Histone modifications

- A **histone modification** is a covalent post-translational modification (PTM) to histone proteins which includes **methylation, phosphorylation, acetylation, ubiquitylation, ribosylation, citrullination and sumoylation**.

- PTMs made to histones can impact gene expression by **altering chromatin structure or recruiting histone modifiers**.

- Histone modifications act in diverse biological processes such as **transcriptional activation/inactivation, chromosome packaging, and DNA damage/repair**.

- In most species, histone H3 is primarily acetylated at lysines 9, 14, 18, 23, and 56, methylated at arginine 2 and lysines 4, 9, 27, 36, and 79, and phosphorylated at ser10, ser28, Thr3, and Thr11. Histone H4 is primarily acetylated at lysines 5, 8, 12 and 16, methylated at arginine 3 and lysine 20, and phosphorylated at serine 1.

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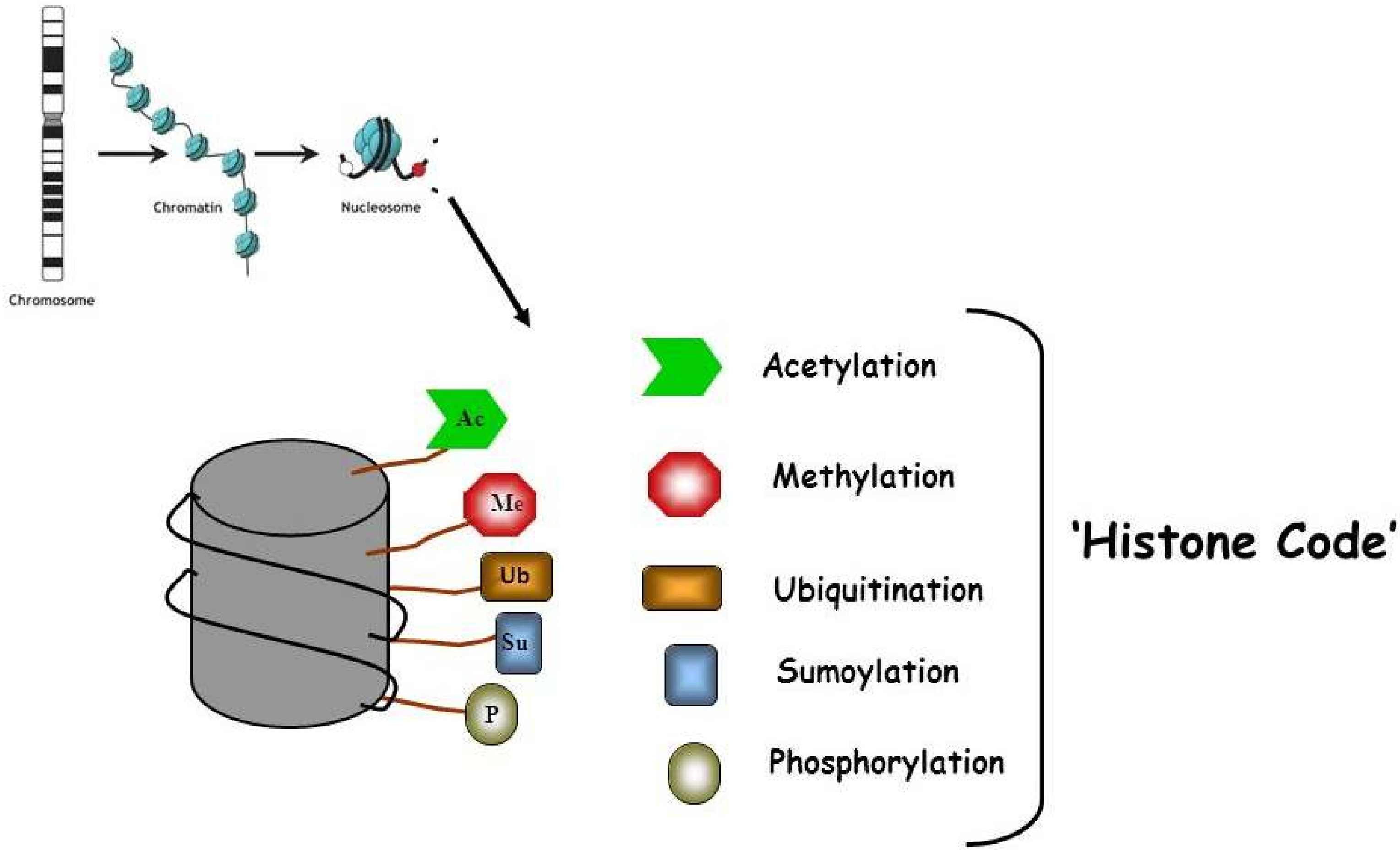
Histone modifications



