Big Idea 3:
Living systems store, retrieve, transmit and respond to information essential to life processes.

Enduring Understanding 3.B:
Expression of genetic information involves cellular and molecular mechanisms.

Learning Objectives:

**Enduring Knowledge 3.B.1**: Gene regulation results in differential gene expression, leading to cell specialization.
- (3.18) The student is able to describe the connection between the regulation of gene expression and observed differences between different kinds of organisms.
- (3.19) The student is able to describe the connection between the regulation of gene expression and observed differences between individuals in a population.
- (3.20) The student is able to explain how the regulation of gene expression is essential for the processes and structures that support efficient cell function.
- (3.21) The student can use representations to describe how gene regulation influences cell products and function.

**Enduring Knowledge 3.B.2**: A variety of intercellular and intracellular signal transmissions mediate gene expression.
- (3.22) The student is able to explain how signal pathways mediate gene expression, including how this process can affect protein production.
- (3.23) The student can use representations to describe mechanisms of the regulation of gene expression.

**Essential Knowledge 2.E.1**: Timing and coordinating of specific events are necessary for the normal development of an organism, and these events are regulated by a variety of mechanisms.
- (2.31) The student can connect concepts in and across domains to show that timing and coordination of specific events are necessary for normal development in an organism and that these events are regulated by multiple mechanisms.
- (2.32) The student is able to use a graph or diagram to analyze situations or solve problems (quantitatively or qualitatively) that involve timing and coordination of events necessary for normal development in an organism.
- (2.33) The student is able to justify scientific claims with scientific evidence to show that timing and coordination of several events are necessary for normal development in an organism and that these events are regulated by multiple mechanisms.
- (2.34) The student is able to describe the role of programmed cell death (apoptosis) in development and differentiation, the reuse of molecules, and the maintenance of dynamic homeostasis.

- 3.B.1 - "031: Gene Regulation
- 3.B.2 - "032: Signal Transmission
- 2.E.1 - "024: Development: Timing and Coordination

**Animated Content Review Videos**:  
- Transcription Promoters: [http://bcs.whfreeman.com/thelifewire/content/chp14/1402002.html](http://bcs.whfreeman.com/thelifewire/content/chp14/1402002.html)
- Lac Operon: [http://www.sumanasinc.com/webcontent/animations/content/lacoperon.html](http://www.sumanasinc.com/webcontent/animations/content/lacoperon.html)
- Cell Proliferation Signaling Pathway: [http://highered.mcgraw-hill.com/sites/dl/free/0072495855/student_view0/chapter24/animation__cytotoxic_t-cell_activity_against_target_cells__quiz_1_.html](http://highered.mcgraw-hill.com/sites/dl/free/0072495855/student_view0/chapter24/animation__cytotoxic_t-cell_activity_against_target_cells__quiz_1_.html)
- Stem Cells: [http://outreach.mcb.harvard.edu/animations/preloaderStemCells.swf](http://outreach.mcb.harvard.edu/animations/preloaderStemCells.swf)
- Cellular Determination: [http://bcs.whfreeman.com/thelifewire/content/chp20/2002002.html](http://bcs.whfreeman.com/thelifewire/content/chp20/2002002.html)
- Apoptosis & Development: [http://sites.sinauer.com/cooper6e/animation1701.html](http://sites.sinauer.com/cooper6e/animation1701.html)
- Apoptosis & Immune Function: [http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter24/animation__cytotoxic_t-cell_activity_against_target_cells__quiz_1_.html](http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter24/animation__cytotoxic_t-cell_activity_against_target_cells__quiz_1_.html)

**Required Readings**  
- 3.B.1 – Ch. 17 (pp. 331-336)
- 3.B.1 & 3.B.2 – Ch. 18
- 2.E.1 – Ch. 18; Ch. 21 (pp. 442-447); Ch. 11 (pp. 223-225)
- Article: miRNA Regulation in the Control of Cell Fate

**Practicing Biology Homework Questions**:  
Questions #23-33
Essential Knowledge 3.B.1: Gene regulation results in differential gene expression, leading to cell specialization.

