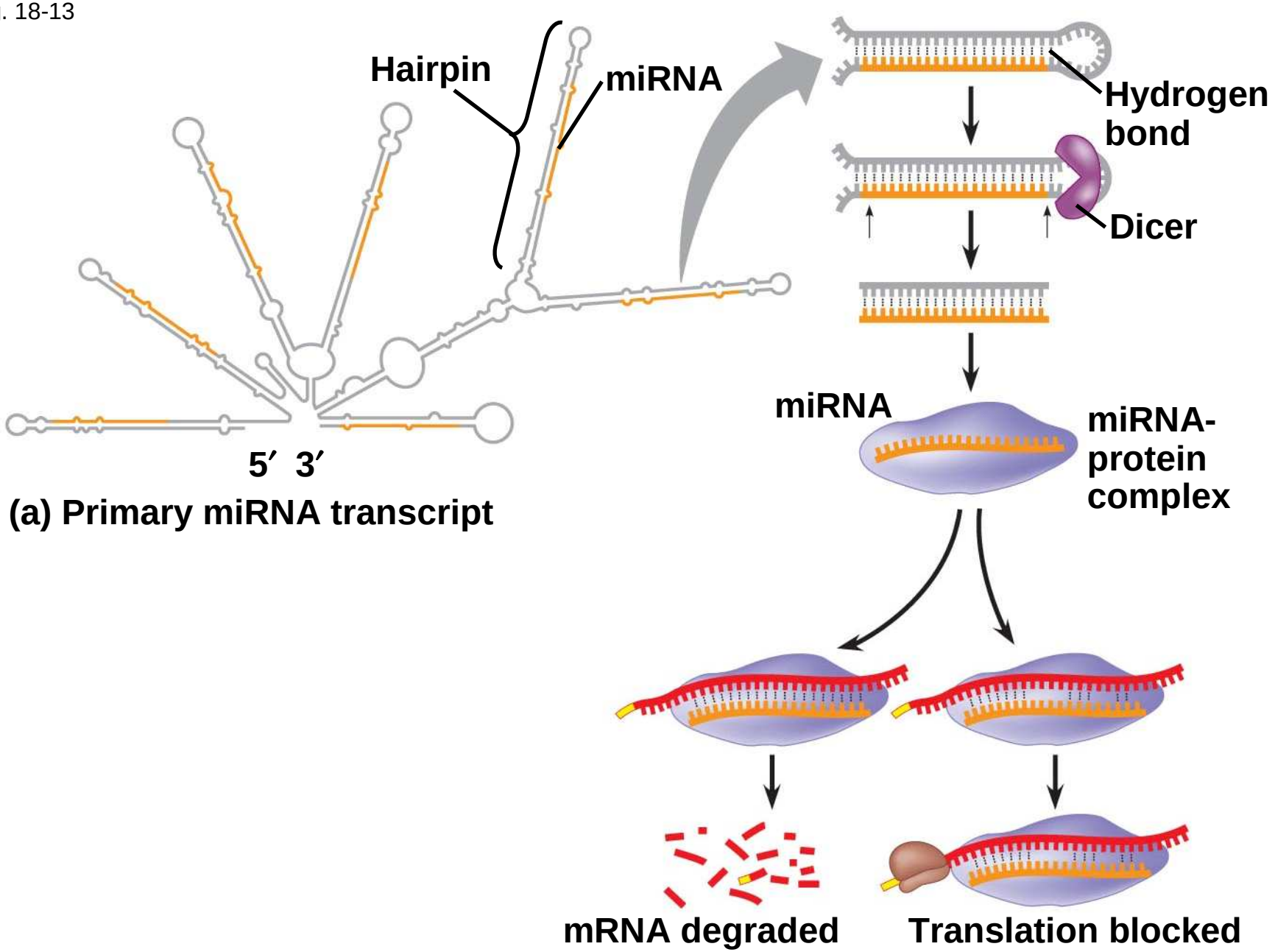
Concept 18.3: Noncoding RNAs play multiple roles in controlling gene expression

- Only a small fraction of DNA codes for proteins, rRNA, and tRNA
- A significant amount of the genome may be transcribed into noncoding RNAs
- 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

Fig. 18-13



- 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

Chromatin Remodeling and Silencing of Transcription by Small RNAs

- siRNAs play a role in heterochromatin formation and can block large regions of the chromosome
- Small RNAs may also block transcription of specific genes

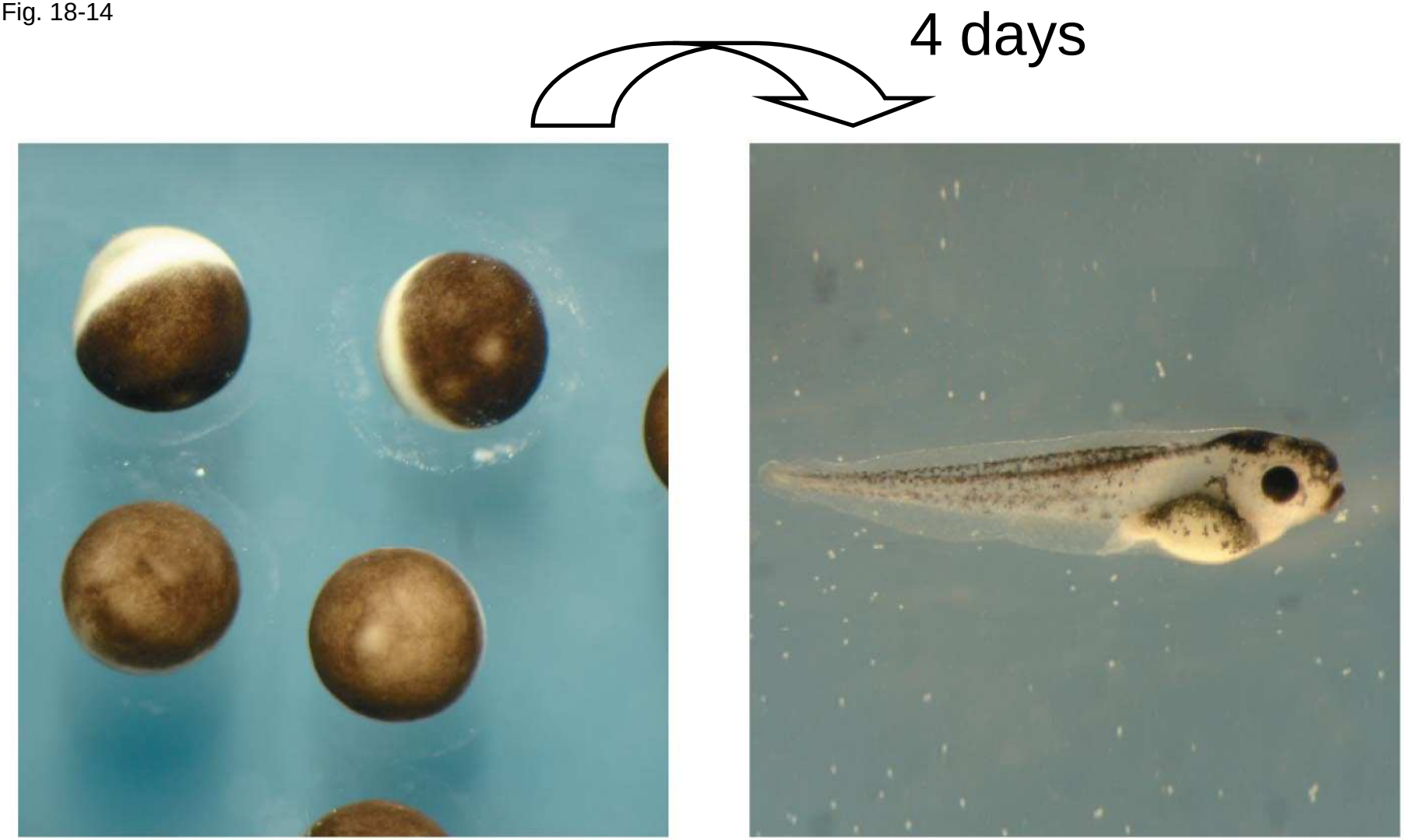
Concept 18.4: A program of differential gene expression leads to the different cell types in a multicellular organism

- 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

Fig. 18-14



(a) Fertilized eggs of a frog

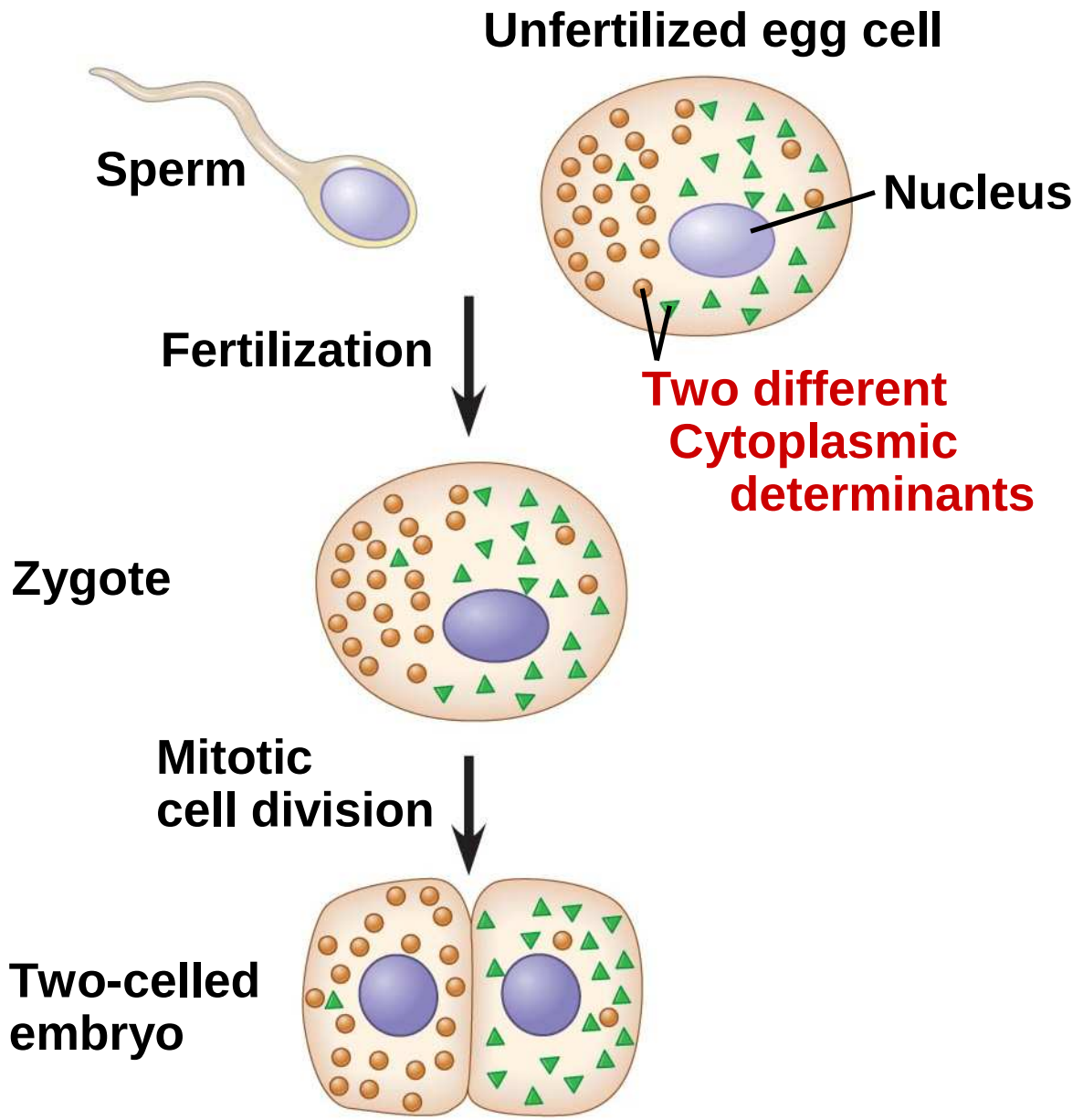
(b) Newly hatched tadpole

- **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 & 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

