Hippo signaling at a glance

Bin Zhao*, Li Li and Kun-Liang Guan*

Department of Pharmacology and Moores Cancer Center, University of California at San Diego, La Jolla, CA 92093-0815, USA

*Authors for correspondence (bizhao@ucsd.edu; kuguan@ucsd.edu)

Journal of Cell Science 123, 4001-4006

doi:10.1242/jcs.069070

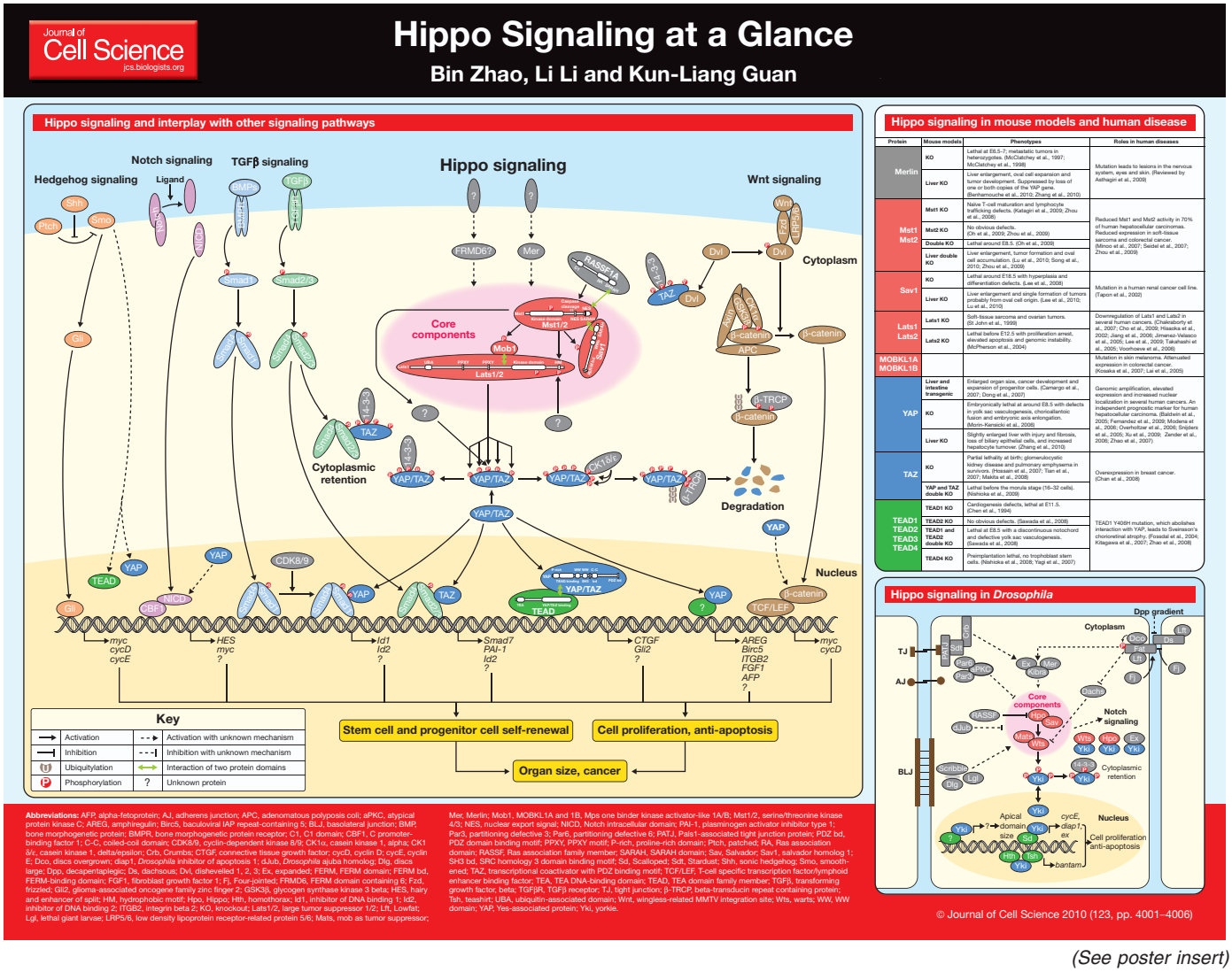
How the organs of multicellular organisms develop to a pre-defined size is a fundamental question in biology, but little is known about the underlying mechanisms. In the past decade, the Hippo pathway has been revealed to play a crucial role in organ size control (reviewed by Zhao et al., 2010a). Furthermore, studies of mouse models and clinical samples have demonstrated the significance of the Hippo pathway for the development of human cancers (Dong et al., 2007; Steinhardt et al., 2008; Xu et al., 2009; Zhou et al., 2009). Thus, the Hippo pathway has attracted broad interest in both basic and clinical research efforts. Here, we summarize the current understanding of the composition, regulation and function of the Hippo tumor-suppressor pathway, with emphasis on the interplay of Hippo signaling with other signaling pathways.

Organization of the Hippo pathway

Most of the Hippo pathway components are highly conserved across species and can be categorized into the following groups.

Core components of the Hippo pathway

Lats1 and Lats2 (collectively referred to as Lats below) are nuclear Dbf2-related (NDR) family protein kinases homologous to *Drosophila* Warts (Wts) (Justice et al., 1995; Xu et al., 1995). They are activated by association with the highly homologous scaffold proteins Mps one binder kinase activator-like 1A (MOBKL1A) and 1B (MOBKL1B), which are collectively referred to as Mob1 below and are homologues of *Drosophila* mob as tumor suppressor (Mats) (Chow et al., 2010; Hergovich et al., 2006; Lai et al., 2005; Wei et al., 2007). Lats kinases are also activated by phosphorylation by the STE20 family protein kinases Mst1 and Mst2 (collectively referred to as Mst below), which are homologues of Hippo (Hpo) in *Drosophila* (Harvey et al., 2003; Jia et al., 2003; Pantalacci et al., 2003; Udan et al., 2003; Wu et al., 2003). The requirement for Mst in Lats activation might be cell-type dependent, as ablation of Mst1 and Mst2 in mouse embryonic fibroblast (MEF) cells does not affect Lats phosphorylation (Zhou et al., 2009), indicating that a different kinase is responsible for Lats activation in MEF cells. Mob1 is also phosphorylated by Mst, which results in