Structure and function in biology result from the presence of genetic information and the correct expression of this information. The expression of the genetic material controls cell products, and these products determine the metabolism and nature of the cell. Most cells within an organism contain the same set of genetic instructions, but the differential expression of specific genes determines the specialization of cells.

Some genes are continually expressed, while the expression of most is regulated; regulation allows for more efficient energy utilization, resulting in increased metabolic fitness. Gene expression is controlled by environmental signals and developmental cascades that involve both regulatory and structural genes.

A variety of different gene regulatory systems are found in nature. Two of the best studied are the inducible and the repressible regulatory systems (i.e., operons) in bacteria, and several regulatory pathways that are conserved across phyla use a combination of positive and negative regulatory motifs. In eukaryotes, gene regulation and expression are more complex and involve many factors, including a suite of regulatory molecules.

→Both DNA regulatory sequences, regulatory genes, and small regulatory RNAs are involved in gene expression.

Specific sequences of nucleotides along the DNA of a gene mark where transcription of that gene begins and ends. Regulatory sequences are stretches of DNA that interact with regulatory proteins to control transcription. A regulatory gene is a sequence of DNA encoding a regulatory protein or RNA. Regulatory proteins are those that regulate or are involved in gene expression. Small regulatory RNAs are noncoding RNAs that can form complexes with proteins and influence gene expression. Illustrative examples of regulatory sequences include:

- **Promoters:** the DNA regulatory sequence where RNA polymerase attaches and initiates transcription.
- **Terminators:** the DNA regulatory sequence that signals the end of transcription in bacteria.
- **Enhancers:** segments of regulatory eukaryotic DNA containing multiple control elements, usually located far from the gene whose transcription it regulates.

→Promoters:

http://bcs.whfreeman.com/thelifewire/content/chp14/1402002.html

1) A eukaryotic promoter commonly includes a TATA box, a nucleotide sequence containing TATA, about 25 nucleotides upstream from the transcription start point.
2) Several transcription factors, one recognizing the TATA box, must bind to the DNA before RNA polymerase II can do so.
3) Additional transcription factors bind to the DNA along with RNA polymerase II, forming the transcription initiation complex. The double helix then unwinds and RNA synthesis begins at the start point on the template strand.

→Terminators:

In bacteria, transcription proceeds through a terminator sequence in the DNA. The transcribed terminator functions as the termination signal, causing the polymerase to detach from the DNA and release the transcript (mRNA).
Enhancers:
An enhancer is a transcription control element that may be located thousands of nucleotides upstream or downstream of a gene. A given gene may have multiple enhancers, each activated at a different time or in a different cell type or location in the organism.

Example (Figure 18.10): Both liver cells and lens cells have the genes for making the protein albumin and crystallin, but only liver cells make albumin (a blood protein) and only lens cells make crystallin (a lens protein). The specific transcription factors made in a cell determine which genes are expressed.

Notice in this example that each gene has its own enhancer, which has a unique combination of elements. All the activators required for expression of the albumin gene are present only in liver cells, whereas the activators needed for expression of the crystallin gene are present only in lens cells.

Both positive and negative control mechanisms regulate gene expression in bacteria and viruses.
The expression of specific genes can be turned on by the presence of an inducer. The expression of specific genes can be inhibited by the presence of a repressor. Inducers and repressors are small molecules that interact with regulatory proteins and/or regulatory sequences. Regulatory proteins inhibit gene expression by binding to DNA and blocking transcription (negative control). Regulatory proteins stimulate gene expression by binding to DNA and stimulating transcription (positive control) or binding to repressors to inactivate repressor function. Certain genes are continuously expressed; that is, they are always turned “on”. For example, the ribosomal genes.

Control of Gene Expression in Bacteria
Bacteria often respond to environmental change by regulating transcription. In bacteria, genes are often clustered into operons, with one promoter serving several adjacent genes. An operator site on the DNA switches the operon on or off, resulting in coordinate regulation of the genes.

- An operon is essentially a set of genes and the switches that control the expression of those genes.
- An operon consists of:
  - an operator;
  - a promotor;
  - and genes that they control
- All together, the operator, the promoter, and the genes they control – the entire stretch of DNA required for enzyme production for the pathway – is called an operon.

