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Mammalian Hippo pathway: from development to cancer and beyond

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The Hippo pathway was discovered as a signal transduction pathway that regulates organ size in *Drosophila melanogaster*. It is composed of three components: cell surface upstream regulators including cell adhesion molecules and cell polarity complexes; a kinase cascade comprising two serine-threonine kinases with regulators and adaptors; and a downstream target, a transcription coactivator. The coactivator mediates the transcription of cell proliferation-promoting and anti-apoptotic genes. The pathway negatively regulates the coactivator to restrict cell proliferation and to promote cell death. Thus, the pathway prevents tissue overgrowth and tumourigenesis. The framework of the pathway is conserved in mammals. A dysfunction of the pathway is frequently detected in human cancers and correlates with a poor prognosis. Recent works indicated that the Hippo pathway plays an important role in tissue homoeostasis through the regulation of stem cells, cell differentiation and tissue regeneration.

Keywords: apoptosis/cancer/kinase/regeneration/signal transduction.

Abbreviations: AMOT, angiomotin; AMOTL, AMOT-like; ATM, ataxia telangiectasia mutated; aPKC, atypical protein kinase C; App, approximated; ALL, acute lymphocytic leukaemia; ASPP, apoptosis-stimulating protein of p53; CDC, cell division cycle; DCO, discs overgrown; EBP50, Ezrin-radixin-moesin-binding phosphoprotein 50; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; Fj, Four-jointed; FERM, 4.1 ezrin radixin moesin; FRMD6, FERM domain-containing protein 6; GTP, guanosine 5′-triphosphate; JNK, c-Jun N-terminal kinase; LATS, large tumour suppressor; Lgl, lethal giant larvae; MOAP, modulator of apoptosis; MOB, Mps one binder; MST, mammalian Ste20-like kinase; NDR, Nuclear Dbf2-related; Nf2, neurofibromin 2 in human and neurofibromatosis 2 in mouse; NHERF, Na^+/H^+ exchanger regulatory factor; NIMA, never in mitosis A; PML, promyelocytic leukaemia; RA, Ras-association; RASSF, Ras-association domain family; SARAH, Salvador/RASSF/Hippo; Shh, Sonic hedgehog; TAZ, Transcriptional coactivator with PDZ-binding motif; TEAD, TEA domain family; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α; Trc, tricornered; YAP, Yes-associated protein.

The Hippo pathway is a signalling pathway that regulates cell proliferation and cell death. It was originally discovered in *Drosophila melanogaster* as a pathway that determines organ size and of which mutations lead to tumourigenesis. The pathway is conserved and plays a role as a tumour suppressor in mammals. Disorders of the pathway are very frequently detected in human cancers. Its down-regulation correlates with the aggressive properties of cancer cells. The pathway regulates the self-renewal and differentiation of stem cells and progenitor cells. As the pathway cross-talks with other signallings such as Wnt, Notch and Sonic hedgehog (Shh), it influences various biological events and its dysfunction possibly underlies many human diseases besides cancer. Accordingly, the Hippo pathway now fascinates researchers. The number of related papers is rapidly increasing. The research progress is enormous. It is difficult to cover everything, so we briefly introduce and occasionally refer to the *Drosophila* Hippo pathway in order to discuss the complexity of the mammalian Hippo pathway, but the main subject of this review is the mammalian Hippo pathway. We do not go into the details of molecular structures and biochemical properties of components. We refer readers to the other recent reviews (*1*–*7*).

Drosophila Hippo pathway

The studies of the pathway have been constantly fuelled by *Drosophila* genetics. Table I lists the currently identified components of the *Drosophila* Hippo pathway (Fig. 1). First, Fat and Expanded were identified as genes that regulate cell proliferation, followed by Warts (*8*–*11*). Merlin was identified as a homologue of human Merlin/neurofibromin 2 (Nf2), which is responsible for neurofibromatosis type 2 (*12*). However, the term Hippo pathway was not coined until the discovery of Salvador (*13*, *14*). Hippo was reported immediately after Salvador (*15*–*19*). The resemblance of the phenotypes led researchers to the idea that these genes function in the same pathway. The physical interactions of the gene products were also confirmed. Mats was identified as a general inhibitor of tissue growth and found to function with Warts (*20*). These four founding members (Hippo, Mats, Salvador and Warts) are called the core complex and form a kinase

Table I. Components of the *Drosophila* Hippo pathway

Components of the *Drosophila* Hippo pathway (gene symbol)	Notes
Upstream regulators	
Fat/Dachsous complex	
Fat (ft)	Protocadherin.
Dachsous (ds)	Protocadherin.
Four-jointed (fj)	Golgi kinase. Modulator of the interaction between Fat and Dachsous.
Low fat (lft)	Fat- and Dachsous-interacting protein.
Dachs (d)	Unconventional myosin. Inhibitor of Warts. No corresponding homologue has been identified in mammals.
Approximated (app)	DHHC palmitoyltransferase.
Discs overgrown (dco)	Casein kinase.
Crumbs	
Crumbs (crb)	A component of the apical polarity complex (Crumbs/Patj/Stardust).
Kibra–Expanded–Merlin complex.	
Kibra (kibra)	WW domain-containing protein.
Expanded (ex)	FERM domain-containing protein. Willin/FRMD6 is a candidate for the homologue in mammals.
Merlin (Mer)	FERM domain-containing protein. Homologue of human Merlin/Nf2.
Core complex	
Hippo (hpo)	Ste20-like kinase. Homologue of MST1 and MST2.
Salvador (sav)	WW domain-containing adaptor. Homologue of Sav1 (WW45).
Mats (mats)	Activator of Warts. Homologue of MOB1 and MOB2.
Warts (wts)	Nuclear Dbf2-related kinase. Homologue of LATS1 and LATS2 (Kpm).
Downstream targets	
Yorkie (yki)	Transcription coactivator. Homologue of YAP and TAZ (WWTR1).
Scalloped (sd)	Transcriptional factor. Homologue of TEAD1–4.
Other related molecules	
dRASSF (Rassf)	Homologue of RASSF1–RASSF6.
dSTRIPAK (mts)	Phosphatase.
djub (jub)	LIM domain-containing protein. Homologue of Ajuba.
Atrophin (atro)	Transcription repressor.
Lgl [l(2)gl]	WD40 repeat containing protein. Component of the basal polarity complex (Lgl/Scrib/Dlg).
aPKC (aPKC)	Component of the apical polarity complex (aPKC/Par3/Par6).

