17

Regulation and Mutations

Learning Objectives

In this chapter, you will learn:

- ➜ Regulation of Gene Expression in Prokaryotes
- ➜ Regulation of Gene Expression in Eukaryotes
- ➜ Gene Expression Helps Cells Specialize
- ➜ Mutations

Overview

The phenotype of an organism is determined by the genes that are expressed and the levels at which those genes are expressed. Regulation of gene expression is important in determining an organism's phenotype. Genes can be regulated by the interaction of regulatory proteins with regulatory sequences in the genome. **Regulatory proteins** are proteins that can turn on or turn off genes by binding to specific nucleotide sequences. The nucleotide sequences to which these regulatory proteins bind are called **regulatory sequences.** Mutations in the genome may also affect gene expression. This chapter will review how the expression of genes is regulated (in prokaryotes and in eukaryotes) and the different types of mutations that can affect an organism's phenotype.

Regulation of Gene Expression in Prokaryotes

Prokaryotes use operons to regulate gene expression. An **operon** is a cluster of genes with a common function under the control of a common promoter. Operons contain regulatory sequences, genes for regulatory proteins, and genes for structural proteins (which are responsible for the function of the operon). An example of an operon is shown in Figure 17.1.

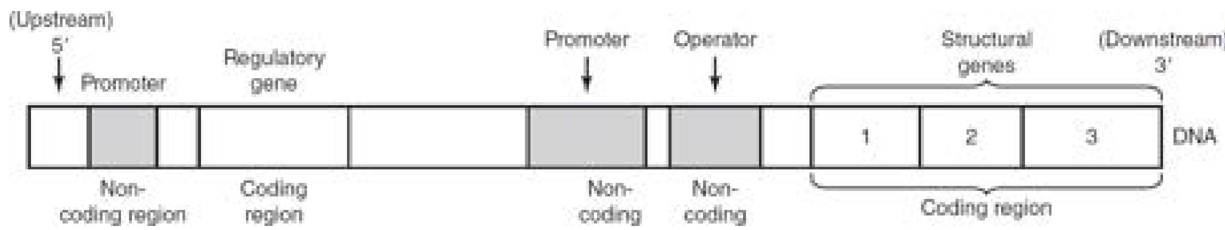


Figure 17.1 The Operon

Promoters are noncoding regulatory sequences that serve as binding sites for RNA polymerase. **Operators** are noncoding regulatory sequences that serve as binding sites for repressor proteins (a type of regulatory protein). **Structural genes** are coding sequences that contain the genetic code for the proteins required to perform the function of the operon.

The two types of prokaryotic operons you need to understand for the AP Biology exam are inducible operons and repressible operons.

When determining whether an operon is turned “on” or “off,” consider what would be most advantageous to the bacteria in its environment. If an operon’s function is to digest a molecule, it is advantageous to the bacteria to turn “off” the operon if the molecule is not present and to turn “on” the operon if the molecule is present. If an operon’s function is to synthesize a molecule, it is advantageous to turn “on” the operon if the molecule is not present but advantageous to turn “off” the operon if the molecule is present.

Inducible Operons

Inducible operons usually have a catabolic function (digesting molecules) and are turned off unless the appropriate inducer molecule is present. The repressor protein in an inducible operon binds to the operator sequence, blocking transcription of the operon by RNA polymerase. However, when an inducer molecule is present, the **inducer** binds to the repressor protein, changing its shape so that it can no longer bind to the operator sequence. This allows RNA polymerase to begin transcribing the operon.

The classic example of an inducible operon is the ***lac* operon**, as shown in Figure 17.2. The function of the *lac* operon is to produce the proteins required to digest the sugar lactose. If no lactose is present, the *lac* repressor protein will bind to the operator, blocking transcription of the operon by RNA polymerase. Lactose serves as the inducer molecule for the *lac* operon. When lactose is present, it binds to the *lac* repressor protein, changing its shape so that it no longer can bind to the operator sequence. This allows RNA polymerase to transcribe the genes for the proteins that digest lactose. After all the lactose has been digested, the repressor can again bind to the operator sequence, shutting down the operon. This type of feedback mechanism allows the cell to manufacture the proteins needed to digest lactose only when they are needed, saving valuable resources in the cell.

