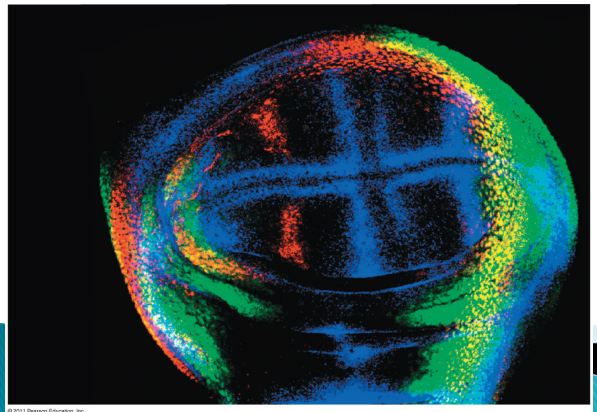
Regulation of Gene Expression

Chapter 13



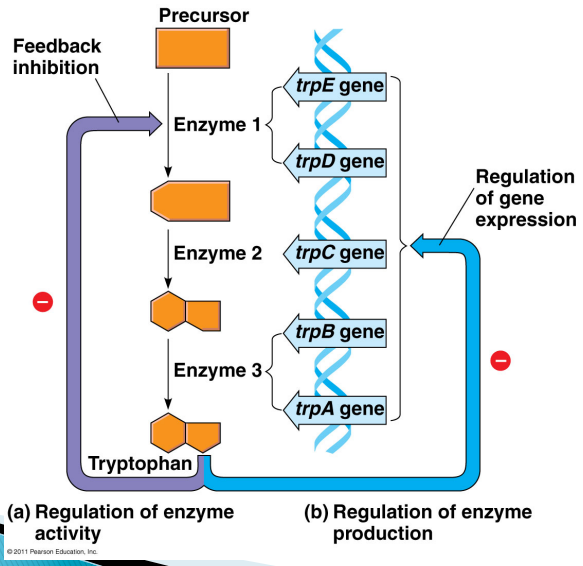
What you must know:

- Genes can be activated by inducer molecules, or they can be inhibited by the presence of a repressor as they interact with regulatory proteins or sequences.
- A regulatory gene is a sequence of DNA that codes for a regulatory protein such as a repressor protein.
- How the components of an operon function to regulate gene expression in both repressible and inducible operons.
- How positive and negative control function in gene expression.
- The impact of DNA methylation and histone acetylation on gene expression.
- How timing and coordination of specific events are regulated in normal development, including pattern formation and induction.
- The role of miRNAs in control of cellular functions.
- The role of gene regulation in embryonic development and cancer.

Regulation of Gene Expression by Bacteria

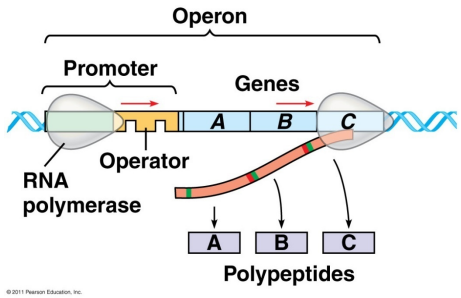
- Transcription

Regulation of metabolic pathways



Bacterial control of gene expression

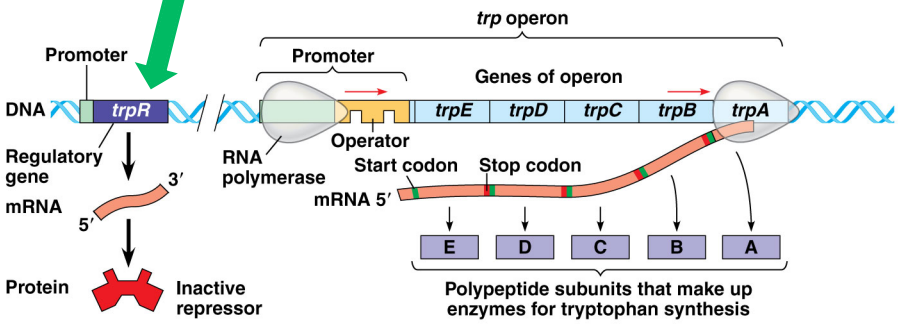
Operon: cluster of related genes with on/off switch



Three Parts:

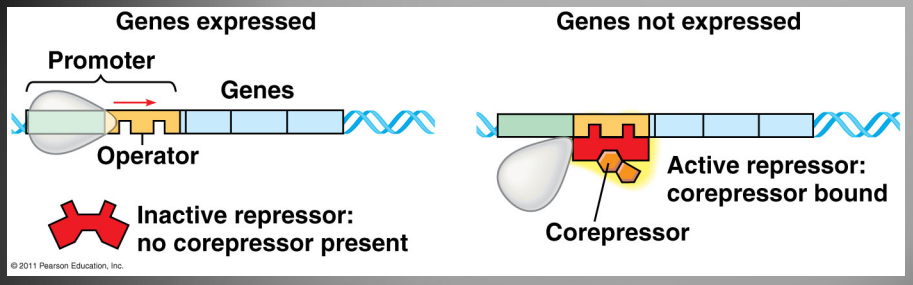
1. Promoter – where RNA polymerase attaches
2. Operator – "on/off", controls access of RNA poly
3. Genes – code for related enzymes in a pathway

Regulatory gene: produces repressor protein that binds to operator to block RNA polymerase

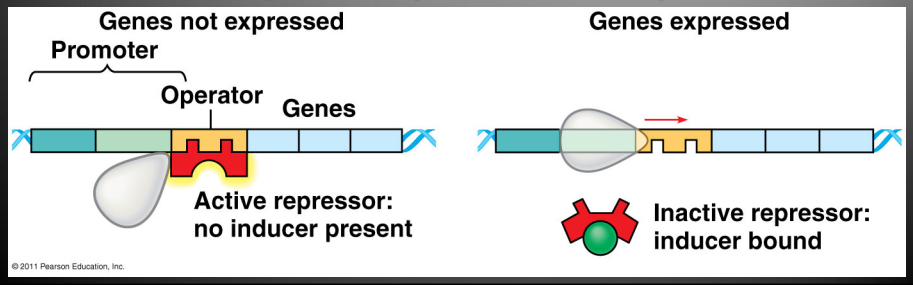


(a) Tryptophan absent, repressor inactive, operon on

Repressible Operon (ON → OFF)

