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YAP/TAZ Signaling and Resistance to Cancer Therapy

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Abstract

Drug resistance is a major challenge in cancer treatment. Emerging evidence indicates that deregulation of YAP/TAZ signaling may be a major mechanism of intrinsic and acquired resistance to various targeted and chemotherapies. Moreover, YAP/TAZ-mediated expression of PD-L1 and multiple cytokines is pivotal for tumor immune evasion. While direct inhibitors of YAP/TAZ are still under development, FDA-approved drugs that indirectly block YAP/TAZ activation or critical downstream targets of YAP/TAZ have shown promise in the clinic in reducing therapy resistance. Finally, BET inhibitors, which reportedly block YAP/TAZ-mediated transcription, present another potential venue to overcome YAP/TAZ-induced drug resistance.

Keywords

Hippo pathway; YAP; TAZ; Cancer therapy resistance

CANCER THERAPY RESISTANCE AND REGULATION OF YAP/TAZ SIGNALING

Despite the dramatic improvement in treatment outcomes for several highly aggressive cancer types in the recent decade, complete and sustained response remains rare in most malignancies due to development of primary or acquired resistance [1]. It is thus essential to identify mechanisms of resistance to design optimal treatment strategies to prevent or overcome relapse. Emerging literature indicates that the Hippo-YAP/TAZ pathway might play a central role in mediating resistance to major classes of cancer therapeutics.

The Hippo pathway was originally discovered in *Drosophila* as a major developmental pathway that controls organ size and later found to be conserved in mammals [2–5]. The core mammalian Hippo pathway consists of a kinase cascade in which MST1/2 kinases (orthologs of Hippo in *Drosophila*), facilitated by scaffold proteins such as SAV1 and NF2/MERLIN, phosphorylate and activate LATS1/2 kinases and the regulatory protein MOB1 [2,5,6]. Activated LATS1/2 in turn phosphorylate YAP and TAZ, priming binding to 14-3-3

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and β -TrCP, which mediate cytoplasmic retention and proteasomal degradation, respectively. Parallel or upstream of MST1/2, the MAP4K family of Ste20-like kinases and TAOK1–3 can also directly or indirectly phosphorylate and activate LATS1/2, thereby inhibiting YAP/TAZ activity [7]. Additionally, many cellular processes such as mechanotransduction and various metabolic pathways have been shown to regulate YAP/TAZ nuclear translocation independent of the core Hippo kinases [8–13]. Once inside the nucleus, YAP/TAZ function as co-activators to multiple transcription factors including TEAD1–4, RUNX2, p73, etc [14–17]. In particular, the TEA-Domain family transcription factors, TEAD1–4, share significant overlap with YAP/TAZ in genomic binding sites and are primary partners of YAP/TAZ in transcribing genes that regulate growth, survival, inflammation, angiogenesis, mechanotransduction, oxidative stress response and stemness [16–18].

A growing body of literature implicates YAP/TAZ activation in resistance to targeted therapies, chemotherapy, radiation, and also, potentially immunotherapies. Though detailed mechanisms vary, they converge on YAP/TAZ-mediated transcription, either through inactivation of upstream YAP/TAZ negative regulators or by direct activation of YAP and/or TAZ. Here, we provide a brief overview of numerous reported YAP/TAZ-dependent mechanisms that lead to therapy resistance. We also address caveats and gaps in existing literature and offer our perspective on potential strategies to overcome YAP/TAZ-mediated resistance to cancer therapy.

YAP/TAZ SIGNALING AND RESISTANCE TO TARGETED THERAPY

Targeted therapies inhibit specific molecules and pathways that are crucial for growth and survival of cancer cells. Effective targeted therapy in cancer was first demonstrated with inhibition of Bcr-Abl, a product of the Philadelphia chromosome fusion oncogene, with Imatinib in Chronic Myelogenous Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), which resulted in objective and durable response in more than 50% of patients [19,20]. Other dependencies in tumors have been also exploited, including EGFR in *EGFR* mutant non-small-cell lung cancer (NSCLC) with cetuximab, erlotinib; VEGFR in *VHL* mutant clear cell renal cell carcinoma (ccRCC) with bevacizumab, axitinib; BRAF (vemurafenib, dabrafenib) or MEK in BRAF-mutant melanoma with vemurafenib, dabrafenib or with trametinib, cobimetinib, respectively; or estrogen receptor (ER) in ER⁺ breast cancer with tamoxifen, fulvestrant [21]. However, most patients develop primary or acquired resistance to targeted therapies. Deregulation of Hippo signaling and subsequent activation of YAP/TAZ is a major resistance mechanism to multiple targeted therapies, particularly against EGFR and MAPK inhibitors (MAPKi). Below, we will discuss how dysregulation of Hippo-YAP/TAZ signaling helps tumor cells bypass pathway inhibition by activation of alternative survival pathways or antiapoptotic signaling (Figure 1).

