Chapter 11

How Genes Are Controlled

PowerPoint® Lectures for
Campbell Essential Biology, Fifth Edition, and
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Fourth Edition
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During the 1900s, doctors noticed that

- smoking increased and
- lung cancer increased.
In 1996, researchers studying lung cancer found that, in human lung cells growing in the lab, a component of tobacco smoke, BPDE, binds to DNA within a gene called $p53$, which codes for a protein that normally helps suppress the formation of tumors.

This work directly linked a chemical in tobacco smoke with the formation of human lung tumors.
• Every somatic cell in an organism contains identical genetic instructions.
  – They all share the same genome.
  – So what makes cells different from one another?
In **cellular differentiation**, cells become specialized in

- structure and

- function.

Certain genes are turned on and off in the process of **gene regulation**.
Patterns of Gene Expression in Differentiated Cells

• In gene expression,
  – a gene is turned on and transcribed into RNA and
  – information flows from
    – genes to proteins and
    – genotype to phenotype.

• Information flows from DNA to RNA to proteins.

• The great differences among cells in an organism must result from the selective expression of genes.
Gene for a glycolysis enzyme

Antibody gene

Insulin gene

Hemoglobin gene
Gene Regulation in Bacteria

- Natural selection has favored bacteria that express
  - only certain genes
  - only at specific times when the products are needed by the cell.

- So how do bacteria selectively turn their genes on and off?
Gene Regulation in Bacteria

- An operon includes:
  - a cluster of genes with related functions and
  - the control sequences that turn the genes on or off.

- The bacterium *E. coli* uses the *lac* operon to coordinate the expression of genes that produce enzymes used to break down lactose in the bacterium’s environment.
A typical operon

- Regulatory gene
- Promoter
- Operator
- Gene 1
- Gene 2
- Gene 3

DNA

- Produces repressor that in active form attaches to operator
- RNA polymerase binding site
- Switches operon on or off
- Code for proteins
Gene Regulation in Bacteria

• The lac operon uses
  – a **promoter**, a control sequence where the transcription enzyme attaches and initiates transcription,
  – an **operator**, a DNA segment that acts as a switch that is turned on or off, and
  – a **repressor**, which binds to the operator and physically blocks the attachment of RNA polymerase and transcription.
Operon turned on (lactose inactivates repressor)

Lactose
Protein
mRNA
DNA

Operon turned off (lactose absent)

DNA
mRNA
Protein

Lactose

Operon turned on (lactose inactivates repressor)
Gene Regulation in Eukaryotic Cells

- Eukaryotic cells have more complex gene regulating mechanisms with many points where the process can be turned on or off.

- The multiple mechanisms that control gene expression are like the many control valves along a water supply.
DNA unpacking

Transcription

RNA processing

RNA transport

mRNA breakdown

Translation

Protein activation

Protein breakdown
The Regulation of DNA Packing

• Cells may use DNA packing for long-term inactivation of genes.

• **X chromosome inactivation**
  – takes place early in embryonic development,
  – occurs in female mammals, and
  – is when one of the two X chromosomes in each cell is inactivated at random.
• All of the descendants of each cell will have the same X chromosome turned off.

• If a female is heterozygous for a gene on the X chromosome,
  – about half her cells will express one allele and
  – the others will express the alternate allele.
Figure 11.4

Early embryo:

- Two cell populations in adult cat:
  - Orange fur
  - Black fur

Allele for orange fur
Allele for black fur

Cell division and X chromosome inactivation
The Initiation of Transcription

• The initiation of transcription is the most important stage for regulating gene expression.

• In prokaryotes and eukaryotes, regulatory proteins
  – bind to DNA and
  – turn the transcription of genes on and off.
• Transcription in eukaryotes, unlike in prokaryotes, is complex, involving many proteins, called transcription factors, that bind to DNA sequences called enhancers.
Figure 11.5

Enhancers (DNA control sequences)

Bend in the DNA

Transcription factor

Promoter

Gene

RNA polymerase

Transcription
The Initiation of Transcription

• Repressor proteins called **silencers**
  – bind to DNA and
  – inhibit the start of transcription.

• **Activators**
  – are more typically used by eukaryotes than silencers and
  – turn genes on by binding to DNA.
RNA Processing and Breakdown

• The eukaryotic cell
  – localizes transcription in the nucleus and
  – processes RNA in the nucleus.

