CHAPTER

8

Targeting the Hippo Pathway to Improve Response to Chemotherapy

Yulei Zhao, Xiaolong Yang

Queen's University, Kingston, ON, Canada

Abstract

The Hippo pathway plays an essential role in tumorigenesis, stem-cell self-renewal and differentiation, organ size control, and many other biological processes. Currently, increasing studies also suggest that the components of the Hippo pathway are involved in the sensitivities of different cancer types to various chemotherapies. As a major approach for cancer treatments, chemotherapeutic therapies can sometimes effectively suppress tumor growth in cancer patients. However, a significant proportion of patients are either intrinsically resistant or later develop acquired resistance to primary chemotherapy, leading to disease relapse and patient mortality. The best way to conquer this resistance is through a better understanding of the molecular networks that are activated in cancer cells in response to drugs. Therefore, identification of signaling pathways and molecules involved in drug resistance is essential for successful treatment of cancers. Here, we will discuss the specific roles of the Hippo pathway in chemotherapy, potential applications for studying this network in response to drugs, and the future strategies to increase chemotherapy efficiency through targeting the Hippo pathway.

ABBREVIATIONS

AC	Adenylate cyclase
AMPK	5' AMP-activated protein kinase
BC	Breast cancer
CDK	Cyclin-dependent kinase
CSC	Cancer stem cell
ER	Estrogen receptor
Ex	Expanded
5-FU	5-Fluorouracil
GPCR	G protein-coupled receptor
HCC	Hepatocellular carcinoma
Hpo	Hippo
LIFR	Leukemia inhibitory factor receptor
LKB1	Liver kinase B1
Lats	Large tumor suppressor
Mats	Mob as tumor suppressor

Targeting Cell Survival Pathways to Enhance Response to Chemotherapy. http://dx.doi.org/10.1016/B978-0-12-813753-6.00008-1

MDR	Multi-drug resistance
MST1/2	Mammalian Ste-20 like kinase ½
NF2	Neurofibromatosis 2
NSCLC	Non-small cell lung cancer
PKA	Protein kinase A
PKB	Protein kinase B
PKC	Protein kinase C
RASSF1A	Ras-associated domain family member 1A
SMDs	Small molecular drugs
TEAD	Transcriptional enhancer associated domain
UPS	Ubiquitin proteasome system
VP	Verteporfin
YKI	Yorkie

8.1 INTRODUCTION

8.1.1 The Hippo Signaling Pathway

8.1.1.1 Canonical Core Cascade of the Hippo Pathway

The Hippo pathway, which was first identified in *Drosophila* and later in mammals [1], is a recently discovered signaling pathway that plays essential roles in both physiological and pathological processes, such as organ size control, tissue regeneration, stem-cell renewal and differentiation, and tumorigenesis [1–9]. The core components of the Hippo pathway were first identified in *Drosophila* (Fig. 8.1) with the development of a new technique called the mosaic genetic screen [10]. The first player of the Hippo pathway detected through this screening was the tumor suppressor and serine/threonine (S/T) kinase named *lats* (large tumor suppressor) or *wts* (Warts) [11,12]. Loss of *lats/wts* causes cell overproliferation and tissue overgrowth [11,12]. Using a similar genetic screen, the S/T kinase *Hpo* (Hippo) was identified with similar functions and as an upstream regulator of *lats/wts* [13–15]. At the same time, scaffold protein Sav (Salvador) was found to promote the functions of Hpo [13] and 2 years later, Mats (Mob as tumor suppressor) was identified as another scaffold protein interacting and potentiating the functions of lats/Wts [16,17]. All these proteins were found to work together as a size-control phosphorylation cascade to regulate the downstream effector Yki (Yorkie), which is a transcriptional co-activator [18,19] (Fig. 8.1).

With increasing studies later on, the Hippo pathway was identified and found to be well conserved in mammals. In the mammalian Hippo pathway (Fig. 8.1), the core components are as follows: kinases MST1/2 (Mammalian Ste-20-like kinase 1/2; homolog of *Drosophila* Hpo; MST will be used instead of MST1/2 in the following text) and LATS1/2 (homolog of *Drosophila* lats/Warts; LATS will be used for LATS1/2 in the following text), scaffold proteins WW45/Sav (homolog of Sav in *Drosophila*) and Mob1 (homolog of *Drosophila* Mats), as well as the transcriptional co-activators YAP (Yes-associated protein; homolog of *Drosophila* Yki) and its paralog TAZ (transcriptional co-activator with PDZ-binding motif) [6,20]. Similar to *Drosophila* Hippo signaling, the mammalian Hippo pathway functions through phosphorylation. When the Hippo pathway is activated in certain conditions such as increased cell–cell contact caused by high cell density, the upstream core component MST first gets phosphorylated and activated, which further phosphorylates and activates the downstream kinase

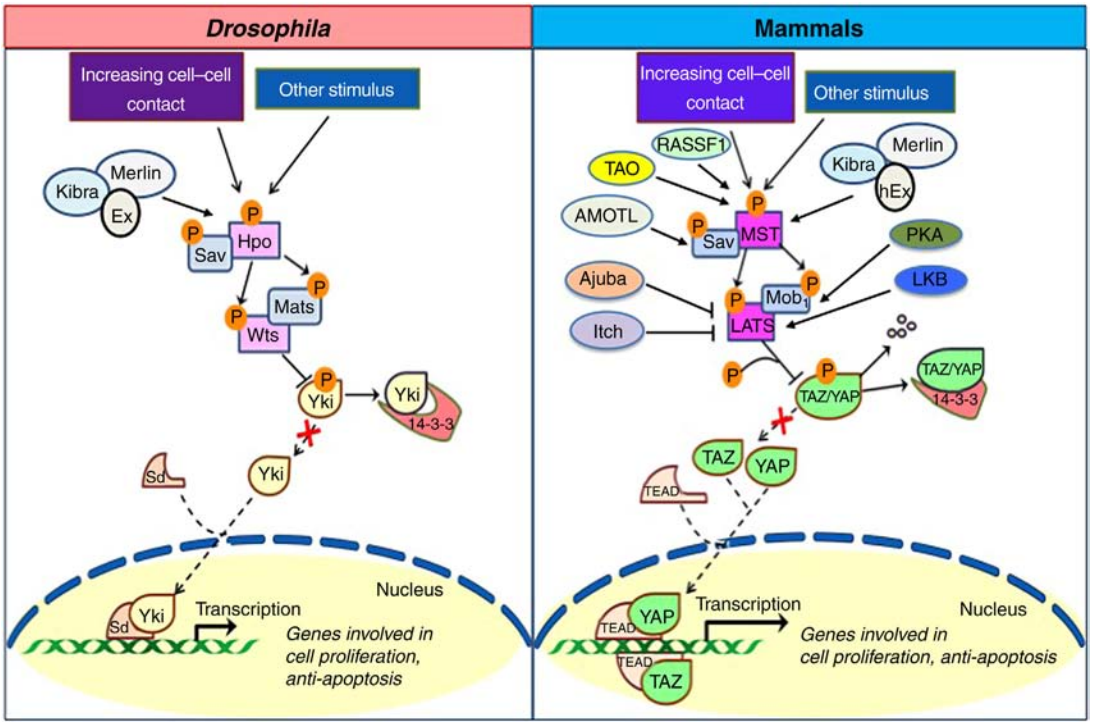

FIG. 8.1 **Hippo pathway in *Drosophila* and mammals.** Abbreviations: Ex, expanded; Sav, Salvador; Hpo, Hippo; Wts, Warts; Yki, Yorki; MST, mammalian Ste-20 like kinase; LATS, large tumor suppressor; hEx, human expanded; RASSF1, Ras-association domain family member 1; PKA, protein kinase A; LKB, liver kinase B.

LATS [1,6]. The phosphorylated LATS can inhibit the transactivating functions of YAP and TAZ through phosphorylation of specific S sites in the motif of "HxH/R/KxxS/T" (H, histidine; R, arginine; K, lysine) on YAP and TAZ [21–23]. As a result, TAZ and YAP are anchored in the cytoplasm [21–23] and/or degraded [24,25], which interrupt their interactions with the transcription factor TEAD (transcriptional enhancer associate domain) family to block their roles in assisting the transcription of downstream target genes involved in cell-cycle progression, cell proliferation, and anti-apoptosis (Fig. 8.1) [21,23–27]. Therefore, dysregulation of the Hippo pathway is involved in tumorigenesis and metastasis [28–31], which mainly depend on cell proliferation and cell survival.