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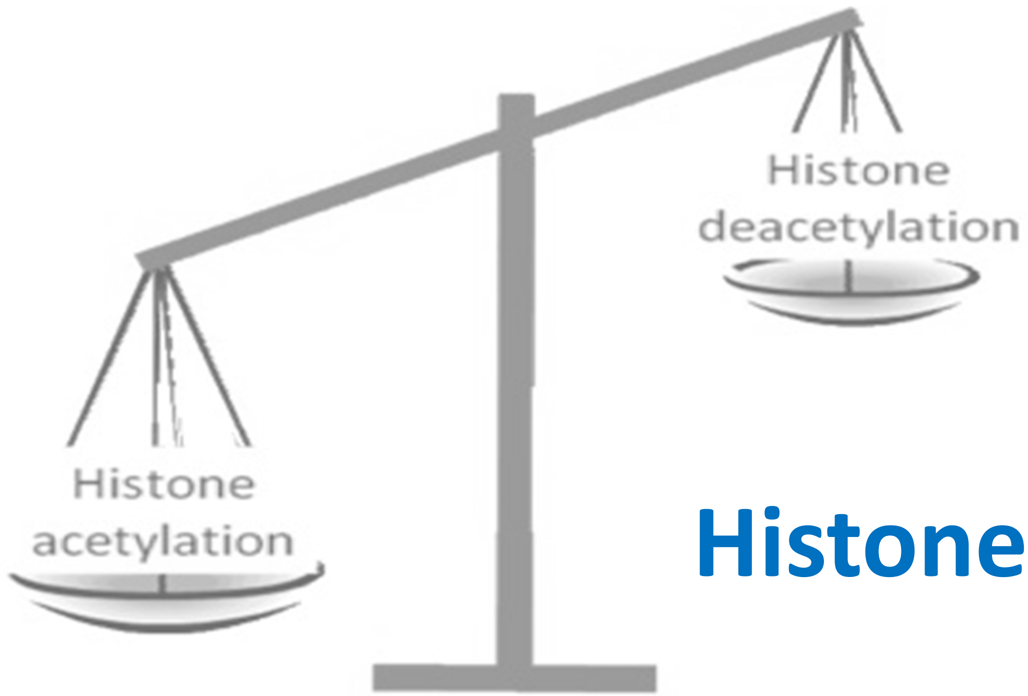

Histone Acetylation

Open chromatin structure
Gene Transcription

Closed chromatin structure
Gene Repression

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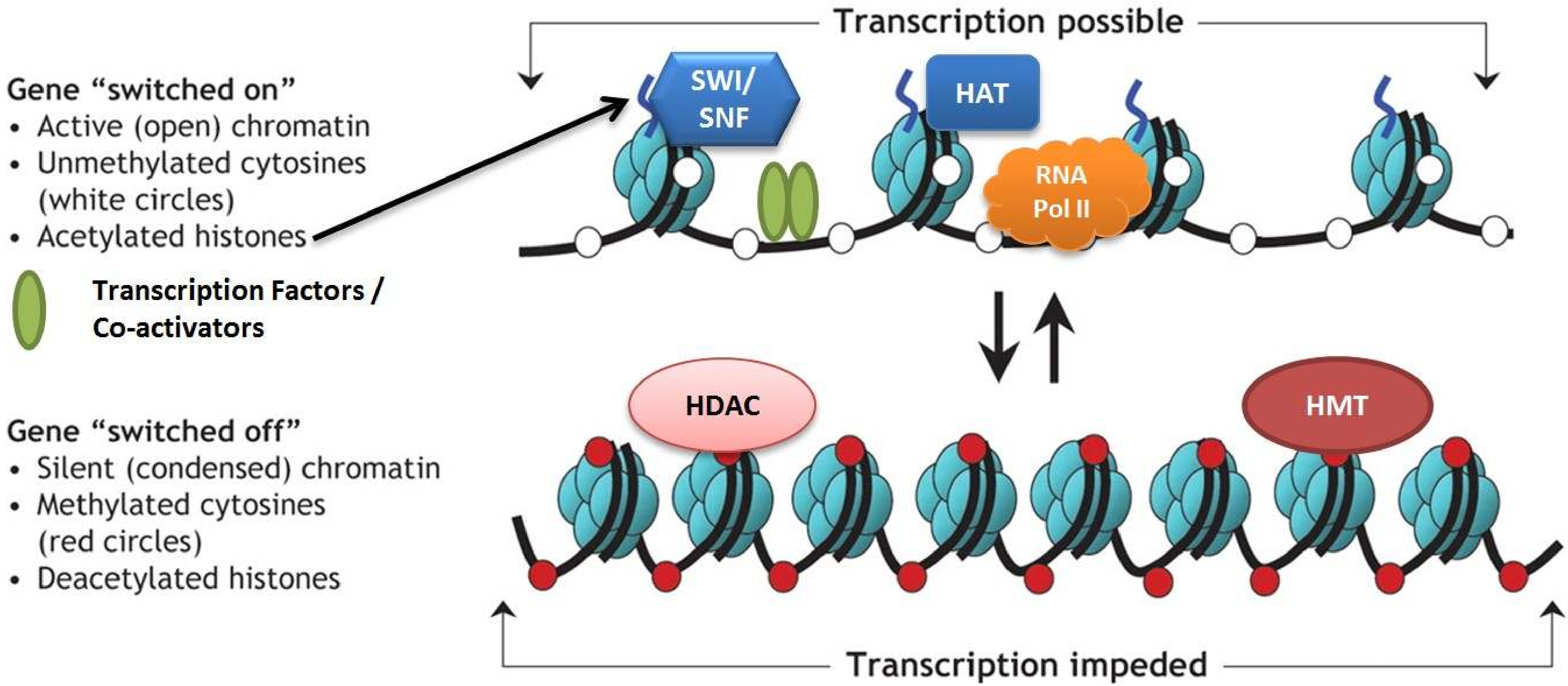
Histone Acetylation and altered chromosome packaging



