CHAPTER 17: CELLULAR MECHANISMS OF DEVELOPMENT

CHAPTER SYNOPSIS

Multicellular eukaryotes depend on cell specialization and have evolved complex developmental processes to ensure that the adult is formed properly. Plant development is flexible and highly influenced by the environment, while animal development is rigidly controlled and much less dependent on the environment. The ties to the environment between plants and animals is greatly a result of their mobility. Plants are immobile, they need to work within the strict confines of a changing habitat. Animals are mobile and can leave their habitat if it is not to their liking, they do not have to adjust to it to survive in the same manner as plants.

After cleavage of the initial zygote, vertebrate animals go through an involved series of stages of cell movement and tissue formation. Although a greater number of cells are produced, each cell is progressively smaller in size and the embryo stays roughly the same size through the formation of the blastula and the gastrula. Neurulation is unique to vertebrate animals as only they possess the neural tube formed in this process. Insect development begins before the egg is even fertilized. The actions of maternal genes control early development since nurse cells distribute mRNA to the egg. The syncytial blastoderm is formed as a result of nuclear divisions without production of intervening cell membranes. These two events are paramount in terms of pattern formation and the development of segment polarity in insects. Insect larva have a single purpose, to accumulate nutrients. Upon formation of the hard-shelled pupa, the cells which were the larva break down and reconstitute themselves into the adult tissues. This metamorphosis is controlled by the insect's imaginal disks.

In the first division of a plant, one cell is destined to become the embryo while the other becomes the suspensor. The embryo differentiates into three germ layers (epidermis, ground tissue, and vascular tissue), like animals, but there is no ensuing cell migration. Development halts with the formation of the seed and resumes with germination. The two events may be separated by many years. The seed enables a plant to be dispersed a great distance from the parent and allows it to wait out unfavorable environmental conditions that would only end in death. Plants produce various meristems which become the components of the adult plant. These meristems are influenced by hormones which are, in turn, controlled by the environment.

Cell migration is of great importance in animal development. What a cell becomes is greatly influenced by where it has been and where it is going. These movements occur as a result of interactions with cadherins and integrins. Cells can be switched from one developmental path to another via the process of induction. Inducing cells secrete proteins, intercellular signals that determine what kind of tissue a cell will become. The same signal can effect different results through variations in concentration. A cell is said to be determined when it has become committed to a particular developmental path. Differentiation is the cell specialization that exists at the end of that path. Therefore cells can be determined, but not yet differentiated. Partial commitment may reflect a cell's location in an embryo and is associated with positional labels. Until recently, the process of determination was thought to be irreversible. Numerous nuclear transplant experiments were performed and failed unless the nucleus came from an early, undetermined embryo cell. A sheep has been successfully cloned using a nucleus from an adult mammary cell (thus the name "Dolly" for Dolly Parton). The key to this attempt was getting both donor and recipient cells in the beginning stage of the cell cycle through starvation of the cell cultures.

Although first discovered in *Drosophila*, homeotic genes have been found in mice and humans and similarly functioning genes also exist in plants. Homeotic genes contain a homeobox sequence of amino acids that ensure certain genes are transcribed at the proper time. These genes are found in clusters and are aligned in the same order as the segments that they control. The ordered nature of these gene clusters is highly conserved over the course of evolution. Many cells produced in the process of development are

ultimately destined to die. It may not make sense in the isolated context of the end result, but there is a logical, progressive reason for it when the developmental process is examined in greater depth.

It is said that the only certainties in life are death and taxes. Substantial research is being done to investigate the process of cell aging and death. There are currently four strong hypotheses involved with four different cell processes. These include accumulated mutations, telomere depletion, cell wear and tear, and the gene clock hypothesis. This last hypothesis suggests that many aspects of aging are regulated by genes in much the same way that development is gene regulated.

CHAPTER OBJECTIVES

- In general terms, compare and contrast plant and animal developmental processes.
- Understand the stages of development, from cleavage to organogenesis, in a model vertebrate.
- Describe the stages of development in a representative insect from the influence of maternal genes to metamorphosis.
- Explain the stages of development in a typical plant from early divisions through morphogenesis.
- Know how cell movement and cadherins are involved in the developmental process.
- Understand the process of induction and the importance of cell-cell interactions.
- Explain the role of organizers in animal development.
- Define and compare determination, differentiation, and commitment.
- Explain the reversibility of determination using the cloned sheep Dolly as an example.
- Understand pattern formation in *Drosophila* and the involvement of positional labels and the syncytial blastoderm.
- Know the importance of homeotic genes.
- Know why programmed cell death is necessary and differentiate between necrosis and apoptosis.
- Describe the four model developmental systems and their representative specimen.
- Compare the four major theories of aging.

