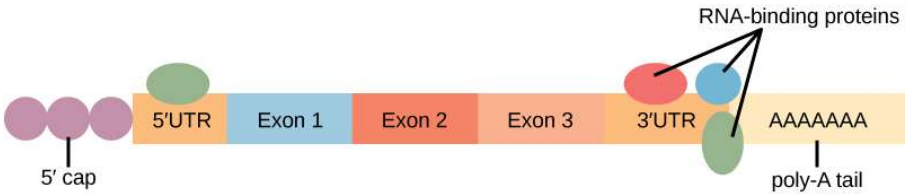



**Figure 16.13** The protein-coding region of mRNA is flanked by 5' and 3' untranslated regions (UTRs). The presence of RNA-binding proteins at the 5' or 3' UTR influences the stability of the RNA molecule.

### *RNA Stability and microRNAs*

In addition to RBPs that bind to and control (increase or decrease) RNA stability, other elements called microRNAs can bind to the RNA molecule. These **microRNAs**, or miRNAs, are short RNA molecules that are only 21–24 nucleotides in length. The miRNAs are made in the nucleus as longer pre-miRNAs. These pre-miRNAs are chopped into mature miRNAs by a protein called **dicer**. Like transcription factors and RBPs, mature miRNAs recognize a specific sequence and bind to the RNA; however, miRNAs also associate with a ribonucleoprotein complex called the **RNA-induced silencing complex (RISC)**. RISC binds along with the miRNA to degrade the target mRNA. Together, miRNAs and the RISC complex rapidly destroy the RNA molecule.

# 16.6 | Eukaryotic Translational and Post-translational Gene Regulation

In this section, you will explore the following question:

- What are different ways in which translational and post-translational control of gene expression take place?

## Connection for AP® Courses

Changing the status of the RNA or the protein itself can affect the amount of protein produced, the function of the protein, or how long the protein resides in the cell. Modifications such as phosphorylation and environmental stimuli can affect the stability and function of the protein.

Information presented and the examples highlighted in the section support concepts outlined in Big Idea 4 of the AP® Biology Curriculum Framework. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

| | |
|---|---|
| **Big Idea 4** | Biological systems interact, and these systems and their interactions possess complex properties. |
| **Enduring Understanding 4.A** | Interactions within biological systems lead to complex properties. |
| **Essential Knowledge** | **4.A.3** Interactions between external stimuli and regulated gene expression result in specialization of cells, tissues and organs. |
| **Science Practice** | **1.3** The student can refine representations and models of natural or man-made phenomena and systems in the domain. |
| **Learning Objective** | **4.7** The student is able to refine representations to illustrate how interactions between external stimuli and gene expression result in specialization of cells, tissues, and organs. |

After the RNA has been transported to the cytoplasm, it is translated into protein. Control of this process is largely dependent on the RNA molecule. As previously discussed, the stability of the RNA will have a large impact on its translation into a protein. As the stability changes, the amount of time that it is available for translation also changes.

## The Initiation Complex and Translation Rate

Like transcription, translation is controlled by proteins that bind and initiate the process. In translation, the complex that assembles to start the process is referred to as the **initiation complex**. The first protein to bind to the RNA to initiate translation is the **eukaryotic initiation factor-2 (eIF-2)**. The eIF-2 protein is active when it binds to the high-energy molecule **guanosine triphosphate (GTP)**. GTP provides the energy to start the reaction by giving up a phosphate and becoming **guanosine diphosphate (GDP)**. The eIF-2 protein bound to GTP binds to the small **40S ribosomal subunit**. When bound, the methionine initiator tRNA associates with the eIF-2/40S ribosome complex, bringing along with it the mRNA to be translated. At this point, when the initiator complex is assembled, the GTP is converted into GDP and energy is released. The phosphate and the eIF-2 protein are released from the complex and the large **60S ribosomal subunit** binds to translate the RNA. The binding of eIF-2 to the RNA is controlled by phosphorylation. If eIF-2 is phosphorylated, it undergoes a conformational change and cannot bind to GTP. Therefore, the initiation complex cannot form properly and translation is impeded (Figure 16.14). When eIF-2 remains unphosphorylated, it binds the RNA and actively translates the protein.

visual CONNECTION

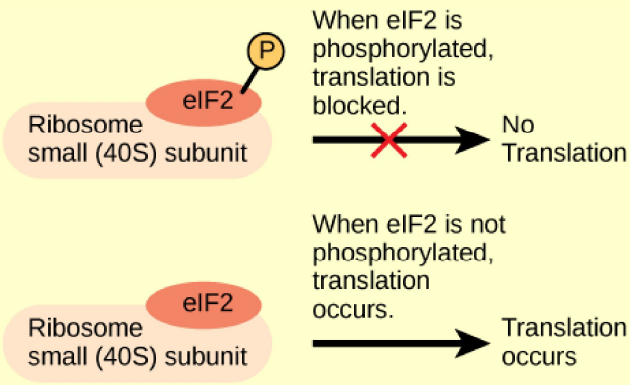



**Figure 16.14** Gene expression can be controlled by factors that bind the translation initiation complex.

An increase in phosphorylation levels of eIF-2 has been observed in patients with neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's. What impact do you think this might have on protein synthesis?

a. It will increase the rate of translation.
b. It will not affect the translation process.
c. It will block the translation of certain proteins.
d. It will produce multiple fragments of polypeptides.

## Chemical Modifications, Protein Activity, and Longevity

Proteins can be chemically modified with the addition of groups including methyl, phosphate, acetyl, and ubiquitin groups. The addition or removal of these groups from proteins regulates their activity or the length of time they exist in the cell. Sometimes these modifications can regulate where a protein is found in the cell—for example, in the nucleus, the cytoplasm, or attached to the plasma membrane.

Chemical modifications occur in response to external stimuli such as stress, the lack of nutrients, heat, or ultraviolet light exposure. These changes can alter epigenetic accessibility, transcription, mRNA stability, or translation—all resulting in changes in expression of various genes. This is an efficient way for the cell to rapidly change the levels of specific proteins in response to the environment. Because proteins are involved in every stage of gene regulation, the phosphorylation of a protein (depending on the protein that is modified) can alter accessibility to the chromosome, can alter translation (by altering transcription factor binding or function), can change nuclear shuttling (by influencing modifications to the nuclear pore complex), can alter RNA stability (by binding or not binding to the RNA to regulate its stability), can modify translation (increase or decrease), or can change post-translational modifications (add or remove phosphates or other chemical modifications).

The addition of an ubiquitin group to a protein marks that protein for degradation. Ubiquitin acts like a flag indicating that the protein lifespan is complete. These proteins are moved to the **proteasome**, an organelle that functions to remove proteins, to be degraded (Figure 16.15). One way to control gene expression, therefore, is to alter the longevity of the protein.

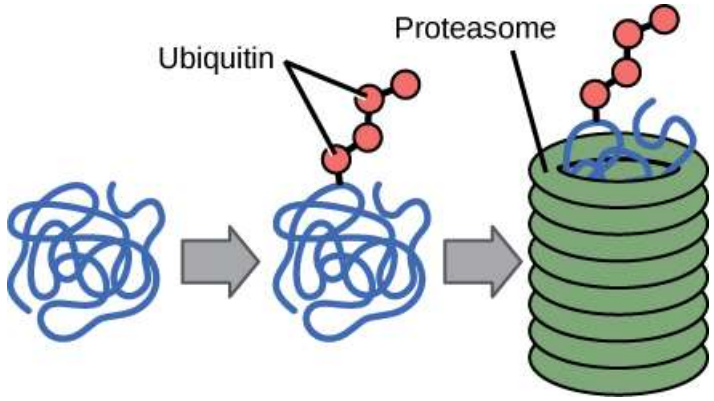



**Figure 16.15** Proteins with ubiquitin tags are marked for degradation within the proteasome.

science practices CONNECTION for AP® Courses

### Think About It

How can environmental stimuli such as ultraviolet light exposure or nutrient deficiency modify gene expression?