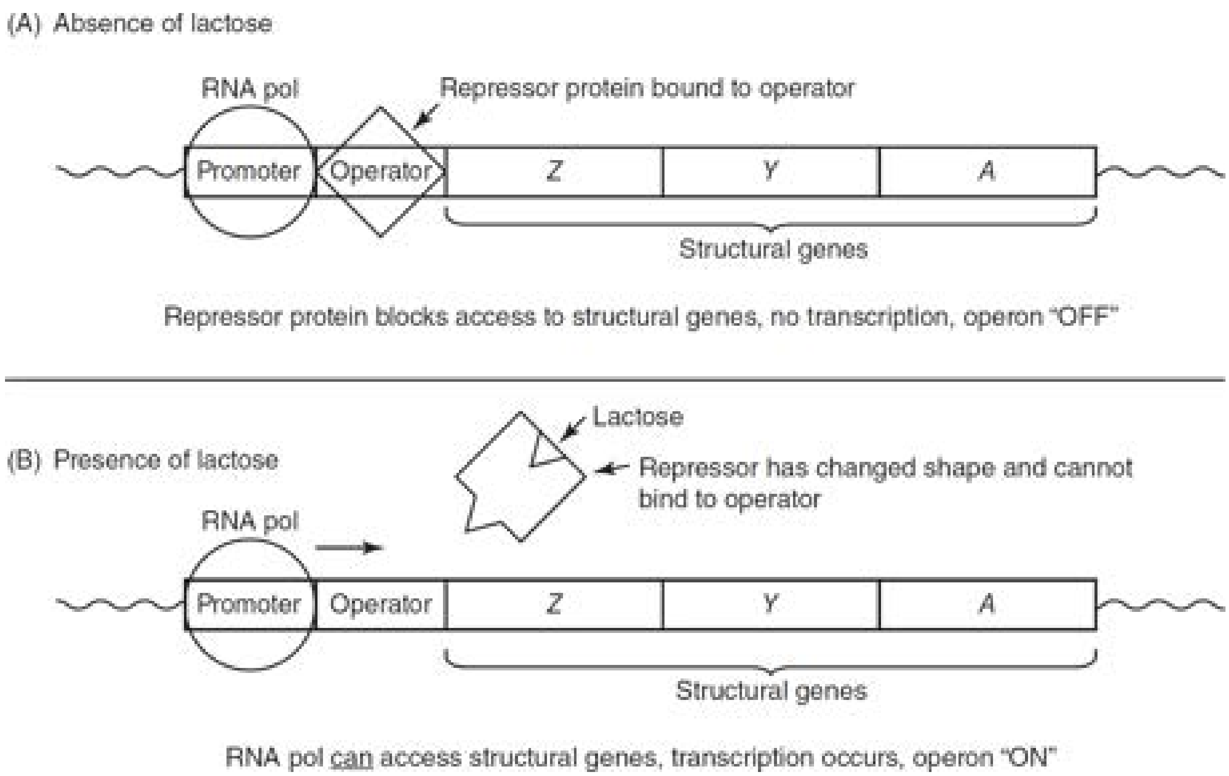


Figure 17.2 *Lac* Operon

While the binding of repressor proteins to the operator sequence can negatively regulate gene expression, there are also ways to positively “upregulate” gene expression. An example of this is the interaction between cyclic AMP (cAMP) and the catabolite activator protein (CAP) in the *lac* operon. When glucose levels are low, cAMP levels in the cell increase. cAMP binds to the catabolite activator protein (CAP), stimulating CAP to bind at a CAP binding site near the promoter. This increases the affinity of RNA polymerase for the promoter, stimulating transcription. So transcription of the *lac* operon is increased when glucose, another food source for the bacteria, is absent, allowing the cell to utilize the energy in lactose more efficiently.

Repressible Operons

Repressible operons usually have an anabolic function (synthesizing molecules) and are turned on unless the product of the operon is in abundance in the cell. The ***trp*** **operon** is an example of a repressible operon. (See Figure 17.3.) The function of the *trp* operon is to produce the enzymes needed to synthesize the amino acid tryptophan. In the *trp* operon, the amino acid tryptophan functions as a **corepressor**. The *trp* repressor protein cannot bind to the operator sequence on its own; the *trp* repressor must be bound to the amino acid tryptophan before it can bind to the operator. Therefore, if no tryptophan is present, the *trp* repressor will not be bound to the operator and RNA polymerase can transcribe the operon. When tryptophan is present, it will bind to the *trp* repressor, which will then bind to the operator, stopping transcription of the operon. This type of feedback mechanism allows the cell to make the enzymes needed to synthesize tryptophan only when the cell needs them, again saving valuable resources in the cell.

