The Hippo pathway in organ size control, tissue regeneration and stem cell self-renewal

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Precise control of organ size is crucial during animal development and regeneration. In *Drosophila* and mammals, studies over the past decade have uncovered a critical role for the Hippo tumour-suppressor pathway in the regulation of organ size. Dysregulation of this pathway leads to massive overgrowth of tissue. The Hippo signalling pathway is highly conserved and limits organ size by phosphorylating and inhibiting the transcription co-activators YAP and TAZ in mammals and Yki in *Drosophila*, key regulators of proliferation and apoptosis. The Hippo pathway also has a critical role in the self-renewal and expansion of stem cells and tissue-specific progenitor cells, and has important functions in tissue regeneration. Emerging evidence shows that the Hippo pathway is regulated by cell polarity, cell adhesion and cell junction proteins. In this review we summarize current understanding of the composition and regulation of the Hippo pathway, and discuss how cell polarity and cell adhesion proteins inform the role of this pathway in organ size control and regeneration.

Organ size regulation is a highly coordinated process involving complex mechanisms in response to physiological cues. On the organismal level, circulating factors such as hormones and insulin-like growth factors (IGF) play important roles in promoting organ size[1]. In contrast, physiological perturbations, such as prolonged starvation, cause profound reduction of organ size[1]. Additionally, an intrinsic mechanism limits organ size, which was first demonstrated in salamander limbs by classical transplantation experiments[1]. The underlying mechanism of organ-autonomous size determination remained largely unknown until the past decade. Extensive research led to the identification of the Hippo tumour-suppressor pathway as a key regulator of organ size in *Drosophila* and mammals[2]. It is also known that mutations of genes that are involved in patterning, cell polarity and cell adhesion cause marked alternations of organ size[3]. Thus, the recent finding that the Hippo pathway is regulated by cell polarity and cell adhesion proteins is a promising basis for the potential crosstalk of the Hippo pathway and cell polarity proteins in the regulation of organ size[4]. Several studies have also demonstrated important roles for the Hippo pathway in stem cell/progenitor cell expansion and tissue regeneration[5–13]. These findings will be discussed here.

The Hippo pathway in *Drosophila*

In *Drosophila*, the first core components of the Hippo pathway to be identified, using genetic mosaic screens, were the tumour-suppressor genes *warts* (*wts*)[14,15], *hippo* (*hpo*)[16–20] and *salvador* (*sav*)[21,22]. These genes belong to the hyperplastic group of *Drosophila* tumour-suppressors. Mutation of these genes results in robust tissue overgrowth without alteration of cell fate determination or cell polarity. Biochemical studies revealed that Hpo directly interacts with Sav to phosphorylate and activate the complex formed by Wts and another core Hippo pathway protein, Mats[16,23] (Fig. 1a). The kinase activity of Hpo is antagonized by a PP2A phosphatase complex, dSTRIPAK[24]. The Hippo pathway is known to limit organ size partly by transcriptional regulation of *cyclin E* and *diap1* (refs 16,17,20,21,23), suggesting the existence of a transcriptional regulator as a downstream effector of the pathway. By performing a yeast two-hybrid screen using Wts as bait, the transcription co-activator Yorkie (Yki) was identified as a potent effector of the Hippo pathway[25]. Subsequent biochemical studies showed that Wts directly phosphorylates and inhibits Yki[26].