Abbreviations: AFP, alpha-fetoprotein; AJ, adherens junction; APC, adenomatous polyposis coli; aPKC, atypical protein kinase C; AREG, amphiregulin; Birc5, baculoviral IAP repeat-containing 5; BLJ, basolateral junction; BMP, bone morphogenetic protein; BMPR, bone morphogenetic protein receptor; C1, C1 domain; CBF1, C promoter-binding factor 1; C-C, coiled-coil domain; CDK8/9, cyclin-dependent kinase 8/9; CK1ε, casein kinase 1, alpha; CK1 δ/ε, casein kinase 1, delta/epsilon; Crb, Crumbs; CTGF, connective tissue growth factor; cycD, cyclin D; cycE, cyclin E; Dco, discs overgrown; diap1, *Drosophila* inhibitor of apoptosis 1; dJub, *Drosophila* ajuba homolog; Dlg, discs large; Dpp, decapentaplegic; Ds, dachsous; Dvl, dishevelled 1, 2, 3; Ex, expanded; FERM, FERM domain; FERM bd, FERM-binding domain; FGF1, fibroblast growth factor 1; Fj, Four-jointed; FRMD6, FERM domain containing 6; Fzd, frizzled, Gli2, glioma-associated oncogene family zinc finger 2; GSK3β, glycogen synthase kinase 3 beta; HES, hairy and enhancer of split; HM, hydrophobic motif; Hpo, Hippo; Hth, homothorax; Id1, inhibitor of DNA binding 1; Id2, inhibitor of DNA binding 2; ITGB2, integrin beta 2; KO, knockout; Lats1/2, large tumor suppressor 1/2; Lft, Lowfat; Lgl, lethal giant larvae; LRP5/6, low density lipoprotein receptor-related protein 5/6; Mats, mob as tumor suppressor; Mer, Merlin; Mob1, MOBKL1A and 1B, Mps one binder kinase activator-like 1A/B; Mst1/2, serine/threonine kinase 4/3; NES, nuclear export signal; NICD, Notch intracellular domain; PAI-1, plasminogen activator inhibitor type 1; Par3, partitioning defective 3; Par6, partitioning defective 6; PATJ, Pals1-associated tight junction protein; PDZ bd, PDZ domain binding motif; PPXY, PPXY motif; P-rich, proline-rich domain; Ptch, patched; RA, Ras association domain; RASSF, Ras association family member; SARAH, SARAH domain; Sav, Salvador; Sav1, salvador homolog 1; SH3 bd, SRC homology 3 domain binding motif; Sd, Scalloped; Sdt, Stardust; Shh, sonic hedgehog; Smo, smoothened, TAZ, transcriptional coactivator with PDZ binding motif; TCF/LEF, T-cell specific transcription factor/lymphoid enhancer binding factor; TEA, TEA DNA-binding domain; TEAD, TEA domain family member; TGFβ, transforming growth factor, beta; TGFβR, TGFβ receptor; TJ, tight junction; β-TRCP, beta-transducin repeat containing protein; Tsh, teashirt; UBA, ubiquitin-associated domain; Wnt, wingless-related MMTV integration site; Wts, warts; WW, WW domain; YAP, Yes-associated protein; Yki, yorkie.

(See poster insert)

enhanced Mob1–Lats interaction (Praskova et al., 2008). Mst is activated by binding of Salvador (Sav1, Sav in *Drosophila*), which is, in turn, also phosphorylated by Mst (Callus et al., 2006; Kango-Singh et al., 2002; Tapon et al., 2002).

Upstream components of the Hippo pathway

Many regulatory proteins upstream of the Hippo pathway core components have been uncovered, but their mechanism of action is unclear in most cases. *Drosophila* epigenetic studies indicate that Merlin (Mer) and Expanded (Ex), proteins that contain FERM domains and are responsible for membrane and actin cytoskeleton association, act upstream of core components of the Hippo pathway (Hamaratoglu et al., 2006). Remarkably, loss of one or two copies of the downstream effector Yes-associated protein (YAP) largely suppresses Mer-deficiency-induced liver overgrowth and tumor formation in murine models, suggesting that the function of Mer within the Hippo pathway is conserved in mammals (Zhang et al., 2010). However, in a study that used cultured cells from Mer knockout livers, Mer-deficiency-induced over-proliferation is not inhibited by YAP knockdown using small hairpin RNA (shRNA) and, in contrast to YAP overexpression, ablation of Mer alone in adult mice is insufficient to induce liver tumors (Benhamouche et al., 2010), which suggest that the regulation of YAP by Mer might be context dependent. In this study, Mer-deficiency-induced over-proliferation was attributed to aberrant epidermal growth factor receptor (EGFR) activity (Benhamouche et al., 2010). In *Drosophila*, the protein Kibra, which interacts with Mer and Ex, might positively regulate the Hippo pathway by mediating or promoting the interaction of Mer and Ex with Hpo and Sav (Baumgartner et al., 2010; Genevet et al., 2010; Yu et al., 2010). Many other *Drosophila* proteins were shown to regulate the activity of the Hippo pathway (reviewed by Grusche et al., 2010), including the proteins Fat, Dachsous (Ds), Four-jointed (Fj) and Lowfat (Lft) (Bennett and Harvey, 2006; Cho et al., 2006; Mao et al., 2009; Rogulja et al., 2008; Silva et al., 2006; Simon et al., 2010; Tyler and Baker, 2007; Willecke et al., 2006; Willecke et al., 2008), which regulate planar cell polarity. Other regulatory proteins include the LIM-domain-containing protein dJub (Das Thakur et al., 2010), the cell apical proteins atypical protein kinase C (aPKC) and Crumbs (Crb), and the basolateral Scribble–discs large (Dlg)–lethal giant larvae (Lgl) protein complex (Grzeschik et al., 2010; Ling et al., 2010; Robinson et al., 2010). These proteins are conserved in mammals, although their function in regulating the mammalian Hippo pathway is yet to be determined. It will be interesting to further investigate the relationship between cell polarity proteins and the Hippo pathway, which might link cell architecture to cell proliferation and apoptosis.

The mammalian tumor-suppressor protein Ras association family member 1A (RASSF1A) interacts with Mst through SARAH (for Sav-Rassf-Hpo) domains present in both proteins, resulting in Mst activation. By contrast, RASSF1A was shown to inhibit Mst in vitro (Guo et al., 2007; Oh et al., 2006; Praskova et al., 2004). Moreover, *Drosophila* RASSF antagonizes Hpo by competing with Sav for Hpo binding (Polesello et al., 2006). Detailed investigations of the molecular mechanisms underlying Mst activation by RASSF1A and further studies of other RASSF family members might help to resolve this apparent discrepancy between studies performed in *Drosophila* and mammalian cells.

Downstream effectors of the Hippo pathway

Lats and Wts kinases are known to phosphorylate the downstream effectors YAP, the YAP paralog transcriptional coactivator with PDZ-binding motif (TAZ) and Yorkie (Yki), which results in the inhibition of their activity as transcription coactivators in mammals and in *Drosophila* (Huang et al., 2005; Lei et al., 2008; Zhao et al., 2007), as discussed in further detail below. The major target transcription factors of YAP, TAZ and Yki are the four proteins of the TEA-domain-containing (TEAD) family (TEAD1–TEAD4), which correspond to a single homologue in *Drosophila*, Scalloped (Sd) (Goulev et al., 2008; Wu et al., 2008; Zhang, H. et al., 2009; Zhang et al., 2008; Zhao et al., 2008). Crystallographic data revealed that the N-terminal TEAD-binding domain of YAP wraps around a globular structure formed by the C-terminal domains of TEAD1, 2 and 4 (Chen et al., 2010; Li et al., 2010; Tian et al., 2010). YAP also binds to other transcription regulators, such as Runt-related transcription factor (RUNX), the cytoplasmic domain of ErbB4 and p73, but none of these interactions has been shown so far to mediate the function of YAP in organ size control and tumorigenesis (Komuro et al., 2003; Omerovic et al., 2004; Strano et al., 2001; Yagi et al., 1999).

