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REVIEW

The mammalian Hippo pathway: regulation and function of YAP1 and TAZ

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Abstract The Hippo pathway was originally identified as the signaling that controls organ size in *Drosophila*, with the core architecture conserved in mammals. In the mammalian Hippo pathway, mammalian Ste20-like kinases (MST1/2) and large tumor suppressor kinases (LATS1/2) regulate transcriptional co-activators, Yes-associated protein (YAP1) and Transcriptional co-activator with a PDZ-binding motif (TAZ). The Hippo pathway was initially thought to be quite straightforward; however, the identification of additional components has revealed its inherent complexity. Regulation of YAP1 and TAZ is not always dependent on MST1/2 and LATS1/2. MST1/2 and LATS1/2 play various YAP1/TAZ-independent roles, while YAP1 and TAZ cross-talk with other signaling pathways. In this review we focus on YAP1 and TAZ and discuss their regulation, function, and the consequences of their dysregulation.

Keywords Cancer · Stem cell · Cell differentiation · Development · Regeneration · Tumor suppressor

Introduction: a short history of the Hippo pathway

Mosaic genetic screens in *Drosophila melanogaster* identified Warts (wts) gene about 20 years ago. This gene encodes a tumor suppressor that is a kinase of the nuclear Dbf-2-related kinase family [1, 2]. Cells with wts mutations exhibit tumor phenotypes, as they over-proliferate and are defective with respect to apoptosis. Further screens revealed that the deletion of three genes, Hippo (hpo), Salvador (sav), and Mats (mats), result in similar phenotypes [3–9]. The HPO protein is a Ste20-like serine/threonine kinase that phosphorylates and activates WTS. The protein products of sav and mats interact with HPO and WTS to facilitate WTS activation. Therefore, these four gene products form a kinase cassette that restricts cell growth and proliferation and determines organ size. The downstream target, Yorkie (yki), was found as a WTS-interacting protein [10]. The product of yki is a transcriptional co-activator that is phosphorylated and negatively regulated by WTS. Analysis via genetic epistasis verified yki to be downstream of sav, wts, and hpo. Initially this pathway was referred to as the warts pathway, or the Salvador-Warts-Hippo pathway, but is now referred to as the Hippo pathway.

The components of the Hippo pathway that were first identified are conserved in mammals. Mice that lack the mammalian homolog of wts develop soft tissue sarcoma and ovarian tumors [11]. The human ortholog of sav (WW45) is mutated in colon and renal cancer cell lines [8]. Mutations in mats homologs have been identified in human melanomas and mouse mammary gland carcinomas [9]. Merlin (also called neurofibromatosis 2) is the etiological gene of a familial cancer syndrome and its *Drosophila* homolog was shown to be an upstream regulator of the Hippo pathway [12]. All these findings indicate that the pathway plays an important tumor suppression role in mammals.

Upon activation of the Hippo pathway, mammalian Ste20-like kinases (MST1 and MST2, HPO homologs) phosphorylate and activate large tumor suppressor kinases

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(LATS1 and LATS2, WTS homologs). These in turn phosphorylate Yes-associated protein (YAP1) and transcriptional co-activator with PDZ-binding motif (TAZ, also known as WWTR1) [13, 14]. YAP1 and TAZ are considered YKI homologs, and when phosphorylated, are segregated in the cytoplasm and undergo protein degradation. Originally, the pathway was thought to be relatively straightforward.

Later studies revealed numerous additional components that control YAP1 and TAZ. Researchers found that YAP1 and TAZ are regulated independently of MST or LATS kinases. The pathway was named after HPO. However, researchers are currently studying the Hippo pathway independent of HPO. In this review we have focused on YAP1 and TAZ and discussed MST and LATS kinases with respect to YAP1 and TAZ. MST and LATS kinases regulate molecules other than YAP1 and TAZ and play other Hippo pathway-independent roles. Detailed information regarding MST and LATS kinases can be found in other reviews [15, 16].

Molecular structures of YAP1 and TAZ

The N-terminal regions of YAP1 and TAZ interact with TEAD family transcriptional factors [13, 14] (Fig. 1). YAP1 and TAZ contain one or two WW domains in their middle region and a transactivation domain at the C-terminus. They also share a coiled-coil domain and PDZ-binding motif. There are eight isoforms of human YAP1 that are classified into two main groups: YAP1-1 (α, β, γ, and δ) and YAP1-2 (α, β, γ, and δ) [17]. YAP1-1 proteins contain one WW domain, while YAP1-2 members have two WW domains. In this review the amino acid residues we refer to correspond with those of human YAP1-2γ and human TAZ. Three variants of human TAZ are registered in GenBank, yet all of them encode the same protein. Medaka has TAZ isoform with two WW domains; however, human TAZ harbors only a single WW domain [18]. YAP1 has a proline-rich domain at the extreme end of the N-terminus (aa 1–57) and an SH3-binding motif after the second WW domain. YAP1 interacts with heterogeneous nuclear ribonuclear protein U (hnRNP U) via the N-terminal region and with Yes tyrosine kinase via the SH3-binding motif [13, 19]. As TAZ does not have the N-terminal proline-rich domain and the SH3-binding motif, it is unlikely for TAZ to interact with these proteins.

YAP1 and TAZ modifications

Phosphorylation by LATS kinases and subsequent ubiquitination are the most important and well-characterized negative regulatory mechanisms of YAP1 and TAZ. YAP1 up-regulates pro-apoptotic transcription under certain conditions. The phosphorylation of YAP1 by c-Abl and c-Jun N-terminal kinase (JNK) is related to pro-apoptotic

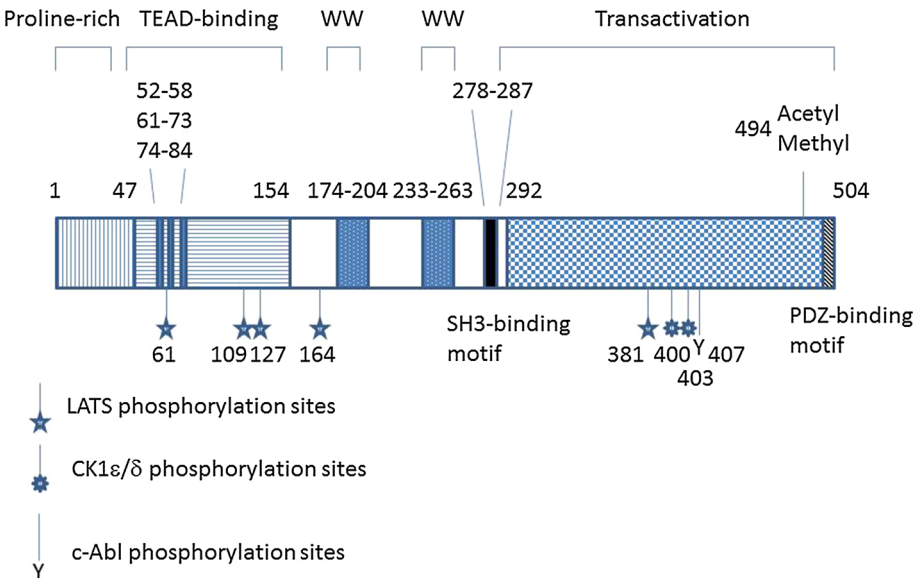

Fig. 1 Molecular structure of YAP1. In this review, amino acid residues for human YAP1-2γ are used. The TEAD-binding domain has three interfaces for interaction with TEAD (aa 52–58, β-strand; aa 61–73, α-helix; and aa 74–84, Ω-loop). Stars indicate the five LATS-dependent phosphorylation sites. S127 could also be phosphorylated by Akt. S127 phosphorylation generates the 14-3-3-binding site. Residue S381 phosphorylation primes the phosphorylation of S400 and S403 and leads to protein degradation by the SCFβ-TrCP pathway. Residue Y407 phosphorylation by c-Abl promotes p73-dependent pro-apoptotic transcription

properties. The significance of acetylation, methylation, and sumoylation upon YAP1 is not yet fully understood.

Phosphorylations and ubiquitination

YAP1 and TAZ have five and four HXRXXS sequences (H, histidine; R, arginine; S, serine; and X, any amino acid), respectively, that are phosphorylated by LATS kinases. Residues S127 of YAP1 and S89 of TAZ are the most important [10, 14, 20, 21]. Phosphorylation at these sites generates 14-3-3-binding sites (RXXXpSXP and RSXpSXP) (pS, phospho-serine; P, proline) and causes segregation of YAP1 and TAZ in the cytoplasm. When LATS kinases phosphorylate S397 of YAP1 and S311 of TAZ, casein kinase 1ε/δ subsequently phosphorylates S400 and S403 of YAP1 and S314 of TAZ. This then leads ubiquitination of YAP1 and TAZ, and their degradation via an SCF β-TrCP pathway [22, 23]. Phosphorylation of TAZ at S66 by LATS kinases induces phosphorylation by GSK3β at S58 and S62, providing the additional phosphodegron [24].

