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REVIEW

Non-hippo kinases: indispensable roles in YAP/TAZ signaling and implications in cancer therapy

Jun Zhu[1] · Tiantian Wu[1] · Qiong Lin[1]

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Abstract

The transcriptional co-activators Yes-associated protein (YAP) and PDZ-binding domain (TAZ) are the known downstream effectors of the Hippo kinase cascade. YAP/TAZ have been shown to play important roles in cellular growth and differentiation, tissue development and carcinogenesis. Recent studies have found that, in addition to the Hippo kinase cascade, multiple non-Hippo kinases also regulate the YAP/TAZ cellular signaling and produce important effects on cellular functions, particularly on tumorigenesis and progression. In this article, we will review the multifaceted regulation of the YAP/TAZ signaling by the non-Hippo kinases and discuss the potential application of the non-Hippo kinase-regulated YAP/TAZ signaling for cancer therapy.

Keywords YAP/TAZ · Non-hippo kinases · Kinase inhibitors · Cancer therapy

Abbreviations

ALL	Acute lymphoblastic leukemia
AMPK	AMP-activated protein kinase
CCA	Cholangiocarcinoma
CDK	Cyclin-dependent kinase
CK1	Casein kinase 1
CML	Chronic myeloid leukemia
EGFR	Epidermal growth factor receptor
GBM	Glioblastoma
GSK3	Glycogen synthase kinase 3
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinomas
IHC	Immunohistochemistry
IKK	IκB kinase
LATS1/2	Large tumor suppressor kinase 1/2
LKB1	Liver kinase B1
MAP4Ks	Mitogen-activated protein kinase kinase kinase kinases
MAPKs	Mitogen-activated protein kinases
MOB1	Mps one binder kinase activator 1
MPM	Malignant pleural mesothelioma
MST1/2	Mammalian Ste20-like kinase 1/2
mTOR	Mammalian target of rapamycin
NDR1/2	Nuclear Dbf2-related kinase 1/2
NGF	Nerve growth factor
NF-κB	Nuclear factor-κB
NLK	Nemo-like kinase
NSCLC	Non-small cell lung cancer
NTRK1	Neurotrophic receptor tyrosine kinase 1
PDGFR	Platelet derived growth factor receptor
PDK1	3-phosphoinositide-dependent protein kinase-1
PDX	Patient-derived xenograft
Ph +	Philadelphia chromosome-positive
ROCK1/2	Rho-associated protein kinase 1 and 2
RTK	Receptor tyrosine kinase
SAV1	Salvador homologue 1
SFK	Src family tyrosine kinase
SH3	Src homology domain 3
STK38	Serine/threonine kinase 38
TCF/LEF	T-cell factor/lymphoid enhancer factor
TEADs	TEA domain family members
TFIIH	Transcriptional initiation factor II-H
TKI	Tyrosine kinase inhibitor
TNBC	Triple-negative breast cancer
UPS	Ubiquitin-proteasome system
VGLL4	Vestigial-like protein 4

✉ Qiong Lin
qlin@ujs.edu.cn

[1] School of Medicine, Jiangsu University, 301 Xuefu Road, Zhenjiang, China

Introduction

YAP/TAZ, the mammalian homologues of Yorkie in *Drosophila melanogaster*, are vital effectors of the Hippo pathway to regulate cell proliferation and tissue growth [1]. As transcriptional co-activators, YAP/TAZ are found to mediate both differentiation and immortalization signaling pathways upon interaction with functionally differentiated transcription factors, such as TEADs, p53/p73, SMAD and RUNX2 [2]. For example, YAP interacts with TEAD and β-catenin-TCF3 to induce *Oct4* transcription thus maintain stemness or binding to p53/p73 which can promote BMP4 expression during differentiation [3]. YAP/TAZ may participate in immortalization by activation transcription of CDK6 and hTERT [4, 5], the two key proteins that are involved in immortalization. Thus, YAP/TAZ have multifaceted effects on differentiation and immortalization dependent on their transcriptional context. Apparently, differences between differentiation and immortalization regulated by the YAP/TAZ signaling pathways are determined by the distinct transcription factors and the specific downstream target genes activated by YAP/TAZ.

Dysregulation of YAP/TAZ signaling frequently observed in various cancers, commonly related to uncontrolled YAP/TAZ activity. Inappropriate activation of YAP/TAZ results in up-regulated expression of target genes that have profound effects on cell proliferation, migration, metabolism and tumorigenesis [6]. It is known that YAP/TAZ are regulated by the Hippo kinase cascade. Recently, mounting research reports found that many kinases that are not in canonical Hippo kinase cascade regulate the YAP/TAZ signaling. We categorize these kinases as non-Hippo kinases. Most of non-Hippo kinases have function in other signaling pathways, such as mTOR signaling, MAPK and NF-κB signaling pathway. Simultaneously, they play indispensable roles in regulating the YAP/TAZ signaling in response to various stimulations or in specific contexts [7–9]. The phosphorylation of YAP/TAZ conducted by non-Hippo kinases occurs not only in the cytoplasm, but also in the nucleus. These non-Hippo kinases directly phosphorylate YAP/TAZ at specific residues to modulate the protein abundance or transcriptional activity of YAP/TAZ or indirectly regulate YAP/TAZ signaling by interacting with the Hippo kinase cascade.

In this review, we will briefly overview the canonical Hippo-YAP/TAZ signaling and focus on the non-Hippo kinase-regulated YAP/TAZ signaling. We will introduce regulation of YAP/TAZ by non-Hippo kinases in three aspects: (1) direct activation and inhibition of the YAP/TAZ signaling; (2) indirect regulation of the YAP/TAZ signaling; and (3) application of the non-Hippo kinase-regulated YAP/TAZ signaling for cancer therapy.

Overview of canonical hippo-YAP/TAZ signaling

The Hippo signaling pathway was initially identified in a genetic screen searched for overgrowth mutants in *Drosophila* and found to play important roles in modulating both cell cycle and survival [1, 2]. In mammals, core components of the Hippo signaling consist of Mammalian Ste20-like kinase 1/2 (MST1/2, the homologues to Hpo in *Drosophila*) with their adaptor protein Salvador homologue 1 (SAV1, the homologue to Sav in *Drosophila*), and large tumor suppressor kinase 1/2 (LATS1/2, the homologues to Wts in *Drosophila*) with adaptor protein Mps one binder kinase activator 1 (MOB1, the homologue to Mats in *Drosophila*) [10].