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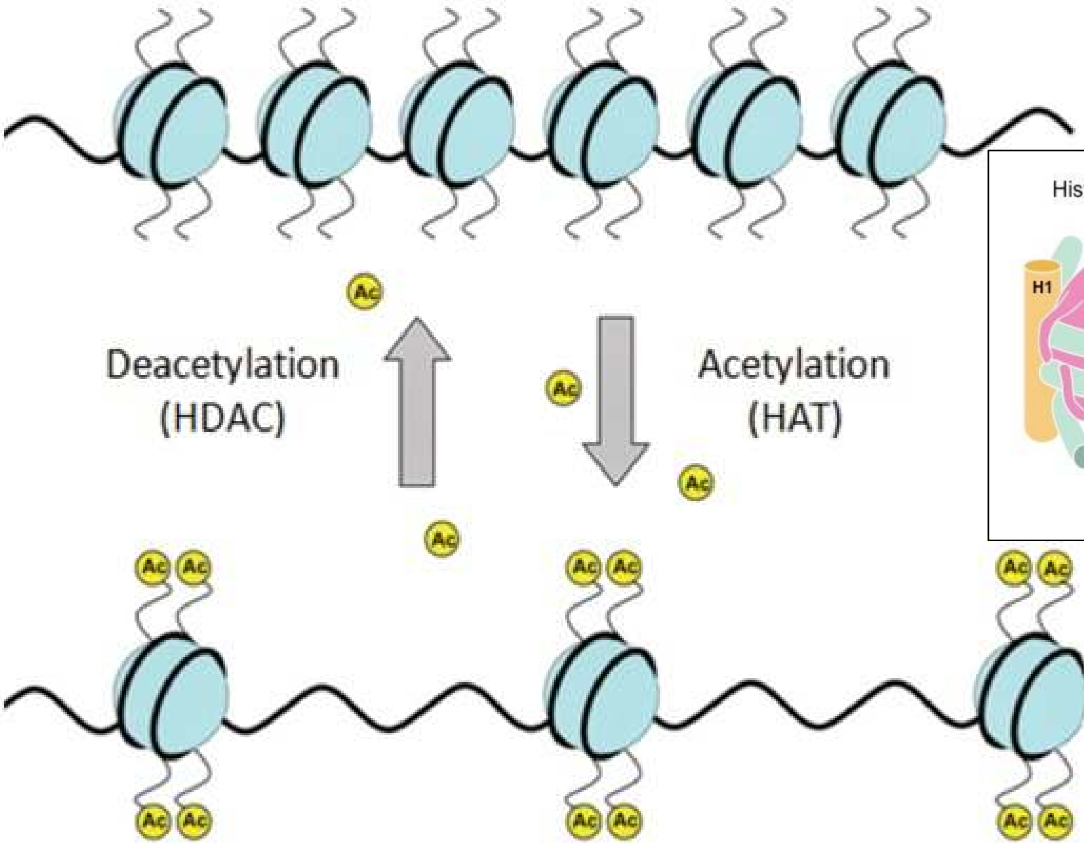
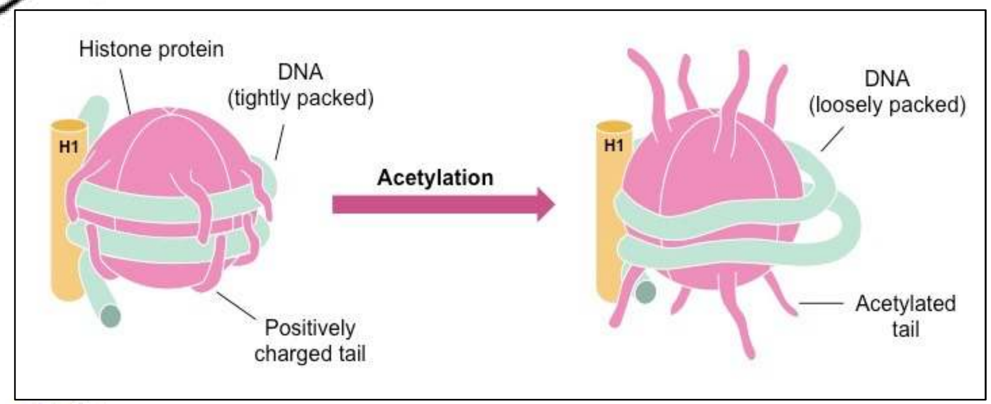
Histone Acetylation and altered chromosome packaging





HAT and HDAC

- Histone acetyltransferases (**HATs**) are enzymes, which catalyze **the transfer of an acetyl group from acetyl-CoA to the lysine ϵ amino groups** on the N-terminal tails of histones.

- More than **20 HATs** have been identified which can be classified into **five families**: GNAT1, MYST, TAFII250, P300/CBP, and nuclear receptor coactivators such as ACTR.

- HATs come in two flavors, **cytoplasmic and nuclear.**

- Histone deacetylaces (**HDACs**) catalyze the **hydrolytic removal of acetyl groups** from histone lysine residues.

- Class I HDACs include 1, 2, 3, and 8. Class II HDACs are comprised of 4, 5, 6, 7, 9, and 10. Class III enzymes, known as sirtuins, require NAD+ cofactors and include SIRTs 1-7. The Class IV enzyme, which contains only HDAC11, has features of both Class I and II.

