histone acetylase complex binds to acidic activation domains in yeast activator proteins such as GCN4. Maximal transcription activation by GCN4 depends on these histone acetylase complexes, which thus function as co-activators. The model shown in Figure 11-32b is consistent with the observation that nucleosomes near the promoter region of a gene regulated by the GCN4 activator are specifically hyperacetylated, as determined by the chromatin immunoprecipitation method. The activator-directed hyperacetylation of nucleosomes near a promoter region changes ("opens") the chromatin structure so as to facilitate the binding of other proteins required for transcription initiation.

A similar activation mechanism operates in higher eukaryotes. For example, mammals express two related ≈400-kD, multidomain proteins called *CBP* and *P300*, which are thought to function similarly. As noted earlier, one domain of CBP binds the phosphorylated acidic activation domain in the CREB transcription factor. Other domains of CBP interact with different activation domains in other transcription factors. Yet another domain of CBP has histone acetylase activity, and another CBP domain associates with a multiprotein histone acetylase complex that is homologous to the yeast GCN5-containing complex. CREB and many other mammalian activators are thought to function in part by directing CBP and the associated histone acetylase complex to specific nucleosomes, where they acetylate histone tails, facilitating the interaction of general transcription factors with promoter DNA. In addition, the largest TFIID subunit also has histone acetylase activity and may function as a co-activator by acetylating histone N-terminal tails in the vicinity of the TATA box.

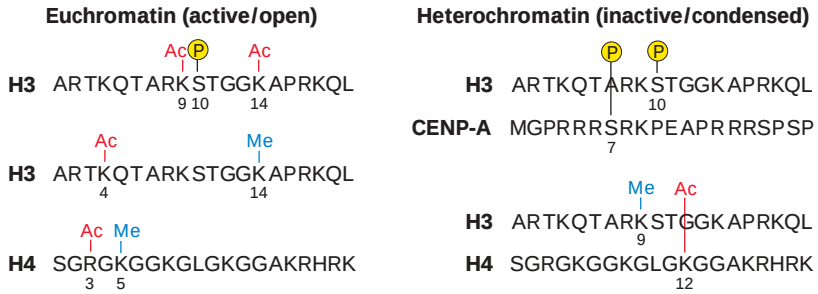
Modifications of Specific Residues in Histone Tails Control Chromatin Condensation

In addition to reversible acetylation, histone tails in chromatin can undergo reversible phosphorylation of serine and threonine residues, reversible monoubiquitination of a lysine residue in the H2A C-terminal tail, and irreversible methylation of lysine residues. Evidence is accumulating that it is not simply the overall level of histone acetylation that controls the condensation of chromatin and hence the accessibility of DNA. Rather the precise amino acids in the tails that are acetylated or otherwise modified may constitute a "*histone code*" that helps control the condensation of chromatin (Figure 11-33). For instance, the lysine at position 9 in histone H3 often is methylated in heterochromatin.

The histone code is "read" by proteins that bind to these specific modifications and in turn promote condensation or decondensation of chromatin, forming "closed" or "open" chromatin structures. For example, higher eukaryotes express a number of heterochromatin-associated proteins containing a so-called *chromodomain*, which binds to the histone H3 tail when it is methylated at lysine 9. These proteins are postulated to contribute to the higher-order folding characteristic of heterochromatin, somewhat like the SIR proteins at yeast telomeres (see Figure 11-30). Alternatively, the *bromodomain* found in a number of euchromatin-associated proteins binds to acetylated histone tails. The largest subunit of TFIID, for example, contains two closely spaced bromodomains, which may help it to associate with chromatin containing an active code, while the histone acetylase activity of this same subunit maintains the chromatin in a hyperacetylated state.

Chromatin-Remodeling Factors Help Activate or Repress Some Genes

In addition to histone acetylase complexes, another type of multiprotein complex, called the *SWI/SNF chromatin-remodeling complex*, is required for activation at some yeast promoters. Several of the SWI/SNF subunits have homology to DNA helicases, enzymes that use energy from ATP hydrolysis to disrupt interactions between base-paired nucleic acids or between nucleic acids and proteins. The SWI/SNF complex is thought to transiently dissociate DNA from the surface of nucleosomes, permitting nucleosomes to "slide" along the DNA and promoting the unfolding of condensed,



▲ FIGURE 11-33 **Examples of the histone code.** Specific post-translational modifications of the N-terminal tails in histones H3 and H4 are found in euchromatin, which is accessible to proteins and transcriptionally active. Different modifications are found in heterochromatin, which is condensed and thus largely inaccessible to proteins and transcriptionally inactive. Histone tail sequences are shown in the one-letter amino acid code. CENP-A is a variant form for H3 found in nucleosomes associated with the centromeres of mammalian chromosomes. [Adapted from T. Jenuwein and C. D. Allis, 2001, *Science* **293**:1074.]