Targeting the Hippo/YAP1 signaling pathway in hepatocellular carcinoma: From mechanisms to therapeutic drugs (Review)

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Abstract. The Hippo signaling pathway plays a pivotal role in regulating cell growth and organ size. Its regulatory effects on hepatocellular carcinoma (HCC) encompass diverse aspects, including cell proliferation, invasion and metastasis, tumor drug resistance, metabolic reprogramming, immunomodulatory effects and autophagy. Yes-associated protein 1 (YAP1), a potent transcriptional coactivator and a major downstream target tightly controlled by the Hippo pathway, is influenced by various molecules and pathways. The expression of YAP1 in different cell types within the liver tumor microenvironment exerts varying effects on tumor outcomes, warranting careful consideration. Therefore, research on YAP1-targeted therapies merits attention. This review discusses the composition and regulation mechanism of the Hippo/YAP1 signaling pathway and its relationship with HCC, offering insights for future research and cancer prevention strategies.

Contents

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1. Introduction

Liver cancer ranks among the most common malignancies and is the third leading cause of cancer-related death worldwide (1). The incidence and mortality of liver cancer are high, with >900,000 newly diagnosed cases and >800,000 deaths each year. Common types include hepatocellular carcinoma (HCC), cholangiocarcinoma (CC), and mixed HCC/CC (2). HCC accounts for 75-85% of primary liver cancers (3). While the etiology of HCC is well-established, the pathogenesis leading to its development remains unclear.

The Hippo signaling pathway was initially identified in *Drosophila melanogaster* and its composition, biological function and molecular mechanism of action were highly conserved during evolution. It plays a crucial role in liver size, regeneration, stem cell self-renewal and controlling liver cancer (4). Furthermore, the Hippo signaling pathway interacts with the Wnt signaling pathway and the Notch signaling pathway, thereby exerting significant regulatory effects on tumor formation and development.

Yes-associated protein 1 (YAP1) serves as a downstream effector of the Hippo pathway, undergoing phosphorylation and inactivation via the Hippo signaling cascade. Inhibition of the Hippo signaling pathway reduces YAP1 phosphorylation, promoting its nuclear localization. Within the nucleus, YAP1 binds to multiple transcription factors and activates multiple genes involved in cell proliferation, survival and invasion. The present study explores the role of the Hippo/YAP1 signaling pathway and the regulatory mechanism of YAP1 in HCC development. In addition, it reviews the impact of small-molecule compounds on YAP1 regulation in HCC. This research underscores YAP1's pivotal role in HCC and its regulatory mechanisms, providing new insight into HCC progression. These findings highlight YAP1 as a critical oncogenic driver in liver carcinogenesis, emphasizing the potential clinical utility of developing drugs targeting YAP1 and its downstream signaling targets for HCC treatment.

2. Hippo signaling pathway

The Hippo pathway was initially discovered and proposed in *Drosophila melanogaster*, where its tumor suppressor effect was also identified (5-7). In mammals, a core component of the Hippo pathway includes a kinase cascade primarily composed of mammalian STE20-like kinase 1/2 (MST1/2) and large tumor suppressor kinase 1/2 (LATS1/2) (Fig. 1). MST1/2, together with protein salvador homologue 1 (SAV1), phosphorylates and activates LATS1/2 kinase. Subsequently, LATS1/2 kinase, in association with MOB kinase activator 1A (MOB1), phosphorylates downstream effector molecules YAP1 and transcriptional co-activator with PDZ-binding motif (TAZ) (8). Phosphorylated YAP1 and TAZ bind to 14-3-3 and remain in the cytoplasm, thereby losing their transcriptional co-activation capability (9).

Inhibition of the Hippo signaling pathway leads to YAP1 and TAZ dephosphorylation, allowing their translocation into the nucleus. In this location, they interact with various transcription factors, including TEA domain transcription factor (TEAD), SMAD and RUNX family transcription factor, thereby promoting gene expression that facilitates cell proliferation and inhibits apoptosis (10,11). Notably, targets such as cellular communication network factor 1 (CCN1), CCN2 and others have been identified for YAP1 and TAZ (12). In addition, YAP1 and TAZ sense extracellular mechanical stimuli, such as extracellular matrix (ECM) hardness, and integrate and convert them into intracellular molecular signals that influence cell proliferation and migration (13).

3. Hippo/YAP1 pathway and HCC

The Hippo/YAP signaling pathway controls organ size during development and mediates the expansion of tissue-specific progenitor cells during tissue regeneration and normal cell proliferation (14). Increasing evidence indicates that YAP1/TAZ, Hippo kinase or other molecules are abnormally expressed in various cancers, including HCC (2,15,16). The regulatory effects of the Hippo signaling pathway on HCC are primarily reflected in the regulation of cell proliferation, invasion and metastasis, tumor drug resistance, metabolic reprogramming, immunomodulatory effects and autophagy. The connection between YAP1 and the hallmarks of cancer is depicted in Fig. 2.

Cell proliferation. YAP1 is an oncogene (17) and its overexpression can lead to the development of liver cancer (18-21), including HCC (22-32), CC (33,34) and hepatoblastoma (HB) (35,36). Elevated nuclear YAP1 expression is observed in HCC (37). Enhanced YAP1 activity promoted the proliferation of HCC (38,39). High YAP1 expression drives HCC proliferation (40-43). The overexpression of YAP1, combined with the knockdown of serine/arginine-rich splicing factor 1 (also known as SF2) further promotes tumor growth (44). YAP1 promotes cancer progression (45). Furthermore, YAP1/TAZ may play an early role in HCC progression (46). Studies have also shown that YAP1 and TAZ are highly expressed and activated in HCC, cholangiocarcinoma (CCA) and combined HCC-CCA (47,48). Of note, studies have also shown that YAP1 and TAZ eliminate tumor cells through cellular competition mechanisms. Normal hepatocytes surrounding liver tumors show activation of YAP1 and TAZ, and the absence of YAP1 and TAZ in these surrounding hepatocyte tumors accelerates tumor growth (49). Stathmin 1 (also known as oncoprotein-18), is a cytoplasmic phosphorylated protein that controls cell microtubule dynamics. Its upregulation promotes HCC development by activating the YAP1 signaling pathway (50). Glypican-3 (GPC3) is a protein that plays a crucial role in HCC development and progression. Inhibition of GPC3 inhibits the proliferation of HCC cells and induces apoptosis by decreasing YAP1 (51). Rac GTPase-activating protein 1 (RACGAP1) is a cytokinetic regulatory protein highly expressed in various cancers. RACGAP1 promotes HCC proliferation by decreasing the activation of the Hippo and YAP1 pathways (52). RNA binding motif protein 3, part of a family of RNA binding proteins rich in glycine, promotes HCC cell proliferation by upregulating YAP1 expression (53). The decrease in succinate dehydrogenase enzyme (SDH) is associated with increased succinate level and poor prognosis in patients with HCC. The decrease of SDH subunits A and B was reported to promote HCC proliferation by preventing the proteasome degradation of YAP1/TAZ (54).