Many kinases are reported to phosphorylate YAP1 and TAZ, including Yes, Src, Akt, c-Abl, JNK, p38, CDK1, and Nima-related protein kinase 1 (Nek1). As its name indicates, YAP1 interacts with the Yes protein [13]. In embryonal stem (ES) cells, leukemia inhibitor factor (LIF) induces tyrosine phosphorylation of YAP1 through Yes and enhances YAP1-TEAD2-dependent transcription [25]. Yes-mediated phosphorylation induces formation of a YAP1-β-catenin-T-box5 (TBX5) complex on the promoters of anti-apoptotic genes and is involved in the survival of β-catenin-active cell lines [26]. Phosphorylation by Src kinase regulates the repression of Runx2 by YAP1 [27]. Residue S127 of YAP1 does not conform to the consensus sequence for Akt phosphorylation but is referred to as an atypical phosphorylation site [21]. Phosphorylation by Akt also results in YAP1 being trapped by cytoplasmic 14-3-3 and YAP1-regulated transcription being switched off. Akt is a pro-survival kinase; YAP1 that is negatively regulated by Akt is thought to up-regulate transcription of pro-apoptotic genes. It is not entirely clear how YAP1 decides to up-regulate transcription of pro- or anti-apoptotic genes; however, c-Abl and JNK are implicated. In response to DNA damage, c-Abl phosphorylates YAP1 at Y407 [28]. Tyrosine phosphorylation enhances the affinity of the interaction between YAP1 and p73, prevents Itch-mediated ubiquitination of p73, and activates pro-apoptotic transcription [29–31]. JNK phosphorylates T119, S138, T154, S317, and T362 in vitro [32, 33]. In skin cancer BWT cells, ultraviolet radiation induces JNK-dependent phosphorylation of YAP1 and promotes apoptosis. In contrast, in HaCaT cells, JNK-phosphorylated YAP1 interacts with ΔNp63α, stabilizes ΔNp63α by blocking the binding of Itch, and protects cells from p73-dependent apoptosis. CDK1 phosphorylates T119, S289, and S367 when the cell cycle is arrested at G2/M phase [34]. Expression of a phospho-mimetic mutant at these three sites causes mitotic defects. Residues T119 and S289 are phosphorylated during normal mitosis. These findings suggest that CDK1 regulates the cell cycle through phosphorylation of YAP1. Nek1 phosphorylates TAZ at S314 to form phosphodegron. Nek1-dependent phosphorylation of TAZ also triggers degradation of polycystin 2 and is required to suppress the expression of polycystin 2 [35]. ATM triggers the activation of YAP1-Promyelocytic leukemia protein (PML)-p53. YAP1 and ATM are co-immunoprecipitated and YAP1 is phosphorylated in this complex; however, it remains unknown whether YAP1 is a direct substrate of ATM [36].

Protein phosphatases, PP1A and PP2A, counteract LATS kinases; PP1A dephosphorylates TAZ at S89 and S311, and YAP1 at S127 [37, 38]. PP2A dephosphorylates YAP1 at S127 [38]. It has been found that α-catenin blocks the interaction of YAP1 with PP2A and functions as a negative regulator of YAP1 [39]. Non-receptor protein tyrosine phosphatase 14 (PTPN14) binds to the WW domains of YAP1 and dephosphorylates src-induced tyrosine phosphorylation [40–42]. PTPN14 increases cytoplasmic phosphorylated YAP1 during contact inhibition. This negative regulation depends on physical interaction with YAP1 and does not require the phosphatase activity of PTPN14.

Other modifications

Methyl methanesulfonate-induced DNA damage causes acetylation of K494 and K497 of YAP1 [43]. The acetylation does not affect the nuclear localization of YAP1 but its deletion enhances TEAD-reporter activity in HEK293 cells and methyl methanesulfonate-induced cell death in HeLa cells. Residue K494 is methylated by SET-domain-containing lysine methyltransferase (SET7) [44]. This methylation is necessary for the cytoplasmic retention of YAP1. YAP1 is modified by sumoylation [45]; in CDDP-treated H1299 cells, PML stabilizes YAP1 by blocking ubiquitylation and inducing sumoylation.

YAP1 and TAZ regulators

We have summarized the upstream regulators of YAP1 and TAZ. Some of these work through MST1/2 or LATS1/2, while others directly regulate YAP1 and TAZ. The former mode of regulation is referred to as the canonical Hippo pathway (Table 1).

Table 1 Core components of *Drosophila* and mammalian Hippo pathways

Drosophila	Mammal	Brief description
Hpo	Mammalian Ste20-like kinases (MST1/2)	Serine/threonine kinases
Sav	WW45/Sav1	Adaptor protein
Mats	MOB1	Adaptor protein
Wts	Large tumor suppressor kinases (LATS1/2)	Serine/threonine kinases
Yki	Yes-associated protein (YAP1)	Transcriptional co-activator
	Transcriptional co-activator with PDZ-binding motif (TAZ/WWTR1)	

For simplicity, only the core founding components of the pathway are listed

Cell adhesion molecules

In *Drosophila* protocadherin FAT and Dachsous are upstream of the Hippo pathway. Fat4 is a homolog of FAT, and mutations in Fat4 or DCHS1 (human homolog of Dachsous) cause Van Maldergem syndrome [46]. Reduction in Fat4 or DCHS1 in mouse embryonic neuroepithelial cells increases the number of progenitor cells and decreases the rate of differentiation into neurons. YAP1 suppression recovers this phenotype. In kidney progenitor cells of $Fat4^{-/-}$ mice, nuclear and dephosphorylated YAP1 levels are increased [47]. These findings support that Fat4 and DCHS1 negatively regulate YAP1. $Fat4^{-/-}$ mice develop polycystic kidneys, as do $TAZ^{-/-}$ mice [48–50]. This coincidence is intriguing but paradoxical and needs to be further studied, because Fat4 depletion should impair the Hippo pathway and activate TAZ. CD44, a hyaluronan receptor and cancer stem cell marker, blocks phosphorylation of YAP1 in response to H_2O_2 treatment in human glioblastoma U87MG cells [51]. In contrast CD44 depletion increases nuclear YAP1 levels in endothelial cells [52]. This discrepancy may be due to the different isoforms of CD44 expressed in U87MG and endothelial cells.

Receptors

Dobutamine induces the recruitment of YAP1 into the cytoplasm of U2OS cells via β-adrenergic receptors [53]. Protease-activated receptor (PAR) 1-activating peptide decreases phosphorylation of YAP1 and TAZ and increases the occurrence of nuclear localization [54]. Lysophosphatidic acid (LPA) and Sphigosine-1-P also trigger YAP1 and TAZ dephosphorylation [55, 56]. Experiments using various G-protein-coupled receptors (GPCRs) revealed that Gs signaling increases YAP1 and TAZ phosphorylation, whereas G12/13, Gq/11, and Gi/o signaling decreases phosphorylation [55]. Cyclic AMP (cAMP) generated by Gs activation stimulates LATS1 via protein kinase A (PKA) in breast cancer cells [57]. PKA does not enhance LATS1 activity in vitro, suggesting that PKA does not directly phosphorylate LATS1 (Fig. 2; Table 2). As the dominant active Rho blocks the effect of cAMP, and PKA represses the phosphorylation of ROCK kinase substrate, cAMP and PKA presumably activate LATS1 through suppression of Rho signaling. Kim et al. studied the effects of cAMP generated by cell detachment [58]; in this scenario, the production of cAMP was independent of Gs. They identified putative PKA phosphorylation sites of LATS2 (S172, S380, S592, and S598) and demonstrated that PKA directly activates LATS2. Among four putative phosphorylation sites, the sequences around S172 and S380 contain the optimal consensus sequence. These sites are not conserved in LATS1. This could possibly explain why PKA does not directly activate LATS1. Regulation by G12/13 signaling is also mediated by Rho and the actin cytoskeleton. Gq/11 mutants detected in human uveal melanoma activate YAP1 via Rho [59, 60]. LIF enriches Scribble at the plasma membrane and activates LATS kinases [61]. Down-regulation of the p130 LIF receptor results in up-regulation of YAP1, and is a prognostic marker of breast cancer metastasis.

Membrane-associated proteins and cell junction proteins

In *D. melanogaster*, the molecules that determine apical-basal polarity regulate the Hippo pathway. These molecules, and their interactions, are mostly conserved in mammals and regarded as upstream regulators.