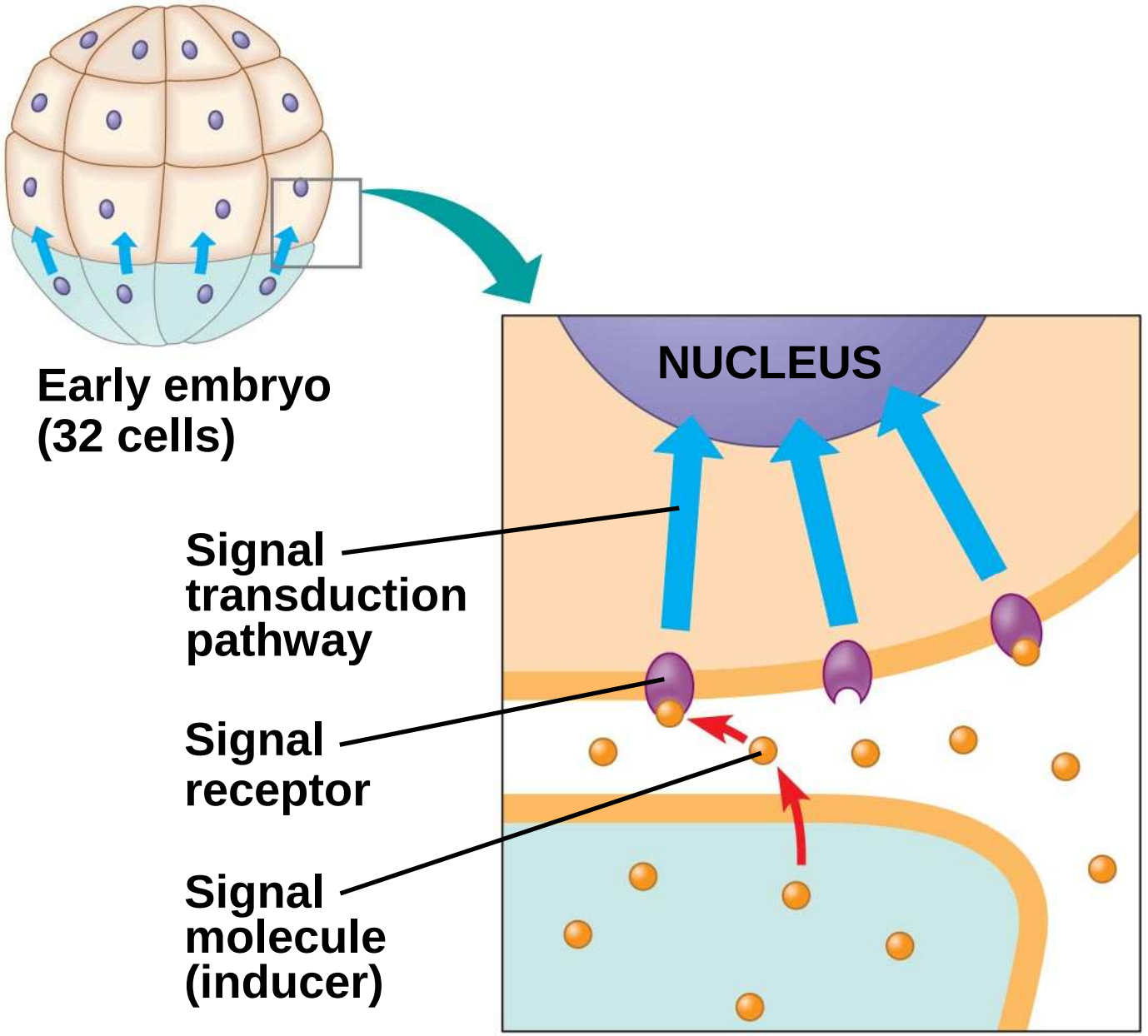
Fig. 18-15a



(a) Cytoplasmic determinants in the egg

Sources of developmental information for the early embryo

Fig. 18-15b



(b) Induction by nearby cells

Sources of developmental information for the early embryo

- 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

Sequential Regulation of Gene Expression During Cellular Differentiation

- **Determination** commits a cell to its final fate
- Determination precedes differentiation
- Cell differentiation is marked by the production of *tissue-specific proteins*

Master regulatory gene

- Myoblasts produce muscle-specific proteins and form skeletal muscle cells
- *MyoD* is one of several "master regulatory genes" that produce proteins that commit the cell to becoming *skeletal muscle*
- The MyoD protein is a transcription factor that binds to enhancers of various target genes

Fig. 18-16-1

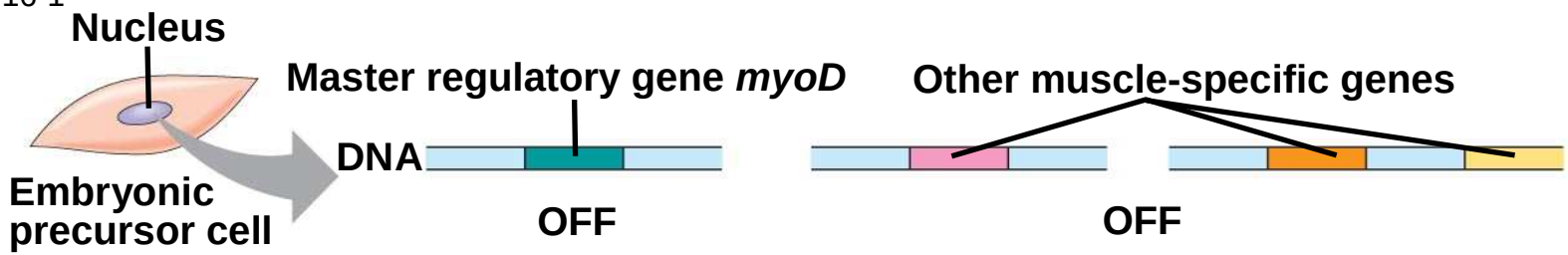


Fig. 18-16-2

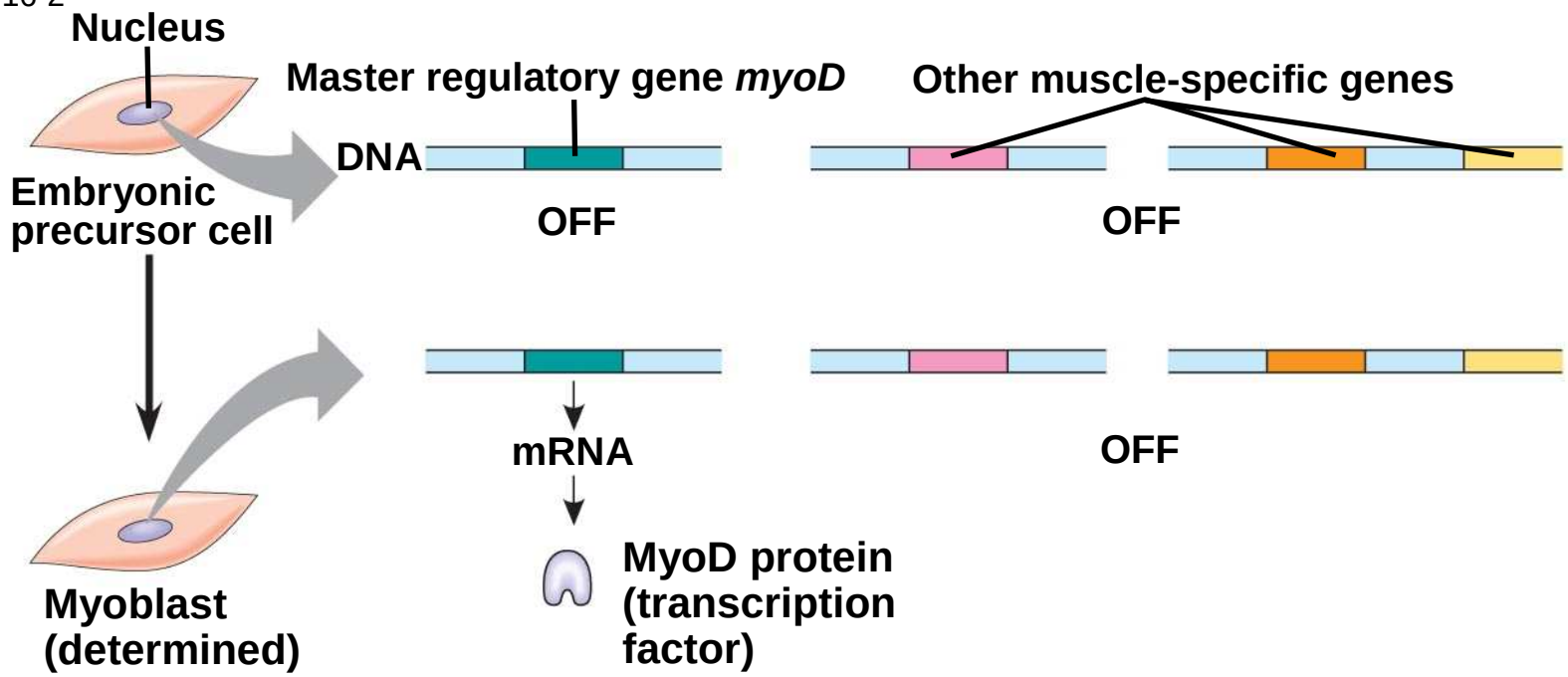
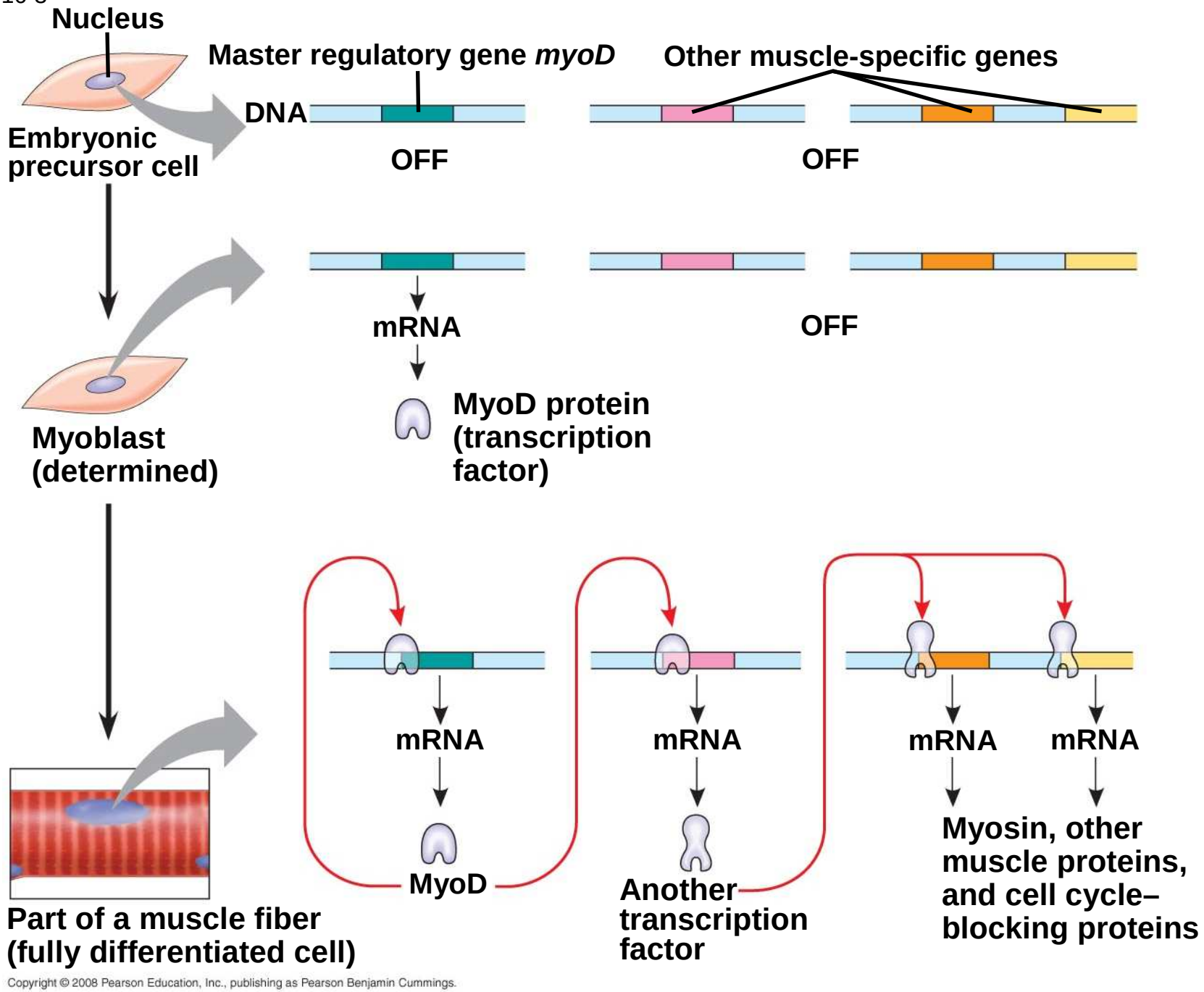


