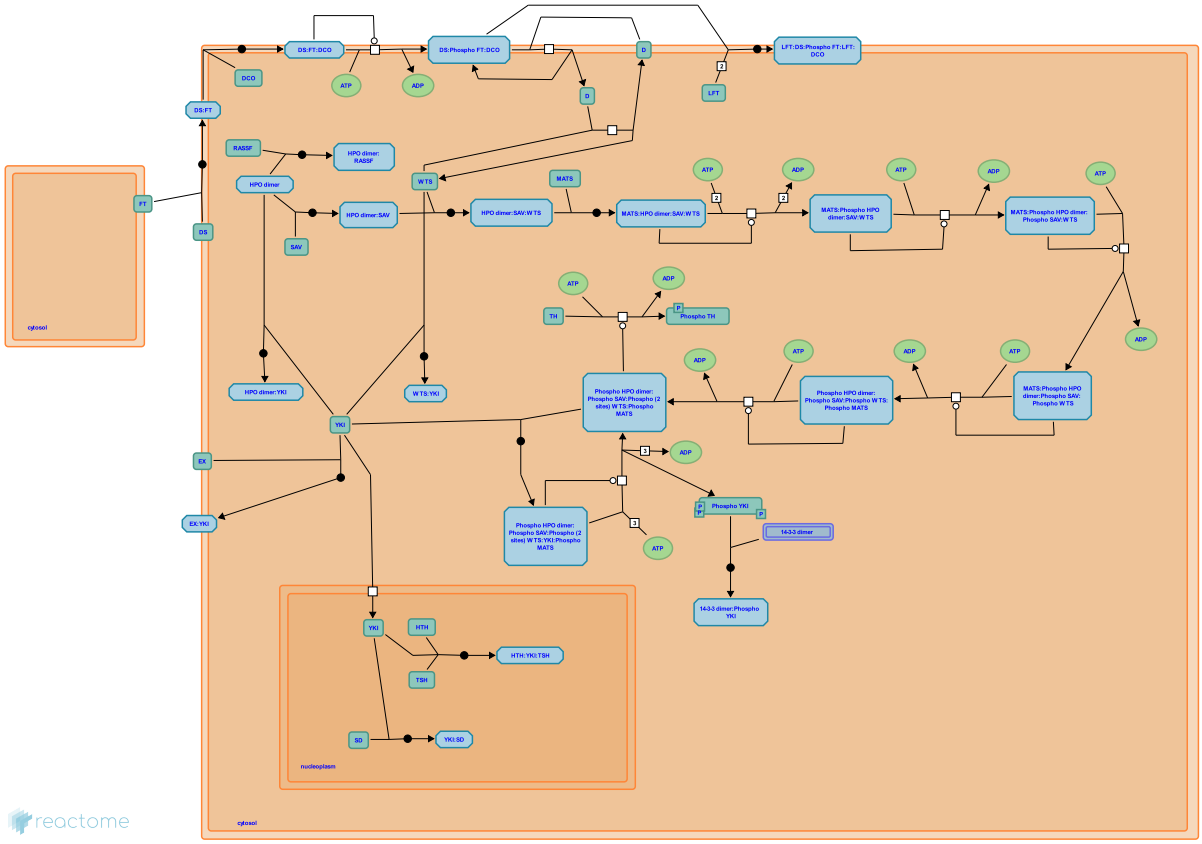
Hippo/Warts pathway



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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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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. ↗

