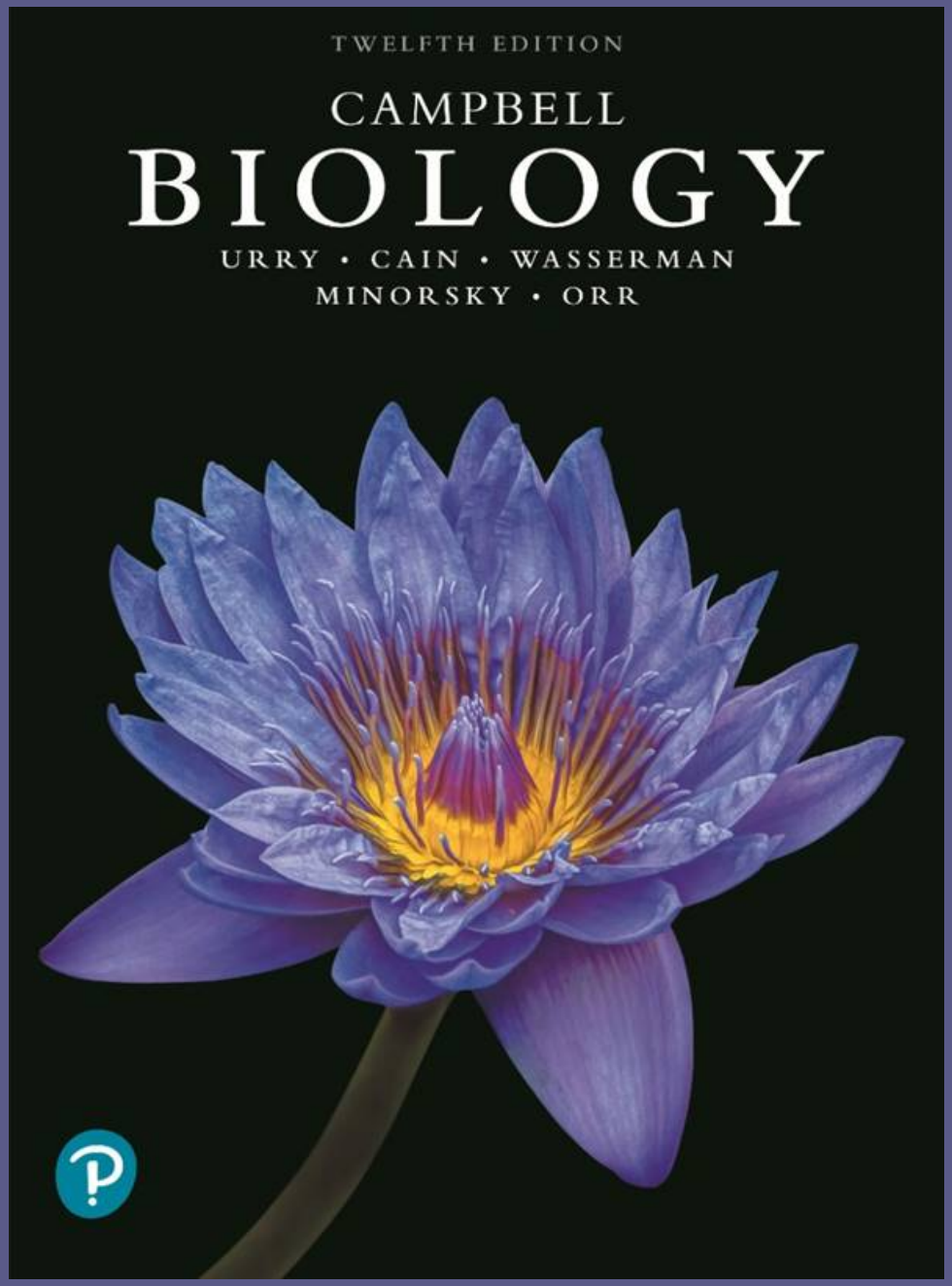


Chapter 18

Regulation of Gene Expression

Lecture Presentations by
Nicole Tunbridge and
Kathleen Fitzpatrick

Figure 18.1a

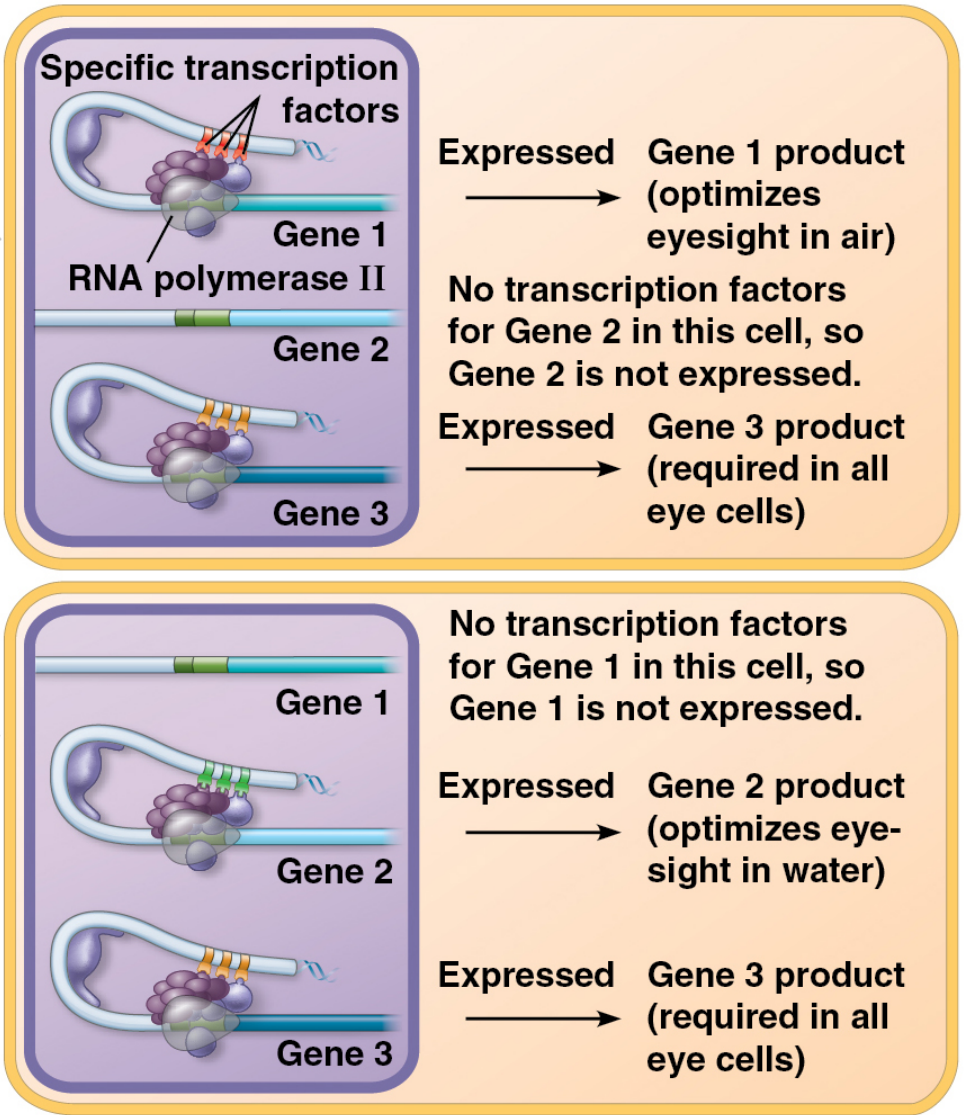
Figure 18.1b

How can two cells with the same set of genes function differently?

Each gene requires particular transcription factors. Different cells have different transcription factors.

Eye cell specialized for aerial vision

Eye cell specialized for aquatic vision



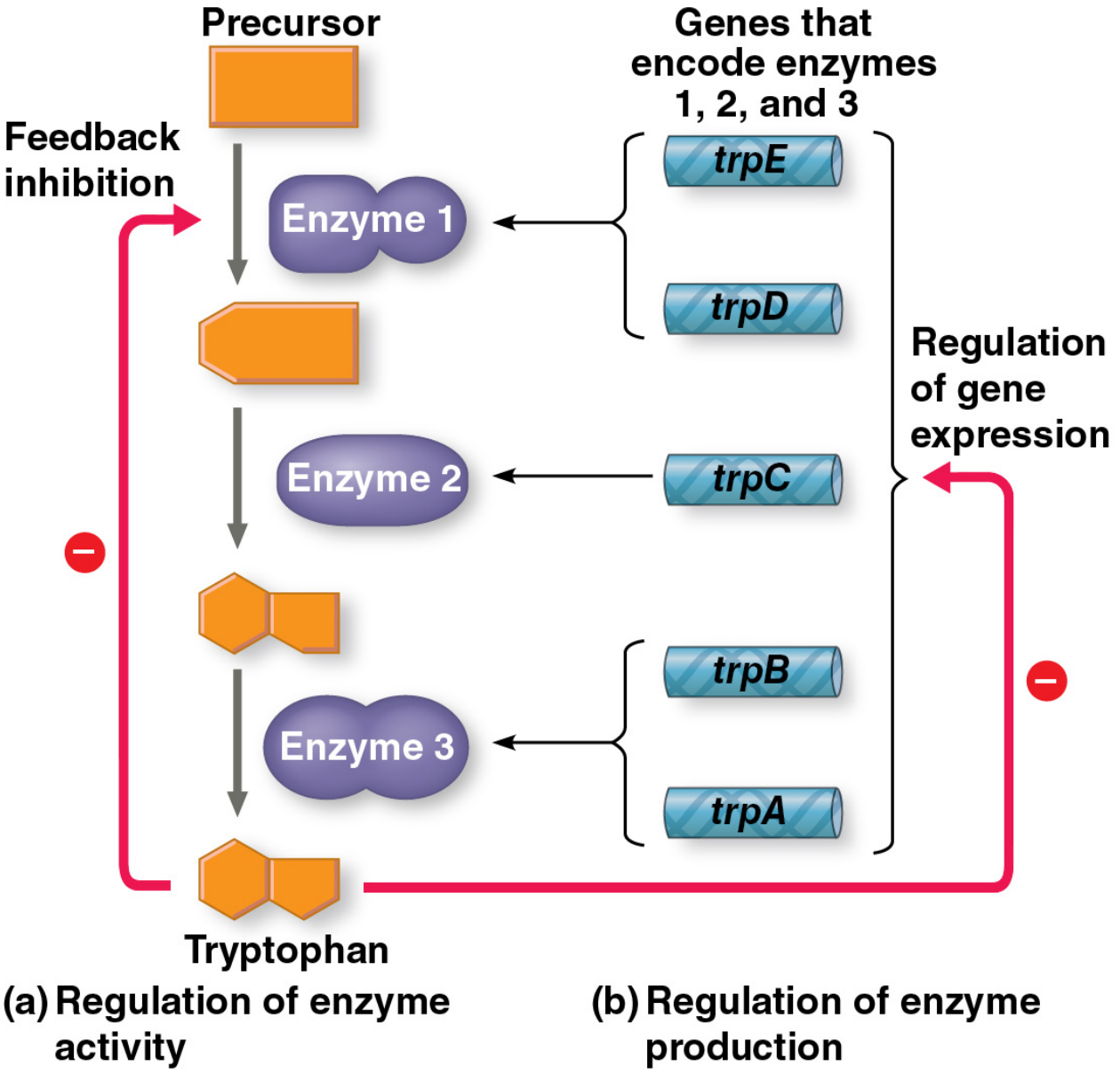
Differential gene expression is the expression of different genes, allowing cells to carry out their specific function.

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

- Natural selection has favored bacteria that express only the genes that encode products needed by the cell
- A cell can regulate the production of enzymes by feedback inhibition or by gene regulation
- In feedback inhibition, the end product of a metabolic pathway shuts down further synthesis of the product by inhibiting enzyme activity

- Cells can adjust the production level of certain enzymes by regulating expression of the genes encoding the enzymes
- The control of enzyme production is thus at the level of transcription
- One basic mechanism for this type of regulation of groups of genes is called the operon model

Figure 18.2


Precursor
Feedback inhibition
Enzyme 1
Enzyme 2
Enzyme 3
Tryptophan
Genes that encode enzymes 1, 2, and 3
trpE
trpD
trpC
trpB
trpA
Regulation of gene expression
(a) Regulation of enzyme activity
(b) Regulation of enzyme production

Operons: The Basic Concept

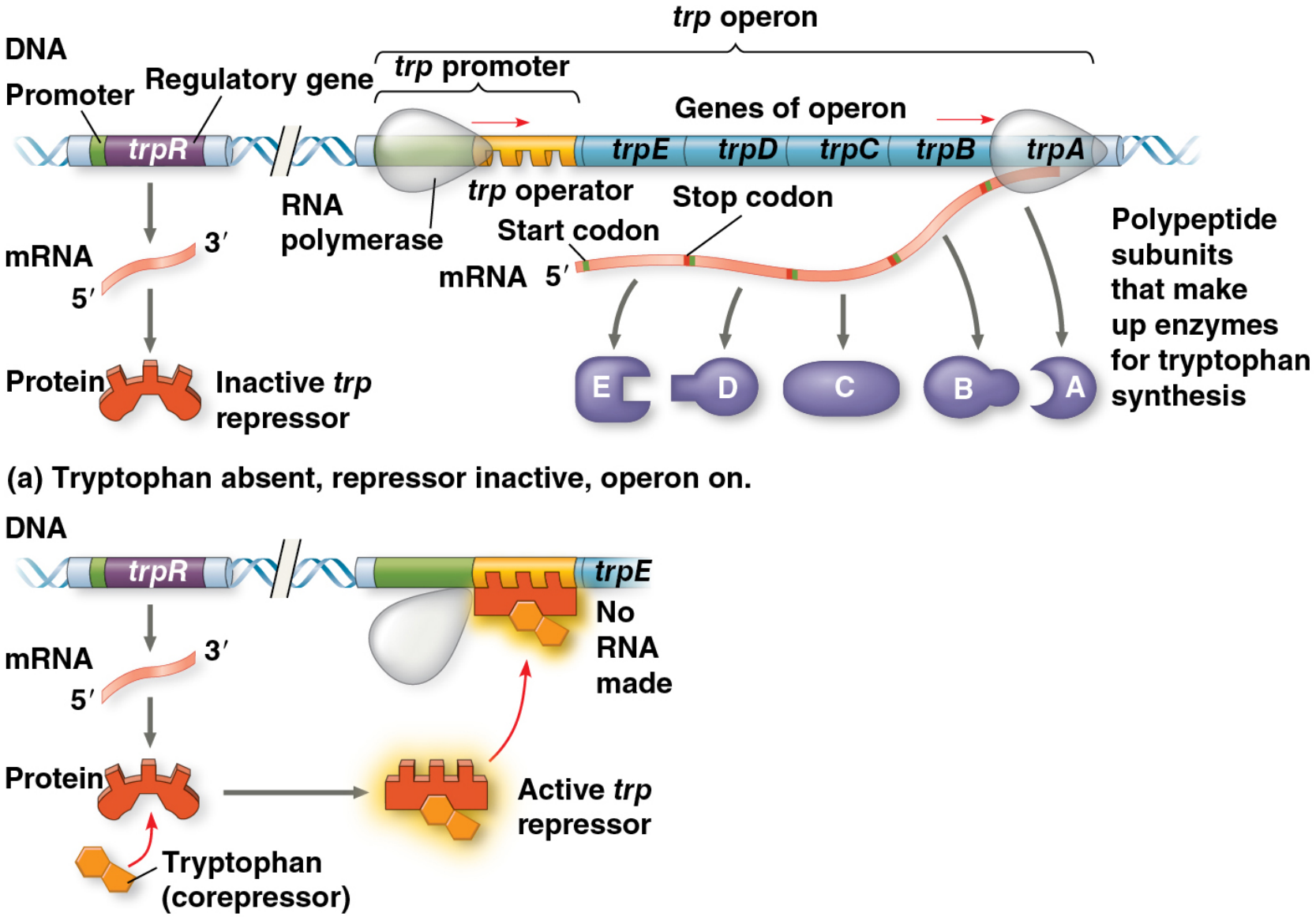
- A cluster of functionally related genes can be coordinately controlled by a single "on-off switch"
- The switch is a segment of DNA called an **operator**, positioned within the promoter or, sometimes, between the promoter and enzyme-coding genes
- An **operon** is the entire stretch of DNA that includes the operator, the promoter, and the genes that they control

- 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**, located some distance from the operon itself

- 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 when it has insufficient tryptophan

- By default, 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 in the active state only in the presence of its corepressor tryptophan
- Thus the *trp* operon is turned off (repressed) if tryptophan levels are high

Figure 18.3


trp operon
DNA
Promoter
Regulatory gene
trp promoter
Genes of operon
trpR
trpE
trpD
trpC
trpB
trpA
RNA polymerase
trp operator
Stop codon
Start codon
mRNA 5′
mRNA
3′
5′
Polypeptide subunits that make up enzymes for tryptophan synthesis
Protein
Inactive trp repressor
E
D
C
B
A
(a) Tryptophan absent, repressor inactive, operon on.
DNA
trpR
trpE
No RNA made
mRNA
3′
5′
Protein
Active trp repressor
Tryptophan (corepressor)
(b) Tryptophan present, repressor active, operon off.

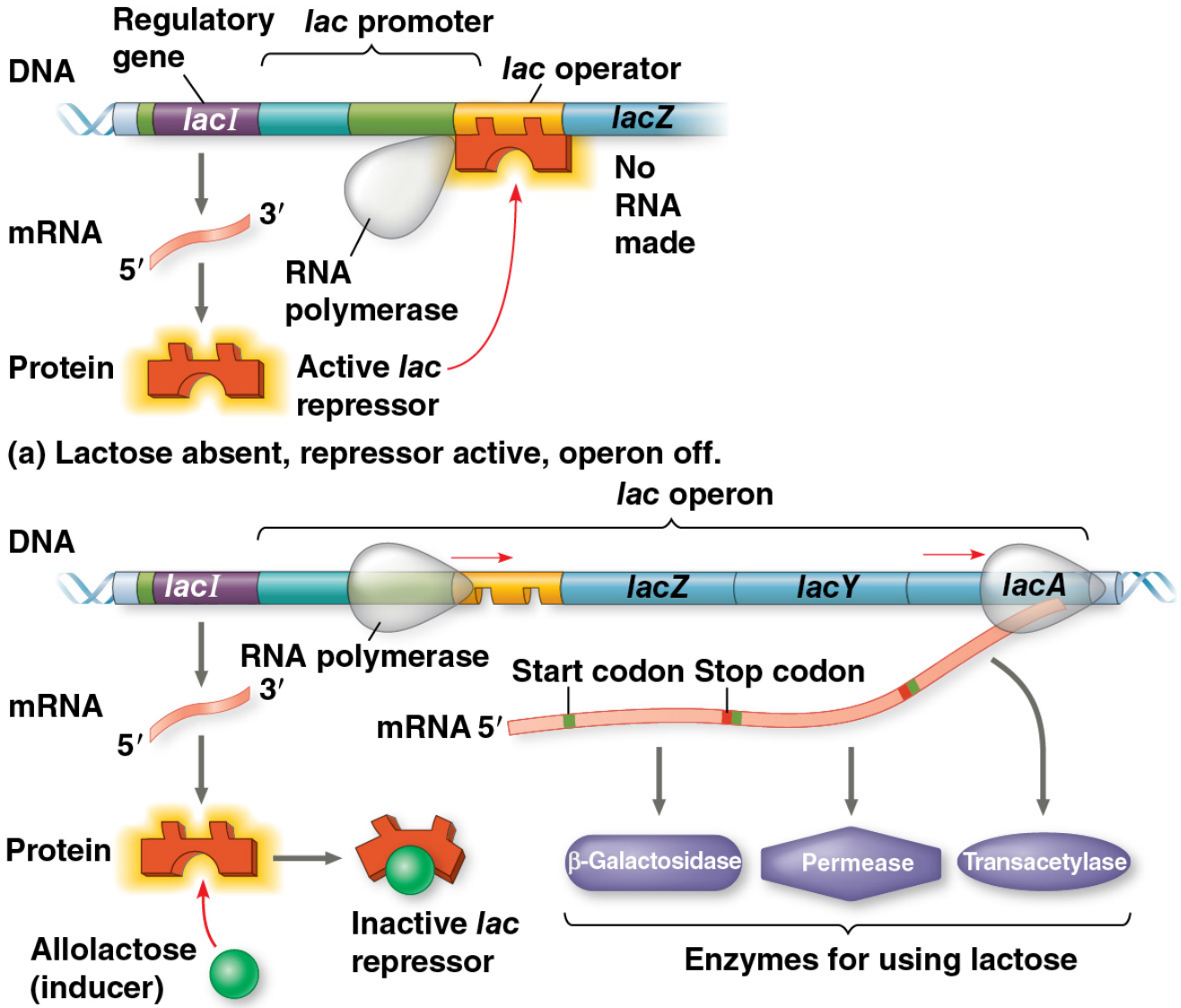
Repressible and Inducible Operons: Two Types of Negative Gene Regulation

- 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

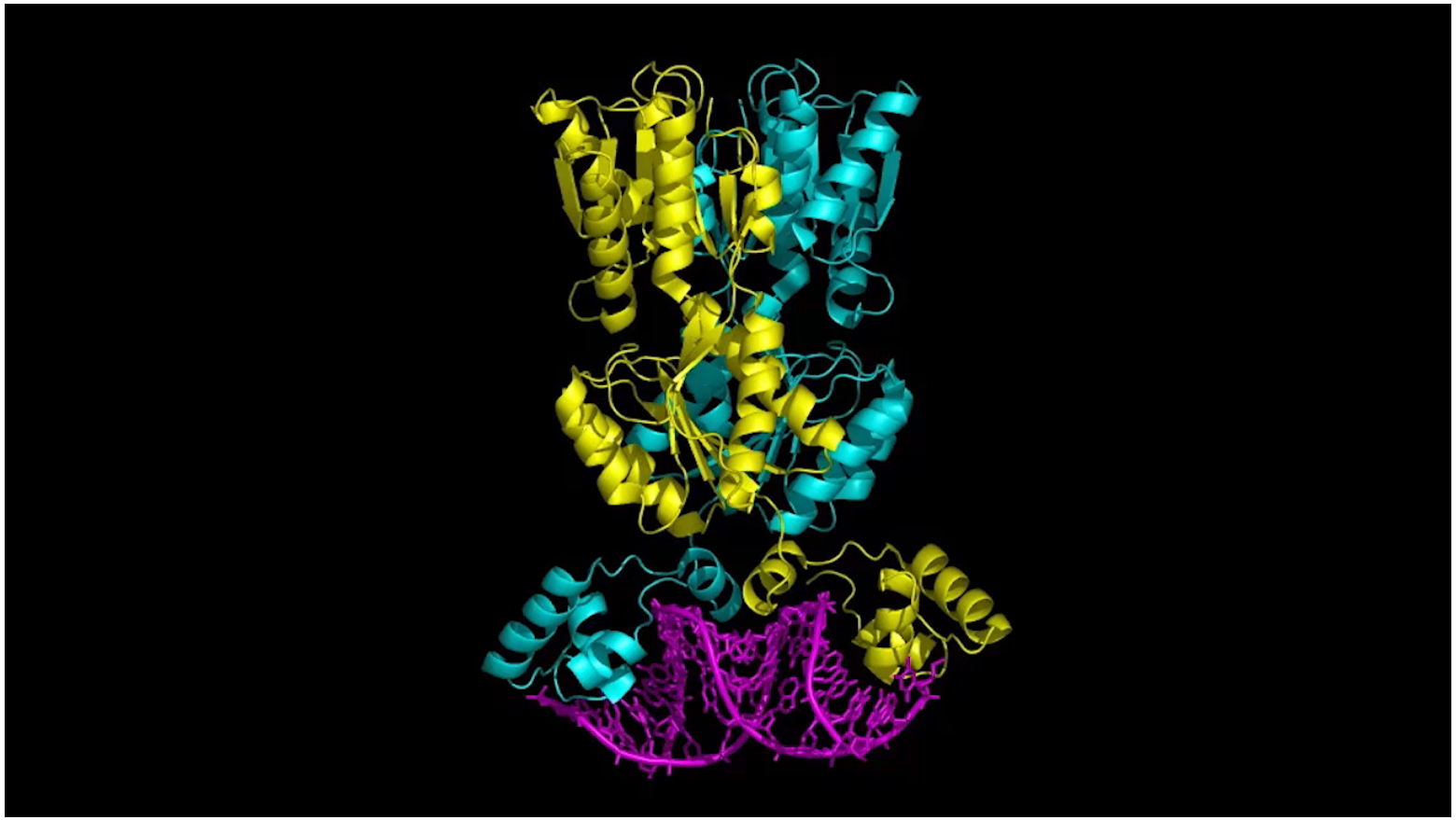
- The *lac* operon is an inducible operon and contains genes that code for enzymes used in the hydrolysis and metabolism of lactose
- The entire transcription unit is under the control of one main operator and promoter
- A regulatory gene, *lacI*, located outside the operon encodes a repressor protein that can switch off the operon

- 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
- In the case of the lac operon, the inducer is allolactose, an isomer of lactose
- Allolactose binds the repressor protein, altering its shape of the repressor so it can no longer bind to the operator sequence

Figure 18.4


Regulatory gene
lac promoter
lac operator
DNA
lacI
lacZ
No RNA made
mRNA
3′
5′
RNA polymerase
Protein
Active lac repressor
(a) Lactose absent, repressor active, operon off.
lac operon
DNA
lacI
lacZ
lacY
lacA
RNA polymerase
3′
mRNA
5′
Start codon
Stop codon
mRNA 5′
Protein
β-Galactosidase
Permease
Transacetylase
Inactive lac repressor
Allolactose (inducer)
Enzymes for using lactose
(b) Lactose present, repressor inactive, operon on.