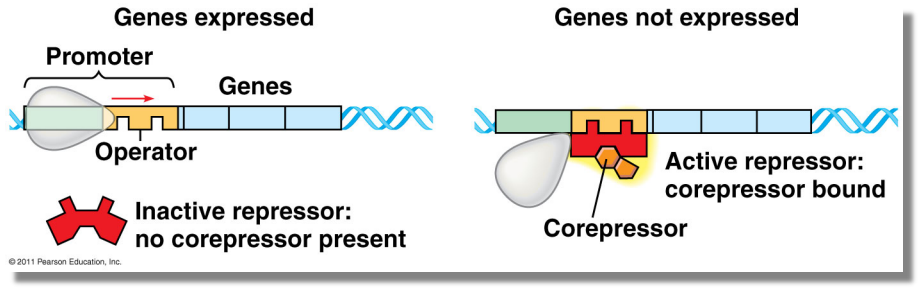


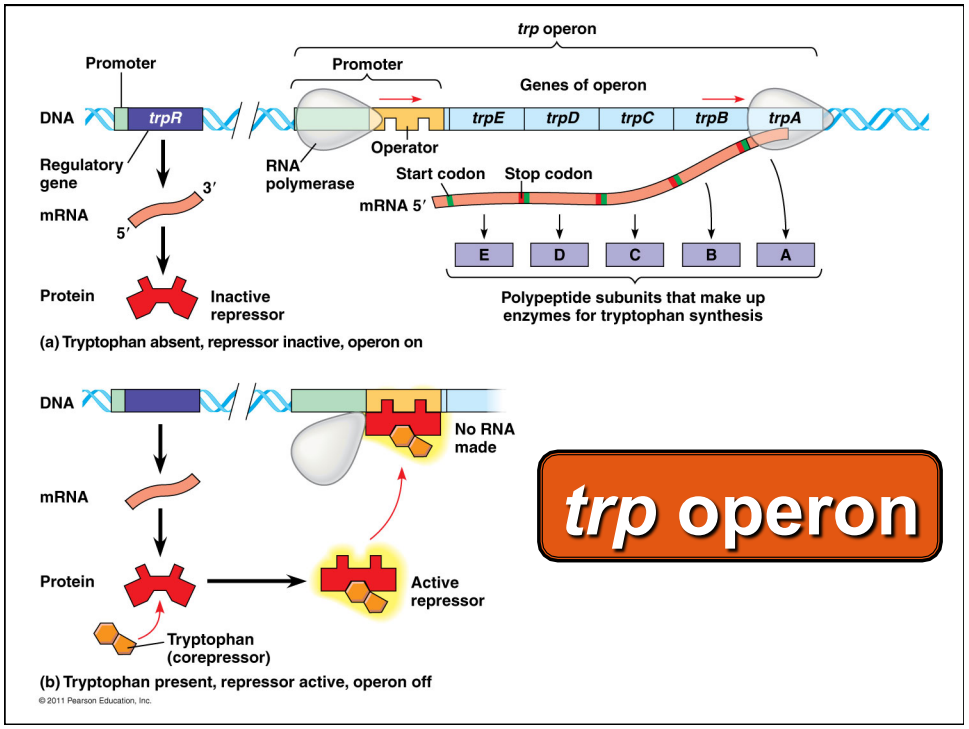
Inducible Operon (OFF → ON)



Repressible Operon

- Normally ON
- Anabolic (build organic molecules)
- Organic molecule product acts as corepressor → binds to repressor to activate it
- Operon is turned OFF
- Eg. *trp* operon

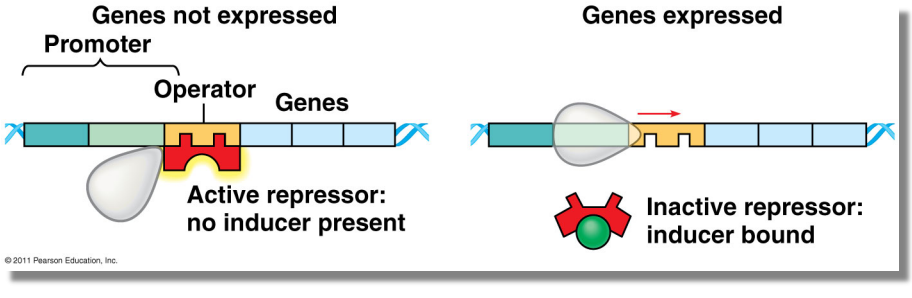


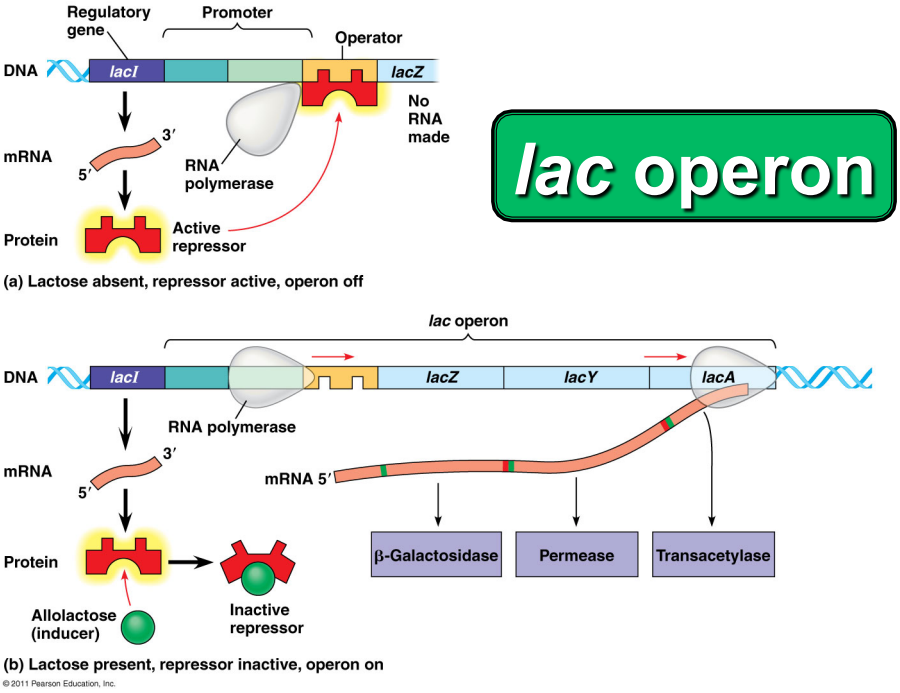


trp operon

Inducible Operon

- Normally OFF
- Catabolic (break down food for energy)
- Repressor is active → inducer binds to and inactivates repressor
- Operon is turned ON
- Eg. *lac* operon



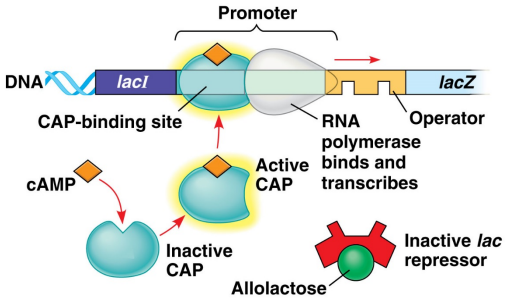


Gene Regulation: Positive vs. Negative Control

- *Negative control*: operons are switched off by active form of repressor protein
  - Eg. *trp* operon, *lac* operon
- *Positive control*: regulatory protein interacts directly with genome to increase transcription
  - Eg. cAMP & CAP

cAMP + CAP = Positive Control

- cAMP: accumulates when glucose is scarce
- cAMP binds to CAP (catabolite activator protein)
- Active CAP → binds to DNA upstream of promoter, ↑ affinity of RNA polymerase to promoter, ↑ transcription

