Chapter 16

Development, Stem Cells, and Cancer

Chapter Focus

Much of what has been learned about the genetic basis of development has come from experiments using **model organisms**, species that are easy to study and grow in the lab.

Chapter Review

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

A Genetic Program for Embryonic Development The three key processes of embryonic development are (1) cell division, the production of large numbers of cells; (2) cell **differentiation**, the formation of cells specialized in structure and function; and (3) **morphogenesis**, the physical processes that produce body structures and shape. All three processes are based on differential gene expression resulting from differences in gene regulation in cells.

Cytoplasmic Determinants and Inductive Signals 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 the nuclei in these new cells to different environments. These maternal components of the egg that influence early development by regulating gene expression are called **cytoplasmic determinants**.

The other important source of developmental control is signals from other embryonic cells in the form of contact with cell-surface molecules or secreted molecules. Change in the gene expression of target cells resulting from signals from other cells is called **induction**.

Sequential Regulation of Gene Expression During Cellular Differentiation A cell's developmental history leads to its eventual differentiation as a cell with a specific structure and function. The term **determination** is used to describe the condition in which a cell is irreversibly committed to its fate, even if it has not yet developed its final structure. When a cell becomes differentiated, it expresses genes for *tissue-specific proteins*, and that expression is usually controlled at the level of transcription.

How do muscle cells become determined and differentiated? 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 identified several "master regulatory genes" that cause myoblast determination. One of these is *myoD*, which codes for MyoD protein, a transcription factor that binds to specific control elements and initiates transcription of other muscle-specific transcription factors. These secondary transcription factors then activate muscle-protein genes. MyoD protein also turns on genes that block the cell cycle and stop cell division, and it activates its own transcription, thereby maintaining the cell's differentiated state.

FOCUS QUESTION 16.1

What is the difference between determination and differentiation?

Apoptosis: A Type of Programmed Cell Death In the best understood type of "programmed cell death," called **apoptosis**, cellular components are chopped up and packaged into vesicles that are released as "blebs" and then engulfed by scavenger cells.

Apoptosis occurs 131 times during normal development in *C. elegans*, a nematode that is a model organism for studies of embryonic development and

genetics. Signal transduction pathways activate a cascade of "suicide" proteins. There are similarities in genes encoding apoptotic proteins in all animals, and this process is essential to development as well as maintenance.

Pattern Formation: Setting Up the Body Plan **Pattern formation** is the spatial ordering of cells and tissues into their characteristic structures and locations. An animal's three major body axes are laid out early in development. Cytoplasmic determinants and inductive signals provide the molecular cues, called **positional information**, that tell a cell where it is located relative to the body axes and neighboring cells and determine how the cell and its progeny will develop.

Anatomical, genetic, and biochemical studies of *Drosophila* development have led to the discovery of some common developmental principles. 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. Nurse cells and follicle cells surrounding each egg supply mRNAs and nutrients needed for development. A fertilized egg develops into a segmented larva. The third larval stage forms a cocoon, in which the larva metamorphoses into an adult fly.

In the 1940s, E. B. Lewis studied developmental mutants and was able to map certain mutations that control pattern formation to specific genes, called **homeotic genes**. In the 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 that caused the death of embryos or resulted in larvae with abnormal segmentation. They identified 120 genes involved in pattern formation leading to normal segmentation.

Maternal effect genes are genes of the mother that, when mutant, result in a mutant offspring, regardless of the offspring's genotype. They 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 of the embryo.

One egg-polarity gene is *bicoid*. The product of the *bicoid* gene is concentrated at one end of the embryo and responsible for determining its anterior end. Offspring of a mother with two mutant alleles for this gene have two tail regions and lack the front half of the body. Researchers located 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. Gradients of such substances, which are called **morphogens**, establish an embryo's axes or other features—an example of the *morphogen gradient hypothesis*. Gradients of proteins transcribed from maternal mRNAs also determine the posterior end and establish the dorsal-ventral axis. Positional information encoded by the embryo's genes then establishes the proper number of segments and finally triggers the formation of each segment's characteristic structures.