Video: Cartoon Rendering of the *lac* Repressor from *E. coli*



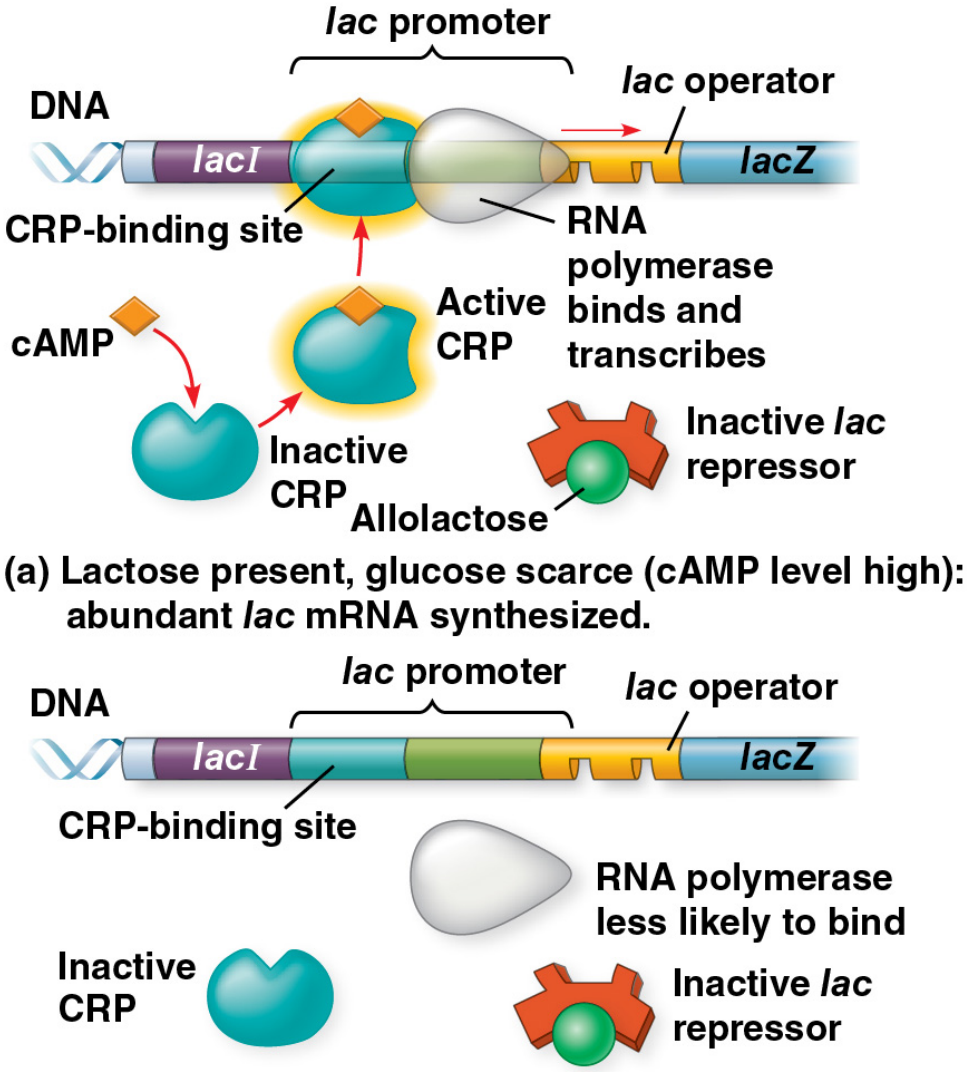
- Inducible enzymes usually function in catabolic pathways; their synthesis is induced by a chemical signal
- Repressible enzymes usually function in anabolic pathways; their synthesis is repressed by high levels of the end product
- Regulation of both the *trp* and *lac* operons involves negative control 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 cyclic AMP receptor protein (CRP), an **activator** of transcription
- When glucose (a preferred food source of *E. coli*) is scarce, CRP is activated by binding with **cyclic AMP (cAMP)**
- Activated CRP attaches to the promoter of the *lac* operon and increases the affinity of RNA polymerase, thus accelerating transcription

- When glucose levels increase, CRP detaches from the *lac* operon, and transcription returns to a normal, low level
- CRP helps regulate other operons that encode enzymes used in catabolic pathways
- The ability to catalyze compounds like lactose enables cells deprived of glucose to survive
- The compounds present in any given cell determine which genes are switched on

Figure 18.5


lac promoter
lac operator
DNA
lacI
lacZ
CRP-binding site
RNA polymerase binds and transcribes
Active CRP
cAMP
Inactive CRP
Inactive lac repressor
Allolactose
(a) Lactose present, glucose scarce (cAMP level high): abundant lac mRNA synthesized.
lac promoter
lac operator
DNA
lacI
lacZ
CRP-binding site
RNA polymerase less likely to bind
Inactive CRP
Inactive lac repressor
(b) Lactose present, glucose present (cAMP level low): little lac mRNA synthesized.

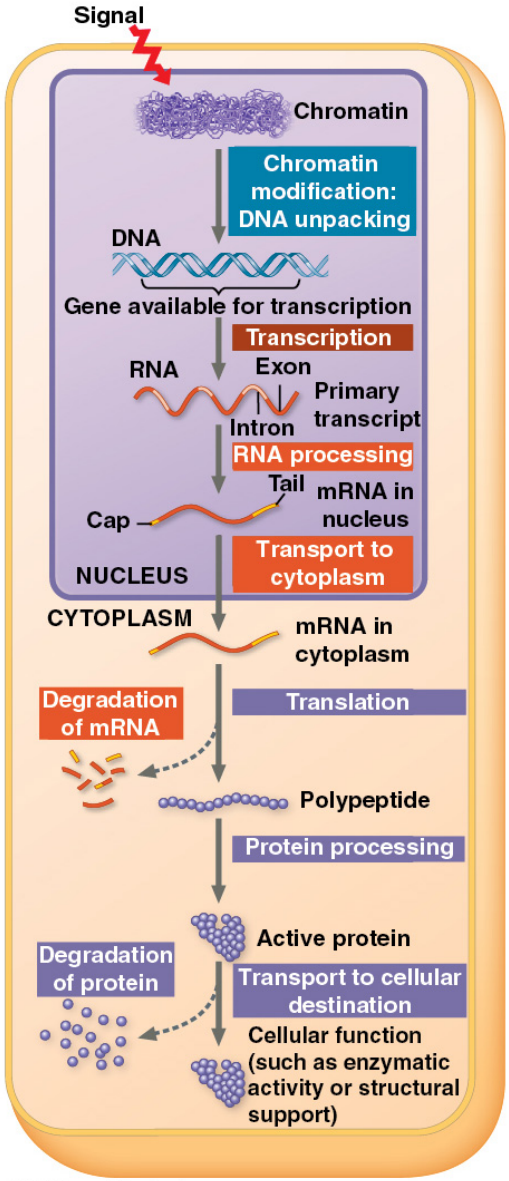
CONCEPT 18.2: Eukaryotic gene expression is regulated at many stages

- All organisms must regulate which genes are expressed at any given time
- Genes are turned on and off in response to signals from their external and internal environments
- In multicellular organisms, regulation of gene expression is essential for cell specialization

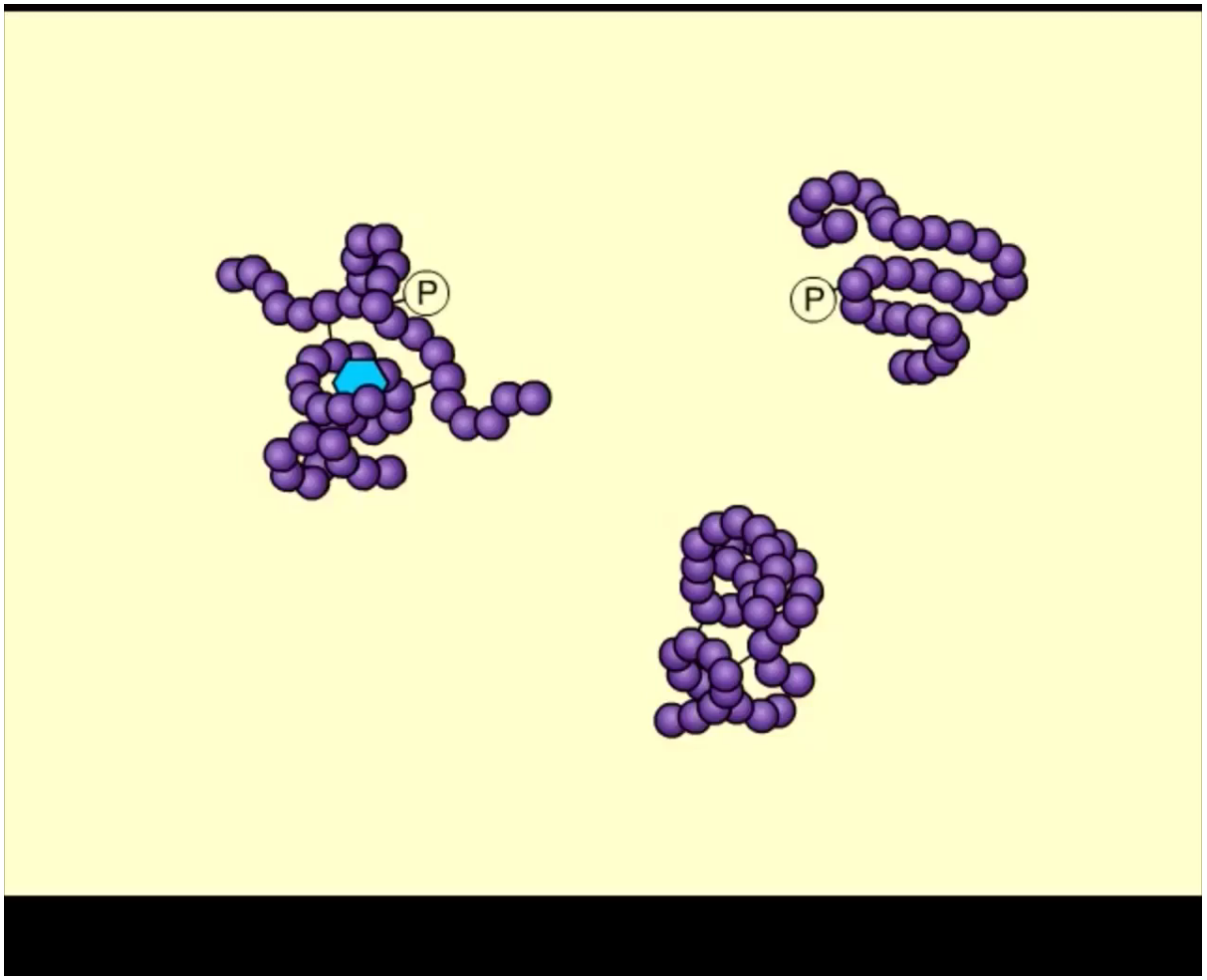
Differential Gene Expression

- Almost all the cells in an organism contain an identical genome
- 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, but is often equated with transcription

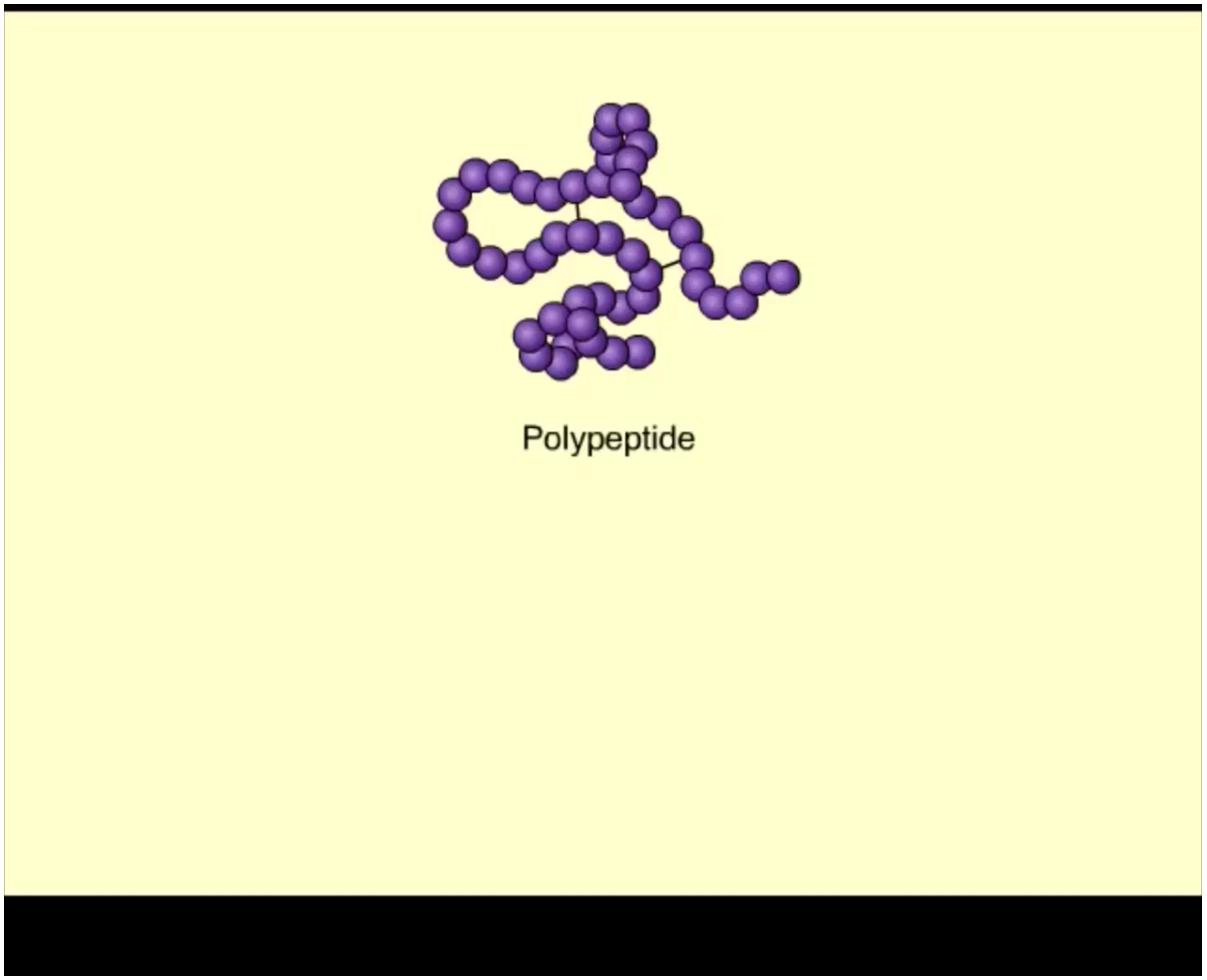
Figure 18.6


Signal
Chromatin
Chromatin modification: DNA unpacking
DNA
Gene available for transcription
Transcription
RNA
Exon
Primary transcript
Intron
RNA processing
Tail
mRNA in nucleus
Cap
Transport to cytoplasm
NUCLEUS
CYTOPLASM
mRNA in cytoplasm
Degradation of mRNA
Translation
Polypeptide
Protein processing
Active protein
Degradation of protein
Transport to cellular destination
Cellular function (such as enzymatic activity or structural support)

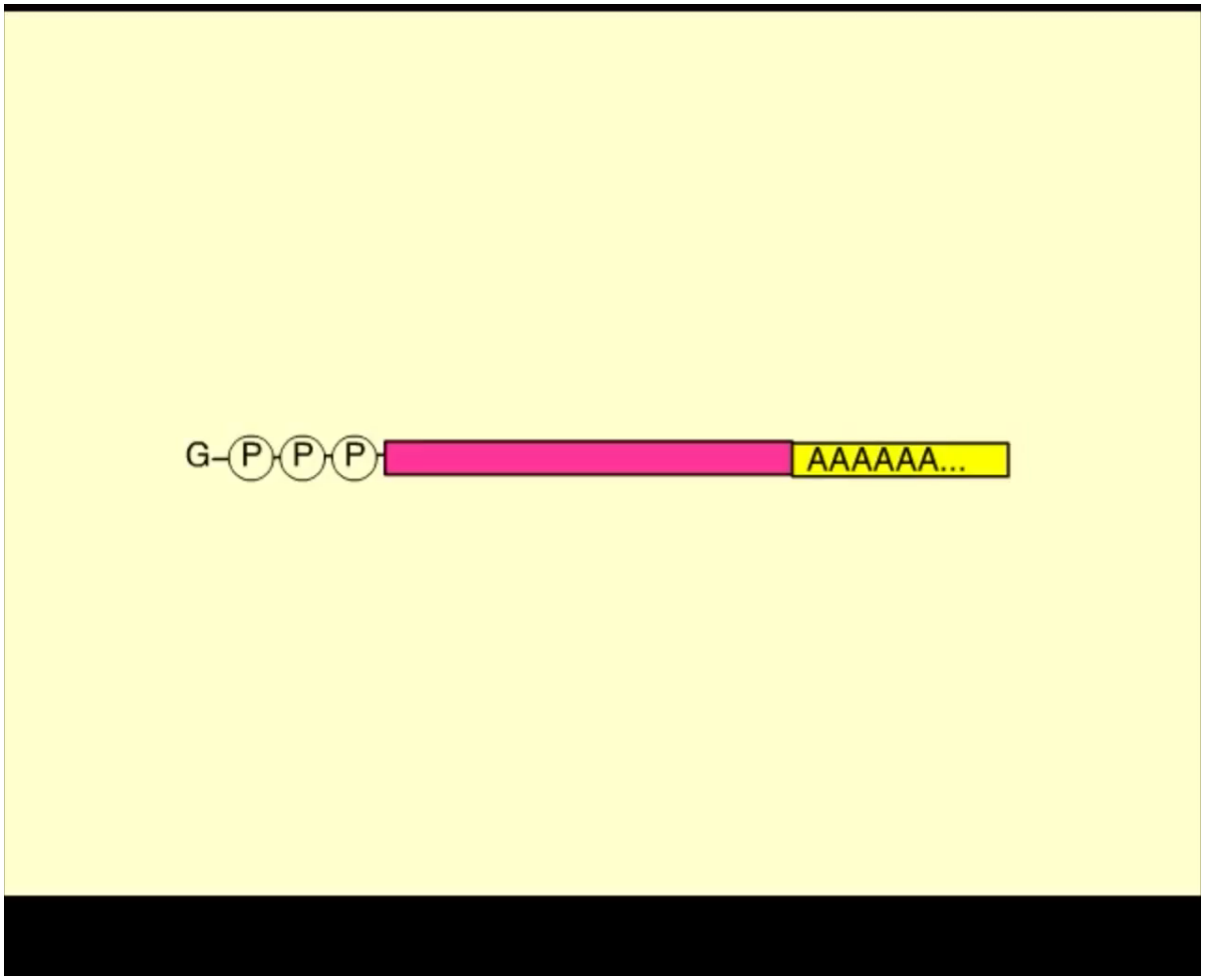
Animation: Protein Degradation



Animation: Protein Processing



Animation: Blocking Translation



Regulation of Chromatin Structure

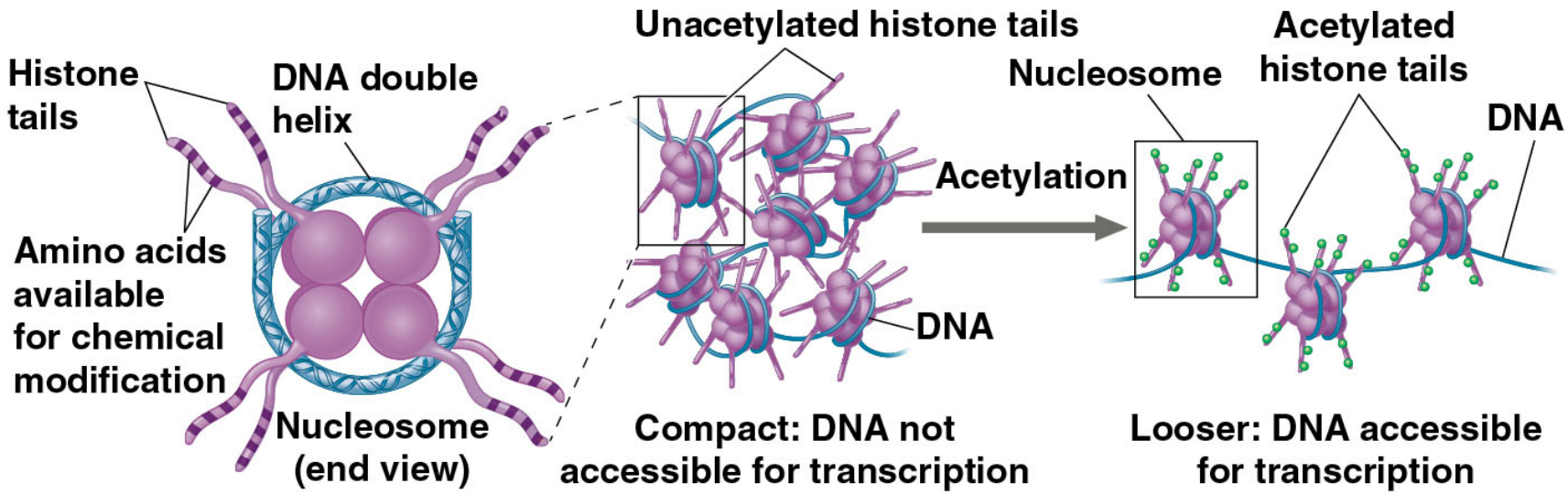
- The structural organization of chromatin helps regulate gene expression in several ways
- Genes within highly packed heterochromatin are usually not expressed
- In euchromatin, gene transcription is affected by the location of nucleosomes along the promoter and the sites where DNA attaches to the protein scaffolding of the chromosome

- Chromatin structure and gene expression can be influenced by chemical modifications of the histone proteins of the nucleosome
- These modifications are catalyzed by specific enzymes

Histone Modifications and DNA Methylation

- In **histone acetylation**, acetyl groups are attached to an amino acid in a histone tail
- This appears to open up the chromatin structure, thereby promoting the initiation of transcription
- The addition of methyl groups (methylation) can condense chromatin and reduce transcription

Figure 18.7



(a) Histone tails protrude outward from a nucleosome.

