



BIOLOGY I

**Chapter 18: REGULATION
OF GENE EXPRESSION**

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Instructor

Introduction: Regulation of Gene Expression

- **Gene expression** is the process of expressing specific protein(s) from DNA (* Remember: *DNA* → *RNA* → *protein*).
- Both prokaryotic and eukaryotic organisms must continually regulate their patterns of gene expression (**they must “turn genes on and off”**) in response to changes in their external and internal environments.
 - ✓ Gene expression is often regulated during **transcription** (synthesis of RNA from DNA) but control at other levels is also important.
- In addition, **multicellular organisms** must also develop and maintain different cell types. Cells undergo a process of **specialization** in form and function called **cell differentiation**.
 - ✓ Each cell type contains the same genome but expresses a different subset of genes.

Introduction: Regulation of Gene Expression

- Gene expression controls include **regulatory proteins** that intervene before, during, or after gene transcription or translation. Examples: *hormones*.
- **Negative control:** Regulatory proteins slow or stop gene action.
- **Positive control:** Regulatory proteins promote or enhance gene action.

Regulation of Gene Expression in Bacteria (Prokaryotes):

Review of General Characteristics of Prokaryotes

- Bacteria are **unicellular** microorganisms, but they form colonies.
- Found **everywhere**, in all types of environments.
- **Prokaryotic** organisms; with **no true nucleus**: Their genetic material is one double-stranded circular DNA molecule that is associated with a small amount of protein and is not bounded by membrane; the region of DNA is called the **nucleoid**.
- Many bacteria have **plasmids**, small independent circles of DNA.
- No membrane-enclosed organelles.
- Bacteria have cell walls containing **peptidoglycan** (a complex of carbohydrates and protein).
- Most common way of reproduction is by **binary fission** (division into two identical daughter cells; it is asexual reproduction).

Bacteria

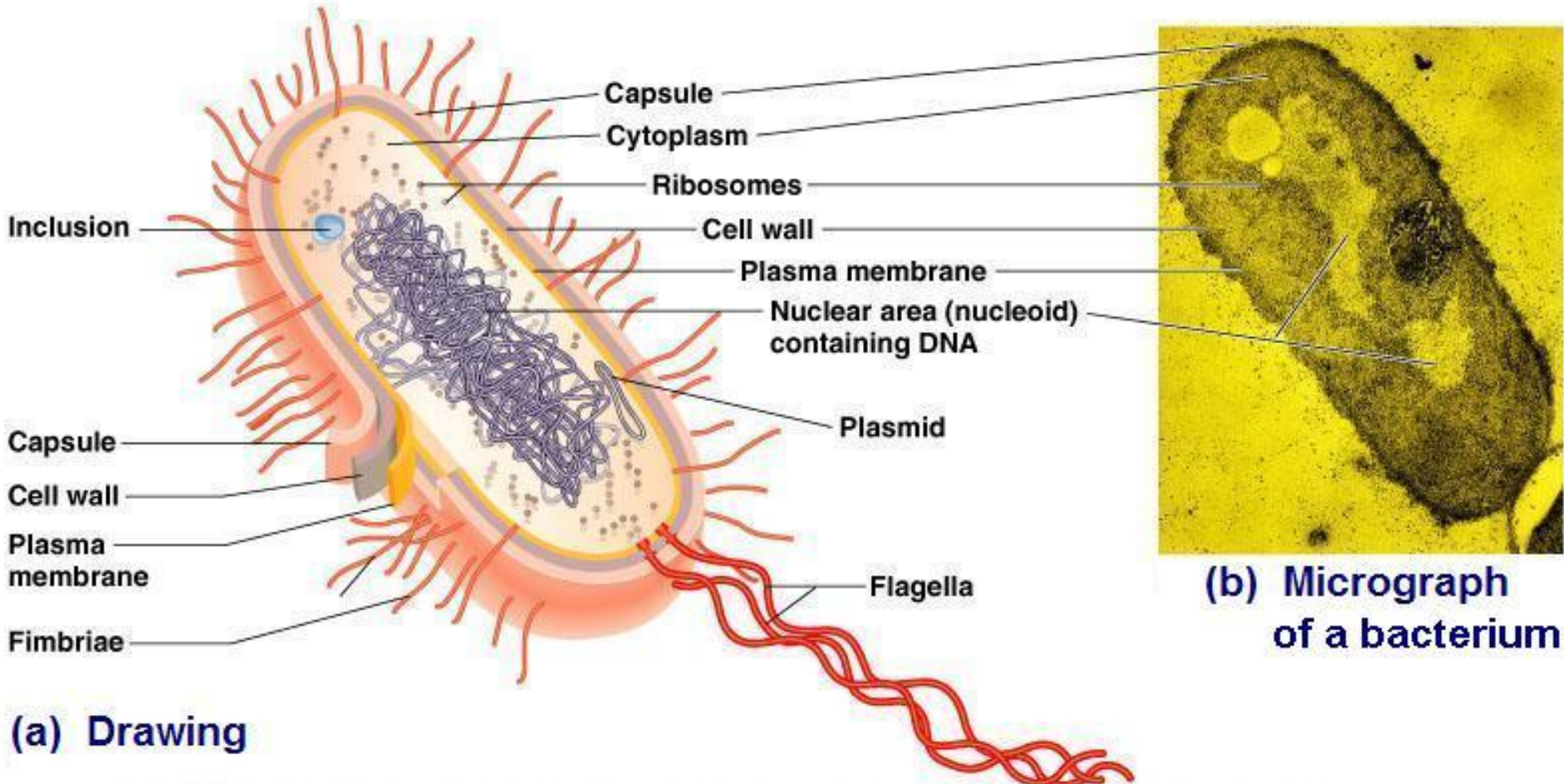
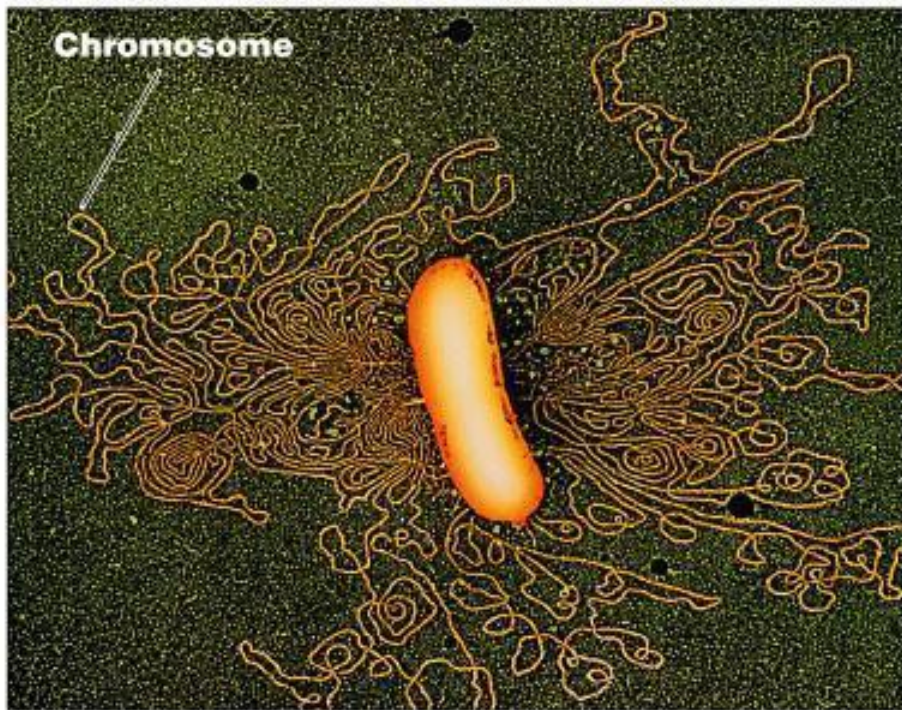
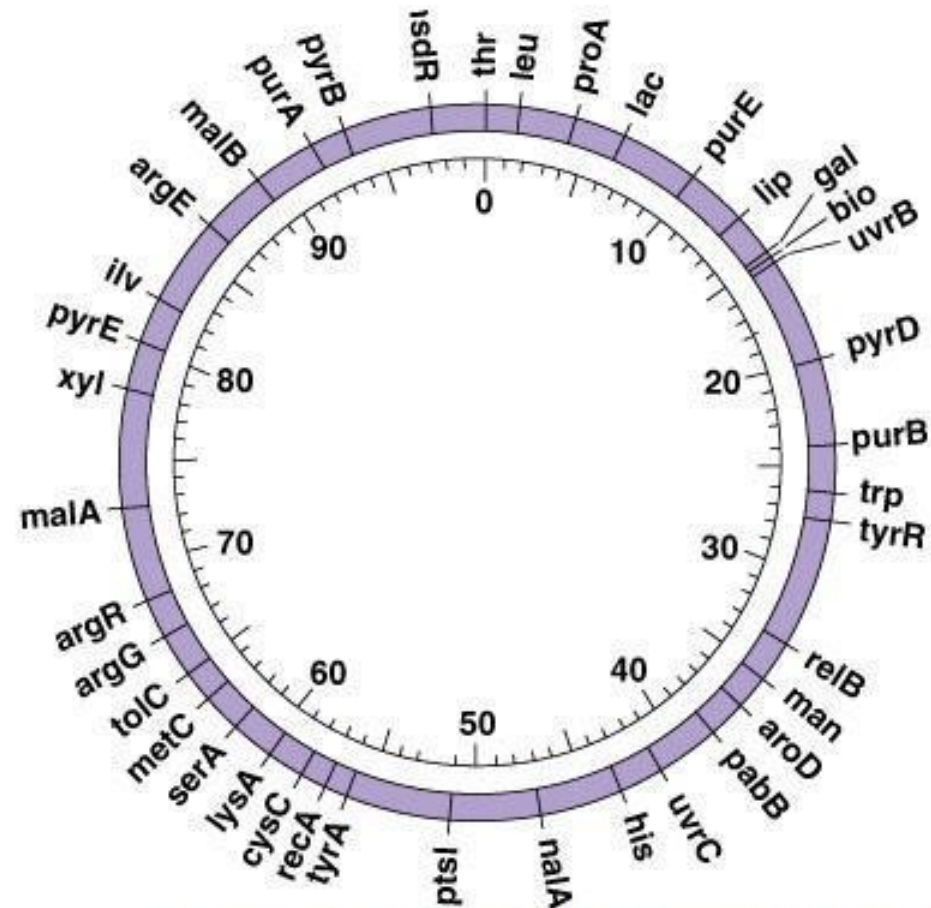


FIGURE 4.6 - A prokaryotic cell showing typical structures.

FIGURE 8.1 - Chromosomes.



(a) A prokaryotic chromosome, emerging from a disrupted *E. coli* cell.



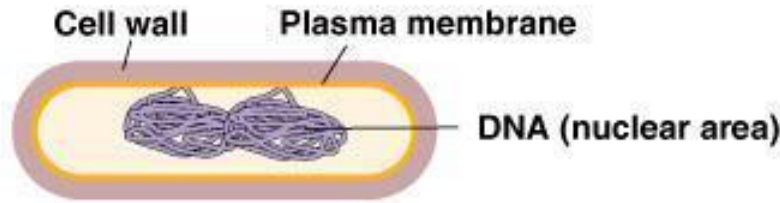
(b) A genetic map of the chromosome of *Escherichia coli*.

- Bacteria typically have a single circular “chromosome”, a single circular molecule of DNA.
- In part b, the numbers inside the circle are minutes based on the length of time it takes to transfer the genes during mating between two cells.

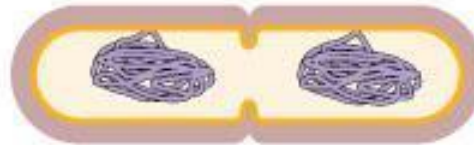
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FIGURE 6.11 - Binary fission in bacteria.

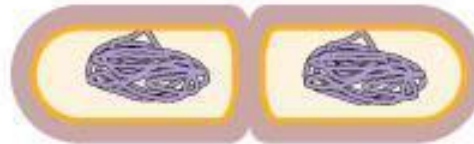
1 Cell elongates and DNA is replicated



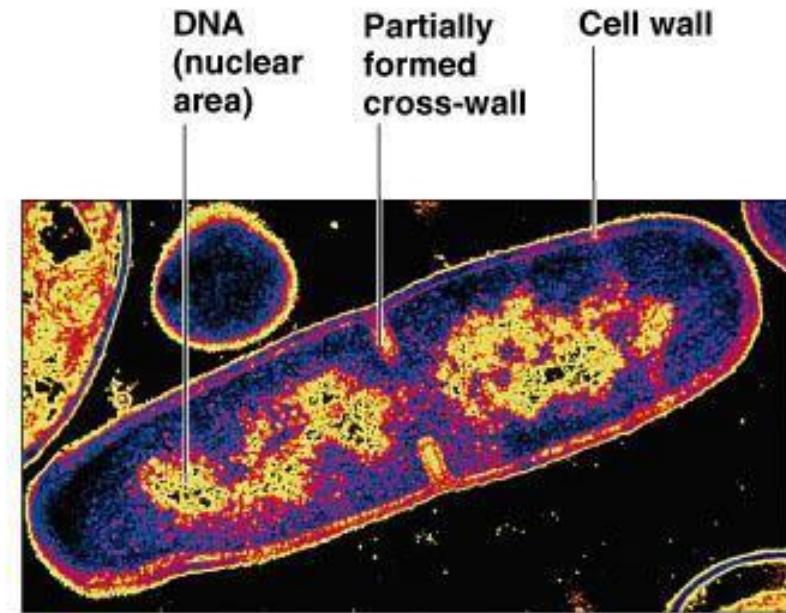
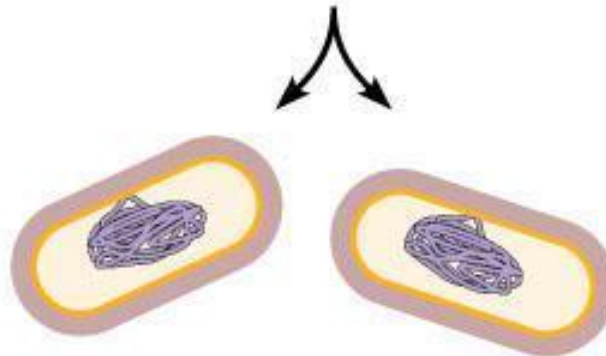
2 Cell wall and plasma membrane begin to divide