Invasion and metastasis. Overexpression of YAP1 promotes HCC migration and invasion (55). Contrarily, YAP1 knockdown inhibits the invasion of HCC cells by modulating the characteristics of epithelial-mesenchymal transition (EMT) (56). YAP1 enhances HCC metastasis and mobilization by restricting the JNK/BCL2 interacting protein 3/ATPase sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting/calcium/calmodulin dependent protein kinase II pathway, which mediates the activation of cofilin/F-actin/lamellipodium axis (57). Zinc finger protein 191 inhibits the activation of YAP1 and metastasis of HCC by upregulating DLG1 (58). Integrin-αV is a TAZ target gene and its inhibition reduces nuclear YAP1/TAZ protein levels and suppresses HCC migration (59). The interaction of α-catenin with YAP1/FoxM1/TEAD induces centrosomal protein 55 to promote HCC cell migration (60). Septin 6 promotes F-actin formation, upregulates YAP1 expression and enhances its nuclear translocation, thereby driving HCC progression (61).

Tumor drug resistance. YAP1 promotes sorafenib resistance by upregulating survivin expression in HCC cells (62). Silencing *YAP1* and insulin-like growth factor 2 mRNA binding protein 3 restores transforming growth factor-β (TGF-β) signaling, suppresses pluripotent genes and tumorigenesis and eliminates chemotherapy resistance in tumor-initiating stem-like cells (TICs) (63). Dual downregulation of TAZ/YAP1 reduces chemotherapy resistance and tumorigenicity (64,65). Mex-3 RNA binding family member A (MEX3A), an RNA-binding protein, has been implicated in cancer development (66). MEX3A may promote HCC progression and hinder sorafenib sensitivity by inactivating the Hippo signaling pathway (67). Claudin 6 (CLDN6) is highly expressed in a variety of cancers (68). Overexpression of CLDN6 increases YAP1 and TAZ abundance, making sorafenib treatment less effective (69).

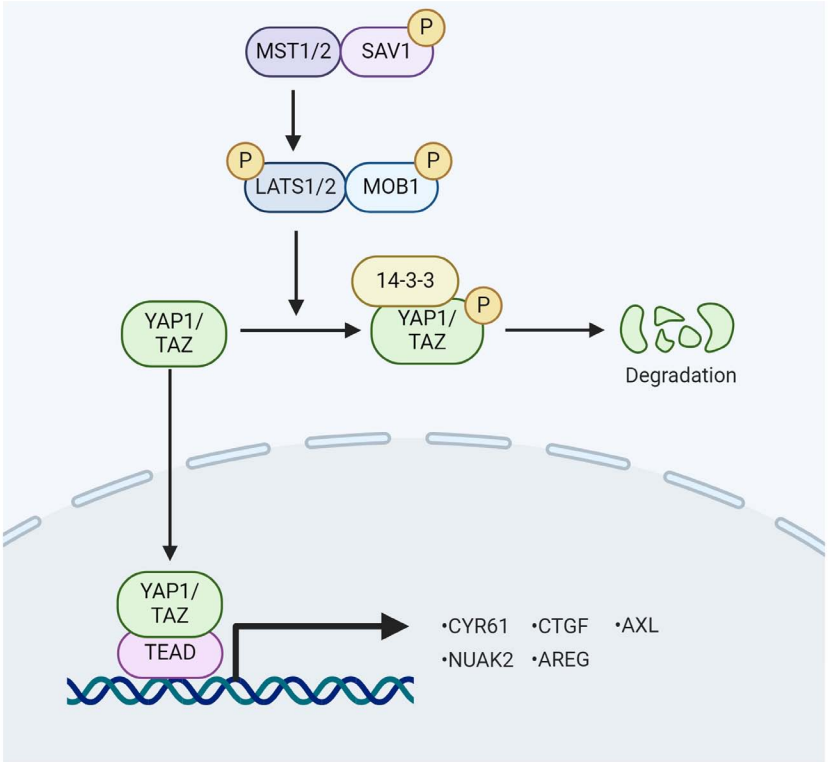

Figure 1. Core components of the Hippo pathway in mammals. The core of the Hippo pathway is a kinase cascade primarily composed of MST1/2 and LATS1/2. MST1/2, in conjunction with SAV1, phosphorylates and activates LATS1/2 kinase. Subsequently, LATS1/2 kinase binds to MOB1 to phosphorylate the downstream effector molecules YAP1 and TAZ. Phosphorylated YAP1 and TAZ bind to 14-3-3 and remain in the cytoplasm, losing their transcriptional co-activation abilities. When Hippo signaling pathway activity is inhibited, YAP1 and TAZ undergo dephosphorylation. The dephosphorylated YAP1/TAZ translocate to the nucleus, where they interact with other transcription factors, including TEAD, to induce gene expression that promotes cell proliferation and inhibits apoptosis. CTGF and CYR61 are among the targets identified for YAP1 and TAZ. MST1/2, mammalian STE20-like 1/2; SAV1, salvador homologue 1; LATS1/2, large tumor suppressor 1/2; YAP1, yes-associated protein 1; TAZ, transcriptional coactivator with PDZ-binding motif; TEAD, TEA domain family member; AREG, amphiregulin; CTGF, connective tissue growth factor; CYR61, cysteine-rich angiogenic inducer 61; AXL, AXL receptor tyrosine kinase; NUAK2, NUAK family SNF1-like kinase 2; MOB1, MOB kinase activator 1; P, phosphate.

Metabolic reprogramming. Tumor development is also a result of metabolic reprogramming (70). Studies have indicated that YAP1 can reprogram cellular metabolism (71). Glycogen accumulation is a key oncogenic event in the malignant transformation of the liver. Deficiency in glucose-6-phosphatase or liver glycogen phosphorylase leads to glycogen storage disease, liver enlargement and tumorigenesis in a YAP1-dependent manner (72). Enolase 1 (ENO1), a glycolytic enzyme, shows abnormal activation in the ENO1/YAP1/PLCB pathway in clinical HCC samples (73). High mobility group box 1 (HMGB1) is a chromosomal protein that promotes HCC development by inducing YAP1/HIF1α-dependent aerobic glycolysis (74). In addition, *Hmgb1* accelerates HCC by activating YAP1 in Hippo signaling-deficient mice (75). YAP1 reprograms glutamine metabolism and YAP1 activation stimulates nucleotide biosynthesis by enhancing the expression and activity of glutamine synthetase (GLUL). Genetic or pharmacological inhibition of GLUL inhibits Yap1-induced hepatomegaly and HCC development (76). YAP1/TAZ regulates amino acid metabolism by upregulating the expression of amino acid transporters solute carrier family 38 member 1 (SLC38A1) and SLC7A5, which are critical for tumor cell formation, growth and progression (77). Bile acids (BAs) act as signaling molecules and tumor promoters by driving YAP1 activation. Studies have shown that the ability of BAs to activate YAP1 is concentration-dependent (78). Loss of the nuclear receptors nuclear receptor subfamily 1 group H member 4 and small heterodimer partner leads to YAP1 activation in mice, resulting in severe deficiencies in BA homeostasis liver enlargement and liver tumorigenesis (78). BAs act as an upstream regulator of YAP1 through a pathway dependent on the induction of scaffold protein IQ motif-containing GTPase-activating protein 1 (IQGAP1) (78). IQGAP1 is a driver of HCC tumors by enhancing YAP1 (79). Cholesterol metabolism has an important role in maintaining membrane integrity and combating diseases such as obesity and cancer. COP9 signalosome subunit 6 antagonizes speckle-type POZ protein ubiquitin ligase to stabilize hydroxymethylglutaryl-CoA synthase 1, thereby activating YAP1 and promoting tumor growth (80).

