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YAP and TAZ Take Center Stage in Cancer

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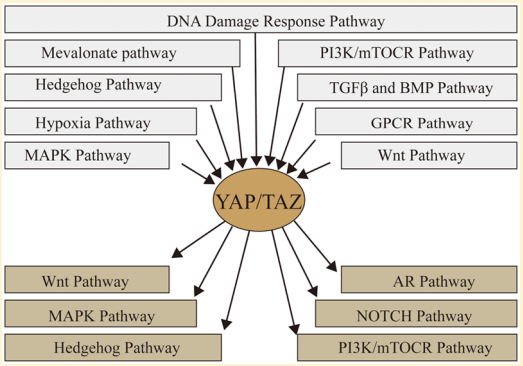
ABSTRACT: The Hippo pathway was originally identified and named through screening for mutations in Drosophila, and the core components of the Hippo pathway are highly conserved in mammals. In the Hippo pathway, MST1/2 and LATS1/2 regulate downstream transcription coactivators YAP and TAZ, which mainly interact with TEAD family transcription factors to promote tissue proliferation, self-renewal of normal and cancer stem cells, migration, and carcinogenesis. The Hippo pathway was initially thought to be quite straightforward; however, recent studies have revealed that YAP/TAZ is an integral part and a nexus of a network composed of multiple signaling pathways. Therefore, in this review, we will summarize the latest findings on events upstream and downstream of YAP/TAZ and the ways of regulation of YAP/TAZ. In addition, we also focus on the crosstalk between the Hippo pathway and other tumor-related pathways and discuss their potential as therapeutic targets.



Cancer is a leading cause of death in the world. About 14.1 million new cancer cases and 8.2 million deaths occurred in 2012 worldwide.[1] Understanding the molecular mechanism of human cancer is essential to improve the diagnosis and treatment of cancer. Tumor progression often involves deregulated signaling pathways that play crucial roles in controlling growth and cell fate decisions during normal development, thus leading to unchecked proliferation and evasion of apoptosis, which are considered as two important hallmarks of cancer development. One of such pathways is the highly conserved Hippo tumor suppressor signaling pathway, which restricts organ size and proliferation and has emerged as a prominent pathway which is "switched off" in many types of cancers, including colon cancer,[2] hepatocellular carcinoma,[3−7] breast cancer,[8−11] ovarian cancer,[12,13] nonsmall cell lung cancer,[14] prostate cancer,[15−17] pancreatic ductal adenocarcinoma,[18] osteosarcoma,[19] glioblastoma,[20] uveal melanoma,[21] medulloblastoma,[22] and malignant mesothelioma.[23]

The Hippo pathway was originally identified and named through screening for mutations in Drosophila, in which loss-of-function mutations of components of the Hippo pathway revealed organomegaly.[24] The Hippo pathway is highly conserved in mammals and acts as a major regulator of tissue growth and organ size. In humans, the central components of the canonical Hippo pathway consists of the mammalian sterile20-like kinases serine/threonine kinases 1/2 (MST1/2), the large tumor suppressor serine/threonine protein kinases1/2 (LATS1/2), as well as their adaptor proteins Salvador homologue 1 (SAV1; also called WW45) and Mps One Binder kinase activator proteins (MOBs). Mechanistically, MST1/2 (Hpo in Drosophila) serves as upstream kinases associated with its scaffolding partner SAV1 (Salvador in Drosophila) and phosphorylates LATS1/2 (Warts in Drosophila) and MOB1 (Mats in Drosophila). MOB1A and MOB1B function to enhance the kinase activity of LATS1/2.[25−27] Activated LATS1/2 kinases then phosphorylate the transcriptional regulators including yes-associated protein (YAP) and transcriptional coactivators with PDZ-binding motif (TAZ), leading to the inactivation of YAP/TAZ (Yki in Drosophila) by sequestering in the cytoplasm via interaction with 14-3-3 proteins or proteasome mediated degradation.[28,29] Thus, the Hippo signaling functions to inhibit the activity of YAP/TAZ by changing its protein level and distribution.

More recently, the complexity of YAP/TAZ regulation has expanded considerably, including MST and LATS-independent phosphorylation of YAP/TAZ, phosphorylation-independent modalities of YAP/TAZ, and more and more evidence showed that the Hippo pathway is interlinked with other tumor-related pathways. This highlights that the experimental modus operandi for investigating the Hippo pathway is moving away from the idea of a simple linear pathway to a view in which YAP/TAZ is an integral part and a nexus of a network composed of multiple signaling pathways. Therefore, we summarize the latest findings on events upstream and downstream of YAP/TAZ and the ways of regulation of