Approximately half of all melanoma tumors harbor activating mutation in the BRAF gene, which leads to constitutive activation of MAPK (MEK-ERK) signaling [22]. Combined therapy with BRAF and MEK inhibitors can lead to rapid tumor regression and significant long-term benefit in patients with metastatic BRAF^{V600E} melanoma, although development of acquired resistance remains a formidable obstacle [23–25]. In an effort to identify

mechanisms of resistance to BRAF inhibitor (BRAFi), a pooled genome-scale CRISPR knockout screen in human melanoma cells identified NF2 sgRNAs among the most enriched after BRAFi treatment [26]. NF2 encodes Merlin, a member of the ERM protein family that functions as a scaffold bridging cytoskeletal dynamics with activation of the MST1/2-LATS1/2 kinase cascade, negatively regulating YAP/TAZ activity [27,28]. Another genome-scale CRISPR activation screen targeting >10,000 long-noncoding RNA (lncRNA) identified lncRNA *EMICER1* as a mediator of BRAFi resistance [29]. Intriguingly, it showed that *EMICER1* confers resistance to BRAFi resistance by promoting the expression of its genomic neighbor MOB3B - a component of the STRIPAK (striatin-interacting phosphatase and kinase) complex that inhibits MST1/2 and LATS1/2 [29–31]. Finally, genome-wide shRNA screens confirmed that YAP mediates resistance to BRAFi and MAPKi in BRAF mutant cancer cells [32–34]. Interestingly, BRAFi treatment was shown to induce actin cytoskeleton remodeling, which induces activation of YAP via Rho-mediated LATS1/2 inhibition in BRAF-mutant melanoma cells [33,34].

The RAS family of small GTPases - KRAS, HRAS and NRAS, which directly activate the MAPK and other pathways are also frequently mutated in cancer [35]. While RAS inhibitors are still under preclinical development, genetic studies were carried out to identify potential bypass mechanisms of oncogenic Ras ablation. Studies assessing tumor relapse following extinction of oncogenic Kras in a genetically engineered mouse model of advanced Pancreatic Ductal Adenocarcinoma (PDAC), and detected amplification of the *Yap* gene locus in three out of eight relapsed tumors analyzed [36]. Independently, in genome-scale cDNA screens, Yap was the top hit in promoting survival upon KRAS knockdown in a human KRAS mutant colon cancer cell lines [37]. Finally, a recent study showed that YAP ablation was sufficient to overcome resistance of Kras mutant lung cancer cells to the combined treatment with Selumetinib, a MEK inhibitor, and Mometinib, a TBK/JAK inhibitor [38]. Together, these studies establish YAP as a key driver of escape from KRAS/ MAPK dependency.

Several studies explored the mechanisms underlying YAP-mediated resistance to blockade of KRAS-MAPK signaling. While Yap was shown to cooperate with Tead2 and E2F transcription factors to promote cell cycle progression in Kras-ablated PDAC cells [36], it was reported to rescue the loss of oncogenic KRAS in human lung cancer cells by partnering with AP-1 transcription factor FOS to promote epithelial-mesenchymal transition (EMT) independent of TEADs [37]. In response to treatment with MAPKi, YAP was found to prevent apoptosis in BRAF or KRAS mutant tumor cells through TEAD-mediated transcription of *BCL2L1*, which encodes anti-apoptotic protein Bcl-xL [32]. Yet according to another study, depletion of YAP sensitizes KRAS mutant PDAC cells to a pan-RAF inhibitor LY3009120 by blocking the compensatory activation of PI3K-AKT signaling [39]. These findings indicate that Yap likely induces therapy resistance through multiple downstream effectors, and targeting one particular Yap-mediated bypass mechanism will unlikely be sufficient to overcome resistance to KRAS/ MAPK pathway blockade. For example, while combination treatment of BRAF/MEK and PI3K inhibition demonstrated remarkable results in preclinical models of Kras-mutant NSCLC [40–42], clinical trials were plagued with heterogeneous response [43–45], in part due to reduction in ratio between pro-apoptotic BIM and anti-apoptotic Bcl-2 proteins, resulting in reduced apoptotic propensity [46]. Thus,

it would be important in further studies to determine the relative contributions of various Yap effector pathways to the overall resistance development under different contexts and how differences in mutation profiles, epigenetic states and tumor microenvironment may cause subpopulations of tumor cells to activate distinct bypass mechanisms to the same treatment.