# 16.7 | Cancer and Gene Regulation

In this section, you will explore the following questions:

- How can changes in gene expression cause cancer?
- How can changes to gene expression at different levels disrupt the cell cycle?

## Connection for AP® Courses

Cancer is a disease of altered gene expression that can occur at every level of control, including at the levels of DNA methylation, histone acetylation, and activation of transcription factors. By understanding how each stage of gene regulation works in normal cells, we can understand what goes wrong in diseased states. For example, changes in the activity of the tumor suppressor gene *p53* can result in cancer. Phosphorylation and other protein modifications have also been implicated in cancer.

Information presented and the examples highlighted in the section support concepts outlined in Big Idea 3 of the AP® Biology Curriculum Framework. The learning objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

| | |
|---|---|
| **Big Idea 3** | Living systems store, retrieve, transmit and respond to information essential to life processes. |
| **Enduring Understanding 3.B** | Expression of genetic information involves cellular and molecular mechanisms. |

| | |
|---|---|
| **Essential Knowledge** | **3.B.2** A variety of intercellular and intracellular signal transmissions mediate gene expression. |
| **Science Practice** | **6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices. |
| **Learning Objective** | **3.22** The student is able to explain how signal pathways mediate gene expression, including how this process can affect protein production. |
| **Essential Knowledge** | **3.B.2** A variety of intercellular and intracellular signal transmissions mediate gene expression. |
| **Science Practice** | **1.4** The student can use representations and models to analyze situations or solve problems qualitatively and quantitatively. |
| **Learning Objective** | **3.23** The student can use representations to describe mechanisms of the regulation of gene expression. |

Cancer is not a single disease but includes many different diseases. In cancer cells, mutations modify cell-cycle control and cells don't stop growing as they normally would. Mutations can also alter the growth rate or the progression of the cell through the cell cycle. One example of a gene modification that alters the growth rate is increased phosphorylation of cyclin B, a protein that controls the progression of a cell through the cell cycle and serves as a cell-cycle checkpoint protein.

For cells to move through each phase of the cell cycle, the cell must pass through checkpoints. This ensures that the cell has properly completed the step and has not encountered any mutation that will alter its function. Many proteins, including cyclin B, control these checkpoints. The phosphorylation of cyclin B, a post-translational event, alters its function. As a result, cells can progress through the cell cycle unimpeded, even if mutations exist in the cell and its growth should be terminated. This post-translational change of cyclin B prevents it from controlling the cell cycle and contributes to the development of cancer.

## Cancer: Disease of Altered Gene Expression

Cancer can be described as a disease of altered gene expression. There are many proteins that are turned on or off (gene activation or gene silencing) that dramatically alter the overall activity of the cell. A gene that is not normally expressed in that cell can be switched on and expressed at high levels. This can be the result of gene mutation or changes in gene regulation (epigenetic, transcription, post-transcription, translation, or post-translation).

Changes in epigenetic regulation, transcription, RNA stability, protein translation, and post-translational control can be detected in cancer. While these changes don't occur simultaneously in one cancer, changes at each of these levels can be detected when observing cancer at different sites in different individuals. Therefore, changes in **histone acetylation** (epigenetic modification that leads to gene silencing), activation of transcription factors by phosphorylation, increased RNA stability, increased translational control, and protein modification can all be detected at some point in various cancer cells. Scientists are working to understand the common changes that give rise to certain types of cancer or how a modification might be exploited to destroy a tumor cell.

### *Tumor Suppressor Genes, Oncogenes, and Cancer*

In normal cells, some genes function to prevent excess, inappropriate cell growth. These are tumor suppressor genes, which are active in normal cells to prevent uncontrolled cell growth. There are many tumor suppressor genes in cells. The most studied tumor suppressor gene is p53, which is mutated in over 50 percent of all cancer types. The p53 protein itself functions as a transcription factor. It can bind to sites in the promoters of genes to initiate transcription. Therefore, the mutation of p53 in cancer will dramatically alter the transcriptional activity of its target genes.


Watch **this animation (http://openstaxcollege.org/l/p53_cancer)** to learn more about the use of p53 in fighting cancer.

Treatment of cancer is often called a "fight against biology." Explain why the use of p53 supports this statement.

a. because normal cells are often negatively affected by cancer treatments, including p53

b. because cancer cells are always affected by current cancer treatments, including p53

c. because normal cells are often negatively affected by cancer treatments, with the exception of p53

d. because cancer cells often aren't affected by cancer treatments, with the exception of p53

Proto-oncogenes are positive cell-cycle regulators. When mutated, proto-oncogenes can become oncogenes and cause cancer. Overexpression of the oncogene can lead to uncontrolled cell growth. This is because oncogenes can alter transcriptional activity, stability, or protein translation of another gene that directly or indirectly controls cell growth. An example of an oncogene involved in cancer is a protein called myc. **Myc** is a transcription factor that is aberrantly activated in Burkett's Lymphoma, a cancer of the lymph system. Overexpression of myc transforms normal B cells into cancerous cells that continue to grow uncontrollably. High B-cell numbers can result in tumors that can interfere with normal bodily function. Patients with Burkett's lymphoma can develop tumors on their jaw or in their mouth that interfere with the ability to eat.

## Cancer and Epigenetic Alterations

Silencing genes through epigenetic mechanisms is also very common in cancer cells. There are characteristic modifications to histone proteins and DNA that are associated with silenced genes. In cancer cells, the DNA in the promoter region of silenced genes is methylated on cytosine DNA residues in CpG islands. Histone proteins that surround that region lack the acetylation modification that is present when the genes are expressed in normal cells. This combination of DNA methylation and histone deacetylation (epigenetic modifications that lead to gene silencing) is commonly found in cancer. When these modifications occur, the gene present in that chromosomal region is silenced. Increasingly, scientists understand how epigenetic changes are altered in cancer. Because these changes are temporary and can be reversed—for example, by preventing the action of the histone deacetylase protein that removes acetyl groups, or by DNA methyl transferase enzymes that add methyl groups to cytosines in DNA—it is possible to design new drugs and new therapies to take advantage of the reversible nature of these processes. Indeed, many researchers are testing how a silenced gene can be switched back on in a cancer cell to help re-establish normal growth patterns.

Genes involved in the development of many other illnesses, ranging from allergies to inflammation to autism, are thought to be regulated by epigenetic mechanisms. As our knowledge of how genes are controlled deepens, new ways to treat diseases like cancer will emerge.

## Cancer and Transcriptional Control

Alterations in cells that give rise to cancer can affect the transcriptional control of gene expression. Mutations that activate transcription factors, such as increased phosphorylation, can increase the binding of a transcription factor to its binding site in a promoter. This could lead to increased transcriptional activation of that gene that results in modified cell growth. Alternatively, a mutation in the DNA of a promoter or enhancer region can increase the binding ability of a transcription factor. This could also lead to the increased transcription and aberrant gene expression that is seen in cancer cells.

Researchers have been investigating how to control the transcriptional activation of gene expression in cancer. Identifying how a transcription factor binds, or a pathway that activates where a gene can be turned off, has led to new drugs and new ways to treat cancer. In breast cancer, for example, many proteins are overexpressed. This can lead to increased phosphorylation of key transcription factors that increase transcription. One such example is the overexpression of the epidermal growth factor receptor (EGFR) in a subset of breast cancers. The EGFR pathway activates many protein kinases that, in turn, activate many transcription factors that control genes involved in cell growth. New drugs that prevent the

activation of EGFR have been developed and are used to treat these cancers.

## Cancer and Post-transcriptional Control

Changes in the post-transcriptional control of a gene can also result in cancer. Recently, several groups of researchers have shown that specific cancers have altered expression of miRNAs. Because miRNAs bind to the 3' UTR of RNA molecules to degrade them, overexpression of these miRNAs could be detrimental to normal cellular activity. Too many miRNAs could dramatically decrease the RNA population leading to a decrease in protein expression. Several studies have demonstrated a change in the miRNA population in specific cancer types. It appears that the subset of miRNAs expressed in breast cancer cells is quite different from the subset expressed in lung cancer cells or even from normal breast cells. This suggests that alterations in miRNA activity can contribute to the growth of breast cancer cells. These types of studies also suggest that if some miRNAs are specifically expressed only in cancer cells, they could be potential drug targets. It would, therefore, be conceivable that new drugs that turn off miRNA expression in cancer could be an effective method to treat cancer.