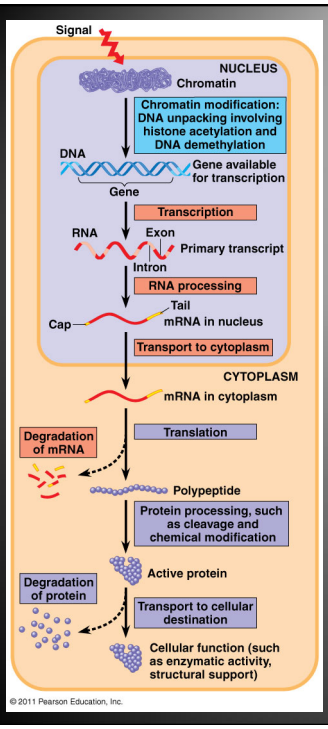


(a) Lactose present, glucose scarce (cAMP level high): abundant *lac* mRNA synthesized

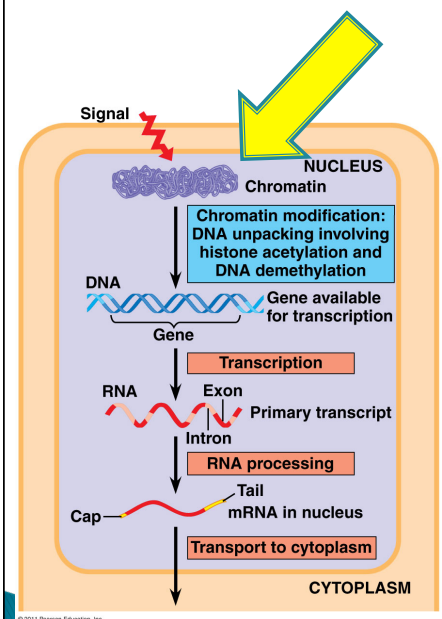
Regulation of Gene Expression by Eukaryotes

- Many stages

- Typical human cell: only 20% of genes expressed at any given time
- Different cell types (with identical genomes) turn on different genes to carry out specific functions
- Differences between cell types is due to differential gene expression

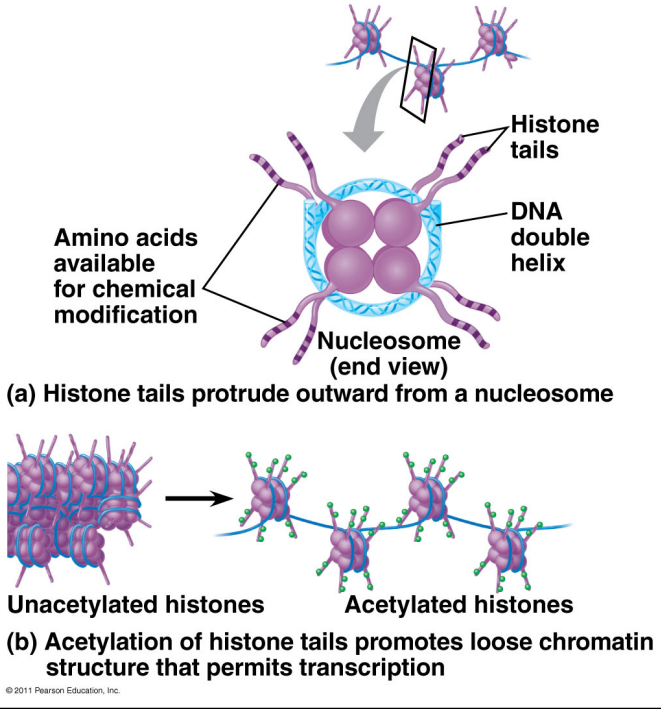


Eukaryotic gene expression regulated at different stages



Chromatin Structure:

- Tightly bound DNA → less accessible for transcription
- DNA methylation: methyl groups added to DNA; tightly packed; ↓ transcription
- Histone acetylation: acetyl groups added to histones; loosened; ↑ transcription



Epigenetic Inheritance

- Modifications on chromatin can be passed on to future generations
- Unlike DNA mutations, these changes to chromatin can be reversed (de-methylation of DNA)
- Explains differences between identical twins
- Eg. DNA methylation (gene silencing), histone acetylation, X chromosome inactivation, heterochromatin (silent chromatin)

Video: The Epigenome at a Glance

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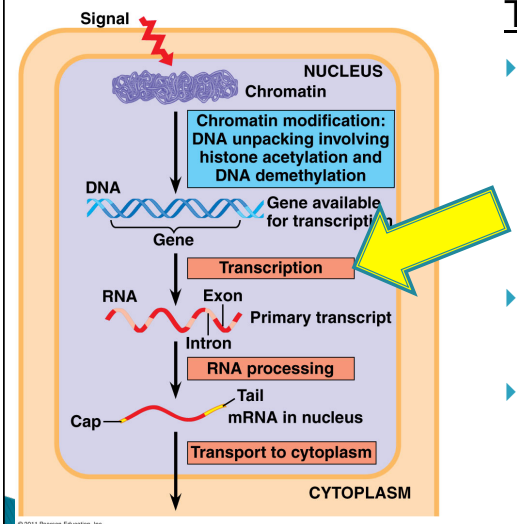
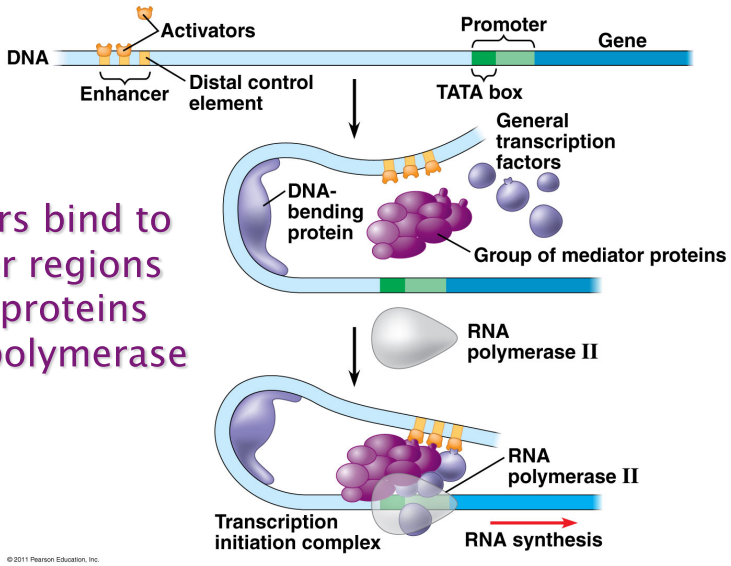


Transcription Initiation:

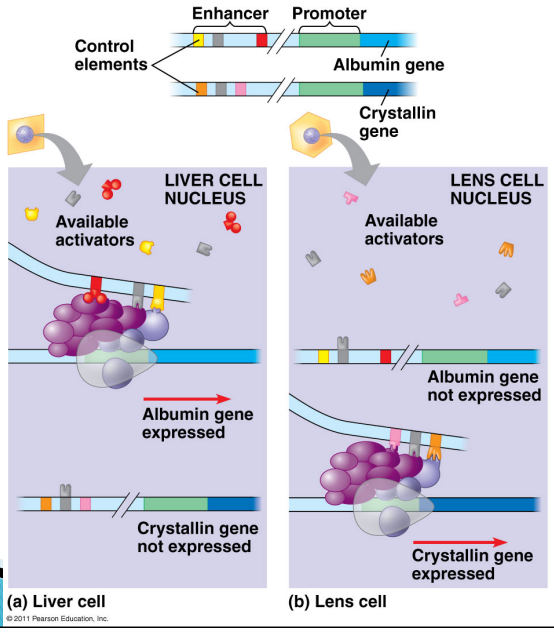
- Specific transcription factors (activators or repressors) bind to control elements (enhancer region)
- Activators: increase transcription
- Repressors: decrease transcription