Research in the past years has uncovered many proteins that act upstream in the *Drosophila* Hippo pathway. Two apical cytoskeleton-binding proteins, Merlin (Mer) and Expanded (Ex)[27], and their interacting protein Kibra[28–30], were found to activate the Hippo pathway. The Fat protocadherin, a cell-surface molecule, was also identified as an upstream regulator of the Hippo pathway[31–35]. Fat activity is regulated by binding to another protocadherin, Dachsous (Ds)[36], and is modulated by several proteins, such as the casein kinase Discs overgrown (Dco)[37,38], the Golgi-resident kinase Four-jointed (Fj)[39–41] and the Fat/Ds-interacting protein Lowfat (Lft)[42]. Fat/Hippo pathway activity may also be influenced by Decapentaplegic (Dpp) and Wingless (Wg) morphogen gradients[40,41,43], which affect the expression of Fj and Ds. It has been proposed that Fat activates the Hippo pathway by regulating the protein level and localization of the protein Ex[31–33,35]. Another study suggests that Fat may control the abundance of Wts through Dachs[34,44]. Recently, dJub, a LIM-domain-containing protein that physically interacts with Wts and Sav, was shown to negatively regulate Hippo signalling, although the detailed mechanism has not been delineated[45]. A number of proteins that determine cell

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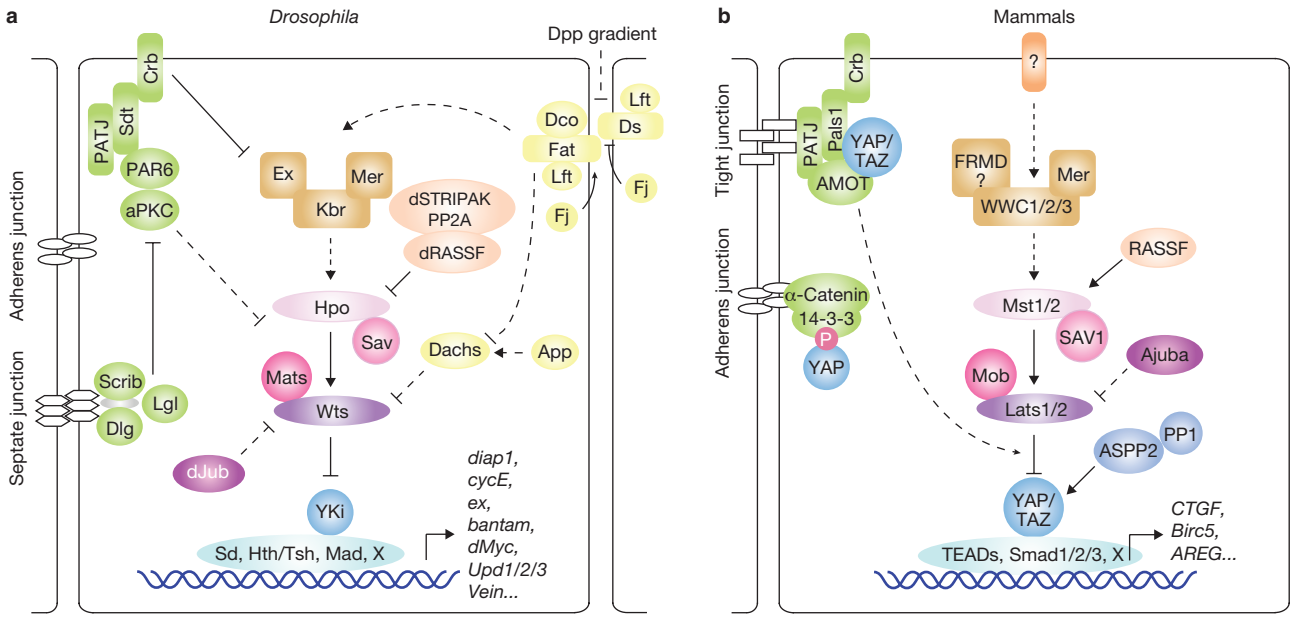

Figure 1 The Hippo pathway in *Drosophila* and mammals. Corresponding proteins in *Drosophila* (**a**) and mammals (**b**) are indicated by matching colours. Arrowed or blunted ends indicate activation or inhibition, respectively. Dashed lines indicate unknown mechanisms.

polarity were also found to regulate the Hippo pathway. These include the Scribble (Scrib)–Discs large (Dlg)–Lethal giant larvae (Lgl) complex, atypical protein kinase C (aPKC) and Crumbs (Crb)[46–49], indicating a role of cell polarity in the regulation of Hippo signalling.

