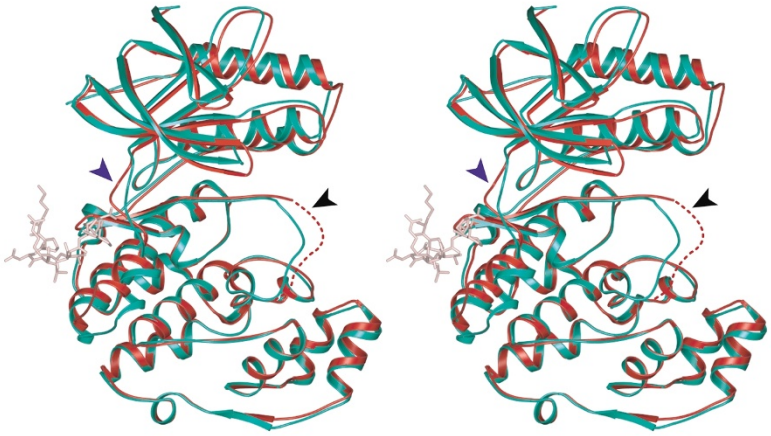
MAPping p38 binding interactions

The mitogen-activated protein kinases, or MAP kinases, mediate cellular responses to extracellular signals by phosphorylation of downstream factors. Members of the p38 MAP kinase family are activated in response to physical and chemical stresses and are regulated by many different extracellular signaling molecules, including cytokines, growth factors and neuropeptides. Although more and more structural data is becoming available for the MAP kinases, our understanding of how a specific pathway is selected during the signaling process is complicated by the fact that MAP kinases are notoriously promiscuous. A single kinase may be involved in multiple signaling cascades and interact with numerous substrates and activators, as well as scaffolding proteins and inactivating enzymes. Understanding how multiple and diverse proteins interact with p38 and affect p38 kinase activity is an area of intense study.

In a recent issue of *Molecular Cell* (*Mol. Cell* **9**, 1241–1249; 2002), Chang *et al.* investigate the structural changes in p38 MAP kinase that arise upon binding to peptides comprising the docking sites of p38 substrate MEF2A and activator MKK3b. Comparison (*via* superposition) of the structures of p38 with (red) and without (green) the MEF2A peptide revealed some interesting features. The peptide, shown in pink, binds to p38 in a groove in the C-terminal domain. The binding groove is near, though distinct from, the active site (indicated by blue arrowhead).



The activator MKK3b peptide binds at the same site, which is perhaps not unexpected. Docking site sequences similar to those identified in p38 substrates had been identified in activating enzymes and MAP kinase scaffolding proteins as well as the inactivating protein tyrosine phosphatases, suggesting similar modes of interaction between these diverse proteins and p38. Substrate docking is thought to be important for determining signaling pathway. If activating enzymes (or inactivating enzymes or scaffolding proteins) are interacting in a similar fashion, how is it that they elicit their specific response in p38? From the structures reported by Chang *et al.*, it seems that these different responses may be linked to conformational changes in the p38 active site and phosphorylation lip (black arrowhead), which differ according to the identity of the docked protein (or, in this case, peptide).

Both the transcription factor substrate MEF2A peptide and the activating enzyme MKK3b peptide induce large conformational changes in the binding groove. However, both peptides also induce separate and distinct changes at the active site, which may have implications in p38 activation. The phosphorylation lip, which contains the sites where phosphorylation occurs during kinase activation, exhibits perhaps the most significant change on binding of either peptide. In both cases, peptide binding induces disorder in the phosphorylation lip (signified with a dashed line in the MEF2A peptide-bound p38). Although the physiological relevance of these conformational changes is so far unclear, Chang *et al.* suggest that in the case of MKK3b, binding of the activating enzyme may release this loop for binding into the MKK3b active site allowing for phosphorylation — and thus activation — of p38.

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