Immunomodulatory effects. Tumor-associated macrophages (TAM) are the most abundant immune-associated stromal cells in the tumor microenvironment. TAM exhibit great phenotypic heterogeneity and have various functions, such as promoting tumor growth, metastasis and angiogenesis (81). Previous studies have shown that M2-type macrophages in HCC induce cell proliferation and angiogenesis (82). In addition, M2-type macrophage-derived extracellular

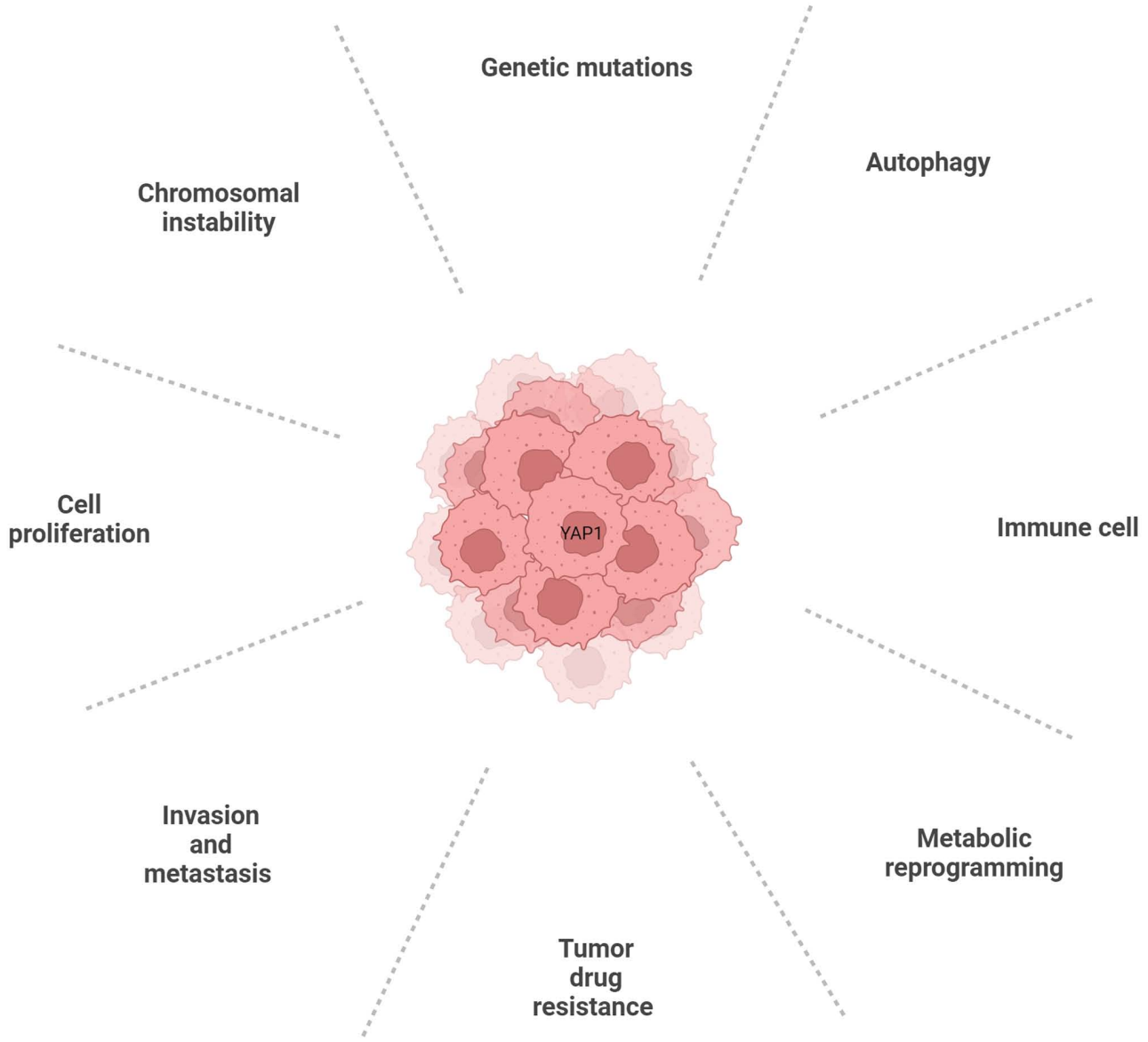

Figure 2. YAP1 and the hallmarks of cancer. When YAP1 is active and not phosphorylated by the Hippo pathway, it translocates from the cytoplasm into the nucleus. In the nucleus, YAP1 can act as an oncogene by inducing the transcription of genes that contribute to cancer development. YAP1 activation promotes cell proliferation, invasion and metastasis, tumor drug resistance, metabolic reprogramming, immune cells, autophagy, genetic mutations and chromosomal instability. YAP1, yes-associated transcriptional regulator.

vesicles promote T-cell exhaustion in HCC by activating the YAP1/β-catenin pathway (83). The interaction between ETS variant transcription factor 4 and YAP1 promotes the growth of HCC, resulting in an increase in macrophages and a decrease in T-cell and natural killer-cell infiltration in the tumor (84). Nogo-B promotes HCC progression by enhancing *YAP1*/*TAZ*-mediated polarization of M2-type TAM (85). IL-6 secreted by YAP1-activated HCC cells may induce TAM recruitment (86). The activation of YAP1 is essential for the recruitment of M2-type macrophages by TICs in the liver and TAM protect TIC from immune clearance (87). RACGAP1 promotes HCC development through immunosuppression mediated by YAP1activation (88). In patients with HCC, YAP1 overexpression in peripheral blood T cells is associated with an increased percentage of T-regulatory cells in peripheral blood mononuclear cells, indicating a poor prognosis (31).

Autophagy. YAP1 activity is associated with the autophagy process in HCC (89,90). In HCC, activation of YAP1 expression promotes autophagy, while downregulation of YAP1 expression inhibits autophagy (91,92). A previous studies by our group found that YAP1 and autophagy produced positive feedback in HCC cells (93). Furthermore, inhibition of YAP1 reduces autophagy activity and improves the efficacy of anti-programmed cell death 1 (PD-1) treatment in HCC (93). It was also reported that chaperone-mediated autophagy impairment leads to YAP1 and IL-6 cytokine family signal transducer degradation, promoting the proliferation and migration of both normal and HCC cells (89). In HCC stem cells, fluid shear stress induces cell migration through the ras homolog family member A-YAP1 autophagy pathway (94).

Genetic mutations and chromosomal instability (CIN). CIN can induce polyploidy and aneuploidy of cells, which are

hallmarks of cancer. The increase in CIN, polyploid and aneuploid is closely related to the occurrence and development of HCC (95). Studies have shown that YAP1 induces forkhead box (FOX)M1 to drive the expression of CIN-related genes and promote the development of HCC (96). YAP1 promotes diploid-polyploid transformation and polyploid cell growth through the protein kinase B (Akt)-S-phase kinase associated protein 2 (Skp2) axis. YAP1 strongly induces acetyltransferase p300-mediated acetylation of the E3 ligase Skp2 through Akt signaling. Acetylated Skp2 is localized only to the cytoplasm, leading to excessive accumulation of the cyclin-dependent kinase inhibitor p27, resulting in mitotic arrest and cell polyploidy. In addition, the pro-apoptotic factor FOXO1/3 is over-degraded by acetylated Skp2, leading to polyploid cell division, genomic instability and tumorigenesis (97). Leucine rich pentatricopeptide repeat containing inhibits genomic instability and HCC by maintaining *Yap1*-p27-mediated cell ploidy and p62-histone deacetylase 6-controlled autophagy maturation (98).

