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Structural Studies of BTB Domains from Transcription Factors and their Complexes with Corepressors.

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The human oncogene *BCL6* is a BTB-zinc finger transcriptional repressor involved in the pathogenesis of B-cell lymphomas. The N-terminal BTB domain of *BCL6* forms an obligate homodimer that associates with BTB binding domains (BBDs) of various corepressors, including SMRT and BCoR. Our previous crystallographic work revealed that the 17 residue SMRT BBD binds into the *BCL6* BTB lateral groove. We have now determined the 2.4 Å crystal structure of *BCL6* BTB in complex with the BCoR BBD. The space group is P6(1)22, the unit cell dimensions are (a,b) = 150 Å, c = 312 Å, and each asymmetric unit contains 8 BTB chains and 8 BCoR BBD peptides. The structure was solved with PHASER using a *BCL6* BTB dimer as a search model. The BBDs of SMRT and BCoR share no sequence similarity, yet the peptides follow very similar surfaces along the *BCL6* BTB lateral groove. The majority of BTB-BBD interactions involve conserved mainchain interactions, however alanine scanning mutagenesis showed that each BBD has a unique set of side-chain that are essential for BTB binding. We also find that histidine 116 of *BCL6* acts as a toggle switch that is flipped in or out upon SMRT and BCoR binding, respectively. In conclusion, our results illustrate a mechanism by which one binding site can recognize multiple non-conserved sequences.