Upstream regulators of the *Drosophila* Hippo pathway comprise Fat/Dachsous complexes, Crumbs, and Kibra–Expanded–Merlin complex. The core complex includes four founding members of the pathway (Hippo, Salvador, Mats and Warts). The downstream targets are Yorkie and Scalloped. The pathway is also regulated by other molecules such as dRASSF, dSTRIPAK, djub, Atrophi, Lgl and aPKC.

cascade. After that, downstream, Yorkie, a transcriptional coactivator, and Scalloped, a transcriptional factor, were identified (*21–24*), which led to the important dogma of the pathway. Upon activation of the pathway, Yorkie is phosphorylated and is transported from the nucleus to the cytosol, so that Yorkie-dependent transcription is shut down, which results in cell cycle arrest and apoptosis. Upstream, three regulators, the Fat/Dachsous complex, Crumbs and the Kibra–Expanded–Merlin complex, were identified. Fat and Dachsous are protocadherins that interact with each other and have been studied in the context of planar cell polarity (*8*, *25–28*). First, Fat was demonstrated to act upstream of Hippo and to be involved in the localization of Expanded (*29–31*). Four-jointed (Fj), Approximated (App), discs overgrown (DCO), Dachs and Lowfat modulate Fat/Dachsous complex. Fj, a Golgi kinase, phosphorylates Fat and Dachsous to tune their interaction (*32–35*). Dachs and App are negative regulators. Dachs, an unconventional myosin, interacts with and negatively regulates Warts (*36*, *37*). App is a DHHC palmitoyltransferase that controls the apical localization of Dachs (*38*). DCO, a casein kinase, phosphorylates the intracellular domain of Fat (*39*, *40*). Lowfat interacts with the intracellular domains of Fat and Dachsous, and increases the expression of these proteins (*41*). Although whether or not atrophin is a component of the Hippo pathway has not been discussed, it binds to the intracellular domain of Fat and regulates the transcription of Fj (*42*). Crumbs, which forms the apical polarity complex with Patj and Stardust, interacts with Expanded and determines its apical localization (*43*, *44*). The over-expression of the intracellular domain of Crumbs depletes apical Expanded in a dominant-negative manner and increases Yorkie activity (*45*, *46*). Chronologically speaking, Expanded and Merlin were demonstrated before Crumbs to function upstream of Hippo (*47*, *48*). Latter, Kibra was found to form a complex with Expanded and Merlin (*49–51*). The Kibra–Expanded–Merlin complex directly interacts with the core complex. Kibra and Merlin bind Salvador, whereas Expanded binds Hippo. Kibra interacts with Merlin, and Expanded potentiates this interaction. Kibra also binds Warts. Additional factors include *Drosophila* Ras-association domain family (dRASSF), dSTRIPAK and djub. dRASSF competes with Salvador for the binding to Hippo (*52*). dRASSF

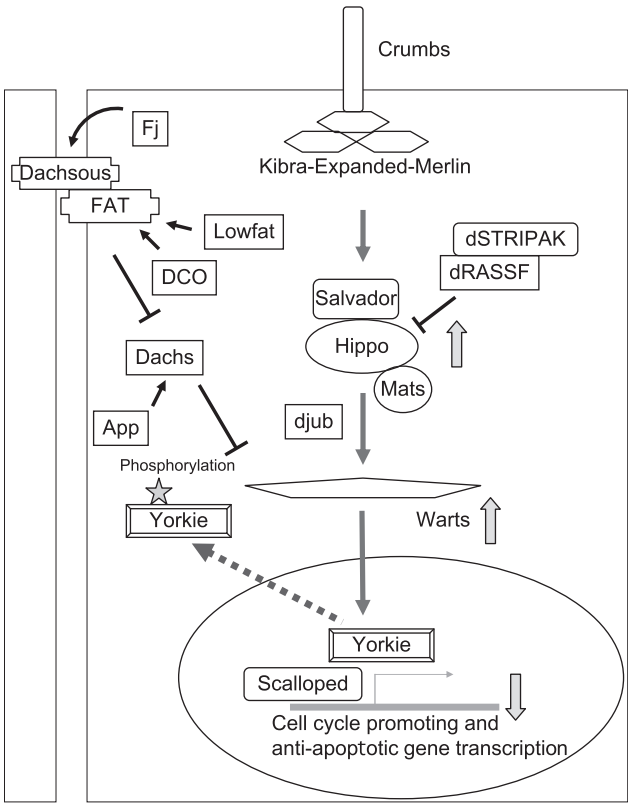

Fig. 1 ***Drosophila*** **Hippo pathway.** The core of the pathway is a kinase cascade comprising Hippo and Warts. When the pathway is activated, Hippo activates Warts, which phosphorylates Yorkie and turns off Yorkie-dependent transcriptions (block arrows). The pathway is regulated by the Fat/Dachsous complex, Crumbs and the Kibra–Expanded–Merlin complex. Fj, Lowfat and DCO modulate Fat/Dachsous complex. dRASSF suppresses the pathway. Dachs inhibits Warts and App affects the localization of Dachs. Djub functions downstream of Hippo and upstream of Warts. In addition, aPKC and Lgl also influence the pathway.

interacts with dSTRIPAK, a phosphatase, which may inhibit the phosphorylation of Hippo (*53*). Thus, dRASSF antagonizes Hippo signalling. A homologue of mammalian Ajuba, djub, functions downstream of Hippo and upstream of Warts to decrease the phosphorylation of Yorkie (*54*). Lethal giant larvae (Lgl), a component of the lateral polarity complex, and atypical protein kinase C (aPKC), a component of another apical polarity complex, indirectly influence the Hippo pathway. Depletion of Lgl and over-expression of aPKC result in the mislocalization of Hippo and dRASSF to the lateral membranes, and induce the activation of Yorkie (*55*). The feedback loop is an important feature of the pathway. Kibra, Merlin, Fj and Dachsous are transcriptional targets of the pathway. Disruption of the Hippo pathway increases Crumbs, aPKC and Patj, and leads to apical membrane hypertrophy, which is independent of the regulation of cell proliferation (*56*, *57*). In addition to cell adhesion and cell polarity, the pathway is activated by ionizing radiation in a *Drosophila melanogaster* p53-dependent manner (*58*). Overall, the *Drosophila* Hippo pathway instructs each cell as to whether or not it should proliferate and how to build itself according to the extrinsic information from the neighbouring cells and the intrinsic information about the cell condition.

Basal architecture of the mammalian Hippo pathway

Mammalian homologues have been identified for all components of the *Drosophila* Hippo pathway except Dachs. Most of the core components had been identified and studied before the emergence of the Hippo pathway. Merlin was identified as the gene responsible for neurofibromatosis type 2 (*59*, *60*). Its inhibitory role in cell proliferation and its biochemical properties including intramolecular interaction and cell density- and Rac-dependent phosphorylation have been analysed (*61–63*). Mammalian Ste20-like kinases (MST1 and MST2) were initially cloned as homologues of yeast Ste20 kinase and later purified as kinases that respond to cell stress (*64*, *65*). Large tumour suppressor (LATS) 1 and LATS2 were cloned as homologues of *Drosophila* Warts, and their tumour suppressive properties were studied (*66–68*). Mps one binder (MOB) 1 was identified in the gene database as a homologue of yeast MOB1 and proposed to be a potential substrate of protein phosphatase 2A (*69*, *70*). Yes-associated protein (YAP) was discovered as a protein that interacts with Yes tyrosine kinase (*71*). Interactions with various proteins such as Na^+/H^+ exchanger regulatory factor (NHERF) 1/Ezrin–radixin–moesin-binding phosphoprotein (EBP) 50, p73, Runx1, Runx2, SMAD7, TEA domain family member (TEAD) 1–4, and ErbB4, have been reported (*72*). Transcriptional coactivator with PDZ-binding motif (TAZ), a paralogue of YAP, was identified as a 14-3-3-interacting protein (*73*). The discovery of the *Drosophila* Hippo pathway prompted researchers to combine the mammalian homologues into one pathway based on these preceding studies. The rough draft of the mammalian Hippo pathway is as follows (Fig. 2, centre): Merlin activates the Hippo pathway at high cell density; MST kinases co-operate with MOB1 and Sav1, a homologue of Salvador, to activate LATS kinases, resulting in the phosphorylation of YAP/TAZ; and eventually, YAP/TAZ is recruited from the nucleus and YAP/TAZ-dependent transcription is shut off to stop cell proliferation and induce apoptosis.

