CAMPBELL BIOLOGY IN FOCUS

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16

Development, Stem Cells, and Cancer

Lecture Presentations by
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SECOND EDITION

Overview: Orchestrating Life's Processes

- The development of a fertilized egg into an adult requires a precisely regulated program of gene expression
- Understanding this program has progressed mainly by studying **model organisms**
- Stem cells are key to the developmental process
- Orchestrating proper gene expression by all cells is crucial for life

Concept 16.1: A program of differential gene expression leads to the different cell types in a multicellular organism

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

A Genetic Program for Embryonic Development

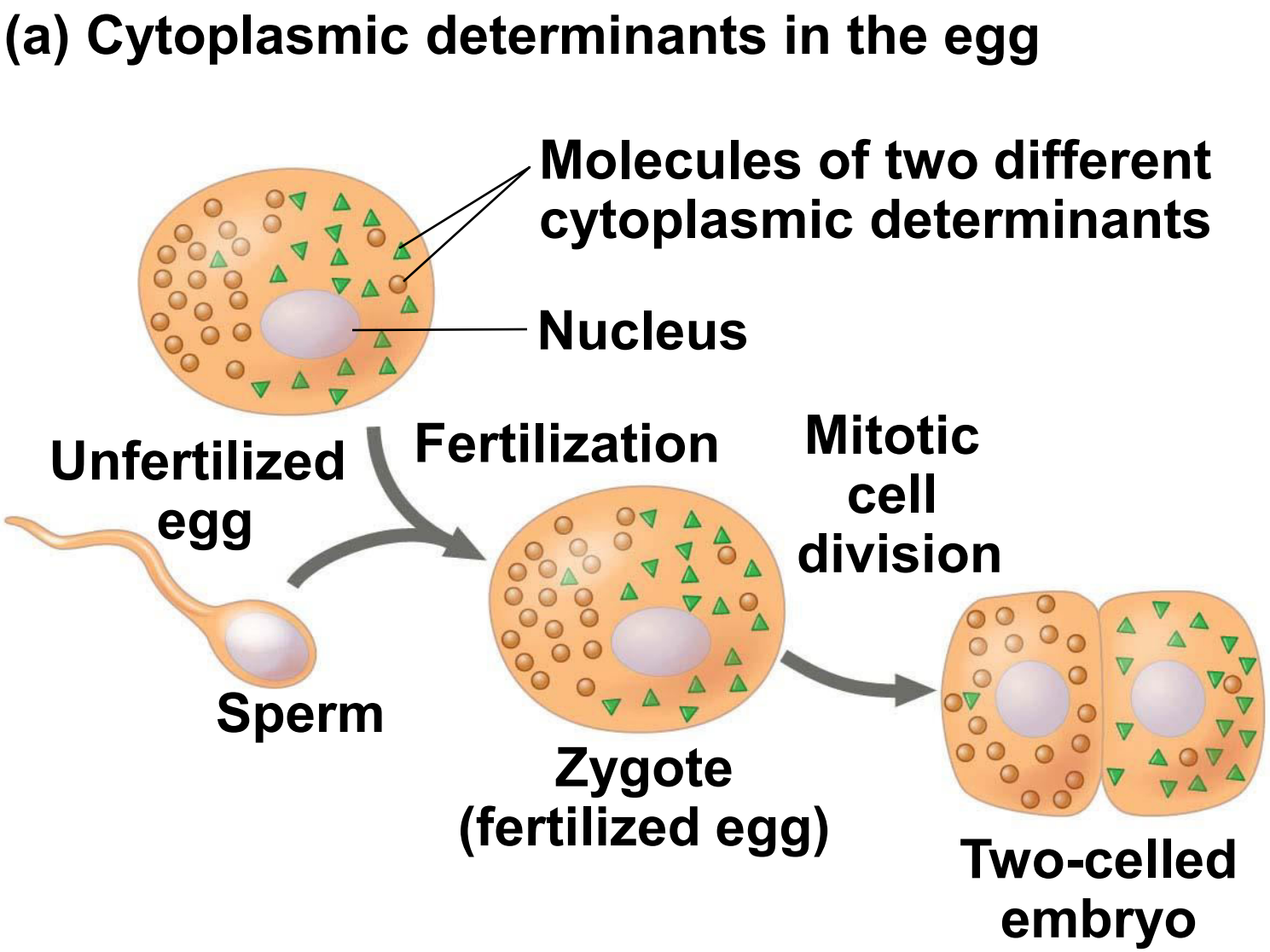
- The transformation from zygote to adult results from cell division, cell differentiation, and morphogenesis

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

Cytoplasmic Determinants and Inductive Signals

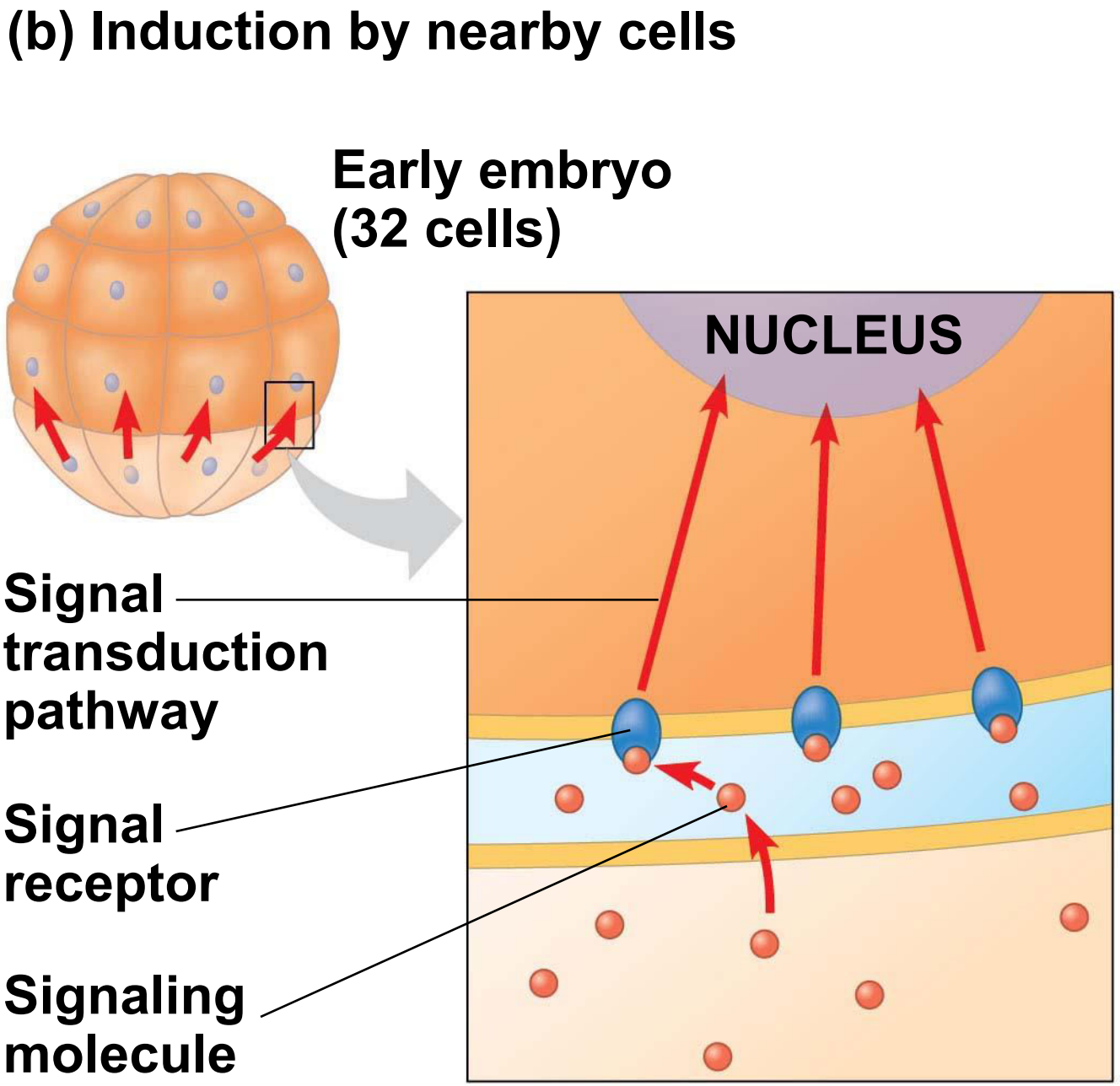
- An egg's cytoplasm contains RNA, proteins, and other substances that are distributed unevenly in the unfertilized egg
- **Cytoplasmic determinants** are maternal substances in the egg that influence early development
- As the zygote divides by mitosis, the resulting cells contain different cytoplasmic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

Figure 16.3-1



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

Figure 16.3-2



Sequential Regulation of Gene Expression During Cellular Differentiation

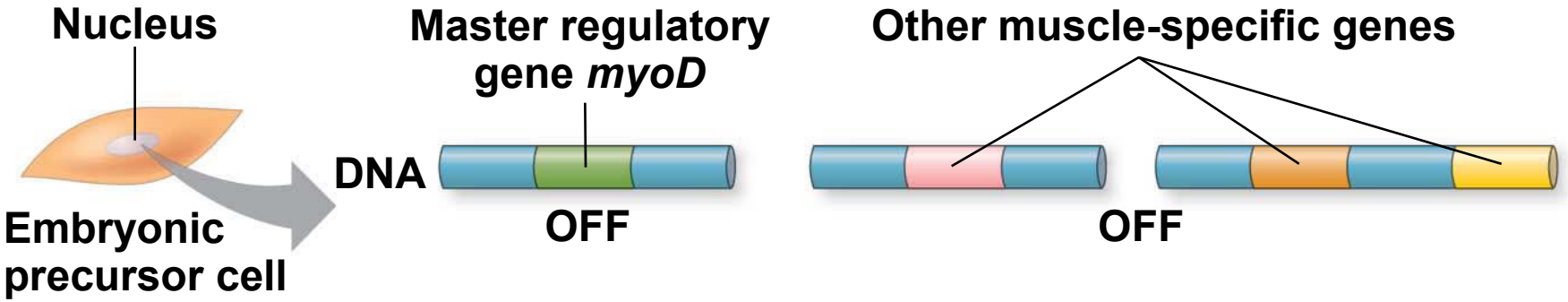
- **Determination** commits a cell irreversibly to its final fate
- Determination precedes differentiation, the process by which a cell attains its determined fate

Differentiation of Cell Types

- Today, determination is understood in terms of molecular changes, the expression of genes for tissue-specific proteins
- The first evidence of differentiation is the production of mRNAs for these proteins
- Eventually, differentiation is observed as changes in cellular structure

- To study muscle cell determination, researchers grew embryonic precursor cells in culture and analyzed them
- They identified several “master regulatory genes,” the products of which commit the cells to becoming skeletal muscle
- One such gene is called *myoD*

Figure 16.4-s1



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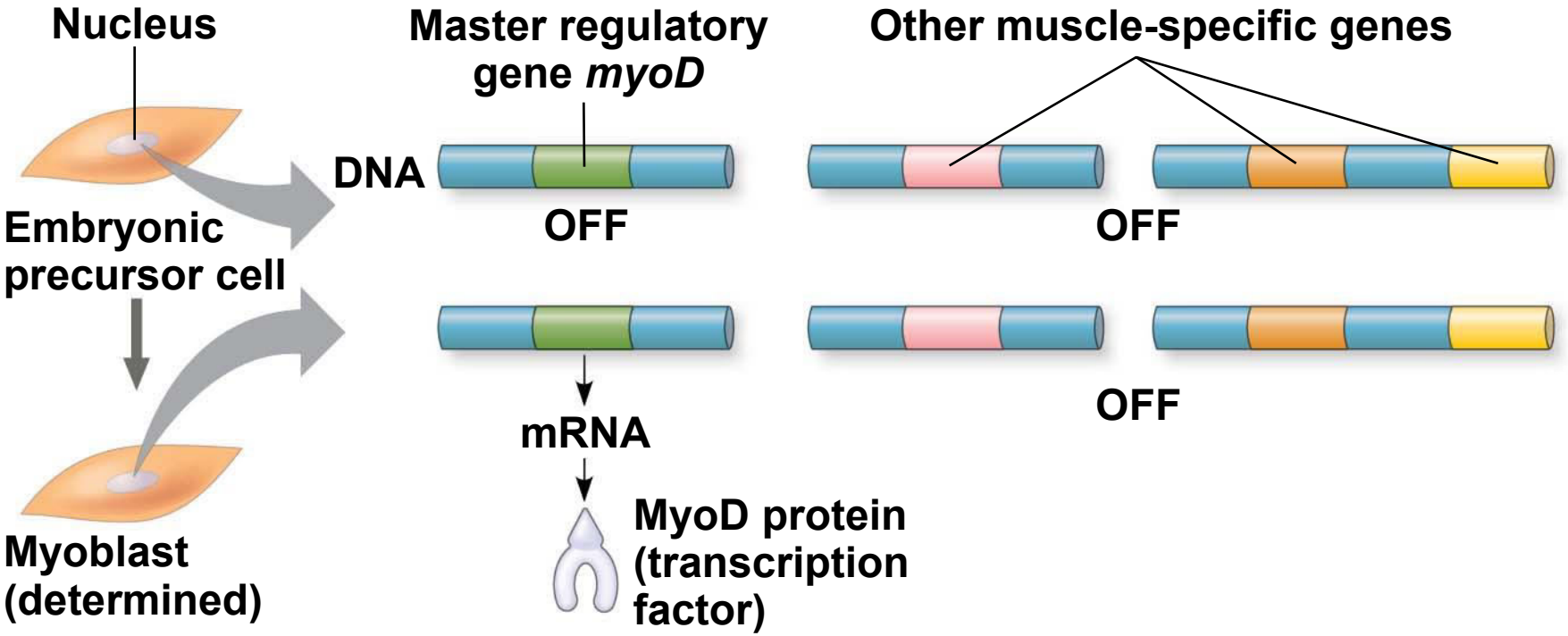

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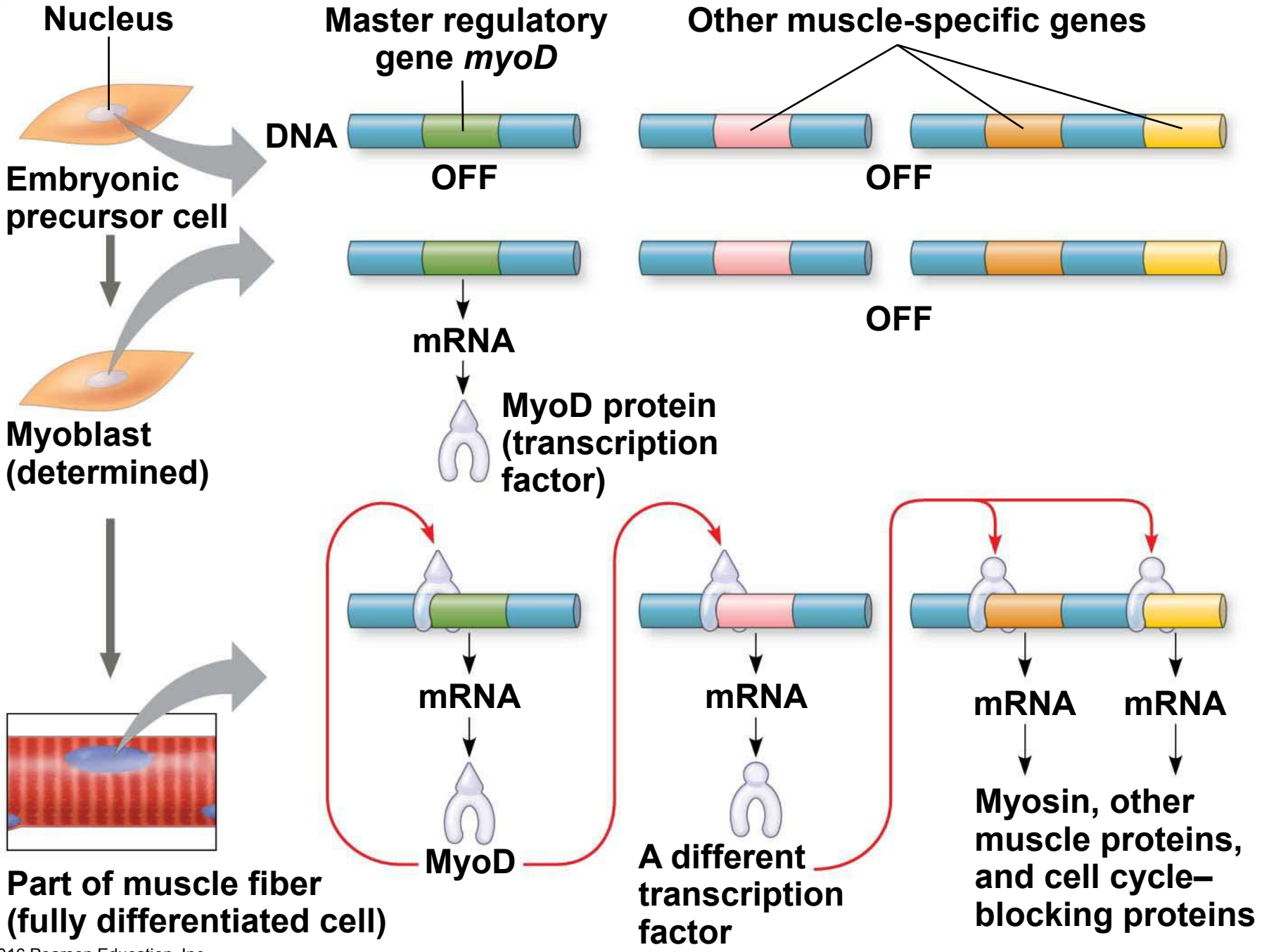
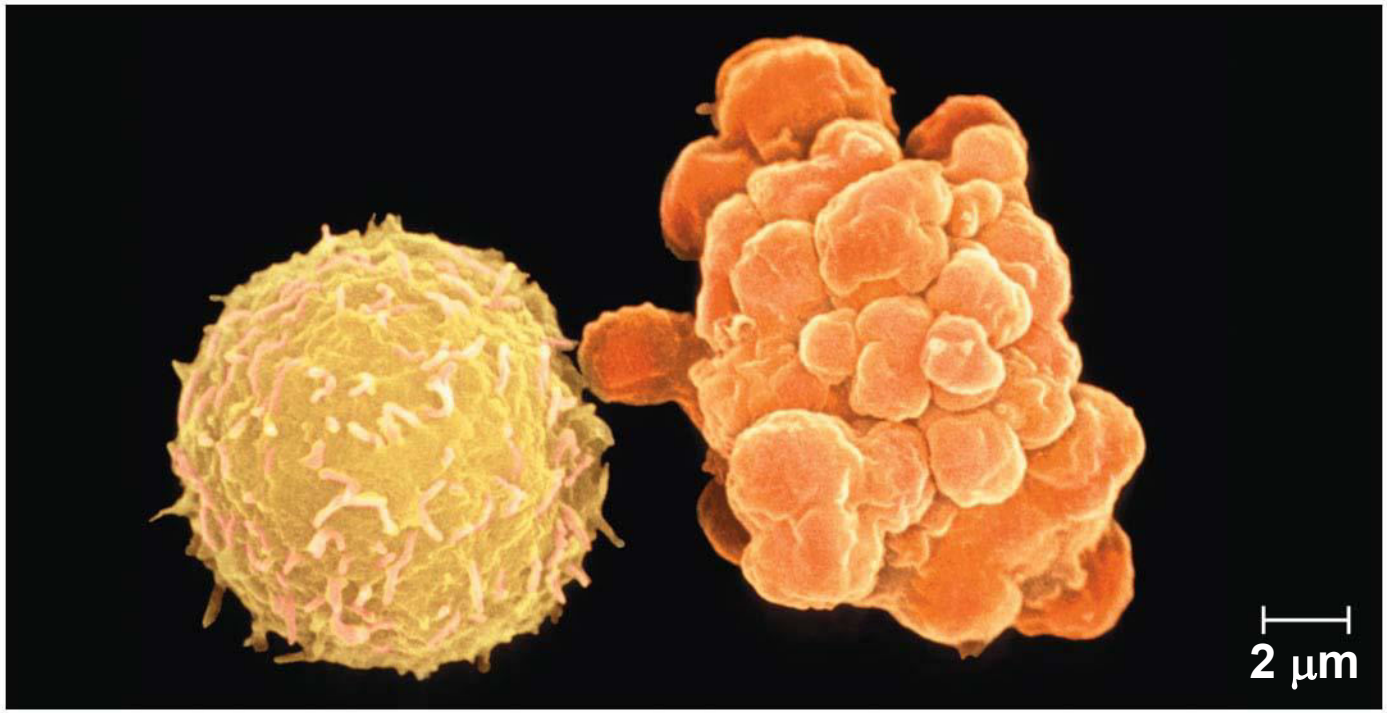


Apoptosis: A Type of Programmed Cell Death

- While most cells are differentiating in a developing organism, some are genetically programmed to die
- **Apoptosis** is the best-understood type of "programmed cell death"
- Apoptosis also occurs in the mature organism in cells that are infected, damaged, or at the end of their functional lives

- During apoptosis, DNA is broken up and organelles and other cytoplasmic components are fragmented
- The cell becomes multilobed and its contents are packaged up in vesicles
- These vesicles are then engulfed by scavenger cells
- Apoptosis protects neighboring cells from damage by nearby dying cells