The Hippo pathway in mammals

The core components and downstream effectors of the *Drosophila* Hippo pathway are highly conserved in mammals: Mst1/2 (homologues of Hpo), Sav1 (Sav homologue), Lats1/2 (Wts homologues), MOBKL1A and MOBKL1B (collectively referred to as Mob1; homologues of Mats), and YAP and its paralogue TAZ (also called WWTR1; homologues of Yki) (Fig. 1b). Expression of human YAP, Lats1, Mst2 and Mob1 can rescue the phenotypes of their corresponding *Drosophila* mutants *in vivo*[16,23,25,50]. The core components Mst1/2 are pro-apoptotic kinases that are activated by caspase cleavage under apoptotic stress[51]. Sav1 interacts with Mst1/2 through the SARAH domains present in both Sav1 and Mst1/2 (ref. 52). Although Sav1 has been shown to activate Mst1/2, the underlying mechanism is unclear, but might involve regulation of Mst1 nuclear translocation[53]. Mst1/2 is also activated by binding to Ras association domain family (RASSF) proteins[54], possibly owing to alteration of Mst1/2 subcellular localization[55]. In *Drosophila*, however, dRASSF inhibits Hpo possibly through competition with Sav for Hpo binding[56] and through recruitment of the dSTRIPAK–PP2A complex[24]. Activation of Mst1/2 leads to phosphorylation and activation of their direct substrates, Lats1/2 (ref. 57). Mob1, which forms a complex with Lats1/2, is also phosphorylated by Mst1/2, resulting in an enhanced Lats1/2–Mob1 interaction[58]. Activated Lats1/2 in turn phosphorylate and inhibit YAP/TAZ transcription co-activators[26,59–62].

Functions of the Hippo pathway in organ size determination and tumour suppression have been confirmed in genetically engineered mouse models. For instance, liver-specific overexpression of YAP results in enlarged livers that return to their normal size after cessation of YAP expression[12,26]. However, sustained YAP overexpression leads to tumour formation[26]. Genomic amplification of YAP is also observed in human cancers and a mouse model of breast cancer[63,64]. Furthermore, elevated YAP protein levels and nuclear localization have been observed in multiple human cancers[59,63,65], and the alterations of YAP may have prognostic value for certain human cancers[66]. Overexpression of TAZ, the paralogue of YAP, has been noted in human breast cancer samples and non-small-cell lung-cancer cell lines[67,68]. Ablation of the Hippo pathway components *Mer* and *Sav* and double knockout of *Mst1/2* in mice also result in liver enlargement and tumour formation[69–74]. Remarkably, loss of one or both copies of *YAP* can suppress liver expansion and tumorigenesis induced by Mer deficiency[69]. Aberrant Mst1/2 and Lats1/2 expression and *Lats2*, *Sav1* and *Mob1* mutation were also observed in human cancers or cancer cell lines[2]. Together, these studies highlight a significant role of the Hippo pathway in organ size regulation and tumorigenesis.

Mechanisms of YAP/TAZ/Yki inhibition

Activation of the Hippo pathway leads to phosphorylation and inhibition of YAP, TAZ and Yki transcription co-activators. In mammals, YAP and TAZ are phosphorylated by Lats1/2 *in vitro* and *in vivo*[59,60,75]. The mechanism of inhibition by Hippo signalling involves phosphorylation of Ser 127 in YAP or the corresponding sites in TAZ and Yki, which promotes 14-3-3 binding and subsequent cytoplasmic sequestration and inactivation[26,59,60,62,76] (Fig. 2a). Indeed, mutation of Ser 127 and disruption of 14-3-3 binding activate YAP[59], confirming the inhibitory nature of this phosphorylation. In *Drosophila*, Yki phosphorylation on two other sites by Wts similarly results in Yki inhibition, although the mechanism is yet to be determined[77].