3 Cross-wall forms completely around divided DNA



4 Cells separate

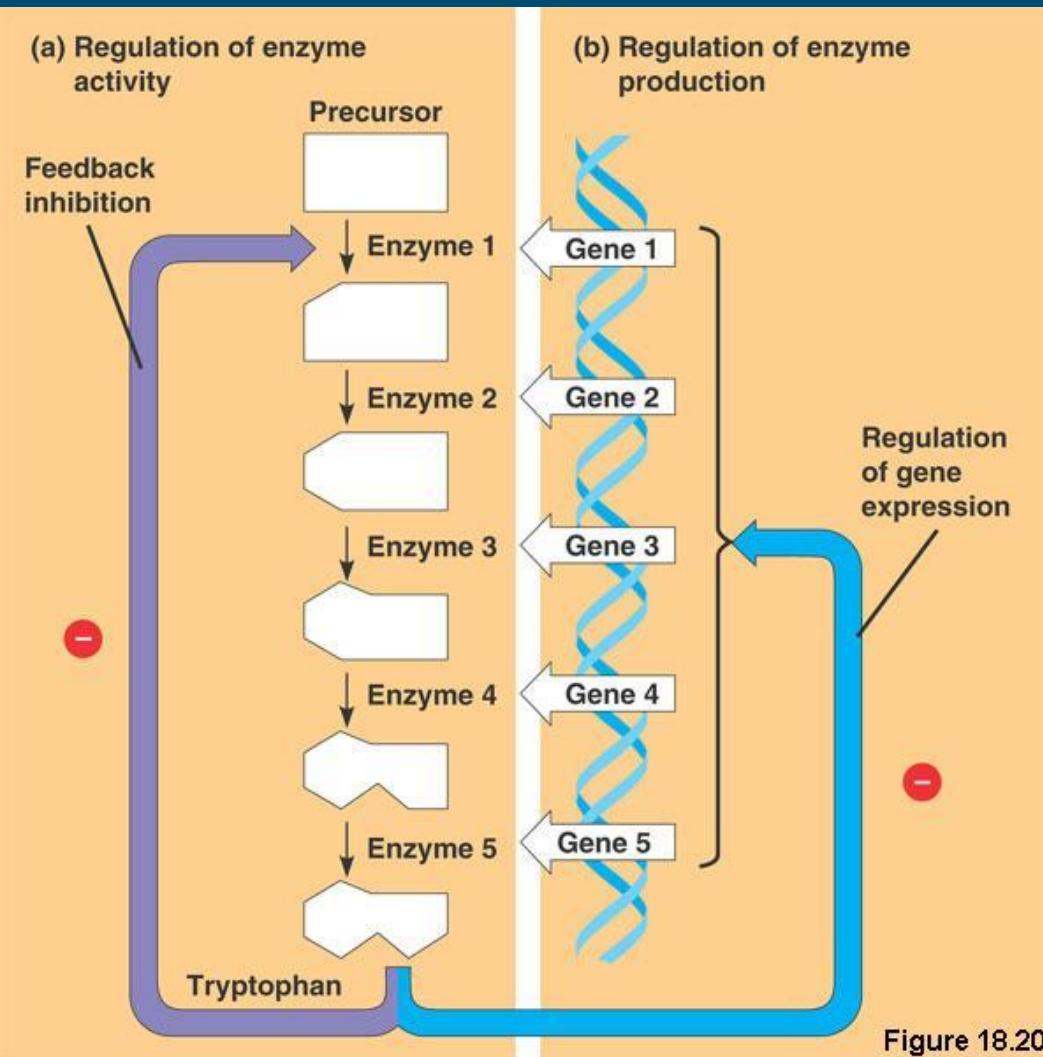


(b) A thin section of a cell of *Bacillus licheniformis* starting to divide.

(a) A diagram of the sequence of cell division.

Bacteria Often Respond to Environmental Change by Regulating Transcription

- Bacteria tune their metabolism to changing environments.
- Metabolic control occurs on two levels in cells:
 - ✓ Cells can adjust the **activity of enzymes** already present. This is a fairly fast response, which relies on the sensitivity of many enzymes to chemical signals that increase or decrease their catalytic activity. (Remember: An *enzyme* is a biological catalyst that accelerates a specific chemical reaction.)
 - ◆ Example: feedback inhibition (product inhibits an enzyme)
 - ✓ Cells can adjust the **production level of certain enzymes**; that is, they can regulate the **expression of the genes** encoding the enzymes.
 - ✓ Genes that are constantly transcribed are called **constitutive genes** (they are *constitutively expressed*).

Regulation of Gene Expression: *Regulation of A Metabolic Pathway*

- Cells control metabolism by regulating **enzyme activity** or the **expression of genes** coding for enzymes.
- **Figure 18.2.** In the pathway for synthesis of **tryptophan** (an amino acid), an abundance of tryptophan can both (a) inhibit the activity of the first enzyme in the pathway (**feedback inhibition**), a rapid response, and (b) **repress expression of the genes** for all the enzymes needed for the pathway, a longer-term response. The red symbol (--) stands for inhibition.

The Regulation of Gene Expression in Bacteria (Prokaryotes)

- 1) **Repression:** The process by which a repressor protein can **stop the synthesis of a protein**. It controls the synthesis of one or several enzymes (inhibits gene expression).
 - ✓ **Repressor:** The regulatory protein that blocks the RNA polymerase, **preventing transcription** (synthesis of mRNA coding for the enzymes).
- 2) **Induction:** The process that **turns on the transcription of a gene** or genes.
 - ✓ **Inducer:** The chemical substance that acts to **induce transcription** of specific genes.

The Regulation of Gene Expression in Bacteria:

The Operon Model

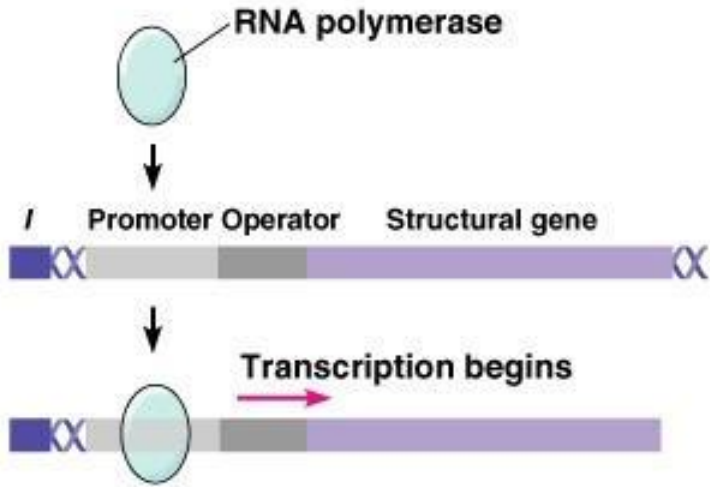
- **Operon:** A group of structural and regulating genes that function as a single unit (encoding proteins of the same metabolic pathway). A **regulator gene**, located outside the operon, codes for a **repressor** that controls whether the operon is active or not.
- An operon includes the following elements:
 - ✓ **Promoter**—A short sequence of DNA where RNA polymerase first attaches when a gene is to be transcribed. Basically, the promoter signals the start of a gene.
 - ✓ **Operator**—A short portion of DNA where an active repressor binds. When an active repressor is bound to the operator, RNA polymerase cannot attach to the promoter, and transcription does not occur. In this way, the operator controls mRNA synthesis.
 - ✓ **Structural genes**—One to several genes coding for the primary structure of enzymes of a metabolic pathway that are transcribed as a unit.

The Regulation of Gene Expression in Bacteria

Figure 8.13 – A model for repression.

- ✓ The repressor protein is encoded by the “*I*” gene. When a **repressor** protein is present, it either blocks RNA polymerase from binding to the promoter, or blocks its progress along the DNA. In either case, the repressor effectively stops transcription of the gene.

Without repressor:



With repressor:

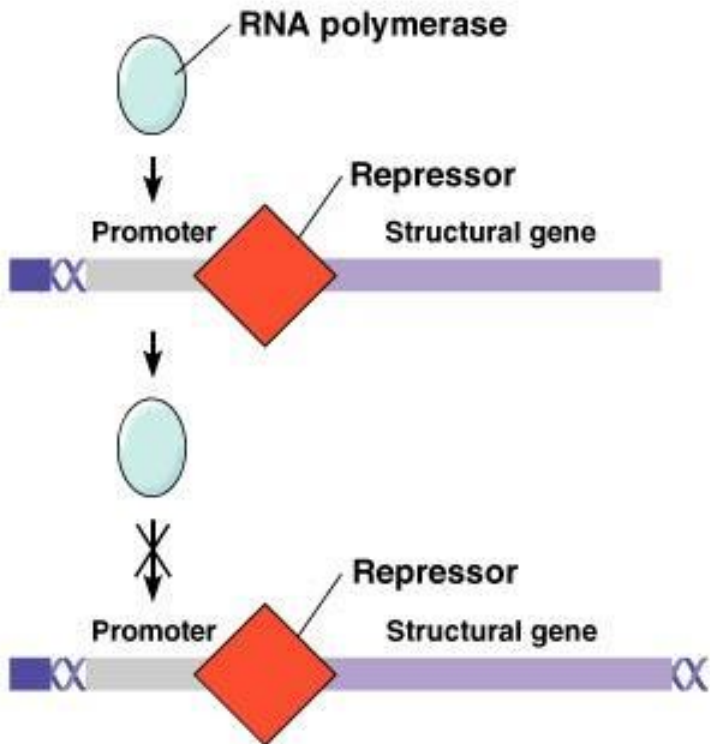


FIGURE 8.13 - A model for repression

The Regulation of Gene Expression in Bacteria: Repressive and Inducible Operons – Negative Gene Regulation

- ↗ **Repressible operon** = Operon that is normally **active** because the repressor is normally inactive. Repressible operons are usually involved in anabolic pathways that synthesize a substance needed by the cell.
- ✓ Example: The **trp operon**. This operon is involved in the synthesis of the amino acid **tryptophan**. When excess tryptophan is present, tryptophan acts as a **corepressor**.
- ↗ **Inducible operon** = Operon that is ordinarily **turned off**; when it is turned on, it causes transcription of the genes controlling the enzymes in a catabolic pathway to break down a nutrient.
- ✓ Example: The **lac operon**. This operon is involved in the synthesis of enzymes that break down the sugar **lactose**. When present, lactose acts as an **inducer** of enzyme synthesis.

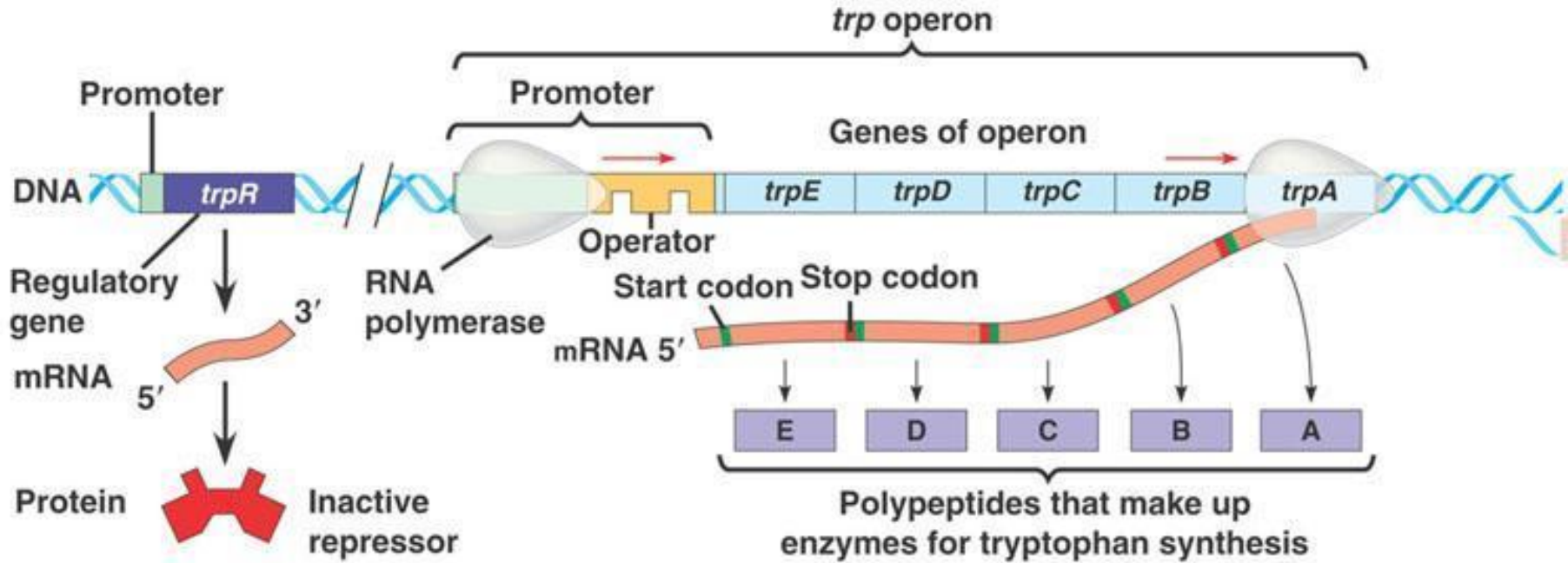
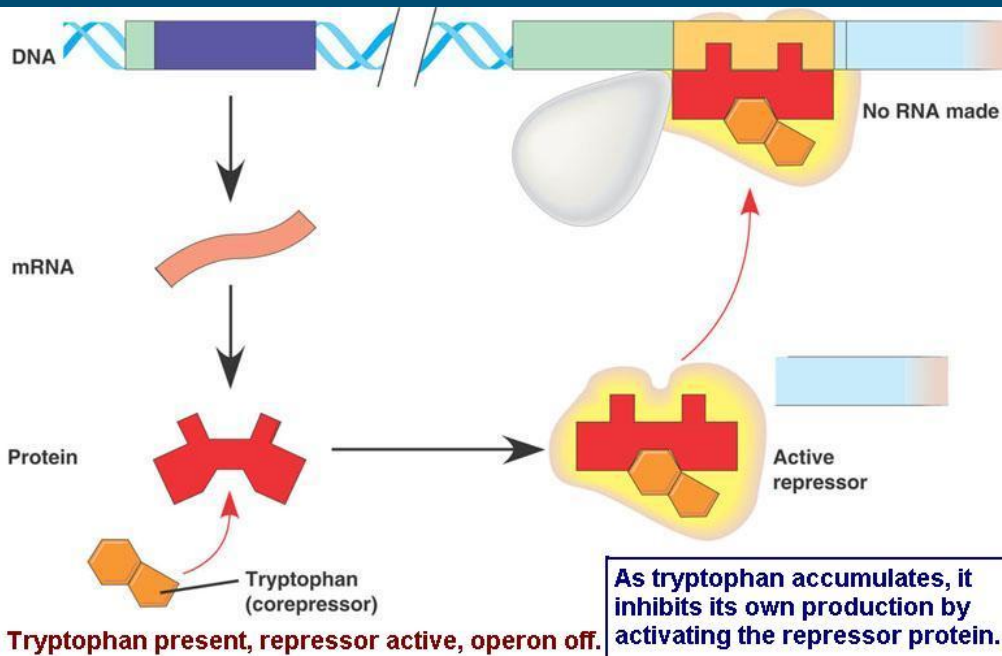


Figure 18.21. The *trp* operon. (a) Tryptophan absent, repressor inactive, operon on.