## Cancer and Translational/Post-translational Control

There are many examples of how translational or post-translational modifications of proteins arise in cancer. Modifications are found in cancer cells from the increased translation of a protein to changes in protein phosphorylation to alternative splice variants of a protein. An example of how the expression of an alternative form of a protein can have dramatically different outcomes is seen in colon cancer cells. The c-Flip protein, a protein involved in mediating the cell death pathway, comes in two forms: long (c-FLIPL) and short (c-FLIPS). Both forms appear to be involved in initiating controlled cell death mechanisms in normal cells. However, in colon cancer cells, expression of the long form results in increased cell growth instead of cell death. Clearly, the expression of the wrong protein dramatically alters cell function and contributes to the development of cancer.

## New Drugs to Combat Cancer: Targeted Therapies

Scientists are using what is known about the regulation of gene expression in disease states, including cancer, to develop new ways to treat and prevent disease development. Many scientists are designing drugs on the basis of the gene expression patterns within individual tumors. This idea, that therapy and medicines can be tailored to an individual, has given rise to the field of personalized medicine. With an increased understanding of gene regulation and gene function, medicines can be designed to specifically target diseased cells without harming healthy cells. Some new medicines, called targeted therapies, have exploited the overexpression of a specific protein or the mutation of a gene to develop a new medication to treat disease. One such example is the use of anti-EGF receptor medications to treat the subset of breast cancer tumors that have very high levels of the EGF protein. Undoubtedly, more targeted therapies will be developed as scientists learn more about how gene expression changes can cause cancer.

career CONNECTION

### Clinical Trial Coordinator

A clinical trial coordinator is the person managing the proceedings of the clinical trial. This job includes coordinating patient schedules and appointments, maintaining detailed notes, building the database to track patients (especially for long-term follow-up studies), ensuring proper documentation has been acquired and accepted, and working with the nurses and doctors to facilitate the trial and publication of the results. A clinical trial coordinator may have a science background, like a nursing degree, or other certification. People who have worked in science labs or in clinical offices are also qualified to become a clinical trial coordinator. These jobs are generally in hospitals; however, some clinics and doctor's offices also conduct clinical trials and may hire a coordinator.

science practices CONNECTION for AP® Courses

## Think About It

New drugs are being developed that decrease DNA methylation and prevent the removal of acetyl groups from histone proteins. Explain how these drugs could affect gene expression to help kill tumor cells.

How can understanding the gene expression in a cancer cell tell you something about that specific form of cancer?

## KEY TERMS

**3' UTR** 3' untranslated region; region just downstream of the protein-coding region in an RNA molecule that is not translated

**5' cap** a methylated guanosine triphosphate (GTP) molecule that is attached to the 5' end of a messenger RNA to protect the end from degradation

**5' UTR** 5' untranslated region; region just upstream of the protein-coding region in an RNA molecule that is not translated

**activator** protein that binds to prokaryotic operators to increase transcription

**catabolite activator protein (CAP)** protein that complexes with cAMP to bind to the promoter sequences of operons that control sugar processing when glucose is not available

***cis*-acting element** transcription factor binding sites within the promoter that regulate the transcription of a gene adjacent to it

**dicer** enzyme that chops the pre-miRNA into the mature form of the miRNA

**DNA methylation** epigenetic modification that leads to gene silencing; commonly found in cancer cells

**enhancer** segment of DNA that is upstream, downstream, perhaps thousands of nucleotides away, or on another chromosome that influence the transcription of a specific gene

**epigenetic** heritable changes that do not involve changes in the DNA sequence

**eukaryotic initiation factor-2 (eIF-2)** protein that binds first to an mRNA to initiate translation

**gene expression** processes that control the turning on or turning off of a gene

**guanine diphosphate (GDP)** molecule that is left after the energy is used to start translation

**guanine triphosphate (GTP)** energy-providing molecule that binds to eIF-2 and is needed for translation

**histone acetylation** epigenetic modification that leads to gene silencing; commonly found in cancer cells.

**inducible operon** operon that can be activated or repressed depending on cellular needs and the surrounding environment

**initiation complex** protein complex containing eIF2-2 that starts translation

**lac operon** operon in prokaryotic cells that encodes genes required for processing and intake of lactose

**large 60S ribosomal subunit** second, larger ribosomal subunit that binds to the RNA to translate it into protein

**microRNA (miRNA)** small RNA molecules (approximately 21 nucleotides in length) that bind to RNA molecules to degrade them

**myc** oncogene that causes cancer in many cancer cells

**negative regulator** protein that prevents transcription

**operator** region of DNA outside of the promoter region that binds activators or repressors that control gene expression in prokaryotic cells

**operon** collection of genes involved in a pathway that are transcribed together as a single mRNA in prokaryotic cells

**poly-A tail** a series of adenine nucleotides that are attached to the 3' end of an mRNA to protect the end from degradation

**positive regulator** protein that increases transcription

**post-transcriptional** control of gene expression after the RNA molecule has been created but before it is translated into

protein

**post-translational** control of gene expression after a protein has been created

**proteasome** organelle that degrades proteins

**repressor** protein that binds to the operator of prokaryotic genes to prevent transcription

**RISC** protein complex that binds along with the miRNA to the RNA to degrade it

**RNA stability** how long an RNA molecule will remain intact in the cytoplasm

**RNA-binding protein (RBP)** protein that binds to the 3' or 5' UTR to increase or decrease the RNA stability

**small 40S ribosomal subunit** ribosomal subunit that binds to the RNA to translate it into protein

***trans*-acting element** transcription factor binding site found outside the promoter or on another chromosome that influences the transcription of a particular gene

**transcription factor** protein that binds to the DNA at the promoter or enhancer region and that influences transcription of a gene

**transcription factor binding site** sequence of DNA to which a transcription factor binds

**transcriptional start site** site at which transcription begins

**trp operon** series of genes necessary to synthesize tryptophan in prokaryotic cells

**tryptophan** amino acid that can be synthesized by prokaryotic cells when necessary

**untranslated region** segment of the RNA molecule that are not translated into protein. These regions lie before (upstream or 5') and after (downstream or 3') the protein-coding region

## CHAPTER SUMMARY

### 16.1 Regulation of Gene Expression

While all somatic cells within an organism contain the same DNA, not all cells within that organism express the same proteins. Prokaryotic organisms express the entire DNA they encode in every cell, but not necessarily all at the same time. Proteins are expressed only when they are needed. Eukaryotic organisms express a subset of the DNA that is encoded in any given cell. In each cell type, the type and amount of protein is regulated by controlling gene expression. To express a protein, the DNA is first transcribed into RNA, which is then translated into proteins. In prokaryotic cells, these processes occur almost simultaneously. In eukaryotic cells, transcription occurs in the nucleus and is separate from the translation that occurs in the cytoplasm. Gene expression in prokaryotes is mostly regulated at the transcriptional level, whereas in eukaryotic cells, gene expression is regulated at the epigenetic, transcriptional, post-transcriptional, translational, and post-translational levels.

### 16.2 Prokaryotic Gene Regulation

The regulation of gene expression in prokaryotic cells occurs at the transcriptional level. There are three ways to control the transcription of an operon: repressive control, activator control, and inducible control. Repressive control, typified by the *trp* operon, uses proteins bound to the operator sequence to physically prevent the binding of RNA polymerase and the activation of transcription. Therefore, if tryptophan is not needed, the repressor is bound to the operator and transcription remains off. Activator control, typified by the action of CAP, increases the binding ability of RNA polymerase to the promoter when CAP is bound. In this case, low levels of glucose result in the binding of cAMP to CAP. CAP then binds the promoter, which allows RNA polymerase to bind to the promoter better. In the last example—the *lac* operon—two conditions must be met to initiate transcription. Glucose must not be present, and lactose must be available for the *lac* operon to be transcribed. If glucose is absent, CAP binds to the operator. If lactose is present, the repressor protein does not bind to its operator. Only when both conditions are met will RNA polymerase bind to the promoter to induce transcription.