KEY TERMS

animal pole
Antennapedia complex
antioxidant
apoptosis
bithorax complex
blastocyst
blastomere
blastula
chimera
cleavage
cotyledon
determinant
determination
differentiation
epidermal cell
gap gene
gastrula
gastrulation
germ layer
ground tissue
homeobox
homeotic gene
imaginal disk
induction
instar
larva
meristem
metamorphosis
morphogen
mosaic development
nanos protein
necrosis
neural crest
neural tube
neurulation
organizer
pair-rule gene
positional label
pupa
regulative developmentsegment
polarity gene
somite
suspensor
syncytial blastoderm
telomeric region
totipotent
vascular tissue
vegetal pole

CHAPTER OUTLINE

17.0 Introduction

I. ALL CELLS IN A MULTICELLULAR ORGANISM DESCEND FROM A SINGLE CELL

A. Particular Lines of Cells Proceed Along Different Developmental Paths

B. The Developmental Program Unfolds With Precision fig 17.1

17.1 Development is a regulated process

I. OVERVIEW OF DEVELOPMENT

A. Multicellular Cell Specialization Controlled by Gene Expression
1. Different cells express different genes at different times
2. Cells determine which genes to activate when
3. In fungi, only reproductive cells are specialized
4. Plant development is flexible and influenced by the environment
5. Animal development is rigidly controlled with less influence by environment fig 17.2
   a. Study an animal with complexly arranged body – a mammal
   b. Study a less complex animal with intricate development – an insect
   c. Study a simple animal – a nematode
   d. Study a flowering plant

II. VERTEBRATE DEVELOPMENT

A. Dynamic Series of Stages of Cell Movement and Organ Formation fig 17.3

B. Cleavage
1. Zygote is the initial vertebrate being
2. One cell divides rapidly forming blastomeres, and solid ball of cells fig 17.4
3. Embryo stays same size, cell number increases, cell size decreases
   a. Cells at animal pole form external body tissues
   b. Cells at vegetal pole from internal tissues
4. Initial dorsal-ventral orientation associated with position of sperm entry
   a. Sperm entry corresponds to future belly
5. After 12 divisions cleavage slows, gene transcription begins

C. Formation of the Blastula
1. Outer blastomeres connected by tight junctions fig 17.5a
   a. Junctions are belts of protein encircling cell, welding it to neighbor
   b. Cell mass effectively separated from environment
2. At sixteen-cell stage, cells at interior pump Na^+ from interior to intercellular spaces
   a. Forms osmotic gradient in intercellular spaces
   b. Water moves from cells to enlarging intercellular spaces
   c. Spaces combine to form a cavity in cell mass
3. Resulting hollow ball of cells is the blastula or blastocyst fig 17.5b

D. Gastrulation
1. Gastrula forms when wall of blastula at vegetal pole pushes inward fig 17.5c
   a. Cell extensions called lamellipodia help in cell movement
   b. Resembles collapsed tennis ball, process called gastrulation
   c. Embryo becomes bilaterally symmetrical

   d. Has central gut tube that opens to outside
2. Embryo develops three germ layers
   a. Endoderm forms tube of primitive gut, most internal organs
   b. Outer cells are ectoderm, form skin and nervous system
   c. Mesoderm forms notochord, bones, blood vessels, connective tissue, muscles

E. Neurulation
1. Presence of notochord triggers thickening of an ectodermal zone fig 17.5d
2. Cells elongate, form wedge shape, and roll into a tube
3. Neural tube formed through this process of neurulation

F. Cell Migration
1. Variety of cells migrate to form distant tissues fig 17.5e
   a. Follow specific path to particular location
   b. Neural crest pinches off from neural tube and forms sense organs
   c. Somites migrate from central blocks of muscle forming skeletal muscles
2. Receptor proteins of migrating cells interact with destination tissues to cease movement

