Molecular & Cellular Biology Faculty Search

"The mechano-responses of a non-canonical Hippo kinase cascade"

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Hosted By: Guang Yao

The Hippo pathway plays a central role in tissue homoeostasis, and its dysregulation contributes to tumorigenesis. Core components of the Hippo pathway include a kinase cascade of MST1/2 and LATS1/2 and the transcription co-activators YAP/TAZ. Through a kinome screening, we identified MAP4K family members--Drosophila Happyhour homologues MAP4K1/2/3 and Misshapen homologues MAP4K4/6/7-as the non-canonical Hippo kinases that directly phosphorylate and activate LATS1/2-activating kinases. Combined deletion of MAP4Ks and MST1/2 abolishes YAP/TAZ phosphorylation by growth-inhibiting signals. We further discovered that extracellular matrix (ECM) stiffness regulates activities of MAP4Ks through RAP2 small GTPases. RAP2 is activated by low ECM stiffness, and deletion of RAP2 blocks the regulation of YAP and TAZ by stiffness signals and promotes aberrant cell growth. Moreover, deletion of RAP2 or LATS1/2 abolishes the ECM stiffness-responsive transcriptome. Our findings show that RAP2 is a molecular switch in mechanotransduction, thereby defining a mechanosignalling pathway from ECM stiffness to the nucleus.

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