Upstream of RAS-MAPK signaling, receptor tyrosine kinases (RTKs) such as EGFR are also frequently mutated or amplified to drive tumorigenesis and drug resistance [47,48]. Monoclonal antibodies or small-molecule tyrosine kinase inhibitors (TKI) have shown efficacy in patients with RTK-addicted tumors, although resistance develops in most patients [21]. Numerous studies linked activation of YAP/TAZ to TKI resistance, including first and second generations of EGFR inhibitors (EGFRi) and the multi-kinase TKI sorafenib [49–60]. The precise mechanisms by which YAP/TAZ drive TKI resistance remain poorly understood. However, given that RTK functions directly upstream of the MAPK pathway, it is likely that that a similar set of YAP/TAZ transcriptional targets confer resistance to both TKI and MAPK pathway inhibitors. Indeed, AXL, a direct transcriptional target of YAP/TAZ, mediates resistance to both BRAFi and EGFRi [49,50,55,61–63]. Besides AXL, other YAP/TAZ targets linked to RTKi inhibition include CTGF, EGFR, ERBB3, EGFR and EMT genes [55,56,58,64–66].

Other targeted therapies with resistance mechanisms associated with Hippo signaling include mTOR, TBK/IGF1R, imatinib, CDK4/6, WEE1 and Aurora-A inhibitors [38,67–71]. Taken together, these studies provide concrete evidence for the involvement of Hippo-YAP/TAZ signaling in development of resistance to targeted therapies across multiple malignancies.

YAP/TAZ SIGNALING AND RESISTANCE TO CHEMOTHERAPY

Chemotherapy encompasses a broad range of drugs that non-specifically inhibit cell division. There are multiple subtypes of chemotherapy, including anti-microtubule, anti-metabolites, and DNA damage agents, all designed to cause damage to highly proliferative cells. A vast body of literature links Hippo-YAP/TAZ signaling to resistance to chemotherapy in numerous solid cancers. Below, we will summarize the known upstream mechanisms that activate YAP/TAZ in response to cytotoxic agents and how notable YAP/TAZ targets enable tumor cells to overcome the detrimental effects of chemotherapy drugs (Figure 2).

Anti-Microtubule Drugs

Anti-microtubule compounds block mitosis and induce apoptosis by disrupting the assembly or disassembly of microtubules. Taxane (Paclitaxel, Docetaxel) is a major class of anti-microtubule drugs widely used in treatment of ovarian, lung, breast, cervical and prostate cancer and acts to stabilize GDP-bound tubulin, thereby preventing microtubule disassembly during cell cycle [72,73]. Resistance to taxane has been associated with deregulation of upstream YAP/TAZ regulators involving various mechanism, particularly microRNAs (miRNAs) [64,74–84]. miRNA-363, which is upregulated in taxane-resistant ovarian cancer cells, confers resistance by directly targeting LATS2 mRNA translation, which in turn activates YAP [81]. miR-181c is upregulated in PDAC and promotes taxane resistance by

directly suppressing the translation of multiple Hippo pathway components including MST1, LATS2, MOB1 and SAV1 [85]. Activation of Protease-activated receptor-1 (PAR1), a G-protein coupled receptor (GPCR), induces stemness and multi-drug chemoresistance in gastric cancer cells by promoting YAP dephosphorylation and nuclear translocation through Rho-mediated inactivation of LAST1/2 [34,83]. Conversely, Cyclin-dependent kinase 1 (CDK1), sensitizes ovarian cancer cells to taxanes by phosphorylating LATS1/2 and YAP/TAZ [75,78,80,84,86,87]. On one hand, CDK1-mediated phosphorylation of LATS1/2 does not appear to interfere with their ability to phosphorylate YAP/TAZ, but rather cause LATS1/2 to associate with PIN1, a peptidyl-prolyl cis/trans isomerase (PPIase), and promotes drug sensitivity through yet-to-be-defined mechanisms [80]. On the other hand, following taxane treatment, CDK1 directly phosphorylates YAP/TAZ at sites distinct from those targeted by LATS1/2, reducing TAZ protein stability while suppressing YAP transcriptional activity by reducing its interaction with TEADs [75,84].