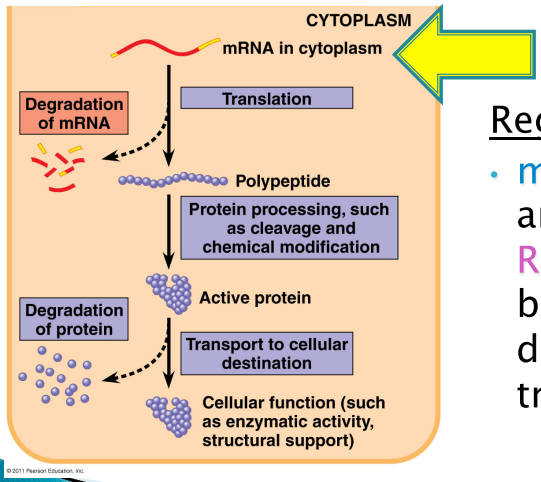
Transcription Initiation Complex



Activators bind to enhancer regions
+ other proteins
+ RNA polymerase

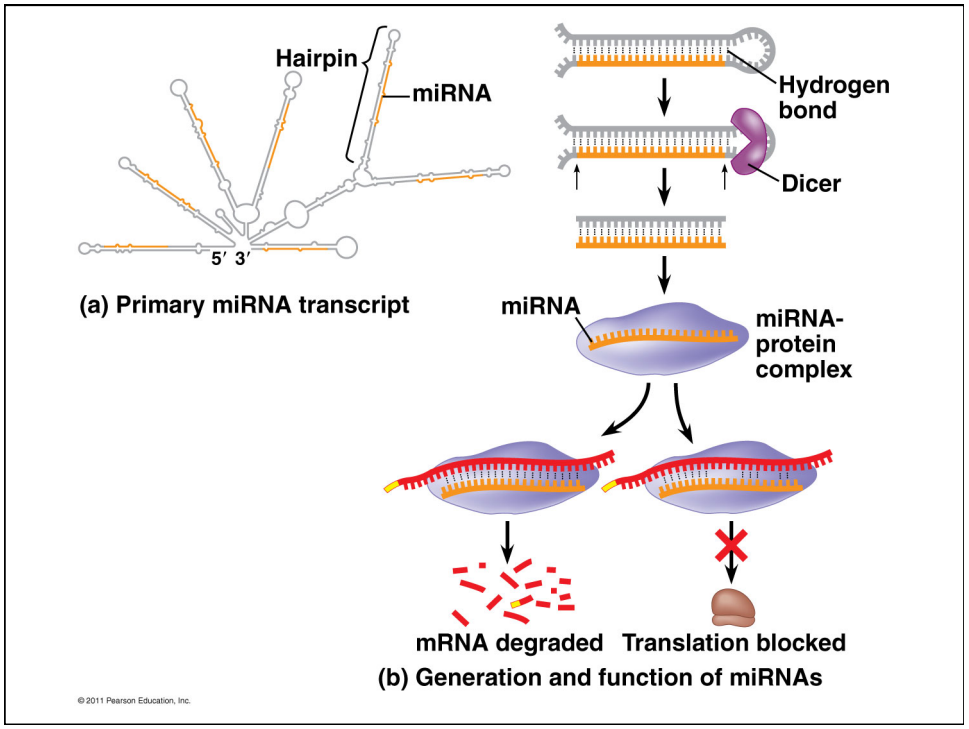
Cell type-specific transcription





Regulation of mRNA:

- micro RNAs (miRNAs) and small interfering RNAs (siRNAs) can bind to mRNA and degrade it or block translation


Hairpin
miRNA
5′ 3′
(a) Primary miRNA transcript
Hydrogen bond
Dicer
miRNA
miRNA-protein complex
mRNA degraded
Translation blocked
(b) Generation and function of miRNAs
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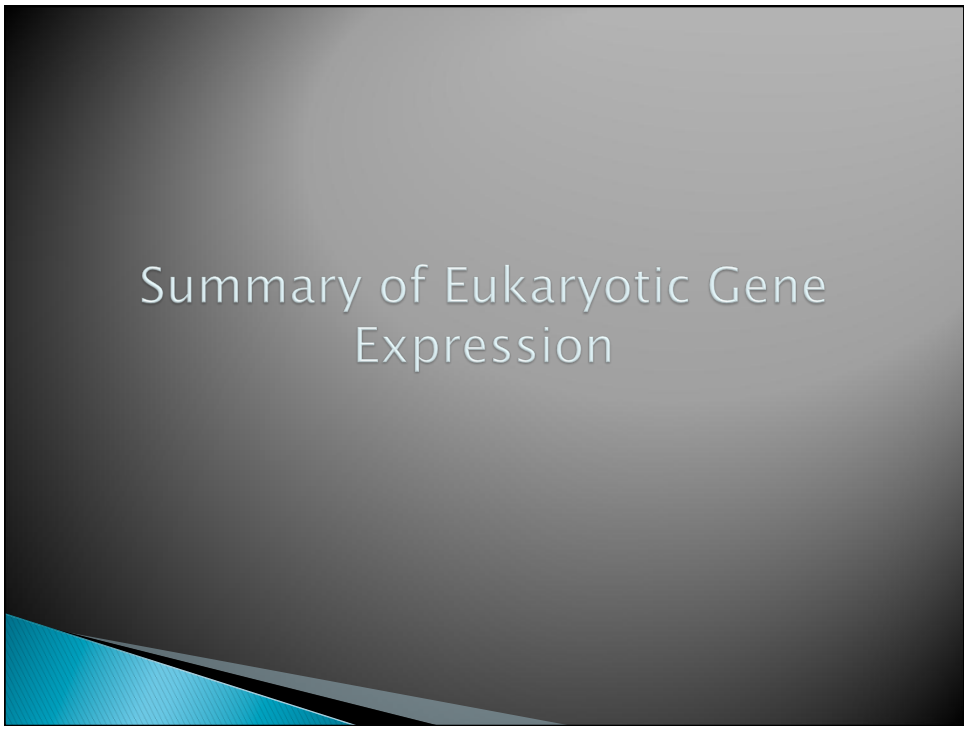
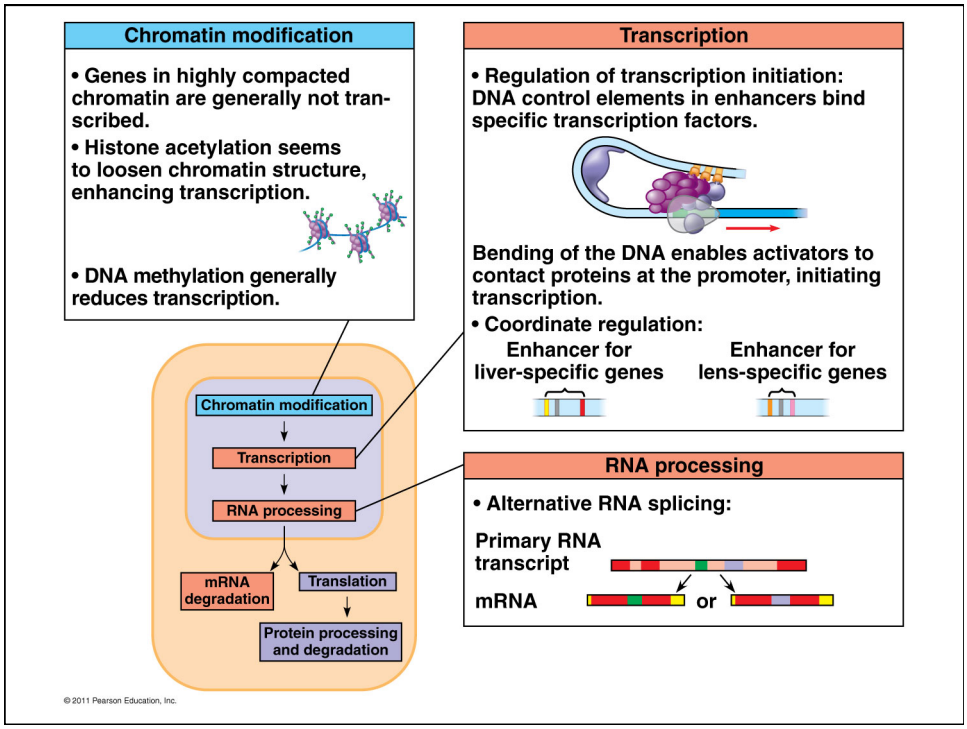