Unresolved upstream regulators of the mammalian Hippo pathway

In spite of the apparent similarities between the *Drosophila* and mammalian Hippo pathways, there are potential differences. The molecular link between upstream regulators and the core complex has not been clarified in mammals as well as in *Drosophila*. Willin/4.1 ezrin radixin moesin (FERM) domain-containing protein 6 (FRMD6) is regarded as an Expanded homologue, but its molecular structure is significantly different (*74*). Kibra binds Expanded, but mammalian Kibra does not bind Willin/FRMD6 (*50*). While Expanded binds Hippo, the interaction between Willin/FRMD6 and MST kinases has not been

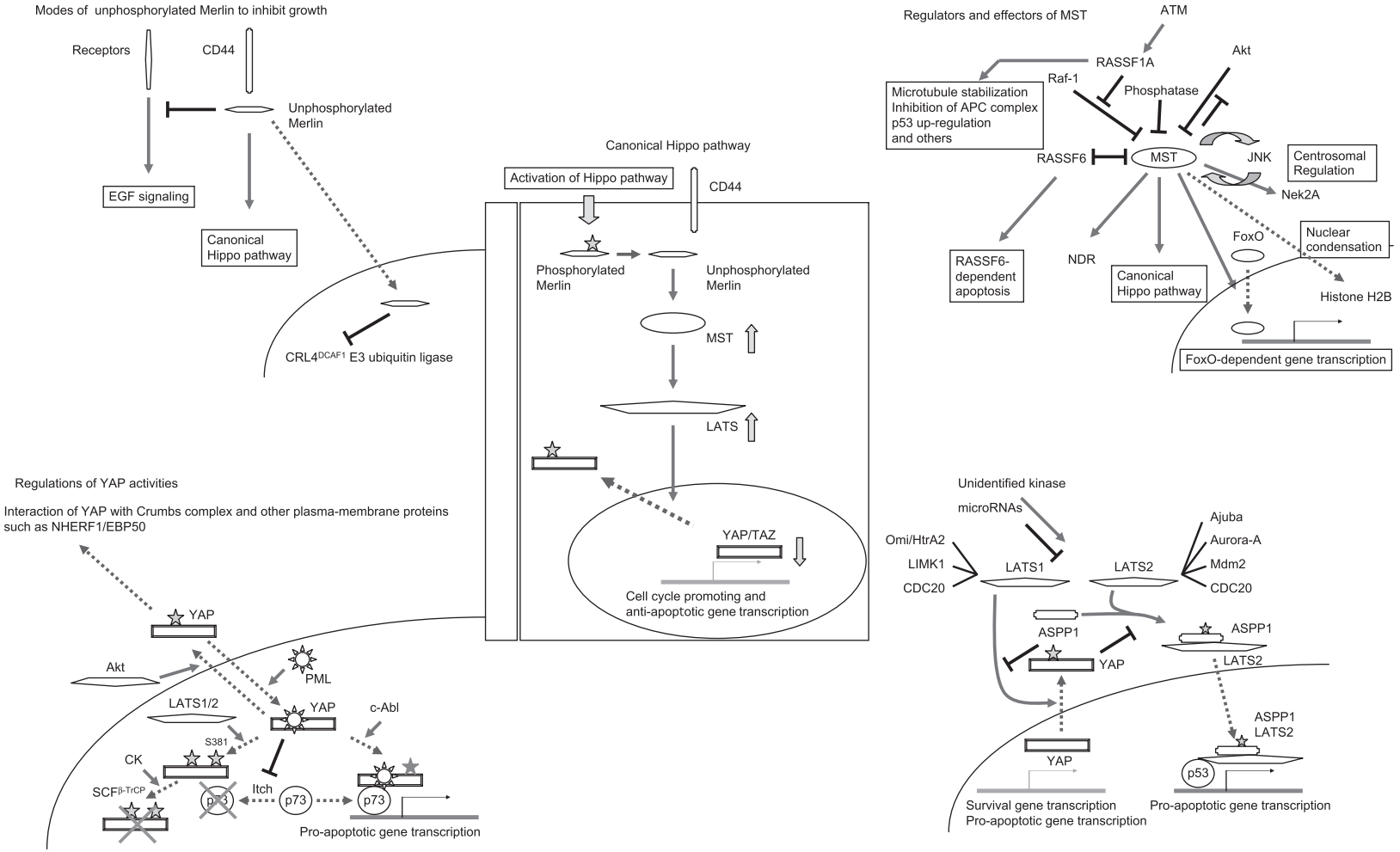

Fig. 2 Mammalian Hippo pathway. Centre: The canonical Hippo pathway. A kinase cascade comprising MST and LATS phosphorylates YAP and TAZ. The phosphorylated YAP and TAZ bind to 14-3-3 (not shown) and are sequestered in the cytosol. YAP and TAZ are predisposed to mediate cell cycle promoting and anti-apoptotic gene transcription. The activation of the Hippo pathway results in cell cycle arrest and apoptosis. CD44 is one of the candidates of upstream regulators of the mammalian Hippo pathway. For simplification, other components such as Sav1 and MOB1 are not depicted. Top left: Merlin inhibits cell growth via the activation of the Hippo pathway, the inhibition of EGF signalling, and the inhibition of $CRL4^{DCAF1}$ E3 ubiquitin ligase. Top right: MST phosphorylates not only the components of the Hippo pathway (MOB1, Sav1 and LATS) but also NDR, FoxO, Histone H2B, JNK and Nek2A. Under the condition that the Hippo pathway is activated, all these substrates can also be phosphorylated. MST is negatively regulated by Raf-1, Akt and phosphatases, and actively regulated by RASSF1A. RASSF6 and MST mutually inhibit each other. The Hippo pathway and RASSF6-dependent apoptosis are simultaneously activated. Bottom left: Pro-apoptotic aspect and regulation of YAP. In some cells, YAP mainly mediates p73-dependent pro-apoptotic gene transcription. c-Abl promotes the association of YAP with p73. PML recruits YAP to the nuclear body and stabilizes p73. The YAP phosphorylated by Akt binds to 14-3-3 (data not shown) and is sequestered in the cytosol. Thus, Akt promotes cell survival, while YAP functions as a tumour suppressor. The phosphorylation of YAP by LATS results in the degradation of YAP. The Crumbs complex interacts with YAP and sequesters it in the cytosol. YAP also interacts with plasma-membrane proteins such as NHERF1/EBP50. Bottom right: Regulation and targets of LATS1 and LATS2. LATS1 and LATS2 are regulated by an unknown kinase other than MST and microRNAs. They interact with various molecules to regulate the cell cycle, apoptosis and the p53 level. ASPP1 is known to be a tumour suppressor. It is mainly localized in the cytosol. Oncogenic stress (not shown) induces the nuclear translocation of ASPP1 with LATS2, so that p53 is shifted from cell cycle regulating gene promoters to pro-apoptotic gene promoters. YAP competes with ASPP1 for the binding to LATS2. Cytosolic ASPP1 inhibits the phosphorylation of YAP by LATS1 and increases the nuclear YAP.

