Chapter 21

The Genetic Basis of Development

Key Concepts

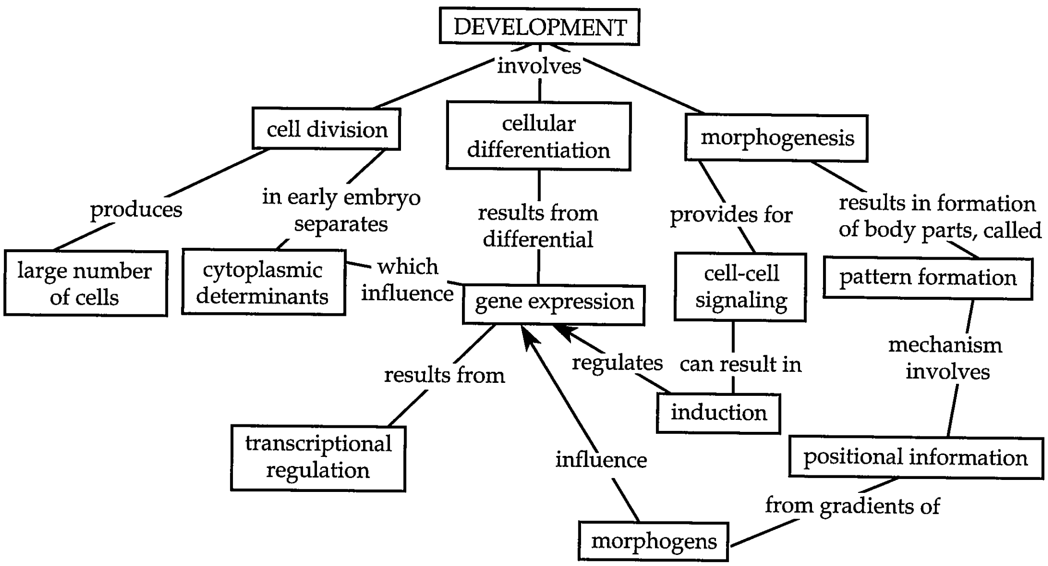
21.1 Embryonic development involves cell division, cell differentiation, and morphogenesis

21.2 Different cell types result from differential gene expression in cells with the same DNA

21.3 Pattern formation in animals and plants results from similar genetic and cellular mechanisms

21.4 Comparative studies help explain how the evolution of development leads to morphological diversity

Framework



Chapter Review

The application of molecular genetics and DNA technology, along with the study of developmental mutants, has revolutionized the field of development. In order to study broad biological principles, researchers often choose a **model organism** that is representative of a larger group, well suited for answering particular types of research questions, and easy to grow in the lab.

The fruit fly *Drosophila melanogaster* has a long history as a model organism for genetic studies. Its genome is 180×10^6 base pairs long (180 millionbases, Mb) and contains about 13,700 genes. Although its early embryology differs from that of other animals, research on *Drosophila* development has provided key information about animal development.

The transparent nematode *Caenorhabditis elegans* has several advantages as a model organism: its ease of culture and short generation time, its hermaphroditic reproduction that allows for easy detection of recessive mutations, and its small number of cells that has allowed researchers to reconstruct the ancestry of every adult cell. Its genome is 97 Mb long and has about 19,000 genes.

Researchers have already developed a great deal of knowledge of the mouse *Mus musculus* and are now able to manipulate genes to make transgenic mice and mice in which certain genes are "knocked out" by mutation. Their large genome (2,600 Mb with 25,000 genes) and in utero development are disadvantages.

The zebrafish *Danio rerio* reproduces in large numbers and has transparent embryos that develop outside the mother. Its genome is estimated at 1,700 Mb and is still being mapped and sequenced.

Arabidopsis thaliana, a small plant in the mustard family, is easily grown in test tubes, is self-fertilizing, produces large numbers of offspring, and has a relatively small genome—about 118 Mb with an estimated 25,500 genes.

21.1 Embryonic development involves cell division, cell differentiation, and morphogenesis

The three key processes of embryonic development are cell division, the production of large numbers of cells; **cell differentiation,** the formation of cells specialized in structure and function; and **morphogenesis,** the physical processes that produce body shape and form.