G. Organogenesis and Growth
1. Basic vertebrate plan established when body is only a few millimeters long
2. Tissues develop into organs fig 17.5f
3. Size increases enormously, number of cells increases by a million times fig 17.5g

III. INSECT DEVELOPMENT

A. Insect Development Quite Different from that of Mammals
1. Many insects possess two distinctly different body forms
   a. Tubular eating machine called a larva
   b. Second form has wings and legs
   c. Change in body form called metamorphosis
   d. Exemplified by the fruit fly, *Drosophila* fig 17.6

B. Maternal Genes
1. Construction of egg begins development before fertilization
2. Nurse cells move their mRNA into end of egg nearest them fig 17.7a
3. Maternal gene mRNAs positioned in specific locations in egg
4. After divisions, daughter cells contain different maternal products
5. Action of maternal, not zygotic, genes controls initial development

C. Syncytial Blastoderm
1. Nuclear divisions without cytokinesis produce syncytial blastoderm fig 17.7b
   a. Twelve round of division produce 400 nuclei within a single cytoplasm
   b. Nuclei in different sections communicate freely
   c. But experience different maternal products
2. Nuclei spread apart and grow intervening membranes, form hollow ball of cells
3. Followed by embryo folding and development of primary tissues
4. Development similar to that of vertebrates
5. Tubular body form called a larva

D. Larval Instars
1. As larva feeds, it grows, sheds its outer chitinous skin
2. Body size expands before exoskeleton hardens
3. Drosophila produce three larval instar stages in four days fig 17.7c

E. Imaginal Disks
   1. A dozen groups of cells are set aside in the abdomen of the larva — fig 17.7d
   2. Called imaginal disks
   3. Have no role in the larva, form key parts of adult body

F. Metamorphosis
   1. Hard shell forms around larva, now called pupa — fig 17.7e
   2. Cells break down, release nutrients then used by imaginal disks
   3. Disks associate with each other to assemble adult fly
   4. Metamorphosis of larva to pupa to adult takes four days
   5. Adult emerges from split pupal shell

IV. PLANT DEVELOPMENT

A. A Comparison of Plant and Animal Development
   1. Share key developmental elements with animals
   2. Developmental mechanisms different between plants and animals
      a. Animal cells move, plant cells encased in immoveable stiff cellulose walls
      b. Plants develop by building bodies outward from meristems
      c. Dividing meristems produce cells that differentiate into tissues
   3. Animals and plants have different reactions to their environment
      a. Animals move away from unfavorable circumstances
      b. Plants endure environment, change developmental strategies
         1) Assemble body from few simple parts like leaves, roots, branches, flowers
         2) Each module has rigid structure and organization
         3) Utilization of modules is flexible
         4) Adjusts path of its development to local circumstances

B. Early Cell Division
   1. First division off-center, one daughter cell is small, cytoplasm dense — fig 17.8a
   2. Small cell becomes embryo, divides rapidly forming ball of cells
   3. Other daughter cell forms suspensor linking embryo to nutrient tissue
   4. Cells near suspensor form roots, opposite end becomes shoot

C. Tissue Formation
   1. Plant embryo differentiates into three basic tissues — fig 17.8b
      a. Outermost cells become epidermal cells
      b. Bulk of interior becomes ground tissue
      c. Cells at core of embryo become vascular tissue
   2. No cell movement occurs

D. Seed formation
   1. First set of leaves called cotyledons
   2. Development arrested, embryo packaged into a seed — fig 17.8c
      a. Embryo may be surrounded by nutritive tissue
      b. May amass food stores in cotyledons
   3. Seed allows for dispersal and survival in harsh conditions

E. Germination
   1. Occurs in response to environmental changes
   2. Embryo resumes development with germination
   3. Roots grow downward, shoot upward — fig 17.8d

F. Meristematic Development
   1. Apical meristems generate cells to make all components of adult plant fig 17.8e
   2. Secondary meristems produce wood and secondary growth (increase girth)
   3. Meristematic activity influenced by hormones
   4. Hormones allow plant to adjust to its environment

G. Morphogenesis
   1. Form of plant body determined by two events
      a. Plane in which cells divide
      b. Changes in cell shape due to osmotic expansion fig 17.8e
   2. Plant growth-regulating hormones affect morphogenesis
      a. Influence orientation of microtubules on interior of membrane
      b. Microtubules guide deposition of cellulose in cell wall
      c. Orientation of cellulose fibers determines elongation of cell as it grows