Promoter Region: a base sequence that signals the start site for gene transcription; this is where RNA polymerase binds to begin the process. Operator: a short sequence near the promoter that controls the access of RNA polymerase to the genes. Repressor: a molecule that binds to the operator and blocks attachment of RNA polymerase to the promoter. Inducer: a molecule that binds to and inactivates a repressor (i.e. lactose for the lac operon). Corepressor: a molecule that cooperates with a repressor protein and activates the repressor to switch an operon off

There are basically two types of operons found in prokaryotes: repressible operons and inducible operons. Both the repressible and inducible operon are types of NEGATIVE gene regulation because both are turned OFF by the active form of the repressor protein. In either type of operon, binding of a specific repressor protein to the operator shuts off transcription.

- trp operon – repressible operon is always in the on position until it is not needed and becomes repressed or switched off.
- lac operon – inducible operon is always off until it is induced to turn on.
- Repressible operons are normally anabolic, building essential organic molecules. Inducible operons are normally catabolic, breaking down food molecules for energy.
The trp Operon

Tryptophan is an amino acid produced by an anabolic pathway catalyzed by repressible enzymes. If tryptophan is absent, the repressor is inactive, the operon is on, and RNA polymerase attaches to the DNA at the promoter and transcribes the operon’s genes. As tryptophan accumulates, it inhibits its own production by activating the repressor protein. The repressor switches the operon off by binding to the operator and blocking access of RNA polymerase to the promoter. Tryptophan binds to an allosteric site on the protein, causing its conformation to change to the active form. REMEMBER: The trp operon is an example of a repressible operon because it is always in the ON position until not needed – then it is switched off.

The lac Operon

The lactose operon services a series of three genes involved in the process of lactose metabolism. These genes help bacteria to digest lactose. It makes sense for these bacteria to express these genes only when lactose is present...otherwise, they waste energy on unneeded enzymes. This is where OPERONS come in to play...the lac repressor is innately active, and in the absence of lactose it switches off the operon by binding to the operator on the promoter region and blocking transcription from occurring.

When lactose is present, there is a binding site on the repressor where lactose attaches, causing the repressor to let go of the promoter region. RNA polymerase is then free to bind to that site and initiate transcription of the genes. IN THIS EXAMPLE...alolactose, an isomer of lactose, de-represses the operon by inactivating the repressor. In this way, the enzymes for lactose utilization are induced. REMEMBER: the lac operon is an example of an inducible operon because it is always off until it is induced to turn on.
When glucose and lactose are both present in its environment, *E. coli* prefer to use glucose. Only when lactose is present AND glucose is in short supply does *E. coli* use lactose as an energy source, and only then does it synthesize appreciable quantities of the enzymes for lactose breakdown.

How does the *E. coli* cell sense the glucose concentration and relay this information to its genome?

If glucose is scarce, the high level of cAMP activates CAP, and the lac operon produces large amounts of mRNA coding for the enzymes in the lactose pathway. cAMP is an allosteric regulatory protein (cyclic AMP) – which accumulates when glucose is scarce. When glucose is present, cAMP is scarce, and CAP is unable to stimulate transcription.

This type of gene regulation is POSITIVE because a regulatory protein interacts directly with the genome to switch transcription ON.

**Factors Affecting the Ability of a Repressor to Bind to an Operator**

1. **Co-Repressor**: activates a repressor:
   - Seen in the trp Operon
   - Co-Repressor is tryptophan
   - Turns normally “on” Operon “off”

2. **Inducer**: inactivates a repressor, *induces* the gene to be transcribed:
   - Seen in the lac Operon
   - Inducer is allolactose
   - Turns normally “off” Operon “on”

