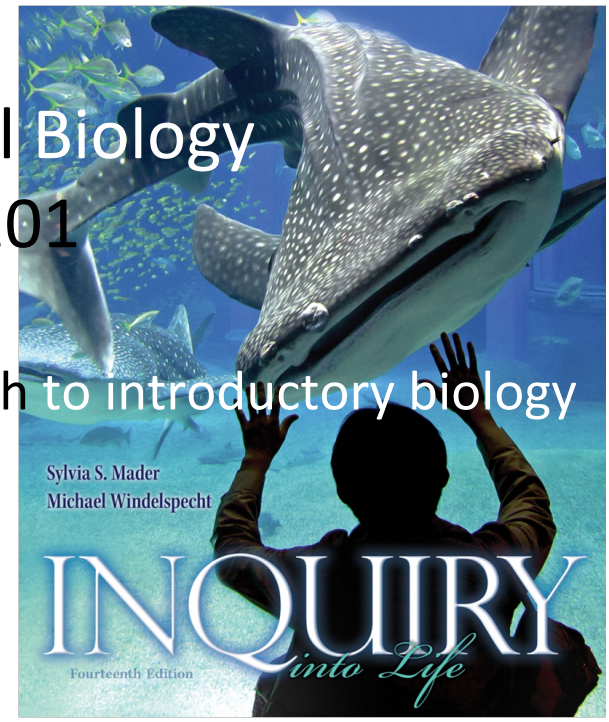
Fundamental Biology
BI 1101

an interdisciplinary approach to introductory biology



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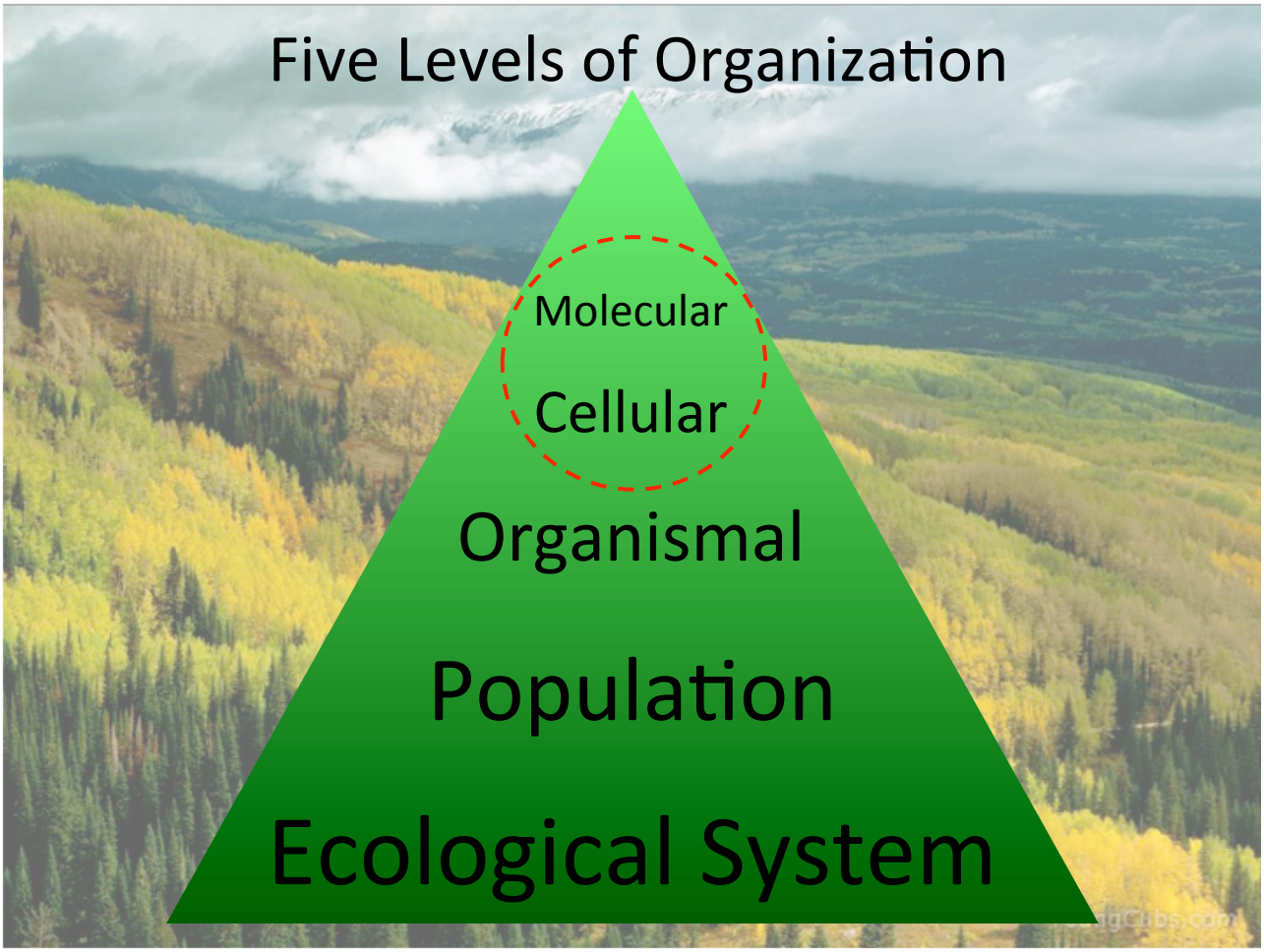


HOW GENES ARE CONTROLLED

Learning outcome

After learning this chapter, students are able to:

- Describe gene regulation and expression
- Explain transcription and translation
- Describe some application concerning gene regulation and expression

Introduction

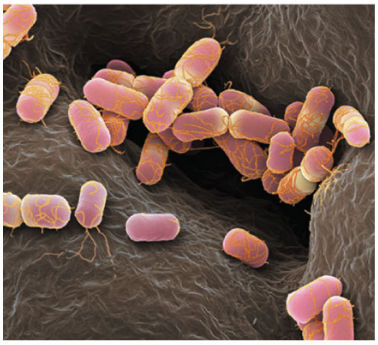
- Cloning is the creation of an individual by asexual reproduction.
- The ability to clone an animal from a single cell demonstrates that every adult body cell
  - contains a complete genome that is
  - capable of directing the production of all the cell types in an organism.

Introduction

- Cloning has been attempted to save endangered species.
- However, cloning
  - does not increase genetic diversity and
  - may trivialize the tragedy of extinction and detract from efforts to preserve natural habitats.

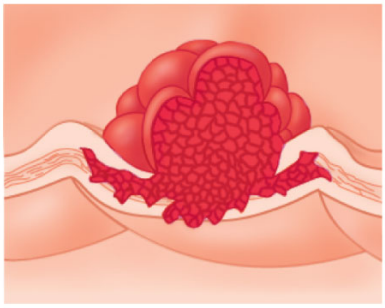
Figure 11.0_1

Chapter 11: Big Ideas



Control of Gene Expression

Cloning of Plants and Animals



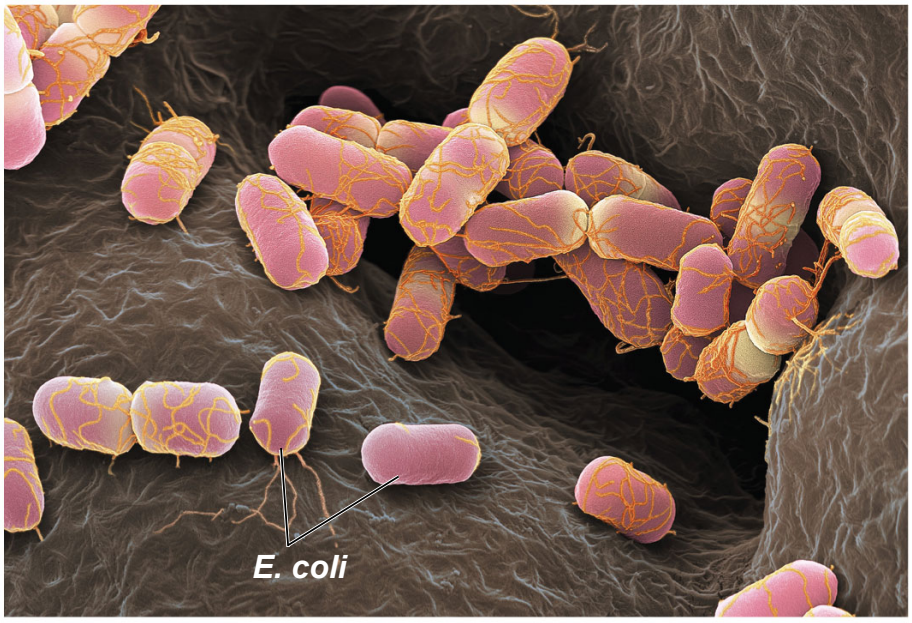
The Genetic Basis of Cancer

CONTROL OF GENE EXPRESSION

Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- **Gene regulation** is the turning on and off of genes.
- **Gene expression** is the overall process of information flow from genes to proteins.
- The control of gene expression allows cells to produce specific kinds of proteins when and where they are needed.
- Our earlier understanding of gene control came from the study of *E. coli*.

Figure 11.1A



Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- A cluster of genes with related functions, along with the control sequences, is called an **operon**.
- With few exceptions, operons only exist in prokaryotes.