(b) Tryptophan present, repressor active, operon off.

➤ **Repressible operons: the *trp* operon.**

➤ Binding of a specific repressor protein to the operator shuts off transcription. The repressor is active when bound to a **corepressor**, usually the end product of an anabolic pathway (such as tryptophan here).

Inducible operons: the *lac* operon.

Binding of an inducer to an innately active repressor (such as the *lactose repressor*) inactivates the repressor and turns on transcription. Inducible enzymes usually function in catabolic pathways.

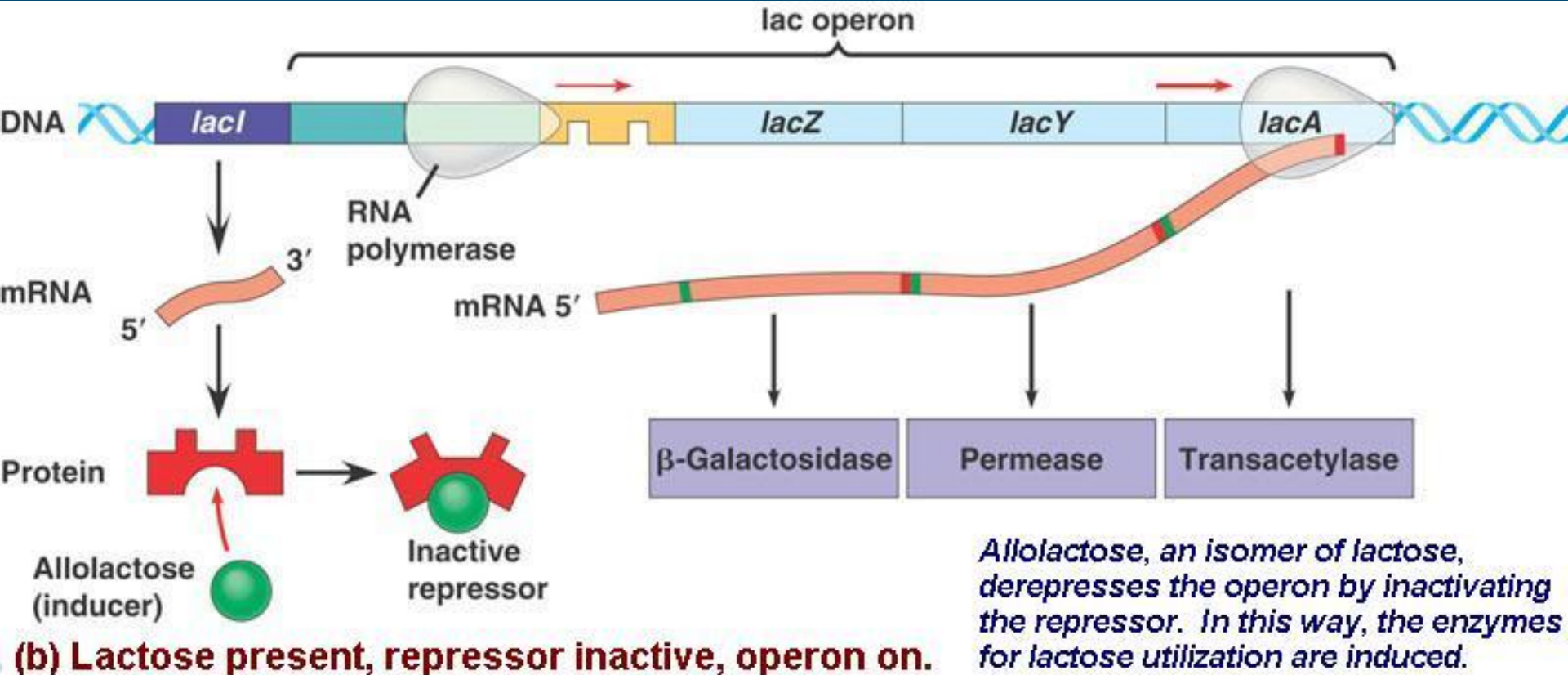
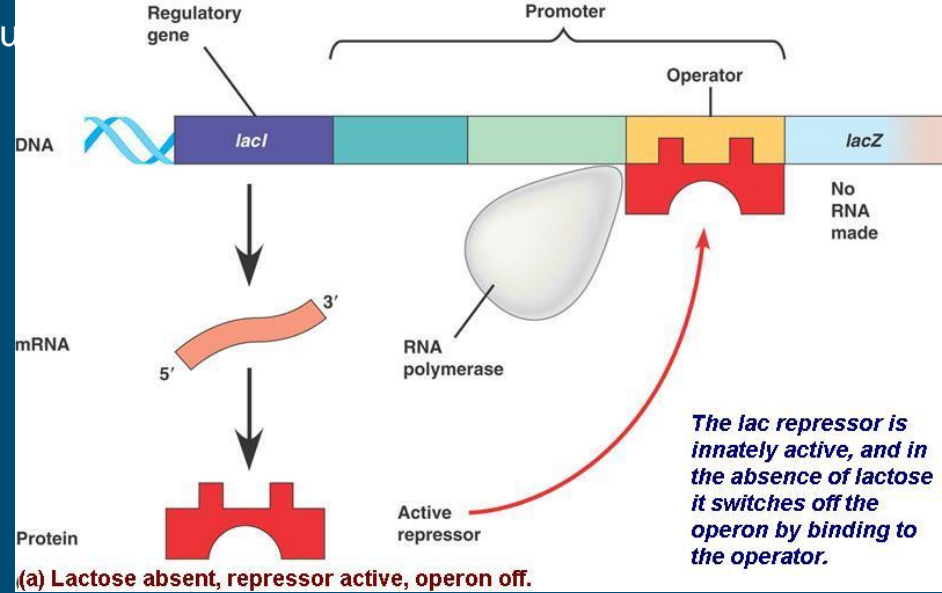
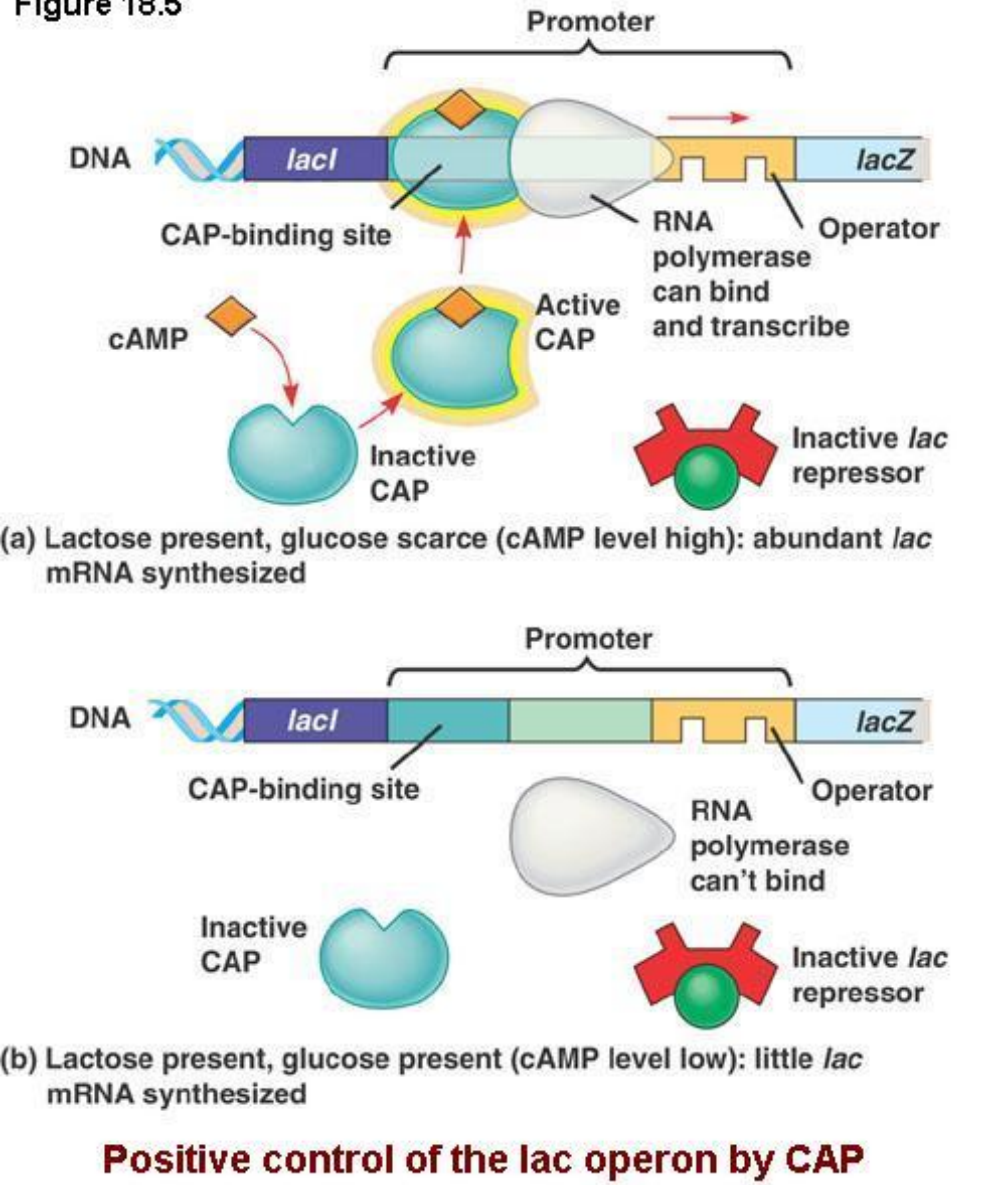


Figure 18.5



Positive Regulation of Bacterial Gene Expression

- Some operons are also subject to positive control via a stimulatory *activator protein*, such as **catabolite activator protein (CAP)**, which promotes transcription when bound to a site within the promoter.
- RNA polymerase has high affinity for the ***lac* promoter** only when CAP is bound to a DNA site at the upstream end of the promoter. CAP attaches to its DNA site only when associated with **cyclic AMP (cAMP)**, whose concentration in the cell rises when the glucose concentration falls. Thus, when glucose is present, even if lactose also is available, the cell preferentially catabolizes glucose and makes very little of the lactose-utilizing enzymes.

TABLE 14-1

Transcriptional Control in Bacteria*

Negative Control	Result
Inducible genes	
Repressor protein alone Lactose repressor alone	Active repressor turns off regulated gene(s) <i>lac</i> operon not transcribed
Repressor protein + inducer Lactose repressor + allolactose	Inactive repressor-inducer complex fails to turn off regulated gene(s) <i>lac</i> operon transcribed
Repressible genes	
Repressor protein alone Tryptophan repressor alone	Inactive repressor fails to turn off regulated gene(s) <i>trp</i> operon transcribed
Repressor protein + corepressor Tryptophan repressor + tryptophan	Active repressor-corepressor complex turns off regulated gene(s) <i>trp</i> operon not transcribed
Positive Control	Result
Activator protein alone CAP alone	Activator alone cannot stimulate transcription of regulated gene(s) Transcription of <i>lac</i> operon not stimulated
Activator complex CAP + cAMP	Functional activator complex stimulates transcription of regulated gene(s) Transcription of <i>lac</i> operon stimulated

*A general description of each type is followed by a specific example.

Regulation of Gene Expression in Eukaryotes: *Review of General Characteristics of Eukaryotes*

- Eukaryotic organisms (domain Eukarya) can be **unicellular or multicellular**. They include:
 - ✓ Protists, fungi, plants, animals
- Multiple chromosomes, inside a **nucleus**.
 - ✓ The typical eukaryotic genome is much larger than prokaryotic genomes. In multicellular eukaryotes **cell specialization** is crucial.
- Have **histones** (special chromosomal proteins).
- Have **membrane-enclosed organelles** specialized for different functions.
- Simple **polysaccharide cell walls in some** (algae, fungi, plants).
- Cell division by **mitosis** (nuclear division).
- Eukaryotic cells are **larger** than prokaryotic cells.

