

Signals that Induce or Repress Transcription of the *lac* Operon

Glucose	CAP binds	Lactose	Repressor binds	Transcription
+	-	+	-	Some
-	+	-	+	No
-	+	+	-	Yes

Table 16.2



Watch an animated tutorial about the workings of *lac* operon here. (This multimedia resource will open in a browser.) (<http://cnx.org/content/m66504/1.3/#eip-id1165239273914>)

16.3 | Eukaryotic Epigenetic Gene Regulation

By the end of this section, you will be able to do the following:

- Explain how chromatin remodeling controls transcriptional access
- Describe how access to DNA is controlled by histone modification
- Describe how DNA methylation is related to epigenetic gene changes

Eukaryotic gene expression is more complex than prokaryotic gene expression because the processes of transcription and translation are physically separated. Unlike prokaryotic cells, eukaryotic cells can regulate gene expression at many different levels. Epigenetic changes are inheritable changes in gene expression that do not result from changes in the DNA sequence. Eukaryotic gene expression begins with control of access to the DNA. Transcriptional access to the DNA can be controlled in two general ways: chromatin remodeling and DNA methylation. Chromatin remodeling changes the way that DNA is associated with chromosomal histones. DNA methylation is associated with developmental changes and gene silencing.

Epigenetic Control: Regulating Access to Genes within the Chromosome

The human genome encodes over 20,000 genes, with hundreds to thousands of genes on each of the 23 human chromosomes. The DNA in the nucleus is precisely wound, folded, and compacted into chromosomes so that it will fit into the nucleus. It is also organized so that specific segments can be accessed as needed by a specific cell type.

The first level of organization, or **packing**, is the winding of DNA strands around histone proteins. Histones package and order DNA into structural units called nucleosome complexes, which can control the access of proteins to the DNA regions (Figure 16.6a). Under the electron microscope, this winding of DNA around histone proteins to form nucleosomes looks like small beads on a string (Figure 16.6b).

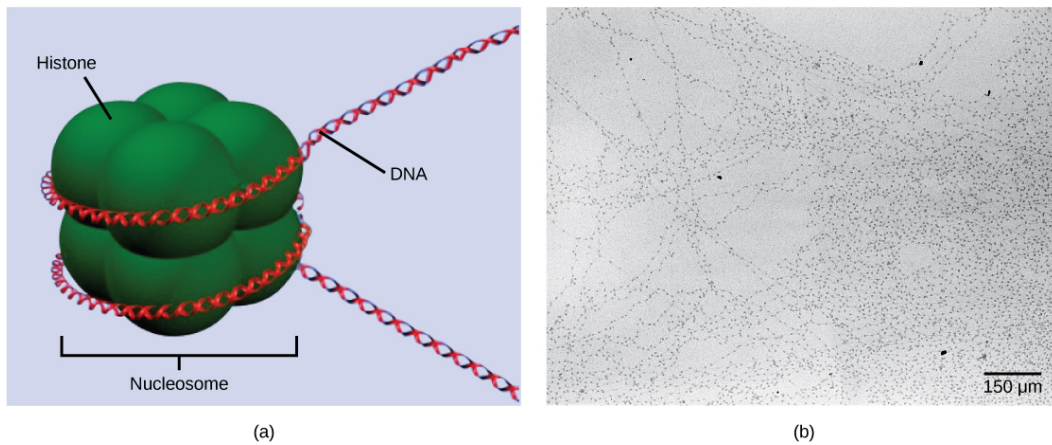


Figure 16.6 DNA is folded around histone proteins to create (a) nucleosome complexes. These nucleosomes control the access of proteins to the underlying DNA. When viewed through an electron microscope (b), the nucleosomes look like beads on a string. (credit “micrograph”: modification of work by Chris Woodcock)

These beads (histone proteins) can move along the string (DNA) to expose different sections of the molecule. If DNA encoding a specific gene is to be transcribed into RNA, the nucleosomes surrounding that region of DNA can slide down the DNA to open that specific chromosomal region and allow for the transcriptional machinery (RNA polymerase) to initiate transcription (**Figure 16.7**).

visual
CONNECTION

Methylation of DNA and histones causes nucleosomes to pack tightly together. Transcription factors cannot bind the DNA, and genes are not expressed.