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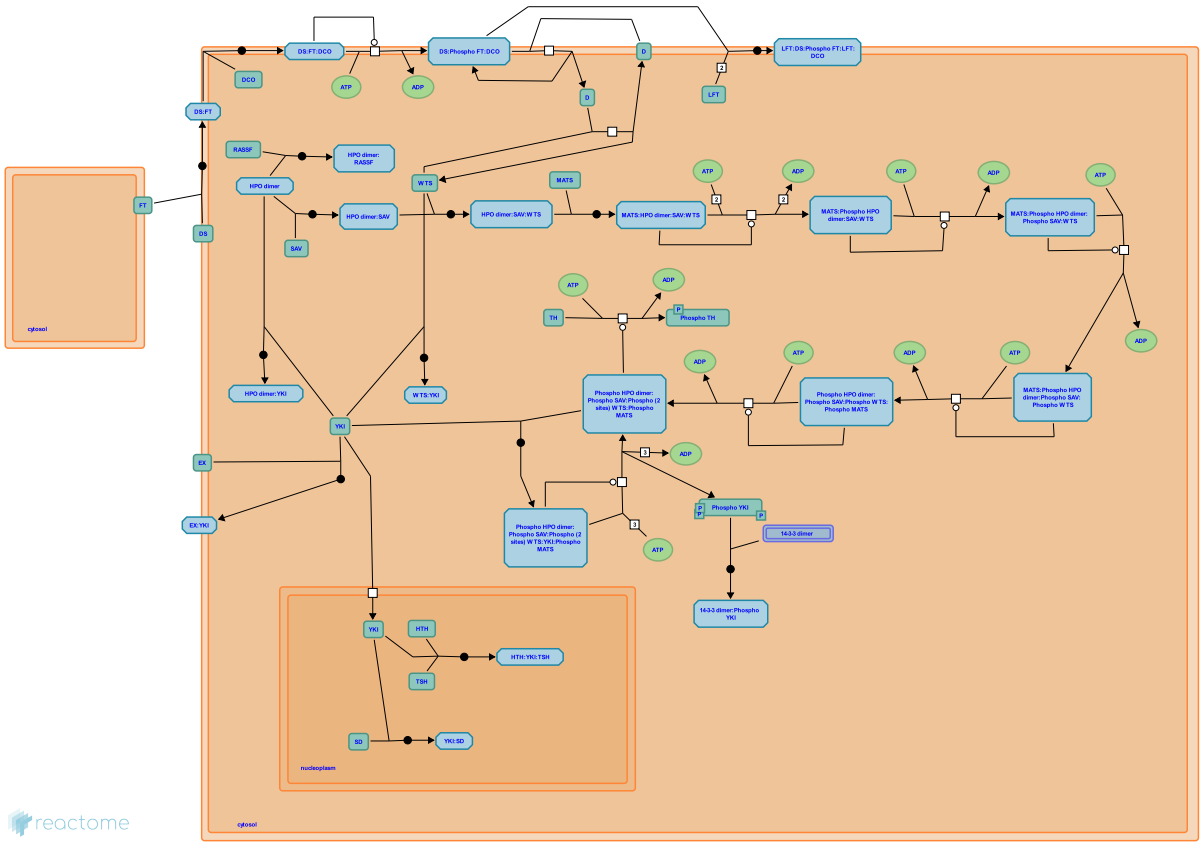
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Hippo/Warts pathway ↗

Stable identifier: R-DME-390146



The Hippo/Warts signalling pathway has been shown to be crucial in control of organ size in both Drosophila and mammals. Such regulation is achieved by transcriptional activation of target genes such as cyclins A, B, and E; E2F1; Diap1; and bantam microRNA.

The cadherin domain containing transmembrane protein Fat (FT) interacts with another cadherin domain containing protein Dachsous (DS). FT inhibits the unconventional myosin, Dachs (D), by reducing its accumulation at the plasma membrane. So, D fails to get access to and interact with the serine/threonine kinase Warts (WTS). WTS is a key component in the Hippo kinase cassette. In this, the active Ser/Thr kinase Hippo (HPO) homodimer interacts and activates the scaffolding protein Salvador (SAV). This in turn recruits WTS which correspondingly recruits its the protein Mob as tumor suppressor (MATS) which activates WTS. Active WTS recruits the transcriptional co-activator Yorkie (YKI) to this complex assembly. YKI is phosphorylated and and binds to a 14-3-3 dimer so that it is retained in the cytosol and unable to enter the nucleus and activate it's target genes and consequently growth can be stopped. Recently, phosphorylation-independent negative regulation of YKI has been observed. Binding of its WW domains to PPXY sequence motifs found in HPO, WTS, and the FERM domain containing Expanded (EX) means that YKI remains in the cytosol and does not enter the nucleus to activate its target genes.

In the absence of the FT:DS interaction, D accumulates at the plasma membrane where it interacts with WTS and inhibits it. D also reduces levels of EX at the plasma membrane. Merlin (MER) is in its inactive phosphorylated state. HPO homodimer, SAV, and WTS remain unphosphorylated and inactive. YKI is not phosphorylated and translocates to the nucleus where it complexes with Scalloped (SD) or Homothorax (HTH) and Teashirt (TSH) to promote the transcription of its target genes.