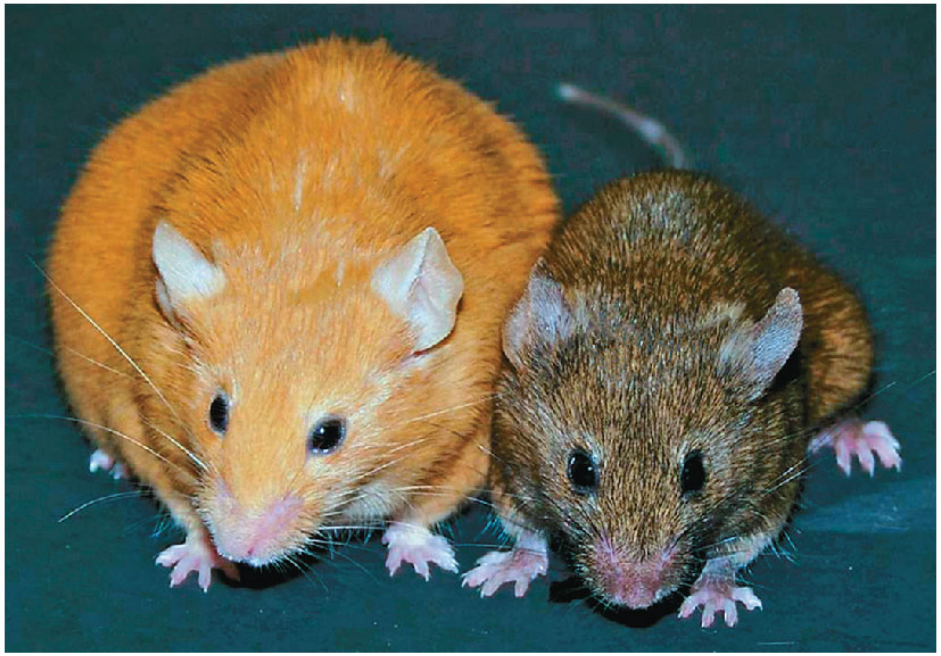
(b) Acetylation of histone tails promotes loose chromatin structure that permits transcription.

- **DNA methylation**, the addition of methyl groups to certain bases in DNA, is associated with reduced transcription
- 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**
- Epigenetic variations might explain cases where one identical twin develops a genetically based disease, while the other does not

Figure 18.8



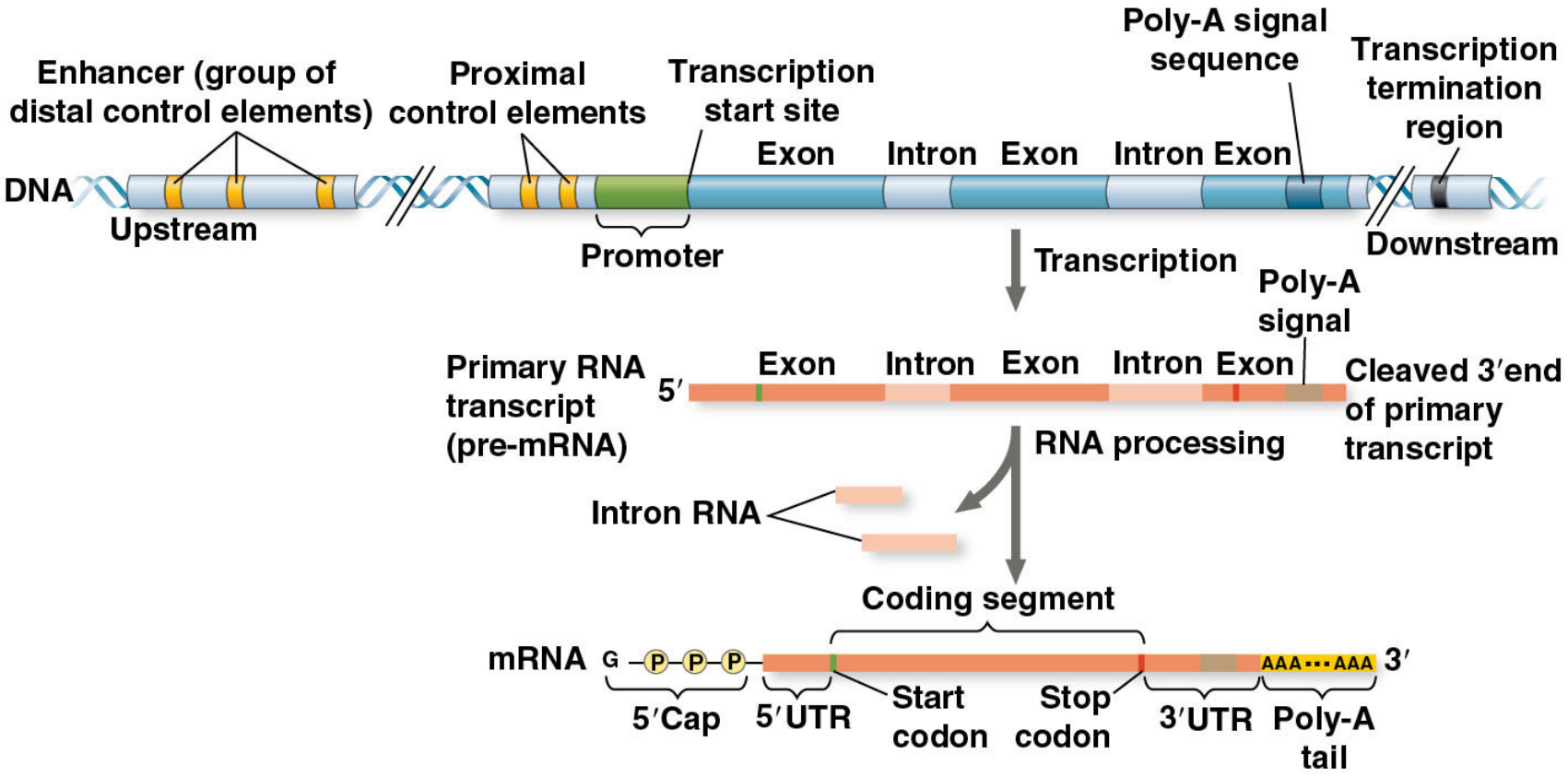
Regulation of Transcription Initiation

- 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

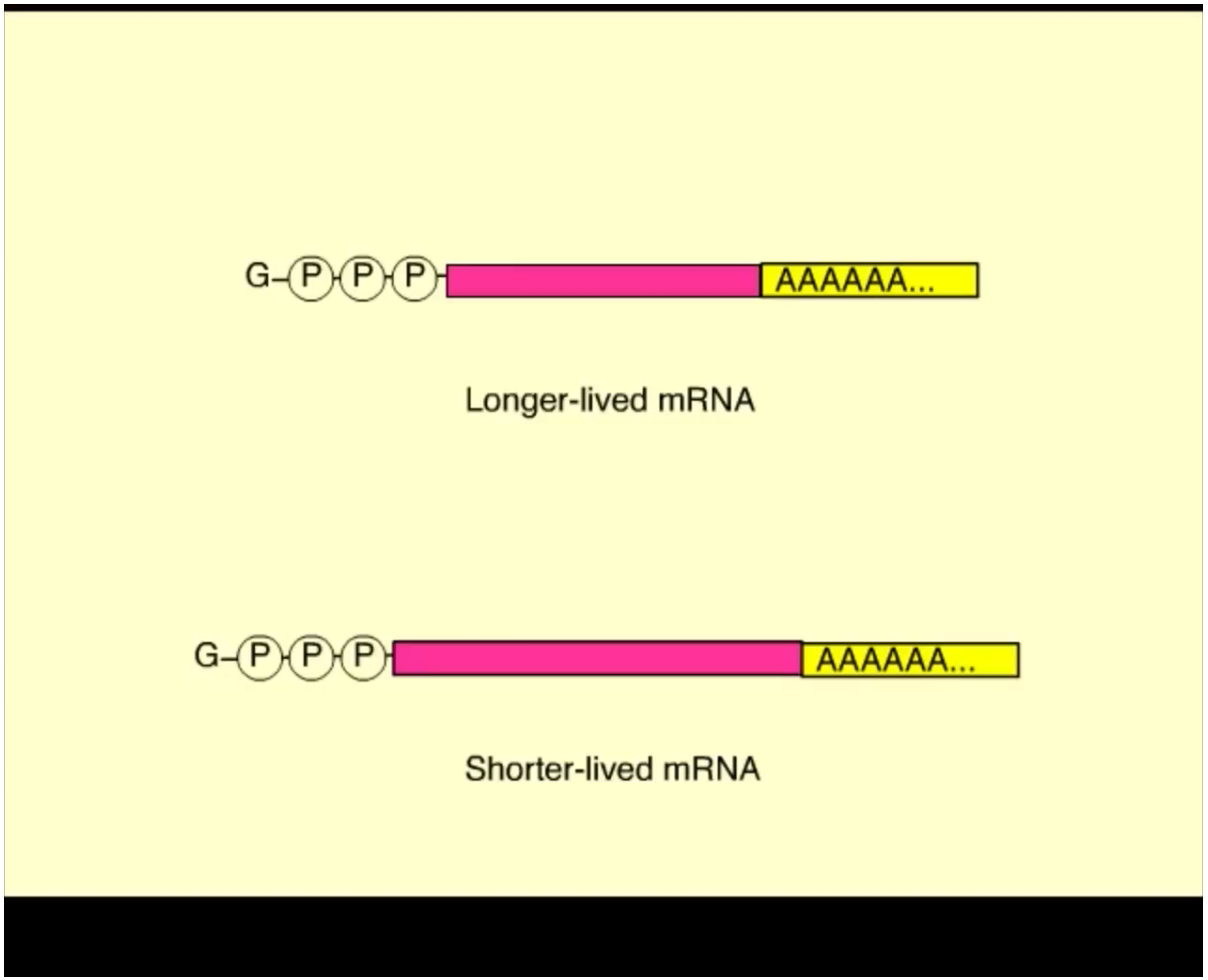
Organization of a Typical Eukaryotic Gene and Its Transcript

- 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 18.9


Enhancer (group of distal control elements)
Proximal control elements
Transcription start site
Poly-A signal sequence
Transcription termination region
DNA
Exon
Intron
Exon
Intron
Exon
Upstream
Promoter
Downstream
Transcription
Poly-A signal
Primary RNA transcript (pre-mRNA)
5′
Exon
Intron
Exon
Intron
Exon
Cleaved 3′end of primary transcript
RNA processing
Intron RNA
Coding segment
mRNA
G
P
P
P
AAA···AAA
3′
5′Cap
5′UTR
Start codon
Stop codon
3′UTR
Poly-A tail

Animation: mRNA Degradation



The Roles of General and Specific Transcription Factors

- General transcription factors are essential for the transcription of all protein-coding genes
- Some genes require specific transcription factors that bind to control elements that may be close to or farther away from the promoter

General Transcription Factors at the Promoter

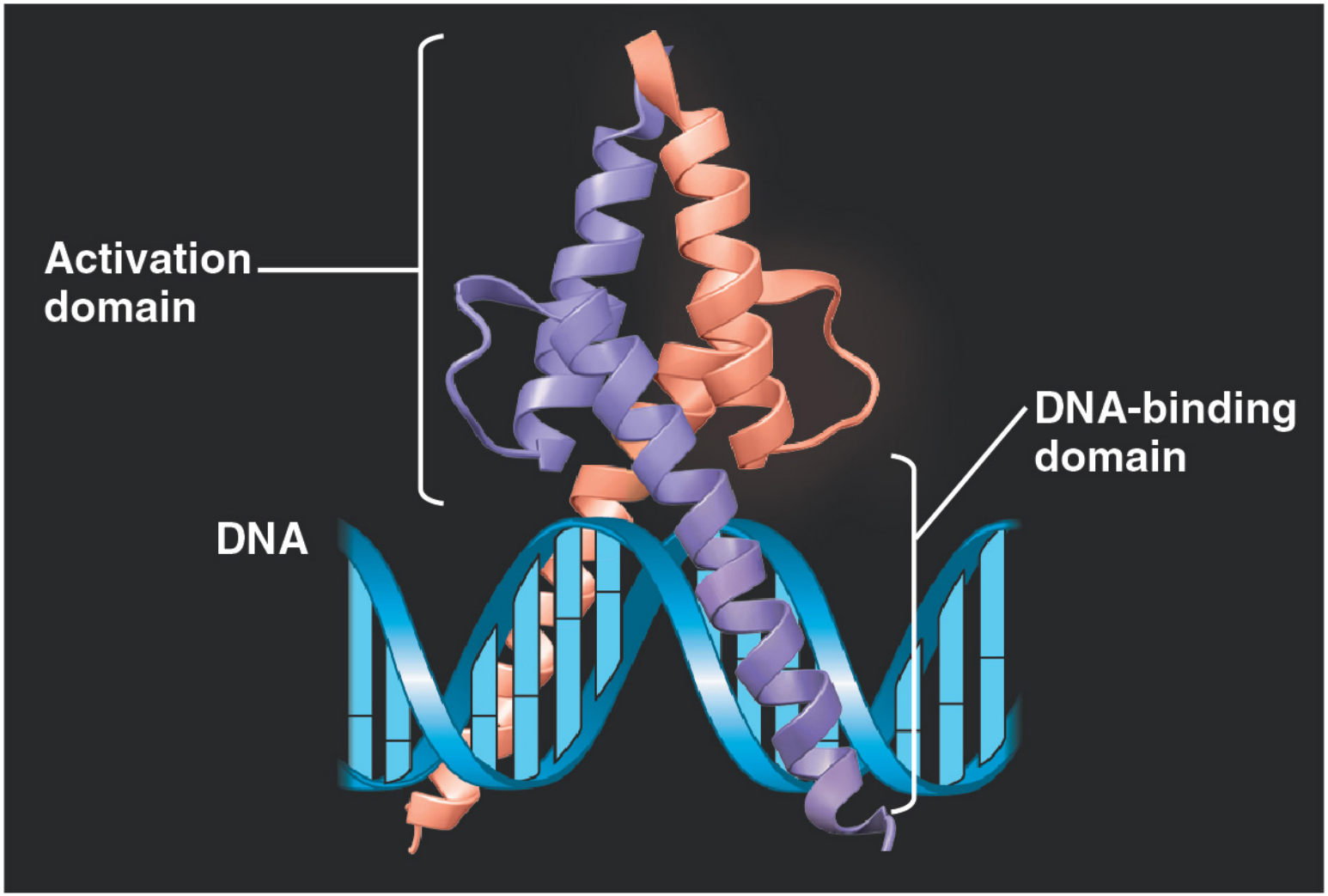
- RNA polymerase II requires the assistance of transcription factors to initiate transcription
- General transcription factors are essential for the transcription of all protein-coding genes
- A few bind to the TATA box within the promoter
- Many bind to proteins, including other transcription factors and RNA polymerase II

- Only when the complete initiation complex has assembled can the RNA polymerase begin to move along the template strand of the DNA
- It produces a complementary strand of RNA
- For genes that are not expressed all the time, high levels of transcription depend on the presence of another set of factors, 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
- Each enhancer is generally associated with only one gene and no other

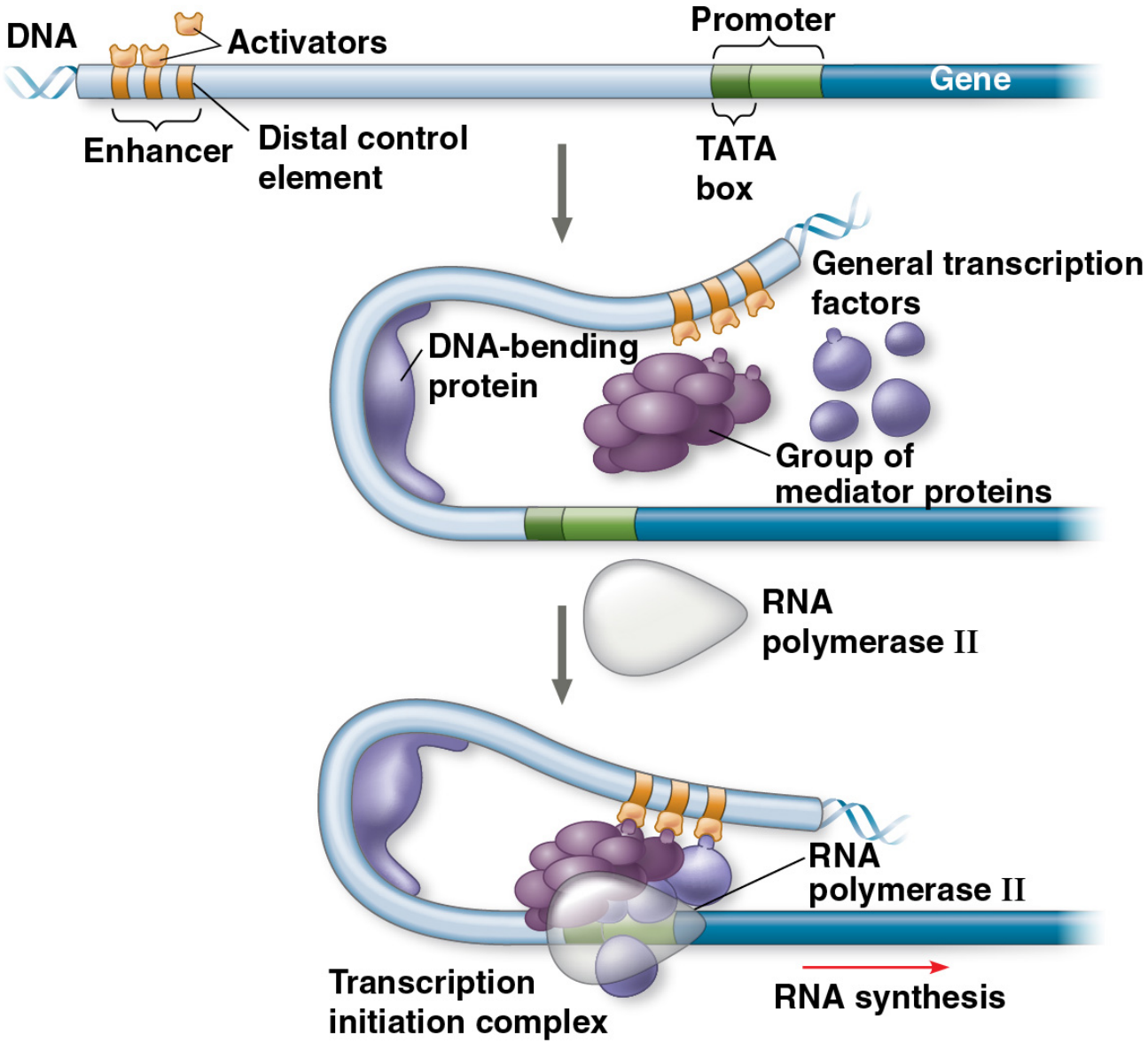
Figure 18.10



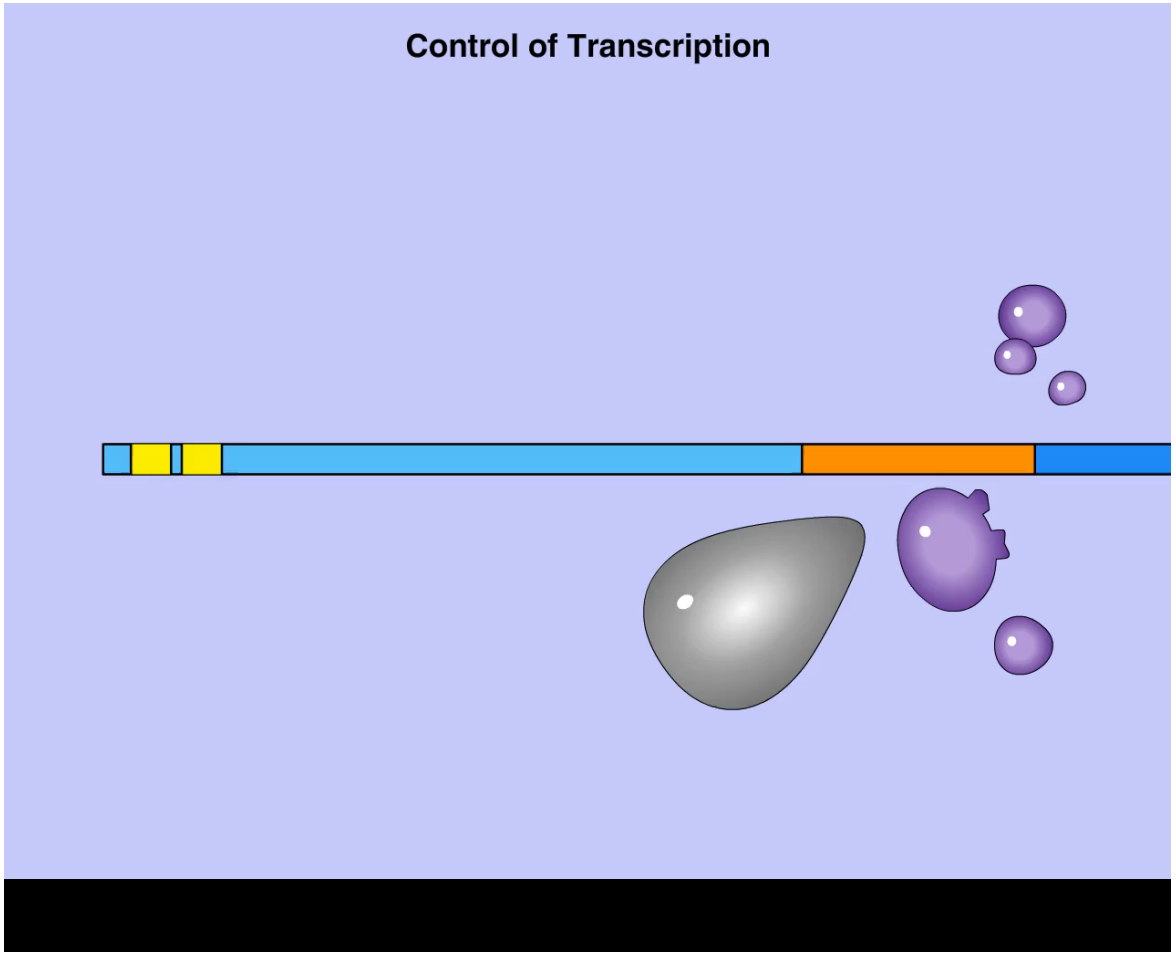
- An activator is a protein that binds to an enhancer and stimulates transcription of a gene
- Activators have two domains, one that binds DNA and a second that activates transcription
- Bound activators facilitate a sequence of protein−protein interactions that result in enhanced transcription of a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