Fig. 18-16-3



Pattern Formation: Setting Up the Body Plan

- **Pattern formation** is the development of a spatial organization of tissues and organs
- In animals, pattern formation begins with the establishment of the major axes
- **Positional information**, the molecular cues that control pattern formation, tells a cell its location relative to the body axes and to neighboring cells

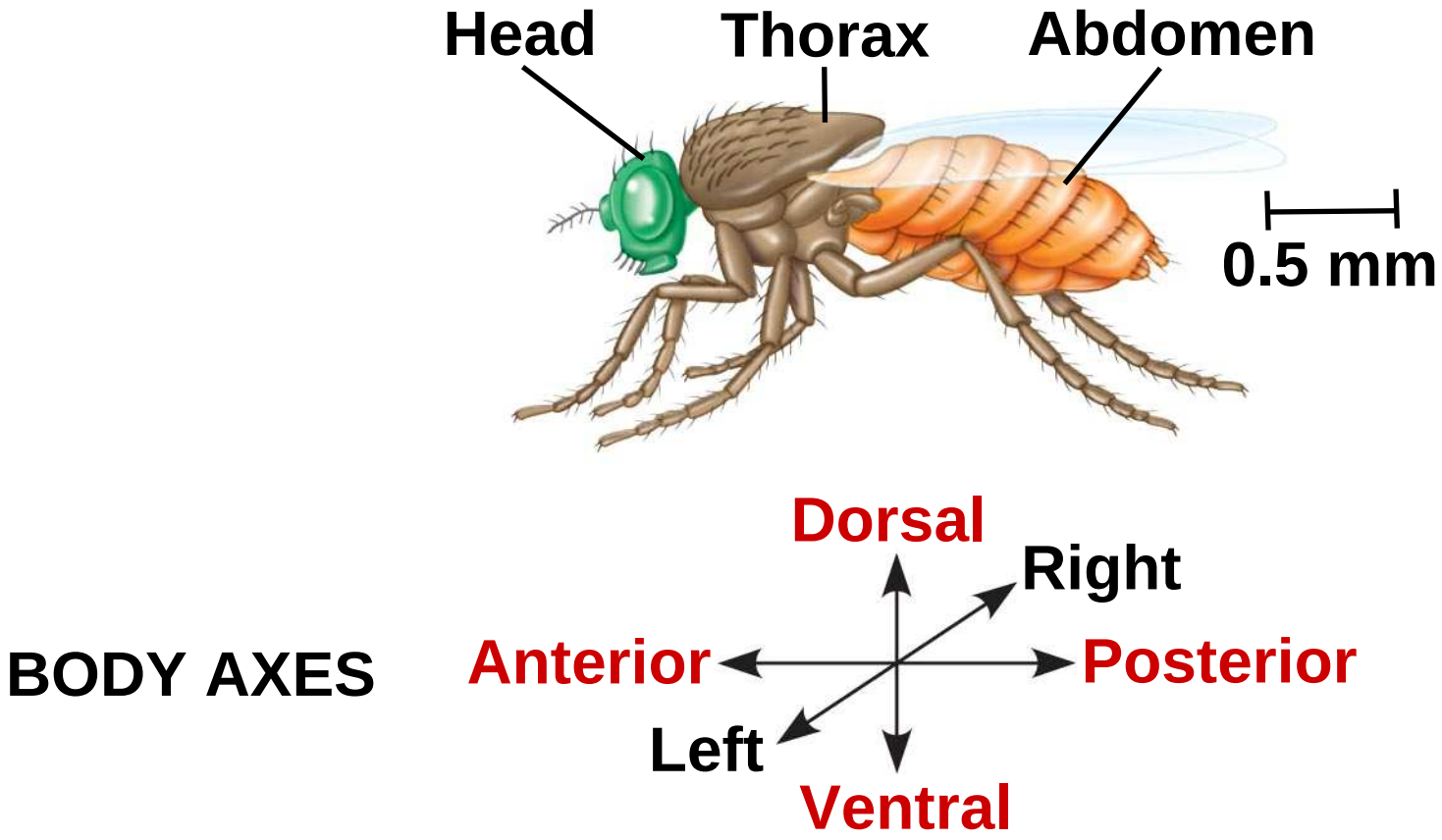
- Pattern formation has been extensively studied in the fruit fly *Drosophila melanogaster (~13700 genes)*
- Combining anatomical, genetic, and biochemical approaches, researchers have discovered developmental principles common to many other species, including humans

The Life Cycle of Drosophila

- In *Drosophila*, cytoplasmic determinants in the unfertilized egg determine the axes before fertilization
- After fertilization, the embryo develops into a segmented larva with three larval stages