Merlin has long been known to play a role in contact inhibition [62]. It interacts with numerous proteins, and it is not clear whether its tumor suppressive role is solely dependent on YAP1. It is, however, clear that Merlin exerts some of its function through the Hippo pathway [63]. Merlin interacts with α-catenin and Par3 in keratinocytes and is involved in the maturation of adherens junctions [64]. It has been shown that α-catenin interacts with phosphorylated YAP1 via 14-3-3 and eventually sequesters YAP1 from the nucleus, implying that Merlin recruits YAP1 into the cytoplasm via α-catenin [39].

FRMD6/Willin is thought to be the ortholog of *Drosophila* Expanded. FRMD6/Willin expression increases phosphorylation of MST kinases, LATS1, and YAP1 in HEK293 cells. This observation supports the theory that FRMD6/Willin is partially equivalent to Expanded [65]. However, there are some differences between expanded and FRMD6/Willin. Expanded interacts with Merlin but FRMD6/Willin lacks the C-terminal Merlin-binding

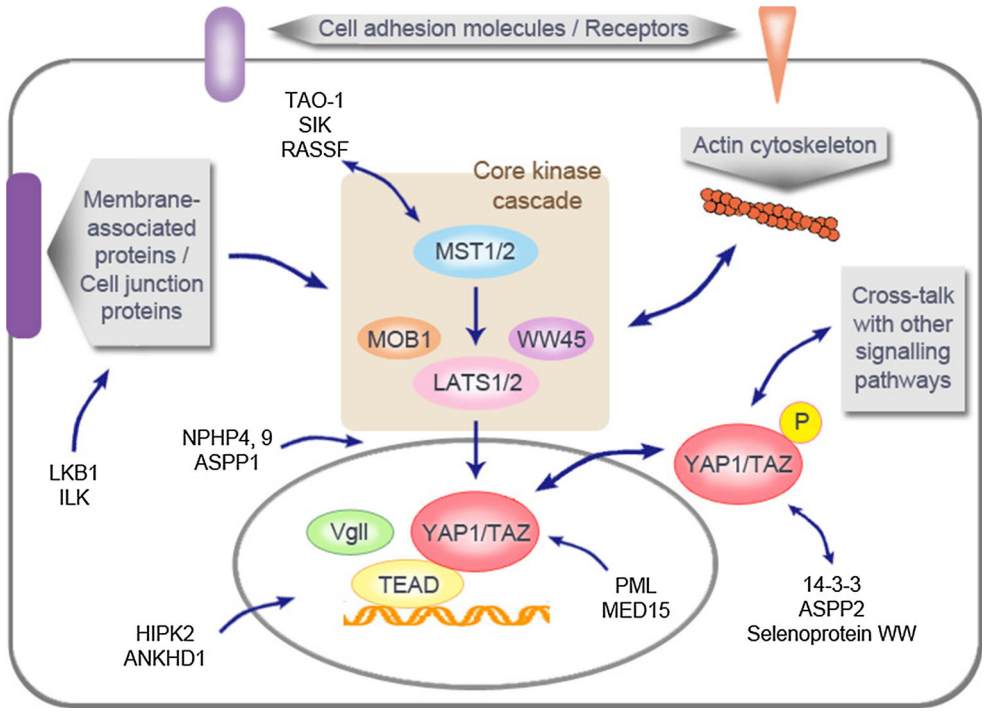

Fig. 2 Summary of YAP1 and TAZ regulation. The core kinase cassette, comprising MST1/2, WW45, MOB1, and LATS1/2, negatively regulates YAP1 and TAZ by phosphorylation. In the nucleus YAP1 and TAZ interact with various transcription factors. TEAD interacts with Vgll. YAP1 and TAZ are regulated by "Membrane-associated proteins and cell junction proteins", "Cell adhesion molecules and receptors", "Actin cytoskeleton" and "Cross-talk with other signaling pathways". The components are summarized in Table 2. LKB1 alters the localization of Scribble. ILK inactivates Merlin. TAO-1, SIK, and RASSF regulate MST1/2 activities. NPHP4, NPHP9, and ASPP1 directly interact with TAZ or YAP1. HIPK2 and ANKHD1 modulate transcription mediated by YAP1. Cytoplasmic YAP1 and TAZ interact with 14-3-3 and several other proteins. Nuclear YAP1 and TAZ interact with several proteins including PML and MED15 along with transcription factors

region, therefore FRMD6/Willin and Expanded possibly work in different ways.

KIBRA forms a complex with Merlin and Expanded and functions upstream of the Hippo pathway in *Drosophila* [66, 67]. In mammals, KIBRA interacts with Merlin, AMOT, and PTPN14, although the significance of these interactions has not been clarified at the molecular level. KIBRA also binds to and activates LATS kinases [68]. KIBRA depletion reduces YAP1 phosphorylation, supporting the view that KIBRA functions upstream of YAP1. Given that KIBRA is up-regulated by YAP1, there is a feedback loop between KIBRA and YAP1.

The AMOT family of proteins comprises AMOT-p80, AMOT-p130, AMOTL1, and AMOTL2 [69]. AMOT interacts with the PDZ domain of Patj, a component of Crb complex (Crb, Pals1, and Patj), via the PDZ-binding motif and is localized at tight junctions. AMOT also interacts with Merlin via the coiled-coil region and bridges Merlin and Patj [70, 71]. AMOT binds Rich1, a GTPase-activating protein for Rac1 and Cdc42. AMOT functions downstream of Merlin and upstream of Rich1 to activate Rac1 in HEK293 cells. The AMOT family of proteins, with the exception of AMOT-p80, directly bind to YAP1 and TAZ. Overexpression of AMOT recruits YAP1 and TAZ to tight junctions or the actin cytoskeleton and reduces nuclear levels of YAP1 and TAZ [72, 73]. The interaction of AMOT with YAP1 and TAZ does not depend on the phosphorylation of YAP1 and TAZ, but does increase their phosphorylation levels. The AMOT family of proteins bypass LATS1/2, and negatively regulate YAP1 and TAZ. Yi et al. [74] reported that AMOT is necessary for tumorigenesis in Merlin$^{-/-}$ mice. They showed that AMOT-p130 inhibits the interaction betweenYAP1 and LATS1/2 and increases nuclear YAP1 in HEK293 cells. Their results are inconsistent with those reported by others; they argued that in previous studies, researchers used cells that do not endogenously express AMOT-p130 and, therefore, might obtain artificial observations.

Ajuba LIM proteins [Ajuba, LIM domain-containing 1 (LIMD1) and Wilms tumor protein 1-interacting protein (WTIP)] interact with LATS 1/2. Ajuba and WTIP bind to WW45 [75]. LIMD1 reduces YAP1 phosphorylation, while combined knockdown of Ajuba and LIMD1 increases YAP1 phosphorylation in MDCK cells. MAPK signals enhance the interaction between WTIP, LATS1, and WW45 [76]. JNK phosphorylates LIMD1 and WTIP and

Table 2 Direct and indirect regulators of YAP1 and TAZ

Category	Name	Effect on YAP1 and/or TAZ	Brief description
Cell adhesion molecule	Fat4	Down	Protocadherin
	DCHS1	Down	Protocadherin
	CD44	Up	Hyaluronan receptor
Receptor	Gs-coupled receptor	Down	Mediated by PKA and Rho
	G12/13-, Gq/11-, Gi/o-coupled receptor	Up	Mediated by Rho
	LIF receptor	Down	Mediated by Scribble
Membrane-associated protein, cell junction protein	Merlin/NF2	Down	Interacts with α-catenin and Par3
	FRMD6/Willin	Down	Putative homolog of Drosophila expanded
	KIBRA	Down	Interacts with Merlin, AMOT, PTPN14, and LATS kinases
	AMOT (AMOT-p80, AMOT-p130, AMOTL1, AMOTL2)	Down or up	Interacts with Patj, Merlin, and Rich AMOT-p130, AMOTL1, and AMOTL2 interact with YAP1 and TAZ
	Ajuba (Ajuba, LIMD1, WTIP)	Down or up	All three interact with LATS kinases. LIMD1 reduces YAP1 phosphorylation in MDCK cells, while Ajuba inreases it in mesothelioma cells
	ZO-2	Down (TAZ) or up (YAP1)	Interacts with YAP1 and TAZ and promotes nuclear localization
	PTPN14	Down	Interacts with YAP1
	α-Catenin	Down	Blocks dephosphorylation of YAP1
Actin cytoskeleton	High mechanical stress	Up	Rho and CDC42 activation
	Low mechanical stress	Down	F-actin capping/severing proteins
Cross-talk with other signaling pathway	Wnt pathway	Up	Phosphorylated β-catenin promotes TAZ degradation Wnt signaling increases PP1A-dependennt dephosphorylation of TAZ β-Catenin mutant stabilizes YAP1
	Sonic hedgehog pathway	Up	Sonic hedgehog increases nuclear YAP1 via IRS
Others	LKB1	Down	Mediated by Scribble, MARK, and LATS2
	ILK	Up	Inhibits Merlin via MYPT1-PP1
	PP2A	Up	Dephosphorylates YAP1
	TAO-1	Down	Activates MST2
	SIK	Up	Phosphorylates WW45
	RASSF	Down	RASSF1A, RASSF2, and RASSF5 function as upstream regulators of the Hippo pathway. RASSF6 works as a tumor suppressor in parallel to the Hippo pathway. RASSF4 may have a similar mode of function
	NPHP4	Up (TAZ)	Inhibits the interaction between LATS1 and TAZ
	NPHP9	Up (TAZ)	Translocates TAZ into the nucleus
	ASPP1	Up (YAP1)	Blocks the interaction between YAP1 and LATS1
	ASPP2	Up (TAZ)	Promotes the interaction between TAZ and PP1A
	HIPK2	Up (YAP1)	Increases YAP1 independently of LATS kinases
	ANKHD1	Up (YAP1)	Forms a complex with YAP1 and is necessary for YAP1 full activity
	PML	Up (YAP1)	Stabilizes YAP1 by sumoylation and enhances p73-dependent anscription
	WRN	Down (YAP1)	Suppresses YAP1 expression

