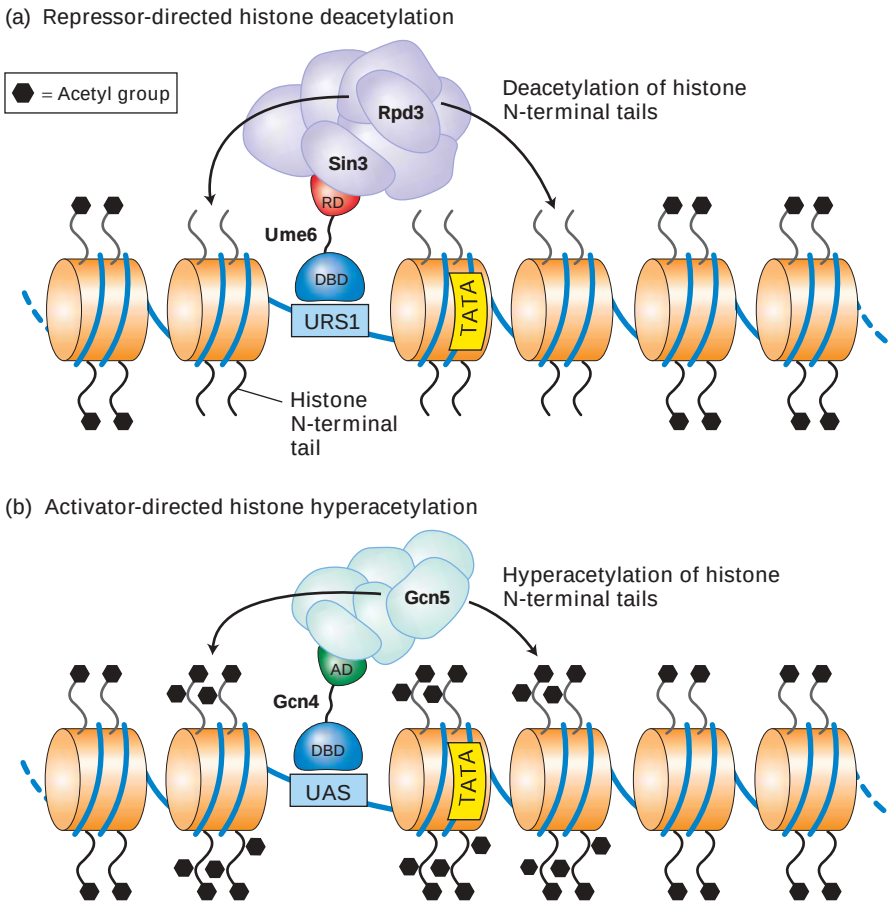

◀ FIGURE 11-32 **Proposed mechanism of histone deacetylation and hyperacetylation in yeast transcription control.** (a) Repressor-directed deacetylation of histone N-terminal tails. The DNA-binding domain (DBD) of the repressor UME6 interacts with a specific upstream control element (URS1) of the genes it regulates. The UME6 repression domain (RD) binds SIN3, a subunit of a multiprotein complex that includes RPD3, a histone deacetylase. Deacetylation of histone N-terminal tails on nucleosomes in the region of the UME6-binding site inhibits binding of general transcription factors at the TATA box, thereby repressing gene expression. (b) Activator-directed hyperacetylation of histone N-terminal tails. The DNA-binding domain of the activator GCN4 interacts with specific upstream activating sequences (UAS) of the genes it regulates. The GCN4 activation domain (AD) then interacts with a multiprotein histone acetylase complex that includes the GCN5 catalytic subunit. Subsequent hyperacetylation of histone N-terminal tails on nucleosomes in the vicinity of the GCN4-binding site facilitates access of the general transcription factors required for initiation. Repression and activation of many genes in higher eukaryotes occurs by similar mechanisms.

RPD3. SIN3 also binds to the repression domain of UME6, thus positioning the RPD3 histone deacetylase in the complex so it can interact with nearby promoter-associated nucleosomes and remove acetyl groups from histone N-terminal lysines. Additional experiments, using the *chromatin immunoprecipitation* technique outlined in Figure 11-31, demonstrated that in wild-type yeast, one or two nucleosomes in the immediate vicinity of UME6-binding sites are hypoacetylated. These DNA regions include the promoters of genes repressed by UME6. In *sin3* and *rpd3* deletion mutants, not only were these promoters derepressed, but the nucleosomes near the UME6-binding sites were hyperacetylated.

All these findings provide considerable support for the model of repressor-directed deacetylation shown in Figure 11-32a. In this model, the SIN3-RPD3 complex functions as a co-repressor. Co-repressor complexes containing histone deacetylases also have been found associated with many repressors from mammalian cells. Some of these complexes contain the mammalian homolog of SIN3 (mSin3), which interacts with the repressor protein. Other histone deacetylase complexes identified in mammalian cells appear to contain additional or different repressor-binding proteins. These various repressor and co-repressor combinations are thought to mediate histone deacetylation at specific promoters by a mechanism similar to the yeast mechanism (see Figure 11-32a). However, the observation that a number of eukaryotic repressor proteins inhibit in vitro transcription in the absence of histones indicates that more direct repression mechanisms, not involving histone deacetylation, also operate.

The discovery of mSin3-containing histone deacetylase complexes provides an explanation for earlier observations that in vertebrates transcriptionally inactive DNA regions often contain the modified cytidine residue *5-methylcytidine* (mC) followed immediately by a G, whereas transcriptionally active DNA regions lack mC residues. DNA containing 5-methylcytidine has been found to bind a specific protein that in turn interacts specifically with mSin3. This finding suggests that association of mSin3-containing co-repressors with methylated sites in DNA leads to deacetylation of histones in neighboring nucleosomes, making these regions inaccessible to general transcription factors and Pol II, and hence transcriptionally inactive.

Activators Can Direct Histone Acetylation at Specific Genes

Genetic and biochemical studies in yeast led to discovery of a large multiprotein complex containing the protein GCN5, which has histone acetylase activity. Another subunit of this