• RNA processing includes the
  – addition of a cap and tail to the RNA,
  – removal of any introns, and
  – splicing together of the remaining exons.
In **alternative RNA splicing**, exons may be spliced together in different combinations, producing more than one type of polypeptide from a single gene.
A typical human gene contains about ten exons, with
- nearly all human genes spliced in at least two different ways and
- some spliced hundreds of different ways!
Figure 11.6-3

Exons

DNA

Introns

RNA transcript

RNA splicing

mRNA

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Eukaryotic mRNAs

- can last for hours to weeks to months and
- are all eventually broken down and their parts recycled.
microRNAs

- Small single-stranded RNA molecules, called microRNAs (miRNAs), bind to complementary sequences on mRNA molecules in the cytoplasm.
- Some trigger the breakdown of their target mRNA, and others block translation.
- It has been estimated that miRNAs may regulate the expression of up to one-third of all human genes, yet miRNAs were unknown 20 years ago!
The Initiation of Translation

- The process of translation offers additional opportunities for regulation by regulatory molecules.
Protein Activation and Breakdown

- Post-translational control mechanisms in eukaryotes
  - occur after translation and
  - often involve cutting polypeptides into smaller, active final products.
Initial polypeptide (inactive) → Cutting → Insulin (active hormone)
• The selective breakdown of proteins is another control mechanism operating after translation.
• In a multicellular organism, gene regulation can cross cell boundaries.

• A cell can produce and secrete chemicals, such as hormones, that affect gene regulation in another cell.
Figure 11.8

SIGNALING CELL

1. Secretion
   Signal molecule

Plasma membrane

Signal molecule

TARGET CELL

2. Receptor protein

3. Transcription factor (activated)

Nucleus

4. Transcription

mRNA

5. Response

Translation

New protein

6. Response
Homeotic genes

- Master control genes called **homeotic genes** regulate groups of other genes that determine what body parts will develop in which locations.

- Mutations in homeotic genes can produce bizarre effects.
Figure 11.9

Normal head

Mutant fly with extra legs growing from head
Homeotic genes

- Similar homeotic genes help direct embryonic development in nearly every eukaryotic organism examined so far.
Figure 11.10

Fruit fly chromosome

Mouse chromosomes

Fruit fly embryo (10 hours)

Mouse embryo (12 days)

Adult fruit fly

Adult mouse
DNA Microarrays: Visualizing Gene Expression

- A DNA microarray allows visualization of gene expression.
- The pattern of glowing spots enables the researcher to determine which genes were being transcribed in the starting cells.
- Researchers can thus learn which genes are active
  - in different tissues or
  - in tissues from individuals in different states of health.
Figure 11.11

1. mRNA isolated
2. cDNA made from mRNA
3. cDNA mixture added to wells
4. Unbound cDNA rinsed away

Reverse transcriptase combined with fluorescently labeled DNA nucleotides

Fluorescent cDNA

DNA microarray (each well contains DNA from a particular gene)

Unbound cDNA rinsed away

Nonfluorescent spot

Fluorescent spot

Fluorescent cDNA

DNA microarray (6,400 genes)

DNA of an expressed gene

DNA of an unexpressed gene

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Differentiated cells

- all contain a complete genome and
- have the potential to express all of an organism’s genes.

Differentiated plant cells can develop into a whole new organism.
Figure 11.12-5

- Cells removed from orchid plant
- Cells in growth medium
- Cell division in culture
- Young plant
- Adult plant
The somatic cells of a single plant can be used to produce hundreds or thousands of identical organisms—clones from a single plant.

Plant cloning demonstrates that cell differentiation in plants
- is reversible and
- does not cause irreversible changes in the DNA.

Plant cloning is now used extensively in agriculture.
The Genetic Potential of Cells

• **Regeneration**
  
  – is the regrowth of lost body parts and
  
  – occurs, for example, in the regrowth of the legs of salamanders.
During regeneration of the leg, cells in the leg stump

- reverse their differentiated state,
- divide, and
- then differentiate again to give rise to a new leg.
Reproductive Cloning of Animals

- **Nuclear transplantation** involves
  - replacing the nucleus of an egg cell with the nucleus from a differentiated cell from an adult body and
  - allowing the egg to develop into an adult.
Reproductive Cloning of Animals

- In 1997, Scottish researchers produced Dolly, a sheep, by replacing the nucleus of an egg cell with the nucleus of an adult somatic cell.
- This procedure is called **reproductive cloning**, because it results in the birth of a new animal.
Reproductive cloning

Therapeutic cloning

Donor cell

Nucleus from donor cell

Implant embryo in surrogate mother

Clone of donor is born

Remove nucleus from egg cell

Add somatic cell from adult donor

Grow in culture to produce a blastocyst (early embryo)