As downstream effectors of the Hippo signaling, YAP and TAZ (Yorkie in *Drosophila*) are transcriptional co-activators which shuttle between the cytoplasm and the nucleus [2]. Mechanistically, activation of MST1/2 initiates the canonical Hippo signaling (Fig. 1). The activation of MST1/2 is induced by autophosphorylation/*trans*-autophosphorylation or upstream kinases on Thr183 and Thr180 of the activation loop [11]. As adaptor protein, SAV1 forms a heterodimer with MST1 or MST2 through SARAH domains. Two SAV1-MST1/2 heterodimers form a heterotetramer via binding of SAV1 WW domains to stabilize MST1/2 *trans*-autophosphorylation status [12]. MST1/2 are the canonical upstream kinases activating LATS1/2. It has been proved that activation of LATS1/2 by MST1/2 contains three events [2, 13] (I) WWC proteins (WWC1/2/3) modulate the interaction between SAV1 and LATS1/2, in turn, SAV1 recruits MST1/2 to phosphorylate LATS1/2 at hydrophobic motif, (II) MST1/2 phosphorylate MOB1 on Thr12 and Thr35 to potentiate the interaction between MOB1 and LATS1/2, (III) the binding of MOB1 to LATS1/2 stimulates the conformational change in LATS1/2, resulting in autophosphorylation of the LATS1/2 activation loop for its full activation. Additionally, the mitogen-activated protein kinase kinase kinase kinases (MAP4Ks) phosphorylate and activate LATS1/2 as well [14]. Activated LATS1/2 phosphorylate downstream effectors YAP/TAZ, resulting in YAP/TAZ cytoplasmic retention via binding to 14-3-3 protein. YAP has five of the LATS phosphorylation consensus HXRXXS motifs, the serine residue in these five motifs, i.e. S61, S109, S127, S164 or S397, is phosphorylated by LATS. It is noted that the phosphorylation of YAP at S127 or TAZ at S89 by LATS promotes YAP/TAZ cytoplasmic sequestration by binding to 14-3-3. Phosphorylation of YAP/TAZ by LATS1/2 primes them for further phosphorylation by casein kinase 1 (CK1), causing ubiquitination and degradation of YAP/TAZ via a ubiquitin-proteasome system (UPS) [15, 16]. Once the Hippo kinase cascades are inhibited, YAP/TAZ translocate into the nucleus, interact with the TEA domain family

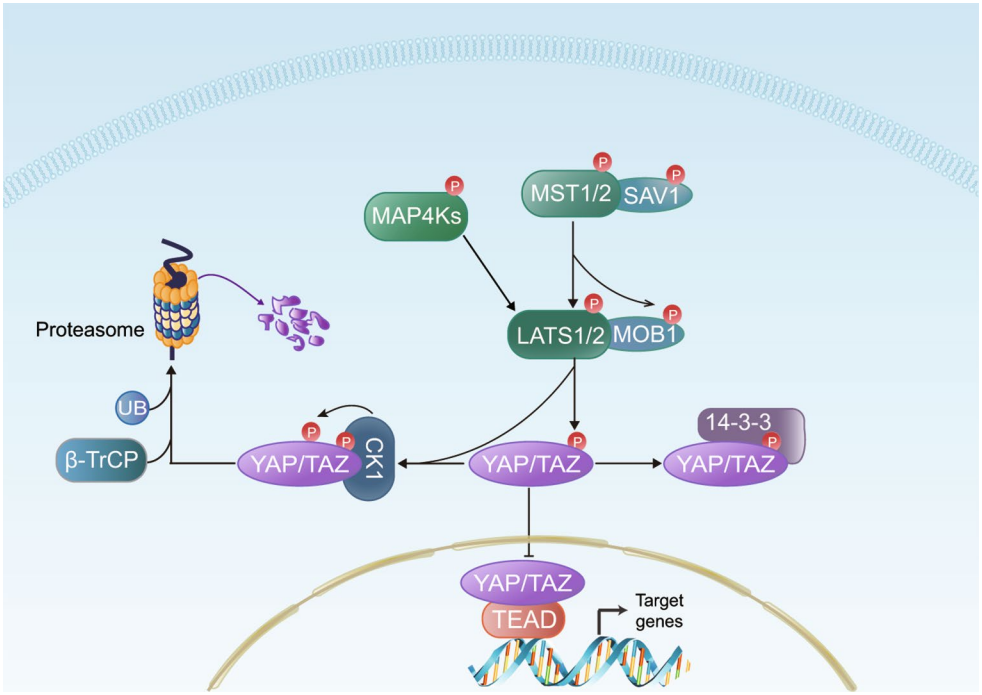

Fig. 1 The core components and regulation of Hippo-YAP/TAZ signaling. When Hippo signaling is activated, the core components of Hippo pathway are phosphorylated sequentially, phosphorylated YAP/TAZ are separated in the cytoplasm by binding to 14-3-3 protein. Further phosphorylation induced by CK1 promotes YAP/TAZ proteasome degradation. YAP/TAZ are dephosphorylated once Hippo signaling is inhibited, resulting in YAP/TAZ translocate to the nucleus and then induce target gene expression by binding to TEADs

Table 1 Non-Hippo kinases that activate YAP/TAZ

Kinase	Target	Phosphorylation site (s)	Mechanism of action	References
CDK1	YAP	T119, S289, S367	Up-regulates YAP activity	[17]
	Vgll4	S58, S155, T159, S280	Reduces Vgll4-TEAD affinity	[21]
CDK7	YAP	S128	Prevents YAP from proteasomal degradation mediated by $CRL4^{DCAF12}$ (phosphorylation in the nucleus)	[27]
	TAZ	S90	Prevents TAZ from proteasomal degradation mediated by $CRL4^{DCAF12}$ (phosphorylation in the nucleus)	[27]
CDK8	YAP	T119, S128, S289, S367	Up-regulates YAP activity	[24]
mTORC2	MST1	S438	Abrogates MST1 homodimerization and activation	[30]
	YAP	S436	Elevates YAP protein level, interaction between YAP and TEAD, enhances transactivation ability of YAP	[7]
ERK	YAP	S289, S367	Elevates YAP activity and target gene expression	[31]
	14-3-3	S37	Disassembles 14-3-3 from YAP (ERK2)	[32]
NLK	YAP	S128	Suppresses interaction between YAP and 14-3-3	[34]
MK5	YAP		Physically binds to YAP to block the proteasomal degradation induced by CK1	[35]
YES	YAP	Y407	Potentiates YAP protein stabilization, nuclear localization and target gene expression	[36]
Src	YAP	Y407	Potentiates YAP protein stabilization, nuclear localization and target gene expression	[37]
LCK	YAP	Y407	Potentiates YAP protein stabilization, nuclear localization and target gene expression	[38, 39]

members (TEAD1-4) transcription factors, induce the transcription of the target genes and produce promoting effects on cell growth, survival and tumorigenesis [2].