### 16.3 Eukaryotic Epigenetic Gene Regulation

In eukaryotic cells, the first stage of gene expression control occurs at the epigenetic level. Epigenetic mechanisms control access to the chromosomal region to allow genes to be turned on or off. These mechanisms control how DNA is packed into the nucleus by regulating how tightly the DNA is wound around histone proteins. The addition or removal of chemical modifications (or flags) to histone proteins or DNA signals to the cell to open or close a chromosomal region. Therefore, eukaryotic cells can control whether a gene is expressed by controlling accessibility to transcription factors and the binding of RNA polymerase to initiate transcription.

### 16.4 Eukaryotic Transcriptional Gene Regulation

To start transcription, general transcription factors, such as TFIID, TFIIH, and others, must first bind to the TATA box and recruit RNA polymerase to that location. The binding of additional regulatory transcription factors to *cis*-acting elements will either increase or prevent transcription. In addition to promoter sequences, enhancer regions help augment transcription. Enhancers can be upstream, downstream, within a gene itself, or on other chromosomes. Transcription factors bind to enhancer regions to increase or prevent transcription.

### 16.5 Eukaryotic Post-transcriptional Gene Regulation

Post-transcriptional control can occur at any stage after transcription, including RNA splicing, nuclear shuttling, and RNA stability. Once RNA is transcribed, it must be processed to create a mature RNA that is ready to be translated. This involves the removal of introns that do not code for protein. Spliceosomes bind to the signals that mark the exon/intron border to remove the introns and ligate the exons together. Once this occurs, the RNA is mature and can be translated. RNA is created and spliced in the nucleus, but needs to be transported to the cytoplasm to be translated. RNA is transported to the cytoplasm through the nuclear pore complex. Once the RNA is in the cytoplasm, the length of time it resides there before being degraded, called RNA stability, can also be altered to control the overall amount of protein that is synthesized. The RNA stability can be increased, leading to longer residency time in the cytoplasm, or decreased, leading to shortened time and less protein synthesis. RNA stability is controlled by RNA-binding proteins (RPBs) and microRNAs (miRNAs). These RPBs and miRNAs bind to the 5' UTR or the 3' UTR of the RNA to increase or decrease RNA stability. Depending on the RBP, the stability can be increased or decreased significantly; however, miRNAs always decrease stability and promote decay.

### 16.6 Eukaryotic Translational and Post-translational Gene Regulation

Changing the status of the RNA or the protein itself can affect the amount of protein, the function of the protein, or how long it is found in the cell. To translate the protein, a protein initiator complex must assemble on the RNA. Modifications (such as phosphorylation) of proteins in this complex can prevent proper translation from occurring. Once a protein has been synthesized, it can be modified (phosphorylated, acetylated, methylated, or ubiquitinated). These post-translational modifications can greatly impact the stability, degradation, or function of the protein.

### 16.7 Cancer and Gene Regulation

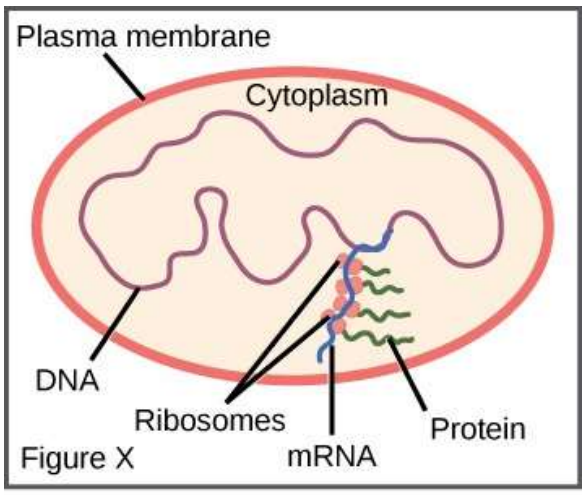
Cancer can be described as a disease of altered gene expression. Changes at every level of eukaryotic gene expression can be detected in some form of cancer at some point in time. In order to understand how changes to gene expression can cause cancer, it is critical to understand how each stage of gene regulation works in normal cells. By understanding the mechanisms of control in normal, non-diseased cells, it will be easier for scientists to understand what goes wrong in disease states including complex ones like cancer.

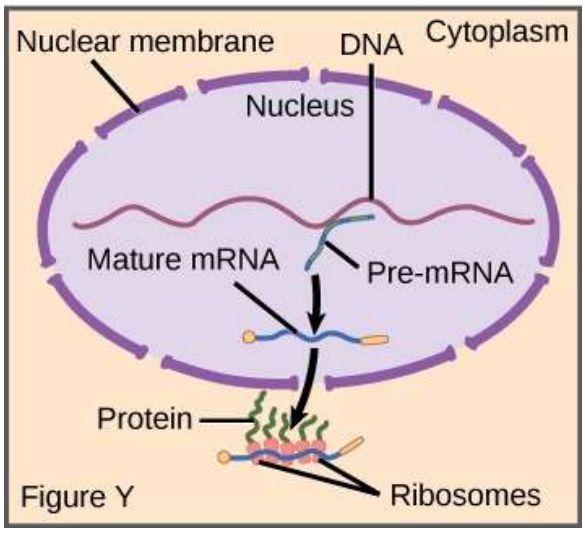
## REVIEW QUESTIONS

**1.** Control of gene expression in eukaryotic cells occurs at which level(s)?

a. only the transcriptional level
b. epigenetic and transcriptional levels
c. epigenetic and transcriptional and translational levels
d. epigenetic and transcriptional, translational, and post-translational levels

**2.**




What do figures X and Y in the graphic illustrate?

a. Transcription and translation in a eukaryotic cell (figure X) and a prokaryotic cell (figure Y).

b. Transcription and translation in a prokaryotic cell (figure X) and a eukaryotic cell (figure Y).

c. Transcription in a eukaryotic cell (figure X) and translation in a prokaryotic cell (figure Y).

d. Transcription in a prokaryotic cell (figure X) and translation in a eukaryotic cell (figure Y)

**3.** If glucose is absent but lactose is present, the *lac* operon will be:

a. activated

b. repressed

c. partially activated

d. mutated

**4.** What would happen if the operator sequence of the *lac* operon contained a mutation that prevented the repressor protein from binding the operator?

a. In the presence of lactose, the lac operon will not be transcribed.

b. In the absence of lactose, the lac operon will be transcribed.

c. The cAMP-CAP complex will not increase RNA synthesis.

d. The RNA polymerase will not bind the promoter.

**5.** What would happen if the operator sequence of the *trp* operon contained a mutation that prevented the repressor protein from binding to the operator?

a. In the absence of tryptophan, the genes trpA-E will not be transcribed.

b. In the absence of tryptophan, only genes trpE and trpD will be transcribed.

c. In the presence of tryptophan, the genes trpA-E will be transcribed.

d. In the presence of tryptophan, the trpE gene will not be transcribed.

**6.** What are epigenetic modifications?

a. the addition of reversible changes to histone proteins and DNA

b. the removal of nucleosomes from the DNA

c. the addition of more nucleosomes to the DNA

d. mutation of the DNA sequence

**7.** Which of the following statements about epigenetic regulation is false?

a. Histone protein charge becomes more positive when acetyl groups are added.

b. DNA molecules are modified within CpG islands.

c. Methylation of DNA and histones causes nucleosomes to pack tightly together.

d. Histone acetylation results in the loose packing of nucleosomes.

**8.** Which of the following is true of epigenetic changes?

a. They only allow gene expression.

b. They allow movement of histones.

c. They change the DNA sequence.

d. They are always heritable.