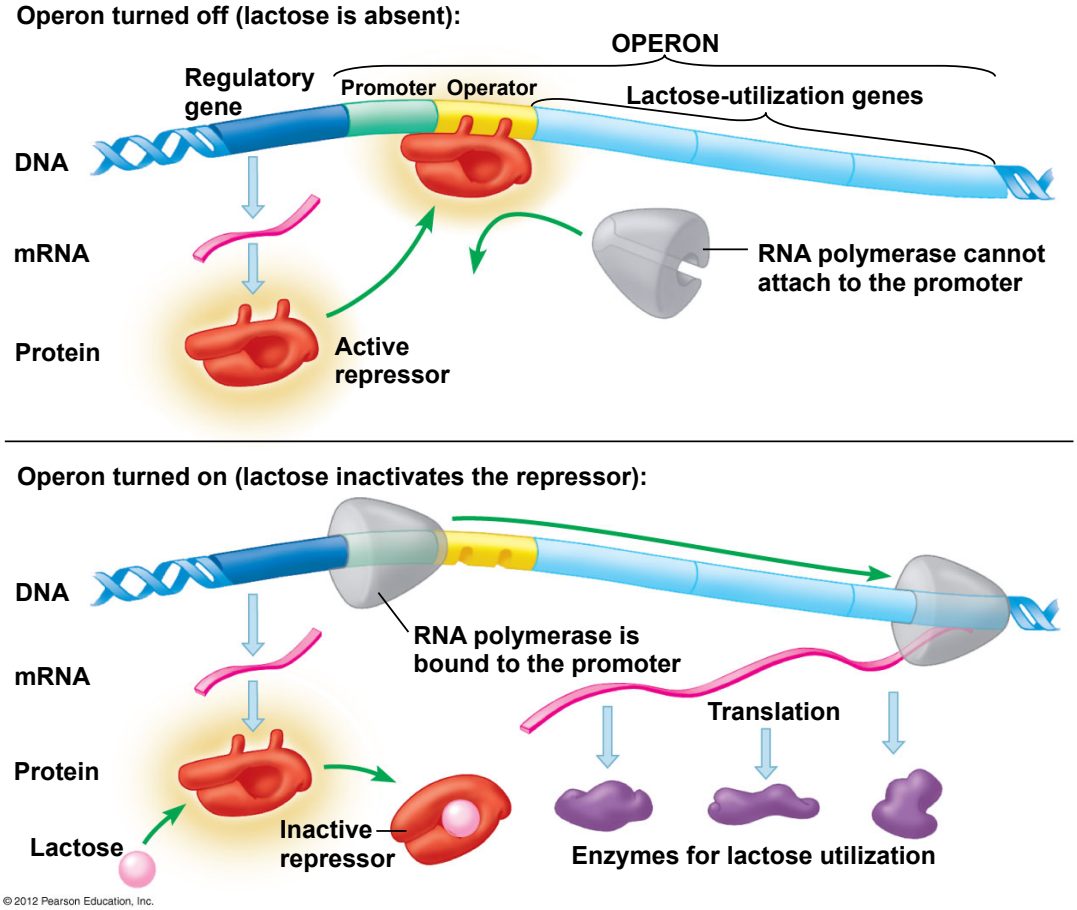
Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- When an *E. coli* encounters lactose, all the enzymes needed for its metabolism are made at once using the lactose operon.
- The lactose (*lac*) operon includes
  1. three adjacent lactose-utilization genes,
  2. a **promoter** sequence where RNA polymerase binds and initiates transcription of all three lactose genes, and
  3. an **operator** sequence where a **repressor** can bind and block RNA polymerase action.

Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- Regulation of the *lac* operon
  - A **regulatory gene**, located outside the operon, codes for a repressor protein.
  - In the absence of lactose, the repressor binds to the operator and prevents RNA polymerase action.
  - Lactose inactivates the repressor, so
    - the operator is unblocked,
    - RNA polymerase can bind to the promoter, and
    - all three genes of the operon are transcribed.

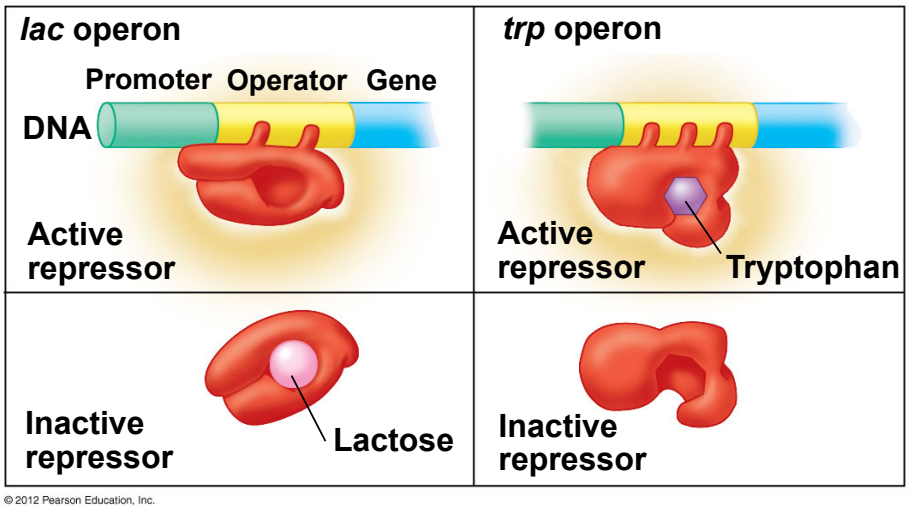
Figure 11.1B



Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- There are two types of repressor-controlled operons.
  - In the *lac* operon, the repressor is
    - active when alone and
    - inactive when bound to lactose.
  - In the *trp* bacterial operon, the repressor is
    - inactive when alone and
    - active when bound to the amino acid tryptophan (Trp).

Figure 11.1C



Proteins interacting with DNA turn prokaryotic genes on or off in response to environmental changes

- Another type of operon control involves **activators,** proteins that turn operons on by
  - binding to DNA and
  - making it easier for RNA polymerase to bind to the promoter.
- Activators help control a wide variety of operons.

Chromosome structure and chemical modifications can affect gene expression

- **Differentiation**
  - involves cell specialization, in structure and function, and
  - is controlled by turning specific sets of genes on or off.
- Almost all of the cells in an organism contain an identical genome.
- The differences between cell types are
  - not due to the presence of different genes but instead
  - due to selective gene expression.

Chromosome structure and chemical modifications can affect gene expression

- Eukaryotic chromosomes undergo multiple levels of folding and coiling, called DNA packing.
  - **Nucleosomes** are formed when DNA is wrapped around **histone** proteins.
    - This packaging gives a “beads on a string” appearance.
    - Each nucleosome bead includes DNA plus eight histones.
    - Stretches of DNA, called linkers, join consecutive nucleosomes.
  - At the next level of packing, the beaded string is wrapped into a tight helical fiber.
  - This fiber coils further into a thick supercoil.
  - Looping and folding can further compact the DNA.

Chromosome structure and chemical modifications can affect gene expression

- DNA packing can prevent gene expression by preventing RNA polymerase and other transcription proteins from contacting the DNA.
- Cells seem to use higher levels of packing for long-term inactivation of genes.
- Highly compacted chromatin, found in varying regions of interphase chromosomes, is generally not expressed at all.

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Chromosome structure and chemical modifications can affect gene expression

- Chemical modification of DNA bases or histone proteins can result in epigenetic inheritance.
  - Certain enzymes can add a methyl group to DNA bases, without changing the sequence of the bases.
  - Individual genes are usually more methylated in cells in which the genes are not expressed. Once methylated, genes usually stay that way through successive cell divisions in an individual.
  - Removal of the extra methyl groups can turn on some of these genes.
  - Inheritance of traits transmitted by mechanisms not directly involving the nucleotide sequence is called **epigenetic inheritance**. These modifications can be reversed by processes not yet fully understood.

Chromosome structure and chemical modifications can affect gene expression

- **X-chromosome inactivation**
  - In female mammals, one of the two X chromosomes is highly compacted and transcriptionally inactive.
  - Either the maternal or paternal chromosome is randomly inactivated.
  - Inactivation occurs early in embryonic development, and all cellular descendants have the same inactivated chromosome.
  - An inactivated X chromosome is called a **Barr body**.
  - Tortoiseshell fur coloration is due to inactivation of X chromosomes in heterozygous female cats.