augments their interaction with LATS1, but not with WW45 [77]. YAP1 is regulated by a mechanical cue; a cyclic stretch increases the binding of LIMD1 to LATS1 via JNK and activates YAP1 [78]. Ajuba is down-regulated in human mesothelioma cells that are associated with YAP1 activation [79]. Ajuba expression consistently enhances YAP1 phosphorylation in mesothelioma cells, suggesting a tumor suppressive role of Ajuba.

ZO-2 is a tight junction protein with PDZ domains that interacts with TAZ and YAP1 [80, 81]. ZO-2 facilitates the nuclear localization of YAP1 and promotes apoptosis in HEK293 cells. ZO-2 co-localizes with TAZ in the nucleus and represses TAZ transactivation.

Actin cytoskeleton

G-protein-coupled receptor signaling activates and inhibits YAP1 via the actin cytoskeleton. Other stimuli that influence the actin cytoskeleton similarly modulate YAP1 and TAZ activities, with Rho involved in most cases. Soft matrix inhibits YAP1 and TAZ, while stiff matrix or cell spreading increases nuclear YAP1 and TAZ through the activation of Rho [82]. The importance of Rho is highlighted by a report showing that inhibition of geranylgeranyl pyrophosphate synthesis impairs the modification of Rho and reduces YAP1 and TAZ nuclear localization [83]. CDC42 inactivation shows a similar phenotype to a YAP1 depletion phenotype in nephrogenesis, supporting that CDC42, a regulator of the actin cytoskeleton, regulates YAP1 [84]. High mechanical stress, such as stretching, activates YAP1 and TAZ. In contrast, under low mechanical stress, YAP1 and TAZ are inhibited by F-actin-capping/severing proteins, such as Cofilin, CapZ, and Gelsolin [85]. Regulation of YAP1 by the extracellular matrix is important in cancer biology and regenerative medicine. YAP1 is activated in cancer-associated fibroblasts and promotes matrix stiffening, which in turn further up-regulates YAP1 [86]. Aging affects the mechanosensing activities of YAP1 and TAZ. In aged mammary epithelial progenitors, YAP1 and TAZ become less sensitive to mechanical cues. Under these conditions, progenitors show biased differentiation towards a luminal-like phenotype [87]. Sun et al. [88] seeded human ES cells on soft matrix to differentiate them into motor neurons by inhibiting YAP1.

Other regulators

Kinases

All molecules that modulate the activities of MST1/2 and LATS1/2 potentially regulate YAP1 and TAZ activities. The Ste20-like kinase TAO-1 phosphorylates and activates MST2 [89, 90]. In *Drosophila,* salt-inducible kinases (SIK) phosphorylate Salvador and negatively regulate the Hippo pathway [91]. Human SIK2 enhances YAP1-mediated transcription, although the mechanisms involved are not clear. Liver kinase B1 (LKB1) and its substrates, microtubule affinity-regulating kinases (MARK), suppress YAP1 [92]. Knockdown of LATS2 or Scribble cancels the inhibitory effect of LKB1, showing that LKB1 acts via LATS2 and Scribble. Deficiencies in LKB1 activate YAP1 and cause *trans*-differentiation from adenocarcinoma to squamous cell carcinoma [93]. Integrin-linked kinase (ILK) phosphorylates myosin phosphatase MYPT1-PP1 at the inhibitory site, inactivates Merlin by increasing S518 phosphorylation, and activates YAP1 [94]. Homeodomain-interacting protein kinase (HIPK)2 increases the abundance of YAP1 in parallel with LATS1/2 and enhances TEAD2-depdendent transcription [95]. Kinase activity is necessary, but the direct substrate of HIK2 has not been identified yet.

RASSF

Drosophila dRASSF has the Ras-association (RA) domain and the Salvador/RASSF/Hippo (SARAH) domain [96]. Humans have 10 RASSF proteins (RASSF1-10) [97]; RASSF1-6 have the SARAH domain and are orthologs of dRASSF. RASSF1A activates MST2 in response to DNA damage [98, 99]. RASSF2 and RASSF5 activate the Hippo pathway as upstream regulators [98, 100–102]. In contrast, RASSF6 forms a complex with MST2 and inhibits its activity [103]. When cells are exposed to stress, RASSF6 is dissociated from MST2 and the Hippo pathway is activated. At the same time RASSF6 facilitates auto-ubiquitination of MDM2 and stabilizes p53 to induce cell cycle arrest and apoptosis [104]. The Hippo pathway and RASSF6 are simultaneously activated and accomplish tumor suppressive roles in a parallel manner. In alveolar rhabdomyosarcoma (aRMS), PAX3-FOXO enhances RASSF4 expression, which leads to MST1 inhibition and YAP1 activation [105]. This finding implies that RASSF4 is oncogenic in aRMS. We should consider the possibility that aRMS might harbor p53 mutations. If this is the case, RASSF4 cannot function as a p53-dependent tumor suppressor and apparently plays an oncogenic role. In *Drosophila*, PP2A negatively regulates the Hippo pathway, and dRASSF is important for HPO to interact with *Drosophila* Striatin-interacting phosphatase and kinase (dSTRIPAK), a *Drosophila* PP2A complex [106]. In mammals, RASSF1A inhibits PP2A-dependent dephosphorylation of MST1/2 and activates the Hippo pathway [107].

Cilia-related proteins

The interaction of TAZ with cilia-related proteins is interesting because $TAZ^{-/-}$ mice develop polycystic kidneys. Nek1 phosphorylates TAZ and is important in ciliogenesis and the regulation of polycystin 2 expression. Nephronophthisis (NPHP) is a group of autosomal recessive kidney cystic diseases with 11 causative genes (NPHP1–11). NPHP4, a cilia-associated protein, inhibits interaction between LATS1 and TAZ to activate TAZ

[108]. NPHP9, also known as Nek8, directly binds to TAZ and translocates it to the nucleus [109]. Phosphorylation of TAZ by NPHP9 has not been reported, and the kinase-dead mutant of NPHP9 can activate TAZ. Therefore, the physical interaction between NPHP9 and TAZ is important.

Miscellaneous

Vigneron et al. [110] reported that cytoplasmic apoptosis-stimulating protein of p53 (ASPP1) binds to YAP1 and blocks interaction between YAP1 and LATS1. ASPP2 promotes the interaction of TAZ with PP1A to facilitate dephosphorylation of TAZ [37]. In C2C12 cells, selenoprotein WW, which might be an anti-oxidant protein, is reported to regulate the binding of TAZ and 14-3-3 [111]. In *Drosophila,* multiple ankyrin repeats single KH domain (Mask) functions downstream of Wts and is necessary for Yki-dependent transcription [112, 113]. The human Mask homolog (ANKHD1) forms a complex with YAP1 and is required for full YAP1 activity. ANKHD1 is highly expressed in various prostate cancer cell lines and its depletion suppresses YAP1 expression [114]. PML binds p73 and YAP1, promotes acetylation of p73 by p300, and stabilizes YAP1 by sumoylation [115]. The PML gene is up-regulated by p73/YAP1 [45]; therefore, there is a positive feedback loop between PML and p73/YAP1. WRN is a human RecQ helicase and a causative gene of Werner syndrome characterized by premature aging. In WRN-depleted cells YAP1 expression is augmented, activating p53-dependent transcription and contributing to senescence [36].