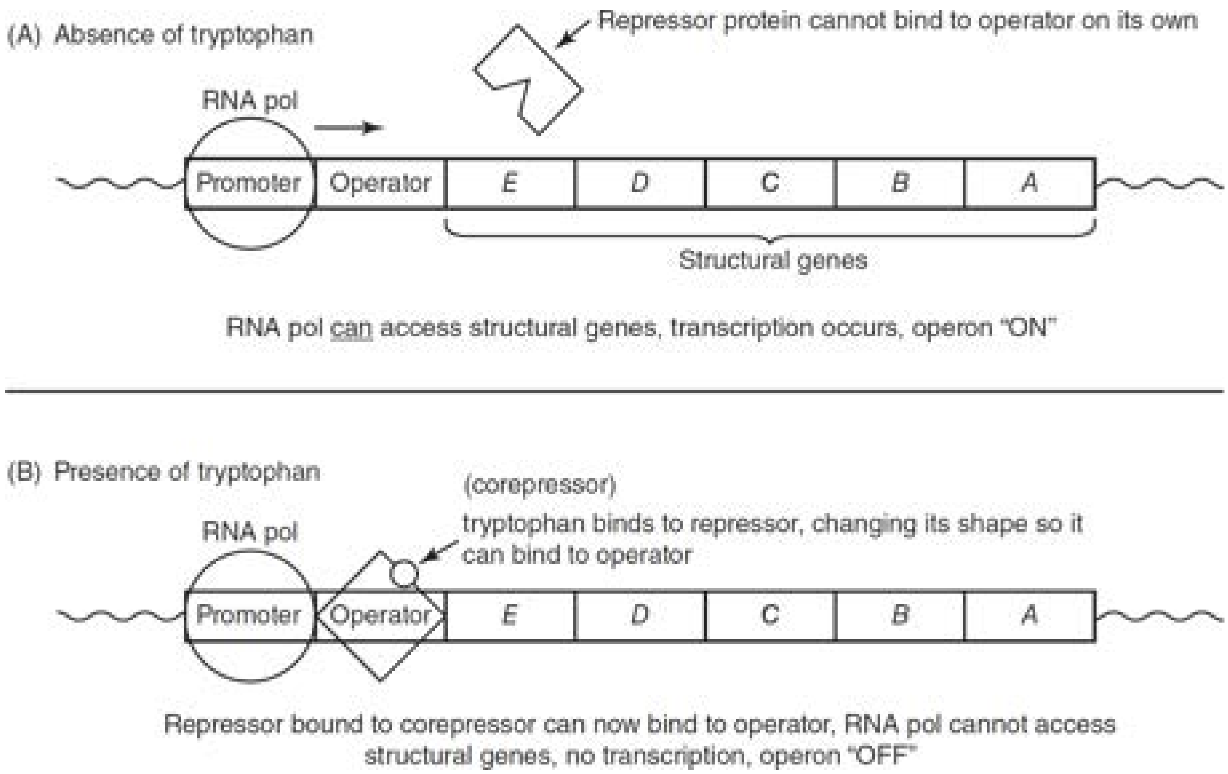


Figure 17.3 *Trp* Operon

In summary, there are some key differences between inducible operons and repressible operons:

- The function of the operon (catabolic or anabolic)
- Whether the repressor protein can bind to the operator on its own, or whether the repressor protein needs a corepressor to bind to the operator

For the AP Biology exam, you are not required to memorize which operons are inducible or repressible, but you do need to understand how inducible and repressible operons work. You must be able to apply your knowledge about operons to novel scenarios. For example, if a question on the exam is about the arabinose operon, the question will tell you the type of operon it is (inducible). Then you should apply your knowledge of how the *lac* operon works to answer the question about the arabinose operon.

Regulation of Gene Expression in Eukaryotes

Eukaryotes can also use the interactions between regulatory sequences and regulatory proteins to turn genes on or off and to regulate the levels of gene expression.

The following are some examples of regulatory sequences used in eukaryotes:

- **Promoters**—sequences that serve as binding sites for RNA polymerase.
- **Regulatory switches**—sequences to which activator proteins or repressor proteins may bind. **Enhancers** are regulatory switches to which activator proteins or transcription factors bind. **Silencers** are regulatory switches to which repressor proteins bind.