4. Regulatory mechanism of YAP1

YAP1, a key downstream effector of the Hippo pathway, is regulated at both the transcriptional and post-translational levels. Transcription factor CP2 (TFCP2) has been identified as an oncogenic protein in HCC, acting as a YAP1 cofactor to stimulate YAP1-dependent liver malignancies (99). Serotonin (5-HT) promotes the proliferation and metastasis of HCC (100). High levels of 5-HT and YAP1/vestigial like family member 4 ratios in patients with HCC are closely associated with HCC progression and poor prognosis (101). The elevated expression of 5-HT and YAP1 may synergistically promote HCC progression (100). Ablation of stearoyl CoA desaturase 2 (*Scd2*) suppresses YAP1 and prevents liver tumorigenesis (102). In HCC, knockdown of aldo-keto reductase 1C3 reduces YAP1 nuclear translocation, inhibits SLC7A11 expression and induces ferroptosis (103).

Studies have shown that YAP1/TAZ activity can be regulated through various post-translational mechanisms, including acetylation, methylation, phosphorylation, O-GlcNAacylation and ubiquitination. Lysine acetyltransferase 6A, a histone acetyltransferase, is involved in drug resistance by inducing YAP1 (104). YAP1 acetylation occurs on specific and highly conserved C-terminal lysine residues and is mediated by the nuclear acetyltransferases CREB binding protein and p300 (105). The nuclear deacetylase sirtuin 1 (SIRT1) is responsible for YAP1 deacetylation (105). In HCC cells, high levels of p300 promote the binding of YAP1 to the melanoma cell adhesion molecule promoter, thereby promoting tumor development (106). SIRT1 is a deacetylase responsible for YAP1 deacetylation. In HCC, SIRT1-induced deacetylation of YAP1 in HCC contributes to tumor progression (107). Downregulation of SIRT1 blocks cisplatin-induced YAP2 nuclear translocation and enhances cisplatin sensitivity (108).

Histone lysine methyltransferase SET domain containing 1A (SETD1A) is a member of the histone methyltransferase family. SETD1A enhances YAP1 activation and induces drug resistance in HCC (109). Loss of spectrin β, non-erythrocytic 1 inhibits hepatocyte autophagy through SETD7-mediated YAP1 methylation, promoting the initiation and development of HCC (110). Overexpression of Menin and YAP1 in human HCC specimens is associated with poor prognosis, suggesting H3K4me3 as a potential therapeutic target for HCC (111). Ten-eleven translocation 1 physically interacts with TEAD to cause regional DNA demethylation, histone H3K27 acetylation and chromatin opening of YAP1 target genes, promoting transcriptional activation (112).

Highly expressed lipolysis-stimulated lipoprotein receptor binds to YAP1 via the PPPY motif, increases YAP1 phosphorylation and inhibits the growth of HCC (113). Overexpression of estrogen receptor α enhances the phosphorylation of YAP1 and reduces its nuclear translocation, inhibiting the growth of HCC (114).

Increased O-GlcNAcylation has been observed in the progression of liver tumors. O-GlcNAcylation is catalyzed by O-linked β-N-acetylglucosamine transferase, which transfers O-GlcNAc to the hydroxyl group of the serine or threonine residue of the target protein. O-GlcNAcylation induces the transforming phenotype of HCC cells in a YAP1-dependent manner (115).

YAP1 post-translational modification, which facilitates ubiquitination and apoptosis, is a favorable prognostic factor in HCC (116). Ubiquitin-specific protease 46 (USP46) interacts with MST1, causing YAP1 inactivation and inhibiting HCC proliferation and metastasis (117). USP10 promotes HCC proliferation by deubiquitinating and stabilizing YAP1/TAZ (118). USP19 reduces K11 and K48-linked multi-ubiquitination of YAP1 at the K76 and K90 sites, stabilizing YAP1 and promoting HCC cell proliferation (119). Ubiquitin ligase RNF219-mediated degradation of α-catenin promoted epigenetic modification of the YAP1/β-catenin complex-dependent lectin galactoside-binding soluble 3 promoter, facilitating HCC metastasis (120). Tribbles homolog 2 promotes YAP1 transcriptional coactivator stabilization by interacting with β-transducin repeat containing E3 ubiquitin protein ligase (β-TrCP), which was important for HCC cell survival (121). Chaperonin containing TCP1 subunit 3 extends the half-life of YAP1 and TFCP2 by blocking ubiquitination caused by poly(rC) binding protein 2 via β-TrCP (122). Overexpression of E3 ubiquitin ligase F-box and WD repeat domain-containing 7 reduces YAP1 expression, thereby inhibiting HCC proliferation (123). These studies suggested that YAP1 is regulated extensively at the post-translational level.

Crosstalk of Hippo signal pathways with other signal pathways to regulate YAP1. Numerous signaling pathways, including Wnt, mitogen-activated protein kinase (MAPK), phosphatidylinositol-3-kinase (PI3K) and Notch, have been shown to regulate YAP1/TAZ activity in HCC through crosstalk with the Hippo signaling pathway (2). The crosstalk of Hippo signaling pathways with other signaling pathways to regulate YAP1 is illustrated in Fig. 3. Activation of Wnt/β-catenin signaling inhibits HCC formation by disrupting the positive feedback loop between YAP1/TAZ and Notch signaling (124). Overexpression of R-spondin 2 activates both typical Wnt/β-catenin and Hippo/YAP1 signaling, promoting HCC formation (125). Various mutations in β-catenin combined with YAP1 drive HB development (126). The upregulation of YAP1 and β-catenin expression is observed in HCC (127,128). The role of MYC and β-catenin in liver tumorigenesis are dependent on Yap1/WW

