**Chapter 18: Regulation of Gene Expression**

**Overview**

The overview for Chapter 18 introduces the idea that while all cells of an organism have all genes in the genome, not all genes are expressed in every cell. What regulates gene expression? Gene expression in prokaryotic cells differs from that in eukaryotic cells. How do disruptions in gene regulation lead to cancer? This chapter gives you a look at how genes are expressed and modulated.

**Concept 18.1 Bacteria often respond to environmental change by regulating transcription**

1. All genes are not “on” all the time. Using the metabolic needs of *E. coli*, explain why not.

   If the environment of the *E. coli* cell is lacking in the amino acid tryptophan, which the bacterium needs to survive, the cell responds by activating a metabolic pathway that makes tryptophan from another compound. Later, if the human host eats a tryptophan-rich meal, the bacterial cell stops producing tryptophan, this saving itself from squandering its resources to produce a substance that is available from the surrounding solution in prefabricated form. This is just one example of how bacteria tune their metabolism to changing environments.

2. What are the two main ways of controlling metabolism in bacterial cells?

   1. Cells can adjust the activity of enzymes already present. This is a fairly fast response, which relies on the sensitivity of many enzymes to chemical cues that increase or decrease their catalytic activity.

   2. Second, cells can adjust the production level of certain enzymes; that is, they can regulate the expression of the genes encoding the enzymes.

3. *Feedback inhibition* is a recurring mechanism throughout biological systems. In the case of *E. coli* regulating tryptophan synthesis, is it *positive* or *negative inhibition*? Explain your choice.

   This is an example of negative inhibition, which is a form of regulation in which accumulation of an end product of a process slows the process. In this case, the accumulation of tryptophan in the cell shuts down the synthesis of more tryptophan.

4. What is a **promoter**?

   A *promoter* is a specific nucleotide sequence in the DNA of a gene that binds RNA polymerase, positioning it to start transcribing RNA at the appropriate place.

5. What is the **operator**? What does it do?

   The operator, in bacterial and phage DNA, is a sequence of nucleotides near the start of an operon to which an active repressor can attach. The binding of the repressor prevents RNA polymerase from attaching to the promoter and transcribing the genes of the operon.
6. What is an operon?

An operon is a unit of genetic function found in bacteria and phages, consisting of a promoter, an operator, and a coordinately regulated cluster of genes whose products function in a common pathway.

7. List the three components of an operon, and explain the role of each one.

1. Operator: The segment of DNA that operates as the “switch”
2. Promoter: The site where RNA polymerase can bind with DNA to begin transcription
3. Genes: Nucleotide sequences that specifically encode subunits of the enzyme

8. How does a repressor protein work?

The repressor binds to the operator and blocks attachment of RNA polymerase to the promoter, preventing transcription of the genes. A repressor protein is specific for the operator of a particular operon.

9. What are regulatory genes?

A regulatory gene is a gene that codes for a protein, such as a repressor, that controls the transcription of another gene or group of genes.

10. Distinguish between inducible and repressible operons, and describe one example of each type.

A repressible operon is usually on, but can be inhibited (repressed) when a specific small molecule binds allosterically to a regulatory protein. One example of a repressible operon is the trp operon (trp for tryptophan).

An inducible operon is usually off but can be stimulated (induced) when a specific small molecule interacts with a regulatory protein. One example of an inducible operon is the lac operon (for lactose).

11. Label this sketch of the lac operon with the terms at right. Know the function of each structure.

See page 354 in your text for the labeled figure.

- operon genes
- operon
- RNA polymerase
- mRNA
- repressor protein
- operator
repressor
regulatory gene
inducer

12. Compare and contrast the lac operon and the trp operon.

In both lac and trp operons, the entire transcription unit is under the command of one main operator and promoter. The lac operon is an inducible operon, while the trp operon is repressible. In both operons, regulation involves negative control of genes, because operons are switched off by the active form of the repressor protein.