8.1.1.2 Upstream Regulators of the Hippo Pathway

With increasing studies on the Hippo pathway, many regulators of the Hippo pathway have been identified in addition to the core components. Studies on *Drosophila* determined that a protein complex consisting of the FERM domain proteins Merlin (NF2, neurofibromatosis 2) and Ex (Expanded) as well as Kibra (kidney and brain expressed protein) activate Hippo/MST [32–34]. A conserved association of Merlin and Kibra exists in human cells to trigger activation of the Hippo pathway via activation of MST [34] (Fig. 8.1). However, unlike *Ex* in *Drosophila*,

hEx (*human Expanded*), which is also named *FRDM6* and *Willin*, functions as a tumor suppressor gene (TSG) in both Hippo pathway-dependent and -independent mechanisms [35,36]. In addition to forming a complex with Kibra, Merlin is also shown to recruit MST and LATS to the plasma membrane to activate the pathway [37]. In addition, AMOTL2, which is a member of AMOT (angiomotin) family, functions as an adapter protein to interact with MST, LATS2, and YAP to promote the activation of LATS2 by MST [38]. Besides, the apicobasal polarity of epithelial cells also plays a role in the activation of the Hippo pathway through basolateral membrane-located protein Scribble, which is required for recruiting MST to the LATS-TAZ/YAP complex [39]. Furthermore, leukemia-inhibitory factor receptor inhibits YAP-promoted metastasis through Scribble involved Hippo pathway activation [40]. In addition, as a tumor suppressor, RASSF1A (Ras-association domain family member 1A) interacts with MST1 to induce apoptosis [41]. Further studies indicate that this protein can protect activated MST from dephosphorylation/inactivation to trigger the Hippo pathway [42,43]. Furthermore, the STE-20 family kinase TAO1, PKA (protein kinase A), and LKB1 (liver kinase B1) can activate the Hippo pathway through phosphorylation of MST and/or LATS (Fig. 8.1) [44–48].

In addition to the positive regulators, kinase Akt [also known as PKB (protein kinase B)] has been shown to inhibit the Hippo pathway through phosphorylation of MST [49,50]. In addition, the proteins of Ajuba Lim family can interact with and inhibit LATS activity to block the Hippo pathway [51–53]. Moreover, LATS can be specifically targeted by Itch ubiquitin ligase to be degraded through ubiquitin proteasome system [54], which also suppresses the activity of the Hippo pathway.

Besides, as a cell-surface glycoprotein and a marker for cancer stem cells (CSCs), CD44 is found to attenuate the activity of the Hippo pathway through association with Merlin in glioblastoma cells [55–57]. Further, CD44 can also directly activate YAP independent of the Hippo pathway [58]. In addition to CD44, several recent studies propose that some extracellular ligands can regulate the Hippo pathway through different G protein-coupled receptors (GPCRs) [2,59–61]. Moreover, a variety of stimuli (e.g., increasing cell density, DNA damage, energy stress, mechanotransduction, etc.) activate or inhibit the Hippo pathway [2,62–67].

8.1.2 Hippo Signaling in Human Cancer

The Hippo pathway is a tumor suppressor pathway. Dysregulation of the Hippo pathway is involved in tumorigenesis and metastasis [1,2,40]. Evidence of the involvement of the Hippo pathway in tumorigenesis comes from the mouse models with gene knockout of upstream components in the Hippo pathway. These mice develop variable types of tumors. For example, LATS1 knockout mice develop soft tissue sarcoma and ovarian carcinoma [68], whereas MST1/2 knockout mice exhibit several types of tumors including hepatocellular carcinoma (HCC) [69], which is the same as mice with YAP overexpression in livers [18]. Moreover, the core components in the Hippo pathway are clinically involved in diverse human cancers. For example, YAP and/or TAZ overexpressions are identified in tumor tissues from patients with breast cancer (BC) [31,70,71], non-small-cell lung cancer (NSCLC) [72,73], HCC [74], colorectal cancer [75,76], head and neck cancer [77,78], oral squamous cell carcinoma [79,80], ovarian cancer [81–85], prostate cancer [86], and so on. On the other hand, downregulation of LATS is detected in BC [87] and NSCLC [88,89].

8.2 HIPPO PATHWAY IN CHEMOTHERAPEUTIC DRUG RESISTANCE

Abnormal expression levels and dysfunctions of components in the Hippo pathway have been implicated in the resistance of cells to different chemotherapeutic drugs and we will discuss how each component of the core Hippo pathway is involved in chemoresistance during cancer treatment in the following text.

MST

MST1 and its homolog MST2 are located upstream of the core Hippo pathway to control the activity of this pathway (Fig. 8.1). Downregulation of MST causes resistance of prostate cancer cells to the DNA-damaging reagent cisplatin, whereas increasing levels of MST sensitize these cells to cisplatin [90]. However, how reduced MST contributes to cisplatin resistance is not clear. One possibility is that decreased MST may cause drug resistance by inactivating the Hippo pathway, which subsequently activates its downstream targets YAP and/or TAZ (see below).

LATS

As the core kinases in the Hippo pathway, *LATS1* and its homolog *LATS2* are well-known TSGs and loss of their functions is found in various human cancers [91]. We have previously shown that knockdown of LATS1 by small interference RNAs can dramatically decrease the sensitivity of HeLa cervical cancer cells to Taxol, an antimicrotubule drug commonly used for treatment of breast and lung cancers [92]. In addition, *LATS1* has been identified as a gene causing Taxol resistance through a functional genomic screen using short-hairpin RNA (shRNA) library targeting TSGs in the lung cancer cell line A549 [93]. In addition, knockdown of ITCH, which is a ubiquitin ligase causing LATS1 degradation [54], increases cell sensitivity to doxorubicin [94]. This suggests that ITCH may play a role in the chemosensitivity of cells through regulation of LATS1. However, the molecular mechanism of how LATS1 is involved in chemoresistance remains unknown. Similar to LATS1, LATS2 is found to be negatively regulated in leukemia and the low level of LATS2 contributes to the resistance of leukemic cells to the DNA-damaging agents doxorubicin and etoposide (standard drugs for leukemia treatment) [95]. In addition, silencing of LATS2 can upregulate the transcription of ERα (estrogen receptor alpha)-regulated genes, which may render patients with ER+ BC resistant to Tamoxifen and other ER antagonists [96]. In contrast to the above studies, by examination of *LATS2* mRNA levels in tissues from chemotherapy-treated patients, one study found that BC patients with low levels of LATS2 mRNA are more sensitive to epirubicin plus cyclophophamide (EC). A potential explanation for these conflicting findings is that EC treatment functions most effectively in cancer cells that are in S phase of replication. LATS2 can inhibit CDK2 function, indirectly preventing cells from entering S phase and being targeted by EC efficiently [97]. These results suggest that a gene may function differently in response to different types of drugs. Therefore, it is necessary to consider the mechanisms of action for different drug treatments when studying the role of LATS2 in chemotherapeutic drug resistance.

YAP

YAP was identified in 1994 as a protein interacting with Yes and Src tyrosine kinases [98]. Later studies indicated that YAP functions as a transcriptional co-activator and an oncoprotein by interacting with many transcription factors and initiating the expression of downstream oncogenic genes [27,28,99]. In 2007, YAP was identified as a major downstream component of the Hippo pathway. The regulation of YAP by LATS in the Hippo pathway determines its subcellular location, which further affects its oncogenic functions through transactivation of a variety of genes involved in anti-apoptosis and cell proliferation [21,22,24].

The expression of YAP is associated with resistance to various chemotherapeutic drugs confirmed in several studies. Upregulation of YAP causes resistance of mammary and ovarian cancer cells to the chemotherapeutic drugs Taxol and cisplatin [30,81,82,85]. Besides, YAP is found de-acetylated by SIRT1 and translocated into the nucleus in HCC during cisplatin treatment, which leads to cisplatin resistance in HCC [100]. YAP nuclear translocation induced by hypoxia in HCC also causes cells to become less sensitive to sorafenib, a first-line treatment drug for HCC [101]. HCC with high levels of YAP expression are also resistant to doxorubicin [102]. Besides, overexpression of YAP mediates the resistance of senescent cells to doxorubicin through upregulation of the anti-apoptotic protein survivin [103]. Additionally, high levels of nuclear-localized YAP has been found in colon cancer cells that are resistant to antimetabolite 5-flurouracil as well as castration-resistant prostate tumor samples [104,105]. Moreover, YAP also mediates the resistance of BRAF mutant cancer cells to either BRAF inhibitor vemurafenib or MEK inhibitor trametinib through upregulation of the downstream anti-apoptotic protein BCL-XL [106]. However, YAP also transcriptionally upregulates *RAS* genes through TEAD in NF2-loss thyroid cancers and sensitizes cells to MEK inhibitor AZD6244 [107]. In addition, enhanced YAP is associated with the resistance of lung cancer cells to EGFR tyrosine kinase inhibitors through upregulation of the downstream target AXL and the activation of ERK [108]. Consistently, reduced levels of YAP in various cancer cells sensitize these cells to cisplatin and the EGFR inhibitors erlotinib and cetuximab [85,109,110].