The non-hippo kinases that activate YAP/TAZ

In this section, we will address the non-Hippo kinases that directly activate YAP/TAZ (Table 1). The mechanisms underlying the activation of YAP/TAZ by non-Hippo kinases are summarized as following four types: (I) to disturb LATS phosphorylation at YAP S127 and TAZ S89 by occupying adjacent phosphorylation residues; (II) to obliterate the interaction between YAP/TAZ and 14-3-3 protein; (III) to block YAP/TAZ proteasome degradation executed by E3 ubiquitin ligase such as β-TrCP and $CRL4^{DCAF12}$; and (IV) to stabilize YAP/TAZ protein in both cytoplasm and nucleus.

CDKs

The phosphorylation of YAP/TAZ is observed during mitosis and is vital for normal mitotic progression. Abnormal activation of YAP contributes to mitotic defects owing to dysregulated spindle checkpoint, and leads to oncogenic phenotypes [17, 18]. There are several cyclin-dependent kinases (CDKs) reported to phosphorylate and activate YAP/TAZ.

Cyclin-dependent kinase 1 (CDK1) belongs to CDKs cell-cycle-related subfamilies, is a mitotic CDK activated during G2/M and sufficient for driving the cell cycle. Cdk1 is the only Cdk that is able to govern the cell cycle in mouse embryos even when all interphase Cdks are absent [19]. In response to anti-mitotic drugs such as taxol and nocodazole which arrest cells in G2/M, YAP is observed phosphorylated independent of Hippo kinases [17]. By administration of taxol and specific kinase inhibitors, CDK1 was identified executing the phosphorylation of YAP during G2/M arrest. CDK1 phosphorylates YAP at T119, S289 and S367 in vitro and at T119, S289 in cells. The phosphorylation mediated by CDK1 is critical for cell migration and invasion driven by YAP [17]. Besides direct phosphorylation, CDK1 may enhance YAP activity via phosphorylating vestigial-like protein 4 (VGLL4). VGLL4 is an antagonist of YAP via binding to TEAD competitively [20]. CDK1 phosphorylates VGLL4 and reduces the affinity of VGLL4 binding to TEAD [21]. Consistently, expression of the YAP-TEAD target gene *CTGF* is reduced in cells overexpressing the CDK1-phosphorylation-defective mutant of VGLL4. Hence, CDK1 acts as a positive regulator in the YAP-mediated oncogenic functions.

Cyclin-dependent kinase 8 (CDK8) belongs to the CDKs transcriptional subfamilies and is a homologue to yeast protein Srb10. CDK8 functions as an enzymatic module of the Mediator complex and involves in basal transcription process [19, 22]. Previous study found that CDK8 displays oncogenic properties in colon tumorigenesis [23]. Knockout of CDK8 leads to elevated phosphorylation of YAP at S127. Consistently, expression of the YAP target gene *CTGF* is suppressed in a LATS-independent manner [24]. Furthermore, CDK8 was identified directly phosphorylates YAP at T119, S128, S289 and S367 in vitro. In mitotic-arrest cells treated with nocodazole, CDK8 contributes to hyperphosphorylation of YAP at S128 along with phosphorylation of T119 and S289 [24]. As S128 is adjacent to the key LATS-phosphorylation site S127, phosphorylation of S128 elevates the YAP transcriptional activity. In turn, YAP activity is essential for the CDK8-driven tumorigenesis. Taken together, CDK8 modulates YAP activity as a positive activator via two mechanisms: (I) to reduce the phosphorylation of YAP at S127; and (II) directly to phosphorylate YAP at T119, S128, S289 and S367, which is vital for YAP activation [24].

Cyclin-dependent kinase 7 (CDK7) is a member of CDKs transcriptional subfamilies, the same as CDK8. CDK7 has essential roles in mediating both the cell cycle via functioning as a CDK-activating kinase and the transcription via assembly of transcriptional initiation factor II-H (TFIIH) [19, 25]. Recent research reports evaluated a functional connection of CDK7 to YAP, given that both CDK7 and YAP are co-localized in nucleus [26, 27]. Immunohistochemistry (IHC) staining in human malignant pleural mesothelioma (MPM) tissue showed a positive correlation between expression of CDK7 and YAP. Additionally, inhibition of CDK7 promotes YAP degradation thus diminishes the protein level of YAP in MPM cells [26]. Further investigation found that CDK7 phosphorylates YAP/TAZ in the nucleus and prevents YAP/TAZ from proteasomal degradation mediated by $CRL4^{DCAF12}$ E3 ubiquitin ligase complex. CDK7 phosphorylates YAP at S128 and TAZ at S90, resulting in enhancement of the YAP/TAZ protein stability and activity [27]. When treating cells with THZ1, a pharmacological inhibitor of CDK7, the level of YAP protein and the expression of the YAP target genes are repressed accordantly [26, 27]. Moreover, growth of tumor in the triple-negative breast cancer (TNBC) xenograft mice models and overgrowth of liver induced by the YAP dysregulation are suppressed upon administration of THZ1 [27].

mTOR

mTOR is a serine/threonine kinase highly conserved from yeast to mammals. Both mTOR and Hippo signaling modulate cell growth and organ size. Dysregulation of these two pathways may lead to tumorigenesis. mTOR has two multiprotein complex forms, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), with different subunits and sensitivity to rapamycin [28]. Previous study has shown that activation of mTORC1 up-regulates YAP protein expression in both cytoplasm and nucleus, in conjunction with enhanced YAP transcriptional activity [29]. mTORC2 has the similar effects on YAP. Sciarretta et al. [30] reported that mTORC2 plays a role as the upstream kinase of MST1 in heart, phosphorylates MST1 at S438 in SARAH domain, thus abrogates MST1 homodimerization and activation. Most recent research found that mTORC2 interacts with YAP via Sin1 and directly phosphorylates YAP at S436 independent of the Hippo kinases [7]. The phosphorylation of YAP at S436 by mTORC2 elevates the YAP protein level and transcriptional activity and strengthens the interaction between YAP and TEAD. YAP promotes glioblastoma (GBM) cell proliferation, migration and invasion while activated by mTORC2. Moreover, the positive correlation between expression of