Multiple transcription targets may contribute to taxane resistance downstream of YAP/TAZ. Several studies suggest that YAP/TAZ are enriched in cancer cells (CSCs) and promote pluripotent transcription program resulting in increased tumor initiating ability and chemotherapy resistance [15,77,82,83,88]. In particular, the YAP/TAZ/TEAD transcription complexes induce expression of multidrug transporters ABCB1 and ABCC1 in ovarian and liver CSCs and potentially mediate PAR1-induced upregulation of ABCG2 in gastric CSCs [82,83,88]. Upregulation of multidrug transporters is expected to increase drug efflux. Indeed, overexpression of a constitutively active TAZ enhances the ability of breast cancer cells to exclude Hoechst dye, which could be reversed with the multidrug transporter inhibitor Verapamil [77]. Finally, YAP/TAZ may also indirectly promote taxane resistance through canonical transcriptional targets CTGF and CYR61, which inhibit taxane-induced apoptosis by upregulating anti-apoptotic proteins Bcl-xL, cIAP1 and Survivin while suppressing p53 via integrin-mediated activation of MAPK or NF- κ B signaling [89–92].

Anti-Metabolites

Anti-metabolites represent another major class of cytotoxic drugs mainly composed of metabolite analogs designed to interfere with critical metabolic pathways necessary for cell proliferation and survival. Fluorouracil (5-FU) and gemcitabine, the respective nucleoside analogs of Uracil and Cytidine, are commonly used as first-line treatment in pancreatic, breast, ovarian and colorectal cancer with variable benefits and predictable relapse [93–99]. Antifolates such as methotrexate and pemetrexed are the other major class of anti-metabolites that antagonize the actions of folic acid (Vitamin B9), whose derivatives fuel the folate cycle that supports serine, methionine, thymidine and purine de novo biosynthesis [100]. Hippo signaling was implicated in resistance to both types of anti-metabolite drugs [64,83,85,101–110].

Similar to anti-microtubule resistance, multiple explorative studies linked miRNA-mediated deregulation of Hippo signaling to resistance to 5-FU and gemcitabine in cancer cells, including miR-181c and miR-455–3p in pancreatic cancer and miR-874–3p in colorectal cancer [85,101,102,109]. Downstream of YAP/TAZ, CTGF and CYR61 were also found to play major roles in anti-metabolite resistance through the activation of Integrin signaling

[92,111]. Furthermore, several studies implicated YAP/TAZ as positive regulators of multidrug transporters (ABCs) [82,83,88]. However, contrary to these reports, a recent study found that expression of a constitutively active YAP or knockdown of MERLIN or LATS2 downregulates multidrug transporters such as ABCB4, ABCC3 and ABCG2 and reverts gemcitabine resistance induced by high cell density in pancreatic cancer cells [107]. This study differs from others in that most of the experiments were performed under high confluence conditions. Because no knockdown of YAP was done in low confluent cells when YAP is presumably active, it is difficult to assess whether the effects induced by forcing YAP activation in conditions where it is normally suppressed reflect the physiological function of YAP. Finally, YAP/TAZ were recently reported to induce the expression of high affinity glucose and AA transporters [112–116], which may indirectly blunt the effects of anti-metabolite drugs.