confirmed (*49*). The reintroduction of Merlin into Merlin-deficient Schwannoma cells induces apoptosis, but RNAi silencing of MST2 does not influence this apoptosis (*75*). Although the possibility that MST1 mediates apoptosis instead of MST2 has not been excluded, this observation suggests that Merlin does not function upstream of MST2. In *Drosophila*, Fat influences Warts activity through not only Expanded but also Dachs (*36*, *37*). Mammals appear to have no Dachs homologue. *Drosophila* Fat is proteolytically processed, is phosphorylated by DCO in a Dachsous-dependent manner, and interacts with atrophin (*39*, *40*, *42*). Mammalian Fat4 and Dachsous1 organize the apical membrane (*76*). Fat4 is proposed to be a putative tumour suppressor (*77*). Therefore, Fat4 is likely to be a Fat homologue. Nevertheless, it has not yet been directly demonstrated that Fat4 is regulated in a similar manner to Fat at the molecular level. Mammals may have alternative upstream regulators. Merlin binds CD44, which is involved in contact inhibition (*78*, *79*). CD44 is over-expressed in glioblastoma multiforme and the suppression of CD44 augments the response of Hippo signalling to H_2O_2 (*80*). CD44 is likely to be an integral component of the mammalian Hippo pathway. NHERF1/EBP50 is also a well-known binding partner of Merlin, and is an important player in cancer (*81*, *82*). The interaction of Merlin with NHERF/EBP50 may be more relevant to the regulation of epidermal growth factor (EGF) signalling, which is one of the important functions of Merlin, than to the Hippo pathway (*83*). However, as YAP and TAZ interact with NHERF1/EBP50 and NHERF2, respectively, we may as well regard NHERF proteins as components of the mammalian Hippo pathway (*73*, *84*). Thus, the mammalian Hippo pathway may have additional upstream regulators.

Complexities of the mammalian Hippo pathway

The mammalian Hippo pathway is more complicated than the *Drosophila* Hippo pathway. One of the reasons for this complexity is that mammals have more than one paralogue for each *Drosophila* component. These paralogues sometimes play redundant roles but in most cases exhibit distinct properties. Second and more importantly, the components of the mammalian Hippo pathway undergo many molecular interactions, so they exert additional functions and are subject to additional regulation. For instance, the substrates of MST kinases include not only LATS kinases and MOB1, but also c-Jun N-terminal kinase (JNK), histone H2B and FoxO, as discussed below (*85*, *86*). All of them are implicated in apoptosis. LATS1 interacts with LIM domain kinase 1 to inhibit its kinase activity and thereby affects cytokinesis (*87*). It also binds mitochondrial serine protease Omi/HtrA2 to promote the protease activity (*88*, *89*). Omi/HtrA2 controls cell proliferation through LATS1. If we define the final outputs of the Hippo pathway as the regulation of cell proliferation and cell death, it can be argued that these molecular interactions also mediate Hippo signalling. No matter how we demarcate the Hippo pathway, we need to consider that activation of the MST–LATS–YAP/TAZ axis is associated with parallel activation of other pathways, which co-operate with the canonical Hippo pathway. In the previous section, we discussed the potential difference from the *Drosophila* Hippo pathway in the upstream regulators. We will here discuss the divergent molecular interactions mediated by the components of the mammalian Hippo pathway that may add twists to the overview of the pathway (Fig. 2).

Merlin

Merlin is a FERM domain-containing protein (*90–92*) (Fig. 2, top left). Merlin is phosphorylated by p21-activated kinase at Ser518 and is dephosphorylated by myosin phosphatase MYPT1-PP1δ, which is inhibited by CPI-17 (*93–95*). Cadherin-based cell contact activates MYPT1-PP1δ and increases the unphosphorylated growth-inhibitory Merlin. The molecular mechanism underlying the contact inhibition has been intensively studied. In Merlin$^{-/-}$ cells, EGF receptor activation and internalization are maintained even at high cell density (*96*). Similarly, in *Drosophila*, Merlin together with Expanded regulates endocytosis and signalling by receptors such as Notch (*97*). These findings suggest that Merlin mediates this contact inhibition through the control of membrane receptor distribution and signalling. After the rediscovery of Merlin as a Hippo pathway component, the effect of Merlin depletion on the Hippo pathway was studied. In one study, liver-specific Merlin$^{-/-}$ mice exhibited extensive proliferation of hepatocytes and bile ducts, and developed hepatocellular carcinomas and bile duct hamartomas (*98*). The phosphorylation of YAP and LATS kinases was reduced and nuclear YAP increased. Cell over-proliferation and tumour growth were suppressed by loss of YAP. This study supports that YAP is a major effector of Merlin and that the Hippo pathway mediates the contact inhibition. However, in another study, Merlin$^{-/-}$ liver exhibited progenitor cell expansion and did not show any alteration of YAP phosphorylation or localization (*99*). The knockdown of YAP did not recover the contact inhibition. Alternatively, an EGF receptor inhibitor blocked the over-proliferation of liver progenitors. The authors consider that the regulation of EGF signalling is the mechanism underlying the contact inhibition. A recent study revealed that growth-inhibitory unphosphorylated Merlin is translocated into the nucleus, where Merlin binds and inhibits E3 ubiquitin ligase CRL4^{DCAF1} to activate growth-inhibitory gene transcription (*100*). These three functions are not mutually exclusive. Once dephosphorylated, Merlin can act as a tumour suppressor through the up-regulation of the canonical Hippo pathway, the restriction of EGF signalling, and the inhibition of CRL4^{DCAF1}.

MST1 and MST2

MST1 mediates apoptosis through cleavage, autophosphorylation and nuclear translocation (*85*, *86*, *101–103*) (Fig. 2, top right). MST2 is also

