Mechanisms of Eukaryotic Gene Regulation

2 Terms before we get started: Types of Chromatin

• **Heterochromatin:**
  – Highly condensed
  – Not expressed = Off!

• **Euchromatin:**
  – Less condensed
  – Available for transcription = On!
DNA, the double helix | Histones | Nucleosomes, or “beads on a string” (10-nm fiber)

Fig. 16-21a

30-nm fiber | Looped domains (300-nm fiber) | Metaphase chromosome

Fig. 16-21b
Prokaryotic gene regulation is at the level of transcription, for the most part = The Operons!

Eukaryotic gene regulation occurs at multiple levels – see this figure. ALL the boxes represent possible control points.

Histone Acetylation

(a) Histone tails protrude outward from a nucleosome

(b) Acetylation of histone tails promotes loose chromatin structure that permits transcription

Acetyl groups = turn on! De-acetylate = turn off!
DNA Methylation

(Chromatin modification mechanism)

• DNA methylation, the addition of methyl groups to certain bases in DNA (usually cytosine), is associated with reduced transcription in some species
• DNA methylation can cause long-term inactivation of genes in cellular differentiation

Methyl groups = turn off!
De-methylate = turn on!

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
• (...watching a video on this later this week...
**The Roles of Transcription Factors**

- To initiate transcription, eukaryotic RNA polymerase requires the assistance of proteins called transcription factors.
- General transcription factors are essential for the transcription of all protein-coding genes.
- In eukaryotes, high levels of transcription of particular genes depend on control elements interacting with specific transcription factors.
Enhancers and Specific Transcription Factors

- Proximal control elements are located close to the promoter
- Distal control elements, groups of which are called **enhancers**, may be far away from a gene or even located in an intron
- An activator is a protein that binds to an enhancer and stimulates transcription of a gene
- Bound activators cause mediator proteins to interact with proteins at the promoter
Fig. 18-10

Control elements

Enhancer

Promoter

Available activators

Albumin gene

Crystallin gene

(a) Liver cell

(b) Lens cell

Fig. 18-6

Signal

NUCLEUS

Chromatin modification

Gene available for transcription

Chromatin

DNA

RNA

mRNA in nucleus

Transport to cytoplasm

mRNA in cytoplasm

Translation

Polypeptide

Protein processing

Active protein

Transport to cellular destination

Cellular function

Degradation of mRNA

Degradation of protein

Cap
RNA Processing

- In alternative RNA splicing, different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns.
**mRNA Degradation**

- The life span of mRNA molecules in the cytoplasm is a key to determining protein synthesis
- Eukaryotic mRNA is more long lived than prokaryotic mRNA
- The mRNA life span is determined in part by sequences in the leader and trailer regions – UTR’s
Protein Processing and Degradation

• After translation, various types of protein processing, including cleavage and the addition of chemical groups, are subject to control
• Proteasomes are giant protein complexes that bind protein molecules and degrade them
Proteasome and ubiquitin to be recycled

Protein to be degraded

Ubiquitin

Proteasome

Ubiquitinated protein

Protein entering a proteasome

Protein fragments (peptides)
Concept 18.3: Noncoding RNAs play multiple roles in controlling gene expression

• Only a small fraction of DNA codes for proteins, rRNA, and tRNA
• A significant amount of the genome is transcribed into noncoding RNAs
• Noncoding RNAs regulate gene expression at two points: degrade mRNA or block its translation
• **MicroRNAs (miRNAs)** are small single-stranded RNA molecules that can bind to mRNA

• The phenomenon of inhibition of gene expression by RNA molecules is called **RNA interference (RNAi)**
• RNAi is caused by **small interfering RNAs (siRNAs)**
• siRNAs and miRNAs are similar but form from different RNA precursors
• Prokaryotic and eukaryotic cells use small RNA’s to regulate gene expression
Summary of Several Eukaryotic Gene Regulation Mechanisms

**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 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

**RNA processing**
- Alternative RNA splicing:
  - Primary RNA transcript
  - mRNA
  - or

**Translation**
- Initiation of translation can be controlled via regulation of initiation factors.

**Protein processing and degradation**
- Protein processing and degradation by proteasomes are subject to regulation.

2 ways that miRNA's interfere with gene expression:
- Translation blocked
- mRNA degraded

**Fig. 18-13**

(a) Primary miRNA transcript

(b) Generation and function of miRNAs
Concept 18.5: Cancer results from genetic changes that affect cell cycle control

- The gene regulation systems that go wrong during cancer are the very same systems involved in embryonic development.
Oncogenes and Proto-Oncogenes

- **Oncogenes** are cancer-causing genes
  - Analogy: Foot on the gas pedal!
- **Proto-oncogenes** are the corresponding normal cellular genes that are responsible for normal cell growth and division
- Conversion of a proto-oncogene to an oncogene can lead to abnormal stimulation of the cell cycle
  - Analogy: Putting the pedal to the metal!

Fig. 18-20

![Diagram showing the transition from proto-oncogene to oncogene](image)
Tumor-Suppressor Genes

- Tumor-suppressor genes help prevent uncontrolled cell growth
  - Analogy: Foot on the brake pedal!
- Mutations that decrease protein products of tumor-suppressor genes may contribute to cancer onset
  - Analogy: Taking the foot of the brake pedal!
- Tumor-suppressor proteins
  - Repair damaged DNA
  - Control cell adhesion
  - Inhibit the cell cycle in the cell-signaling pathway

- Suppression of the cell cycle can be important in the case of damage to a cell’s DNA
- The p53 gene prevents a cell from passing on mutations due to DNA damage
- Mutations in the p53 gene prevent suppression of the cell cycle
Interference with Normal Cell-Signaling Pathways
...add to lecture...

- Mutations in the ras proto-oncogene and p53 tumor-suppressor gene are common in human cancers
- Mutations in the ras gene can lead to production of a hyperactive Ras protein and increased cell division

![Fig. 18-21a](image-url)

(a) Cell cycle–stimulating pathway

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Protein kinases

DNA damage in genome

1. DNA damage

2. Protein kinases

3. Active form of p53

MUTATION

Defective or missing transcription factor, such as p53, cannot activate transcription

Protein that inhibits the cell cycle

UV light

(c) Effects of mutations

<table>
<thead>
<tr>
<th>EFFECTS OF MUTATIONS</th>
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<tr>
<td>Protein overexpressed</td>
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<tr>
<td>Cell cycle overstimulated</td>
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(b) Cell cycle–inhibiting pathway

(c) Effects of mutations
The Multistep Model of Cancer Development

- Multiple mutations are generally needed for full-fledged cancer; thus the incidence increases with age
- At the DNA level, a cancerous cell is usually characterized by at least one active oncogene and the mutation of several tumor-suppressor genes
Summary of Several Eukaryotic Gene Regulation Mechanisms

Chromatin modification
- Genes in highly compacted chromatin are generally not transcribed.
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- DNA methylation generally reduces transcription.

Chromatin modification
DNA methylation: reduces transcription.
Histone acetylation: loosens chromatin structure, enhancing transcription.

Transcription
- Regulation of transcription initiation: DNA control elements bind specific transcription factors.
- Bending of the DNA enables activators to contact proteins at the promoter, initiating transcription.
- Coordinate regulation: enhancers for liver-specific genes, enhancers for lens-specific genes

RNA processing
- Alternative RNA splicing:
  - Primary RNA transcript
  - mRNA

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.

Summary Roles of Small RNA’s in Gene Regulation of Eukaryotic Cells

Chromatin modification
- Small 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.