Figure 16.5



- Apoptosis is essential to development and maintenance in all animals
- It is known to occur also in fungi and yeasts
- In vertebrates, apoptosis is essential for normal nervous system development and morphogenesis of hands and feet (or paws)

Figure 16.6

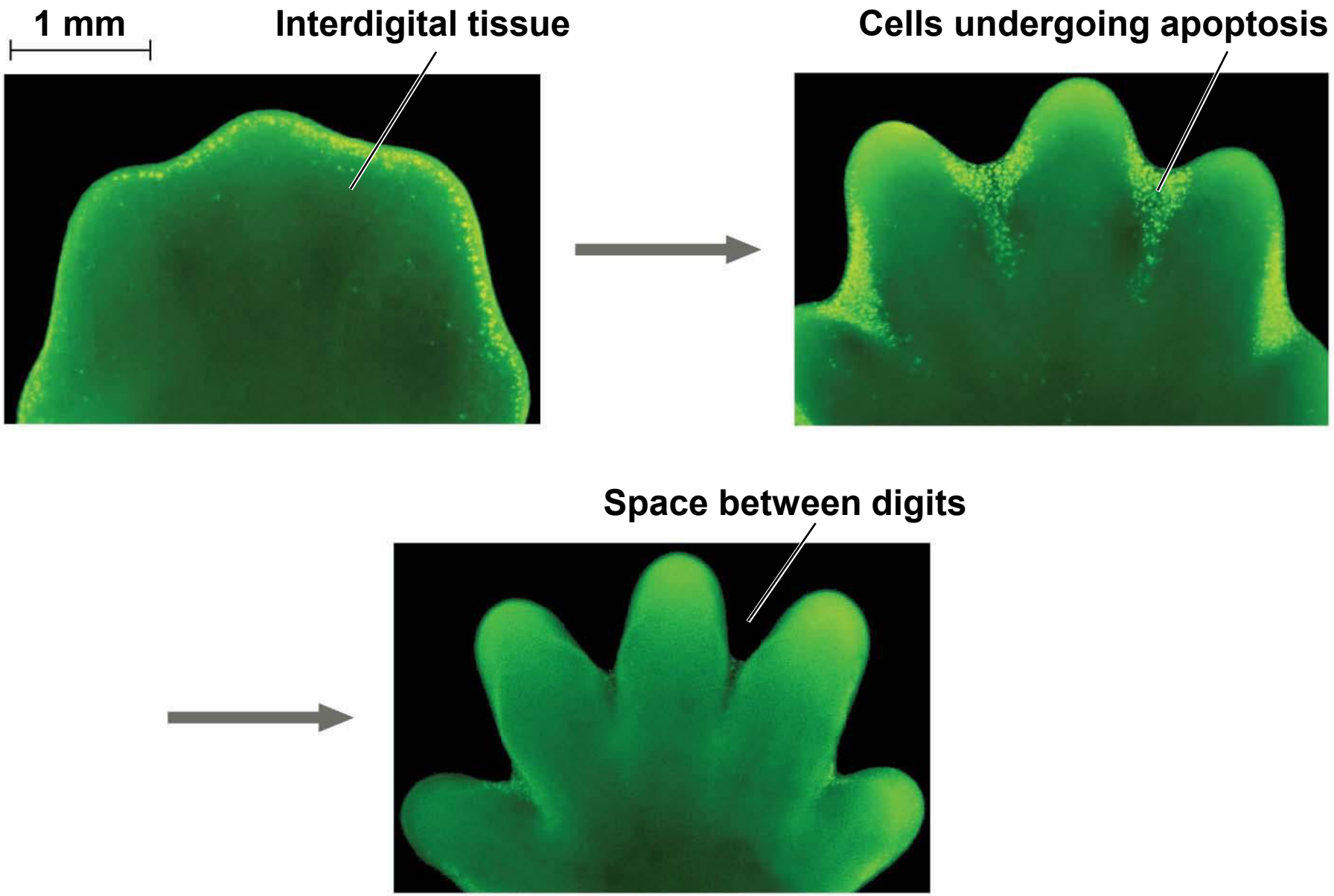
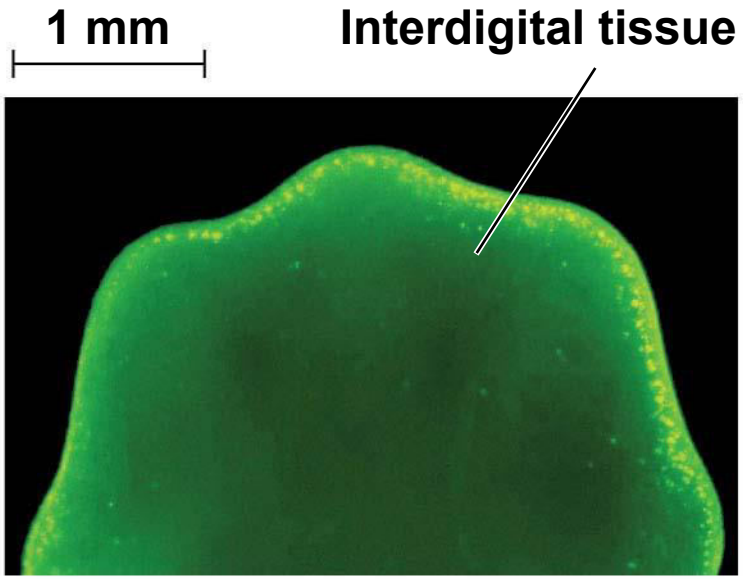


Figure 16.6-1



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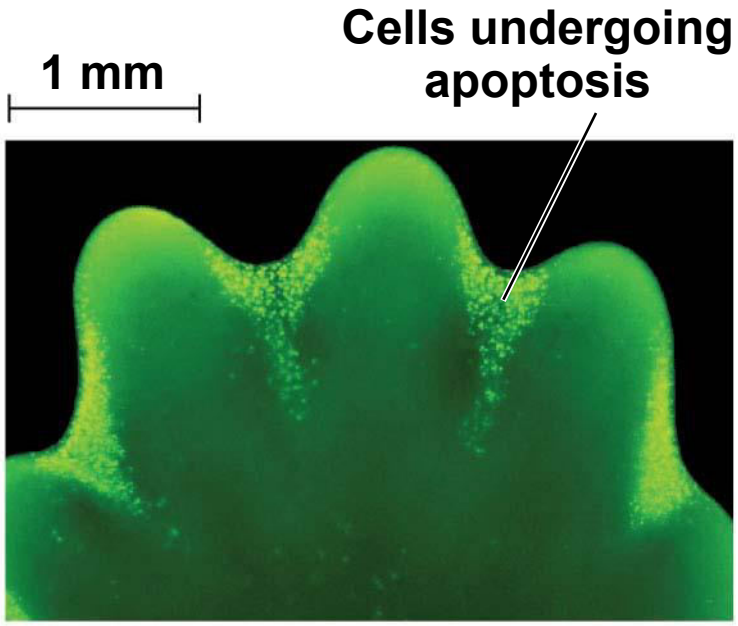
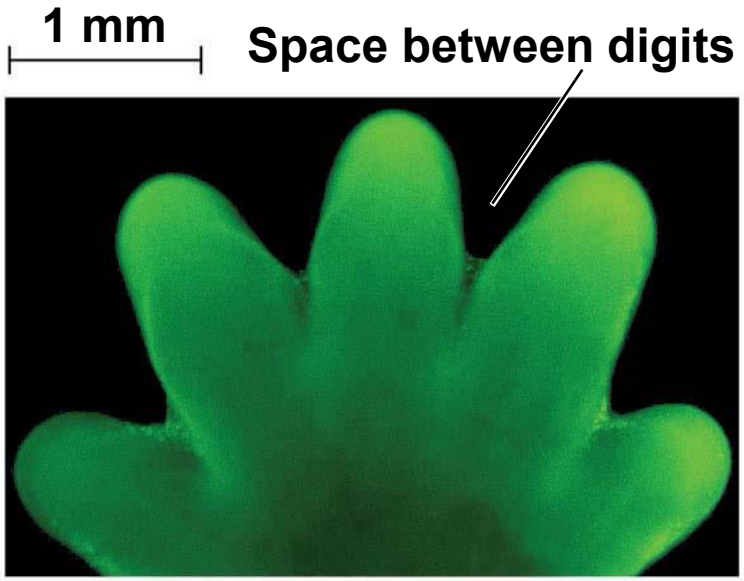


Figure 16.6-3



Pattern Formation: Setting Up the Body Plan

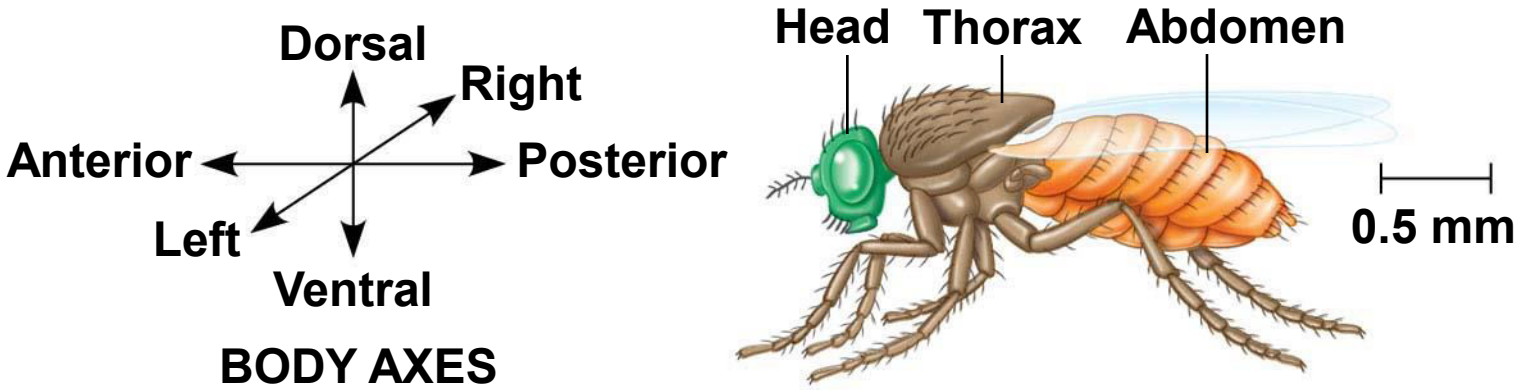
- **Pattern formation** is the development of a spatial organization of tissues and organs
- In animals, pattern formation begins with the establishment of the major axes
- **Positional information**, the molecular cues that control pattern formation, tells a cell its location relative to the body axes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

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

The Life Cycle of Drosophila

- Fruit flies and other arthropods have a modular structure, composed of an ordered series of segments
- In *Drosophila*, cytoplasmic determinants in the unfertilized egg determine the axes before fertilization

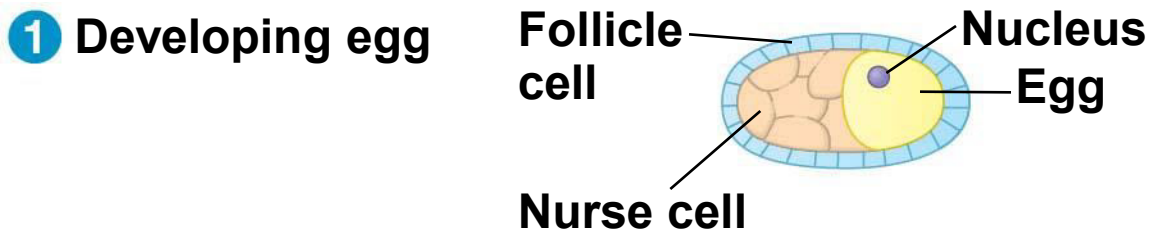
Figure 16.7-1



(a) Adult

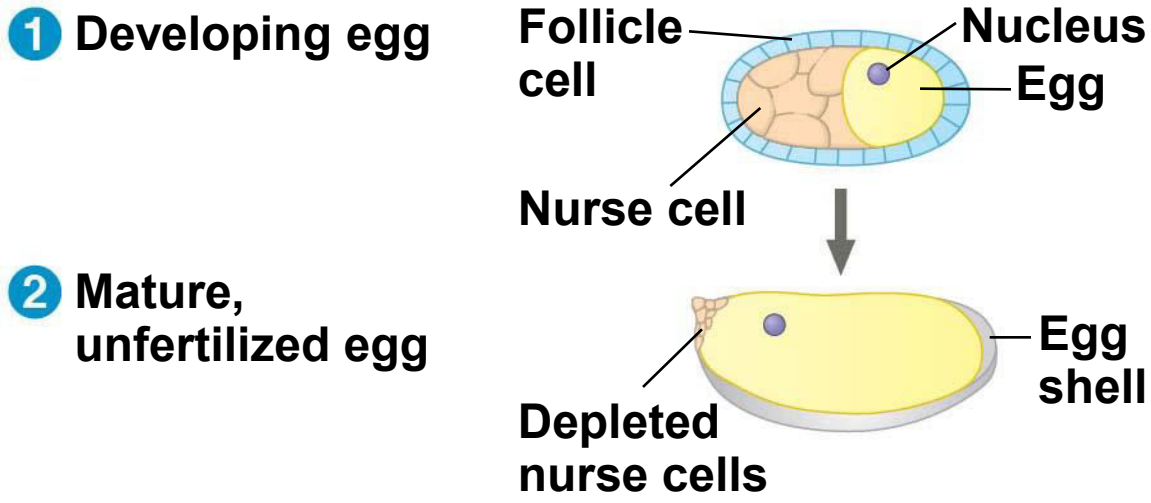
- The *Drosophila* eggs develop in the female's ovary, surrounded by ovarian cells called nurse cells and follicle cells
- After fertilization, embryonic development results in a segmented larva, which goes through three stages
- Eventually, the larva forms a pupa within which it metamorphoses into an adult fly

Figure 16.7-2-s1



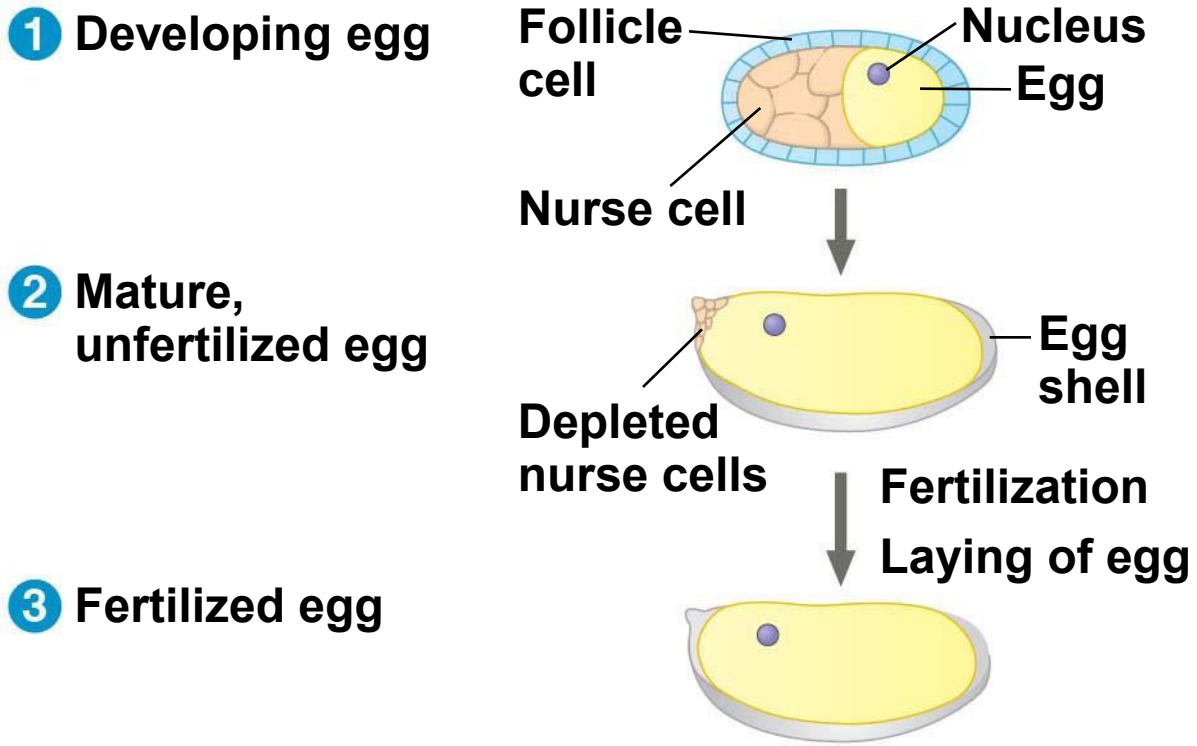
(b) Development from egg to larva

Figure 16.7-2-s2



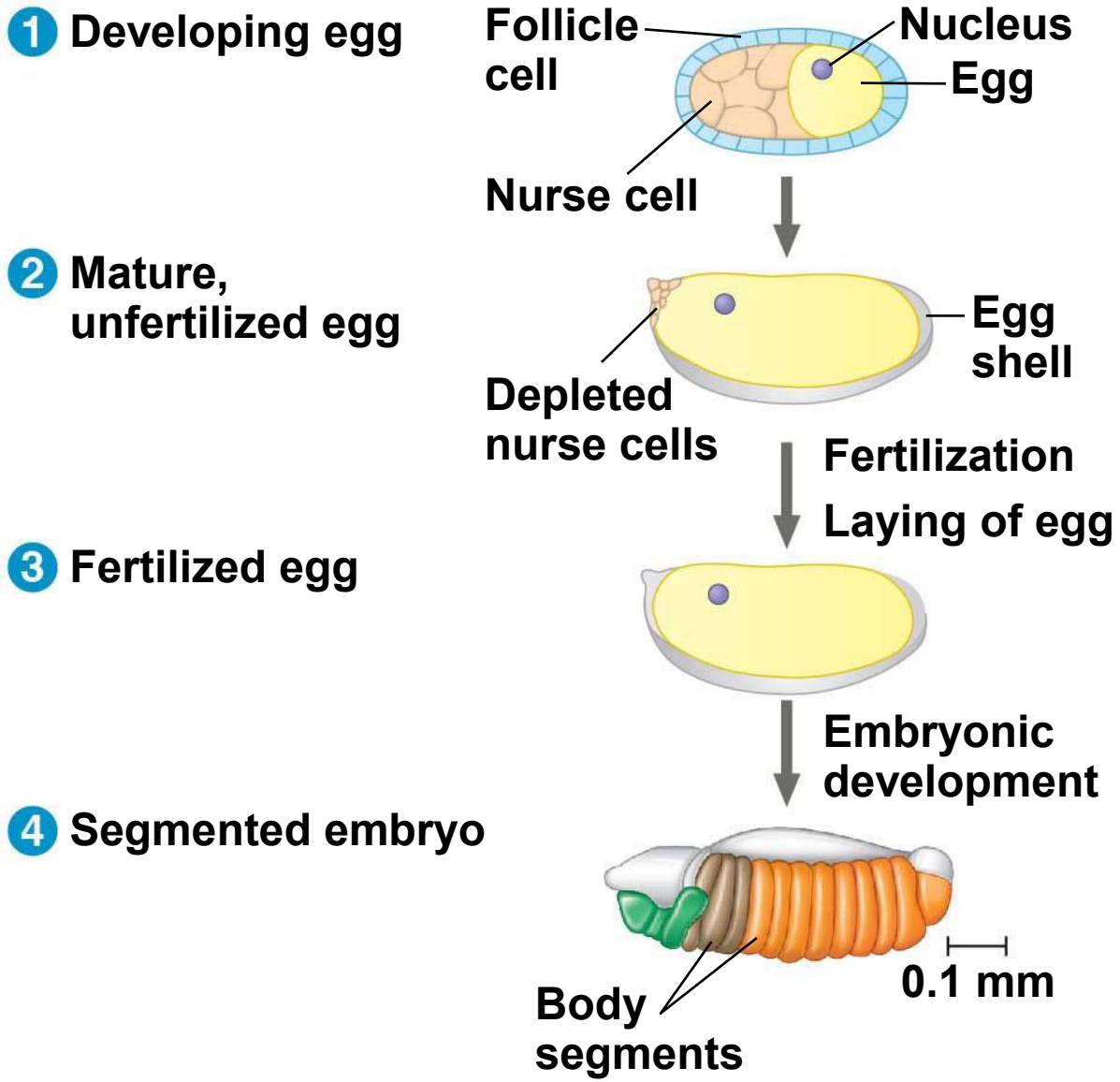
(b) Development from egg to larva

Figure 16.7-2-s3



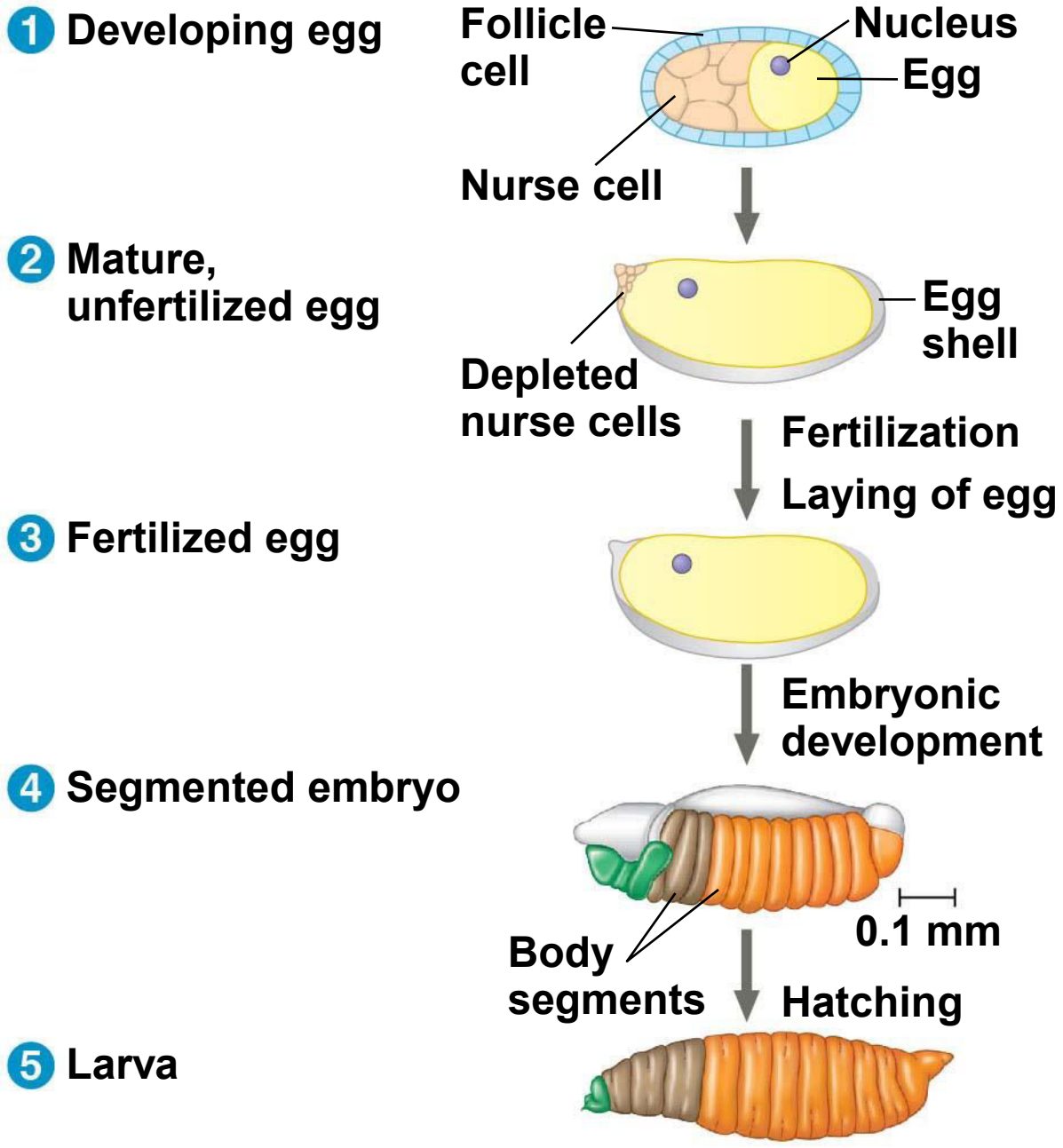
(b) Development from egg to larva

Figure 16.7-2-s4



(b) Development from egg to larva

Figure 16.7-2-s5



(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 the **homeotic genes**, which control pattern formation in late embryo, larva, and adult stages

