



# Role of YAP/TAZ transcriptional regulators in resistance to anti-cancer therapies

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**Abstract** A diverse range of drug resistance mechanisms in cancer cells and their microenvironment significantly reduces the effectiveness of anti-cancer therapies. Growing evidence suggests that transcriptional effectors of the Hippo pathway, YAP and TAZ, promote resistance to various anti-cancer therapies, including cytotoxic chemotherapy, molecular targeted therapy, and radiation therapy. Here, we overview the role of YAP and TAZ as drug resistance mediators, and also discuss potential upstream regulators and downstream targets of YAP/TAZ in cancer. The widespread involvement of YAP and TAZ in resistance mechanisms suggests that therapeutic targeting of YAP and TAZ may expedite the development of effective anti-resistance therapies.

**Keywords** Drug · Resistance · YAP · TAZ · Hippo pathway · Biomarker

## Introduction

Advances in cancer therapies have improved patient survival in many types of cancer, but resistance against therapies crucially limits the opportunity of complete tumor remission or further survival improvement. Malignant tumors are based on complex, redundant, and heterogeneous survival mechanisms that prevent tumor

death by single pathway blockade [1–3]. Moreover, the initial response to anti-cancer therapy varies from patients to patients according to biologic properties of their tumors. Researchers are trying to identify clinical and biological markers predicting therapeutic responses, and to block innate resistance mechanisms to enhance drug efficiency. Anti-cancer therapy is also hampered by acquired resistance where tumors initially respond to therapies, but become resistant during treatment through various genetic and epigenetic changes. Several mechanisms have been implicated in acquired resistance, including amplification of therapeutic targets, emergence of gatekeeper mutations in targeted kinases, acquired mutations in upstream and downstream genes of the same pathway, activation of alternative signaling pathways, and changes in drug uptake or efflux [1, 4]. Acquired resistance in cancer cells also comes from adaptive responses such as epigenetic activation of prosurvival signaling and epithelial–mesenchymal transition (EMT), as well as from their interactions with the tumor microenvironment [5–8]. Surviving cancer cells upon anti-cancer therapies are often originated from intratumoral genetic heterogeneity and clonal selection, which make the distinction between innate and acquired resistance somewhat blurred.

It is clear that overcoming therapy resistance will benefit the majority of cancer patients, and thus developing anti-cancer agents that are free of resistance is one of the most important goals in current cancer research. A recent clinical trial showed a promising result in treating non-small cell lung cancer (NSCLC) exhibiting acquired resistant to epithelial growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs), using a new compound specific for EGFR with the T790M gatekeeper mutation [9]. In addition, a combination of an MEK inhibitor and a BRAF inhibitor has been shown to be effective for overcoming

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BRAF inhibitor resistance in melanoma [10], and various new drug combinations are now tested by clinical trials. These results demonstrate that targeting drug resistance is clinically feasible and effective in improving patient survival. However, although specific resistance mechanisms have been revealed for selected population of cancer patients, major mechanisms to explain widespread emergence of resistance are still unknown and efficient strategies to overcome resistance have not been developed for majority of anti-cancer agents.

Yes-associated protein (YAP) and its paralog transcriptional co-activator with a PDZ-binding domain (TAZ) are transcriptional regulators that play key roles in embryonic development and tissue regeneration [11, 12]. Recent findings indicate that YAP and TAZ are deeply implicated in cancer pathogenesis across multiple cancer types [13–15]. This review will highlight the role of YAP/TAZ in cancer with a special focus on their involvement in anti-cancer therapy resistance.

## The Hippo-YAP/TAZ pathway

Components of the Hippo pathway were first discovered as organ size regulators in *Drosophila* [16, 17]. Inactivation of Hippo pathway genes *Warts*, *Hippo*, *Salvador*, and *Mats* has been shown to cause significant increases in the size of multiple organs as a result of excessive cell proliferation and defective cell death [16, 18–23]. A screen for Warts-interacting proteins also identified Yorkie (Yki), the *Drosophila* ortholog of the mammalian YAP, as a key link between the Hippo pathway and transcriptional control [24]. Subsequent studies have revealed analogous composition and function of the mammalian Hippo-YAP/TAZ pathway.

Detailed regulatory mechanisms and updated findings on the Hippo-YAP/TAZ pathway have been thoroughly reviewed in recent articles [12, 13, 25]. Briefly, the central components of the mammalian Hippo pathway comprise serine/threonine kinases MST1/2 (Hippo orthologs) and LATS1/2 (Warts orthologs), and scaffold proteins SAV1 (Salvador ortholog) and MOB1A/B (Mats orthologs). Upon activation by MST1/2, LATS1/2 phosphorylate serine residues in multiple HXRXXS motifs of YAP and TAZ, leading to their cytoplasmic retention and degradation [26, 27]. When the Hippo pathway is inactivated, YAP/TAZ translocate into the nucleus and upregulate the transcription of genes associated with the cell cycle, cell proliferation, and cell survival. YAP/TAZ do not bind to DNA by themselves, but they are potent transcriptional co-activators that mainly support the activity of TEA domain family member (TEAD) transcription factors [28]. In addition, YAP/TAZ interact with AP-1 [29], RUNX2 [30]

and SMADs [31], and can also suppress gene transcription via their interaction with the NuRD complex [32]. Transcriptional targets of YAP/TAZ include CTGF, ANKRD1, CYR61, ITGB2 and AXL, which have been identified by YAP/TAZ overexpression studies [28, 33]. Chromatin immunoprecipitation followed by DNA sequencing (ChIP-seq) analyses further identified a group of YAP/TAZ target genes whose major functional categories are cell proliferation, RNA metabolism, extracellular matrix (ECM) and actin cytoskeleton organization, and cell migration [29, 34]. Remarkably, it appears that specific ligands and designated transmembrane receptors are not involved in the mammalian Hippo pathway. Instead, Hippo pathway activity is controlled by various intrinsic and environmental inputs including cell polarity [35], cell–cell and cell–matrix adhesion [36, 37], matrix stiffness [38, 39], actin cytoskeleton architecture and contractility [36–38, 40], mechanical stress, and cell metabolism [41–43]. Moreover, the Hippo-YAP/TAZ pathway cross-talks with multiple other signaling pathways such as GPCR [44], EGF [45, 46], and TGF $\beta$  pathways [47], as well as canonical and non-canonical WNT pathways [48–50].