DNA Damaging Agents

DNA damaging agents refers to compounds that induce cell cycle arrest and apoptosis by either directly alkylating DNA (cisplatin, temolozomide, etc.) or inhibiting topoisomerases - the enzymes that unwind the double-stranded DNA during replication and DNA repair (doxorubicin, etoposide). Hippo signaling was linked to resistance to DNA damaging agents in numerous studies [77,82,83,88,104,108,110,117–134]. While YAP/TAZ confer resistance to DNA damaging agents through a similar set of transcriptional targets as to other chemo drugs [66,77,82,89,92,118,119,127,128,135,136], distinct upstream mechanisms appear to underlie YAP/TAZ activation. Three studies reported downregulation of MST1 following doxorubicin or cisplatin treatment either due to Hsp70-mediated degradation or translation blockade caused by miR-149–5p, which also targets the scaffolding protein SAV1 [110,123,129]. In addition, AJUBA, a negatively regulator of LATS1/2, is upregulated along with YAP/TAZ in cisplatin-resistant cervical cancer cells [132]. Finally, Hippo-independent mechanisms were also reported to contribute to YAP activation. Doxorubicin-induced increase in YAP expression was linked to downregulation of miR-590–5p, which directly inhibits YAP translation [88]. Furthermore, SIRT1-mediated-deacetylation of YAP increases its nuclear translocation and interaction with TEAD following cisplatin treatment [122]. Similarly, overexpression of an acetylation-resistant YAP mutant modestly boosted resistance to another DNA-alkylating agent methyl methanesulfonate (MMS), although YAP acetylation driven by CBP/p300 was increased in response to MMS and did not affect YAP nuclear translocation [137].

YAP/TAZ SIGNALING AND RESISTANCE TO IMMUNE THERAPY

Immune evasion presents a major challenge but also an opportunity in cancer treatment. Most notably, PD-L1 and CTLA-4 are cell surface markers often expressed on tumor cells that bind to their cognate receptors on cytotoxic T cells (CTLs), inducing T cell exhaustion and preventing CTL-mediated tumor-specific killing. Monoclonal antibodies targeting PDL1/CTLA-4 (Artezolizumab, Ipilimumab, etc.) or PD-L1 receptor PD-1 (Nivolumab, Pembrolizumab.) are successfully used to reactivate T cells in certain tumors, although they fail to work in most tumors due to the existence of additional immune suppressive

mechanisms [138–140]. Here, we will explore the potential roles of Hippo-YAP/TAZ signaling in modulating cancer immunotherapy response (Figure 3).

Multiple studies identified PD-L1 as a direct transcriptional target of YAP/TAZ/TEAD and showed that YAP and/or TAZ activation upregulates PD-L1 in human breast cancer, NSCLC, mesothelioma and melanoma cells, although it was reported that the TEAD binding sites are not conserved on the mouse PD-L1 promoter [141–146]. Besides promoting PD-L1 expression, YAP may also suppress T cell function by inducing the expression of cytokines that drive polarization and recruitment of myeloid-derived suppressing cells (MDSCs) and tumor-associated macrophages (TAMs), which inactivate T cells and induce T cell apoptosis through multiple mechanisms [147]. Yap promotes the recruitment of MDSCs in syngeneic prostate cancer models by directly transcribing Cxcl5, which attracts CXCR2-expressing MDSCs to the tumor microenvironment [148]. Yap also drives the recruitment and systematic polarization of MDSCs by promoting the expression of Il-6, Csf1–3, Tnfa, Il-3, Cxcl1/2, and Ccl2 in genetically engineered PDAC models [149]. Yap-induced tumor secretome is also responsible for recruitment of TAMs in pancreatic and liver tumor models [149–151].

CONCLUDING REMARKS

In summary, YAP/TAZ signaling is a pivotal regulator of response to targeted, chemo, and immune therapies in many types of solid tumors. However, there are currently no clinically viable drugs that directly target this pathway. Verteporfin (VP), a photosensitizing medication used to treat abnormal blood vessels in the eye, was the first compound identified to directly inhibit YAP-TEAD binding and reduce organ overgrowth caused by Yap overexpression or *Nf2* knockout [152]. A number of studies showed that VP could mimic YAP knockdown to overcome resistance to RAFi, TKI or chemo drugs [39,50,51,53,56,64,118,121,134,153]. However, Verteporfin only blocks YAP-TEAD binding at high micromolar concentrations and has YAP-independent effects and therefore is not a clinically viable YAP inhibitor [152,154,155]. A number of drugs were found to indirectly inhibit YAP/TAZ by targeting upstream regulators of Hippo signaling [156]. In particular, Statins, which target HMG-CoA reductase, inhibit YAP nuclear translocation and mimic genetic YAP ablation in sensitizing cells to TKI or MAPKi [52,53,60,157–159]. However, similar to VP, Statins exert pleiotropic cellular effects and require high concentrations to block YAP-mediated transcription [157,158,160], rendering them unsuitable as clinical YAP inhibitors.

