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Johnson 2011; Zhao et al. 2011). Many components of the pathway were identified as a result of mutations in the fruit fly *Drosophila melanogaster* that resulted in tissue overgrowth (Table 1). The pathway is conserved in

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Table 1. Components of the *Drosophila melanogaster* Salvador-Warts-Hippo pathway and their human homologues

<i>Drosophila</i>	Human
Upstream	
Fat (FT)	FAT1—FAT4
Dachsous (DS)	DCHS1 and DCHS2
Discs overgrown (DCO)	CK1ε and CK1δ
Lowfat (LFT)	LIX1 and LIX1L
Four-jointed (FJ)	FJX1
Dachs (D)	?
Approximated (APP)	ZDHHC9, ZDHHC14 and ZDHHC18
Zyxin (ZYG)	Zyxin, LPP and TRIP6
Merlin (MER)	Merlin (also known as NF2)
Expanded (EX)	Willin/FRMD6 and FRMD1
Kibra	Kibra
Crumbs (CRB)	CRB1—CRB3
Lethal giant larvae (LGL)	LGL1 and LGL2
Discs large (DLG)	DLG1—DLG4
Scribble (SCRIB)	SCRIB
aPKC	aPKC α and aPKC ζ
STRIPAK (PP2A)	PP2A (STRIPAK)
RASSF	RASSF1-RASSF6
Myopic (MOP)	HD-PTP
JUB	Ajuba, LIMD1, WTIP
TAO1	TAO1—TAO3
Core	
Hippo (HPO)	MST1 and MST2
Salvador (SAV)	SAV1
Mats (MTS)	MOBKL1A and MOBKL1AB
Warts (WTS)	LATS1 and LATS2
Downstream	
Yorkie (YKI)	YAP and TAZ
WBP2	WBP2
Scalloped (SD)	TEAD1—TEAD4
MAD	SMADs
TSH	TSHZ1—TSHZ3
HTH	MEIS1—MEIS3

vertebrates, including mammals (Fig. 2), and changing the activity of the pathway can result in dramatic changes in the size of certain organs, most notably the liver (Pan 2010; Halder and Johnson 2011). In addition to its role in regulating tissue growth, the pathway has been implicated in the control of other biological processes, such as cell-fate determination, mitosis, and pluripotency. Deregulation of Hippo pathway activity has been reported in many human cancers. The human homolog of *D. melanogaster* Merlin (MER), also known as Neurofibromatosis Type 2 (NF2) is a bona fide tumor suppressor, while altered activity of several Hippo pathway components has been implicated in human tumorigenesis (Harvey and Tapon 2007).

At the core of the pathway is a module composed of two kinases—Hippo (HPO) (Harvey et al. 2003; Jia et al. 2003; Pantalacci et al. 2003; Udan et al. 2003; Wu et al. 2003) and

Warts (WTS; also known as LATS) (Justice et al. 1995; Xu et al. 1995)—and two other proteins—Salvador (SAV) (Kango-Singh et al. 2002; Tapon et al. 2002) and Mob as Tumor Suppressor (MATS) (Lai et al. 2005). HPO functions upstream of WTS and can directly phosphorylate it. Mutations that inactivate any of these four proteins result in tissue overgrowth. The first indication that some of these proteins might function in a pathway was the observation that *sav* and *wts* mutants display similar phenotypic abnormalities and that the two proteins can interact with each other (Tapon et al. 2002). More recently it has been shown that activity of this module can be regulated by RASSF, a scaffold protein that promotes tissue growth by recruiting the serine-threonine phosphatase complex STRIPAK to inhibit HPO autophosphorylation, and hence HPO activity (Ribeiro et al. 2010).

The main output of the module involves the transcriptional coactivator Yorkie (YKI) (Huang et al. 2005). Phosphorylation of YKI by WTS induces binding of 14-3-3 proteins to YKI that limit YKI activity by preventing nuclear accumulation. Phosphatases that counter the activity of WTS have not been discovered but the Myopic (MOP) tyrosine phosphatase regulates YKI activity, repressing it (Gilbert et al. 2011). YKI promotes tissue growth by increasing expression of positive regulators of cell growth and inhibitors of apoptosis. YKI, itself does not bind DNA but functions together with several transcription factors, including Scalloped (SD; the homolog of TEAD transcription factors in vertebrates), Homothorax (HTH), Teashirt (TSH), and Mothers against DPP (MAD). Transcriptional regulatory proteins such as WBP2 also control Hippo-pathway-dependent tissue growth (Zhang et al. 2011). WBP2 and other as-yet-unidentified proteins have been predicted to interact with YKI via its WW domains, which are important for YKI's transcription activation function (Oh and Irvine 2010).

The HPO and WTS kinases appear to receive multiple inputs. The first upstream regulators to be discovered were the Band 4.1 proteins Expanded (EX) and MER (Hamaratoglu et al. 2006). These function together with the WW-domain-containing protein Kibra to activate the core kinase cassette by an unknown mechanism. EX is also thought to repress YKI by physical interaction and sequestration. The Fat/Dachsous branch of the pathway consists of the atypical cadherins Fat (FT) and Dachsous (DS) as well as the downstream effector proteins Discs overgrown (DCO, a serine-threonine kinase also known as casein kinase 1ε), Dachs (D, an atypical myosin), Approximated (APP, a palmitoyltransferase), Lowfat (LFT), and Zyxin (ZYG) (Grusche et al. 2010; Rauskolb et al. 2011). The Fat/Dachsous branch impinges on pathway activity by modulating the abundance of WTS and also modulates

Figure 2. The mammalian Hippo pathway.

the Kibra-EX-MER branch by regulating EX levels. The sterile 20-like kinase, TAO1, phosphorylates and activates HPO (MST1/2 in mammals) although it is unclear whether TAO1 activity is regulated (Boggiano et al. 2011; Poon et al. 2011).

Increasing evidence underlines the importance of cell junctions for regulation of Hippo pathway activity. In *D. melanogaster* epithelial cells, many Hippo pathway proteins reside, at least partially, at the sub-apical region (SAR), adherens junction (AJ) or septate junction (SJ). Examples of such junctional proteins include the AJ protein Jub and the apical-basal polarity proteins Discs large (DLG), Lethal giant larvae (LGL), Scribble (SCRIB), Crumbs (CRB), and

atypical protein kinase C (aPKC). In mammalian epithelial cells, several other junctional proteins regulate Hippo pathway activity (see Table 2), including angiomin and

Table 2. Components of the human Salvador-Warts-Hippo pathway and their *Drosophila melanogaster* homologs

Human	<i>Drosophila</i>
Upstream	
α-Catenin	α-Catenin
PATJ	Discs lost
PALS1	Stardust
AMOTs	?
β-TRCP	Slimb

α -catenin (Schlegelmilch et al. 2011; Zhao et al. 2011). The Hippo pathway may therefore help couple tissue growth to mechanical stresses or cell–cell contact, which might be important for organ size regulation.

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