13. What happens when a repressor is bound to the operator?

When a repressor is bound to the operator, it blocks attachments of RNA polymerase to the promoter, preventing transcription of the genes.

14. What is CAP? How does CAP work?

CAP refers to catabolite activator protein, and is a regulatory protein that binds to DNA and stimulates transcription of a gene.

15. Explain why CAP binding and stimulation of gene expression is positive regulation.

By facilitating the binding of RNA polymerase to the promoter and thereby increasing the rate of transcription, the attachment of CAP to the promoter directly stimulates gene expression, qualifying CAP as positive regulation.

16. Describe the relationship between glucose supply, cAMP, and CAP.

If the amount of glucose in the cell increases, the cAMP concentration falls, and without cAMP, CAP detaches from the operon. Because CAP is inactive, RNA polymerase binds less efficiently to the promoter, and transcription proceeds only at a low level.

17. How can both repressible and inducible operons be negative regulators?

Both repressible and inducible operons can be negative regulators as long as the operons are switched off by the active form of the repressor protein. In the case of the lac operon, allolactose induces enzyme synthesis not by acting directly on the genome, but by freeing the lac operon from the negative effect of the repressor. Remember that gene regulation is said to be positive only when a regulatory protein interacts directly with the genome to switch transcription on.

**Concept 18.2 Eukaryotic gene expression can be regulated at any stage**

18. Even though all cells of an organism have the same genes, there is differential gene expression. What does this mean?

Differential gene expression is the expression of different sets of genes by cells with the same
19. What percentage of the genes of a typical human cell is expressed at any given time? 
20% 

20. What is the common control point of gene expression for all organisms? 
Transcription 

21. Gene expression can be regulated by modifications of the chromatin. Distinguish between heterochromatin and euchromatin as to their structure and activity. 

Heterochromatin: Eukaryotic chromatin that remains highly compacted during interphase and is generally not transcribed. 

Euchromatin: The less condensed form of eukaryotic chromatin that is available for transcription. 

22. What occurs in histone acetylation? How does it affect gene expression? 
Histone acetylation is the attachment of acetyl groups to certain amino acids of histone proteins. Such binding promotes the folding of chromatin into a more compact structure; when this binding does occur, chromatin has a looser structure. As a result, transcribing proteins have easier access to genes in an acetylated region. 

23. What is DNA methylation? What role may it play in gene expression? 
DNA methylation is the process of adding methyl groups to DNA bases. At least in some species, DNA methylation seems to be essential for the long-term inactivation of genes that occurs during normal cell differentiation in the embryo. 

24. The inactive mammalian X chromosome is heavily methylated. What is the result of this methylation? 
After an X chromosome is inactivated in a particular cell, all mitotic descendants of that cell have the same inactive X. Thus, if a female is heterozygous for a sex-linked trait, about half her cells will express one allele, while the others will express the alternative allele. 

25. What is genomic imprinting, and how is it maintained? Give an example discussed earlier in human genetics. 
Genomic imprinting is the phenomenon in which expression of an allele in offspring depends on whether the allele is inherited from the male or female parent. Examples may vary. 

26. Explain what is meant by epigenetic inheritance, and give an example of epigenetic changes discussed in the text or in class. 
Inheritance of traits transmitted by mechanisms not directly involving the nucleotide sequence of a genome. Examples may vary.
27. Use the sketch below to explain how enhancers and activators interact with transcription factors to affect gene expression. Label the following elements: TATA box, promoter, gene, enhancer, activators, transcription factors, transcription initiation complex, RNA polymerase II, and DNA. Then place your explanation to the right of the figure.

See page 360 of your text for the labeled figure.

28. In prokaryotes, functionally related genes are usually clustered in a single operon. What has been found to be the case in eukaryotes?