Phosphorylation of YAP can also induce its degradation. Lats1/2 phosphorylates YAP at Ser 381, which primes YAP for subsequent phosphorylation by another kinase, possibly casein kinase 1 (CK1δ/ε), activating a phosphorylation-dependent degradation motif termed a phosphodegron. Subsequently, the E3 ubiquitin ligase SCFβ–TRCP is recruited to YAP, leading to its polyubiquitylation and degradation[75] (Fig. 2c). Consistently, decreased YAP phosphorylation in sparsely cultured NIH-3T3 cells, as well as in Mst1/2-deficient mouse liver, correlates with increased YAP

protein levels[73,75]. This mechanism is conserved in TAZ but not in Yki[78], which lacks a residue equivalent to Ser 381.

YAP, TAZ and Yki can also be inhibited through protein–protein interactions that result in their cytoplasmic sequestration (Fig. 2b). Yki contains two WW domains that can interact with PPXY motifs present in Mop[79] and the Hippo pathway components Ex, Wts and Hpo[80,81]. Recently, YAP/TAZ and angiomotin (AMOT) family proteins were shown to interact[82–85], resulting in YAP/TAZ localization to tight junctions and inhibition through phosphorylation-dependent and -independent mechanisms[82]. In addition, YAP and TAZ interact with another tight junction protein ZO-2, which was reported to increase nuclear localization of YAP and tight-junction localization of TAZ[86,87]. It will be important to investigate the relationship between phosphorylation and these physical interactions in YAP regulation, and whether disruption of these interactions alters organ growth.

Transcriptional regulation of Hippo pathway target genes by YAP, TAZ and Yki

The TEAD family transcription factors were found to be critical partners of YAP and TAZ in the regulation of gene expression (the *Drosophila* TEAD homologue Scalloped (Sd) is partner of Yki) [88–92]. Knockdown of TEADs or disruption of the YAP–TEAD interaction abolishes YAP-dependent gene transcription and largely diminishes YAP-induced cell proliferation, oncogenic transformation and the epithelial-to-mesenchymal transition (EMT)[88]. In *Drosophila*, Sd was shown to genetically interact with Yki and to be required for Yki-induced target gene expression *in vivo*[88,89,91,92]. Intriguingly, a mutation of TEAD1 Tyr 406, which forms a hydrogen bond with YAP, results in loss of interaction with YAP and leads to the human genetic disease Sveinsson's chorioretinal atrophy[93–96]. Precise regulation of YAP–TEAD interaction is therefore important in maintaining normal physiology.

Several direct target genes of YAP–/TAZ–TEAD and Yki–Sd have been identified, including *CTGF* and *Cyr61* in mammalian cells[88,97], and *diap1* and *dMyc* in *Drosophila*[89,91,98,99]. CTGF was shown to have an important role in YAP-induced proliferation and anchorage-independent growth[88]. In *Drosophila*, diap1 is essential for Yki-induced overgrowth, but is not sufficient to explain all Yki phenotypes. Recently, Yki–Sd was shown to induce transcription of *dMyc*, a potent promoter of ribosome biogenesis and cell growth[98,99]. *dMyc* expression also mediates a cell phenomenon induced by imbalance of Hippo pathway activity, referred to as cell competition — wherein the contact between fast- and slow-growing cells in genetic mosaics favours the positive selection and clonal expansion of fast-dividing cells at the expense of slow-dividing cells[98,99]. YAP also induces *Myc* in transgenic mouse liver[26], although the mechanism remains to be investigated.

Despite a major role for TEADs in YAP/TAZ function, other transcription factors containing PPXY motifs are known to interact with the WW domains of YAP/TAZ. These include Smad1, RUNX, ErbB4 and p73 for YAP[100–104], and RUNX, PPARγ, Pax3, TBX5 and TTF-1 for TAZ[105–109]. The interaction of YAP with Smad1 is believed to be important for BMP-mediated maintenance of pluripotency of mouse embryonic stem cells[104]. YAP and TAZ also bind Smad2/3 through the coiled-coil region, and this interaction is believed to dictate the subcellular localization of Smad2/3 (refs 85,110). YAP also interacts with p73, a p53 family pro-apoptotic transcription factor, to induce expression of genes such as *Bax*, *puma* and *PML*[111]. However, there are contradictory