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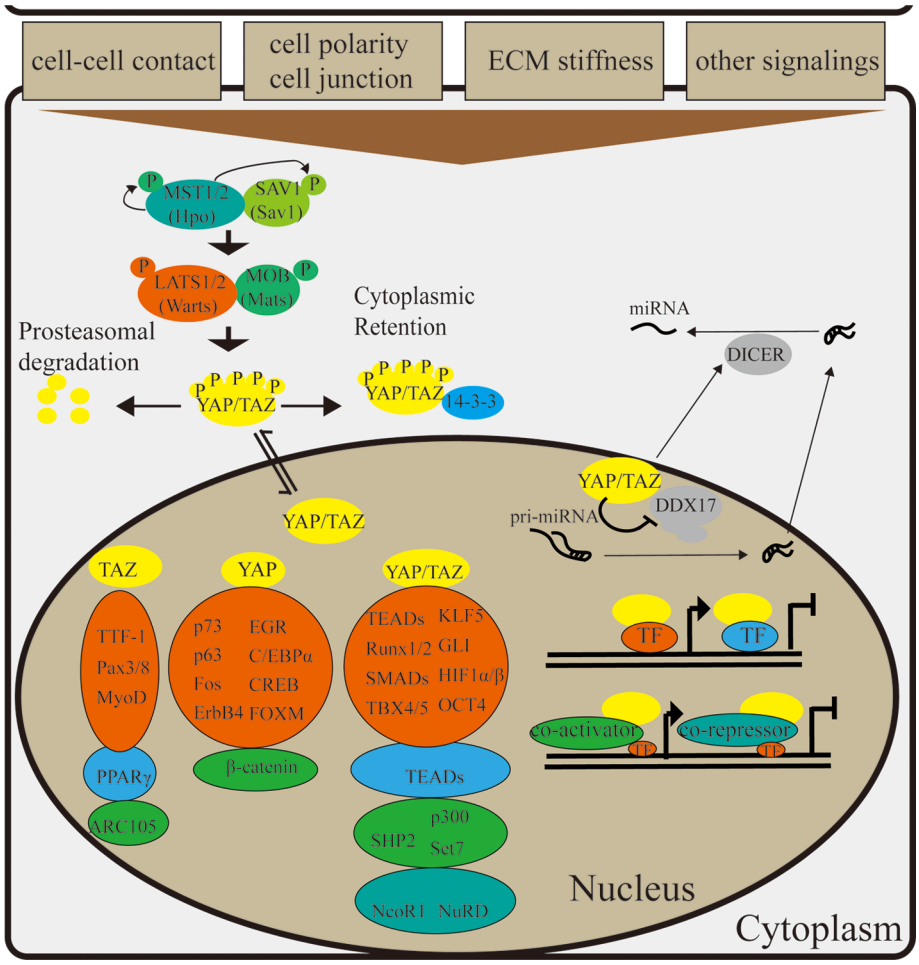

Figure 1. Schematic models of the Hippo pathway in mammals. The Hippo pathway is regulated by various upstream regulators such as cell−cell contacts, apical-basal polarity and junction proteins, mechanical cues from neighboring cells and the extracellular matrix and various signals from other signaling pathways, and then, MST1/2 (Hpo in Drosophila) serve as upstream kinases associate with their scaffolding partner SAV1 (Salvador in Drosophila) and phosphorylates LATS1/2 (Warts in Drosophila) and MOB1 (Mats in Drosophila). Activated LATS1/2 kinases then phosphorylate the transcriptional coactivator YAP/TAZ (Yki in Drosophila), leading to the inactivation of YAP/TAZ by sequestering in the cytoplasm via interaction with 14-3-3 proteins or proteasome mediated degradation. In the nucleus, YAP/TAZ regulates target genes via binding with transcription factors, coactivators, and corepressors. In addition, YAP/TAZ also regulates the expression of miRNAs through the Microprocessor component DDX17 and DICER.

YAP/TAZ, which focus on the crosstalk between the Hippo pathway and other tumor-related pathways and discuss their potential as therapeutic targets in this review (Figure 1).

UPSTREAM REGULATORS OF YAP/TAZ

Although the core signaling cascade from MST1/2 to YAP/TAZ is well understood; however, how these kinases are activated and recruited to YAP/TAZ is poorly understood. Accumulating evidence from both Drosophila and mammals has shown that cell−cell contacts, adhesion and apical-basal polarity proteins, mechanical cues from neighboring cells and the extracellular matrix, as well as various signals acting through other signaling pathways have all been identified as regulators of the localization and phosphorylation of YAP/TAZ through MST1/2 or LATS1/2, while some of them regulate YAP/TAZ independent of the canonical Hippo pathway. Cell−cell contact is one of the first identified regulators of Hippo signaling and is sensed and transmitted to the pathway by proteins, such as E-cadherin, α- and β-catenins, Crumbs and Scribble, which are involved in adherens junction and apical-basal polarity.[28−31] Moreover, FAT tumor suppressor homolog1-4 (FAT1-4) receptor and its ligands Dachsous1/2 (DCHS1/2), which regulate apical membrane organization, have also been identified as negative upstream regulators of the Hippo pathway. Cells are experiencing different mechanical inputs caused by differential ECM stiffness, cell shape, and geometry and are a crucial regulator of YAP/TAZ activity. Accumulating evidence has shown that nuclear translocation of YAP/TAZ is promoted when the cells are "stretched" or growing on a stiff extracellular matrix and repressed when cells are compressed or growing on a soft surface.[32,33] In addition, a large number of membrane receptors, including GPCRs,[34] EGFR,[13,35] gp130,[36] LIFR,[37] ILK,[38] and LKB1,[39] and intracellular signaling pathways, such as Wnt,[2,40−42] TGFβ,[9,31,43] Hedgehog,[19,22] Hypoxia pathway,[44−47] and mevalonate pathway,[8,48,49] have also been reported to regulate YAP/TAZ phosphorylation and nucleocytoplasmic localization.

DOWNSTREAM EFFECTORS OF YAP/TAZ

When signals perceived at the plasma membrane inactivate the Hippo pathway, dephosphorylated YAP/TAZ translocates to the nucleus to initiate transcription by interacting with the