Figure 16.8

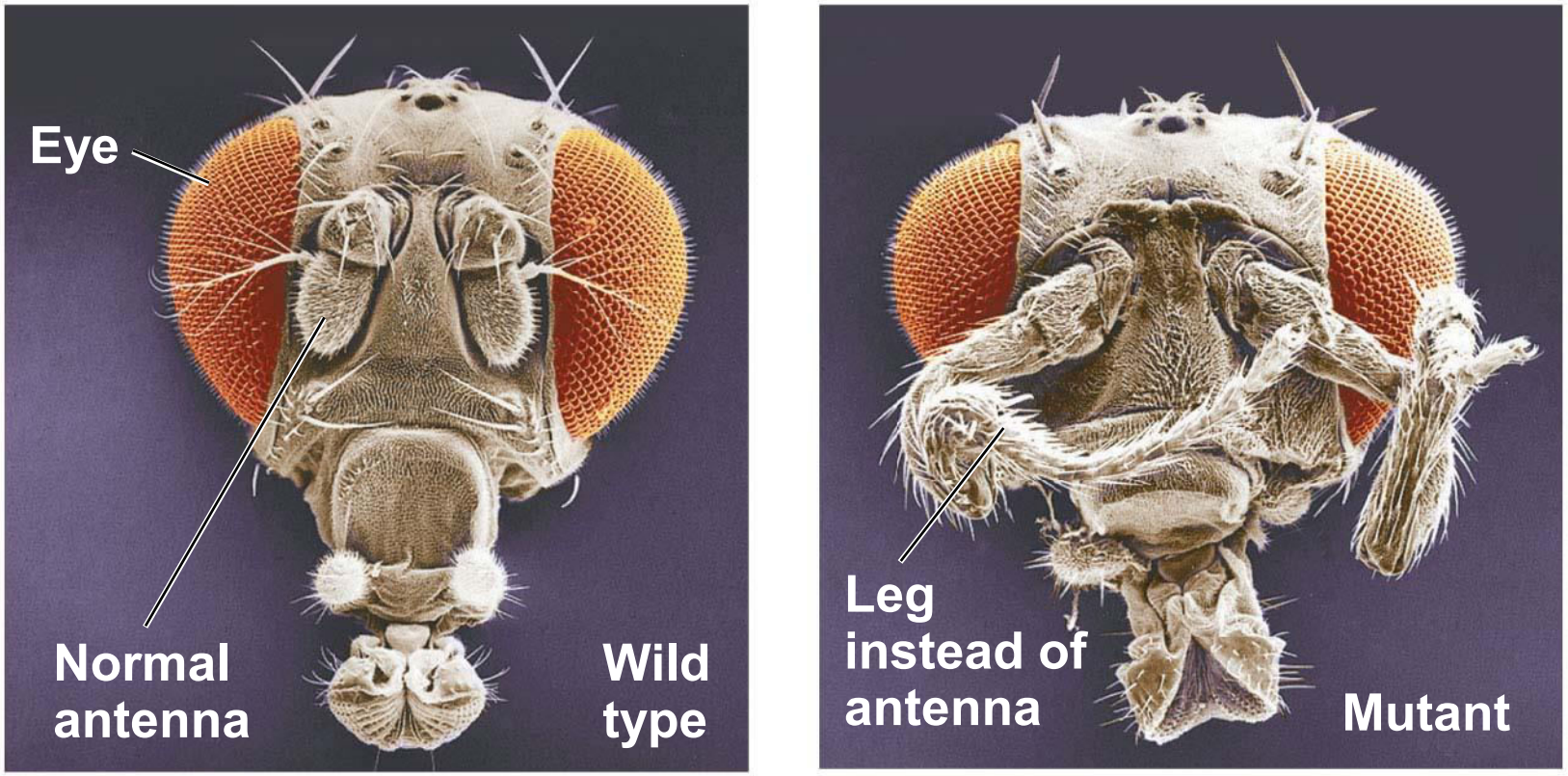


Figure 16.8-1

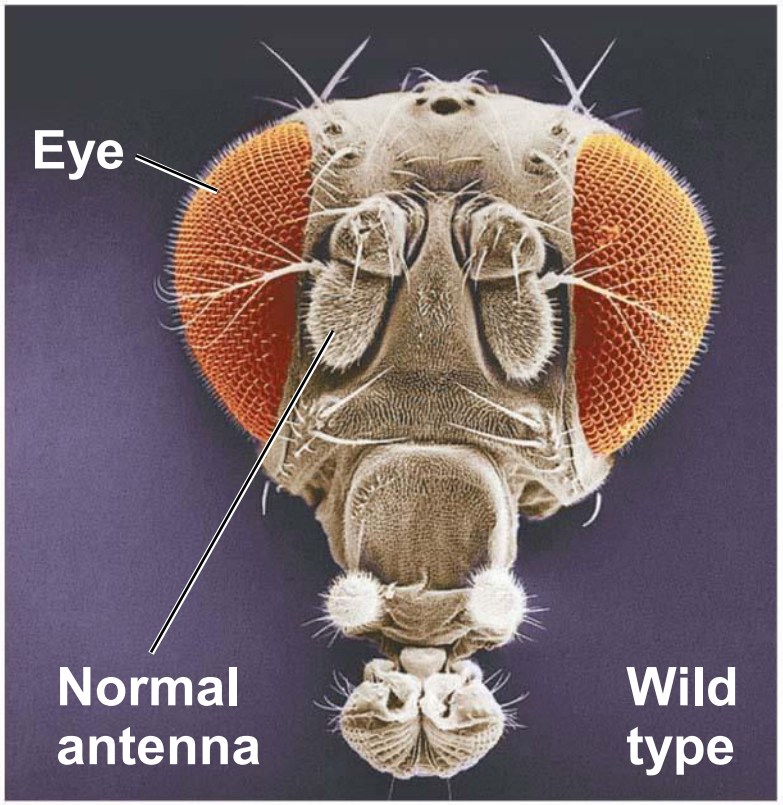
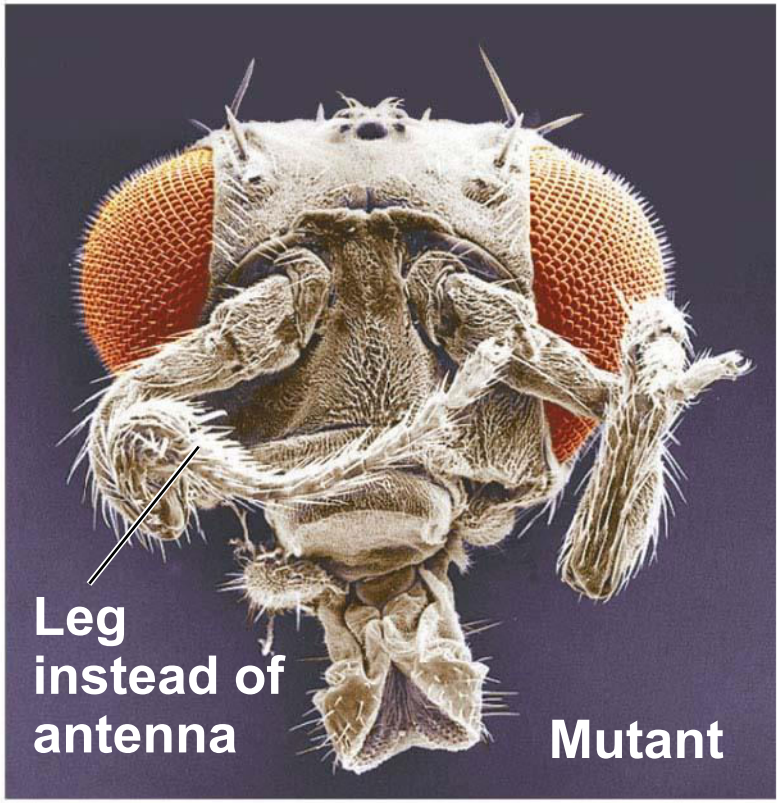


Figure 16.8-2



- Nüsslein-Volhard and Wieschaus set out to identify all genes that affected segment formation in *Drosophila*
- Many of the identified mutations were **embryonic lethals**, causing death during embryogenesis
- They identified 120 genes essential for normal segmentation

Axis Establishment

- **Maternal effect genes** encode cytoplasmic determinants that initially establish the axes of the body of *Drosophila*
- When these genes are mutant in the mother, the resulting phenotype is seen in the offspring
- 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, ***bicoid***, 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 posterior structures at both ends

Figure 16.9

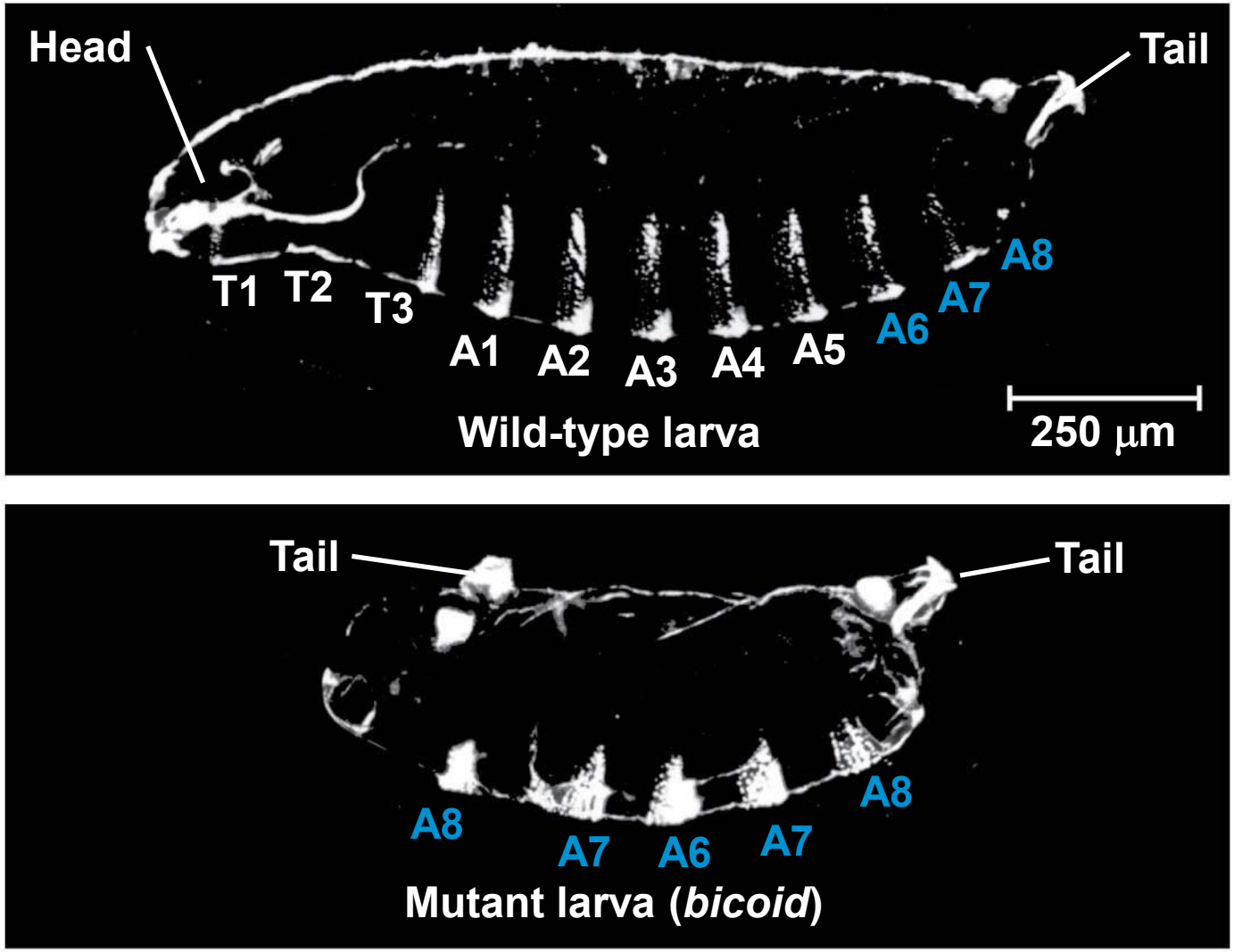


Figure 16.9-1

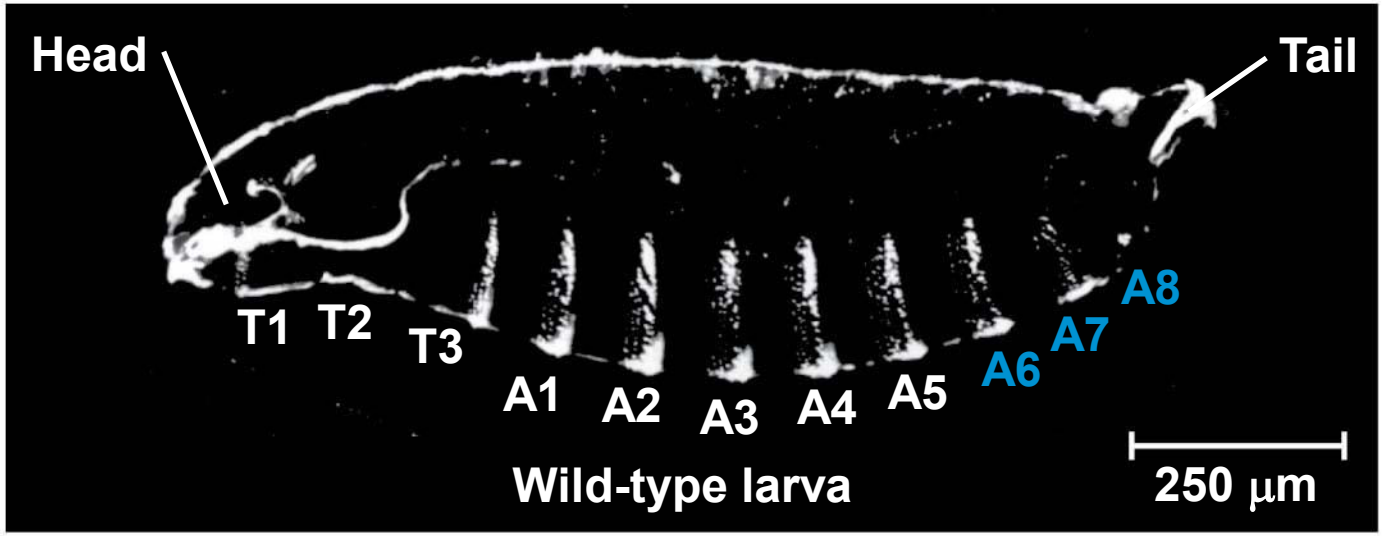
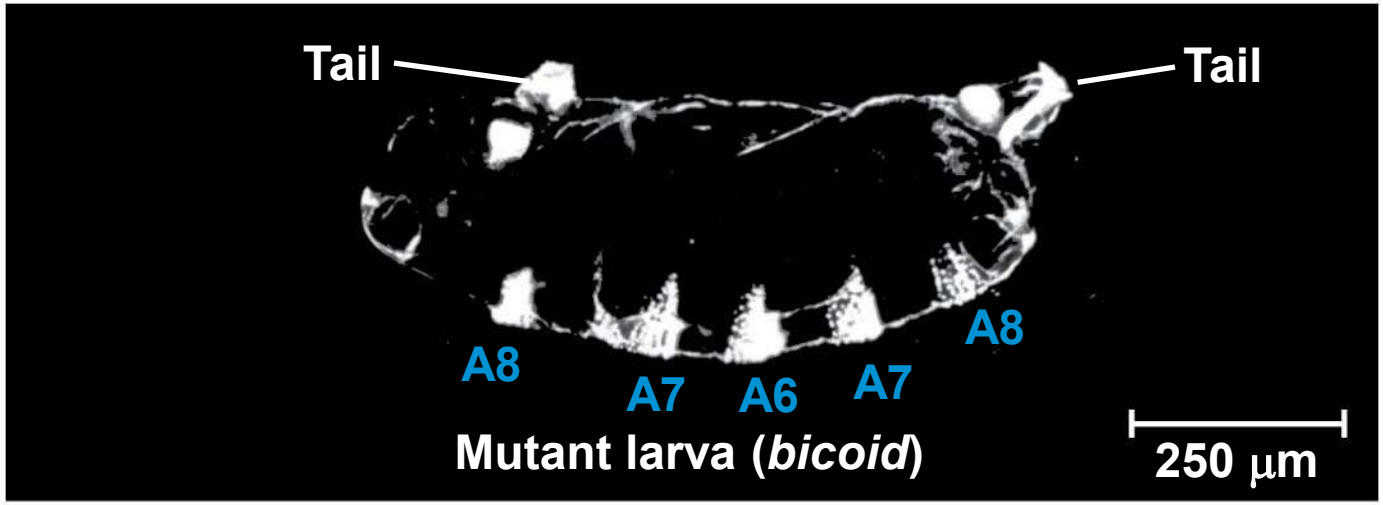


Figure 16.9-2



- This phenotype suggested that the product of the mother's *bicoid* gene is concentrated at the future anterior end and is required for setting up the anterior end of the fly
- This hypothesis is an example of the morphogen gradient hypothesis; gradients of substances called **morphogens** establish an embryo's axes and other features

- The *bicoid* mRNA is highly concentrated at the anterior end of the embryo
- After the egg is fertilized, the mRNA is translated into Bicoid protein, which diffuses from the anterior end
- The result is a gradient of Bicoid protein
- Injection of *bicoid* mRNA into various regions of an embryo results in the formation of anterior structures at the site of injection