**Structure & Function of PROKARYOTIC Genomes**

1. shape (*circular*, nonlinear, loop)
2. less complex than eukaryotes (no histones/less elaborate structure/folding)
3. size (*smaller size*, less genetic information/fewer genes)
4. replication method (*single origin of replication*, rolling circle replication)
5. transcription/translation may be *coupled*
6. generally few or no *introns* (noncoding segments)
7. majority of genome expressed
8. **Operons** are used for gene regulation and control
   - NOTE: *plasmids* – more common but not unique to prokaryotes/not part of prokaryote chromosome
   - The bacterial chromosome is a double-stranded, *circular* DNA molecule associated with a small amount of protein
   - In a bacterium, the DNA is “supercoiled” and found in a region of the cell called the **nucleoid**
In EUKARYOTES, gene expression is complex and control involves regulatory genes, regulatory elements and transcription factors that act in concert. Transcription factors bind to specific DNA sequences and/or other regulatory proteins. Some of these transcription factors are activators (increase expression), while others are repressors (decrease expression). The combination of transcription factors binding to the regulatory regions at any one time determines how much, if any, of the gene product will be produced. A typical human cell probably expresses about 20% of its genes at any given time. Almost all cells in an organism contain an identical genome. However, the subset of genes expressed in the cells of each type is unique, allowing these cells to carry out their specific function. The differences between cell types, therefore, are due not to different genes being present, but to differential gene expression, the expression of different genes by cells with the same genome.

Key Stages in the Expression of a Protein-Coding Gene in Eukaryotes
In eukaryotes, gene expression can be regulated at any stage. The expression of eukaryotic genes can be turned off and on at any point along the pathway from gene to functional protein. Further, the difference between cell types is NOT due to different genes being present, but to differential gene expression. This is the expression of DIFFERENT genes by cells with the SAME genome.

Opportunities for the control of gene expression in eukaryotes include:
(1) Chromatin Packing, modification; (2) Assembling of Transcription Factors; (3) RNA Processing; (4) Regulation of mRNA degradation and Control of Translation; and (5) Protein Processing and Degradation

Chromatin structure is based on successive levels of DNA packing. Eukaryotic chromatin is composed mostly of DNA and histone proteins that bind to the DNA to form nucleosomes, the most basic units of DNA packing. Additional folding leads ultimately to highly compacted heterochromatin, the form of chromatin in a metaphase chromosome. In interphase cells, most chromatin is in a highly extended form, called euchromatin.

Chromatin Modifications
The relationship between DNA and its histones is governed by two chemical interactions:

- **DNA methylation**: (-CH$_3$) the addition of methyl groups to DNA – causes DNA to be more TIGHTLY packaged, thus REDUCING gene expression. *Methylation occurs primarily on DNA and reduces gene expression.*

- **Histone acetylation**: (-COCH$_3$) the addition of acetyl groups to amino acids of histone proteins – makes chromatin LESS TIGHTLY packed and STIMULATES transcription. *Acetylation occurs on histones and increases gene expression.*

Chromatin modifications affect the availability of genes for transcription. The physical state of DNA in or near a gene is important in helping control whether the gene is available for transcription. Genes of heterochromatin (highly condensed) are usually not expressed because transcription proteins cannot reach the DNA. **Example:** Highly methylated DNA can be seen in that of the inactivated mammalian X chromosome, whereas active X chromosome tends to be heavily acetylated. **THESE ARE BOTH EXAMPLES OF EPIGENETIC INHERITANCE!!!**
A Eukaryotic Gene and its Transcript

In eukaryotes, transcription is controlled by the presence or absence of particular transcription factors, which bind to the DNA and affect the rate of transcription. Thus, transcription initiation is controlled by proteins that interact with DNA and with each other. Once a gene is “unpacked”, the initiation of transcription is the most important and universally used control point in gene expression.

Assembling of Transcription Factors

1) **Activator** proteins bind to enhancer sequences in the DNA and help position the initiation complex on the promoter.
2) **DNA bending** brings the bound activators closer to the promoter. Other transcription factors and RNA polymerase are nearby.
3) **Protein-binding domains** on the activators attach to certain transcription factors and help them form an active transcription initiation complex on the promoter.
4) Control elements are simply segments of noncoding DNA that help regulate transcription of a gene by binding proteins (transcription factors).

Alternative Splicing

http://highered.mcgraw-hill.com/olc/dl/120080/bio31.swf

Transcription alone DOES NOT constitute gene expression! **Post-transcriptional mechanisms** play supporting roles in the control of gene expression: **Alternative RNA splicing** — where different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns. Regulatory proteins specific to a cell type control intron-exon choices by binding to regulatory sequences within the primary transcript.
Further Control of Gene Expression

After RNA processing, other stages of gene expression that the cell may regulate are:

1. **mRNA degradation**: The life span of mRNA molecules in the cytoplasm is important in determining the pattern of protein synthesis in a cell. In bacteria, mRNA are typically degraded within a few minutes of their synthesis – enables bacteria to change quickly in response to environmental changes. In eukaryotes, mRNA typically survive for days or weeks. Breakdown begins by shortening the poly-A tail and removing the 5’ cap.