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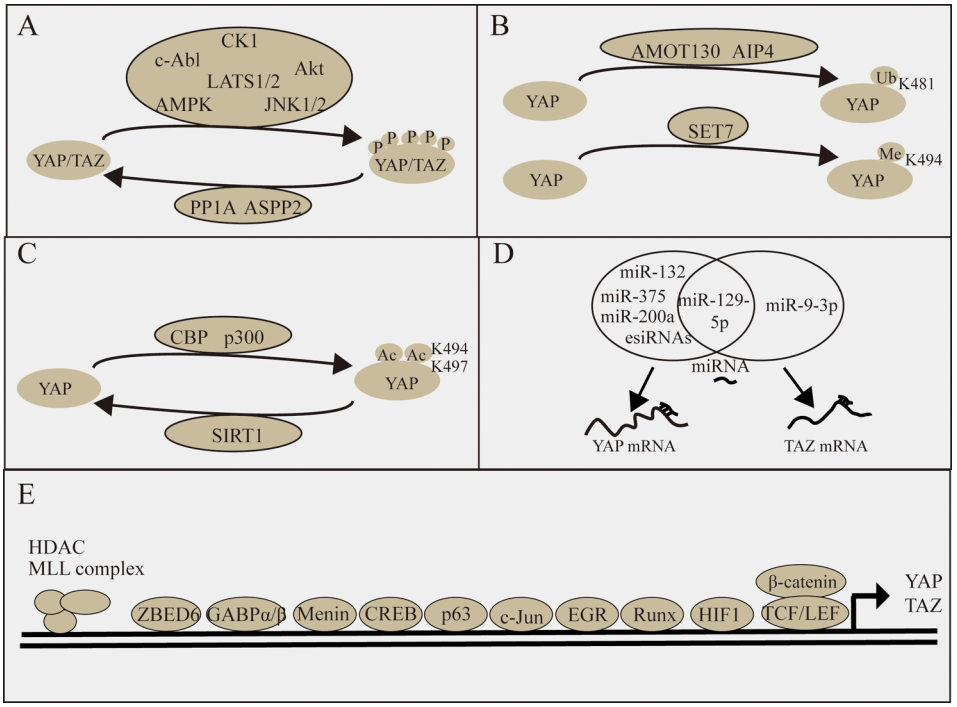

Figure 2. Ways of regulation of YAP/TAZ: (A) YAP/TAZ is phosphorylated by proteins such as LATS1/2, CK1, c-Abl, Akt, JNK1/2, and AMPK. On the other hand, PP1A and ASPP2 dephosphorylate YAP/TAZ. (B) YAP is methylated at K494 by SET-7, whereas the adaptor protein Amot130 works coordinately with the Nedd4 (neural precursor cell expressed developmentally down-regulated 4) family ubiquitin ligase AIP4 to promote the ubiquitination of YAP. (C) YAP is acetylated by CBP/p300 acetyltransferase, occurs on conserved C-terminal lysine residues, and can be reversed by SIRT1 deacetylase. (D) MicroRNAs mediated YAP/TAZ mRNA degradation. (E) Several transcription factors and cofactors regulate the transcription of YAP/TAZ in nucleus.

transcription factors and other transcriptional cofactors. In addition, YAP/TAZ has also been found to regulate the expression of noncoding RNAs including miRNAs and long noncoding RNAs (lncRNAs).

The current view in YAP/TAZ is primarily regarded as oncogene. However, YAP/TAZ also functions as tumor suppressor in certain cancers. Current evidence suggests that oncogenic or tumor suppressive functions of YAP/TAZ depend on the transcription factors binding with YAP/TAZ. Another point worth mentioning is that YAP/TAZ does not always function as transcriptional coactivators. In certain instances, YAP/TAZ also operates as transcriptional corepressors for additional target genes.[50,51] The best-described transcription factors regulated by YAP/TAZ are the TEAD/TEF family transcription factors.[52,53] Besides TEAD, YAP/TAZ also interacts with other transcription factors, including Runx1/2,[50,54] Smad2/3/4,[23,31,43,55] Smad1/7,[56,57] p73,[58−60] p63,[60−62] HIF1α/β,[44−46,63] Fos,[18] ErbB4,[64] EGR1,[15,16] C/EBPα,[65] CREB,[6,66] FOXM1,[67] TBX4/5,[2,68] OCT4,[69] Gli1,[70] Glis3,[71] KLF5,[72−74] TTF-1/Nkx-2.1,[75] Pax3/8,[76,77] PPARγ[50] and MyoD,[78] to regulate the transcription of target genes. In addition, YAP/TAZ also interacts with other proteins that are required for regulation of downstream target genes. A recent study reported that ARC105, a component of the mediator complex, associates with TAZ in the nucleus, thus controlling Smad nucleocytoplasmic localization.[55] Other reports showed that YAP interacts with β-catenin on the promoter of target genes.[2,79,80] Intriguingly, YAP/TAZ can also regulate gene expression at the epigenetic level. Recent studies showed that YAP/TAZ directly associates with histone acetyltransferase (HAT) p300,[23,68] SWI/SNF chromatin-remodeling complex (BRM),[81] transcriptional corepressors NCoR1,[10,82] and NuRD[51,69] to regulate numerous target genes.

Global suppression of miRNAs is commonly observed in cancers. A recent study revealed that YAP/TAZ governs miRNA biogenesis in a cell density-dependent manner. At low cell density, nuclear YAP/TAZ represses miRNA biogenesis through sequestering the microprocessor component p72 (DDX17). At higher cell density, YAP/TAZ is inactivated by exclusion from the nucleus, thereby facilitating p72 enhances pri-miRNA processing.[83] Interestingly, another report showed that cell contact-induced YAP/TAZ cytoplasm retention decreases Dicer levels and leads to aberrant maturation of miRNAs through regulating the Let-7/LIN28 axis.[84] The reasons for these discrepancies are currently not well understood. In addition, other studies reported that YAP/TAZ can also regulate the expression of lncRNAs such as *MALAT1*,[80] *UCA1*,[9] *MT1DP*,[7] and *H19*.[19]

■ WAYS OF REGULATION OF YAP/TAZ

As the centerpiece of Hippo pathway, the expression of YAP/TAZ can be regulated through epigenetic, transcriptional, and post-transcriptional ways, including phosphorylation and dephosphorylation, methylation, acetylation and deacetylation, ubiquitination, and miRNAs mediated degradation. This may provide invaluable insights into regulation of organ size and cancer development (Figure 2).