Animation: Head and Tail Axis of a Fruit Fly

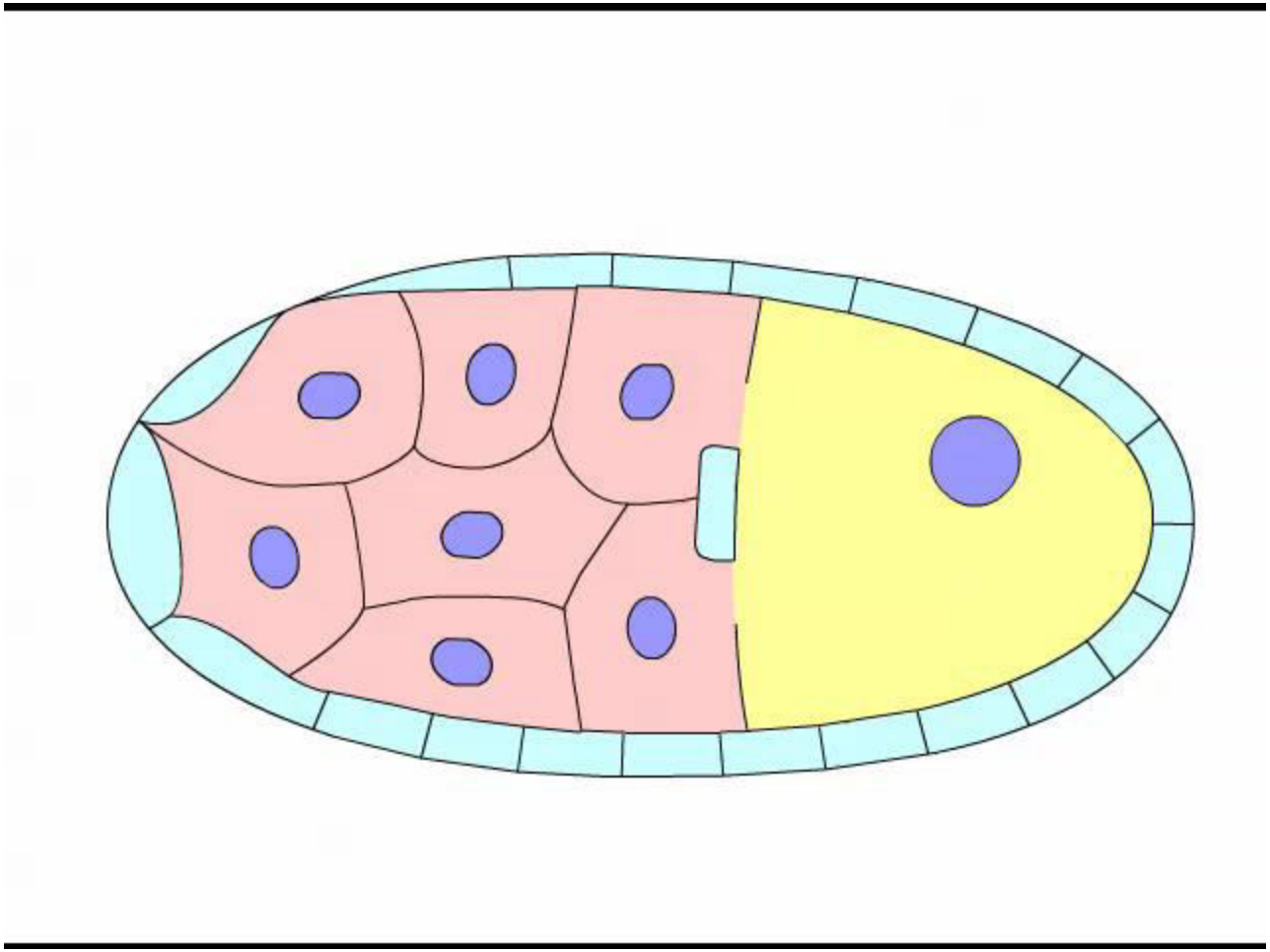


Figure 16.10

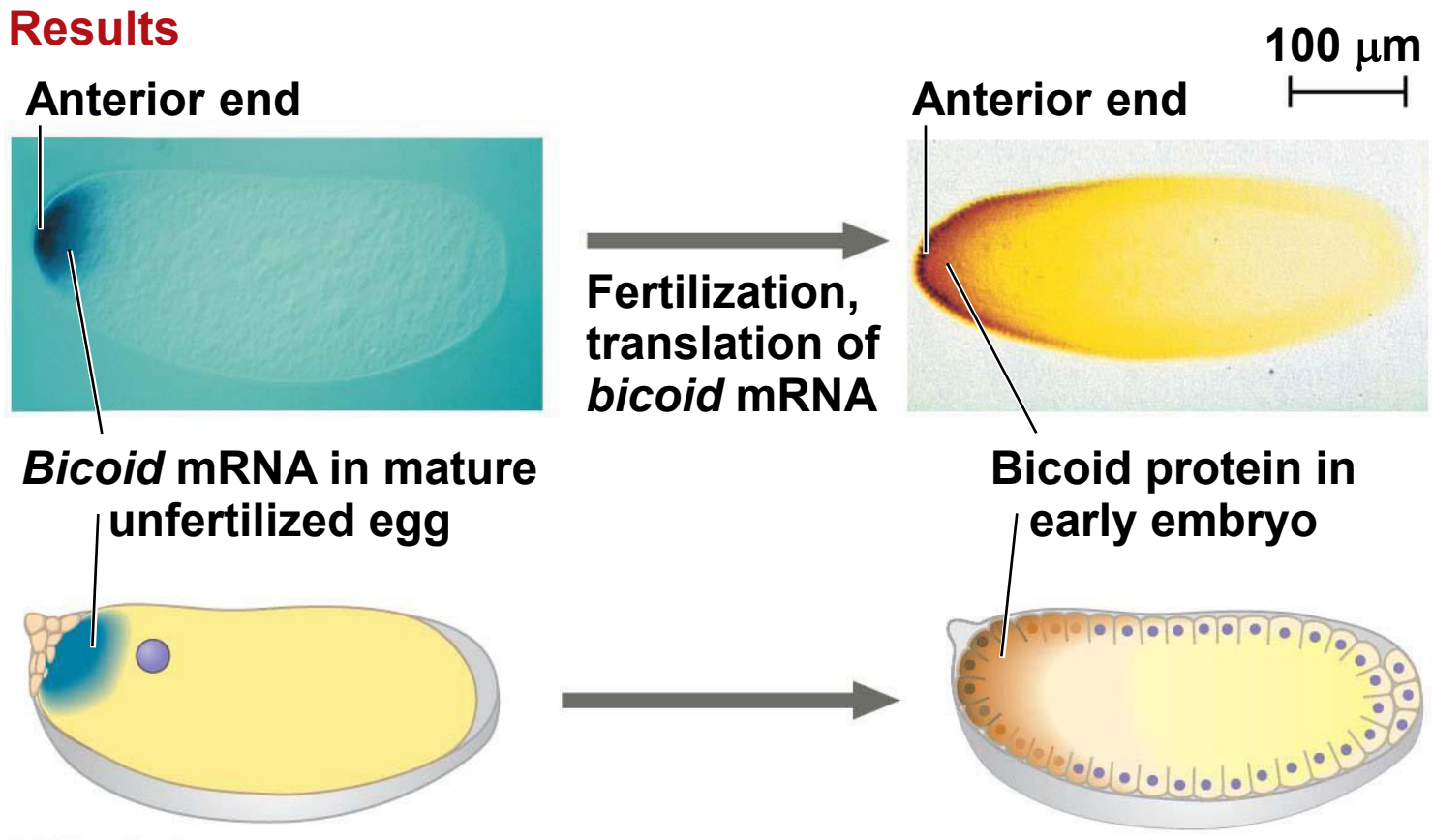


Figure 16.10-1

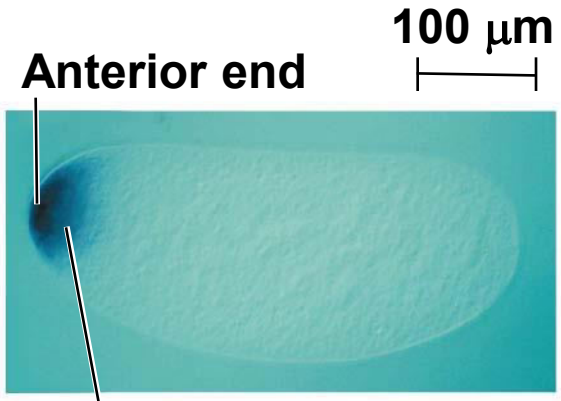
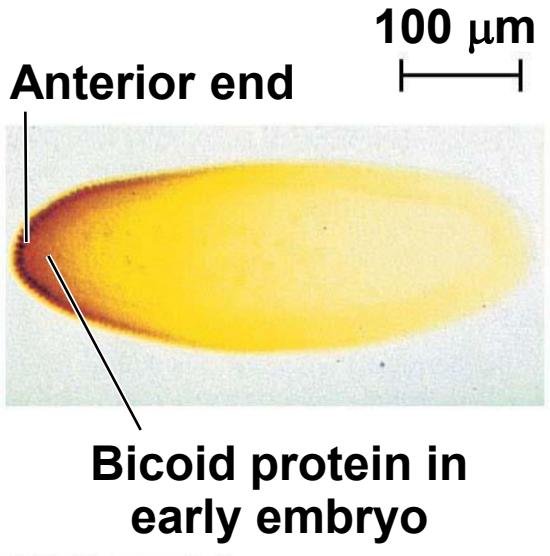


Figure 16.10-2



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

Concept 16.2: Cloning organisms showed that differentiated cells could be reprogrammed and ultimately led to the production of stem cells

- In organismal cloning one or more organisms develop from a single cell without meiosis or fertilization
- The cloned individuals are genetically identical to the "parent" that donated the single cell
- The current interest in organismal cloning arises mainly from its potential to generate **stem cells**

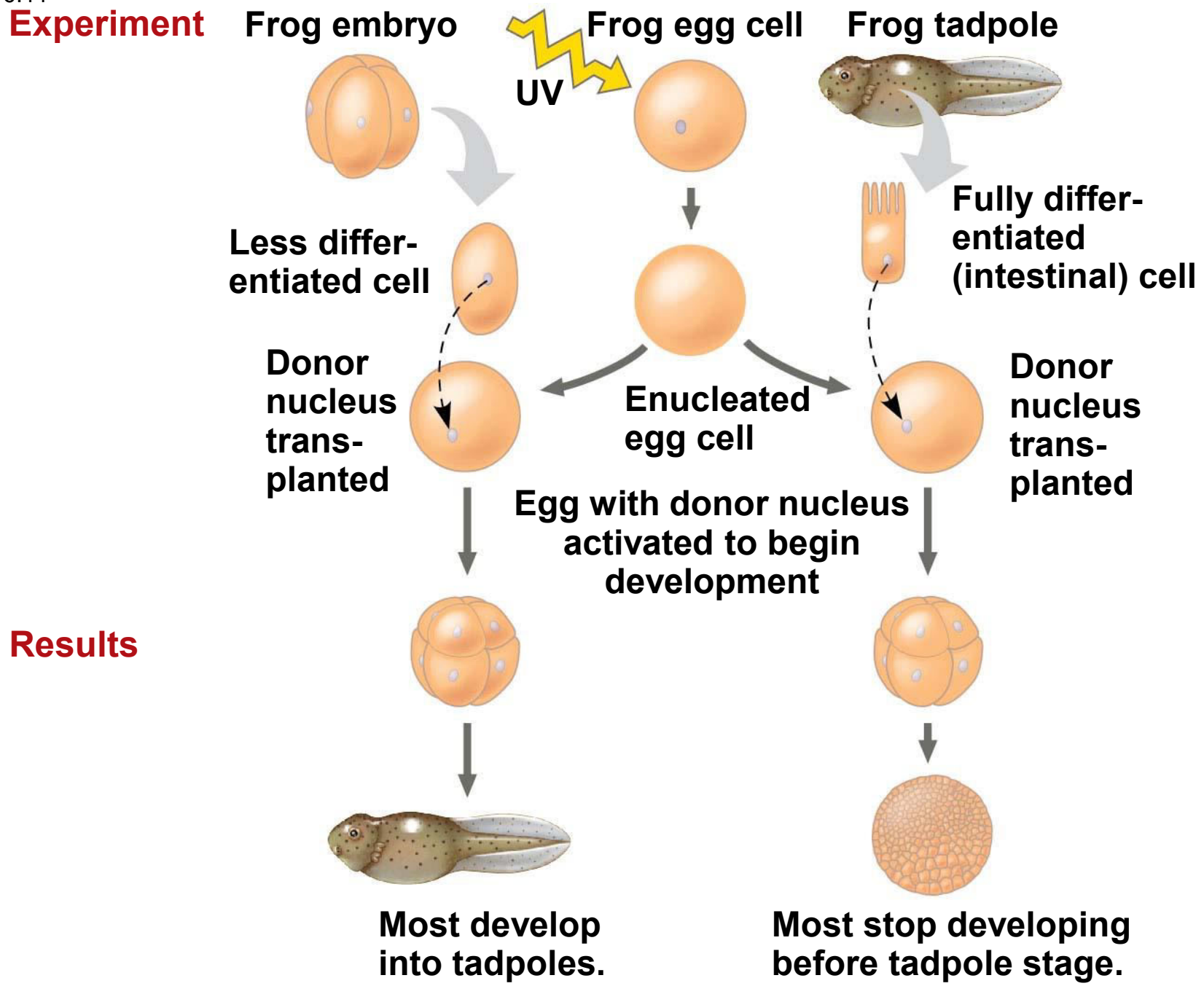
Cloning Plants: Single-Cell Culture

- F. C. Steward and his students first cloned whole carrot plants in the 1950s
- Single differentiated cells from the root incubated in culture medium were able to grow into complete adult plants
- This work showed that differentiation is not necessarily irreversible
- Cells that can give rise to all the specialized cell types in the organism are called **totipotent**

Cloning Animals: Nuclear Transplantation

- In cloning of animals, the nucleus of an unfertilized egg cell or zygote is replaced with the nucleus of a differentiated cell, called nuclear transplantation
- Experiments with frog embryos showed that a transplanted nucleus can often support normal development of the egg
- The older the donor nucleus, the lower the percentage of normally developing tadpoles
- John Gurdon concluded from this work that nuclear potential is restricted as development and differentiation proceed

Figure 16.11



Reproductive Cloning of Mammals

- In 1997, Scottish researchers announced the birth of Dolly, a lamb cloned from an adult sheep by nuclear transplantation from a differentiated cell
- Dolly's premature death in 2003, and her arthritis, led to speculation that her cells were not as healthy as those of a normal sheep, possibly reflecting incomplete reprogramming of the original transplanted nucleus

Figure 16.12

© Photo courtesy of the Roslin Institute, The University of Edinburgh

- Since 1997, cloning has been demonstrated in many mammals, including mice, cats, cows, horses, pigs, dogs, and monkeys
- CC (for Carbon Copy) was the first cat cloned; however, CC differed somewhat from her female "parent"
- Cloned animals do not always look or behave exactly the same as their "parent"

Figure 16.13

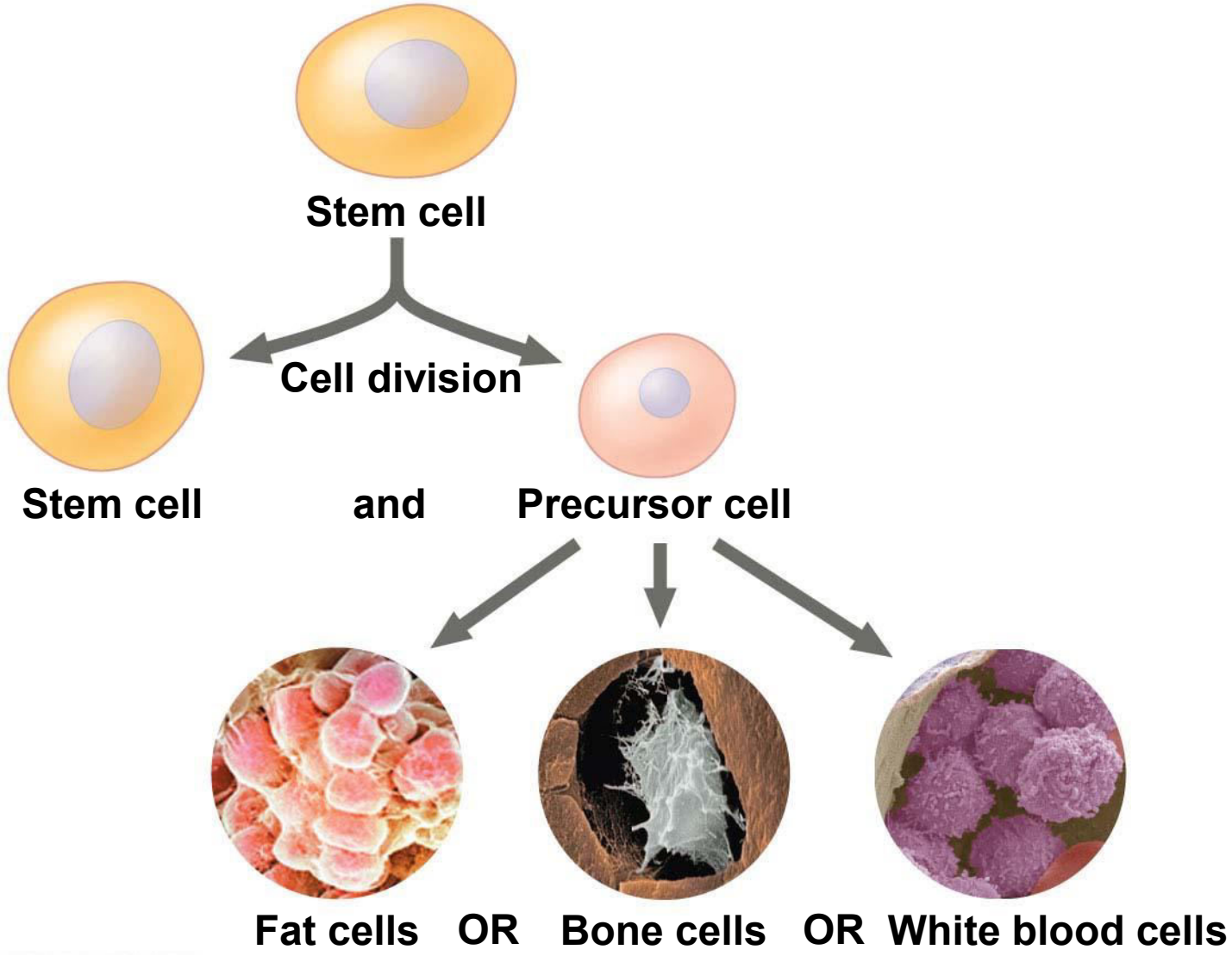
Faulty Gene Regulation in Cloned Animals

- In most nuclear transplantation studies, only a small percentage of cloned embryos have developed normally to birth
- Many cloned animals exhibit defects
- Epigenetic changes must be reversed in the nucleus from a donor animal in order for genes to be expressed or repressed appropriately for early stages of development

Stem Cells of Animals

- A stem cell is a relatively unspecialized cell that can reproduce itself indefinitely and differentiate into specialized cells of one or more types

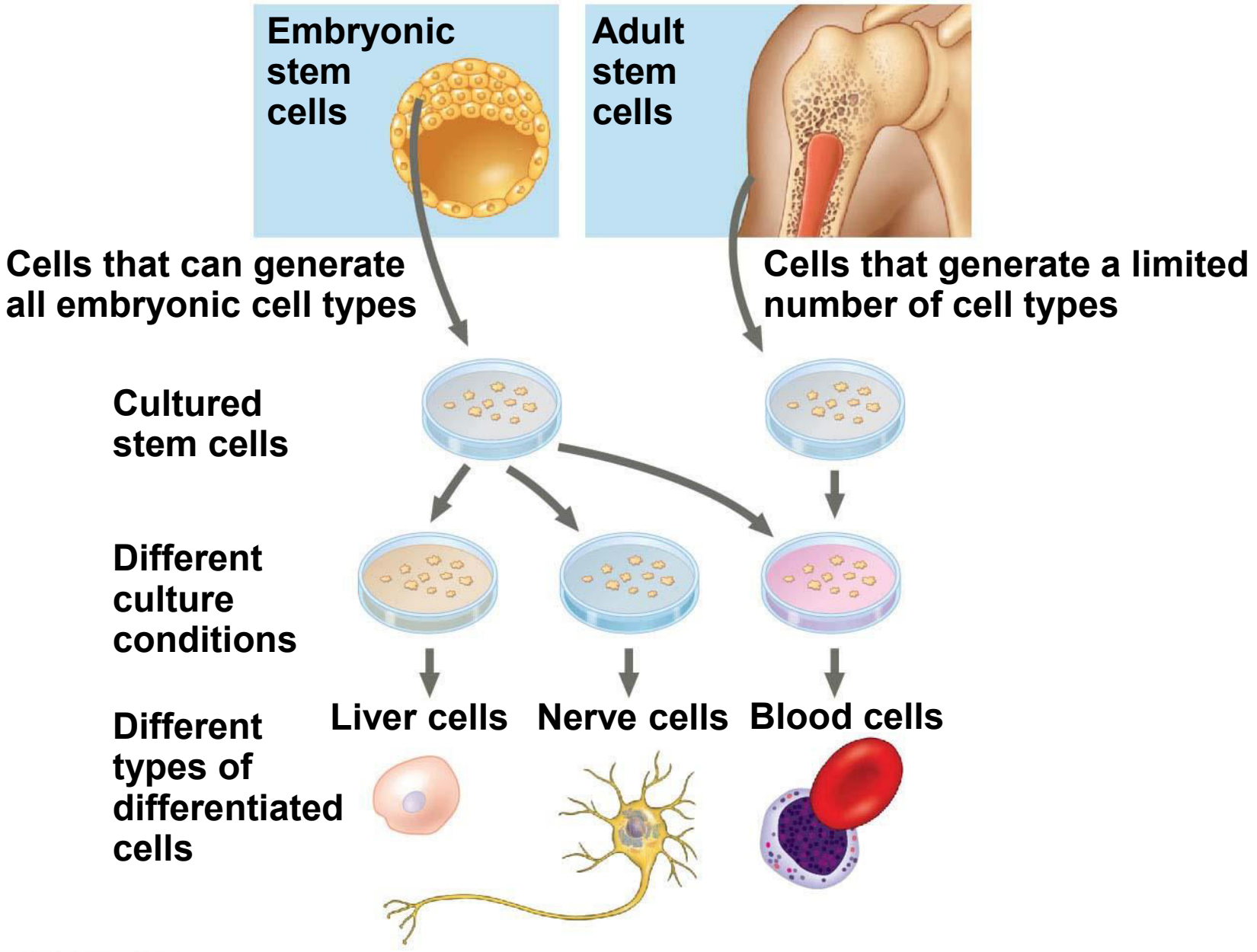
Figure 16.14



Embryonic and Adult Stem Cells

- Many early animal embryos contain stem cells, able to differentiate into any cell type (**pluripotent**)
- These embryonic stem (ES) cells can reproduce indefinitely
- The adult body also has stem cells, which replace nonreproducing specialized cells as needed

