Section C: The Control of Gene Expression

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1. Each cell of a multicellular eukaryote expresses only a small fraction of its genes

• Like unicellular organisms, the tens of thousands of genes in the cells of multicellular eukaryotes are continually turned on and off in response to signals from their internal and external environments.

• Gene expression must be controlled on a long-term basis during **cellular differentiation**, the divergence in form and function as cells specialize.
  
  • Highly specialized cells, like nerves or muscles, express only a tiny fraction of their genes.
• Problems with gene expression and control can lead to imbalance and diseases, including cancers.

• Our understanding of the mechanisms controlling gene expression in eukaryotes has been enhanced by new research methods and technology.

• Controls of gene activity in eukaryotes involves some of the principles described for prokaryotes.
  
  • The expression of specific genes is commonly regulated at the transcription level by DNA-binding proteins that interact with other proteins and with external signals.
  
  • With their greater complexity, eukaryotes have opportunities for controlling gene expression at additional stages.
2. The control of gene expression can occur at any step in the pathway from gene to functional proteins: an overview

- Each stage in the entire process of gene expression provides a potential control point where gene expression can be turned on or off, speeded up or slowed down.

- A web of control connects different genes and their products.
• These levels of control include chromatin packing, transcription, RNA processing, translation, and various alterations to the protein product.
3. Chromatin modifications affect the availability of genes for transcription

- In addition to its role in packing DNA inside the nucleus, chromatin organization impacts regulation.
  - Genes of densely condensed heterochromatin are usually not expressed, presumably because transcription proteins cannot reach the DNA.
  - A gene’s location relative to nucleosomes and to attachments sites to the chromosome scaffold or nuclear lamina can affect transcription.

- Chemical modifications of chromatin play a key role in chromatin structure and transcription regulation.
• **DNA methylation** is the attachment by specific enzymes of methyl groups (-CH$_3$) to DNA bases after DNA synthesis.

• Inactive DNA is generally highly methylated compared to DNA that is actively transcribed.
  • For example, the inactivated mammalian X chromosome in females is heavily methylated.
  • Genes are usually more heavily methylated in cells where they are not expressed.
  • Demethylating certain inactive genes turns them on.
  • However, there are exceptions to this pattern.
• In some species DNA methylation is responsible for long-term inactivation of genes during cellular differentiation.

• Once methylated, genes usually stay that way through successive cell divisions.

• Methylation enzymes recognize sites on one strand that are already methylated and correctly methylate the daughter strand after each round of DNA replication.

• This methylation patterns accounts for **genomic imprinting** in which methylation turns off either the maternal or paternal alleles of certain genes at the start of development.
• **Histone acetylation** (addition of an acetyl group - COCH$_3$) and deacetylation appear to play a direct role in the regulation of gene transcription.

• Acetylated histones grip DNA less tightly, providing easier access for transcription proteins in this region.

• Some of the enzymes responsible for acetylation or deacetylation are associated with or are components of transcription factors that bind to promoters.

• In addition, some DNA methylation proteins recruit histone deacetylation enzymes, providing a mechanism by which DNA methylation and histone deacetylation cooperate to repress transcription.
4. Transcription initiation is controlled by proteins that interact with DNA and with each other

- Chromatin-modifying enzymes provide a coarse adjustment to gene expression by making a region of DNA either more available or less available for transcription.

- Fine-tuning begins with the interaction of transcription factors with DNA sequences that control specific genes.

- Initiation of transcription is the most important and universally used control point in gene expression.
• A eukaryotic gene and the DNA segments that control transcription include introns and exons, a promoter sequence upstream of the gene, and a large number of other **control elements**.

• **Control elements** are noncoding DNA segments that regulate transcription by binding *transcription factors*.

• The *transcription initiation complex* assembles on the promotor sequence and one component, RNA polymerase, then transcribes the gene.
Fig. 19.8
• Eukaryotic RNA polymerase is dependent on transcription factors before transcription begins.
  • One transcription factor recognizes the TATA box.
  • Others in the initiation complex are involved in protein-protein interactions.

• High transcription levels require additional transcription factors binding to other control elements.

• Distant control elements, **enhancers**, may be thousands of nucleotides away from the promoter or even downstream of the gene or within an intron.
• Bending of DNA enables transcription factors, *activators*, bound to enhancers to contact the protein initiation complex at the promoter.