Summary of Eukaryotic Gene Expression


Chromatin modification
• Genes in highly compacted chromatin are generally not transcribed.
• Histone acetylation seems to loosen chromatin structure, enhancing transcription.
• DNA methylation generally reduces transcription.
Transcription
• Regulation of transcription initiation: DNA control elements in enhancers bind specific transcription factors.
Bending of the DNA enables activators to contact proteins at the promoter, initiating transcription.
• Coordinate regulation:
Enhancer for liver-specific genes
Enhancer for lens-specific genes
Chromatin modification
Transcription
RNA processing
mRNA degradation
Translation
Protein processing and degradation
RNA processing
• Alternative RNA splicing:
Primary RNA transcript
mRNA
or
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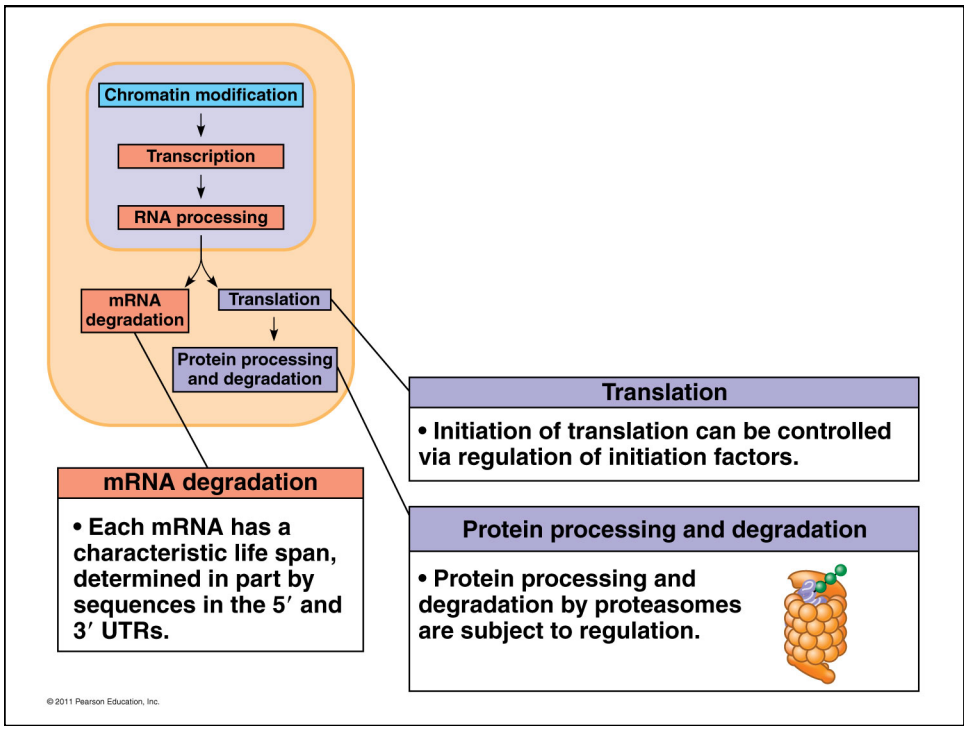
Chromatin modification
Transcription
RNA processing
mRNA degradation
Translation
Protein processing and degradation
Translation
• Initiation of translation can be controlled via regulation of initiation factors.
mRNA degradation
• Each mRNA has a characteristic life span, determined in part by sequences in the 5′ and 3′ UTRs.
Protein processing and degradation
• Protein processing and degradation by proteasomes are subject to regulation.
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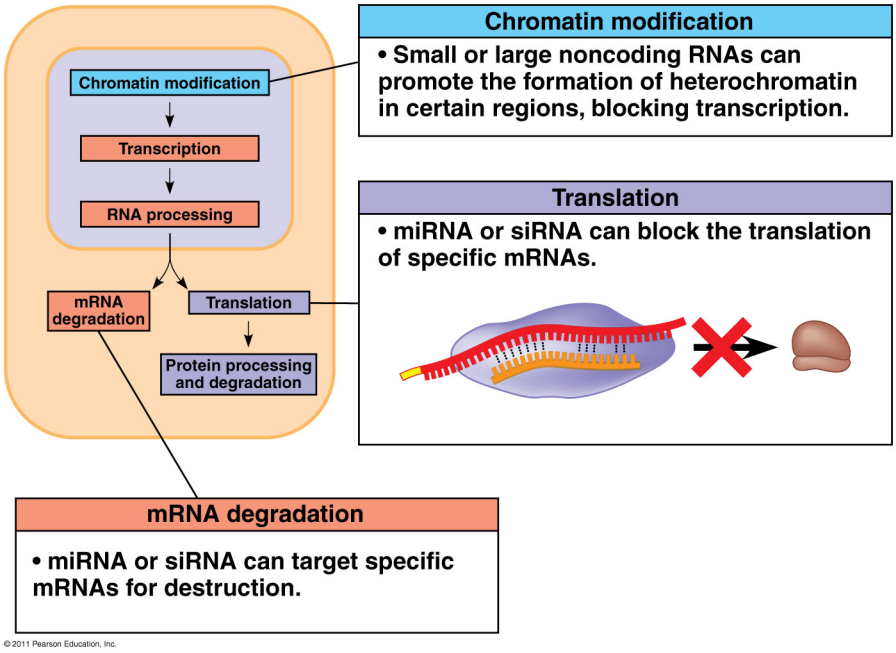
Chromatin modification
Transcription
RNA processing
mRNA degradation
Translation
Protein processing and degradation
Chromatin modification
• Small or large noncoding RNAs can promote the formation of heterochromatin in certain regions, blocking transcription.
Translation
• miRNA or siRNA can block the translation of specific mRNAs.
mRNA degradation
• miRNA or siRNA can target specific mRNAs for destruction.
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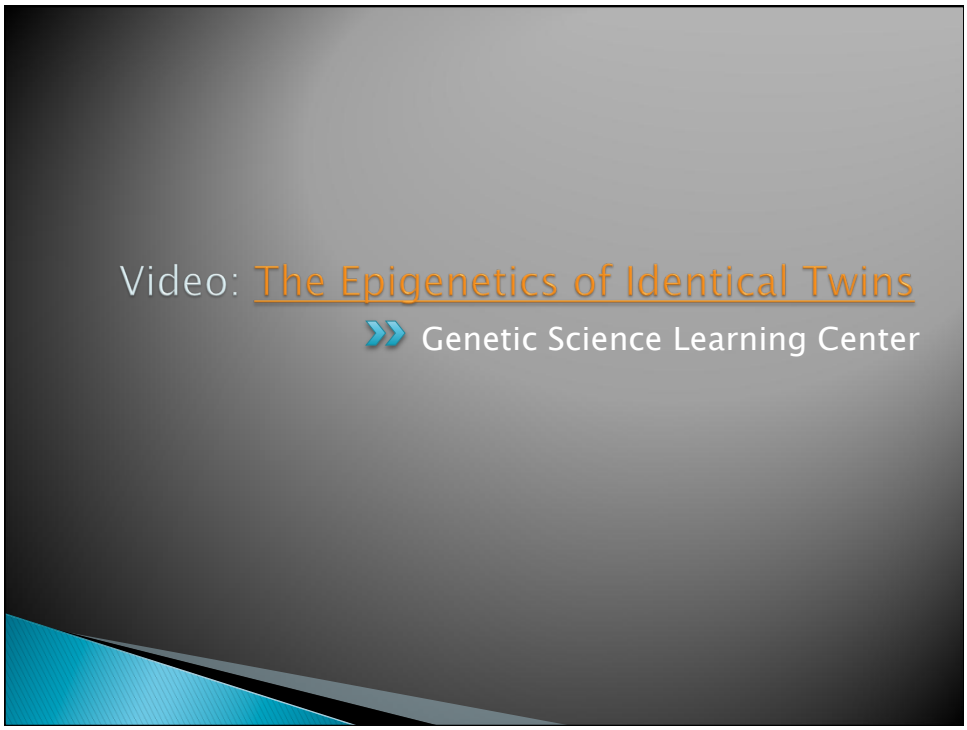
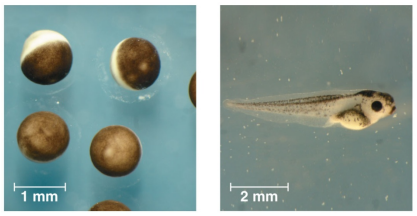