Remove embryonic stem cells from embryo and grow in culture

Induce stem cells to form specialized cells for therapeutic use

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Reproductive cloning

Implant embryo in surrogate mother  Clone of donor is born

Therapeutic cloning

Remove embryonic stem cells from embryo and grow in culture  Induce stem cells to form specialized cells for therapeutic use
Since Dolly, reproductive cloning has been used to clone many species of mammals, including mice, horses, dogs, mules, cows, pigs, rabbits, ferrets, and cats.
Reproductive cloning has been used to restock populations of endangered species including:

- a wild mouflon (a small European sheep),
- a banteng (a Javanese cow),
- a gaur (an Asian ox), and
- gray wolves.
However, cloning does not increase genetic diversity, which may be essential to long-term species survival.
Figure 11.14

(a) The first cloned cat

(b) Cloning for medical use

(c) Clones of endangered animals

- Mouflon lamb with mother
- Banteng
- Gaur
- Gray wolf
Human Cloning

• Cloning of mammals
  – has heightened speculation about human cloning and
  – is very difficult and inefficient.

• Critics raise practical and ethical objections to human cloning.
Therapeutic Cloning and Stem Cells

• The purpose of therapeutic cloning is
  – not to produce a viable organism but
  – to produce embryonic stem cells.
Embryonic Stem Cells

• Embryonic stem cells (ES cells)
  – are derived from blastocysts and
  – can give rise to all the specialized cells in the body.
• Adult stem cells
  – are cells in adult tissues and
  – generate replacements for some of the body’s cells.
Unlike embryonic ES cells, adult stem cells

- are partway along the road to differentiation and
- usually give rise to only a few related types of specialized cells.
Figure 11.15

Adult stem cells in bone marrow

Cultured embryonic stem cells

Different culture conditions

Different types of differentiated cells

Blood cells

Nerve cells

Heart muscle cells
Umbilical Cord Blood Banking

- Umbilical cord blood
  - can be collected at birth,
  - contains partially differentiated stem cells, and
  - has had limited success in the treatment of a few diseases.

- The American Academy of Pediatrics recommends cord blood banking only for babies born into families with a known genetic risk.
Cancer is a variety of diseases in which cells

– experience changes in gene expression and

– escape from the control mechanisms that normally limit their growth and division.
Genes That Cause Cancer

• As early as 1911, certain viruses were known to cause cancer.

• **Oncogenes** are
  
  – genes that cause cancer and
  
  – found in viruses.
Oncogenes and Tumor-Suppressor Genes

- **Proto-oncogenes** are
  - normal genes with the potential to become oncogenes,
  - found in many animals, and
  - often genes that code for **growth factors**, proteins that stimulate cell division.
Oncogenes and Tumor-Suppressor Genes

• A cell can acquire an oncogene
  – from a virus or
  – from the mutation of one of its own proto-oncogenes.
Figure 11.17

Proto-oncogene

Mutation within gene

Multiple copies of gene

Gene in new position, under new controls

DNA

Oncogene

Hyperactive growth-stimulating protein

New promoter

Normal growth-stimulating protein in excess
Tumor-suppressor genes

- inhibit cell division,
- prevent uncontrolled cell growth, and
- may be mutated and contribute to cancer.

Researchers have identified many mutations in both tumor-suppressor and growth factor genes that are associated with cancer.
Figure 11.18

(a) Normal cell growth

(b) Uncontrolled cell growth (cancer)
Proto-oncogene (normal) → Oncogene

- Normal protein

- Normal regulation of cell cycle

- Normal growth-inhibiting protein

- Tumor-suppressor gene (normal) → Mutated tumor-suppressor gene

- Mutant protein

- Out-of-control growth (leading to cancer)

- Defective protein

Mutation
The Process of Science: Are Childhood Tumors Special?

• Observations: Specific mutations can lead to cancer.

• Question: Are different kinds of cancer associated with specific mutations?

• Hypothesis: Young patients with medulloblastoma (MB) harbor unique mutations. (MB is the most common pediatric brain cancer and the deadliest form of childhood cancer.)
The Process of Science: Are Childhood Tumors Special?

• **Prediction**: The genetic map of MB cells from childhood tumors would have cancer-associated mutations not found in adult brain cancer tissue.

• **Experiment**: Researchers sequenced all the genes in tumors from 22 pediatric MB patients and compared the genes with normal tissue from these same patients.
The Process of Science: Are Childhood Tumors Special?

• **Results:**
  
  – Each tumor had an average of 11 mutations.
  
  – This is 5–10 times fewer mutations than are found in adult MB patients.
  
  – Therefore, younger MB patients have fewer but more deadly mutations.
Figure 11.19

Tumor
The Progression of a Cancer

- Nearly 150,000 Americans will be stricken by cancer of the colon (the main part of the large intestine) this year.