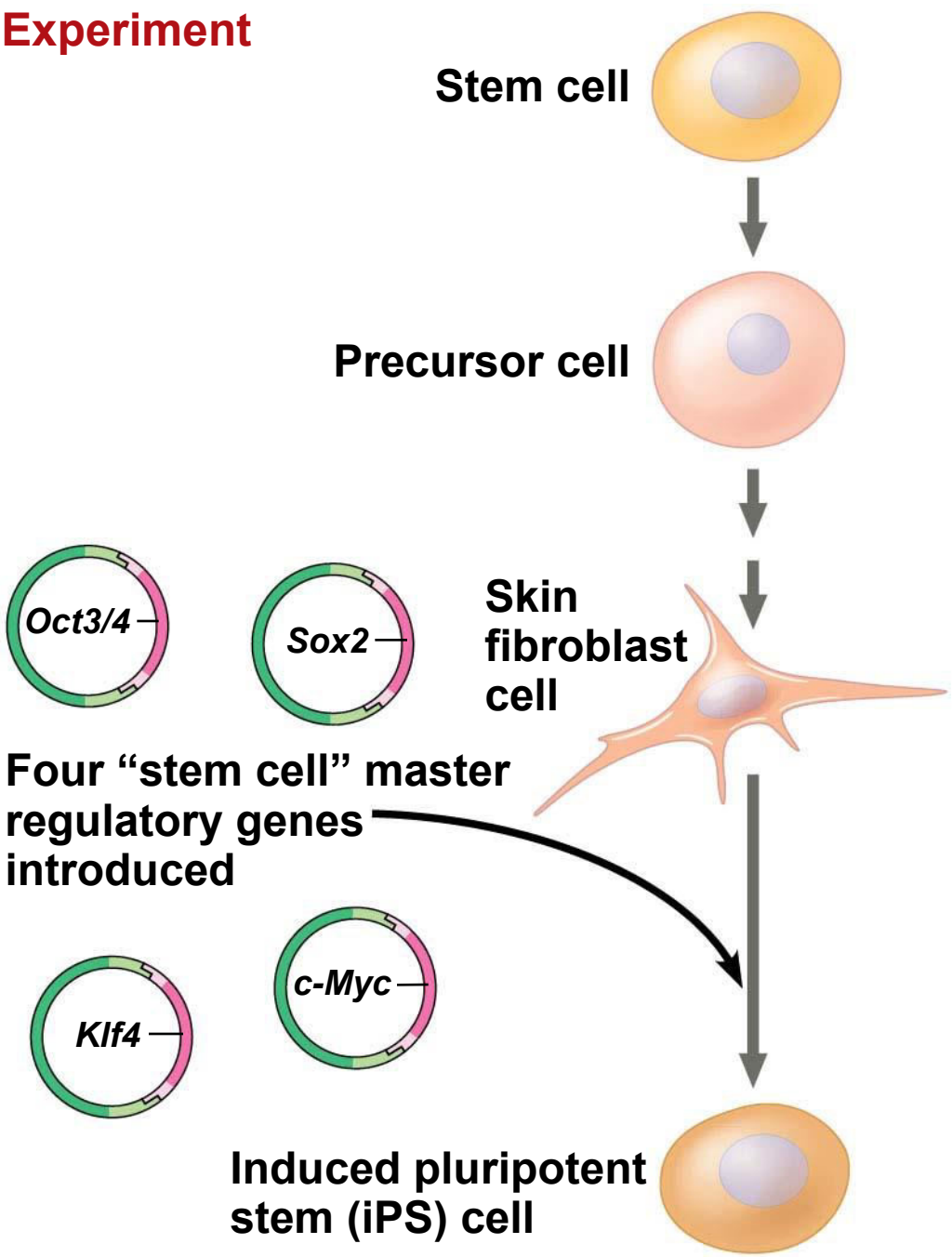
Figure 16.15



Induced Pluripotent Stem (iPS) Cells

- Researchers are able to “deprogram” fully differentiated cells to act like ES cells using retroviruses
- Cells transformed this way are called iPS, or induced pluripotent stem cells
- Gurdon and Yamanaka received the Nobel Prize in 2012 for this work

Figure 16.16



- Cells of patients suffering from certain diseases can be reprogrammed into iPS cells for use in studying the disease and potential treatments
- In the field of regenerative medicine, a patient's own cells might be reprogrammed into iPS cells to potentially replace nonfunctional (diseased) cells

Concept 16.3: Abnormal regulation of genes that affect the cell cycle can lead to cancer

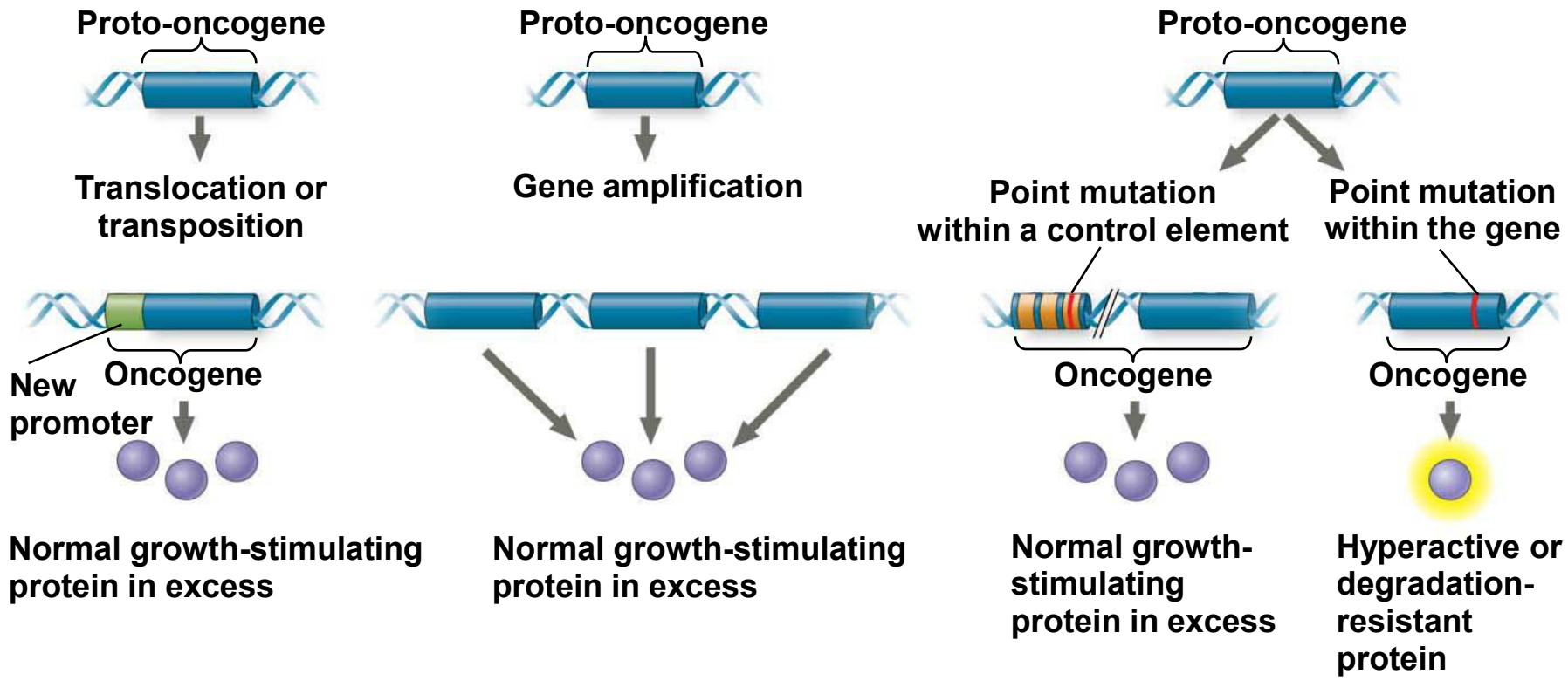
- The gene regulation systems that go wrong during cancer are the same systems involved in embryonic development

Types of Genes Associated with Cancer

- Cancer research led to the discovery of cancer-causing genes called **oncogenes** in certain types of viruses
- The normal version of such genes, called **proto-oncogenes**, code for proteins that stimulate normal cell growth and division
- An oncogene arises from a genetic change leading to an increase in either the amount or the activity of the protein product of the gene

- Proto-oncogenes can be converted to oncogenes by
  - Movement of the oncogene to a position near an active promoter, which may increase transcription
  - Amplification, increasing the number of copies of a proto-oncogene
  - Point mutations in the proto-oncogene or its control elements, causing an increase in gene expression

Figure 16.17



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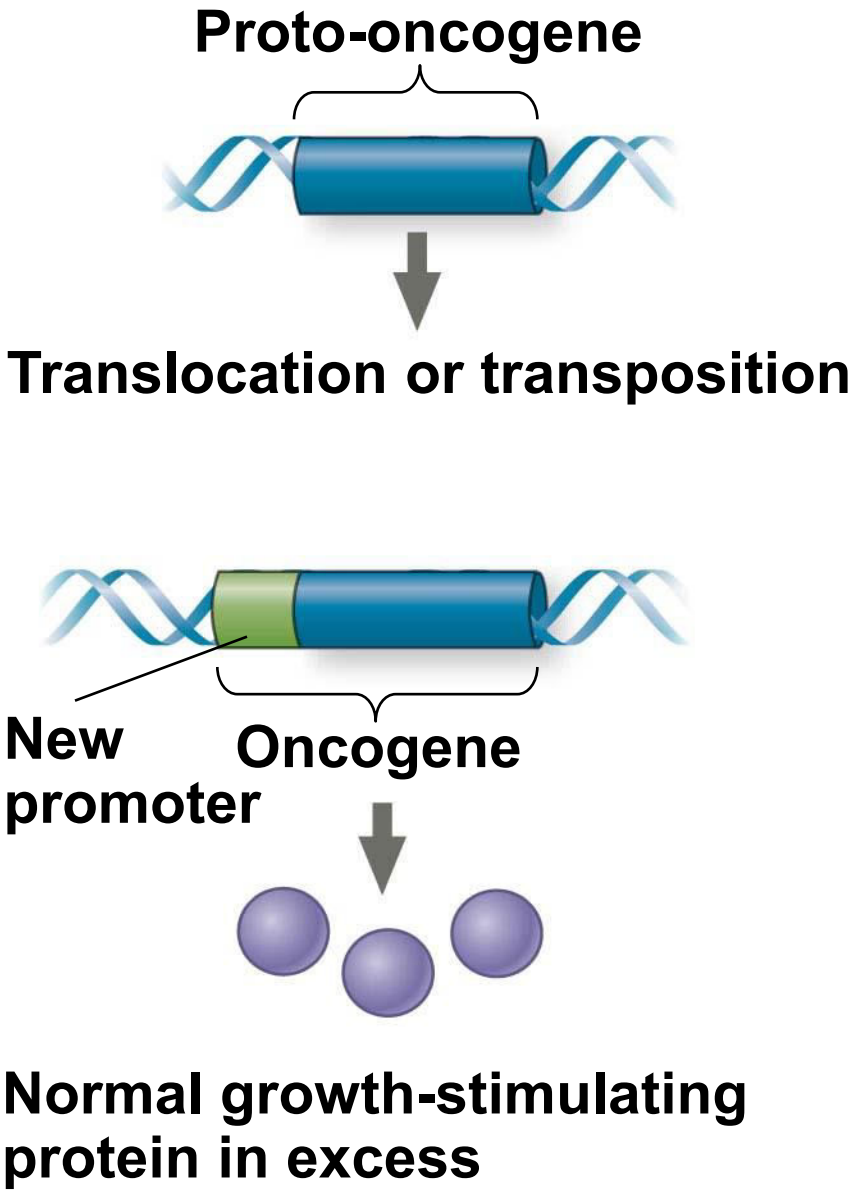
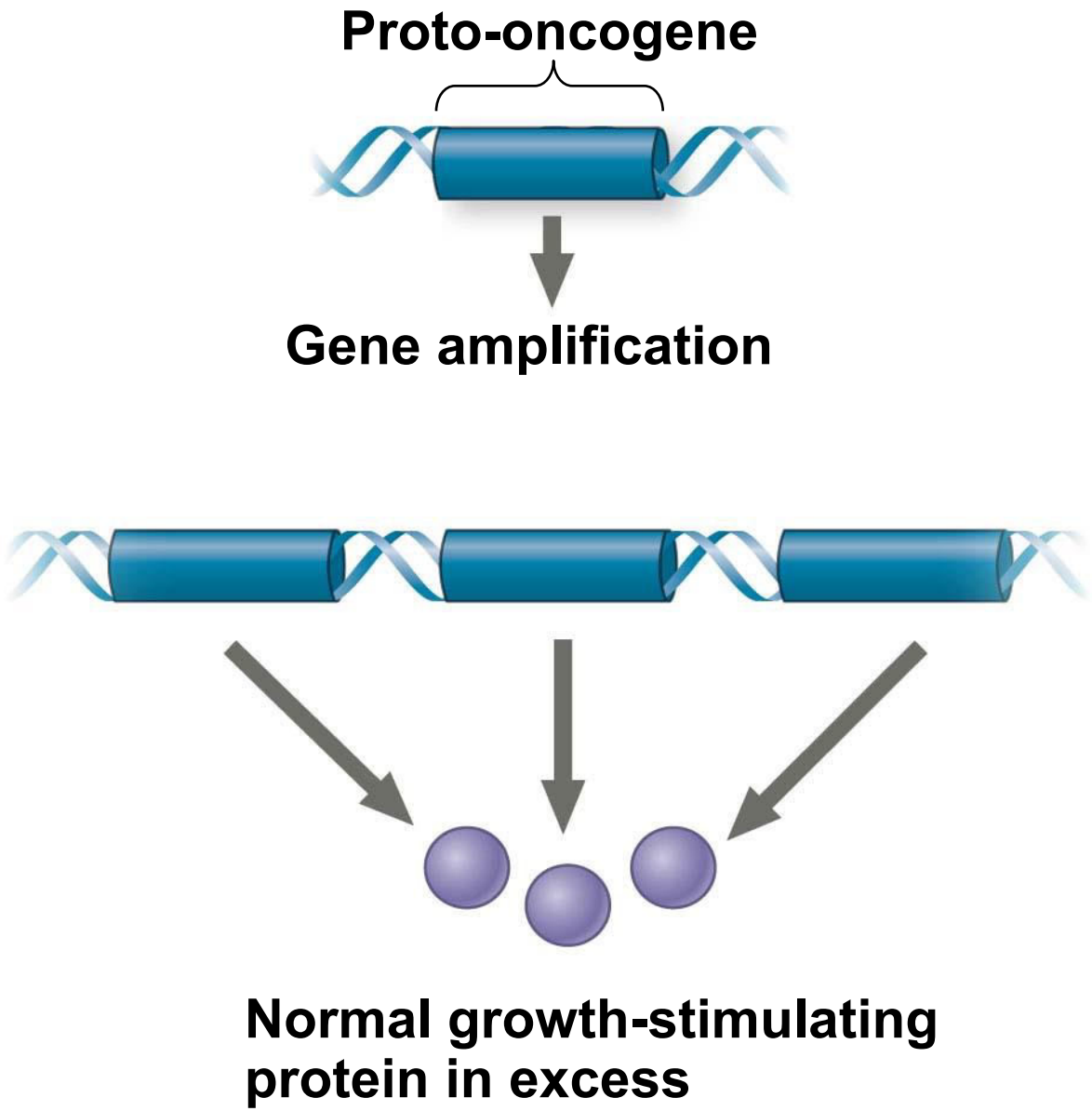


Figure 16.17-2



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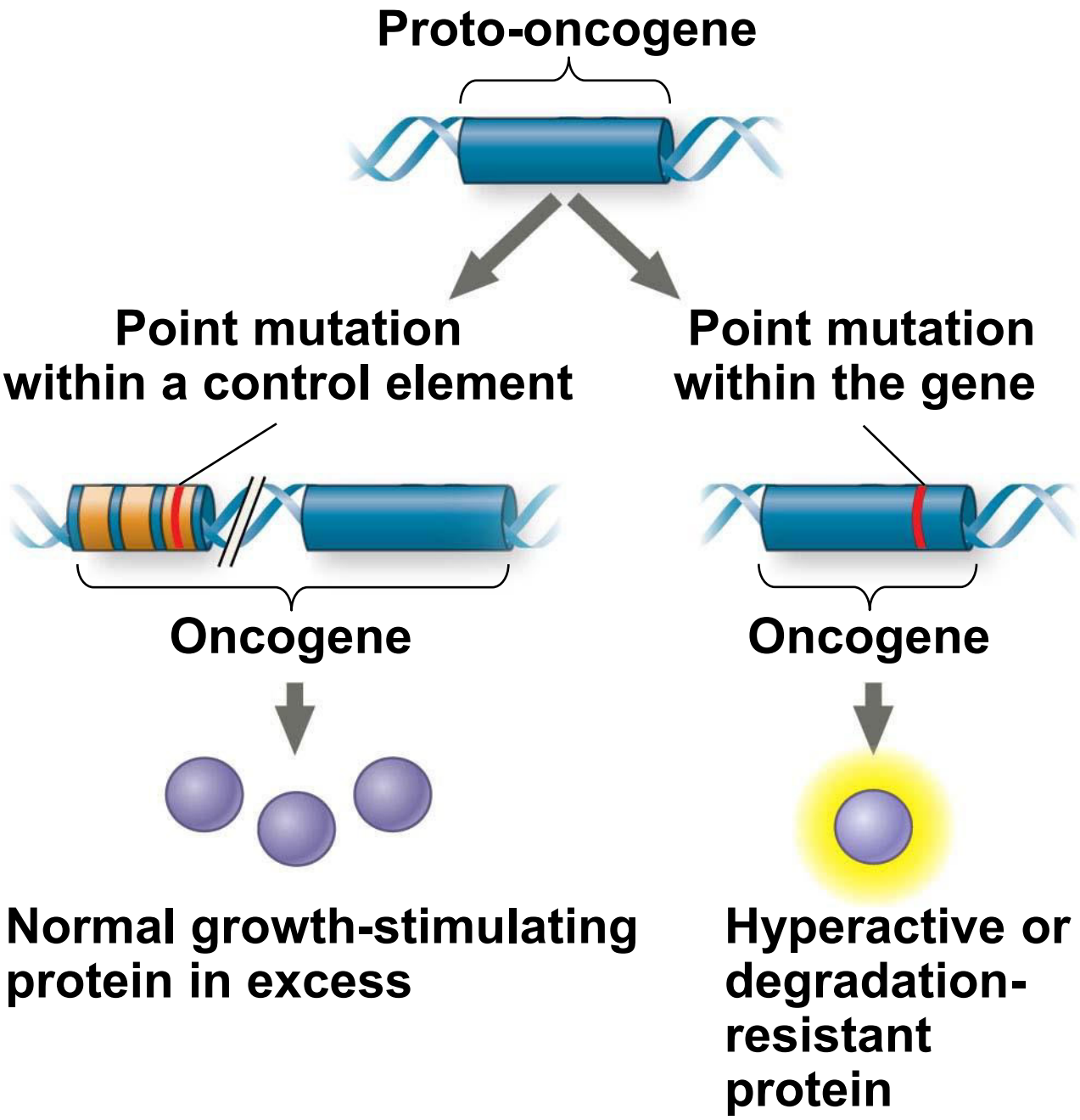
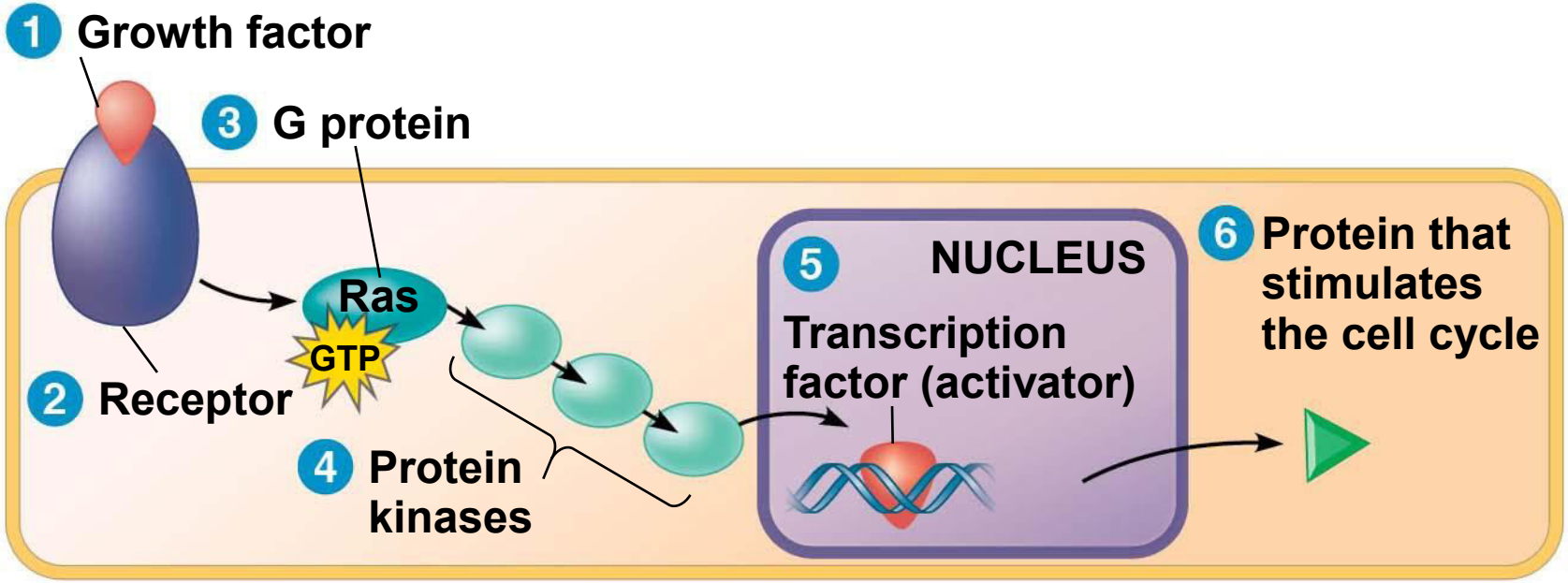