cleaved (*102*). Akt blocks the caspase-dependent cleavage through phosphorylation at Thr120 and Thr387 in MST1, and at Thr117 and Thr384 in MST2 (*104–107*). Thr387 of MST1 is dephosphorylated by PHLPP1 and PHLPP2 phosphatases (*108*). MST1 activates JNK, and this activation causes nuclear condensation (*101*, *109*). MST1 phosphorylates histone H2B and H2AX directly or via JNK (*110*, *111*). MST1-FoxO signalling is not simple. A study involving $MST1^{-/-}$ mice demonstrated that MST1-FoxO signalling augments the resistance to oxidative stress in T cells and promotes survival not apoptosis (*112*). However, in the prevailing view, MST1 induces the translocation of FoxO proteins and mediates FoxO-dependent apoptosis (*113*, *114*). A recent paper reported that MST1 and MST2 phosphorylate never in mitosis A (NIMA) kinase, Nek2A, to recruit it to the centrosome, and to promote the phosphorylation of centrosomal linker proteins and centrosome splitting (*115*). As Sav1 also interacts with Nek2A and is necessary for the effect of MST kinases on Nek2A, this centrosomal function of MST kinases may also be relevant to the Hippo pathway. MST1 phosphorylates and inhibits Aurora-B (*116*). This inhibition promotes the stability of kinetochore–microtubule attachment and prevents chromosomal missegregation. P53 is phosphorylated by MST1 in the presence of death-associated protein 4 (*117*). MST1 directly inhibits Akt1, a pro-survival kinase (*118*). RCC1 is a newly identified substrate of MST1 and MST2 (*119*). The phosphorylation of RCC1 is enhanced by RASSF1A and results in the accumulation of guanosine 5′-triphosphate (GTP)-bound RAN. GTP-bound RAN is involved in the stabilization of microtubules. All these interactions and phosphorylations may be related to the tumour-suppressive function of MST kinases. Intriguingly, one paper reported that in $MST1^{-/-}$ $MST2^{-/-}$ liver, LATS1 and LATS2 are phosphorylated in the activation loop but the phosphorylation of YAP is reduced (*120*). These findings mean that LATS kinases can be phosphorylated by a kinase distinct from MST kinases, and more importantly, that MST kinases negatively regulate YAP independently of LATS kinases.

Upstream regulation of MST kinases is likewise manifold. Raf-1 prevents the dimerization and auto-phosphorylation of MST2 (*121*). RASSF1A releases MST2 from the inhibition by Raf-1 to induce apoptosis (*122*). Other RASSF proteins also modulate MST kinases, which we will discuss later. Akt promotes the interaction between MST2 and Raf-1, which means that the inhibition of cleavage is not the sole way for Akt to regulate MST2 (*106*). JNK, which is a substrate of MST1, phosphorylates MST1 at Ser82 and enhances its activity (*123*). In *Drosophila*, JNK functions upstream of Hippo, but in a different manner. Tissue damage activates *Drosophila* JNK in enterocytes, which increases nuclear Yorkie (*124*). Although, it has not been directly examined, it can be inferred that *Drosophila* JNK suppresses Hippo or that *Drosophila* JNK regulates Yorkie independently of Hippo. *Drosophila* JNK induces cytokine Unpaired to activate Jak/Stat signalling and to mediate tissue regeneration (*125*, *126*).

NDR1 and NDR2

Drosophila Warts and mammalian LATS kinases belong to the Nuclear Dbf2-related (NDR) kinases, which are conserved from yeast, and play important roles in cell cycle regulation and cell proliferation (*127*) (Fig. 2, top right). *Drosophila* has an additional NDR kinase named Tricornered (Trc) (*128*). Trc is regulated by Hippo and Mats (*129*, *130*). Even so, Trc is not considered to be a component of the Hippo pathway, because the Trc mutant shows different phenotypes from those of Hippo pathway mutants (*128*, *130*). Mammals have two Trc homologues, NDR1 and NDR2, which are activated by MST kinases and MOB1. NDR1 and NDR2 mediate apoptosis downstream of MST1 and RASSF1A (*131*). NDR1 is involved in the regulation of centrosome and chromosome alignment (*116*, *132*, *133*). NDR1 knockout mice are predisposed to the development of T cell lymphomas (*134*). These findings suggest that NDR1 functions as a tumour suppressor through regulation of cell division and apoptosis. As NDR1 is activated by MST kinases and MOB1, upon activation of the Hippo pathway, NDR kinases are supposedly activated as well as LATS kinases, and contribute to apoptosis and cell cycle regulation.

LATS1 and LATS2

LATS1 and LATS2 negatively regulate cell division cycle (CDC) 2 and induce G2/M arrest (*135–137*) (Fig. 2, bottom right). LATS1 interacts with zyxin during mitosis, and this interaction is necessary for normal mitotic progression (*138*). A dysfunction of LATS1 induces mitotic delay and the development of tetraploidity (*139*). LATS2 has also been reported to induce G1/S arrest (*140*). Both are localized at the centrosome. The centrosomal localization of LATS2 is regulated by Aurora-A (*141*). LATS2 is associated with Ajuba and recruits γ-tubulin to centrosomes during mitosis (*142*). LATS2 binds Mdm2 and inhibits its E3 ubiquitin ligase activity to stabilize p53, which in turn up-regulates the transcription of LATS2 (*143*). Two papers have reported the implication of apoptosis-stimulating protein of p53 (ASPP) 1 in the functions of LATS and YAP (*144*, *145*). LATS2 phosphorylates cytoplasmic ASPP1 to induce nuclear translocation (*144*). In the nucleus, LATS2 and ASPP1 shift the binding of p53 to pro-apoptotic gene promoters from cell cycle regulating gene promoters. In the cytosol, YAP competes with ASPP1 for the interaction with LATS2 and prevents apoptosis. The second paper reported that cytoplasmic ASPP1 inhibits the phosphorylation of YAP and TAZ by LATS1, and increases nuclear YAP and TAZ to promote survival (*145*). The authors discuss the possibility that ASPP1 promotes apoptosis if YAP mediates pro-apoptotic gene transcription in the nucleus. In short, LATS kinases regulate the cell cycle and apoptosis not only through the phosphorylation of YAP but also in other ways. As described above, LATS1 and LATS2 are still phosphorylated in the activation loop in the absence of MST1 or MST2, suggesting that MST1 and MST2 are not the sole regulators of LATS kinases (*120*). Their expression levels are

regulated by microRNA-31, -372 and -373, and Heat Shock Protein 90 (*146–148*).