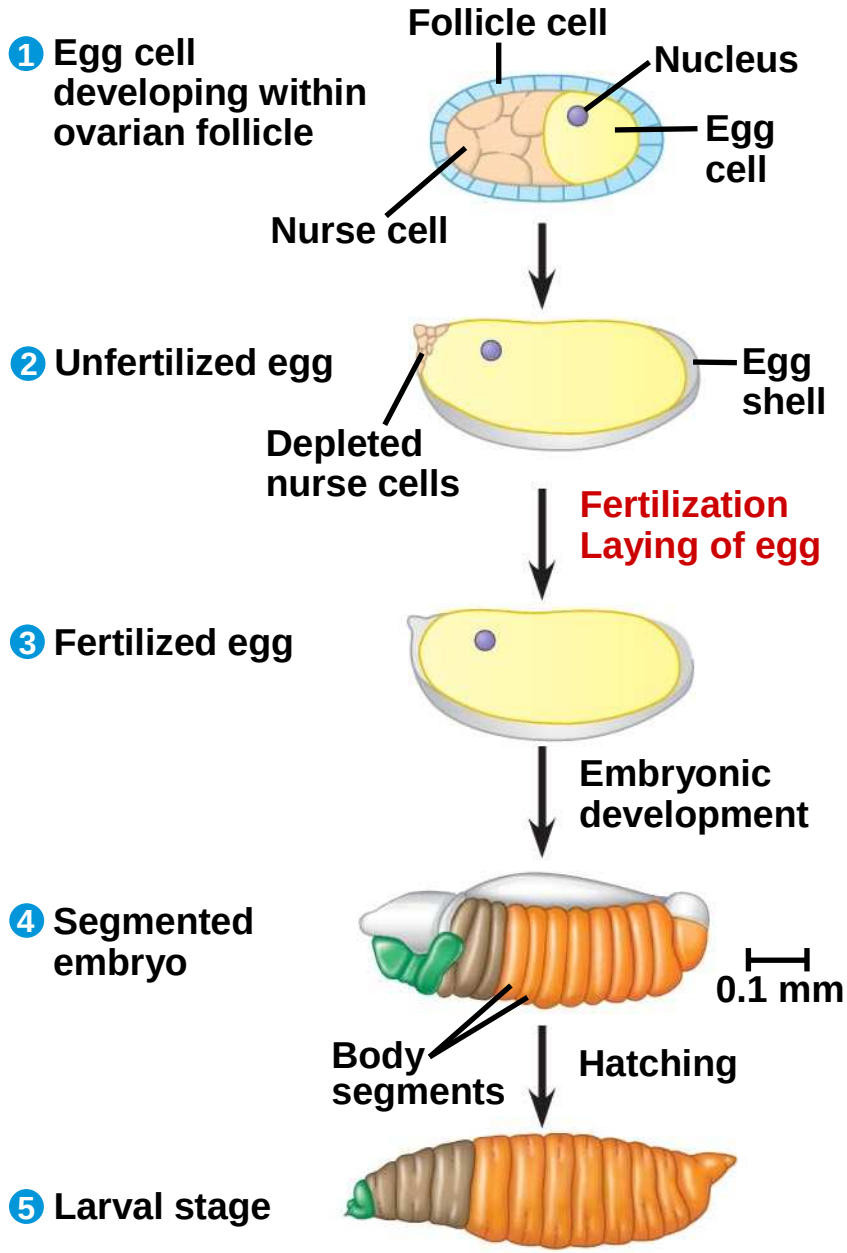
Fig. 18-17a

Key developmental events in the life cycle of *Drosophila*



(a) Adult

Fig. 18-17b



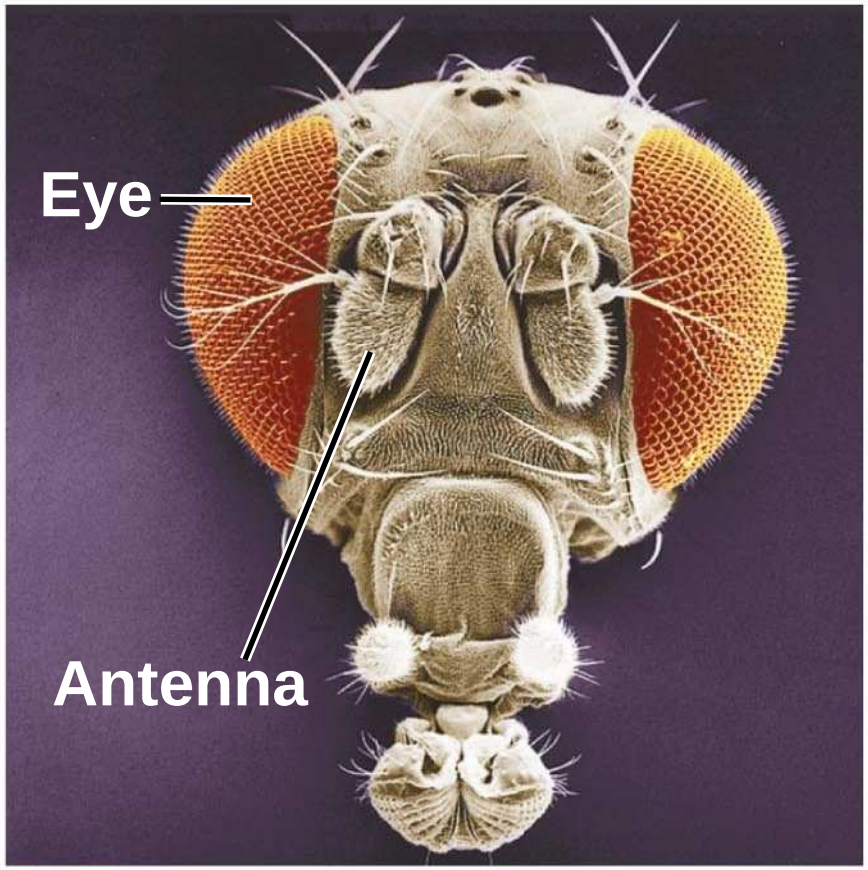
(b) Development from egg to larva

Genetic Analysis of Early Development: Scientific Inquiry

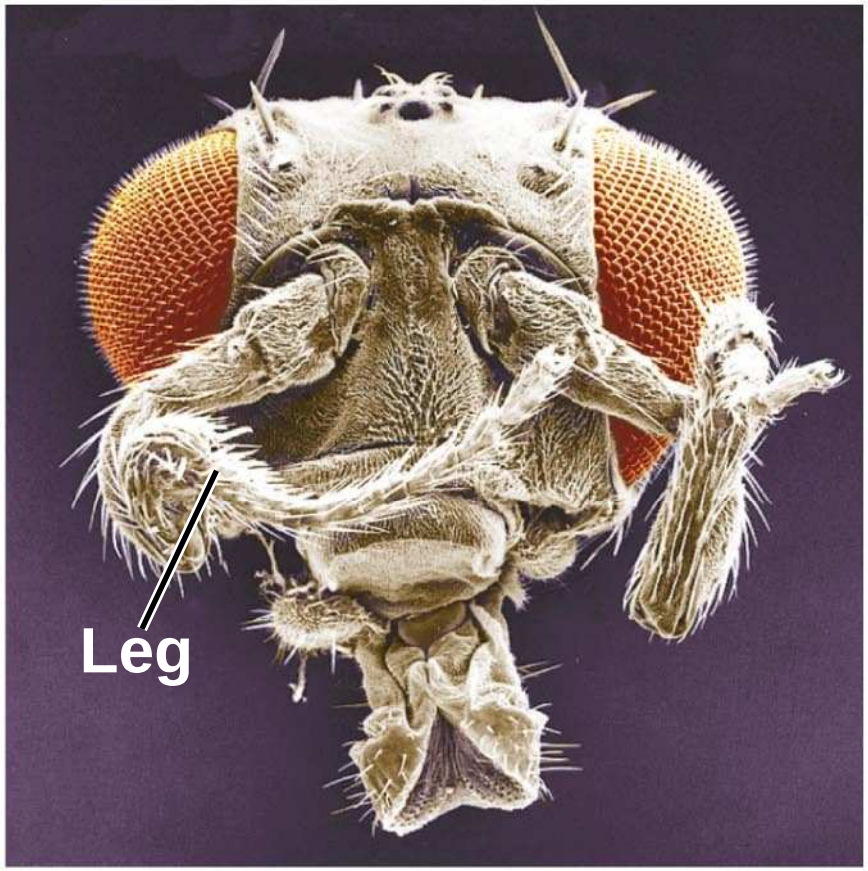
- Edward B. Lewis, Christiane Nüsslein-Volhard, and Eric Wieschaus won a Nobel 1995 Prize for decoding pattern formation in *Drosophila*
- Lewis demonstrated that genes direct the developmental process

Fig. 18-18

Abnormal pattern formation in *Drosophila*



Wild type



Mutant

- Nüsslein-Volhard and Wieschaus studied segment formation
- They created mutants, conducted breeding experiments, and looked for corresponding genes
- Breeding experiments were complicated by **embryonic lethals,** embryos with lethal mutations
- They found 120 genes essential for normal segmentation

Axis Establishment

- **Maternal effect genes** encode for cytoplasmic determinants that initially establish the axes of the body of *Drosophila*
- These maternal effect genes are also called **egg-polarity genes** because they control orientation of the egg and consequently the fly

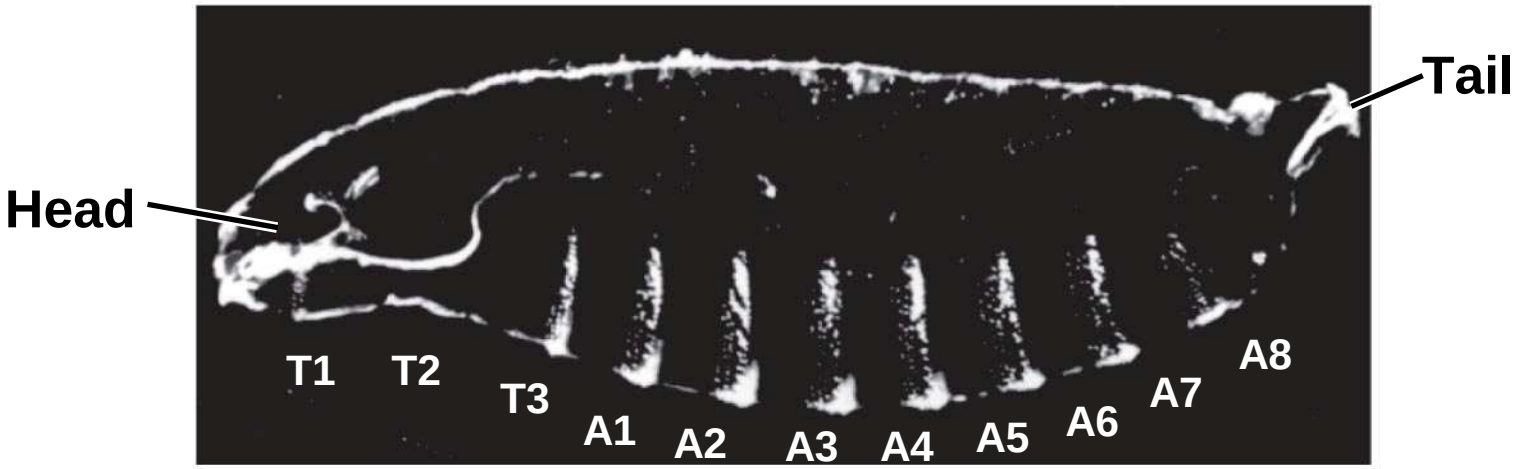
PLAY Animation: Development of Head-Tail Axis in Fruit Flies

Bicoid: A Morphogen Determining Head Structures

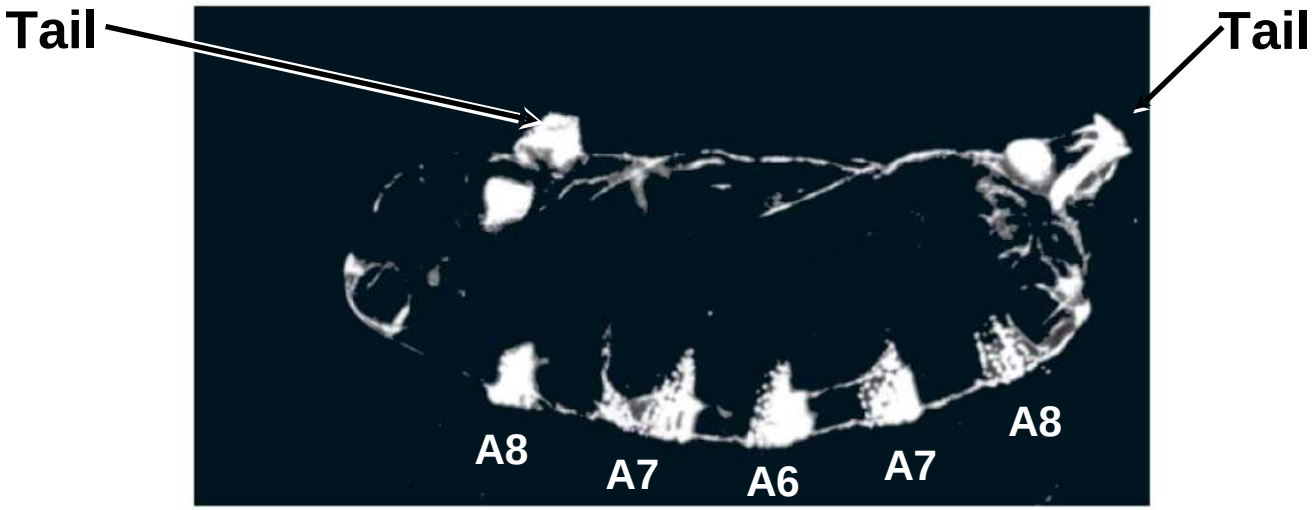
- One maternal effect gene, the ***bicoid*** gene, affects the front half of the body
- An embryo whose mother has a mutant *bicoid* gene lacks the front half of its body and has duplicate posterior structures at both ends

Fig. 18-19a

EXPERIMENT **Is Bicoid a morphogen that determines the anterior end of a fruit fly?**



Wild-type larva

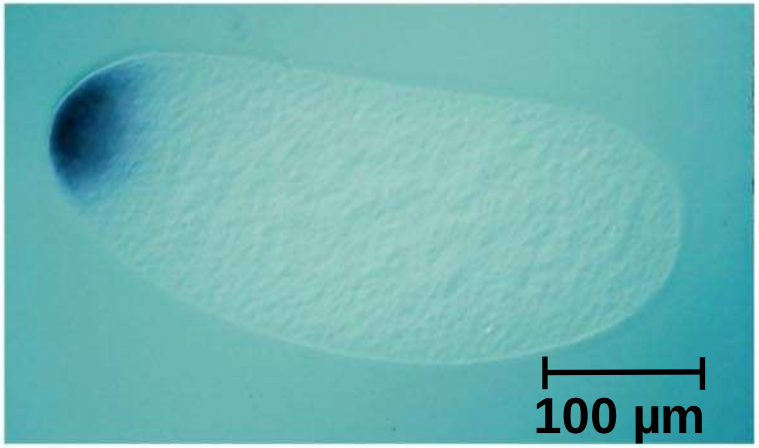


Mutant larva (*bicoid*)

Fig. 18-19b

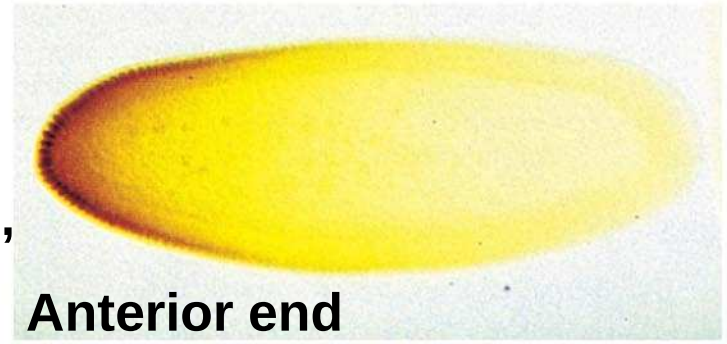
Is Bicoid a morphogen that determines the anterior end of a fruit fly?

RESULTS



***Bicoid* mRNA in mature unfertilized egg**

Fertilization, translation of *bicoid* mRNA

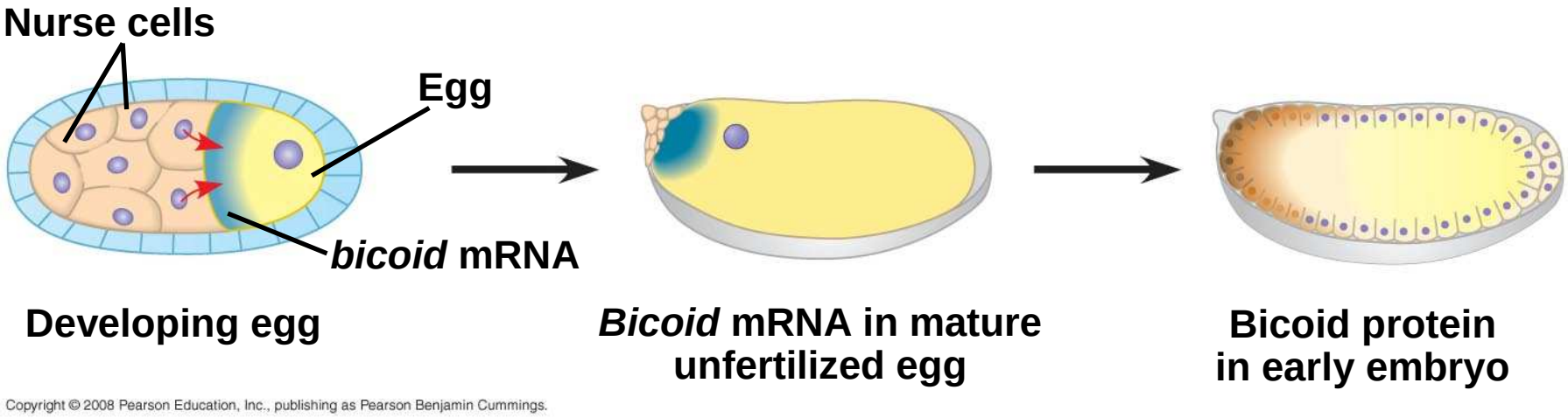


Bicoid protein in early embryo

Fig. 18-19c

Is Bicoid a morphogen that determines the anterior end of a fruit fly?