The activation of YAP may play a critical role in the resistance of cancer cells to various therapeutic drugs. For example, we have recently demonstrated that in response to antitubulin drug treatments, activated CDK1 can negatively regulate YAP by directly phosphorylating YAP on five sites with an SP (S, Serine; P, Proline) motif. This phosphorylation can dramatically decrease the interaction between YAP and TEAD transcription factor and sensitize cancer cells to antimicrotubule drug treatments [111]. Therefore, the identification of the upstream regulators and downstream mediators of YAP during chemotherapeutic drug response may be critical to understanding how activation of YAP causes resistance to different drug treatments.

TAZ

TAZ was identified as a 14-3-3 binding protein in 2000 [112]. Further studies have indicated that TAZ is a paralog of YAP in mammals and regulated by the Hippo pathway [23]. Therefore, TAZ shares many functions with YAP. TAZ has been identified as an oncogene and is involved in the development and metastasis of various types of cancers [23,113]. High levels of TAZ are detected in basal-like BC cells and patient tissues [31,70,114].

Overexpression of TAZ causes resistance of mammary cells to Taxol, whereas knockdown of TAZ by shRNA in BC cells sensitizes these cells to Taxol [114]. Besides, we also found that TAZ can be directly phosphorylated by CDK1, which further causes TAZ degradation and therefore reverses TAZ-related cell resistance to antitubulin drugs [115]. Moreover, TAZ overexpression in Ras-transformed MCF10A-T1K cells increases multidrug resistance protein levels and results in cellular resistance to paclitaxel and doxorubicin [39]. Besides, TAZ is required for maintaining the properties of breast CSCs and causes resistance of these cells to Taxol and doxorubicin [31,39].

Our laboratory provided first evidence that overexpression of TAZ causes resistance of mammary cells to Taxol treatment by upregulating its downstream target genes, CTGF and Cyr61, through activation of transcription factor TEAD [114]. It has previously been shown that Cyr61 reduces chemosensitivity to Taxol by activating an integrin-MAPK pathway [116]. Therefore, it is possible that TAZ induces Taxol resistance through a novel TEAD-Cyr61/CTGF-integrin-MAPK pathway. However, it remains to be explored whether this pathway is also important in mediating TAZ-mediated resistance to other drugs.

8.3 TARGETING THE HIPPO PATHWAY FOR CANCER CHEMOTHERAPY

As stated above, dysregulation of the Hippo pathway plays important roles in the development and progression of a wide variety of human cancers and is critical for their response to chemotherapeutic drug treatments. Therefore, targeting the Hippo pathway will be a novel strategy for cancer therapy.

8.3.1 Drugs Targeting the Hippo Pathway

Currently, most of the drugs that target the Hippo pathway act by either activating the TSGs MST/LATS or inactivating the oncogenes YAP/TAZ directly or indirectly (Table 8.1 and Fig. 8.2).

8.3.1.1 MST and LATS Activation

Activation of MST or LATS can inhibit cancer cell growth by promoting the phosphorylation and inactivation of YAP and TAZ (Fig. 8.1). Although no drug has been developed so far to directly activate MST/LATS, many drugs have been used to indirectly activate MST/LATS by modulating its upstream signaling (Table 8.1; Fig. 8.2). For example, since F-actin has been shown to inhibit MST/LATS [117,118], inhibition of F-actin polymerization directly [Cytochalasin (Cyt D) and Latrunculin (Lat) A/B] or indirectly through inhibition of upstream regulators such as Rho (Botulinum toxin C3) and ROCK (Y27632 or HA1077) can activate the Hippo pathway by activating MST/LATS [60,119] (Fig. 8.2). In addition, statins and simvastatin can also activate LATS through Rho inhibition by suppressing HMG-CoA reductase activity in the mevalonate pathway [120,121]. Moreover, dobutamine or epinephrine, agonists of GPCRs (coupled with Gs), can also activate LATS and the Hippo pathway through activation of PKA, whereas QLT0267, an ILK inhibitor, reduces BC cell growth by activating MST [122,123] (Fig. 8.2).

TABLE 8.1 Drugs Targeting the Hippo Pathway

Target	Drugs	Working mechanism	References
AMPK (5' AMP-activated protein kinase)	Metformin, C19	Inhibiting YAP activity by activating AMPK	[62–64,134,135]
Cdk1	Taxol	Inhibiting YAP/TAZ activity by activating Cdk1	[111,115]
F-actin	Latrunculin A/B	Activating LATS through regulating F-actin polymerization	[117]
	Cytochalasin D	Activating LATS through regulating F-actin polymerization	[117,118]
GPCR	Dobutamine, epnephrine	Activating LATS by regulating its upstream regulator GPCR	[59,123]
HMG-CoA reductase, Rho	Statins, Simvastatin	Activating MST/LATS activity through Rho GTPases	[60]
		by inhibiting HMG-CoA in the mevalonate pathway	[120,121]
ILK	QLT0267	Activating MST by inhibiting ILK activity	[122]
MST	C19	Activating MST	[136]
PKA	Ibudilast, rolipram	Activating LATS by increasing PKA activity	[47,59,60]
PKC	Auranofin	Inhibiting YAP through AMOT by inhibiting PKC	[135]
Rho	Botulinum toxin C3	Activating LATS through inhibition of Rho GTP activity	[66,118]
ROCK	Y27632,HA1077	Activating LATS though inhibition of ROCK	[66,119]
Tankyrase	XAV939	Inhibiting YAP activity by activating its inhibitor angiomotin	[110]
YAP	Super-TDU	Peptides inhibiting YAP-TEAD interaction	[127]
	Cyclic peptides	Peptides disrupting YAP-TEAD interaction	[125,126]
	C108	Promoting YAP degradation	Guan Patent
	Flufenamic acid	Disrupting YAP-TEAD interacting	[124]
	Verteporfin	Disrupt YAP-TEAD interaction	[128–130]
TAZ	Rottlerin	TAZ inhibitor	[136]
VEGFR PDGFR	Pazopanib	Inhibit YAP/TAZ nuclear localization by inhibiting VEGFR and PDGFR	[142]
Yes	Dasatinib	Activating kinase activity of Yes (YAP/TAZ activator)	[143]

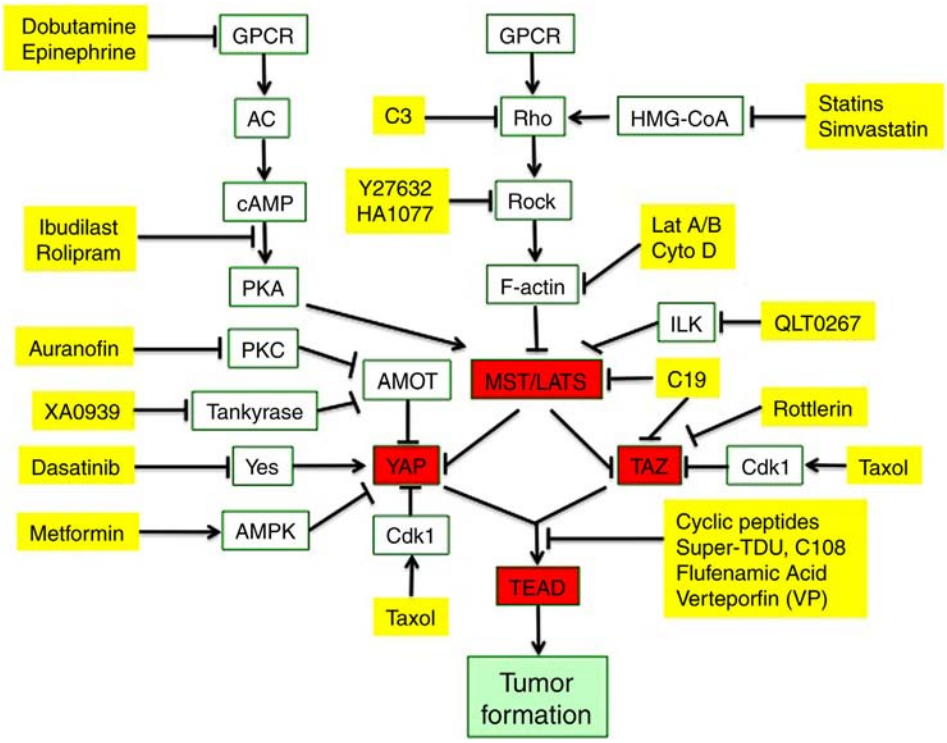

FIG. 8.2 **Regulators of the Hippo pathway and relevant drugs targeting the Hippo pathway.** Abbreviations: GPCR, G protein-coupled receptor; ILK, integrin-linked kinase; PKC, protein kinase C; AC, adenylate cyclase; cAMP, cyclic adenosine monophosphate; AMPK, 5′ AMP-activated protein kinase.