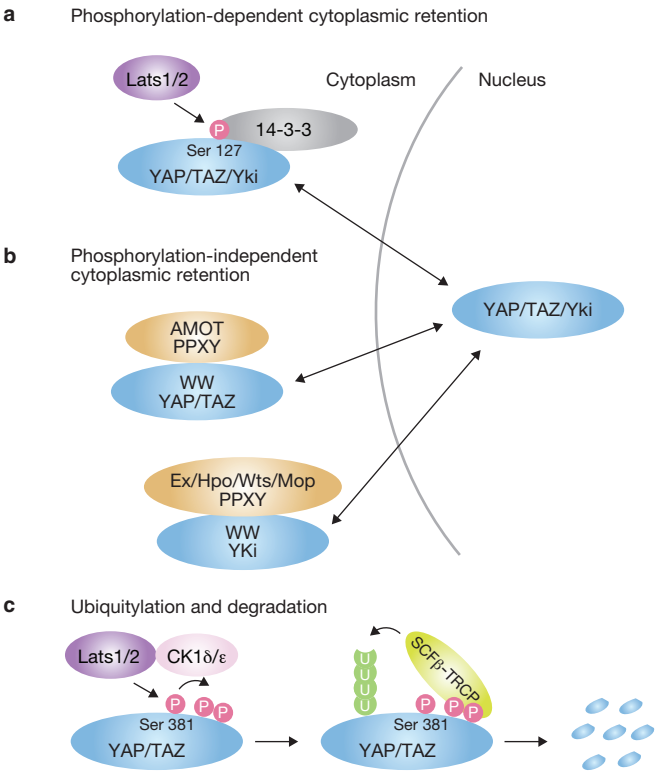

Figure 2 Mechanisms of YAP/TAZ/Yki inhibition by the Hippo pathway. (**a**) Phosphorylation-dependent cytoplasmic retention. Phosphorylation of YAP on Ser 127 by Lats1/2 induces 14-3-3 binding and cytoplasmic retention of YAP. The mechanism is conserved in TAZ and Yki. (**b**) Phosphorylation-independent cytoplasmic retention. Through WW domain–PPXY motif interactions, Yki binds to Mop, Ex, Hpo and Wts, and YAP/TAZ binds to AMOT family proteins. These interactions physically sequester Yki and YAP/TAZ in the cytoplasm. (**c**) Phosphorylation-induced ubiquitylation and degradation. Phosphorylation of YAP on Ser 381 by Lats1/2 primes further phosphorylation of YAP by CK1δ/ε, which induces interaction with SCFβ–TRCP and finally leads to YAP ubiquitylation and degradation. The mechanism is conserved in TAZ.

reports on the role of the Hippo pathway in activating[112] or inhibiting[61] this activity. Recently, YAP was also shown to interact with β-catenin and induce expression of canonical Wnt target genes such as *Sox2* and *Snai2* in mouse heart tissue[113].

bantam microRNA is a target gene of the Hippo pathway and promotes cell survival and proliferation[114,115]. Homothorax (Hth) and Teashirt (Tsh) are two transcription factors mediating *bantam* expression anterior to the morphogenetic furrow[116]. In addition, the expression of *bantam* is also directly induced by a transcriptional complex formed by Yki and Mad, an effector of the *Drosophila* Dpp signalling pathway[117]. The existence of a *bantam* counterpart and the functions of Hth and Tsh homologues in the Hippo pathway in mammals remain to be investigated.