Table 2 Non-Hippo kinases that inactivate YAP/TAZ

Kinase	Target	Phosphorylation site (s)	Mechanism of action	References
NDR1/2	YAP	S61, S109, S127, S164	Inhibit YAP nuclear localization and target gene transcription	[40]
AMPK	YAP	S61, S94, T119	Disrupts the interplay between YAP and TEAD (S94); inhibits YAP transcriptional activity (S61)	[42, 43]
	LATS		Activates LATS to phosphorylate YAP at S127, thus promoting YAP degradation	
TAK1	YAP	Multiple sites, including S127	Induces YAP degradation via β-TrCP and represses YAP activity (in osteoarthritis pathogenesis)	[9]
IKKε	YAP	S419	Induces YAP degradation through lysosomes in response to viral stimulation	[50]
MEKK3	YAP	S371	Down-regulates YAP activity	[52]
	LAST1/2		Activates LATS1/2 to inhibit YAP/TAZ activity	
MEKK5	TAZ		Interacts with and inactivates TAZ by cytoplasmic retention of TAZ	[54]
GSK3	TAZ	S58, S62	Promotes TAZ degradation by UPS	[55, 56]

mTORC2 and YAP in GBM patient tumor samples was observed by IHC staining [7].

MAPKs

Besides mTOR kinases, mitogen-activated protein kinases (MAPKs) also play important roles in modulating YAP/TAZ activity. Previous studies have demonstrated that MAPKs are involved in mediating the mechanical tension-induced YAP activity [8]. A recent report found that ERK phosphorylates YAP at S274 and S352 (conserved in human S289 and S367) during metaphase in ERBB2-overexpressed cardiomyocytes in a mouse heart failure model study, the phosphorylation of YAP on these sites by ERK elevates activity of YAP and expression of the YAP target genes [31]. Besides direct phosphorylation, ERK2 interacts with and phosphorylates 14-3-3 protein at S37, releases YAP from the YAP/14-3-3 complex, and promotes translocation of YAP into the nucleus in response to hypoxia [32].

Nemo-like kinase (NLK), the ortholog of Nemo in *Drosophila*, is an atypical MAPK. The kinase domain of NLK displays 45% identity to that of ERK and 38% identity to CDK1 [33]. In response to osmotic stress, NLK phosphorylates and activates YAP [34]. NLK phosphorylates YAP at S128 that is adjacent to the key LATS-phosphorylation site S127, suppresses interaction between YAP and 14-3-3, and enhances YAP nuclear translocation [34].

MK5, another member of atypical MAPKs and also known as MAPKAPK5, has been identified as an activator of YAP [33, 35]. MK5 physically binds to YAP in a kinase-dependent manner. The interaction between MK5 and YAP reduces the proteasomal degradation of YAP induced by CK1 due to disrupting interaction between YAP and β-TrCP [35].

SFKs

The activation of YAP/TAZ is regulated by tyrosine kinases as well. YAP was initially identified as the interactive protein of Yes, a Src family tyrosine kinase (SFK) [36]. SFKs are non-receptor protein tyrosine kinases and function in a wide range of cellular processes. SFKs share similar structural architecture. In addition to Yes, Src and LCK also interact with YAP [37–39]. Yes binds to YAP via its Src homology domain 3 (SH3) domain and phosphorylates YAP at Y407 in a kinase-dependent manner [36]. Similar to Yes, Src phosphorylates and activates YAP [37]. SFKs are activated in cholangiocarcinoma (CCA) cells because of the up-regulated platelet derived growth factor receptor (PDGFR) signaling [38]. In CCA cells, activated SFKs induce tyrosine phosphorylation of YAP at Y407, promote association of YAP with transcription factor TBX5, elevate expression of the YAP target gene Mcl-1, and enhance survival of CCA cells [38]. It has been identified that LCK is the kinase phosphorylates YAP at Y407 in CCA [39].

The non-hippo kinases that inactivate YAP/TAZ

YAP/TAZ play fundamental roles in cellular biological processes. Meanwhile, the activity of YAP/TAZ is inhibited to sustain cellular homeostasis when cells are response to nutrient shortage, viral infections or inflammatory cytokines such as TNFα and IL-1β. The inhibitory regulation of YAP/TAZ by non-Hippo kinases is normally via following three aspects (Table 2): (I) phosphorylation of YAP at S127 and TAZ at S89 to promote the proteasomal degradation of YAP/TAZ; (II) disruption of interaction between YAP/TAZ and TEAD to down-regulate the transcriptional activity of YAP/TAZ; and (III) induction of the YAP/TAZ degradation through lysosomes.

NDR1/2

Nuclear Dbf2-related kinase 1 and 2 (NDR1/2) are the closest homologs of LATS1/2 in the AGC (protein kinase A (PKA)/PKG/PKC-like) family of serine/threonine protein kinases. NDR1/2 directly phosphorylate YAP at S61, S109, S127 and S164 in vitro [40]. All these four sites are phosphorylated by LATS1/2 as well [15]. Through direct phosphorylation, NDR1/2 inhibit nuclear localization of YAP and expression of the YAP target genes in human colorectal cancer cells, thus repress colon cancer cell proliferation [40].

AMPK

The AMP-activated protein kinase (AMPK) is a trimeric serine/threonine protein kinase and the major cellular sensor in response to energy stress [41]. AMPK signaling pathway interplays with mTOR signaling pathway to ensure cellular energy homeostasis. mTORC1 and mTORC2 function as the positive regulators and promote cell growth in response to nutrient abundance, whereas AMPK as the negative regulator that inhibits cell growth under condition of nutrient shortage [41]. Contrary roles in controlling cellular energy status of mTORC1/mTORC2 and AMPK are consistent with their modulation of the YAP activity. As mentioned before, mTORC1/mTORC2 phosphorylate and activate YAP [7, 29], while AMPK negatively regulates YAP activity. Under energy stress, the phosphorylation of YAP S61, S94, T119 and S127 is elevated [42, 43]. S127 of YAP is phosphorylated by LATS and phosphorylation of S61, S94 and T119 is dependent on AMPK [43, 44]. YAP S94 is a critical residue for interaction with TEAD [45]. Phosphorylation of YAP S94 by AMPK disrupts interaction of YAP with TEAD upon shortage of energy [42]. In addition to S94, S61 and T119 are also the AMPK phosphorylation sites. Phosphorylation of S61 by AMPK also inhibits the YAP transcriptional activity, however, the mechanism underlying the inhibition remains unknown [43].

