

SBS Seminar Announcement

Structural insights into non-canonical activation modes of p38 α MAP kinase

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Abstract

MAP kinases are involved in numerous signaling processes that are crucial for normal function of cells and organisms. MAP kinases are mainly activated via the canonical three-tiered cascade leading to dual phosphorylation on adjacent Thr-180 and Tyr-182 (p38 α numbering) located on the phosphorylation lip. For p38 α several alternative activation pathways and modes have been identified where one is induced by T-cell receptor activation and subsequent phosphorylation of p38 α on the distinctive Tyr-323 distal from the phosphorylation lip by ZAP-70 tyrosine kinase. Consequent to Tyr-323 phosphorylation, autoactivation occurs in trans, resulting in monophosphorylation of Thr-180. This alternative pathway differs in its substrate selectivity profile from the canonical one. The structures of intrinsically active 232-site mutants considered to emulate the phosphorylated form, exhibit conformational changes depicting the molecular basis for autophosphorylation and subsequent activation. An additional activation mode was revealed while screening for Akt phosphatidyl inositol analogues (PIAs) inhibitors. It was also shown that these lipid molecules bind and activate p38 α inducing autoactivation and apoptosis. Perifosine, an Akt inhibitor, also exhibit p38 α activation properties similarly to those of PIAs. The crystal structures of p38 α in complex with activating lipid molecules identify a new activation site in the p38 α C-lobe. In addition conformational changes in the α EF/ α F loop could play an essential role in the autoactivation properties. This site could become a platform towards the design of specific inhibitors and activators of p38 α .

Thursday, 04 Jul 2013 11am to 12pm SBS Classroom 2 (SBS-01n-22)

Host: Associate Professor Julien Lescar