2. **Translation Initiation**: Translation presents another opportunity for regulating gene expression in eukaryotes – particularly at the translation initiation stage. This type of regulation typically occurs at the 5’ cap or poly-A tail. If regulatory protein binds to 5’ region, ribosome cannot attach to mRNA – thus no translation occurs. If mRNA lacks a poly-A tail of sufficient length, translation initiation will not occur because poly-A tail facilitates attachment of rRNA to mRNA during translation.

3. **Protein Processing & Degradation**: Often, eukaryotic polypeptides must be processed to yield functional proteins, and regulation can occur at any stage of protein processing:
   - Proper folding is required;
   - Chemical modification is required;
   - Protein must be transported to proper location within or outside the cell;
   - Selective degradation regulates the length of time a particular protein functions in a cell. Proteins to be degraded are tagged with ubiquitin, and proteasomes recognize these and chop them apart.

Noncoding RNAs & Gene Expression

A significant amount of the eukaryotic genome may be transcribed into small non-protein-coding RNAs. These play crucial roles in regulating gene expression – generally during mRNA translation and chromatin configuration.

- **MicroRNAs** (miRNAs): bind to mRNA sequences and degrade the mRNA before translation or block its translation.
- **Small Interfering RNAs** (siRNAs): can be crucial for the formation of heterochromatin at the centromeres of chromosomes.

Structure & Function of EUKARYOTIC Genomes

- **Chromatids**: 2/sister/pari/identical DNA/ genetic information; distribution of one copy to each new cell
- **Centromere**: noncoding/uncoiled/narrow/constricted region; joins/holds/attaches chromatids together
- **Nucelosome**: histones/DNA wrapped arround special proteins; packaging compacting
- **Chromatin Form (heterochromatin/euchromatin)**: heterochromatin is condensed/supercoiled / proper distribution in cell division (not during replication); euchromatin is loosely coiled/ gene expression during interphase/replication occurs when loosely packed
- **Kinetochores**: disc-shaped proteins; spindle attachment/alignment
- **Genes or DNA**: brief DNA description; codes for proteins or for RNA
- **Telomeres**: tips, ends, noncoding repetitive sequences; protection against degradation/ aging, limits number of cell divisions

Gene regulation accounts for some of the phenotypic differences between organisms with similar genes.

When considering phenotypes, it is often useful to focus on genes that code for polypeptides, and the control mechanisms that switch these genes on and off in cells.

- Proteins bring about an organism’s observable phenotype.
- Regardless of the genes found in the organism, phenotypes are only produced when gene products are made by genes that are switched on.
- Thus, two organisms with basically the same genome may have very different phenotypes due to differential gene expression.
Essential Knowledge 3.B.2: A variety of intercellular and intracellular signal transmissions mediate gene expression.

Multicellular organisms have developmental pathways from zygote to adult, yet all cells in the organism start with the same complement of DNA. The developmental sequences are predominately determined and programmed by differential gene expression. Which gene gets expressed and the level of expression are determined by both internal and external signals. In multicellular organisms, cell-to-cell interactions and cell-to-cell signaling via small molecules modulate and control gene expression and cell function. For example, morphogens help to determine spatial development, and hormones can influence cell metabolism.

Developmental gene sequences have an evolutionary origin and are conserved across species; for example, HOX genes are present in the genome sequences from Drosophila to humans. Errors or changes in regulation of genes involved in development often lead to severe, detrimental and even bizarre consequences.

→ Signal transmission within and between cells mediates gene expression.

External signals are converted to responses within a cell. This phenomenon is known as signal transmission. Signal transmission within and between cells mediates the function of cells. Illustrative Examples include:

- Cytokines regulate gene expression to allow for cell replication and division (REVIEW CONTROL OF THE CELL CYCLE).
- Ethylene levels cause changes in the production of different enzymes, allowing fruits to ripen (REVIEW NOTES FROM BIG IDEA 2).
- Levels of cAMP regulate metabolic gene expression in bacteria (REVIEW OPERONS).