YAP, TAZ and Yki also induce many other genes directly or indirectly. In *Drosophila*, Yki induces: *cycE* (ref. 21) and *E2F1* (ref. 92), which may be involved in cell-autonomous regulation of cell proliferation; the EGFR (epidermal growth factor receptor) ligands *Vein*, *Keren* and *Spitz*[11,118] and the Jak–Stat pathway ligands *Unpaired1/2/3* (*Upd1/2/3*)[8–11], which might mediate non-cell-autonomous functions of the Hippo pathway; and the Hippo pathway genes *Ex*, *Kibra*, *Crb*, and *Fj*[27,29,34,119], which may

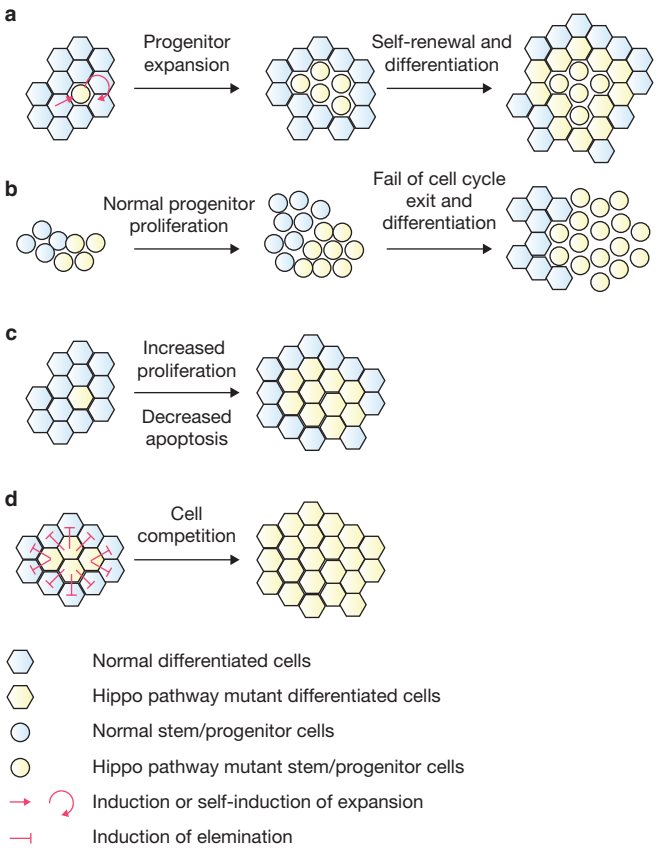

Figure 3 Mechanisms of the Hippo pathway in regulation of organ size and regeneration. Hexagons denote differentiated cells and circles denote stem/progenitor cells. Blue colour indicates wild-type and yellow colour indicates Hippo-pathway mutant cells. (**a**) Hippo pathway inactivation leads to stem/progenitor cell expansion in both cell-autonomous and non-autonomous manners. (**b**) Hippo pathway inactivation leads to cell cycle exit defects in some cellular contexts. (**c**) Hippo pathway mutations promote proliferation and decrease apoptosis in non-stem/progenitor cells. (**d**) Imbalance of Hippo pathway activity in neighbouring cells induces cell competition.

constitute a signal feedback loop. In mammals, YAP and TAZ also induce the expression of *AREG*[118] and *FGF1* (ref. 60), which may also mediate non-cell-autonomous functions of the Hippo pathway. However, the mechanisms underlying the induction of these genes, including the responsible transcription factors, are mostly unclear.

Regulation of the Hippo pathway by cell polarity and cell adhesion complexes

In *Drosophila*, mutations of several genes that are involved in cell polarity and cell junction lead to massive overgrowth. The Dlg–Lgl–Scrib protein complex localizes to the basal–lateral membrane of epithelial cells, where it is required for the lateral exclusion of apical proteins, including the Par3–Par6–aPKC complex and the Crb–Stardust (Sdt)–PATJ complex. Interestingly, *Lgl* mutations lead to nuclear translocation of Yki and upregulation of Hippo pathway target genes in *Drosophila* epithelium[47]. Expression of dominant-negative aPKC rescued the tissue overgrowth in *Lgl*-mutant tissues[47]. In zebrafish, Scrib was shown to interact genetically with and suppress the activity of the YAP homologue during embryonic kidney development[120]. The tumour-suppressor function of the Dlg–Lgl–Scrib complex is possibly conserved in mammals, as depletion of Scrib in mammary epithelium results in disruption of apoptosis inhibition by cell polarity, and induction of dysplasia *in vivo* that progresses to tumours after long latency[121]. It would be interesting to determine whether the mammalian Hippo pathway mediates the tumour-suppressor function of the Dlg–Lgl–Scrib complex.