**9.** The binding of what is required for transcription start?

a. a protein

b. DNA polymerase

c. RNA polymerase

d. a transcription factor

**10.** What would be the outcome of a mutation that prevented DNA binding proteins from being produced?

a. decreased transcription because transcription factors would not bind to transcription binding sites
b. decreased transcription because enhancers would not be able to bind to transcription factors
c. increased transcription because repressors would not be able to bind to promoter regions
d. increased transcription because RNA polymerase would be able to increase binding to promoter regions

**11.** What will result from the binding of a transcription factor to an enhancer region?

a. decreased transcription of an adjacent gene
b. increased transcription of a distant gene
c. alteration of the translation of an adjacent gene
d. initiation of the recruitment of RNA polymerase

**12.** Which of the following are involved in post-transcriptional control?

a. control of RNA splicing
b. ubiquitination
c. proteolytic cleavage
d. phosphorylation

**13.** Gene A is thought to be associated with color blindness. The protein corresponding to gene A is isolated. Analysis of the protein recovered shows there are actually two different proteins that differ in molecular weight that correspond to gene A. What is one reason why there may be two proteins corresponding to the gene?

a. One protein had a 5’ cap and a poly-A tail in its mRNA, and the other protein did not.
b. One protein had a 5’ UTR and a 3’ UTR in its RNA, and the other protein did not.
c. The gene was alternatively spliced.
d. The gene produced mRNA molecules with differing stability.

**14.** Binding of an RNA binding protein will change the stability of the RNA molecule in what way?

a. increase
b. decrease
c. neither increase nor decrease
d. either increase or decrease

**15.** A mutation in the 5’UTR that prevents any proteins from binding to the region will:

a. increase or decrease the stability of the RNA molecule
b. prevent translation of the RNA molecule
c. prevent splicing of the RNA molecule
d. increase or decrease the length of the poly-A tail

**16.** Post-translational modifications of proteins can affect which of the following?

a. mRNA splicing
b. 5’capping
c. 3’polyadenylation
d. chemical modifications

**17.** A mutation is found in eIF-2 that impairs the initiation of translation. The mutation could affect all but one of the following functions of eIF-2. Which one would not be affected?

a. The mutation prevents eIF-2 from binding to RNA.
b. The mutation prevents eIF-2 from being phosphorylated.
c. The mutation prevents eIF-2 from binding to GTP.
d. The mutation prevents eIF-2 from binding to the 40S ribosomal subunit.

**18.** The addition of a ubiquitin group to a protein does what?

a. increases the stability of the protein
b. decreases translation of the protein
c. increases translation of the protein
d. marks the protein for degradation

**19.** What are cancer-causing genes called?

a. transformation genes
b. tumor suppressor genes
c. oncogenes
d. protooncogenes

**20.** Targeted therapies are used in patients with a certain gene expression pattern. A targeted therapy that prevents the activation of the estrogen receptor in breast cancer would be beneficial to what type of patient?

a. patients who express the EGFR receptor in normal cells
b. patients with a mutation that inactivates the estrogen receptor
c. patients with over-expression of ER alpha in their tumor cells
d. patients with over-expression of VEGF, which helps in tumor angiogenesis

**21.** In a new cancer treatment, a cold virus is genetically

modified so that it binds to, enters, and is replicated in cells, causing them to burst. The modified cold virus cannot replicate when wildtype p53 protein is present in the cell. How does this treatment treat cancer without harming healthy cells?

a. The modified virus only infects and enters cancer cells.
b. The modified virus replicates in normal and cancer cells.
c. The modified virus only infects and enters normal cells.
d. The modified virus replicates only in cancer cells.

**22.** A drug designed to switch silenced genes back on in cancer cells would result in what?

a. prevent methylation of DNA and deacetylation of histones
b. prevent methylation of DNA and acetylation of histones
c. prevent deacetylation of DNA and methylation of histones
d. prevent acetylation of DNA and demethylation of histones

**23.** What are positive cell-cycle regulators that can cause cancer when mutated called?

a. transformation genes
b. tumor suppressor genes
c. oncogenes
d. mutated genes

## CRITICAL THINKING QUESTIONS

**24.** Which best distinguishes prokaryotic and eukaryotic cells?

a. Prokaryotes possess a nucleus whereas eukaryotes do not, but eukaryotes show greater compartmentalization that allows for greater regulation of gene expression.
b. Eukaryotic cells contain a nucleus whereas prokaryotes do not, and eukaryotes show greater compartmentalization that allows for greater regulation of gene expression.
c. Prokaryotic cells are less complex and perform highly-regulated gene expression whereas eukaryotes perform less-regulated gene expression.
d. Eukaryotic cells are more complex and perform less-regulated gene expression whereas prokaryotic cells perform highly-regulated gene expression.

**25.** Which statement is correct regarding the distinction between prokaryotic and eukaryotic gene expression?

a. Prokaryotes regulate gene expression at the level of transcription whereas eukaryotes regulate at multiple levels including epigenetic, transcriptional and translational.
b. Prokaryotes regulate gene expression at the level of translation whereas eukaryotes regulate at the level of transcription to manipulate protein levels.
c. Prokaryotes regulate gene expression with the help of repressors and activators whereas eukaryotes regulate expression by degrading mRNA transcripts, thereby controlling protein levels.
d. Prokaryotes control protein levels using epigenetic modifications whereas eukaryotes control protein levels by regulating the rate of transcription and translation.

**26.** All the cells of one organisms share the genome. However, during development, some cells develop into skin cells while others develop into muscle cells. How can the same genetic instructions result in two different cell types in the same organism? Thoroughly explain your answer.

**27.** Which of the following statements describes prokaryotic transcription of the lac operon?

a. When lactose and glucose are present in the medium, transcription of the lac operon is induced.
b. When lactose is present but glucose is absent, the lac operon is repressed.
c. Lactose acts as an inducer of the lac operon when glucose is absent.
d. Lactose acts as an inducer of the lac operon when glucose is present.

**28.** The lac operon consists of regulatory regions such as the promoter as well as the structural genes lacZ, lacY, and lacA, which code for proteins involved in lactose metabolism. What would be the outcome of a mutation in one of the structural genes of the *lac* operon?

a. Mutation in structural genes will stop transcription.

b. Mutated lacY will produce an abnormal β galactosidase protein.

c. Mutated lacA will produce a protein that will transfer an acetyl group to β galactosidase.

d. Transcription will continue but lactose will not be metabolized properly.

**29.** In some diseases, alteration to epigenetic modifications turns off genes that are normally expressed. Hypothetically, how could you reverse this process to turn these genes back on?

**30.** Flowering Locus C (FLC) is a gene that is responsible for flowering in certain plants. FLC is expressed in new seedlings, which prevents flowering. Upon exposure to cold temperatures, FLC expression decreases and the plant flowers. FLC is regulated through epigenetic modifications. What type of epigenetic modifications are present in new seedlings and after cold exposure?

a. In new seedlings, histone acetylations are present; upon cold exposure, methylation occurs.

b. In new seedlings, histone deacetylations are present; upon cold exposure, methylation occurs.

c. In new seedlings, histone methylations are present; upon cold exposure, acetylation occurs.

d. In new seedlings, histone methylations are present; upon cold exposure, deacetylation occurs.

**31.** A mutation within the promoter region can alter gene transcription. Describe how this can happen.

a. Mutated promoters decrease the rate of transcription by altering the binding site for the transcription factor.

b. Mutated promoters increase the rate of transcription by altering the binding site for the transcription factor.

c. Mutated promoters alter the binding site for transcription factors to increase or decrease the rate of transcription.

d. Mutated promoters alter the binding site for transcription factors and thereby cease transcription of the adjacent gene.

**32.** What could happen if a cell had too much of an activating transcription factor present?

a. The transcription rate would increase, altering cell function.

b. The transcription rate would decrease, inhibiting cell functions.

c. The transcription rate decreases due to clogging of the transcription factors.

d. The transcription rate increases due to clogging of the transcription factors.

