

Chapter 11: Gene Expression

Objectives

1. Define operon, operator, repressor
2. Predict whether an operon will be on/off/in between based on presence of certain chemicals (ex. lactose, glucose in lac operon)
3. Define stem cells, differentiation, master genes
4. Name and explain the different types of transcriptional control
5. Name and explain the different types of mRNA processing control
6. Name and explain the different types of mRNA transport control
7. Name and explain the different types of translational control
8. Name and explain the different types of post-translational control
9. How master genes are evidence for evolution (common ancestry)
10. Explain X-chromosome inactivation
11. Explain how epigenetics (specifically methylation of DNA) is related to gene expression

Regulation of Gene Expression

- ❖ 11.1: Introduction
 - Gene Expression - processes that control the turning on or turning off of a gene; allows stem cells to specialize/differentiate
 - DNA to the final product, typically a protein
 - Transcription and translation
 - Regulation of gene expression conserves energy and space
 - Turns them on and off like a breaker box
 - Only expressing a subset of genes in each cell saves space because DNA must be unwound from its tightly coiled structure to transcribe and translate the DNA
- ❖ 11.1a: Prokaryotic vs. Eukaryotic Gene Expression
 - How (Prokaryotic) Genes Code for Functional Proteins
 - Transcription and translation occur almost simultaneously
 - When the resulting protein isn't needed anymore, transcription stops
 - As a result, the *primary method to control* what type of protein and how much of each protein is expressed in a prokaryotic cell is the *regulation of DNA transcription*
 - All the subsequent steps occur automatically
 - How (Eukaryotic) Genes Code for Functional Proteins
 - DNA is transcribed into RNA in the cell's nucleus
 - RNA travels to the cytoplasm where it becomes proteins
 - Transcription and translation are physically separated by the nuclear membrane
 - Transcription only occurs in the nucleus
 - Translation occurs only outside the nucleus in the cytoplasm
 - Gene expression regulation occurs in all stages

Level	Occurrence
Epigenetic	when the DNA is uncoiled and loosened from nucleosomes to bind transcription factors
Transcriptional	when the RNA is transcribed
Post-Transcriptional	when the RNA is processed and exported to the cytoplasm after it is transcribed
Post-Translational	when the RNA is translated into protein (translational level), or after the protein has been made

- Epigenetic - heritable changes that do not involve changes in the DNA sequence
- Transcriptional - control of gene expression before it has been transcribed into mRNA
- Post-Transcriptional - control of gene expression after the RNA molecule has been created but before it is translated into protein
- Post-Translational - control of gene expression after a protein has been created

Differences in the Regulation of Gene Expression of Prokaryotic and Eukaryotic Organisms

<i>Prokaryotes</i>	<i>Eukaryotes</i>
No nucleus	Nucleus
DNA in cytoplasm	DNA is confined to nuclear compartment
RNA transcription and protein formation occur almost simultaneously	RNA transcription occurs prior to protein formation and takes place in the nucleus; translation of RNA to protein occurs in the cytoplasm
Gene expression is regulated primarily at the transcriptional level	Gene expression is regulated at many levels

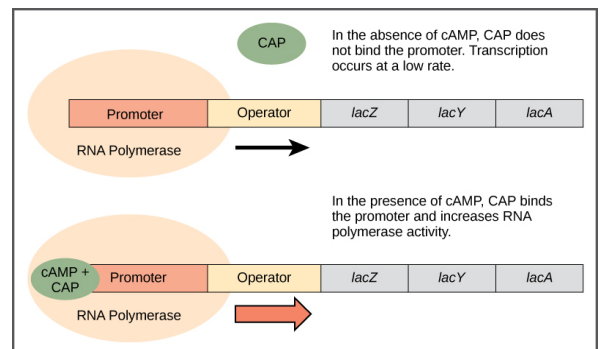
Prokaryotic Gene Regulation

❖ 11.2: Introduction

- **Operon** - a unit made up of linked genes that regulates other genes responsible for protein synthesis
 - Three Types of Operons in Prokaryotes: Repressors, Activators, and Inducers
 - **Repressors** - proteins that suppress transcription of a gene in response to an external stimulus; negative regulators
 - **Activators** - proteins that increase the transcription of a gene in response to an external stimulus
 - **Inducers** - small molecules that either activate or repress transcription depending on the needs of the cell and the availability of substrate
- **Coding Region** - DNA sequence that codes for proteins
- **Transcriptional Start Site** - region just before the coding region; the region of DNA to which RNA polymerase binds to initiate transcription
- **Promoter Sequence** - DNA sequences that define where transcription of a gene by RNA polymerase begins; upstream from the transcriptional start site
 - Each operon has a sequence within or near the promoter to which proteins (activators or repressors) can bind and regulate transcription
 - **Operator** - DNA sequence encoded between the promoter region and the first coding gene; contains the DNA code to which the repressor protein can bind