FOCUS QUESTION: 16.2

What type of evidence established that Bicoid protein is a morphogen that determines the anterior end of a fruit fly?

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

Research established the *genomic equivalence* of all the cells of an organism, but is each cell able to express all of its genes? *Organismal cloning* involves producing genetically identical individuals (clones) from a single cell of a multicellular organism.

Cloning Plants and Animals F. C. Steward demonstrated that differentiation does not necessarily irreversibly change the DNA of a cell by growing new carrot plants from root cells. Most plant cells remain **totipotent**, retaining the ability to give rise to a complete new organism.

Early evidence of the totipotency of differentiated animal cells 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.

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 it in a nutrient-poor medium.

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.

FOCUS QUESTION 16.3

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 of Animals **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 (ES) cells* taken from early embryos can be cultured indefinitely and can differentiate into all cell types. Thus, ES cells are **pluripotent**. *Adult stem cells* have been isolated from various tissues and grown in culture. Such cells are capable of producing multiple (but not all) types of 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 and political issues. The transformation of adult stem cells into *induced pluripotent stem (iPS) cells* may provide sources of model cells for studying diseases and potential treatments, and may someday provide a patient's own iPS cells for regenerative treatments.

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

Types of Genes Associated with Cancer Chemical carcinogens, X-rays, or certain viruses most often cause the changes in the genes that regulate cell growth and division that lead to cancer. **Oncogenes**, or cancer-causing genes, were first found in certain types of viruses. Similar genes were later recognized in the genomes of humans and other animals. Cellular **proto-oncogenes**, which code for proteins that stimulate cell growth and division, may become oncogenes by several mechanisms, resulting in an overproduction or increased activity of growth-stimulating proteins.

Mutations in **tumor-suppressor genes** can contribute to the onset of cancer when they result in a decrease in the activity of proteins that prevent uncontrolled cell growth.

FOCUS QUESTION 16.4

a. Describe three genetic changes that can convert a proto-oncogene into an oncogene.

b. List three possible functions of tumor-suppressor proteins.

Interference with Cell-Signaling Pathways In about 30% of human cancers, the *ras* proto-oncogene is mutated. The ***ras* gene** codes for a G protein that connects a growth-factor receptor on the plasma membrane to a cascade of protein kinases that leads to the production of a cell cycle stimulating protein. A mutation may create a hyperactive version of the Ras protein that relays a signal without the binding of a growth factor.

The ***p53* gene** is mutated in about 50% of human cancers. It codes for a tumor-suppressor protein that is a specific transcription factor for several genes. It often activates the *p21* gene, whose product binds to cyclin-dependent kinases, halting the cell cycle and allowing time for the cell to repair damaged DNA. It also activates several miRNAs that inhibit the cell cycle. The p53 protein can also activate genes involved in DNA repair. Should DNA damage be irreparable, p53 activates "suicide genes" that initiate apoptosis.

The Multistep Model of Cancer Development More than one mutation appears to be needed to produce a cancerous cell. Mutation of a single proto-oncogene can stimulate cell division, but usually both alleles for several tumor-suppressor genes must be defective to allow uncontrolled cell growth.

Inherited Predisposition and Other Factors Contributing to Cancer A genetic predisposition to certain cancers may involve the inheritance of an oncogene or a recessive mutant allele for a tumor-suppressor gene. Approximately 15% of colorectal cancers involve inherited mutations, often in the tumor-suppressor gene *APC*, which regulates cell migration and adhesion.

About 5–10% of breast cancer cases are linked to an inherited mutant allele for either *BRCA1* or *BRCA2*, both of which appear to be tumor-suppressor genes involved in a cell's DNA damage repair pathway.

The ultraviolet radiation in sunlight and the chemicals in cigarette smoke may contribute to cancer through their DNA-damaging effects.

Tumor viruses appear to be involved in about 15% of human cancers. Viruses can interfere with gene regulation when the insertion of their genetic material into a cell's DNA introduces an oncogene or affects a proto-oncogene or tumor-suppressor gene. Viral proteins may also inactivate p53 or other tumor-suppressor proteins.