CONCLUSION



- This phenotype suggests that the product of the mother's *bicoid* gene is concentrated at the future anterior end
- This hypothesis is an example of the gradient hypothesis, in which gradients of substances called **morphogens** establish an embryo's axes and other features

- The *bicoid* research is important for three reasons:
  - It identified a specific protein required for some early steps in pattern formation
  - It increased understanding of the mother's role in embryo development
  - It demonstrated a key developmental principle that a gradient of molecules can determine polarity and position in the embryo

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

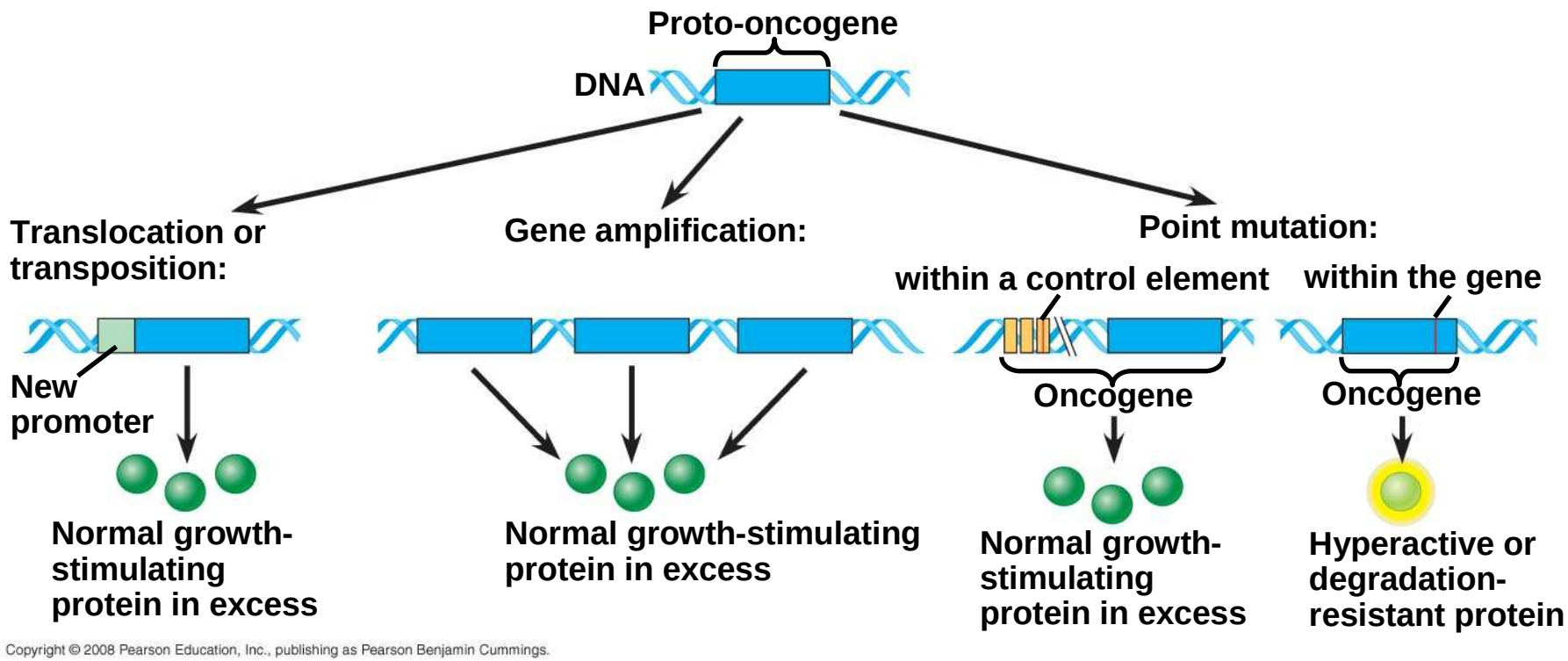
Types of Genes Associated with Cancer

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

Oncogenes and Proto-Oncogenes

- **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

Fig. 18-20



- 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: causes an increase in gene expression