❖ 11.2a: Catabolite Activator Protein (CAP): An Activator Regulator

- *E. coli* Bacteria Example
 - *E. coli* can use sugars as a source of fuel
 - Needs new genes are transcribed to process these alternate genes
 - Cyclic AMP (cAMP) accumulates in the cell, a reaction to the scarcity of glucose
 - The cAMP molecule is a signaling molecule that is involved in glucose and energy metabolism in *E. coli*
 - Accumulating cAMP binds to the positive regulator catabolite activator protein (CAP)
 - **Catabolite Activator Protein (CAP)** - a protein that binds to the promoters of operons that control the processing of alternative sugars
 - As cAMP binds to CAP, the complex binds to the promoter region of the genes that are needed to use the alternate sugars
 - In these operons, a CAP binding site is located upstream of the RNA polymerase binding site in the promoter
 - This increases the binding ability of RNA polymerase to the promoter region and the transcription of the genes
 - The cAMP–CAP protein complex serves as a *positive regulator to induce* transcription



❖ 11.2b: The *lac* Operon: An Inducer Operon

➤ **Inducible Operons** - have proteins that bind to activate or repress transcription depending on the local environment and the needs of the cell; ex.: *lac* operon

➤ ***lac* Operon** - encodes the genes necessary to acquire and process the lactose from the local environment

- CAP binds to the operator sequence upstream of the promoter that initiates transcription of the *lac* operon
- Can only be activated when 2 conditions are met
 - Glucose levels must be low or nonexistent
 - Lactose must be present
- Results in the transcription of the *lac* operon
- Makes sense for the cell because it would be energetically wasteful to create the proteins to process lactose if glucose was plentiful or lactose was not available
- Condition Combinations
 - If glucose is absent, the CAP binds to the operator sequence (activates transcription)
 - If lactose is absent, the repressor binds to the operator (prevents transcription)
 - If either of these requirements is met, then transcription remains off; only when both conditions are satisfied is the *lac* operon transcribed

Signals that Induce or Repress Transcription of the <i>lac</i> Operon				
Glucose	CAP binds	Lactose	Repressor binds	Transcription
✓	×	×	✓	No
✓	×	✓	×	Some
×	✓	×	✓	No
×	✓	✓	×	Yes

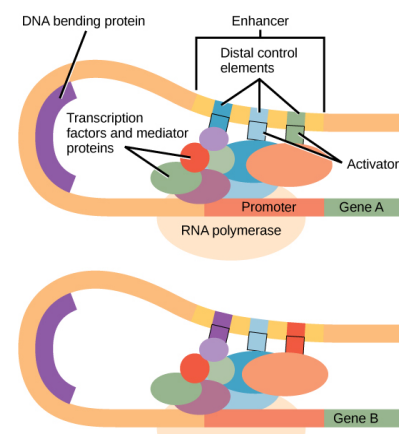
Eukaryotic Transcription Gene Regulation

❖ 11.3: Introduction

- Prokaryotes and eukaryotes require the actions of an RNA polymerase to bind to a sequence upstream of a gene to initiate transcription
- However, unlike prokaryotic cells, eukaryotic RNA polymerase requires other proteins, or *transcription factors*, to facilitate transcription initiation
 - **Transcription Factors** - proteins that bind to the promoter sequence and other regulatory sequences to control the transcription of the target gene; proteins that help turn specific genes "on" or "off" by binding to nearby DNA
 - RNA polymerase on its own can't initiate transcription in eukaryotes
- Transcription factors must bind to the promoter region first and recruit RNA polymerase to the site for transcription to be established

❖ 11.3a: Enhancers and Transcription

- **Enhancers** - *binding sequences* that help increase or enhance transcription; location varies
 - **Binding Sequence** - sites for transcription factors
- When a DNA-bending protein binds, the shape of the DNA changes
 - This shape change allows for the interaction of the activators bound to the enhancers with the transcription factors bound to the promoter region and the RNA polymerase