→ Signal transmission within and between cells mediates cell function.


Certain genes normally regulate growth and division — the cell cycle — and mutations that alter those genes in somatic cells can lead to cancer.

- Proto-Oncogenes are normal genes that code for proteins which stimulate normal cell growth and division.
- Oncogenes — cancer causing genes; lead to abnormal stimulation of cell cycle. Oncogenes arise from genetic changes in proto-oncogenes:
  1. Amplification of proto-oncogenes
  2. Point mutation in proto-oncogene
  3. Movement of DNA within genome

In addition to genes whose products normally promote cell division, cells contain genes whose normal products inhibit cell division. These genes are referred to as tumor-suppressor genes because the proteins they encode help prevent uncontrolled cell growth. Cancer can be caused by a mutation in a tumor-suppressor gene if the mutation causes the gene to fail to prevent uncontrolled division.

- Two important tumor-suppressor genes: p53 and ras. Mutations in ras occur in 30% of human cancers. Mutations in p53 occur in more than 50% of human cancers.

The **p53 gene** is an important tumor-suppressor gene. This gene may suppress cancer in three ways:

1. The p53 gene halts the cell cycle by binding to cyclin-dependent kinases — allows time for DNA to be repaired before the resumption of cell division.
2. The p53 genes turns on genes directly involved in DNA repair.
3. When DNA damage is too severe to repair, the p53 gene activates suicide genes whose products cause apoptosis (cell death). In many cancer patients, the p53 gene product does not function properly.
Multiple mechanisms regulate the timing and coordination of molecular, physiological and behavioral events that are necessary for an organism’s development and survival. Cell differentiation results from the expression of genes for tissue-specific proteins, and the induction of transcription factors during development results in sequential gene expression. For example, homeotic genes determine developmental patterns and sequences. Genetic transplantation experiments support the link between gene expression, mutations and development. Programmed cell death (apoptosis) plays a role in normal development and differentiation (i.e. morphogenesis).

Observable cell differentiation results from the expression of genes for tissue-specific proteins.
Almost all cells in an organism have the same genome; therefore, differential gene expression result from genes being regulated differently in each cell type. This program of differential gene expression leads to the different cell types in a multicellular organism.
A zygote typically undergoes transformation in three interrelated processes:
1. **Cell Division**: the series of mitotic divisions that increases the number of cells.
2. **Cell Differentiation**: the process by which cells become specialized in structure & function.
3. **Morphogenesis**: the organization of cells into tissues and organs.

All three processes have their basis in cellular behavior. The activities of a cell depend on the genes it expresses and the proteins it produces. Each differentiated cell in a multicellular organism has a particular mix of specific activators that turn on the collection of genes whose products are required in the cell. Materials placed into the egg by the MOTHER set up a sequential program of gene regulation that is carried out as cells divide, and this program makes the cells become different from each other in a coordinated fashion.

*From Fertilized Egg to Animal*
In the embryonic development of multicellular organisms, a fertilized egg (zygote) gives rise to cells of many different types, each with a different structure and corresponding function. Typically, cells are organized into tissues, tissues into organs, organs into organ systems, and organ systems into the whole organism. Thus, any developmental program must produce cells of different types that form higher-level structures arranged in a particular way.

**Cytoplasmic Determinants in the Egg**
How do different sets of activators come to be present in two cells? Materials placed into the egg by the mother set up a sequential program of gene regulation that is carried out as cells divide – and this program makes cells become different from each other in a coordinated fashion. An unfertilized egg has molecules called **cytoplasmic determinants** in its cytoplasm – and these molecules are unequally distributed in the unfertilized egg. These materials include RNA and proteins encoded by the mother’s DNA. The uneven distribution of these determinants has a profound impact on the development of the future embryo. After fertilization and early mitotic division, the cell nuclei of the embryo are exposed to different sets of cytoplasmic determinants and, as a result, express different genes.
Induction by Nearby Cells
The other major source of developmental information, which becomes increasingly important as the number of embryonic cells increases, is the environment around a particular cell.

