

X chromosomes in females (X-inactivation). Alterations in methylation can also be acquired, e.g., in cancer cells. Covalent posttranslational modifications of histones play an important role in altering DNA accessibility and chromatin structure and hence in regulating transcription. Histones can be reversibly modified in their amino-terminal tails, which protrude from the nucleosome core particle, by acetylation of lysine, phosphorylation of serine, methylation of lysine and arginine residues, and sumoylation. Acetylation of histones by histone acetylases (HATs), e.g., leads to unwinding of chromatin and accessibility to transcription factors. Conversely, deacetylation by histone deacetylases (HDACs) results in a compact chromatin structure and silencing of transcription.

Histone methylation involves the addition of a methyl group to lysine residues in histone proteins (Fig. 466-7). Depending on the specific lysine residue being methylated, this alters chromatin configuration, making it either more open or tightly packed. Acetylation of histone proteins is another well-characterized mechanism that results in an open chromatin configuration, which favors active transcription. Acetylation is generally more dynamic than methylation, and many transcriptional activation complexes have histone acetylase activity, whereas repressor complexes often contain deacetylases and remove acetyl groups from histones. Other histone modifications include, among others, phosphorylation and sumoylation.

Furthermore, noncoding RNAs and RNA regulatory networks that bind to DNA have a significant impact on transcriptional activity.

Physiologically, epigenetic mechanisms play an important role in several instances. For example, X-inactivation refers to the relative silencing of one of the two X chromosome copies present in females. The inactivation process is a form of dosage compensation such that females (XX) do not generally express twice as many X-chromosomal gene products as males (XY). In a given cell, the choice of which chromosome is inactivated occurs randomly in humans. But once the maternal or paternal X chromosome is inactivated, it will remain inactive, and this information is transmitted with each cell division. The *X-inactive specific transcript (Xist)* gene encodes a large noncoding RNA that mediates the silencing of the X chromosome from which it is transcribed by coating it with *Xist* RNA. The inactive X chromosome is highly methylated and has low levels of histone acetylation. While the majority of X-chromosomal genes