Co-expressed eukaryotic genes, such as genes coding for the enzymes of a metabolic pathway, are typically scattered over different chromosomes. In these cases, coordinate gene expression depends on the association of a specific combination of control elements with every gene of a dispersed group.

29. Operons have not been found in eukaryotic cells, and the genes coding for the enzymes of a particular metabolic pathway are often scattered over different chromosomes. What is a plausible mechanism for the coordination of gene expression?

Coordinate control of dispersed genes in a eukaryotic cell often occurs in response to chemical signals from outside the cell. A steroid hormone, for example, enters a cell and binds to a specific intracellular receptor protein, forming a hormone-receptor complex that serves as a transcription activator.

30. How can alternative RNA splicing result in different proteins derived from the same initial RNA transcript?

Different mRNA molecules are produced from the same primary transcript, depending on which RNA segments are treated as exons and which as introns. Regulatory proteins specific to cell type control intron-exon choices by binding to regulatory sequences within the primary transcript.

31. Posttranscriptional control includes regulation of mRNA degradation. Explain how this affects translation.

The central idea is that the longer mRNA is in the cytoplasm, the more protein that can be formed by translation. In general, prokaryotes degrade their mRNA more quickly than eukaryotes.

32. How can proteins be activated, processed, and degraded? Give an example or describe each process.

The process of making proteins through activation can best be seen in the developing embryo. Many mRNA molecules are made ahead of fertilization, but they do not have a poly-A tail and are therefore not active. At the appropriate time, an enzyme in the cytoplasm adds the adenines, activating the mRNA and producing proteins. A second method of activation is the zygote wide release of translation initiation factors that triggers a burst of protein synthesis. Proteins are often processed by altering amino acids or changing the sequence of amino acids to form an active, functioning protein. Finally, the length of time each protein functions in the cell is strictly regulated by means of selective degradation utilizing proteasomes.
33. An article in *Scientific American* about proteasomes was entitled “Little Chamber of Horrors.” Explain how proteins are targeted for degradation, and give a specific example of when this might occur.

To mark a particular protein for destruction, the cell commonly attaches molecules of a small protein ubiquitin to the protein. Proteasomes then recognize ubiquitin-tagged proteins and degrade them. The importance of proteasomes is underscored by the findings that mutations making specific cell cycle proteins impervious to proteasome degradation can lead to cancer.

34. How do these “little chambers of horrors” function? Annotate the sketch below to describe their action. Then explain their role in regulation of gene expression.

See page 364 of your text for the labeled figure.

Multiple ubiquitin molecules are attached to a protein by enzymes in the cytosol. The ubiquitin-tagged protein is recognized by a proteasome, which unfolds the protein and sequesters it within a central cavity. Enzymatic components of the proteasome cut the protein into small peptides, which can be further degraded by other enzymes in the cytosol.

**Concept 18.3 Noncoding RNAs play multiple roles in controlling gene expression**

35. It is now known that much of the RNA that is transcribed is not translated into protein. These RNAs are called noncoding RNAs. Read carefully to discern a crucial role played by these RNAs. What is this role?

Regulating gene expression

36. One of the noncoding RNAs that regulate gene expression is microRNA. On the sketch below, follow an RNA loop, called a “hairpin,” from its creation. Be sure to label the location of hydrogen bonds and Dicer. Explain the two modes of action of microRNAs.

See page 365 of your text for the labeled figure.

If mRNA and mRNA bases are complementary all along their length, the mRNA is degraded (left side of figure); if the match is less complete, translation is blocked (right side of figure).

**Concept 18.4 A program of differential gene expression leads to the different cell types in a multicellular organism**

This concept deals with the regulation of gene expression in development. Animal development is also discussed in Chapter 47.

37. What three processes lead to the transformation of a zygote into the organism?

1. Cell division
2. Cell differentiation
3. Morphogenesis
38. Explain what occurs in cell differentiation and morphogenesis.

Cell differentiation is the process by which cells become specialized in structure and function.