Studies using genetically engineered mouse models have demonstrated functional conservation between the *Drosophila* Hippo–Warts–Yki pathway and the mammalian Hippo-YAP/TAZ pathway. Loss of Hippo components or hyperactivation of YAP in mice causes organ size enlargement, although they may not drive growth in every tissue. For example, liver-specific knockout of MST1/2 or overexpression of YAP results in a significant increase in liver size with increased cell numbers [51–53]. Similarly, conditional SAV knockout or YAP hyperactivation promotes heart growth through cardiomyocyte proliferation [54]. Notably, YAP activation is also involved in maintaining undifferentiated status of progenitor and stem cells. Knockout of Hippo components or hyperactivation of YAP in mouse skin epidermis causes an expansion of basal progenitor cells and epidermal thickening [51, 55]. Moreover, maintenance of pluripotency in embryonic stem (ES) cells depends on YAP activity, and transcriptional targets of YAP in ES cells include a group of genes known to promote stemness [56]. In line with its role in stemness control, the Hippo-YAP/TAZ pathway has been shown to modulate the regeneration of multiple tissues [57–61].

## Role of YAP/TAZ in cancer pathogenesis

Growing evidence indicates that YAP and TAZ play important roles in pathogenic mechanisms of cancer including tumorigenesis, metastasis, and drug resistance [13–15]. It has been shown that overexpression of YAP in

mammary epithelial cells induces multiple hallmarks of cancers such as anchorage- and growth factor-independent growth, suppression of apoptosis, and EMT [62]. In vivo tumorigenic potential of YAP/TAZ activation has been validated in a number of mouse models. Long-term YAP activation or MST1/2 double knockout in the liver causes not only the enlargement of the organ but also the development of hepatocellular carcinoma [51–53]. MST1/2 double knockout also causes epithelial hyperplasia and adenoma in the colon [63]. Moreover, MOB1-depleted (*Mob1a<sup>null</sup>*; *Mob1b<sup>het</sup>* or *Mob1a<sup>het</sup>*; *Mob1b<sup>null</sup>*) mice are susceptible to developing cancers of various origins including skin cancer, osteosarcoma, fibrosarcoma, liver cancer, and breast cancer [64]. A number of xenograft studies in mice further demonstrated that inactivation of YAP or TAZ decreases tumor mass in YAP/TAZ-dependent cancers [65–69]. Together, these evidences indicate that activation of YAP/TAZ can induce cellular transformation that gives features of malignancy to non-transformed cells.

Although the overall frequency is not dramatic, recurrent mutations in genes encoding Hippo-YAP/TAZ pathway components have been reported in several types of human cancers. Germline loss-of-function mutations in *NF2* (encoding Merlin, which facilitates activation of LATS1/2 by MST1/2) are common in neurofibromatosis type 2 [70], and germline and somatic mutations of *NF2* are also reported in mesothelioma [71, 72]. Germline *YAP R331W* mutation has been reported to increase NSCLC risk [73]. *YAP* gene amplification is observed in a subset of hepatocellular carcinomas [74], esophageal squamous cell carcinomas [75], and medulloblastomas [76]. Gene fusions that occurred in *YAP* or *TAZ* are also commonly observed in epithelioid hemangioendotheliomas [77, 78]. Gene fusion and deletion in *LATS2* have been found in mesothelioma [79], and a recent cancer genome analysis identified recurrent mutations in *LATS1* gene in skin basal cell carcinoma [80]. In addition, YAP hyperactivation induced by activating mutations in *GNAQ* or *GNA11* (encoding GPCR signaling components  $G\alpha_q$  and  $G\alpha_{11}$ , respectively) is the major oncogenic driver of uveal melanomas [81, 82].

Notably, when compared with gene mutation rate, elevations of YAP/TAZ expression and their nuclear enrichment are detected much more frequently in human cancers, including liver, ovary, breast, lung, and colon cancers [83–87]. Because the Hippo-YAP/TAZ pathway receives signaling inputs from diverse sources, it is likely that multiple genetic and epigenetic perturbations in upstream regulators of YAP/TAZ may exist in various cancers independent of Hippo pathway genetic alterations, comprehensively supporting tumor development. Moreover, recent studies also found that YAP activity is required

in colon and pancreatic cancer tumorigenesis induced by KRAS and APC mutation, suggesting that YAP/TAZ activity cooperates with other oncogenic pathways in the tumorigenic process [88, 89]. Therefore, YAP and TAZ may contribute to a broad range of pathogenic mechanisms in cancer with various genetic and epigenetic alterations.

A recent genome-wide chromatin occupancy analysis done in human cholangiocarcinoma cells revealed that YAP binds to a subset of enhancers with high transcriptional outputs and recruits the mediator complex, an integrator of signals from multiple transcriptional regulators [90]. In this way, YAP plays a major role in defining transcriptional state and cell identity, and YAP/TAZ-driven transcriptional program in cancer cells appears to impose stem cell-like properties as well as to support cell proliferation [35, 91, 92]. It has been demonstrated that high levels of TAZ expression and activity are associated with higher grade histology and poor prognosis of breast cancer [35]. Loss of cell polarity protein Scribble in breast cancer stem cells enhances sustained self-renewal and tumor-initiation capacities by releasing TAZ from tumor suppressive Hippo kinases. Another recent study also demonstrated that increased interactions between YAP and transcription factor SRF in breast cancer cells induce a gene expression signature specific for mammary stem cells, and YAP-induced stemness acquisition involves IL-6 upregulation [91]. SRF–YAP–IL6 signaling is activated in basal-like breast cancer, and YAP/TAZ expression levels inversely correlate with patient survival.

YAP/TAZ activation also promotes invasion and metastasis of cancer cells. YAP/TAZ activation induces EMT, and rescues cancer cells from anoikis to promote their survival during circulation and spread from the primary sites [37, 62, 93]. YAP or TAZ knockdown in melanoma cells interferes with anchorage-independent growth, matrix invasion, and lung metastasis in xenograft models [94]. Conversely, overexpression of constitutively active YAP increases metastatic and invasive potential of breast cancer and melanoma cells, and the metastasis activity of breast cancer and melanoma cells is highly dependent on YAP-TEAD transcriptional activity [95]. Moreover, *Lats1/2* expression levels are significantly lower in metastatic prostate cancer when compared with benign prostate tissues or localized prostate cancer, implying that Hippo downregulation and YAP/TAZ upregulation may play a role in prostate cancer metastasis [37].

Although oncogenic properties of YAP/TAZ have been revealed in a number of cancer types, studies on hematologic malignancies and breast cancer suggest tumor-suppressive roles of YAP/TAZ. YAP has been shown to bind and positively regulate p73, a tumor suppressive and pro-apoptotic protein, and this interaction is countered by AKT activation [96–98]. In addition, a study reported

downregulation of YAP protein levels in breast cancer tissues, and demonstrated enhanced tumor growth after YAP knockdown [99]. Moreover, YAP expression levels are significantly reduced in hematologic cancers, and YAP downregulation prevents ABL1-induced YAP-p73 interaction which promotes DNA damage-induced apoptosis in hematologic cancers [100]. It is likely that YAP/TAZ behave either as oncogenic drivers or tumor suppressors, depending on the cellular context such as the abundance of transcriptional regulators interacting with YAP/TAZ in the nucleus.