**33.** The *wnt* transcription pathway is responsible for key changes during animal development. Based on the transcription pathway shown below. In this diagram, arrows indicate the transformation of one substance into another. Square lines, or the lines with no arrowheads, indicate inhibition of the product below the line. Based on this, how would increased *wnt* gene expression affect the expression of Bar-1?

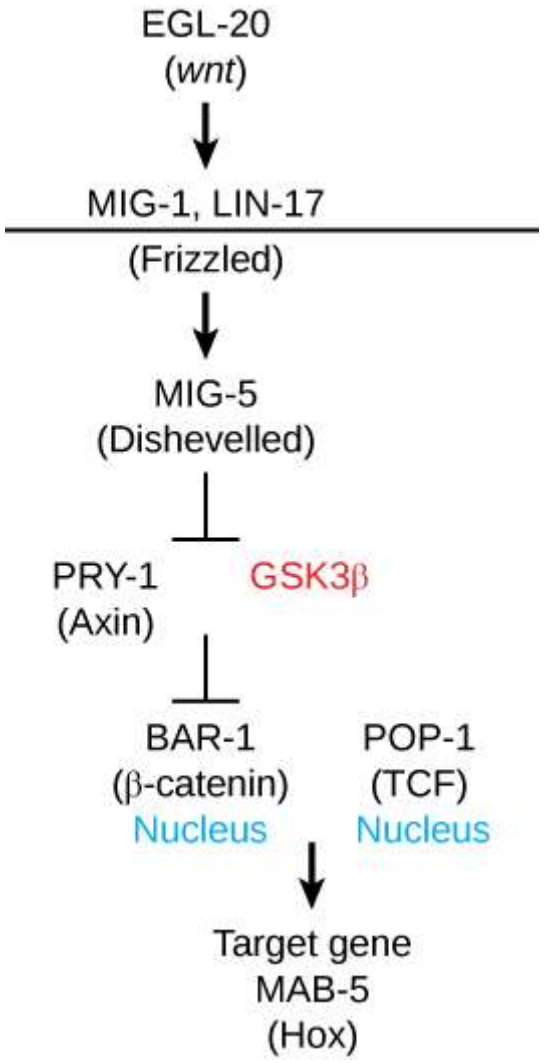



**Figure 16.16**

**34.** Describe how RBPs can prevent miRNAs from degrading an RNA molecule.

a. RBPs can bind first to the RNA, thus preventing the binding of miRNA, which degrades RNA.

b. RBPs bind the miRNA, thereby protecting the mRNA from degradation.

c. RBPs methylate miRNA to inhibit its function and thus stop mRNA degradation.

d. RBPs direct miRNA degradation with the help of a DICER protein complex.

**35.** How can external stimuli alter post-transcriptional control of gene expression?

a. UV rays can alter methylation and acetylation of proteins.

b. RNA binding proteins are modified through phosphorylation.

c. External stimuli can cause deacetylation and demethylation of the transcript.

d. UV rays can cause dimerization of the RNA binding proteins.

**36.** Protein modifications can alter gene expression in many ways. Describe how phosphorylation of proteins can alter gene expression.

a. Phosphorylation of proteins can alter translation, RNA shuttling, RNA stability or post transcriptional modification.

b. Phosphorylation of proteins can alter DNA replication, cell division, pathogen recognition and RNA stability.

c. Phosphorylated proteins affect only translation and can cause cancer by altering the p53 function.

d. Phosphorylated proteins affect only RNA shuttling, RNA stability, and post-translational modifications.

**37.** Changes in epigenetic modifications alter the accessibility and transcription of DNA. Describe how environmental stimuli, such as ultraviolet light exposure, could modify gene expression.

a. UV rays could cause methylation and deacetylation of the genes that could alter the accessibility and transcription of DNA.

b. The UV rays could cause phosphorylation and acetylation of the DNA and histones which could alter the transcriptional capabilities of the DNA.

c. UV rays could cause methylation and phosphorylation of the DNA bases which could become dimerized rendering no accessibility of DNA.

d. The UV rays can cause methylation and acetylation of histones making the DNA more tightly packed and leading to inaccessibility.

**38.** New drugs are being developed that decrease DNA methylation and prevent the removal of acetyl groups from histone proteins. Explain how these drugs could affect gene expression to help kill tumor cells.

a. These drugs maintain the demethylated and the acetylated forms of the DNA to keep transcription of necessary genes “on”.

b. The demethylated and the acetylated forms of the DNA are reversed when the silenced gene is expressed.

c. The drug methylates and acetylates the silenced genes to turn them back “on”.

d. Drugs maintain DNA methylation and acetylation to silence unimportant genes in cancer cells.

**39.** How can understanding the gene expression pattern in a cancer cell tell you something about that specific form of cancer?

a. Understanding gene expression patterns in cancer cells will identify the faulty genes, which is helpful in providing the relevant drug treatment.

b. Understanding gene expression will help diagnose tumor cells for antigen therapy.

c. Gene profiling would identify the target genes of the cancer-causing pathogens.

d. Breast cancer patients who do not express EGFR can respond to anti-EGFR therapy.

**40.** Explain what personalized medicine is and how it can be used to treat cancer.

a. Personalized medicines would vary based on the type of mutations and the gene’s expression pattern.

b. The medicines are given based on the type of tumor found in the body of an individual.

c. The personalized medicines are provided based only on the symptoms of the patient.

d. The medicines tend to vary depending on the severity and the stage of the cancer.

## TEST PREP FOR AP® COURSES

**41.** Which of the following is found in both prokaryotes and eukaryotes?

a. 3’ poly-A tails
b. 5’ caps
c. promoters
d. introns

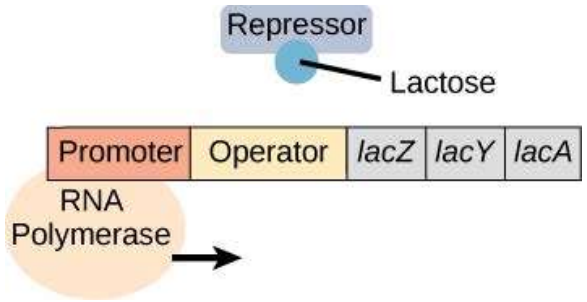
**42.** The enzyme ployadenylate polymerase catalyzes the addition of adenosine monophosphate to the 3’ ends of mRNAs to form a poly-A tail. If the enzyme were blocked so that it could not function, the result would be:

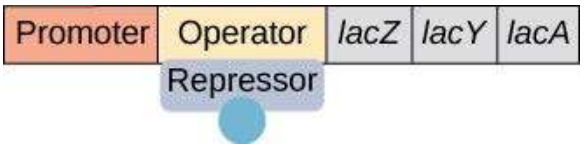
a. increased mRNA stability in eukaryotes, and decreased mRNA stability in prokaryotes
b. decreased mRNA stability in eukaryotes, and no effect in prokaryotes
c. no effect in eukaryotes, and increased mRNA stability in prokaryotes
d. no effect in eukaryotes, and decreased mRNA stability in prokaryotes

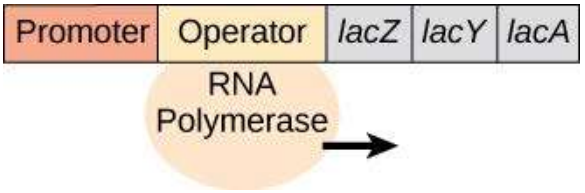
**43.** Describe two ways in which gene regulation differs and two ways in which it is similar in prokaryotes and eukaryotes.

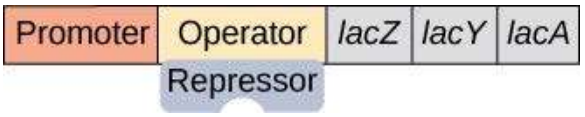
a. Prokaryotes show co-transcriptional translation whereas eukaryotes perform transcription prior to translation; in both cell types, regulation occurs through the binding of transcription factors, activators, and repressors.
b. Prokaryotes perform transcription prior to translation whereas eukaryotes show co-transcriptional translation (the processes occur in the same organelle).
c. Prokaryotes show co-transcriptional translation that is regulated prior to translation whereas eukaryotes perform transcription prior to translation that is regulated only at the level of transcription. In both domains, transcription factors, activators, and repressors provide regulation.
d. Prokaryotes show co-transcriptional translation that occurs in the nucleus whereas eukaryotes show transcription prior to translation. In both cell types, regulation occurs using transcription factors, activators, and repressors.