- The currently accepted model suggests that protein-mediated bending of the DNA brings the bound activators into contact with a group of mediator proteins
- The mediator proteins interact with general transcription factors at the promoter
- This helps assemble and position the preinitiation complex

Figure 18.11


DNA
Activators
Promoter
Gene
Enhancer
Distal control element
TATA box
General transcription factors
DNA-bending protein
Group of mediator proteins
RNA polymerase II
RNA polymerase II
Transcription initiation complex
RNA synthesis

Animation: Regulation of Transcription by Transcription Activators and Enhancers

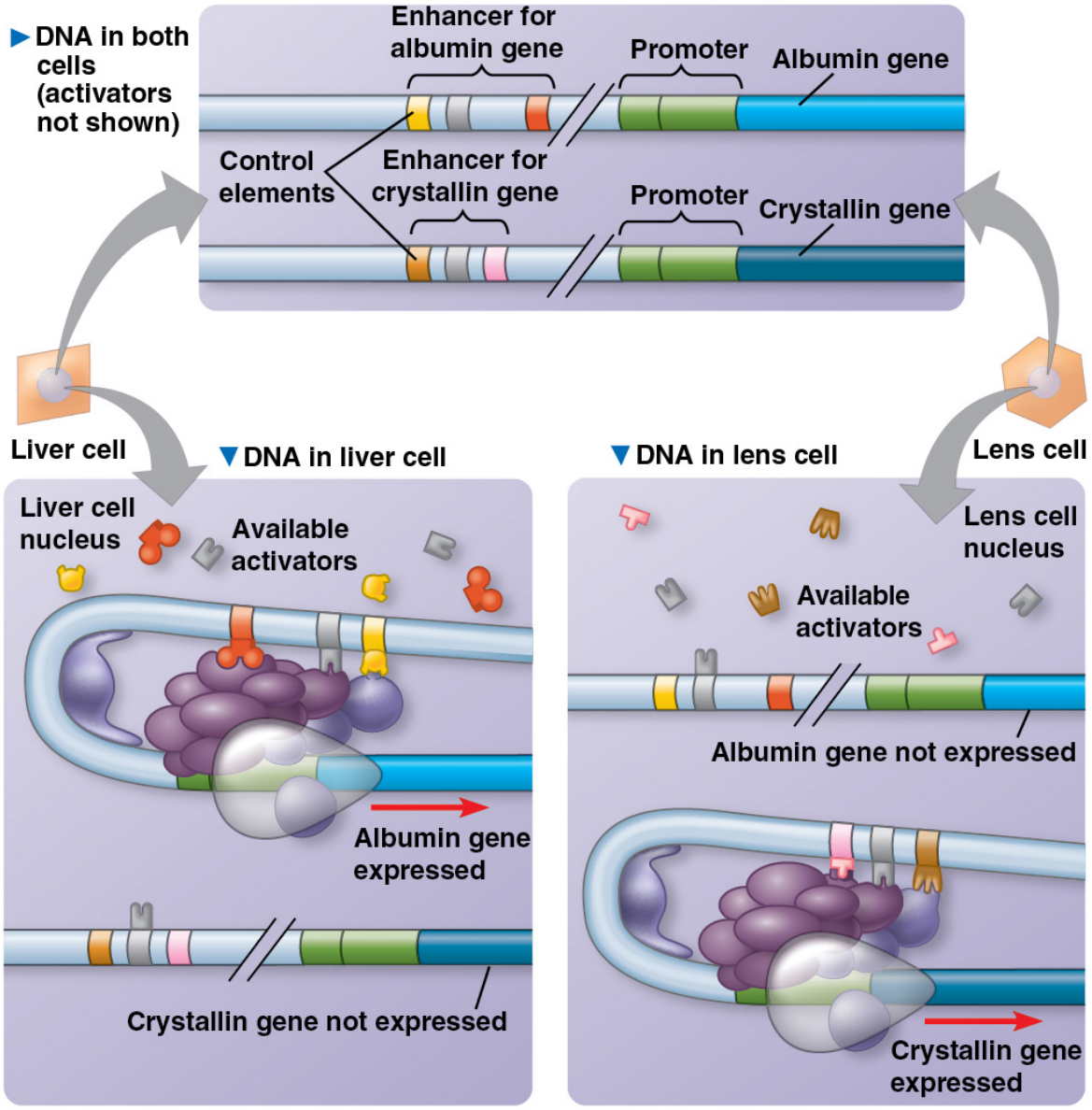


- Some transcription factors function as repressors, inhibiting expression of a particular gene in several different ways
- Some repressors bind directly to control elements, and block activator binding
- Others interfere with activators, so they cannot bind the DNA
- Some activators and repressors my indirectly affect transcription by altering chromatin structure

Combinatorial Control of Gene Activation

- A particular combination of control elements can activate transcription only when the appropriate activator proteins are present
- With only a dozen or so control elements, a large number of potential combinations is possible

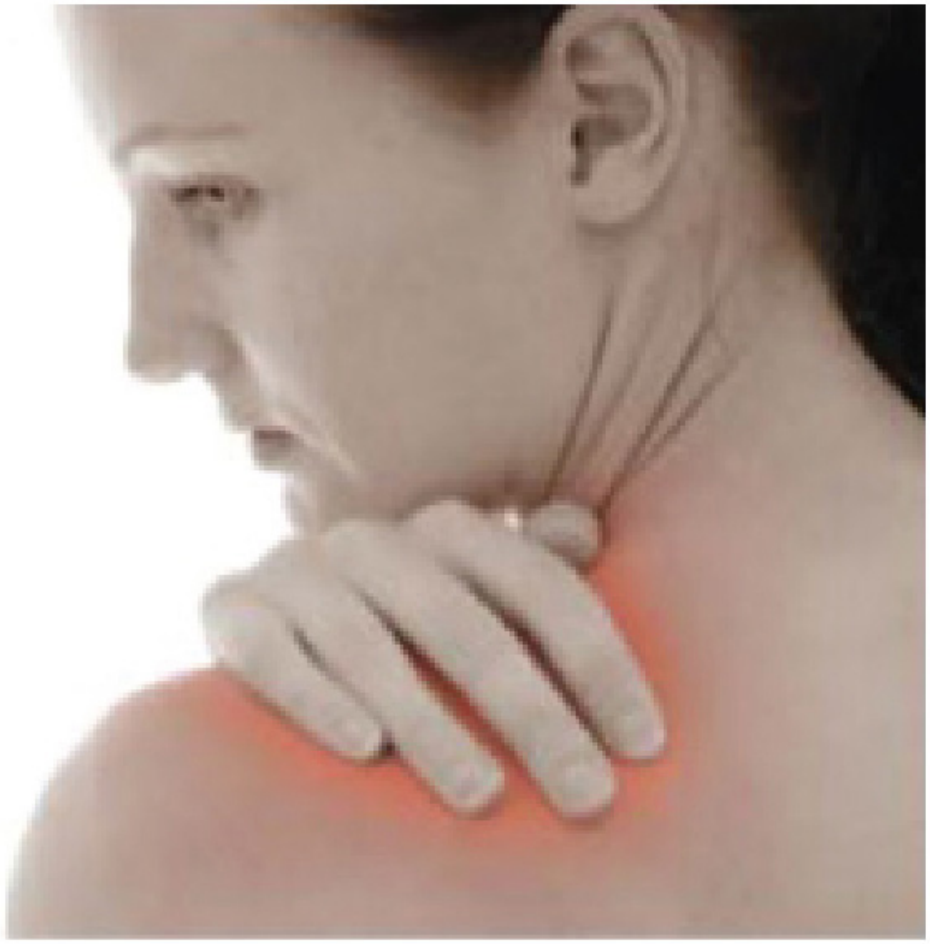
Figure 18.12


DNA in both cells (activators not shown)
Enhancer for albumin gene
Promoter
Albumin gene
Control elements
Enhancer for crystallin gene
Promoter
Crystallin gene
Liver cell
DNA in liver cell
Liver cell nucleus
Available activators
Albumin gene expressed
Crystallin gene not expressed
DNA in lens cell
Lens cell
Lens cell nucleus
Available activators
Albumin gene not expressed
Crystallin gene expressed

Coordinately Controlled Genes in Eukaryotes

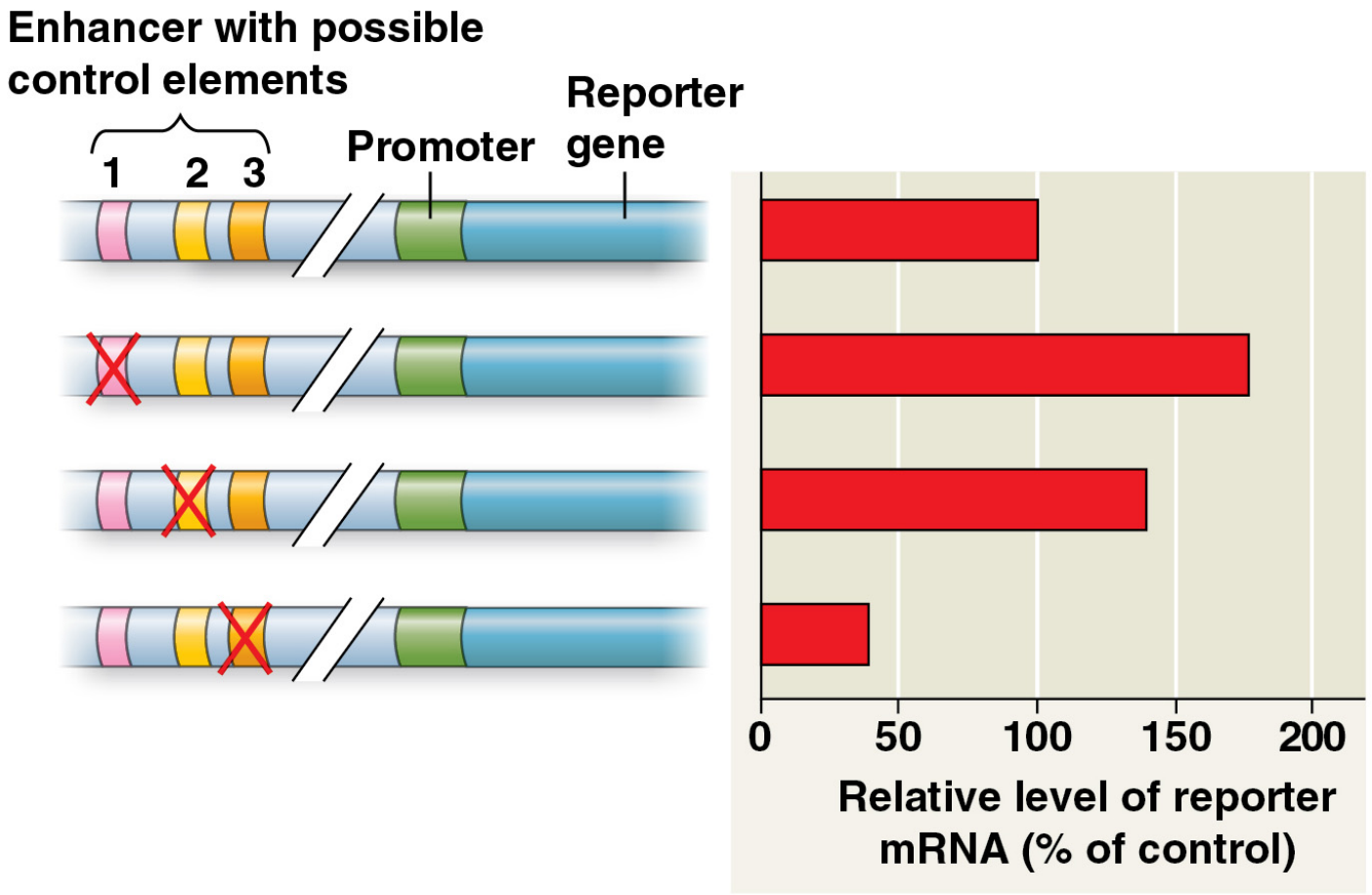
- Co-expressed eukaryotic genes are not organized in operons (with a few exceptions)
- These genes can be scattered over different chromosomes, but each has the same combination of control elements
- Activator proteins in the nucleus recognize specific control elements and promote simultaneous transcription of the genes

Figure 18.UN01



Tissue inflammation

Figure 18.UN02

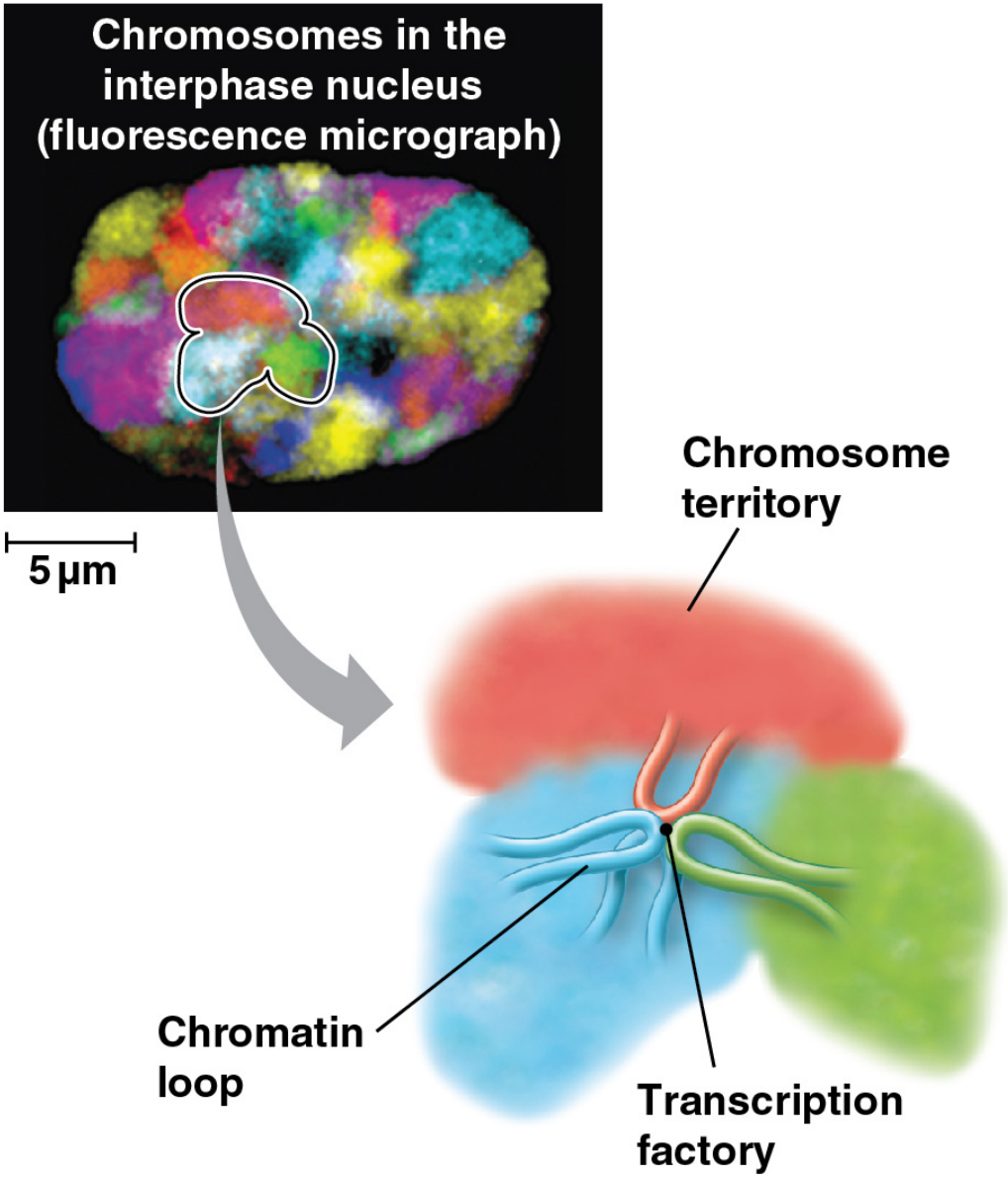


Data from J. N. Walters et al., Regulation of human microsomal prostaglandin E synthase-1 by IL-1b requires a distal enhancer element with a unique role for C/EBPb, *Biochemical Journal* 443:561–571 (2012).