Histone acetylation results in loose packing of nucleosomes. Transcription factors can bind the DNA and genes are expressed.

Figure 16.7 Nucleosomes can slide along DNA. When nucleosomes are spaced closely together (top), transcription factors cannot bind and gene expression is turned off. When the nucleosomes are spaced far apart (bottom), the DNA is exposed. Transcription factors can bind, allowing gene expression to occur. Modifications to the histones and DNA affect nucleosome spacing.

In females, one of the two X chromosomes is inactivated during embryonic development because of epigenetic changes to the chromatin. What impact do you think these changes would have on nucleosome packing?

How closely the histone proteins associate with the DNA is regulated by signals found on both the histone proteins and on the DNA. These signals are functional groups added to histone proteins or to DNA and determine whether a chromosomal region should be open or closed (**Figure 16.8** depicts modifications to histone proteins and DNA). These tags are not permanent, but may be added or removed as needed. Some chemical groups (phosphate, methyl, or acetyl groups) are attached to specific amino acids in histone "tails" at the N-terminus of the protein. These groups do not alter the DNA base sequence, but they do alter how tightly wound the DNA is around the histone proteins. DNA is a negatively charged molecule and unmodified histones are positively charged; therefore, changes in the charge of the histone will change how tightly wound the DNA molecule will be. By adding chemical modifications like acetyl groups, the charge becomes less positive, and the binding of DNA to the histones is relaxed. Altering the location of nucleosomes and the tightness of histone binding opens some regions of chromatin to transcription and closes others.

The DNA molecule itself can also be modified by methylation. DNA methylation occurs within very specific regions called CpG islands. These are stretches with a high frequency of cytosine and guanine dinucleotide DNA pairs (CG) found in the promoter regions of genes. The cytosine member of the CG pair can be methylated (a methyl group is added). Methylated genes are usually silenced, although methylation may have other regulatory effects. In some cases, genes that are silenced during the development of the gametes of one parent are transmitted in their silenced condition to the offspring. Such genes are said to be imprinted. Parental diet or other environmental conditions may also affect the methylation patterns of genes, which in turn modifies gene expression. Changes in chromatin organization interact with DNA methylation. DNA methyltransferases appear to be attracted to chromatin regions with specific histone modifications. Highly methylated (*hypermethylated*) DNA regions with deacetylated histones are tightly coiled and transcriptionally inactive.

