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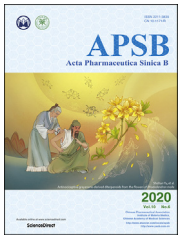

REVIEW

Yes-associated protein (YAP) and transcriptional coactivator with a PDZ-binding motif (TAZ): a nexus between hypoxia and cancer

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Abstract Hypoxia is a common feature of solid tumors. As transcription factors, hypoxia-inducible factors (HIFs) are the master regulators of the hypoxic microenvironment; their target genes function in tumorigenesis and tumor development. Intriguingly, both yes-associated protein (YAP) and its paralog transcriptional coactivator with a PDZ-binding motif (TAZ) play fundamental roles in the malignant progression of hypoxic tumors. As downstream effectors of the mammalian Hippo pathway, YAP and/or TAZ (YAP/TAZ) are phosphorylated and sequestered in the cytoplasm by the large tumor suppressor kinase 1/2 (LATS1/2)-MOB kinase activator 1 (MOB1) complex, which restricts the transcriptional activity of YAP/TAZ. However, dephosphorylated YAP/TAZ have the ability to translocate to the nucleus where they induce transcription of target genes, most of which are closely related to cancer. Herein we review the tumor-related signaling crosstalk between YAP/TAZ and hypoxia, describe current agents and therapeutic strategies targeting the hypoxia–YAP/TAZ axis, and highlight questions that might have a potential impact in the future.

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1. Introduction

A hypoxic microenvironment is a common feature of most solid tumors. In response to oxygen deprivation, tumors activate genes involved in processes such as angiogenesis, cell survival, cell proliferation, and glucose metabolism[1]. This hypoxia phenomenon indicates that hypoxia-targeting strategies are attractive for cancer therapy. In the past few years, studies on signaling in response to hypoxia have been centered on hypoxia-inducible factors (HIFs)[2–4], the unfolded protein response (UPR)[5], and the mTOR pathway[6–9]. Among them, HIFs are critical hallmarks of hypoxia. Under normoxia, HIF1A and HIF2A (HIF1A/HIF2A) are hydroxylated by prolyl hydroxylase domain-containing proteins (PHDs) at two different prolines (P402 and P564 of HIF1A; P405 and P531 of HIF2A). The hydroxylation of prolines recruits the von Hippel-Lindau tumor suppressor (VHL, an ubiquitin E3 ligase) and marks HIF1A/HIF2A to degradation *via* the ubiquitin−proteasome pathway. Meanwhile, the hydroxylation of the asparagines (N803 of HIF1A; N847 of HIF2A) by the factor inhibiting HIF1 (FIH1) suppresses transcriptional activation of HIFs by blocking the interaction between HIF1A/HIF2A and coactivators, such as P300 and the CREB binding protein (CBP). However, the hydroxylation of HIF1A/HIF2A is attenuated under hypoxia, which confers HIF1A/HIF2A stability. Subsequently, HIF1A/HIF2A translocates to the nucleus and dimerize with HIF1B to form functional complexes. The complexes can bind to the hypoxia response elements (HRE) of target genes (vascular endothelial growth factor A, *VEGFA*; insulin like growth factor 1, *IGF1*; lysyl oxidase, *LOX*), which results in angiogenesis, cell survival, and metastasis (Fig. 1A)[3,10–12]. These results indicate that the HIFs play a key role in a variety of tumor phenotypes. However, by far, HIFs-targeting intervention strategies have been challenged by the lack of effective drug candidates and insufficient *in vivo* cancer-killing abilities. Furthermore, some research has shown that inhibition of HIFs could not abrogate malignant phenotypes related to hypoxia[13–16]. Therefore, other therapeutic targets in the HIFs-dependent signaling pathways and novel targets in the HIFs-independent hypoxia-related axis should be investigated.

Notably, some recent studies have revealed that yes-associated protein (YAP) and transcriptional coactivator with a PDZ-binding motif (TAZ) play pivotal roles in hypoxia-induced tumorigenesis and tumor development[17,18], and might be potential therapeutic targets against cancer. In mammalian cells yes-associated protein 1 (*YAP1*) and WW domain containing transcription regulator 1 (*WWTR1*) encode oncoprotein YAP and TAZ respectively. As a transcriptional coactivator, dephosphorylated YAP escapes proteasomal degradation and translocates into the nucleus where it interacts with transcription factors (TFs) from transcriptional enhancer factor-1 and abaA (TEA) domain family members (TEADs)[19] or TFs possessing a PPXY (where P is proline, X is any amino acid, and Y is tyrosine) motif (runt-related transcription factor, RUNX[20]; P73[21] and ERB-B2 receptor tyrosine kinase 4, ERBB4[22]). Subsequently, YAP induces transcription of target genes such as connective tissue growth factor (*CTGF*), amphiregulin (*AREG*) and cysteine-rich angiogenic inducer 61 (*CYR61*). Similarly, TAZ also has the ability to activate some TFs, including TEADs and RUNX2 (Fig. 1B)[23,24].