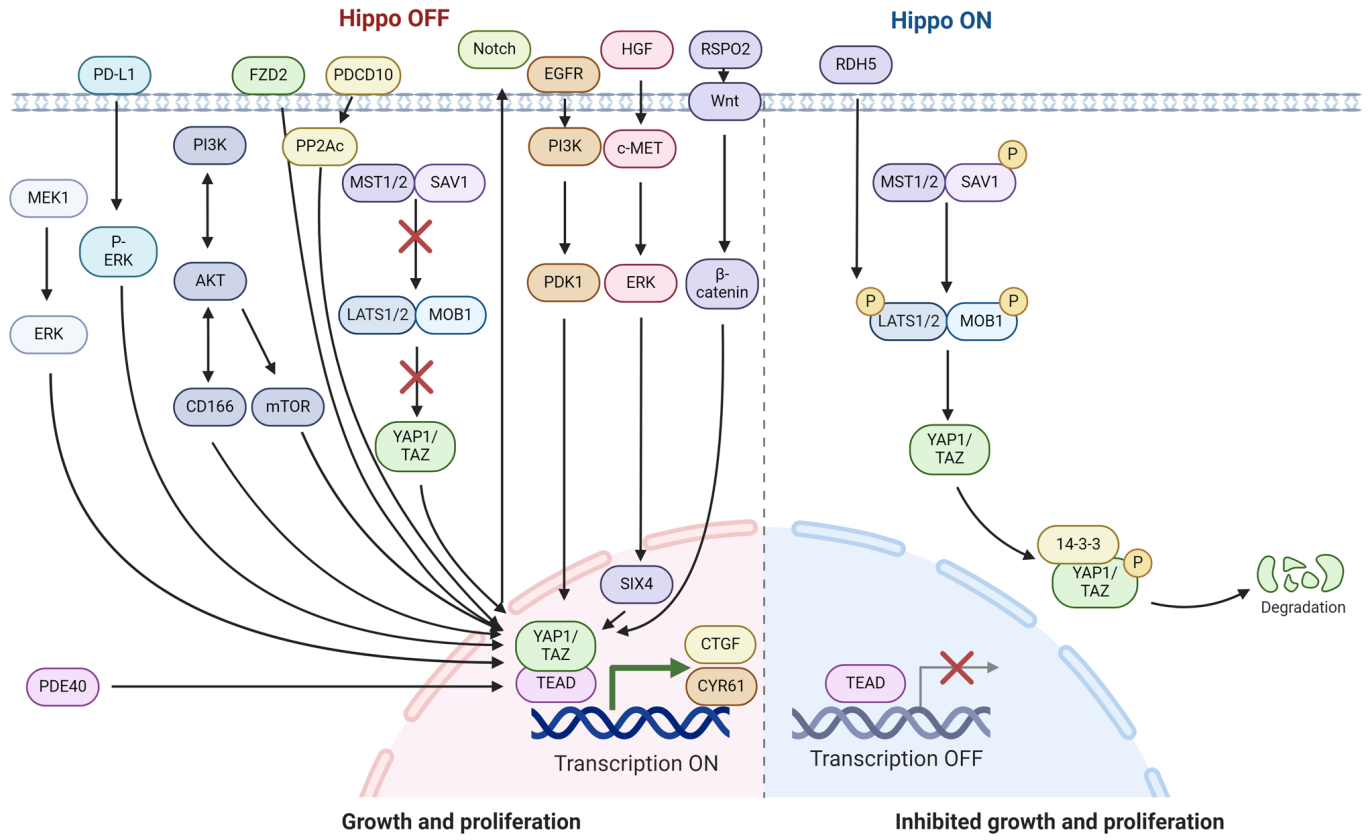

Figure 3. Crosstalk of Hippo signal pathway with other signaling pathways to regulate YAP1. When Hippo signaling is active, MST1/2 kinase phosphorylates the SAV1 complex, which then activates LATS1/2 and its regulatory protein MOB1/2 complex. Subsequently, LATS1/2 phosphorylates YAP1 at a highly conserved residue within a specific sequence. Phosphorylation at Ser-127 promotes cytoplasmic retention of YAP1, while phosphorylation at Ser-397 induces degradation. In the absence of Hippo pathway activity, YAP1 is dephosphorylated and translocates into the nucleus. There, YAP1 binds to and activates TEAD transcription factors, promoting the expression of genes such as CTGF and CYR61. The Wnt, MAPK, PI3K, EMT, Notch, EGFR, TNF, cAMP and HGF/c-MET signaling pathways affect the expression of YAP1 in tumor cells. X indicates inhibition. YAP1, yes-associated protein 1; MST1/2, mammalian STE20-like 1/2; SAV1, salvador homologue 1; LATS1/2, large tumor suppressor 1/2; TEAD, TEA domain family member; MOB1, MOB kinase activator 1; CTGF, connective tissue growth factor; CYR61, cysteine-rich angiogenic inducer 61; EMT, epithelial mesenchymal transition; HGF, hepatocyte growth factor; cAMP, cyclic adenosine monophosphate.

domain containing transcription regulator 1 activity (129). Frizzled 10 (FZD10) enhances the self-renewal, tumorigenicity and metastasis of liver cancer stem cells (CSCs) by activating β-catenin and YAP1 (130). Tribbles homolog 2 is a direct target of Wnt/T-cell factor in HCC, promoting the stabilization and nuclear localization of YAP1 and contributing to the development of fibrosis-associated HCC (131).

The MAPK signaling pathway has a key role in numerous human diseases, including cancer. It is activated in numerous tumors, with various components identified as oncogenes (132). A previous study by our group found that tumor cells promoted phosphorylated (p-)ERK and expression of YAP1 through cell surface PD-1/programmed death ligand-1 (PD-L1) interactions. Therefore, blocking the binding of PD-1 and PD-L1 inhibited the p-ERK/YAP1 pathway and reduced tumor cell proliferation (133). Studies have also shown that MAPK kinase 1 interacts with YAP1 to promote YAP1 expression, which supports the proliferation and phenotypic transformation of hepatoma cells (134). In lenvatinib-resistant HCC cells, the ERK/YAP1 signaling pathway mediates the upregulation of cyclin-dependent kinase 6 (135).

Simultaneous activation of PI3K and YAP1 pathways often occurs in HCC and their combined inhibition is unfavorable to HCC growth (136). PI3K/AKT signaling regulates CD166 (also known as Alcam), playing an anti-apoptotic role in HCC via YAP1 (137). Standard CD44 (CD44S) positively regulates the expression of YAP1 and its target genes in HCC cells through the PI3K/AKT pathway (138). The mTOR complex 1 (mTORC1) pathway is a major oncogenic pathway acting downstream of PI3K and AKT (139). The mTORC1/AT-rich interaction domain 1A axis promotes carcinogenic chromatin remodeling and YAP1-dependent transcription, thus promoting HCC development (140).

EMT is important for HCC metastasis (141,142). FZD2 promotes the progression of EMT and HCC by activating the Hippo/YAP1 pathway (143). Programmed cell death 10 activates YAP1 through interaction with protein phosphatase 2A (PP2Ac), promoting the progression of EMT and HCC (144). Overexpression of retinal dehydrogenase 5 activates the Hippo/YAP1 signaling pathway, promotes YAP1 nuclear translocation and alleviates metastasis of HCC (145). Snail family transcriptional repressor 1 is a primary regulator of EMT and its overexpression promotes the expression of YAP1 (146).

In addition, transcriptional regulator YAP1 has been found to upregulate Notch ligand Jagged-1 (Jag-1), thereby activating Notch signaling in HCC cells and mouse hepatocytes. In

human HCC and colorectal tumor samples, the activity of YAP1-dependent Jag-1 and Notch was observed to correlate with patient survival time. These results show that YAP1 and Notch inhibitors can be used as therapeutics for gastrointestinal cancers (147).

The ECM is a major component of tumors, playing a vital role in mechanical support, microenvironment regulation and as a source of signaling molecules (148). The Hippo pathway effector molecules YAP1 and TAZ function as nuclear sensors for mechanical signals in response to ECM signals. The ECM proteoglycan Agrin promotes tumorigenesis by activating YAP1 (149). Collagens, a key component of ECM, play a significant role as well. Collagen I-discoidin domain receptor 1 signaling inhibits the Hippo pathway by promoting the recruitment of protein phosphatase 2 scaffold subunit Aα to MST1, which activates YAP1 and enhances the stem cell properties of HCC (150).

