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Structural and Biophysical Characterization of Two hEphB4 Complexes: Insights into Modulating Protein-Protein Interactions. Jill E. Chrencik, Alexei Brooun, Michael I. Recht, Michelle L. Kraus, Anand R. Kolatkar, Peter Kuhn, Dept. of Cellular Biology, The Scripps Research Institute, La Jolla, CA 92037.

The Eph family of receptor tyrosine kinases and their ligands, the ephrins, regulate numerous biological processes in developing and adult tissues, and have more recently been implicated in cancer progression and in pathological forms of angiogenesis. Recent biochemical studies suggest that agonizing EphB4 signaling, or antagonizing ephrin-B2 signaling, results in the inhibition of cellular proliferation *in vitro*. Here we present the 1.65 Å crystal structure of the ligand binding domain of EphB4 in complex with an antagonistic peptide that inhibits ephrin-B2 binding and exhibits anti-tumorigenic properties *in vivo*. Further, we present the 1.9 Å crystal structure of the EphB4-ephrin-B2 complex. A thorough comparative analysis of the two structures reveals how subtle differences in the amino acid composition of the receptor G-H and J-K loops results in the recruitment of a unique set of ligands to the cell surface. ITC and FP studies further reveal the molecular determinants for the directed specificity unique to the EphB4 receptor, allowing the first insights into modulating pathways resulting in tumorigenesis and angiogenesis that rely on EphB4-ephrinB2 signaling.