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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142.

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467.

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655.

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968.

Reactome database release: 82

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**

Lei, Q., Guan, KL., Li, L., Zhao, B. (2010). The Hippo-YAP pathway in organ size control and tumorigenesis: an updated version. *Genes Dev*, 24, 862-74.

Pan, D. (2010). The hippo signaling pathway in development and cancer. *Dev Cell*, 19, 491-505.

Tsubuki, S., Yajima, N., Lee, KK., Ohyama, T., Yonehara, S. (2001). MST, a physiological caspase substrate, highly sensitizes apoptosis both upstream and downstream of caspase activation. *J Biol Chem*, 276, 19276-85.

Meerschaert, K., Vandekerckhove, J., Remue, E., Gettemans, J., Sudol, M., Boucherie, C. et al. (2010). TAZ interacts with zonula occludens-1 and -2 proteins in a PDZ-1 dependent manner. *FEBS Lett*, 584, 4175-80.

Chen, Y., Ji, M., Dong, J., Xiao, L. (2011). KIBRA regulates Hippo signaling activity via interactions with large tumor suppressor kinases. *J Biol Chem*, 286, 7788-96.

**Editions**

| Date       | Action       | Author       |
|------------|--------------|--------------|
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| 2012-02-03 | Authored     | D'Eustachio, P. |
| 2012-02-03 | Reviewed     | Sudol, M. |

https://reactome.org
The serine/threonine kinase STK3 (MST2) catalyzes its own autophosphorylation as well as the phosphorylation of SAV1. These two reactions are annotated here as a single concerted process that takes place in a tetrameric complex containing two STK3 (MST2) subunits and two SAV1 subunits, based on the observations that STK3 (MST2) can catalyze both phosphorylation reactions in vitro, as well as the observations that each protein dimerizes and that STK3 (MST2) and SAV1 associate to form a complex. The order in which the various components associate, the stoichiometry of the complex ultimately formed, and the point(s) in this association process at which phosphorylation occurs have not been established in vitro or in vivo, however (Callus et al. 2006; Praskova et al. 2004).

Followed by: Phosphorylation of LATS1 and 2 by p-STK3 (p-MST2), Phosphorylation of MOB1A and B by p-STK3 (p-MST2), Cleavage of p-STK3 (p-MST2) by caspase 3

Literature references

Ortiz-Vega, S., Khoklatchev, A., Praskova, M., Avruch, J. (2004). Regulation of the MST1 kinase by autophosphorylation, by the growth inhibitory proteins, RASSF1 and NORE1, and by Ras. Biochem J, 381, 453-62.

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Callus, BA., Vaux, DL., Verhagen, AM. (2006). Association of mammalian sterile twenty kinases, Mst1 and Mst2, with hSalvador via C-terminal coiled-coil domains, leads to its stabilization and phosphorylation. FEBS J, 273, 4264-76.
Phosphorylation of STK4 (MST1) and SAV1 by STK4

Location: Signaling by Hippo

Stable identifier: R-HSA-2028284

Type: transition

Compartments: cytosol

The serine/threonine kinase STK4 (MST1) catalyzes its own autophosphorylation as well as the phosphorylation of SAV1. These two reactions are annotated here as a single concerted process that takes place in a tetrameric complex containing two STK4 (MST1) subunits and two SAV1 subunits, based on the observations that STK4 (MST1) can catalyze both phosphorylation reactions in vitro, as well as the observations that each protein dimerizes and that STK4 (MST1) and SAV1 associate to form a complex. The order in which the various components associate, the stoichiometry of the complex ultimately formed, and the point(s) in this association process at which phosphorylation occurs have not been established in vitro or in vivo, however (Callus et al. 2006; Creasy et al. 1996; Praskova et al. 2004).

Followed by: Phosphorylation of LATS1 and 2 by p-STK4 (p-MST1), Phosphorylation of MOB1A and B by p-STK4 (p-MST1), Cleavage of p-STK4 (p-MST1) by caspase 3

Literature references

Ortiz-Vega, S., Khoklatchev, A., Praskova, M., Avruch, J. (2004). Regulation of the MST1 kinase by autophosphorylation, by the growth inhibitory proteins, RASSF1 and NORE1, and by Ras. Biochem J, 381, 453-62.

Ambrose, DM., Creasy, CL., Chernoff, J. (1996). The Ste20-like protein kinase, Mst1, dimerizes and contains an inhibitory domain. J Biol Chem, 271, 21049-53.

