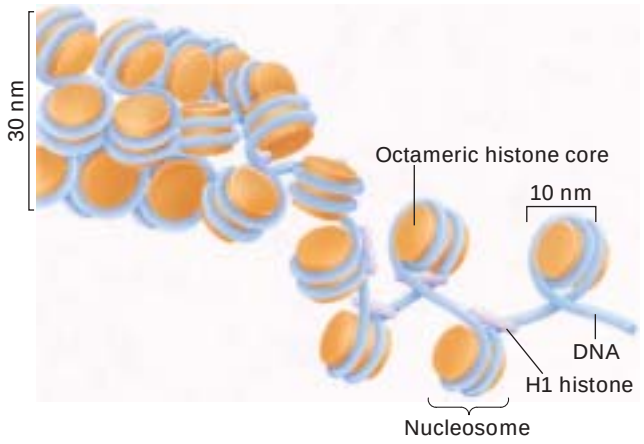

▲ FIGURE 10-21 **Solenoid model of the 30-nm condensed chromatin fiber in a side view.** The octameric histone core (see Figure 10-20) is shown as an orange disk. Each nucleosome associates with one H1 molecule, and the fiber coils into a solenoid structure with a diameter of 30 nm. [Adapted from M. Grunstein, 1992, *Sci. Am.* **267**:68.]

fibers, nucleosomes are thought to be packed into an irregular spiral or solenoid arrangement, with approximately six nucleosomes per turn (Figure 10-21). H1, the fifth major histone, is bound to the DNA on the inside of the solenoid, with one H1 molecule associated with each nucleosome. Recent electron microscopic studies suggest that the 30-nm fiber is less uniform than a perfect solenoid. Condensed chromatin may in fact be quite dynamic, with regions occasionally partially unfolding and then refolding into a solenoid structure.

The chromatin in chromosomal regions that are not being transcribed exists predominantly in the condensed, 30-nm fiber form and in higher-order folded structures whose detailed conformation is not currently understood. The regions of chromatin actively being transcribed are thought to assume the extended beads-on-a-string form.

Modification of Histone Tails Controls Chromatin Condensation

Each of the histone proteins making up the nucleosome core contains a flexible amino terminus of 11–37 residues extending from the fixed structure of the nucleosome; these termini are called *histone tails*. Each H2A also contains a flexible C-terminal tail (see Figure 10-20b). The histone tails are required for chromatin to condense from the beads-on-a-string conformation into the 30-nm fiber. Several positively charged lysine side chains in the histone tails may interact with linker DNA, and the tails of one nucleosome likely interact with neighboring nucleosomes. The histone tail lysines, especially those in H3 and H4, undergo reversible acetylation and deacetylation by enzymes that act on specific lysines in the N-termini. In the acetylated form, the positive charge of the lysine ϵ-amino group is neutralized, thereby eliminating its interaction with a DNA phosphate group. Thus the greater the acetylation of histone N-termini, the less likely chromatin is to form condensed 30-nm fibers and possibly higher-order folded structures.

The histone tails can also bind to other proteins associated with chromatin that influence chromatin structure and processes such as transcription and DNA replication. The interaction of histone tails with these proteins can be regulated by a variety of covalent modifications of histone tail amino acid side chains. These include acetylation of lysine ϵ-amino groups, as mentioned earlier, as well as methylation of these groups, a process that prevents acetylation, thus maintaining their positive charge. Arginine side chains can also be methylated. Serine and threonine side chains can be phosphorylated, introducing a negative charge. Finally, a single 76-amino-acid ubiquitin molecule can be added to some lysines. Recall that addition of multiple linked ubiquitin molecules to a protein can mark it for degradation by the proteasome (Chapter 3). In this case, the addition of a single ubiquitin does not affect the stability of a histone, but influences chromatin structure. In summary, multiple types of covalent modifications of histone tails can influence chromatin structure by altering histone-DNA interactions and interactions between nucleosomes and by controlling interactions with additional proteins that participate in the regulation of transcription, as discussed in the next chapter.

The extent of histone acetylation is correlated with the relative resistance of chromatin DNA to digestion by nucleases. This phenomenon can be demonstrated by digesting isolated nuclei with DNase I. Following digestion, the DNA is completely separated from chromatin protein, digested to completion with a restriction enzyme, and analyzed by Southern blotting (see Figure 9-26). An intact gene treated with a restriction enzyme yields characteristic fragments. When a gene is exposed first to DNase, it is cleaved at random sites within the boundaries of the restriction enzyme cut sites. Consequently, any Southern blot bands normally seen with that gene will be lost. This method has been used to show that the transcriptionally inactive β-globin gene in nonerythroid cells, where it is associated with relatively unacetylated histones, is much more resistant to DNase I than is the active, transcribed β-globin gene in erythroid precursor cells, where it is associated with acetylated histones (Figure 10-22). These results indicate that the chromatin structure of nontranscribed DNA is more condensed, and therefore more protected from DNase digestion, than that of transcribed DNA. In condensed chromatin, the DNA is largely inaccessible to DNase I because of its close association with histones and other less abundant chromatin proteins. In contrast, actively transcribed DNA is much more accessible to DNase I digestion because it is present in the extended, beads-on-a-string form of chromatin.

Genetic studies in yeast indicate that specific histone acetylases are required for the full activation of transcription of a number of genes. Consequently, as discussed in