Use the given information to explain how histones help to control DNA compaction and function?


About 200 nucleotide DNA bases wrap around 8 histone proteins which helps compact the DNA so it can fit inside a cell nucleus (about 10^{-5} m in diameter). There are about 3 billion base pairs measuring 6 linear feet of DNA (coil is about 1 nm in diameter). Short protein tails (in the histone proteins) have various amino acids that allow attachment of other groups (acetyl groups, methyl groups, phosphate groups, sugars, lipids or other small proteins) that affect the activity of the genes along the strands of DNA (about 20,000 genes, but each gene can lead to multiple proteins via post translational modification). Amino acids that allow attachments of the various small groups include serine, threonine, tyrosine, lysine, arginine and cysteine. (In DNA / histone chemistry this is called epigenetics.)

Examples of amino acids with modifiable heteroatoms in the side chains,

- **threonine**
- **serine**
- **cysteine**
- **lysine**
- **arginine**
- **tyrosine**

All amino acids have “S” absolute configuration at Cα position, except cysteine (S changes the priority)

Examples of possible modifications of side chains on amino acids - in DNA chemistry = epigenetics

- **Methylation**
- **Acetylation**
- **Phosphorylation**

The positive charge on the amine group of a lysine in a histone disappears when it is converted to an amide. This causes a looser association of histone with the negatively charged DNA, and allows greater access by enzymes that turn on a gene, or correct errors in the DNA. (See the bottom of the next page.) Modification of DNA and the histones that interact with DNA is called “epigenetics.” Acetylation of histones seems to increase gene activity (turn them on) and deacylation seems to decrease gene activity (turn them off). Either of these can be good or bad. Turning on an “apotosis” gene (suicide gene) can be good in a cancer cell, but turning off an oncogene (cancer gene) is good in a cancer cell, but turning off a functional gene in a healthy cell is bad. It is also proposed that acetylation might allow complexation with other proteins that allow transcription to occur (RNA synthesis), which is followed by translation (protein synthesis from the RNA template). Methylation of the nucleoside bases (with SAM = S-adenosyl methionine) seems to more permanently turn off gene activity. This may be the case when particular genes are not part of a cells primary duties, e.g. vision, liver, pancreas, blood, bone, lung, heart, etc. However, to replicate a cell, these “add-on” groups all have to be removed. They then have to be added back on in the newly divided cells. Living cells survive and die using mind boggling complexity!
Henderson-Hasselbach Equation
\[
\text{pH} = pK_a + \log \frac{[A^-]}{[HA]}
\]

extracellular blood pH \( \approx 7.4 \)
intracellular \( \approx 6.8 \)
stomach \( \approx 1.5 - 3.5 \)
small intestines \( \approx 8.5 \)

What do the amino acids look like?

lysine side chain looks like this in the body (cation)
lysine side chain looks like this in the body (neutral amide)

acylated lysine side chain looks like this in the body (neutral amide)

DNA highly negative from phosphates
histones positive with lysine amine groups
histones neutral with lysine amide groups

When lysine is acylated the positive charge is lost and the binding is much weaker. The DNA is more exposed and approachable by gene starter proteins or repair proteins.

Ionic interactions between histones "lysines" and DNA phosphates bind tightly to one another. Compact DNA is less active.

The amide groups are neutral (but polar) along the protein backbone.

The amide groups are neutral (but polar) along the protein backbone.

The conjugate base lies outside the normal range of possibilities in water.
How can enzyme pockets affect the pKₐ of acids?

Assume enzyme active site intracellular pH ≈ 6.8

Typical pKₐ(RCO₂H) ≈ 4 (in acid protein side chain)

\[
\log \frac{[\Theta]}{[HA]} = (6.8 - 4) = 2.8 \\
[\Theta] = 10^{2.8} = 630 / 1
\]

Typical pKₐ(RNH₃⁺) ≈ 10 (in amine protein side chain)

\[
\log \frac{[A]}{[HA]} = (6.8 - 10) = -3.2 \\
\frac{[A]}{[H^+]A} = 10^{-3.2} = 1 / 1600
\]

Assume pKₐ(RCO₂H) is lower by 2 near RNH₃⁺

\[
\log \frac{[A]}{[HA]} = (6.8 - 2) = 4.8 \\
[\Theta] = 10^{4.8} = 63,000 / 1
\]

Assume pKₐ(RNH₃⁺) is higher by 2 near RCO₂⁻

\[
\log \frac{[A]}{[HA]} = (6.8 - 12) = -5.2 \\
\frac{[A]}{[H^+]A} = 10^{-5.2} = 1 / 160,000
\]

Assume pKₐ(RCO₂H) is higher by 2 near RCO₂⁻

\[
\log \frac{[A]}{[HA]} = (6.8 - 6) = 0.8 \\
[\Theta] = 10^{0.8} = 6 / 1
\]

Much higher concentration of neutral acid

Assume pKₐ(RNH₃⁺) is lower by 2 near RNH₃⁺

\[
\log \frac{[A]}{[HA]} = (6.8 - 8) = -1.2 \\
\frac{[A]}{[H^+]A} = 10^{-1.2} = 1 / 16
\]

Much higher concentration of neutral amine

Assume enzyme active site intracellular pH ≈ 6.8

Postive charge makes conjugate base more stable, thus acid has a lower pKₐ

\[
\log \frac{[A]}{[HA]} = (6.8 - 4) = 2.8 \\
[\Theta] = 10^{2.8} = 630 / 1
\]

Negative charge makes conjugate acid more stable, thus acid has a higher pKₐ

\[
\log \frac{[A]}{[HA]} = (6.8 - 10) = -3.2 \\
\frac{[A]}{[H^+]A} = 10^{-3.2} = 1 / 1600
\]

Postive charge makes conjugate acid less stable, thus acid has a lower pKₐ

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\log \frac{[A]}{[HA]} = (6.8 - 6) = 0.8 \\
[\Theta] = 10^{0.8} = 6 / 1
\]

Negative charge makes conjugate base less stable, thus acid has a higher pKₐ

\[
\log \frac{[A]}{[HA]} = (6.8 - 12) = -5.2 \\
\frac{[A]}{[H^+]A} = 10^{-5.2} = 1 / 160,000
\]