Phosphorylation, Methylation, Acetylation, and Ubiquitination. Besides phosphorylation-dependent inhibition of YAP/TAZ by the canonical Hippo pathway, YAP/TAZ is also phosphorylated by other proteins such as CK1,[85] c-Abl,[59] Akt,[58] JNK1/2,[60,86] and AMPK.[87] On the other hand, recent studies

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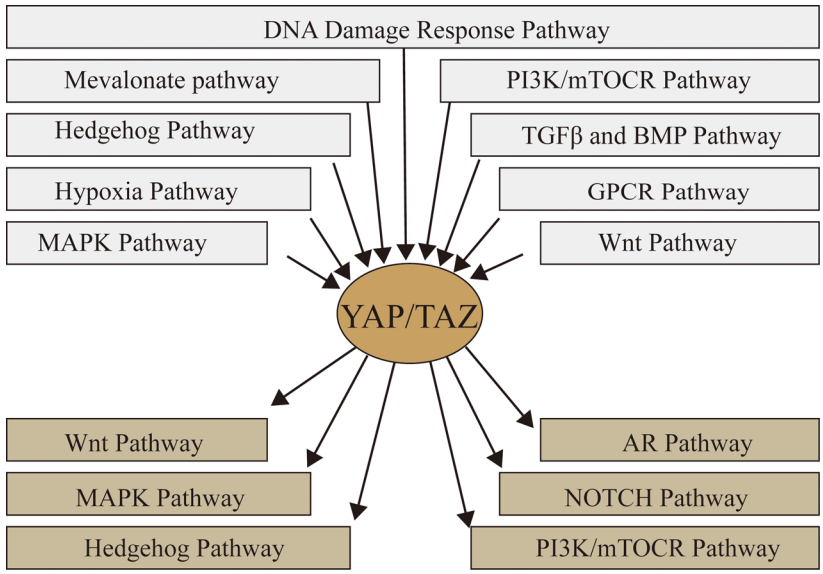

Figure 3. Summary of YAP/TAZ signaling interactions in mammals. MAPK, Wnt, TGFβ/BMP, GPCR, PI3K-mTOR, Hedgehog, Mevalonate pathway, Hypoxia pathway and DNA Damage Response Pathway regulate the Hippo signaling pathway via YAP/TAZ. On the other hand, the Hippo signaling pathway can also modulate MAPK, Wnt, PI3K-mTOR, Hedgehog, Notch, and AR pathway. See text for further details.

have shown that PP1A dephosphorylates YAP/TAZ and dissociates it from 14-3-3 binding. What is more, ASPP2 facilitates the interaction between TAZ and PP1A, thus leading to its nuclear retention and transcriptional activation.[88,89] Several other modifications have been reported to play regulatory roles on YAP in various contexts. YAP is reported to be methylated at K494 by Set-7, leading cytoplasmic retention.[90]Furthermore, it was recently discovered that the adaptor protein Amot130 works coordinately with the Nedd4 family ubiquitin ligase AIP4 to promote the ubiquitination of YAP.[91] Besides phosphorylation, methylation and ubiquitination, in respond to DNA-damaging stimuli *S*N2 alkylating agents, YAP translocates to cell nuclei and is acetylated by CBP/p300 acetyltransferase, which can be reversed by SIRT1 deacetylase. Importantly, this acetylation deacetylation cycle may be essential for YAP transcription coactivator activity.[92]

MicroRNAs Mediated Degradation. MicroRNAs are important regulators in gene expression at post-transcriptional level. Recent studies have showed that miR-132[3] and miR-375[4] significantly reduce the expression of *YAP* through a specific target site within the 3′untranslated region (3′ UTR) of *YAP* mRNA. Similarly, it has been reported that miR-129-5p directly represses *YAP/TAZ* expression, which leads to the inactivation of TEAD and subsequently inhibits ovarian cancer cell proliferation, survival, and tumorigenicity.[93] Another report has shown that overexpression of miR-200a promotes whereas inhibition of miR-200a suppresses anoikis resistance and tumor metastasis-promoting effect via reducing the expression of *YAP*.[94] In addition to that, *TAZ* is negatively regulated by miR-9-3p at post-transcriptional level. Overexpression of miR-9-3p using a mimic decreased *TAZ* expression and resulted in suppressed cell proliferation in HCC.[95] Interestingly, a recently study of Gao et al.[96] showed that a hairpin within *YAP* mRNA 3′ UTR functions in regulation at post-transcription level through generating endogenous siRNAs (esiRNAs), which is able to target mRNA 3′ UTR of *NF2* and *YAP* mRNA 3′ UTR itself, providing a new insight into the mechanism of mRNAs in regulatory function.

Regulation of YAP/TAZ Transcription. The ways of regulation of *YAP/TAZ* mRNA transcription have been reported in a number of different mechanisms. The transcriptional factors, including HIF-1α,[63] ZBED6,[97] ERG,[15] GABPα/GABPβ,[98] CREB,[6,66] FoxA1,[7] c-Jun,[86] ΔNp63,[99] and Runx2,[7] have been reported to regulate the expression of YAP/TAZ. Interestingly, it has also been revealed that β-catenin associated with TCF/LEF directly regulate *YAP* expression through binding a DNA enhancer element within the first intron of the *YAP* gene.[42] On the other hand, a recent study reported that Menin, as a scaffold protein, regulates *YAP* transcription through epigenetic mechanisms, which is regulated by the menin−mixedlineage leukemia (MLL) complex.[100] It has also been reported that the HDAC inhibitor LBH589 and the BET protein inhibitor I-BET151 has synergistic effects in the treatment of melanoma in vitro and in vivo, which are associated with downregulation of *YAP* mRNA expression.[101]

■ CROSS-TALK WITH OTHER SIGNALING PATHWAY

The Hippo kinase cascade is the major regulator of YAP/TAZ by phosphorylating YAP/TAZ and thereby inhibiting their nuclear activities. However, many studies have revealed YAP/TAZ as a nexus and integrator for multiple prominent pathways such as MAPK, Wnt, TGFβ/BMP, GPCR, PI3K-mTOR, Notch, Hedgehog, Mevalonate pathway, AR and Hypoxia pathway, identifying new upstream-downstream regulatory components that coordinately control the progression of cancer (Figure 3).