Video: The Epigenetics of Identical Twins
Genetic Science Learning Center

Embryonic Development of Multicellular Organisms

» Section 18.4

Embryonic Development:

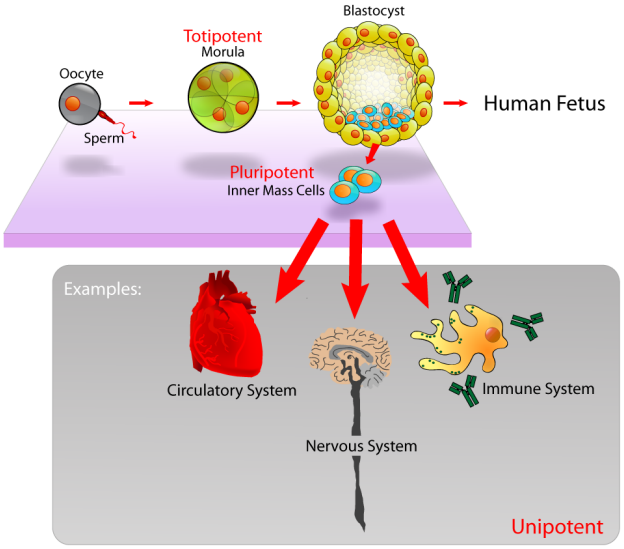
Zygote → Organism

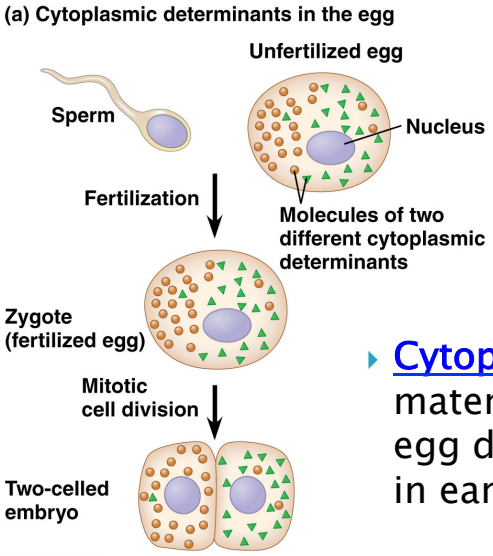


(a) Fertilized eggs of a frog (b) Newly hatched tadpole

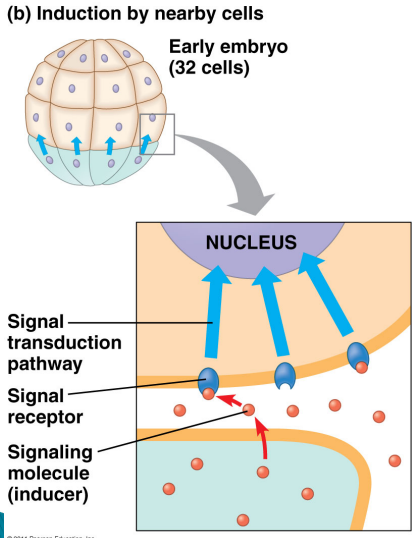
1. Cell Division: large # identical cells through mitosis
2. Cell Differentiation: cells become specialized in structure & function
3. Morphogenesis: "creation of form" – organism's shape