RASSFs

RASSFs are proteins with a Ras-association (RA) domain (*149*, *150*) (Fig. 2, top right). The human genome contains 10 RASSF genes. RASSF1–RASSF6 have the RA domain in middle regions and the Salvador/RASSF/Hippo (SARAH) domain in C-terminal regions. The SARAH domain is a coiled-coil motif that mediates protein interactions. Sav1, MST1, MST2 and Nek20 have this domain. RASSF5 is better known as Nore1. RASSF7–RASSF10 have the RA domain in N-terminal regions and lack the SARAH domain. RASSF1–RASSF6 correspond to *Drosophila* dRASSF. RASSF1 was identified as a gene encoded on chromosome 3p21, which shows allelic loss in lung cancer (*151*). It has two major isoforms: RASSF1A and RASSF1C. The suppression of RASSF1A by hypermethylation of CpG islands is quite often associated with human cancers. RASSF1A mutant mice are susceptible to carcinogens and irradiation (*152*, *153*). These properties established RASSF1A as a tumour suppressor. Nore1 was identified as an Ras effector and implicated in Ras-dependent apoptosis (*154*, *155*). The interaction of RASSF1 and Nore1 with MST1 has also been reported (*156*). The effect of RASSF1A and Nore1 on MST1 activity is controversial. RASSF1A and Nore1 seemingly inhibit the activity *in vitro* but stimulate it *in vivo*. RASSF1A mediates Fas-induced MST1-dependent apoptosis, which is associated with the activation of MST1 *in vivo* (*157*). The RASSF protein was accepted as an integral component of the Hippo pathway when the genetic and physical interaction of dRASSF with Hippo was demonstrated (*52*). dRASSF competes with Salvador for binding to Hippo and acts as a negative regulator of the pathway. Researchers have noticed, however, that dRASSF suppresses the overgrowth phenotype of the Hippo mutant lacking the SARAH domain but not of the kinase-dead Hippo mutant. This observation means that dRASSF has a tumour-suppressor function and paradoxically antagonizes the tumour suppressor Hippo pathway. In mammals, RASSF1A has been recognized as a part of the complex including MST2, Sav1 and LATS1 (*158*). The *in vivo* activation of MST2 by RASSF1A has been confirmed (*122*, *158*). In response to DNA damage, RASSF1A is phosphorylated by ataxia telangiectasia mutated (ATM) to activate MST2 and LATS1 (*159*). Thus, RASSF1A functions as an upstream activator and mediates Hippo-dependent apoptosis. As RASSF1A is a well-established tumour suppressor, this observation is comprehensible but is inconsistent with the report on dRASSF. We and others have studied RASSF6 that mediates apoptosis in various cells (*160*, *161*). RASSF6 interacts with MST1 and MST2 through the C-terminal SARAH domain [(*162*), M. Ikeda's unpublished results]. A C-terminal truncated mutant of RASSF6, which does not bind MST kinases, still promotes apoptosis. The knockdown of LATS1 or LATS2 does not affect RASSF6-induced apoptosis. These findings indicate that RASSF6 mediates apoptosis independently of the Hippo pathway. The underlying mechanism is not yet clear enough, but RASSF6-induced apoptosis partially depends on modulator of apoptosis (MOAP) 1, which is also involved in RASSF1A-induced apoptosis (*163*, *164*). MST2 blocks the interaction between RASSF6 and MOAP1, and inhibits RASSF6-mediated apoptosis. This inhibition does not require kinase activity. Conversely, RASSF6 suppresses the activity of MST2, possibly by inhibiting homo-oligomerization. Based on these data, we have proposed a new model. RASSF6 and MST2 form a complex and mutually inhibit their functions. Upon activation of MST2, RASSF6 is released from MST2 and then induces apoptosis. MST2, which is free of RASSF6, together with Sav1 activates LATS kinases. If dRASSF behaves like RASSF6, this scenario explains why dRASSF does not function as a tumour suppressor in the kinase-dead Hippo mutant. As RASSF6 is highly pro-apoptotic, the RASSF6-mediated process should significantly contribute to apoptosis under the condition that the Hippo pathway is activated.

Because of its importance as a tumour suppressor, RASSF1 has been intensively studied and diverse functions are attributed to it. RASSF1A stabilizes microtubules through various interactions (*165*, *166*). RASSF1A–MST2–RAN complex is also involved in this stabilization (*119*). RASSF1A interacts with CDC20 and inhibits an anaphase-promoting complex (*167*). RASSF1A interacts with Aurora-A and Aurora-B, which are important for prometaphase progression and cytokinesis (*168–170*). RASSF1A promotes the self-ubiquitination of Mdm2 and activates the p53-dependent checkpoint (*171*). RASSF1A interacts with F-box protein Skp2 and is degraded by the SCF complex at the G1/S transition (*172*). RASSF1C, a splice variant of RASSF1A, is anchored by Daxx to a promyelocytic leukaemia (PML) nuclear body and is released when Daxx is degraded in response to DNA damage (*173*). RASSF1C is translocated to the cytosol and activates stress activated protein kinase/JNK. It is unclear whether or not these functions of RASSF1A and RASSF1C are relevant to the Hippo pathway. However, all these properties can contribute to the restriction of cell cycle and cell death.

YAP and TAZ

Mammals have two Yorkie homologues: YAP and TAZ (*71*, *174–176*) (Fig. 2, bottom left). YAP and TAZ have similar molecular structures and share interacting proteins. However, YAP and TAZ are distinct in some aspects. The most remarkable difference is that YAP promotes pro-apoptotic gene transcription (*177*). In the central dogma, it is presumed that Yorkie or YAP mediates cell cycle-promoting and anti-apoptotic gene transcription and that the phosphorylation of Yorkie by Warts or YAP by LATS kinases turns off this transcription. However, this premise is too simple for YAP. WW domains are necessary for YAP to induce transformation in NIH3T3 cells, whereas the same domains show an inhibitory effect in MCF10A cells (*178*). YAP functions in a cell context-dependent manner. The keys are p73 and

Akt. In some cells, YAP is mainly localized in the cytosol and its recruitment to the cytosol depends on the phosphorylation by Akt, not LATS kinases (*179*). Likewise, in some cells, YAP mediates p73-dependent pro-apoptotic gene transcription. In these cells, the nuclear accumulation of YAP leads to apoptosis, while cytosolic sequestration results in cell survival. Indeed, YAP plays a tumour suppressive role in some cancers (*180*). In HCT116 or H1299 cells, PML interacts with YAP and recruits it to the nuclear bodies (*181*). Then, p73 is stabilized through sumoylation, so that p73-dependent transcription is up-regulated. As PML is a target of p73, a positive feedback loop exists here. Akt negatively regulates this PML transcriptional activation by sequestering YAP in the cytosol. In breast cancer MCF7 cells, YAP forms a complex with LATS1 in the cytosol (*122*). RASSF1A releases YAP from LATS1, and facilitates the nuclear translocation and complex formation of YAP and p73. YAP competes with E3 ubiquitin ligase Itch for binding to p73, and promotes p73-dependent transcription and apoptosis (*182*). In H1299 cells, DNA damage induces the phosphorylation of YAP by c-Abl and the phosphorylated YAP strongly interacts with p73 (*183*). Neurons express a neuron-specific isoform of YAP, which mediates atypical neuronal death at least partially depending on p73 (*184*). Under all these conditions, YAP is predisposed to promote apoptosis and thus the naïve idea that the Hippo pathway mediates apoptosis by down-regulating YAP is not valid.

The subcellular localization of YAP and TAZ is modulated through various protein interactions. Tight junction protein ZO-1 and its isoform, ZO-2, bind TAZ (*185*). ZO-2 also binds YAP (*186*). Unlike ZO-1, ZO-2 is localized in the nucleus and is involved in the nuclear localization of YAP. ZO-2 affects TAZ-mediated transcription. Mass spectrometry analysis revealed the co-immunoprecipitation of YAP and TAZ with the Crumbs complex comprising Pals1, Patj, MUPP1, Lin7c and Angiomotin (AMOT) (*187*). In Eph4 cells, when the cell density is high, the Crumbs complex is assembled at tight junctions, facilitates the phosphorylation of YAP and TAZ, and causes their accumulation in the cytosol. As the initial studies suggested, YAP and TAZ may be anchored to the plasma membrane via NHERF proteins. These molecular interactions as well as the binding to 14-3-3 can determine the subcellular localization of YAP and TAZ, and regulate their functions.

Moreover, the regulation of YAP and TAZ does not necessarily depend only on their subcellular localization. When LATS kinases phosphorylate YAP at Ser381, YAP is further phosphorylated by casein kinase 1 δ/ε, and targeted for ubiquitination by $SCF^{\beta\text{-}TrCP}$ and degradation (*188*). TAZ is also a substrate of $SCF^{\beta\text{-}TrCP}$ (*189*). Thus, YAP and TAZ are regulated through protein degradation.