Morphogenetic events establish body axes early in development. In animals, but not in plants, movements of cells and tissues produce body form. Growth and morphogenesis continue throughout the life of a plant, relying on the perpetually embryonic regions in root and shoot tips known as **apical meristems** to produce new organs and growth.

■ INTERACTIVE QUESTION 21.1

What are some of the important criteria for model organisms chosen for the study of developmental genetics?

21.2 Different cell types result from differential gene expression in cells with the same DNA

Evidence for Genomic Equivalence Nearly all cells of an organism have the same genes; they have *genomic equivalence*. F. C. Steward demonstrated genomic equivalence in plants by growing new carrot plants from differentiated root cells. Most plant cells remain **totipotent,** retaining the ability to form a complete new organism.

Cloning involves producing genetically identical individuals (**clones**) from a single somatic cell of a multicellular organism.

Early evidence of genomic equivalence in animals was provided by the work of Briggs, King, and Gurdon, who transplanted nuclei from embryonic and tadpole cells into enucleated frog egg cells, a method called *nuclear transplantation*. The ability of the transplanted nucleus to direct normal development was inversely related to its developmental age. The base sequence of an animal cell's DNA usually does not change during differentiation, but its chromatin structure may be modified and thus its nuclear potency restricted.

In 1997, Scottish researchers reported cloning an adult sheep by transplanting a nucleus from a fully differentiated mammary cell into an unfertilized enucleated egg cell, and then implanting the resulting early embryo into a surrogate mother. The mammary cell was induced to dedifferentiate by culturing in a nutrient-poor medium that arrested the cell cycle in the G_0 phase.

The *reproductive cloning* of numerous mammals has shown that cloned animals do not always look and behave identically. Environmental influences and random events play a role in development.

■ INTERACTIVE QUESTION 21.2

Although numerous mammals have now been cloned successfully, most cloned embryos fail to develop normally, and many cloned animals have various defects. What is a likely cause of these developmental failures?

Stem cells are relatively unspecialized cells that continue to reproduce themselves and can, under proper conditions, differentiate into one or more types of cells. *Embryonic stem cells* taken from early embryos can be cultured indefinitely. They are totipotent and can differentiate into cells of any type. Adult stem cells have been isolated from various tissues and grown in culture. Such cells, capable of producing multiple but not all types of cells, are called **pluripotent.** Both types of stem cells can be induced to differentiate into specialized cells. Stem cell research has the potential to provide cells to repair organs that are damaged or diseased. *Therapeutic cloning* of embryonic stem cells, although different from reproductive cloning of humans, still raises ethical debates.

Transcriptional Regulation of Gene Expression During Development A cell's developmental history leads to its eventual differentiation as a cell with a specific structure and function. **Determination** is a term used to describe the condition when a cell is irreversibly committed to its fate. When a cell becomes differentiated, it expresses genes for *tissue-specific proteins*, and that expression is usually controlled at the level of transcription.

The embryonic precursor cells from which muscle cells arise have the potential to develop into a number of different cell types. Once they become committed to becoming muscle cells, they are called *myoblasts.* Researchers have isolated mRNA from myoblasts, prepared a library of cDNA genes, and inserted them into separate embryonic precursor cells in order to identify "master regulatory genes." One of these is *myoD,* which codes for a transcription factor named MyoD that binds to control elements and initiates transcription of other muscle-specific transcription factors. These secondary transcription factors then activate muscle-protein genes. MyoD also turns on genes that block the cell cycle and stop cell division, and it activates its own transcription, thus maintaining the cell's differentiated state.

■ INTERACTIVE QUESTION 21.3

The MyoD protein has been shown to be able to transform some, but not all, differentiated cells into muscle cells. Why doesn't it work on all kinds of cells?