**44.** Lactose digestion in *E. coli* begins with its hydrolysis by the enzyme β-galactosidase. The gene encoding β-galactosidase, lacZ, is part of a coordinately regulated operon containing other genes required for lactose utilization. Which of the following figures correctly depicts the interactions at the *lac* operon when lactose is not being utilized?

a.



b.



c.



d.



**45.** What would be the result of a mutation in the repressor protein that prevented it from binding lactose?

a. The repressor will bind to lactose when it is removed from the operator.
b. The repressor will bind the operator in the presence of lactose.
c. The repressor will not bind the operator in the presence of lactose.
d. The repressor will not bind the operator in the absence of lactose.

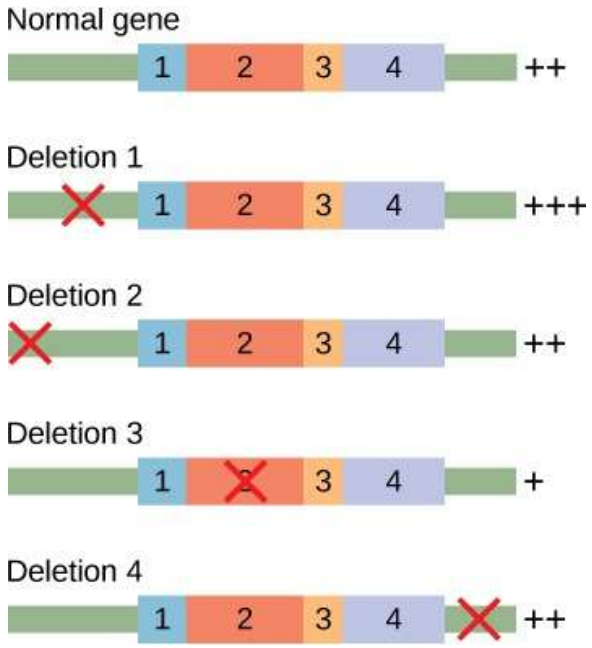
**46.** What type of modification might be observed in the GR gene in all newborn rats?

a. The DNA will have many methyl molecules.
b. The DNA will have many acetyl molecules.
c. The DNA will have few methyl groups.
d. The histones will have many acetyl groups.

**47.** What type of modification will be observed in the GR gene in the highly nurtured rats?

a. The DNA will have many methyl molecules.
b. The DNA will have many acetyl molecules.
c. The DNA will have few methyl groups.
d. The histones will have few acetyl groups.

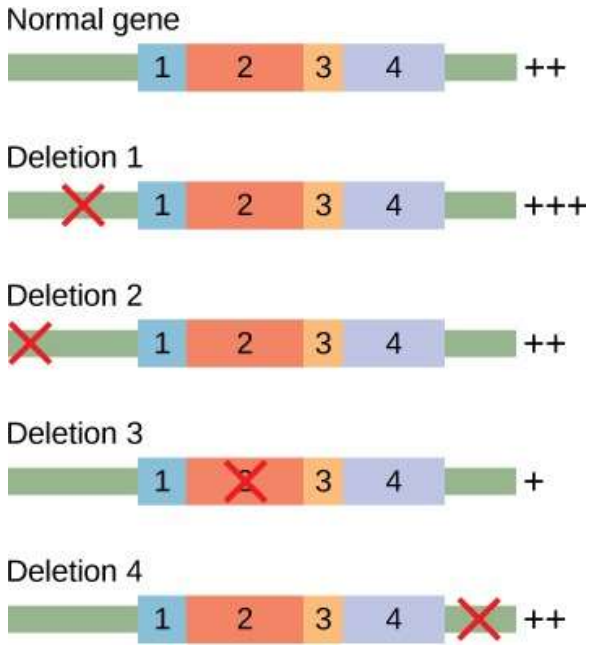
**48.**




The level of transcription of a gene is tested by creating deletions in the gene as shown in the illustration. These modified genes are tested for their level of transcription: (++) normal transcription levels; (+) low transcription levels; (+++) high transcription levels. Which deletion is in an enhancer involved in regulating the gene?

a. deletion 1
b. deletion 2
c. deletion 3
d. deletion 4

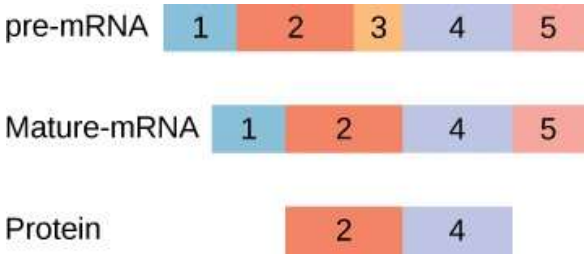
**49.**




Which deletion is in a repressor involved in regulating the gene?

a. deletion 1
b. deletion 2
c. deletion 3
d. deletion 4

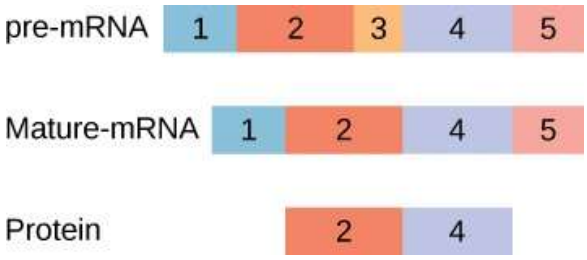
**50.**




The diagram provided shows different regions (1-5) of a pre-mRNA molecule, a mature-mRNA molecule, and the protein corresponding to the mRNA. A mutation in which region is most likely to be damaging to the cell?

a. 1
b. 2
c. 3
d. 5

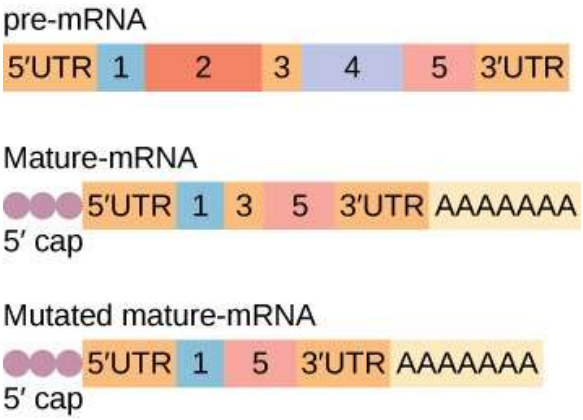
**51.**




What do regions 1 and 5 correspond to?

a. exons
b. introns
c. promoters
d. untranslated regions

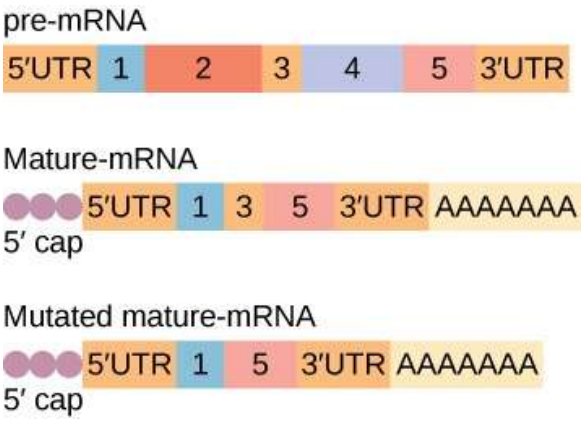
**52.**




What are regions 1 through 5 in the diagram?

a. 1, 3, and 5 are exons; 2 and 4 are introns.
b. 2 and 4 are exons; 1,3, and 5 are introns.
c. 1 and 5 are exons; 2, 3, and 4 are introns.
d. 2, 3, and 4 are exons; 1 and 5 are introns.