8.3.1.2 Inhibition of YAP/TAZ-TEAD Interaction

The YAP/TAZ oncogene is a major output of the Hippo pathway (Fig. 8.1). Since YAP/TAZ is a transcriptional co-activator with no enzymatic activity, directly inhibiting YAP/TAZ is challenging. However, it has been shown that YAP/TAZ causes tumorigenic phenotypes through interaction and activation of transcription factor TEAD [27]. Therefore, disruption of YAP/TAZ interaction with TEAD to inhibit YAP/TAZ tumorigenic function represents an attractive strategy to target the Hippo pathway for cancer therapy [124]. Based on the crystallographic structure of the YAP-TEAD4 complex and using a combination of engineering approaches, a series of cyclic peptide mimics have been designed and shown to be able to effectively block YAP-TEAD interaction [125,126]. In addition, a 48-mer peptide called "Super-TDU", which is derived from the sequence of VGLL4 that is critical for inhibition of YAP, was also designed and found to specifically disrupt YAP-TEAD interaction [127]. Significantly, these peptides were shown to suppress tumor growth both *in vitro* in cell lines and *in vivo* in a xenograft mouse model. However, since the cost of manufacturing peptide-based compounds is high and peptide-based compounds can be quickly degraded *in vivo*, it is still challenging to administer these peptide drugs to cancer patients.

Small molecular drugs (SMDs) are easy to synthesize and relatively stable *in vivo*. Therefore, they are the cost-effective drugs commonly used for targeted therapies. Currently, Verteporfin (VP) is the only SMD that has been shown to directly disrupt the YAP–TEAD interaction. In a search for SMDs blocking YAP–TEAD interaction, Pan and colleagues used a YAP–TEAD transcriptional activating luciferase reporter to screen a library of 3300 FDA-approved SMDs. VP was identified from the screen [128]. VP can directly disrupt YAP-TEAD interaction *in vitro* and *in vivo* in a dose-dependent manner and inhibit YAP-TEAD transcriptional activation function. Most significantly, this and later studies showed that VP treatment dramatically suppressed the growth of various cancers caused by YAP overexpression in xenograft mouse models *in vivo* [128–130].

8.3.1.3 Targeting Proteins Regulating YAP/TAZ

(1) Kinases: Since direct targeting of YAP/TAZ is difficult, targeting the positive or negative regulators of YAP/TAZ becomes one of the important strategies targeting the Hippo pathway. Since kinases are druggable by SMDs, they are attractive targets for inhibiting YAP/TAZ activity. Recently, Yes proto-oncogene was found to be crucial for the formation of a transcriptional complex including YAP and β-catenin [131]. Interestingly, inhibition of Yes by Dasatinib can suppress cancer cell growth by inhibiting YAP–catenin complex function. In addition, 5' AMP-activated protein kinase (AMPK) has also been shown to phosphorylate YAP and inhibit its function under energy (e.g., glucose) deprivation. Metformin, a drug used for the treatment of diabetes, can suppress YAP through activation of AMPK [62–64]. Moreover, we have recently shown that antitubulin drugs such as Taxol can activate Cdk1, which subsequently phosphorylates and inactivates YAP/TAZ to induce cancer cell death [111,115]. In this case, studies on drugs modulating the activity of Cdk1 could also be used to identify drugs that regulate YAP/TAZ functions.

(2) Proteins regulating YAP/TAZ nuclear localization and stability: Since YAP/TAZ functions as a transcriptional co-activator in the nucleus, inhibition of their nuclear localization is another strategy for inhibiting YAP/TAZ function. The AMOT family of proteins has recently been shown to negatively regulate the oncogenic properties of YAP/TAZ by inhibiting its nuclear localization through direct protein–protein interactions [132–134]. Therefore, activation of AMOT could be another strategy to inhibit YAP/TAZ in cancer (Fig. 8.2). It has been recently reported that XA0939, an inhibitor of tankyrase that can cause AMOT degradation through E3 ligase RNF146, can inhibit YAP nuclear localization through AMOT [110]. On the other hand, atypical protein kinase C (PKCι) can directly phosphorylate AMOT, whose phosphorylation inhibits YAP1 binding and increases YAP nuclear localization. Therefore, treatment of tumor cells with the PKCι inhibitor Auranofin can decrease YAP nuclear localization and tumor growth *in vitro* and *in vivo* through activation of AMOT [135].

Another way to inhibit YAP/TAZ function is to induce YAP/TAZ protein degradation [136]. Recently, C19, a newly identified SMD, was shown to cause TAZ degradation by activation of GSK3β, a negative regulator of TAZ [137,138]. In addition, in a screen for YAP/TAZ inhibitors, the SMD C108 was shown to inhibit YAP/TAZ by promoting their degradation (Guan Patent). The molecular mechanism underlying C108-induced YAP/TAZ degradation is unclear. However, it is suggested that C108 may be targeting the de-ubiquitinating enzymes critical for regulating YAP/TAZ protein stability [139].

8.3.2 Targeting Hippo Pathways to Improve Response to Chemotherapy

As discussed above, mounting evidence suggests that inactivation of the Hippo pathway by upregulating oncoproteins such as YAP/TAZ or downregulating TSGs such as LATS1/2 or MST1/2 may represent a major event leading to resistance of cancer cells to various chemotherapeutic drugs. Therefore, activation of the Hippo pathway by activating MST/LATS or inactivating YAP/TAZ may sensitize drug-resistant cancer cells to chemotherapeutic drug treatments. Since MST/LATS is not druggable, YAP and TAZ are the potential therapeutic targets to improve response to chemotherapy.

Many studies have shown that knockdown of YAP or TAZ genetically by RNA interference (RNAi) in various cancer cells leads to improved response to a wide variety of chemotherapeutic drugs including antitubulin drugs (Taxol, vinblastine, etc.), cisplatin, EGFR inhibitors (e.g., erlotinib, gefitinib, and cetuximab), c-Abl inhibitor (e.g., imatinib), and RAF and MEK inhibitors [106,108,114,140]. One good example of these findings is the manipulation of YAP in coping with RAF and MEK inhibitor drug resistance. Although RAF- and MEK-targeted therapy has been widely used for the treatment of melanoma and NSCLC, resistance to this therapy is a major obstacle for successful treatment. Through a genetic screen, YAP was identified as a gene-promoting resistance of cancer cells to RAF and MEK inhibitors [106]. Most significantly, knockdown of YAP by RNAi in drug-resistant melanoma, colon, and thyroid cells caused synthetically lethal with RAF/MEK inhibitor treatment, suggesting that inactivation of YAP is an attractive strategy to treat cancers resistant to RAF and MEK inhibitors.

Other studies demonstrate that targeting YAP/TAZ using SMDs may sensitize cancers to various chemotherapies. For example, the levels of YAP and TAZ are negatively correlated with the sensitivity of cancer cells to Taxol [111,114]. Most significantly, it has recently been shown that treatment of Taxol-resistant colon cancer cells with the YAP inhibitor VP reverses the resistance to Taxol [141]. In addition, combined treatment of BC cells with the YAP/TAZ inhibitors Dasatinib and pazopanib also sensitizes BC cells to both doxorubicin and Taxol [142]. Moreover, activation of YAP was found to be responsible for hypoxia-induced resistance of HCC to Sorafenib, a multikinase inhibitor [101]. Treatment of drug-resistant HCC cells with VP sensitizes these cells to Sorafenib treatment. Similarly, treatment of Sorafenib-resistant HCC cells with statins, which inactivate YAP through activation of the Hippo pathway (Fig. 8.2), overcomes Sorafenib resistance, leading to improved response to Sorafenib therapy [101].