Cytoplasmic Determinants and Cell-Cell Signals in Cell Differentiation The cytoplasm of an unfertilized egg cell contains maternal mRNA, proteins, and other substances that are unevenly distributed, and the first few mitotic divisions separate these components and expose cell nuclei to different environments. These maternal components of the egg cell that influence early development by regulating gene expression are called **cytoplasmic determinants.**

The other important source of developmental control comes from signals received from other embryonic cells. Change in the gene expression of target cells resulting from chemical or physical signals from other cells is called **induction.**

21.3 Pattern formation in animals and plants results from similar genetic and cellular mechanisms

Pattern formation is the ordering of cells and tissues into their characteristic structures and locations. In animals, pattern formation takes place in embryos and juveniles; in plants, it occurs continually in the apical meristems.

An animal's three major body axes are laid out early in development. Cells and their progeny develop in response to molecular cues called **positional information** that tell a cell where it is located relative to the body axes and neighboring cells.

Drosophila Development: A Cascade of Gene Activations A fruit fly's body consists of a series of segments grouped into the head, thorax, and abdomen. The anterior-posterior and dorsal-ventral axes are determined by positional information provided by cytoplasmic determinants localized in the unfertilized egg. After fertilization, positional information establishes the proper number of segments and then triggers the formation of each segment's characteristic structures.

Each egg cell in the mother's ovary is surrounded by nurse cells and follicle cells that supply nutrients and other molecules needed for development. Eggs are laid following fertilization, and the first ten mitotic divisions occur without cytokinesis, yielding a multinucleated embryo. In the blastoderm stage, nuclei migrate to the periphery, and plasma membranes divide the nuclei into separate cells. Segments become visible, organs form, and a wormlike larva hatches out of the egg shell. Following three larval stages and molts, the larva becomes a pupa. Metamorphosis produces an adult fly, with distinct segments bearing characteristic appendages.

In the 1940s, E. B. Lewis studied developmental mutants and was able to map certain mutations that control development in the late embryo to specific genes. In the late 1970s, C. Nüsslein-Volhard and E. Wieschaus undertook a search for the genes that control segment formation. They studied mutations that were **embryonic lethals,** which prevented the development of viable larvae. They exposed flies to a chemical mutagen and then performed many thousands of crosses to detect recessive mutations causing death of embryos or larvae with abnormal segmentation. They identified

1,200 genes essential for development, 120 of which were involved in pattern formation leading to normal segmentation.

Maternal effect genes are genes of the mother that code for proteins or mRNA that are deposited in the unfertilized egg. These genes are also called **egg-polarity genes** because they determine the anterior-posterior and dorsal-ventral axes of the egg and consequently the embryo.

One egg-polarity gene is *bicoid*. The product of the *bicoid* gene is concentrated at one end of the larva and responsible for determining its anterior end. Offspring of a mother defective for this gene have two tail regions and lack the front half of the body. Researchers used the cloned *bicoid* gene as a probe and found *bicoid* mRNA concentrated in the most anterior end of egg cells. Following fertilization, the mRNA is translated into Bicoid protein, which diffuses posteriorly, forming a gradient in the early embryo. Proteins whose gradients determine the posterior end and establish the dorsal-ventral axis have also been identified. Such substances, whose gradients establish an embryo's axes or other features, are called **morphogens.**

The products of the egg-polarity genes are transcription factors. Gradients of these morphogens affect the expression of the embryo's **segmentation genes,** which direct the formation of segments. In a cascade of gene activations, products of the *gap genes* control the localized expression of *pair-rule genes,* which in turn activate specific *segment polarity genes.* The products of many of these segmentation genes are transcription factors; others code for cell-signaling molecules or their receptors, which are necessary for the cell-cell communication needed once plasma membranes have separated the cells of the embryo.

Master regulatory genes called **homeotic genes** next determine each segment's anatomical fate by encoding transcription factors that control the expression of genes that build a segment's characteristic structures.

INTERACTIVE QUESTION 21.4

a. What could cause a mutant fly embryo to develop two tail ends but no head?

b. What could cause a mutant embryo to have half the normal number of segments?

c. What could cause a fruit fly to have legs growing out of its head in place of antennae?

C. elegans: *The Role of Cell Signaling* Inductive signaling from one group of cells to nearby cells influences the gene expression that leads to cellular differentiation. Researchers have determined the complete cell lineage of *C. elegans*. As early as the four-cell stage, cell signaling is involved in directing the developmental fate of cells. The binding of a cell-surface protein produced by cell 4 to a receptor protein on cell 3 triggers cellular events in cell 3 that lead to different fates for its two daughter cells—the posterior one will form the intestine, the anterior one develops into muscle and gonads.