Callus, BA., Vaux, DL., Verhagen, AM. (2006). Association of mammalian sterile twenty kinases, Mst1 and Mst2, with hSalvador via C-terminal coiled-coil domains, leads to its stabilization and phosphorylation. FEBS J, 273, 4264-76.

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Cleavage of p-STK3 (p-MST2) by caspase 3

Location: Signaling by Hippo

Stable identifier: R-HSA-2028697

Type: transition

Compartments: cytosol

Cytosolic caspase 3 cleaves p-STK3 (p-MST2) to yield an active amino-terminal fragment (p-STK3/N) and a carboxy-terminal fragment (p-STK3/C) (Lee et al. 2001). The association of p-STK3 (p-MST2) with other proteins at the time of its cleavage by caspase has not been studied experimentally. Here, it is inferred to be dimerized and in a complex with SAV1 because that is the form of the molecule that becomes phosphorylated and phosphorylation appears normally to precede caspase cleavage. The effect of the cleavage is to increase the kinase activity of p-STK3 (p-MST2).

Preceded by: Phosphorylation of STK3 (MST2) and SAV1 by STK3

Followed by: Phosphorylation of LATS1 and 2 by p-STK3 (MST2)/N, Phosphorylation of MOB1A and B by p-STK3(MST2)/N

Literature references

Tsubuki, S., Yajima, N., Lee, KK., Ohyama, T., Yonehara, S. (2001). MST, a physiological caspase substrate, highly sensitizes apoptosis both upstream and downstream of caspase activation. *J Biol Chem*, 276, 19276-85.

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Cleavage of p-STK4 (p-MST1) by caspase 3

Location: Signaling by Hippo

Stable identifier: R-HSA-2028692

Type: transition

Compartments: cytosol

Cytosolic caspase 3 cleaves p-STK4 (p-MST1) to yield an active amnio-terminal fragment (p-STK4/N) and a carboxy-terminal fragment (p-STK4/C) (Graves et al. 1998; Lee et al. 2001). The association of p-STK4 (p-MST1) with other proteins at the time of its cleavage by caspase has not been studied experimentally. Here, it is inferred to be dimerized and in a complex with SAV1 because that is the form of the molecule that becomes phosphorylated and phosphorylation appears normally to precede caspase cleavage. The effect of the cleavage is to increase the kinase activity of p-STK4 (p-MST1).

Preceded by: Phosphorylation of STK4 (MST1) and SAV1 by STK4

Followed by: Phosphorylation of LATS1 and 2 by p-STK4(MST1)/N, Phosphorylation of MOB1A and B by p-STK4(MST1)/N

Literature references

Tsubuki, S., Yajima, N., Lee, KK., Ohyama, T., Yonehara, S. (2001). MST, a physiological caspase substrate, highly sensitizes apoptosis both upstream and downstream of caspase activation. J Biol Chem, 276, 19276-85.

Ambrose, DM., Krebs, EG., Han, DK., Gotoh, Y., Clark, EA., Draves, KE. et al. (1998). Caspase-mediated activation and induction of apoptosis by the mammalian Ste20-like kinase Mst1. EMBO J, 17, 2224-34.

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Cytosolic KIBRA (WWC1) binds LATS proteins. The stoichiometry of the resulting complex is unknown. The interaction of KIBRA with LATS directly or indirectly stimulates the phosphorylation of the latter proteins, so this interaction may promote LATS activation and, ultimately, YAP1 and TAZ sequestration in vivo (Xiao et al. 2011).

**Literature references**

Chen, Y., Ji, M., Dong, J., Xiao, L. (2011). KIBRA regulates Hippo signaling activity via interactions with large tumor suppressor kinases. *J Biol Chem*, 286, 7788-96.
NPHP4 protein binds LATS proteins

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2059926

**Type:** binding

**Compartments:** cytosol

Cytosolic NPHP4 protein binds LATS proteins to form a complex. The stoichiometry of the resulting complex is unknown. When bound to NPHP4, LATS is unable to phosphorylate YAP1 and WWTR1 (TAZ) proteins, so the effect of NPHP4 binding is to antagonize this aspect of the Hippo cascade (Habbig et al. 2011).

**Literature references**

Schermer, B., Bartram, MP., Sägmüller, JG., Hoehne, M., Habbig, S., Burst, V. et al. (2011). NPHP4, a cilia-associated protein, negatively regulates the Hippo pathway. *J Cell Biol, 193*, 633-42.