Crb is another cell polarity protein that regulates the *Drosophila* Hippo pathway[46,48,49]. The intracellular domain of Crb contains a juxtamembrane FERM-binding motif (FBM) and a carboxy-terminal PDZ-binding motif (PBM). The PBM is important for polarity formation[122], whereas the FBM regulates Hippo-pathway-dependent proliferation and apoptosis by promoting apical localization of the upstream component Ex[46,48,49]. Thus, Crb regulates cell polarity and tissue growth through distinct mechanisms. In addition, it seems that the functions of the Dlg–Lgl–Scrib complex in cell polarity and tissue growth are also separable[47,123]. It is therefore important to determine whether, and how, the two functions of these proteins are coupled to regulate tissue homeostasis.

In mammalian cells, Hippo pathway activation is triggered in part by cell–cell contact. In tissue culture, high cell density induces YAP phosphorylation and cytoplasmic translocation[59]. And in mouse blastocysts, YAP is nuclear in outer layer cells, and cytoplasmic in the inner blastocyst layer cells[124]. Consistently, it has been observed that disruption of cell–cell junctions in epithelium results in the nuclear localization of YAP and TAZ[85]. Collectively, these studies suggest that maintenance of cell–cell junctions is important for mammalian Hippo pathway function.

Recent studies shed some light into the mechanisms of YAP/TAZ regulation by cell–cell contact. First, a tight-junction protein complex, composed of the AMOT family proteins, PALS1, PATJ/MPDZ and Lin7, was found to interact with YAP and TAZ[82–85]. This interaction inhibits YAP and TAZ by promoting their localization to tight junctions and their phosphorylation by the Hippo pathway. In addition, α-catenin was shown to interact with YAP[125,126], possibly through a 14-3-3 protein, in a phosphorylation-dependent manner[126]. This interaction may prevent YAP dephosphorylation by PP2A and results in YAP inhibition[126]. Thus, it is possible that the tight junction and adherens junction are critically important for relaying cell contact signals to the Hippo pathway. Such a hypothesis needs to be further investigated.

The Hippo pathway in tissue regeneration, and stem cell self-renewal and expansion

The Hippo pathway was initially thought to limit organ size by inhibiting proliferation and promoting apoptosis[16–20]. However, emerging evidence suggests that the Hippo pathway may also regulate stem cell and progenitor cell self-renewal and expansion. For instance, YAP and TAZ regulate embryonic stem cell self-renewal in response to TGFβ/BMP (transforming growth factor beta/bone morphogenetic protein) signalling[104,110]. In addition, YAP is inactivated during mouse embryonic stem cell differentiation and activated in induced pluripotent stem (iPS) cells[5]. YAP knockdown in mouse embryonic stem cells leads to loss of pluripotency, whereas ectopic expression of YAP prevents embryonic stem cell differentiation[5].

Additionally, the Hippo pathway also regulates tissue-specific progenitor cells. YAP expression is generally restricted to the progenitor cells in normal mouse intestines, and transgenic expression of YAP in mouse intestines causes a marked expansion of the progenitor cell compartment[12]. Activation of YAP–TEAD also results in the expansion of neural progenitor cells in a chicken neural tube model[13]. Similarly,

YAP expression expands basal epidermal progenitors in mouse skin and inhibits their terminal differentiation[127]. In contrast, conditional knockout of YAP or knock-in of a TEAD-binding-deficient YAP mutant in mouse skin leads to decreased proliferation of basal cells, thinner epidermis and failure of skin expansion[126]. Consistently, adult liver stem cells known as oval cells accumulate in *Mst1/2*-, *Sav1*- and *Mer*-knockout mice liver[70–73]. It should be noted that these genetic manipulations are applied at the whole organ level and not specifically to the progenitor cell compartment. However, the contribution of progenitor cell expansion in YAP-induced organ overgrowth is likely to be tissue-dependent. For instance, overgrown hearts induced by *Sav1* knockout showed excessive proliferation in cardiomyocytes but normal proliferation level of cardiac progenitors[113]. In addition, in certain cancers, such as a subtype of medulloblastomas, YAP expression is highly elevated in the perivascular cancer stem cell compartment[128].