Yki induces the expression of *cyclin E* (*cycE*), *Drosophila inhibitor of apoptosis 1* (*diap1*) and the microRNA *bantam* (Huang et al., 2005; Nolo et al., 2006; Thompson and Cohen, 2006). However, YAP, together with TEAD, induces the expression of another set of genes, including the connective tissue growth factor (CTGF) and Gli2 (Fernandez et al., 2009; Zhao et al., 2008). YAP also induces expression of the *diap1* homologues *baculoviral IAP repeat-containing 5* and *2* (*Birc5* and *Birc2*) and of cytokines such as *fibroblast growth factor 1* (*FGF1*) and *amphiregulin* (*AREG*) (Dong et al., 2007; Hao et al., 2008; Zhang, J. et al., 2009). However, the transcription factors responsible for the expression of these genes have thus far remained elusive.

YAP, TAZ and Yki are phosphorylated and inhibited by the Hippo pathway

Phosphorylation and inhibition of the transcription coactivators YAP, TAZ and Yki by the Lats and Wts kinases are crucial events within the Hippo signaling pathway, as discussed below.

Phosphorylation leads to cytoplasmic retention of YAP, TAZ and Yki

Lats phosphorylates five consensus HXRXXS motifs in YAP (Zhao et al., 2010b) and this results in YAP inhibition. Phosphorylation of YAP Ser127 and of the corresponding sites in Yki and TAZ generates a protein-binding motif for the 14-3-3 family proteins, which, upon binding by a 14-3-3 protein, leads to their cytoplasmic retention (Lei et al., 2008; Oh and Irvine, 2008; Zhao et al., 2007). This results in these transcription coactivators becoming separated from their target gene promoters. Mutation of Ser127 in YAP or of the equivalent residues in TAZ and Yki is thus able to enhance their function as transcription coactivators (Lei et al., 2008; Zhao et al., 2007).

Phosphorylation leads to YAP degradation

In addition to promoting its translocation, phosphorylation by Lats also destabilizes YAP. Phosphorylation of YAP Ser381 primes it for subsequent phosphorylation by another kinase, possibly casein kinase 1 (CK1δ/ε). This activates a phosphorylation-dependent degradation motif termed the phosphodegron and results in the recruitment of the E3 ubiquitin ligase β-TRCP, thereby leading to polyubiquitylation and subsequent degradation of YAP (Zhao et al., 2010b). This Hippo-pathway-dependent destabilization of YAP is supported by the observation of an increase in YAP protein level that accompanies decreased YAP phosphorylation in the liver of mice in which Mst1 and Mst2 have been knocked out (Song et al., 2010). This mechanism, which provides the cell with a means to inhibit YAP on a long-term basis, is conserved in TAZ, but not in Yki, which lacks a residue equivalent to Ser381. It is worth noting that phosphorylation of YAP Tyr391, which is close to the phosphodegron, by the

tyrosine kinase c-Abl results in YAP stabilization (Levy et al., 2008). It is unclear whether phosphorylation at Tyr391 stabilizes YAP through modulation of Ser381-phosphorylation-mediated YAP degradation.

Hippo pathway components can bind to and inhibit Yki

Apart from phosphorylation-dependent inhibition, components of the Hippo pathway can also inhibit Yki in a phosphorylation-independent manner. The WW domain in Yki can interact with the PPXY motifs that are present in the Hippo pathway components Ex, Wts and Hpo (Badouel et al., 2009; Oh et al., 2009). These interactions might inhibit Yki activity by sequestering it in the cytoplasm, thus adding another layer of complexity to Yki regulation.

The interplay between the Hippo pathway and other signaling pathways

Organ development is a coordinated process of increase in organ size and morphogenesis that is mediated by extensive crosstalk between signaling pathways. Pioneer studies have now begun to reveal the interplay of the Hippo pathway with other established signaling cascades, as discussed below.

The Hippo pathway and TGF-β signaling

Transforming growth factor (TGF)-β and bone morphogenetic protein (BMP) signaling play crucial roles in morphogenesis and tumorigenesis through the activation of Smad proteins as their downstream nuclear effectors. In developing *Drosophila* wings, clonal activation of TGF-β family member Decapentaplegic (Dpp) signaling by expression of an activated form of the Dpp receptor leads to activation of the expression of Hippo pathway target genes around the clone edge, presumably by modulating the expression and localization of the upstream Hippo pathway components Fj, Ds and Dachs (Rogulja et al., 2008). The link between Hippo and TGF-β or BMP signaling might be more direct in mammals, as phosphorylation of Smad1 following BMP stimulation enhances the interaction of Smad1 with the WW domains of YAP, which promotes the self-renewal capability of mouse embryonic stem cells (ESCs) (Alarcon et al., 2009). Interestingly, TAZ has been shown to interact with Smad2 and Smad3 through its coiled-coil region, and to be important in maintaining the nuclear localization of Smad2 and Smad3 as well as the expression of their target genes in response to TGF-β signaling and, thus, in the maintenance of human ESC self-renewal (Varelas et al., 2008). However, it is unclear how YAP and TAZ achieve binding specificity for only certain Smads and whether these interactions contribute to the control of organ size and tumorigenesis.

The Hippo pathway and Wnt signaling

Wnt signaling plays an important role in tissue development. Aberrant activation of the Wnt pathway has been implicated in driving the formation of various human cancers, in particular those of the digestive tract (Barker and Clevers, 2006). Stimulation of cell-surface receptors by Wnt ligands results in the disassembly of the so-called 'β-catenin destruction complex', an axin–APC–GSK3–CK1α–β-catenin complex that normally promotes the proteolytic degradation of β-catenin, which is followed by nuclear accumulation of β-catenin and activation of the Wnt target genes. Interestingly, according to a recent report, cytoplasmic TAZ negatively regulates the Wnt–β-catenin signaling pathway by binding to dishevelled (Dvl) 2, 1 and 3, which might interfere with Dvl phosphorylation, an event that precedes β-catenin stabilization and activation (Varelas et al., 2010). Mst and Lats can also inhibit Wnt signaling, presumably by promoting the phosphorylation of TAZ and its subsequent cytoplasmic localization. Consistent with this observation, *wts* or *hpo* mutants have elevated levels of Armadillo, the β-catenin ortholog in *Drosophila* (Varelas et al., 2010). Moreover, TAZ knockout mice develop renal cysts that lead to end-stage renal disease (Hossain et al., 2007; Makita et al., 2008; Tian et al., 2007). Interestingly, excessive Wnt signaling in mouse kidneys also yields polycystic kidney lesions (Saadi-Kheddouci et al., 2001; Sansom et al., 2005). These data suggest that inhibition of Wnt signaling by TAZ could be the cause of TAZ-ablation-induced mouse kidney cystic disease, whose underlying mechanism was hitherto unknown. An interesting question that remains is whether and to what extent cytoplasmic TAZ-mediated inhibition of Wnt signaling can contribute to the function of the Hippo pathway in regulating organ size and cancer. In this context, it is worth noting that an independent report showed that YAP overexpression in mouse intestinal epithelium increased total and nuclear β-catenin levels, presenting further evidence for activation of Wnt signaling by Hippo pathway components (Camargo et al., 2007).