As an alternative to targeting upstream Hippo signaling, drugs that inhibit downstream effectors of YAP/TAZ showed promise in the clinic. For example, multiple small molecule AXL inhibitors (bemcentinib, TP-0903) and pamrevlumab (FG-3019) - a monoclonal CTGF antibody - are currently in clinical trials in combination with EGFRi and other cytotoxic drugs [161,162]. However, given the diverse functions of YAP/TAZ targets, it is unlikely that targeting one downstream effector will fully recapitulate the effects of direct blockade of YAP/TAZ. Thus, it is important to further decipher the relative contributions of druggable YAP/TAZ targets to YAP/TAZ-mediated resistance to various types of cancer drugs (see outstanding questions).

Notably, two recent studies reported that BET family protein BRD4 inhibitors (BRD4-i) could block YAP-mediated transcription and overcome resistance to MAPKi in BRAF mutant melanoma and KRAS mutant lung cancer cells [38,62]. Mechanistically, BRD4 was found to not only promote the expression of YAP but also directly interact with YAP/TAZ and function as a required co-factor for the YAP/TAZ/TEAD transcriptional complexes [38,62]. However, all the existing BRD4-i also inhibit BRD2 and BRD3, which have distinct functions and transcriptional targets [163]. Consequently, toxicity is a major concern for this type of drugs, and clinical utility is being investigated in trials of single agents or combinations with other agents [164]. Moreover, as a general transcription co-activator, BRD4 has numerous other transcriptional partners besides YAP/TAZ [163]. Conversely, YAP/TAZ are also known to partner with other epigenetic regulators to promote or suppress gene transcription [18,165–169]. Thus, the full extent of functional overlaps between YAP/TAZ and BRD4 in different cancer types represents another critical gap in knowledge (see outstanding questions).

Direct YAP/TAZ/TEAD inhibitors are currently under development [170]. Through function-based or in silico screenings, a number of lead compounds targeting various YAP/TAZ/TEAD binding interfaces or various functional pockets of TEADs have been reported [170]. Furthermore, emerging evidence indicates that the activity of YAP/TAZ/TEAD transcriptional complexes are tightly controlled by extensive posttranslational modifications (PTMs) [122,137,171–177], an example of which is TEAD. Utilizing predicted 3D topography and solved crystal structures of TEAD interaction with many co-activators, TEAD homologs are shown to be consistently palmitoylated at an internal Cysteine and this modification is required for TEAD stability and binding propensity [175–177]. Due to significant functional overlaps between YAP and TEAD, targeting TEAD can potentially recapitulate full effects of YAP/TAZ inhibition [16–18]. However, It remains to be determined whether potent and specific small molecule inhibitors could be developed against critical PTM events, and whether targeting PTMs represents a viable approach to effectively block the activities of YAP/TAZ/TEAD transcription complexes (see outstanding questions).

While Hippo pathway's relevance to immunotherapy resistance has not been formally confirmed, the prospect is promising. Regulation of the expression of PD-L1 and other immune suppressive cytokines by YAP/TAZ implies that tumors can rely on Hippo signaling deregulation to evade immune surveillance, which further supports strategies targeting this pathway. However, it was reported that YAP/TAZ's regulation of PD-L1 transcription is human-specific [141], making it difficult to model this aspect of YAP/TAZ functions using the traditional syngenic or GEMM mouse models. Moreover, while YAP/TAZ are highly expressed across most solid tumor types, they are strongly silenced in blood malignancies [178,179]. Further complicating the matter is that Hippo-YAP/TAZ signaling in haematopoietic cells appears to be divergent in many aspects from non-haematopoietic cells and may be even different among different immune subtypes [180]. Thus, further studies are needed to fully anticipate systemic effect of targeting the Hippo-YAP/TAZ pathway, especially of the immune system (see outstanding questions).