Later in development, six precursor cells of the second-stage larva become destined to give rise to the vulva. An *anchor cell* of the embryonic gonad secretes a signal protein that reaches the closest precursor cell in high concentration. This inducer stimulates the cell to divide and differentiation to form the inner part of the vulva. Lower concentrations of the signal reach the two adjacent precursor cells. These cells are stimulated to divide and differentiate into the outer vulva. The remaining three cells are too distant to receive the signal; they develop into epidermal cells.

INTERACTIVE QUESTION 21.5

Developmental studies of *Drosophila* and *C. elegans* support the following generalizations regarding the role of induction in development:

a. The pathway to organ formation often follows a series of steps that involve ________ ________.

b. The effect of an inducer on its possible target cells often depends on the ________ of the inducer.

c. Inducers often initiate ________ ________ in the target cell that lead to ________ ________ of important developmental genes.

Lineage analysis of *C. elegans* has established that cell suicide or **apoptosis** occurs numerous times during normal development. Signals activate a cascade of "suicide" proteins, the cell shrinks and forms blebs, and neighboring cells engulf the membrane-bound remains. Genetic screening has identified three key genes involved in cell death: *ced-9* that produces a protein that inhibits the activity of the protein products of *ced-3* and *ced-4*. In the case of apoptosis, protein activity is regulated, not transcription or translation. When a cell receives a "death" signal on its membrane receptor, Ced-9 protein becomes inactivated, and the apoptosis pathway activates enzymes that hydrolyze the cell's proteins and DNA. Ced-3 is the main *caspase* (protease) of apoptosis in the nematode. One of several apoptosis pathways in mammals involves proteins, including cytochrome *c*, that are released from mitochondria.

■ INTERACTIVE QUESTION 21.6

a. What can one conclude from the fact that some mammalian apoptosis proteins are homologous to the Ced-3, Ced-4, and Ced-9 proteins of nematodes?

b. Give some examples of programmed cell death in humans.

Plant Development: Cell Signaling and Transcriptional Regulation The developmental fates of plant cells depend less on cell lineage and more on positional information. Embryonic development occurring in a seed is difficult to study, but research on apical meristems has provided insight into the genetics and control of plant development.

Environmental cues trigger signal-transduction pathways through which shoot meristems are transformed to floral meristems. A floral meristem consists of three cell layers, from which the organs of the flower—the carpels, stamens, petals, and sepals-arise. Grafting stems of *fascinated (f)* mutant tomato plants onto wild-type plants produces shoots from the graft site that are **chimeras,** having a mixture of cells from different genetic backgrounds. The number of organs produced in flowers of the chimeras depends on the parental source of the innermost cell layer, which must somehow induce the two outer layers to produce its specified number of organs.

Analogous to homeotic genes in animals are plant **organ identity genes** that determine what type of structure develops from a particular outgrowth from the floral meristem. These genes have been most extensively studied with floral mutants in *Arabidopsis.* The organ identity genes encode transcription factors that control the transcription of many other genes responsible for organ development.

21.4 Comparative studies help explain how the evolution of development leads to morphological diversity

Biologists in the field of evolutionary developmental biology ("evo-devo") compare development processes to understand how they have evolved and how minor changes may lead to diverse forms of life.

Widespread Conservation of Developmental Genes Among Animals A sequence of 180 nucleotides called a **homeobox** has been found in each *Drosophila* homeotic gene. The same or very similar homeobox nucleotide sequences have been identified in homeotic genes of many animals. These are often called *Hox* genes in mammals. Related sequences are found in regulatory genes of yeast, plants, and even prokaryotes. These similarities indicate that the homeobox must have arisen early and been conserved through evolution as part of genes involved in regulation of gene expression and development.

The homeobox sequence is translated into a 60-amino-acid sequence known as a *homeodomain*. This portion of the resulting transcription factor binds to DNA, while other domains interact with other transcription factors to recognize specific enhancers or promoters. Proteins with homeodomains probably coordinate the transcription of groups of developmental genes and thus control pattern formation.