Interestingly, a screen for genetic markers associated with sensitivity or resistance to SMDs revealed a combination of two FDA-approved SMDs, statins and Dasatinib, as an effective cotreatment strategy to potently inhibit YAP/TAZ in cancer cells [143]. Compared to single drug treatment, combined treatment of BC cells with these two drugs significantly sensitized cancer cells to Taxol treatment. Therefore, combined treatment of cancer cells with inhibitors targeting the Hippo pathway may result in better outcomes in the treatment of drug-resistant cancers.

8.4 CONCLUSION

In conclusion, dysregulation of the Hippo pathway plays important roles not only in tumorigenesis, but also in drug resistance. Newly published data strongly suggest that targeting the Hippo pathway is a novel and attractive strategy to improve the response of drug-resistant cancer cells to chemotherapy. Therefore, the development of more SMDs directly

targeting the core Hippo components will significantly enhance our ability to treat drug-resistant cancer patients in the future.

Acknowledgments

We would like to thank Canadian Institute of Health Research (#119325, 148629) (XY), the Canadian Breast Cancer Foundation/Canadian Cancer Society (XY) and the Ontario Trillium Scholarship (OTS, Canada) and the CIHR/Terry Fox Foundation Training Program in Transdisciplinary Cancer Research (YZ) for their financial support.

Conflict of Interest: No potential conflicts of interest were disclosed.

References

[1] Pan D. The hippo signaling pathway in development and cancer. Dev Cell 2010;19:491–505.
[2] Yu F, Guan K. The Hippo pathway: regulators and regulations. Genes Dev 2013;27:355–71.
[3] Chan SW, Lim CJ, Huang C, Chong YF, Gunaratne HJ, Hogue KA, et al. WW domain-mediated interaction with Wbp2 is important for the oncogenic property of TAZ. Oncogene 2011;30:600–10.
[4] Halder G, Johnson RL. Hippo signaling: growth control and beyond. Development 2011;138(1):9–22.
[5] Harvey KF, Zhang X, Thomas DM. The Hippo pathway and human cancer. Nat Rev Cancer 2013;13:246–57.
[6] Harvey K, Tapon N. The Salvador–Warts–Hippo pathway—an emerging tumour-suppressor network. Nat Rev Cancer 2007;7:182–91.
[7] Hiemer SE, Varelas X. Stem cell regulation by the Hippo pathway. Biochim Biophys Acta 2013;1830:2323–34.
[8] Zhao B, Lei Q, Guan K. The Hippo–YAP pathway: new connections between regulation of organ size and cancer. Curr Opin Cell Biol 2008;20:638–46.
[9] Zhao B, Tumaneng K, Guan K-L. The Hippo pathway in organ size control, tissue regeneration and stem cell self-renewal. Nat Cell Biol 2011;13:877–83.
[10] Xu T, Rubin GM. Analysis of genetic mosaics in developing and adult Drosophila tissues. Development 1993;117(4):1223–37.
[11] Xu T, Wang W, Zhang S, Stewart RA, Yu W. Identifying tumor suppressors in genetic mosaics: the *Drosophila* lats gene encodes a putative protein kinase. Development 1995;121(4):1053–63.
[12] Justice RW, Zilian O, Woods DF, Noll M, Bryant PJ. The *Drosophila* tumor suppressor gene warts encodes a homolog of human myotonic dystrophy kinase and is required for the control of cell shape and proliferation. Genes Dev 1995;9(5):534–46.
[13] Wu S, Huang J, Dong J, Pan D. Hippo encodes a Ste-20 family protein kinase that restricts cell proliferation and promotes apoptosis in conjunction with salvador and warts. Cell 2003;114(4):445–56.
[14] Harvey KF, Pfleger CM, Hariharan IK. The *Drosophila* Mst ortholog, hippo, restricts growth and cell proliferation and promotes apoptosis. Cell 2003;114:457–67.
[15] Udan RS, Kango-Singh M, Nolo R, Tao C, Halder G. Hippo promotes proliferation arrest and apoptosis in the Salvador/Warts pathway. Nat Cell Biol 2003;5(10):914–20.
[16] Chan EHY, Nousiainen M, Chalamalasetty RB, Schäfer A, Nigg EA, Silljé HHW. The Ste20-like kinase Mst2 activates the human large tumor suppressor kinase Lats1. Oncogene 2005;24:2076–86.
[17] Lai Z-C, Wei X, Shimizu T, Ramos E, Rohrbaugh M, Nikolaidis N, et al. Control of cell proliferation and apoptosis by Mob as tumor suppressor Mats. Cell 2005;120(5):675–85.
[18] Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, et al. Elucidation of a universal size-control mechanism in *Drosophila* and mammals. Cell 2007;130:1120–33.
[19] Huang J, Wu S, Barrera J, Matthews K, Pan D. The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the *Drosophila* homolog of YAP. Cell 2005;122:421–34.
[20] Saucedo LJ, Edgar BA. Filling out the Hippo pathway. Nat Rev Mol Cell Biol 2007;8(8):613–21.
[21] Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, et al. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev 2007;21:2747–61.
[22] Hao Y, Chun A, Cheung K, Rashidi B, Yang X. Tumor suppressor LATS1 is a negative regulator of oncogene YAP. J Biol Chem 2008;283:5496–509.
[23] Lei Q-Y, Zhang H, Zhao B, Zha Z-Y, Bai F, Pei X-H, et al. TAZ promotes cell proliferation and epithelial–mesenchymal transition and is inhibited by the hippo pathway. Mol Cell Biol 2008;28:2426–36.

[24] Zhao B, Li L, Tumaneng K, Wang C, Guan K. A coordinated phosphorylation by Lats and CK1 regulates YAP stability through. Genes Dev 2010;24:72–85.
[25] Liu C-Y, Zha Z-Y, Zhou X, Zhang H, Huang W, Zhao D, et al. The hippo tumor pathway promotes TAZ degradation by phosphorylating a phosphodegron and recruiting the SCF{beta}-TrCP E3 ligase. J Biol Chem 2010;285:37159–69.
[26] Thompson BJ, Cohen SM. The Hippo pathway regulates the bantam microRNA to control cell proliferation and apoptosis in *Drosophila*. Cell 2006;126(4):767–74.
[27] Zhao B, Ye X, Yu J, Li L, Li W, Li S, et al. TEAD mediates YAP-dependent gene induction and growth control. Genes Dev 2008;22:1962–71.
[28] Lamar JM, Stern P, Liu H, Schindler JW, Jiang Z-G, Hynes RO. The Hippo pathway target, YAP, promotes metastasis through its TEAD-interaction domain. Proc Natl Acad Sci USA 2012;109:E2441–50.
[29] Yang N, Morrison CD, Liu P, Miecznikowski J, Bshara W, Han S, et al. TAZ induces growth factor-independent proliferation through activation of EGFR ligand amphiregulin. Cell Cycle 2012;11(15):2922–30.
[30] Overholtzer M, Zhang J, Smolen GA, Muir B, Li W, Sgroi DC, et al. Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. Proc Natl Acad Sci USA 2006;103:12405–10.
[31] Bartucci M, Dattilo R, Moriconi C, Pagliuca A, Mottolese M, Federici G, et al. TAZ is required for metastatic activity and chemoresistance of breast cancer stem cells. Oncogene 2014;34:681–90.
[32] Yu J, Zheng Y, Dong J, Klusza S, Deng W-M, Pan D. Kibra functions as a tumor suppressor protein that regulates Hippo signaling in conjunction with Merlin and Expanded. Dev Cell 2010;18:288–99.
[33] Baumgartner R, Poernbacher I, Buser N, Hafen E, Stocker H. The WW domain protein Kibra acts upstream of Hippo in *Drosophila*. Dev Cell 2010;18:309–16.
[34] Genevet A, Wehr MC, Brain R, Thompson BJ, Tapon N. Kibra is a regulator of the Salvador/Warts/Hippo signaling network. Dev Cell 2010;18:300–8.
[35] Visser-Grieve S, Hao Y, Yang X. Human homolog of *Drosophila* expanded, hEx, functions as a putative tumor suppressor in human cancer cell lines independently of the Hippo pathway. Oncogene 2011;31:1189–95.
[36] Angus L, Moleirinho S, Herron L, Sinha A, Zhang X, Niestrata M, et al. Willin/FRMD6 expression activates the Hippo signaling pathway kinases in mammals and antagonizes oncogenic YAP. Oncogene 2012;31:238–50.
[37] Yin F, Yu J, Zheng Y, Chen Q, Zhang N, Pan D. Spatial organization of Hippo signaling at the plasma membrane mediated by the tumor suppressor Merlin/NF2. Cell 2013;154:1342–55.
[38] Murugan P, Sarkeshik A, Yates JR, McCollum D. Angiomotin family proteins are novel activators of the LATS2 kinase tumor suppressor. Mol Biol Cell 2011;22:3725–33.
[39] Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, et al. The Hippo transducer TAZ confers cancer stem cell-related traits on breast cancer cells. Cell 2011;147:759–72.
[40] Chen D, Sun Y, Wei Y, Zhang P, Rezaeian AH, Teruya-Feldstein J, et al. LIFR is a breast cancer metastasis suppressor upstream of the Hippo–YAP pathway and a prognostic marker. Nat Med 2012;18:1511–7.
[41] Khokhlatchev A, Rabizadeh S, Xavier R, Nedwidek M, Chen T, Zhang X, et al. Identification of a novel Ras-regulated proapoptotic pathway. Curr Biol 2002;12:253–65.
[42] Guo C, Zhang X, Pfeifer GP. The tumor suppressor RASSF1A prevents dephosphorylation of the mammalian STE20-like kinases MST1 and MST2. J Biol Chem 2011;286:6253–61.
[43] Guo C, Tommasi S, Liu L, Yee J-K, Dammann R, Pfeifer GP. RASSF1A is part of a complex similar to the *Drosophila* Hippo/Salvador/Lats tumor-suppressor network. Curr Biol 2007;17:700–5.
[44] Poon CLC, Lin JI, Zhang X, Harvey KF. The sterile 20-like kinase Tao-1 controls tissue growth by regulating the Salvador–Warts–Hippo pathway. Dev Cell 2011;21:896–906.
[45] Boggiano JC, Vanderzalm PJ, Fehon RG. Tao-1 phosphorylates Hippo/MST kinases to regulate the Hippo–Salvador–Warts tumor suppressor pathway. Dev Cell 2011;21:888–95.
[46] Mohseni M, Sun J, Lau A, Curtis S, Goldsmith J, Fox VL, et al. A genetic screen identifies an LKB1-MARK signalling axis controlling the Hippo–YAP pathway. Nat Cell Biol 2014;16:108–17.
[47] Yu F-X, Zhang Y, Park HW, Jewell JL, Chen Q, Deng Y, et al. Protein kinase A activates the Hippo pathway to modulate cell proliferation and differentiation. Genes Dev 2013;27:1223–32.
[48] Kim M, Kim M, Lee S, Kuninaka S, Saya H, Lee H, et al. cAMP/PKA signalling reinforces the LATS–YAP pathway to fully suppress YAP in response to actin cytoskeletal changes. EMBO J 2013;32:1543–55.
[49] Romano D, Matallanas D, Weitsman G, Preisinger C, Ng T, Kolch W. Proapoptotic kinase MST2 coordinates signaling crosstalk between RASSF1A, Raf-1, and Akt. Cancer Res 2010;70:1195–203.

