Changes in the environment can regulate cell activity

- Natural selection has favored single-celled organisms that produce only the products needed by that cell

- The fastest way is to directly control enzyme cascades

- In bacteria it is nearly as fast to change gene expression. This is controlled by the operon model – one promoter, many genes

- Eukaryotes also have coordinately controlled gene expression – but, like everything else about them it’s more complicated (more on that later....)
Operons: the entire stretch of DNA that includes ...

- The **promoter** which binds RNA polymerase.
- The **operator**: a regulatory “switch” in the promoter that reacts to environmental change
- All of the **related genes** that they control

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**Negative vs. Positive Operons**

- Two Types of Negative, or “Repressor”, Gene Regulation
  - Operons that involve negative control of genes are switched off by the active form of a **repressor**
  - A **repressible operon** is one that is usually on; binding of a repressor to the operator shuts off transcription
  - An **inducible operon** is one that is usually off; a molecule called an inducer inactivates the repressor and turns on transcription

- One Type of Positive, or “Activator”, Gene Regulation
  - An **activator of transcription** is a stimulatory protein that acts to bind RNA polymerase much like an eukaryotic transcription factor

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**Example 1 of Negative, or “Repressor”, Gene Regulation**

- **Repressible** enzymes usually function in **anabolic** pathways; their synthesis is repressed by high levels of the end product
  - The **tryptophan operon** is a repressible operon: By default it is on and the genes for tryptophan synthesis are transcribed
  - Tryptophan is a **corepressor** and when it is present, it binds to the try repressor protein, which turns the operon off
Polypeptide subunits that make up enzymes for tryptophan synthesis

Tryptophan absent, repressor inactive, operon on

Tryptophan present, repressor active, operon off

Tryptophan present, repressor active, operon off
Inducible enzymes usually function in catabolic pathways: their synthesis is induced by a chemical signal.

- The lac operon is an inducible operon and by itself, the lac repressor is active and switches the lac operon off.
- Lactose is an inducer and inactivates the repressor to turn the lac operon on.

**Figure 18-4a**
Lactose absent, repressor active, operon off

**Figure 18-4b**
Lactose present, repressor inactive, operon on
Positive Gene Regulation

- Positive secondary control of the speed of an operon
- Sometimes lactose is present but glucose is scarce
- Catabolite Activator Protein (CAP) is activated by binding with cyclic AMP
- Activated CAP attaches to the promoter of the lac operon and increases the affinity of RNA polymerase, thus accelerating transcription
- When glucose levels increase, CAP detaches from the lac operon, and transcription returns to a normal rate
- CAP helps regulate other operons that encode enzymes used in catabolic pathways

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Differential gene expression in multicellular development and cell specialization

- Regulation of Chromatin Structure
- Regulation of Transcription Initiation
- Mechanisms of Post-Transcriptional Regulation
- Mechanisms of Post-Translational Regulation
Regulation of Chromatin Structure

- Genes within tightly packed heterochromatin are usually not expressed.
- Chemical modifications to histones and DNA influence chromatin structure and gene expression by making a region of DNA either more or less able to bind the transcription machinery.
- The histone code hypothesis proposes that specific combinations of modifications help determine chromatin configuration and influence transcription.
**Slide 19**

In histone acetylation, acetyl groups are attached to positively charged lysines in histone tails. This process loosens chromatin structure, thereby initiating transcription.

The addition of methyl groups (methylation) can condense chromatin.

The addition of phosphate groups (phosphorylation) next to a methylated amino acid can loosen chromatin.

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**DNA Methylation**

- DNA methylation, the addition of methyl groups to certain bases in DNA, is associated with reduced transcription in some species.
- DNA methylation can cause long-term inactivation of genes in cellular differentiation.
- In genomic imprinting, methylation regulates expression of either the maternal or paternal alleles of certain genes at the start of development.