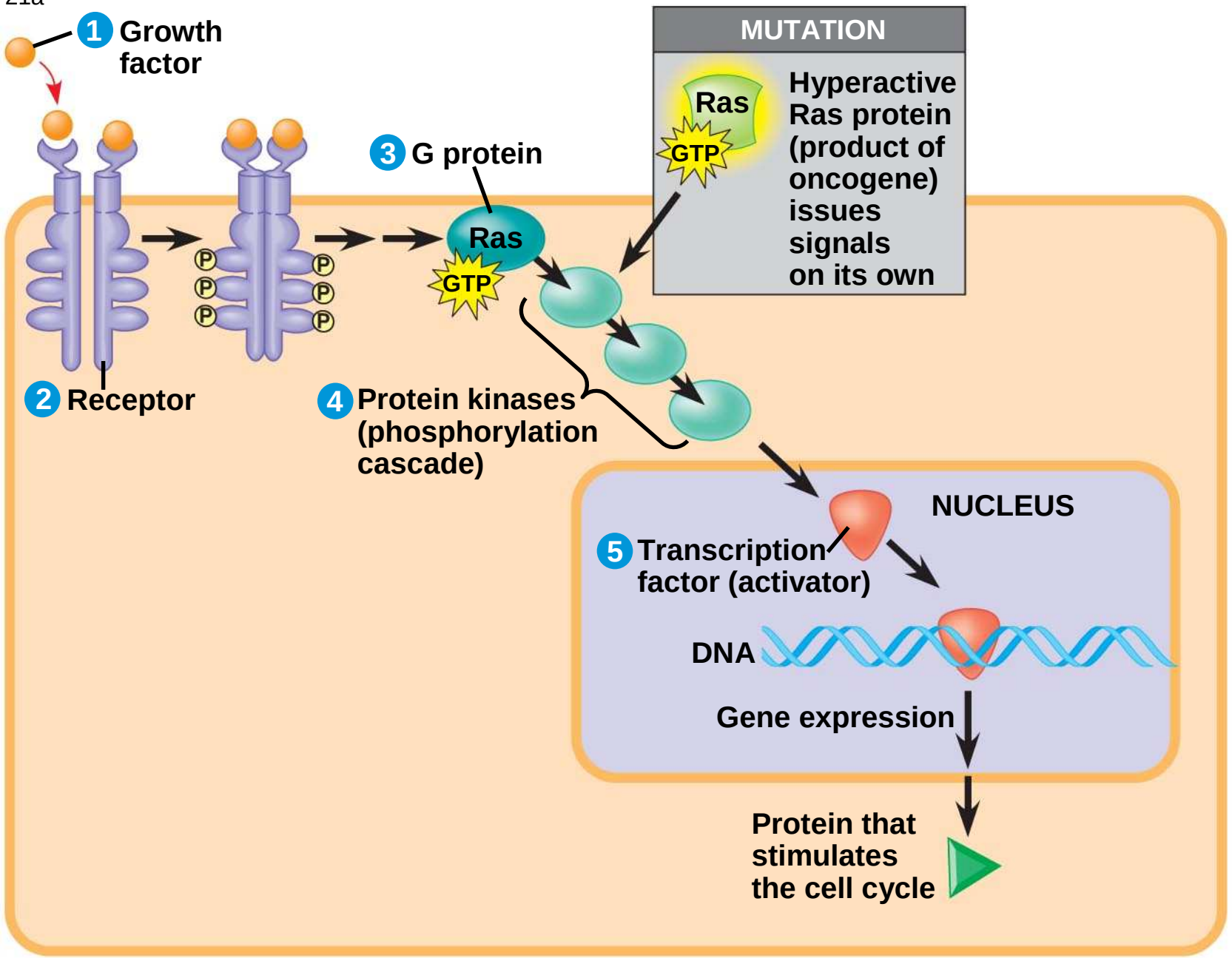
Tumor-Suppressor Genes

- **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

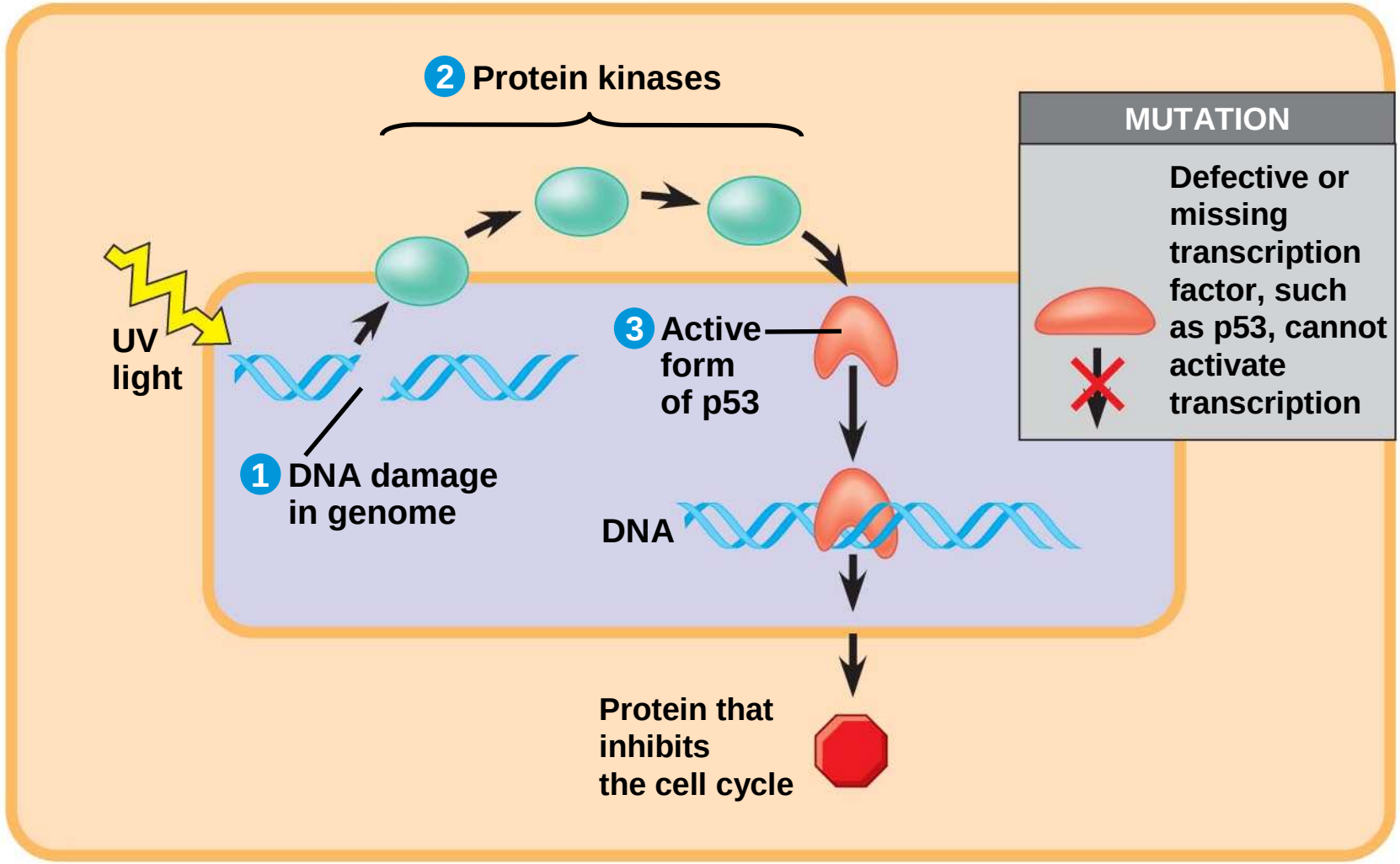
Fig. 18-21a



(a) Cell cycle–stimulating pathway

Signaling pathways that regulate cell division

Fig. 18-21b

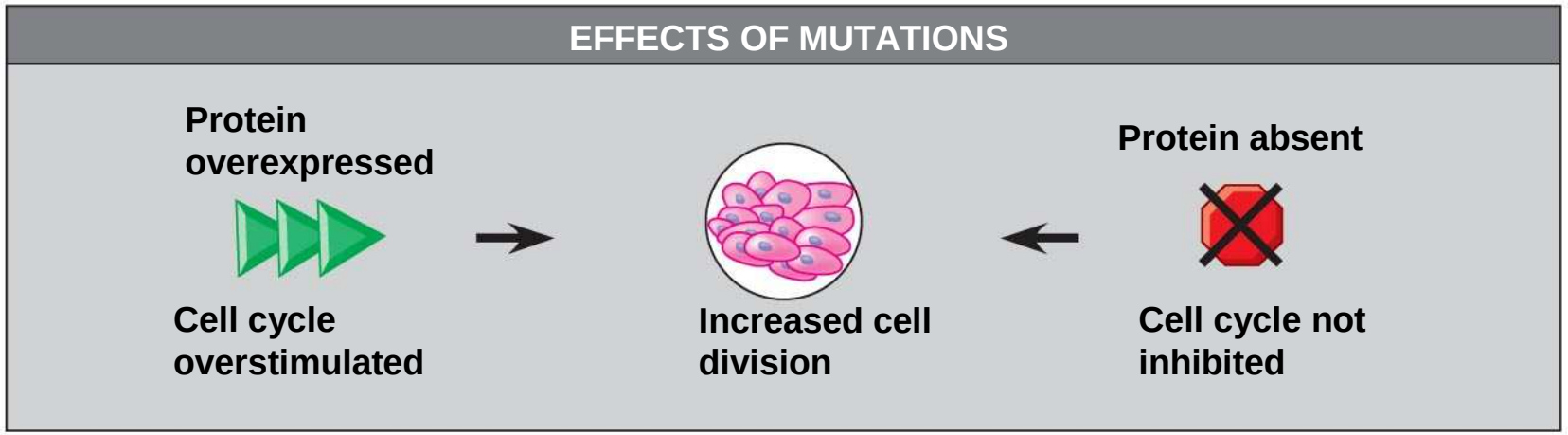


(b) Cell cycle–inhibiting pathway

Signaling pathways that regulate cell division

Fig. 18-21c

Signaling pathways that regulate cell division



(c) Effects of mutations

- 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

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

A multistep model for the development of colorectal cancer

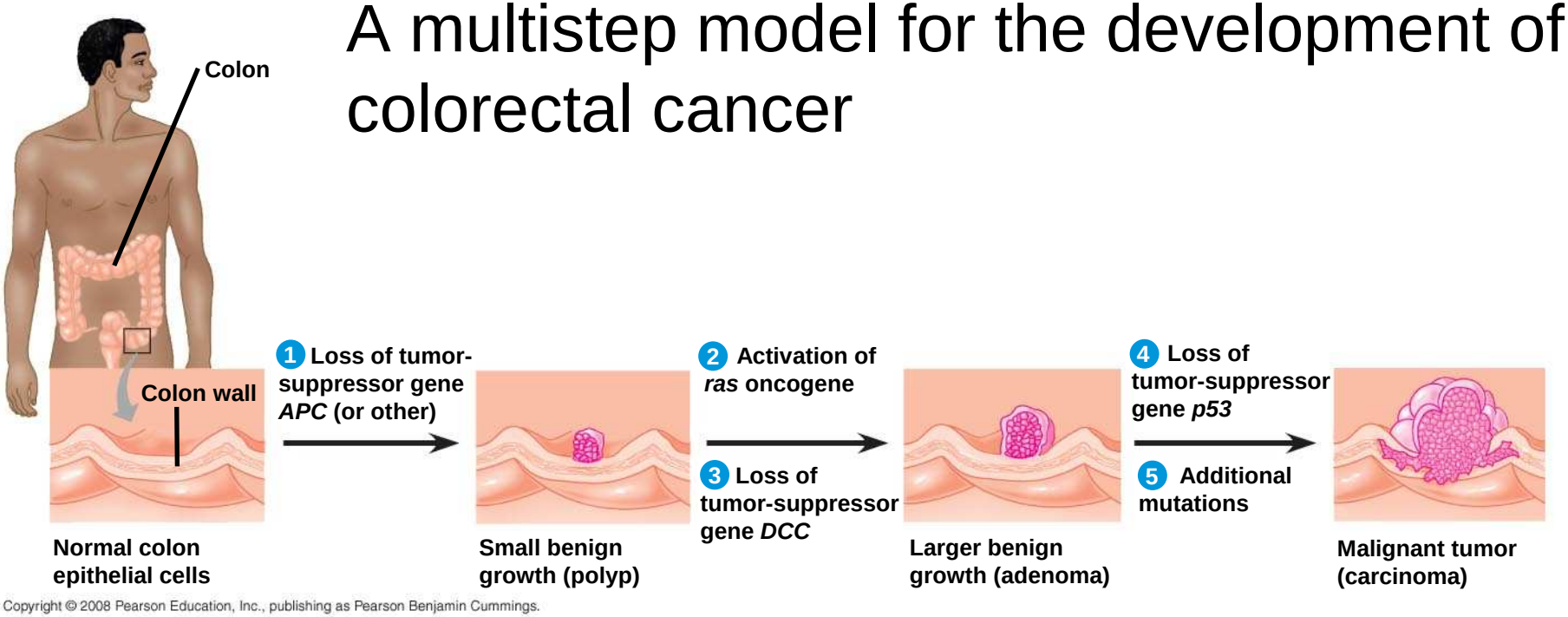
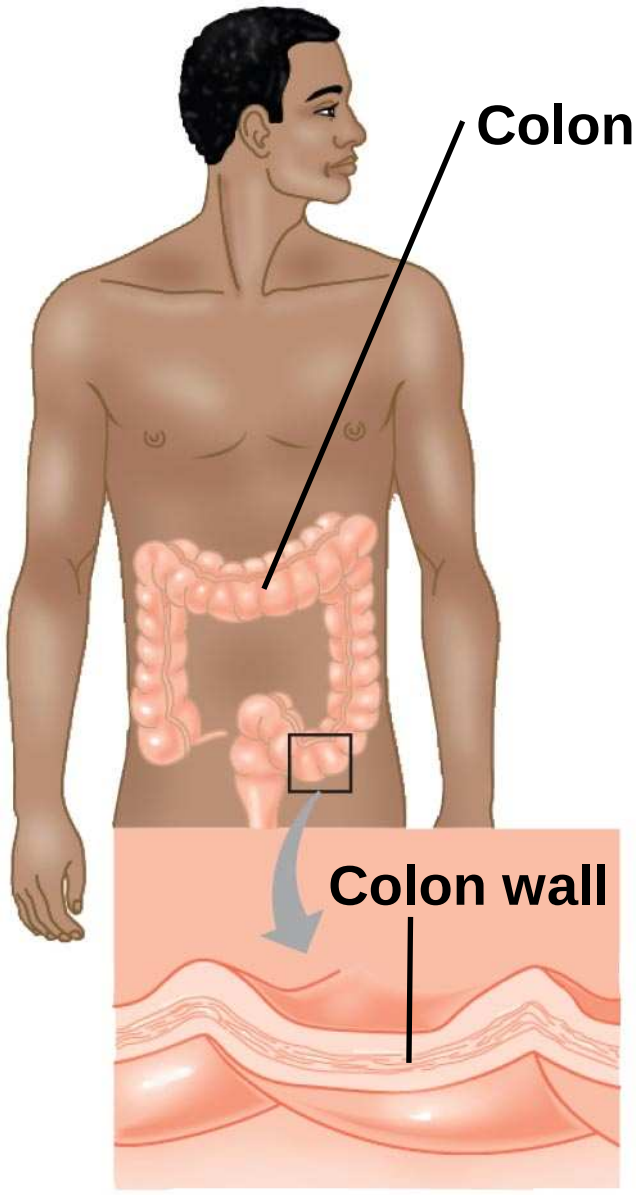


Fig. 18-22a



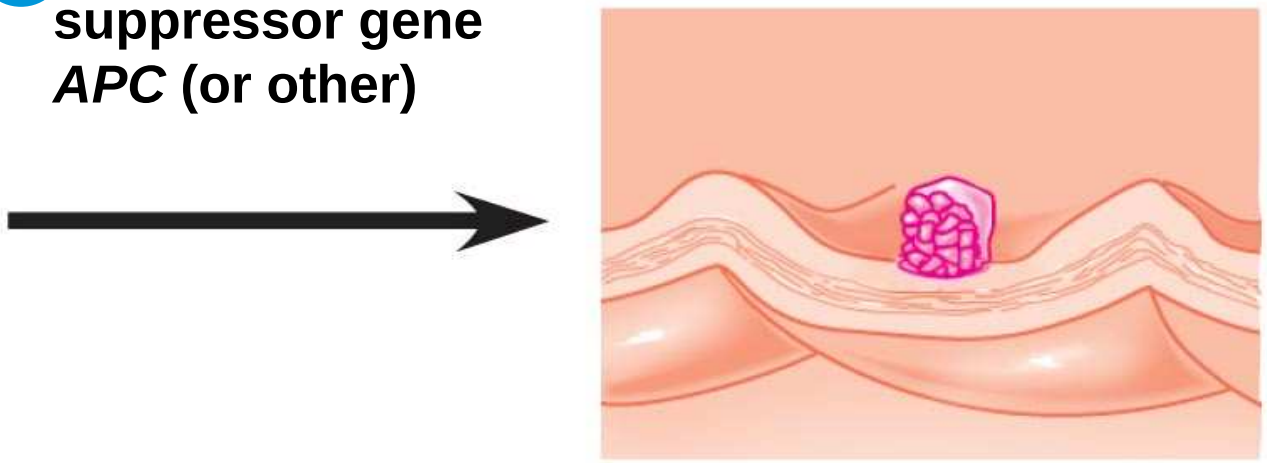
Normal colon epithelial cells

Step 0

Fig. 18-22b

A multistep model for the development of colorectal cancer

1 **Loss of tumor-suppressor gene *APC* (or other)**



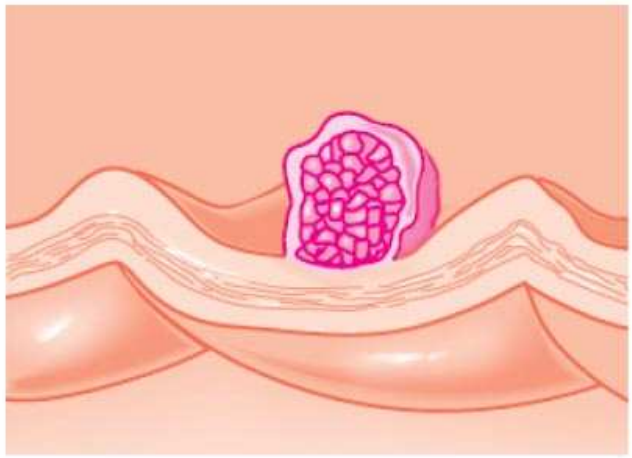
Small benign growth (polyp)

Fig. 18-22c

A multistep model for the development of colorectal cancer

2 **Activation of *ras* oncogene**

3 **Loss of tumor-suppressor gene *DCC***



Larger benign growth (adenoma)

Fig. 18-22d

A multistep model for the development of colorectal cancer

4 **Loss of tumor-suppressor gene *p53***

5 **Additional mutations**

Malignant tumor (carcinoma)

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

Fig. 18-23

In 1990, after 16 years of research, geneticist Mary-Claire King identified BRCA1 to a breast cancer gene.