MAPK Pathway. Tumor formation often involves the inappropriate activation of regulatory pathways that play vital roles in controlling growth and cell fate decisions. One such pathway is MAPK signaling, which has been implicated in some deadly cancers. Three major groups of distinctly regulated MAPK cascades are known in mammals: ERK1/2, JNK, and p38 MAPK. (1) Several studies have been reported that EGFR and Hippo signaling create a positive feedback loop. Hong et al.[102] showed that EGFR/Ras pathway stabilize YAP through downregulation of the ubiquitin ligase complex substrate recognition factors SOCS5/6. Moreover, Urtasun et al.[103]

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revealed that *YAP* expression can be up-regulated through EGFR activation. On the other hand, other reports showed that YAP induces the expression of epidermal growth factor receptors (*EGFR, ERBB3*) and production of EGF-like ligands (*HBEGF, NRG1, NRG2*, and *AREG*), which, in turn, activates YAP and stimulates cancer cell growth.[13] (2) A recent study showed that expression of activated forms of RAF or MEK increases *YAP* levels and reduces YAP phosphorylation through promoting phosphorylation of the Ajuba family protein WTIP binding to LATS.[35] Shao et al.[104] also stated that YAP rescues cell death in KRAS dependent cells upon suppression of KRAS and is required for KRAS-induced cell transformation. Consistently, other reports[14,18] revealed that oncogenic RAS induces posttranscriptional modification of YAP through the MAPK pathway and augments its transcriptional activity. Furthermore, Li et al.[105] showed that MAP4K4 interacts with LATS and promotes inhibition of YAP. On the other hand, several studies have been reported that YAP acts upstream of ERK1/2 to promote cell survival, migration, and invasion in cancer cells.[49,106] (3) It has been shown that JNK1/2 as kinases that robustly phosphorylate YAP and regulate its function in apoptosis. Moreover, Danovi et al.[86] showed that down-regulation of c-Jun using siRNA resulted in reduced levels of endogenous YAP. In addition, other reports showed that JNK promotes binding between LIMD1 and LATS1 through direct phosphorylation of LIMD1, in turn, inhibits YAP.[107,108] (4) Interestingly, it has also been reported that YAP negatively controls phosphorylation of MAPK14/p38 at Thr180/Tyr182 (p-p38) through inhibition of BTRC expression.[6] Taken together, MAPK and Hippo signaling regulate each other and form a positive feedback loop in human cancers.

Wnt/β-Catenin Pathway. Another well studied signaling pathway, Wnt/β-Catenin pathway, is even more closely integrated with Hippo signaling. Growing evidence revealed that the Hippo pathway regulates Wnt/β-Catenin signaling through multiple mechanisms. Heallen et al.[79] revealed that YAP and β-catenin are recruited to Sox2 and Snai2 genes through TEAD and TCF transcription factors, respectively. Consistently, Rosenbluh et al.[2] showed that β-catenin forms a ternary complex with YAP and the transcription factor TBX5. In addition, it has been reported that loss of Hippo pathway activity leads to increased nuclear TAZ and reduced TAZ-DVL binding in the cytoplasm, which results in increased CK1-mediated phosphorylation of DVL, β-Catenin nuclear accumulation, and induction of Wnt-target genes.[109] This is also confirmed by Barry et al.[110] The study revealed that cytoplasmic YAP restricts elevated Wnt signaling partly by limiting the activity of DVL. Imajo et al.[111] also unveiled that phosphorylated YAP/TAZ suppress Wnt signaling by directly binding to β-catenin and retaining it in the cytoplasm. Moreover, Tsutsumi et al.[112] showed that dephosphorylated YAP/TAZ promotes nuclear translocalization of SHP2, which in turn stimulates TCF/LEF- and TEAD-target genes through promoting tyrosine dephosphorylation of parafibromin. On the other hand, Azzolin et al.[40] revealed that in the absence of Wnt signaling, GSK3-phosphorylated β-catenin serves as a critical scaffold for TAZ recognition by the β-TrCP E3 ubiquitin ligase, suggesting that Wnt signaling regulates TAZ in a way that depends on the β-catenin destruction complex. However, Cai et al.[41] showed a novel function of APC as a scaffold protein that facilitates the phosphorylation of YAP/TAZ by interacting with Sav1 and LATS1. Furthermore, Wang et al.[65] revealed that the tribbles homologue 2 (TRIB2), a direct target of Wnt/TCF, promotes protein stabilization of the YAP through interaction with the β-TrCP ubiquitin ligase. Interestingly, a recent study showed that β-Catenin/TCF4 complexes directly regulate *YAP* gene expression through binding a DNA enhancer element within the *YAP* gene.[42] Taken together, these data suggest a closely integration between the Hippo and Wnt/β-Catenin pathways.

