Poster presentations

MS1. Recent experimental developments in synchrotron macromolecular crystallography

Chairs: Gordon Leonard, Marjolein Thunnissen

MS1-P1 The structures of the kinase domain and UBA domain of MPK38 suggest the activation mechanism for kinase activity

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Murine protein serine/threonine kinase 38 (MPK38) is the murine ortholog of human maternal embryonic leucine zipper kinase (MELK), which belongs to the SNF1/AMPK family. MELK is considered as a promising drug target for anticancer therapy, because MELK overexpression and hyper-activation correlate with several human cancers. Activation of MPK38 requires the extended sequence (ExS) containing the ubiquitin-associated (UBA) linker and UBA domain, and phosphorylation of the activation loop. However, the activation mechanism of MPK38 is unknown. This paper reports the crystal structure of MPK38 (T167E), which mimics a phosphorylation state of the activation loop in complex with AMP-PNP. In the MPK38 structure, the UBA linker forces the inward movement of the αC helix into an intermediate conformation, in which the activation loop might not be stabilized. Then, phosphorylation of the activation loop induces movement of the activation loop toward the C-lobe and results in closing of interlobar cleft. These processes generate a fully active state of MPK38. This structure suggests that MPK38 has a similar molecular activation mechanism as that of other kinases of the SNF1/AMPK family. Recently, we also reported the structure of MPK38 in complex with OTSSP167, which is an orally administrative MELK selective inhibitor, conferring an IC_{50} of 0.41 nM. OTSSP167 effectively fits into the active site of MPK38, thus offering an opportunity for structure-based development and optimization of MELK inhibitors.

Keywords: MPK38, UBA Linker, Protein crystal structure