❖ 11.3b: Turning Genes Off: Transcriptional Repressors

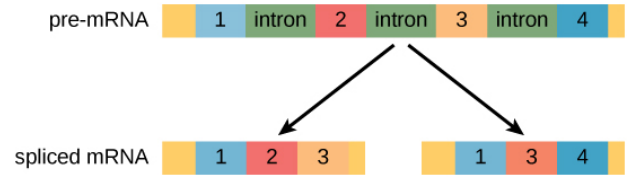
- Transcriptional repressors can bind to promoter or enhancer regions and block transcription
- Repressors respond to external stimuli to prevent the binding of activating transcription factors

Eukaryotic Post-Transcriptional Gene Regulation

❖ 11.4: Introduction

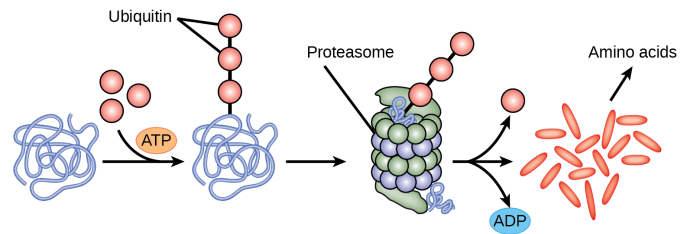
- RNA is transcribed but needs to mature before translation can occur

- Post-Transcriptional Modification - processing after an RNA molecule has been transcribed, but before it is translated into a protein (more in Chapter 10.3a: mRNA Processing/Post-Transcriptional Modification)
 - Can be regulated to control gene expression
- ❖ 11.4a: RNA Splicing, the First Stage of Post-Transcriptional Control
 - Introns - non-coding, intervening sequence of DNA within a gene that is transcribed into mRNA but is removed from the primary gene transcript and rapidly degraded during maturation of the RNA product; regions removed prior to translation
 - Exons - regions of RNA that code for protein
 - After an RNA molecule has been transcribed, but prior to its departure from the nucleus to be translated, the RNA is processed and the introns are removed by splicing



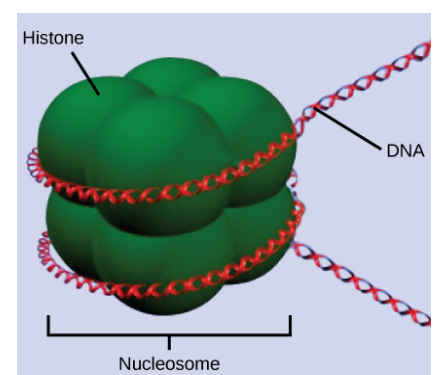
Eukaryotic Translational and Post-Translational Gene Regulation

- ❖ 11.5: Introduction
 - RNA is translated into a protein in the cytoplasm
 - Control of this process is dependent on the RNA molecule
 - As the stability changes, the amount of time that it is available for translation also changes
- ❖ 11.5a: Chemical Modifications, Protein Activity, and Longevity
 - Proteins can be chemically modified with the addition of groups
 - Addition or removal of groups regulates activity or time existing
 - Modifications result from external stimuli and can alter epigenetic accessibility, transcription, mRNA stability, or translation—all resulting in changes in expression of various genes
 - Efficient way to rapidly change protein levels
 - Protein phosphorylation can alter many things
 - Accessibility to the chromosome
 - Translation by altering transcription factor binding or function
 - Nuclear shuttling by influencing modifications to the nuclear pore complex
 - RNA stability by binding or not binding to the RNA to regulate its stability
 - Post-translational modifications
 - Add or remove phosphates or other chemical modifications
 - Ubiquitin - group that signals that a protein is ready for degradation
 - Acts like a flag, signaling that the protein's "life" cycle is up
 - These proteins are moved to the proteasome
 - Proteasome - organelle that degrades proteins
 - One way to alter gene expression is through protein longevity



Eukaryotic Epigenetic Gene Regulation

- ❖ 11.6: Introduction
 - Eukaryotes can regulate gene expression at many different levels, unlike prokaryotes
 - Epigenetic Regulation - controls access to DNA; occurs before transcription is initiated
- ❖ 11.6a: Epigenetic Control: Regulating Access to Genes within the Chromosome
 - DNA Organization
 - The first level of organization/packing is winding of DNA around histone proteins
 - Histones package and order the DNA into structural units called nucleosome complexes, which can control the access of proteins to the DNA regions