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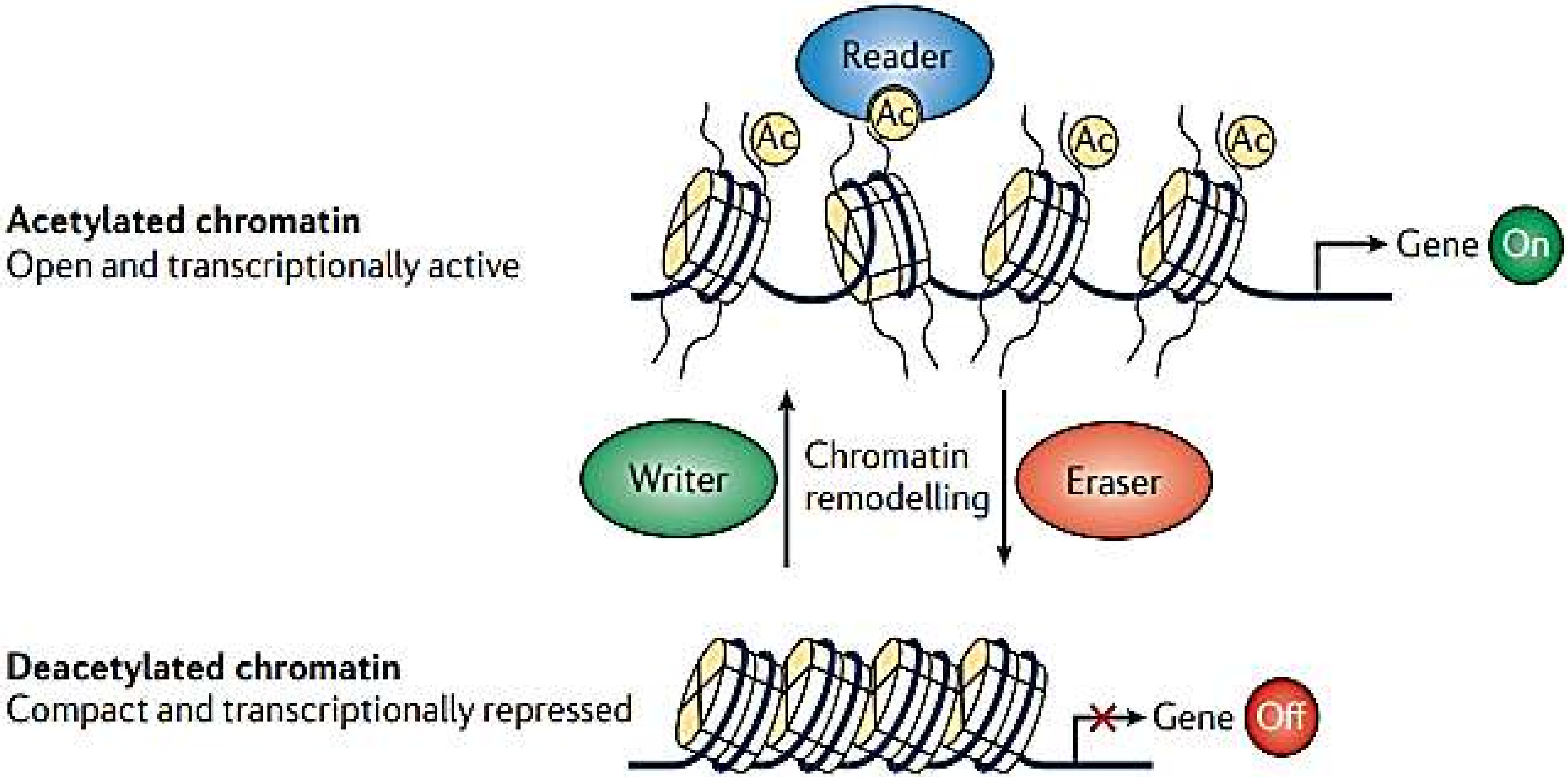
Reader Writer and Eraser



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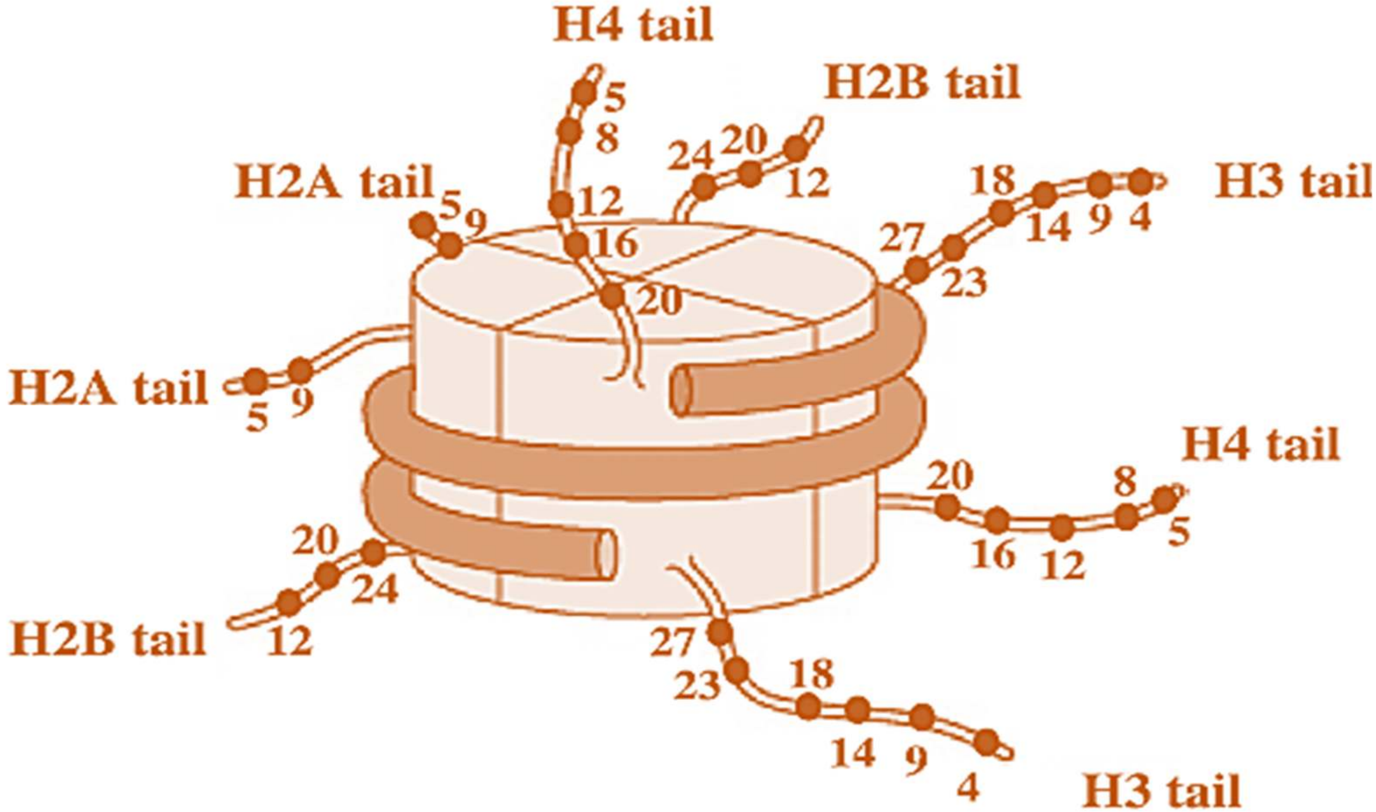
Schematic representation of lysine residues on the histone N-terminal tails