- As the number of cells of an early embryo increases, the most influential signals are those that come from nearby embryonic cells, particularly those in contact with each other.
- The cells at the bottom of the early embryo are releasing chemicals that signal nearby cells to change their gene expression (INDUCTION). This change in gene expression of the target cells results in observable cellular changes, including those that produce differentiated cells in an organism.
- So...interactions between embryonic cells help induce differentiation of the many specialized cell types making up a new organism.

Control of Cell Differentiation & Morphogenesis
http://outreach.mcb.harvard.edu/animations/preloaderStemCells.swf

Cytoplasmic determinants are maternal substances in the egg that influence the course of early development – they are distributed unevenly in the early cells of the embryo and this has a profound impact on early development.

- Cell-cell signals result from molecules, such as growth factors, produced by one cell influencing neighboring cells in a process called induction, which causes cells to differentiate.
- Determination is the series of events that lead to observable differentiation of a cell – caused by cell signaling from neighboring embryonic cells. Once it has undergone determination, an embryonic cell is irreversibly committed to its final fate.
- It is now understood that the outcome of determination, observable cell differentiation, is marked by the expression of genes for tissue-specific proteins.
- Pattern formation sets up the body plan and is a result of cytoplasmic determinants and inductive signals – determines head/tail, left/right, and back/front.

Sequential Regulation of Gene Expression During Cellular Differentiation in a Muscle Cell
http://bcs.whfreeman.com/thelifewire/content/chp20/2002002.html

The outcome of determination (cell differentiation) is marked by the expression of genes for tissues-specific proteins. These proteins are found only in a specific cell type and give the cell its characteristic structure and function. The first evidence of differentiation is the appearance of mRNAs for these proteins. On the molecular level, different sets of genes are sequentially expressed in a regulated manner as new cells arise from division of their precursors. A number of steps in gene expression may be regulated during differentiation, with transcription among the most important. Once differentiated, cells become specialized at making tissue-specific proteins.
Early Development & Homeotic Genes

Homeotic genes are any of the master regulatory genes that control placement and spatial organization of body parts in eukaryotes by controlling the developmental fate of a group of cells.

- The products of one class of homeotic genes, the *Hox* genes, provide positional information in an animal embryo. This information prompts cells to develop into structures appropriate for a particular location.
- Changes in *Hox* genes or in how they are expressed can have a profound impact on morphology.

Pattern Formation: Setting Up the Body Plan

*Pattern formation* is the development of a spatial organization of tissues and organs.

- In animals, pattern formation begins with the establishment of the major axes. *Positional information*, the molecular cues that control pattern formation, tells a cell its location relative to the body axes and to neighboring cells.
- Pattern formation has been extensively studied in the fruit fly *Drosophila melanogaster*.
- Combining anatomical, genetic, and biochemical approaches, researchers have discovered developmental principles common to many other species, including humans.

Figure 18.17 Key developmental events in the life cycle of *Drosophila*

In *Drosophila*, cytoplasmic determinants in the unfertilized egg determine the axes before fertilization. After fertilization, the embryo develops into a segmented larva with three larval stages.

Genetic mutations can result in abnormal development. Mutations in regulatory genes (homeotic gene) can cause misplacement of structures. Wild type head with small antennae. Mutant head with pair of legs in place of antennae.

Axis Establishment

Cytoplasmic determinants in the egg are the substances that initially establish the axes of a body plan (anterior-posterior, right-left, dorsal-ventral). These substances are referred to as *maternal effect genes* because they are encoded by genes of the mother. When there is a mutation in the mother, the mutation will be visible in the offspring REGARDLESS of the offspring’s own genotype.

This is powerful evidence that cytoplasmic determinants, rather than strictly DNA, control the early embryonic development of organisms.

- Mother has a mutation on a gene that codes for cytoplasmic determinants.
- She makes a defective gene product (or none at all).
- Eggs are defective. If eggs are fertilized, they fail to develop properly.
- As it relates to homeotic genes:
  - You should be familiar with the “Scientific Inquiry” on page 370 (read text) and Figure 18.17 & 18.18 in text.
  - You should also be familiar with Inquiry/Figure 18.19 in text.
Is Bicoid a morphogen that determines the anterior end of a fruit fly?