The EGFR signaling pathway and the Hippo signaling pathway play important roles in the carcinogenesis of HCC (151). Studies have shown that the EGFR/PI3K-phosphoinositide-dependent kinase 1 pathway activates YAP1 signaling in HCC. In addition, activated EGFR signaling can also promote the growth of HCC cells in a YAP1-independent manner (151).

TNF receptor II (TNFR2) is required for TNF-α-induced YAP1 activation during malignant transformation of hepatic progenitor cells (HPC) and liver tumorigenesis. In HPC-like cells that drive HCC, the TNFR2/heterogeneous nuclear ribonucleoprotein K/YAP1 signal is activated and associated with poorer prognosis (152).

The cyclic adenosine monophosphate (cAMP) signaling pathway plays a crucial role in cancer development (153). Phosphodiesterase 4D, a major component of cAMP hydrolysis in many cell types, was observed to form a complex with YAP1 to promote HCC progression (154).

The hepatocyte growth factor/cellular-mesenchymal epithelial transition factor (c-MET) signaling pathway is important for promoting HCC growth, angiogenesis and metastasis (155). Overexpression of SIX homeobox 4 promoted the expression of YAP1 and c-MET, thereby enhancing the invasion and metastasis of HCC (156).

5. Hippo pathway and treatment of HCC

Targeting the upstream region of YAP1/TAZ. The upstream components of the Hippo pathway appear to be human tumor suppressors. Studies have shown that overexpression of MST1 promotes the phosphorylation of YAP1 (Ser127), inhibits cell proliferation and induces cell apoptosis (157). Combined *Mst1/2* deficiency results in loss of inhibitory Ser127 phosphorylation of YAP1, massive overgrowth and HCC (158). Studies have shown that serine/threonine protein kinase 25 enhances YAP1 activation through the regulation of MST1/2 (159). α2β1 integrin binds to the collagen ECM, inhibits MST1 kinase phosphorylation and activates YAP1 to promote cancer (160). Knockdown of MST1 or overexpression of YAP1 reverses tripartite motif containing 21 knockdown-induced HCC growth and chemotherapy-sensitive impairment (161). SIRT7 inhibits MST1 transcription by binding to its promoter and inducing H3K18 deacetylation of the promoter region. High SIRT7 expression is associated with increased YAP1 expression and nuclear localization (162). Striatin 3 inhibits the Hippo pathway, promoting YAP1 nuclear translocation (163). As an inhibitor of YAP1, LATS1 is decreased via RNA interference-mediated downregulation of YAP1 (164). Inhibition of LATS2-mediated dephosphorylation increases the YAP1/TEAD2 association, leading to YAP1/TEAD2 transcriptional activation, as well as upregulated invasion of HCC cells (165). DND microRNA-mediated repression inhibitor 1 promotes LATS2 and phosphorylated YAP1 levels, inhibiting the EMT of HCC (166). TGF-β1 increases the phosphorylation of LATS1 and YAP1, inhibiting HCC growth (167). Overexpression of WW and C2 domain containing 2 inhibits the invasion and metastasis of HCC cells by activating LATS1/2 and phosphorylating YAP1 (168). Loss of PDZ and LIM domain protein 1 leads to dephosphorylation of LATS1 and activation of YAP1, promoting HCC metastasis (169). α-actinin 1 reduced LATS1 and YAP1 phosphorylation and promoted HCC cell proliferation through interaction with MOB1 (170). Highly expressed LIM domain only 3 inhibits the Hippo signaling pathway by interacting with LATS1, promoting the invasion and metastasis of HCC cells (171). The diacylglycerol lipase α/2-arachidonoylglycerol axis significantly inhibits LATS1 and YAP1 phosphorylation, promotes YAP1 nuclear translocation and activity, and induces HCC resistance (172). SAV1 is required for the activation of MST1 and subsequent LATS1/2, and SAV1 knockout leads to the development of HCC (173). Studies have shown that low levels of YAP1 phosphorylation can still be observed in the case of SAV1 knockout. Furthermore, almost all liver cancers caused by specific SAV1 knockout in the liver were mixed liver cancers (174). Angiomotin (AMOT), another regulator of YAP1 in the Hippo pathway, forms a typical Hippo core complex with MST and LATS (175). Studies have shown that AMOT acts as a YAP1 stimulator at high glucose levels and as a YAP1 inhibitor at normal glucose levels (176). LIM domain protein Ajuba regulates YAP1 signaling and is associated with tumorigenesis. Depletion of Ajuba led to increased YAP1 expression in HCC cells, promoting their growth (177). Neurofibromin 2 (NF2) is a tumor suppressor gene. NF2 induces LATS1/2 kinase, which inhibits YAP1/TAZ (178). In the absence of *Nf2*, Amot promotes nuclear entry and transcriptional activity of *Yap1* and is required for liver tumorigenesis (179). Together, these studies suggest that the Hippo-YAP1 signaling pathway is involved in the development of HCC. The dysregulation of Hippo signaling pathway components is frequently observed in HCC.

Targeting downstream of YAP1/TAZ. Although the complete range of downstream targets of YAP1 has yet to be fully elucidated, numerous identified targets are linked to cell growth and survival. In addition, TEAD is essential for the oncogenic function of YAP1/TAZ, thus disrupting the interaction between TEAD and YAP1/TAZ can inhibit YAP1 activity. Silencing TEAD4 in the TEAD gene persistently inhibited tumor growth in HB cell lines and decreased the expression of YAP1 target genes (180). TEAD4 was found to mitigate TGF-β signaling and HCC progression independently of YAP1 (181). Overexpression of hepatocyte nuclear factor 4α significantly impaired the proliferation of YAP1-TEAD-induced HCC

Table I. Drugs targeting YAP1 for the treatment of HCC.