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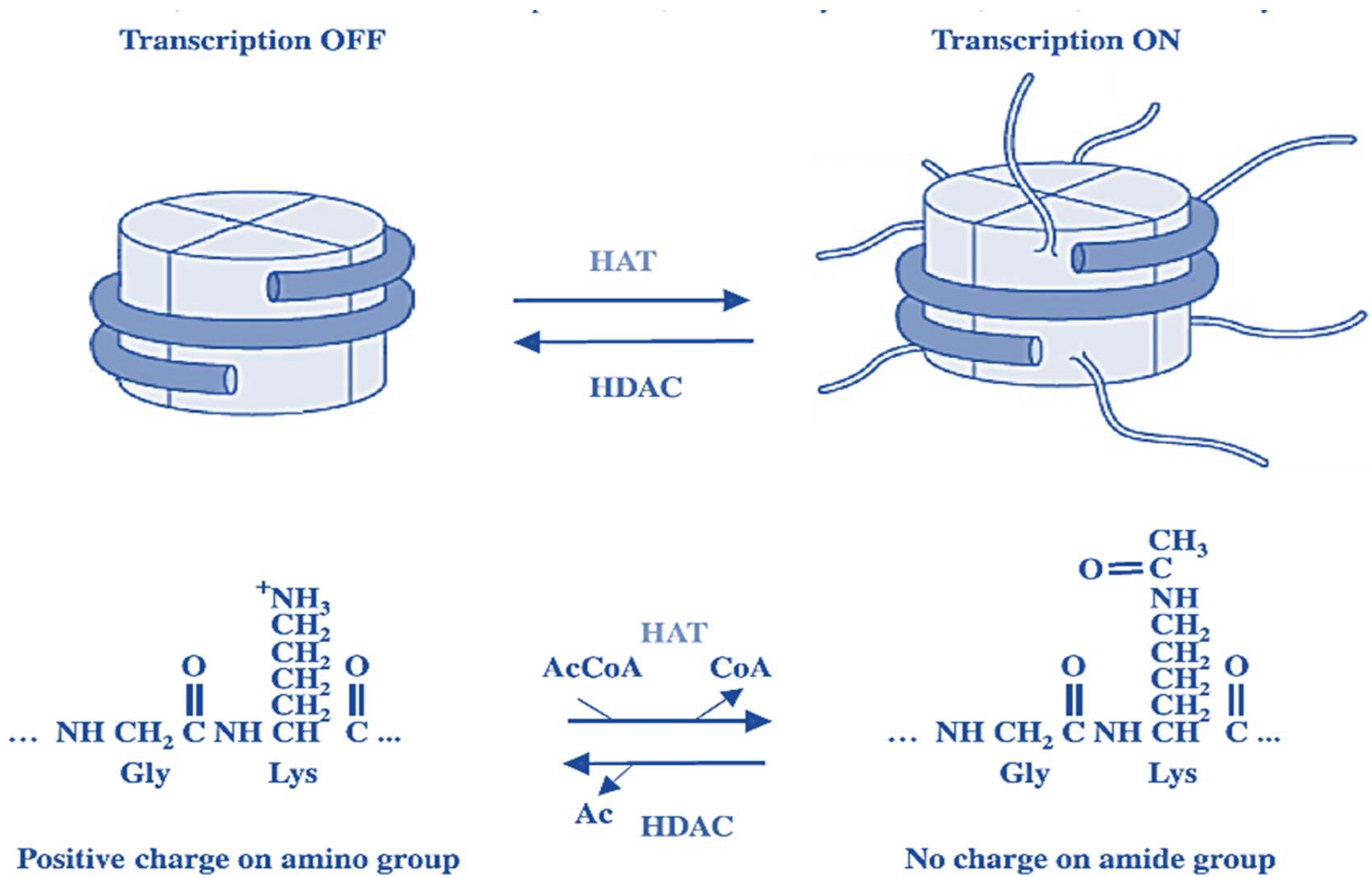
Histone Acetylation: Reaction