**Experiment:** Embryos and larvae were obtained that had defects in their body patterns, some due to mutations in the mother’s genes. One such gene was termed the “bicoid” gene because its mutation resulted in larvae with two tails and no head.

- **Hypothesis:** bicoid normally codes for a morphogen that specifies the head (anterior) end of the embryo. To test, they used molecular techniques to determine where the mRNA and protein encoded by this gene were found in the fertilized egg and early embryo.
- **Results:** Bicoid mRNA (dark blue) was confined to the anterior end of the unfertilized egg. Later in development, Bicoid protein was seen to be concentrated in cells at the anterior end of the embryo.
- **Conclusion:** The results support the hypothesis that Bicoid protein is a morphogen specifying formation of head-specific structures.

**QUESTION:** If the hypothesis is correct, predict what would happen if you injected bicoid mRNA into the anterior end of an egg from a female mutant for bicoid.

**Genetic transplantation experiments support the link between gene expression and normal development.**

http://bcs.whfreeman.com/thelifewire/content/chp20/2002002.html

Can the dorsal lip of the blastopore induce cells in another part of the amphibian to change their developmental fate?

**Genetic Regulation and the Role of microRNAs**

Genetic regulation by microRNAs plays an important role in the development of organisms and the control of cellular functions. Only a small fraction of DNA codes for proteins, rRNA, and tRNA. A significant amount of the genome may be transcribed into noncoding RNAs. Noncoding RNA molecules in cells play crucial roles in regulating gene expression.

- **MicroRNAs (miRNAs)** are small single-stranded RNA molecules that can bind to complementary mRNA sequences.
- These can degrade mRNA or block its translation.
  - The phenomenon of inhibition of gene expression by RNA molecules is called RNA interference (RNAi).
  - RNAi is caused by small interfering RNAs (siRNAs).
- Noncoding RNAs can regulate gene expression at multiple steps.
- Many miRNAs play important roles in embryonic development by regulating gene expression at crucial times during early embryonic development.
The role of small RNAs as key regulators of mRNA turnover and translation has been well established. Recent advances indicate that the small RNAs termed microRNAs play important roles in animal development and physiology.

- Cellular activities such as proliferation, morphogenesis, apoptosis and differentiation are regulated by microRNAs.
- The expression of various genes are regulated by microRNAs, and several microRNAs act in reciprocal negative feedback loops with protein factors to control cell fate decisions that are triggered by signal transduction activity.
- These observations implicate small RNAs as important mediators of gene regulation in response to cell-cell signaling.
- The mechanism by which microRNAs silence gene expression is post-transcriptional, possibly influencing the stability, compartmentalization and translation of mRNAs. This mechanism is an efficient means to regulate production of a diverse range of proteins.

> **Programmed cell death (apoptosis) plays a role in the normal development and differentiation of organisms.**

http://sites.sinauer.com/cooper5e/animation1701.html

Cells that are infected or damaged or that have simply reached the end of their functional life span often enter a program of controlled cell suicide. During this process, cellular agents chop up the DNA and fragment the organelles and other cytoplasmic components. The cell shrinks, and the cell’s parts are packaged up in vesicles that are engulfed and digested by special scavenger cells. **Illustrative examples** include:

- Morphogenesis of fingers and toes
- *C. elegans* development
- Immune function

*C. elegans* Development

Embryonic development is a period during which apoptosis is widespread and plays a crucial role. The molecular mechanisms underlying apoptosis were worked out in detail by researchers studying embryonic development of a small soil worm, a nematode called *Caenorhabditis elegans*. The timely suicide of cells occurs exactly 131 times during normal development of *C. elegans*, at precisely the same points in the cell lineage of each worm. Research has revealed two key apoptosis genes (*ced-3* & *ced-4*) which encode proteins essential for apoptosis. These and most other proteins involved in apoptosis are continually present in cells, but in inactive form; thus, protein activity is regulated rather than protein synthesis (by way of gene activity).

a) As long as Ced-9, located in the outer mitochondrial membrane, is active, apoptosis is inhibited, and the cell remains alive.

b) When a cell receives a death signal, Ced-9 is inactivated, relieving its inhibition of Ced-3 & Ced-4. Active Ced-3 triggers a cascade of reactions leading to changes in apoptotic cells and eventual cell death.