TGF-β/SMADs and BMP/SMADs Pathway. Several lines of evidence indicate that YAP/TAZ promotes aggressive tumorigenic properties through interconnection with TGF-β/SMADs or BMP/SMADs signaling pathway. Mahoney et al.[113] showed that nuclear YAP/TEAD complexes cooperate with TGFβ-induced cues to control the expression and distribution of Sox2 in airway epithelial cells. Moreover, Fujii et al.[23] revealed that dephosphorylated YAP translocates into the nucleus, where it interacts with TEAD, SMAD3, and p300, forming a complex on the *CTGF* promoter. Similarly, Hiemer et al.[9] unveiled that like YAP/TAZ, the TEAD transcription factors bind with TGFβ-induced SMAD2/3 in the nucleus, directly regulating target genes including *NEGR1* and *UCA1*. This was confirmed by another study with that TGFβ stimulates formation of YAP/TAZ-Smad2/3 complexes in HaCaT keratinocytes. Surprisingly, YAP/TAZ-Smad2/3 complexes cannot be detected in Smad4-deficient HT-29 cells. Further study revealed that Smad4 is not essential for the YAP−Smad2/3 interaction, suggesting that there could be other mechanisms responsible for the lack of YAP−Smad2/3 complexes in HT-29 cells.[114] On the other hand, Varelas et al.[31,55] showed that YAP/TAZ dominates the localization of SMAD complexes in response to cell density-mediated formation of Crumbs polarity complex or TGFβ stimulation. However, it has been reported recently that nuclear translocation of SMAD2/3 in response to TGFβ is independent of YAP/TAZ nuclear exclusion induced by cell density in polarized epithelial cells.[115] Sequentially, another study showed that Hippo signaling pathway activation, which promotes YAP/TAZ cytoplasmic sequestration and reduces SMAD activation, is an early event in polarizing epithelial cells. Prolonged culture can lead to the basal restriction of TGFβRs, thus suppressing the activity of TGFβ/SMAD pathway.[43] These results suggest that receptor sequestration and Hippo control of activated Smads are distinct mechanisms controlling Smad activation in polarized epithelia. In addition to TGFβ, several studies also showed that YAP affects BMP signaling. Sun et al.[32] showed that substrate rigidity regulates the phosphorylation of YAP and coincided with nucleocytoplasmic shuttling of Smad 2/3 and Smad 1/5/8. In addition, another report revealed that YAP interacts with Smad1 at the same binding site specially required by Smurf1, which belong to the HECT family of E3 ubiquitin ligases. Furthermore, YAP is reported to enhance Smad1-dependent transcription and is required for BMP suppression of neural differentiation of mouse embryonic stem cells.[56] Altogether, various mechanisms have described the interconnection between the Hippo pathway and the TGF-β/SMADs or BMP/SMADs signaling pathway.

PI3K/mTOR Pathway. The Hippo and PI3K/mTOR pathways are two major signaling pathways which coordinately regulate cell growth and proliferation in Drosophila and mammals and as such, it is expected that various crosstalk mechanisms exist between these pathways. AKT is reported to be a potential regulator of Ser127 phosphorylation and cellular distribution of YAP.[58,99,116] Moreover, Fan et al.[117] revealed that the PI3K-PDK1 pathway also mediates YAP nuclear

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translocation and transcriptional activation in response to EGF and LPA. A subsequent study showed that mTORC2 promotes YAP signaling via phosphorylating the YAP negative regulator AMOTL2[20] On the other hand, it has been reported that the abundance of PI3K and phosphorylation of Akt are increased in YAP overexpressed cardiomyocytes.[106,118] Furthermore, Tumaneng et al.[119] showed that YAP transcriptionally regulates miR-29 family, which inhibits *PTEN* by targeting its 3′UTR. The inhibition of PTEN by YAP activates PI3K signaling and results in activation of both mTORC1 and mTORC2. Similarly, Lin et al.[120] showed that YAP and TEAD, occupying a conserved enhancer within the first intron of *Pik3cb*, a catalytic subunit of PI3K, increases *Pik3cb* expression, which further induces PI3K/mTORC pathway activation. In addition, Kim et al.[51] showed that YAP/TAZ functions as transcriptional corepressors represses numerous target genes, including DDIT4, a well-established inhibitor of mTORC1, thus promoting mTORC1 activity. Taken together, these observations revealed that the Hippo pathway also exhibits multiple layers of interaction with PI3K/mTORC pathway.

GPCR Pathway. G protein-coupled receptor (GPCR), the largest cell surface receptor family in eukaryotes, is involved in a wide range of physiological regulatory activities and plays important roles in cancer development. Notably, recent studies reported that the Hippo pathway is strongly regulated by GPCR signaling. GPCR signaling can either activate or inhibit YAP activity through various ways including LATS-dependent, MST, and LATS-dependent and MST and LATS-independent manner. Yu et al.[34] first revealed that the Hippo pathway is regulated by GPCR signaling. LPA and S1P act through G12/13- or Gq/11-coupled receptors to repress LATS1/2 thereby resulting in YAP activation. In contrast, stimulation of Gs-coupled receptors by glucagon or epinephrine increases LATS1/2 kinase activity, thereby resulting in inhibition of YAP function. Other GPCRs, including AT1R,[121] PARs,[122] and GPER,[123] also have been reported to regulate the activity of YAP/TAZ dependent on LATS. In addition, a recent study also showed that the Hippo-YAP pathway function as a mediator in mutant Gq/11-induced uveal melanoma tumorigenesis.[21] Independently of these reports, GPCR signaling can regulate YAP activity dependent on MST and LATS. Fan et al.[117] showed that in the absence of growth factors such as LPA and serum, GPCRs inhibit PI3K and PDK1, which form a complex with Hippo pathway proteins including Sav1, MST1, and LATS1, thereby phosphorylating YAP and inducing it cytoplasm retention. However, it has also been reported that LPA dose- and time-dependently induces YAP dephosphorylation in human EOC cell lines via G13, RhoA, ROCK and PP1A. In contrast to results in HEK293 cells, LPA do not inhibit MST and LATS kinase in EOC cells.[12] This discrepancy may be due to the various cell background. Further investigation should be carried out to investigate the detail connection between GPCR signaling and the Hippo pathway.