Nuclear Architecture and Gene Expression

- Chromosome conformation capture techniques allow identification of regions of chromosomes that interact with each other
- Loops of chromatin from different chromosomes may congregate at particular sites, some of which are rich in transcription factors and RNA polymerases
- These transcription factories are thought to be areas specialized for a common function

Figure 18.13


Chromosomes in the interphase nucleus (fluorescence micrograph)
5 µm
Chromosome territory
Chromatin loop
Transcription factory

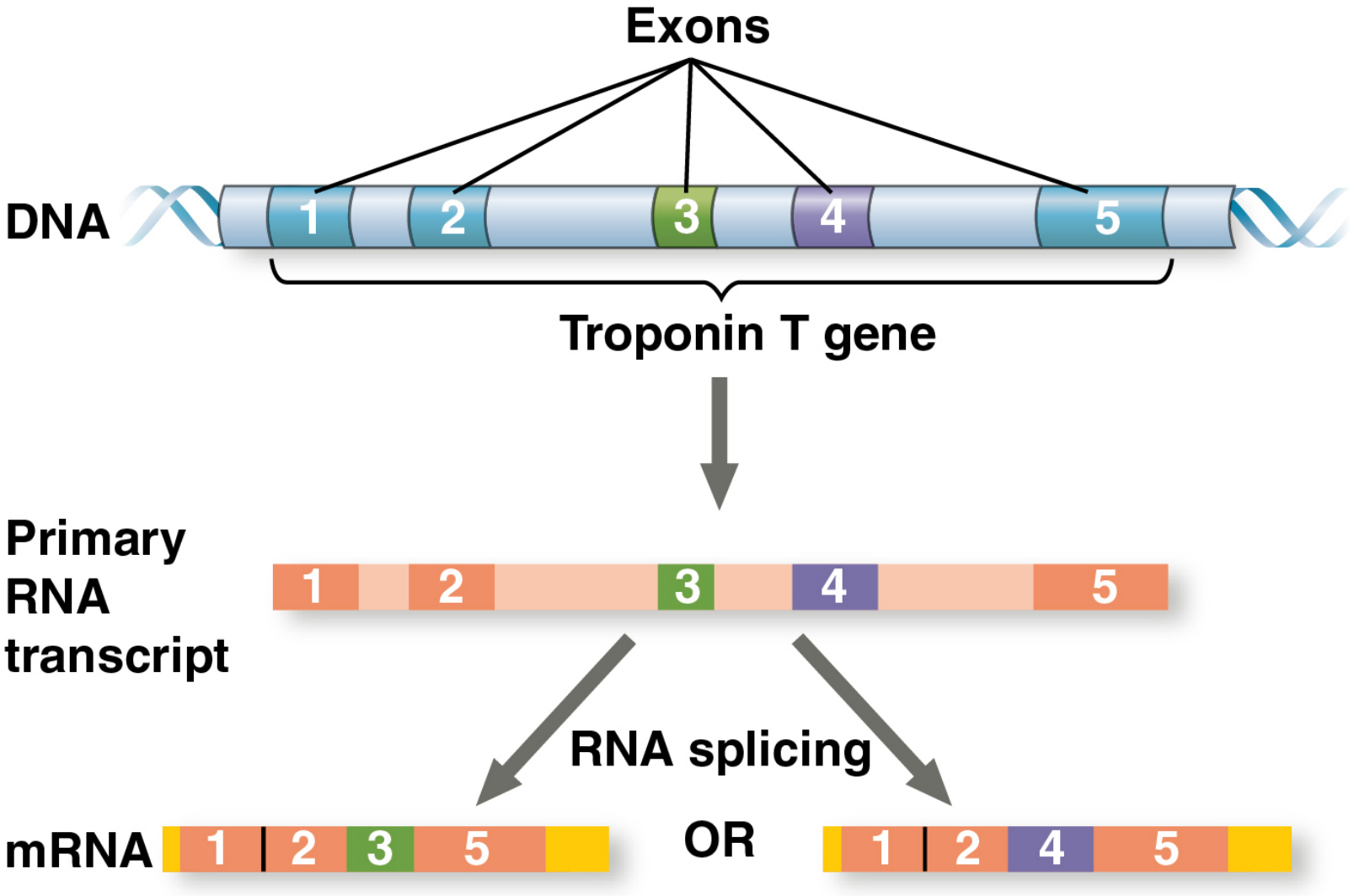
Mechanisms of Post-Transcriptional Regulation

- Transcription alone does not constitute gene expression
- Regulatory mechanisms can operate at various stages after transcription
- Such mechanisms allow a cell to rapidly fine-tune gene expression 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
- Alternative RNA splicing can significantly expand the repertoire of a eukaryotic genome
- It is a proposed explanation for the surprisingly low number of genes in the human genome
- More than 90% of the human protein-coding genes undergo alternative splicing

Figure 18.14


Exons
DNA
1
2
3
4
5
Troponin T gene
Primary RNA transcript
1
2
3
4
5
RNA splicing
mRNA
1
2
3
5
OR
1
2
4
5

Initiation of Translation and mRNA Degradation

- 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

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

Protein Processing and Degradation

- After translation, polypeptides undergo processing, including cleavage, and chemical modifications
- The length of time each protein functions is regulated by selective degradation
- Cells mark proteins for degradation by attaching ubiquitin to them
- This mark is recognized by proteasomes, which recognize and degrade the proteins

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

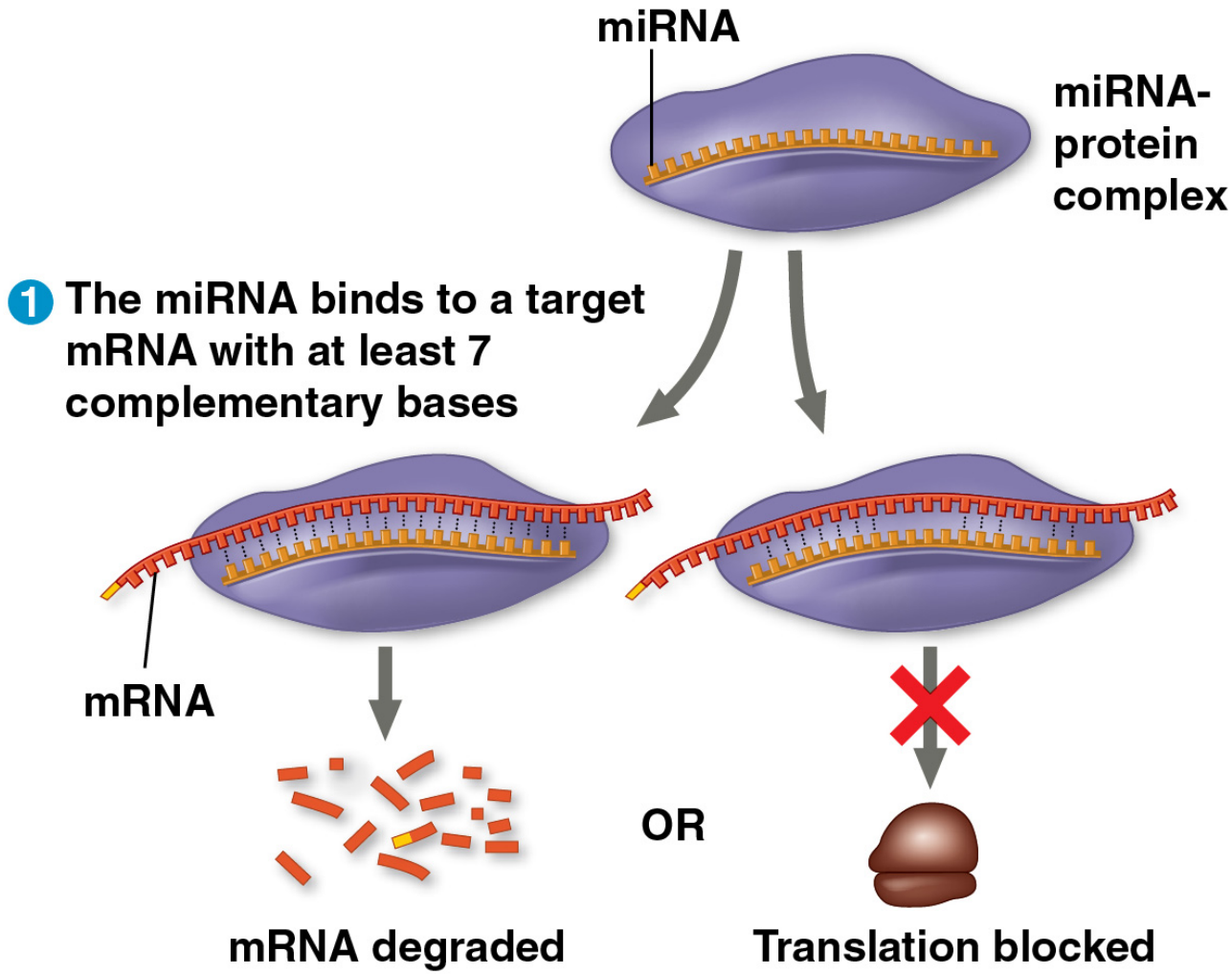
- A small fraction of DNA codes for proteins, and a very small fraction of the non-protein-coding DNA consists of genes for RNA such as rRNA and tRNA
- In the past, genes that did not encode a protein product or known functional RNA were considered "junk DNA"
- Some genomic studies have cast doubt on this description

- Roughly 75% of the human genome is transcribed in at some point in any given cell
- At least some of the genome is transcribed into noncoding RNAs (ncRNAs)
- Researchers are uncovering more evidence of biological roles for these ncRNAs every day
- This represents a major shift in the thinking of biologists

Effects on mRNAs by MicroRNAs and Small Interfering RNAs

- **MicroRNAs (miRNAs)** are small, single-stranded RNA molecules that can bind complementary sequences in mRNA
- The miRNAs and associated proteins cause degradation of the target mRNA or sometimes block its translation
- Biologists estimate that expression of at least one-half of human genes may be regulated by miRNAs

Figure 18.15


miRNA
miRNA-protein complex
1 The miRNA binds to a target mRNA with at least 7 complementary bases
mRNA
OR
mRNA degraded
Translation blocked
2 If bases are all complementary, mRNA is degraded; if the match is less complete, translation is blocked.

- **Small interfering RNAs (siRNAs)** are similar to miRNAs in size and function
- The blocking of gene expression by siRNAs is called **RNA interference (RNAi)**
- RNAi is used in the laboratory as a means of disabling genes to investigate their function
- Small ncRNAs are also used by bacteria as a defense system, called the CRISPR-Cas9 system, against viruses that infect them

Chromatin Remodeling and Effects on Transcription by ncRNAs

- Some ncRNAs can cause remodeling of chromatin structure
- In some yeasts, siRNAs re-form heterochromatin at centromeres after chromosome replication
- In most mammalian cells, siRNAs have not been found, and the mechanisms for centromere DNA condensation is not yet understood

- Small ncRNAs called piwi-interacting RNAs (piRNAs) induce formation of heterochromatin, blocking the expression of parasitic DNA elements in the genome known as transposons
- piRNAs help to reestablish appropriate methylation patterns during gamete formation in many animal species

- **Long noncoding RNAs (lncRNAs)** range from 200 to hundreds of thousands of nucleotides in length
- One type of lncRNA is responsible for X chromosome inactivation
- Because chromatin structure affects transcription and thus gene expression, RNA-based regulation of chromatin must play an important role in gene regulation

- Some experimental evidence suggest that lncRNAs can act as a scaffold, bringing DNA, proteins, and other RNAs together into complexes
- These may consequently promote gene expression, directly or indirectly
- Embryonic development is perhaps the ultimate example of precisely regulated gene expression

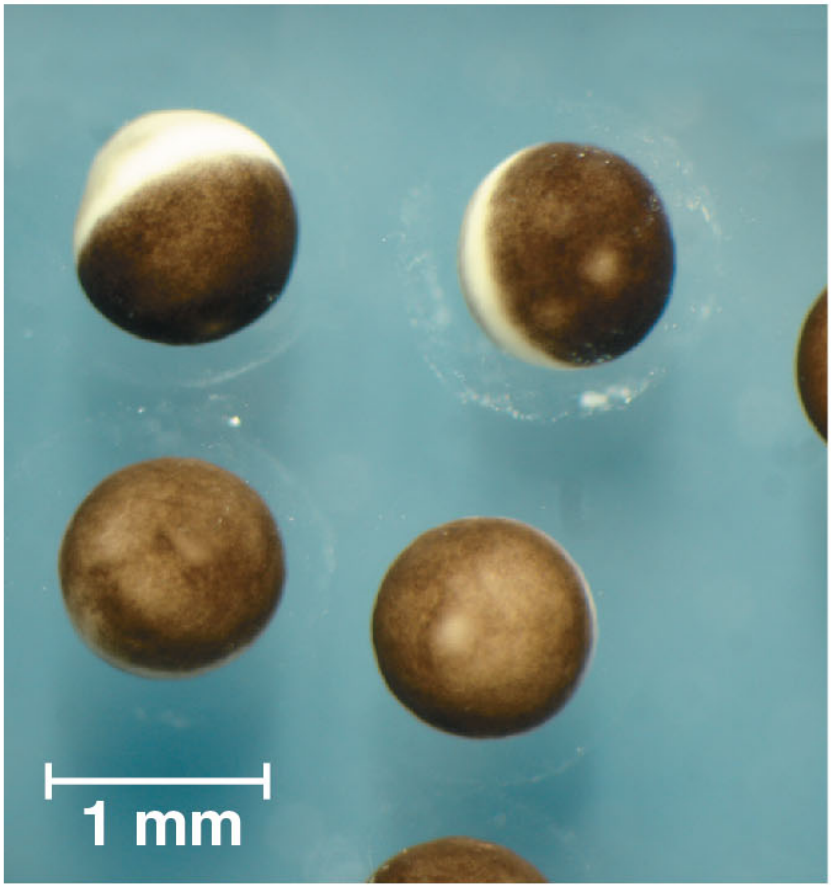
CONCEPT 18.4: A program of differential gene expression leads to the different cell types in a multicellular organism

- During embryonic development, a fertilized egg gives rise to many different cell types
- Cells 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
- 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**

Figure 18.16



(a) Fertilized eggs of a frog

(b) Newly hatched tadpole

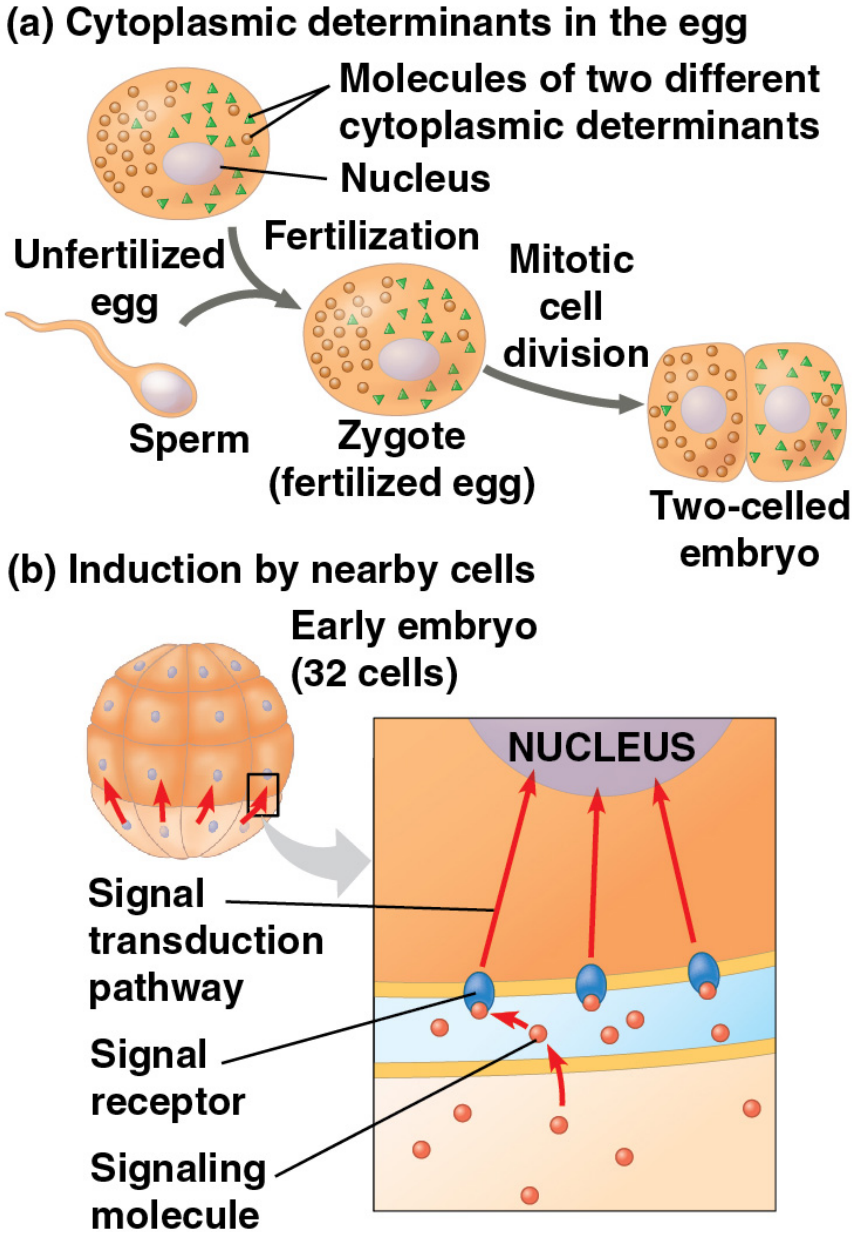
- Differential gene expression results from genes being regulated differently in each cell type
- Materials placed in the egg by maternal cells set up a program of gene regulation that is carried out as cells divide

Cytoplasmic Determinants and Inductive Signals

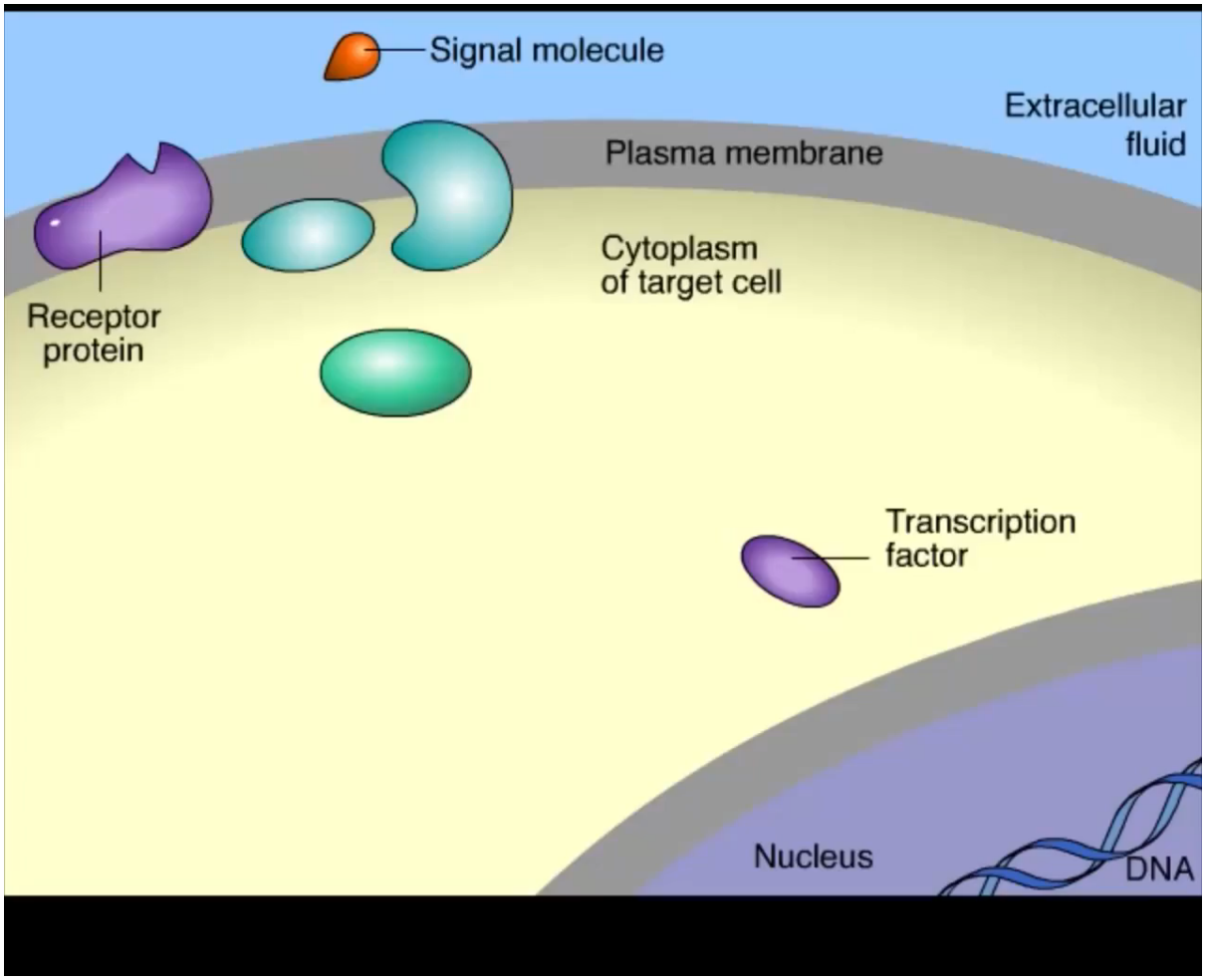
- An egg's cytoplasm contains RNA, proteins, and other substances that are distributed unevenly in the unfertilized egg
- **Cytoplasmic determinants** are maternal substances in the egg that influence early development
- As the zygote divides by mitosis, cells contain different cytoplasmic determinants,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

- The other major 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 changes in nearby target cells
- Thus, interactions between cells induce differentiation of specialized cell types

Figure 18.17


(a) Cytoplasmic determinants in the egg
Molecules of two different cytoplasmic determinants
Nucleus
Unfertilized egg
Fertilization
Mitotic cell division
Sperm
Zygote (fertilized egg)
Two-celled embryo
(b) Induction by nearby cells
Early embryo (32 cells)
NUCLEUS
Signal transduction pathway
Signal receptor
Signaling molecule

Animation: Cell Signaling



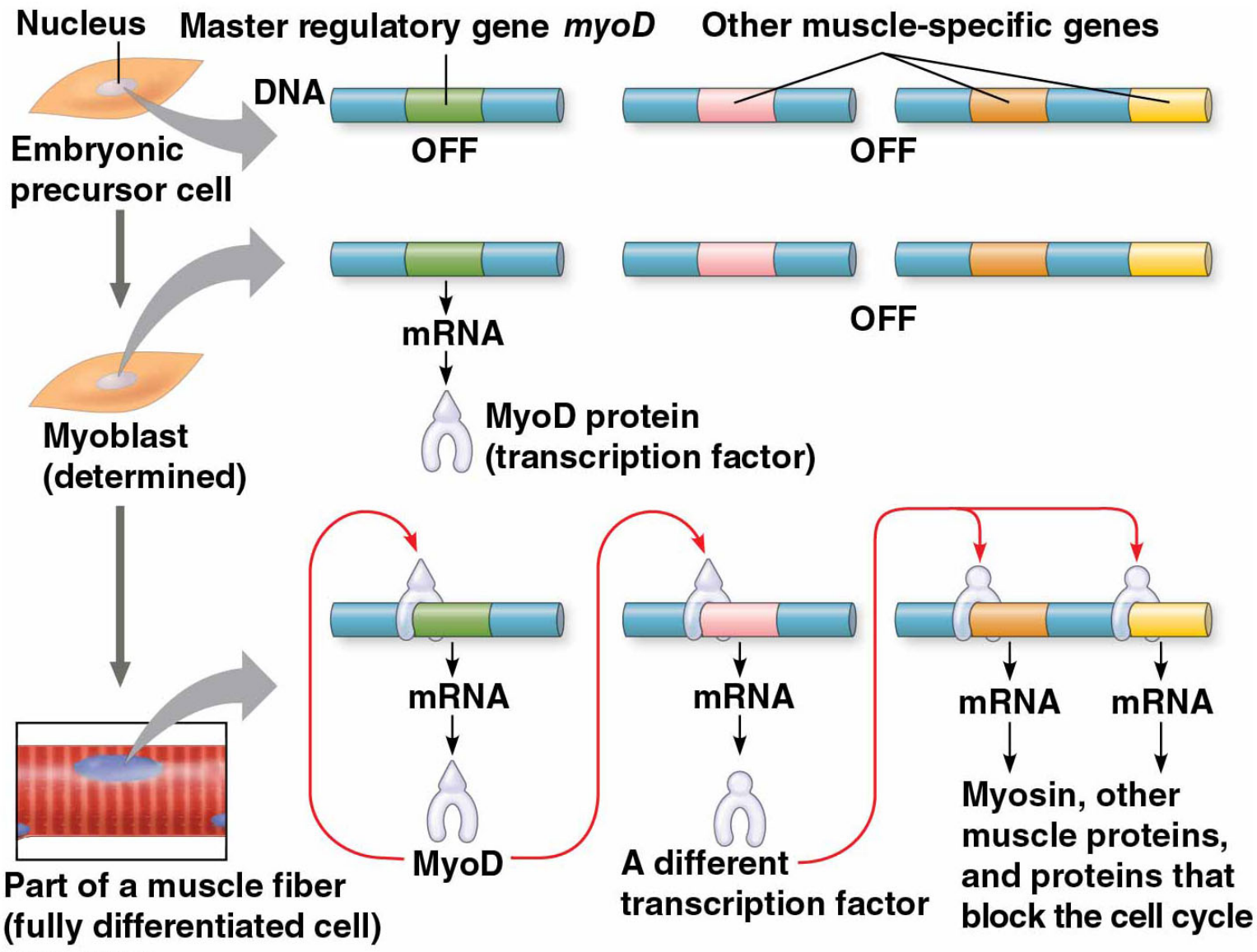
Sequential Regulation of Gene Expression During Cellular Differentiation