[50] Romano D, Nguyen LK, Matallanas D, Halasz M, Doherty C, Kholodenko BN, et al. Protein interaction switches coordinate Raf-1 and MST2/Hippo signalling. Nat Cell Biol 2014;16:673–84.
[51] Reddy B, Irvine KD. Regulation of Hippo signaling by EGFR-MAPK signaling through Ajuba family proteins. Dev Cell 2013;24:459–71.
[52] Das Thakur M, Feng Y, Jagannathan R, Seppa MJ, Skeath JB, Longmore GD. Ajuba LIM proteins are negative regulators of the Hippo signaling pathway. Curr Biol 2010;20:657–62.
[53] Rauskolb C, Sun S, Sun G, Pan Y, Irvine KD. Cytoskeletal tension inhibits Hippo signaling through an Ajuba–Warts complex. Cell 2014;158:143–56.
[54] Ho K, Zhou Z, She Y, Chun A, Cyr TD, Yang X. Itch E3 ubiquitin ligase regulates large tumor suppressor 1 tumor-suppressor stability. PNAS 2011;108:4870–5.
[55] Xu Y, Stamenkovic I, Yu Q. CD44 attenuates activation of the hippo signaling pathway and is a prime therapeutic target for glioblastoma. Cancer Res 2010;70:2455–64.
[56] Sainio M, Zhao F, Heiska L, Turunen O, den Bakker M, Zwarthoff E, et al. Neurofibromatosis 2 tumor suppressor protein colocalizes with ezrin and CD44 and associates with actin-containing cytoskeleton. J Cell Sci 1997;110:2249–60.
[57] Yu S, Cai X, Wu C, Wu L, Wang Y, Liu Y, et al. Adhesion glycoprotein CD44 functions as an upstream regulator of a network connecting ERK AKT and Hippo–YAP pathways in cancer progression. Oncotarget 2015;6:2951–65.
[58] Zhang Y, Xia H, Ge X, Chen Q, Yuan D, Chen Q, et al. CD44 acts through RhoA to regulate YAP signaling. Cell Signal 2014;26:2504–13.
[59] Yu F-X, Zhao B, Panupinthu N, Jewell JL, Lian I, Wang LH, et al. Regulation of the Hippo–YAP pathway by G-protein-coupled receptor signaling. Cell 2012;150(4):780–91.
[60] Mo J-S, Yu F-X, Gong R, Brown JH, Guan K-L. Regulation of the Hippo–YAP pathway by protease-activated receptors (PARs). Genes Dev 2012;26:2138–43.
[61] Zhou X, Wang S, Wang Z, Feng X, Liu P, et al. Estrogen regulates Hippo signaling via GPER in breast cancer. J Clin Invest 2015;125:2123–35.
[62] DeRan M, Yang J, Shen C-H, Peters EC, Fitamant J, Chan P, et al. Energy stress regulates Hippo–YAP signaling involving AMPK-mediated regulation of angiomotin-like 1 protein. Cell Rep 2014;9:495–503.
[63] Wang W, Xiao Z, Li X, Aziz KE, Gan B, Johnson RL, et al. AMPK modulates Hippo pathway activity to regulate energy homeostasis. Nat Cell Biol 2015;17:490–9.
[64] Mo J-S, Meng Z, Kim YC, Park HW, Hansen CG, Kim S, et al. Cellular energy stress induces AMPK-mediated regulation of YAP and the Hippo pathway. Nat Cell Biol 2015;17:500–10.
[65] Calvo F, Ege N, Grande-Garcia A, Hooper S, Jenkins RP, Chaudhry SI, et al. Mechanotransduction and YAP-dependent matrix remodelling is required for the generation and maintenance of cancer-associated fibroblasts. Nat Cell Biol 2013;15(6):637–46.
[66] Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, et al. Role of YAP/TAZ in mechanotransduction. Nature 2011;474:179–83.
[67] Wrighton KH. Mechanotransduction: YAP and TAZ feel the force. Nat Rev Mol Cell Biol 2011;12(7):404.
[68] St John MA, Tao W, Fei X, Fukumoto R, Carcangiu ML, Brownstein DG. Mice deficient of Lats1 develop soft-tissue sarcomas, ovarian tumours and pituitary dysfunction. Nat Genet 1999;21:182–6.
[69] Zhou D, Conrad C, Xia F, Park J-S, Payer B, Yin Y, et al. Mst1 and Mst2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the Yap1 oncogene. Cancer Cell 2009;16:425–38.
[70] Chan SW, Lim CJ, Guo K, Ng CP, Lee I, Hunziker W, et al. A role for TAZ in migration, invasion, and tumorigenesis of breast cancer cells. Cancer Res 2008;68:2592–8.
[71] Wang X, Su L, Ou Q. Yes-associated protein promotes tumour development in luminal epithelial derived breast cancer. Eur J Cancer 2012;48:1227–34.
[72] Su LL, Ma WX, Yuan JF, Shao Y. XW and JS expression of Yes-associated protein in non-small cell lung cancer and its relationship with clinical pathological factors. Chin Med J (Engl) 2012;125:4003–8.
[73] Noguchi S, Saito A, Horie M, Mikami Y, Suzuki HI, Morishita Y, et al. An integrative analysis of the tumorigenic role of TAZ in human non-small cell lung cancer. Clin cancer Res 2014;20:4660–72.
[74] Han S, Bai E, Jin G, He C, Guo X, Wang L, et al. Expression and clinical significance of YAP, TAZ, and AREG in hepatocellular carcinoma. J Immunol Res 2014;2014:261365.

