

The STRIPAK PP2A complex couples upstream inputs to control Hippo kinase activation

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The Hippo pathway is a growth control pathway that plays key roles in organ size control, tissue homeostasis and tumor suppression. The mammalian Hippo pathway contains a core MST-LATS kinase cascade. Recently, we have shown that the STRIPAK PP2A complex is a key negative regulator of Hippo signaling in human cells. MST2 interacts with STRIPAK through the adaptor protein SLMAP. The SLMAP-containing STRIPAK complex specifically blocks MST2 activation by dephosphorylating phospho-T180 (pT180) at its activation loop. Inactivation of STRIPAK-SLMAP leads to spontaneous activation of the Hippo pathway without upstream signals. In our most recent studies, we have defined the core components of the specific STRIPAK complex critical for MST2 inhibition in human cells. We show that phosphorylation of SAV1 by the GCK-III kinase (the kinase component of STRIPAK) blocks STRIPAK-mediated inhibition of MST2. We hypothesize that STRIPAK serves as a major signaling platform that enables the regulation of MST2 activation by upstream regulators.