It is clear that YAP and TAZ exhibit oncogenic activities and contribute to epithelial–mesenchymal transition (EMT), but it is not clear how they do it (*190–192*). The importance of TEAD-mediated transcription has been shown (*193*, *194*). However, the targets of YAP and TAZ, which directly govern oncogenesis and EMT, are not clear enough. AXL receptor tyrosine kinase was recently identified as one of the targets of YAP and its implication in oncogenesis has been reported (*195*). Another paper reported the importance of Wbp2 in TAZ-mediated oncogenesis (*196*). In *Drosophila*, microRNA bantam is well known as a target of Yorkie. However, the target microRNAs of YAP and TAZ have not yet been reported.

Cross-talk with other signallings

The Hippo pathway cross-talks with other signallings (*197*). In *Drosophila*, Yorkie up-regulates dMyc, while dMyc represses Yorkie (*198*, *199*). Hippo signalling activates Notch signalling in posterior follicle cells and neuroepithelial cells (*200–203*). Yorkie induces cytokine-like ligand Unpaired and non-cell autonomously activates the Jak/Stat pathway. In mammals, YAP activation enhances Notch signalling and increases nuclear β-catenin (*204*). TAZ binds Dvl2 and inhibits its phosphorylation by casein kinases (*205*). As this interaction occurs in the cytoplasm, the Hippo pathway, which induces the cytosolic localization of TAZ, appears to antagonize the Wnt pathway. YAP binds SMAD1 and supports SMAD1-dependent transcription (*206*). In human embryonic stem cells, TAZ interacts with SMAD complexes and mediates transforming growth factor-β (TGF-β) signaling (*207*). The Crumbs complex interacts with YAP and TAZ, sequesters SMAD2/3 complexes, and suppresses TGF-β signalling (*187*). YAP is up-regulated in medulloblastomas with aberrant Shh signalling (*208*). Shh increases YAP expression and promotes its nuclear localization. YAP subsequently induces the expression of Gli2, which regulates Gli1. YAP induces amphiregulin and activates EGF receptor signalling in a non-cell autonomous manner (*209*). This cross-talk implies that disruption of the Hippo pathway can cause perturbation in many signal pathways and thereby result in broad spectrum consequences.

Physiological functions of the Hippo pathway

Tissue development

The Hippo pathway plays a role at an early stage of development. During blastocyst formation, the Hippo pathway is activated in the inside cells through cell–cell contacts, but is inactive in the outside cells (*210*). Consequently, YAP is localized in the nucleus in the outside cells and induces the expression of trophectoderm regulators, while the inside cells do not express these regulators and adopt the inner cell mass fate. Homozygous knockout mice of Merlin, Fat4, Sav1, MST1/2 double, LATS1, LATS2 and YAP are embryonic lethal or die soon after birth, which underscores the importance of the Hippo pathway in development (*120*, *137*, *211–217*). $FAT4^{-/-}$ mice develop polycystic kidneys (*212*). Epithelial differentiation is impaired in $Sav1^{-/-}$ mice (*213*). YAP deletion in the liver causes hepatocyte death and abnormal bile ducts (*98*).

Loss of TAZ leads to polycystic kidneys and lung emphysema (*218*, *219*).

Organ size control and tumour suppressive role

Animal models support the importance of the Hippo pathway in suppression of tumourigenesis. Merlin$^{+/-}$ mice develop malignant tumours including osteosarcomas, lymphomas, lung adenocarcinomas, hepatocellular carcinomas and fibrosarcomas (*220*). Conditional knockout of Merlin in Schwann cells causes schwannomas (*221*). MST1$^{-/-}$ mice and MST2$^{-/-}$ mice develop sarcomas and mammary tumours, respectively, but at a low frequency (*120*). Seventy-four percent of Sav1$^{+/-}$ mice have liver tumour (*222*). LATS1$^{-/-}$ mice have sarcomas and ovarian tumours (*215*). Liver-specific conditional knockout of MST1, MST2 and Sav1, and activation of YAP demonstrate that the Hippo pathway indeed regulates the organ size in mammals, and that its dysfunction leads to hepatomegaly and tumourigenesis (*22*, *120*, *204*, *222–224*). Readers should refer to a recent review for detailed comparison of these animals (*225*).

The Hippo pathway is also important for heart size control and apoptosis. Dominant negative MST1 prevents apoptosis in a myocardial infarction model (*226*). Cardiac-specific expression of LATS2 reduces the size of ventricles (*227*). Dominant negative LATS2 causes cardiac hypertrophy and blocks MST1-induced apoptosis, supporting that LATS2 functions downstream of MST1. RASSF1A expression is reduced in the failing human heart (*228*). RASSF1A is up-regulated in response to pressure-overload and activates MST1 to induce cardiomyocyte apoptosis (*229*). The depletion of RASSF1A in mice enhances cardiac hypertrophy, while over-expression of RASSF1A increases apoptosis and exacerbates cardiac dysfunction under pressure overload. RASSF1A suppresses tumour necrosis factor-α (TNF-α) production in cardiac fibroblasts and thereby prevents cardiac fibrosis.

Cell differentiation

Both YAP and TAZ are involved in the maintenance of stemness. YAP mostly inhibits differentiation, but TAZ induces some differentiation. YAP is expressed in the crypt compartment of the small intestine and in the ventricular zone progenitor cells in the mouse neural tube (*204*, *230*). YAP activation expands progenitor cells and decreases differentiated cells. In mesenchymal stem cells, TAZ activates Runx2 to promote osteogenesis, and inhibits peroxisome proliferator-activated receptor γ to suppress adipogenesis (*231*). YAP has been experimentally shown to repress Runx2 gene transcription, but it is unknown whether or not YAP regulates Runx2 in mesenchymal stem cells (*232*). In myoblasts, TAZ activates MyoD-dependent gene transcription to promote myogenesis (*233*). In contrast, during C2C12 cell myogenesis, YAP is phosphorylated and recruited to the cytosol, implying that YAP-dependent transcription is turned off (*234*). The interaction of TAZ with SMAD complexes is necessary for self-renewal (*207*). TAZ depletion induces differentiation into neuroectoderm. YAP is necessary for the pluripotency of mouse embryonic stem cells and is inactivated during their differentiation (*235*). YAP facilitates the generation of iPS cells from mouse embryonic fibroblasts.

Tissue regeneration

The Hippo pathway plays a pivotal role in tissue regeneration. In *Drosophila*, when the intestine is under stress due to bacterial infection or bleomycin, the Hippo pathway is inactivated in enterocytes to activate Yorkie and increase Unpaired, which non-cell autonomously induces intestinal stem cell proliferation (*236*, *237*). Yorkie activation has also been detected in intestinal stem cells. Similarly, YAP expression is increased in regenerating mouse intestinal crypts and YAP depletion impairs regeneration (*238*).