Many other genes involved in development, such as those coding for components of signaling pathways, are highly conserved. The differing patterns of expression of these genes in different body areas may explain the development of animals with different body plans.

■ INTERACTIVE QUESTION 21.7

In *Drosophila*, homeobox sequences have been found not only in the homeotic genes, but also in the egg-polarity gene bicoid, in several segmentation genes, and in the master regulatory gene for eye development. Is this just a coincidence? Explain.

Comparison of Animal and Plant Development The processes of development evolved independently in plants and animals due to their ancient divergence. The rigid cell walls of plants restrict movement, and morphogenesis relies more on the orientation of cell divisions and cell enlargement. Some similarities persist from their common ancestral microbe. In both, development involves a cascade of transcriptional regulators, although the master control genes are different in the two groups.

Word Roots

apic- = tip (*apical meristem:* embryonic plant tissue in the tips of roots and in the buds of shoots that supplies cells for the plant to grow in length)

morph- = form; **-gen** = produce (*morphogen:* a substance that provides positional information in the form of a concentration gradient along an embryonic axis)

toti- = all; **-potent** = powerful (*totipotent:* the ability of a cell to form all parts of the mature organism)

Structure Your Knowledge

1. Describe the cascade of gene activations that leads to the development of a fruit fly.
2. How might the mechanism for transcriptional regulation differ for cytoplasmic determinants and the cell-cell signaling involved in induction?

Test Your Knowledge

MULTIPLE CHOICE: *Choose the one best answer.*

1. Which of the following is descriptive of a cell that is differentiated?
   - **a.** The cell's development fate has been decided, although it may not look any different from another precursor cell.
   - **b.** The cell has definite anterior-posterior and dorsal-ventral axes.
   - **c.** The cell has developed cell surface receptors that allow it to receive signals from other cells.
   - **d.** The cell has been induced to transcribe all its genes.
   - **e.** The cell is producing tissue-specific proteins and has its characteristic structure.
2. Morphogenesis in plants results from
   - **a.** migration of cells from the apical meristems to produce three tissue layers.
   - **b.** differences in the plane of cell division and the direction of cell expansion.
   - **c.** cytoplasmic determinants that were deposited in the egg cell.
   - **d.** the differentiation of cells within the apical meristem.
   - **e.** the production of cell walls and plasmodesmata that communicate between cells.
3. In which of these model organisms has it been possible to create a complete cell lineage?
   - **a.** *Drosophila melanogaster* (fruit fly)
   - **b.** *Danio rerio* (zebrafish)
   - **c.** *Caenorhabditis elegans* (nematode)
   - **d.** *Mus musculus* (mouse)
   - **e.** *Arabidopsis thaliana* (common wall cress)
4. Cytoplasmic determinants are
   - **a.** unevenly distributed cytoplasmic components of an unfertilized egg.
   - **b.** often involved in transcriptional regulation.
   - **c.** often separated in the first few mitotic divisions following fertilization.
   - **d.** maternal contributions that help to direct the initial stages of development.
   - **e.** all of the above.
5. For which of the following can the cloning of Dolly the sheep best be used to provide evidence?
   - **a.** totipotency of most adult animal cells
   - **b.** determination of most adult animal cells
   - **c.** embryonic nature of mammary cells
   - **d.** genomic equivalence of most animal cells
   - **e.** immune tolerance of embryos in mammals
6. The fact that transplanted nuclei from most tadpole cells were unable to direct normal development in an enucleated frog cell gives evidence for
   - **a.** the differentiation of adult cells resulting in the deletion of certain key genes.
   - **b.** the totipotency of adult cells even when they are differentiated.
   - **c.** changes in chromatin during development that may make genes no longer available for transcription.
   - **d.** the dedifferentiation of embryonic cells.
   - **e.** the need for cytoplasmic determinants to direct initial developmental stages.
7. Pattern formation in animals is based on
   - **a.** the first few mitotic divisions.
   - **b.** the induction of cells by the initial fertilized egg.
   - **c.** the locations and activity of apical meristems.
   - **d.** differentiation of cells, which then migrate together to form tissues and organs.
   - **e.** positional information a cell receives from gradients of morphogens.
8. Which of the following developmental processes involves apoptosis?
   - **a.** the development of the vulva in *C. elegans*
   - **b.** the sequential activation of segmentation genes in *Drosophila*
   - **c.** the production of genetically engineered mice with "knockout" genes
   - **d.** the development of separate fingers and toes during mammalian development
   - **e.** the induction of tissue layers in the production of the organs from a floral meristem