Regulation of YAP1 transcription

Our knowledge regarding regulation of YAP1 and TAZ gene expression is limited. GABP and Sox2 bind to the YAP1 promoter and activate its transcription [116]. As GABP is sensitive to the redox state, YAP1 might be a part of the defense mechanisms against oxidants. Sox2 inhibits osteogenesis via YAP1 and induces PPARγ in osteoblastic and adipocytic lineage cells [117]. Induction of adipogenesis by Sox2 is impaired by excessive YAP1 or its depletion and requires the moderate level expression of YAP1. In the developing lung YAP1 controls Sox2 expression [118]. The mutual regulation between YAP1 and Sox2 is likely to be important in determining cell fate.

YAP1 and TAZ functions

As YAP1 and TAZ are transcriptional co-activators, regulation of transcription is an essential part of their functions. However, YAP1 and TAZ also function in the cytoplasm and regulate microRNAs (miRNAs). Cross-talk with other signaling pathways, especially the Wnt pathway, is important for the regulation of stem cells and cancer.

Regulation of transcription

YAP1 and TAZ interact with various transcriptional factors that are overlapped, but are significantly divergent, mirroring the fact that YAP1 and TAZ play distinct roles during development and oncogenesis.

TEAD1–4

TEAD1–4 play important roles in development and cancer cells [119]. All four TEADs have a DNA-binding domain in the N-terminal region and immunoglobulin-like β-sandwich folds in the C-terminal region [120–122]. The C-terminal region functions as a transactivation domain and interacts with YAP1 and TAZ. This domain also binds Vestigial-like (Vgll) proteins and p160 coactivator proteins. The TEAD-interacting domain of YAP1 has a β-strand (aa 52–58), an α-helix (aa 61–73), and an Ω-loop (aa 74–84). YAP1 binds to three interfaces of TEAD1 and TEAD4, whereas Vgll1 uses only the first and second interfaces of TEAD4 [123]. The overall affinities of YAP1 and TAZ for TEAD4 are similar, with closer analysis revealing some differences between YAP1-TEAD4 and TAZ-TEAD4 interactions [124]. In *Drosophila*, the TEAD homolog, Scalloped (Sd), functions as a default repressor. The Vgll homolog, Tgi, is necessary for this repression [125]. YKI competes with Tgi for binding to Sd and abrogates repression; a similar competition between YAP1 and Vgll1 was shown in vitro. Vgll4 negatively regulates the YAP1-TEAD complex in lung cancer [126]. The synthetic peptide mimicking the sequence of Vgll4 interferes with the interaction of YAP1 and TEAD4 and inhibits gastric cancer growth [127]. Based on these findings we reasoned that YAP1, like YKI, activates transcription by blocking Vgll-TEAD-mediated repression.

SMAD proteins

YAP1 and TAZ interact with SMAD proteins. SMAD-mediated transcription is important in the regulation of stem and cancer cells. Not all combinations of YAP1/TAZ and SMAD1–8 have been tested for interaction. The interaction between YAP1 and SMAD1 is well characterized [128]. SMAD1 mediates bone morphogenesis protein (BMP) signals, while BMP induces the CDK8/9-mediated linker phosphorylation of SMAD1. This phosphorylation enhances the interaction between the WW domains of YAP1 and the PPXY motif in the linker region. Subsequent

phosphorylation by GSK3β abrogates YAP1 binding, but overall YAP1 promotes SMAD1-mediated signals. In human mesothelioma cells, the YAP1-TEAD4-SMAD3-p300 complex was detected on the promoter of connective tissue growth factor, suggesting an interaction between YAP1 and SMAD3 [129]. Developing airway epithelial cells are unable to respond to TGFβ in the absence of YAP1 [130], suggesting that YAP1 co-operates with SMAD proteins to transduce TGFβ signaling. YAP1 interacts with SMAD7 in COS-7 cells and potentiates the inhibitory effect against TGFβ signaling [131]. The relationship of YAP1 with SMAD proteins appears to be context-dependent. TAZ interacts with the SMAD2/3–4 complex in a TGFβ-dependent manner, and is necessary for nuclear localization of the complex and TGFβ-induced transcription in human ES cells [132, 133]. TAZ binds to the MH domain of SMAD2. This interaction is not dependent upon the WW domain of TAZ. In mouse mammary epithelial cells seeded at high density, TAZ and YAP1 accumulate in the cytoplasm, with SMAD2/3 concomitantly recruited to the cytoplasm. YAP1 and TAZ regulate SMAD functions at the transcriptional level and in determining subcellular localization.

Other transcription factors

TAZ interacts with Pax3, MyoD, thyroid transcription factor-1 (TTF-1, T-EBP, Nkx2.1), Pax8, Runx2, and peroxisome proliferator-activated receptor (PPAR)γ. The interaction of TAZ with Pax3, TTF-1, or Pax8 is mediated by multiple domains [134, 135]. MyoD binds to the WW domain of TAZ [136]. Runx2 and PPARγ contain the WW domain-binding motif, but it is not known whether interaction of TAZ with Runx2 or PPARγ is dependent on the WW domain [137]. Pax8 and TTF-1 are involved in thyroid development. $TAZ^{-/-}$ mice do not show significant abnormalities during thyroid development. The significance of TAZ interaction with Pax8 and TTF-1 is unclear. In mesenchymal stem cells, TAZ activates Runx2 to promote osteogenesis and represses PPARγ to inhibit adipogenesis [137]. Pax3 and MyoD play important roles in skeletal muscles. In mouse C2C12 cells, TAZ enhances MyoD-mediated myogenesis, but the cellular output of the interaction between TAZ and Pax3 has not been analyzed. YAP1 interacts with Runx2 and p73; however, findings have been inconsistent regarding observed effects [27, 31]. In reporter assays using rat osteosarcoma ROS 17/2.8 and human cervical carcinoma HeLa cells, YAP1 repressed Runx2 [27]. In human bone marrow endothelial cells, YAP1 and Runx2 co-operated to promote cell transformation [138]. Interaction with p73 is required to understand the tumor suppressive properties of YAP1. PML stabilizes YAP1 and p73, and enhances YAP1/p73-mediated transcription [45, 115]. The hnRNP U protein binds to the N-terminal region of YAP1 and suppresses p73-dependent Bax transcription [19]. The interaction of YAP1 with p63 is necessary to regulate p63 target genes in airway basal stem cells [139]. To date, there is no evidence to show interaction between YAP1 and PPARγ, but it has been postulated that because YAP1 overexpression suppresses adipogenesis in 3T3-L1 cells, YAP1 might repress PPARγ [57]. Wbp2, a co-activator of the estrogen receptor (ER), binds to YAP1 and TAZ and is implicated in TAZ-dependent oncogenesis in breast cancers [140, 141]. Wbp2 enhances Scalloped-dependent reporter activity in *Drosophila* S2 cells to a small extent [142]. It has not been reported whether YAP1 and TAZ modulate ER-dependent transcription via Wbp2. TAZ binds to Gli-similar 3 (Glis3), a Kruppel-like zinc finger protein, and enhances Glis3-meditated transcription [143]. Glis3 is localized to primary cilia. As TAZ is modified by NPHP4 and NPHP9 and $TAZ^{-/-}$ mice develop polycystic kidneys, the interaction between TAZ and Glis3 is an attractive area for further studies [49, 50, 108, 109]. YAP1 forms a complex with Foxo1 on the promoter of catalase and manganese superoxide dismutase, protecting cardiomyocytes against irradiation [144]. TAZ activates hypoxia-inducible factor 1α (HIFα)-dependent transcription and confers malignant properties to cancer cells [145].

Regulation of miRNA biogenesis

Two reports have shown that the Hippo pathway regulates miRNA biogenesis, which is relevant to contact inhibition. Chaulk et al. [146] reported that nuclear YAP1 and TAZ increase inhibitory LIN28B levels and suppress Let-7 expression; this is necessary for the processing of pre-miRNA. Mori et al. demonstrated that nuclear YAP1 sequesters p72 (DEAD box helicase 17) from DROSHA and DGCR8 at a low cell density. At a high density, cytoplasmic YAP1 promotes p72 association with Microprocessor [147]. These findings suggest that dysregulation of the Hippo pathway impairs miRNA processing and shed some light on how miRNAs are globally suppressed in cancers.