Others

There was no study that directly addressed whether or not and how the canonical Hippo pathway functions in hemopoietic cells. Lymphocytes express MST1 and RASSF proteins. MST1 interacts with RAPL, which is a short isoform of Nore1 and an effector of Rap1 GTPase, in lymphocytes (*239*). MST1 is activated downstream of Rap1 and RAPL, and is necessary for cell polarization and integrin LFA-1 clustering and adhesion (*240*). MST1$^{-/-}$ lymophocytes do not adhere firmly to high endothelial venules and lack efficient homing capacity. In MST1$^{-/-}$ mice, the egress of mature T cells from the thymus is impaired, and lymphocytes are reduced in the blood and peripheral lymphoid tissues (*241*). MST1 expression induces apoptosis in T cells, but paradoxically, in MST1$^{-/-}$ mice, apoptosis of T cells is enhanced, which may be due to the high activation of T cells (*242*).

The Hippo pathway and human diseases

Cancer

The importance of the Hippo pathway in cancer development is obvious. Mutations of Merlin cause neurofibromatosis type 2, an autosomal dominant multiple neoplasia syndrome. Mutations of Merlin are found in sporadic meningiomas and mesotheliomas (*243*, *244*). RASSF1A and LATS2 are located on chromosomes 3p21.3 and 13q12.11, respectively. Deletion of both regions frequently occurs in human cancers. The RASSF1A promoter is frequently hypermethylated in various cancers (*149*, *150*). The LATS1 and LATS2 promoters are hypermethylated in ~50% of breast cancers and 60–70% of astrocytomas (*245*, *246*). Hypermethylation of the MST1 and MST2 promoters is detected in 37% and 20% of soft tissue sarcomas, respectively (*247*). The RASSF6 promoter is hypermethylated in >90% of childhood B cell acute lymphocytic leukaemia (ALL) and in 40% of T cell ALL (*248*). YAP is encoded on chromosome 11q22, whose amplification has been detected in various cancers (*190*). Activation of YAP or TAZ induces EMT in breast cancer cells and increases their invasiveness (*190*, *192*, *193*). Accordingly, the down-regulation of RASSF1A, LATS1 and LATS2, the reduced cytoplasmic expression of MST1, and the increased nuclear localization of YAP in cancer cells correlate with malignant properties and a poor prognosis (*149*, *246*,

249–251). Most dysfunctions of the Hippo pathway components, except Merlin, are caused not by gene mutations but by epigenetic silencing. This indicates the possibility that the Hippo pathway function may be recovered by epigenetic intervention. As Hippo pathway disorders are common events in cancer and they correlate with a poor prognosis, the Hippo pathway is an important and attractive therapeutic target.

Putative implications for other diseases

The crucial roles of the Hippo pathway in the regulation of stem cells and progenitor cells indicate that dysfunctions of the pathway can cause various diseases besides cancer. Studies on the heart suggested that malfunction of the Hippo pathway leads to cardiac hypertrophy. The observation that both depletion and over-expression of RASS1A are detrimental for cardiac function corroborates that appropriate Hippo signalling is important for tissue homoeostasis. To suppress tumours, the Hippo pathway should be active. However, hyperactivity of the Hippo pathway may increase tissue damage through excessive apoptosis and the prevention of tissue regeneration. The inactivation of TAZ by the Hippo pathway will inhibit osteogenesis and myogenesis. This means that over-activation of the Hippo pathway could cause osteoporosis and muscle atrophy. The suppression of TNF-α by RASSF1A in the heart is an intriguing observation. The down-regulation of RASSF1A predisposes tissues to an inflammatory response, and may facilitate atherosclerosis and insulin resistance. EMT in cancer cells causes metastasis, while EMT in epithelial cells causes fibrosis (*252*). As YAP and TAZ induce EMT, their activation may be involved in tissue fibrosis.

Concluding remarks and future directions

If we discuss only the canonical Hippo pathway, its framework is apparently simple and straightforward. It is a kinase cascade that is activated by the initial input from cell adhesion, cell polarity and cell stress, and transmits signals to restrict cell proliferation and induce apoptosis. The pathway explains the well-known contact inhibition and how damaged tissues are repaired. When some cells undergo apoptosis under stress or are removed mechanically, the neighbouring cells lose cell adhesion, which turns off the Hippo pathway. They start to proliferate and might produce cell proliferation-promoting signals to induce further cell proliferation non-cell autonomously. Proliferation will cease when all cells establish mature cell adhesion and tissues are repaired. However, to complete the whole process correctly, the Hippo pathway needs to be properly regulated at all stages. The Hippo pathway should be constitutively and mildly active to prevent overgrowth but avoid cell death under a static condition. The stimuli that damage tissues activate the Hippo pathway. The pathway is speculated to be more activated in more damaged cells. If the Hippo pathway overwhelms the cell-survival signals, the cells should die. On the other hand, the Hippo pathway must be suppressed in the cells that have lost matured cell adhesion but escaped severe damages. Such cells proliferate to repair tissues. Finally, when tissue repair is completed, the Hippo pathway must be re-activated at the proper time. For simplification, we here consider only the case that differentiated cells proliferate. Tissues are composed of diverse cells. Regeneration is carried out by stem cells or progenitor cells. The Hippo pathway balances cell proliferation and differentiation. Moreover, as we have discussed above, the mammalian Hippo pathway is not necessarily canonical. All circumstances considered the Hippo pathway requires sophisticated and cell context-dependent regulation. In the current boom, new components and new molecular interactions are continuously being added to the pathway. New cross-talks with other signallings have been identified. Each component plays numerous roles and is multifaceted. The network of the Hippo pathway is expanding and intertwined. It has become more difficult to have an overview of the Hippo pathway. So far, our understanding mostly depends on the information obtained from knockout mice, knockdown cells and over-expression of wild-type or mutated components. We guess how the pathway normally functions based on the findings that were collected under extreme conditions. In order to understand the roles of the Hippo pathway in the maintenance of tissue homoeostasis, it is essential to know what results from perturbation of the endogenous normal Hippo pathway in cells, tissues and animals. To this end, we need to have reagents that inhibit or stimulate the Hippo pathway. Such reagents will facilitate the future study in this field and lead to the development of new therapies for human diseases.

Acknowledgements

We thank the editor for giving us the opportunity to write this review. We are grateful especially for the lifting of the limitation to cite references. Even so, we have to apologize for not being able to mention all primary important research publications. During writing this manuscript, a new paper reported the interaction of YAP and TAZ with AMOT (*253*). In this article, the authors mainly studied AMOT-like protein (AMOTL) 2 among AMOT family and revealed that AMOTL2 functions as a tumour suppressor through promoting YAP phosphorylation and inhibiting YAP transcription activity. Together with the paper by Varelas *et al.* (*187*), this work indicates that AMOT family proteins are components of the mammalian Hippo pathway. Two other papers also reported the interaction of YAP or TAZ with AMOT family proteins (*254*, *255*). Chan *et al.* reported that even Hippo refractory TAZ mutant is restricted by AMOT family proteins and argued that the regulation by AMOT family proteins is independent of Hippo pathway. We discussed only the *Drosophila* and mammalian Hippo pathways in this review. We note that several papers have been published on the Hippo pathway in other animals including chicken, frog, zebra fish and cricket.

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Conflict of interest
None declared.

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