The Hippo pathway and Notch signaling

Notch signaling is another important signaling pathway involved in metazoan development and implicated in a wide range of human disorders, including cancer. Upon ligand binding, Notch signaling is activated by a series of proteolysis events, which release an active intracellular Notch fragment (NICD) that translocates to the nucleus to activate the expression of its target genes, such as the *hairy and enhancer of split* (*HES*) genes and *myc*. Interestingly, mutations of Hippo pathway components largely suppress normal Notch signaling in posterior follicle cells during *Drosophila* oogenesis, as indicated by compromised Notch target gene expression (Genevet et al., 2010; Meignin et al., 2007; Polesello and Tapon, 2007; Yu et al., 2010). In *hpo*, *wts* or *mer;ex* double-mutant clones in *Drosophila* eye and wing imaginal disc, Notch abnormally accumulates at the cell apical region and the overall Notch activity is reduced (Genevet et al., 2009; Maitra et al., 2006). This suggests that Notch accumulation at the cell apical region owing to compromised Hippo signaling might result in the inhibition of Notch signaling as a result of reduced NICD internalization (Genevet et al., 2009). In mammals, a connection between YAP and Notch signaling has been observed in an intestine-specific YAP transgenic mouse model, in which expression of YAP results in the rapid stimulation of HES expression; this is indicative of activated Notch signaling. Moreover, inhibition of Notch signaling by a γ-secretase inhibitor largely overcomes YAP-induced dysplasia and differentiation (Camargo et al., 2007). It is currently unclear whether Yki is also involved in the crosstalk between *Drosophila* Hippo and Notch signaling. Deciphering the detailed mechanisms underlying the interplay between Notch and Hippo signaling requires further studies.

The Hippo pathway and Hedgehog signaling

The Hedgehog pathway is a major regulator of cell differentiation, tissue polarity and cell proliferation. Interestingly, overexpression of YAP and TEAD1 was observed specifically in subsets of medulloblastomas that were driven by activated Sonic hedgehog (Shh) or Wnt signaling for their formation (Fernandez et al., 2009), suggesting that crosstalk exists between YAP and Hedgehog signaling as well as between YAP and Wnt signaling (as discussed above). Interestingly, YAP was indeed activated when neuron precursors, which are believed to be the cell of origin for Shh-dependent medulloblastomas (Fernandez et al., 2009), were treated with Shh. Here, activation of YAP was shown to be the result of increased transcription of its mRNA and of increased protein stabilization and nuclear accumulation, indicating a complex underlying mechanism. It has also been suggested that YAP, together with TEAD1, can directly induce the expression of Gli2, a downstream effector of

Shh signaling (Fernandez et al., 2009). Additional studies are required to determine whether other Hippo pathway components, such as TAZ and Yki, are also involved in crosstalk with Hedgehog signaling and, if so, what the underlying mechanisms are.

The Hippo pathway links regulation of organ size to cancer development

The Hippo pathway not only regulates organ size, but also plays an important role in the development of human cancers. This might be due to either its ability to regulate cell proliferation and apoptosis or, alternatively, its functions in the renewal and expansion of stem cells and progenitor cells, as discussed below.

The Hippo pathway and organ size control

In *Drosophila*, mutation of the Hippo pathway results in increased organ size; the ectopic expression of its components leads to an opposite phenotype of reduced organ size, similar to what has been observed for Yki mutations (for a review, see Kango-Singh and Singh, 2009). These alterations of organ size are attributed to a combinatory effect of changes in both cell proliferation and apoptosis (for a review, see Kango-Singh and Singh, 2009). A function of the Hippo pathway in controlling organ size was also confirmed in mammals. For example, liver-specific expression of YAP in transgenic mice leads to an up to fourfold increase in liver size and to the development of liver tumors at a later stage (Camargo et al., 2007; Dong et al., 2007). Similar phenotypes have been observed in liver-specific knockouts of Mst1 and Mst2, Sav1 or Mer (Benhamouche et al., 2010; Lee et al., 2010; Lu et al., 2010; Song et al., 2010; Zhang et al., 2010; Zhou et al., 2009). Taken together, these genetic studies present convincing evidence that the Hippo pathway is indeed a key regulator of organ size.

The Hippo pathway and cancer

Accumulating evidence indicates that the Hippo pathway also plays important roles in cancer development. *Mer* is a well-established human tumor suppressor gene, the mutation of which causes lesions in the nervous system, eyes and skin (Asthagiri et al., 2009). Mutation of *Mob1* and *Sav1*, two other Hippo pathway core components, has also been observed in a human renal cancer cell line and in skin melanoma, respectively (Lai et al., 2005; Tapon et al., 2002). Other Hippo pathway components have also been reported to show abnormal expression levels in cancer samples. For example, RASSF1A is one of the most commonly silenced genes in human cancers, owing to hypermethylation of its promoter (Agathanggelou et al., 2005), and the expression of Mst and Lats is downregulated in several human cancers (Jiang et al., 2006; Minoo et al., 2007; Seidel et al., 2007). By contrast, TAZ was found to be upregulated in breast cancers, especially in invasive ductal carcinomas (Chan et al., 2008). Furthermore, YAP gene amplification was found in various cancers, including hepatocelluar carcinoma (HCC) (Overholtzer et al., 2006; Zender et al., 2006). Consistent with these findings, increased protein levels of YAP and nuclear accumulation was also observed in several cancers (Dong et al., 2007; Steinhardt et al., 2008; Zender et al., 2006; Zhao et al., 2007). Recently, a clinical study identified YAP as a predicting factor for HCC-specific disease-free survival and overall survival through assessing its protein level and nuclear localization (Xu et al., 2009).

The role of the Hippo pathway in stem cells

Recent studies demonstrated previously unknown functions of YAP and TAZ in the renewal and proliferation of ESCs and organ-specific progenitor cells. For instance, YAP is inactivated during ESC differentiation and activated in induced pluripotent stem (iPS) cells (Lian et al., 2010). In addition, knockdown of YAP in murine D3 ESCs leads to loss of pluripotency. By contrast, ectopic expression of YAP prevents ESC differentiation (Lian et al., 2010), but the exact underlying mechanism is not clear. Intriguingly, knockdown of TAZ also leads to differentiation of human CA1 stem cells (Varelas et al., 2008), but it is not clear how these functions of YAP and TAZ are coordinated to maintain 'stemness'. YAP also plays a role in tissue-specific progenitor cells. For instance, in mouse intestines, expression of endogenous YAP is restricted to the progenitor cell compartment, which expands when YAP is overexpressed (Camargo et al., 2007). Consistent with this observation, activation of YAP and TEAD also causes marked expansion of neural progenitor cells in a chicken neural tube model (Cao et al., 2008).