Notch Signaling Pathway. Accumulating evidence supported the notion that the Notch pathway, interacting with the Hippo signaling cascade, increases the likelihood of cancerous transformation. Genetic analyses in Drosophila have also linked the Hippo pathway and Notch signaling. The Fat-Hpo signaling has been shown to regulate the expression of Notch receptor and Notch ligand Delta1.[124−126] On the other hand, the four-jointed (fj) gene, a target gene of Notch signaling, has been showed to regulate the Hpo pathway by directly phosphorylating fat.[127] In vertebrates, Camargo et al.[128] revealed that YAP induced loss of differentiation and expansion of intestinal progenitor cells at least partially through activation of the Notch pathway, as indicated by the increased expression of HES1 after YAP activation. Furthermore, several reports identified that YAP/TEAD directly regulates transcription of Notch1/2, Jag1, and the Notch target genes Hes1 and Sox9.[5,129] Interestingly, a recent study showed that YAP is an important downstream effector of the Notch pathway in neural stem cell self-renewal. Activation of Notch pathway results in elevated *YAP* and *TEAD2* mRNA levels, suggesting that *YAP* and *TEAD2* are the direct targets of RBPJ/N1ICD.[130] Taken together, these data revealed the mutual cross-regulation between the Hippo and Notch pathways.

Hedgehog Signaling Pathway. Evidence of crosstalk between the Hippo and Hedgehog pathways has been widely reported in multiple cancers. A recent study demonstrated that Gli2 knockdown can rescue the neuronal differentiation defect in YAP overexpressing cells, suggesting that Hh signaling functions downstream of YAP to inhibit neuronal differentiation. Similarly, ectopic YAP expression increases the transcription of Ptch1, a downstream target of the Hh signaling.[131] Contradictory to this report, Tariki et al.[70] showed that YAP directly interacts with and negatively controls Gli1, thereby repressing Hh pathway target genes. Despite this negative regulation, Hh signaling facilitates YAP activity post-transcriptionally by increasing its protein levels, resulting in a negative feedback loop. Furthermore, PAR activation promoted simultaneous activation of YAP and Gli1 that results in increased cell proliferation. Furthermore, another study confirmed that aberrant Hh signaling induces *YAP* and *H19* overexpression during osteosarcoma development.[19] Consistently, it has been reported that *YAP* mRNA and protein is upregulated in Shh-driven medulloblastomas in both humans and mice. In addition, another study revealed that Shh induces *YAP* expression and nuclear localization through stabilizing IRS1, which interacts with YAP in cerebellar granule neuron precursors.[22] Altogether, these observations suggest that the Hippo and Hedgehog pathways form a close feedback loop during the development of human cancers.

Mevalonate Pathway. Statins, the specific inhibitors of 3-hydroxyl-3-methylglutaryl-CoA reductase (HMGCR) that is a rate-limiting enzyme in the mevalonate pathway, have been found to induce cytoplasmic relocalization of YAP/TAZ, suggesting that the mevalonate pathway closely integrated with the Hippo pathway. Wang et al.[49] revealed that the mevalonate metabolic pathway, or its inhibitor simvastatin, modulates YAP nuclearcytoplasmic distribution via Rho GTPase activation and actin cytoskeleton rearrangement independent of MST and LATS kinase activity. Similarly, Sorrentino et al.[48] showed that YAP/TAZ activity is controlled by the SREBP factor, the upstream transcriptional regulators of many enzymes in the mevalonate cascade. Mechanistically, the mevalonate pathway provides the geranylgeranyl pyrophosphate (GGPP) essential for activation of Rho GTPases, which in turn activate YAP/TAZ by inhibiting its phosphorylation. Moreover, this was confirmed by another study with that YAP mediates the mevalonate pathway induced PBK geranylgeranylation, thereby promoting breast cancer cell proliferation.[8] Independently of these reports, it has been also showed that the Hippo-YAP/TAZ pathway is essential for GGylation-dependent breast cancer cell proliferation and migration. Further study revealed that inhibition of mevalonate pathway by atorvastatin or GGylation by GGTI-298 enhances phosphorylation of

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MST1/2 and LATS1, suggesting that the mevalonate pathway activates YAP/TAZ dependent on the canonical Hippo pathway.[132] There is a discrepancy with previous reports about whether the effects of statins and GGylation on YAP/TAZ depend on MST1/2 and LATS1. Such discrepancy suggests that further investigation should be carried out to verify the relationship between the Hippo and mevalonate pathways.

Hypoxia Pathway. Hypoxia is an important microenvironmental factor that promotes cancer progression and metastasis. The activation of HIF-1, the principal transcriptional regulator of the responses to hypoxia, is correlated with poor prognosis and chemotherapy resistance of human cancers. Recently, several studies reported that TAZ functions as a coactivator of HIF-1 under hypoxia.[11,46] Xiang et al.[11] revealed that direct protein−protein interaction between HIF-1α and TAZ has reciprocal effects: HIF-1α physically interacts with TAZ and stimulates transactivation mediated TAZ/TEAD and TAZ functions as a coactivator for HIF-1-dependent gene transcription. What is more, Maroni et al.[46] stated that the human homologue of MDM2 (HDM2) interacts with WW-domain containing oxidoreductase (Wwox), preventing HIF-1α degradation under hypoxia, thus, translocation into nuclei and binding with TAZ, inducing the expression of E-cadherin in bone metastatic cells. In addition, emerging evidence showed that the E3 ubiquitin ligase SIAH2 promotes LATS2 ubiquitylation and degradation in response to hypoxia, causing YAP/TAZ dephosphorylation and nuclear translocation. In the nuclei, YAP/TAZ interacts with HIF1α and promotes its stabilization under hypoxia.[45,63] Moreover, Xiang et al.[63] also reported that HIF-1, but not HIF-2, binds directly to the *WWTR1* gene and activates transcription of *TAZ* and *SIAH1*. On the other hand, Yan et al.[47] reported that hypoxic conditions had opposing roles in the level of p-YAP and p-TAZ. Hypoxia induces up-regulation of pTAZ and down-regulation of pYAP in several cell lines derived from different cancers. Taken together, the coordination of YAP/TAZ and HIF1α in response to hypoxia plays a vital role in human cancers, providing insight into therapeutic strategies against diseases that are associated with aberrant activities of these pathways.