Figure 11.2A

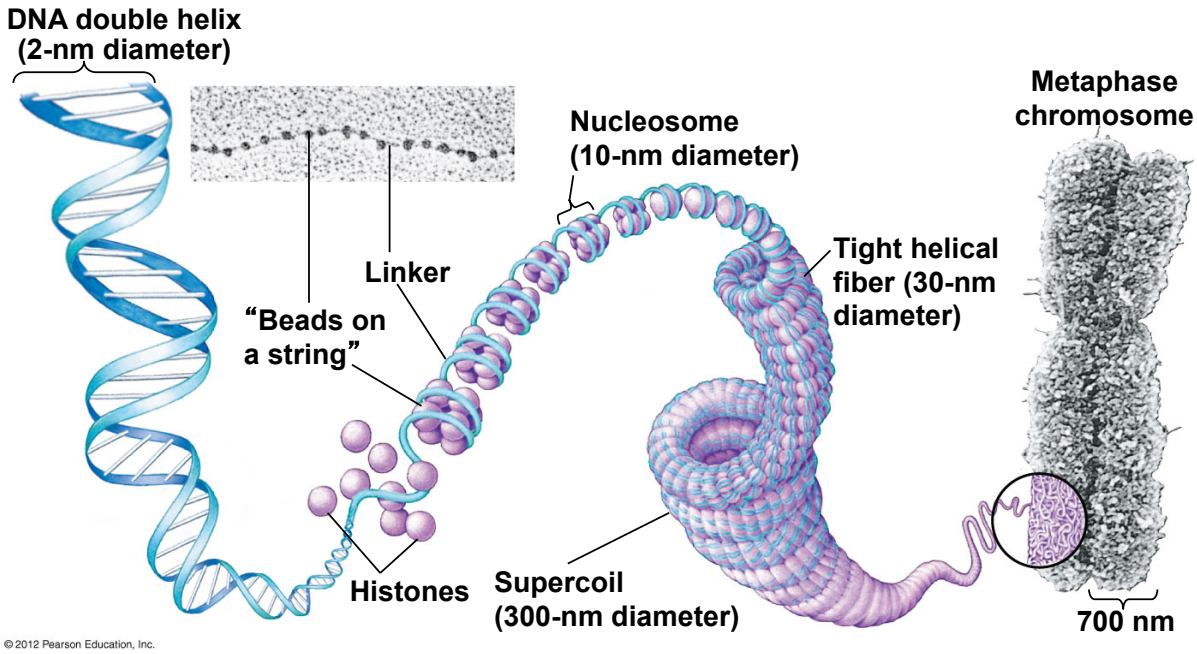
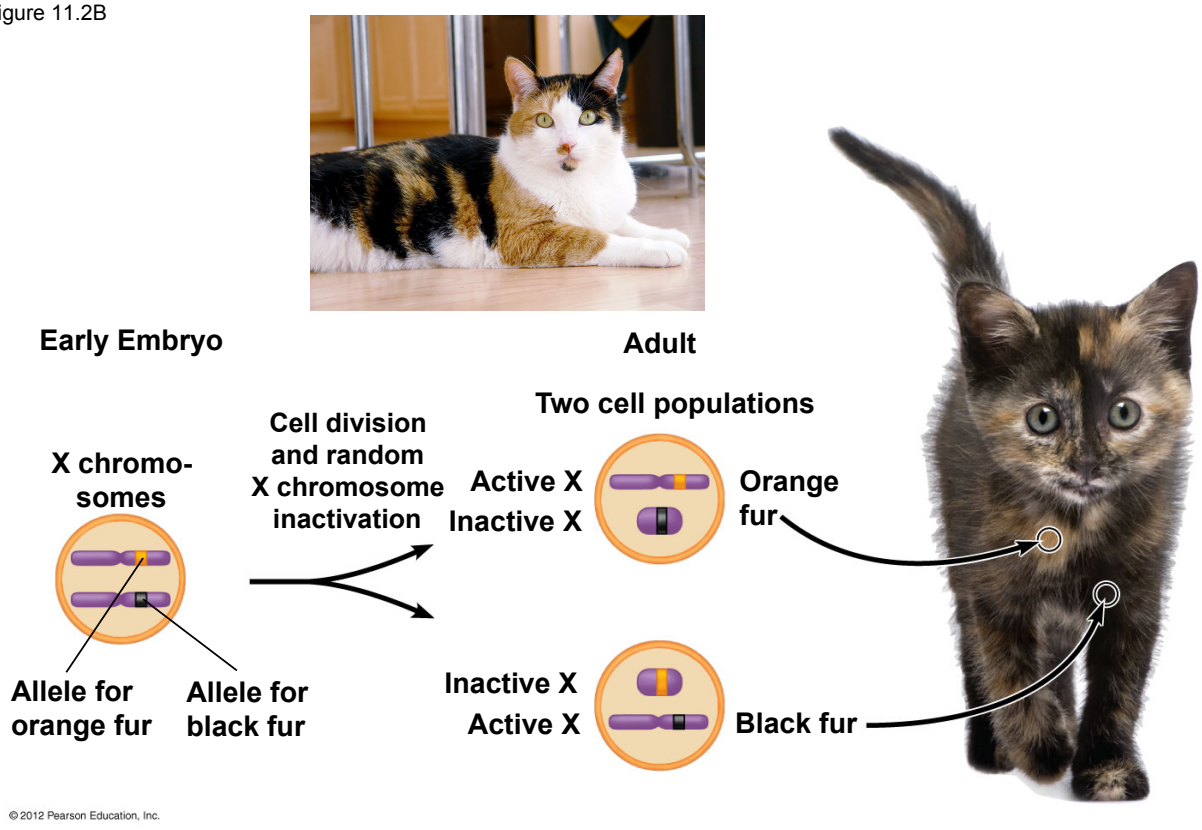


Figure 11.2B



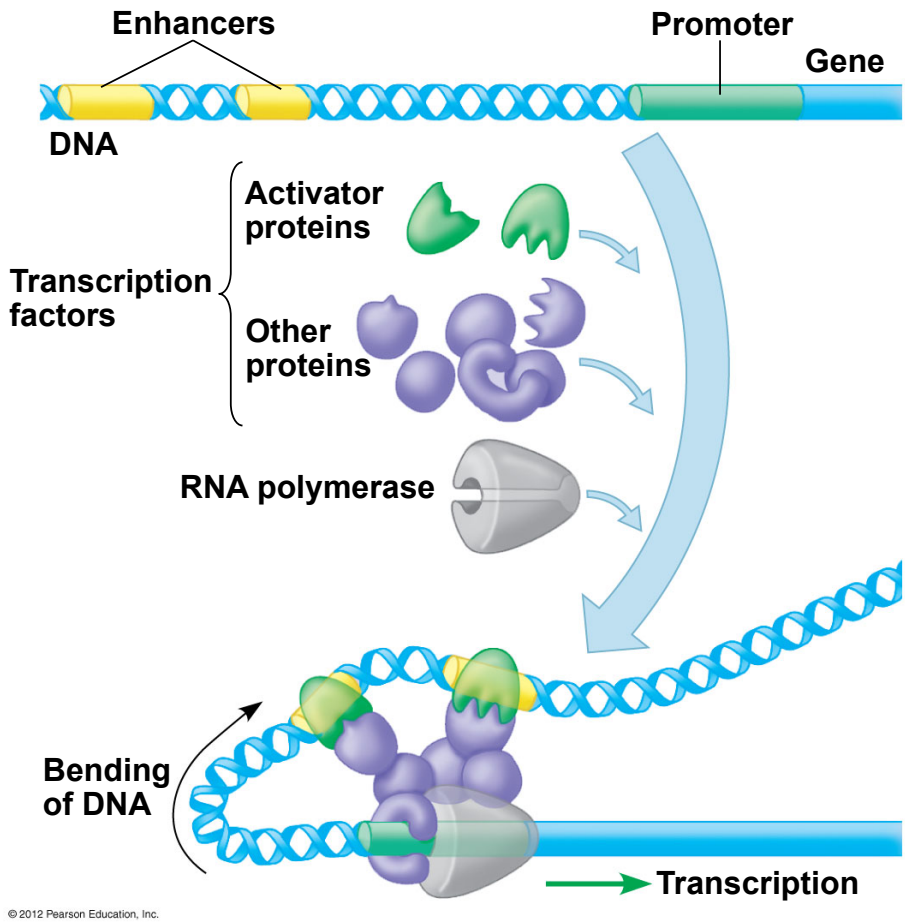
Complex assemblies of proteins control eukaryotic transcription

- Prokaryotes and eukaryotes employ regulatory proteins (activators and repressors) that
  - bind to specific segments of DNA and
  - either promote or block the binding of RNA polymerase, turning the transcription of genes on and off.
- In eukaryotes, activator proteins seem to be more important than repressors. Thus, the default state for most genes seems to be off.
- A typical plant or animal cell needs to turn on and transcribe only a small percentage of its genes.

Complex assemblies of proteins control eukaryotic transcription

- Eukaryotic RNA polymerase requires the assistance of proteins called **transcription factors**. Transcription factors include
  - **activator proteins**, which bind to DNA sequences called enhancers and initiate gene transcription. The binding of the activators leads to bending of the DNA.
  - Other transcription factor proteins interact with the bound activators, which then collectively bind as a complex at the gene's promoter.
- RNA polymerase then attaches to the promoter and transcription begins.