You should now be able to:

- Explain the concept of an operon and the function of the operator, repressor, and corepressor
- Explain the adaptive advantage of grouping bacterial genes into an operon
- Explain how repressible and inducible operons differ and how those differences reflect differences in the pathways they control

- Explain how DNA methylation and histone acetylation affect chromatin structure and the regulation of transcription
- Define control elements and explain how they influence transcription
- Explain the role of promoters, enhancers, activators, and repressors in transcription control

- Explain how eukaryotic genes can be coordinately expressed
- Describe the roles played by small RNAs on gene expression
- Explain why determination precedes differentiation
- Describe two sources of information that instruct a cell to express genes at the appropriate time

- Explain how maternal effect genes affect polarity and development in *Drosophila* embryos
- Explain how mutations in tumor-suppressor genes can contribute to cancer
- Describe the effects of mutations to the *p53* and *ras* genes

Supporting Information

Fig. 18-UN1

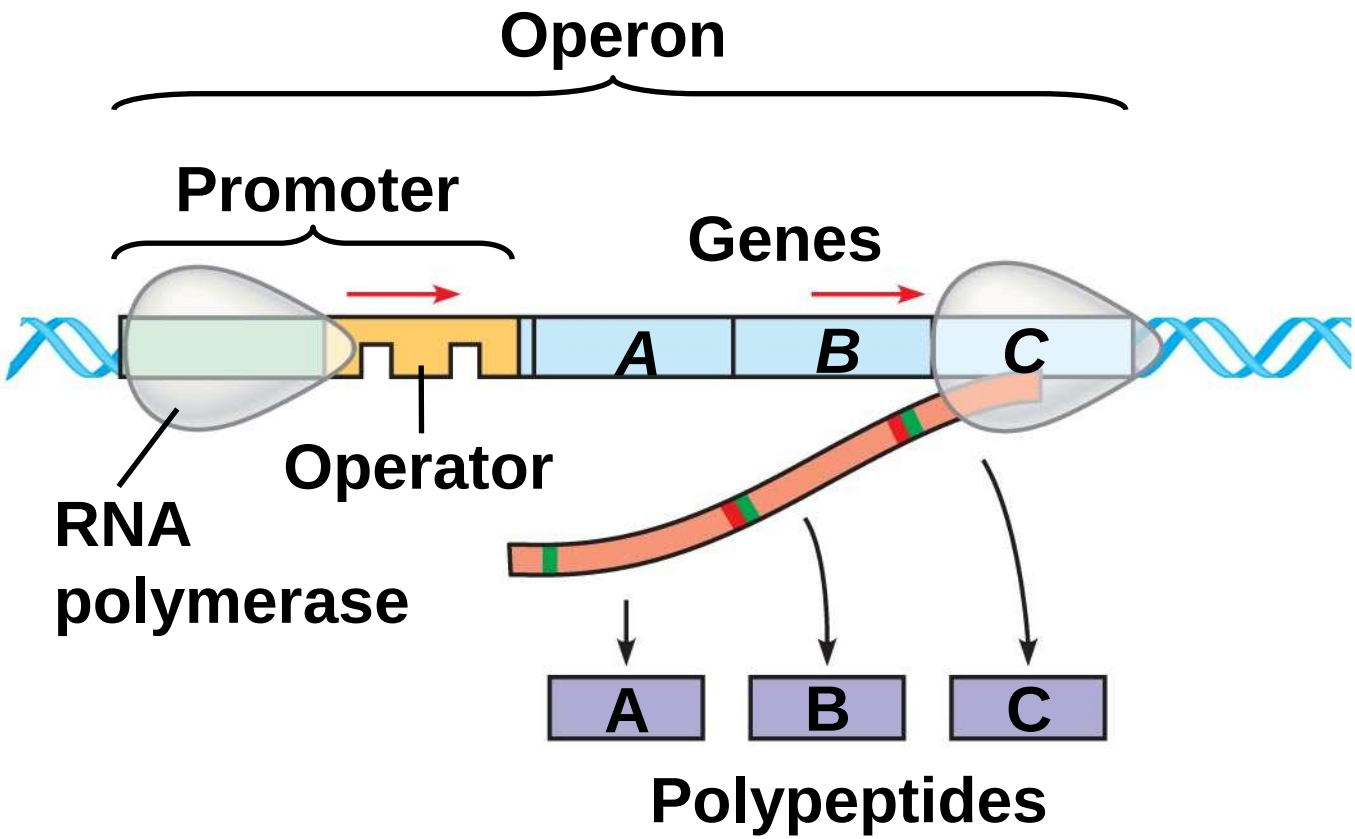


Fig. 18-UN2

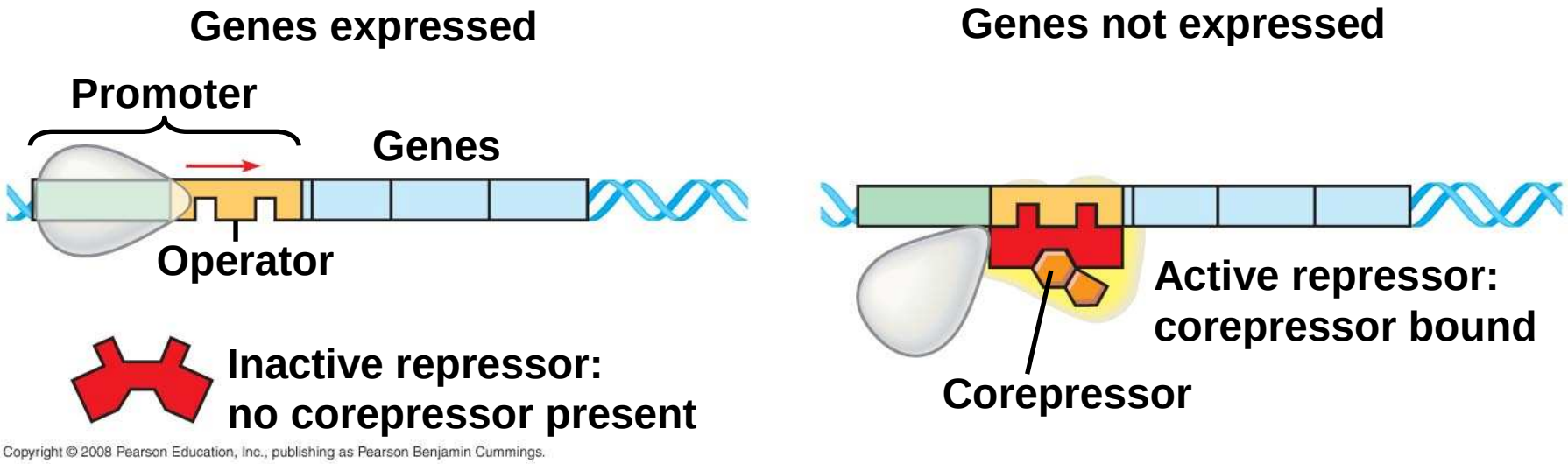


Fig. 18-UN3

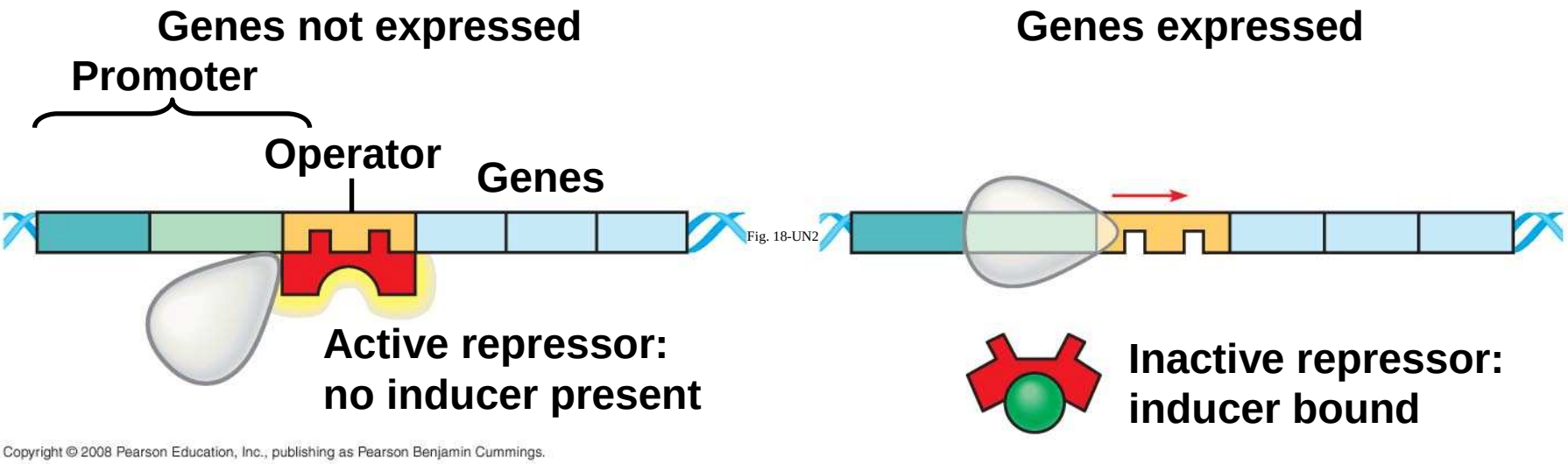


Fig. 18-UN2

Fig. 18-UN4

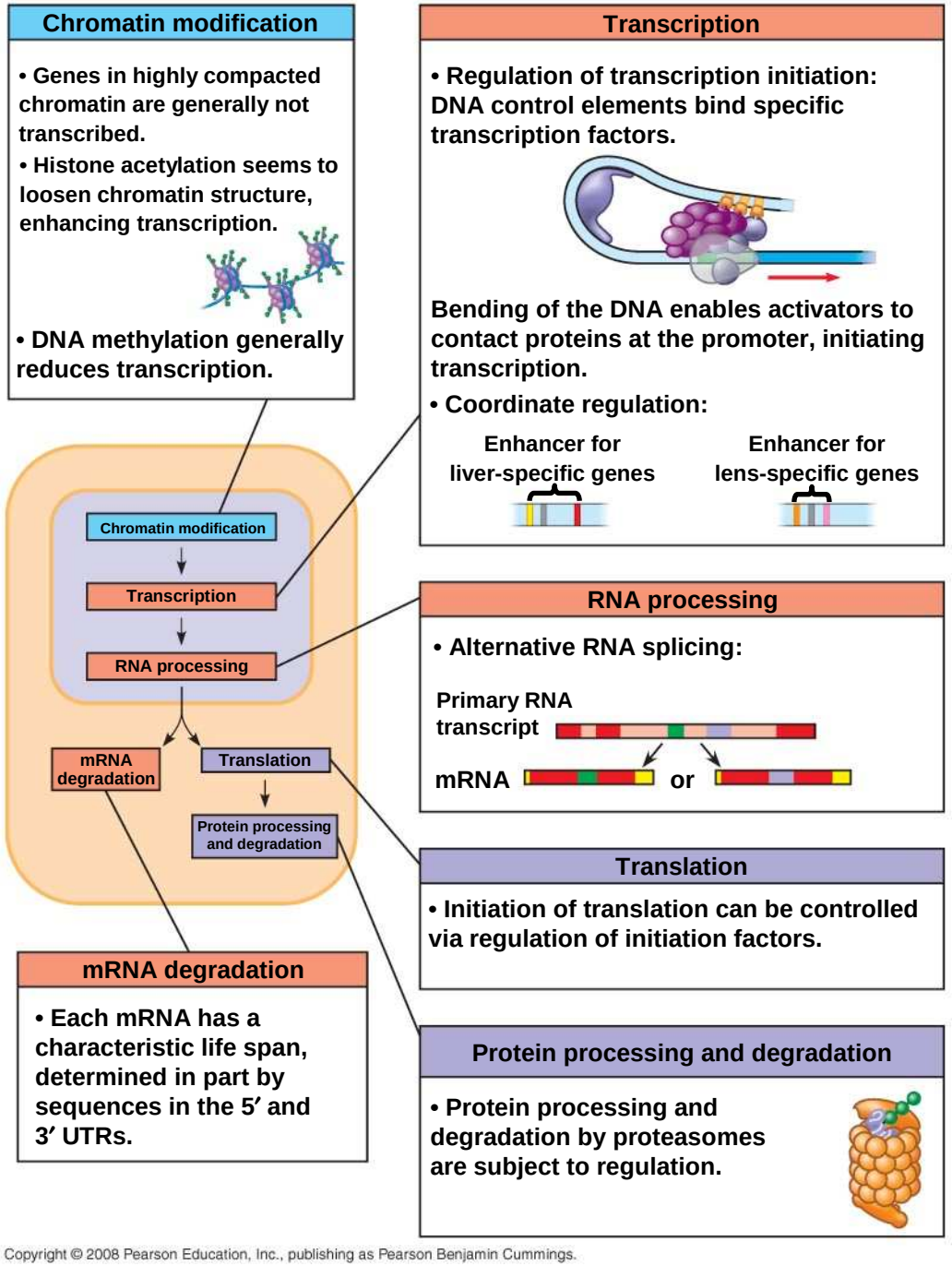


Fig. 18-UN5

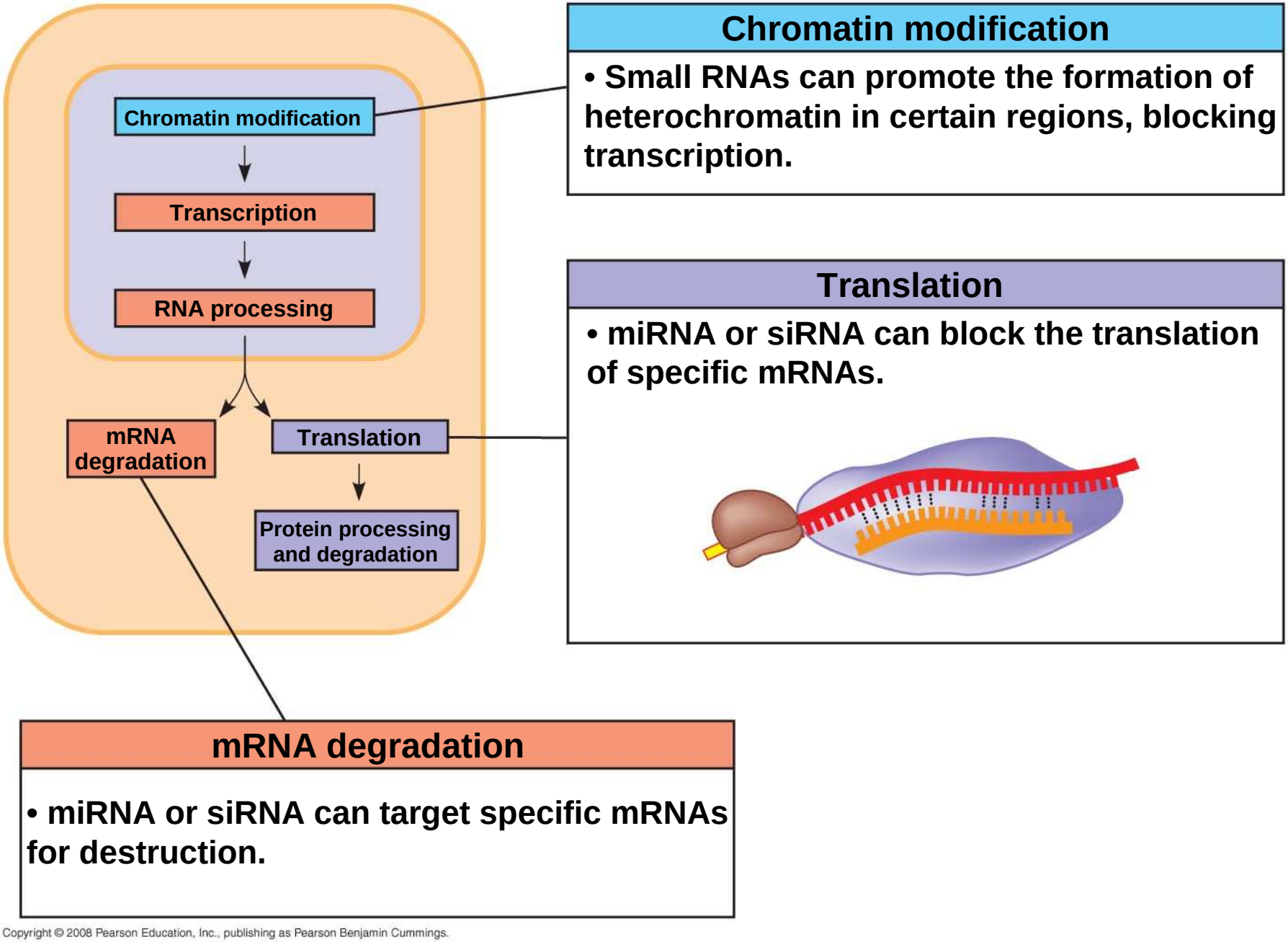


Fig. 18-UN6

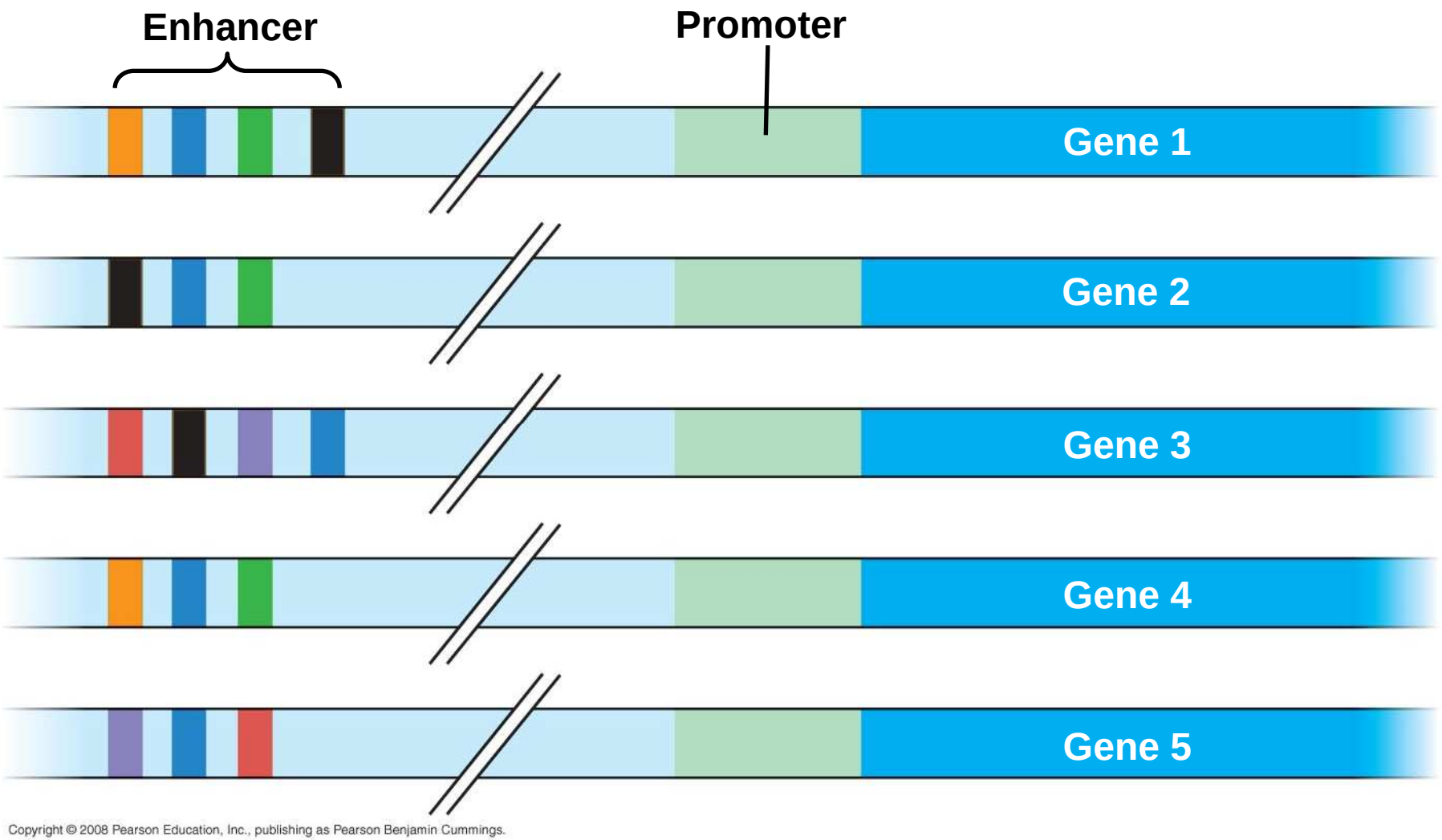


Fig. 18-UN7

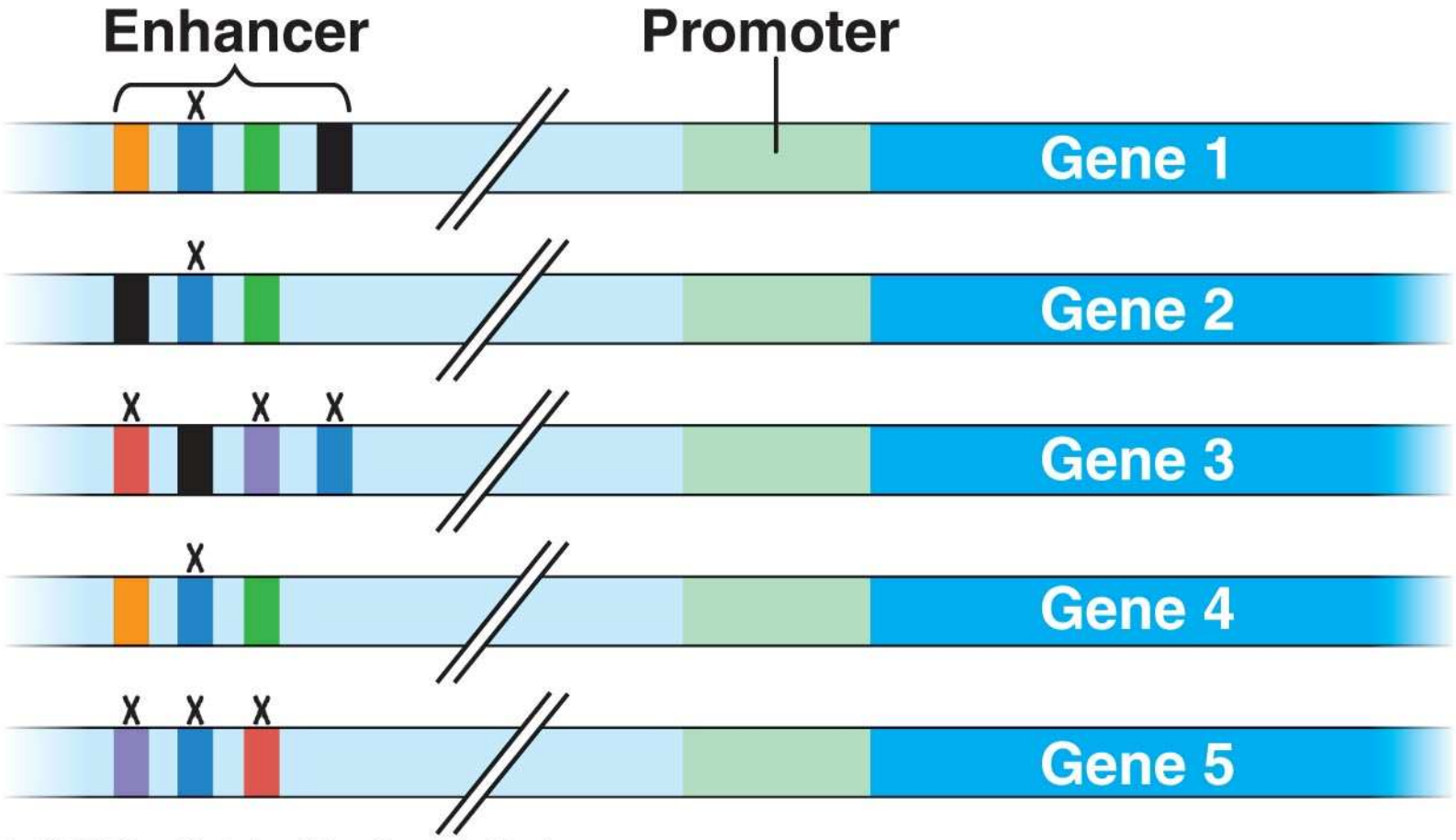


Fig. 18-UN8