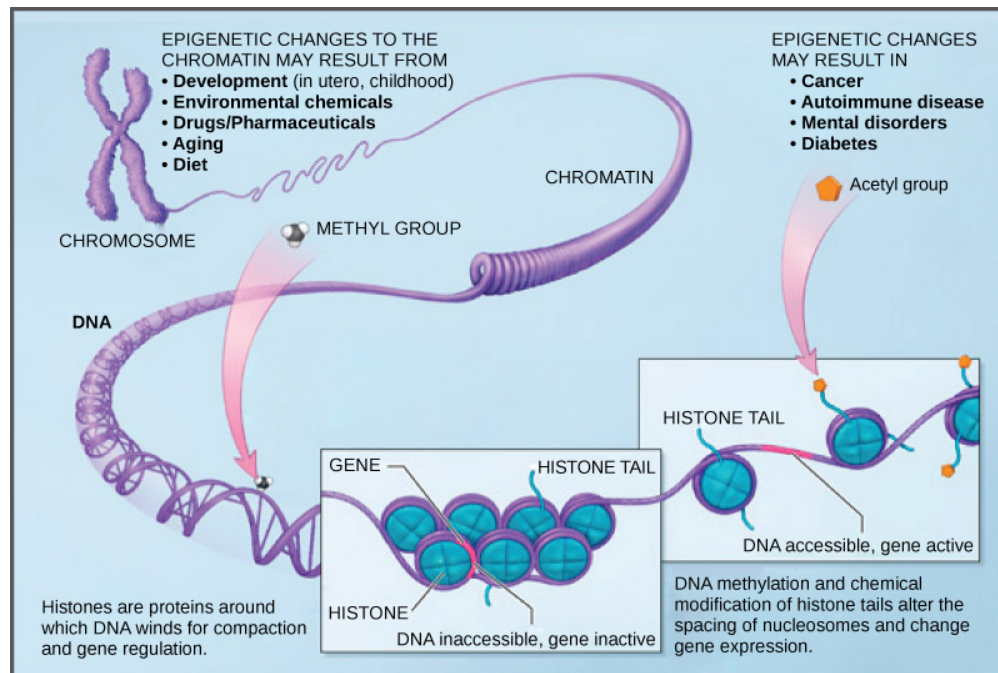


Figure 16.8 Histone proteins and DNA nucleotides can be modified chemically. Modifications affect nucleosome spacing and gene expression. (credit: modification of work by NIH)

Epigenetic changes are not permanent, although they often persist through multiple rounds of cell division and may even cross generational lines. Chromatin remodeling alters the chromosomal structure (open or closed) as needed. If a gene is to be transcribed, the histone proteins and DNA in the chromosomal region encoding that gene are modified in a way that opens the promoter region to allow RNA polymerase and other proteins, called **transcription factors**, to bind and initiate transcription. If a gene is to remain turned off, or silenced, the histone proteins and DNA have different modifications that signal a closed chromosomal configuration. In this closed configuration, the RNA polymerase and transcription factors do not have access to the DNA and transcription cannot occur (**Figure 16.8**).



View this video that describes how epigenetic regulation controls gene expression. (This multimedia resource will open in a browser.) (<http://cnx.org/content/m66505/1.3/#eip-id1169842033590>)

16.4 | Eukaryotic Transcription Gene Regulation

By the end of this section, you will be able to do the following:

- Discuss the role of transcription factors in gene regulation
- Explain how enhancers and repressors regulate gene expression

Like prokaryotic cells, the transcription of genes in eukaryotes requires the action of an RNA polymerase to bind to a DNA sequence upstream of a gene in order to initiate transcription. However, unlike prokaryotic cells, the eukaryotic RNA polymerase requires other proteins, or transcription factors, to facilitate transcription initiation. RNA polymerase by itself cannot initiate transcription in eukaryotic cells. There are two types of transcription factors that regulate eukaryotic transcription: *General (or basal) transcription factors* bind to the core promoter region to assist with the binding of RNA polymerase. *Specific transcription factors* bind to various regions outside of the core promoter region and interact with the proteins at the core promoter to enhance or repress the activity of the polymerase.



View the process of transcription—the making of RNA from a DNA template. (This multimedia resource will open in a browser.) (<http://cnx.org/content/m66506/1.3/#eip-id1168020166468>)

The Promoter and the Transcription Machinery

Genes are organized to make the control of gene expression easier. The promoter region is immediately upstream of the coding sequence. This region can be short (only a few nucleotides in length) or quite long (hundreds of nucleotides long). The longer the promoter, the more available space for proteins to bind. This also adds more control to the transcription process. The length of the promoter is gene-specific and can differ dramatically between genes. Consequently, the level of control of gene expression can also differ quite dramatically between genes. The purpose of the **promoter** is to bind transcription factors that control the initiation of transcription.

Within the core promoter region, 25 to 35 bases upstream of the transcriptional start site, resides the TATA box. The TATA box has the consensus sequence of 5'-TATAAA-3'. The TATA box is the binding site for a protein complex called TFIID, which contains a TATA-binding protein. Binding of TFIID recruits other transcription factors, including TFIIB, TFIIE, TFIIF, and TFIIH. Some of these transcription factors help to bind the RNA polymerase to the promoter, and others help to activate the transcription initiation complex.

In addition to the TATA box, other binding sites are found in some promoters. Some biologists prefer to restrict the range of the eukaryotic promoter to the core promoter, or polymerase binding site, and refer to these