- Colon cancer, like many cancers,
  - spreads gradually and
  - is produced by more than one mutation.
Figure 11.20

Cellular changes:
Increased cell division

Colon wall

DNA changes:
Oncogene activated

Cellular changes:
Growth of benign tumor

Colon wall

DNA changes:
Tumor-suppressor gene inactivated

Cellular changes:
Growth of malignant tumor

DNA changes:
Second tumor-suppressor gene inactivated
The development of a malignant tumor is accompanied by a gradual accumulation of mutations that

- convert proto-oncogenes to oncogenes and
- knock out tumor-suppressor genes.
Figure 11.21-5

Chromosomes 1 mutation 2 mutations 3 mutations 4 mutations

Normal cell → 1 mutation → 2 mutations → 3 mutations → 4 mutations → Malignant cell

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“Inherited” Cancer

• Most mutations that lead to cancer arise in the organ where the cancer starts.

• In familial or inherited cancer,
  – a cancer-causing mutation occurs in a cell that gives rise to gametes and
  – the mutation is passed on from generation to generation.
“Inherited” Cancer

- Breast cancer
  - is usually not associated with inherited mutations
  - in some families can be caused by inherited $BRCA1$ cancer genes.
Cancer Risk and Prevention

• Cancer
  – is the second leading cause of death (after heart disease) in most industrialized countries and
  – can be caused by carcinogens, cancer-causing agents, found in the environment, including
    – tobacco products,
    – alcohol, and
    – exposure to ultraviolet light from the sun.
Table 11.1

Cancer in the United States (Ranked by Number of Cases)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Known or Likely Carcinogens or Factors</th>
<th>Estimated Cases (2011)</th>
<th>Estimated Deaths (2011)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Testosterone; possibly dietary fat</td>
<td>241,000</td>
<td>33,700</td>
</tr>
<tr>
<td>Breast</td>
<td>Estrogen; possibly dietary fat</td>
<td>233,000</td>
<td>40,000</td>
</tr>
<tr>
<td>Lung</td>
<td>Cigarette smoke</td>
<td>221,000</td>
<td>157,000</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>High dietary fat; low dietary fiber</td>
<td>141,000</td>
<td>49,400</td>
</tr>
<tr>
<td>Skin</td>
<td>Ultraviolet light</td>
<td>76,300</td>
<td>12,000</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>Viruses (for some types)</td>
<td>75,200</td>
<td>20,600</td>
</tr>
<tr>
<td>Bladder</td>
<td>Cigarette smoke</td>
<td>69,300</td>
<td>15,000</td>
</tr>
<tr>
<td>Kidney</td>
<td>Cigarette smoke</td>
<td>60,900</td>
<td>13,100</td>
</tr>
<tr>
<td>Uterus</td>
<td>Estrogen</td>
<td>46,500</td>
<td>8,100</td>
</tr>
<tr>
<td>Leukemias</td>
<td>X-rays; benzene; viruses (for some types)</td>
<td>44,600</td>
<td>21,800</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Cigarette smoke</td>
<td>44,000</td>
<td>37,700</td>
</tr>
<tr>
<td>Liver</td>
<td>Alcohol; hepatitis viruses</td>
<td>26,200</td>
<td>19,600</td>
</tr>
<tr>
<td>Brain and nerve</td>
<td>Trauma; X-rays</td>
<td>22,300</td>
<td>13,100</td>
</tr>
<tr>
<td>Ovary</td>
<td>Large number of ovulation cycles</td>
<td>22,000</td>
<td>15,500</td>
</tr>
<tr>
<td>Stomach</td>
<td>Table salt; cigarette smoke</td>
<td>21,500</td>
<td>10,300</td>
</tr>
<tr>
<td>Cervix</td>
<td>Viruses; cigarette smoke</td>
<td>12,700</td>
<td>4,300</td>
</tr>
<tr>
<td>All other types</td>
<td></td>
<td>239,200</td>
<td>100,800</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,596,700</td>
<td>572,000</td>
</tr>
</tbody>
</table>

Source: Cancer Facts and Figures 2011 (American Cancer Society Inc.).
Exposure to carcinogens

- is often an individual choice and
- can be avoided.

Some studies suggest that certain substances in fruits and vegetables may help protect against a variety of cancers.
Evolution Connection: The Evolution of Cancer in the Body

• Evolution drives the growth of a tumor.

• Like individuals in a population of organisms, cancer cells in the body
  – have the potential to produce more offspring than can be supported by the environment and
  – show individual variation, which
    – affects survival and reproduction and
    – can be passed on to the next generation of cells.
Some researchers are attempting to “prime” tumors for treatment by increasing the reproductive success of only those cells that will be susceptible to a chemotherapy drug.