Given the oncogenic abilities of activated YAP and/or TAZ (YAP/TAZ), exploring the regulatory mechanisms of YAP/TAZ holds promising expectation. The Hippo pathway has been fully explored in its regulation of YAP/TAZ. In 1995, researchers uncovered the Hippo pathway, which was shown to be pivotal in the control of organ size and tissue growth[25,26]. In mammals the highly conserved Hippo pathway consists of three interlinked parts, including upstream regulatory components, the Hippo core kinase components and the downstream transcriptional machinery. The mammalian STE20-like protein kinase 1/2 (MST1/2) and the salvador family WW domain containing protein 1 (SAV1), two key Hippo core kinases, interact with each other and phosphorylate the large tumor suppressor kinase 1/2 (LATS1/2)-MOB kinase activator 1 (MOB1) complex. The LATS1/2-MOB1 complex subsequently phosphorylates downstream effectors YAP (S127) and/or TAZ (S89), which sequesters YAP/TAZ in the cytoplasm. Phosphorylated YAP/TAZ interacts with the 14-3-3 proteins and are subject to degradation *via* the ubiquitin-proteasome pathway (Fig. 1B)[27].

In brief, hypoxia plays a key role in tumorigenesis and tumor development, and YAP and TAZ are potential therapeutic targets in cancer therapy. Unfortunately, studies on the interconnections between hypoxia and YAP/TAZ are limited. In this review we summarize the tumor-related crosstalk between hypoxia and YAP/TAZ as well as hypoxia-targeting therapeutic strategies based on YAP/TAZ.

2. The crosstalk between hypoxia and YAP/TAZ

We summarize three aspects of the tumor-related crosstalk between hypoxia and YAP/TAZ: the hypoxia-induced dephosphorylation and activation of YAP/TAZ, the formation of HIF1-YAP/TAZ complexes, and other crosstalk with undefined mechanisms.

2.1. *Hypoxia-induced dephosphorylation and activation of YAP/TAZ*

Current studies have shown that YAP/TAZ could be phosphorylated, ubiquitinated, sumoylated, acetylated, and even methylated[28]. Compared to other posttranslational modifications, dephosphorylation-mediated nuclear translocation plays a more pivotal role in the stability and transcriptional activity of YAP/TAZ. However, the relationship between hypoxia and the dephosphorylation of YAP/TAZ has not been fully elucidated. Herein we summarize current mechanisms mediating the hypoxia-induced dephosphorylation and nuclear translocation of YAP/TAZ.

2.1.1. *Seven in absentia homolog (SIAH) regulates YAP/TAZ under hypoxia*

The SIAH family was first discovered in *Drosophila* and plays a key role in eye development[29,30]. The SIAH family consists of two isoforms, including SIAH1 and SIAH2, both of which are E3 ligases controlling the ubiquitination and degradation of substrates, such as homeodomain-interacting protein kinase 2 (HIPK2) which related to the DNA damage response[31], TNF receptor-associated factor 2 (TRAF2) in apoptosis signaling[32], and Sprouty2, the

regulator of phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2)[33]. Mounting evidence shows that SIAH1 and SIAH2 are extensively involved in cell migration, proliferation, and metastasis[34,35]. Particularly, recent studies have shown that these two factors also participate in hypoxia responses[36,37].

Under hypoxia, HIF1 directly binds to the HRE of *WWTR1* and *SIAH1* and induces the transactivation of the latter two. SIAH1, as an ubiquitin E3 ligase, directs LATS2 to degradation *via* the ubiquitin-proteasome pathway. Thus, LATS2 fails to phosphorylate TAZ resulting in the nuclear translocation of TAZ and the expression of target genes (*CTGF*; plasminogen activator inhibitor 1, *PA11*, and baculoviral IAP repeat containing 5, *BIRC5*), which induces the breast cancer stem cell phenotypes[38]. Notably, the interaction of SIAH1−LATS2 needs further confirmation, because another study conducted by Ma et al.[39] found that SIAH1 fails to interact with LATS2. These seemingly contradictory observations may arise from the different cellular context of the two types of cell models (HEK293T and MDA-MB-231), as well as the varied experimental conditions.

