The Tup1p-Cyc8p corepressor is important for the repression of many genes involved in a wide variety of physiological processes. Tup1p-Cyc8p may also be involved in the derepression of at least some target genes. The active form of the corepressor consists of a protein complex containing four Tup1p subunits and a single Cyc8p subunit. The Tup1 protein comprises three functionally defined domains: an N-terminus involved in the interaction with Cyc8p; a central domain required for the repression activity of the complex; and a C-terminus containing seven WD40 repeats that form a beta-transducin-like propeller structure important for protein interactions and tetramerization. Tup1p-Cyc8p mediates repression of target genes by different molecular mechanisms. Tup1p-Cyc8p can recruit histone deacetylases to genes, which results in deacetylation of histones producing a repressive chromatin structure. Tup1p-Cyc8p can also interact with hypoacetylated N-terminal tails of histones H3and H4that have been programmed for repression by the action of histone deacetylases. In addition, Tup1p-Cyc8p can interfere directly with the transcriptional machinery by interacting with factors important for the repressive activity of the RNA polymerase II mediator subcomplex. Tup1p-Cyc8p is recruited to target genes by interaction with DNA-bound transcriptional repressors that recognize specific sequences within the target gene promoters. Such repressors include MatAlpha2p, which regulates mating-type-specific genes, Mig1p, which regulates glucose-repressed genes, Rfx1p, which is involved in DNA repair, and Sko1p, which is involved in stress responses. This gene-specific role has been complemented by observations that Tup1p might be involved in establishing domains of heterochromatin structure in the subtelomeric regions of chromosomes. These \"HAST\" domains contain clusters of Tup1p- and Cyc8p-repressed genes and coincide with regions that are deacetylated by the histone deacetylase Hda1p. Therefore, Tup1p-Cyc8p may establish the formation of heterochromatin in these regions by recruiting Hda1p. HAST domains are distinct from adjacent heterochromatin regions that are established via Tup1p-independent recruitment of the Sir2p histone deacetylase.