Roles of cytoplasmic YAP1 and TAZ

In the canonical Hippo pathway, only nuclear YAP1 and TAZ were considered to be functional. However, it now appears that cytoplasmic YAP1 and TAZ also have specific functions. Aylon et al. [148] reported that LATS2 phosphorylates cytoplasmic ASPP1, inducing its nuclear translocation, and promoting transcription of pro-apoptotic genes. As YAP1 blocks the binding of LATS2 to ASPP1, cytoplasmic YAP1 antagonizes the tumor suppressive roles

of ASPP1. YAP1, and TAZ affect the subcellular localization of SHP2 tyrosine phosphatase [149]; when YAP1 and TAZ accumulate in the nucleus, SHP2 is recruited to the nucleus and dephosphorylates parafibromin to stimulate TCF/LEF-dependent and TEAD-dependent transcriptions. This is an example of the cross-talk between the Hippo and Wnt pathways. Cytoplasmic YAP1 and TAZ also play an important role in regulating β-catenin [150].

Cross-talk with the Wnt pathway

The yes tyrosine kinase triggers the formation of a YAP1-β-catenin-TBX5 complex [26]. TAZ interacts with DVL in the cytoplasm and inhibits CK1ε/δ-mediated phosphorylation [151]. Similarly, in the intestine, YAP1 interacts with DVL and restricts its nuclear localization to compromise Wnt signaling during regeneration [152]. Imajo et al. [153] found that YAP1 and TAZ bind to β-catenin; they revealed that activation of the Hippo pathway blocks nuclear localization of β-catenin through the cytoplasmic translocation of YAP1. Whether TAZ plays a similar role is not yet clear. In YAP1-induced intestinal dysplasia, increased nuclear β-catenin levels were observed [154]. In WW45-deficient hearts, nuclear β-catenin levels were increased, and YAP1 interacted with β-catenin on Sox2 and Snai2 genes [155]. Azzolin et al. revealed that YAP1 and TAZ interact with Axin1, and recruit β-catenin to the β-TrCP degradation complex. When the Wnt pathway is switched on, YAP1 and TAZ dissociate from Axin1, and β-catenin is stabilized and translocated to the nucleus [150]. These findings suggest that YAP1 and TAZ increase nuclear β-catenin levels, and that the Hippo pathway antagonizes the Wnt pathway. Consistently in $MST^{-/-}$ intestinal epithelia, YAP1 and β-catenin accumulate in the nucleus [156]; however in $WW45^{-/-}$ mice, only YAP1 accumulates in the nucleus [157]. This discrepancy is not yet fully explained. The recent study has revealed that in the Wnt off state, cytoplasmic YAP1 and TAZ regulate β-catenin negatively, while in the Wnt on state, YAP1 and TAZ potentiate the Wnt pathway [150]. It might be possible that in $WW45^{-/-}$ mice, TAZ remains in the cytoplasm to facilitate degradation of β-catenin. It is necessary to detect YAP1 and TAZ with specific antibodies. In YAP1-depleted kidneys, no major changes were observed in the Wnt pathway [84]. Cross-talk between the Hippo and Wnt pathways might vary in different tissues.

Cross-talk between the Hippo and Wnt pathways is bi-directional. Phosphorylated β-catenin bridges TAZ to SCFβ-TrCP and promotes its degradation [158]. Canonical Wnt signaling reduces phosphorylated β-catenin, releases TAZ from SCFβ-TrCP and leads to a concomitant increase of β-catenin and TAZ levels. TRIB2, a pseudokinase, is a target of the Wnt pathway [159]. In liver tumors with β-catenin mutants, TRIB2 levels are increased and it interacts with β-TrCP, thereby stabilizing YAP1. TRIB2 also induces degradation of C/EBPα. As C/EBPα binds to YAP1 and inhibits the interaction between YAP1 and TEAD, TRIB2 enhances YAP1/TEAD-dependent transcription. Wnt signaling dephosphorylates TAZ via PP1A to induce osteogenesis in C3H10T1/2 cells [160]. Hence, the Wnt pathway up-regulates TAZ and YAP1 functions.

Cross-talk with other signaling pathways (Sonic hedgehog, Notch, and EGF)

The cross-talk between the Hippo and Sonic hedgehog pathway is also bi-directional. YAP1 is overexpressed in human Sonic hedgehog (Shh)-dependent medulloblastoma [161]. Shh up-regulates YAP1 expression at the mRNA and protein level and increases nuclear localization via IRS1. In mouse embryonal carcinoma P19 cells and mouse cortical progenitor cells, YAP1 overexpression blocks neuronal differentiation, while knockdown of Gli2 rescues differentiation [162]. In the intestine, YAP1 activates Notch signaling and γ-secretase inhibition prevents YAP1-induced intestinal dysplasia [154]. In hepatocellular carcinomas, YAP1 up-regulates Jagged-1 and stimulates Notch signaling in a non-cell autonomous manner [163]. Amphiregulin, a ligand of the EGF receptor, is a target of YAP1 and TAZ, and dysfunction of the Hippo pathway up-regulates EGF signals in a non-cell autonomous manner [164, 165].

Roles in cancer

In this section we briefly review disorders of the Hippo pathway observed in human cancers. Dysregulation of the Hippo pathway causes epithelial-mesenchymal transition (EMT), provides cancer cells with stemness, and enhances genomic instability. YAP1 functions as a tumor suppressor in certain cancer cells.

Abnormalities of YAP1 and TAZ in human cancers

Dysfunction of the Hippo pathway and hyperactivity of YAP1 and TAZ correlate with poor prognosis in human cancers. Mutants of YAP1 and TAZ, in which LATS-dependent phosphorylation sites have been replaced, are used experimentally, but have not been seen in human cancers. YAP1 and TAZ mutations are very rare. One missense mutation (F29V) in TAZ has been reported in a basal-like breast cancer [166]. Two mutations in YAP1 have been reported in families with autosomal-dominant inheritance of coloboma but no mutation has been detected in cancer so far [167]. Frequently observed abnormalities

of the Hippo pathway include Merlin mutations, down-regulation of Hippo components (KIBRA, RASSF1A, MST2, and LATS1/2) by DNA hypermethylation, and YAP1 gene amplification. Chromosomal rearrangement that results in the fusion of TAZ and CAMTA1, a calmodulin-binding transcription activator, has been detected in epithelioid hemangioendothelioma (EHE) [168]. Fusion of YAP1 and transcription factor 3 (YAP1–TFE3) has also been detected in EHE [169].

How do YAP1 and TAZ hyperactivities lead to oncogenesis?

The WW domains of YAP1 are required for YAP1-induced overgrowth and serum-independent growth in NHI3T3 cells [170]. The WW domain of TAZ is necessary for anchorage-independent growth of MCF10A cells expressing TAZ [141]. The transcription factors interacting with the WW domains play some role in oncogenesis, with TEADs thought to be major contributors to oncogenesis [171–173]. Two studies using a K-ras-driven pancreatic cancer model yielded inconsistent results [174, 175]. Mice with K-ras G12D developed pancreatic ductal adenocarcinoma; suppression of K-ras G12D resulted in tumor regression, but then there was a relapse of K-ras-independent tumors. Both studies found that YAP1 substitutes for the K-ras G12D mutant in tumor relapse cases, but do not agree in the downstream mechanisms. Kapoor et al. compared the mRNA expression profiles between K-ras-dependent and K-ras-independent tumors and focused on TEAD2. They demonstrated that YAP1 and TEAD2 cooperate with E2F to bypass K-ras-oncogenic addiction. Shao et al. observed that the TEAD-binding-deficient YAP1 mutants can rescue proliferation in K-ras G12D-suppressed cells and concluded that AP-1 was a key factor. This discrepancy could be due to differences in experimental methods that the groups used. TEAD is also important in YAP1- and TAZ-induced EMT [172, 176]. Target genes of TEADs include the CCN family (CTGF, Cyr61), Axl, miR-29, and Sox9. CTGF and Cyr61 confer drug resistance to cancer cells [177]. Interleukin-6, metalloproteinase 7, interleukin 1-α, and cyclooxygenase 2 also correlated with YAP1 abundance in pancreatic cancer models [178]. Axl, a receptor tyrosine kinase, determines tumorigenic properties of hepatocellular carcinoma cells [179]. miR-29 suppresses PTEN and activates mTOR [180]. Sox9 provides esophageal cancer cells with stemness [181]. A glioblastoma chromatin immunoprecipitation study demonstrated that TAZ forms a complex with TEAD2 on mesenchymal gene promoters [182]. Considering the importance of TEADs in oncogenesis, YAP1 and TEAD complexes are promising therapeutic targets. Reagents such as verteporfin and Vgll4-mimicking peptide that block the interaction between YAP1 and TAZ with TEADs are tested [127, 183].

EMT is closely related to cancer stemness [184]. Breast cancer cells with mesenchymal properties show cancer stem-like properties. TAZ hyperactivity confers mesenchymal and cancer stem cell-like properties to breast cancer cells [185]. It appears that TAZ introduces molecular signatures into cancer cells that are shared by EMT and cancer stemness. Conversely EMT increases TAZ expression levels; however, when E-cadherin is overexpressed in breast cancer cells with an active TAZ mutant, EMT is reversed but cancer stem cell-like properties are maintained. This indicates that TAZ-mediated cancer stemness is independent of EMT. All these findings suggest that TAZ activation triggers EMT, subsequently activating TAZ to high levels and causing cancer stemness.