Altogether, the evidence strongly supports critical involvement of the Hippo-YAP/TAZ pathway in cancer pathogenesis. The expanded knowledge on the Hippo-YAP/TAZ pathway allows us to understand previously unrecognized mechanisms of cancer behaviors, including stem cell-like properties, EMT, and resistance to therapies.

### Role of YAP/TAZ in resistance to anti-cancer therapies

A series of studies has demonstrated YAP/TAZ activation and concordant induction of anti-cancer therapy resistance in various tumor models, eliciting intense interest in recent years. Here, we overview recent updates on the involvement of YAP/TAZ in resistance to multiple anti-cancer treatment modalities (Table 1).

#### Cytotoxic chemotherapy

Cytotoxic chemotherapy agents interfere with cell division and survival by disturbing essential cellular processes, such as mitotic spindle formation, DNA replication, and the maintenance of DNA integrity. Despite widespread application of cytotoxic chemotherapy for many cancer types, complete cure of patients by cytotoxic agents is exceptional in many solid cancers. Once cancer cells acquire resistance to a certain regimen, they no longer respond to the specific regimen used. Recent studies have consistently suggested that YAP/TAZ upregulation confers resistance against a diverse range of cytotoxic agents such as anti-tubulin, anti-metabolite, and DNA-damaging agents.

TAZ overexpression in breast cancer cells has been shown to induce resistance to taxol and doxorubicin, and upregulation of YAP/TAZ target genes *CYR61* and *CTGF* appears to contribute to resistance development [35, 92, 101]. Similarly, YAP induces resistance to various anti-tubulin drugs, and CDK1-mediated inhibitory phosphorylation on YAP elevates sensitivity to anti-tubulin drugs [102]. In addition, cancer cell lines resistant to 5-fluorouracil (5-FU) exhibit increased YAP expression and activity, and YAP is also upregulated in therapy-

resistant colon and esophageal cancers [103, 104]. Notably, either knockdown or pharmacological inhibition of YAP sensitizes esophageal cancer cells towards 5-FU and docetaxel by suppressing YAP-mediated upregulation of EGFR [104]. Cisplatin and other platinum compounds are widely used DNA-damaging cytotoxic agents, comprising the backbone of chemotherapeutics against many cancers, including ovary, cervix, bladder, and testis cancer [105]. YAP has been reported to promote resistance to cisplatin in oral squamous cell carcinoma, urothelial cell carcinoma, and ovarian cancer [106–108]. Considering pervasive usage of cytotoxic agents in cancer treatment, YAP/TAZ-driven resistance to multiple cytotoxic agents is an issue that deserves intense attention.

#### Molecular targeted therapy

As molecular alterations of cancer have been extensively profiled by recent genomic and proteomic technologies, researchers now focus on the development of anti-cancer drugs targeting recurrently mutated oncogenic drivers. Although several targeted therapy agents against major oncogenic drivers have been developed, the effectiveness of the agents varies widely because of innate and acquired resistance. Remarkably, recent studies have demonstrated that YAP can functionally substitute for oncogenic KRAS, which is one of the most common drivers of human cancer. When the expression of oncogenic KRAS<sup>G12D</sup> was withdrawn in inducible KRAS<sup>G12D</sup>-driven mouse pancreatic ductal adenocarcinoma (PDAC), tumor regression occurred at first, but a major fraction of tumors relapsed [109]. The relapsed tumors acquired YAP amplification, and elevated YAP-TEAD2 activity was shown to enable bypass of oncogenic KRAS activity through upregulation of cell cycle and DNA replication genes. An independent study also showed that YAP activation can rescue KRAS-dependent colon cancer cells from loss of viability induced by shRNA-mediated suppression of KRAS [110]. These findings imply that YAP/TAZ activation may induce resistance to targeted anti-cancer agents specific for RAS signaling pathways.

The MAPK pathway (RAF–MEK–ERK) is a central node in regulating cell proliferation and survival, and oncogenic mutations in MAPK components, including BRAF, constitutively activate cell proliferation. BRAF inhibitors and MEK inhibitors have proved effective in treating BRAF mutant melanoma and NSCLC. However, acquired resistance occurs in the majority of patients in a short time period after initial tumor shrinkage [111, 112]. Lin et al. recently reported that YAP can mediate resistance to RAF and MEK inhibitor therapies [113]. They demonstrated that YAP serves as a parallel survival input to inhibit apoptosis upon RAF and MEK inhibitor treatment,

**Table 1** Published studies on YAP/TAZ-dependent anti-cancer therapy resistance

Type	Evidence	Proposed mechanism	References	
Cytotoxic chemotherapy	Overexpression of TAZ in breast cancer cells promotes taxol and doxorubicin resistance	TAZ induces stem cell-related traits	[35, 92]	
	Overexpression of TAZ in breast cancer cells promotes taxol resistance	TAZ activation induces CYR61/CTGF expression, and CYR61/CTGF knockdown blocks taxol-resistance	[101]	
	YAP mediates resistance to various anti-tubulin drugs in HeLa and other cancer cell lines	Anti-tubulin drug treatment activates Cdk1 to phosphorylate and inactivate YAP	[102]	
	5-FU treated colon cancer liver metastasis shows increased YAP expression, and YAP expression levels predict patient survival	c-Yes activates YAP in 5-FU resistant quiescent colon cancer cells	[103]	
	YAP activation causes resistance to 5-FU and docetaxel. YAP is overexpressed in resistant esophageal cancer tumors and 5-FU resistant cell lines.	YAP increases EGFR expression by binding to its promoter	[104]	
	Cisplatin-resistant oral squamous cancer cell lines show decreased phospho-YAP and increased nuclear YAP. YAP knockdown causes increased sensitivity to cisplatin		[106]	
	YAP activity correlates with cisplatin sensitivity of urothelial carcinoma cells. Nuclear YAP expression predicts poor outcome in urothelial carcinoma patients with chemotherapy	YAP knockdown causes increased DNA damage response and ATM activation upon cisplatin, accumulating DNA damages	[107]	
	YAP and target gene expression are increased in cisplatin-resistant ovarian cancer cells, and YAP knockdown suppresses resistant cell viability	YAP induces increased autophagy by enhancing autolysosome degradation	[108]	
	Molecular targeted therapy	YAP amplification drives tumor maintenance against KRAS withdrawal in inducible KRAS mutant pancreatic ductal adenocarcinoma model	The YAP/TEAD complex cooperates with E2F to activate cell cycle and DNA replication programs	[109]
		YAP overexpression rescues KRAS mutant colon cancer cell lines from KRAS suppression	YAP induces epithelial-mesenchymal transition by interaction with FOS	[110]
Combined YAP and RAF/MEK inhibition is synthetically lethal to BRAF or RAS-mutant tumors. Increased YAP expression is a biomarker of worse response to RAF/MEK inhibition in BRAF-mutant tumors		YAP induces the expression of Bcl-xL to antagonize anti-apoptotic signal	[113]	
BRAF inhibitor resistance of melanoma cells is dependent on YAP/TAZ activity, and inhibition of YAP/TAZ activation by actin modulation suppresses the resistance		Increased YAP/TAZ activity induces expression of E2F1-related cell cycle genes and activates EGFR, MYC, AKT	[114]	
YAP activation induces resistance to EGFR gefitinib in NSCLC cells. EGFR inhibitor resistant human NSCLC tumors show increased nuclear YAP staining compared with their pre-treatment tumors		YAP induces EMT, AXL expression, and ERK activation	[117]	
TAZ is upregulated in lung adenocarcinoma cells with EGFR T790 M mutation, and TAZ depletion sensitizes their response to gefitinib		TAZ depletion inhibits tumorigenicity, EMT, migration, and invasion of gefitinib-resistant NSCLC cells	[118]	
YAP activation signature is associated with poor response to cetuximab treatment in colorectal cancer patients			[119]	
High TAZ expression level is associated with poor response to trastuzumab in HER2-positive breast cancer patients			[120]	
YAP/TAZ inhibition diminishes matrix stiffness-dependent lapatinib resistance. Inhibition of YAP in tumor xenograft model slows the growth of HER2-amplified tumors and increases sensitivity to lapatinib		YAP and TAZ transduce resistant signals from rigid microenvironments	[121]	
Knockdown of YAP sensitizes ovarian cancer cells to cisplatin, EGFR inhibitor, and survivin inhibitor		PTPN14 downregulates YAP activity. PPXY motif containing PTPN14 fragment can sensitizes cancer cells to anti-cancer agents	[122]	