- **Determination** irreversibly commits a cell to becoming a particular cell type
- Once determined, an embryonic cell can be placed in another location in the embryo and will still differentiate into the cell type that is its normal fate
- Cell differentiation is the process by which a cell attains its determined fate

- Determination is understood in terms of molecular changes resulting in expression of tissue-specific proteins
- The first sign of differentiation is the appearance of tissue-specific mRNAs
- Later it is observable as changes in cell structure
- Multiple steps in gene regulation may be regulated during differentiation

- Myoblasts are cells determined to form muscle cells and produce large amounts of muscle-specific proteins
- *MyoD* is a “master regulatory gene” that encodes a transcription factor that commits the cell to becoming skeletal muscle
- Some target genes for MyoD (protein) encode additional muscle-specific transcription factors

Figure 18.18


Nucleus
Master regulatory gene myoD
Other muscle-specific genes
DNA
Embryonic precursor cell
OFF
OFF
mRNA
OFF
MyoD protein (transcription factor)
Myoblast (determined)
mRNA
mRNA
mRNA
mRNA
MyoD
A different transcription factor
Myosin, other muscle proteins, and proteins that block the cell cycle
Part of a muscle fiber (fully differentiated cell)

Pattern Formation: Setting Up the Body Plan

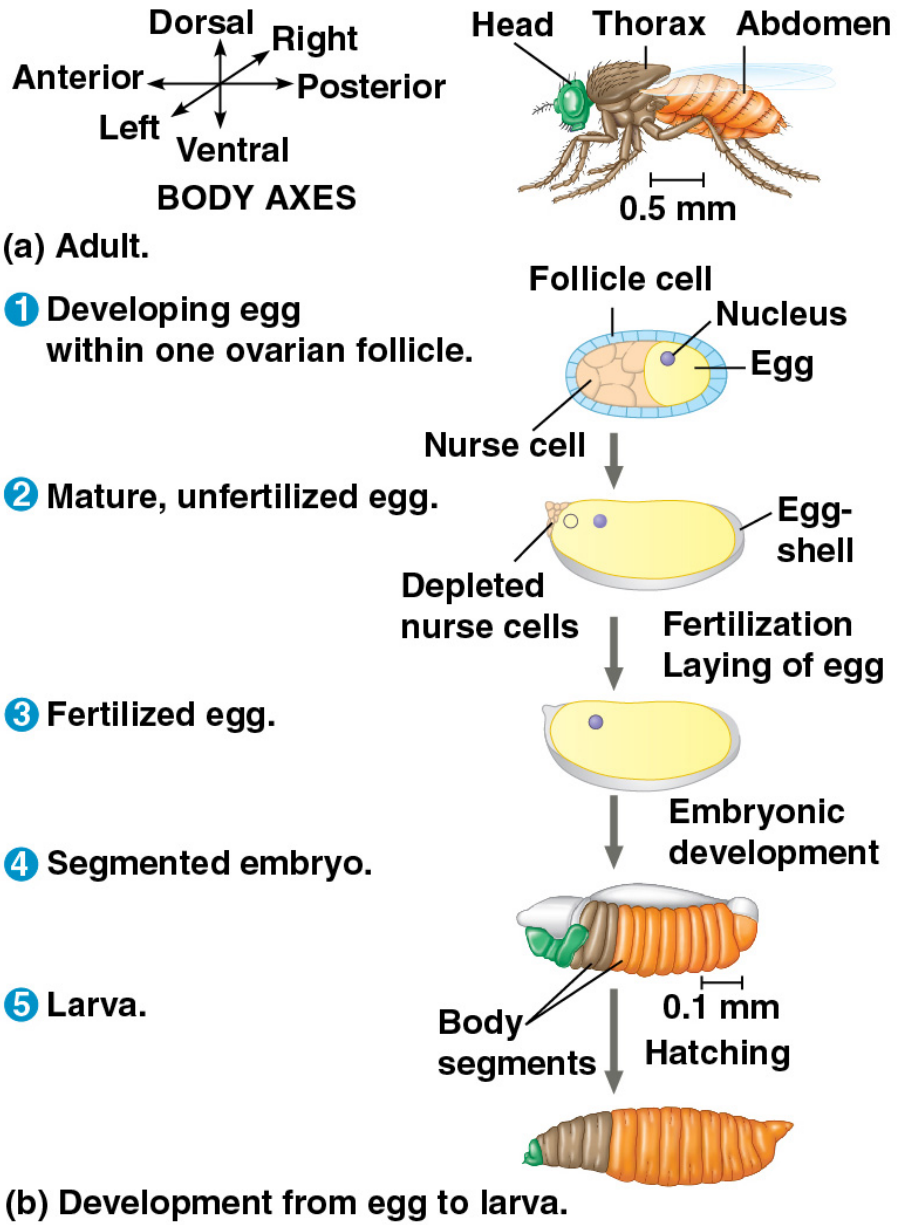
- **Pattern formation** is the development of a spatial organization of tissues and organs
- In animals, pattern formation begins with the establishment of the major axes
- **Positional information**, the molecular cues that control pattern formation, tells a cell its location relative to the body axes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

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

The Life Cycle of Drosophila

- Flies and other organisms have a modular construction, an ordered series of segments
- In Drosophila, cytoplasmic determinants in the unfertilized egg provide positional information for placement of body axes even before fertilization
- After fertilization, the embryo develops into a segmented larva with three larval stages
- The larva then forms a pupa, which undergoes metamorphosis into the adult fly

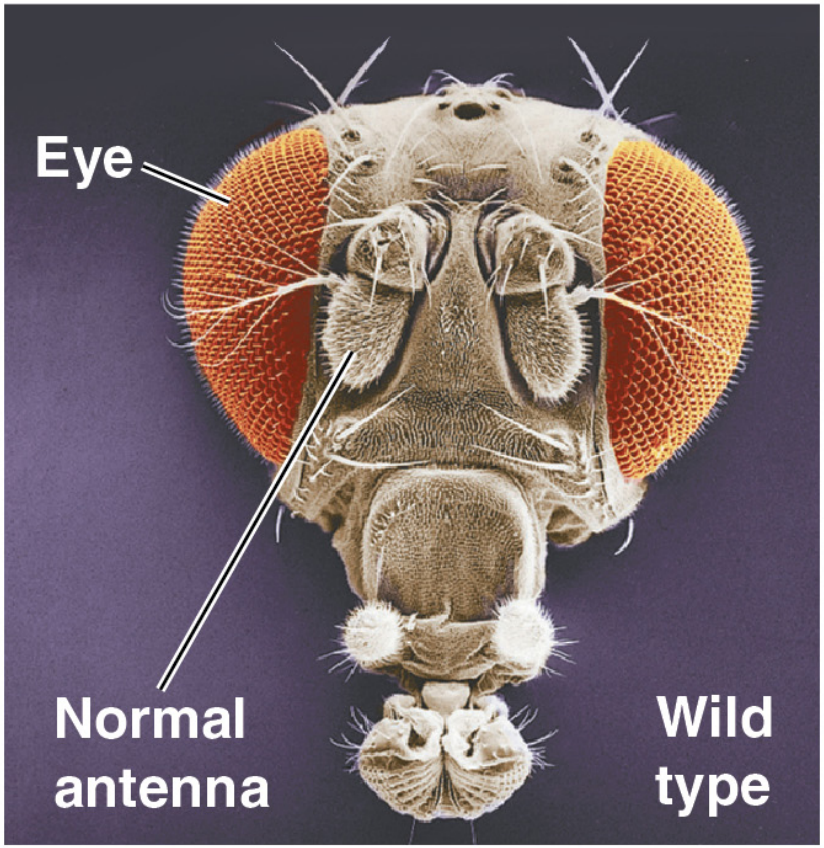
Figure 18.19

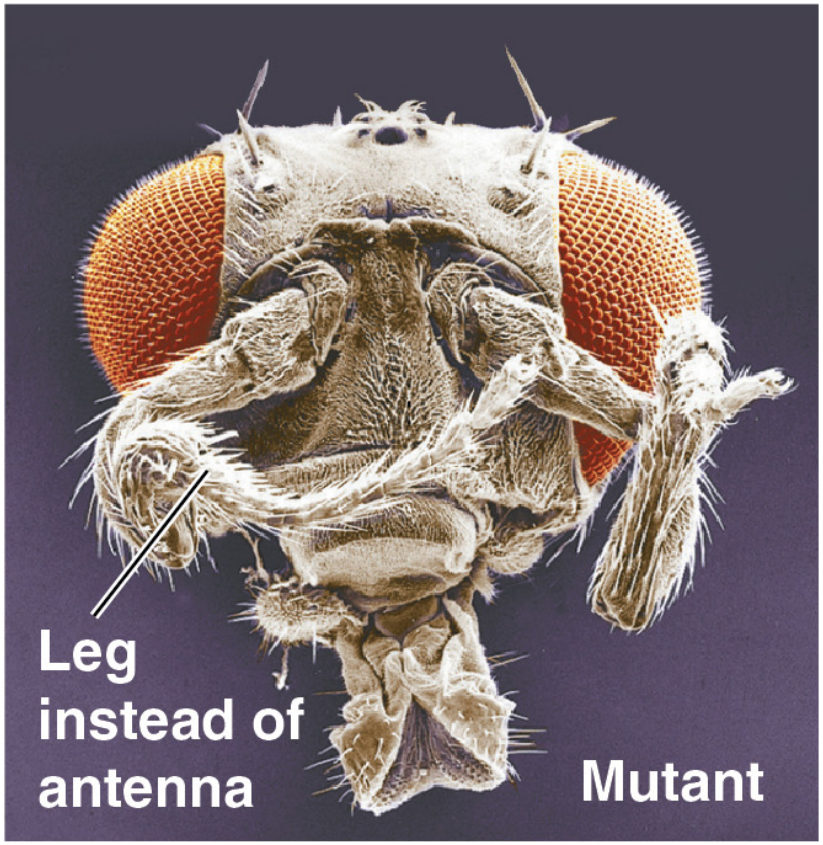

Dorsal
Right
Anterior
Posterior
Left
Ventral
BODY AXES
Head
Thorax
Abdomen
0.5 mm
(a) Adult.
1 Developing egg within one ovarian follicle.
Follicle cell
Nucleus
Egg
Nurse cell
2 Mature, unfertilized egg.
Egg-shell
Depleted nurse cells
Fertilization
Laying of egg
3 Fertilized egg.
Embryonic development
4 Segmented embryo.
0.1 mm
5 Larva.
Body segments
Hatching
(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 Prize in 1995 for decoding pattern formation in *Drosophila*
- Lewis discovered **homeotic genes**, which control pattern formation in the late embryo, larva, and adult stages

Figure 18.20





- Nüsslein-Volhard and Wieschaus studied segment formation
- They created mutants, conducted breeding experiments, and looked for corresponding genes
- Many of the identified mutations were **embryonic lethals**, causing death during embryogenesis
- They found about 120 genes essential for normal segmentation

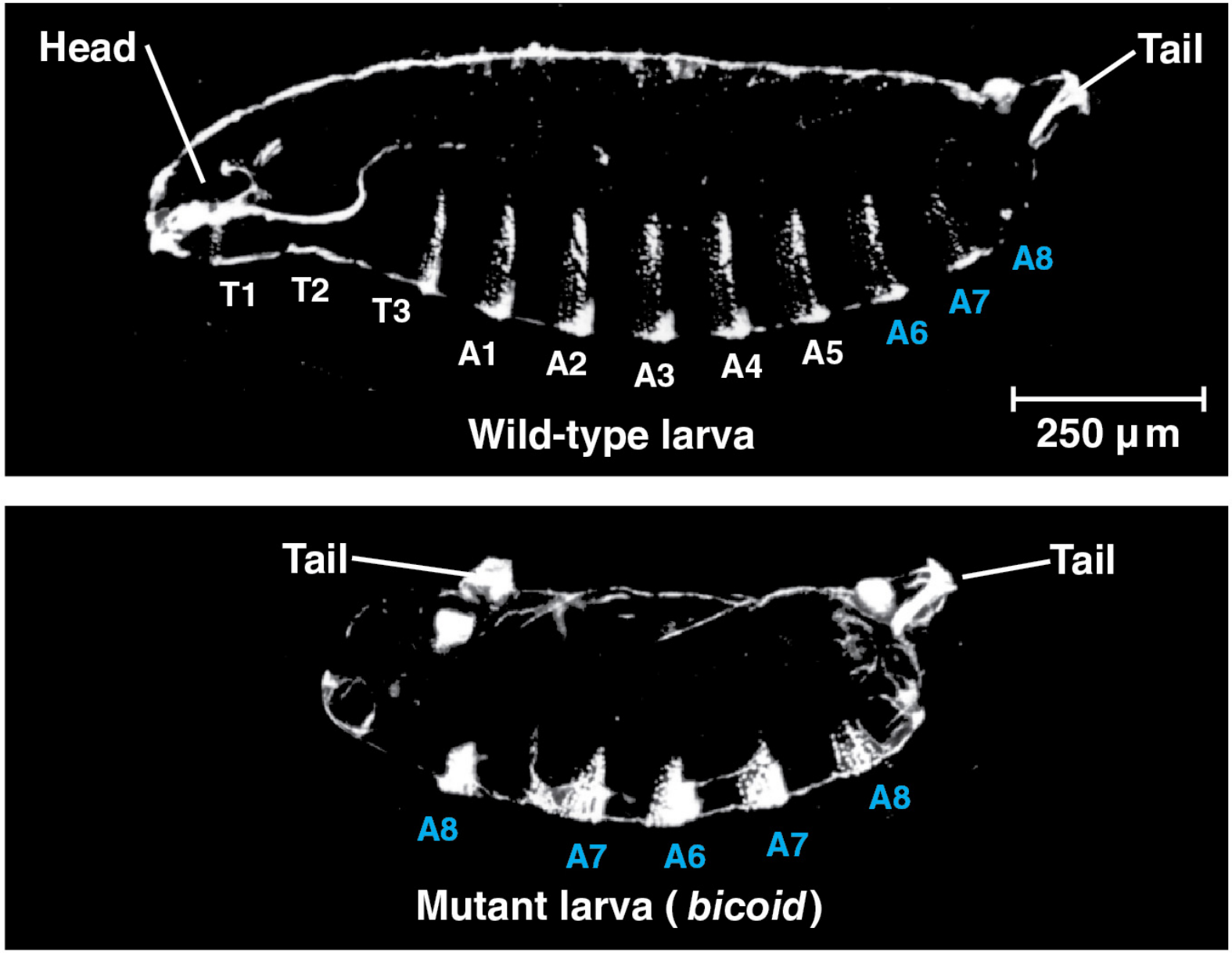
Axis Establishment

- **Maternal effect genes** encode 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

Bicoid: A Morphogen That Determines Head Structures

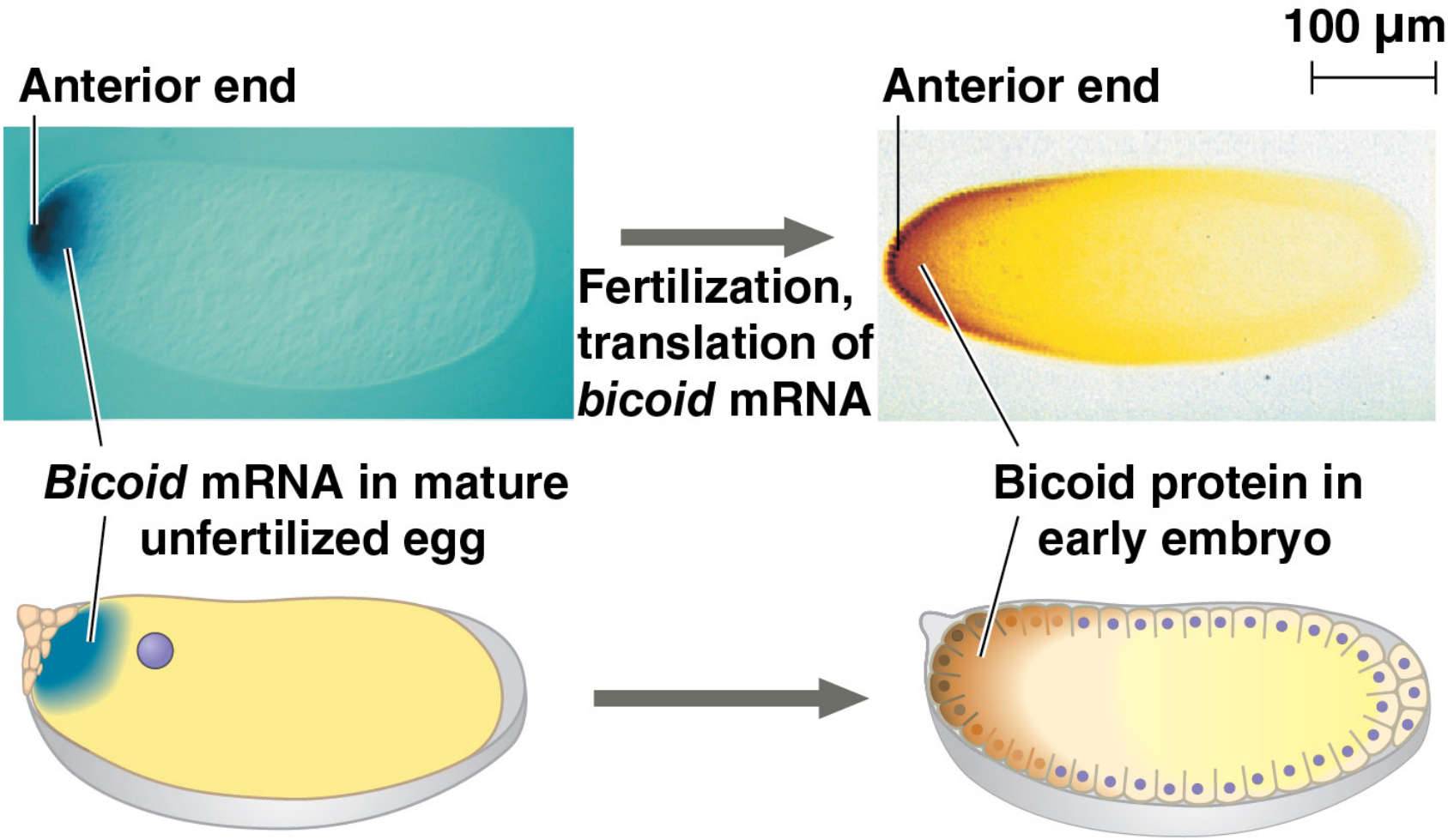
- One maternal effect gene, the ***bicoid*** gene, affects the front half of the body
- An embryo whose mother has no functional *bicoid* gene lacks the front half of its body and has duplicate posterior structures at both ends

Figure 18.21

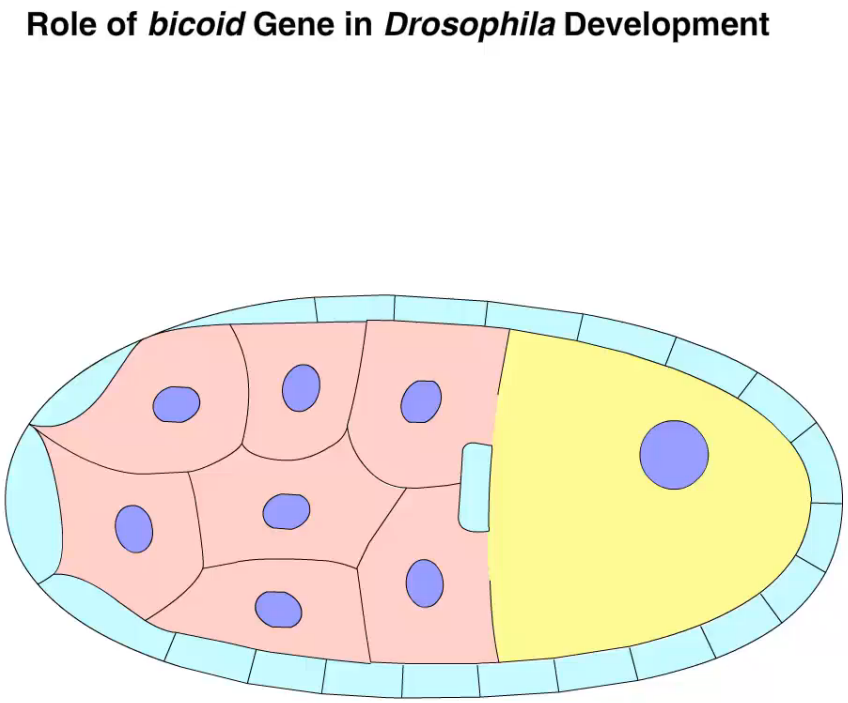

Head
Tail
T1
T2
T3
A1
A2
A3
A4
A5
A6
A7
A8
Wild-type larva
250 µm
Tail
Tail
A8
A7
A6
A7
A8
Mutant larva (*bicoid*)

- This phenotype suggests that the product of the mother's *bicoid* gene is essential for setting up the anterior end of the embryo
- This hypothesis is an example of the morphogen gradient hypothesis, in which gradients of substances called **morphogens** establish an embryo's axes and other features of its form
- Experiments showed that bicoid protein is distributed in an anterior to posterior gradient in the early embryo

Figure 18.22


100 µm
Anterior end
Anterior end
Fertilization, translation of *bicoid* mRNA
Bicoid mRNA in mature unfertilized egg
Bicoid protein in early embryo

Animation: Role of *bicoid* Gene in *Drosophila* Development



- The *bicoid* research was groundbreaking 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 that a gradient of molecules can determine polarity and position in the embryo

Evolutionary Developmental Biology ("Evo-Devo")

- The fly with legs emerging from its head in Figure 18.20 is the result of a single mutation in one gene
- Some scientists considered whether these types of mutations could contribute to evolution by generating novel body shapes
- This line of inquiry gave rise to the field of evolutionary developmental biology, "evo-devo"