It was recently reported that LATS2 is activated in tetraploid cells and is important in arresting the cell-cycle [186]. In tetraploid cells, cytoplasmic YAP1 levels are increased, while TAZ expression is reduced. Expression of constitutively active YAP1 mutants overrides cell cycle arrest and drives tetraploid cells into the cell cycle. Tetraploid cells cannot proliferate while the Hippo pathway is functional; in cancer cells where the Hippo pathway is deficient, YAP1 and TAZ facilitate genomic instability.

YAP1 as a tumor suppressor

Although YAP1 is primarily regarded as an oncogene, it promotes apoptosis in response to DNA damage in some cancer cell lines such as H1299, HCT116, and MCF7 [21, 33]. In human breast cancers, deletion of YAP1 gene locus is observed [187]. In human head and neck squamous carcinoma cells, cytoplasmic YAP1 is abundant, reflecting high Akt activity, with overexpression of nuclear YAP1 causing cell death [188]. In multiple myeloma cells, DNA damage causes nuclear accumulation of c-Abl, but because of low YAP1 expression, these cells evade cell death [189]. If YAP1 is activated in these myeloma cells, cell proliferation is reduced and cell death is induced. YAP1 activation could be beneficial in the treatment of myeloma. Loss of YAP1 expression has also been seen in human colon cancers and is associated with high stage diseases [152]. It is essential to select appropriate cancers for cancer therapies targeting YAP1.

Roles in development and tissue regeneration

YAP1 and TAZ have attracted an increasing amount of interest from researchers in the field of regenerative medicine.

Embryogenesis

It has been shown that YAP1$^{-/-}$ mice die by embryonic day (E) 8.5 due to yolk sac defects [190], while TAZ$^{-/-}$ mice progress through to adulthood, although they suffer from emphysema-like lung defects and polycystic kidneys [49, 50]. The TEAD proteins are expressed at the very early stages of embryogenesis [191, 192]. At the blastocyst stage, blastomeres develop into the outer epithelial trophectoderm (TE) and the inner cell mass (ICM) [193, 194]. In the TE, YAP1 is localized to the nucleus and TEAD4 induces the expression of TE-specific genes such as Cdx2 and Gata3. For the ICM, YAP1 is distributed within the cytoplasm and TEAD4-dependent transcription does not occur. Components of the Hippo pathway, including Merlin, AMOT, and LATS1/2, regulate the subcellular localization of YAP1 in blastomeres [195–197].

ES cells and induced pluripotent stem (iPS) cells

YAP1 is a regulator of mouse ES and iPS cells. In murine ES cells, YAP1 is inactivated during differentiation; YAP1 and TEAD2 promote Oct3/4 and Nanog expression [25]. Depletion of YAP1 and TEAD2 reduces the self-renewal ability and induces differentiation of mouse ES cells. The differentiation of human ES cells into motor neurons is facilitated by the suppression of YAP1 [88]. Overexpression of YAP1 enhances the efficiency of mouse iPS induction [198]. TAZ knockdown has no effect on mouse ES cells [132], but in human ES and iPS cells, TAZ is required. LATS2 knockdown increases the efficiency of reprogramming in human iPS cells, but additional TAZ knockdown counteracts LATS2 knockdown, indicating that TAZ improves efficiency [200]. TAZ controls the shuttling of SMAD2/3–4 between the nucleus and cytoplasm and enhances self-renewal in human ES cells [132]. Proteomic and genomic studies using human ES cells revealed that YAP1 and TAZ form a complex comprising SMAD2/3 and Oct4 and that they repress mesendoderm genes via a nucleosome remodeling and deacetylase (NuRD) complex, and maintain pluripotency [199]. Treatment with activin results in TEAD4 dissociating from the complex, and consequently SMAD2/3 and FOXH1 induce mesendoderm genes. A recent model has shown that the NuRD complex acts as a balance between self-renewal and differentiation [201]. YAP1 promotes self-renewal and blocks differentiation in neural stem cells and myoblasts, whereas TAZ accelerates differentiation in mesenchymal stem cells and in myoblasts. The different properties of YAP1 and TAZ might reflect differing interactions with the NuRD complex.

Roles in adult tissues

YAP1 and TAZ regulate tissue-specific stem cells and are important for tissue homeostasis and regeneration in adult animals. YAP1 is crucial in the liver, intestine, heart, skin, pancreas, lung, and brain. TAZ is involved in the regulation of osteogenesis and adipogenesis in mouse mesenchymal stem cells. YAP1 and TAZ control myogenesis in myoblasts. TAZ plays some role in the heart, but this has not been as widely studied as the role of YAP1 [202]. YAP1$^{-/-}$ mice and TAZ$^{-/-}$ mice show defects in kidney organogenesis [49, 50, 84], but it remains unknown what roles YAP1 and TAZ play in the adult kidney. TAZ$^{-/-}$ mice show emphysema-like changes in the lungs [49], but the role of TAZ in adult lungs is not clear. The size of the pancreas is small in MST1/2 knockout mice because disorganization of the exocrine compartment causes secondary pancreatitis [203, 204]. This observation suggests that proper inactivation of YAP1 is important for development of the pancreas, but the role of YAP1 in the adult pancreas is unknown.

Liver

Various model mice with either liver-specific mutant YAP1 expression or liver-specific ablations of Hippo pathway components (Merlin, WW45, and MST1/2) have been analyzed [63, 154, 205–208]. Although there are differences between models, all animals show proliferation of liver stem cells, known as oval cells, and hepatomegaly, thus supporting the notion that the Hippo pathway controls organ size. In human patients with chronic cholestasis, nuclear YAP1 is prominent in bile duct compartments and induces biliary epithelial cell proliferation [209]. After a hepatectomy, MST1/2, LATS1/2, and MOB1 levels are decreased and YAP1 becomes active during regeneration [210]. It was recently shown that YAP1 activation leads hepatocytes to a ductal fate [211]. YAP1 overexpression induces dedifferentiation of adult hepatocytes into progenitor-like cells. Furthermore, the suppression of YAP1 in hepatocyte-derived progenitor-like cells induces re-differentiation into hepatocytes. These findings imply that during liver damage YAP1 triggers reprogramming of hepatocytes for regeneration.

Intestine

YAP1 hyperactivation expands intestinal progenitors, while YAP1 deletion impairs regeneration in intestines damaged with dextran sodium acetate [154, 157]. There was another report showing that YAP1 antagonizes Wnt signaling and restricts intestinal stem cell expansion [152]. This discrepancy reminds us of the inconsistent nuclear

β-catenin localization in WW45$^{-/-}$ (decreased) and MST$^{-/-}$ (increased) intestinal epithelia [155, 156].

Heart

WW45, MST1/2, or LATS1/2 deficiencies and overexpression of YAP1 result in heart overgrowth [212–214]. In a myocardial infarction model, YAP1 promotes regeneration and improves survival [202, 215]. YAP1 stimulates cardiomyocyte proliferation but not hypertrophy. Cardiomyocyte-specific YAP1 depletion increases apoptosis and fibrosis, leading to dilated cardiomyopathy [155]. In the heart, β-catenin forms a complex with unphosphorylated YAP1 in the nucleus. YAP1 and β-catenin concurrently occupy the promoter of Sox2 and Snai2. YAP1 inhibits GSK3β via the insulin-growth factor pathway and activates β-catenin to proliferate cardiomyocytes [216]. YAP1 co-operates with the Wnt pathway in the heart. In arrhythmogenic cardiomyopathy with mutation in intercalated disc proteins, Merlin was activated. As a consequence of this, YAP1 and β-catenin were suppressed and adipogenesis was enhanced [217]. The requirement of YAP1 for heart homeostasis raises concerns about the potential cardiotoxicity of YAP1-targeted cancer drugs.

Skin

During skin development, YAP1 is expressed in the single-layered epithelium, and then in the bulge of the hair follicle, and in the interfollicular epidermis [218, 219]. Nuclear YAP1 is evident in undifferentiated skin progenitors [39]. YAP1 shifts to the cytoplasm as differentiation occurs, and its overexpression results in the expansion of epidermal stem cells and progenitor cells. These findings are consistent with the view that YAP1 blocks differentiation and is important in maintaining self-renewal. Knockdown of YAP1 and TAZ delays skin wound healing [220]. Activation of YAP1 and TAZ could be beneficial for treating skin injuries.