17.2 Multicellular organisms employ the same basic mechanisms of development

I. MULTICELLULAR ORGANISMS DEVELOP ACCORDING TO MOLECULAR MECHANISMS

A. Mechanisms Similar Among Most Multicellular Animals
   1. Mechanisms evolved early in the history of life
   2. Six mechanisms are of particular importance

II. CELL MOVEMENT AND INDUCTION

A. Cell Movement
   1. Cells migrate during many animal developmental stages
      a. May travel great distances before reaching ultimate destination
      b. Tissues contain cells from very different parts of early embryo
   2. Cells move via cell adhesion molecules like cadherins
      a. Span plasma membrane, protrude into cytoplasm, extend from cell surface
      b. Cytoplasmic portion attached to cytoskeleton actin or intermediate filaments
      c. Extracellular portion has five 100 amino acid segments with Ca^{++} sites
      d. Ca^{++} binding sites attach cadherin to other cells
      e. Cadherin links to another of same type, joining cytoskeletons of two cells
         1) Dozens of different kinds of cadherins discovered
         2) Helps sort cells with different cadherins into separate masses
         3) Cause for assembly of different imaginal disks
      f. Calcium-independent cell adhesion molecules assist cadherins
         1) Include neural cell adhesion molecules (N-CAMs)
         2) Expressed by migrating nerve cells
   3. Much tissue volume is space between cells
      a. Spaces filled with network of molecules secreted by surrounding cells
         1) Include matrix of protein-linked polysaccharides, proteoglycans
         2) Contain embedded fibrous proteins like collagen, elastin, fibronectin
      b. Migrating cells traverse intercellular matrix via integrins
         1) Integrins attach to cytoskeleton actin filaments, protrude like two hands
         2) Protruding integrins attach to (hands grasp) fibrous portion of matrix
         3) Provides anchor and initiates cellular changes
         4) Alter growth of cytoskeleton, change how cell secretes materials into matrix
      c. Migration changes patterns of cell adhesion
         1) Migrating cell extends projections that probe environment
         2) Cell tugged different directions by different temporary attachments
         3) Literally feels its way to ultimate target site

B. Induction
1. Mosaic development
a. Occurs in *Drosophila*
b. Initial cells created by cleavage contain different developmental signals
c. Signals called determinants, pattern called mosaic development
d. Individual cells set off on different developmental paths
2. Regulative development
a. Blastomeres in mammals receive equal sets of determinants
b. Body form determined by cell-cell interactions
3. Demonstration of the importance of cell-cell interactions
a. Separate cells of early blastula and allow to develop
1) Ones from animal pole develop characteristics of ectoderm
2) Ones from vegetal pole develop characteristics of endoderm
3) Neither develop characteristics of mesoderm
4) Mesoderm develops from animal pole cells growing next to vegetal pole cells
b. Induction: Switching cell from one path of development to another fig 17.9
c. Inducing cells secrete proteins that serve as intercellular signals
d. Signals produce abrupt changes in patterns of gene transcription
4. Role of organizers in development
a. Organizers produce signal molecules that convey positional information
b. Have profound effect influence on development of surrounding cells
c. Act as signal beacons, inform surrounding cells of their distance from organizer
d. If close, concentration of signal molecule is greater
e. Signal molecules called morphogens fig 17.10
f. Few morphogens identified, vital for determining relative developmental position
g. Same morphogen can have different effect at different concentrations fig 17.11
1) Dependent on distance from organizer
2) In *Xenopus,* low level of activin morphogen causes cells to become epidermis
3) Slightly higher levels make cells into muscles
4) Still higher level causes cells to become notochord

III. DETERMINATION

A. Developing Cells May Exhibit Totipotency
1. Mammalian egg symmetrical in contents and shape
a. As in all cells of mammalian egg equal up to eight-cell stage
b. Cells are totipotent, capable of expressing all genes of genome
c. If cells separated, can all develop into normal individual
d. Used to produce identical offspring in valuable cattle
2. Can do reverse, combine cells of eight cell stage into one individual
a. Called a chimera fig 17.12
b. Contains cells from different genetic lines
3. After eight-cell stage, mammalian cells become different
a. Due to cell-cell interactions
b. Future developmental fate of cells becomes irreversible
c. Determination is a commitment to a particular developmental path
1) Move cell in brain of early gastrula amphibian embryo, cell undetermined
2) Cell will develop same way as new neighbors
3) Transplant cell from late gastrula stage, cell determined
4) Cell develops into neural tissue regardless of new location
4. Determination versus differentiation
a. Differentiation is cell specialization produced at end of developmental path
b. Cell can be determined but not yet differentiated

c. Example: Cells of *Drosophila* eye imaginal disk
   1) Cells fully determined to produce an eye
   2) Cells undifferentiated through most of development