TAK1 and IKK

TAK1 or MAP3K7, initially identified as TGF-β-activated kinase 1, is a member of mitogen-activated protein kinase kinase kinases (MAP3Ks) family. TAK1 functions in both the nuclear factor-κB (NF-κB) and the MAPK signaling pathways [46]. Because of cellular and microenvironmental complexity, TAK1 was observed to produce opposite cellular effects in different tumor types or pathological stages [46]. TAK1 also produces the similar effects on regulation of YAP activity. For example, TAK1 promoted the formation of the YAP/TAZ-TRAF6 complex thus prevented YAP/TAZ from proteasomal degradation via ubiquitination of K63 [47]. Thus, it was proposed that TAK1 stabilizes YAP/TAZ protein and enhances YAP/TAZ activity [47, 48]. However, it was also observed that TAK1 regulated YAP activity by direct phosphorylation in response to inflammatory cytokines, such as TNFα and IL-1β [9]. TAK1 interacts with and directly phosphorylates YAP at multiple sites including S127, induces YAP degradation via the β-TrCP-mediated ubiquitination, thus represses YAP activity [9].

The IκB kinase (IKK) complex contains kinase subunits IKKα, IKKβ and regulatory subunit IKKγ (Nemo), or IKK-related kinases (TBK1 and IKKε). IKK complex plays essential roles in innate immunity via activating the NF-κB and IRF signaling [49]. It has been reported that IKKε interacts with and directly phosphorylates YAP at S419, induces YAP degradation through lysosomes, resulting in relief of the repression effect of YAP on antiviral immunity upon viral stimulation [50]. Thus, IKKε modulates YAP activity by phosphorylation as a negative regulator.

MEKK3 and MEKK5

MEKK3 (mitogen-activated kinase kinase kinase 3, MAP3K3) is a serine/threonine protein kinase belongs to MAP3K family. MEKK3 has multiple functions including phosphorylation of IKK and activation of the NF-κB signaling [49]. Emerging evidence elucidated MEKK3 has multifaceted roles in modulating YAP activity [51]. Upon stimulation, MEKK3 phosphorylates and activates LATS1/2 in MST1/2 and MAP4Ks independent manners. Moreover, MEKK3 directly interacts with and phosphorylates YAP at S371, resulting in inhibitory regulation of YAP transcriptional activity [52].

MEKK5 (mitogen-activated kinase kinase kinase 5, also ASK1) is a member of MAP3K family. Our previous study has demonstrated that MEKK5 plays inhibitory role in regulation of E3 ligase NEDD4-mediated lung cancer cell migration [53]. Moreover, we identified that MEKK5 participates in regulation of TAZ signaling, MEKK5 interacts with and inactivates TAZ, leads to TAZ cytoplasmic retention in a kinase-dependent manner [54].

GSK3

Glycogen synthase kinase 3 (GSK3) is a serine/threonine kinase that implicated in a number of cellular functions. Similar to β-catenin, which is phosphorylated by GSK3 and subsequently recognized by β-TrCP, TAZ is directly phosphorylated by GSK3 at S58 and S62 that compose its N-terminal phosphodegron, resulting in TAZ degradation by UPS [55]. Meanwhile, Azzolin et al. found that GSK3 destabilizes TAZ in a kinase-dependent but indirect manner

Table 3 Non-Hippo kinases that regulate YAP/TAZ indirectly

Kinase	Target	Mechanism of action	YAP/TAZ signaling	References
LKB1	AMPK	Disrupts the interplay between YAP and TEAD	down	[42, 43, 59]
	MARKs	Activate Hippo-kinases as upstream regulators	down	[59]
NUAK2	LATS	Phosphorylates LAST at T246 and S613, S613 is adjacent to LATS-MOB1 binding site, phosphorylation at S613 inhibits LATS full activation	up	[64]
PDK1	Hippo complex	Forms complex with active MST1/2 and LAST1/2 to inactivate YAP in response to serum-starvation; once PDK1 is activated, complex is dissociated thus activating YAP	up	[65]
Src	PDK1	Functions as upstream kinase to activate PDK1	up	[37, 66]
EGFR	MOB1	Phosphorylates MOB1 at Y95, Y114, Y117, decreases phosphorylation level of LATS (LATS-MOB1 interaction is not disrupted)	up	[70]
	PI3K/PDK1	Activates PI3K/PDK1 to regulate YAP/TAZ	up	[71, 72]
HER2	Ras-Rac1	Activates YAP/TAZ by oncogenic mechanosignaling	up	[73]
NTRK1	LATS	Inhibits LATS phosphorylation (Hippo signaling) to induce YAP activity	up	[75]
ROCK1	Actomyosin cytoskeleton	Upregulates actomyosin cytoskeleton contractility and TEAD/YAP transcription.	up	[76, 77]

[56]. In this vein, GSK3 phosphorylates and endows with β-catenin as a bridge between TAZ and β-TrCP, thus fosters TAZ proteasomal degradation. Collectively, by direct and indirect effects, GSK3 functions as an inhibitory regulator of TAZ.

The non-hippo kinases that regulate YAP/TAZ indirectly

In addition to direct activation or inhibition by phosphorylation of YAP/TAZ, some non-Hippo kinases regulate the YAP/TAZ signaling without direct phosphorylation of YAP/TAZ. These kinases modulate the YAP/TAZ signaling through phosphorylation or regulation of assembly of the Hippo cascade components, thus effect the Hippo signaling and YAP/TAZ (Table 3).

LKB1 and AMPK-related kinase

The liver kinase B1 (LKB1) is a serine/threonine protein kinase ubiquitously expressed. LKB1 is considered as a tumor suppressor that governs cell proliferation, metabolism and polarity [57]. Knockdown of LKB1 is found to decrease phosphorylation of YAP and up-regulate expression of the YAP target genes [58, 59]. The inactivation effect of LKB1 on YAP activity partially depends on its substrates, MARKs. MARK1, 3 and 4 function as the activators of the Hippo kinase, thus inhibit YAP activity [59]. In addition, AMPK is a well-known substrate of LKB1 and the inhibitory regulation of YAP by LKB1 relies on AMPK phosphorylation as well [60].