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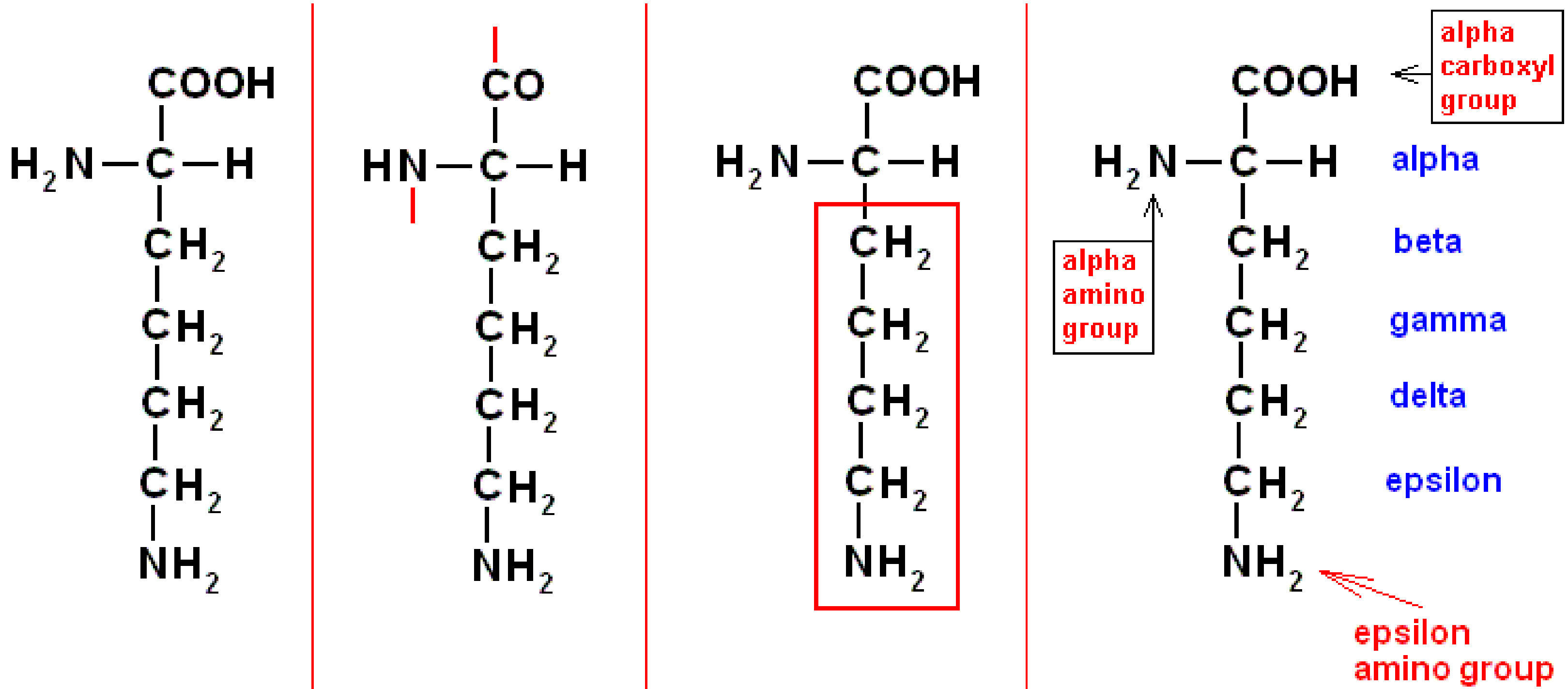

lysine

lysine residue

R-group of lysine

labeling of atoms
of the lysine chain

Types of histone acetylation

- **Broad domain wide histone acetylation**

(The dosage compensated male X chromosome in Drosophila, where the acetylation of histone H4 at lysine 16 (H4K16) by MOF (Males absent on the First) correlates with increased transcription of many genes throughout most of the male X chromosome)

- **Local, targeted histone acetylation**

(These are the patterns of acetylation at specific lysines within the histone N-termini, rather than simple charge neutralization by non-specific modification, receives convincing confirmation)