- **Tumor-suppressor genes** encode proteins that help prevent uncontrolled cell growth
- Mutations that decrease protein products of tumor-suppressor genes may contribute to cancer onset
- Tumor-suppressor proteins
  - Repair damaged DNA
  - Control cell adhesion
  - Inhibit the cell cycle

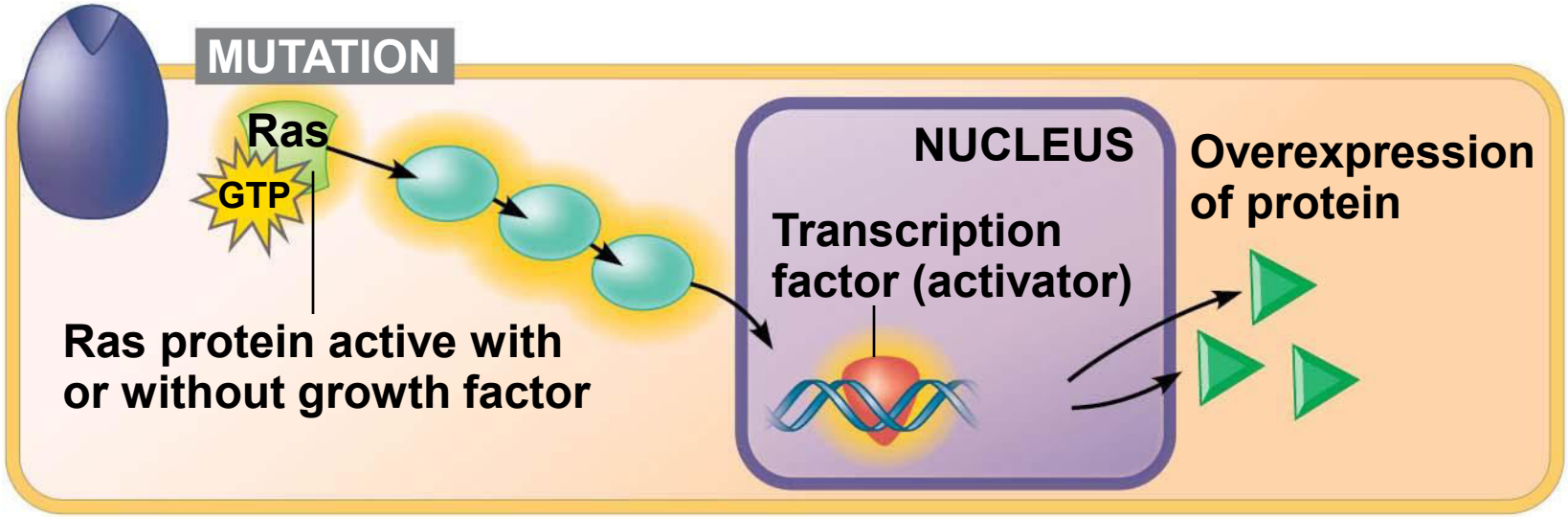
Interference with Cell-Signaling Pathways

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

Figure 16.18



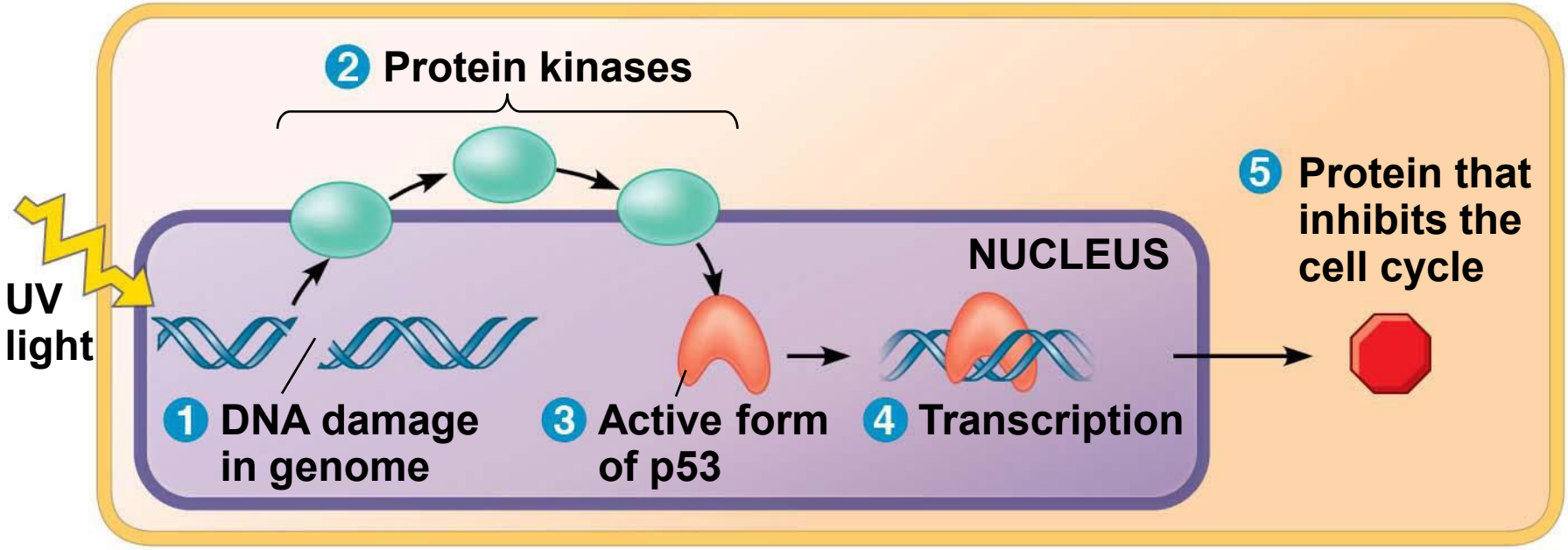
(a) Normal cell cycle–stimulating pathway



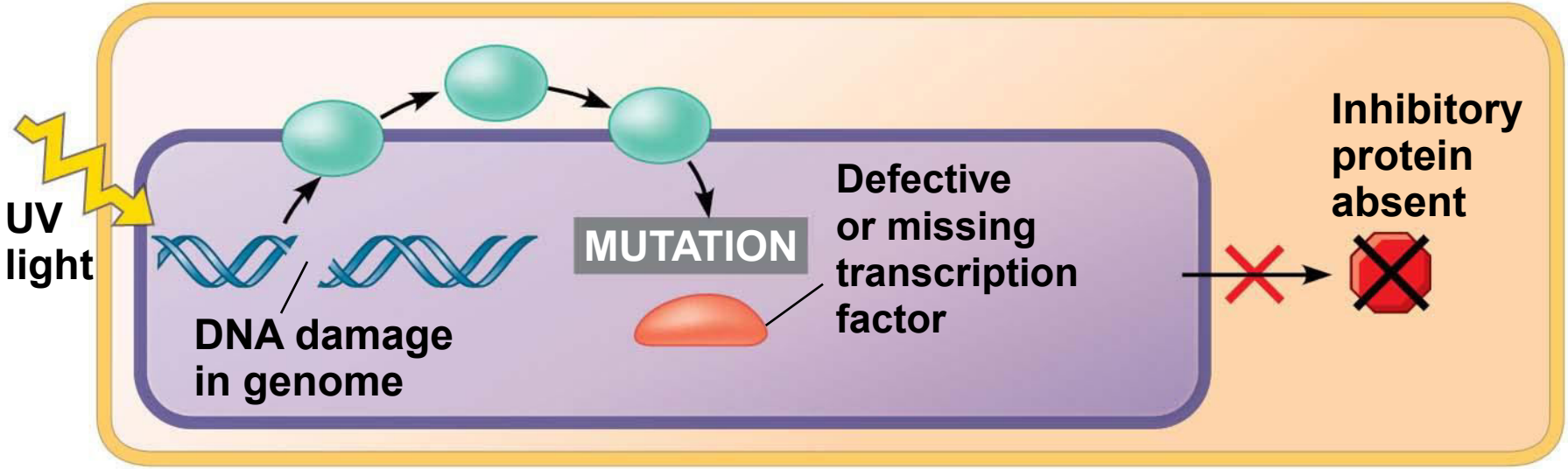
(b) Mutant cell cycle–stimulating pathway

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

Figure 16.19



(a) Normal cell cycle–inhibiting pathway



(b) Mutant cell cycle–inhibiting pathway

The Multistep Model of Cancer Development

- Multiple somatic mutations are generally needed for full-fledged cancer; thus the incidence increases with age
- The multistep path to cancer is well supported by studies of human colorectal cancer, one of the best-understood types of cancer
- The first sign of colorectal cancer is often a polyp, a small benign growth in the colon lining

- About half a dozen changes must occur at the DNA level for a cell to become fully cancerous
- These changes generally include at least one active oncogene and the mutation or loss of several tumor-suppressor genes

Figure 16.20

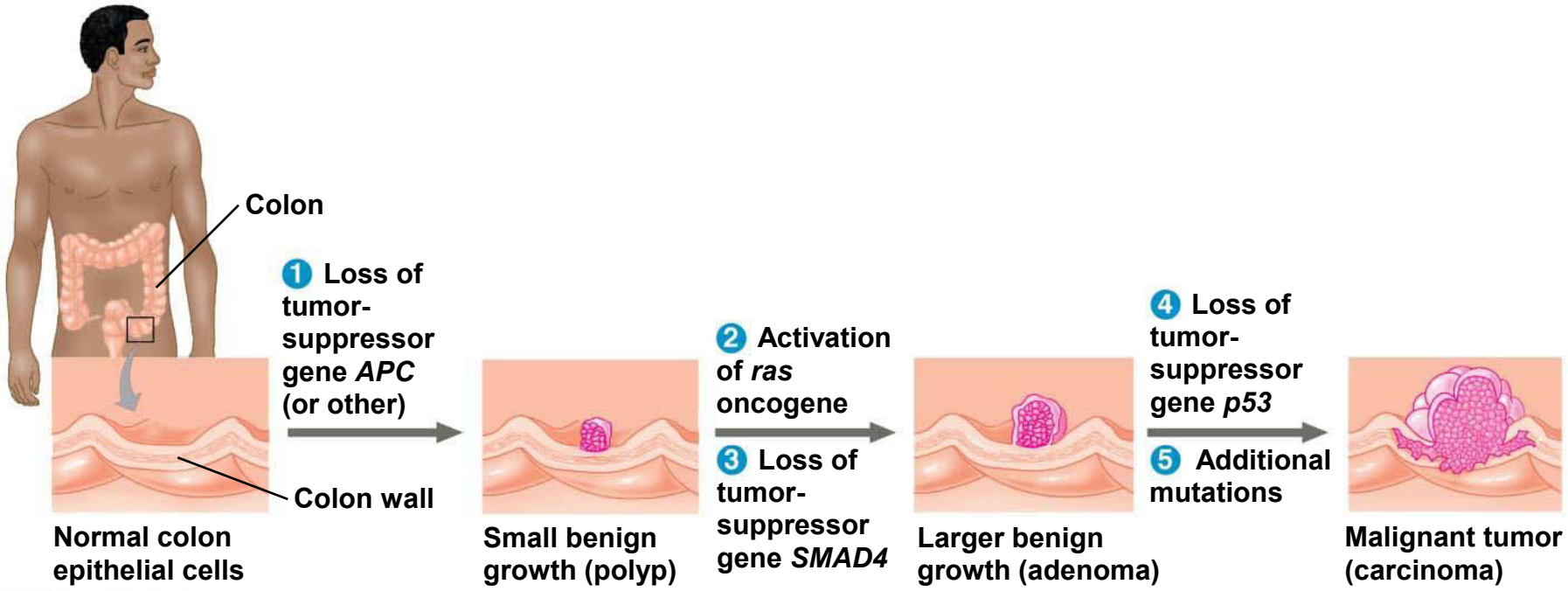
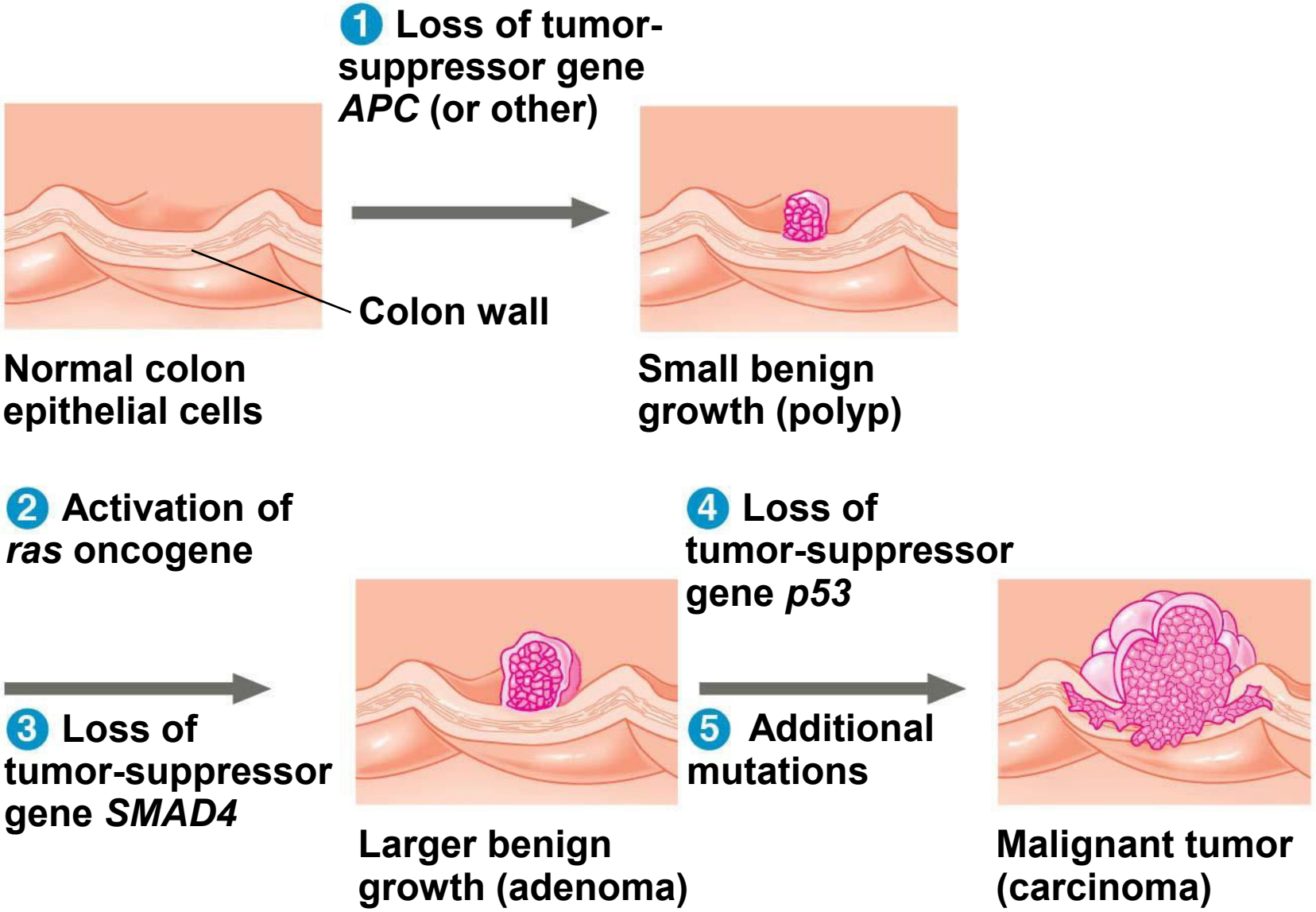


Figure 16.20-1



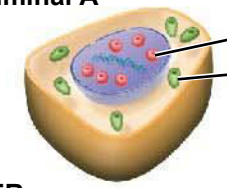
- Breast cancer is the second most common form of cancer in the United States and the most common form among women
- In 2012, the Cancer Genome Atlas Network published results of a genomics approach to profiling types of breast cancer
- Four major types were identified based on their molecular signatures

Figure 16.21

MAKE CONNECTIONS: Genomics, Cell Signaling, and Cancer

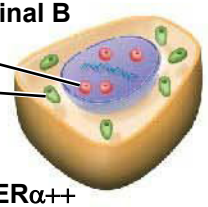
A research scientist examines DNA sequencing data from breast cancer samples.

Luminal A



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

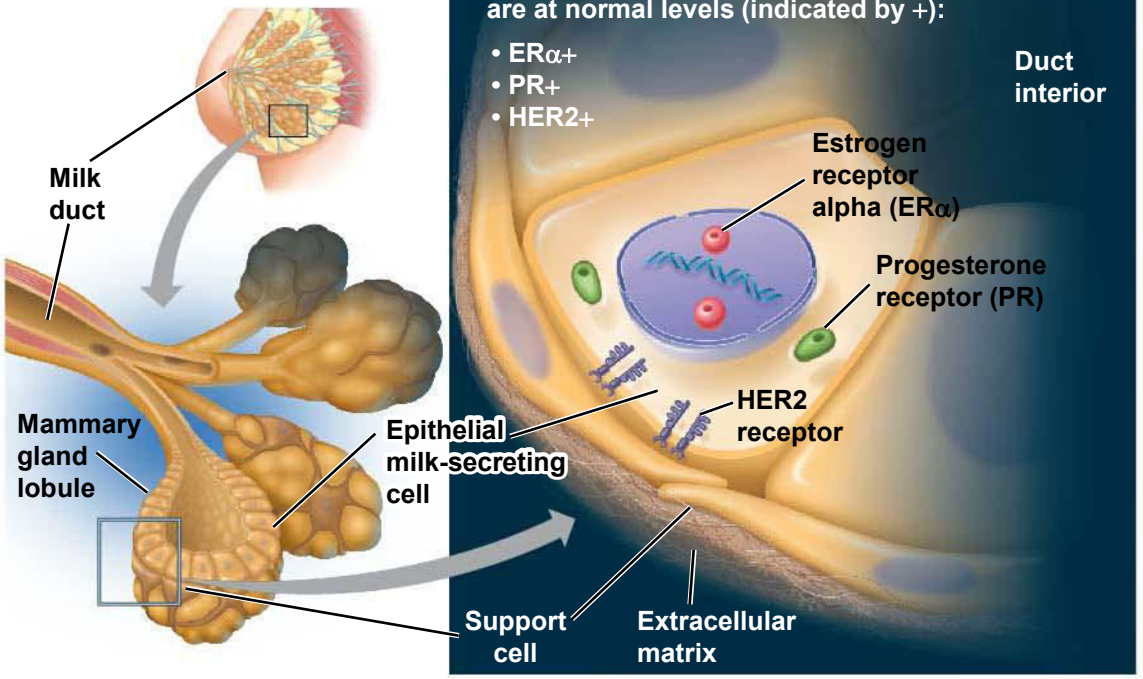
Luminal B



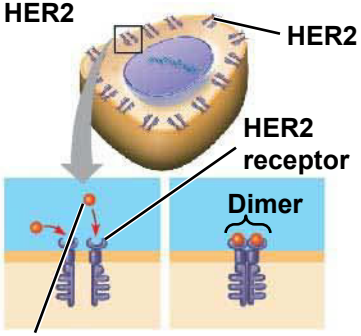
- ERα++
- PR++
- HER2– (shown here); some HER2++
- 15–20% of breast cancers
- Poorer prognosis than luminal A subtype

Basal-like

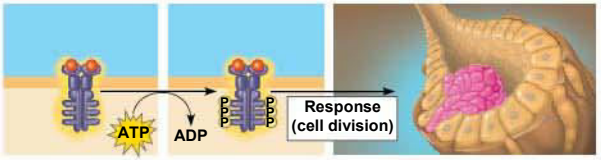
- ERα–
- PR–
- HER2–
- 15–20% of breast cancers
- More aggressive; poorer prognosis than other subtypes