B. The Mechanism of Determination
   1. Gene regulatory proteins initiate development changes
      a. When genes are activated, they further reinforce their own activation
      b. Developmental switch is deterministic, initiates particular chain of events
      c. Cells may not undergo differentiation until later time
         1) Requires interaction of other factors with regulatory protein
         2) Cause protein to activate additional genes
      d. When switch is thrown cell is fully committed to certain developmental path
   2. Partial commitment to development associated with positional labels
      a. Reflect cell's location in embryo
      b. Influence how pattern of body develops
      c. Example: Chick embryo cell transplantation
         1) Leg bud cell (to become thigh) transplanted to wing bud (produces wing tip)
         2) Cell becomes toe rather than thigh or wing tip
         3) Cell committed to be leg, but not committed to be particular part of leg

C. Is Determination Irreversible?
   1. Once thought to be irreversible
      a. Research in 1950-60 provided supporting information
      b. Removed nucleus from frog egg, replaced it with nucleus from body cell fig 14.3
      c. Transplanted nucleus from advanced embryo, developed into tadpole and died
   2. Nuclear transplant experiments unsuccessful till 1984, sheep cloned
      a. Used cell from embryo cell very early in development
      b. Experiment replicated in other animals, pigs, monkeys
      c. Only successful if early embryo nucleus used
      d. Animal cells appeared to become committed after only few cell divisions
   3. Research in 1996 by Campbell and Wilmut produced sheep from adult nucleus
      a. Synchronized cell cycle stage of egg and donated nucleus fig 17.13
      b. Mammary cells removed from adult sheep, clone cells named "Dolly"
         1) Cells grown in tissue culture, starved just prior to implantation experiment
         2) Caused cells to pause at beginning of cell cycle
      c. Eggs from ewe enucleated
      d. Egg and nucleus surgically combined, brief electric shock applied
         1) Shock causes plasma membrane to become leaky
         2) Nucleus of mammary cell passed into egg cell
         3) Also kick starts cell cycle, resulting in cell division
      e. 30 of 277 tries showed formation of blastula stage, 29 implanted into ewes
      f. Five months later one sheep gave birth to lamb named Dolly
         1) First clone derived from fully differentiated animal cell
         2) Determination is, therefore, fully reversible

IV. PATTERN FORMATION

A. Encoding of Positional Information
   1. Use of positional labels in pattern formation in *Drosophila*
      a. Egg has initial asymmetry due to maternal mRNA deposited by nurse cells
      b. Maternal mRNA from bicoid gene marks embryo's front end
         1) mRNA translated into bicoid protein upon fertilization
         2) Diffuses through syncytial blastoderm, forming morphogen gradient
         3) Without protein, no head or thorax develops, embryo is two-tailed (bicaudal)

4) Injection of protein into anterior end causes embryo to be normal
5) Injection at other end causes head to develop there

2. Effect of bicoid protein occurs by activating gap genes fig 17.14
   a. Gap genes, set of six genes, map out subdivisions of embryo
   b. *Hunchback* gene associated with development of thorax
      1) *Nanos* gene associated with development of abdominal segments
      2) Nanos protein binds to hunchback mRNA, stopping its translation
      3) Hunchback only made at anterior end, away from region with nanos
      4) Hunchback diffuses backward, establishing gradient for thoracic and abdominal segments
   c. Other gap genes work in posterior regions of embryo
   d. Activate eleven sets of pair-rule genes
   e. Pair-rule genes alter every other body segment into zones
      1) One set named *hairy* produces seven stripe-like bands
      2) Bands divide embryo into seven zones
   f. Segment polarity genes subdivide these zones
      1) *Engrailed* gene divides hairy zones into anterior and posterior compartments
      2) 14 resulting compartments = 3 head + 3 thorax + 8 abdominal segments
3. Cascade of gene activity results in segmentation of fly's body plan
4. Activation of genes depends on morphogen diffusion in syncytial blastoderm fig 17.15