**Table 1** continued

Type	Evidence	Proposed mechanism	References
Radiotherapy	YAP expression level in pre-treatment tumor tissue correlates with poor survival of head and neck squamous cell carcinoma patients		[123]
	YAP overexpression promotes medulloblastoma tumorigenesis, and promotes survival of cerebellar granule neuron precursors cells after irradiation	YAP enables cells to enter mitosis with un-repaired DNA through driving IGF2/AKT activation, resulting in ATM/Chk2 inactivation	[124]
	YAP knockdown in urothelial carcinoma cells increases DNA damage response induced by $\gamma$ -irradiation	YAP knockdown causes increased DNA damage response and ATM activation, promoting accumulation of DNA damage	[107]

and YAP suppression significantly enhances sensitivity to RAF or MEK inhibitors. In addition, they supported their findings by confirming an increase of YAP protein levels in clinical samples of melanoma and NSCLC resistant to a BRAF inhibitor. Our group added another layer upon this discovery, using an *in vitro* model of BRAF inhibitor resistance [114]. BRAF inhibitor-resistant melanoma cells generated by chronic drug administration exhibited increased nuclear accumulation of YAP/TAZ when compared with parental melanoma cell lines. Concordant with Lin et al.'s findings, the viability of resistant melanoma cells was highly dependent on YAP/TAZ activity. We further found that the upregulation of YAP/TAZ activity in resistant melanoma cells is associated with marked actin cytoskeleton remodeling induced by BRAF inhibitor treatment. Oncogenic mutations in MAPK pathways frequently occur throughout cancer types [115], and MAPK inhibition appears to be effective in several cancers beyond melanoma [116]. Therefore, we speculate that combined YAP and MAPK inhibition may yield fruitful outcome in preventing resistance development in multiple cancer types.

Activating EGFR mutations are an important oncogenic driver in a subset of lung adenocarcinoma, and EGFR-TKIs are effective in treating tumors with EGFR mutations. It has been shown that EGFR inhibitor-resistant NSCLC cells exhibit both increased expression and nuclear enrichment of YAP [117]. In addition, YAP overexpression decreases EGFR-TKI sensitivity. Similarly, another study proposed TAZ as a mediator of intrinsic EGFR-TKI resistance in lung adenocarcinoma with EGFR T790M mutation [118]. Monoclonal antibody cetuximab is another important EGFR targeting modality, and YAP activation signature predicts fast tumor progression and poor disease control in colorectal cancer patients treated with cetuximab [119]. Moreover, in HER2-positive breast cancer, high TAZ expression levels were associated with poor therapeutic

response to HER2 monoclonal antibody, trastuzumab, as well as chemotherapy combinations [120]. Concordantly, a study also demonstrated that the anti-proliferative effect of HER2 inhibitor lapatinib is influenced by YAP activity *in vitro* and *in vivo* [121]. Reduction of YAP activity suppresses the growth of HER2-positive tumors, and a trend of increasing sensitivity to lapatinib is observed as YAP activity decrease. Knockdown of YAP has been also shown to sensitize cancer cells to EGFR-TKI erlotinib as well as to a small-molecule antagonist of survivin [122]. These studies collectively suggest that YAP and TAZ mediate resistance to a variety of molecular-targeted agents against oncogenic EGFR–RAS–MAPK signaling pathways, which are central targets of recent cancer drug development.

### Radiation therapy

Radiation therapy accounts for another important axis of cancer therapy. Ionizing radiation to cancer cells causes DNA double-strand break, inducing cell cycle exit and apoptosis. Recent studies indicate that YAP mediates radiotherapy resistance, in addition to chemotherapy resistance, in several cancers. Microarray analyses of head and neck squamous cell carcinoma, comparing tumors with complete response and incomplete response to radiotherapy, revealed that high levels of YAP expression predict poor response to radiation therapy [123]. Concordant with this clinical finding, *in vitro* and *in vivo* YAP modulation in cancer models has also shown to affect radiation sensitivity. YAP knockdown in urothelial cell carcinoma potentiates DNA damage response and apoptosis by  $\gamma$ -irradiation, as well as by other DNA-damaging agents [107]. By contrast, YAP activation in medulloblastoma induces resistance to radiation [124]. In Shh-induced mouse medulloblastoma model, YAP overexpression maintains cell proliferation and prevents apoptosis after irradiation.

Moreover, YAP acts to override cell cycle checkpoints in irradiated cerebellar granule neuron precursors, which are the origin of medulloblastoma. In another study on endometrial cancer, which is an important clinical target of radiation therapy, YAP nuclear expression levels were shown to be correlated with poor prognosis of patients, and YAP suppression in endometrial cancer cells increased sensitivity to radiation treatment [125]. Together, these results indicate that YAP/TAZ activity is implicated in the promotion of cell survival and growth in response to a wide range of anti-cancer therapies.