Some examples of regulatory proteins include:

- **Repressors**—These bind to regulatory switches and turn off or suppress gene expression.
- **Activators**—These bind to regulatory switches and upregulate gene expression.
- **Transcription factors**—These help RNA polymerase bind to the promoter and start transcription.
- **Mediators**—These serve as "connectors" between other regulatory proteins and allow regulatory proteins to communicate.

Epigenetic changes can also affect gene expression in eukaryotes. **Epigenetic changes** can be reversible modifications to the nucleotides of the DNA sequence, such as methylation (adding a methyl group) of nucleotides. A methylated nucleotide is much less likely to be transcribed, so the cell can modify gene expression by changing the level of methylation of the nucleotides in various genes.

The **histone proteins** around which DNA is packaged into chromosomes can also be epigenetically modified by adding acetyl groups (acetylation) to the histone proteins. If histone proteins are acetylated, DNA will be more loosely wound around the histone proteins, more accessible to RNA polymerase, and more likely to be expressed. **Euchromatin** is DNA that is more loosely wound around the histone proteins, is more accessible to RNA polymerase, and usually results in more expression of the genes in the euchromatin. DNA in chromosomes may be tightly wound around the histone proteins, forming **heterochromatin**, which is less accessible to RNA polymerase and results in reduced gene expression.

Small interfering RNA (siRNA) molecules can also affect gene expression. siRNA is single-stranded and binds to complementary mRNA molecules, forming double-stranded RNA (dsRNA) molecules. Enzymes in the cell detect and destroy these dsRNA molecules, resulting in no translation of the targeted mRNA molecules and reduced gene expression.

Gene Expression Helps Cells Specialize

The regulation of gene expression results in different genes being expressed in different cells (also known as **differential gene expression**). This differential gene expression influences the functions of cells and the resulting phenotype of the organism. Different tissue types express different genes, which results in cell differentiation.

The phenotype of an organism is determined not only by which genes are expressed but also by the levels at which the genes are expressed. For example, a skin cell expressing higher levels of the melanin protein would appear darker in color than a skin cell expressing lower levels of the melanin protein.

The timing of the expression of different transcription factors during development is critical to the formation of specialized tissues and organs from a single-celled zygote. Errors in the timing of the expression of these genes can result in errors in the body plan or structures of an organism. A family of genes that codes for transcription factors called the *Hox* genes were discovered in *Drosophila* flies. The *Hox* gene coding for antennapedia controls the formation of legs in *Drosophila* during development. Mutations in this gene or expression of this gene at the wrong time can result in legs not forming or legs being located in the wrong body segment.

Mutations

Mutations are changes in the genetic material of an organism. Mutations may result in changes to the organism's phenotype. Phenotypes can change if the mutation interferes with or changes the function of a protein. Mutations that change the amount of a protein produced can also change the phenotype of an organism. Mutations provide genetic variation in populations. These variations are acted upon by natural selection and can lead to the evolution of populations.

Two of the most common aneuploidies in humans are Klinefelter syndrome and Down syndrome (also known as trisomy 21). Individuals with Klinefelter syndrome have three sex chromosomes: two X and one Y. Individuals with Down syndrome typically have three copies of chromosome 21.

Not all mutations are harmful. The organism's environment determines whether a mutation is beneficial, harmful, or has no effect on the survival of the organism. If the organism's environment changes, the benefit or harm a mutation confers on the organism can change. Some mutations do not change the amino acid sequence of a protein at all because of the redundancy of the genetic code.

Mutations can be caused by environmental factors, such as chemicals or radiation, or by random errors in DNA replication or DNA repair mechanisms.

Mistakes in mitosis or meiosis can also lead to mutations. Failure of homologous chromosomes to separate during meiosis can lead to an **aneuploidy** (an incorrect number of chromosomes). Aneuploidies in animals can be fatal or may cause sterility or other disorders. However, in plants, aneuploidies that result in polyploids (an entire extra set of chromosomes) can confer an advantage to the plant, making it more likely to survive.