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| Date       | Action   | Author         |
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| 2012-01-19 | Edited   | D'Eustachio, P.|
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Phosphorylation of LATS1 and 2 by p-STK3 (p-MST2)

Location: Signaling by Hippo

Stable identifier: R-HSA-2028589

Type: transition

Compartments: cytosol

Cytosolic LATS1 and LATS2 are phosphorylated by phospho-STK3 (p-MST2). LATS proteins are known to form complexes with MOB1 proteins and this reaction is annotated with LATS:MOB1 complexes as its substrate. Likewise, phosphorylated (active) STK3 (p-MST2) and SAV1 are known to form a complex and that complex is annotated as the catalyst of this reaction. Serine-909 and threonine-1097 have been identified as LATS1 residues phosphorylated by STK4 kinase (MST1); STK3 (MST2) is inferred to act similarly. The target residues of LATS2 have not been identified experimentally but are inferred to be serine-871 and threonine-1041 based on sequence similarity (Chan et al. 2005).

Preceded by: Phosphorylated MOB1A proteins associate with LATS proteins, Phosphorylation of STK3 (MST2) and SAV1 by STK3

Followed by: Phosphorylation of YAP by LATS2, Phosphorylation of YAP by LATS1, Phosphorylation of WWTR1 (TAZ) by LATS1, Phosphorylation of WWTR1 (TAZ) by LATS2

Literature references

Chalamalasetty, RB., Nigg, EA., Nousiainen, M., Chan, EH., Silljé, HH., Schäfer, A. (2005). The Ste20-like kinase Mst2 activates the human large tumor suppressor kinase Lats1. Oncogene, 24, 2076-86.
Phosphorylation of LATS1 and 2 by p-STK3 (MST2)/N

Location: Signaling by Hippo

Stable identifier: R-HSA-2028673

Type: transition

Compartments: cytosol

Cytosolic LATS1 and LATS2 are phosphorylated by phospho-STK3 (MST2)/N (Lee et al. 2001). LATS proteins are known to form complexes with MOB1 proteins and this reaction is annotated with LATS:MOB1 complexes as its substrate. Serine-909 and threonine-1097 have been identified as LATS1 residues phosphorylated by STK4 (MST1) kinase; STK3(MST2)/N is inferred to act similarly. The target residues of LATS2 have not been identified experimentally but are inferred to be serine-871 and threonine-1041 based on sequence similarity.

Preceded by: Phosphorylated MOB1A proteins associate with LATS proteins, Cleavage of p-STK3 (p-MST2) by caspase 3

Followed by: Phosphorylation of YAP by LATS2, Phosphorylation of YAP by LATS1

Literature references

Tsubuki, S., Yajima, N., Lee, KK., Ohyama, T., Yonehara, S. (2001). MST, a physiological caspase substrate, highly sensitizes apoptosis both upstream and downstream of caspase activation. J Biol Chem, 276, 19276-85.

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Phosphorylation of LATS1 and 2 by p-STK4 (p-MST1)

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028555

**Type:** transition

**Compartments:** cytosol

Cytosolic LATS1 and LATS2 are phosphorylated by phospho-STK4 (p-MST1). LATS proteins are known to form complexes with MOB1 proteins and this reaction is annotated with LATS:MOB1 complexes as its substrate. Likewise, phosphorylated (active) STK4 (p-MST1) and SAV1 are known to form a complex and that complex is annotated as the catalyst of this reaction. Serine-909 and threonine-1097 have been identified as LATS1 residues phosphorylated by STK4 (MST1) kinase. The target residues of LATS2 have not been identified experimentally but are inferred to be serine-871 and threonine-1041 based on sequence similarity (Chan et al. 2005).

**Preceded by:** Phosphorylated MOB1A proteins associate with LATS proteins, Phosphorylation of STK4 (MST1) and SAV1 by STK4

**Followed by:** Phosphorylation of YAP by LATS2, Phosphorylation of YAP by LATS1, Phosphorylation of WWTR1 (TAZ) by LATS1, Phosphorylation of WWTR1 (TAZ) by LATS2

**Literature references**

Chalamalasetty, RB., Nigg, EA., Nousiainen, M., Chan, EH., Silljé, HH., Schäfer, A. (2005). The Ste20-like kinase Mst2 activates the human large tumor suppressor kinase Lats1. *Oncogene, 24*, 2076-86.