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**Epigenetic Inheritance**

- Although the chromatin modifications just discussed do not alter DNA sequence, they may be passed to future generations of cells.
- The inheritance of traits transmitted by mechanisms not directly involving the nucleotide sequence is called epigenetic inheritance.
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Organization of a Typical Eukaryotic Gene

Enhancer (distal control elements)
Proximal control elements
Poly-A signal
Termination region
Downstream
Promoter
Upstream
DNA
Exon Exon Exon Intron Intron

Slide 23

Organization of a Typical Eukaryotic Gene

Enhancer (distal control elements)
Proximal control elements
Poly-A signal
Termination region
Downstream
Promoter
Upstream
DNA
Exon Exon Exon Intron Intron
Exon Exon Exon Intron Intron
Cleaved 3′ end of primary transcript
Primary RNA transcript
Poly-A signal
Transcription
5′RNA processing
Intron RNA
Coding segment
mRNA
5′ Cap
5′ UTR
Start codon
Stop codon 3′ UTR
Poly-A tail
3′

Slide 24

Organization of a Typical Eukaryotic Gene

Enhancer (distal control elements)
Proximal control elements
Poly-A signal
Termination region
Downstream
Promoter
Upstream
DNA
Exon Exon Exon Intron Intron
Exon Exon Exon Intron Intron
Cleaved 3′ end of primary transcript
Primary RNA transcript
Poly-A signal
Transcription
5′RNA processing
Intron RNA
Coding segment
mRNA
5′ Cap
5′ UTR
Start codon
Stop codon 3′ UTR
Poly-A tail
3′

What do the GTP Cap and Poly-A Tail do again?
A particular combination of control elements can activate transcription only when the appropriate activator proteins and transcription factors are present.

Unlike prokaryotes, coordinately controlled eukaryotic genes can be scattered over different chromosomes, but each has the same combination of control elements.

Proteasomes are giant protein complexes that bind protein molecules and degrade them.

After translation, various types of protein processing, including cleavage and the addition of chemical groups, are subject to control.
Noncoding RNAs can control gene expression through RNA Interference (RNAi).

- Only a small fraction of DNA codes for proteins; rRNA, and tRNA. A significant amount of the genome may be transcribed into noncoding RNAs.
- MicroRNAs (miRNAs) are small single-stranded RNA molecules that can bind to mRNA and degrade it or block its translation.
- siRNAs and miRNAs are similar but form from different RNA precursors.
- siRNAs play a role in heterochromatin formation and can block large regions of the chromosome.
- Small RNAs may also block transcription of specific genes.

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**Fig. 18-UN5**

- Chromatin modification
- RNA processing
- Translation
- mRNA degradation
- Protein processing and degradation

- miRNA or siRNA can target specific mRNAs for destruction.
- miRNA or siRNA can block the translation of specific mRNAs.
- Small RNAs can promote the formation of heterochromatin in certain regions, blocking transcription.

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**Fig. 18-13**

- miRNA-protein complex
- (a) Primary miRNA transcript
- (b) Generation and function of miRNAs
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The differentiation of cell types in a multicellular organism results from orchestrated changes in gene expression.

Fertilized eggs are single cells. This tadpole has neurons, muscle, gills, fins, etc.

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An egg's cytoplasm contains RNA, proteins, and other substances that are distributed unevenly in the unfertilized egg.

Sperm
Fertilization
Mitotic cell division
Two-celled embryos have two different cell types

Unfertilized egg cell

Signal molecule (inducer)
Signal transduction pathway
Signal receptor
Signal molecule (inducer)

In the process called induction, signal molecules from nearby cells cause transcriptional changes in embryonic target cells.

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Ovary cells can tell the unfertilized egg which end is which.

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Bicoid: Nurse cells help localize the mRNA for a protein that is required to make head structures.

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EXPERIMENT

Wild-type larva

Mutant larva (bicoid)
Embryonic precursor cell

Nucleus

OFF

DNA

Master regulatory gene

myoD

Other muscle-specific genes

OFF

OFF

mRNA

MyoD protein (transcription factor)

Myoblast (determined)

mRNA

Myosin, other muscle proteins, and cell cycle-blocking proteins

Part of a muscle fiber (fully differentiated cell)

MyoD Another transcription factor