• This helps position the initiation complex on the promoter.

Fig. 19.9
• Eukaryotic genes also have *repressor* proteins that bind to DNA control elements called *silencers*.

• At the transcription level, activators are probably more important than repressors, because the main regulatory mode of eukaryotic cells seems to be activation of otherwise silent genes.

• Repression may operate mostly at the level of chromatin modification.
The hundreds of eukaryotic transcription factors follow only a few basic structural principles.

Each protein generally has a **DNA-binding domain** that binds to DNA and a protein-binding domain that recognizes other transcription factors.

![Fig. 19.10](image-url)

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• A surprisingly small number of completely different nucleotide sequences are found in DNA control elements.

• Members of a dozen or so sequences about four to ten base pairs long appear again and again in the control elements for different genes.

• For many genes, the particular combination of control elements associated with the gene may be more important than the presence of a control element unique to the gene.
• In prokaryotes, coordinately controlled genes are often clustered into an operon with a single promoter and other control elements upstream.

• The genes of the operon are transcribed into a single mRNA and translated together

• In contrast, only rarely are eukaryotic genes organized this way.

• Genes coding for the enzymes of a metabolic pathway may be scattered over different chromosomes.

• Even if genes are on the same chromosome, each gene has its own promoter and is individually transcribed.
• Coordinate gene expression in eukaryotes probably depends on the association of a specific control element or collection of control elements with every gene of a dispersed group.

• A common group of transcription factors bind to them, promoting simultaneous gene transcription.
  • For example, steroid hormones enter a cell and bind to a specific receptor protein in the cytoplasm or nucleus.
  • After allosteric activation of these proteins, they functions as transcription activators.
  • Other signal molecules can control gene expression indirectly by triggering signal-transduction pathways that lead to transcription activators.
5. Post-transcriptional mechanisms pay supporting roles in the control of gene expression

- Gene expression may be blocked or stimulated by any post-transcriptional step.
- By using regulatory mechanisms that operate after transcription, a cell can rapidly fine-tune gene expression in response to environmental changes without altering its transcriptional patterns.
• RNA processing in the nucleus and the export of mRNA to the cytoplasm provide opportunities for gene regulation that are not available in bacteria.

• 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.

![Diagram of RNA splicing](image)

Fig. 19.11
• The life span of a mRNA molecule is an important factor determining the pattern of protein synthesis.

• Prokaryotic mRNA molecules may be degraded after only a few minutes.

• Eukaryotic mRNAs endure typically for hours or even days or weeks.
  
  • For example, in red blood cells the mRNAs for the hemoglobin polypeptides are unusually stable and are translated repeatedly in these cells.
• A common pathway of mRNA breakdown begins with enzymatic shortening of the poly(A) tail.
  • This triggers the enzymatic removal of the 5’ cap.
  • This is followed by rapid degradation of the mRNA by nucleases.

• Nucleotide sequences in the untranslated trailer region at the 3’ end affect mRNA stability.
  • Transferring such a sequence from a short-lived mRNA to a stable mRNA results in quick mRNA degradation.
• Translation of specific mRNAs can be blocked by regulatory proteins that bind to specific sequences or structures within the 5’ leader region of mRNA.
  • This prevents attachment to ribosomes.

• Protein factors required to initiate translation in eukaryotes offer targets for simultaneously controlling translation of all the mRNA in a cell.
  • This allows the cell to shut down translation if environmental conditions are poor (for example, shortage of a key constituent) or until the appropriate conditions exist (for example, until after fertilization or during daylight in plants).
Finally, eukaryotic polypeptides must often be processed to yield functional proteins.

- This may include cleavage, chemical modifications, and transport to the appropriate destination.

Regulation may occur at any of these steps.

- For example, cystic fibrosis results from mutations in the genes for a chloride ion channel protein that prevents it from reaching the plasma membrane.
- The defective protein is rapidly degraded.
• The cell limits the lifetimes of normal proteins by selective degradation.

  • Many proteins, like the cyclins in the cell cycle, must be short-lived to function appropriately.

• Proteins intended for degradation are marked by the attachment of ubiquitin proteins.

• Giant **proteosomes** recognize the ubiquitin and degrade the tagged protein.

![Diagram of protein degradation](Fig. 19.12)