Small molecule drugs	Mechanisms	(Refs.)
Cisplatin	Promotes the expression of PD-L1 and induces immune tolerance through YAP1	(192)
Verteporfin	Decreases the PD-1^{+}CD8^{+}T cell percentage while increasing the PD-1^{-}CD8^{+}T cell percentage in the spleen	(218)
Statins	After Statins treatment, YAP1 protein is extruded from the nucleus to the cytoplasm	(197)
EZH2 inhibitors	Induces apoptosis of HCC cells by inhibiting YAP1	(198)
TPA	Inhibits YAP1 and HCC cells through AMOT	(200)
Dichloroacetate	Reduces the stemness of HCC cells by promoting the cytoplasmic translocation of YAP1	(204)
Fingolimod	Inhibits HCC proliferation by downregulating YAP1 expression	(206)
Metformin	Inhibits LATS1/2, activates MST1/2 and phosphorylates YAP1; increases sensitivity to chemotherapeutic agents by inhibiting YAP1	(207,208)
Tadalafil	Reduces YAP1/TAZ by targeting the PDE5/PKG/Hippo/YAP1/TAZ axis	(210)
Artemisinin	Inhibits the growth, migration and invasion of HCC by targeting cell bioenergetics and the Hippo/YAP1 signaling pathway	(213)
DHA	Regulates lipid metabolism, TME, glycolysis and intestinal microflora of the immune microenvironment through YAP1 in HCC, enhancing the effect of anti-PD-1 treatment	(214-217,219)
Decursin	Inhibits HCC cell proliferation by upregulating phosphorylation of LATS1 and β-TRCP and degradation of YAP1	(220)
Myricetin	Activates LATS1/2 kinase, which directly phosphorylates YAP1 on serine residues and inhibits the proliferation of HCC cells	(221)
Evodiamine	Inhibits the expression of YAP1 by upregulating the phosphorylation of LATS1	(222,226)
Wogonin	Inhibits the expression of YAP1	(223)
WZ35	Inhibits the growth of HCC cells by downregulating YAP1-controlled autophagy	(92)
Ginsenoside CK	Inhibits the proliferation and growth of HCC by inhibiting YAP1/TEAD2 interaction	(224)
Apigenin	Decreases the expression of YAP1	(225)
4AALT3	Inhibits HepG2 cell growth by targeting YAP1/TAZ	(227)
Tanshinone IIA	Inhibits the proliferation of HCC by downregulating YAP1 expression in a TGF-β signaling pathway-dependent manner	(228)
Chinese propolis	Inhibits HepG2 cell proliferation and promotes apoptosis by inactivating the Hippo/YAP1 and PI3K/AKT pathways	(229)
Salvianolic acid B	Inhibits HCC by upregulating the expression of MST1 protein, degrading YAP1 in cytoplasm	(230)
Ovatodiolide	Reduces YAP1 expression	(231)
Corosolic acid	Inhibits tumor progression by transferring YAP1from the nucleus	(232)
Actinomycin D	Inhibits the expression of YAP1	(233)
Luteolin	Inhibits the biological effects of matrix stiffness induction and the CXCR4-mediated YAP1 signaling pathway	(238)
HS-OA	Decreases the expression of YAP1	(239)
YHC1	Inhibits the binding of YAP1 and TEAD1	(240)

YAP1, yes-associated protein 1; HCC, hepatocellular carcinoma; DHA, dihydroartemisinin; 4AALT3, 4-acetylantrocamol LT3; HS-OA, hydrogen sulfide-releasing oleanolic acid; YHC,12-O-debenzoyl-yuanhuacine; TPA, 12-O-tetradecanoylphorbol-13-acetate; AKT, protein kinase B; AMOT, angiomotin; CXCR4, C-X-C motif chemokine receptor type 4; LATS1, large tumor suppressor kinase 1; LATS2, large tumor suppressor kinase 2; MST1, mammalian STE20-like kinase 1; MST2, mammalian STE20-like kinase 2; PDE5, phosphodiesterase type 5; PD-L1, programmed death ligand-1; PI3K, phosphatidylinositol-3-kinase; TEAD1, TEA domain transcription factor 1; TGF-β, transforming growth factor-β; β-TRCP, β-transducin repeat containing E3 ubiquitin protein.

cells (182). Targeting downstream effectors of YAP1 could be a potential strategy to inhibit its oncogenic properties. The AXL receptor tyrosine kinase (AXL), a downstream target of YAP1, is involved in cell invasion and metastasis (183). It has been demonstrated that RNA interference-mediated down-regulation of AXL expression reduces the proliferation and invasion capabilities of YAP1-expressing HCC cell lines (184). CTGF, a multifunctional signal regulator, promotes cancer occurrence, progression and metastasis by regulating cell proliferation, migration, invasion and drug resistance (185). Sphingosine-1-phosphate (S1P) has been shown to stimulate cell proliferation through YAP1 activation and upregulation

of CTGF expression mediated by S1P receptor 2 (186). Overexpression of TNF-α-induced protein 8 (TNFAIP8) increases the nuclear localization and stability of YAP1, upregulates CTGF and promotes HCC progression (187). Furthermore, the loss of CYR61 enhances TGF-β-or YAP1-mediated growth and migration of HCC cells (188). Amphiregulin (AREG), another downstream target of YAP1, has been shown to play a crucial role in inhibiting HCC by inactivating YAP1 (189). NUAK family SNF1-like kinase 2 (NUAK2), also known as sucrose nonfermenting-like kinase, is a member of the AMPK protein kinase family and a direct downstream target of YAP1 (190). Pharmacological inactivation of NUAK2 inhibits YAP1-dependent cancer cell proliferation and liver overgrowth (191). These findings suggest that targeting the downstream effectors of YAP1, such as AXL, CTGF, TNFAIP8, CYR61, AREG and NUAK2, may be an effective strategy for inhibiting YAP1-mediated oncogenesis.

Small molecule drugs. Given the critical role of YAP1 in cancer development, the existing small molecule compounds targeting YAP1 and their mechanisms of action were summarized (Table I). A previous study by our group demonstrated that YAP1 blocked the immunosuppressive microenvironment, thereby enhancing the efficacy of HCC chemotherapy. For instance, cisplatin promotes PD-L1 expression and induces immune tolerance through YAP1 in the HCC microenvironment (192). Verteporfin, a photodynamic drug approved for treating macular degeneration, has shown promising preclinical antitumor effects by inhibiting the YAP1/TAZ pathway (193). In addition, verteporfin exhibited antitumor effects in both intrahepatic and extrahepatic CCA and enhanced tumor growth inhibition when combined with anti-PD-1 (194). Verteporfin significantly improved the efficacy of transcatheter arterial chemoembolization in the treatment of transplanted HCC by inhibiting the Hippo/YAP1 signaling pathway (195). Statins, widely used for treating dyslipidemia and preventing cardiovascular diseases, were found to be associated with a reduced incidence of HCC (196). Statins treatment resulted in the extrusion of YAP1 protein from the nucleus to the cytoplasm (197). The synergistic effect of fibroblast growth factor receptor 4 and EZH2 inhibitors induced the apoptosis of HCC cells by inhibiting YAP1 (198). The compound 12-O-tetradecanoylphorbol-13-acetate, a known carcinogen in rodent skin (199), inhibited YAP1 and HCC cells through AMOT (200). Talazoparib, a potent poly(ADP-ribose) polymerase 1 inhibitor used for treating patients with breast cancer with BRCA1 DNA repair associated (BRCA1) or BRCA2 mutations (201), induced the expression of the tumor suppressor long non-coding RNA polo-like kinase 4, which inhibited HCC cell viability and growth by inactivating YAP1 and inducing cell senescence (202). Dichloroacetate, used for treating mitochondrial genetic diseases and lactic acid poisoning (203), reduced the stemness of HCC cells by promoting the cytoplasmic translocation of YAP1 (204). Fingolimod, a Food and Drug Administration-approved immunomodulator for multiple sclerosis (205), inhibited HCC proliferation by downregulating YAP1 expression (206). Metformin, a first-line treatment for type 2 diabetes, exhibited promising anti-tumor effects by directly inhibiting LATS1/2, activating MST1/2 and phosphorylating YAP1, thereby inhibiting HCC progression (207). Furthermore, metformin increased the sensitivity to chemotherapeutic agents by inhibiting YAP1 in HCC (208). Tadalafil, a phosphodiesterase type 5 (PDE5) inhibitor used for treating pulmonary hypertension and erectile dysfunction (209), reduced YAP1/TAZ levels by targeting the PDE5/PKG/Hippo/YAP1/TAZ axis in HCC (210). Vincristine sulfate, a common chemotherapy drug, inhibited YAP1 transcriptional activity and cell proliferation when the tumor supernatant was briefly treated with the drug *in vitro* (211).

