Molecular Basis for the Allosteric Inhibition of JNKs by the Peptide Fragment from the Scaffolding Protein JIP1

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The c-jun N-terminal kinase (JNK) signaling pathway is regulated by JNK-interacting protein-1 (JIP1), which is a scaffolding protein assembling the components of the JNK cascade. Overexpression of JIP1 deactivates the JNK pathway selectively by cytoplasmic retention of JNK and thereby inhibits gene expression mediated by JNK, which occurs in the nucleus. Here, we report the crystal structures of human JNK1, 2, and 3 complexed with pepJIP1, the peptide fragment of JIP1, revealing its selectivity for JNKs over other MAPKs and the allosteric inhibition mechanism. The specific hydrogen bonds between JNKs and pepJIP1 can provide the selective regulation. Binding of the peptide also induces a hinge motion between the N- and C-terminal domains of JNKs and distorts the ATP-binding cleft, reducing the affinity of the kinase for ATP. Considering the value of JNKs as therapeutic targets for several diseases, the information from these structures can contribute to the optimization of JNK inhibitors of high affinity and specificity, which can be derived from pepJIP1. In addition, we also determined the ternary complex structures of pepJIP1-bound JNK1, 2, and 3 complexed with SP600125, an ATP-competitive inhibitor of JNKs, providing the basis for the JNK specificity of the compound.

Keywords: JNK, scaffolding protein, JIP1