V. EXPRESSION OF HOMEOTIC GENES

A. Homeotic Genes Determine the Form Each Segment Will Take

1. Code for proteins that function as transcription factors
2. Activates a particular module of the genetic program producing body parts

B. Homeotic Mutations

1. Mutations in *Drosophila* homeotic genes
   a. *Bithorax*: Fly grows extra set of wings fig 17.16
   b. *Antennapedia*: Legs grow out of head instead of antennae
2. Bithorax complex affect body parts of thorax and abdomen
   a. Discovered by Lewis in 1950 on third chromosome
   b. Control development of body parts in rear of thorax, all of abdomen
   c. Order of genes is order of body parts, as if genes are activated in order
      1) Genes at beginning switch on development of thorax
      2) Genes in middle affect anterior part of abdomen
      3) Genes at end affect tip of abdomen
3. Antennapedia complex
   a. Discovered by Kaufman in 1980
   b. Governs anterior end, also serially activated fig 17.17

C. The Homeobox

1. Homeotic *Drosophila* genes typically contain homeobox sequence of amino acids
   a. Codes for homeodomain: An amino acid DNA-binding peptide domain fig 17.18
   b. Function as transcription factors, ensuring genes are transcribed at right time
   c. *Bicoid* and *engrailed* also contain homeobox sequence
2. Distinguishes portion of genome devoted to pattern formation

D. Evolution of Homeobox Genes

1. Homeotic genes also found in mice and humans
   a. Genes governing positioning of body parts established early in animal evolution
   b. Similar genes function in flowering plants
2. *Drosophila* gene probes identify similar sequences in myriads of organisms

a. Mice and humans have four clusters of homeobox-containing genes
b. Called *Hox* genes in mice
c. Genes in mammals aligned in same order as segments they control fig 17.19

3. Ordered nature of homeotic gene clusters is highly conserved in evolution fig 17.20

VI. PROGRAMMED CELL DEATH

A. Many Cells Produced in Development Are Destined to Die
1. Examples: Webbing between digits, excess vertebrate neurons
2. Presence of cells and death required for proper development
3. Necrosis
a. Cell death due to injury
b. Cell swells and bursts, contents released into extracellular spaces
4. Apoptosis
a. Planned cell death
b. Cell shrinks, surrounding cells absorb remains

B. Gene Control of Apoptosis
1. Animals all experience developmentally regulated suicide
a. Example: Nematode worm fig 17.21a
1) Same 131 cells die during development
2) Controlled by three genes: *ced-3*, *ced-4*, *ced-9*
3) *ced-3* and *ced-4* constitute death program itself
4) If either mutated, 131 cells do not die, become nervous and other tissues
5) *ced-9* represses death program
b. Example: Human cells fig 17.21b
1) *bax* gene encodes cell death program
2) Oncogene *bcl-2* represses cell death program
c. Mechanism of apoptosis highly conserved during animal evolution
1) Protein made by *bcl-2* is 25% identical to protein made by *ced-9*
2) Human *blc-2* transferred into nematode with defective *ced-9*
3) *bcl-2* suppresses cell death program of *ced-3* and *ced-4*
d. Prevention of cell death by *bcl-2*
1) *bcl-2* may prevent damage by destroying free radicals
2) Antioxidant: Molecule that destroys free radicals
3) Antioxidants are almost as effective as *bcl-2* in blocking apoptosis

17.3 Four model developmental systems have been extensively researched

I. THE MOUSE

A. Mammalian Model System
1. Mouse possesses battery of homeotic *Hox* genes fig 17.22
a. Closely related to homeotic genes of *Drosophila*
b. Same genes seem to operate in same order
c. Homeotic gene system highly conserved
2. Creation of chimeric mice
a. Contain cells from two genetic lines
b. Mammalian embryos are chemically symmetrical, contain no gradients
c. All daughter cells identical after first division
1) Any individual cell, up to eight-cell stage, will produce complete adult
2) Two different eight-cell cells combined to form normal adult
d. Chimeric mice essentially have four parents