NUAK2 (also known as SNARK) is a serine/threonine protein kinase, belongs to AMPK kinase family and is regulated by LKB1. NUAK2 participates in various cellular processes including proliferation, migration, cell adhesion and metabolism [61]. It has been observed that NUAK2 responds to nutrient stress similar to AMPK [62]. Intriguingly, a positive feed-forward loop between YAP/TAZ and NUAK2 was identified. NUAK2 is the target gene of YAP/TAZ and mediates the YAP-dependent cancer cell and tumor growth [63, 64]. Inhibition of NUAK2 activity by its specific inhibitors represses the YAP-mediated cancer cell or organ growth [63]. NUAK2 regulates the YAP/TAZ activity by phosphorylation and inhibition of LATS [64]. NUAK2 interacts with LATS and phosphorylates LATS at S613 and T246. Because LATS S613 is adjacent to MOB1-LATS binding site, phosphorylation at S613 by NUAK2 inhibits LATS activity and the YAP phosphorylation by LATS [64]. Given the vital roles of NUAK2 in promoting the YAP/TAZ oncogenic function, inhibitors of NUAK2 may be applied for cancer therapy.

PDK1

PDK1 (3-phosphoinositide-dependent protein kinase-1) modulates YAP/TAZ activity as well. Fan and colleagues [65] identified PDK1 interacts with MST and LATS via SAV1 in serum-starved confluent MCF-10 A cells. PDK1 forms a complex with active Hippo components in response to serum-starvation, thus impairs nuclear translocation of YAP. PDK1 is activated and recruited to plasma membrane upon EGF stimulation, resulting in the dissociation of PDK1 from the Hippo kinase complex and inactivation of LATS. As a consequence, YAP is trans-localized in nucleus. The effect of PDK1 on YAP is independent of the PI3K/AKT signaling [65]. Subsequent research found that Src might be the upstream kinase of PDK1 in this regulation [66].

Receptor tyrosine kinases (RTKs)

Mounting evidence has demonstrated that receptor tyrosine kinases (RTKs) are associated with the Hippo signaling pathway and regulate YAP/TAZ activity.

The epidermal growth factor receptor (EGFR, also known as ERBB1 and HER1), a member of the ERBB tyrosine kinase family, is ubiquitously expressed in epithelial and fibroblast cells. The EGFR signaling pathway is well studied and known as a driver of tumorigenesis in human non-small cell lung cancer (NSCLC) and breast cancer [67, 68]. EGFR is activated by its ligands such as EGF, TGFα, epiregulin and neuregulin [69]. In head and neck squamous cell carcinomas (HNSCC) cells, the EGFR signaling activates YAP/TAZ independent of MST1/2. Further study found that EGFR phosphorylates MOB1 at Y95, Y114 and Y117 upon EGF stimulation or by overexpression of EGFR or EGFR active mutants [70]. Although interaction of MOB1 with LATS1 is not disrupted by the tyrosine phosphorylation, activity of LATS1 is reduced and expression of the YAP/TAZ target genes is elevated. Treatment of HNSCC cells with the EGFR inhibitor erlotinib enhanced phosphorylation of YAP and repressed expression of the YAP target genes [70]. It has been found that the EGFR signaling promotes the YAP/TAZ activity through activation of PI3K and PDK1 in hepatocellular carcinoma (HCC) cells. The oncogenic effect of EGFR in HCC is partially mediated by the YAP/TAZ signaling [71, 72].

HER2, another member of the ERBB tyrosine kinase family, was reported to reprogram normal cells into tumor-initiating cells by regulating cell's mechanical properties by activation of Ras and Rac1 [73]. Mechanical signals transducted by the HER2-Ras-Rac1 cascade activates YAP/TAZ activity, and transcription of oncogenic genes. Meanwhile, YAP/TAZ sustain HER2 and Ras induced oncogenic reprogramming [73]. With the crucial roles played in mechanotransduction, YAP/TAZ function as key mediators in mechanosignaling.

Neurotrophic receptor tyrosine kinase 1 (NTRK1, also known as TRKA), a member of the tropomyosin receptor kinase family, was initially identified in colon carcinoma. Expression of NTRK1 and its ligand nerve growth factor (NGF) in nervous system were found a few years later [74]. The pro-oncogenic role of NTRK1 has been demonstrated in multiple tumor types, and NTRK1 promotes tumorigenesis mostly by activation of the MAPK and PI3K signaling [74]. Recently, a report has shown that NTRK1 promotes tumorigenesis through regulating the Hippo-YAP signaling [75]. Inhibition of NTRK1 induces activation of LATS that leads to increase in phosphorylation at S127 and cytoplasmic localization of YAP. Consistently, stimulation of NTRK1 with NGF suppresses the YAP phosphorylation, enhances YAP activity, and promotes cancer cell proliferation and migration [75].

ROCK1/2

Rho-associated protein kinase 1 and 2 (ROCK1 and ROCK2) are serine/threonine kinases that belong to AGC family and initially identified as downstream effectors of small GTPase RhoA. Plenty of evidence has demonstrated that YAP/TAZ nuclear localization and transcriptional activity are regulated by ROCK1/2 [76, 77]. Depletion of ROCK2 severely reduced YAP oncogenic activity [76]. Moreover, pharmacological inhibition of ROCK1 markedly impaired TEAD/YAP transcription that is mediated by mechano-signaling [77].

Targeting the YAP/TAZ signaling by kinase inhibitors in cancer therapy

Inhibitors of the PI3K signaling

In MCF-10 A breast cancer cells, inhibition of PI3K with wortmannin/LY294002 or PDK1 with BX795 impairs nuclear localization of YAP, while the AKT inhibitor VIII has an insignificant effect [65, 66]. The similar results were obtained in HCC, PI3K and PDK1 inhibitors abolish the EGFR-induced reduction of pYAP-S127 [71], suggesting that inhibitors of the PI3K-PDK1 axis may be applied for targeting the YAP signaling in cancer therapy.

Inhibitors of the src family kinases (SFKs)

SFKs have been demonstrated to enhance the YAP-oncogenic activity, not only via activating the PI3K-PDK1 signaling, but also through directly phosphorylation and stabilization of YAP/TAZ [37, 66]. PP2 is a selective inhibitor of SFKs, treatment with PP2 in human renal proximal tubule epithelial (HK-2) and MCF-10 A cells elevated phosphorylation of YAP at S127 and reduced YAP activity [66, 78]. In triple-negative breast cancer MDA-MB231 and MDA-MB468 cells, PP2 suppresses cell viability, migration and invasion, suggesting that PP2 may have a therapeutic effect on the YAP/TAZ-dependent cancer [79].