[75] Wang L, Shi S, Guo Z, Zhang X, Han S, Yang A, et al. Overexpression of YAP and TAZ is an independent predictor of prognosis in colorectal cancer and related to the proliferation and metastasis of colon cancer cells. PLoS ONE 2013;8:e65539.
[76] Yuen H-F, McCrudden CM, Huang Y-H, Tham JM, Zhang X, Zeng Q, et al. TAZ expression as a prognostic indicator in colorectal cancer. PLoS ONE 2013;8:e54211.
[77] Ehsanian R, Brown M, Lu H, Yang XP, Pattatheyil A, Yan B, et al. YAP dysregulation by phosphorylation or ΔNp63-mediated gene repression promotes proliferation, survival and migration in head and neck cancer subsets. Oncogene 2010;29(46):6160–71.
[78] Ge L, Smail M, Meng W, Shyr Y, Ye F, Fan K-H, et al. Yes-associated protein expression in head and neck squamous cell carcinoma nodal metastasis. PLoS ONE 2011;6(11). e27529.
[79] Wei Z, Wang Y, Li Z, Yuan C, Zhang W, Wang D, et al. Overexpression of Hippo pathway effector TAZ in tongue squamous cell carcinoma: correlation with clinicopathological features and patients' prognosis. J Oral Pathol Med 2013;42(10):747–54.
[80] Hiemer SE, Zhang L, Kartha VK, Packer TS, Almershed M, Noonan V, et al. A YAP/TAZ-regulated molecular signature is associated with oral squamous cell carcinoma. Mol Cancer Res 2015;13(6):957–68.
[81] Jeong W, Kim S-B, Sohn BH, Park Y-Y, Park ES, Kim SC, et al. Activation of YAP1 is associated with poor prognosis and response to taxanes in ovarian cancer. Anticancer Res 2014;34:811–7.
[82] Zhang X, George J, Deb S, Degoutin JL, Takano EA, Fox SB, et al. The Hippo pathway transcriptional co-activator, YAP, is an ovarian cancer oncogene. Oncogene 2011;30:2810–22.
[83] Hall CA, Wang R, Miao J, Oliva E, Shen X, Wheeler T, et al. Hippo pathway effector Yap is an ovarian cancer oncogene. Cancer Res 2010;70:8517–25.
[84] He C, Lv X, Hua G, Lele SM, Remmenga S, Dong J, et al. YAP forms autocrine loops with the ERBB pathway to regulate ovarian cancer initiation and progression. Oncogene 2015;34(50):6040–54.
[85] Xia Y, Chang T, Wang Y, Liu Y, Li W, Li M, et al. YAP promotes ovarian cancer cell tumorigenesis and is indicative of a poor prognosis for ovarian cancer patients. PLoS ONE 2014;9(3). e91770.
[86] Zhang L, Yang S, Chen X, Stauffer S, Yu F, Lele SM, et al. The Hippo pathway effector, YAP, regulates motility, invasion and castration-resistant growth of prostate cancer cells. Cell Biol 2015;35:00102–15.
[87] Takahashi Y, Miyoshi Y, Takahata C, Irahara N, Taguchi T. Down-regulation of LATS1 and LATS2 mRNA expression by promoter hypermethylation and its association with biologically aggressive phenotype in human breast cancers. Clin Cancer Res 2005;11:1380–5.
[88] Lin X-Y, Zhang X-P, Wu J-H, Qiu X-S, Wang E-H. Expression of LATS1 contributes to good prognosis and can negatively regulate YAP oncoprotein in non-small-cell lung cancer. Tumour Biol 2014;35:6435–43.
[89] Sasaki H, Hikosaka Y, Kawano O, Yano M, Fujii Y. Hypermethylation of the large tumor suppressor genes in Japanese lung cancer. Oncol Lett 2010;1:303–7.
[90] Ren A, Yan G, You B, Sun J. Down-regulation of mammalian sterile 20-like kinase 1 by heat shock protein 70 mediates cisplatin resistance in prostate cancer cells. Cancer Res 2008;68:2266–74.
[91] Visser S, Yang X. LATS tumor suppressor: a new governor of cellular homeostasis. Cell Cycle 2010;9:3892–903.
[92] Visser S, Yang X. Identification of LATS transcriptional targets in HeLa cells using whole human genome oligonucleotide microarray. Gene 2010;449:22–9.
[93] Ji D, Deeds SL, Weinstein EJ. A screen of shRNAs targeting tumor suppressor genes to identify factors involved in A549 paclitaxel sensitivity. Oncol Rep 2007;18(6):1499–505.
[94] Hansen TM, Rossi M, Roperch JP, Ansell K, Simpson K, Taylor D, et al. Itch inhibition regulates chemosensitivity *in vitro*. Biochem Biophys Res Commun 2007;361(1):33–6.
[95] Kawahara M, Hori T, Chonabayashi K, Oka T, Sudol M, Uchiyama T. Kpm/Lats2 is linked to chemosensitivity of leukemic cells through the stabilization of p73. Blood 2008;112(9):3856–66.
[96] Lit LC, Scott S, Zhang H, Stebbing J, Photiou A, Giamas G. LATS2 is a modulator of estrogen receptor alpha. Anticancer Res 2013;33:53–63.
[97] Takahashi Y, Miyoshi Y, Morimoto K, Taguchi T, Tamaki Y, Noguchi S. Low LATS2 mRNA level can predict favorable response to epirubicin plus cyclophosphamide, but not to docetaxel, in breast cancers. J Cancer Res Clin Oncol 2007;133(8):501–9.
[98] Sudol M. Yes-associated protein (YAP65) is a proline-rich phosphoprotein that binds to the SH3 domain of the Yes proto-oncogene product. Oncogene 1994;9:2145–52.