Figure 11.3



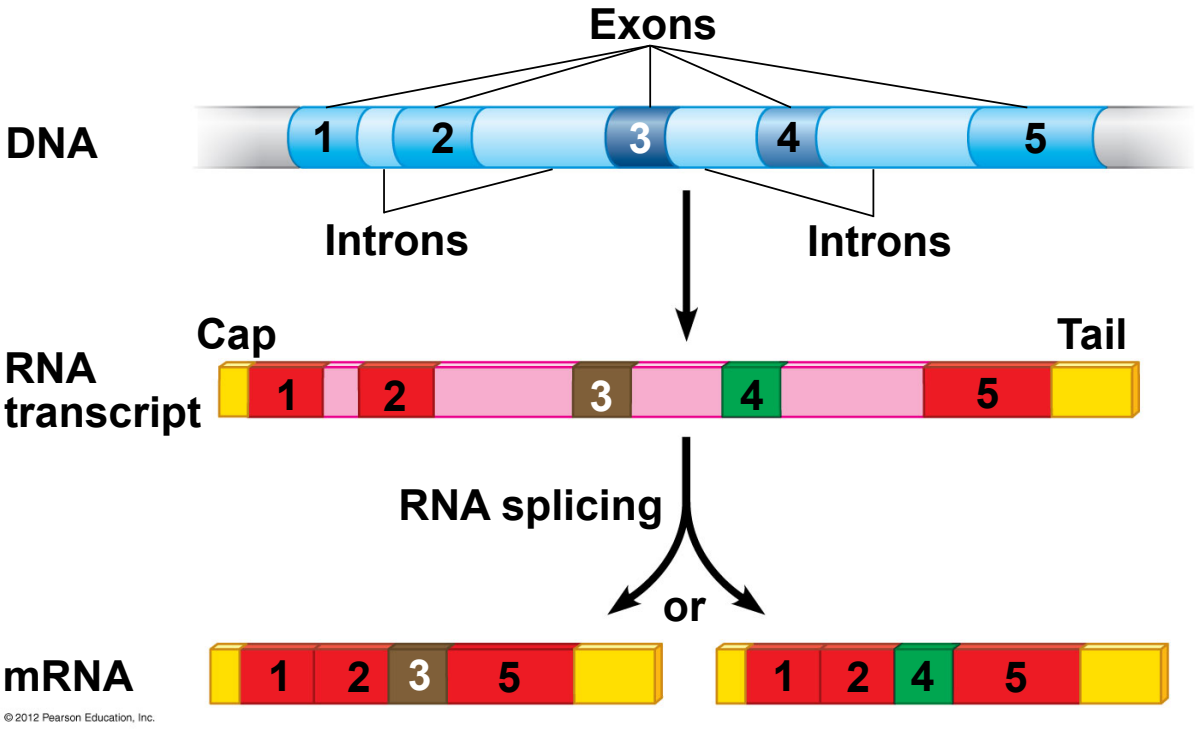
Complex assemblies of proteins control eukaryotic transcription

- **Silencers** are repressor proteins that
  - may bind to DNA sequences and
  - inhibit transcription.
- Coordinated gene expression in eukaryotes often depends on the association of a specific combination of control elements with every gene of a particular metabolic pathway.

Eukaryotic RNA may be spliced in more than one way

- **Alternative RNA splicing**
  - produces different mRNAs from the same transcript,
  - results in the production of more than one polypeptide from the same gene, and
  - may be common in humans.

Figure 11.4



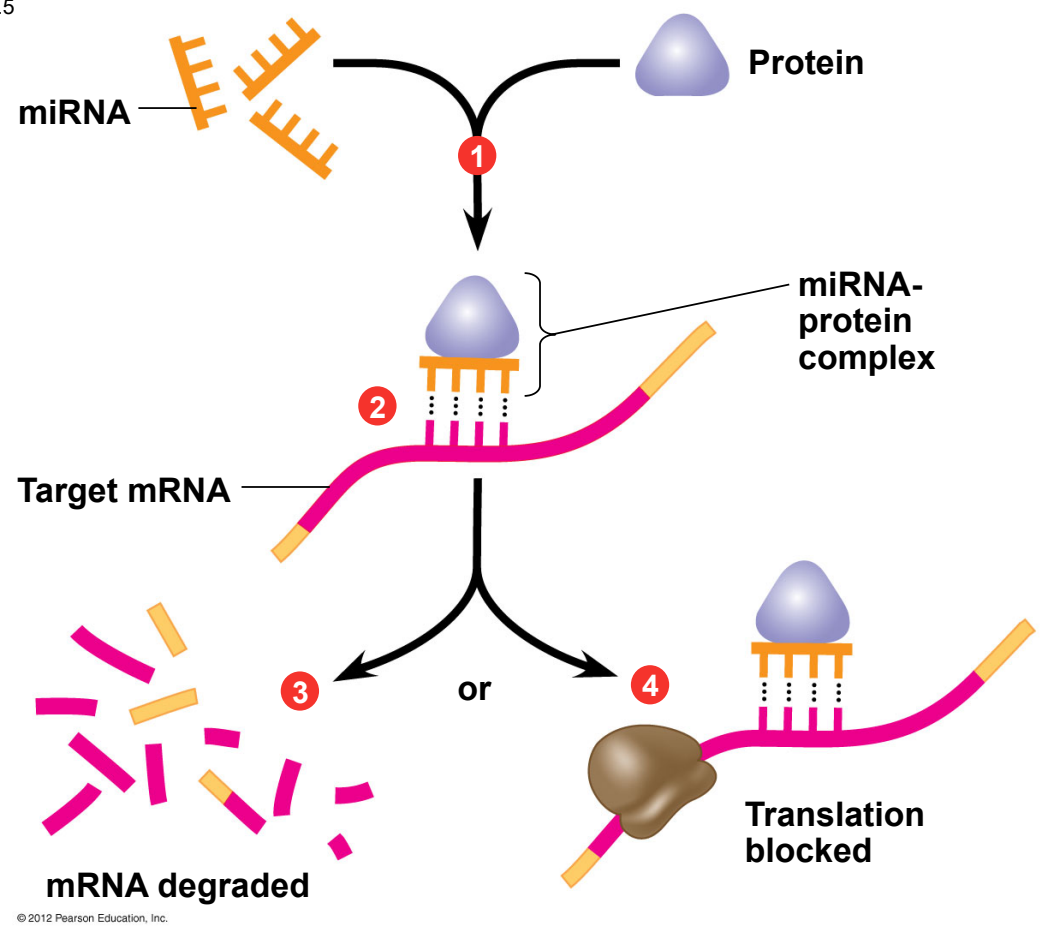
Small RNAs play multiple roles in controlling gene expression

- Only about 1.5% of the human genome codes for proteins. (This is also true of many other multicellular eukaryotes.)
- Another small fraction of DNA consists of genes for ribosomal RNA and transfer RNA.
- A flood of recent data suggests that a significant amount of the remaining genome is transcribed into functioning but non-protein-coding RNAs, including a variety of small RNAs.

Small RNAs play multiple roles in controlling gene expression

- **microRNAs** (**miRNAs**) can bind to complementary sequences on mRNA molecules either
  - degrading the target mRNA or
  - blocking its translation.
- **RNA interference** (**RNAi**) is the use of miRNA to artificially control gene expression by injecting miRNAs into a cell to turn off a specific gene sequence.

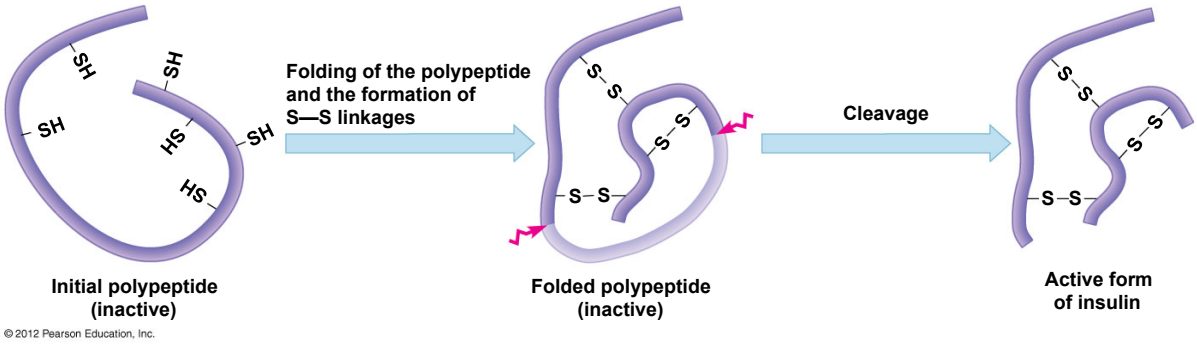
Figure 11.5



Later stages of gene expression are also subject to regulation

- After mRNA is fully processed and transported to the cytoplasm, gene expression can still be regulated by
  - breakdown of mRNA,
  - initiation of translation,
  - protein activation, and
  - protein breakdown.

Figure 11.6



Review: Multiple mechanisms regulate gene expression in eukaryotes

- Multiple control points exist where gene expression in eukaryotes can be
  - turned on or off or
  - speeded up, or slowed down.
- These control points are like a series of pipes carrying water from your local water supply to a faucet in your home. Valves in this series of pipes are like the control points in gene expression.