Lung

In the developing lung, YAP1 is located in the nucleus of distal bud progenitors and in the cytoplasm of airway epithelial progenitors [118]. YAP1 regulates Sox2 expression, with Sox2 controlling the differentiation of airway epithelial cells. YAP1 depletion expands aberrant distal progenitors. YAP1 is further necessary for the differentiation of adult airway progenitors. Parallel work has also demonstrated that YAP1 is indispensable for the maintenance of adult airway basal stem cells [139]. Overexpression of YAP1 causes dedifferentiation of secretory cells, which echoes the dedifferentiation of hepatocytes by YAP1.

Brain and nerve tissues

Our knowledge of the roles of YAP1 in mammalian brain is still limited. However, there was a report that increased YAP1 activity was associated with the expansion of neural progenitors in chickens [221]; therefore, YAP1 is thought to be important for the maintenance of neural progenitors. The expansion of neural progenitors has been observed in Fat4$^{-/-}$ mice and in Merlin$^{-/-}$ mice [46, 222]. Suppression of YAP1 in human ES cells facilitates differentiation into motor neurons, which mirrors the inhibitory effect of YAP1 on differentiation [88]. Expression of YAP1 and TAZ is enhanced in the spinal cord after peripheral nerve injury [223]. Researchers have discussed the potential implication of YAP1 and TAZ in neuropathic pain; however, the physiological significance needs to be further investigated.

Mesenchymal stem cells

TAZ promotes osteogenesis and inhibits adipogenesis in mouse mesenchymal stem cells [137]. Kaempferol, a flavonoid, enhances the interaction of TAZ with Runx2 and PPARγ to promote osteogenesis and inhibit adipogenesis [224]. LATS2 overexpression in 3T3-L1 cells induces the recruitment of TAZ to the cytoplasm. Eventually PPARγ regains the activity and the Wnt pathway is suppressed, such that cell proliferation is repressed and adipogenesis is enhanced [225]. Kaempferol and another TAZ activator, TM-25659, are expected to play protective roles against osteoporosis and obesity [224, 226]. Sox2 overexpression in mesenchymal stem cells and C3H10T1/2 cells induces YAP1 expression, with YAP1 inhibiting osteogenesis and adipogenesis [117]. YAP1 overexpression in 3T3-L1 cells also inhibits adipogenesis [198]. As the Hippo pathway is activated by cAMP, serum glucose level should alter YAP1 and TAZ activities. It would be interesting to study whether and how YAP1 and TAZ are involved in the regulation of adipogenesis.

Skeletal muscles

TEADs take part in the regulation of myogenesis. TEAD1 and TEAD4 bind to the Myf5 promoter and regulate its expression [227]. TEAD4 also regulates myogenin expression [228]. As TEAD2 regulates Pax3 in the neural crest, TEAD2 might also regulate Pax3 in skeletal muscles [229]. As YAP1 and TAZ interact with TEADs, it is postulated that they are involved in myogenesis. YAP1 is recruited from the nucleus to the cytoplasm during differentiation in C2C12

cells [230]. When YAP1 activity is augmented in C2C12 cells, the expressions of Myf5 and cyclinD1 remain high, but those of myogenin and Mef2c are low; therefore, myogenesis is inhibited. In Pax7-positive quiescent satellite cells, YAP1 expression is low, while it is high in MyoD-positive active satellite cells and Pax7-positive self-renewal reentering cells [231]. Consistently, YAP1 hyperactivity enhances satellite cell proliferation, increases the number of Pax7-positive MyoD-positive active satellite cells, and inhibits myogenesis from skeletal muscle progenitors. In a mouse model, skeletal muscle fiber-specific expression of an active YAP1 mutant causes muscle degeneration [232]. Lamin A/C gene mutations cause congenital muscle dystrophy. Myoblasts with such mutations are defective in mechanosensing and YAP1 is hyperactive in these cells [233]. All these findings suggest that the moderate and timely activation of YAP1 is important for homeostasis of skeletal muscles. TAZ interacts with Pax3 and MyoD [134, 136]. The precise roles of TAZ in satellite cells are not fully known but its expression is increased in regenerating muscles after injury [136]. In C2C12 cells, TAZ enhances MyoD-mediated myogenesis. TAZ activators promote muscle repair after injury [234, 235]. Unlike YAP1, TAZ activation seemingly enhances self-renewal and replenishment of satellite cells, along with myogenesis.

Others

The study of the Hippo pathway now covers a large number of fields and has provided researchers with many unexpected yet interesting findings. During development of the salivary submandibular gland, TAZ becomes phosphorylated and associated with E-cadherin and α-catenin [236]. Perturbation of the Hippo pathway results in dysmorphogenesis of the gland. In patients with Sjögren's syndrome, TAZ is mislocalized from cell junctions. Although TAZ mislocalization could be a secondary result of cell junction disruption, it is also possible that dysregulation of the Hippo pathway is implicated in the pathophysiology of Sjögren's syndrome. Fragmentation of the mouse ovary disrupts the Hippo pathway and promotes follicle formation [237]. Based on this observation, the fragmentation of the ovary with Akt stimulation is used to treat primary ovarian insufficiency.

Conclusions and future perspectives

Almost 10 years ago, the Hippo pathway started with four members (hpo, sav, wts, and mats) that partook in five interactions (HPO-SAV, HPO-WTS, HPO-Mats, SAV-WTS, and WTS-Mats). However, since then, new components have continued to be identified. There have been five recent papers reporting the proteome-scale analysis of the Hippo pathway (one for *Drosophila*, four for mammals) [238–242]. These papers illustrate the daunting and complicated protein network underlying the Hippo pathway. The original founding members are obscured among numerous proteins. It needs to be discussed which part is the most essential for the Hippo pathway. The pathway was initially defined as the organ size controlling pathway. To build up an organ with its proper size, cells need to behave as players in the mass games. They should receive the information from without, judge their own places, know what the neighboring cells do, and determine whether to proliferate, differentiate, or not. YAP1 and TAZ sense external cues such as cell density, stretching, cell geometry, and matrix rigidity; they are also regulated by the maturity of cell junctions. This combination of properties allows the placement of YAP1 and TAZ at the center of the Hippo pathway.

YAP1 and TAZ are frequently discussed together but have distinct properties. The phenotypes of YAP1 and TAZ knockout mice differ. During development, especially in the early phase, YAP1 appears to be more important than TAZ. In ES cells and tissue progenitor cells, YAP1 promotes self-renewal and inhibits differentiation. This is in sharp contrast to TAZ, which tends to facilitate differentiation. YAP1 and TAZ are both considered to be oncogenes. However, TAZ is more oncogenic. A study using Ha-ras-transformed immortalized human mammalian epithelial MCF10A cells revealed that TAZ, but not YAP1, is up-regulated in malignant subtypes with higher tumor-initiating capacity [185]. In our hands, MCF10A cells expressing the active TAZ mutant can survive under floating conditions and form spheres; MCF10A cells expressing the active YAP1 mutant cannot form spheres (unpublished observation). YAP1 and TAZ differ in their interactions with transcription factors. Unfortunately researchers do not publish the negative data. TAZ interacts with MyoD, but there are no reports to indicate that YAP1 does not interact with MyoD. Likewise, it is not reported that TAZ does not interact with p73. It is important to study YAP1 and TAZ in parallel and compare the results. If YAP1 shifts stem cells towards self-renewal and TAZ shifts them towards differentiation, YAP1 and TAZ are likely to interact with the NuRD complex in different ways. It is essential to detect YAP1 and TAZ with specific antibodies in the interaction with the NuRD complex. To use YAP1- and TAZ-targeted drugs for cancer therapy and in regenerative medicine, it will be necessary to collect baseline information about YAP1 and TAZ. The combined use of YAP1 and TAZ activators could enable us to control tissue regeneration more efficiently.

We also question whether the mammalian Hippo pathway has other function not related to the control of organ size. DNA damage switches on the Hippo pathway to

trigger the checkpoint. Genomic instability is a hallmark of cancer, while maintenance of genomic integrity is a central role of the mammalian Hippo pathway. The Hippo pathway functions in hemopoietic cells, but it is not known how the Hippo pathway is activated in these cells. It is possible that they receive signals from cell–cell contacts, cell–matrix contacts, and/or soluble ligands. We now know that glucagon and epinephrine activate the Hippo pathway. This prompts us to ask whether the Hippo pathway is activated in the human body in response to serum glucose levels and sympathetic nerve stimuli. If we reconsider the roles of YAP1 and TAZ as mechanosensors, we need to study how YAP1 and TAZ respond to exercise in skeletal muscles; blood pressure changes in the heart and arteries; shear forces in ciliated epithelial cells; skin stretching, and loads placed upon bone. We hope that the next decade of the Hippo pathway research will allow us to answer these questions.

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