In the past few years, it has been suggested that cancer could arise from a small population of cancer cells that have stem-cell-like properties, the so-called cancer stem cells. A function of YAP and thus of the Hippo pathway in cancer stem cells is also emerging. In a subtype of medulloblastomas, YAP expression was found to be strikingly high in the perivascular cancer stem cell compartment, suggesting a role for YAP in maintaining cancer stem cells (Fernandez et al., 2009). In addition, double knockout of Mst1 and Mst2, knockout of Sav1 or knockout of Mer in mice liver also induces abundant accumulation of oval cells, the adult liver stem cells, which possibly are the cell type of origin for subsequent tumor formation (Benhamouche et al., 2010; Lee et al., 2010; Lu et al., 2010; Zhang et al., 2010). Further investigations are necessary to address how regulation of cell proliferation, apoptosis and stem cell self-renewal contributes to the functions of the Hippo pathway in organ size control and cancer development.

Perspectives

Over the past decade, our understanding of the Hippo signaling pathway has progressed rapidly, and has lead to the delineation of the Hippo pathway kinase cascade and insights into the regulation of its downstream effectors – YAP, TAZ and Yki. Functions of the Hippo pathway in controlling organ size and in cancer development have been described, and recent pioneering work has revealed insights into the interplay of the Hippo pathway with other signaling cascades. However, many key questions remain, including but not limited to the identity of the upstream signals of the Hippo pathway, the mechanisms of the interplay between the Hippo pathway and other signaling pathways, the existence of as-yet-unidentified Hippo pathway effectors, and the dysfunction of the Hippo pathway in human cancers. Answers to these questions will further advance our understanding of normal development and might help to develop new cancer therapies.

We apologize to authors whose primary work we could not cite because of space constraints. We thank Ryan Russell for critical reading of the manuscript, and the NIH and CIRM for funding (K.-L.G.). Deposited in PMC for release after 12 months.

References

Agathanggelou, A., Cooper, W. N. and Latif, F. (2005). Role of the Ras-association domain family 1 tumor suppressor gene in human cancers. *Cancer Res.* **65**, 3497-3508.

Alarcon, C., Zaromytidou, A. I., Xi, Q., Gao, S., Yu, J., Fujisawa, S., Barlas, A., Miller, A. N., Manova-Todorova, K., Macias, M. J. et al. (2009). Nuclear CDKs drive Smad transcriptional activation and turnover in BMP and TGF-beta pathways. *Cell* **139**, 757-769.

Asthagiri, A. R., Parry, D. M., Butman, J. A., Kim, H. J., Tsilou, E. T., Zhuang, Z. and Lonser, R. R. (2009). Neurofibromatosis type 2. *Lancet* **373**, 1974-1986.

Badouel, C., Gardano, L., Amin, N., Garg, A., Rosenfeld, R., Le Bihan, T. and McNeill, H. (2009). The FERM-domain protein Expanded regulates Hippo pathway activity via direct interactions with the transcriptional activator Yorkie. *Dev. Cell* **16**, 411-420.

Barker, N. and Clevers, H. (2006). Mining the Wnt pathway for cancer therapeutics. *Nat. Rev. Drug Discov.* **5**, 997-1014.

Baumgartner, R., Poernbacher, I., Buser, N., Hafen, E. and Stocker, H. (2010). The WW domain protein Kibra acts upstream of hippo in Drosophila. *Dev. Cell* **18**, 309-316.

Benhamouche, S., Curto, M., Saotome, I., Gladden, A. B., Liu, C. H., Giovannini, M. and McClatchey, A. I. (2010). Nf2/Merlin controls progenitor homeostasis and tumorigenesis in the liver. *Genes Dev.* **24**, 1718-1730.

Bennett, F. C. and Harvey, K. F. (2006). Fat cadherin modulates organ size in Drosophila via the Salvador/Warts/Hippo signaling pathway. *Curr. Biol.* **16**, 2101-2110.

Callus, B. A., Verhagen, A. M. and Vaux, D. L. (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**, 4264-4276.

Camargo, F. D., Gokhale, S., Johnnidis, J. B., Fu, D., Bell, G. W., Jaenisch, R. and Brummelkamp, T. R. (2007). YAP1 increases organ size and expands undifferentiated progenitor cells. *Curr. Biol.* **17**, 2054-2060.

Cao, X., Pfaff, S. L. and Gage, F. H. (2008). YAP regulates neural progenitor cell number via the TEA domain transcription factor. *Genes Dev.* **22**, 3320-3334.

Chan, S. W., Lim, C. J., Guo, K., Ng, C. P., Lee, I., Hunziker, W., Zeng, Q. and Hong, W. (2008). A role for TAZ in migration, invasion, and tumorigenesis of breast cancer cells. *Cancer Res.* **68**, 2592-2598.

Chen, L., Chan, S. W., Zhang, X., Walsh, M., Lim, C. J., Hong, W. and Song, H. (2010). Structural basis of YAP recognition by TEAD4 in the hippo pathway. *Genes Dev.* **24**, 290-300.

Cho, E., Feng, Y., Rauskolb, C., Maitra, S., Fehon, R. and Irvine, K. D. (2006). Delineation of a Fat tumor suppressor pathway. *Nat. Genet.* **38**, 1142-1150.

Chow, A., Hao, Y. and Yang, X. (2010). Molecular characterization of human homologs of yeast MOB1. *Int. J. Cancer* **126**, 2079-2089.

Das Thakur, M., Feng, Y., Jagannathan, R., Seppa, M. J., Skeath, J. B. and Longmore, G. D. (2010). Ajuba LIM proteins are negative regulators of the Hippo signaling pathway. *Curr. Biol.* **20**, 657-662.

Dong, J., Feldmann, G., Huang, J., Wu, S., Zhang, N., Comerford, S. A., Gayyed, M. F., Anders, R. A., Maitra, A. and Pan, D. (2007). Elucidation of a universal size-control mechanism in Drosophila and mammals. *Cell* **130**, 1120-1133.

Fernandez, L. A., Northcott, P. A., Dalton, J., Fraga, C., Ellison, D., Angers, S., Taylor, M. D. and Kenney, A. M. (2009). YAP1 is amplified and up-regulated in hedgehog-associated medulloblastomas and mediates Sonic hedgehog-driven neural precursor proliferation. *Genes Dev.* **23**, 2729-2741.

Genevet, A., Polesello, C., Blight, K., Robertson, F., Collinson, L. M., Pichaud, F. and Tapon, N. (2009). The Hippo pathway regulates apical-domain size independently of its growth-control function. *J. Cell Sci.* **122**, 2360-2370.

Genevet, A., Wehr, M. C., Brain, R., Thompson, B. J. and Tapon, N. (2010). Kibra is a regulator of the salvador/warts/hippo signaling network. *Dev. Cell* **18**, 300-308.