Figure 11.7_1

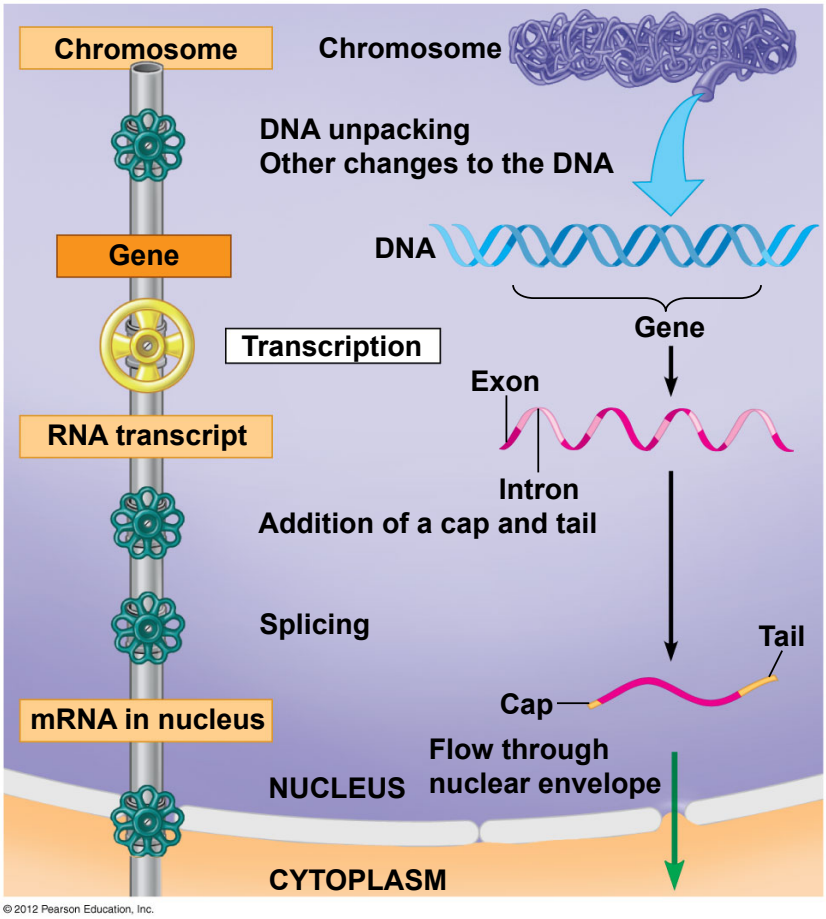
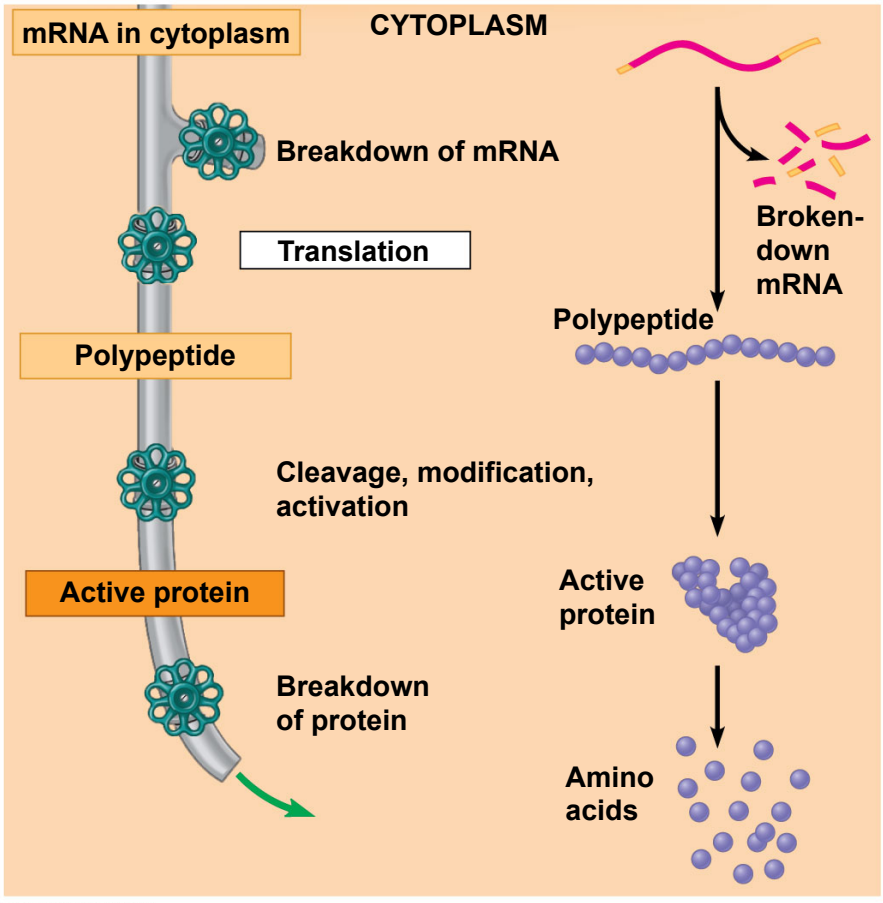


Figure 11.7_2



Cell signaling and cascades of gene expression direct animal development

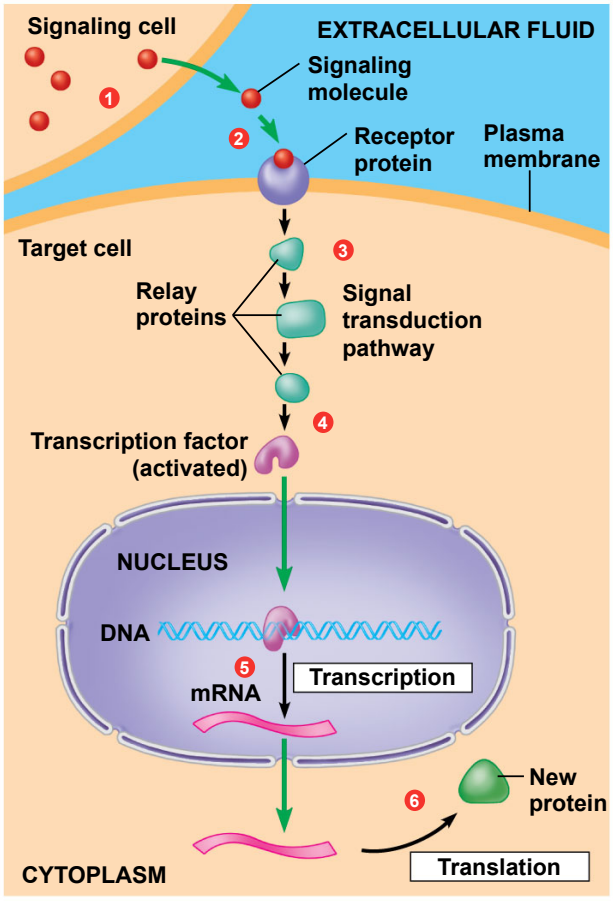
- Early research on gene expression and embryonic development came from studies of a fruit fly, revealing the control of these key events.

1. Orientation of the head-to-tail, top-to-bottom, and side-to-side axes are determined by early genes in the egg that produce proteins and maternal mRNAs.
2. Segmentation of the body is influenced by cascades of proteins that diffuse through the cell layers.
3. Adult features develop under the influence of **homeotic genes**, master control genes that determine the anatomy of the parts of the body.

Signal transduction pathways convert messages received at the cell surface to responses within the cell

- A **signal transduction pathway** is a series of molecular changes that convert a signal on the target cell's surface to a specific response within the cell.
- Signal transduction pathways are crucial to many cellular functions.

Figure 11.10



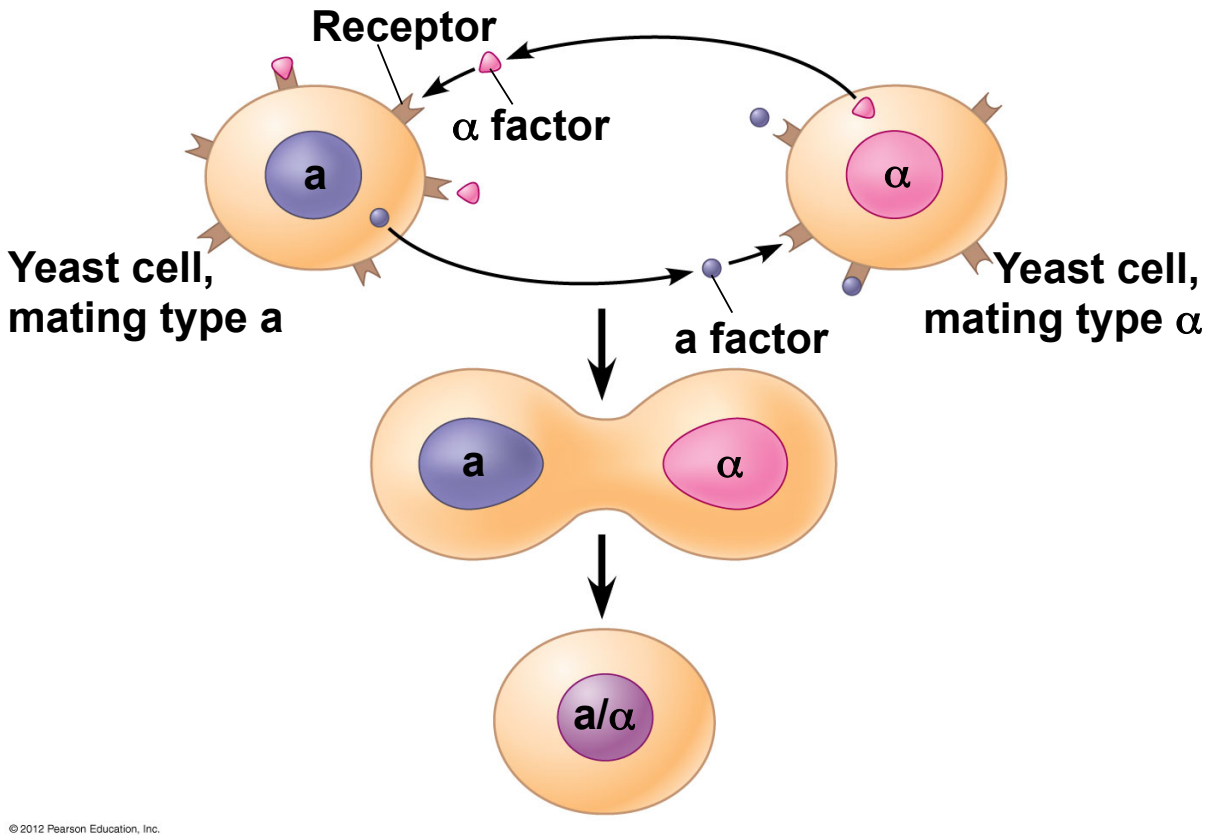
EVOLUTION CONNECTION: Cell-signaling systems appeared early in the evolution of life

- In the yeast used to make bread, beer, and wine, mating is controlled by a signal transduction pathway.
- These yeast cells identify their mates by chemical signaling.