Genetic mutations can also be transmitted horizontally between members of the same generation. Some methods of **horizontal transmission** of genetic information include:

- **Transformation**—the uptake of naked foreign DNA by a cell

- **Transduction**—the transmission of DNA from one organism to another by viruses; as the virus transfers the DNA, the DNA sequence may be recombined or otherwise changed, leading to new mutations and variations
- **Conjugation**—the transmission of DNA through cell-to-cell contact, usually through a connection called a pilus
- **Transposition**—the movement of DNA between chromosomes or within a chromosome; these are sometimes referred to as “jumping genes”

Practice Questions

Multiple-Choice

1. A repressible operon in bacteria codes for the genes required to produce the amino acid serine. Serine functions as a corepressor for the operon. If serine is present in the bacteria's environment, which of the following is most likely?

   (A) increased digestion of serine
   (B) increase in the levels of serine
   (C) increased production of the repressor protein
   (D) increased binding of the repressor protein to the operator

2. The arabinose operon is an inducible operon that codes for the genes required to digest the sugar arabinose. Arabinose functions as an inducer molecule for the operon. If arabinose is present in the bacteria's environment, which of the following is most likely?

   (A) increased digestion of arabinose
   (B) increase in the levels of arabinose
   (C) increased production of the repressor protein
   (D) increased binding of the repressor protein to the operator

3. Which sequences in bacterial operons are noncoding sequences?

   (A) operators and promoters only
   (B) operators, promoters, and genes for regulatory proteins
   (C) operators, promoters, and genes for structural proteins
   (D) promoters, genes for regulatory proteins, and genes for structural proteins

4. Which of the following is a key difference between inducible operons and repressible operons?

(A) Inducible operons have promoter sequences, and repressible operons do not have promoter sequences.

(B) Inducible operons have operator sequences, and repressible operons do not have operator sequences.

(C) The repressor in an inducible operon can bind to the operator sequence on its own, but the repressor in a repressible operon requires a corepressor in order to bind to the operator.

(D) In inducible operons, RNA polymerase requires the presence of a corepressor in order to bind to the promoter; in repressible operons, RNA polymerase does not require a corepressor.

5. Under which of the following conditions will transcription of the *lac* operon be at its highest level?

(A) low glucose, low lactose

(B) low glucose, high lactose

(C) high glucose, low lactose

(D) high glucose, high lactose

6. Adding a methyl group to a DNA nucleotide is a type of ______________ and will make a DNA sequence much less likely to be transcribed.

(A) mutation

(B) epigenetic change

(C) aneuploidy

(D) transposition

7. Which of the following are proteins in eukaryotes that bind to regulatory switches and upregulate gene expression?

(A) activators

(B) repressors

(C) transcription factors

(D) mediators

8. Not every change in the DNA sequence results in a change in the amino acid sequence of a protein. Which of the following explains this?

(A) Each organism lives in a different environment, which changes the expression of its genes.
(B) The genetic code is redundant, and more than one codon codes for most amino acids.
(C) The proofreading function of ribosomes corrects changes in the DNA sequence.
(D) Differential gene expression adapts to these changes in the DNA sequence.

9. Which of the following does not affect the phenotype of an organism?

(A) the genes that are expressed
(B) the level at which genes are expressed
(C) the timing of gene expression
(D) the number of genes in the organism

10. Which of the following methods of horizontal transmission of genetic material would be most likely to lead to new variants of the COVID-19 virus?

(A) transformation
(B) transduction
(C) transposition
(D) conjugation

Short Free-Response

11. One way that organisms respond to changing environmental conditions is through the regulation of gene expression.

(a) **Describe** the function of operators and promoters in prokaryotes.

(b) **Explain** how the operator and repressor interact to control the expression of the inducible *lac* operon.

(c) Bacteria are placed in an environment that has low levels of glucose and high levels of lactose. **Predict** the level of expression of the *lac* operon in this environment.

(d) **Justify** your prediction from part (c).

12. A student conducts an experiment in an effort to determine whether a specific bacterial operon is inducible or repressible. The level of transcription of the operon was measured after the addition of different molecules to the bacteria's environment. Data are shown in the table.

Fructose	Lysine	Level of Transcription
Absent	Absent	High
Absent	Present	Low
Present	Absent	High
Present	Present	Low

(a) **Describe** what, if any, effect levels of fructose have on the level of transcription of the operon.

