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Crystal Structure of a Biologically Active Peptide Complexed with G-Protein Beta:Gamma Subunits. Tara Davis¹, T. Bonacci², A. M. Smrcka², Stephen R. Sprang¹, ¹The Univ. of Texas Southwestern Medical Center, Dallas, TX, 75390, ²Univ. of Rochester, Rochester, NY, 14627.

Heterotrimeric G proteins function in diverse pathways in eukaryotic cells. Much attention has been paid to the interactions of activated (GTP-bound) α ; however, $\beta\gamma$ subunits also participate in multiple signaling interactions when released from α . We have solved the crystal structure of $\beta_1\gamma_2$ bound to a peptide obtained from a randomized library. This peptide inhibits multiple $\beta\gamma$ mediated signaling events and binds $\beta\gamma$ with sub-micromolar IC_{50} . The structure has been solved by molecular replacement to a resolution of 2.7Å; the peptide is well ordered – 13 of the 15 amino acids have clear electron density. This structure has four complexes in the asymmetric unit; the crystal exhibits P2₁2₁2 pseudosymmetry but is actually P1. Cell parameters are a=45.419 Å, b=74.297 Å, c=107.673 Å; $\alpha=90.03^\circ$, $\beta=90.03^\circ$, $\gamma=89.82^\circ$. R_{work} is 22.5% and R_{free} is 27.0%. $\beta_1\gamma_2$ binds the peptide by utilizing an interface important for other $\beta\gamma$ target binding and suggests an explanation for the biological effects of the peptide. More importantly this structure may lead to a greater understanding of one way that a general binding surface is able to sustain a wide range of interactions with multiple protein partners.