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Phosphorylation of LATS1 and 2 by p-STK4(MST1)/N

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028679

**Type:** transition

**Compartments:** cytosol

Cytosolic LATS1 and LATS2 are phosphorylated by phospho-STK4(MST1)/N (Graves et al. 1998; Lee et al. 2001). LATS proteins are known to form complexes with MOB1 proteins and this reaction is annotated with LATS:MOB1 complexes as its substrate. Serine-909 and threonine-1097 have been identified as LATS1 residues phosphorylated by STK4 (MST1) kinase. The target residues of LATS2 have not been identified experimentally but are inferred to be serine-871 and threonine-1041 based on sequence similarity.

**Preceded by:** Phosphorylated MOB1A proteins associate with LATS proteins, Cleavage of p-STK4 (p-MST1) by caspase 3

**Followed by:** Phosphorylation of YAP by LATS2, Phosphorylation of YAP by LATS1

**Literature references**

Tsubuki, S., Yajima, N., Lee, KK., Ohyama, T., Yonehara, S. (2001). MST, a physiological caspase substrate, highly sensitizes apoptosis both upstream and downstream of caspase activation. *J Biol Chem*, 276, 19276-85.

Ambrose, DM., Krebs, EG., Han, DK., Gotoh, Y., Clark, EA., Draves, KE. et al. (1998). Caspase-mediated activation and induction of apoptosis by the mammalian Ste20-like kinase Mst1. *EMBO J*, 17, 2224-34.

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Phosphorylation of MOB1A and B by p-STK3 (p-MST2)

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028635

**Type:** transition

**Compartments:** cytosol

Cytosolic MOB1A and MOB1B are phosphorylated by phospho-STK3 (p-MST2). Phosphorylated (active) STK3 (p-MST2) and SAV1 are known to form a complex and that complex is annotated as the catalyst of this reaction. Threonine residues 12 and 35 have been experimentally identified as the targets of MOB1A phosphorylation; the homologous residues of MOB1B are inferred likewise to be targets (Praskova et al. 2008).

**Preceded by:** Phosphorylation of STK3 (MST2) and SAV1 by STK3

**Followed by:** Phosphorylated MOB1A proteins associate with LATS proteins

**Literature references**

Xia, F., Praskova, M., Avruch, J. (2008). MOBK1A/MOBKL1B phosphorylation by MST1 and MST2 inhibits cell proliferation. *Curr Biol*, 18, 311-21.

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Phosphorylation of MOB1A and B by p-STK3(MST2)/N

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028675

**Type:** transition

**Compartments:** cytosol

Cytosolic MOB1A and MOB1B are phosphorylated by phospho-STK3(MST2)/N (Lee et al. 2001). Threonine residues 12 and 35 have been experimentally identified as the targets of MOB1A phosphorylation; the homologous residues of MOB1B are inferred likewise to be targets.

**Preceded by:** Cleavage of p-STK3 (p-MST2) by caspase 3

**Followed by:** Phosphorylated MOB1A proteins associate with LATS proteins

**Literature references**

Tsubuki, S., Yajima, N., Lee, KK., Ohyama, T., Yonehara, S. (2001). MST, a physiological caspase substrate, highly sensitizes apoptosis both upstream and downstream of caspase activation. *J Biol Chem*, 276, 19276-85.

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Phosphorylation of MOB1A and B by p-STK4 (p-MST1)

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028629

**Type:** transition

**Compartments:** cytosol

Cytosolic MOB1A and MOB1B are phosphorylated by phospho-STK4 (p-MST1). Phosphorylated (active) STK4 (p-MST1) and SAV1 are known to form a complex and that complex is annotated as the catalyst of this reaction. Threonine residues 12 and 35 have been experimentally identified as the targets of MOB1A phosphorylation; the homologous residues of MOB1B are inferred likewise to be targets (Praskova et al. 2008).

**Preceded by:** Phosphorylation of STK4 (MST1) and SAV1 by STK4

**Followed by:** Phosphorylated MOB1A proteins associate with LATS proteins

**Literature references**

Xia, F., Praskova, M., Avruch, J. (2008). MOBKL1A/MOBKL1B phosphorylation by MST1 and MST2 inhibits cell proliferation. *Curr Biol*, 18, 311-21.