Various studies have shown that natural products play an important role in HCC. Artemisinin and its derivative dihydroartemisinin (DHA) have been found to inhibit HCC (212). Artemisinin inhibits the growth, migration and invasion of HCC by targeting cell bioenergetics and the Hippo/YAP1 signaling pathway (213). Our research group has been studying the anti-HCC mechanism of DHA and found that DHA reduced lipid droplet deposition by YAP1, thereby enhancing the anti-PD-1 effect (214). In addition, DHA inhibited the Warburg effect in HCC via the YAP1/solute carrier family 2 member 1 pathway (215). The present study also showed that DHA increased FXR expression decreased YAP1, and inhibited BA metabolism (216). A previous study by our group found that YAP1 was positively correlated with IL-18, and DHA was effective against HCC by inhibiting both YAP1 and IL-18 (217). Furthermore, DHA disrupted the tumor immunosuppressive microenvironment by inhibiting YAP1 expression, enhancing the efficacy of anti-PD-1 (218). Another study by our group found that DHA increased the abundance of *Akkermansia muciniphila* by downregulating YAP1, which increased the efficacy of anti-PD-1 (219). These studies confirmed that DHA inhibited HCC progression by inhibiting YAP1. Decursin, a component of Korean Dang-gui (*Angelica gigas* Nakai) root, significantly inhibited HCC-cell proliferation by upregulating the phosphorylation of LATS1 and β-TrCP and promoting the degradation of YAP1 (220). Myricetin activated LATS1/2 kinase, which directly phosphorylates YAP1 on serine residues, thereby inhibiting HCC cell proliferation (221). Evodiamine significantly inhibited YAP1 expression by upregulating LATS1 phosphorylation, leading to inhibited proliferation and induced apoptosis of HCC cells (222). Wogonin, an ingredient extracted from the *Scutellaria baicalensis Georgi* root, effectively induced cell cycle arrest and promoted apoptosis in HCC cells by activating MOB1-LATS1 and inhibiting YAP1 and TAZ (223). A study reported that WZ35, a derivative of curcumin, significantly inhibits HCC cell growth by downregulating YAP1-controlled autophagy (92). Ginsenoside CK, an intestinal microbial metabolite of panaxadiol saponins, inhibited HCC proliferation and growth by blocking YAP1/TEAD2 interaction (224). Apigenin decreased YAP1expression by regulating autophagy-related genes, reducing HCC cell migration and invasion (225). Evodiamine, isolated from the *Evodia rutaecarpa* fruit, is an effective anti-cancer agent that reduces YAP1 levels (226). 4-acetylantrocamol LT3, a new ubiquinone from the mycelium of *Antrodia cinnamomea* (Polyporaceae), inhibited HepG2 cell growth by targeting the YAP1/TAZ, mTOR and Wnt/β-catenin signaling pathways (227). Tanshinone IIA, an ingredient

of *Salvia miltiorrhiza*, inhibited HCC proliferation by downregulating YAP1 expression in a TGF-β signaling pathway-dependent manner (228). Chinese propolis, a resin-like substance collected by *Apis mellifera* from various tree buds, inhibited HepG2 cell proliferation and promoted apoptosis by inactivating the Hippo/YAP1 and PI3K/AKT pathways (229). Salvianolic acid B, an active ingredient of *Salvia miltiorrhiza*, inhibited HCC by upregulating MST1 protein expression, degrading YAP1 in the cytoplasm and inhibiting the expression of downstream genes in the Hippo pathway (230). Ovatodiolide, an active ingredient of *Anisomeles indica (L.) Kuntze (Labiatae)*, significantly reduced YAP1 expression and inhibited the CSC phenotype and associated disease progression (231). Corosolic acid, an extract of *Actinidia chinensi*, inhibited tumor progression by relocating YAP1 from the nucleus (232). Inhibition of YAP1 by actinomycin D enhanced the efficacy of corosolic acid in HCC treatment (233). Ligustilide, the main ingredient of *Angelica sinensis* and *Ligusticum chuanxiongs* (234), antagonized macrophage recruitment and M2 polarization induced by HCC cells by inhibiting YAP1/IL-6-induced IL-6R/STAT3 signaling activation (235). Myricetin, a flavonoid compound found in a wide variety of natural plants (236) and Luteolin, a flavonoid contained in a variety of fruits, vegetables and herbs (237), both showed potential in HCC treatment. Luteolin inhibited the biological effects of matrix stiffness induction and C-X-C motif chemokine receptor type 4-mediated YAP1 signaling pathway in HCC (238). Hydrogen sulfide-releasing oleanolic acid (HS-OA) decreased the expression of YAP1 and its downstream targets CTGF and CYR61, promoting cell apoptosis (239). Daphnane diterpenoids, specifically 12-O-debenzoyl-yuanhuacine, prepared from dried flower buds of the *Daphne genkwa* plant, effectively inhibited the binding of YAP1 and TEAD1 (240).

6. Conclusion and perspective

In recent years, our research group has conducted in-depth and comprehensive studies on the relationship between YAP1 and HCC. This included the role of YAP1 in lipid metabolism (214), glucose metabolism (215) and BA metabolism (216) of HCC, as well as its relationship with autophagy and immune cells, particularly T cells. Much of our research has focused on HCC cells. However, the occurrence of HCC is influenced not only by hepatocellular lesion but also by the entire HCC microenvironment. Therefore, we should broaden our focus on YAP1 to gain new insights. For instance, in 2019, a study published in Science reported that differences in YAP1/TAZ expression between HCC tissues and adjacent tissues could determine the prognosis of HCC (49). Therefore, it is important to consider the level of YAP1 expression in non-tumor cells within the HCC microenvironment. Drug development should not only focus on the effect of drugs on tumor cells but also consider their impact on non-tumor cells. Our subsequent study reflects this approach. When investigating the therapeutic effects of DHA on HCC in mice, DHA's effects on YAP1 were examined in both HCC cells and adjacent tissues (218). In the absence of YAP1 in hepatocytes and biliary epithelial cells, YAP1 is expressed in non-parenchymal cells (NPCs) in a cholestasis-independent manner. YAP1expression was detected in both Kupffer cells and endothelial cell subgroups. Serum secretion of pro-inflammatory chemokines and cytokines increased in YAP1KO animals, suggesting that YAP1 activation in NPCs may promote inflammation through TEAD-dependent transcriptional regulation of secretory factors (241).

In summary, the Hippo signaling pathway and its downstream effector YAP1 play crucial roles in the development and progression of HCC. While many regulatory mechanisms of YAP1 have been identified, interactions between YAP1and HCC have remained to be fully elucidated, necessitating further research. In addition, various factors, such as hepatitis B virus (242,243), hypoxia (244-246) and ECM, can influence YAP1 expression (247), mechanotransduction (248). The study of the Hippo-YAP1 signaling pathway in relation to HCC provides new strategies for understanding the pathogenesis, diagnosis and treatment of HCC. This research also provides new directions for the development of YAP1-related drugs, highlighting both the challenges and opportunities in this area. Further clarification of the relationship between YAP1 and HCC is essential.

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Availability of data and materials

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Authors' contributions

XH and ED designed the study; SL, LH, NL, and XS performed the literature search; SL, LH, NL and XS wrote the manuscript with contributions from all authors. XH, HY and ED revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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