The Hippo pathway was recently shown to be involved in tissue regeneration. In the *Drosophila* midgut, Yki expression is largely restricted to intestinal stem cells (ISC)[10]. Under resting conditions, Yki is mostly localized to the cytoplasm and seems to be inactive[10]. In contrast, Yki displays increased nuclear localization and reporter activity, and has an important and cell-autonomous role in ISC proliferation in response to injury[9,10]. Interestingly, the Hippo pathway also has a non-cell-autonomous function during regeneration[8,9,11]. In response to damage, the Hippo pathway is inactivated in enterocytes, a differentiated cell type in the *Drosophila* midgut, resulting in Yki activation and subsequent expression of Upd1/2/3 (refs 8,9,11), as well as EGFR ligands[11]. This results in increased ISC proliferation in a non-cell-autonomous manner. Yki activation in enterocytes and in wing discs (where Yki also plays a role in regeneration[6]) seems to involve JNK signalling[8,129].

In mammals, there is also evidence for a role of YAP in tissue regeneration. Intestinal damage markedly induces YAP expression, and loss of YAP severely impairs dextran sodium sulfate-induced intestinal regeneration[7]. In the mouse liver, *Yap* knockout causes a defect in bile duct development[69]. Interestingly, most adult mouse biliary ductal epithelial cells express Sox9 and these cells make a significant contribution to liver regeneration after injury as shown by lineage tracing[130]. It remains to be determined whether ablation of *YAP* also results in compromised liver regeneration, and more importantly, whether the Hippo pathway activity is regulated during regeneration in mammals.

Conclusions and perspectives

Extensive studies in the past decade have elucidated the importance of the Hippo pathway in organ size control and regeneration in both *Drosophila* and mammals. Several mechanisms have been proposed, and it is clear that cell adhesion and polarity complexes play a key role in Hippo pathway regulation. YAP and Yki may promote organ size and regeneration by inducing stem cell and progenitor cell proliferation through both cell-autonomous and non-cell-autonomous mechanisms (Fig. 3a). In addition, inactivation of the Hippo pathway may block cell-cycle exit, leading to hyperplasia and differentiation defects[53] (Fig. 3b). The Hippo pathway can also inhibit proliferation and promote apoptosis in non-stem cells/non-progenitor cell types (Fig. 3c). Lastly, an imbalance of Hippo pathway activity in neighbouring cells may induce cell competition through differential expression of *dMyc* in *Drosophila*[98,99] (Fig. 3d). How these mechanisms fit into organ size regulation and regeneration *in vivo* is yet to be determined.

Despite these insights into the critical role of this pathway in stem cell expansion and tissue regeneration, many important questions await answers. These include the role and mechanism of cell polarity and cell adhesion proteins in sensing organ size to regulate the Hippo pathway and the position of the Hippo pathway in the known signalling networks regulating cell proliferation, apoptosis and stem cell function. In addition, the mechanism by which upstream regulators of the Hippo pathway are integrated to initiate or terminate signalling is not yet fully understood. Importantly, Hippo pathway dysregulation in cancer remains to be fully elucidated. The Hippo–YAP pathway holds great promise as a target in cancer therapy and regenerative medicine. Insights into the upstream regulators and downstream targets of this pathway, and their mechanism of regulation, are crucial in translating our basic knowledge of this pathway into therapeutic designs.

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COMPETING FINANCIAL INTERESTS

The authors declare that they have no competing financial interests.

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