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Phosphorylation of MOB1A and B by p-STK4(MST1)/N

Location: Signaling by Hippo

Stable identifier: R-HSA-2028670

Type: transition

Compartments: cytosol

Cytosolic MOB1A and MOB1B are phosphorylated by phosho-STK4(MST1)/N (Graves et al. 1998; Lee et al. 2001). Threonine residues 12 and 35 have been experimentally identified as the targets of MOB1A phosphorylation; the homologous residues of MOB1B are inferred likewise to be targets.

Preceded by: Cleavage of p-STK4 (p-MST1) by caspase 3

Followed by: Phosphorylated MOB1A proteins associate with LATS proteins

Literature references

Tsubuki, S., Yajima, N., Lee, KK., Ohyama, T., Yonehara, S. (2001). MST, a physiological caspase substrate, highly sensitizes apoptosis both upstream and downstream of caspase activation. *J Biol Chem*, 276, 19276-85.

Ambrose, DM., Krebs, EG., Han, DK., Gotoh, Y., Clark, EA., Draves, KE. et al. (1998). Caspase-mediated activation and induction of apoptosis by the mammalian Ste20-like kinase Mst1. *EMBO J*, 17, 2224-34.

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Phosphorylated MOB1A proteins associate with LATS proteins

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028626

**Type:** binding

**Compartments:** cytosol

Phosphorylated MOB1A proteins are able to associate with LATS proteins (Praskova et al. 2008).

**Preceded by:** Phosphorylation of MOB1A and B by p-STK3(MST2)/N, Phosphorylation of MOB1A and B by p-STK4 (p-MST1), Phosphorylation of MOB1A and B by p-STK3 (p-MST2), Phosphorylation of MOB1A and B by p-STK4(MST1)/N

**Followed by:** Phosphorylation of LATS1 and 2 by p-STK4(MST1)/N, Phosphorylation of LATS1 and 2 by p-STK4 (p-MST1), Phosphorylation of LATS1 and 2 by p-STK3 (p-MST2), Phosphorylation of LATS1 and 2 by p-STK3 (MST2)/N

**Literature references**

Xia, F., Praskova, M., Avruch, J. (2008). MOBKL1A/MOBKL1B phosphorylation by MST1 and MST2 inhibits cell proliferation. *Curr Biol, 18*, 311-21.

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Translocation of YAP1 to the nucleus

Location: Signaling by Hippo

Stable identifier: R-HSA-2032770

Type: transition

Compartments: nucleoplasm, cytosol

In its unphosphorylated state, the YAP1 transcriptional coactivator moves freely into the nucleus. Phosphorylated YAP1, in contrast, is sequestered in the cytosol (Hao et al. 2008).

Literature references

Cheung, K., Rashidi, B., Yang, X., Hao, Y., Chun, A. (2008). Tumor suppressor LATS1 is a negative regulator of oncoprotein YAP. J Biol Chem, 283, 5496-509.

Editions

| Date     | Action   | Author      |
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YAP1 binds ZO-2 (TJP2)

Location: Signaling by Hippo

Stable identifier: R-HSA-2064421

Type: binding

Compartments: cytosol

Cytosolic ZO-2 (TJP2) binds YAP1 to form a complex (Oka et al. 2010). The phosphorylation state of the YAP1 protein involved in this interaction has not been determined experimentally; it is inferred to be unphosphorylated.

Followed by: Translocation of YAP1:ZO-2 (TJP2) to the nucleus

Literature references

Meerschaert, K., Bader, GD., Vandekerckhove, J., Remue, E., Gettemans, J., Sudol, M. et al. (2010). Functional complexes between YAP2 and ZO-2 are PDZ domain-dependent, and regulate YAP2 nuclear localization and signalling. *Biochem J*, 432, 461-72.

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Translocation of YAP1:ZO-2 (TJP2) to the nucleus

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2064406

**Type:** transition

**Compartments:** nucleoplasm, cytosol

The YAP1:ZO-2 (TJP2) complex can translocate to the nucleus (Oka et al. 2010).

**Preceded by:** YAP1 binds ZO-2 (TJP2)

**Literature references**

Meerschaert, K., Bader, GD., Vandekerckhove, J., Remue, E., Gettemans, J., Sudol, M. et al. (2010). Functional complexes between YAP2 and ZO-2 are PDZ domain-dependent, and regulate YAP2 nuclear localization and signalling. *Biochem J*, 432, 461-72.