EVOLUTION CONNECTION: Cell-signaling systems appeared early in the evolution of life

- Yeast have two mating types: **a** and α.
  - Each produces a chemical factor that binds to receptors on cells of the opposite mating type.
  - Binding to receptors triggers growth toward the other cell and fusion.
- Cell signaling processes in multicellular organisms are derived from those in unicellular organisms such as bacteria and yeast.

Figure 11.11

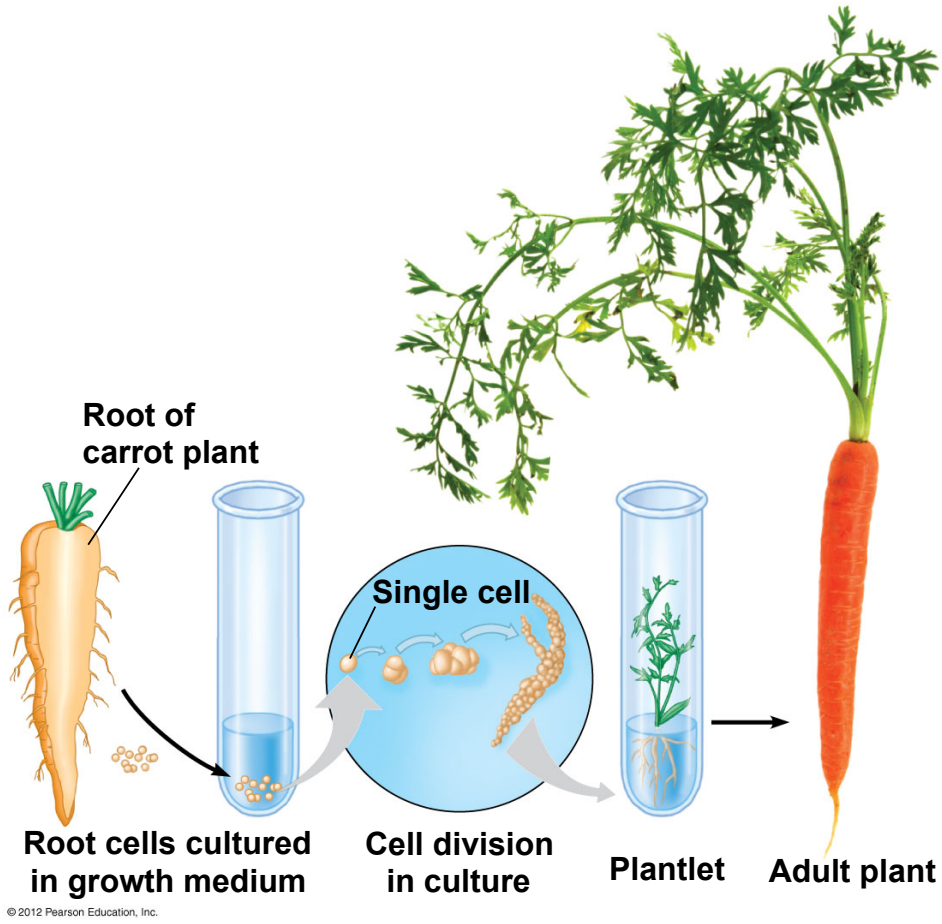


CLONING OF PLANTS AND ANIMALS

Plant cloning shows that differentiated cells may retain all of their genetic potential

- Most differentiated cells retain a full set of genes, even though only a subset may be expressed. Evidence is available from
  - plant cloning, in which a root cell can divide to form an adult plant and
  - salamander limb **regeneration**, in which the cells in the leg stump dedifferentiate, divide, and then redifferentiate, giving rise to a new leg.

Figure 11.12



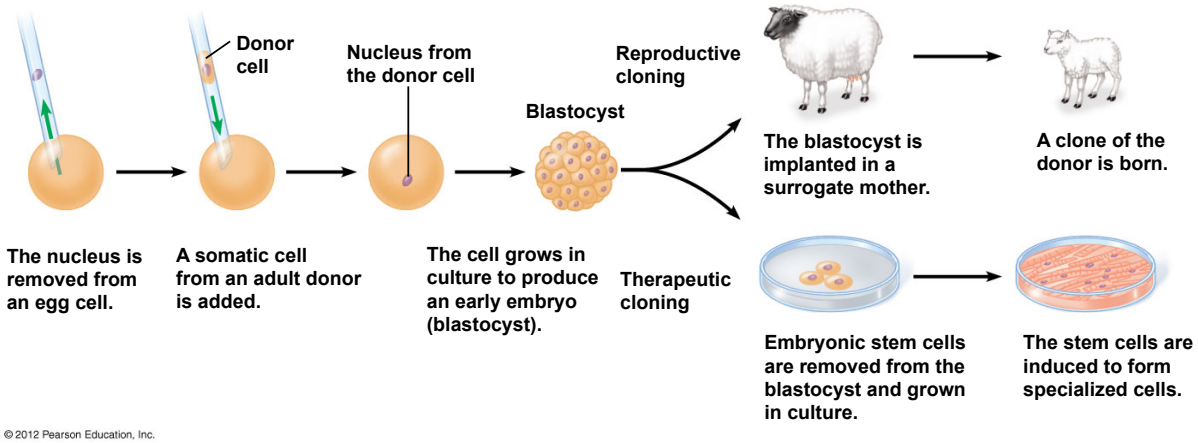
Nuclear transplantation can be used to clone animals

- Animal cloning can be achieved using **nuclear transplantation**, in which the nucleus of an egg cell or zygote is replaced with a nucleus from an adult somatic cell.
- Using nuclear transplantation to produce new organisms is called **reproductive cloning**. It was first used in mammals in 1997 to produce the sheep Dolly.

Nuclear transplantation can be used to clone animals

- Another way to clone uses **embryonic stem** (**ES**) **cells** harvested from a blastocyst. This procedure can be used to produce
  - cell cultures for research or
  - stem cells for therapeutic treatments.

Figure 11.13



CONNECTION: Reproductive cloning has valuable applications, but human reproductive cloning raises ethical issues

- Since Dolly's landmark birth in 1997, researchers have cloned many other mammals, including mice, cats, horses, cows, mules, pigs, rabbits, ferrets, and dogs.
- Cloned animals can show differences in anatomy and behavior due to
  - environmental influences and
  - random phenomena.

CONNECTION: Reproductive cloning has valuable applications, but human reproductive cloning raises ethical issues

- Reproductive cloning is used to produce animals with desirable traits to
  - produce better agricultural products,
  - produce therapeutic agents, and
  - restock populations of endangered animals.
- Human reproductive cloning raises many ethical concerns.

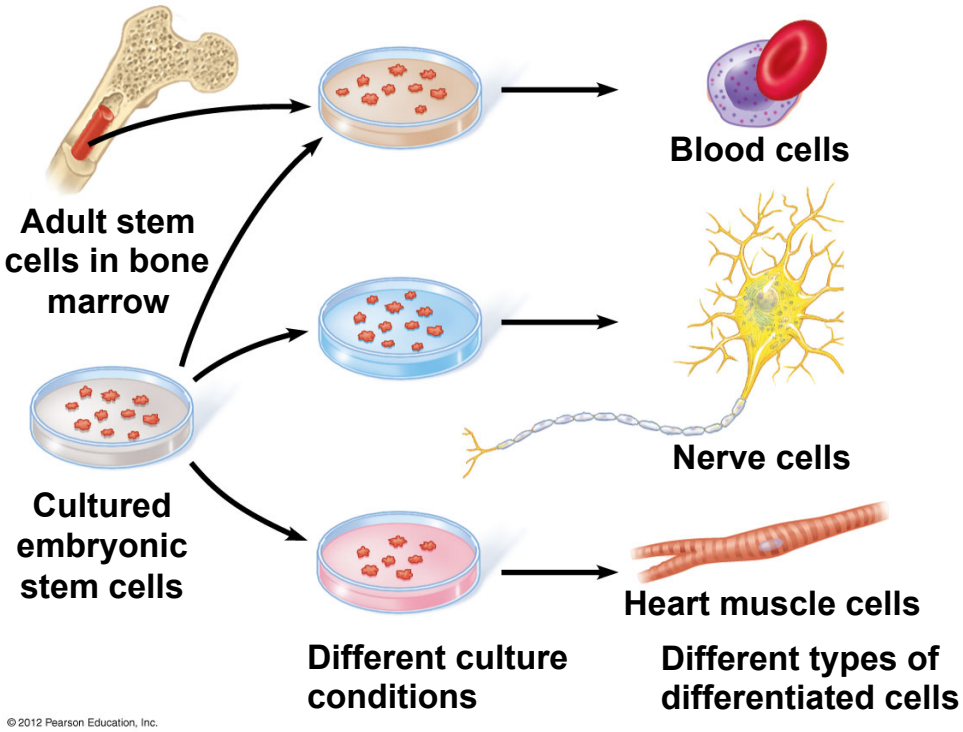
CONNECTION: Therapeutic cloning can produce stem cells with great medical potential

- When grown in laboratory culture, stem cells can
  - divide indefinitely and
  - give rise to many types of differentiated cells.
- **Adult stem cells** can give rise to many, but not all, types of cells.