Dasatinib is an SFK inhibitor approved by FDA and EMA for treatment of Philadelphia chromosome-positive (Ph +) chronic myeloid leukemia (CML) and Ph + acute lymphoblastic leukemia (ALL) [80]. Recent reports have demonstrated that overexpression of Yes contributes to tumor growth and metastasis in NSCLC both in vitro and in vivo. By inhibiting Yes kinase activity, dasatinib represses the tyrosine phosphorylation of YAP, impairs the nuclear

translocation of YAP, and reduces expression of the YAP target genes [81]. Datasinib significantly inhibits proliferation of MDA-MB-231 cells that are the YAP/TAZ-dependent breast cancer cells [82]. Consistently, tumors with activated YAP have high sensitivity to dasatinib [83]. In a CCA patient-derived xenograft (PDX) model, treatment with dasatinib elevates cancer cell death and decreases tumor volume in mice [39]. The inhibitory effects of dasatinib on cancer cell proliferation partially rely on its inhibition of the YAP/TAZ signaling, suggesting that dasatinib has potential therapeutic efficacy for the YAP/TAZ-driven cancer. However, some studies have shown that treatment with dasatinib alone did not have a significant effect on growth of the PDX tumors in vivo [84, 85]. Treatment of cancer patients with dasatinib failed in lung cancer clinical trial [86]. Combination with other anti-cancer drugs may be an approach for application of dasatinib for cancer therapy.

Inhibitors of EGFR

EGFR is frequently mutated to drive lung and breast cancer tumorigenesis and progression. EGFR tyrosine kinase inhibitors (TKIs) have been used as the first-line treatment for patients with advanced EGFR-mutant NCSLC [87]. Currently, the third-generation EGFR-TKI osimertinib has been demonstrated superior over the first-generation (erlotinib and gefitinib) and the second-generation EGFR-TKIs (afatinib) with a lower rate of serious adverse events and the similar safety profile [88]. Inhibition of EGFR with the TKI erlotinib enhances YAP phosphorylation at S127 and reduces expression of the YAP target genes in HNSCC cells bearing the EGFR mutation [70]. However, clinical trials frequently observed resistance to treatment with EGFR-TKIs in NSCLC patients [89]. Some studies have shown that YAP plays a role in resistance to EGFR-TKIs [90, 91]. YAP signaling is activated in the EGFR-TKI-resistant cells and knockout or inhibition of YAP enhances the sensitivity of cancer cells to EGFR-TKIs [92].

Inhibitors that disrupt interaction of YAP/TAZ with TEAD

Verteporfin (VP) is a small molecular weight chemical and used to antagonize YAP/TAZ binding to TEAD [93]. However, application of VP for therapy of the YAP-driven cancer is limited due to the off-target effect [94].

Approaches with combination of inhibitors

In preclinical studies, inhibition of YAP/TAZ with VP combined with EGFR-TKIs has shown more effective in suppressing proliferation of cancer cells [92]. In combination of the EGFR-TKI gefitinib with simvastatin that inhibits YAP, the anti-tumor effect is more significant than the single agent administration alone in HCC cells [71]. Trametinib is a MEK inhibitor has been approved for treatment of BRAF-mutant melanoma and applied for multiple cancer therapy [95]. Treatment of HCC cells with simvastatin and trametinib significantly enhanced the cytostatic effects in the cell proliferation and colony formation assays [71]. MYF-01-37 is a newly developed TEAD inhibitor that covalently binds to TEAD, thus disrupts interaction between YAP and TEAD [96]. In a recent study inhibition of both the EGFR/MEK and the YAP signaling pathways overcomes dormant therapy-resistant cancer cells by promoting cellular apoptosis. Treatment of NSCLC cells with MYF-01-37, osimertinib (EGFR-TKI), and trametinib (MEK inhibitor) results in complete repression of YAP activity and a significant increase in apoptosis [96].

The SFKs inhibitor dasatinib in combination with EGFR-TKI erlotinib or afatinib has been used in phase I/II trial for lung cancer patients with the acquired EGFR-TKIs resistance. However, objective response in patients to the treatment in these clinical trials was not observed [97, 98]. The third-generation EGFR-TKI osimertinib is a preferred option for treatment of the EGFR-mutant NSCLC. When osimertinib combined with dasatinib, the anti-tumor effect was displayed in NSCLC patients with the EGFR-mutation [99], suggesting that combination of these two inhibitors is effective for NSCLC therapy.

Recent research revealed that oncogenic Hippo-YAP and PI3K signaling is elevated and activated in high-grade gliomas derived from the Pten/Tp53-lossed Olig1/2-expressing intermediate lineage precursors of mice. While targeting the YAP signaling with VP or the PI3K signaling with the analog of wortmannin PX-866 alone partially inhibited tumor cell proliferation, targeting both the YAP and PI3K signaling pathways by combination treatment with VP and PX-866 completely inhibited the growth of tumor cells [100], suggesting that targeting YAP signaling combined with other oncogenic signaling may significantly enhance cancer therapeutic efficacy.

Conclusion

As essential transcriptional co-activators, YAP/TAZ have pivotal functions in cellular homeostasis, tissue development and carcinogenesis. Dysregulation of YAP/TAZ activity resulting from either elevation of protein abundance or activation promotes tumorigenesis, cancer progression, and resistance to cancer therapy.