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Highlights

- Hippo-YAP/TAZ signaling pathway has emerged as a linchpin in targeted-, chemo-, and potentially immune-therapy resistance
- In response to various therapies, numerous upstream signals could impinge on various components of the Hippo pathway to activate YAP/TAZ
- YAP/TAZ activation represents a central bypass mechanism to EGFR and RAS/MAPK blockade
- YAP/TAZ promote immune suppression by transcribing PD-L1 and cytokines required for polarization and recruitment of MDSCs
- Inhibitors targeting key YAP/TAZ transcriptional targets such as CTGF, AXL and Bcl-xl are under clinical trials in combination with standard therapies
- BET inhibitors have emerged as proxy inhibitors for YAP/TAZ

- Given YAP/TAZ's roles in transcribing a diverse set of target genes, what are relative contributions of druggable YAP/TAZ targets to YAP/TAZ-mediated resistance to various cancer drugs in different cancer subtypes?
- Given the impact of PTMs on the folding, stability, subcellular localization, and binding affinities of YAP, TAZ and TEAD proteins, could small molecular inhibitors be designed to block PTMs that are essential for the activities of YAP/TAZ/TEAD?
- Given that BRD4 has recently emerged as a critical co-activator of the YAP/TAZ/TEAD transcriptional complexes, could BET inhibitors fully recapitulate the effects of YAP/TAZ blockade?
- What are the broader impacts of YAP/TAZ on the tumor microenvironment, particularly of the immune system?

Figure 1. YAP/TAZ signaling and resistance to targeted therapy.

The Hippo pathway, which consists of a core MST1/2-LATS1/2 kinase cassette and numerous regulatory proteins including *NF2/Merlin*, SAV1, MOB1, MOB3B, phosphorylates and inhibits YAP/TAZ by targeting them for cytoplasmic retention and proteasomal degradation mediated by 14-3-3 and β -TrCP, respectively. Inactivation of Hippo signaling promotes stabilization and nuclear entry of YAP/TAZ, where they form transcription complexes with TEAD1–4, AP-1, BRD4, ZEB1, E2F and possibly other transcription factors to induce the expression of pro-survival/anti-apoptotic genes such as CTGF, CYR61, Bcl-xL and Survivin. YAP/TAZ have been identified as major drivers of resistance to RAF and MEK inhibitors as single agents or in combination with TBK1 inhibitor in BRAF and KRAS mutant cancer cells. BRAFi treatment induces actin cytoskeletal remodeling and promotes Rho-mediated YAP nuclear entry in BRAF-mutant melanoma cells. YAP induces E2F and AP-1-mediated cell cycle and EMT transcriptional programs to promote survival following ablation of oncogenic Kras in pancreatic and colon cancer cells. Additionally, YAP/TAZ induce EGFRi resistance by increasing the expression of AXL, ERBB3 and EGFR.

Figure 2. YAP/TAZ signaling and resistance to chemotherapy.

Multiple miRNAs are up- or down-regulated in response to various chemo drugs and induce chemo resistance by targeting different components of the Hippo pathway (MST1, SAV1, LATS2, MOB1, YAP) in various cancer types. Anti-microtubule treatment activates CDK1, which phosphorylates and promotes LATS binding to and inhibition of Pin1, an oncoprotein that induces taxane resistance in multiple malignancies. Furthermore, CDK1 directly phosphorylates and inhibits YAP/TAZ by disrupting their binding to TEADs and destabilizing TAZ, sensitizing tumor cells to anti-microtubule drugs. The transcriptional activity of YAP is further modulated by CBP/p300-mediated acetylation and SIRT1-mediated deacetylation in response to various chemo agents. YAP/TAZ induce the transcription of antiapoptotic proteins (Bcl-xL, IAP1, Survivin.) and ABC multi-drug transporters to promote tumor cell survival and drug efflux, respectively. In addition, CTGF and CYR61, two canonical transcription targets of YAP/TAZ, can act through integrin receptors to activate MAPK and NF- κ B signaling to further boost chemotherapy resistance.

Figure 3. YAP/TAZ signaling and resistance to immune checkpoint therapy.

YAP/TAZ/TEAD directly transcribe PD-L1 and multiple cytokines (CSF1–3, IL6, CXCL5). YAP/TAZ-mediated PD-L1 expression on tumor cells binds to PD-1 expressed on effector T cells (CTLs), leading to inactivation of CTLs. Furthermore, YAP-induced upregulation of IL-6 and CSF1–3 skew the monocyte polarization in favor of tumor-promoting MDSCs and TAMs in bone marrow. On the other hand, YAP-mediated expression of CXCL5 by tumor cells attracts MDSCs and TAMs through its cognate receptor CXCR2 expressed on MDSCs and TAMs. Once recruited into the tumor microenvironment, MDSCs and TAMs inactivate CTLs both directly via PD-L1-PD1 interaction and indirectly by upregulating Arg1 and various other mechanisms.