Mechanisms of Epigenetics

Recap: chromatin structure

Each somatic human cell contains two meters of DNA, which has to be efficiently packaged into nuclei 10-20 μm in diameter. If we were to scale the nucleus up to the size of a tennis ball, then the length of the DNA to be packaged would correspond to 9 km! This DNA is however very thin: just 2 nm, which following our analogy would be 9 μm = 0.009 mm – ~10 times thinner than a human hair.

DNA is wrapped around “spools” – complexes of **histone** proteins (the protein from your earlier task!), – forming **nucleosomes** (Figure 1). Nucleosomes can be positioned at varying distances from each other, like beads on a string. Those beads are further folded and compacted, with the degree of compaction varying along the genome. The substance that is formed of DNA, histones and other DNA-binding proteins is called **chromatin** (it was first identified by W. Fleming as a substance that absorbed basic dyes – hence the prefix “chromo”). In most human cells, there are 46 **chromosomes**, which are individual DNA molecules in complex with proteins.

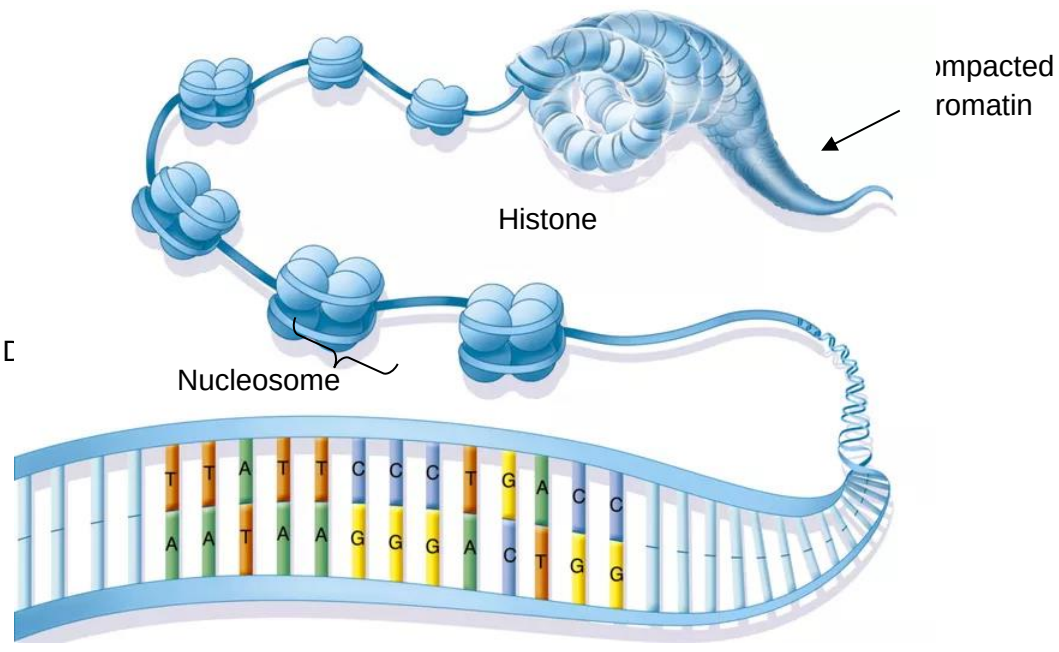

Figure 1. Chromatin structure. Adapted from https://www.thoughtco.com/chromatin-373461.

DNA methylation

In addition to the familiar “genetic code”, there are other ways information can be stored on DNA. **DNA methylation** is a chemical modification that can be applied to cytosine, one of the DNA bases. Close to the start sites of genes, there exist areas termed “**CpG islands**”,

which contain a high amount of “CG” sequences. These serve as a signal for methylation, and the methylation status of the CpG islands drastically influences the expression of the downstream gene. Methylation brings about gene silencing, while unmethylated CpG islands are active (Figure 2).