HER2



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



Treatment with Herceptin for the HER2 subtype

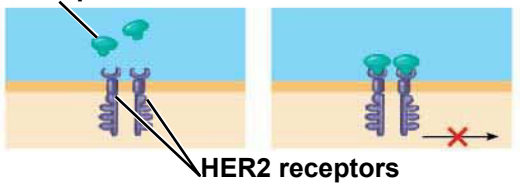
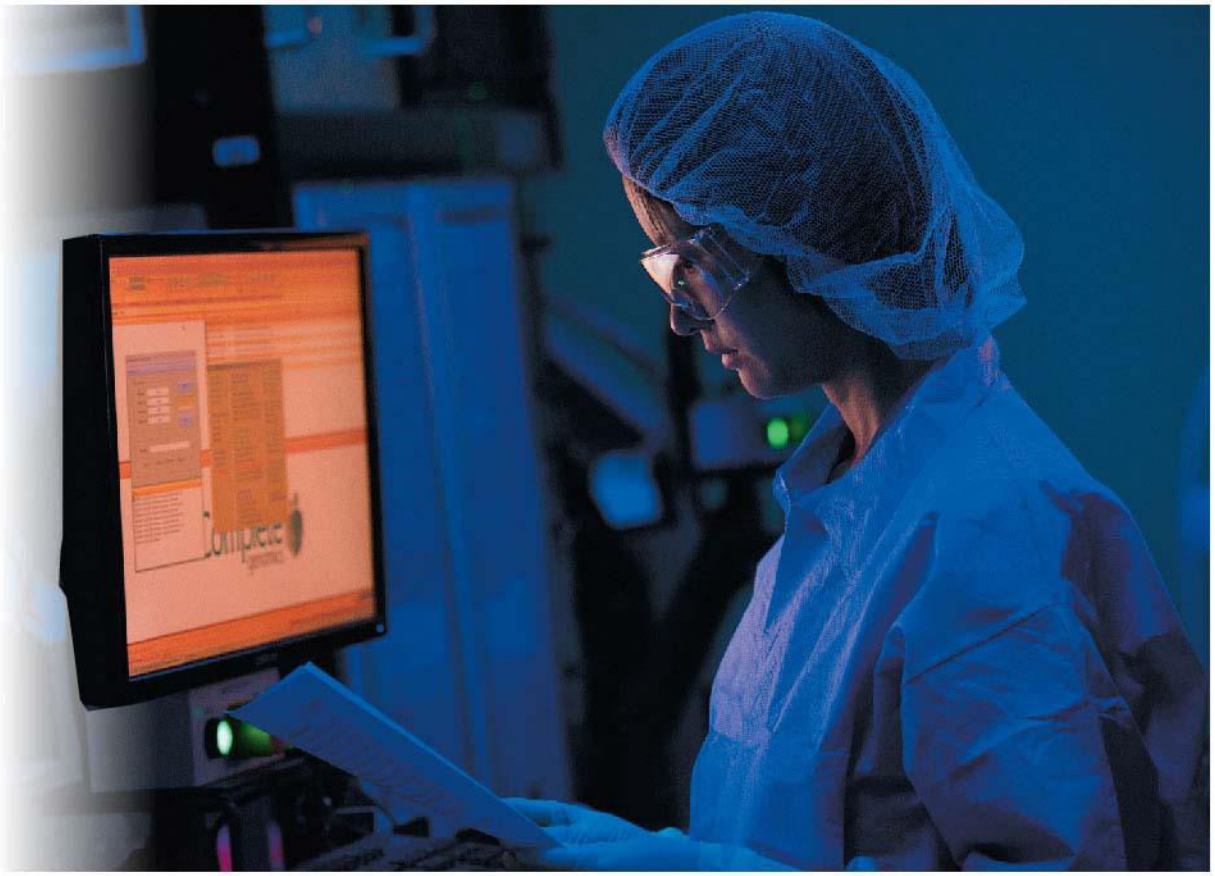


Figure 16.21-1



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

Figure 16.21-2

MAKE CONNECTIONS: Genomics, Cell Signaling, and Cancer

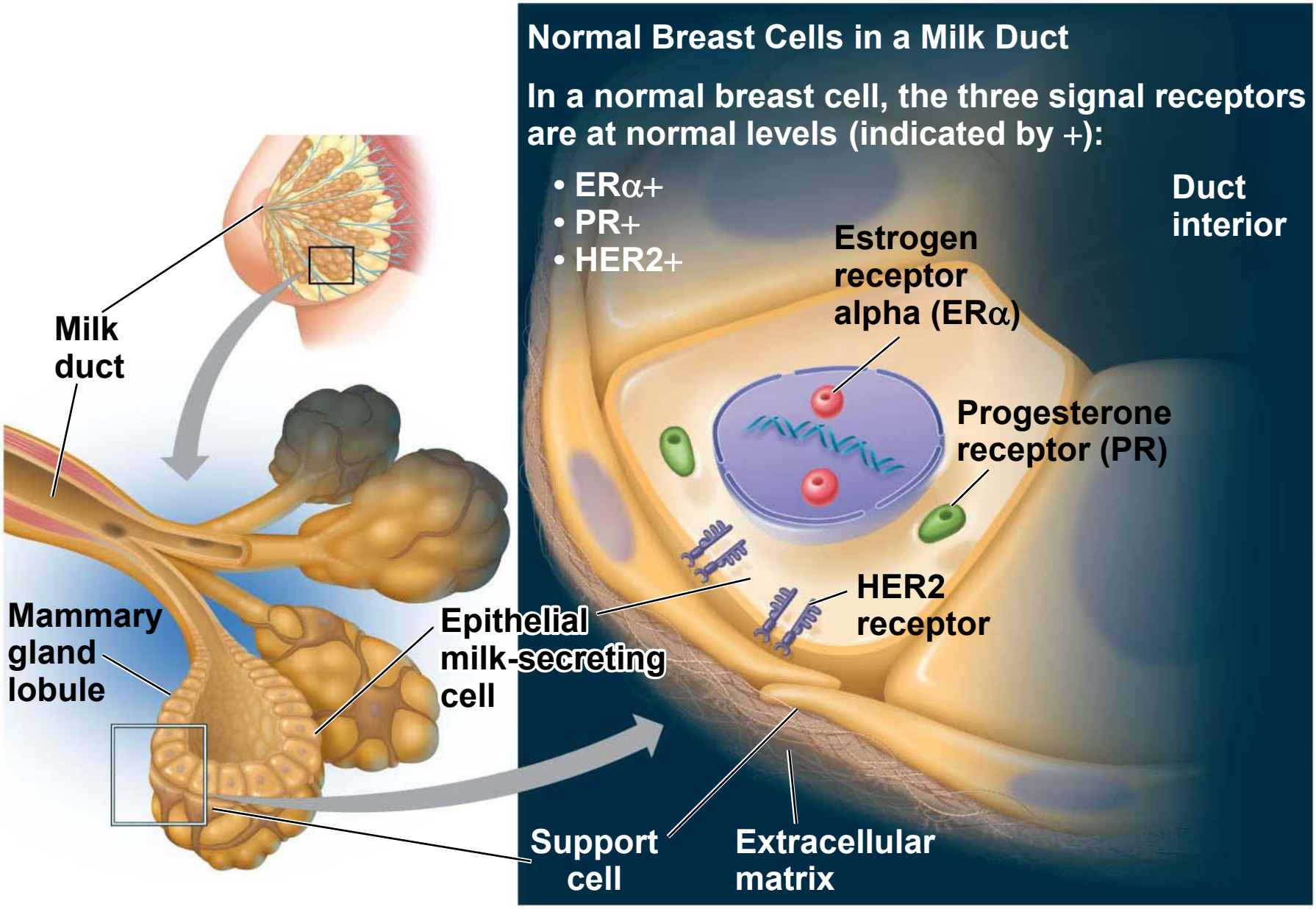


Figure 16.21-2a

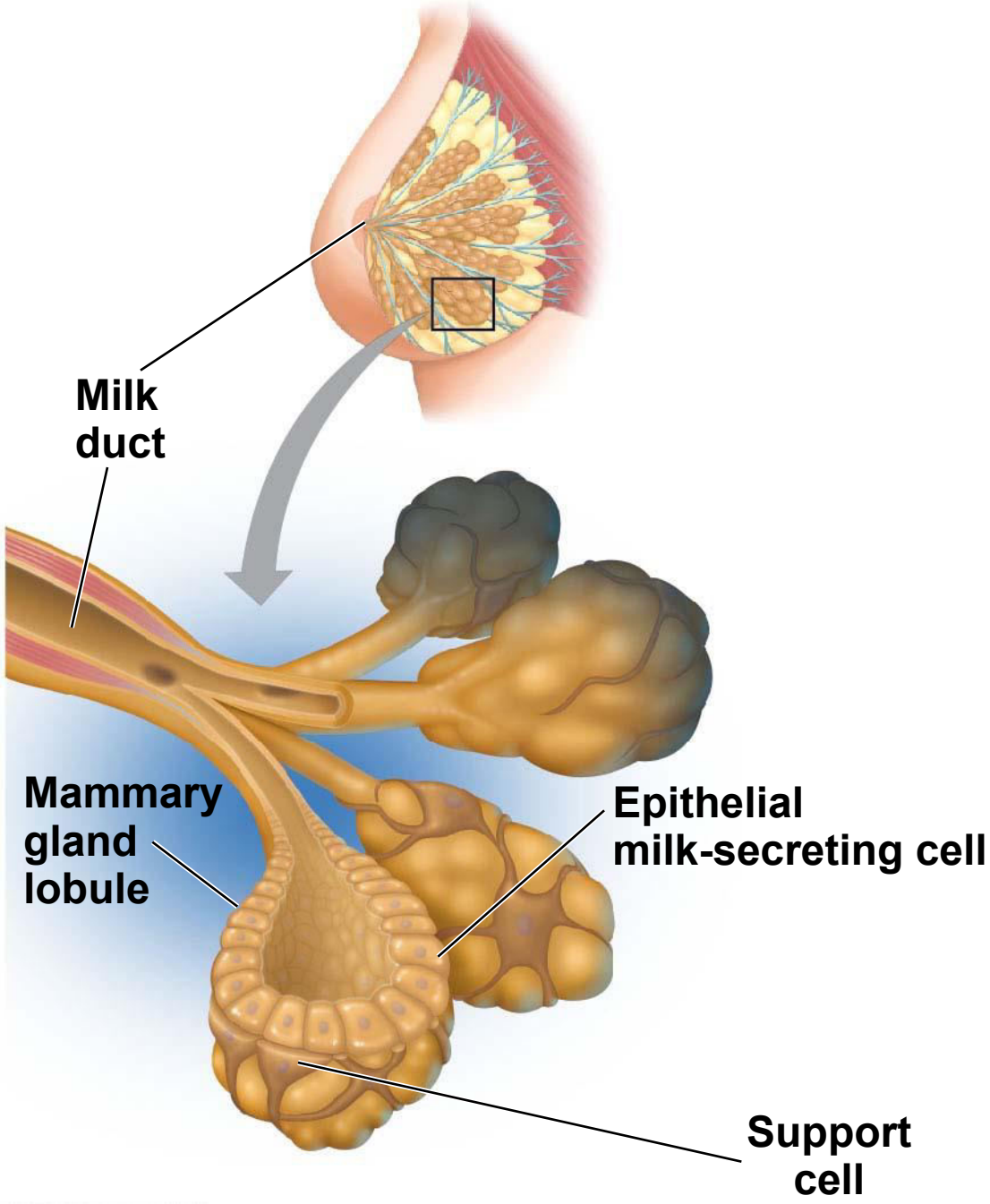


Figure 16.21-2b

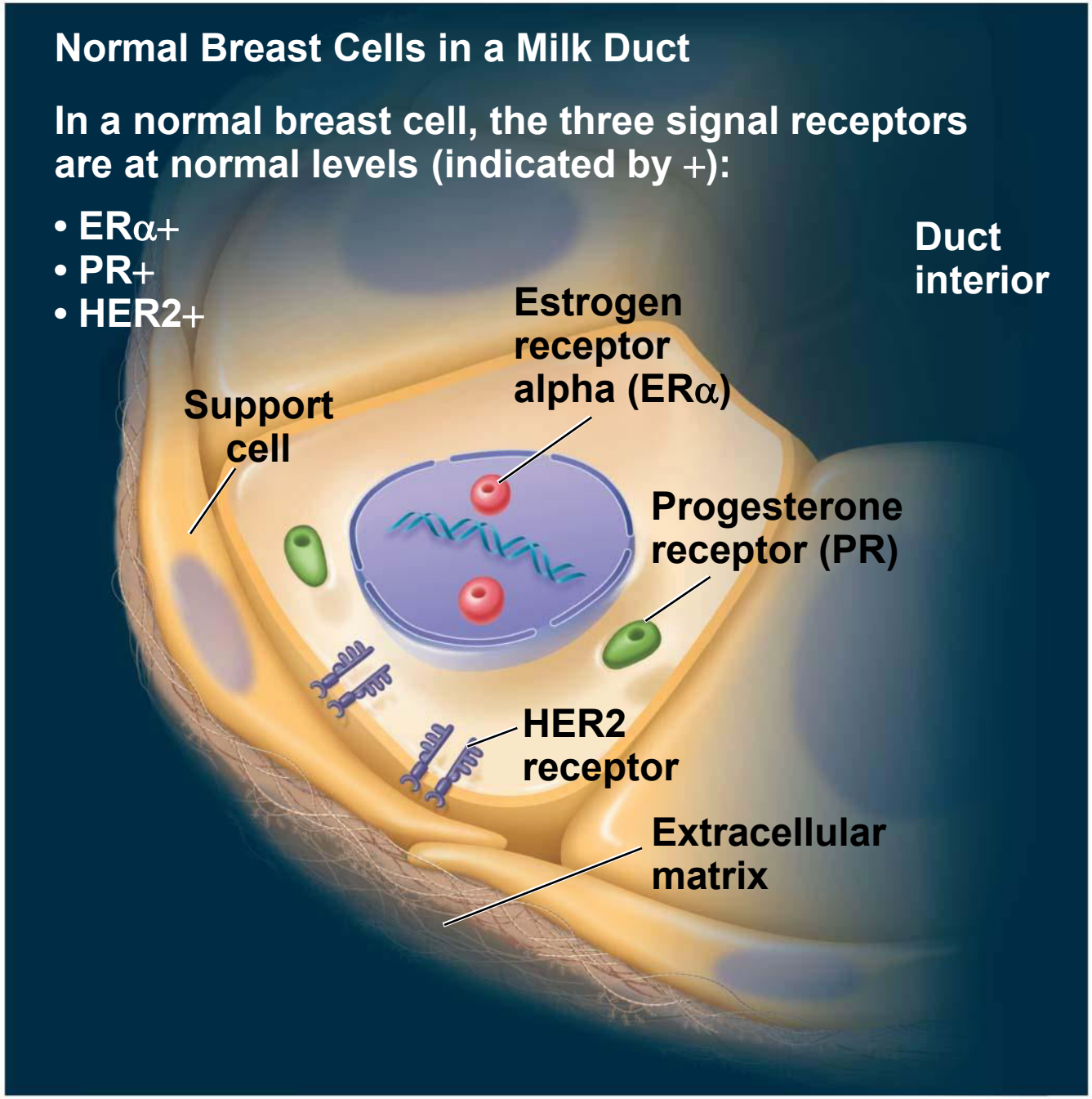
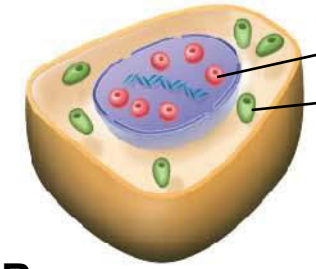


Figure 16.21-3

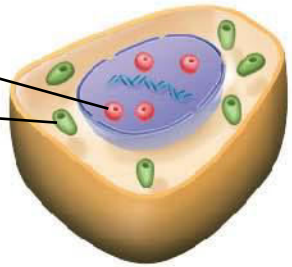
MAKE CONNECTIONS: Genomics, Cell Signaling, and Cancer

Luminal A



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

Luminal B

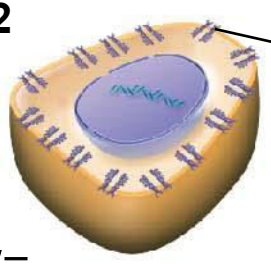


- ERα++
- PR++
- HER2– (shown here); some HER2++
- 15–20% of breast cancers
- Poorer prognosis than luminal A subtype

Basal-like

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

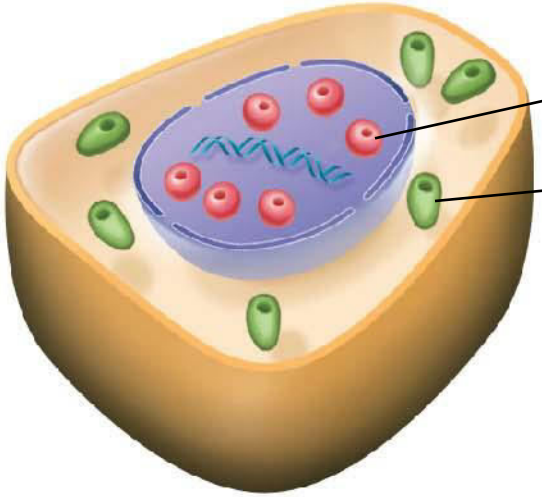
HER2



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

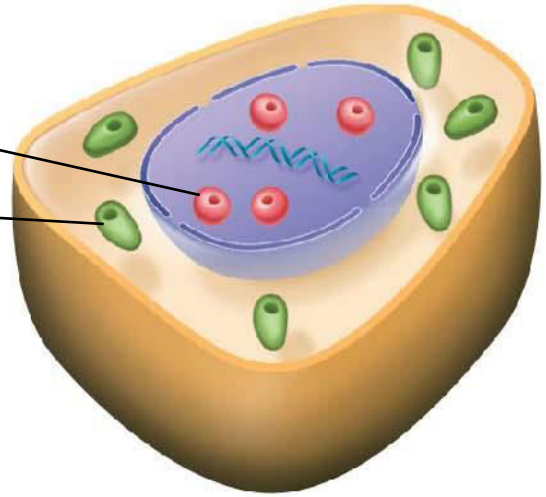
Figure 16.21-3a

Luminal A



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

Luminal B



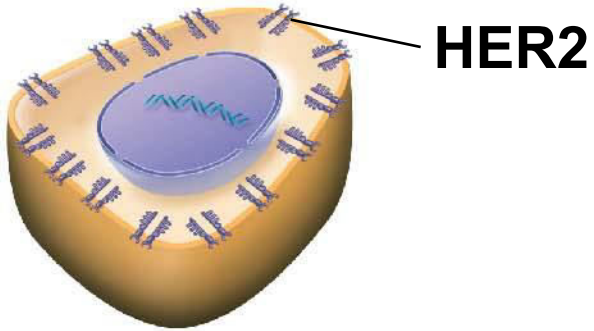
- ERα++
- PR++
- HER2– (shown here); some HER2++
- 15–20% of breast cancers
- Poorer prognosis than luminal A subtype

Figure 16.21-3b

Basal-like

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

HER2

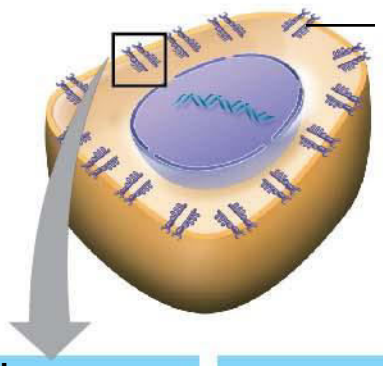


- ERα–
- PR–
- HER2++
- 10–15% of breast cancers
- Poorer prognosis than luminal A subtype