Determination: irreversible series of events that lead to cell differentiation

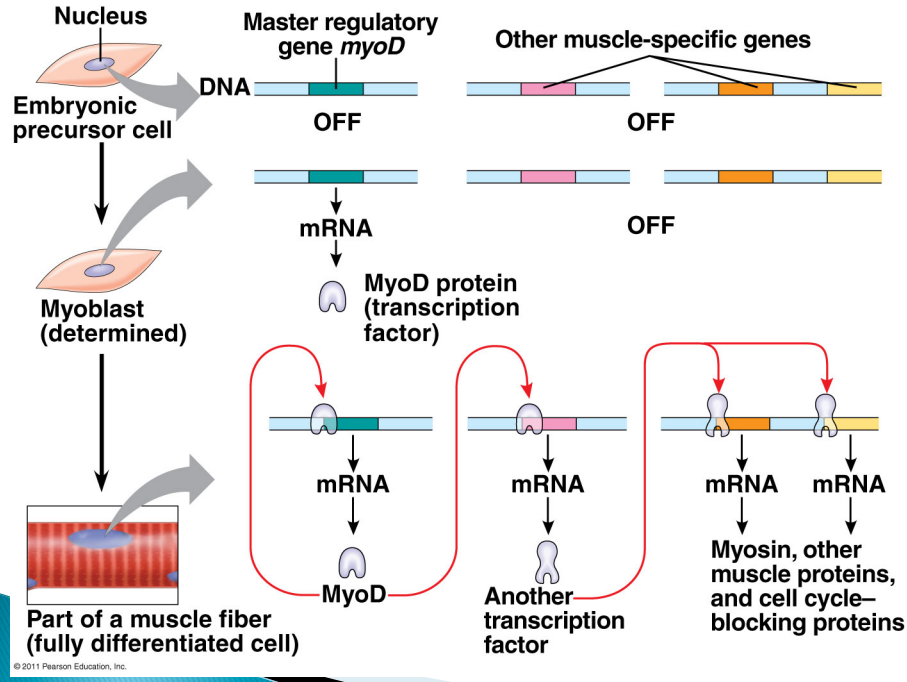




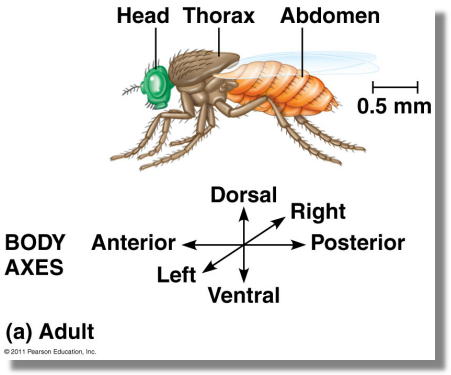
- Cytoplasmic determinants: maternal substances in egg distributed unevenly in early cells of embryo

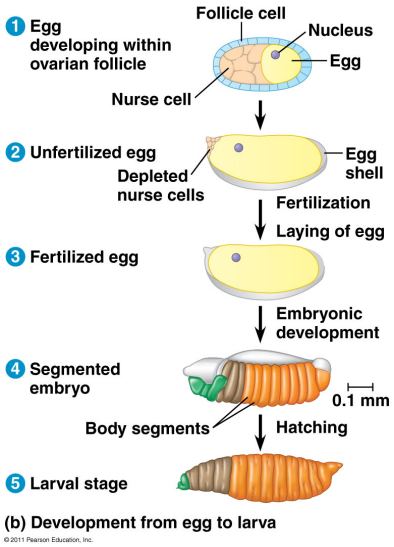


- Induction: cells triggered to differentiate
- Cell–Cell Signals: molecules produced by one cell influences neighboring cells
  - Eg. Growth factors

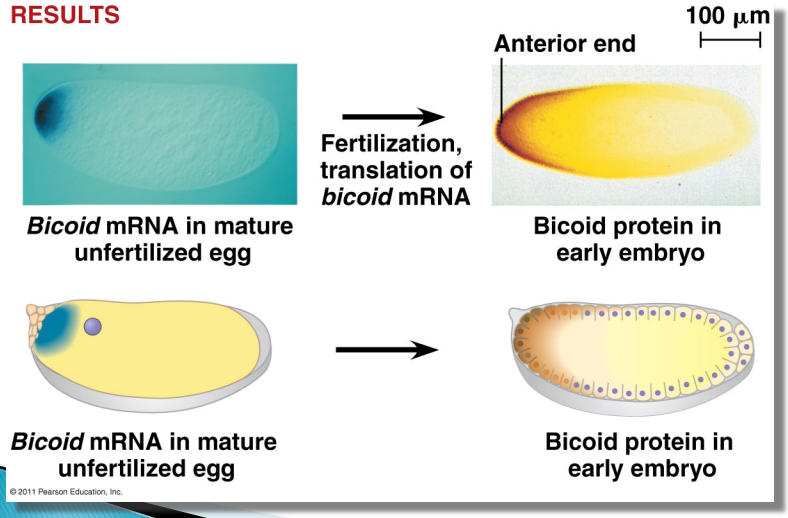


Pattern formation: setting up the body plan (head, tail, L/R, back, front)

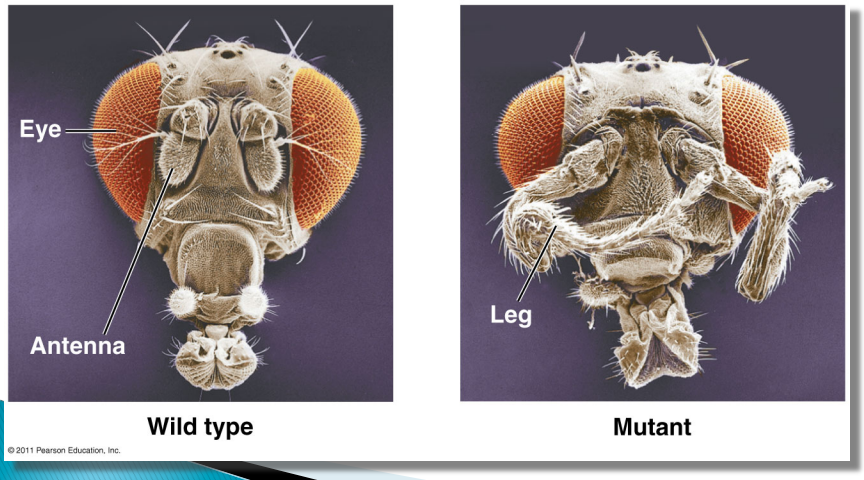




Morphogens: substances that establish an embryo's axes



Homeotic genes: master control genes that control pattern formation (eg. Hox genes)



Wild type | Mutant

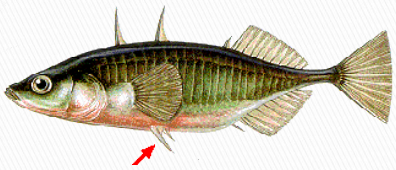
Evolving Switches, Evolving Bodies

- HHMI Short Film

Pitx1 Gene = Homeotic/Hox Gene

Stickleback Fish

- Development of pelvic bone

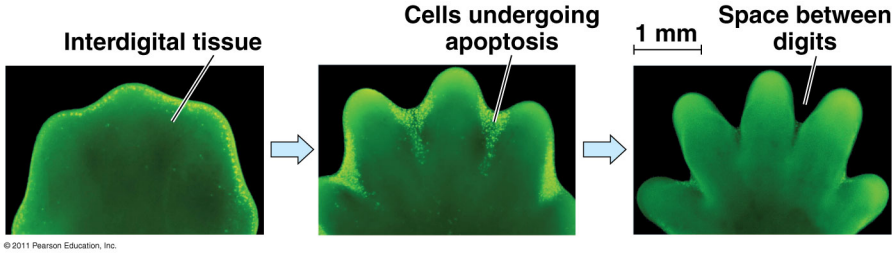


Humans

- Development of anterior structures, brain, structure of hindlimb
- Mutation may cause clubfoot, polydactyly (extra fingers/toes), upper limb deformities