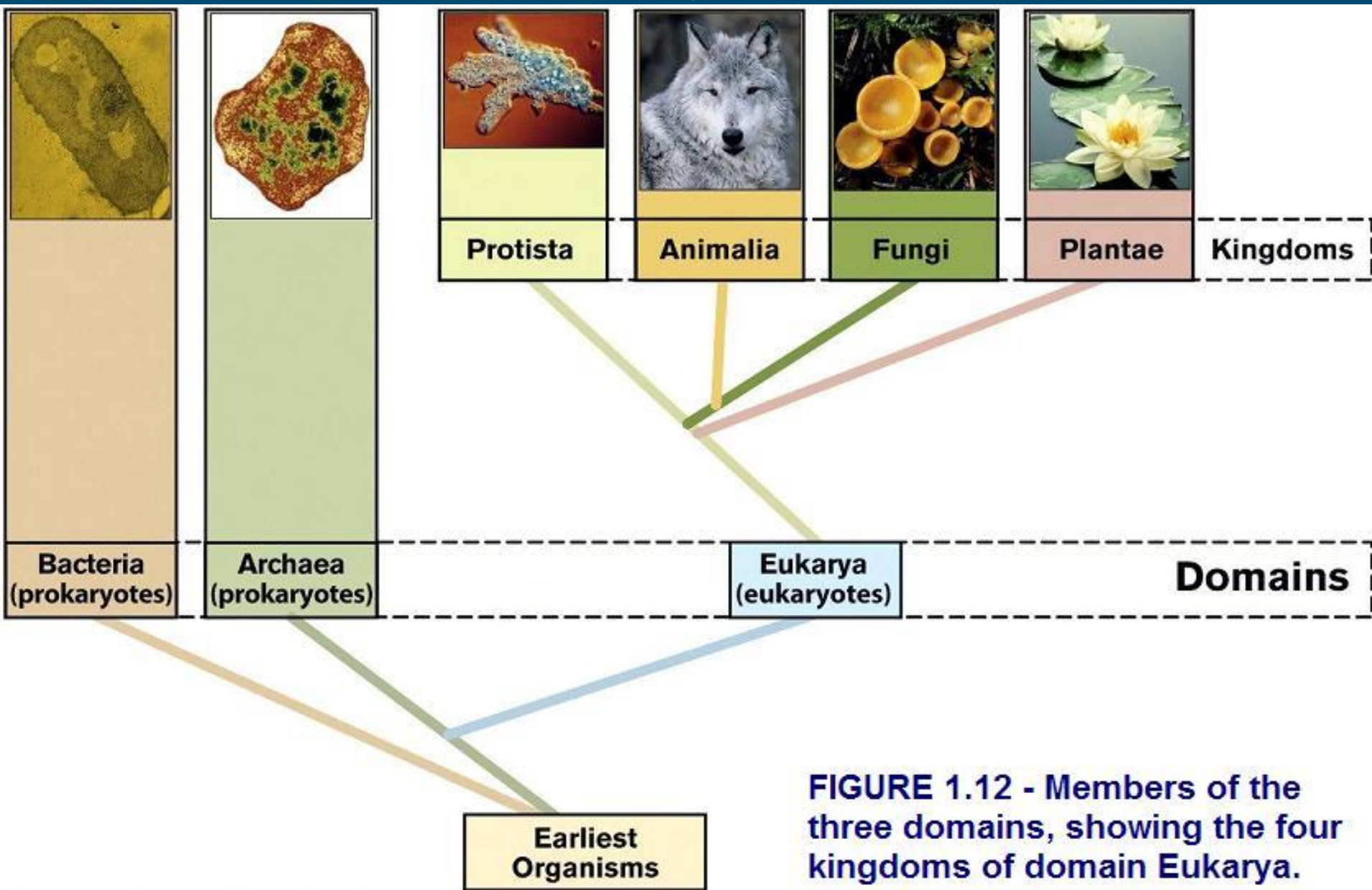
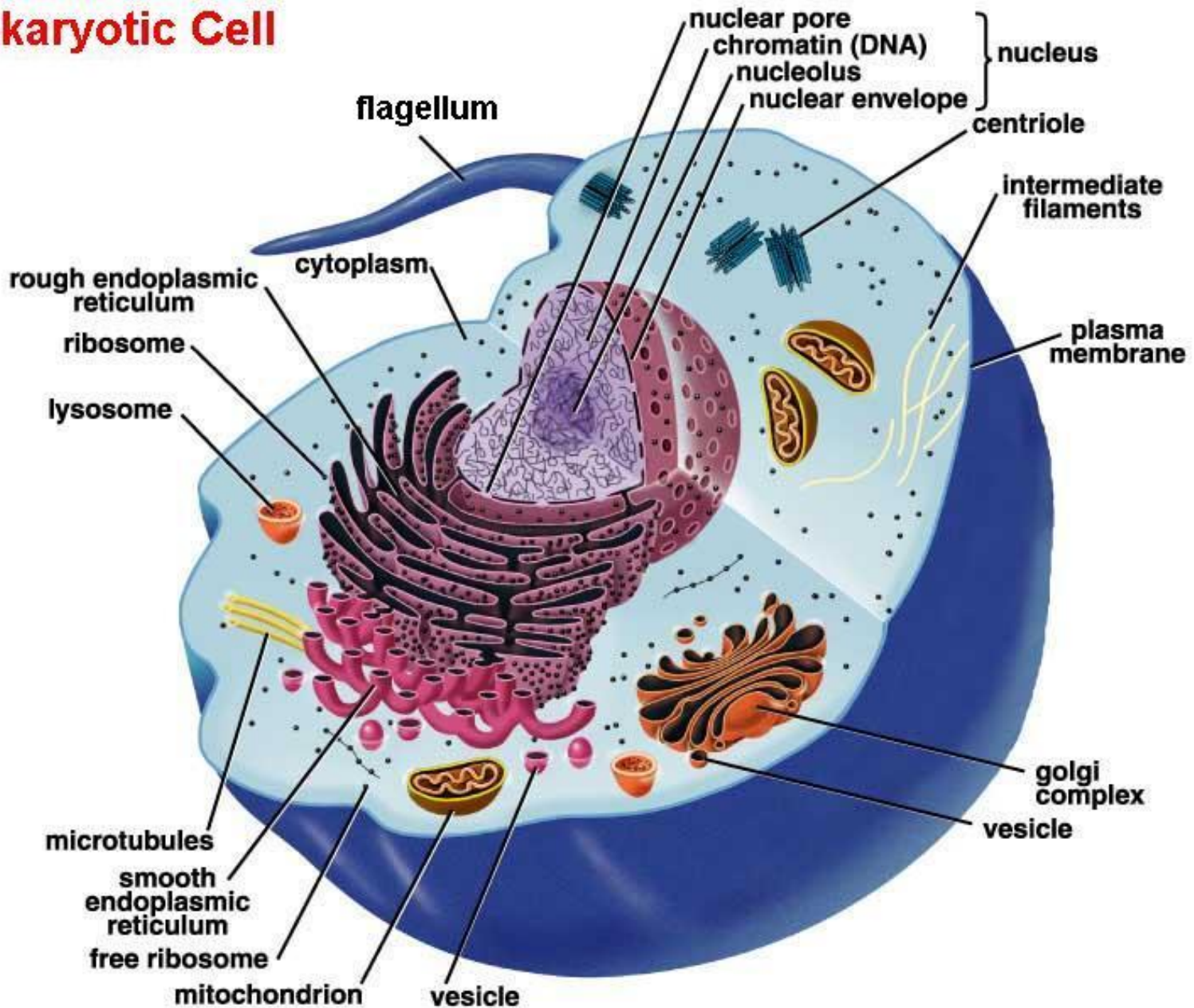


FIGURE 1.12 - Members of the three domains, showing the four kingdoms of domain Eukarya.

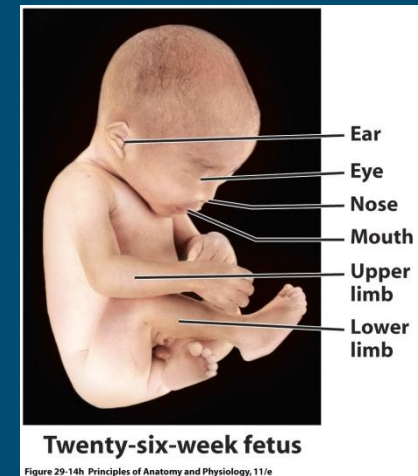
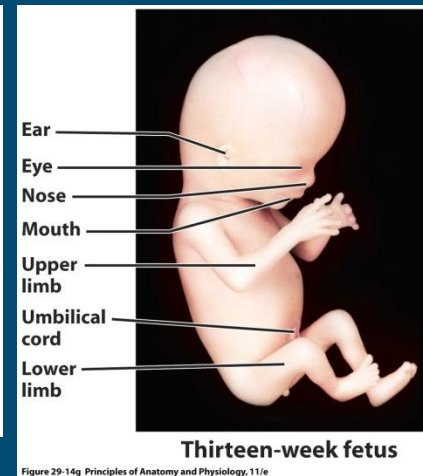
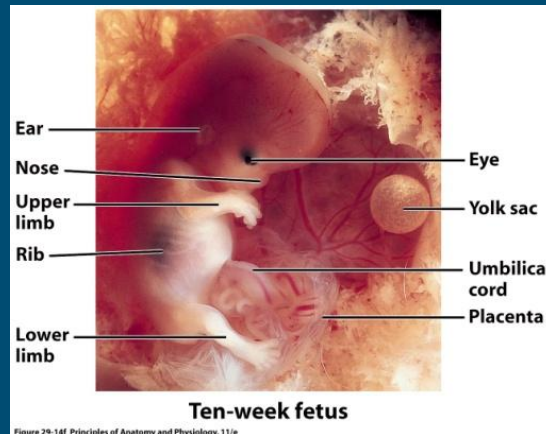
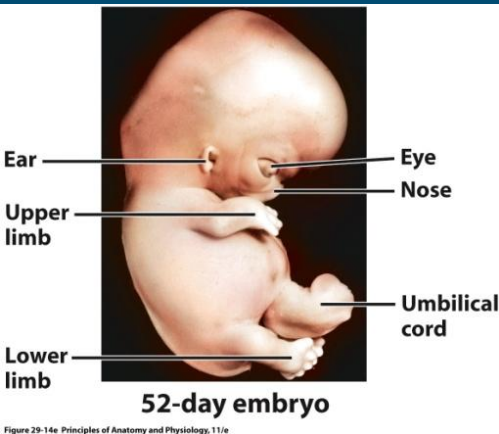
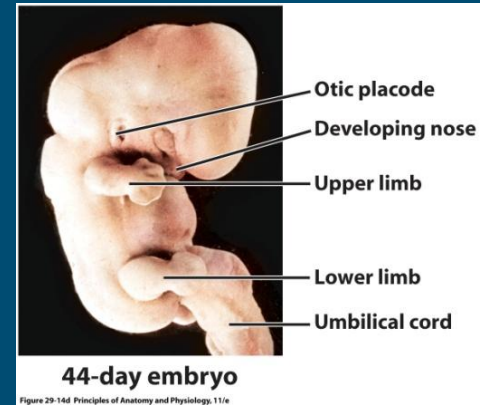
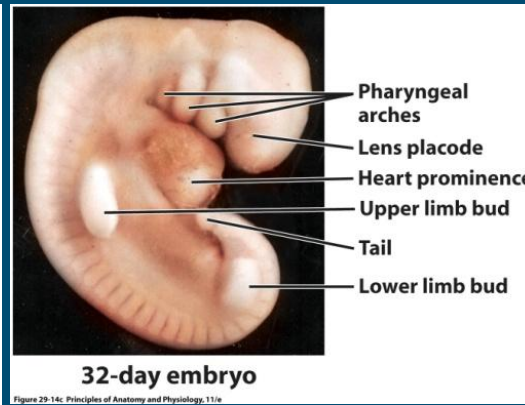
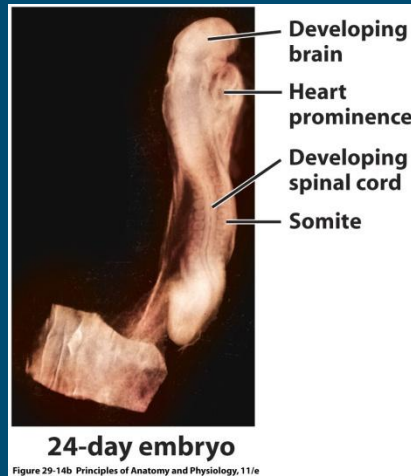
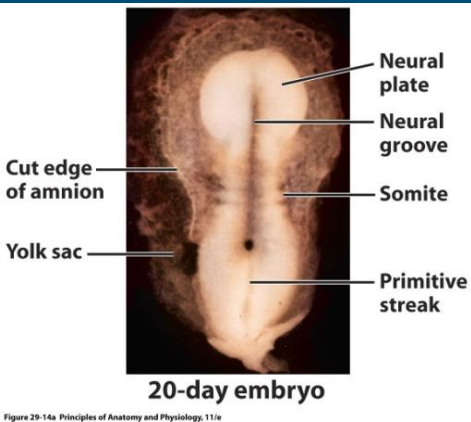
Eukaryotic Cell



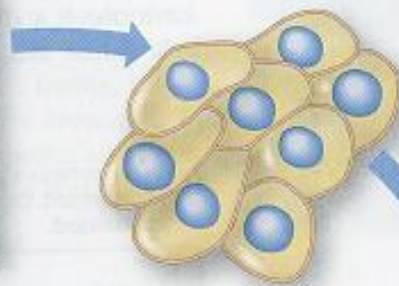
Regulation of Gene Expression in Eukaryotes

- ↗ Both unicellular organisms and the cells of multicellular organisms must continually **turn genes on and off** in response to signals from their external and internal environments.
- ↗ In multicellular organisms, cells undergo a process of **specialization** in form and function called **cell differentiation**.
- ↗ A program of **differential gene expression**—the expression of different sets of genes by cells with the same genome—leads to the different cell types in a multicellular organism.
 - ✓ In other words, each cell of a multicellular eukaryote expresses only a fraction of its genes. In each type of differentiated cell, **a unique subset of genes is expressed**.

Human Embryonic Development: Cell Division and Cell Differentiation

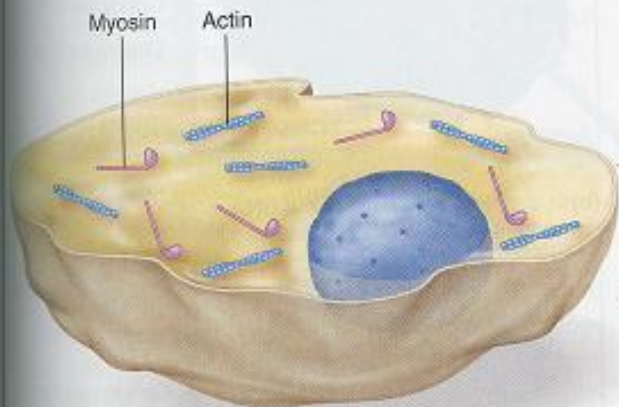
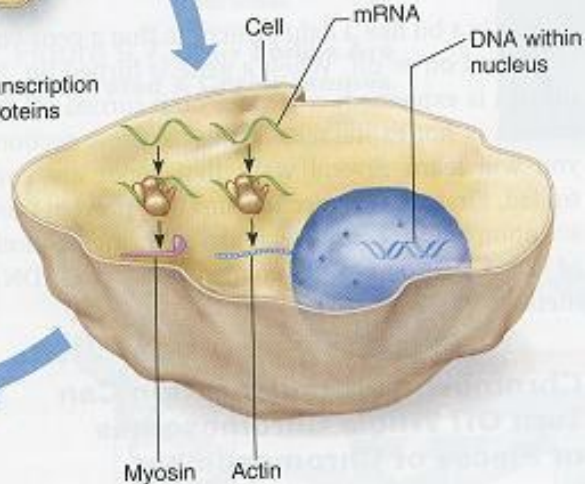


The process of **cell differentiation** does not happen all at once. Body parts and organs emerge gradually.



(a) Embryonic cells that eventually differentiate into a muscle fiber.

(b) DNA directs the transcription of mRNA for the proteins actin and myosin.



(c) As the cell makes more and more actin, myosin, and other muscle proteins, the cell differentiates into muscle fiber. Actin and myosin become organized into contractile units of the muscle fiber.

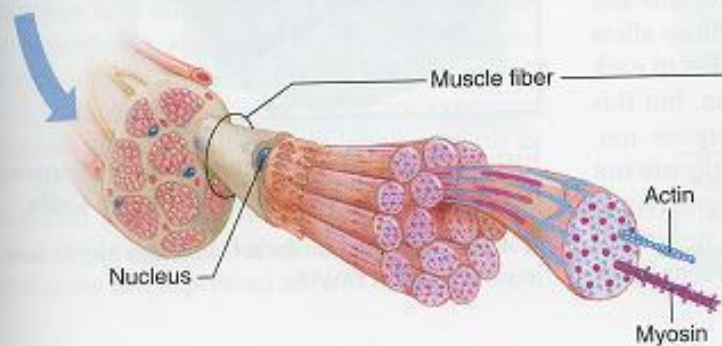


Figure 9.5 DNA Controls the Traits of a Cell by Providing the Instructions for Making Specific Proteins. The expression of specific proteins turns a group of embryonic cells into muscle tissue.