II. THE FRUIT FLY

A. Model System for Invertebrates
1. Key organism to understand cellular mechanisms of development
   a. Examine how genes expressed early in development form adult plan fig 17.23
   b. Imaginal disks float in larva, grow into adult body parts in pupa
2. Characteristic segmentation of adult established early in development
   a. Body divided into 17 segments, some bear jointed appendages
   b. Segments established before nuclei of blastoderm fully separated
      1) Chemical gradients established within egg by maternal material
      2) Create polarity that directs embryonic development
   c. Series of segmentation genes react to chemical gradient, subdivide embryo
      1) First divided into 4 broad areas
      2) Further divided into 7, 14, then finally 17 segments
3. Two clusters of homeotic genes
   a. Anterior end = antennapedia complex; posterior end = bithorax complex
   b. Organization of genes corresponds to order of segments
   c. Similar set of homeotic genes govern body architecture in mice and humans

III. THE NEMATODE

A. Model Describes Development in Many Animals
1. Tiny roundworm composed of 959 somatic cells
2. Entire genome mapped, complete DNA sequencing in progress
3. Organism is transparent
   a. Division and migration of cells easy to follow
   b. Complete linage map determined for each cell and its divisions fig 17.24
      1) Horizontal line on map shows one round of cell division
      2) Length of line represents time between divisions
      3) End of vertical line shows one fully differentiated cell
      4) Linage map is color coded
4. Cells are "born" after varying numbers of cell divisions
   a. Some differentiated cuticle cells "born" after 8 rounds of division
   b. Other cuticle cells require 14 divisions
   c. Pharynx cells born after 9 to 11 divisions
   d. Cells in gonads need up to 17 divisions
5. Each worm has exact same number of cells with identical program
   a. 302 nerve cells become nervous system
   b. 131 cells programmed to die
   c. Only cells that become eggs and sperm have unique fate

IV. THE FLOWERING PLANT

A. Small relative of the mustard plant *Arabidopsis thaliana*
1. Easy to grow and cross, has short generation time
2. Able to self-fertilize
3. Can produce thousands of offspring in two months
4. Genome sequenced in 1999, same size as *C. elegans* and *Drosophila*

B. Pattern Formation
1. Library of gene clones available to researchers, complete genome by 1998
2. Numerous gene mutations altering pattern formation are known
3. Mechanisms in early development broadly similar to animals

C. Organ Formation
   1. Development of organs parallels that of animals
   2. Possess similar sets of homeotic genes fig 17.25

17.4 Aging can be considered a developmental process

I. THEORIES OF AGING

A. Aging and Death Are Certainties
   1. Oldest human was 122 in 1997
   2. Age at which individual is least likely to die is puberty, 10-15 years old fig 17.26
      a. Death rate increases rapidly after puberty
      b. Mortality rate increases exponentially, as function of increasing age
      c. Log scale plotting shows mortality increasing in straight line from 15 to 90 years
      d. Mortality rate doubles every 8 years
      e. At age 100, risk of dying reaches 50% per year
   3. Wide variety of theories to explain why animals age

B. Accumulated Mutation Hypothesis
   1. Cells accumulate mutations as they age, lead to eventual lethal damage
      a. Somatic mutations accumulate during aging
      b. Aging cells build up 8-hydroxyguanine, OH-group added to guanine base
   2. Little evidence that these mutations cause aging
      a. No acceleration in aging when individuals experience increased mutation rate
      b. Unlikely that there is relationship between mutation and aging

C. Telomere Depletion Hypothesis
   1. In 1961, Hayflick demonstrated cultured cells only divided a certain number of times
      a. After 50 population doublings, cell division stops fig 17.27
      b. Cell cycle blocked just before DNA replication
      c. Take sample after 20 doublings and freeze
      d. Will resume growth for 30 more doublings and stops
   2. Previous explanation for Hayflick limit
      a. Cells could only replicate chromosomes a certain number of times
      b. Enzymes copying DNA have problems with chromosomes telomeres
      c. As cells divided, thought that telomeres got shorter with each DNA replication
      d. After 50 replications, the telomeres on the chromosome tips disappeared
      e. Cell enters senescence
      f. Cancer cells avoid telomeric shortening
   3. Research in 1998, direct evidence relating telomeric shortening and cell senescence
      a. Transferred gene into human primary cell cultures
      b. Gene leads to expression of telomerase, enzyme that builds TTAGGG caps
      c. New caps added when gene is present in cells
      d. Cells did not senesce at Hayflick limit showed 20 more generations