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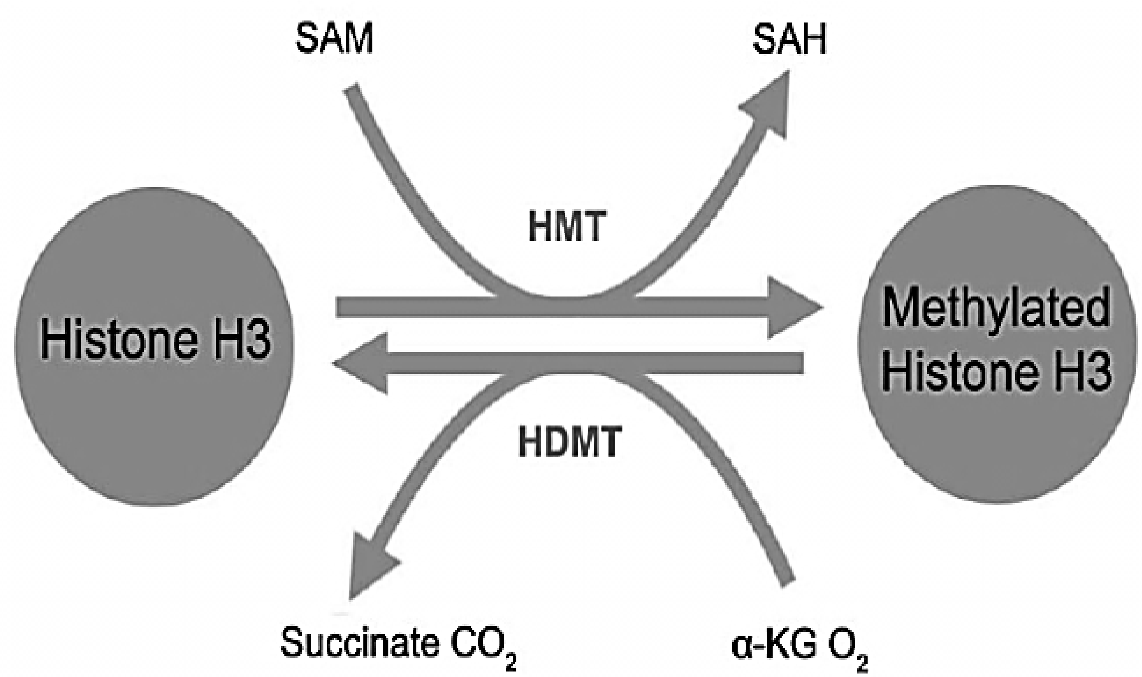
Histone Methylation and Demethylation



Histone methylation

- **There are two types of HMTs: histone lysine N-methyltransferase (KMT) and histone arginine N-methyltransferase (PRMTs).**

- **Generally, trimethylation of lysine 4 on histone H3 (H3K4me3) is associated with a fully activated promoter, which correlates with gene transcription, whereas dimethylation (H3K4me2) occurs at both inactive and active euchromatic genes.**

- **Dimethylation at lysine 9 (H3K9me2) marks the silence of gene expression in euchromatin, important in proliferating cells, whereas H3K9me3 is enriched in regions of "gene-poor" pericentric heterochromatin.**

- **Methylation at lysine 27 on histone H3 (H3K27me) is associated with transcriptional repression in many developmental processes. Increased global H3K27 methylation is also found to be involved in some pathological processes such as cancer progression.**

- **Arginine methylation of histones H3 and H4 promotes transcriptional activation.**

Histone demethylation

- Two major families of demethylases have been discovered: Lysine specific demethylase 1 (LSD1) and Jumonji domain containing (JmjC domain) histone demethylases (JMJD2, JMJD3/UTX and JARIDs).

- Histone H3, mono- and di-methylated lysine 4 are demethylated by LSD1 (BHC110, KDM1) and tri-methylated lysine 4 by JARID (1A-1D); di- and tri-methylated lysine 27 are demethylated by JMJD3 and UTX (KDM6A) and mono- and di-methylated lysine 9 are demethylated by JMJD1 and tri-methylated lysine 9 is demethylated by JMJD2.

Histone phosphorylation

- All four nucleosomal histone tails contain acceptor sites that can be phosphorylated by a number of **protein kinases** and dephosphorylated by **phosphatases.**
- Histone phosphorylation can occur on **serine, threonine and tyrosine** residues.
- Phosphorylation of **H2A(X)** is an important histone modification that plays a major role in **DNA damage response.**
- Phosphorylation of **serines 10 and 28 of H3 and serine 32 of H2B** has been associated with **regulation of epidermal growth factor (EGF)-responsive gene transcription.**
- Phosphorylation of **tyrosine (Y) 41 on H3 by Janus Kinase 2** (JAK2) has also been described to **influence transcription**.
- **H2B** has also been recently shown to be phosphorylated on **tyrosine 37** in yeast and mammalian cells. This mark is added by the **WEE1 kinase** and is important for **suppression of replication-dependent core histone gene transcription.**

Histone sumoylation

- Small ubiquitin-related modifier (SUMO) **shares 18% identity with ubiquitin** and adopts a similar 3D structure. Ubiquitylation has a role in protein degradation, whereas SUMO does not.

- The SUMO paralogs are synthesized as precursor proteins that are cleaved by a family of SUMO isopeptidases referred to as SENPs. Mature SUMO is subsequently activated by a heterodimeric E1 activating enzyme (Aos1/Uba2), transferred to an E2 conjugating enzyme (Ubc9), and finally transferred to lysine residues in target proteins.

- Sumoylation of proteins can affect **protein stability, enzymatic activity, alter localization, or mediate novel protein-protein interactions with other proteins containing SUMO-interacting motifs (SIMs).**

- Although invertebrates express only a single SUMO, **vertebrates express four paralogs (SUMO-1, SUMO-2, SUMO-3 and SUMO-4),** each with the potential to act as unique signals by interacting with distinct downstream factors

Histone ubiquitination

- It is estimated that **5–15%** of **H2A** and **1–2% of H2B** are conjugated with ubiquitin in vertebrate cells.

- The **dominant form** of ubiquitinated histones are **mono-ubiquitinated** H2A (H2Aub) and H2B (H2Bub). A single molecule of **ubiquitin** is added to the highly conserved lysine residues: **Lys-119 for H2A,** and **Lys-123 in yeast** or **Lys-120 in vertebrate for H2B**.

Ubiquitination types

- Poly-ubiquitination
  For degradation via the 26S proteasome
- Mono-ubiquitination
  Mono-ubiquitination of histones
  H2A at Lys-119
  H2B at Lys-120

K48-linked UQ chains on histones targets them for proteasome mediated degradation. For example, during spermatogenesis, histones are degraded through this mechanism and replaced by transition proteins to permit chromatin condensation.