Additional resources:

https://www.whatisepigenetics.com/dna-methylation/

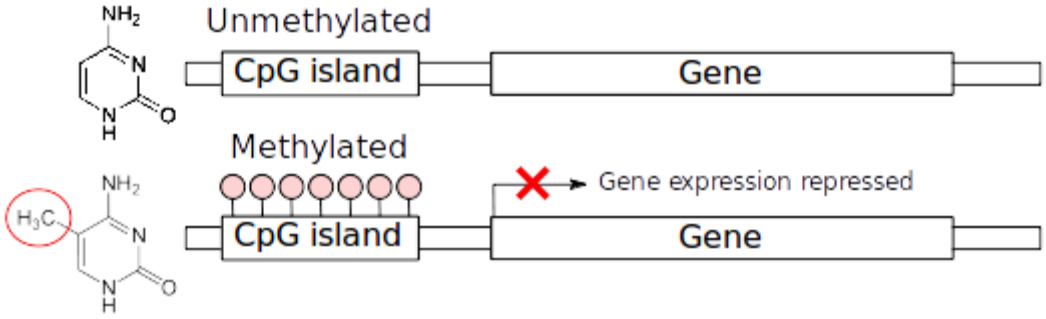

Figure 2. DNA methylation at CpG islands represses the downstream gene. On the left, unmethylated and methylated cytosines are shown.

Task

Outside of CpG islands, the CG sequence is actually rare – much more rare than one would expect by chance. Given that the total percentage of C’s and G’s in the human genome is about 40%, calculate the expected occurrence of the CG sequence. In reality, this sequence only appears at a frequency of ~0.8%. What could be the reason for this combination being under-represented?

(Hint: think about the mechanisms by which the genome sequence evolves).

Histone modification

Histone proteins serve not only as DNA spools. They have protruding parts - "**tails**" - which just as DNA can be chemically modified. Histone tails serve as platforms for a variety of modifications, such as mono-, di- or trimethylation, acetylation, etc. Both the nature and the position of the modification matter, giving rise to a large variety of possibilities, often referred to as the "**histone code**" (Figure 3). Some modifications can directly alter the local chromatin structure. In addition, all such marks can be recognised and/or modified by other proteins, leading to various downstream effects. For example, heterochromatin protein 1 (HP1) binds to di- and trimethylated lysine 9 on histone H3 (abbreviated H3K9me2/3, where H3 means the histone, K9 is lysine 9 and me is the methyl group). It seems to physically make chromatin more compact, and it also recruits a variety of other repressive proteins, such as DNA methyltransferase that methylates cytosines. Often these processes can be linked in a positive feedback loop, which can bring about modification of a whole genomic region.

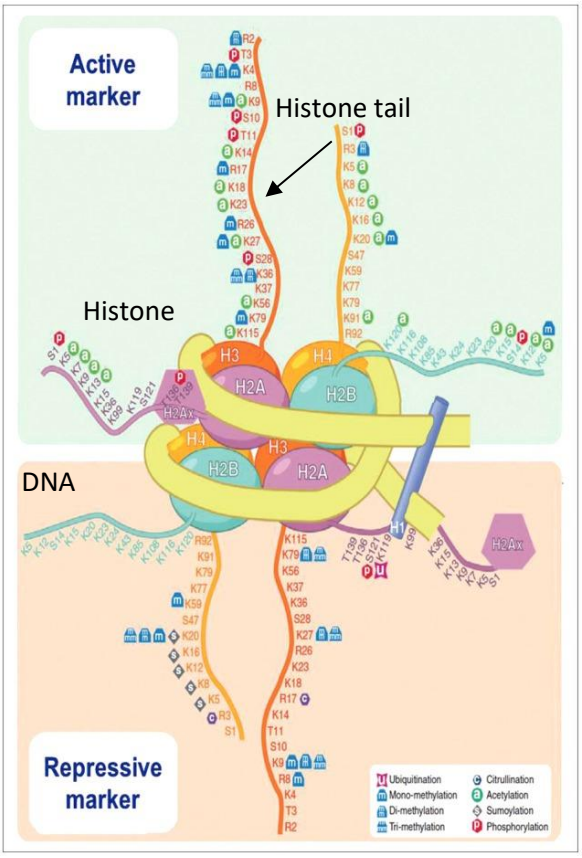

Figure 3. The histone code is based on various modifications of histone tails. Adapted from Kim, Brain Tumor Res Treat 2014.