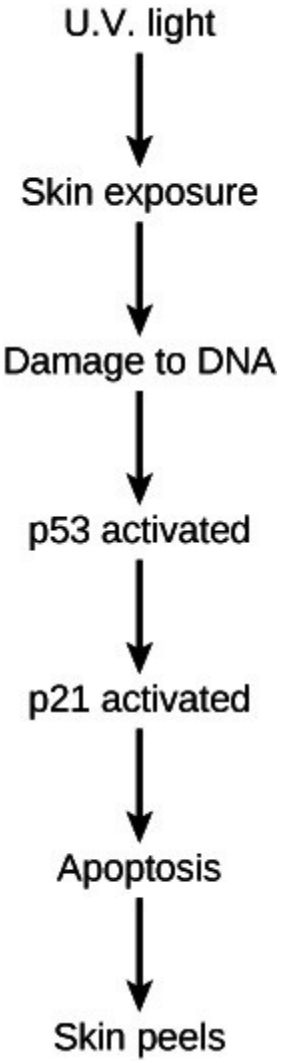
**53.**




A mutation results in the formation of the mutated mature-mRNA as indicated in the diagram. Describe what type of mutation occurred and what the likely outcome of the mutation is.

a. Mutation in the GU-AG sites of introns produced a non-functional protein.
b. A transversion mutation in the introns led to alternative splicing, producing a functional protein.
c. A transversion mutation in the GU-AG site mutated this mRNA, producing a non-functional protein.
d. Transition mutations in the introns could produce a functional protein.

**54.**




The diagram illustrates the role of p53 in response to UV exposure. What would be the result of a mutation in the p53 gene that inactivates it?

a. Skin will peel in response to UV exposure.
b. Apoptosis will occur in response to UV exposure.
c. No DNA damage will occur in response to UV exposure.
d. No peeling of skin will occur in response to UV exposure.

**55.** Which of the following will not occur in response to UV exposure if a p53 mutation inactivates the p53 protein?

1. Damage to DNA
2. p53 activation
3. p21 activation
4. Apoptosis

a. 1, 2, and 3
b. 3 and 4
c. 3
d. 2, 3, and 4

**56.**


What happens when tryptophan is present?

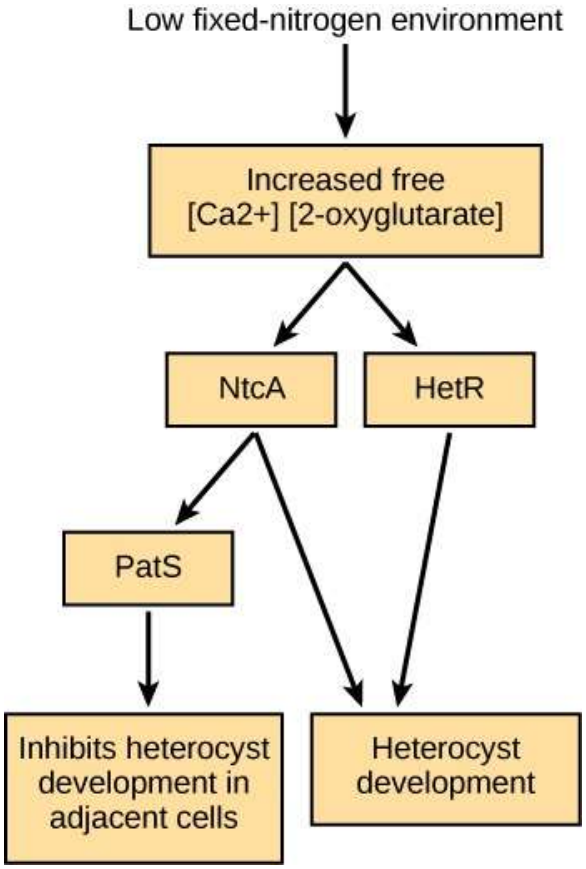
a. The repressor binds to the operator, and RNA synthesis is blocked.
b. RNA polymerase binds to the operator, and RNA synthesis is blocked.
c. Tryptophan binds to the repressor, and RNA synthesis proceeds.
d. Tryptophan binds to RNA polymerase, and RNA synthesis proceeds.

**57.**


What happens in the absence of tryptophan?

a. RNA polymerase binds to the repressor
b. the repressor binds to the promoter
c. the repressor dissociates from the operator
d. RNA polymerase dissociates from the promoter

**58.**




*Anabaena* is a simple multicellular photosynthetic cyanobacterium. In the absence of fixed nitrogen, certain newly developing cells along a filament express genes that code for nitrogen-fixing enzymes and become non-photosynthetic heterocysts. The specialization is advantageous because some nitrogen-fixing enzymes function best in the absence of oxygen. Heterocysts do not carry out photosynthesis but instead provides adjacent cells with fixed nitrogen and receives fixed carbon and reduced energy carriers in return. As shown in the diagram above, when there is low fixed nitrogen in the environment, an increase in the concentration of free calcium ions and 2-oxyglutarate stimulates the expression of genes that produce two transcription factors (NtcA and HetR) that promote the expression of genes responsible for heterocyst development. HetR also causes production of a signal, PatS, that prevents adjacent cells from developing as heterocysts. Based on your understanding of the ways in which signal transmission mediates cell function, which of the following predictions is most consistent with the information given above?

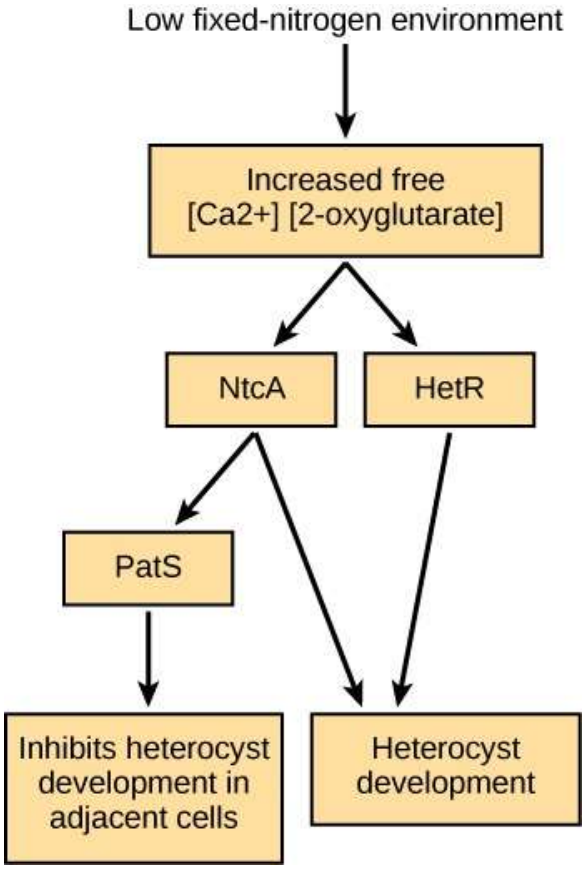
a. In an environment with low fixed nitrogen, treating the *Anabaena* cells with a calcium-binding compound should prevent heterocyst differentiation.

b. A strain that overexpresses the patS gene should develop many more heterocysts in a low nitrogen environment.

c. In an environment with abundant fixed nitrogen, free calcium levels should be high in all cells, preventing heterocysts from developing.

d. In environments with abundant fixed nitrogen, loss of the hetR gene should induce heterocyst development.

**59.**




Which of the following statements about *Anabaena* is false?

a. Decreasing the concentration of free calcium ions will prevent heterocyst development.

b. In the presence of fixed nitrogen, NtcA will not be expressed.

c. Low fixed nitrogen levels result in increased PatS levels.

d. A mutation in NtcA that makes it nonfunctional will also allow adjacent cells to develop as heterocysts.

## SCIENCE PRACTICE CHALLENGE QUESTIONS

**60.** The operon model describes expression in prokaryotes. **Describe** this model and the essential difference in the way in which expression is regulated in eukaryotes.