The proteins that a cell expresses determine the cell's traits.

gene expression the process of expressing specific protein from DNA

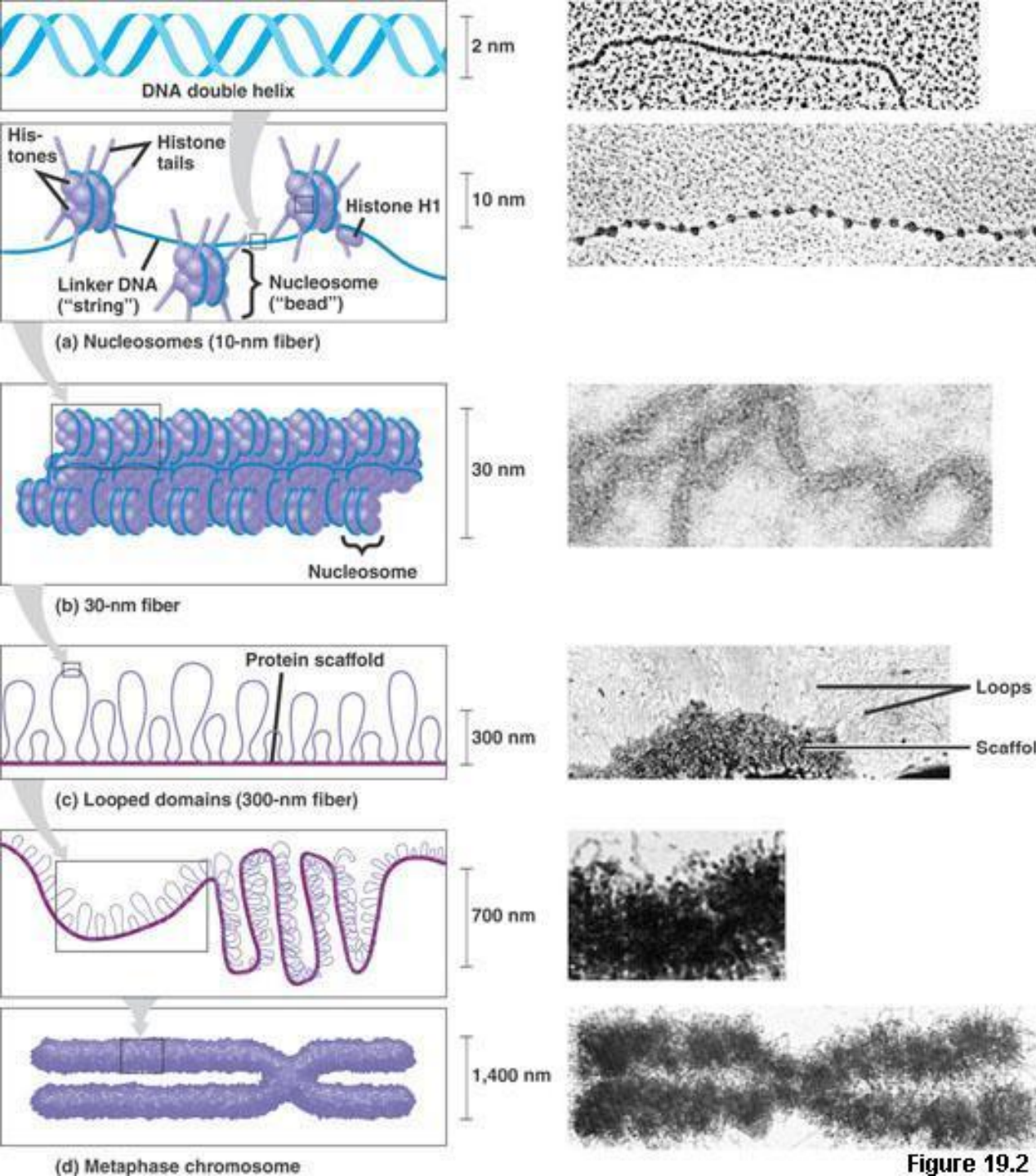
Regulation of Gene Expression in Eukaryotes

- Key stages at which gene expression may be regulated include:
 - ✓ Chromatin modification (changes in chromatin structure)
 - ✓ Transcription initiation
 - ✓ RNA processing
 - ✓ mRNA degradation
 - ✓ Translation
 - ✓ Protein processing and degradation (post-translational control)
- *** Gene expression can be regulated at any stage, but the key step is **transcription**.

Regulation of Gene Expression in Eukaryotes

Regulation of Chromatin Structure

- ⇒ The structural organization of chromatin not only packs a cell's DNA into a compact form that fits inside the nucleus but also helps regulate gene expression in several ways.
- ✓ The **location** of a gene's **promoter** (region where RNA polymerase binds) can affect whether the gene is transcribed.
 - ✓ Genes within **heterochromatin**, which is highly condensed, are usually not expressed.
 - ✓ Active genes are within a more loosely packed chromatin structure called **euchromatin**.
 - ✓ Certain **chemical modifications** to the **histones** (special chromosomal proteins) and DNA of chromatin can influence both chromatin structure and gene expression.



pression

Organization of a Eukaryotic Chromosome

These diagrams and transmission electron micrographs depict a current model for the progressive stages of DNA coiling and folding.

Eukaryotic chromosomes have several levels of organization. The DNA is associated with **histones** (basic proteins) to form **nucleosomes**, each of which consists of a histone bead with DNA wrapped around it. The nucleosomes are organized into large, coiled loops held together by non-histone **scaffolding proteins**.

Figure 19.2

Regulation of Gene Expression in Eukaryotes

Regulation of Chromatin Structure

↗ Histone Modifications – Histone Acetylation

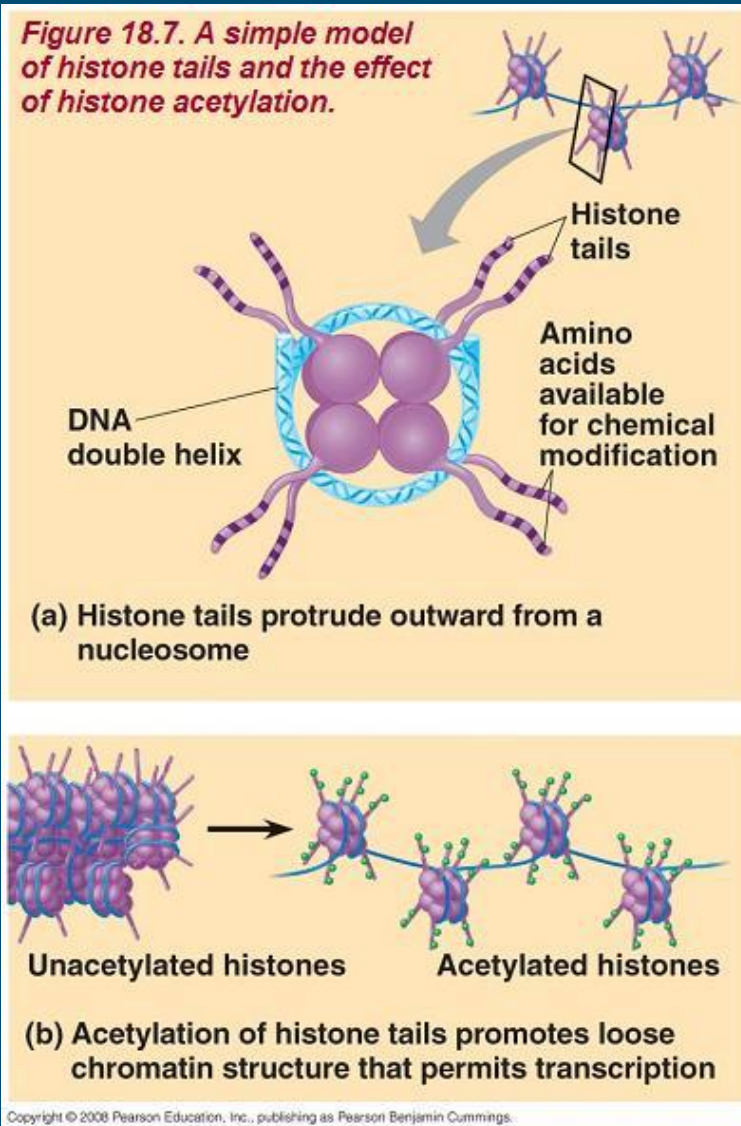
- ✓ **Acetyl groups** ($--COCH_3$) are attached to *lysine* (an amino acid) in histone tails. It promotes loose chromatin structure that **permits transcription**.
- ✓ In addition to acetylation, histones can undergo other types of modifications that also help determine the chromatin configuration of a region.

↗ DNA Methylation

- ✓ Attaching a **methyl group** ($--CH_3$) to a *cytosine* nucleotide base **prevents the stretch of DNA from being transcribed**.

Regulation of Gene Expression in Eukaryotes

Regulation of Chromatin Structure: **Histone Acetylation**



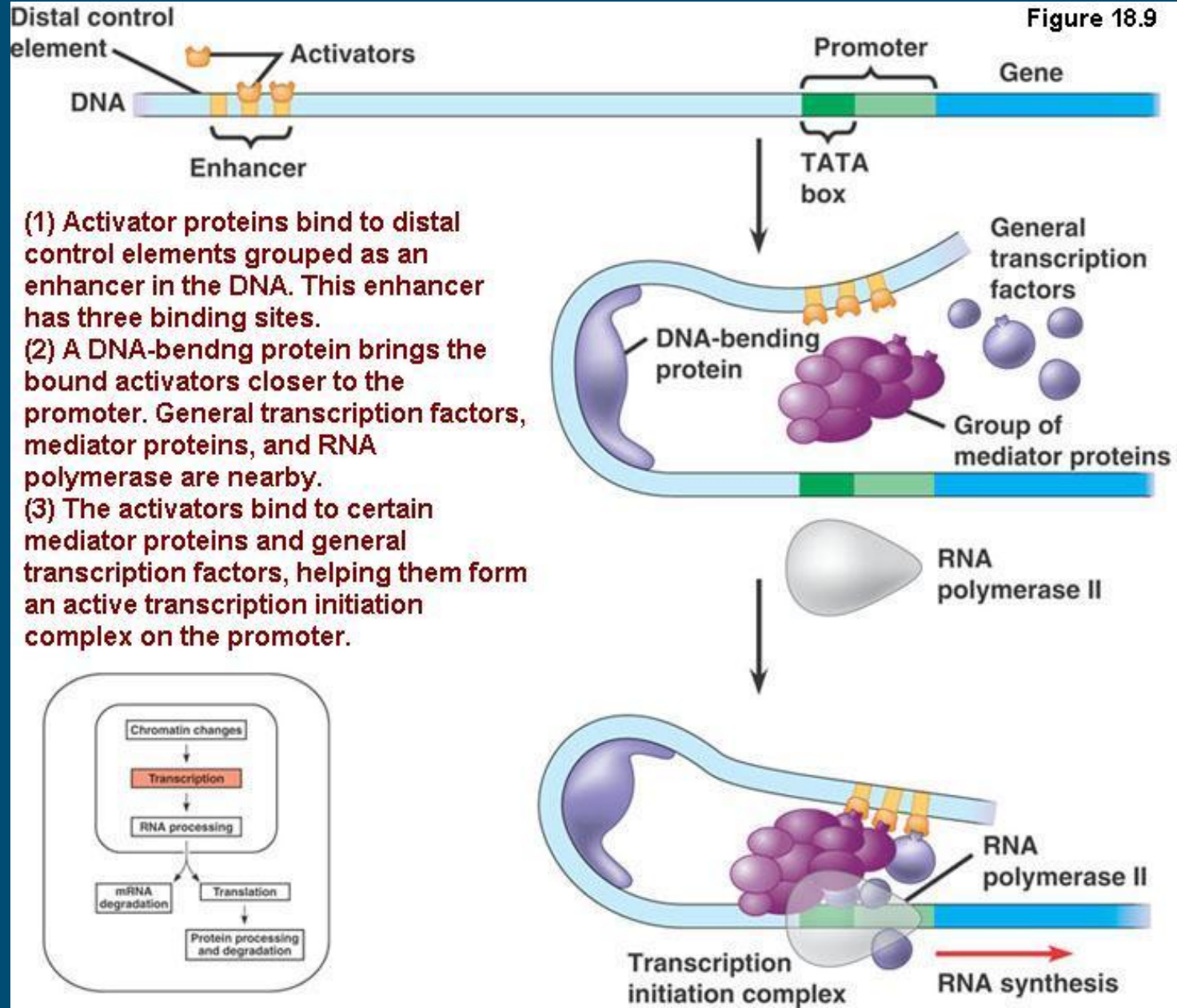
- a) **End view of histone tails protruding outward from a nucleosome.** The amino acids in the N-terminal tails are accessible for chemical modification.
- b) **Acetylation of histone tails promotes loose chromatin structure that permits transcription.** A region of chromatin in which nucleosomes are unacetylated forms a compact structure (left) in which the DNA is not transcribed. When nucleosomes are highly acetylated (right), the chromatin becomes less compact, and the DNA is accessible for transcription.

Regulation of Gene Expression in Eukaryotes

Regulation of Transcription Initiation

- **Transcription factors** are *regulatory proteins* that bind to DNA and affect transcription of specific genes. They bind to **DNA control elements**, segments of noncoding DNA that help regulate transcription.
- **Proximal control elements** are located close to the **promoter**.
- **Enhancer (distal control elements)**: A segment of eukaryotic DNA containing multiple control elements, located far from the gene whose transcription it regulates.
- Bending of the DNA enables activators to contact proteins close to the **promoter**, initiating transcription.
 - ✓ In multicellular eukaryotes, RNA polymerase binds to a promoter called a **TATA box**, which is required for transcription to begin.