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AMOT proteins bind YAP1

Location: Signaling by Hippo

Stable identifier: R-HSA-2028724

Type: binding

Compartments: cytosol

AMOT (130 KDa isoform), AMOTL1, and AMOTL2 can each bind YAP1 and sequester it in the cytosol. This interaction is not dependent on YAP1 phosphorylation and may thus be a means of negatively regulating YAP activity in addition to the ones dependent on Hippo pathway-dependent phosphorylation. AMOT-YAP1 binding is dependent on sequence motifs in the amino terminal portions of the AMOT proteins (and that are absent from the AMOT 80 KDa isoform, which does not bind YAP1) (Wang et al. 2010; Chan et al. 2011).

Literature references

Wang, W., Chen, J., Huang, J. (2011). Angiomotin-like proteins associate with and negatively regulate YAP1. J Biol Chem, 286, 4364-70.

Pobbati, AV., Lim, CJ., Hong, W., Huang, C., Chan, SW., Chong, YF. (2011). Hippo pathway-independent restriction of TAZ and YAP by angiomotin. J Biol Chem, 286, 7018-26.

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Phosphorylation of YAP by LATS1

Location: Signaling by Hippo

Stable identifier: R-HSA-2028598

Type: transition

Compartments: cytosol

Cytosolic phospho-LATS1, complexed with MOB1, catalyzes the phosphorylation of YAP on five serine residues (Hao et al. 2008).

Preceded by: Phosphorylation of LATS1 and 2 by p-STK3 (MST2)/N, Phosphorylation of LATS1 and 2 by p-STK4(MST1)/N, Phosphorylation of LATS1 and 2 by p-STK4 (p-MST1), Phosphorylation of LATS1 and 2 by p-STK3 (p-MST2)

Followed by: YWHAB (14-3-3 beta/alpha) dimer binds phosphorylated YAP1

Literature references

Cheung, K., Rashidi, B., Yang, X., Hao, Y., Chun, A. (2008). Tumor suppressor LATS1 is a negative regulator of oncogene YAP. J Biol Chem, 283, 5496-509.

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Phosphorylation of YAP by LATS2

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028583

**Type:** transition

**Compartments:** cytosol

Cytosolic phospho-LATS2, complexed with MOB1, catalyzes the phosphorylation of YAP on serine residue 127 (and possibly other serine residues) (Zhao et al. 2007). This reaction is positively regulated by the angiomotin proteins AMOT (130 kd form), AMOTL1, and AMOTL2, which may function by physically bridging LATS2 and YAP (Paramasivam et al. 2011; Zhao et al. 2011).

**Preceded by:** Phosphorylation of LATS1 and 2 by p-STK3 (MST2)/N, Phosphorylation of LATS1 and 2 by p-STK4(MST1)/N, Phosphorylation of LATS1 and 2 by p-STK4 (p-MST1), Phosphorylation of LATS1 and 2 by p-STK3 (p-MST2)

**Followed by:** YWHAB (14-3-3 beta/alpha) dimer binds phosphorylated YAP1

**Literature references**

Sarkeshik, A., Yates, JR 3rd., Paramasivam, M., McCollum, D., Fernandes, MJ. (2011). Angiomotin family proteins are novel activators of the LATS2 kinase tumor suppressor. *Mol Biol Cell*, 22, 3725-33.

Lei, Q., Guan, KL., Liu, CY., Li, L., Wang, LH., Lu, Q. et al. (2011). Angiomotin is a novel Hippo pathway component that inhibits YAP oncoprotein. *Genes Dev*, 25, 51-63.

Zheng, P., Halder, G., Ye, K., Lai, ZC., Yu, J., Wei, X. et al. (2007). Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev*, 21, 2747-61.

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https://reactome.org
YWHAB (14-3-3 beta/alpha) dimer binds phosphorylated YAP1

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028644

**Type:** binding

**Compartments:** cytosol

YWHAB (14-3-3 beta/alpha) binds phosphorylated YAP1 proteins, sequestering them in the cytosol. Structural studies indicate that the active form of YWHAB (14-3-3 beta/alpha) is a homodimer (Yang et al. 2006); the stoichiometry of its complex with YAP1 is unknown and has been annotated arbitrarily here to involve one YAP1 molecule and a YWHAB (14-3-3 beta/alpha) dimer. While YAP1 can be phosphorylated on several serine residues, phosphorylation of serine-127 appears to be critical for YWHAB(14-3-3 beta/alpha) binding (Zhao et al. 2007).