Androgen Receptor Signaling Pathway. It is now well established that the AR signaling pathway plays a critical role in prostate cancer development and progression and remains a relevant target in patients with metastatic castration-resistant prostate cancer (mCRPC). More recently, it has been reported that ectopic expression of YAP promotes cellular transformation, motility, and invasiveness in immortalized prostate epithelial cells and induces migration, invasion, and androgen-insensitive growth in cancerous prostate cells. What is more, the AR targets PSA, NKX3.1, PGC-1, and KLK2 are all greatly induced by YAP overexpression, while YAP knockdown reduces basal levels of PSA and NKX3.1 mRNA and partially blocks the AR targets induced by R1881(a testosterone analogue), suggesting that YAP promotes AR activation.[17] In addition, another study has been revealed that MST1 antagonizes AKT-mediated AR activation via a mechanism that involves a tripartite protein complex formation between MST1, AR, and AKT1.[133] Therefore, these findings suggest that the Hippo pathway functions as a novel negative regulator of AR signaling. However, whether androgen signaling could affect YAP activity needs further study.

In addition to the pathways described above, some other pathways also integrated with Hippo signaling such as the DNA Damage Response Pathway, AMPK signaling pathway, and JAK-STAT pathway. In response to DNA damage, c-Abl directly phosphorylates YAP at position Y357, which in turn displays higher affinity to p73 and selectively coactivates p73 proapoptotic target genes.[59,134] Moreover, endogenous YAP is acetylated in response to a specific type of DNA damage.[92] Mo et al. identified that cellular energy stress can inhibit YAP by two mechanisms: AMPK inhibits YAP activity via activation of the LATS and directly induces YAP phosphorylation at Ser 94, a residue essential for the interaction with TEAD, thus disrupting the YAP−TEAD interaction.[87] In addition, several reports have shown that loss of Hpo signaling or overexpression of Yki in Drosophila epithelial cells increases the production of cytokines of the upd family that activate the JAK-STAT pathway in intestinal epithelial cells (ISCs), suggesting that Yki activates JAK-STAT signaling.[105,135,136] However, a recent study reported that YAP is not required for STAT3 activation in mammal ISCs.[36] Further understanding of this discrepancy will require additional studies.

CONCLUSION

A huge amount of information has accumulated and our understanding of the molecular mechanism and the physiological function of the Hippo signaling pathway in tumors have increased orders of magnitude in the past several years. These studies have firmly established the Hippo signaling pathway, especially the core effector YAP/TAZ, as a central mechanism that regulates tumor growth in mammals. Understanding the organ and context specific functions of the Hippo pathway in human cancers is essential to the development of effective and personalized therapies. In this review, we summarize the latest findings on events upstream and downstream of YAP/TAZ and the ways of regulation of YAP/TAZ. In addition, we also focus on the crosstalk between the Hippo pathway and other tumor-related pathways such as the MAPK, Wnt, TGFβ/BMP, GPCR, PI3K-mTOR, Notch, Hedgehog, Mevalonate pathway, AR, Hypoxia pathway, and DNA Damage Response Pathway. The discoveries of the events upstream and downstream of YAP/TAZ greatly expanded the complexity of YAP/TAZ regulation and have sparked interest in the development of potential therapeutics that could target key effectors of the signaling cascade. Not surprisingly, members of the Hippo pathway are emerging targets in anticancer treatments. Verteporfin (VP), a member of the porphyrin family, binds to YAP and inhibits its interaction with TEAD.[52] Recently, verteporfin was shown to suppress growth in many types of human cancers.[21,137] Intriguingly, a newly characterized tumor suppressor gene, VGLL4, directly competes with YAP for binding TEADs, suggesting that disruption of YAP-TEADs interaction by a VGLL4-mimicking peptide may be a promising therapeutic strategy against YAP-driven human cancers.[138] In addition, other drugs targeting other members of the Hippo signal transduction network, such as GPCRs,[21] the mevalonate pathway,[8,48,139] the Notch pathway[128] and the MAPK pathway,[140] have also been reported. Taken together, continued molecular exploration of the Hippo pathway is likely to be an active and exciting topic.

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■ ABBREVIATIONS
AMOT, angiomotin; F-actin, filamentous actin; ECM, extra cellular matrix; βPix, PAK-interacting exchange factor beta; Ang II, angiotensin II; PDK, phosphoinositide-dependent kinase; LIF, leukemia inhibitory factor; miRNA, microRNA; 3′ UTR, 3′untranslated region; esiRNAs, endogenous siRNAs; lncRNAs, long noncoding RNAs; ZBED6, zinc finger, BED-type containing 6; MEN1, endocrine neoplasia type 1; MLL, menin-mixed lineage leukemia; C/EBPα, CCAAT-enhancer-binding protein α; CREB, cyclic adenosine monophosphate response element-binding protein; FOXM1, forkhead box M1; TBX, T-box transcription factor; KLF, Krüppel-like factor; TTF-1, Thyroid transcription factor-1; PPARγ, peroxisome proliferator-activated receptorγ; H3K4, histone H3 lysine 4; GSK-3β, glycogen synthase kinase-3β; APC, adenomatous polyposis coli; CK1, casein kinase 1; DVL, Dishevelled; TβRI, TGF-β receptor type I; GPER, G protein-coupled estrogen receptor; GGTIs, GGTase inhibitors; AR, androgen receptor

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