- If DNA that encodes for a specific gene is to be transcribed into RNA, the nucleosomes surrounding that region of DNA can slide down the DNA to open that specific chromosomal region
 - Allow for the transcriptional machinery (RNA polymerase) to initiate transcription
 - Nucleosomes can move to open the chromosome structure to expose a segment of DNA in a very controlled process
 - Histone movement is dependent on signals on the histone and DNA
 - These tags tell the histones if a chromosomal region should be opened or closed
 - Not permanent tags; can be added and removed as necessary
 - They are chemical modifications (phosphate, methyl, or acetyl groups) that are attached to specific amino acids in the protein or to the nucleotides of the DNA
 - ◆ Do not alter the DNA base sequence, but they do alter how tightly wound the DNA is around the histone proteins
 - DNA itself can also be modified
 - Occurs within CpG islands
 - ◆ CpG Island - stretches with a high frequency of cytosine and guanine dinucleotide DNA pairs (CG) found in the promoter regions of genes
 - Presence of the CpG island can cause the cytosine member of the pair to get methylated
 - ◆ Methylated - addition of a methyl group
 - This modification changes how the DNA interacts with proteins
 - ◆ Highly methylated (hypermethylated) DNA regions with deacetylated histones are tightly coiled and transcriptionally inactive
- The changes that occur to the histone proteins and DNA do not alter the nucleotide sequence and are not permanent
 - Changes are temporary but may persist through several rounds of cell division
 - Changes alter chromosomal structure (open or closed)
 - Genes can be switched on and off depending on location and modifications to the histone proteins and DNA
 - If a gene is to be transcribed, the histone proteins and DNA are modified surrounding the chromosomal region encoding that gene
 - Opens chromosomal region to allow RNA polymerase and transcription factors access to bind to the promoter region
 - ◆ Transcription Factors - protein that binds to the DNA at the promoter or enhancer region and that influences transcription of a gene
 - If the gene is off, the histone proteins and DNA have different modifications that signal a closed chromosomal configuration
 - In this closed configuration, the RNA polymerase and transcription factors do not have access to the DNA and transcription cannot occur

X Chromosome Inactivation

- ❖ 11.7: Introduction
 - Every human has an X-chromosome
 - Generally, females have XX, and males have XY
 - Autosome - any of the chromosome not considered as a sex chromosome
 - Monosomy - condition in which there is 1 instance of a particular chromosome, instead of 2
 - Trisomy - condition in which there are 3 instances of a particular chromosome, instead of 2
 - Humans display dramatic deleterious effects with autosomal trisomies and monosomies
- ❖ 11.7a: Difference in Expression in Males and Females
 - Rather than a gain or loss of autosomes, variations in the number of sex chromosomes are associated with relatively mild effects
 - X Inactivation - condensation of X-chromosomes into Barr bodies during embryonic development in females to compensate for the double genetic dose
 - Female Development and the X Chromosome: How Females Compensate for 2 Xs

- When a female is just a mammalian embryo (only a few thousand cells as opposed to the trillions in a newborn), one X chromosome in each cell inactivates by tightly condensing into a Barr body
 - ◆ Barr Body - a small, quiescent (dormant), densely staining structure in the cell nuclei of female mammals, consisting of a condensed, inactive X chromosome; regarded as diagnostic of genetic femaleness
- The chance that an X chromosome (maternally or paternally derived) is inactivated in each cell is random
 - ◆ Once the inactivation occurs, all cells derived from that one will have the same inactive X-chromosome or Barr body
- Intersex Cases
 - [Intersex TED Talk](#)
 - An individual carrying an abnormal number of X chromosomes will inactivate all but one X chromosome in each of her cells
 - ◆ Even inactivated X chromosomes express some genes
 - ◆ X-chromosomes must reactivate for the proper maturation of female ovaries
 - Triplo-X - individual with 3 Xs; corresponds to phenotypically female but express developmental delays and reduced fertility
 - XXY Genotype - corresponds to phenotypically male individuals with small testes, enlarged breasts, and reduced body hair
 - ◆ Corresponding to one type of Klinefelter syndrome
 - Klinefelter Syndrome - the set of symptoms that result from two or more X chromosomes in males
 - ◆ The individual has as many as five X chromosomes
 - Turner Syndrome/Xo Genotype - individual with only one sex chromosome; corresponds to a phenotypically female individual with short stature, webbed skin in the neck region, hearing and cardiac impairments, and sterility
- X-Chromosomal Abnormalities
 - Typically associated with mild mental and physical defects, as well as sterility
 - If the X chromosome is absent altogether, the individual will not develop in utero
- Every X chromosome except one undergoes inactivation to compensate for the excess genetic dosage