Morphogenesis is the physical process that gives an organism its shape.

39. Differential gene expression results from different activators in different cells. How do different sets of activators come to be present in two cells? Explain how each of these occurs:

a. distribution of cytoplasmic determinants

   After fertilization, early mitotic divisions distribute the zygote’s cytoplasm into separate cells. The nuclei of these cells may thus be exposed to different cytoplasmic determinants, depending on which portions of the zygotic cytoplasm a cell received. The combination of cytoplasmic determinants in a cell helps determine its developmental fate by regulating expression of the cell’s genes during the course of cell differentiation.

b. different inductive signals

   The molecules conveying these signals within the target cell are cell-surface receptors and other proteins expressed by the embryo’s own genes. In general, the signaling molecules send a cell down a specific developmental path by causing changes in its gene expression that eventually result in observable cellular changes.

40. What is meant by determination? Explain what this means within an embryonic cell.

   Determination is the progressive restriction of developmental potential in which the possible fate of each cell becomes more limited as an embryo develops. At the end of determination, a cell is committed to its fate.

41. What process ensures that all the tissues and organs of an organism are in their characteristic places? Where do the molecular cues that control this process arise?

   Pattern formation. The molecular cues that control pattern formation, collectively called positional information, are provided by cytoplasmic determinants and inductive signals.

42. What is controlled by homeotic genes?

   Homeotic genes control placement and spatial organization of body parts in animals, plants, and fungi by controlling the developmental fate of groups of cells.

43. What mechanism is involved in the beginning of tumor growth? Discuss oncogenes and proto-oncogenes.

   Mutations in the genes that normally regulate cell growth and division in somatic cells can lead to cancer. An oncogene is a gene found in viral or cellular genomes that is involved in triggering
molecular events that can lead to cancer. A proto-oncogene is a normal cellular gene that has the potential to become an oncogene.

44. What are three mechanisms for converting a proto-oncogene to an oncogene?

In general, an oncogene arises from a genetic change that leads to an increase either in the amount of the proto-oncogene’s protein product or in the intrinsic activity of each protein molecule. The genetic changes that convert proto-oncogenes to oncogenes are movement of DNA within the genome, amplification of a proto-oncogene, and point mutations in a control element or in the proto-oncogene itself.

45. There seem to be two categories of genes involved in cancer: oncogenes, which code for proteins to regulate cell growth, and should not be stuck “on,” much like the accelerator in a car; and tumor-suppressor genes, which work like the brakes on a car and must function! Let’s begin with a look at the ras gene, which codes for a G protein and is an oncogene. Label the sketch below to explain how a ras mutation leads to cancer.

See page 375 in your text for the labeled figure.

46. Tumor-suppressor genes help prevent uncontrolled cell growth. One that is found mutated (and therefore nonfunctional) in more than 50% of human cancer is p53. So important is the p53 gene that it is sometimes called the “guardian angel of the genome.” Describe the double whammy that results from mutation of p53.

p53 acts in several ways to prevent a cell from passing on mutations due to DNA damage. If mutations do accumulate and the cell survives through many divisions—as is more likely if the p53 tumor-suppressor gene is defective or missing—cancer may ensue.

47. Explain the multistep model of cancer development by using the specific example of colorectal cancer. The figure below may be labeled to help in your explanation.

See page 376 of your text for the labeled figure.

Affecting the colon and/or rectum, this type of cancer is one of the best understood. Changes in a tumor parallel a series of genetic changes, including mutations affecting several tumor-suppressor genes (such as p53) the ras proto-oncogene. Mutations of tumor-suppressor genes often entail loss (deletion) of the gene. Other mutation sequences can also lead to colorectal cancer.

Test Your Understanding Answers

Now you should be ready to test your knowledge. Place your answers here:

1. d  2. a  3. a  4. a  5. c  6. d  7. c  8. e  9. b  10. b