CONNECTION: Therapeutic cloning can produce stem cells with great medical potential

- Embryonic stem cells are considered more promising than adult stem cells for medical applications.
- The ultimate aim of therapeutic cloning is to supply cells for the repair of damaged or diseased organs.

Figure 11.15



THE GENETIC BASIS OF CANCER

Cancer results from mutations in genes that control cell division

- Mutations in two types of genes can cause cancer.

1. Oncogenes

- **Proto-oncogenes** are normal genes that promote cell division.
- Mutations to proto-oncogenes create cancer-causing **oncogenes** that often stimulate cell division.

2. Tumor-suppressor genes

- Tumor-suppressor genes normally inhibit cell division or function in the repair of DNA damage.
- Mutations inactivate the genes and allow uncontrolled division to occur.

Figure 11.16A

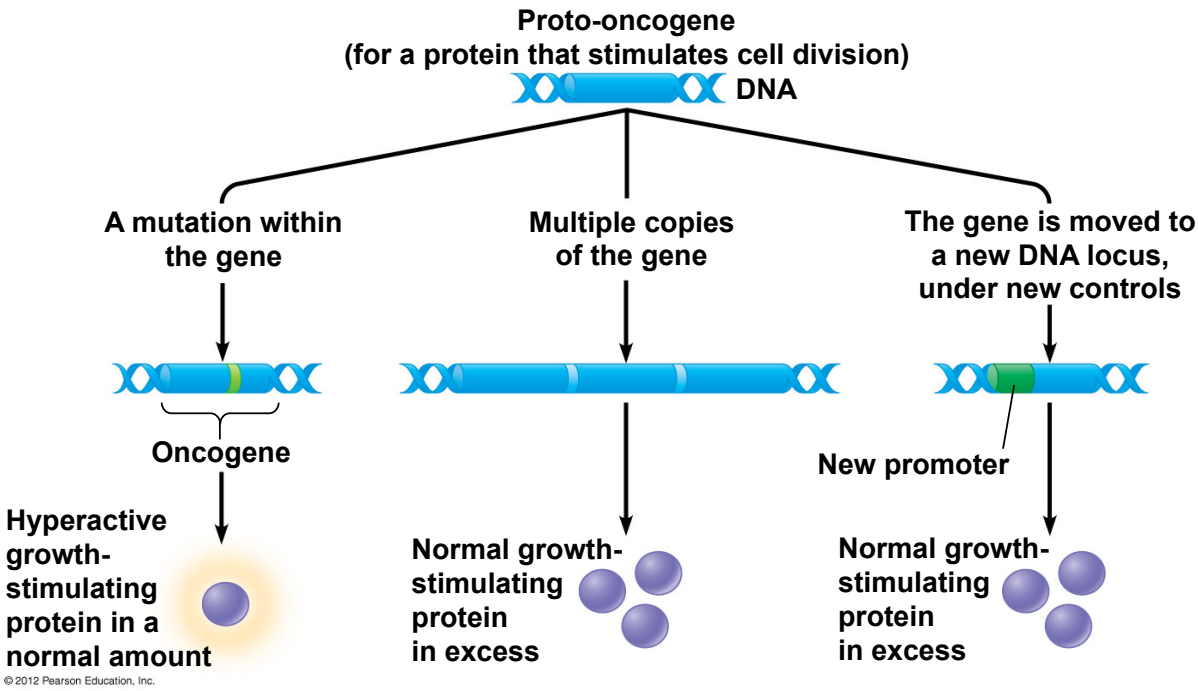
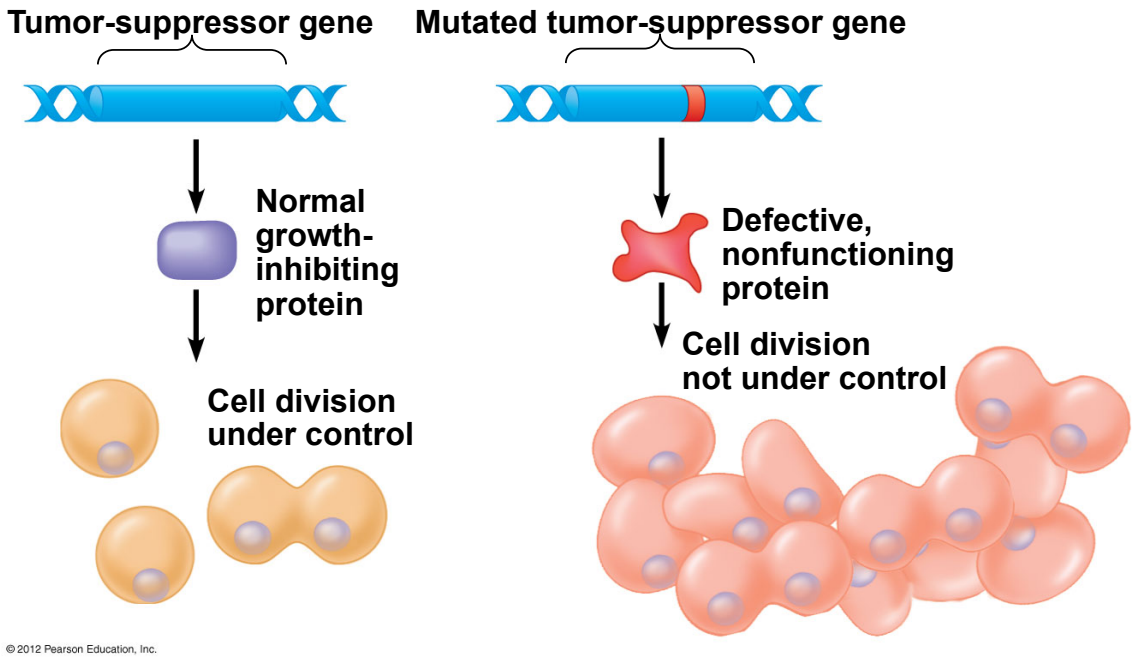


Figure 11.16B



Multiple genetic changes underlie the development of cancer

- Usually four or more somatic mutations are required to produce a full-fledged cancer cell.
- One possible scenario is the stepwise development of colorectal cancer.
  1. An oncogene arises or is activated, resulting in increased cell division in apparently normal cells in the colon lining.
  2. Additional DNA mutations cause the growth of a small benign tumor (polyp) in the colon wall.
  3. Additional mutations lead to a malignant tumor with the potential to metastasize.

Figure 11.17A

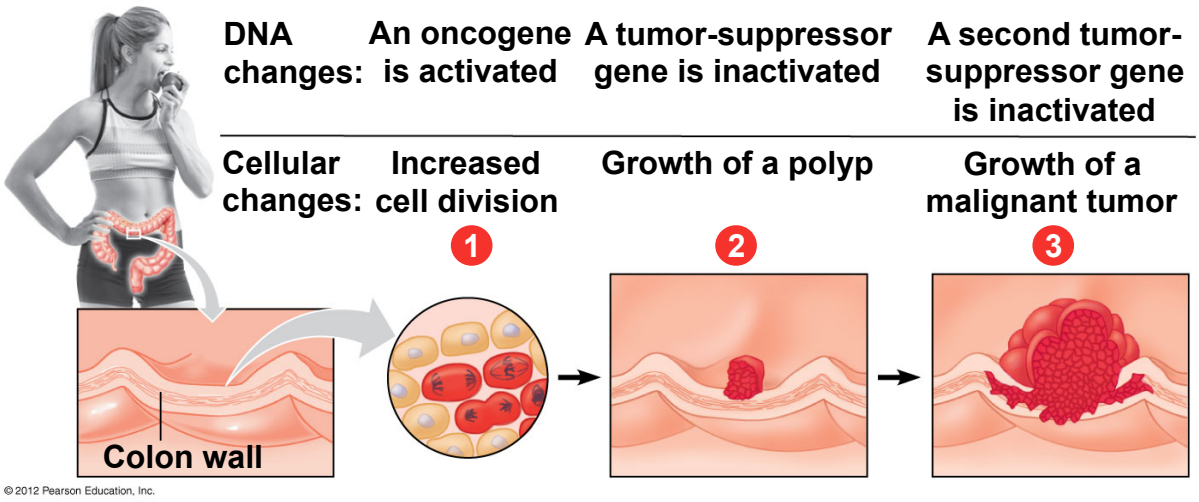
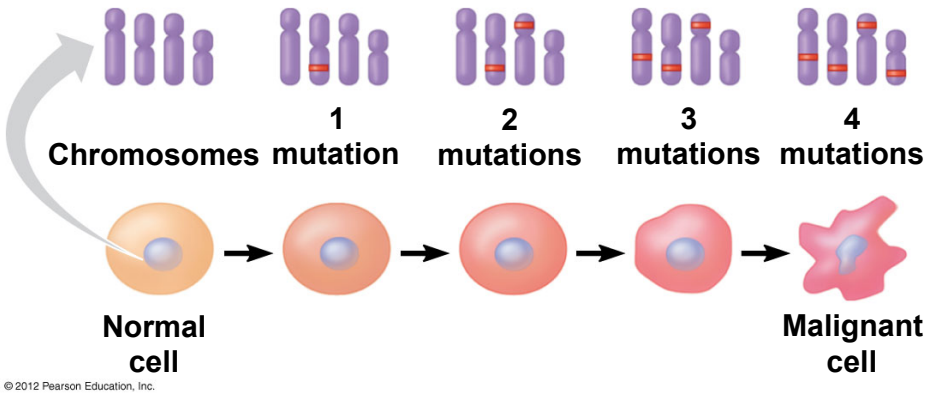