9. A fruit fly that has two sets of wings growing from its thorax (instead of a single pair of wings and a pair of small balancing organs) would probably have mutations in its
   a. gap genes.
   b. segment polarity genes.
   c. homeotic genes.
   d. egg-polarity genes.
   e. pair-rule genes.

10. What would be the fate of a *Drosophila* larva that inherits two copies of a mutant *bicoid* gene (one mutant allele from each heterozygous parent)?
    a. It develops two heads, one at each end of the larva.
    b. It develops two tails, one at each end of the larva.
    c. It develops normally but produces mutant larvae that have two tail regions.
    d. It develops into an adult with legs growing out of its head.
    e. It receives no *bicoid* mRNA from the nurse cells of its mother.

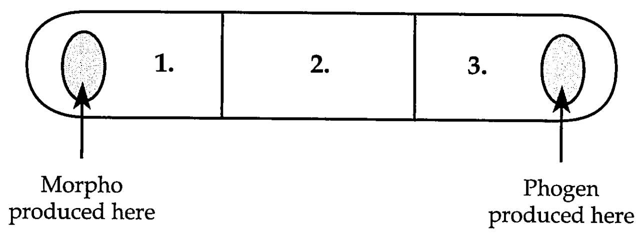
11. A highly conserved nucleotide sequence that has been found in master regulatory genes in many diverse organisms is called a
    a. homeobox.
    b. homeodomain.
    c. transcription factor.
    d. homeotic gene.
    e. morphogen.

12. The gene *ced-9* codes for a protein that inactivates the proteins of suicide genes found in the genome of *C. elegans*. For development to proceed normally, the *ced-9* gene
    a. should be activated in all cells, but its protein product must remain inactive.
    b. should be activated in all cells, but its product will be inactivated when cells programmed to die receive the proper signal.
    c. should be inactivated in all cells except when a cell receives a signal to die.
    d. should be inactivated only in those cells that must die for proper development to occur.
    e. should code for a transcription factor that attaches to the enhancers of other suicide genes.

13. Once the developmental fate of a cell is set, the cell is said to be
    a. determined.
    b. differentiated.
    c. totipotent.
    d. genomically equivalent.
    e. induced.

14. Which of the following is *not* true of adult stem cells?
    a. They have been found not only in bone marrow, but also in other tissues, including the adult brain.
    b. Although more difficult to grow than embryonic stem cells, they have been successfully grown in culture and made to differentiate into specialized cells.
    c. They are differentiated cells that can be induced to dedifferentiate and become totipotent.
    d. As pluripotent cells, they are capable of developing into several different types of cells under appropriate conditions.
    e. These relatively unspecialized cells continually reproduce themselves.

15. In this hypothetical embryo, a high concentration of a morphogen called morpho is needed to activate gene *P*; gene *Q* is active at medium concentrations of morpho or above; and gene *R* is expressed as long as there is any quantity of morpho present. A different morphogen called phogen has the following effects: activates gene *S* and inactivates gene *Q* when at medium to high concentrations. If morpho and phogen are diffusing from where they are produced at the opposite ends of the embryo, which genes will be expressed in region 2 of this embryo? (Assume diffusion through the three regions from high at source to medium to low concentration.)



    a. genes *P*, *Q*, *R*, and *S*
    b. genes *P*, *Q*, and *R*
    c. genes *Q* and *R*
    d. genes *R* and *S*
    e. gene R

16. What do most master regulatory genes do?
    a. produce mRNAs that function as cytoplasmic determinants
    b. code for tissue-specific proteins that differentiate cells
    c. produce proteins that function as inducers to neighboring cells, initiating signaling pathways that activate transcription factors
    d. produce transcription factors that coordinate the expression of other transcription factors and groups of developmental genes
    e. either c or d