Task

Thinking about the physical properties of the DNA and the acetyl group, can you guess what effect histone tail acetylation has on chromatin conformation? *(Hint: think about charge).*

Task

Suggest a mechanism by which HP1-associated chromatin regions can "spread".
(Hint: think about its interaction partners).

Additional resources:

https://www.whatisepigenetics.com/histone-modifications/

EpiGenie on HP1

https://epigenie.com/key-epigenetic-players/chromatin-modifying-and-dna-binding-proteins/heterochromatin-protein-1-hp1/

Chromatin remodeling

You can imagine that nucleosomes can be packaged in different ways. Loose packing allows various proteins, e.g. the ones necessary for transcription, to access these regions easily, and hence it makes sense to have active genes in such open state. Conversely, the gene-poor or repressed genomic regions are usually densely packed. Certain proteins, **chromatin remodelers**, can change the **conformation of chromatin** (Figure 4). For example, they can move or evict a nucleosome such that the beginning of a gene becomes exposed and is able to bind transcriptional machinery, or globally change the spacing between nucleosomes.

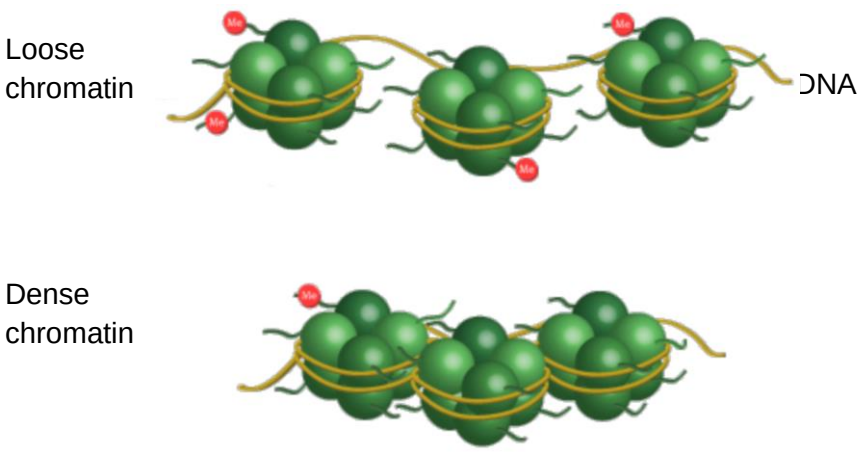

Figure 4. Chromatin remodeling. Adapted from Epigentek Resources.

Additional resources:

https://www.whatisepigenetics.com/chromatin-remodeling/

Non-coding RNA

The “traditional” roles of RNA – messenger, transport and ribosomal – are by far not the only ones it can play. There is a huge variety of non-coding RNA species, which have diverse functions mainly in gene expression regulation. **Short non-coding RNAs** usually regulate gene expression by preventing **translation** of certain mRNAs or even promoting their **degradation**. **Long non-coding RNAs** can interact with **chromatin-modifying proteins** and direct them to specific sites.

Additional resources:

https://www.whatisepigenetics.com/non-coding-rna/

The epigenetic mechanisms do not act in isolation – instead they form a complex and dynamic **system**. For example, histone acetylation makes the chromatin conformation looser and more accessible, while DNA methylation and repressive histone marks are often present in densely packed chromatin regions, acting together to repress gene expression.

Task

True or false?

1. DNA methylation is involved in bacterial protection from viruses.
2. There exist regions with both active and repressive chromatin marks.
3. Chromatin conformation plays a role in silencing endogenous viruses incorporated in our genome.
4. If you inject purple petunias with a gene encoding the purple pigment, they become white.