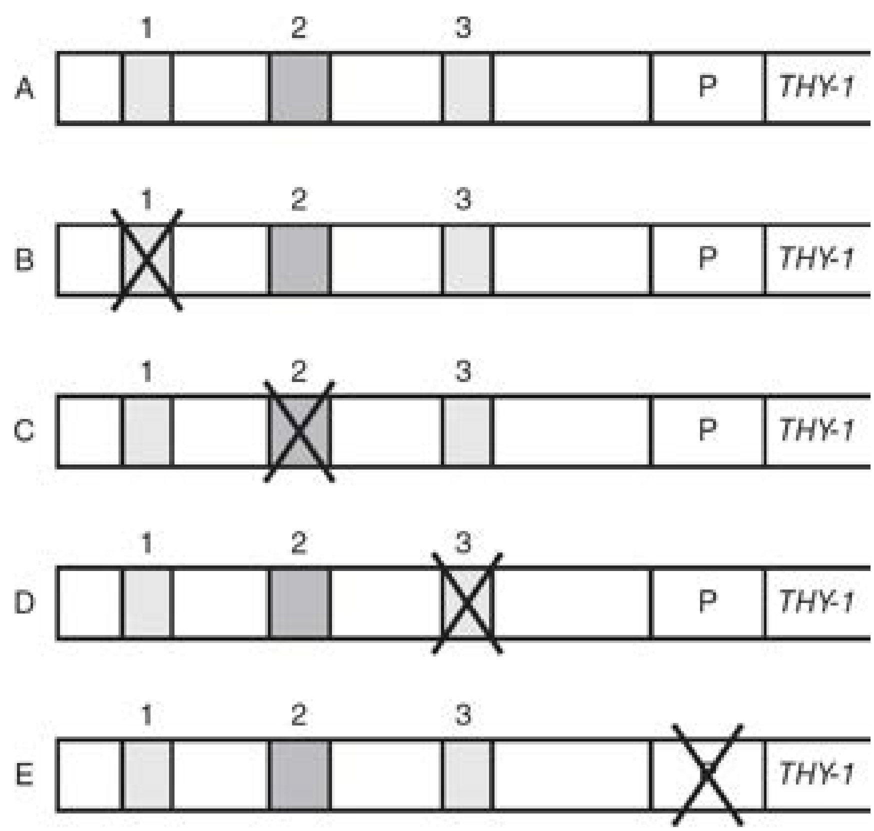
(b) **Describe** what, if any, effect levels of lysine have on the level of transcription of the operon.

(c) **Make a claim** about whether this operon is more likely inducible or repressible.

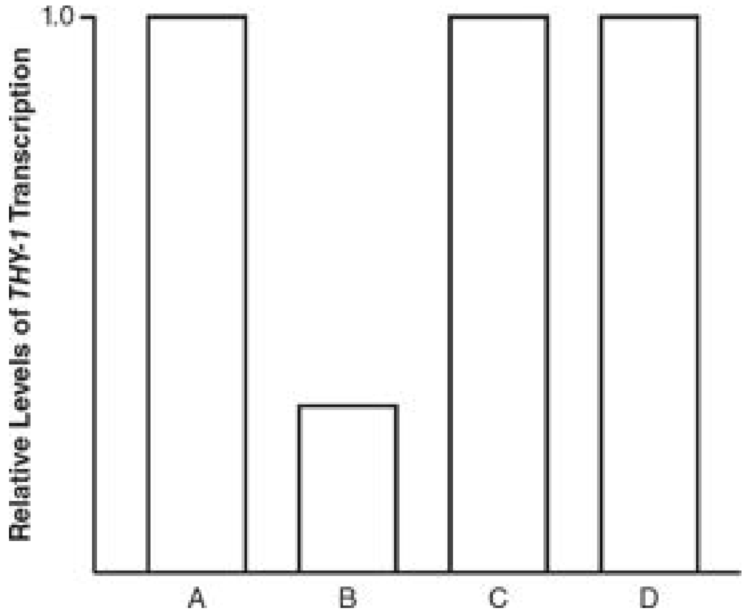
(d) **Justify** your claim from part (c) using evidence from the experiment and your knowledge of inducible and repressible operons.

Long Free-Response

13. The human *THY-1* gene (Thy-1 cell surface antigen) codes for a cell surface glycoprotein that is thought to function as a tumor suppressor in certain types of cancer. In order to find possible locations of enhancer sequences for the *THY-1* gene, scientists performed a series of DNA deletion experiments. In the experiments, different deletions were made in areas that were suspected to function as possible enhancer sequences, and the levels of *THY-1* transcription were measured after each deletion. The following diagram shows the sequences deleted. A, B, C, D, and E represent different DNA sequences. 1, 2, and 3 represent suspected enhancer sequences. *P* is the promoter of the *THY-1* gene. An X represents the deletion of that portion of the DNA sequence.