Goulev, Y., Fauny, J. D., Gonzalez-Marti, B., Flagiello, D., Silber, J. and Zider, A. (2008). SCALLOPED Interacts with YORKIE, the nuclear effector of the hippo tumor-suppressor pathway in *Drosophila*. *Curr. Biol.* **18**, 435-441.

Grusche, F. A., Richardson, H. E. and Harvey, K. F. (2010). Upstream regulation of the hippo size control pathway. *Curr. Biol.* **20**, R574-R582.

Grzeschik, N. A., Parsons, L. M., Allott, M. L., Harvey, K. F. and Richardson, H. E. (2010). Lgl, aPKC, and Crumbs regulate the Salvador/Warts/Hippo pathway through two distinct mechanisms. *Curr. Biol.* **20**, 573-581.

Guo, C., Tommasi, S., Liu, L., Yee, J. K., Dammann, R. and Pfeifer, G. P. (2007). RASSF1A is part of a complex similar to the Drosophila Hippo/Salvador/Lats tumor-suppressor network. *Curr. Biol.* **17**, 700-705.

Hamaratoglu, F., Willecke, M., Kango-Singh, M., Nolo, R., Hyun, E., Tao, C., Jafar-Nejad, H. and Halder, G. (2006). The tumour-suppressor genes NF2/Merlin and Expanded act through Hippo signalling to regulate cell proliferation and apoptosis. *Nat. Cell Biol.* **8**, 27-36.

Hao, Y., Chun, A., Cheung, K., Rashidi, B. and Yang, X. (2008). Tumor suppressor LATS1 is a negative regulator of oncogene YAP. *J. Biol. Chem.* **283**, 5496-5509.

Harvey, K. F., Pfleger, C. M. and Hariharan, I. K. (2003). The Drosophila Mst ortholog, hippo, restricts growth and cell proliferation and promotes apoptosis. *Cell* **114**, 457-467.

Hergovich, A., Schmitz, D. and Hemmings, B. A. (2006). The human tumour suppressor LATS1 is activated by human MOB1 at the membrane. *Biochem. Biophys. Res. Commun.* **345**, 50-58.

Hossain, Z., Ali, S. M., Ko, H. L., Xu, J., Ng, C. P., Guo, K., Qi, Z., Ponniah, S., Hong, W. and Hunziker, W. (2007). Glomerulocystic kidney disease in mice with a targeted inactivation of Wwtr1. *Proc. Natl. Acad. Sci. USA* **104**, 1631-1636.

Huang, J., Wu, S., Barrera, J., Matthews, K. and Pan, D. (2005). The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the Drosophila Homolog of YAP. *Cell* **122**, 421-434.

Jia, J., Zhang, W., Wang, B., Trinko, R. and Jiang, J. (2003). The Drosophila Ste20 family kinase dMST functions as a tumor suppressor by restricting cell proliferation and promoting apoptosis. *Genes Dev.* **17**, 2514-2519.

Jiang, Z., Li, X., Hu, J., Zhou, W., Jiang, Y., Li, G. and Lu, D. (2006). Promoter hypermethylation-mediated down-regulation of LATS1 and LATS2 in human astrocytoma. *Neurosci. Res.* **56**, 450-458.

Justice, R. W., Zilian, O., Woods, D. F., Noll, M. and Bryant, P. J. (1995). The Drosophila tumor suppressor gene warts encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation. *Genes Dev.* **9**, 534-546.

Kango-Singh, M. and Singh, A. (2009). Regulation of organ size: insights from the Drosophila Hippo signaling pathway. *Dev. Dyn.* **238**, 1627-1637.

Kango-Singh, M., Nolo, R., Tao, C., Verstreken, P., Hiesinger, P. R., Bellen, H. J. and Halder, G. (2002). Shar-pei mediates cell proliferation arrest during imaginal disc growth in *Drosophila*. *Development* **129**, 5719-5730.

Komuro, A., Nagai, M., Navin, N. E. and Sudol, M. (2003). WW domain-containing protein YAP associates with ErbB-4 and acts as a co-transcriptional activator for the carboxyl-terminal fragment of ErbB-4 that translocates to the nucleus. *J. Biol. Chem.* **278**, 33334-33341.

Lai, Z. C., Wei, X., Shimizu, T., Ramos, E., Rohrbaugh, M., Nikolaidis, N., Ho, L. L. and Li, Y. (2005). Control of cell proliferation and apoptosis by mob as tumor suppressor, mats. *Cell* **120**, 675-685.

Lee, K. P., Lee, J. H., Kim, T. S., Kim, T. H., Park, H. D., Byun, J. S., Kim, M. C., Jeong, W. I., Calvisi, D. F., Kim, J. M. et al. (2010). The Hippo-Salvador pathway restrains hepatic oval cell proliferation, liver size, and liver tumorigenesis. *Proc. Natl. Acad. Sci. USA* **107**, 8248-8253.

Lei, Q. Y., Zhang, H., Zhao, B., Zha, Z. Y., Bai, F., Pei, X. H., Zhao, S., Xiong, Y. and Guan, K. L. (2008). TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway. *Mol. Cell. Biol.* **28**, 2426-2436.

Levy, D., Adamovich, Y., Reuven, N. and Shaul, Y. (2008). Yap1 phosphorylation by c-Abl is a critical step in selective activation of proapoptotic genes in response to DNA damage. *Mol. Cell* **29**, 350-361.

Li, Z., Zhao, B., Wang, P., Chen, F., Dong, Z., Yang, H., Guan, K. L. and Xu, Y. (2010). Structural insights into the YAP and TEAD complex. *Genes Dev.* **24**, 235-240.

Lian, I., Kim, J., Okazawa, H., Zhao, J., Zhao, B., Yu, J., Chinnaiyan, A., Israel, M. A., Goldstein, L. S. and Abujarour, R. et al. (2010). The role of YAP transcription coactivator in regulating stem cell self-renewal and differentiation. *Genes Dev* **24**, 1106-1118.

Ling, C., Zheng, Y., Yin, F., Yu, J., Huang, J., Hong, Y., Wu, S. and Pan, D. (2010). The apical transmembrane protein Crumbs functions as a tumor suppressor that regulates Hippo signaling by binding to Expanded. *Proc. Natl. Acad. Sci. USA* **107**, 10532-10537.

Lu, L., Li, Y., Kim, S. M., Bossuyt, W., Liu, P., Qiu, Q., Wang, Y., Halder, G., Finegold, M. J., Lee, J. S. et al. (2010). Hippo signaling is a potent in vivo growth and tumor suppressor pathway in the mammalian liver. *Proc. Natl. Acad. Sci. USA* **107**, 1437-1442.

Maitra, S., Kulikauskas, R. M., Gavilan, H. and Fehon, R. G. (2006). The tumor suppressors Merlin and Expanded function cooperatively to modulate receptor endocytosis and signaling. *Curr. Biol.* **16**, 702-709.

