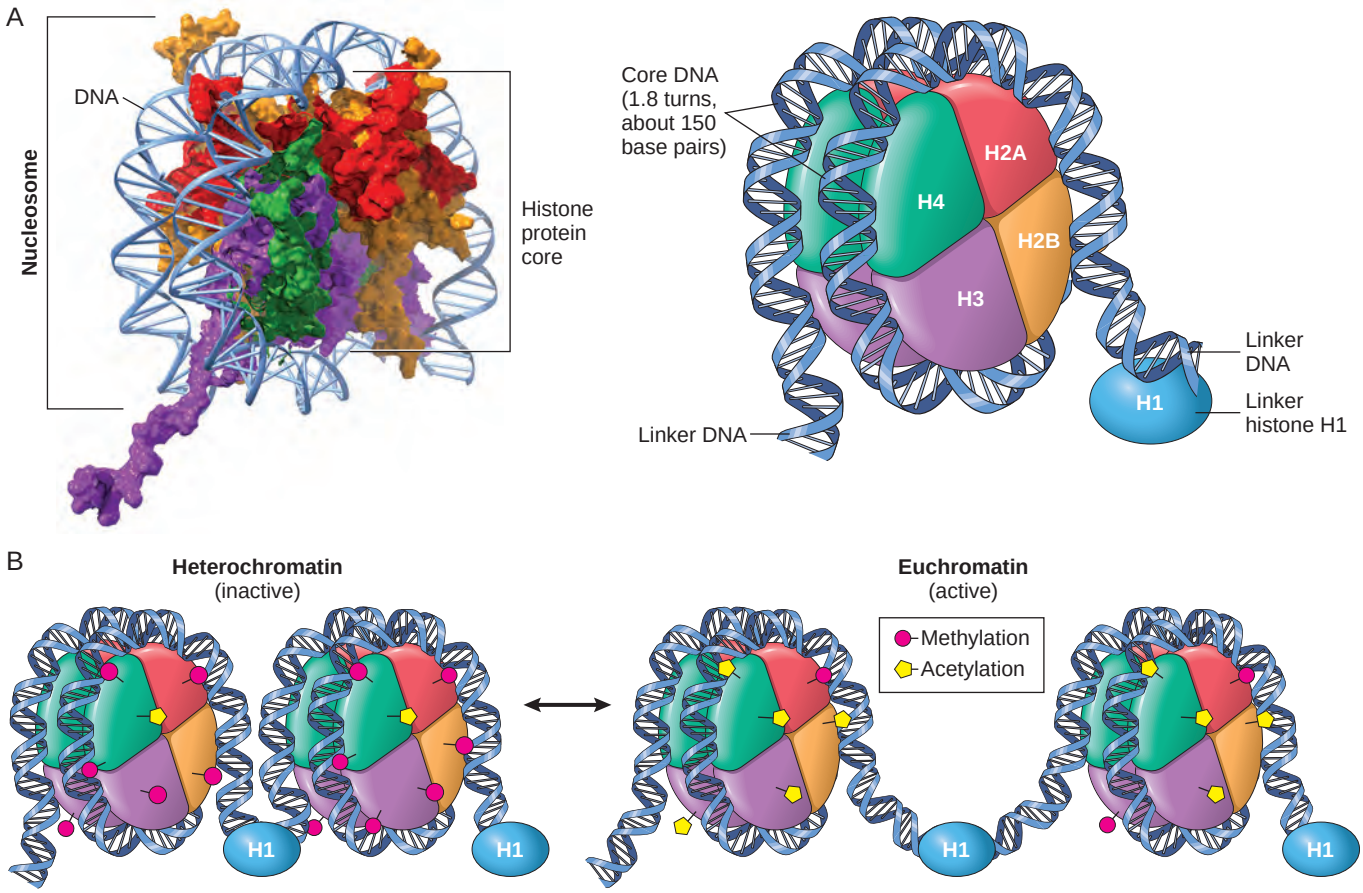

Figure 1-2 Histone organization. **A,** Nucleosomes are comprised of octamers of histone proteins (two each of histone subunits H2A, H2B, H3, and H4) encircled by 1.8 loops of 147 base pairs of DNA; histone H1 sits on the 20-80 nucleotide linker DNA between nucleosomes and helps stabilizes the overall chromatin architecture. The histone subunits are positively charged, thus allowing the compaction of the negatively charged DNA. **B,** The relative state of DNA unwinding (and thus access for transcription factors) is regulated by histone modification, for example, by acetylation, methylation, and/or phosphorylation (so-called "marks"); marks are dynamically written and erased. Certain marks such as histone acetylation "open up" the chromatin structure, whereas others, such as methylation of particular histone residues, tends to condense the DNA and leads to gene silencing. DNA itself can also be also be methylated, a modification that is associated with transcriptional inactivation.

the DNA may be opened up for transcription or condensed to become inactive.

- *DNA methylation.* High levels of DNA methylation in gene regulatory elements typically result in transcriptional silencing. Like histone modifications, DNA methylation is tightly regulated by methyltransferases, demethylating enzymes, and methylated-DNA-binding proteins.
- *Chromatin organizing factors.* Much less is known about these proteins, which are believed to bind to noncoding regions and control long-range looping of DNA, which is important in regulating the spatial relationships between gene enhancers and promoters that control gene expression.

Deciphering the mechanisms that allow epigenetic factors to control genomic organization and gene expression in a cell-type-specific fashion is an extraordinarily complex proposition. Despite the intricacies, there is already ample evidence that dysregulation of the "epigenome" has a central role in malignancy (Chapter 7), and there is growing evidence that many other diseases are associated with inherited or acquired epigenetic alterations. Another reason for excitement is that—unlike genetic changes—many epigenetic alterations (e.g., histone acetylation and DNA methylation) are reversible and are amenable to therapeutic intervention; thus, HDAC inhibitors and DNA methylation inhibitors are already being tested in the treatment of various forms of cancer.

Micro-RNA and Long Noncoding RNA

Another mechanism of gene regulation depends on the functions of noncoding RNAs. As the name implies, these are encoded by genes that are transcribed but not translated. Although many distinct families of noncoding RNAs exist, we will only discuss two examples here: small RNA molecules called *microRNAs,* and *long noncoding RNAs* >200 nucleotides in length.

Micro-RNA (miRNA)

The miRNAs do not encode proteins; instead, they function primarily to modulate the translation of target mRNAs into their corresponding proteins. **Posttranscriptional**