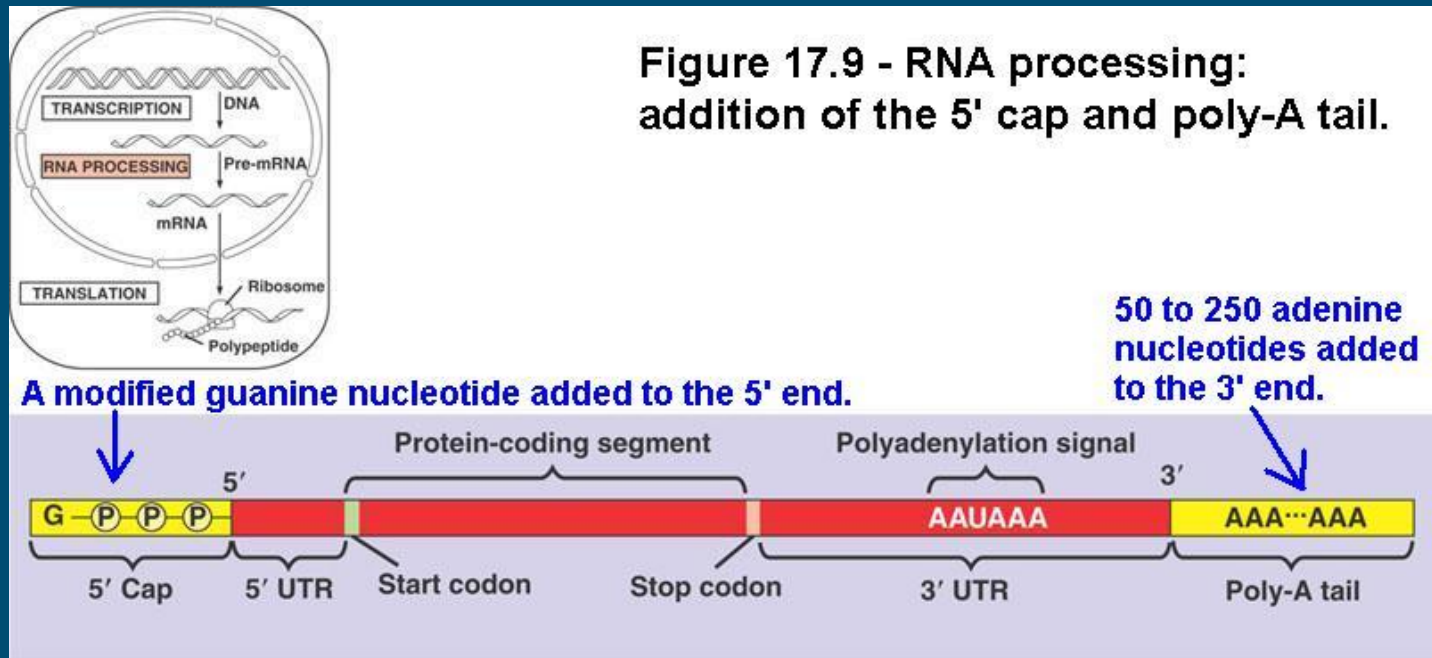
A model for the action of enhancers and transcription activators



Regulation of Gene Expression in Eukaryotes Mechanisms of Post-Transcriptional Regulation

- **RNA Processing (Editing):** Eukaryotic mRNA molecules undergo further modification and processing before they are mature and used in protein synthesis.
 - ✓ Addition of a **5' cap**.
 - ✓ Addition of a **poly-A tail** at the 3'.
 - ✓ **RNA Splicing:** After synthesis of the primary RNA transcript, the removal of **introns**, the portions of the transcript that will not be included in the mRNA.
- Translation
 - ✓ **Initiation factors** (proteins) for translation can be regulated.

Eukaryotic cells modify RNA after transcription



- ✎ **RNA processing: addition of the 5' cap and poly-A tail.** Enzymes modify the two ends of a eukaryotic pre-mRNA molecule. The modified ends may *promote the export of mRNA* from the nucleus, and they help *protect the mRNA* from degradation. When the mRNA reaches the cytoplasm, the modified ends, in conjunction with certain cytoplasmic proteins, facilitate ribosome attachment. The 5' cap and poly-A tail are not translated into protein, nor are the regions called the 5' untranslated region (5' UTR) and 3' untranslated region (3' UTR).

Regulation of Gene Expression in Eukaryotes

Mechanisms of Post-Transcriptional Regulation: **RNA Processing**

- **RNA processing** of the primary transcript into a functional mRNA involves three steps: addition of the **5' cap**, addition of the **poly-A tail**, and **splicing** (removal of introns). In the cell, the 5' cap is added soon after transcription is initiated; splicing and poly-A tail addition may also occur while transcription is still under way.

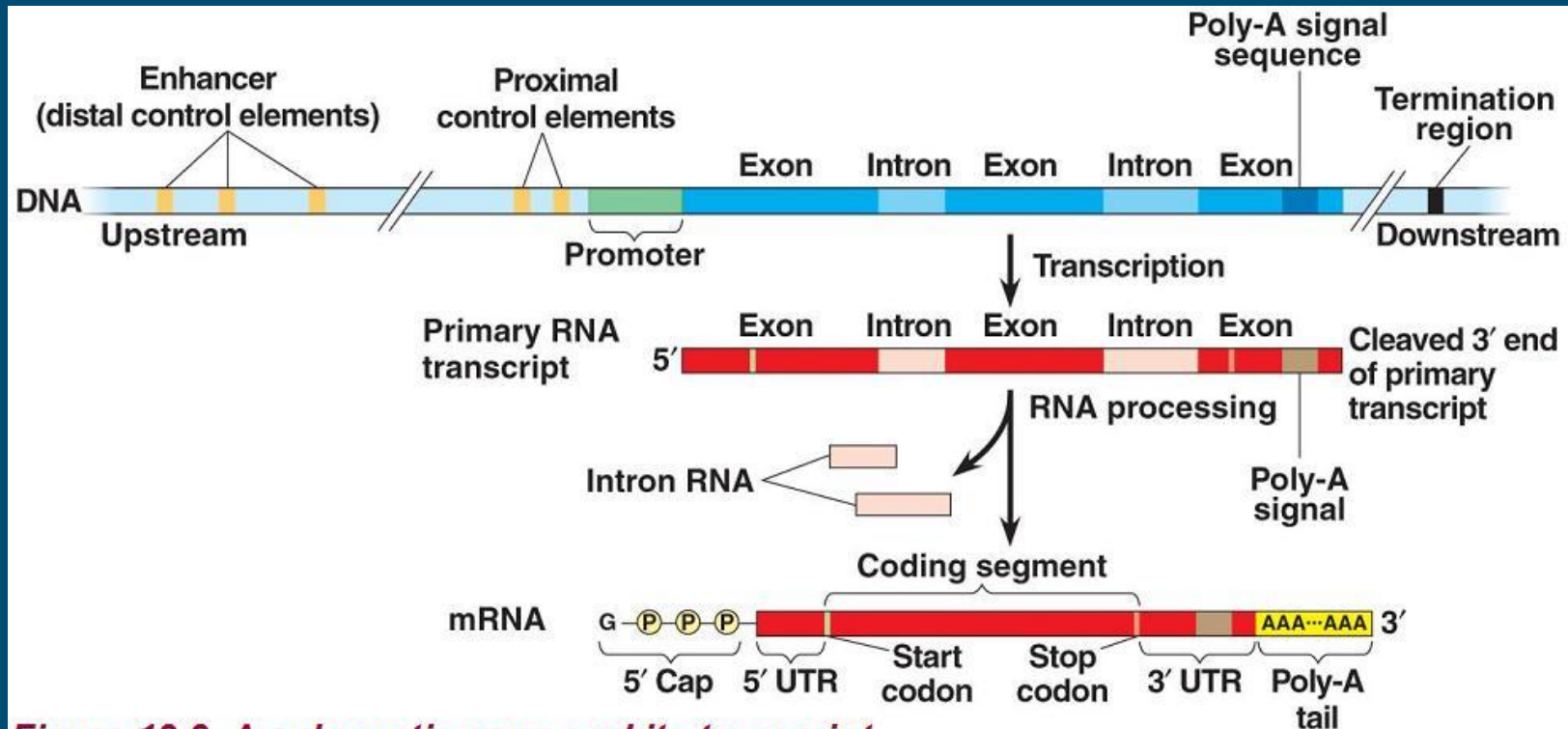


Figure 18.8. A eukaryotic gene and its transcript.

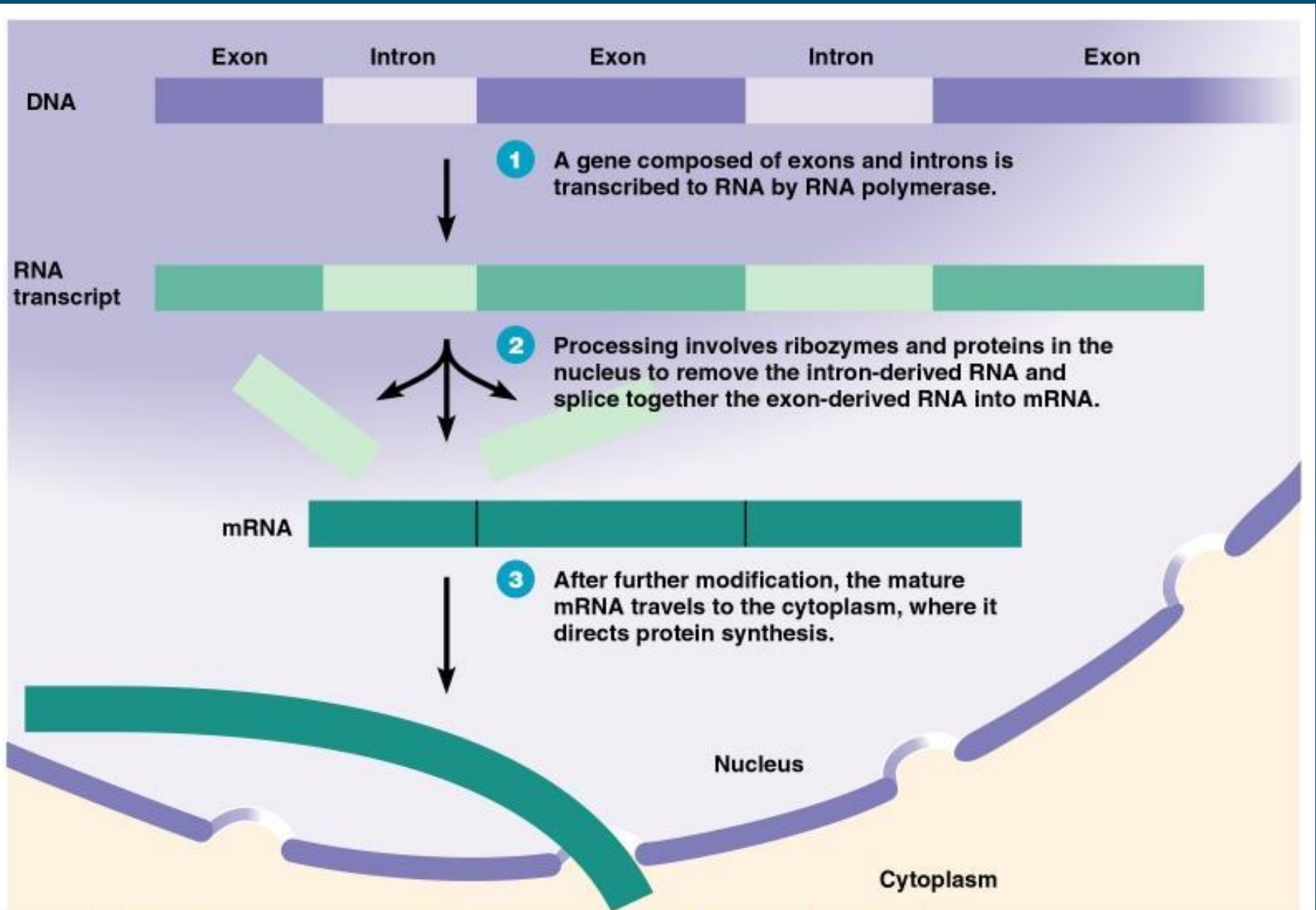


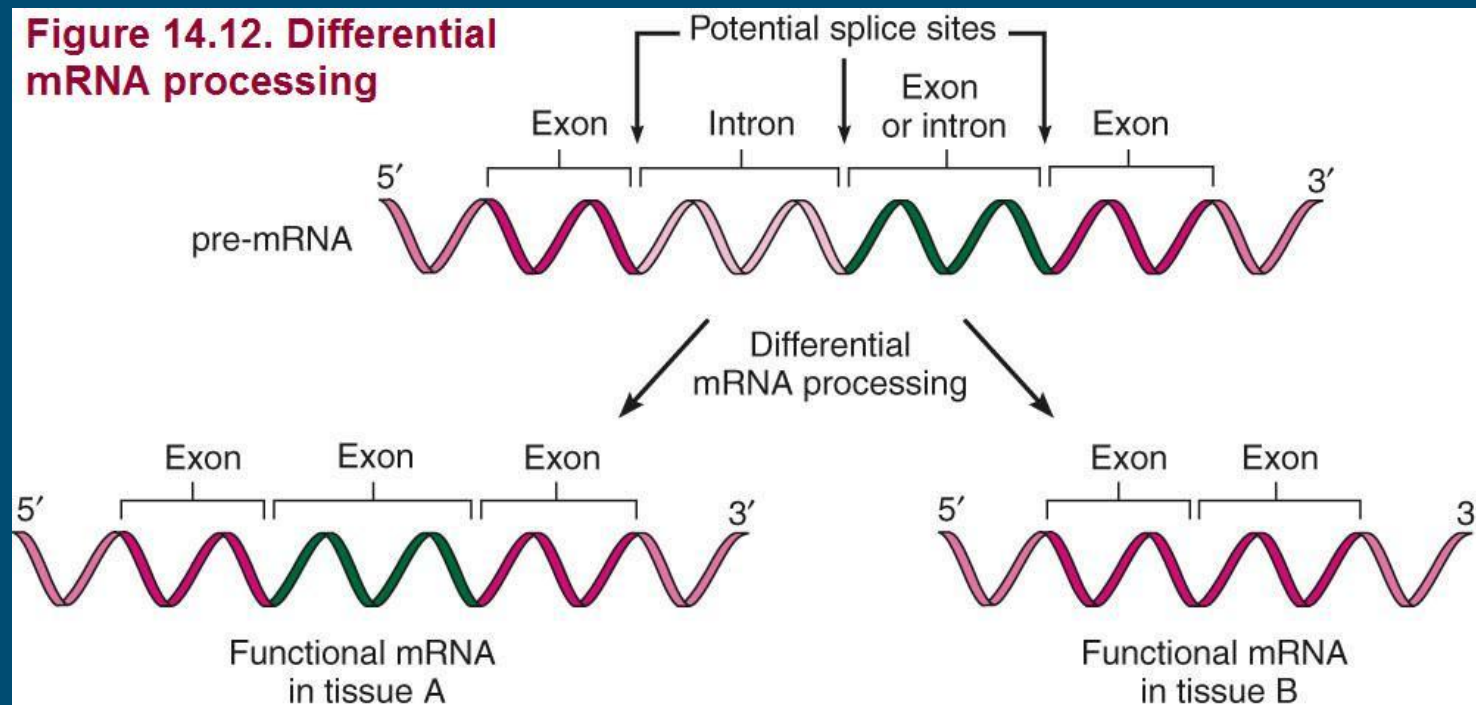
FIGURE 8.11 - RNA processing in eukaryotic cells.