Two cytoplasmic Band 4.1 superfamily members, Merlin (MER) and EX which contain a FERM (Four-point one, Ezrin, Radixin, Moesin) domain are believed to regulate HPO by promoting its phosphorylation, however, the precise mechanism of this and how MER and EX are themselves activated remains unknown. Additionally, unactivated unphosphorylated HPO associates with Ras association family member (RASSF) where it remains in its inactive state.

Two upstream components of the Hippo/Warts pathway are important target genes involved in feedback regulation. These target genes encode the proteins EX and Four-jointed (FJ), a golgi Ser/Thr kinase involved in regulating FT. HPO has been reported as phosphorylating Thread (TH) aka Diap1 affecting its stability. These show that feedback regulation is present in this signalling pathway.

Another example of feedback regulation in this pathway involves the small protein Lowfat (LFT) which binds to and influences levels of both FT and DS, which in turn have influence on levels of LFT.

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Tapon, N., Harvey, K. (2007). The Salvador-Warts-Hippo pathway - an emerging tumour-suppressor network. *Nat Rev Cancer, 7*, 182-91. ↗

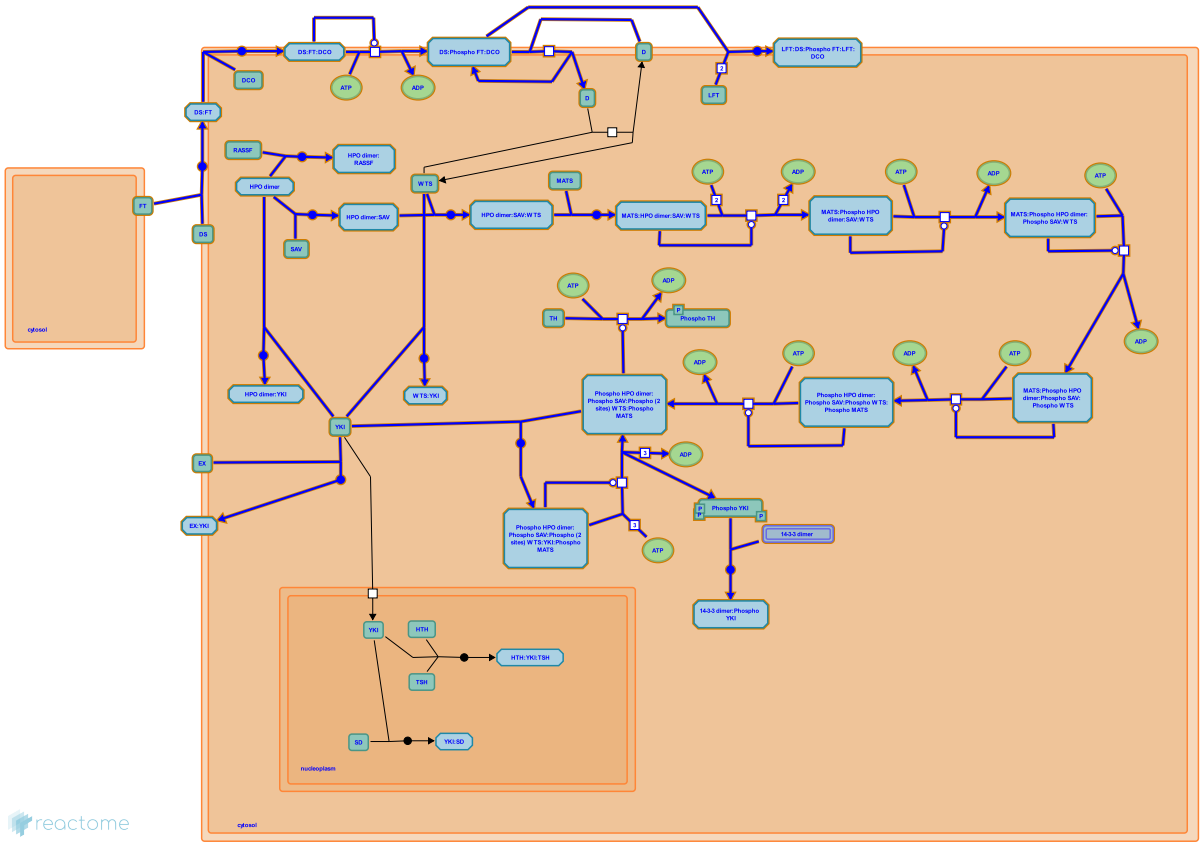
Editions

2009-01-23	Authored, Edited	Williams, MG.
2009-11-25	Reviewed	Irvine, KD.