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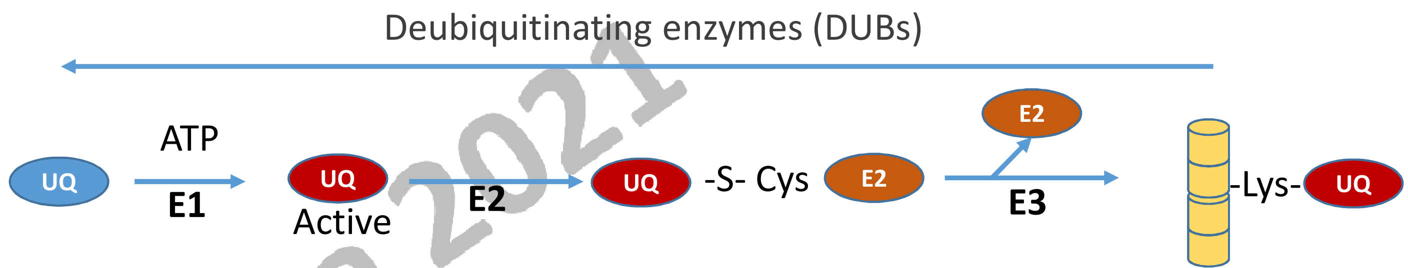
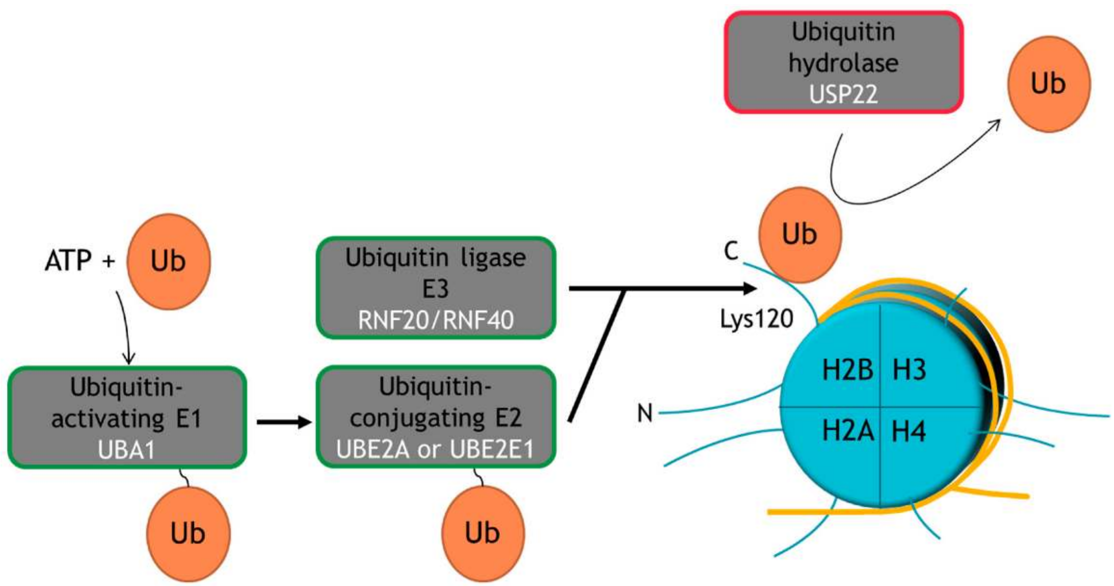


The 76 amino acid protein ubiquitin is conjugated to substrate proteins in a reaction involving three separate enzymatic activities. Ubiquitin is first activated by an ATP-dependent reaction involving a ubiquitin activating enzyme (E1), followed by its conjugation via a thioester bond to a cysteine residue in a ubiquitin-conjugating enzyme (E2). In the final enzymatic step, ubiquitin is transferred from the E2 enzyme to a target lysine residue in a particular substrate protein by a ubiquitin-protein isopeptide ligase (E3).



Function of Mono-ubiquitinization

H2B Mono-ubiquitination:

- Rad6, the E2 ubiquitin conjugase catalyzes H2B monoubiquitination in yeast.
- HR6A and HR6B in mammal.

→ Promotes Lys-4 H3 Methylation
Promotes Lys-79 H3 Methylation

→ UbH2B deubiquitination is required for optimal Transcriptional activation

→ Assists RNA pol II during elongation

H2A Mono-ubiquitination:

- Done by Ring 1B and 2A-HUB in mammal.

→ H2A is mono-ubiquitinated at DNA lesions, and this requires functional nucleotide excision repair

→ Inhibits Lys-4 H3 Methylation

→ Inhibits RNA pol II during elongation

Histone ribosylation

- Histone proteins often undergo ribosylation i.e. the addition of **poly ADP-ribose** units specifically at the **lysine** residues.
- This modification is mediated by **Poly [ADP-ribose] polymerase (PARP)** enzymes.
- PARP1 prefers the **H1** and PARP2 prefers the **core histones.**
- In this case, the **NAD+** acts as substrate.
- **Mono ADP-ribosylation** is done by ADP-ribosyl transferase **(ART).**
- ADP-ribosylation causes **disruption of the nucleosome structure** by loss of histone-DNA interaction on account of charge modification.
- PARP1 acts as a **transcription activator or repressor** by binding its recognition motif.
- Poly (ADP-ribose) polymerase 1 (PARP1) is an ADP-ribosylating enzyme essential for initiating various forms of **DNA repair**.

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Histone ribosylation