Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references


Reactome database release: 79

This document contains 1 pathway and 30 reactions (see Table of Contents)
Human Hippo signaling is a network of reactions that regulates cell proliferation and apoptosis, centered on a three-step kinase cascade. The cascade was discovered by analysis of Drosophila mutations that lead to tissue overgrowth, and human homologues of its components have since been identified and characterized at a molecular level. Data from studies of mice carrying knockout mutant alleles of the genes as well as from studies of somatic mutations in these genes in human tumors are consistent with the conclusion that in mammals, as in flies, the Hippo cascade is required for normal regulation of cell proliferation and defects in the pathway are associated with cell overgrowth and tumorigenesis (Oh and Irvine 2010; Pan 2010; Zhao et al. 2010). This group of reactions is also notable for its abundance of protein:protein interactions mediated by WW domains and PPxY sequence motifs (Sudol and Harvey 2010).

There are two human homologues of each of the three Drosophila kinases, whose functions are well conserved: expression of human proteins rescues fly mutants. The two members of each pair of human homologues have biochemically indistinguishable functions. Autophosphorylated STK3 (MST2) and STK4 (MST1) (homologues of Drosophila Hippo) catalyze the phosphorylation and activation of LATS1 and LATS2 (homologues of Drosophila Warts) and of the accessory proteins MOB1A and MOB1B (homologues of Drosophila Mats). LATS1 and LATS2 in turn catalyze the phosphorylation of the transcriptional co-activators YAP1 and WWTR1 (TAZ) (homologues of Drosophila Yorkie).

In their unphosphorylated states, YAP1 and WWTR1 freely enter the nucleus and function as transcriptional co-activators. In their phosphorylated states, however, YAP1 and WWTR1 are instead bound by 14-3-3 proteins, YWHAB and YWHAE respectively, and sequestered in the cytosol.

Several accessory proteins are required for the three-step kinase cascade to function. STK3 (MST2) and STK4 (MST1) each form a complex with SAV1 (homologue of Drosophila Salvador), and LATS1 and LATS2 form complexes with MOB1A and MOB1B (homologues of Drosophila Mats).

In Drosophila a complex of three proteins, Kibra, Expanded, and Merlin, can trigger the Hippo cascade. A human homologue of Kibra, WWC1, has been identified and indirect evidence suggests that it can regulate the human Hippo pathway (Xiao et al. 2011). A molecular mechanism for this interaction has not
yet been worked out and the molecular steps that trigger the Hippo kinase cascade in humans are unknown.

Four additional processes related to human Hippo signaling, although incompletely characterized, have been described in sufficient detail to allow their annotation. All are of physiological interest as they are likely to be parts of mechanisms by which Hippo signaling is modulated or functionally linked to other signaling processes. First, the caspase 3 protease cleaves STK3 (MST2) and STK4 (MST1), releasing inhibitory carboxyterminal domains in each case, leading to increased kinase activity and YAP1 / TAZ phosphorylation (Lee et al. 2001). Second, cytosolic AMOT (angiomotin) proteins can bind YAP1 and WWTR1 (TAZ) in their unphosphorylated states, a process that may provide a Hippo-independent mechanism to down-regulate the activities of these proteins (Chan et al. 2011). Third, WWTR1 (TAZ) and YAP1 bind ZO-1 and 2 proteins (Remue et al. 2010; Oka et al. 2010). Fourth, phosphorylated WWTR1 (TAZ) binds and sequesters DVL2, providing a molecular link between Hippo and Wnt signaling (Varelas et al. 2010).

**Literature references**


**Editions**

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Phosphorylation of STK3 (MST2) and SAV1 by STK3

Location: Signaling by Hippo

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