DS ligand bound to FT receptor ↗

Location: Hippo/Warts pathway

Stable identifier: R-DME-390150



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Tapon, N., Harvey, K. (2007). The Salvador-Warts-Hippo pathway - an emerging tumour-suppressor network. *Nat Rev Cancer, 7*, 182-91. ↗

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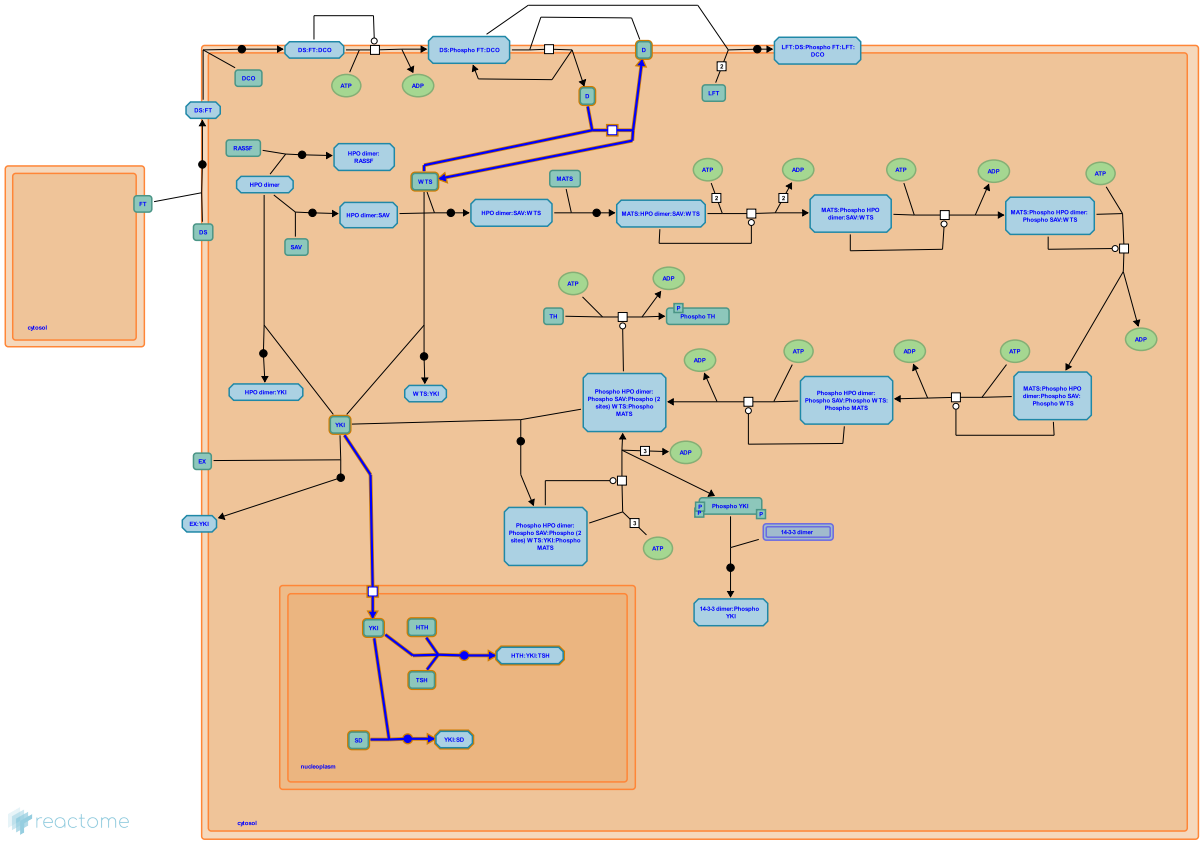
DS ligand not bound to FT receptor ↗

Location: Hippo/Warts pathway

Stable identifier: R-DME-390178



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Tapon, N., Harvey, K. (2007). The Salvador-Warts-Hippo pathway - an emerging tumour-suppressor network. *Nat Rev Cancer, 7*, 182-91. ↗

Editions

2009-01-23	Authored, Edited	Williams, MG.
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