Role of Apoptosis

- Most of the embryonic cells are produced in excess
- Cells will undergo *apoptosis* (programmed cell death) to sculpture organs and tissues
- Carried out by *caspase* proteins



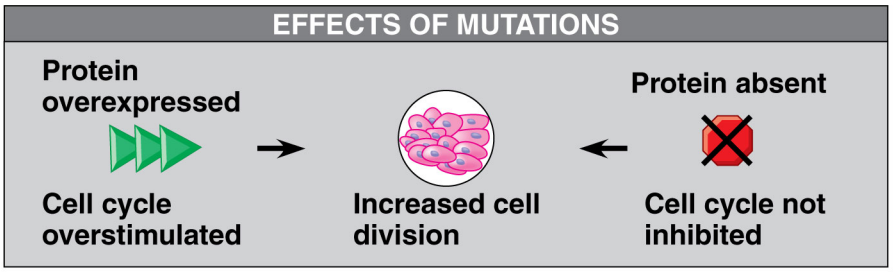
Cancer results from genetic changes that affect cell cycle control

» Section 18.5

Control of Cell Cycle:

1. **Proto-oncogene** = stimulates cell division
2. **Tumor-suppressor gene** = inhibits cell division

- Mutations in these genes can lead to cancer



(c) Effects of mutations

Proto-Oncogene → Oncogene

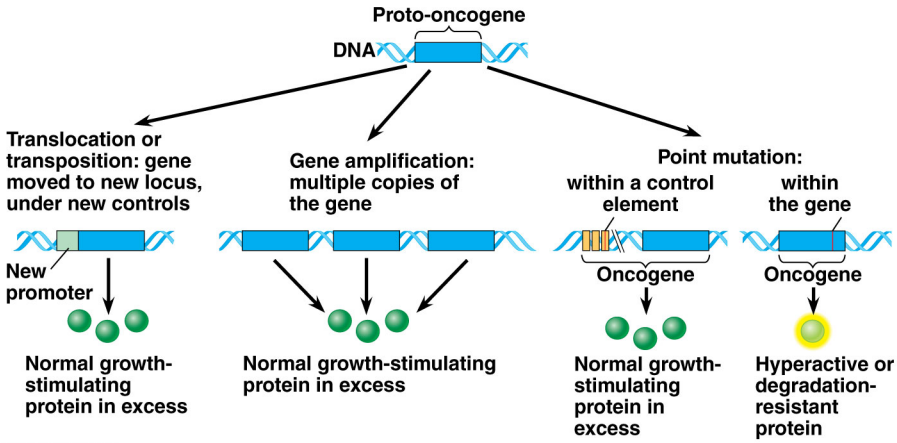
- Gene that stimulates <u>normal</u> cell growth & division

- Mutation in proto-oncogene
- Cancer-causing gene

Effects:

- Increase *product* of proto-oncogene
- Increase *activity* of each protein molecule produced by gene

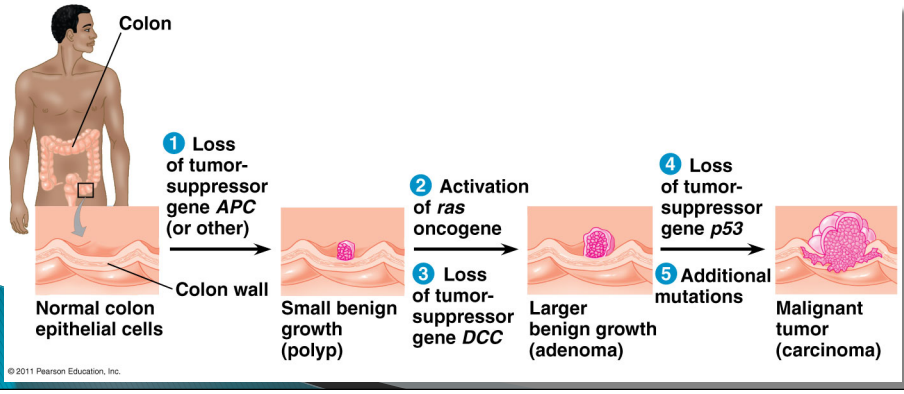
Proto-oncogene → Oncogene



Genes involved in cancer:

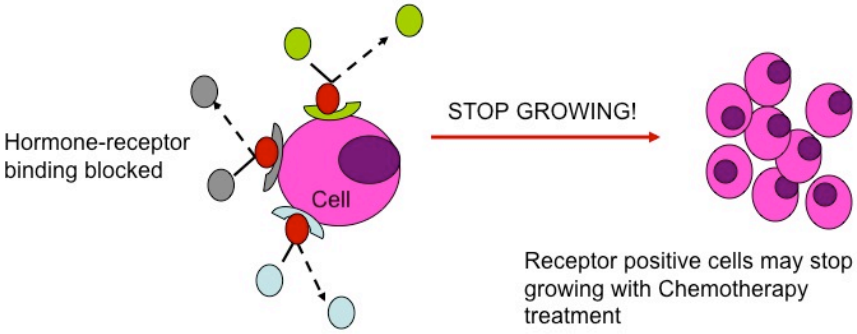
- *Ras* gene: stimulates cell cycle (proto-oncogene)
  - Mutations of *ras* occurs in 30% of cancers
- *p53* gene: tumor-suppresor gene
  - Functions: halt cell cycle for DNA repair, turn on DNA repair, activate apoptosis (cell death)
  - Mutations of *p53* in 50+% of cancers

- Cancer results when mutations accumulate (5-7 changes in DNA)
- Active oncogenes + loss of tumor-suppressor genes
- The longer we live, the more likely that cancer might develop



How does chemotherapy work?

Chemotherapy drugs ( ) can block hormone attachment ("binding") to their receptors and block growth.

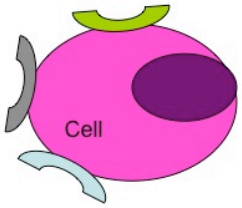


Receptor positive cells may stop growing with Chemotherapy treatment

Chemotherapy blocks hormones from binding to their receptors. This sends a message to the cells to "Stop growing!" Cells that are receptor positive receive the "stop growing" message better than cells that do not have the receptors (triple negative breast cancer cells).

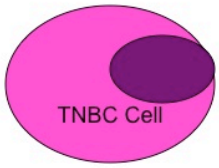
What is Triple Negative Breast Cancer (TNBC)?

Receptor Positive Breast Cancer



Many breast cancer cells have 1, 2 or even all 3 of these important receptors on their surface. These receptors are important targets for Chemotherapy to block hormone attachment and block the growth of the abnormal cells. Doctors take a piece of the tissue to test how many of these receptors are present.

Triple Negative Breast Cancer



In Triple Negative Breast Cancer (TNBC), none of the 3 important receptors are found on the cell surface. This makes it difficult to use traditional chemotherapy to block growth.

Summary

- *Embryonic development* occurs when gene regulation proceeds correctly
- *Cancer* occurs when gene regulation goes awry