Figure 11.17B



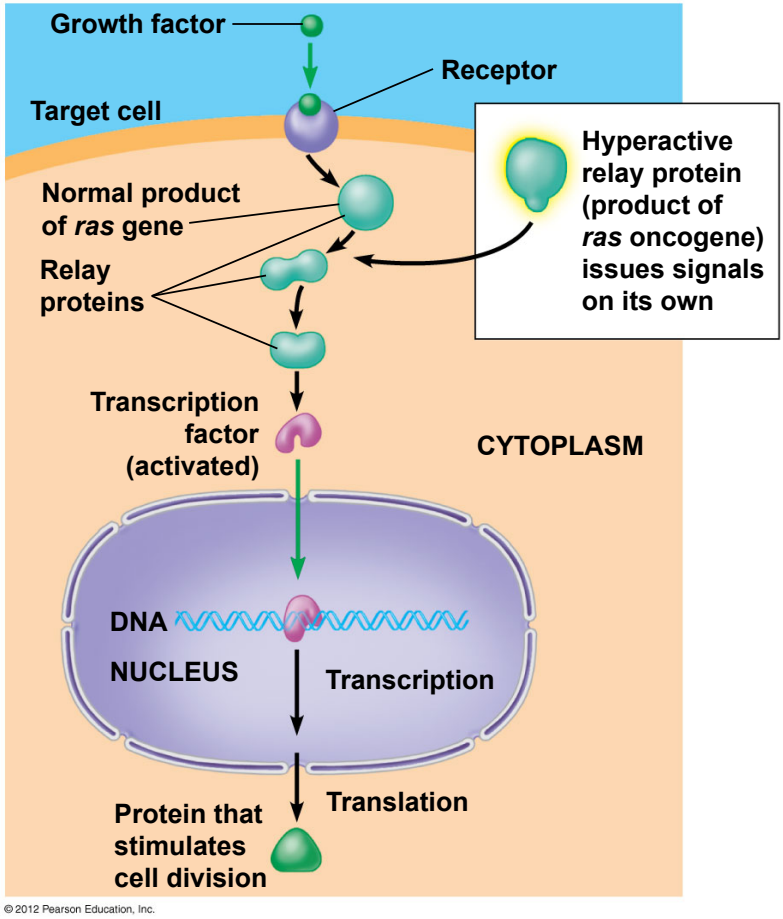
Faulty proteins can interfere with normal signal transduction pathways

- Proto-oncogenes and tumor-suppressor genes often code for proteins involved in signal transduction pathways leading to gene expression.
- Two main types of signal transduction pathways lead to the synthesis of proteins that influence cell division.

Faulty proteins can interfere with normal signal transduction pathways

1. One pathway produces a product that *stimulates* cell division.
   - In a healthy cell, the product of the *ras* proto-oncogene relays a signal when growth factor binds to a receptor.
   - But in a cancerous condition, the product of the *ras* proto-oncogene relays the signal in the absence of a growth factor, leading to uncontrolled growth.
   - Mutations in *ras* occur in more than 30% of human cancers.

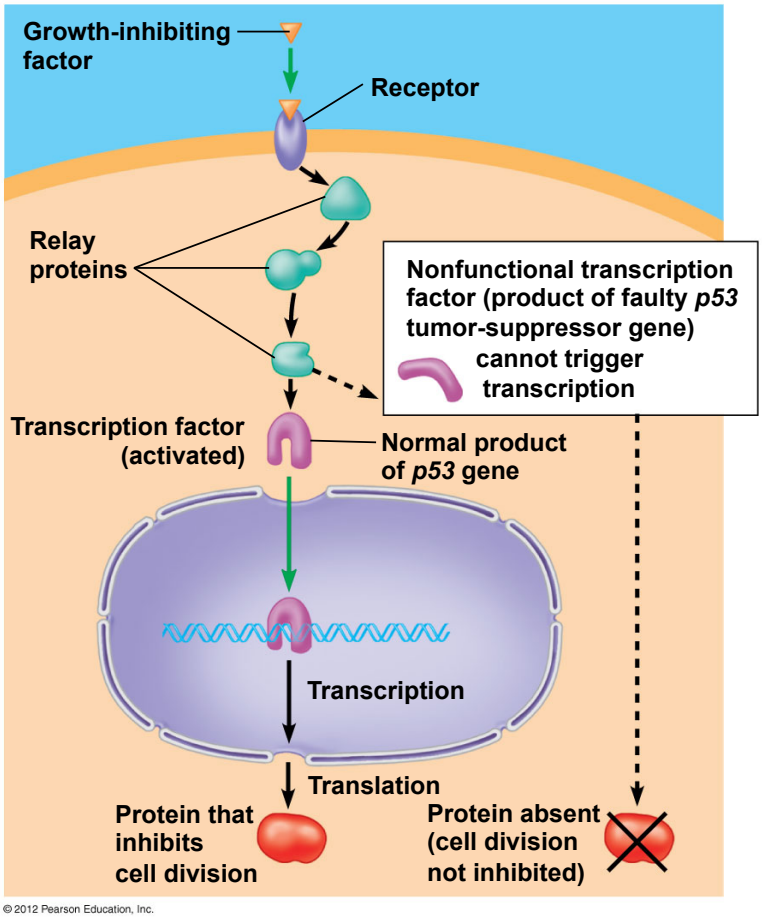
Figure 11.18A



Faulty proteins can interfere with normal signal transduction pathways

2. A second pathway produces a product that *inhibits* cell division.
   - The normal product of the *p53* gene is a transcription factor that normally activates genes for factors that inhibit cell division.
   - In the absence of functional *p53*, cell division continues because the inhibitory protein is not produced.
   - Mutations in *p53* occur in more than 50% of human cancers.

Figure 11.18B



CONNECTION: Lifestyle choices can reduce the risk of cancer

- After heart disease, cancer is the second-leading cause of death in most industrialized nations.
- Cancer can run in families if an individual inherits an oncogene or a mutant allele of a tumor-suppressor gene that makes cancer one step closer.
- But most cancers cannot be associated with an inherited mutation.

CONNECTION: Lifestyle choices can reduce the risk of cancer

- **Carcinogens** are cancer-causing agents that alter DNA.
- Most mutagens (substances that promote mutations) are carcinogens.
- Two of the most potent carcinogens (mutagens) are
  - X-rays and
  - ultraviolet radiation in sunlight.

CONNECTION: Lifestyle choices can reduce the risk of cancer

- The one substance known to cause more cases and types of cancer than any other single agent is tobacco.
  - More people die of lung cancer than any other form of cancer.
  - Although most tobacco-related cancers come from smoking, passive inhalation of second-hand smoke is also a risk.
  - Tobacco use, sometimes in combination with alcohol consumption, causes cancers in addition to lung cancer.

CONNECTION: Lifestyle choices can reduce the risk of cancer

- Healthy lifestyles that reduce the risks of cancer include
  - avoiding carcinogens, including the sun and tobacco products,
  - exercising adequately,
  - regular medical checks for common types of cancer, and
  - a healthy high-fiber, low-fat diet including plenty of fruits and vegetables.

Table 11.19

TABLE 11.19 | CANCER IN THE UNITED STATES

Cancer	Risk Factors	Estimated Number of Cases in 2010
Lung	Tobacco smoke	222,520
Prostate	African heritage; possibly dietary fat	217,730
Breast	Estrogen	209,060
Colon, rectum	High dietary fat; tobacco smoke; alcohol	142,570
Lymphomas	Viruses (for some types)	74,030
Urinary bladder	Tobacco smoke	70,530
Melanoma of the skin	Ultraviolet light	68,130
Kidney	Tobacco smoke	58,240
Uterus	Estrogen	43,470
Pancreas	Tobacco smoke; obesity	43,140
Leukemias	X-rays; benzene; virus (for one type)	43,050
Oral cavity	Tobacco in various forms; alcohol	36,540
Liver	Alcohol; hepatitis viruses	24,120
Brain and nerve	Trauma; X-rays	22,020
Ovary	Obesity; many ovulation cycles	21,880
Stomach	Table salt; tobacco smoke	21,000
Cervix	Sexually transmitted viruses; tobacco smoke	12,200
All others		199,330