D. Wear-and-Tear Hypothesis
   1. General idea that cells wear out over time, accumulate damage until unfunctionable
      a. No inherent designed limit, but a statistical limit
      b. Disruption and damage eventually prevent cell's ability to function properly
   2. Considerable evidence that cells do accumulate damage
      a. Some evidence associated with free radicals
         1) Free radicals are atoms, molecule fragments that have unpaired electron
         2) Chemically very reactive, destructive in a cell
         3) Produced as natural by-product of oxidative metabolism

4) Generally collected by special enzymes
b. Damaging free radical reaction involves glucose
1) Glucose becomes linked to proteins, called glycation
2) Collagen and elastin are proteins often glycated
3) Such molecules are not replaced
c. Glycation produces mix of proteins, advanced glycosylation end products (AGEs)
1) AGEs cross link to one another, reduce flexibility of connective tissues in joints
2) Produce other symptoms characteristic of aging

E. Gene Clock Hypothesis
1. Some aspects of aging under direct gene control
2. Genes regulate aging like they regulate development
3. Mutations in these genes cause premature aging in children
a. Recessive Hutchinson-Gilford syndrome
1) Growth, sexual maturation, skeletal development retarded
2) Death by age 12 due to atherosclerosis, strokes
b. Similar Werner's syndrome not as rare
1) Appears in adolescence, produces death before age 50
2) Death results from heart attack or rare connective tissue cancers
3) Responsible gene located on short arm of chromosome 8
4) Affects helicase enzyme involved in DNA repair
5) Gene codes for 1432 amino acid protein, completely sequenced
6) Four mutant alleles identified, helicases needed to unwind DNA helix
7) Mutant helicase may fail to activate critical tumor suppressor genes
4. Extensive aging research using *C. elegans* nematode
a. Recently discovered genes affect intrinsic genetic clock
b. Combined mutations can increase normal lifespan five times
1) Mutations in *clk-1* cause cells to divide more slowly
2) Animal spends more time in each phase of its life cycle
3) Mutations in *clk-2* and *clk-3* have similar effects
4) Nematodes with two mutations lived 3 to 4 times longer
c. Slowing down life in nematodes extends life
1) Aging may be associated with damage to cells and DNA
2) Caused by destructive by-products of oxidative metabolism
3) Destructive products may be produced less or more slowly with slower life
4) Damage may be repaired more efficiently
5. Similar genes reported in yeasts, attempting to isolate and clone them

INSTRUCTIONAL STRATEGY

PRESENTATION ASSISTANCE:

Many texts relegate plant development to a minuscule part of one chapter in the midst of the "plant biology" section. Here plant development is discussed right in context with animal development making it very easy to compare and contrast the two.

Programmed cell death is like constructing a scaffold while building a house. It's needed for the building process, but eventually will be disassembled since it isn't meant to be incorporated into the final design of the house. Think of other analogies using the building trade. Auto and other mechanical analogies don't work as well with regard to this topic because most auto companies completely retool for each new production year. Parts are pretty specific as to their use. With houses you can create an innumerable amount of different structures from nails and a few two-by-fours. Borrow your kids Legos™ (or buy sets for labs)!

Along the same lines, there is the old story about cooking a turkey for thanksgiving. The granddaughter cuts off the turkey's legs, stuffs it, puts it in the roaster, and slides it in the oven. When her new husband asks her why she replies, "Mom did it this way, silly, it's delicious!" One day he asked his mother-in-law why she cooked turkey in such a unique way and got the same answer "My mother did it this way!" Still curious, he finally asked grandmom. Apparently, her oven wasn't large enough for the whole turkey and she had to chop off its legs to get it in. Similarly, developmental processes simply build upon themselves, often with no immediately apparent reason.

VISUAL RESOURCES:

Transparencies, slides, and videos are essential in presenting this chapter. Note the three Insight Media videos listed in Media Resources: Videos, Part Five: Molecular Genetics.

Douglas Green and Ben Jones have developed two computer simulations associated with this material entitled *Morphogenic Construction Kit* and *Diffusion Laboratories*. The former is designed to facilitate exploration of classical experiments in biological pattern formation. The latter combines two simulations, Particle Diffusion and Pattern Formation, that explore mathematical models of embryological pattern formation. See Media Resources: Computer Programs, Part Five: Molecular Genetics.