The levels of *THY-1* transcription in each part of the experiment are shown in the graph.



(a) **Explain** the function of enhancer sequences in eukaryotic gene expression.

(b) **Identify** which DNA sequence (A, B, C, D, or E) was the control in this experiment.

(c) Which sequence (1, 2, or 3) most likely functions as an enhancer sequence? **Support** your claim using evidence from the data.

(d) **Predict** the effects of the deletion of P, as shown in sequence E, and what the relative level of *THY-1* transcription would be for E. **Justify** your prediction with evidence from the data.

Answer Explanations

Multiple-Choice

1. **(D)** Corepressors help the repressor protein bind to the operator. Since serine is a corepressor, its presence would result in increased binding of the repressor protein to the operator. Choice (A) is incorrect because repressible operons are usually anabolic, not catabolic, in function and thus they would not be involved in the digestion of serine. Since serine functions as a corepressor, the presence of serine would reduce the expression of the operon and would not result in increased levels of serine. Thus, choice (B) is incorrect. The presence of the corepressor does not affect the production of the repressor protein, so choice (C) is incorrect.

2. **(A)** In inducible operons, the inducer molecule binds to the repressor protein, which prevents the repressor protein from binding to the operator, increasing the level of expression of the operon. Choice (B) is incorrect because inducible operons are usually catabolic, not anabolic, and would not be involved in the production of arabinose. The presence of the inducer does not affect the production of the repressor protein, so choice (C) is incorrect. The presence of the inducer results in decreased binding of the repressor protein to the operator, so choice (D) is also incorrect.

3. **(A)** The operators and promoters of operons both serve as noncoding sequences to which regulatory proteins bind. Repressor proteins bind to the operator, and RNA polymerase binds to the promoter. Genes for both regulatory proteins and structural proteins contain sequences that code for proteins, so choices (B), (C), and (D) are incorrect.

4. **(C)** In inducible operons, repressor proteins can bind to the operator without the assistance of a corepressor. In repressible operons, the presence of a corepressor is required in order for the repressor protein to bind to the operator sequence. Choice (A) is incorrect because both inducible and repressible operons have promoter sequences. Operator sequences are present in both inducible and repressible operons, so

choice (B) is incorrect. RNA polymerase does not require a corepressor in order to bind to the promoter in both inducible and repressible operons, so choice (D) is incorrect.

5. **(B)** Lactose is an inducer for the *lac* operon, so high levels of lactose would pull the repressor protein off of the operator, increasing expression of the *lac* operon. Low levels of glucose would cause higher levels of cyclic AMP, which would activate the catabolite activator protein, upregulating the expression of the *lac* operon. Low levels of lactose would not result in high levels of *lac* operon expression, so choices (A) and (C) are incorrect. Glucose is the preferred food source for bacteria, so if high levels of glucose were present, the bacteria would not express the *lac* operon at a high level until all of the glucose was metabolized. Therefore, choice (D) is incorrect.

6. **(B)** Methylating nucleotides is a type of epigenetic change to DNA. Choice (A) is incorrect because mutations change the DNA sequences and do not involve methylation. An aneuploidy is an incorrect number of chromosomes, so choice (C) is incorrect. Choice (D) is incorrect because transposition involves the movement or rearrangement of pieces of DNA and does not involve methylation.

7. **(A)** Activators are proteins in eukaryotes that bind to regulatory switches and upregulate gene expression. Choice (B) is incorrect because repressors downregulate gene expression. Transcription factors help RNA polymerase bind to the promoter and do not bind to regulatory switches, so choice (C) is incorrect. Mediators are proteins that allow communication between the regulatory proteins involved in gene expression; they do not bind to regulatory switches, so choice (D) is incorrect.

8. **(B)** The genetic code contains more than one codon for most amino acids, so a change in a codon does not necessarily result in a change in the amino acid for which it codes. While changes in the environment can affect the expression of genes, the statement in choice (A) does not explain why changes in the DNA sequence may not result in changes in the amino acid found in the final protein. Thus, choice (A) is incorrect.

Ribosomes do not have a proofreading function, so choice (C) is incorrect. Differential gene expression results in cell differentiation but not changes in the DNA sequence, so choice (D) is incorrect.

