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Purification, Crystallization and Structure Solution of the Complex between p38 α and its Substrate MK2.

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The p38 mitogen-activated protein kinase pathway is required for the production of proinflammatory cytokines (TNF α and IL-1) that mediate the chronic inflammatory phases of several autoimmune diseases. p38 transduces signals through downstream effectors, including mitogen-activated protein kinase-activated protein kinases (MKs). Genetic deletion and phosphorylation studies indicated that MK2 participates in p38-dependent modulation of production of inflammatory cytokines. The catalysis and function of the p38 α :MK2 signaling complex have been recently described. We report here the purification, crystallization and 3.1 Å structure of the inactive p38 α :MK2 complex. The interactions between the two kinases involve mainly the previously identified p38 docking groove (residues E160 and E161), and MK2 docking domain peptide. The formation of the complex positions MK2 S272 (one of the residues that need to be phosphorylated for maximal activation of MK2) near the ATP-binding site of p38 α , suggesting that this is indeed a biological complex and not a crystallization artifact. Together with the already available biochemical data, this structure may help in understanding the complex formation and function at the molecular level.