### Molecular mechanisms of YAP/TAZ-driven resistance

The biologic effects of YAP/TAZ mainly originate from their function in transcriptional activation of genes governing cell proliferation, survival, and stemness. The binding of Yki to *Drosophila* genome is enriched in proximal promoter regions [126]. However, YAP and TAZ in mammalian cells interact with a number of TEAD-binding enhancers and superenhancers in addition to gene promoters, driving high levels of transcriptional activity of a group of genes determining cellular state [90]. A genome-wide ChIP-seq study also revealed that YAP/TAZ/TEAD and AP-1 form a complex which binds to enhancers, activating transcription of target genes required for cell cycle entry and mitosis [29]. YAP/TAZ/TEAD complex not only upregulates genes expression, but can also repress gene expression by recruiting the NuRD complex which deacetylates histones at target genes [32]. Therefore, it is likely that YAP and TAZ may orchestrate pro-resistant gene transcription by regulating a complex repertoire of enhancer and promoter activity. Here, we highlight six molecular mechanisms as candidate downstream effectors of YAP/TAZ in the development of anti-cancer therapy resistance (Fig. 1).

#### Activating growth factor signaling

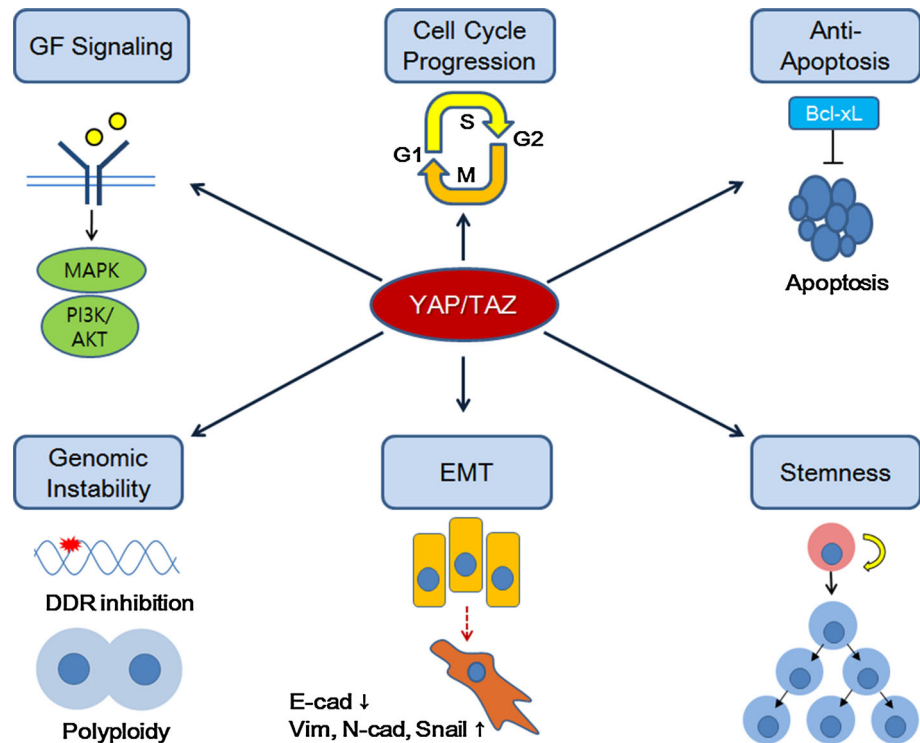
Activation of YAP and TAZ upregulates genes encoding components of growth factor signaling which contributes to anti-cancer therapy resistance. YAP/TAZ have been shown to upregulate EGFR expression in chemoresistant esophageal squamous cell carcinoma and BRAF inhibitor-resistant melanoma [104, 114]. YAP directly binds to the promoter region of EGFR to increase its expression [104]. Moreover, YAP can induce the expression of EGFR ligand Amphiregulin to promote EGF-independent cell survival and migration [46]. Therefore, YAP/TAZ-driven drug resistance may involve potentiation of EGFR signaling and the activation of downstream MAPK and PI3K/AKT

pathways. Activation of the insulin-like growth factor (IGF) pathway has been linked to drug resistance in many types of cancers [127], and a recent study indicated that YAP/TAZ upregulates the IGF pathway to promote cardiomyocyte proliferation [128]. Consistently, YAP-induced IGF2/AKT pathway activation in medulloblastoma promotes cancer cell survival upon irradiation, whereas IGF2 suppression abrogates the effect of YAP-dependent resistance [124]. These results further indicate that upregulation of growth factor signaling is a key mechanism of YAP/TAZ-driven anti-cancer therapy resistance. Inversely, EGFR and IGF signaling have been shown to enhance YAP/TAZ activity [45, 129, 130]. Thus, it is conceivable that a positive feedback loop between YAP/TAZ and EGFR/IGF pathways may further intensify drug resistance process.

#### Promoting cell cycle progression

The Hippo-YAP/TAZ pathway is known to mediate contact inhibition of cell proliferation and determine organ size through its role in the regulation of cell cycle entry and exit [26, 131]. The YAP/TAZ/TEAD complex directly targets enhancers of genes encoding DNA replication/repair machineries and transcriptional regulators required for cell cycle progression and mitosis [29]. In KRAS mutant PDAC model, the cooperation between YAP/TEAD and E2F1 transcription factor is essential for upregulating cell cycle machinery genes to bypass KRAS deprivation [109]. Our group also reported that depletion of YAP/TAZ in melanoma cells resistant to a BRAF inhibitor results in a significant downregulation of cell cycle/mitosis-associated genes, as well as genes with E2F motifs in their promoter [114]. These results suggest that transcriptional upregulation of cell cycle progression genes by YAP/TAZ makes cancer cells resistant to anti-proliferative effect of therapies. It is also noteworthy that LATS1/2 and YAP are involved in the regulation of p53 function. LATS2 has been shown to inhibit E3 ligase activity of MDM2 to stabilize p53 upon mitotic checkpoint activation or cytokinesis failure [132]. Consistently, LATS2 depletion blocks p53 activation in response to cytokinesis defects, allowing the propagation of tetraploid cells [133]. Moreover, LATS1/2 downregulation not only reduces tumor-suppressive role of p53, but also shifts the phosphorylation status and conformation of wild-type p53 to induce transcriptional activity similar to that of oncogenic p53 mutants [134]. YAP has also been shown to cooperate with oncogenic p53 mutants to induce transcriptional activation of cyclins and CDK1, promoting cell cycle progression [135]. Therefore, it is likely that YAP activation or LATS1/2 downregulation can interfere with growth inhibitory effect of anti-cancer therapy by disrupting the tumor-suppressor activity of

**Fig. 1** Downstream effector mechanisms of YAP/TAZ-dependent anti-cancer therapy resistance



wild-type p53 or potentiating the oncogenic activity of p53 mutants.

