16.3C: Epigenetic Control: Regulating Access to Genes within the Chromosome

Both the packaging of DNA around histone proteins, as well as chemical modifications to the DNA or proteins, can alter gene expression.

Learning Objectives

• Discuss how eukaryotic gene regulation occurs at the epigenetic level and the various epigenetic changes that can be made to DNA

Key Points

• DNA is packaged by wrapping around histone proteins into structures called nucleosomes, which resemble beads on a string.

• When DNA is to be transcribed, the nucleosomes can slide away from that region of DNA, opening it up to the transcription machinery of the cell.

• Chemical modifications to either the histone proteins or the DNA itself signals whether or not a particular region of the genome should be “open” or “closed” to the transcription machinery.

• Modifications such as acetylation or methylation of the histones can alter how tightly DNA is wrapped around them, while methylation of DNA changes how the DNA interacts with proteins, including the histone proteins that control access to the region.

• This type of genetic regulation is called epigenetic regulation (“above genetics”) as it does not change the nucleotide sequence of the DNA.
Epigenetic Control: Regulating Access to Genes within the Chromosome

The human genome encodes over 20,000 genes; each of the 23 pairs of human chromosomes encodes thousands of genes. 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. Under the electron microscope, this winding of DNA around histone proteins to form nucleosomes looks like small beads on a string. These beads (histone proteins) can move along the string (DNA) and change the structure 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. Nucleosomes can move to open the chromosome structure to expose a segment of DNA, but do so in a very controlled manner.
Nucleosomes can change position to allow transcription of genes. 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.

How the histone proteins move is dependent on signals found on both the histone proteins and on the DNA. These signals are tags, or modifications, added to histone proteins and DNA that tell the histones if a chromosomal region should be open or closed. These tags are not permanent, but may be added or removed as needed. They are chemical modifications (phosphate, methyl, or acetyl groups) that are attached to specific amino acids in the protein or to the nucleotides of the DNA. The tags 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; therefore, changes in the charge of the histone will change how tightly wound the DNA molecule will be. When unmodified, the histone proteins have a large positive charge; by adding chemical modifications, such as acetyl groups, the charge becomes less positive.

Modifications to histones and DNA can alter gene expression: Histone proteins and DNA nucleotides can be modified chemically. Modifications affect nucleosome spacing and gene expression.

The DNA molecule itself can also be modified. This 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. When this configuration exists, the cytosine member of the pair can be methylated (a methyl group is added). This modification changes how the DNA interacts with proteins, including the histone proteins that control access to the
region. Highly-methylated (hypermethylated) DNA regions with deacetylated histones are tightly coiled and transcriptionally inactive. These changes to DNA are inherited from parent to offspring, such that while the DNA sequence is not altered, the pattern of gene expression is passed to the next generation.

This type of gene regulation is called epigenetic regulation. Epigenetics means “above genetics.” The changes that occur to the histone proteins and DNA do not alter the nucleotide sequence and are not permanent. Instead, these changes are temporary (although they often persist through multiple rounds of cell division) and alter the chromosomal structure (open or closed) as needed. A gene can be turned on or off depending upon the location and modifications to the histone proteins and DNA. If a gene is to be transcribed, the histone proteins and DNA are modified surrounding the chromosomal region encoding that gene. This opens the chromosomal region to allow access for RNA polymerase and other proteins, called transcription factors, to bind to the promoter region, located just upstream of the gene, 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.