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

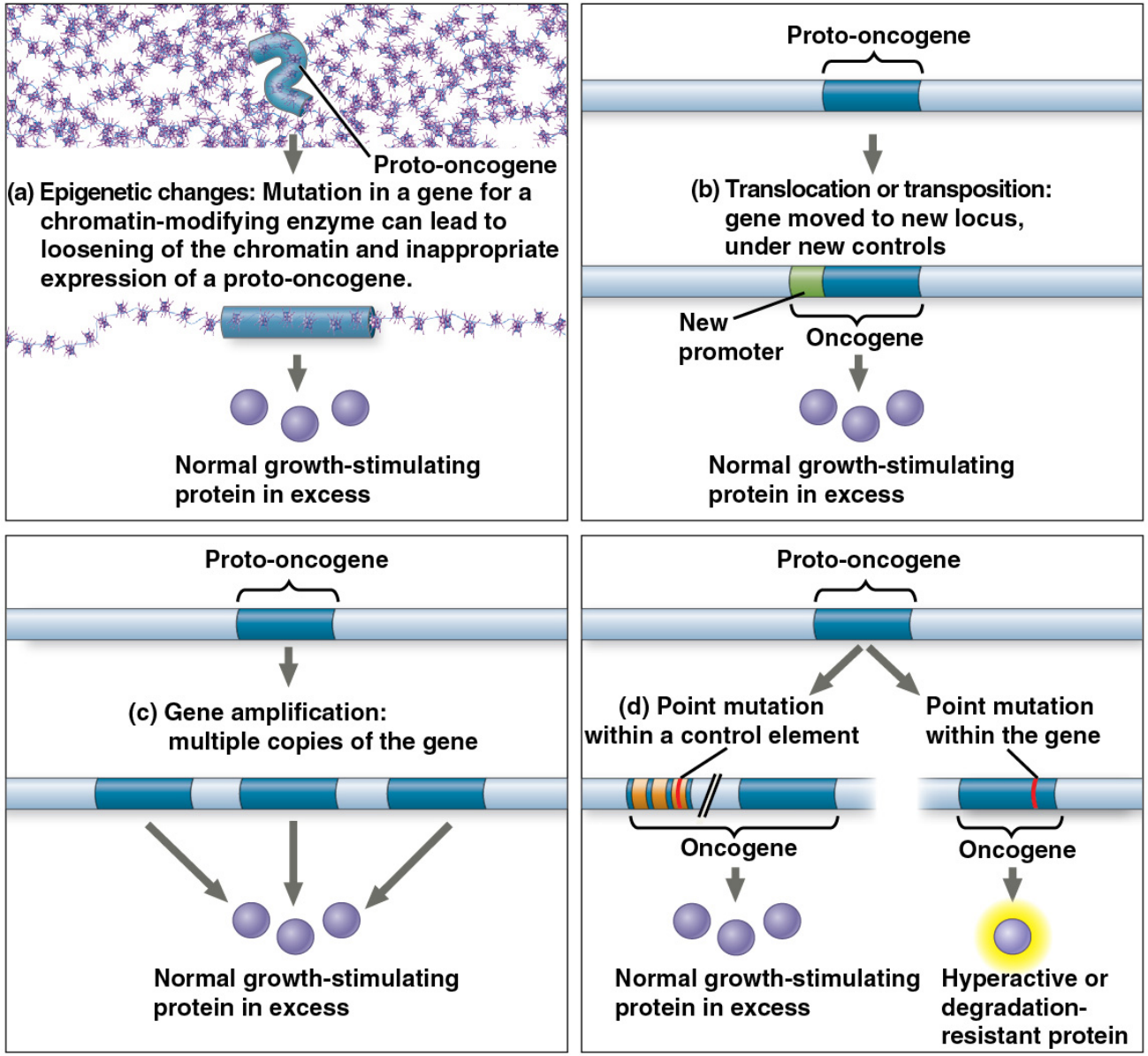
- The gene regulation systems that go wrong during cancer are the very same systems involved in embryonic development

Types of Genes Associated with Cancer

- Mutations that alter normal cell growth and division can lead to cancer
- **Oncogenes** are mutations in genes (called **proto-oncogenes**) that code for proteins that stimulate normal cell growth and division
- An oncogene arises from a change that either increases the amount of the proto-oncogene's product or in the activity of the protein

- The genetic changes that convert proto-oncogenes to oncogenes fall into four main categories
  - Epigenetic changes
  - Translocations
  - Gene amplification
  - Point mutations

Figure 18.23

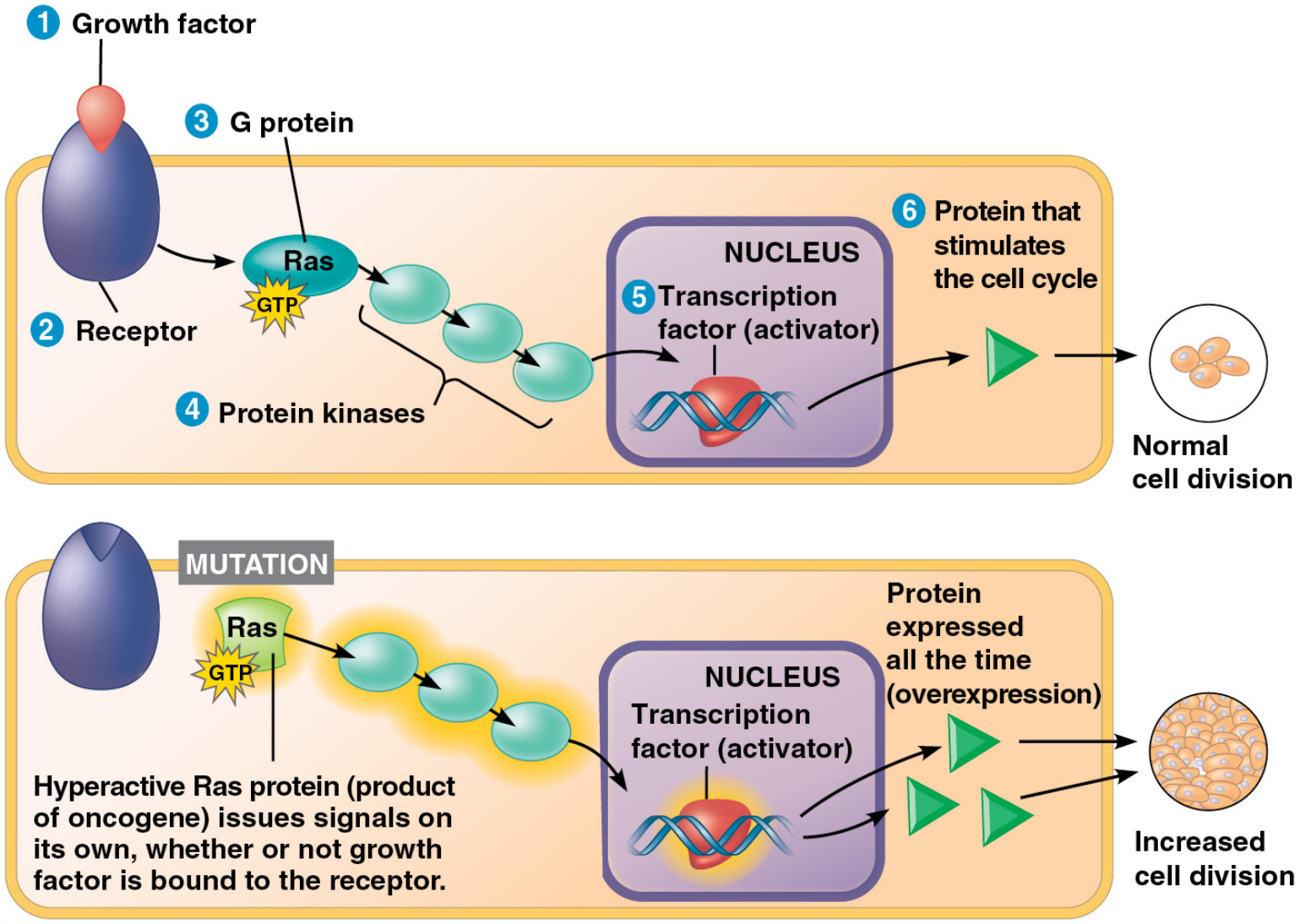

Proto-oncogene
(a) Epigenetic changes: Mutation in a gene for a chromatin-modifying enzyme can lead to loosening of the chromatin and inappropriate expression of a proto-oncogene.
Normal growth-stimulating protein in excess
Proto-oncogene
(b) Translocation or transposition: gene moved to new locus, under new controls
New promoter
Oncogene
Normal growth-stimulating protein in excess
Proto-oncogene
(c) Gene amplification: multiple copies of the gene
Normal growth-stimulating protein in excess
Proto-oncogene
(d) Point mutation within a control element
Point mutation within the gene
Oncogene
Oncogene
Normal growth-stimulating protein in excess
Hyperactive or degradation-resistant protein

- **Tumor-suppressor genes** normally inhibit cell division
- Mutations that decrease protein products of tumor-suppressor genes may contribute to cancer onset
- Tumor-suppressor proteins normally
  - repair damaged DNA
  - control cell adhesion
  - act in cell-signaling pathways that inhibit the cell cycle

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
- The Ras protein is a G protein that relays a signal from a growth factor receptor on the cell surface
- The response to the resulting cascade stimulates cell division

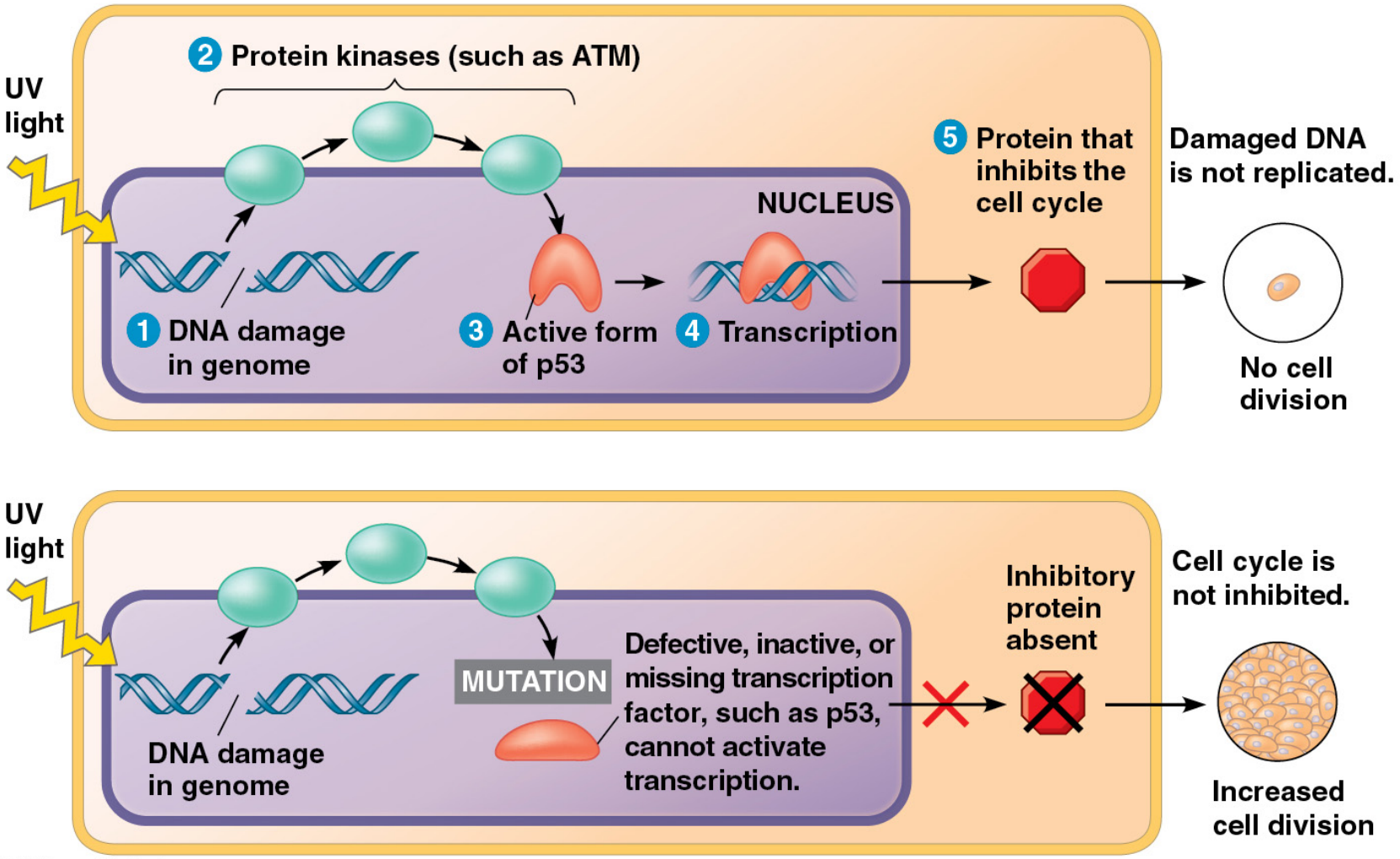
Figure 18.24


1 Growth factor
3 G protein
Ras
GTP
2 Receptor
4 Protein kinases
NUCLEUS
5 Transcription factor (activator)
6 Protein that stimulates the cell cycle
Normal cell division
MUTATION
Ras
GTP
Hyperactive Ras protein (product of oncogene) issues signals on its own, whether or not growth factor is bound to the receptor.
NUCLEUS
Transcription factor (activator)
Protein expressed all the time (overexpression)
Increased cell division

- Mutations in the ***p53* gene** prevent suppression of the cell cycle
- Suppression of the cell cycle can be important in the case of damage to a cell's DNA; normal p53 prevents a cell from passing on mutations
- It also activates expression of miRNAs that inhibit the cell cycle, and can turn on genes directly involved in DNA repair
- If DNA is irreparable, p53 activates cell "suicide" genes

- Elephants have a very low cancer rate (about 3%) compared with humans (closer to 30%)
- Genome sequencing reveals that elephants have 20 copies of the *p53* gene compared to just one copy in humans and other mammals
- This interesting connection bears further investigation

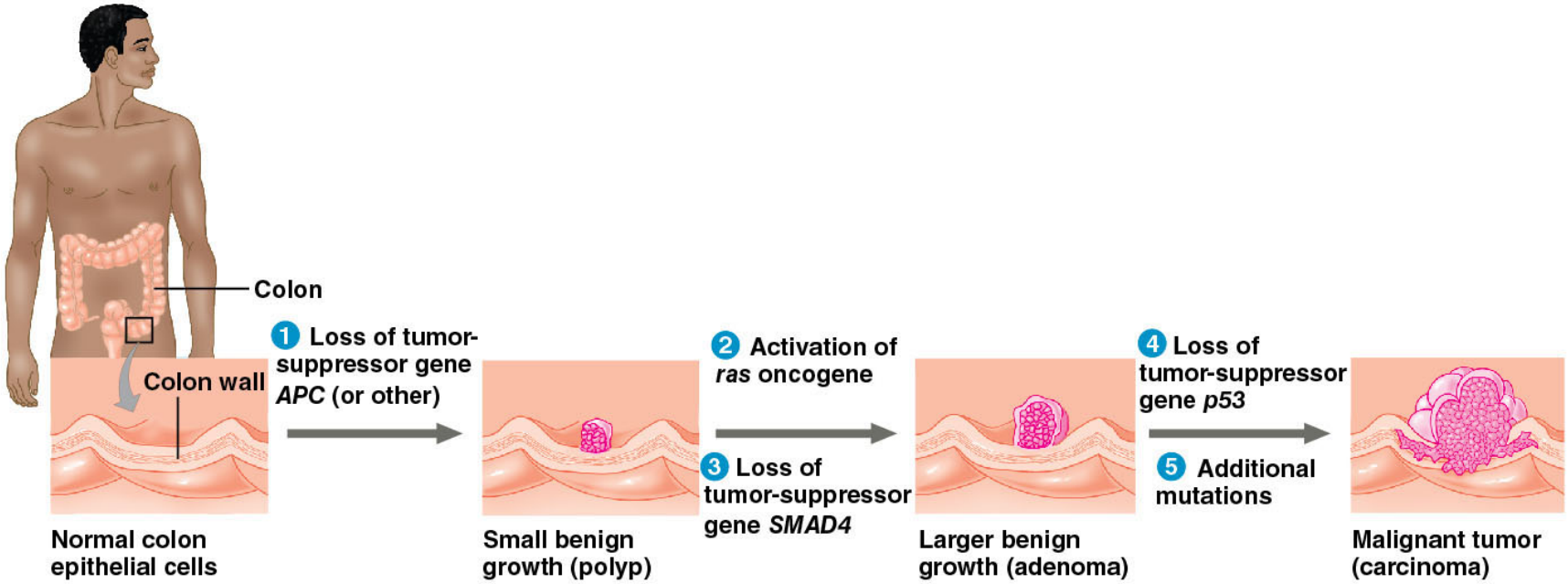
Figure 18.25


UV light
2 Protein kinases (such as ATM)
NUCLEUS
1 DNA damage in genome
3 Active form of p53
4 Transcription
5 Protein that inhibits the cell cycle
Damaged DNA is not replicated.
No cell division
UV light
DNA damage in genome
MUTATION
Defective, inactive, or missing transcription factor, such as p53, cannot activate transcription.
Inhibitory protein absent
Cell cycle is not inhibited.
Increased cell division

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 18.26


Colon
Colon wall
1 Loss of tumor-suppressor gene *APC* (or other)
2 Activation of *ras* oncogene
3 Loss of tumor-suppressor gene *SMAD4*
4 Loss of tumor-suppressor gene *p53*
5 Additional mutations
Normal colon epithelial cells
Small benign growth (polyp)
Larger benign growth (adenoma)
Malignant tumor (carcinoma)

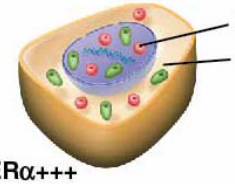
- Routine screening for some cancers, such as colorectal cancer, is recommended
- Suspicious polyps may be removed before cancer progresses
- Breast cancer is a heterogeneous disease that is the second most common form of cancer in women in the United States; it also occurs in some men
- A genomics approach to profiling breast tumors has identified four major types of breast cancer

Figure 18.27

MAKE CONNECTIONS: Genomics, Cell Signaling, and Cancer

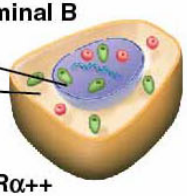
A research scientist examines DNA-sequencing data from breast cancer samples.

Luminal A



- ERα+++
- PR++
- HER2–
- 40% of breast cancers
- Best prognosis

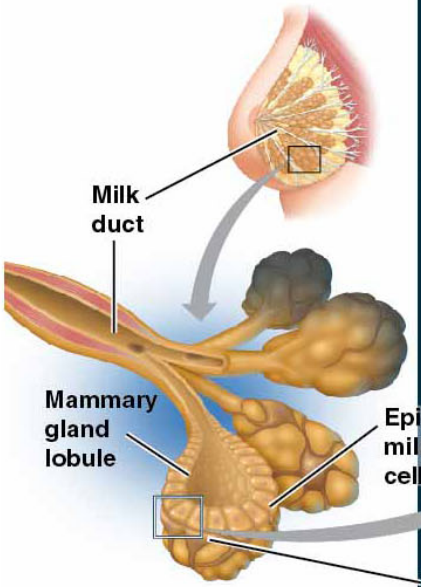
Luminal B



- ERα++
- PR++
- HER2– (shown here); some HER2++
- Divide rapidly
- 15–20% of breast cancers
- Poorer prognosis than luminal A

Basal-like

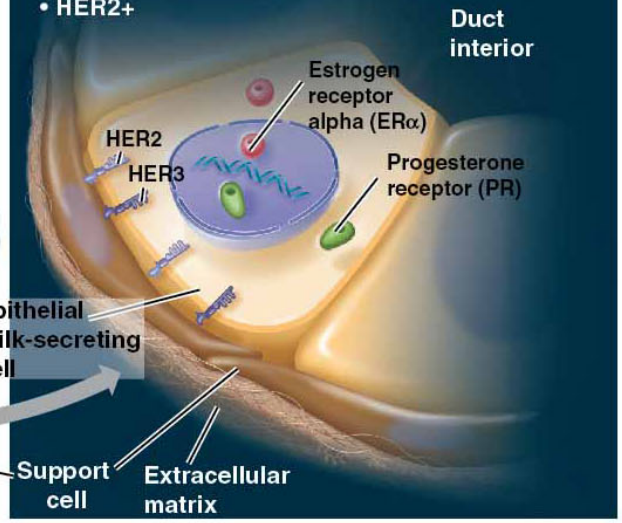
- ERα–
- PR–
- HER2–
- 15–20% of breast cancers
- More aggressive; poorer prognosis than other subtypes

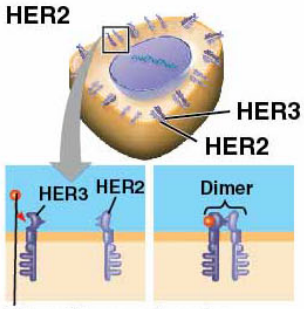


Normal Breast Cells in a Milk Duct

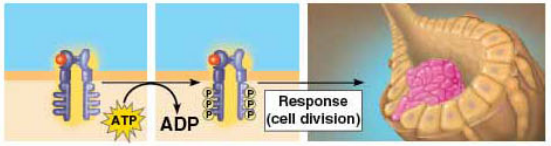
In a normal breast cell, the three signal receptors are at normal levels (indicated by +):

- ERα+
- PR+
- HER2+

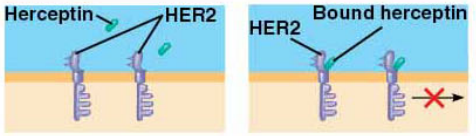




- ERα– or ERα+
- PR–
- HER2++
- 10–15% of breast cancers
- Poorer prognosis than luminal A subtype



Treatment with Herceptin for the HER2 subtype



Inherited Predisposition and Environmental 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

The Role of Viruses in Cancer

- A number of tumor viruses can also cause cancer in humans and animals
- Viruses can interfere with normal gene regulation in several ways if they integrate into the DNA of a cell
- Viruses are powerful biological agents