Makita, R., Uchijima, Y., Nishiyama, K., Amano, T., Chen, Q., Takeuchi, T., Mitani, A., Nagase, T., Yatomi, Y., Aburatani, H. et al. (2008). Multiple renal cysts, urinary concentration defects, and pulmonary emphysematous changes in mice lacking TAZ. *Am. J. Physiol. Renal. Physiol.* **294**, F542-F553.

Mao, Y., Kucuk, B. and Irvine, K. D. (2009). Drosophila lowfat, a novel modulator of Fat signaling. *Development* **136**, 3223-3233.

Meignin, C., Alvarez-Garcia, I., Davis, I. and Palacios, I. M. (2007). The salvador-warts-hippo pathway is required for epithelial proliferation and axis specification in Drosophila. *Curr. Biol.* **17**, 1871-1878.

Minoo, P., Zlobec, I., Baker, K., Tornillo, L., Terracciano, L., Jass, J. R. and Lugli, A. (2007). Prognostic significance of mammalian sterile20-like kinase 1 in colorectal cancer. *Mod. Pathol.* **20**, 331-338.

Nolo, R., Morrison, C. M., Tao, C., Zhang, X. and Halder, G. (2006). The bantam microRNA is a target of the hippo tumor-suppressor pathway. *Curr. Biol.* **16**, 1895-1904.

Oh, H. and Irvine, K. D. (2008). In vivo regulation of Yorkie phosphorylation and localization. *Development* **135**, 1081-1088.

Oh, H., Reddy, B. V. and Irvine, K. D. (2009). Phosphorylation-independent repression of Yorkie in Fat-Hippo signaling. *Dev. Biol.* **335**, 188-197.

Oh, H. J., Lee, K. K., Song, S. J., Jin, M. S., Song, M. S., Lee, J. H., Im, C. R., Lee, J. O., Yonehara, S. and Lim, D. S. (2006). Role of the tumor suppressor RASSF1A in Mst1-mediated apoptosis. *Cancer Res.* **66**, 2562-2569.

Omerovic, J., Puggioni, E. M., Napoletano, S., Visco, V., Fraioli, R., Frati, L., Gulino, A. and Alimandi, M. (2004). Ligand-regulated association of ErbB-4 to the transcriptional co-activator YAP65 controls transcription at the nuclear level. *Exp. Cell Res.* **294**, 469-479.

Overholtzer, M., Zhang, J., Smolen, G. A., Muir, B., Li, W., Sgroi, D. C., Deng, C. X., Brugge, J. S. and Haber, D. A. (2006). Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. *Proc. Natl. Acad. Sci. USA* **103**, 12405-12410.

Pantalacci, S., Tapon, N. and Leopold, P. (2003). The Salvador partner Hippo promotes apoptosis and cell-cycle exit in Drosophila. *Nat. Cell Biol.* **5**, 921-927.

Polesello, C. and Tapon, N. (2007). Salvador-warts-hippo signaling promotes Drosophila posterior follicle cell maturation downstream of notch. *Curr. Biol.* **17**, 1864-1870.

Polesello, C., Huelsmann, S., Brown, N. H. and Tapon, N. (2006). The Drosophila RASSF homolog antagonizes the hippo pathway. *Curr. Biol.* **16**, 2459-2465.

Praskova, M., Khoklatchev, A., Ortiz-Vega, S. and Avruch, J. (2004). Regulation of the MST1 kinase by autophosphorylation, by the growth inhibitory proteins, RASSF1 and NORE1, and by Ras. *Biochem. J.* **381**, 453-462.

Praskova, M., Xia, F. and Avruch, J. (2008). MOBKL1A/MOBKL1B phosphorylation by MST1 and MST2 inhibits cell proliferation. *Curr. Biol.* **18**, 311-321.

Robinson, B. S., Huang, J., Hong, Y. and Moberg, K. H. (2010). Crumbs regulates Salvador/Warts/Hippo signaling in Drosophila via the FERM-domain protein expanded. *Curr. Biol.* **20**, 582-590.

Rogulja, D., Rauskolb, C. and Irvine, K. D. (2008). Morphogen control of wing growth through the Fat signaling pathway. *Dev. Cell* **15**, 309-321.

Saadi-Kheddouci, S., Berrebi, D., Romagnolo, B., Cluzeaud, F., Peuchmaur, M., Kahn, A., Vandewalle, A. and Perret, C. (2001). Early development of polycystic kidney disease in transgenic mice expressing an activated mutant of the beta-catenin gene. *Oncogene* **20**, 5972-5981.

Sansom, O. J., Griffiths, D. F., Reed, K. R., Winton, D. J. and Clarke, A. R. (2005). Apc deficiency predisposes to renal carcinoma in the mouse. *Oncogene* **24**, 8205-8210.

Seidel, C., Schagdarsurengin, U., Blumke, K., Wurl, P., Pfeifer, G. P., Hauptmann, S., Taubert, H. and Dammann, R. (2007). Frequent hypermethylation of MST1 and MST2 in soft tissue sarcoma. *Mol. Carcinog.* **46**, 865-871.

Silva, E., Tsatskis, Y., Gardano, L., Tapon, N. and McNeill, H. (2006). The tumor-suppressor gene fat controls tissue growth upstream of expanded in the hippo signaling pathway. *Curr. Biol.* **16**, 2081-2089.

Simon, M. A., Xu, A., Ishikawa, H. O. and Irvine, K. D. (2010). Modulation of FAt:Dachsous binding by the cadherin domain kinase four-jointed. *Curr. Biol.* **20**, 811-817.

Song, H., Mak, K. K., Topol, L., Yun, K., Hu, J., Garrett, L., Chen, Y., Park, O., Chang, J., Simpson, R. M. et al. (2010). Mammalian Mst1 and Mst2 kinases play essential roles in organ size control and tumor suppression. *Proc. Natl. Acad. Sci. USA* **107**, 1431-1436.

Steinhardt, A. A., Gayyed, M. F., Klein, A. P., Dong, J., Maitra, A., Pan, D., Montgomery, E. A. and Anders, R. A. (2008). Expression of Yes-associated protein in common solid tumors. *Hum. Pathol.* **39**, 1582-1589.

