The WHI5 gene encodes a cell cycle regulated transcriptional repressor that inhibits both SBFand MBFmediated G1/S phase transcription. SBF and MBF complexes both contain the Swi6p transcriptional coactivator and either Swi4por Mbp1p, two sequence specific DNA binding proteins. These complexes bind to SCBor MCBpromoter sites to enhance the transcription of hundreds of genes, including additional transcription factors. This results in the initiation of a complex transcriptional cascade required for coordinated cell cycle progression. Whi5p associates with G1-specific promoters through direct interactions with both SBF and MBF and affects the onset of G1/S phase transcription. The CDK/Cyclin complex, Cln3p/Cdc28p, a key regulator of both MBF- and SBF-dependent gene expression, hyperphosphorylates the WHI5 protein during late G1 causing it to dissociate from SBF and exit the nucleus where it remains until the end of mitosis. Whi5p re-enters the nucleus after CDK activity is eliminated by the mitotic exit network.A regulatory role was originally proposed for WHI5 when the complete set of deletion mutants was screened to identify novel genes that influence cell size and the subset of these that affect the critical cell size threshold required for passage through Start. The whi5 deletion mutant was found to pass through Start at about half the size of congenic wild-type cells, thereby accelerating the G1/S phase transition. Conversely, overexpression of WHI5 causes both a G1 delay and an increase in cell size in wild-type cells. In addition, deletion of WHI5 results in increased resistance to mating pheromone, a phenotype shared by other WHI mutants that regulate Start including: CLN3-1, whi3, and, vps51.Epistatic size interactions place WHI5 upstream of SBF, since the small cell size phenotype of the WHI5 deletion is dependent on the presence of functional copies of SWI4 and SWI6. Deletion of WHI5 partially suppresses the increase in cell size caused by CLN3 inactivation and does not alter the small size phenotype of the CLN3-1 mutation; thus CLN3 functions upstream of WHI5 in keeping with other genetic and biochemical results.Whi5p functions in an equivalent regulatory pathway as that of the retinoblastomafamily proteins in metazoans and appears to be the budding yeast analog of Rb. The tumor suppressor Rb and related proteins function in quiescent cells and during the G1 phase of cycling cells to inhibit S phase entry through direct binding and inhibition of members of the E2F family of transcription factors. Mitogenic stimulation results in the inactivation of Rb proteins through, cyclinD/Cdk4 and cyclinE/Cdk2 dependent hyperphosphoryation, liberating E2F proteins and their heterodimeric partners to activate the transcriptional cascade required for timely S phase entry. Cln3p and Cln1p or Cln2p can mediate the stepwise phosphorylation of mammalian Rb when expressed in yeast and these functions can be complemented in yeast cells lacking G1 cyclins through the heterologous expression of human cyclins, D1 and E1. In addition, mouse embryonic fibroblasts derived from mice with a triple knockout of Rb family members have a small cell size phenotype similar to what is observed when WHI5 is deleted.