In response to multiple stimuli, several non-Hippo kinases directly phosphorylate YAP/TAZ at specific residues

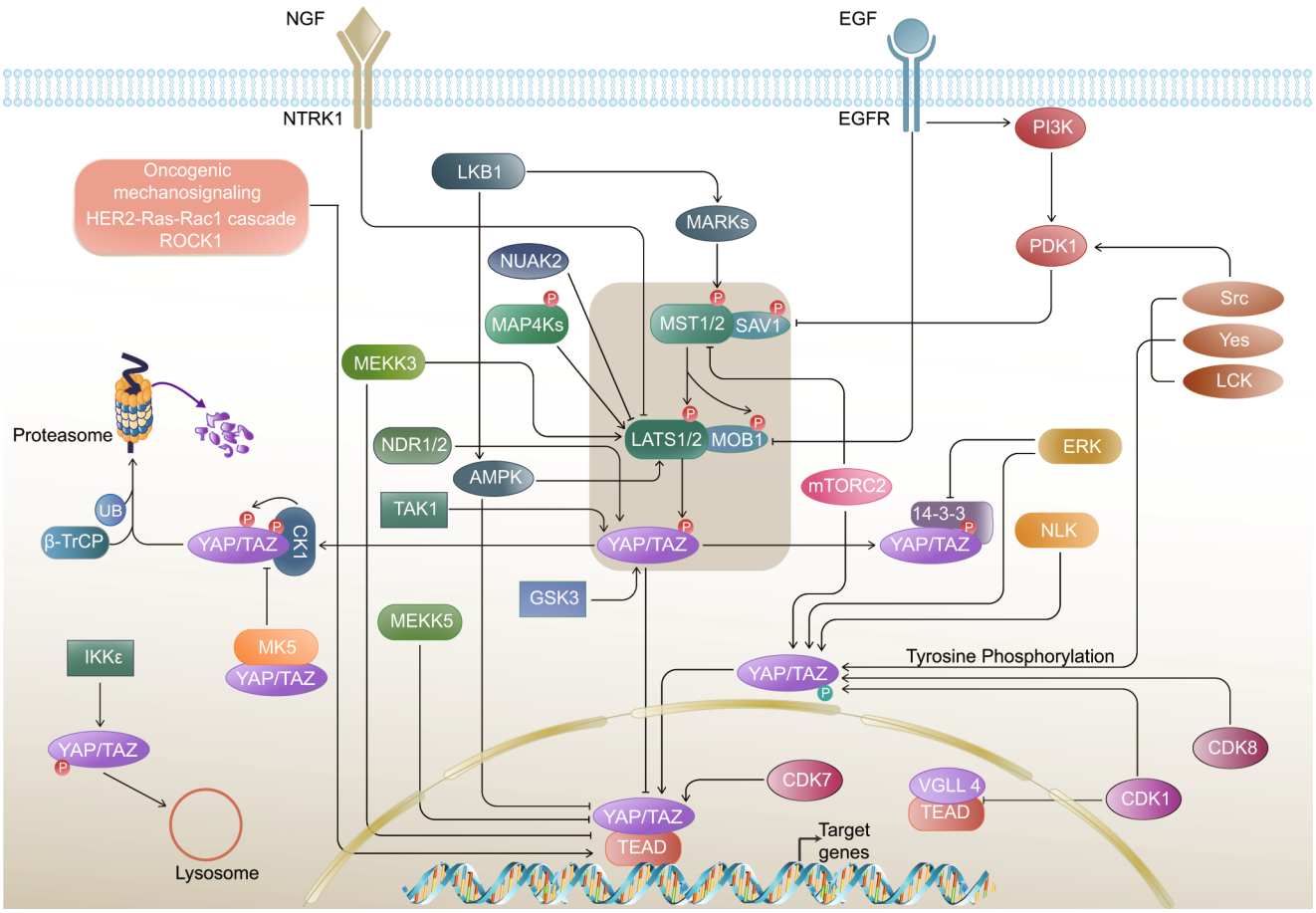

Fig. 2 Regulation of YAP/TAZ by non-Hippo kinases. Activation and inhibition of transcriptional co-activators YAP/TAZ are regulated by multiple non-Hippo kinases both in the cytoplasm and in the nucleus. Non-Hippo kinases induce serine/threonine phosphorylation and tyrosine phosphorylation on YAP specific residues. Generally, CDK7, CDK8 and NLK phosphorylate YAP/TAZ at S128 and S90 to disturb LATS phosphorylation at YAP S127 and TAZ S89, thus prevent YAP/TAZ from proteasomal degradation. SFKs (Src, Yes, LCK) phosphorylate YAP at Y407 to stabilize YAP protein and promote YAP translocation in the nucleus. MK5 physically binds to YAP to stabilize YAP protein as well. Phosphorylation of YAP at S436 by mTORC2 elevates interaction between YAP and TEADs; phosphorylation at T119, S289 and S367 conducted by CDK1, CDK8 and ERK1 (S289 and S367 only) up-regulate YAP transcriptional activity. To inactivate YAP/TAZ, NDR1/2 and TAK1 phosphorylate YAP at S127, IKK phosphorylates YAP at S419, thus induce YAP degradation by proteasomes or lysosomes. S94 phosphorylated by AMPK disrupt the interaction between YAP and TEAD to down-regulate the transcriptional activity of YAP. MAP3Ks, MEKK3, MEKK5 and GSK3 interact with and down-regulate YAP/TAZ activity as well. Some of the non-Hippo kinases regulate YAP/TAZ signaling in a Hippo-dependent manner. NUAK2 and NTRK1 target LATS, EGFR targets MOB1, mTORC2 targets MST1 to inhibit LATS full activation. LKB1 mediates downstream kinases AMPK and MARKs, PDK1 and upstream kinase Src regulate the assembly of Hippo cascade components to affect the Hippo signaling and YAP/TAZ

to sustain YAP/TAZ protein stability and abundance and facilitate the YAP/TAZ nuclear translocation. Under energy stress or viral infection, several non-Hippo kinases interact with and phosphorylate YAP/TAZ to disrupt their interaction with TEAD or promote their degradation, thus inhibit the YAP/TAZ signaling. In addition to direct interaction and phosphorylation, some non-Hippo kinases regulate YAP/TAZ activity through regulation of the Hippo kinase cascade, thus indirectly control YAP/TAZ activity. Taken together, regulation of the YAP/TAZ signaling by the non-Hippo kinases is multifaceted (Fig. 2), depending on cell type and signaling context.

Targeting the YAP/TAZ or the non-Hippo kinases that regulate YAP/TAZ signaling for cancer therapy is still under development by disrupting interaction of YAP/TAZ with TEAD or inhibiting the non-Hippo kinases. Because of heterogeneity and complexity of genetic and epigenetic background of tumors, targeting the YAP/TAZ signaling alone may not be enough to inhibit tumor growth and effective for cancer therapy, particularly in the tumor with a multiple oncogenic signaling pathways. Therefore, targeting the YAP/TAZ signaling or the non-Hippo kinase regulated YAP/TAZ signaling combined with other oncogenic

signaling may be an effective approach for targeted therapy of the YAP/TAZ-driven cancers in future.

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Declarations

Conflict of Interest The authors have no conflicts of interest to declare.

Ethical Approval The review does not cover human participants and animal studies.

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