Animation: Causes of Cancer

Figure 18.UN03

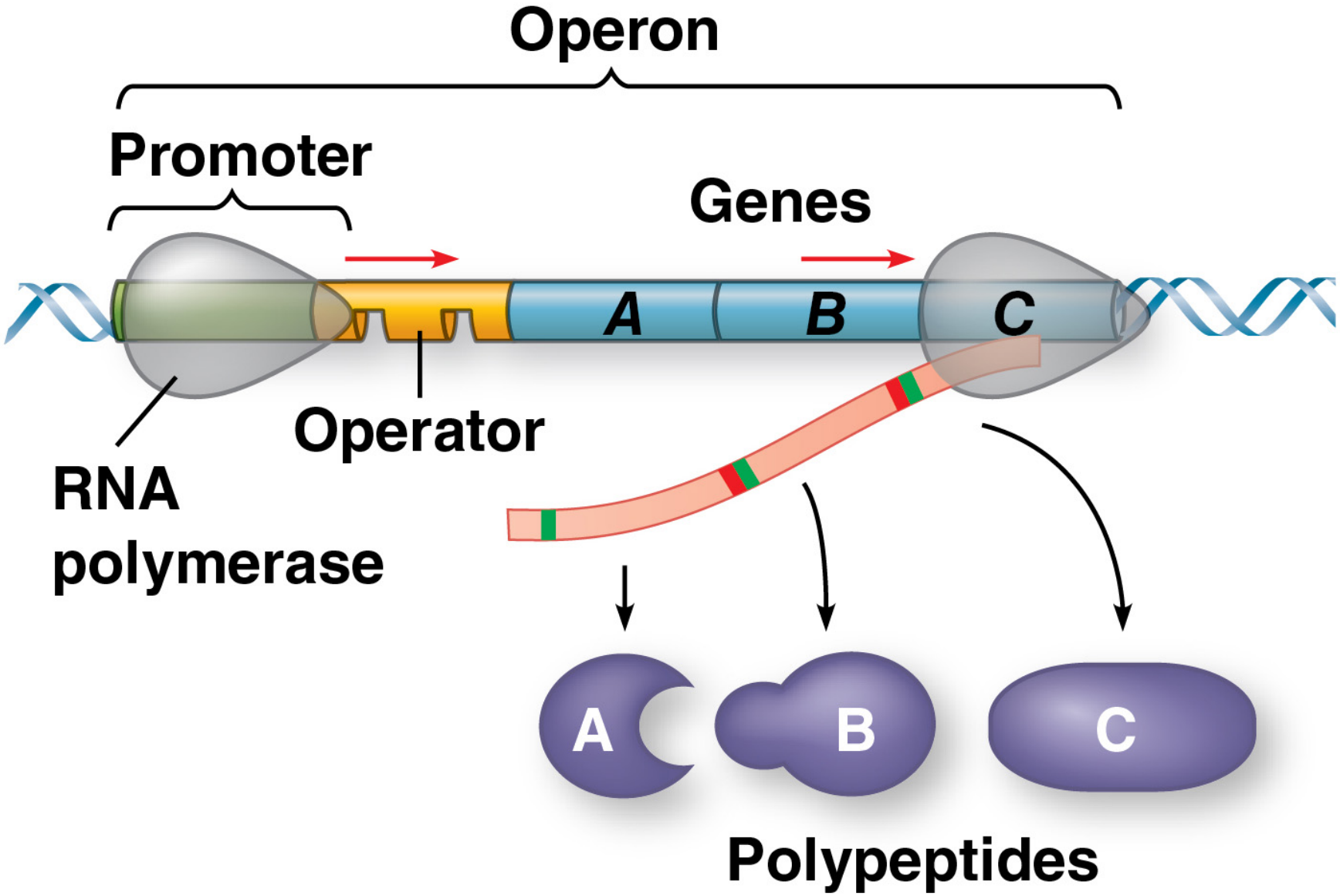


Figure 18.UN04

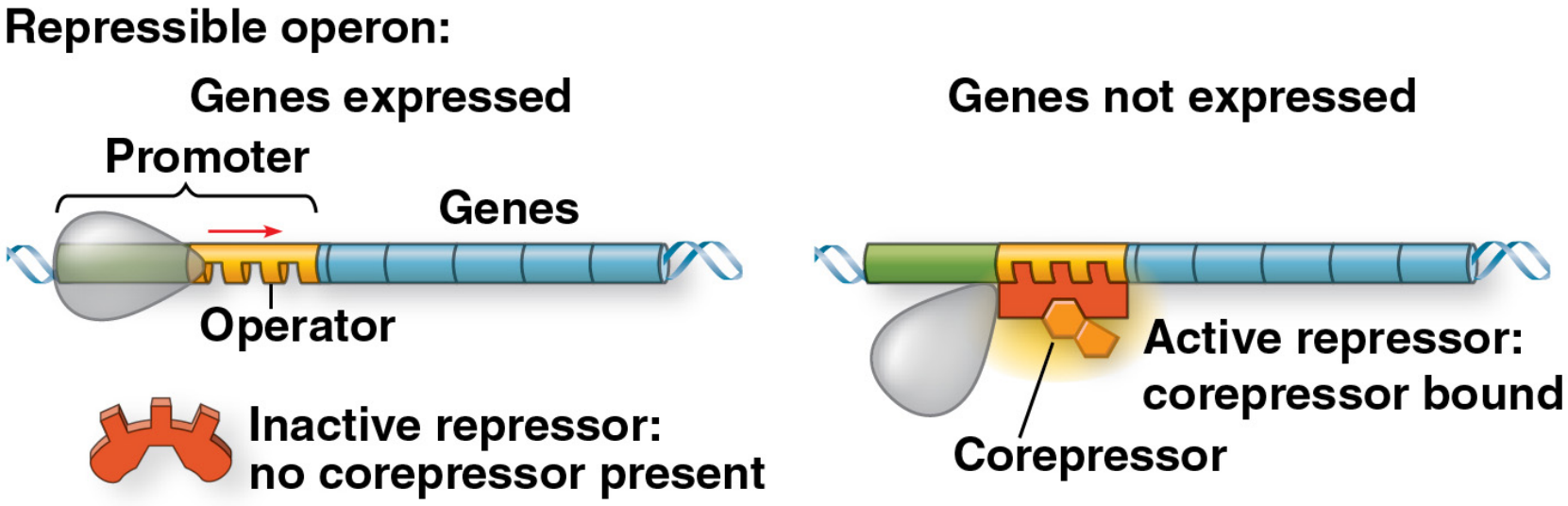


Figure 18.UN05

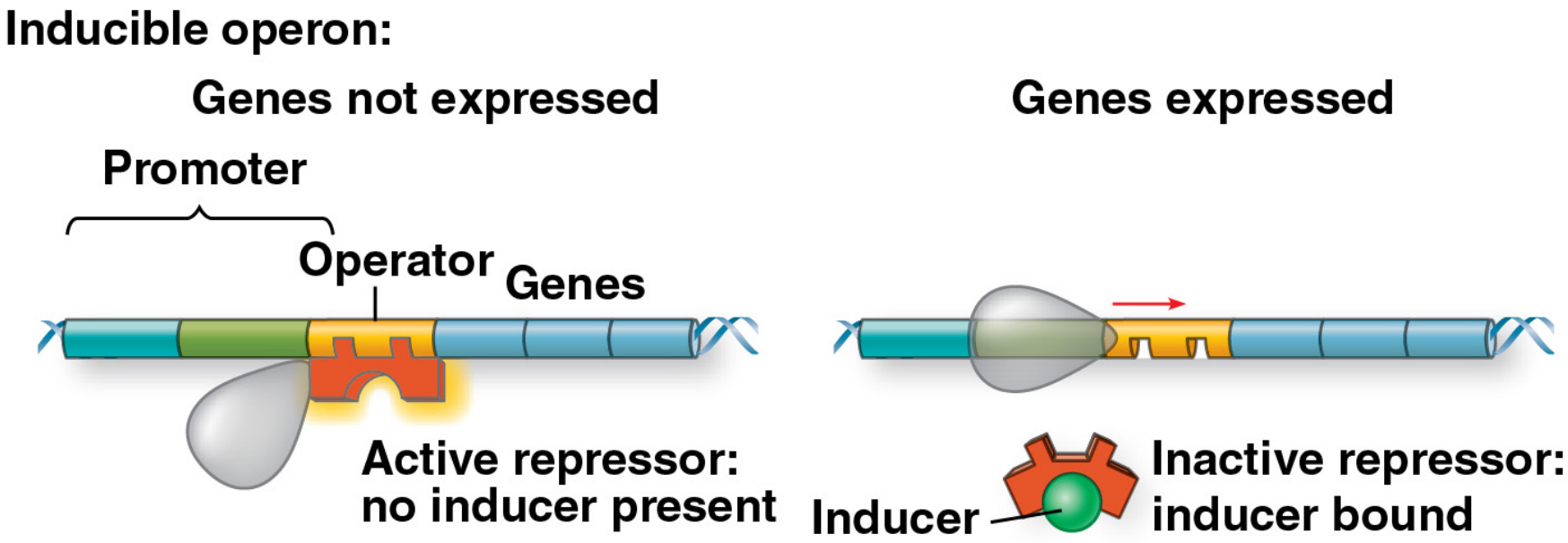


Figure 18.UN06

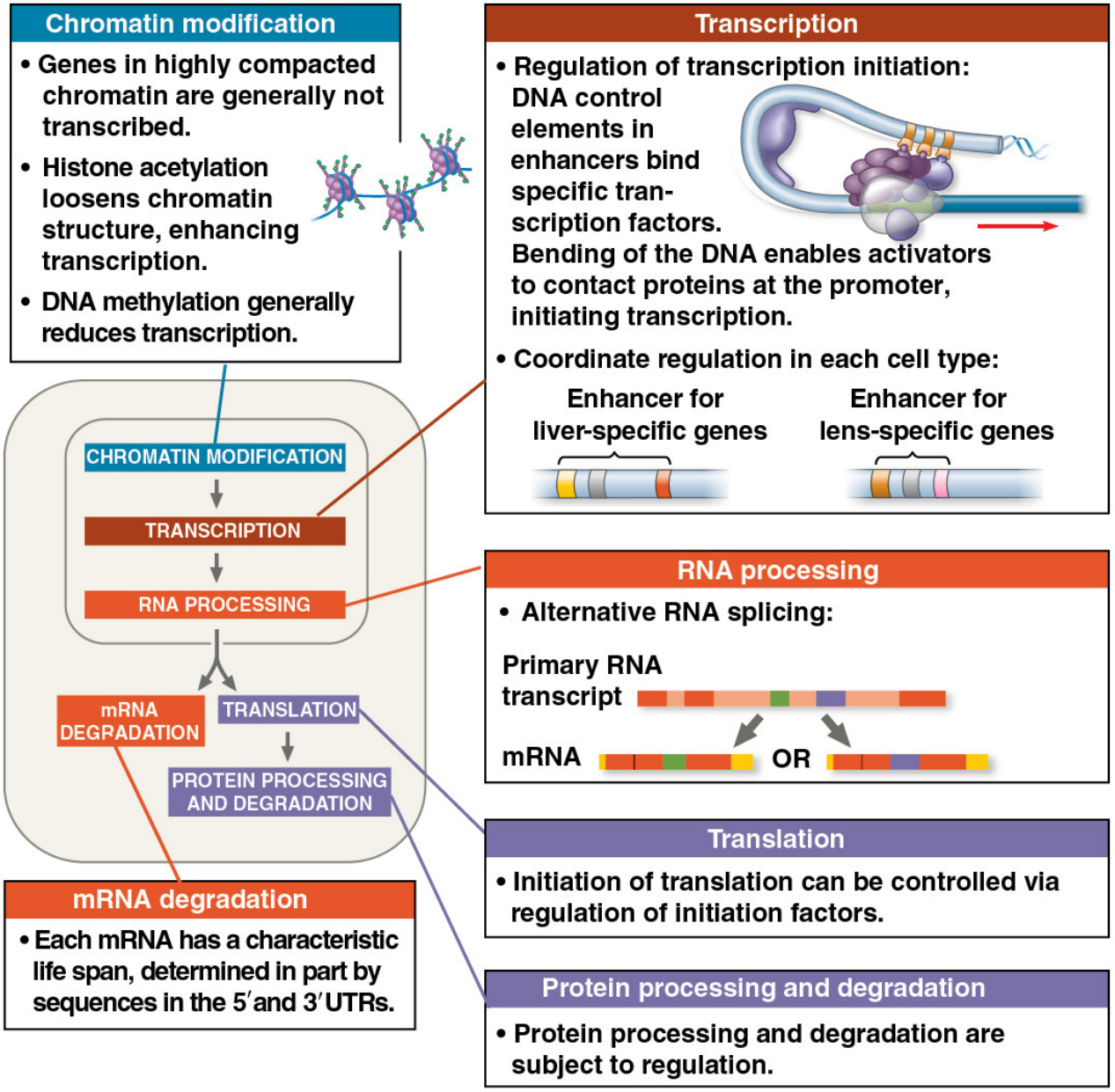


Figure 18.UN07

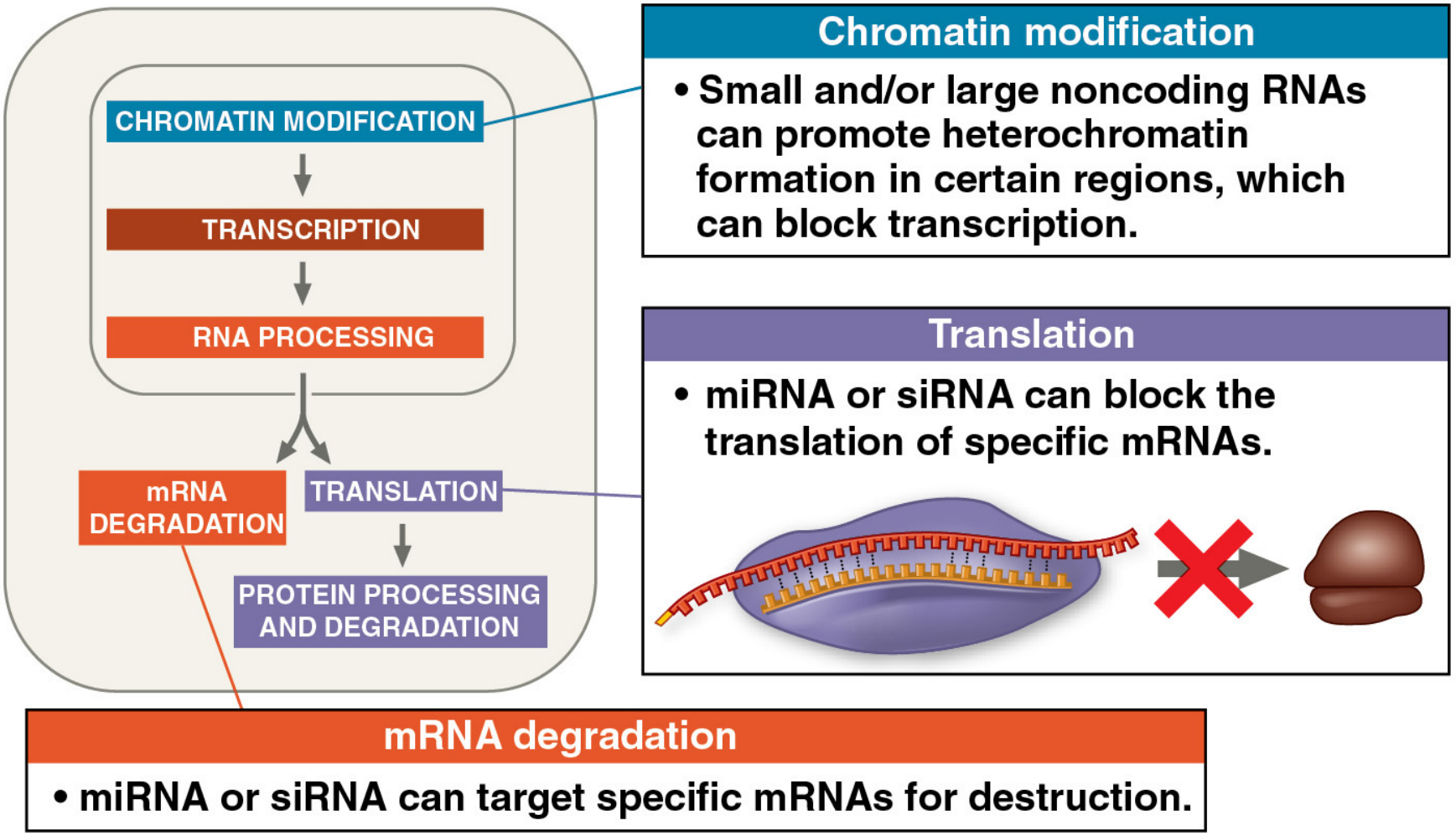


Figure 18.UN08

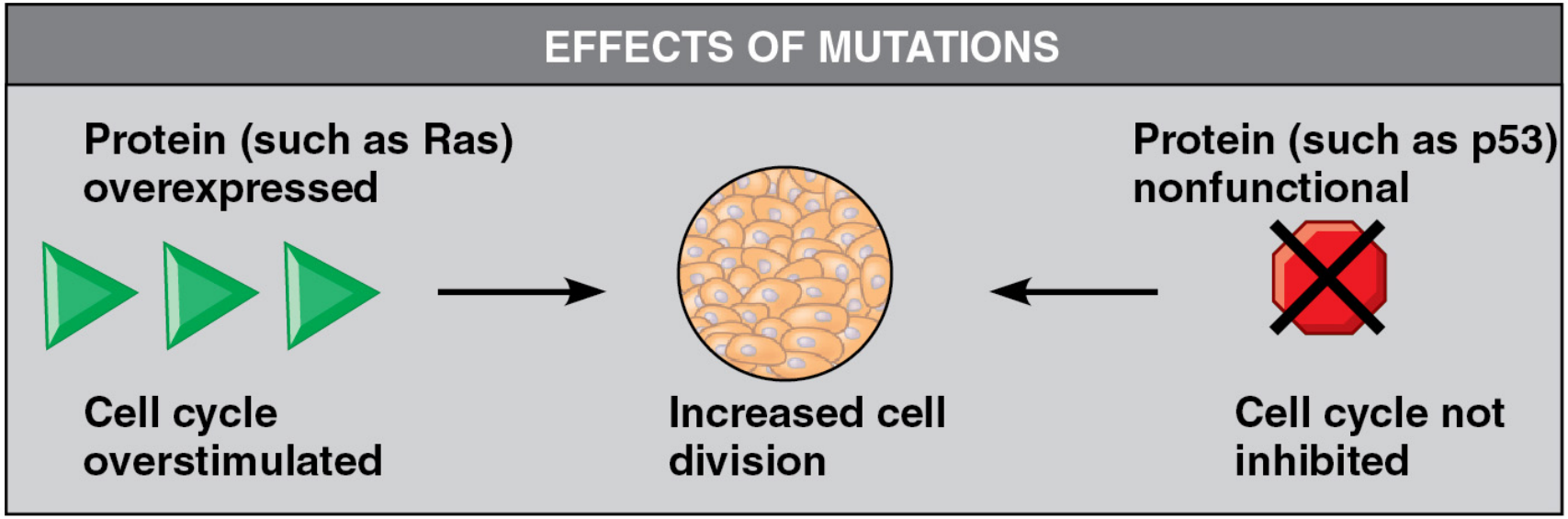


Figure 18.UN09

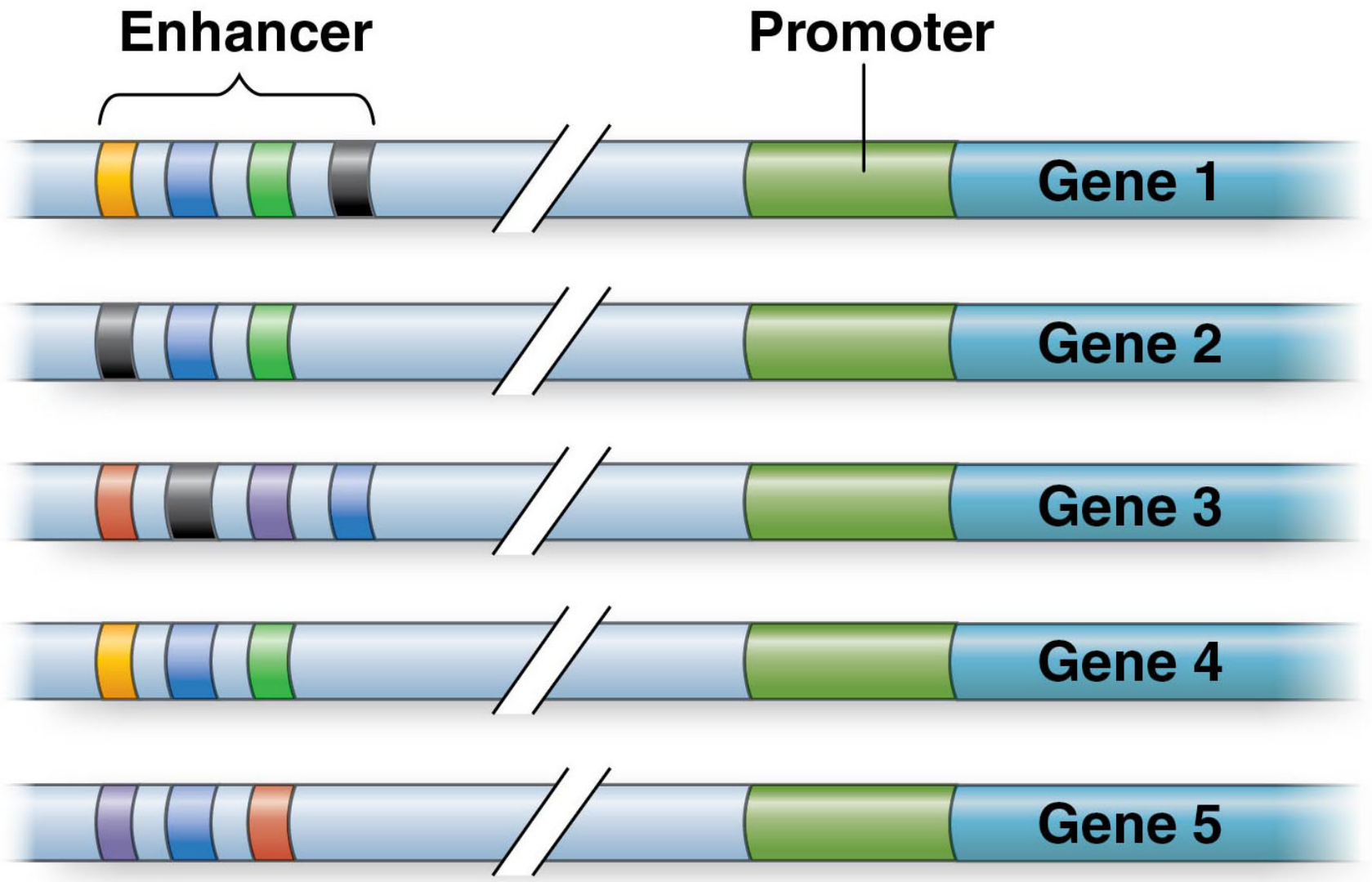


Figure 18.UN10