Strano, S., Munarriz, E., Rossi, M., Castagnoli, L., Shaul, Y., Sacchi, A., Oren, M., Sudol, M., Cesareni, G. and Blandino, G. (2001). Physical interaction with Yes-associated protein enhances p73 transcriptional activity. *J. Biol. Chem.* **276**, 15164-15173.
Tapon, N., Harvey, K. F., Bell, D. W., Wahrer, D. C., Schiripo, T. A., Haber, D. A. and Hariharan, I. K. (2002). salvador Promotes both cell cycle exit and apoptosis in Drosophila and is mutated in human cancer cell lines. *Cell* **110**, 467-478.
Thompson, B. J. and Cohen, S. M. (2006). The Hippo pathway regulates the bantam microRNA to control cell proliferation and apoptosis in Drosophila. *Cell* **126**, 767-774.
Tian, W., Yu, J., Tomchick, D. R., Pan, D. and Luo, X. (2010). Structural and functional analysis of the YAP-binding domain of human TEAD2. *Proc. Natl. Acad. Sci. USA* **107**, 7293-7298.
Tian, Y., Kolb, R., Hong, J. H., Carroll, J., Li, D., You, J., Bronson, R., Yaffe, M. B., Zhou, J. and Benjamin, T. (2007). TAZ promotes PC2 degradation through a SCFbeta-Trcp E3 ligase complex. *Mol. Cell. Biol.* **27**, 6383-6395.
Tyler, D. M. and Baker, N. E. (2007). Expanded and fat regulate growth and differentiation in the Drosophila eye through multiple signaling pathways. *Dev. Biol.* **305**, 187-201.
Udan, R. S., Kango-Singh, M., Nolo, R., Tao, C. and Halder, G. (2003). Hippo promotes proliferation arrest and apoptosis in the Salvador/Warts pathway. *Nat. Cell. Biol.* **5**, 914-920.
Varelas, X., Sakuma, R., Samavarchi-Tehrani, P., Peerani, R., Rao, B. M., Dembowy, J., Yaffe, M. B., Zandstra, P. W. and Wrana, J. L. (2008). TAZ controls Smad nucleocytoplasmic shuttling and regulates human embryonic stem-cell self-renewal. *Nat. Cell Biol.* **10**, 837-848.
Varelas, X., Miller, B. W., Sopko, R., Song, S., Gregorieff, A., Fellouse, F. A., Sakuma, R., Pawson, T., Hunziker, W., McNeill, H. et al. (2010). The Hippo pathway regulates Wnt/beta-catenin signaling. *Dev. Cell* **18**, 579-591.
Wei, X., Shimizu, T. and Lai, Z. C. (2007). Mob as tumor suppressor is activated by Hippo kinase for growth inhibition in Drosophila. *EMBO J.* **26**, 1772-1781.
Willecke, M., Hamaratoglu, F., Kango-Singh, M., Udan, R., Chen, C. L., Tao, C., Zhang, X. and Halder, G. (2006). The fat cadherin acts through the hippo tumor-suppressor pathway to regulate tissue size. *Curr. Biol.* **16**, 2090-2100.
Willecke, M., Hamaratoglu, F., Sansores-Garcia, L., Tao, C. and Halder, G. (2008). Boundaries of Dachsous Cadherin activity modulate the Hippo signaling pathway to induce cell proliferation. *Proc. Natl. Acad. Sci. USA* **105**, 14897-14902.
Wu, S., Huang, J., Dong, J. and Pan, D. (2003). hippo encodes a Ste-20 family protein kinase that restricts cell proliferation and promotes apoptosis in conjunction with salvador and warts. *Cell* **114**, 445-456.
Wu, S., Liu, Y., Zheng, Y., Dong, J. and Pan, D. (2008). The TEAD/TEF family protein Scalloped mediates transcriptional output of the Hippo growth-regulatory pathway. *Dev. Cell* **14**, 388-398.
Xu, M. Z., Yao, T. J., Lee, N. P., Ng, I. O., Chan, Y. T., Zender, L., Lowe, S. W., Poon, R. T. and Luk, J. M. (2009). Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. *Cancer* **115**, 4576-4585.
Xu, T., Wang, W., Zhang, S., Stewart, R. A. and Yu, W. (1995). Identifying tumor suppressors in genetic mosaics: the Drosophila lats gene encodes a putative protein kinase. *Development* **121**, 1053-1063.
Yagi, R., Chen, L. F., Shigesada, K., Murakami, Y. and Ito, Y. (1999). A WW domain-containing yes-associated protein (YAP) is a novel transcriptional co-activator. *EMBO J.* **18**, 2551-2562.
Yu, J., Zheng, Y., Dong, J., Klusza, S., Deng, W. M. and Pan, D. (2010). Kibra functions as a tumor suppressor protein that regulates hippo signaling in conjunction with Merlin and expanded. *Dev. Cell* **18**, 288-299.
Zender, L., Spector, M. S., Xue, W., Flemming, P., Cordon-Cardo, C., Silke, J., Fan, S. T., Luk, J. M., Wigler, M., Hannon, G. J. et al. (2006). Identification and validation of oncogenes in liver cancer using an integrative oncogenomic approach. *Cell* **125**, 1253-1267.
Zhang, H., Liu, C. Y., Zha, Z. Y., Zhao, B., Yao, J., Zhao, S., Xiong, Y., Lei, Q. Y. and Guan, K. L. (2009). TEAD transcription factors mediate the function of TAZ in cell growth and epithelial-mesenchymal transition. *J. Biol. Chem.* **284**, 13355-13362.
Zhang, J., Ji, J. Y., Yu, M., Overholtzer, M., Smolen, G. A., Wang, R., Brugge, J. S., Dyson, N. J. and Haber, D. A. (2009). YAP-dependent induction of amphiregulin identifies a non-cell-autonomous component of the Hippo pathway. *Nat. Cell Biol.* **11**, 1444-1450.
Zhang, L., Ren, F., Zhang, Q., Chen, Y., Wang, B. and Jiang, J. (2008). The TEAD/TEF family of transcription factor Scalloped mediates Hippo signaling in organ size control. *Dev. Cell* **14**, 377-387.
Zhang, N., Bai, H., David, K. K., Dong, J., Zheng, Y., Cai, J., Giovannini, M., Liu, P., Anders, R. A. and Pan, D. (2010). The Merlin/NF2 tumor suppressor functions through the YAP oncoprotein to regulate tissue homeostasis in mammals. *Dev. Cell* **19**, 27-38.
Zhao, B., Wei, X., Li, W., Udan, R. S., Yang, Q., Kim, J., Xie, J., Ikenoue, T., Yu, J., Li, L. et al. (2007). Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. *Genes Dev.* **21**, 2747-2761.
Zhao, B., Ye, X., Yu, J., Li, L., Li, W., Li, S., Lin, J. D., Wang, C. Y., Chinnaiyan, A. M., Lai, Z. C. et al. (2008). TEAD mediates YAP-dependent gene induction and growth control. *Genes Dev.* **22**, 1962-1971.
Zhao, B., Li, L., Lei, Q. and Guan, K. L. (2010a). The Hippo-YAP pathway in organ size control and tumorigenesis: an updated version. *Genes Dev.* **24**, 862-874.
Zhao, B., Li, L., Tumaneng, K., Wang, C. Y. and Guan, K. L. (2010b). A coordinated phosphorylation by Lats and CK1 regulates YAP stability through SCF(beta-TRCP). *Genes Dev.* **24**, 72-85.
Zhou, D., Conrad, C., Xia, F., Park, J. S., Payer, B., Yin, Y., Lauwers, G. Y., Thasler, W., Lee, J. T., Avruch, J. et al. (2009). Mst1 and Mst2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the Yap1 oncogene. *Cancer Cell* **16**, 425-438.

Cell Science at a Glance on the Web
Electronic copies of the poster insert are available in the online version of this article at jcs.biologists.org. The JPEG images can be downloaded for printing or used as slides.