### Suppressing apoptosis

YAP binds to the promoters of anti-apoptosis genes BCL2L1 and BIRC5, and upregulate their expression levels [136]. Moreover, YAP overexpression protects cells from apoptosis upon various agents, including taxol, cisplatin, staurosporine, and UV irradiation [62, 137]. In BRAF and RAS mutated cancer cell lines, the expression of BCL-xL, the anti-apoptotic isoform of BCL2L1, is dependent on YAP activity, and BCL-xL serves as a downstream effector of YAP in the development of resistance to RAF/MEK inhibitors [113]. Pharmacological inhibition of BCL-xL overcomes YAP-dependent resistance to RAF/MEK inhibitors. Therefore, YAP/TAZ activity may decrease apoptotic sensitivity to anti-cancer therapy agents by upregulating the expression of anti-apoptotic genes.

### Modulating DNA damage response

Activation of YAP/TAZ has been shown to allow cancer cells to override DNA damage response induced by DNA-damaging agents and radiotherapy. Medulloblastoma cells in which YAP is activated bypass G1/S and G2/M cell cycle checkpoints induced by DNA damages, and the consequence is persistent DNA breaks and genomic

instability [124]. This checkpoint bypass is ascribed to YAP-mediated activation of the IGF2-AKT pathway, which inactivates DNA damage response transducers ATM and CHK2. By contrast, YAP suppression causes increased DNA damage response and ATM activation upon cisplatin treatment, causing apoptosis of urothelial cancer cells through accumulation of DNA damages [107]. Interestingly, cytokinesis inhibition and resulting polyploidy cause an activation of Hippo kinase LATS2, which is followed by YAP/TAZ suppression and p53 activation in non-transformed cells [133]. By contrast, aberrant YAP/TAZ activation results in cytokinesis defect and polyploidy. In addition, knockout of LATS1 or LATS2 in mouse embryonic fibroblast increases cytokinesis failure and polyploidy [138]. Therefore, we speculate that elevated YAP/TAZ activity in tumors may cause genomic instability by impeding both DNA damage response and polyploidy suppression, and thus contribute to the emergence of drug resistance through mutations or copy number changes of pro-resistance genes.

### Driving mesenchymal transition

In mammary epithelial cells, YAP/TAZ activation induces EMT phenotypes: loss of cell–cell contact, emergence of spindle morphology, and upregulation of mesenchymal markers, such as fibronectin, vimentin, and N-cadherin [62, 131]. EMT process of tumor cells not only underlies increased metastasis, but has also been implicated in



resistance to anti-cancer therapies [139–141]. Notably, in KRAS-dependent colon cancer cell lines and a mouse lung cancer model, YAP rescues a reduction of tumor cell viability after KRAS suppression through its effect on EMT induction [110]. YAP appears to cooperate with c-FOS to activate a transcriptional program governing EMT [110]. This study suggests that YAP activity facilitates bypass of oncogenic drivers by promoting EMT of cancer cells. Although a direct causal link between YAP/TAZ-induced EMT and anti-cancer therapy resistance has not been reported yet, we propose that EMT induction may play a role in YAP/TAZ-mediated drug resistance.

### Inducing stem cell-like properties

Transcriptional activation by YAP/TAZ promotes sustained self-renewal and pluripotency of stem cells, and affects expansion and lineage determination of progenitor cells *in vivo* [56, 142–145]. YAP/TAZ activation also induces stem cell-like properties in cancer cells. Importantly, stemness in cancer cells have been associated with properties enabling resistance to anti-cancer therapy, such as upregulation of drug transporter expression, elevated DNA repair capacity, and higher anti-apoptotic potential [146, 147]. Poorly differentiated breast cancer exhibits higher levels of YAP/TAZ target gene expression, and TAZ activity in breast cancer induces resistance to taxol and doxorubicin through elevation of stemness marker and tumor-initiating potential [35]. In addition, a study showed that Protease-Activated Receptor1 (PAR1) signaling promotes multidrug resistance in stem-like gastric cancer cells by inducing dephosphorylation and nuclear translocation of YAP through Rho GTPase activation [148]. PAR1-induced YAP activity significantly influences stem cell-like properties as well as drug efflux potential of gastric cancer cells. These results support the idea that YAP/TAZ may promote anti-cancer therapy resistance by inducing stem cell-like properties in cancer cells.

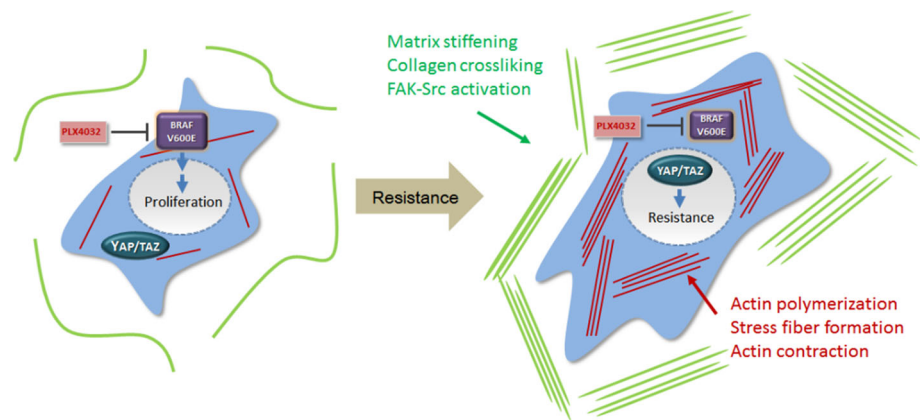
### What drives YAP/TAZ activation against anti-cancer therapies?

Understanding how YAP and TAZ are activated in malignant tumors upon anti-cancer treatment would be imperative to overcome YAP/TAZ-driven resistance. Currently, molecular mechanisms of YAP/TAZ regulation during the development of drug resistance are largely unexplored for many cancer types. Although YAP/TAZ upregulation and nuclear enrichment are frequently observed in clinical samples from cancer patients, genetic alterations in Hippo-YAP/TAZ pathway components are rare. Moreover, acquired mutation in Hippo-YAP/TAZ

pathway components has not yet been reported from analyses of therapy-resistant tumors. Notably, YAP/TAZ activation itself does not induce tumor formation in several tissues, but YAP/TAZ cooperate with other oncogenic pathways in the tumorigenic process [88, 89]. Thus, it is possible that elevated YAP/TAZ activity in resistant tumors might be a consequence of crosstalk with other oncogenic drivers. Importantly, recent studies have demonstrated that mutations in RAS, LKB1, or APC can activate YAP/TAZ [49, 65, 88, 149]. Oncogenic RAS promotes YAP stability by inhibiting ubiquitin ligase substrate recognition factors SOC5/6 [49, 65, 88, 149]. YAP activity is also enhanced by homozygous loss of LKB1 or APC [49, 65, 88, 149]. The emergence of additional mutations is a frequent event in therapy resistance, and thus acquired mutations in RAS, APC, and LKB1 genes, as well as in GPCR, TGF $\beta$ , and Wnt signaling components in resistant tumors may contribute to the activation of YAP/TAZ during resistance development.