[99] Yagi R, Chen LF, Shigesada K, Murakami Y, Ito Y. A WW domain-containing yes-associated protein (YAP) is a novel transcriptional co-activator. EMBO J 1999;18:2551–62.
[100] Mao B, Hu F, Cheng J, Wang P, Xu M, Yuan F, et al. SIRT1 regulates YAP2-mediated cell proliferation and chemoresistance in hepatocellular carcinoma. Oncogene 2014;33:1468–74.
[101] Zhou T, Zhuang L, Hu Y, Zhou Y, Lin W, Wang D, et al. Inactivation of hypoxia-induced YAP by statins overcomes hypoxic resistance tosorafenib in hepatocellular carcinoma cells. Sci Rep 2016;6:30483.
[102] Huo X, Zhang Q, Liu AM, Tang C, Gong Y, Bian J, et al. Overexpression of Yes-associated protein confers doxorubicin resistance in hepatocellullar carcinoma. Oncol Rep 2013;29:840–6.
[103] Ma K, Xu Q, Wang S, Zhang W, Liu M, Liang S, et al. Nuclear accumulation of Yes-associated protein (YAP) maintains the survival of doxorubicin-induced senescent cells by promoting survivin expression. Cancer Lett 2016;375(1):84–91.
[104] Touil Y, Igoudjil W, Corvaisier M, Dessein A-F, Vandomme J, Monté D, et al. Colon cancer cells escape 5FU chemotherapy-induced cell death by entering stemness and quiescence associated with the c-Yes/YAP axis. Clin Cancer Res 2014;20:837–46.
[105] Jiang N, Hjorth-Jensen K, Hekmat O, Iglesias-Gato D, Kruse T, Wang C, et al. *In vivo* quantitative phosphoproteomic profiling identifies novel regulators of castration-resistant prostate cancer growth. Oncogene 2015;34:2764–76.
[106] Lin L, Sabnis AJ, Chan E, Olivas V, Cade L, Pazarentzos E, et al. The Hippo effector YAP promotes resistance to RAF- and MEK-targeted cancer therapies. Nat Genet 2015;47:250–6.
[107] Garcia-Rendueles MER, Ricarte-Filho JC, Untch BR, Landa I, Knauf JA, Voza F, et al. NF2 loss promotes oncogenic RAS-induced thyroid cancers via YAP-dependent transactivation of RAS proteins and sensitizes them to MEK inhibition. Cancer Discov 2015;5(11):1178–93.
[108] Lee JE, Park HS, Lee D, Yoo G, Kim T, Jeon H, et al. Hippo pathway effector YAP inhibition restores the sensitivity of EGFR-TKI in lung adenocarcinoma having primary or acquired EGFR-TKI resistance. Biochem Biophys Res Commun 2016;474(1):154–60.
[109] Huang J, Nagatomo I, Suzuki E, Mizuno T, Kumagai T, Berezov A, et al. YAP modifies cancer cell sensitivity to EGFR and survivin inhibitors and is negatively regulated by the non-receptor type protein tyrosine phosphatase 14. Oncogene 2013;32:2220–9.
[110] Wang H, Castillo J, Zhang Y, Yang Z, McAllister G, Lindeman A, et al. Tankyrase inhibitor sensitizes lung cancer cells to endothelial growth factor receptor (EGFR) inhibition via stabilizing angiomotins and inhibiting yap signaling. J Biol Chem 2016;291(29):15256–66.
[111] Zhao Y, Khanal P, Savage P, She Y, Cyr TD, Yang X. YAP-induced resistance of cancer cells to antitubulin drugs is modulated by a Hippo-independent pathway. Cancer Res 2014;74:4493–503.
[112] Kanai FA, Marignani P, Sarbassova D, Yagi R, Hall RA, Donowitz M, et al. TAZ: a novel transcriptional co-activator regulated by interactions with 14-3-3 and PDZ domain proteins. EMBO J 2000;19:6778–91.
[113] Zhao Y, Yang X. WWTR1 (WW domain containing transcription regulator 1). Atlas Genet Cytogenet Oncol Haematol 2014;18(11):849–52.
[114] Lai D, Ho KC, Hao Y, Yang X. Taxol resistance in breast cancer cells is mediated by the hippo pathway component TAZ and its downstream transcriptional targets Cyr61 and CTGF. Cancer Res 2011;71:2728–38.
[115] Zhao Y, Yang X. Regulation of sensitivity of tumor cells to antitubulin drugs by Cdk1-TAZ signalling. Oncotarget 2015;6:21906–17.
[116] Menendez JA, Vellon L, Mehmi I, Teng PK, Griggs DW, Lupu R. A novel CYR61-triggered "CYR61- alphavbeta3 integrin loop" regulates breast cancer cell survival and chemosensitivity through activation of ERK1/ERK2 MAPK signaling pathway. Oncogene 2005;24:761–79.
[117] Sun S, Irvine KD. Cellular organization and cytoskeletal regulation of the Hippo signaling network. Trends Cell Biol 2016;26(9):694–704.
[118] Zhao B, Li L, Wang L, Wang C-Y, Yu J, Guan K-L. Cell detachment activates the Hippo pathway via cytoskeleton reorganization to induce anoikis. Genes Dev 2012;26:54–68.
[119] Wada K-I, Itoga K, Okano T, Yonemura S, Sasaki H. Hippo pathway regulation by cell morphology and stress fibers. Development 2011;138(18):3907–14.
[120] Sorrentino G, Ruggeri N, Specchia V, Cordenonsi M, Mano M, Dupont S, et al. Metabolic control of YAP and TAZ by the mevalonate pathway. Nat Cell Biol 2014;16(4):357–66.
[121] Wang Z, Wu Y, Wang H, Zhang Y, Mei L, Fang X, et al. Interplay of mevalonate and Hippo pathways regulates RHAMM transcription via YAP to modulate breast cancer cell motility. Proc Natl Acad Sci USA 2014;111(1):E89–98.

[122] Serrano I, McDonald PC, Lock F, Muller WJ, Dedhar S. Inactivation of the Hippo tumour suppressor pathway by integrin-linked kinase. Nat Commun 2013;4:2976.
[123] Bao Y, Nakagawa K, Yang Z, Ikeda M, Withanage K, Ishigami-Yuasa M. A cell-based assay to screen stimulators of the Hippo pathway reveals the inhibitory effect of dobutamine on the YAP-dependent gene transcription. J Biochem 2011;150(2):199–208.
[124] Pobbati AV, Han X, Hung AW, Weiguang S, Huda N, Chen G-Y, et al. Targeting the central pocket in human transcription factor TEAD as a potential cancer therapeutic strategy. Structure 2015;23(11):2076–86.
[125] Zhang Z, Lin Z, Zhou Z, Shen HC, Yan SF, Mayweg AV, et al. Structure-based design and synthesis of potent cyclic peptides inhibiting the YAP-TEAD protein–protein interaction. ACS Med Chem Lett 2014;5(9):993–8.
[126] Zhou Z, Hu T, Xu Z, Lin Z, Zhang Z, Feng T, et al. Targeting Hippo pathway by specific interruption of YAP-TEAD interaction using cyclic YAP-like peptides. FASEB J 2015;29(2):724–32.
[127] Jiao S, Wang H, Shi Z, Dong A, Zhang W, Song X, et al. A peptide mimicking VGLL4 function acts as a YAP antagonist therapy against gastric cancer. Cancer Cell 2014;25(2):166–80.
[128] Liu-Chittenden Y, Huang B, Shim JS, Chen Q, Lee S-J, Anders RA, et al. Genetic and pharmacological disruption of the TEAD-YAP complex suppresses the oncogenic activity of YAP. Genes Dev 2012;26(12):1300–5.
[129] Feng X, Degese MS, Iglesias-Bartolome R, Vaque JP, Molinolo AA, Rodrigues M, et al. Hippo-independent activation of YAP by the GNAQ uveal melanoma oncogene through a trio-regulated rho GTPase signaling circuitry. Cancer Cell 2014;25(6):831–45.
[130] Yu F-X, Luo J, Mo J-S, Liu G, Kim YC, Meng Z, et al. Mutant Gq/11 promote uveal melanoma tumorigenesis by activating YAP. Cancer Cell 2014;25(6):822–30.
[131] Rosenbluh J, Nijhawan D, Cox AG, Li X, Neal JT, Schafer EJ, et al. β-Catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. Cell 2012;151(7):1457–73.
[132] Chan SW, Lim CJ, Chong YF, Pobbati AV, Huang C, Hong W. Hippo pathway-independent restriction of TAZ and YAP by angiomotin. J Biol Chem 2011;286:7018–26.
[133] Zhao B, Li L, Lu Q, Wang LH, Liu C, Lei Q, et al. Angiomotin is a novel Hippo pathway component that inhibits YAP oncoprotein. Genes Dev 2011;25:51–63.
[134] Wang W, Huang J, Chen J. Angiomotin-like proteins associate with and negatively regulate YAP1. J Biol Chem 2011;286(6):4364–70.
[135] Wang Y, Justilien V, Brennan KI, Jamieson L, Murray NR, Fields AP. PKCβ regulates nuclear YAP1 localization and ovarian cancer tumorigenesis. Oncogene 2017;36(4):534–45.
[136] Zhao Z, Zheng N, Wang L, Hou Y, Zhou X, Wang Z, et al. Rottlerin exhibits antitumor activity via down-regulation of TAZ in non-small cell lung cancer. Oncotarget 2017;8(5):7827–38. Available from: http://www.oncotarget.com/abstract/13974.
[137] Basu D, Lettan R, Damodaran K, Strellec S, Reyes-Mugica M, Rebbaa A. Identification, mechanism of action, and antitumor activity of a small molecule inhibitor of Hippo, TGF-, and Wnt signaling pathways. Mol Cancer Ther 2014;13(6):1457–67.
[138] Huang W, Lv X, Liu C, Zha Z, Zhang H, Jiang Y, et al. The N-terminal phosphodegron targets TAZ/WWTR1 protein for SCFβ-TrCP-dependent degradation in response to phosphatidylinositol 3-kinase inhibition. J Biol Chem 2012;287:26245–53.
[139] Gong R, Yu F-X. Targeting the Hippo pathway for anti-cancer therapies. Curr Med Chem 2015;22(35):4104–17.
[140] Zhao Y, Yang X. The Hippo pathway in chemotherapeutic drug resistance. Int J Cancer 2015;137:2767–73.
[141] Pan W, Wang Q, Zhang Y, Zhang N, Qin J, Li W, et al. Verteporfin can reverse the paclitaxel resistance induced by YAP over-expression in HCT-8/T cells without photoactivation through inhibiting YAP expression. Cell Physiol Biochem 2016;39(2):481–90.
[142] Oku Y, Nishiya N, Shito T, Yamamoto R, Yamamoto Y, Oyama C, et al. Small molecules inhibiting the nuclear localization of YAP/TAZ for chemotherapeutics and chemosensitizers against breast cancers. FEBS Open Biol 2015;5:542–9.
[143] Taccioli C, Sorrentino G, Zannini A, Caroli J, Beneventano D, Anderlucci L, et al. MDP, a database linking drug response data to genomic information, identifies dasatinib and statins as a combinatorial strategy to inhibit YAP/TAZ in cancer cells. Oncotarget 2015;6(36):38854–65.