Regulation of Gene Expression in Eukaryotes

Mechanisms of Post-Transcriptional Regulation

➤ **Alternative (differential) mRNA Processing:** In some cases, *a pre-mRNA molecule is processed in more than one way* to yield two or more mature mRNAs, each of which encodes a related, but different, protein.

➤ In this generalized example, the gene contains a segment that can be an **exon** in tissue A (*left*) but an **intron** in tissue B (*right*).



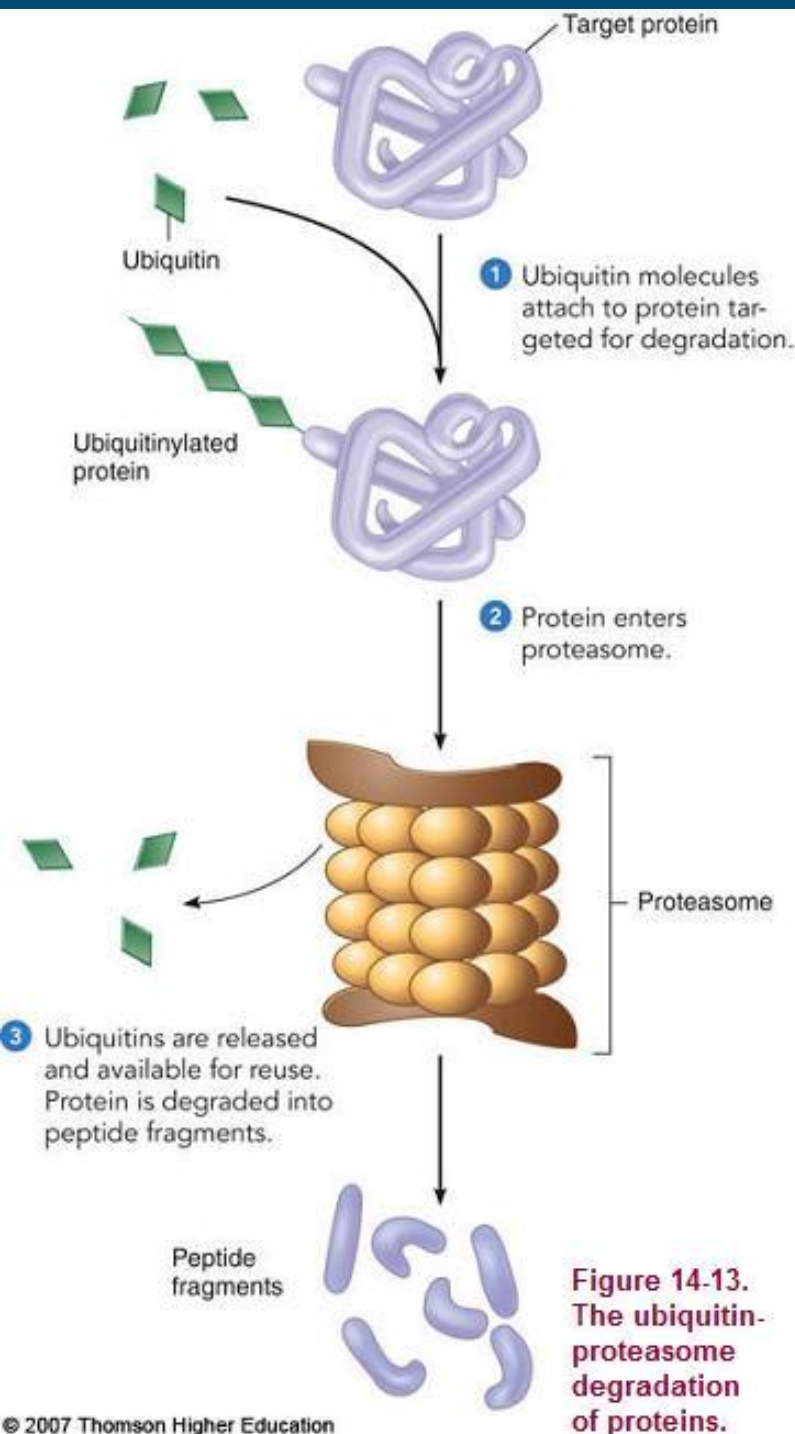
Regulation of Gene Expression in Eukaryotes

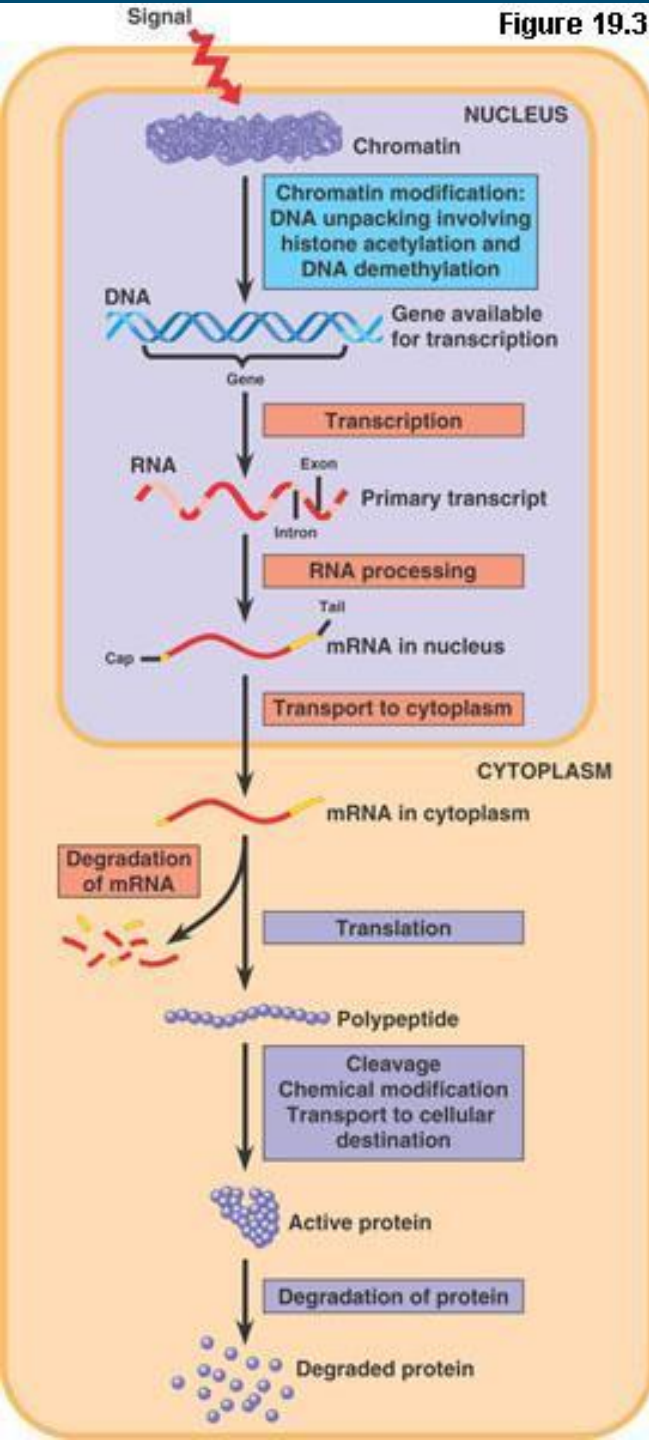
Mechanisms of Post-Translational Regulation

- Post-translational protein processing (modification of protein structure) and protein degradation
 - ✓ **Proteolytic (protein) processing:** inactive protein precursors are converted to an active form by the removal of a portion of the polypeptide chain.
 - ✓ **Chemical modification,** by adding or removing functional chemical groups (for example, phosphate groups), reversibly alters the activity of a protein.
 - ◆ **Kinases** are enzymes that add phosphate groups.
 - ◆ **Phosphatases** remove phosphate groups.
 - ✓ **Protein degradation,** in **proteasomes** (large multiprotein complexes) by **proteases** (enzymes that degrade proteins).

Regulation of Gene Expression in Eukaryotes Mechanisms of Post-Translational Regulation

- Post-translational control of gene expression can also involve **protein degradation**.
- Proteins targeted for destruction are covalently bonded to **ubiquitin**, a small protein that contains 76 amino acids.
- A protein that is tagged by ubiquitin is targeted for degradation in a **proteasome**, a large multiprotein complex that recognizes the ubiquitin tag. **Proteases** (protein-degrading enzymes) associated with proteasomes break some of the peptide bonds, degrading the protein into short, nonfunctional peptide fragments.





Stages in gene expression that can be regulated in eukaryotic cells

- In this diagram, the colored boxes indicate the processes most often regulated.
- The nuclear envelope separating transcription from translation in eukaryotic cells offers an opportunity for post-transcriptional control through **RNA processing** that is absent in prokaryotes.
- In addition, eukaryotes have a greater variety of control mechanisms operating before transcription and after translation.
- The expression of any given gene, however, does not necessarily involve every stage shown; for example, not every polypeptide is cleaved.
- REMEMBER: As in prokaryotes, **transcription initiation is the most important control point.**

TABLE 14-2

Gene Regulation in Eukaryotes

Level of Regulation	Description
Transcriptional control (most common level of gene regulation in eukaryotes)	<p>Chromatin structure regulates transcription; heterochromatin cannot be transcribed</p> <p>DNA methylation regulates transcription; methylated DNA is inaccessible to transcription machinery</p> <p>Selective transcription: promoter and enhancer elements in DNA interact with protein transcription factors to activate or repress transcription</p>
Posttranscriptional control: mRNA processing and transport	<p>Control mechanisms, such as rate of intron/exon splicing, regulate mRNA processing</p> <p>Differential mRNA processing (alternate splicing of exons) produces different proteins from same mRNA</p> <p>Controlling access to, or efficiency of, transport through nuclear pores regulates mRNA transport from nucleus to cytosol</p>
Translational control	<p>Translational controls determine how often and how long specific mRNA is translated</p> <p>Translational controls determine degree to which mRNA is protected from destruction; proteins that bind to mRNA in cytosol affect stability</p>
Posttranslational control of protein product	<p>Chemical modifications, such as phosphorylation, affect activity of protein after it is produced</p> <p>Selective degradation targets specific proteins for destruction by proteasomes</p>

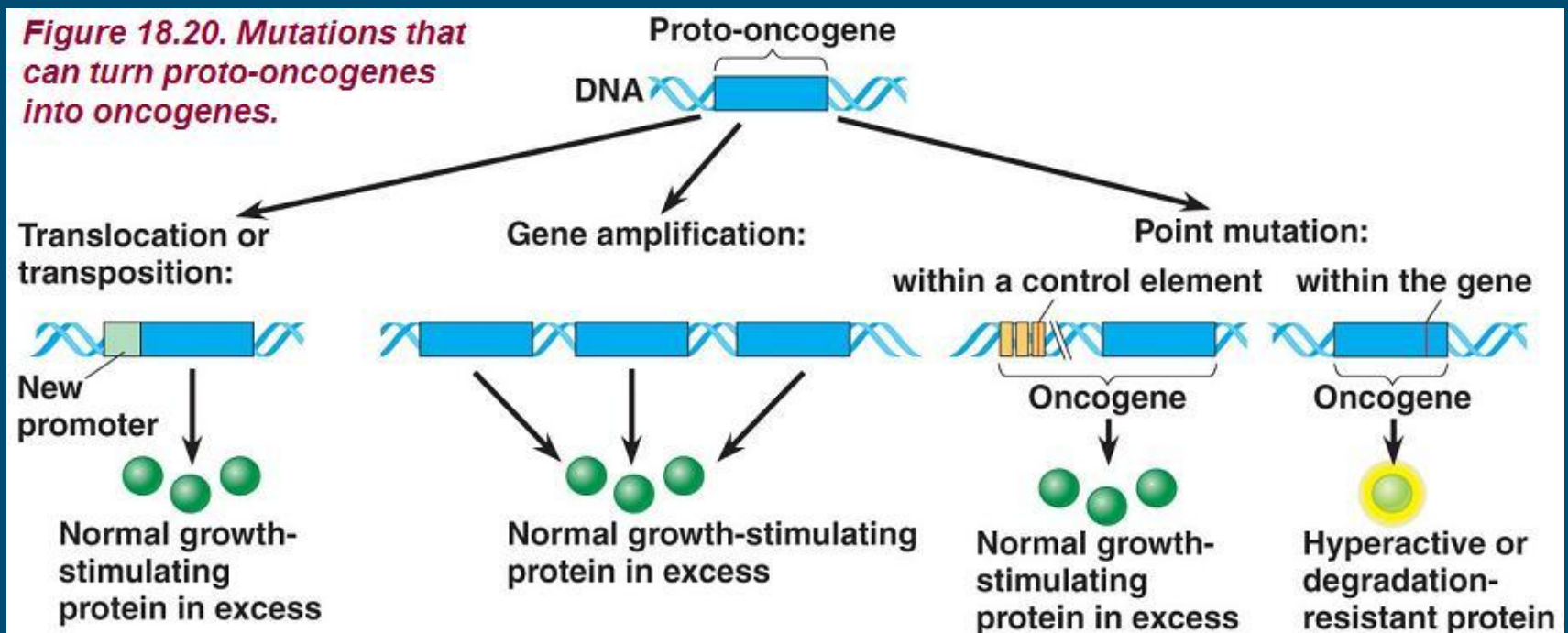
Cancer Results from Genetic Changes that Affect Cell Cycle Control

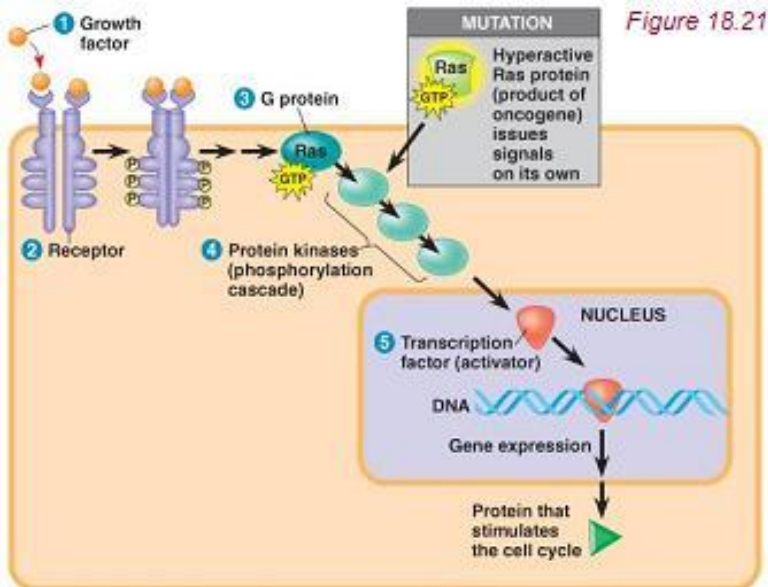
↗ Types of genes associated with cancer:

- ✓ **Proto-oncogenes** and **tumor-suppressor genes** control cell division. (*Review Chapter 12 about the cell cycle*).
- ✓ **Proto-oncogenes** code for proteins that stimulate **normal cell growth and division**. A mutation (DNA change) that makes a proto-oncogene **excessively active** converts it to an **oncogene**, which may promote **excessive cell division and cancer**.
- ✓ **Tumor-suppressor genes** encode proteins that **inhibit abnormal cell division**. A mutation in such a gene that reduces the activity of its protein product may also lead to **excessive cell division** and possibly to **cancer**.