Although underlying mechanisms are not fully elucidated, it is clear that increases in intracellular tension, matrix stiffness, actin polymerization, and actin-myosin contractility result in increased YAP/TAZ nuclear localization and activity [36, 38, 150]. Thus, it is likely that mechanical stimuli and cytoskeletal architecture may influence YAP/TAZ-dependent therapy resistance in certain cancers. Our group reported actin cytoskeletal remodeling in melanoma cells, which promotes YAP/TAZ nuclear localization and consequential BRAF inhibitor resistance [114]. The actin cytoskeletal remodeling was apparently induced by changes in expression levels of multiple actin regulators in response to BRAF inhibitor treatment [114]. Moreover, another study demonstrated that lapatinib resistance in HER2-positive breast cancer cells depends on stroma rigidity-induced YAP/TAZ activation [121]. In line with these findings, BRAF inhibitor treatment makes melanoma tumor stroma stiffer through promotion of cancer-associated fibroblast activation and ECM production/remodeling [151]. Therefore, we speculate that cancer cells can adapt themselves to anti-cancer therapy by changing their mechanical properties in two ways: increasing intracellular actin cytoskeletal tension and stiffening tumor stroma by ECM remodeling (Fig. 2). These two mechanisms may synergize to upregulate YAP/TAZ activity as an adaptive response to anti-cancer therapies. Matrix stiffening and YAP/TAZ activation have also been reported to maintain cancer-associated fibroblasts [39], and a clinical study reported that combined high YAP/TAZ expression levels in non-lymphoid stromal cells and cancer cells correlate with poor neoadjuvant chemotherapy response in triple-negative breast cancer [152]. Altogether, these findings suggest that YAP/TAZ activation mechanisms associated with the tumor

**Fig. 2** YAP/TAZ activation by mechanotransduction in BRAF inhibitor resistance



microenvironment play an important role in the therapy resistance development. Other studies have identified CDK1, PAR-1, and YES as potential YAP/TAZ regulators in drug resistance models [102, 103, 148]. Further research will clarify the relationship between therapy-induced adaptive responses and YAP/TAZ regulators.

### YAP/TAZ as predictive biomarkers

Although preclinical studies have demonstrated that YAP/TAZ are involved in a wide range of therapeutic resistance, clinical application of YAP/TAZ as a predictive biomarker and a drug target is in its early stages. Systematic monitoring of YAP/TAZ activity in pre- and post-therapy tumor biopsy samples will fully establish YAP/TAZ as a useful clinical biomarker for predicting therapy resistance in many cancer types. YAP/TAZ activity in tumor tissues can be measured by YAP/TAZ immunohistochemical (IHC) staining. Because YAP/TAZ activity is regulated by both nuclear translocation and proteosomal degradation, YAP/TAZ scoring by IHC needs to be determined by combining subcellular localization and staining intensity. Indeed, high levels of nuclear YAP/TAZ staining have been reported to correlate with poor prognosis in breast cancer, NSCLC, and bladder cancer [85, 92, 153]. Elevated nuclear TAZ staining in HER2-positive breast cancer was associated with lower rates of pathologic complete response to trastuzumab [120]. In addition, high levels of nuclear YAP expression correlated with poor survival of urothelial cell carcinoma patients [107], and poor response to a BRAF inhibitor in melanoma and NSCLC patients [113]. Table 2 summarizes published studies that reported YAP/TAZ as therapy response markers.

YAP/TAZ activity in non-cancerous cells in the tumor microenvironment also needs to be analyzed, because YAP/TAZ staining in cancer-associated fibroblasts or tumor-infiltrating lymphocytes has been reported to affect therapy response [152, 154].

Recent studies have analyzed genome-wide transcriptional signatures of YAP/TAZ activation, and demonstrated that the signatures are associated with therapy responses. Therefore, YAP/TAZ target gene signatures identified by microarray or RNA-seq analyses can be used as a surrogate marker for YAP/TAZ activation. In colon cancer, a YAP/TAZ target gene signature predicted progression-free survival after cetuximab treatment in KRAS-wild-type colon cancer [119], and YAP activation signature has also been associated with shorter progression-free survival after radiation therapy in head and neck cancer and squamous cell carcinoma [123]. Further studies will be required to establish reliable consensus signatures of YAP/TAZ activation in cancer cells and to confirm the significance of the association between the signature and therapy resistance.

### Therapeutic targeting of YAP/TAZ for overcoming drug resistance

The crucial role of YAP/TAZ in resistance mechanisms proposes that therapeutic targeting of YAP/TAZ will facilitate the development of effective anti-resistance therapies. YAP mainly exerts their transcriptional activity by interaction with TEADs, and YAP-TEAD interaction is an important target for suppressing YAP-induced tumorigenesis and resistance. A screen for pharmacological inhibitors of YAP-TEAD interaction identified three porphyrin compounds [155]. Among them, verteporfin showed the strongest inhibition of the interaction between YAP and TEAD. Importantly, verteporfin suppresses YAP-induced hepatomegaly and hepatocellular carcinoma in vivo, and shows anti-tumor activity in *GNAQ*-mutated uveal melanoma [82]. Verteporfin has been used in photodynamic therapy for macular degeneration and pancreatic cancer, and further clinical indications need to be evaluated in a set of YAP-dependent tumors. Vestigial-like family member 4 (VGLL4) competes with YAP/TAZ for TEAD binding,

**Table 2** YAP/TAZ as clinical biomarkers in predicting response to anti-cancer therapy

Cancer type	Measurement	Predictive value of elevated YAP or TAZ expression/activity	References
Colon cancer	YAP transcript level detected by qRT-PCR	Shorter OS and DFS in colon cancer patients with liver metastasis who received neoadjuvant chemotherapy	[103]
Colon cancer	YAP target gene expression signature	Low response rate and shorter PFS on cetuximab treatment in colon cancer patients	[119]
Breast cancer	TAZ IHC staining scored by combining intensity and cellular localization	Low pCR in HER2-positive breast cancer patients who received trastuzumab-based neoadjuvant therapy	[120]
Urothelial cell carcinoma	Nuclear YAP IHC staining	Shorter OS and RFS in urothelial cell carcinoma patients who received perioperative chemotherapy	[107]
Melanoma and NSCLC	YAP IHC staining	Incomplete response to BRAF inhibitor in BRAF mutant melanoma and NSCLC	[113]
Head and neck squamous cell carcinoma	YAP IHC staining	Incomplete response, shorter RFS, and shorter CSS of head and neck squamous cell carcinoma patients who received primary radiotherapy or chemoradiation	[123]

qRT-PCR quantitative reverse transcriptase polymerase chain reaction, IHC immunohistochemistry, OS overall survival, DFS disease-free survival, PFS progression-free survival, pCR pathologic complete response, RFS recurrence-free survival, CSS cause-specific survival

suppressing transcriptional activity of YAP/TAZ [156]. VGLL4 expression levels in gastric cancer are lower than normal gastric mucosa, and inversely correlate with patient survival [156]. VGLL4 also suppresses cell proliferation and cancer progression in lung cancer [157]. A peptide drug which mimics the TEAD-interacting domain of VGLL4 (super-TDU) has been generated as an inhibitor of YAP/TAZ activity [156]. Super-TDU inhibits YAP-TEAD interaction and significantly decreases tumor growth in *Helicobacter pylori*-induced gastric cancer in mice.