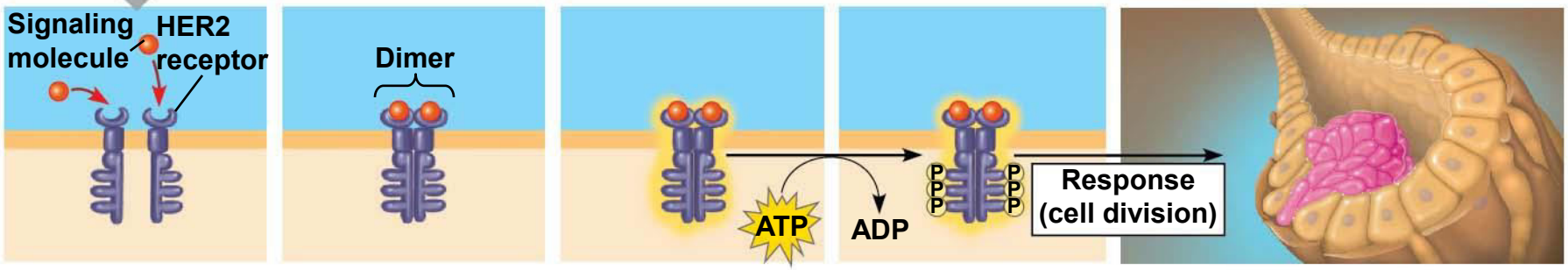
Figure 16.21-4

MAKE CONNECTIONS: Genomics, Cell Signaling, and Cancer

HER2



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



Treatment with Herceptin for the HER2 subtype

Figure 16.21-4a

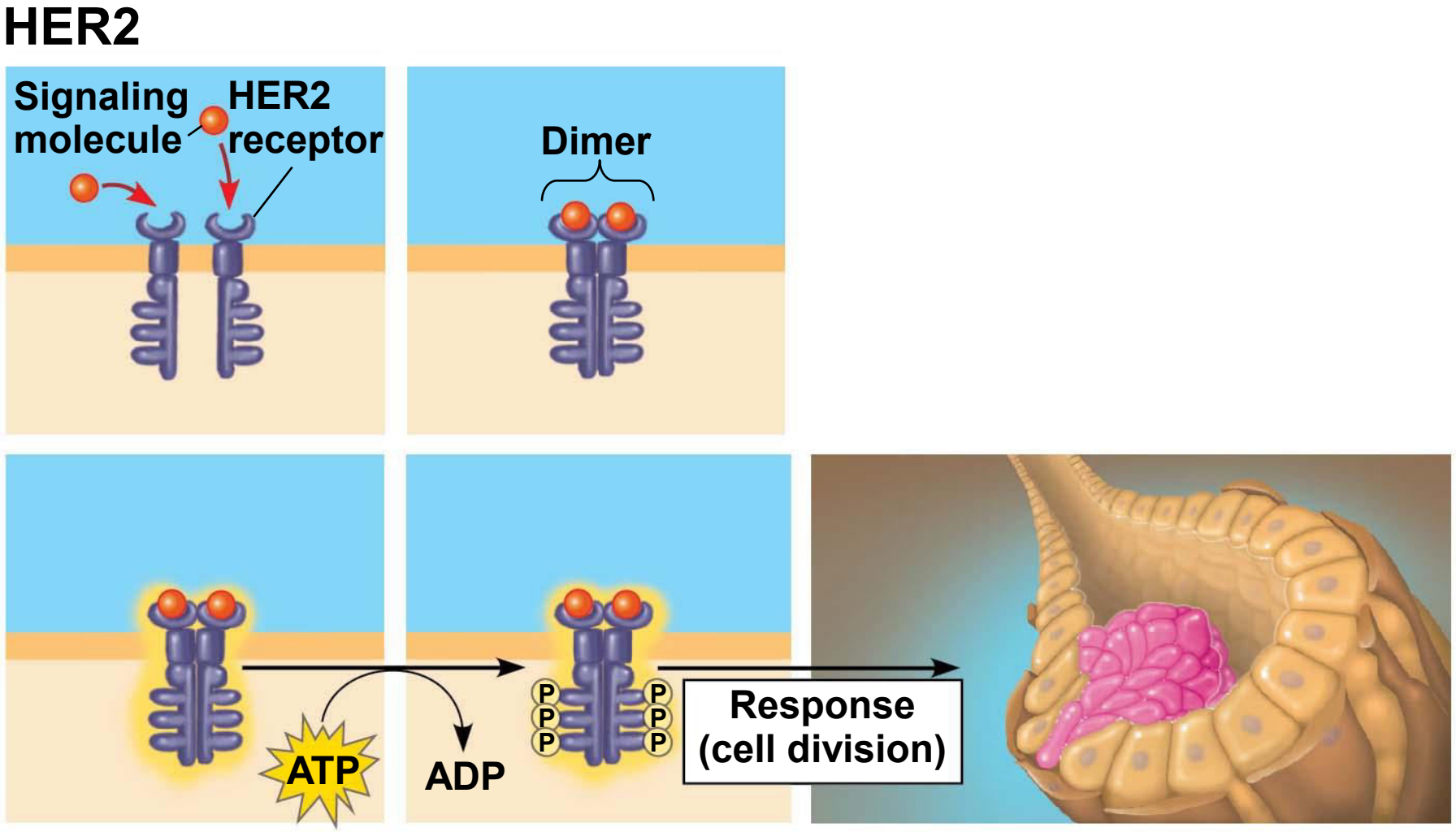


Figure 16.21-4b

Treatment with Herceptin for the HER2 subtype

Inherited Predisposition and Other Factors Contributing to Cancer

- Individuals can inherit oncogenes or mutant alleles of tumor-suppressor genes
- Inherited mutations in the tumor-suppressor gene *adenomatous polyposis coli* (*APC*) 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

- DNA breakage can contribute to cancer, thus the risk of cancer can be lowered by minimizing exposure to agents that damage DNA, such as ultraviolet radiation and chemicals found in cigarette smoke
- Also, viruses play a role in about 15% of human cancers by donating an oncogene to a cell, disrupting a tumor-suppressor gene, or converting a proto-oncogene into an oncogene

Figure 16.3

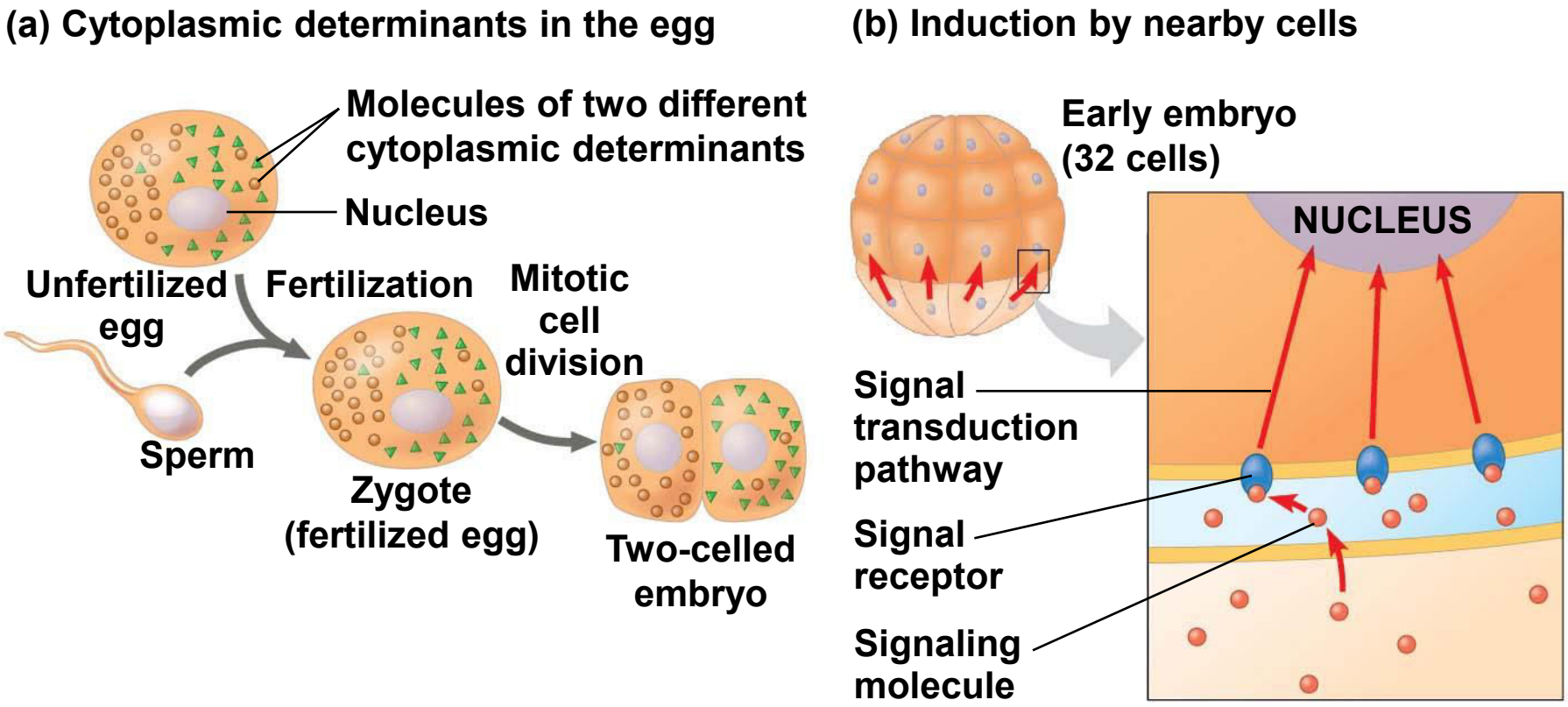
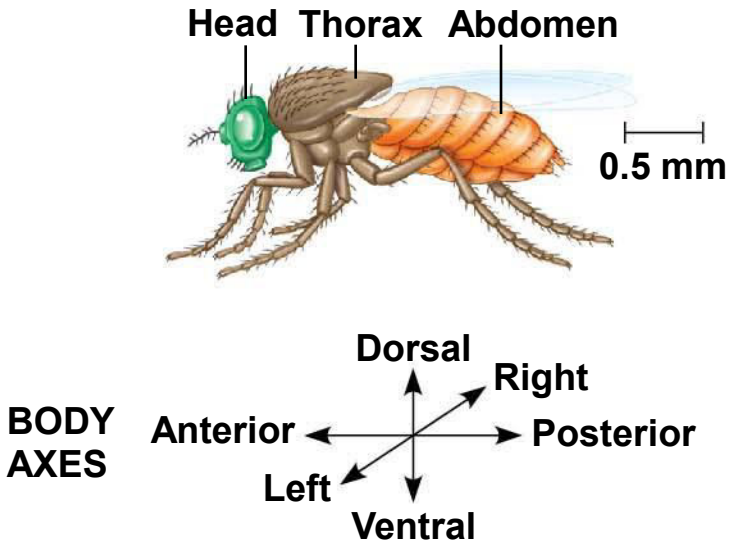
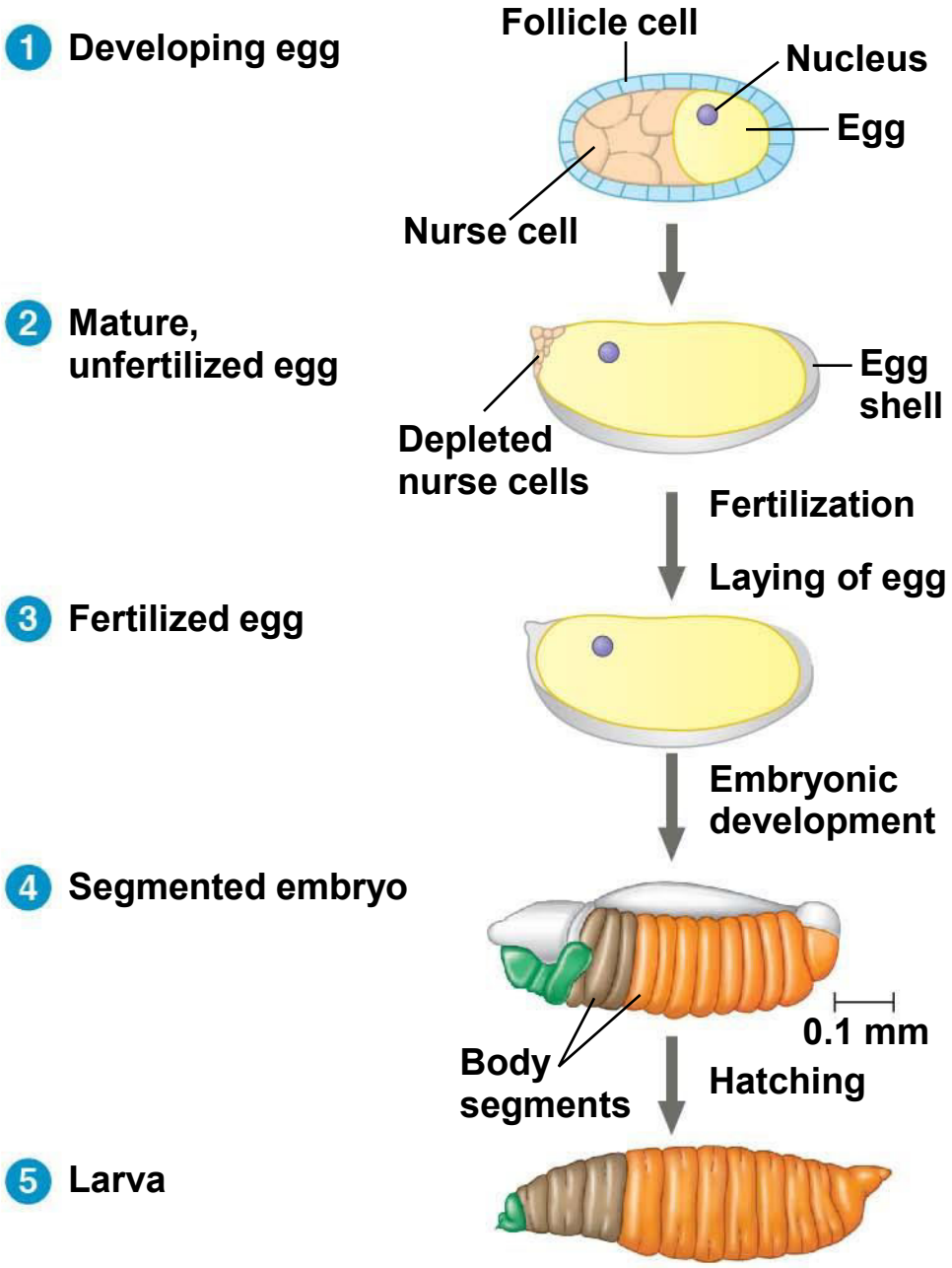


Figure 16.7

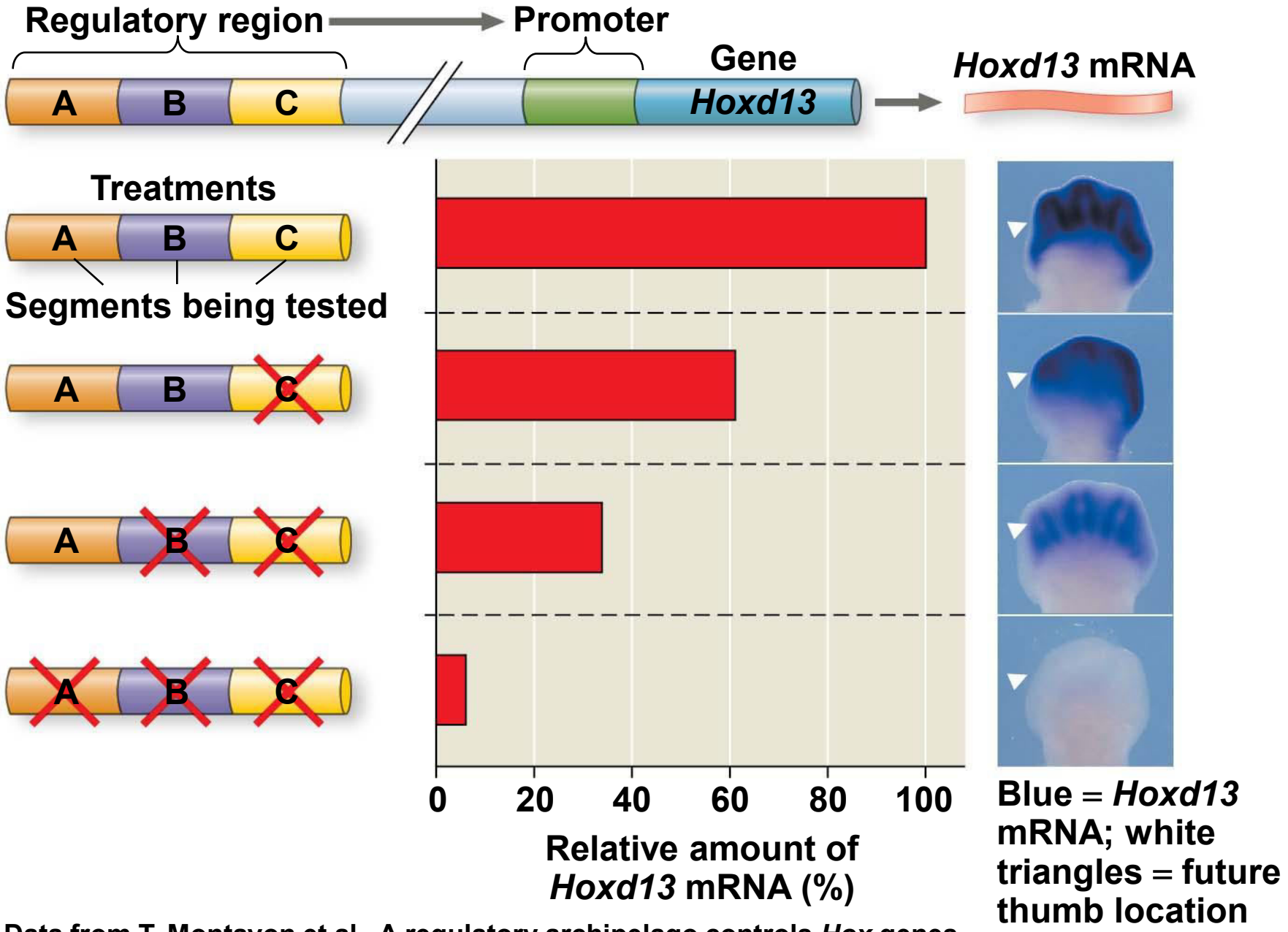


(a) Adult



(b) Development from egg to larva

Figure 16.UN01-1



Data from T. Montavon et al., A regulatory archipelago controls *Hox* genes transcription in digits, *Cell* 147:1132–1145 (2011). doi 10.1016/j.cell.2011.10.023

Figure 16.UN01-2

Figure 16.UN02

Cytoplasmic determinants

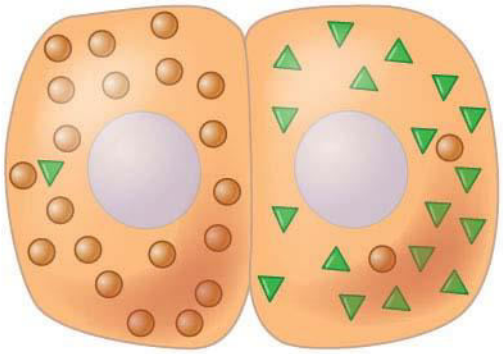


Figure 16.UN03

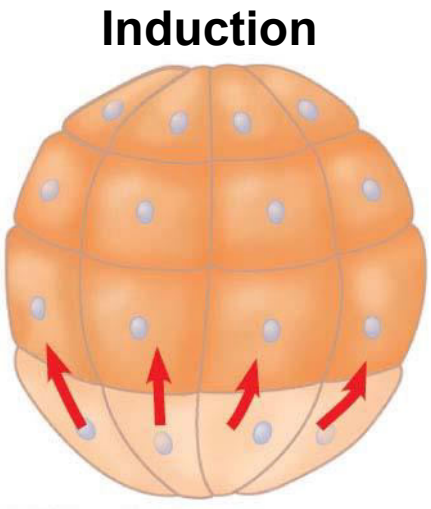


Figure 16.UN04

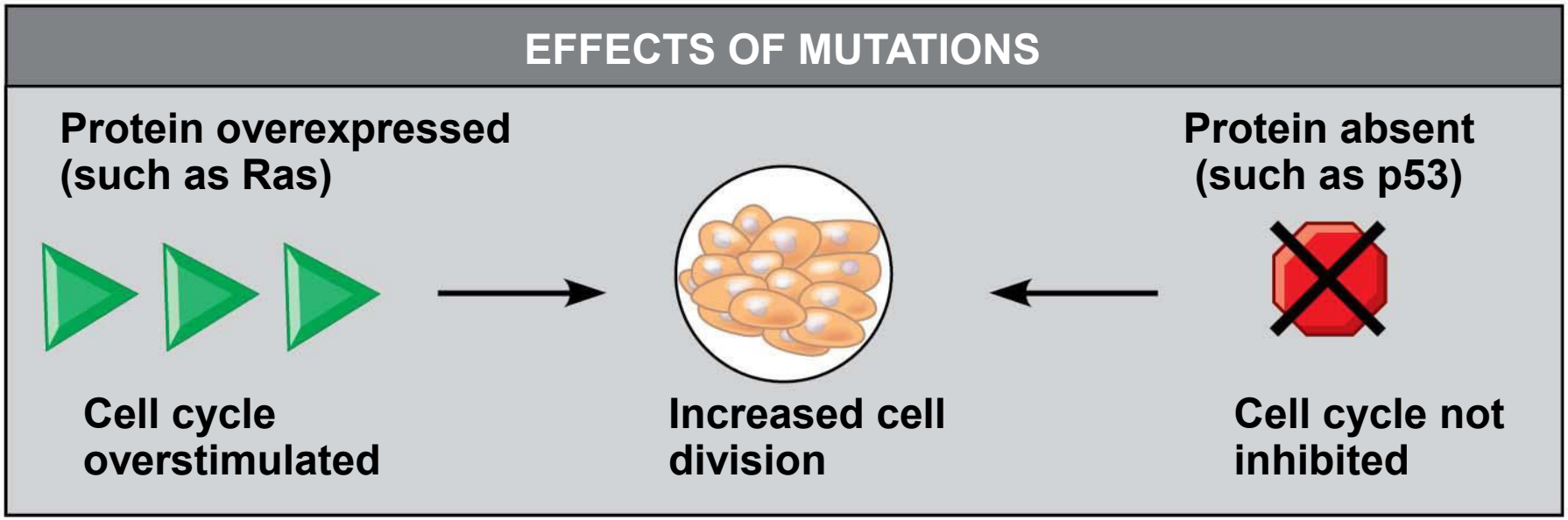


Figure 16.UN05