9. **(D)** The phenotype of an organism is determined by the genes that are expressed, the level of expression of those genes, and the timing of the expression of those genes. The phenotype is not affected by the number of genes in the organism, so choice (D) is the only choice that does not affect the phenotype of an organism.

10. **(B)** Transduction involves the transfer of genetic material by viral transmission. Transformation, transposition, and conjugation do not involve viruses, so choices (A), (C), and (D) are incorrect.

Short Free-Response

11. (a) Operators serve as binding sites for repressor proteins. Promoters are binding sites for RNA polymerase.

    (b) When the repressor is bound to the operator, it blocks RNA polymerase's access to the structural genes, and the operon is shut down.

    (c) The level of expression of the *lac* operon will be high.

    (d) Lactose is the inducer and will bind to the repressor, removing it from the operator and allowing the operon to be expressed. Low glucose levels will lead to high levels of cAMP, which will activate the catabolite activator protein, increasing the expression of the *lac* operon even more.

12. (a) Based on the data in the table, fructose appears to have no effect on the level of transcription.

    (b) The level of transcription is higher when lysine is absent and lower when lysine is present. Therefore, lysine has a negative effect on the level of transcription.

    (c) This operon is more likely repressible.

(d) Repressible operons have a lower level of expression when the corepressor is present. Since the presence of lysine decreases the level of expression of the operon, it is more likely that the operon is repressible.

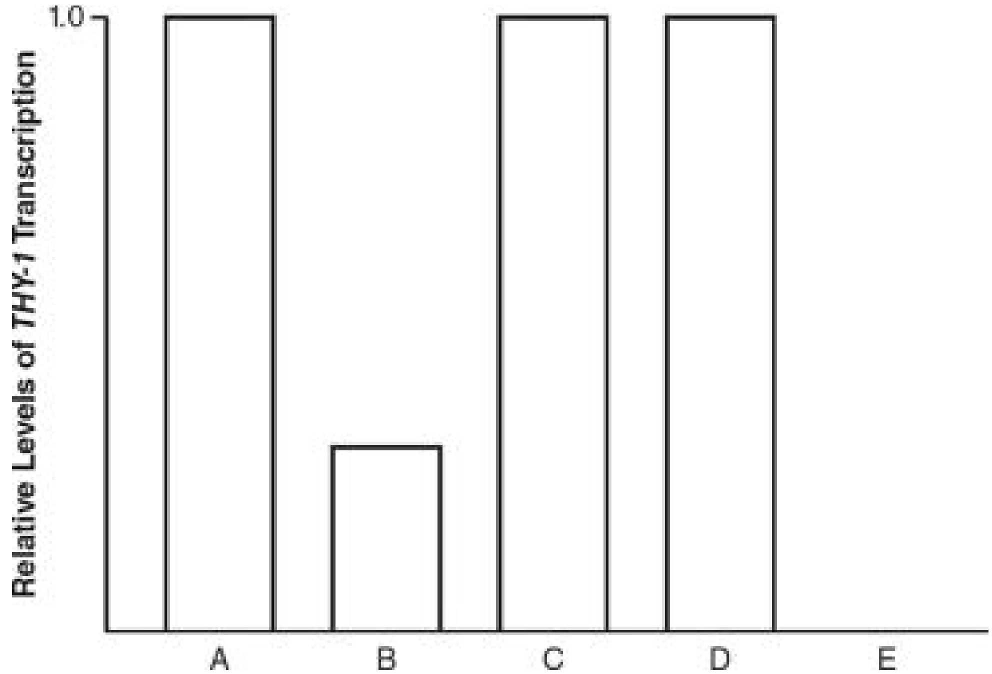
Long Free-Response

13. (a) Enhancer sequences function as binding sites for activator proteins or transcription factors. When an activator or transcription factor binds to an enhancer site, more transcription of the gene occurs.

(b) DNA sequence A is the control because none of the sequences are deleted.

(c) Sequence 1 is most likely the enhancer sequence because the relative levels of *THY-1* gene transcription are lower when sequence 1 is deleted than when sequence 2 or sequence 3 is deleted.

(d) Promoters serve as binding sites for RNA polymerase. If RNA polymerase cannot bind, transcription cannot occur. If P were deleted, no transcription of *THY-1* would occur, as shown in the following figure.



1.0
Relative Levels of THY-1 Transcription
A
B
C
D
E