Although kinases are generally considered druggable, Hippo pathway kinases MST1/2 and LATS1/2 are not valid targets for YAP/TAZ inhibitor development because they suppress YAP/TAZ and are tumor suppressors. YAP was originally recognized as a YES1-associated protein. SRC family kinase YES1 phosphorylates 357 tyrosine residue of YAP to promote YAP- $\beta$ -Catenin-TBX5 complex activity in  $\beta$ -Catenin active cancers, and YES1 inhibition by dasatinib significantly decreases colon cancer cell proliferation [136]. Therefore, YES1 may be an effective target for suppressing  $\beta$ -Catenin/YAP-dependent tumor growth. HIPK2 has been also suggested to be a potential target for YAP/TAZ inhibition [158, 159]. Discovery of additional kinases necessary for YAP/TAZ activity will facilitate the development of pharmacological agents blocking YAP/TAZ-dependent resistance as well as tumorigenesis.

Because the actin cytoskeleton provides important inputs for Hippo-YAP/TAZ activity regulation, actin-modulating drugs would be effective in suppressing YAP/TAZ-mediated therapy resistance. Actin polymerization inhibitor cytochalasin D, actin-myosin contraction inhibitor blebbistatin, and Rho-actin pathway inhibitors C3 transferase and Y27632 have been shown to inhibit YAP/

TAZ nuclear localization and their transcriptional activity [38]. Moreover, our group also showed that cytochalasin D and blebbistatin can suppress YAP-dependent BRAF inhibitor resistance [114]. However, the actin cytoskeleton is involved in a wide variety of cellular activities in addition to YAP/TAZ regulation, and thus actin-modulating drugs commonly present general toxicity. Therefore, it will be necessary to target specific actin regulators that play a direct role in resistance development. Our RNAi-based screening identified TESK1 as a candidate for druggable actin regulators acting in BRAF inhibitor-resistant melanoma [114]. Increased matrix stiffness also upregulates YAP/TAZ activity. Notably, inhibitors for lysyl oxidase-mediated collagen crosslinking have been reported to exert anti-tumor activity [160, 161], suggesting that targeting ECM stiffness would be a feasible strategy for inhibiting YAP/TAZ activity in resistant tumors.

Recent studies have shown that YAP/TAZ activity is modulated by cell metabolism. Inhibition of HMG-CoA reductase in the mevalonate pathway by statin or bisphosphonate suppresses nuclear localization and function of YAP/TAZ [43]. Statin and bisphosphonate block the generation of geranylgeranyl pyrophosphate by inhibiting mevalonic acid catabolism, and geranylgeranyl pyrophosphorylation of Rho GTPase is essential for full activation of Rho, which promotes YAP/TAZ activity [43]. Statin treatment decreases proliferation and stemness of breast cancer cells, and bisphosphonate decreases tumor size in breast cancer xenograft model. Cellular energy stress, such as glucose starvation, also regulates YAP/TAZ activity by AMPK-dependent phosphorylation of LATS and YAP [41, 42]. Thus, altering cellular energy status or AMPK

pathway modulation may provide an alternative strategy to suppress YAP/TAZ in cancer cells.

Future clinical trials will test the effectiveness of YAP/TAZ inhibitors in suppressing anti-cancer therapy resistance. Either initial combination treatment or combination at the time of drug re-challenge after progression can be considered for the trials, depending on YAP/TAZ activation status of tumor tissue. Reduction of both YAP/TAZ nuclear staining and target gene expression levels in post-therapy tissues will confirm the actual blockade of YAP/TAZ activity by YAP/TAZ inhibitors administered. Because YAP/TAZ play important roles in normal physiologic activities in the human body, drug dosing and schedule as well as administration modality should be carefully optimized to minimize drug toxicity. Interestingly, YAP/TAZ inhibiting compounds metformin [41], statins [43], and bisphosphonates [43], which have been prescribed for diabetes, hypercholesterolemia and osteoporosis, respectively, are associated with lower risk of cancer occurrence [162]. Observational studies of comorbidity that investigate the clinical outcomes of cancer patients who take these agents can be designed to estimate the influence of YAP/TAZ blockade on drug resistance and patient survival.

## Conclusions and perspectives

A wealth of experimental evidence now supports that YAP and TAZ constitute a baseline of resistance to multiple anti-cancer therapies. Increased nuclear localization of YAP/TAZ and higher transcriptional activities of YAP/TAZ target genes have been observed in therapy-resistant tumors. Modulation of YAP/TAZ activity in cancer cells clearly influences sensitivities to anti-cancer therapies, and this phenomenon has been consistently reproduced in many resistance models. However, the majority of studies are based on RNAi-mediated knock-down or overexpression of YAP/TAZ, and clinical evidence for the link between YAP/TAZ and drug resistance is convincing in only a few cases. YAP/TAZ activation mechanisms during resistance development in vivo are largely unexplored. Moreover, because downstream effects of YAP/TAZ activity are complex, the resistance mechanism dominant upon each therapy modality remains obscure. It is also an unresolved issue whether YAP/TAZ activation indeed confers universal resistance regardless of the type of anti-cancer therapy. Notably, a recent study has demonstrated that YAP activation in prostate cancer cells recruits CXCR2-expressing myeloid-derived suppressor cells around cancer tissues by upregulating CXCL5 chemokine [163]. It will be intriguing to test whether YAP/TAZ can also induce

resistance to immunotherapy agents by recruiting immune suppressive cells into tumor microenvironment. However, elevated expression of YAP/TAZ in tumor-infiltrating lymphocytes predicts a higher response rate to chemotherapy in cervical cancer [154]. Besides, the non-canonical Hippo/MST pathway is involved in the regulation of T cell development and migration in the thymus [164]. Therefore, both cancer cells and immune cells as well as their interactions should be considered when investigating the effect of pharmacological targeting of YAP/TAZ or Hippo kinases in vivo. Even though the overall portrait of YAP/TAZ-mediated resistance has not been completed yet, it is evident that YAP/TAZ are crucially implicated in the emergence of anti-cancer therapy resistance, and targeting YAP/TAZ will yield valuable source for developing novel anti-resistance strategies.

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