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Processing Conformation of MAP Kinases. E.J. Goldsmith, T. Zhou, J. Humphreys, R. Akella, Dept. of Biochemistry, Univ. of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 90-8816.

MAP kinases interact with docking motifs in activating kinases, phosphatases, and substrates that bind to sites outside the kinase active site. Here we report a 1.9 Å crystallographic analysis of inactive ERK2 bound to a "D-domain" docking motif peptide (pepHePTP) derived from hematopoietic tyrosine phosphatase, a negative regulator of ERK2. In this complex, the complete D-domain docking motif interaction defined by mutagenic analysis is observed for the first time, including extensive electrostatic interactions with the "CD site" of the kinase. Large conformational changes occur affecting the activation loop conformation: the phosphorylation sites, which are buried in the inactive form of ERK2, become exposed to solvent, which may promote processing. Similar conformational changes occur in a complex between ERK2 and a MEK2 (MAP/ERK kinase 2)-derived peptide. The peptide binding interaction and conformational changes are similar yet unique among the MAP kinases ERK2, p38 α and JNK1, offering insights into the mechanisms of specificity determination.