Word Roots

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

proto- = first, original; **onco-** = tumor (*proto-oncogene:* a normal cellular gene that has the potential to become an oncogene, which is involved in triggering molecular events that lead to cancer)

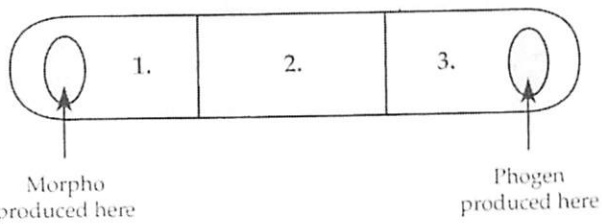
Structure Your Knowledge

1. How might the mechanism of transcriptional regulation differ for cytoplasmic determinants and for the cell-cell signaling involved in induction?
2. What are stem cells? What are the differences between embryonic stem cells, adult stem cells, and induced pluripotent stem cells? Do plants have stem cells? Explain.

Test Your Knowledge

MULTIPLE CHOICE: *Choose the one best answer.*

1. Cytoplasmic determinants are
   a. unevenly distributed cytoplasmic components of an unfertilized egg.
   b. often involved in transcriptional regulation.
   c. usually 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.
2. Pattern formation in animals is based on
   a. positional information a cell receives from gradients of morphogens.
   b. the induction of cells by the nurse cells in the mother's ovary.
   c. the packing of chromatin in the nucleus.
   d. the differentiation of cells that then migrate together to form tissues and organs.
   e. the first few mitotic divisions.
3. 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, if female, 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.
4. In the following hypothetical embryo, a high concentration of a morphogen called morpho is needed to activate gene *P;* gene *Q* is active at or above medium concentrations of morpho; and gene *R* is expressed so long as any quantity of morpho is present. A different morphogen, called phogen, activates gene *S* and inactivates gene *Q* when at medium to high concentrations. If morpho and phogen are diffusing from their sites of production at opposite ends of this embryo, which genes will be expressed in region 2? (Assume a gradient of morphogen concentrations in the three regions, from high at the source, to medium in the middle, and to low at the opposite end.)



   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*
5. Apoptosis is
   a. a cell suicide program that may be initiated by p53 protein in response to DNA damage.
   b. metastasis, or the spread of cancer cells to a new location in the body.
   c. a type of programmed cell death that is a normal part of development.
   d. the transformation of a proto-oncogene to an oncogene by a point mutation.
   e. both a and c.

6. 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. They come from skin cells that have been induced to become pluripotent by the introduction of cloned "stem cell" master regulatory genes.
   c. They are capable of developing into several (but not all) types of cells.
   d. These relatively unspecialized cells continually reproduce themselves in the body.
   e. They have been successfully grown in culture and made to differentiate into specialized cells.

7. Which of the following might a proto-oncogene code for?
   a. DNA polymerase
   b. RNA polymerase
   c. receptor protein for growth factors
   d. an enhancer
   e. transcription factors that inhibit cell division genes

8. A gene can develop into an oncogene when
   a. it is present in more copies than normal.
   b. it undergoes a translocation that removes it from its normal control region.
   c. a mutation results in a more active or resistant protein.
   d. a mutation in a control element increases expression.
   e. any of the above occur.

9. A tumor-suppressor gene could cause the onset of cancer if
   a. both alleles have mutations that decrease the activity of the gene product.
   b. only one allele has a mutation that alters the gene product.
   c. it is inherited from a parent in mutated form.
   d. a proto-oncogene has also become an oncogene.
   e. both a and d have occurred.

10. Which of the following would most likely account for a family history of colorectal cancer?
    a. a diet that is low in fats and high in fiber
    b. inheritance of one mutated *APC* allele that regulates cell adhesion and migration
    c. a family history of breast cancer
    d. inheritance of the *ras* oncogene, which locks the G protein in an active configuration
    e. inheritance of a proto-oncogene