**Preceded by:** Phosphorylation of YAP by LATS2, Phosphorylation of YAP by LATS1

**Literature references**

Elkins, JM., Sobott, F., Papagrorigiou, E., Grossmann, JG., Robinson, CV., Sundström, M. et al. (2006). Structural basis for protein-protein interactions in the 14-3-3 protein family. *Proc Natl Acad Sci U S A*, 103, 17237-42.

Zheng, P., Halder, G., Ye, K., Lai, ZC., Yu, J., Wei, X. et al. (2007). Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev, 21*, 2747-61.

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Translocation of WWTR1 (TAZ) to the nucleus

Location: Signaling by Hippo

Stable identifier: R-HSA-2032768

Type: transition

Compartments: nucleoplasm, cytosol

In its unphosphorylated state, the WWTR1 (TAZ) transcriptional coactivator moves freely into the nucleus. Phosphorylated WWTR1 (TAZ), in contrast, is sequestered in the cytosol (Lei et al. 2008).

Literature references

Lei, Q., Guan, KL., Xiong, Y., Pei, XH., Zhang, H., Zha, ZY. et al. (2008). TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway. *Mol Cell Biol, 28*, 2426-36.

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**WWTR1 (TAZ) binds ZO-1 (TJP1)**

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2064417

**Type:** binding

**Compartments:** cytosol

Cytosolic ZO-1 (TJP1) binds WWTR1 (TAZ) to form a complex. This event may play a role in sequestering WWTR1 in the cytosol (Remue et al. 2010). The phosphorylation state of the WWTR1 protein involved in this interaction has not been determined experimentally; it is inferred to be unphosphorylated.

**Literature references**

Meerschaert, K., Vandekerckhove, J., Remue, E., Gettemans, J., Sudol, M., Boucherie, C. et al. (2010). TAZ interacts with zonula occludens-1 and -2 proteins in a PDZ-1 dependent manner. *FEBS Lett*, 584, 4175-80.

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**WWTR1 (TAZ) binds ZO-2 (TJP2)**

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2064418

**Type:** binding

**Compartments:** cytosol

Cytosolic ZO-2 (TJP2) binds WWTR1 (TAZ) to form a complex. This event may play a role in sequestering WWTR1 in the cytosol (Remue et al. 2010). The phosphorylation state of the WWTR1 protein involved in this interaction has not been determined experimentally; it is inferred to be unphosphorylated.

**Literature references**

Meerschaert, K., Vandekerckhove, J., Remue, E., Gettemans, J., Sudol, M., Boucherie, C. et al. (2010). TAZ interacts with zonula occludens-1 and -2 proteins in a PDZ-1 dependent manner. *FEBS Lett*, 584, 4175-80.

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AMOT proteins bind WWTR1 (TAZ)

Location: Signaling by Hippo

Stable identifier: R-HSA-2028735

Type: binding

Compartments: cytosol

AMOT (130 KDa isoform) and AMOTL1 can each bind WWTR1 (TAZ) and sequester it in the cytosol. AMOTL2 - WWTR1 binding has not been studied but is inferred to occur from the presence of key binding sequence motifs in AMOTL2 protein and from its known binding activity with YAP1, a WWTR1 homolog. These interactions are not dependent on WWTR1 phosphorylation and may thus be a means of negatively regulating WWTR1 activity in addition to the ones dependent on Hippo pathway-dependent phosphorylation. AMOT - WWTR1 binding is dependent on sequence motifs in the amino terminal portions of the AMOT proteins (and that are absent from the AMOT 80 KDa isoform) (Chan et al. 2011).

Literature references

Pobbati, AV., Lim, CJ., Hong, W., Huang, C., Chan, SW., Chong, YF. (2011). Hippo pathway-independent restriction of TAZ and YAP by angiomotin. J Biol Chem, 286, 7018-26.

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Phosphorylation of WWTR1 (TAZ) by LATS1

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2060328

**Type:** transition

**Compartments:** cytosol

Cytosolic phospho-LATS1, complexed with MOB1, catalyzes the phosphorylation of WWTR1 (TAZ) on serine residue 89. This activity of human LATS1 protein has not been demonstrated experimentally but is inferred from the activity of human paralogue LATS2 and of mouse homologue LATS1 (Varelas et al. 2010).

