Structures of Mnk-2 Reveal Novel Aspects of Kinase Regulation

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Human MAP kinase interacting kinase-2 (Mnk-2) targets the translational machinery by phosphorylation of the eukaryotic initiation factor 4e (eIF4E) and plays intricate roles in growth control. Here we present the 2.0 Å crystal structure of the non-phosphorylated Mnk-2 catalytic domain. The results show unique Mnk-specific features such as a zinc binding motif and an atypical open conformation of the activation segment. In addition, the ATP-binding pocket contains Asp-Phe-Asp (DFD) in place of the canonical magnesium-binding Asp-Phe-Gly (DFG) motif. The DFD motif sterically inhibits productive ATP binding as observed with inhibitor-bound p38 kinase. Replacement of DFD by the canonical DFG motif affects the conformation of Mnk-2, but not the ATP-binding and the activity profile of Mnk-2. The results suggest that the ATP binding pocket and the activation segment of Mnk-2 require conformational switches to provide kinase activity.

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