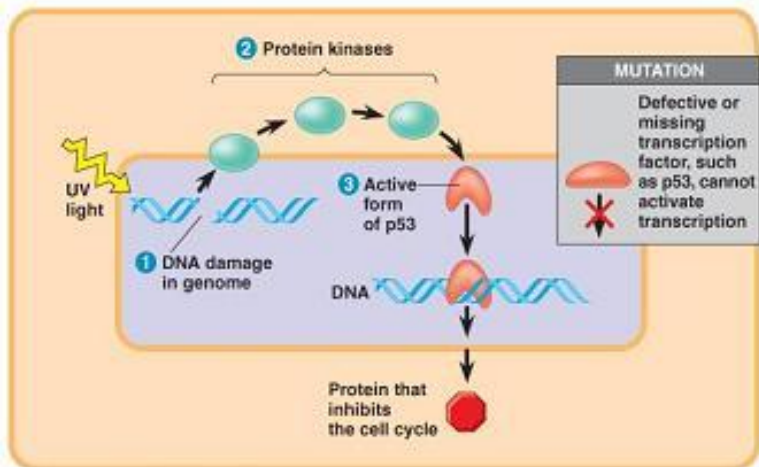
Genetic Changes that Can Turn Proto-Oncogenes into Oncogenes

- **Translocation or transposition:** gene moved to new locus, under new controls.
- **Gene amplification:** multiple copies of the gene.
- **Point mutation:** a nucleotide pair is replaced by another nucleotide pair in the DNA molecule.

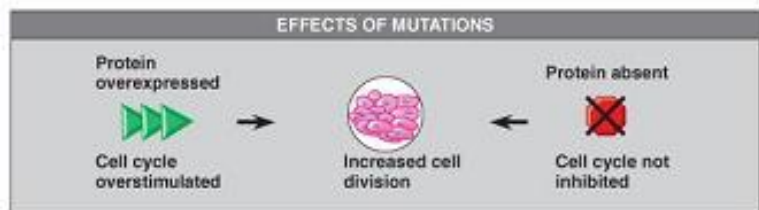




(a) Cell cycle-stimulating pathway



(b) Cell cycle-inhibiting pathway



(c) Effects of mutations

Signaling pathways that regulate cell division.

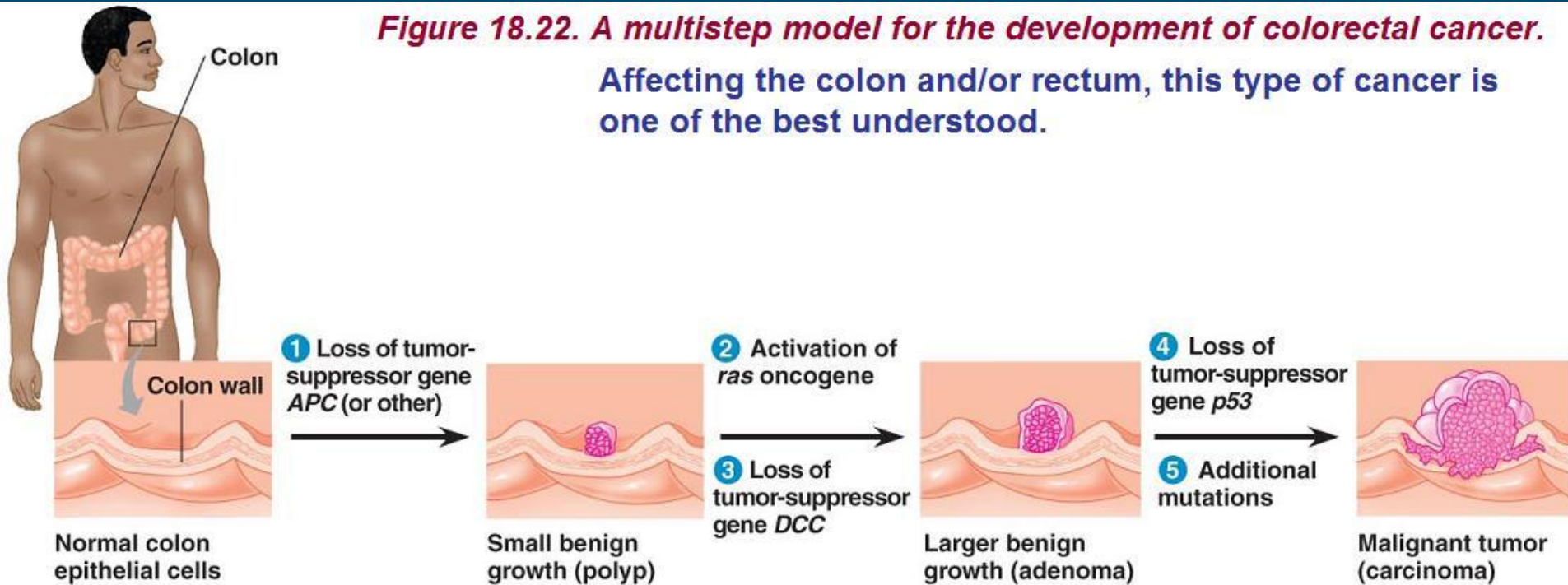
Interference with Normal Cell-Signaling Pathways

➤ The proteins encoded by many proto-oncogenes and tumor-suppressor genes are components of *cell-signaling pathways*.

- Cell cycle-stimulating pathway.** This pathway is triggered by a growth factor (1) and involves a G protein called **Ras** (3).
- Cell cycle-inhibiting pathway.** In this pathway DNA damage is an intracellular signal that is passed via protein kinases (2) and leads to activation of **p53** (3).
- Effects of mutations.** Increased cell division, possibly leading to **cancer**, can result if the cell cycle is **overstimulated**, as in (a) or **not inhibited** when it normally would be, as in (b).





➤ * *Review more details in your textbook.*

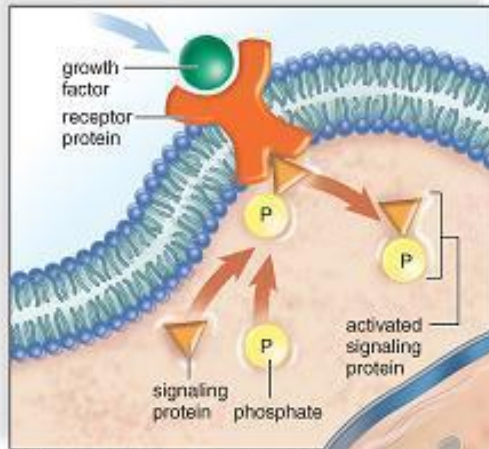
The Multistep Model of Cancer Development



Changes in a tumor parallel a series of genetic changes, including mutations affecting several **tumor-suppressor genes** (such as ***p53***) and the ***ras* proto-oncogene**. Mutations of tumor-suppressor genes often entail loss (deletion) of the gene. ***APC*** stands for “adenomatous polyposis coli”, and ***DCC*** stands for “deleted in colorectal cancer”. Other mutation sequences can also lead to colorectal cancer.

Figure 9.8. Causes of cancer.

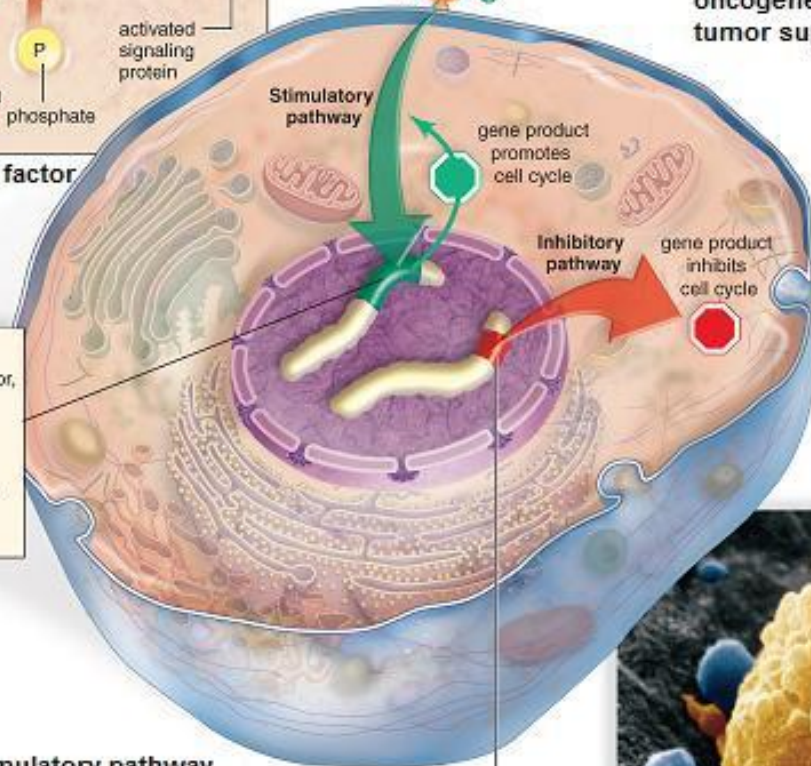
 Heredity	 Radiation sources
 Pesticides and herbicides	 Viruses oncogene



growth factor
Activates signaling proteins in a stimulatory pathway that extends to the nucleus.

a. Influences that cause mutated proto-oncogenes (called oncogenes) and mutated tumor suppressor genes

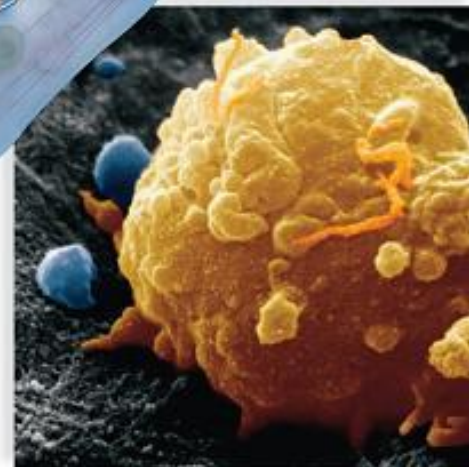
b. Effect of growth factor



proto-oncogene
Codes for a growth factor, a receptor protein, or a signaling protein in a stimulatory pathway. If a proto-oncogene becomes an oncogene, the end result can be active cell division.

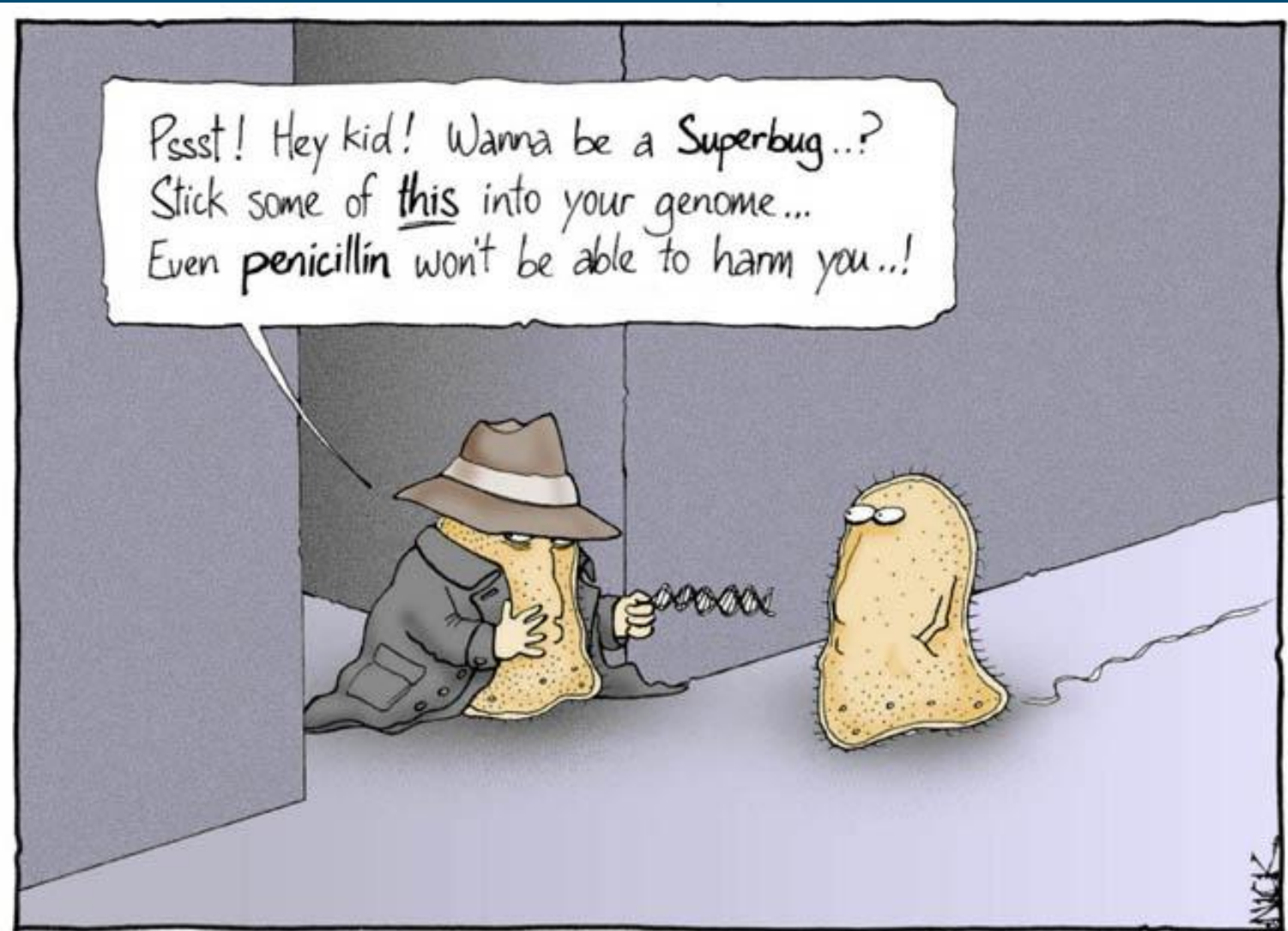
c. Stimulatory pathway and inhibitory pathway

tumor suppressor gene
Codes for a signaling protein in an inhibitory pathway. If a tumor suppressor gene mutates, the end result can be active cell division.



d. Cancerous skin cell

1,100x



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

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