**Preceded by:** Phosphorylation of LATS1 and 2 by p-STK4 (p-MST1), Phosphorylation of LATS1 and 2 by p-STK3 (p-MST2)

**Followed by:** DVL2 binds phosphorylated WWTR1 (TAZ)

**Literature references**

Pawson, T., Wrana, JL., Gregorieff, A., Sakuma, R., Fellouse, FA., Attisano, L. et al. (2010). The Hippo pathway regulates Wnt/beta-catenin signaling. *Dev Cell, 18*, 579-91.

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| 2012-02-03 | Reviewed  | Sudol, M.   |
Phosphorylation of WWTR1 (TAZ) by LATS2

**Location:** Signaling by Hippo

**Stable identifier:** R-HSA-2028661

**Type:** transition

**Compartments:** cytosol

Cytosolic phospho-LATS2, complexed with MOB1, catalyzes the phosphorylation of WWTR1 (TAZ) on serine residue 89 (Lei et al. 2008). This reaction is positively regulated by the angiomotin proteins AMOT (130 kd form), AMOTL1, and AMOTL2, which may function by physically bridging LATS2 and YAP (Zhao et al. 2011).

**Preceded by:** Phosphorylation of LATS1 and 2 by p-STK4 (p-MST1), Phosphorylation of LATS1 and 2 by p-STK3 (p-MST2)

**Followed by:** YWHAE (14-3-3 epsilon) dimer binds phosphorylated WWTR1 (TAZ), DVL2 binds phosphorylated WWTR1 (TAZ)

**Literature references**

Lei, Q., Guan, KL., Xiong, Y., Pei, XH., Zhang, H., Zha, ZY. et al. (2008). TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway. *Mol Cell Biol*, 28, 2426-36.

Lei, Q., Guan, KL., Liu, CY., Li, L., Wang, LH., Lu, Q. et al. (2011). Angiomotin is a novel Hippo pathway component that inhibits YAP oncoprotein. *Genes Dev*, 25, 51-63.

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DVL2 binds phosphorylated WWTR1 (TAZ)

Location: Signaling by Hippo

Stable identifier: R-HSA-2066299

Type: binding

Compartments: cytosol

Phosphorylated WWTR1 (TAZ) and DVL interact to form a complex in the cytosol. Thus sequestered, DVL2 is unable to undergo phosphorylation by casein kinase, inhibiting its role in WNT signaling. WWTR1 - DVL interaction thus appears to link the Hippo and WNT signaling processes (Varelas et al. 2010). The stoichiometry of the WWTR1:DVL complex is unknown.

Preceded by: Phosphorylation of WWTR1 (TAZ) by LATS2, Phosphorylation of WWTR1 (TAZ) by LATS1

Literature references

Pawson, T., Wrana, JL., Gregorieff, A., Sakuma, R., Fellouse, FA., Attisano, L. et al. (2010). The Hippo pathway regulates Wnt/beta-catenin signaling. Dev Cell, 18, 579-91.

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YWHAE (14-3-3 epsilon) dimer binds phosphorylated WWTR1 (TAZ)

Location: Signaling by Hippo

Stable identifier: R-HSA-2028651

Type: binding

Compartments: cytosol

YWHAE (14-3-3 epsilon) binds phosphorylated WWTR1 (TAZ), sequestering it in the cytosol. Structural studies indicate that the active form of YWHAE (14-3-3 epsilon) is a homodimer (Yang et al. 2006); the stoichiometry of its complex with WWTR1 (TAZ) is unknown and has been annotated arbitrarily here to involve one WWTR1 (TAZ) molecule and a YWHAE(14-3-3 epsilon) dimer. Phosphorylation of serine residue 127 of WWTR1 (TAZ) appears to be critical for YWHAE (14-3-3 epsilon) binding (Kanai et al. 2000; Lei et al. 2008).

Preceded by: Phosphorylation of WWTR1 (TAZ) by LATS2

Literature references

Elkins, JM., Sobott, F., Papagrigoriou, E., Grossmann, JG., Robinson, CV., Sundström, M. et al. (2006). Structural basis for protein-protein interactions in the 14-3-3 protein family. Proc Natl Acad Sci U S A, 103, 17237-42.

Lei, Q., Guan, KL., Xiong, Y., Pei, XH., Zhang, H., Zha, ZY. et al. (2008). TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway. Mol Cell Biol, 28, 2426-36.

Ito, Y., Hall, RA., Cantley, LC., Yagi, R., Marignani, PA., Hisaminato, A. et al. (2000). TAZ: a novel transcriptional co-activator regulated by interactions with 14-3-3 and PDZ domain proteins. EMBO J, 19, 6778-91.

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