SIAH2, the homolog of SIAH1, encompasses two zinc finger domains and a really interesting gene domain (RING) in the N-terminal region, and a substrate-binding domain (SBD) in the C-terminal region[40]. Results have shown that the C-terminal and the N-terminal of SIAH2 could both bind to LATS2 at residues 667−720 of LATS2, and residues 403−480 of LATS2 possess abilities to strengthen this interaction, which is more significant under hypoxia. Then SIAH2 promotes the ubiquitination of LATS2 (K670 and K672) and subsequently decreases the protein level of LATS2 *via* the ubiquitin−proteasome pathway, which inhibits the phosphorylation of YAP (S127) under hypoxia (Fig. 2A). Serving as a transcription coactivator, dephosphorylated YAP translocates into the nucleus and induces transcription of downstream genes such as *CYR61* and *CTGF*, which consequently accelerates cell proliferation[39]. Further studies have revealed that the protein level of SIAH2 in tumor tissues is upregulated while LATS is downregulated[39], which indicates the close negative correlation between SIAH2 and LATS in breast cancer patients. Furthermore, the secretion of transforming growth factor beta (TGFB) increases under hypoxia while zyxin (a LIM domain protein), SIAH2 and LATS2 form ternary complexes in response to hypoxia and the stimulation of TGFB. Further studies have shown that zyxin, as a scaffold protein, is capable of strengthening the interaction between SIAH2 and LATS2 (Fig. 2A), which promotes the dephosphorylation of YAP and then induces an epithelial−mesenchymal transition (EMT) and migration of MDA-MB-231 breast cancer cells[41].

The studies mentioned above indicate that both SIAH1 and SIAH2 could be regarded as potential therapeutic targets, as they play essential roles in the hypoxia−YAP/TAZ axis and E3 ligases are feasible intervention targets for small molecule compounds.

2.1.2. G protein-coupled receptor class C group 5 member A (GPRC5A) decreases the inhibitory phosphorylation of YAP under hypoxia

G protein-coupled receptors (GPCRs), the largest family of cell-surface receptors and well-validated drug targets, regulate

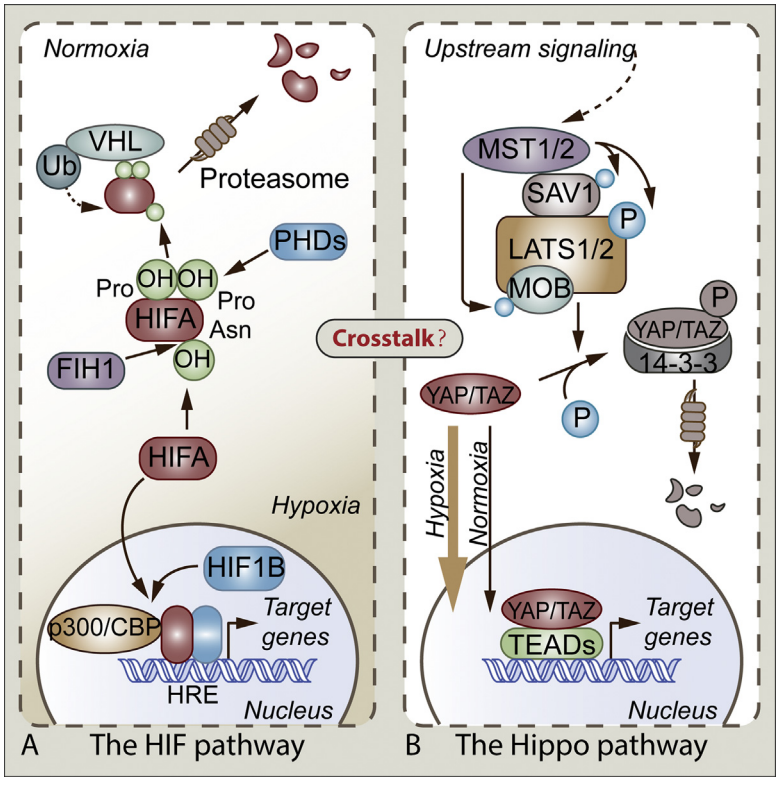


Figure 1 The cores of the HIF pathway and the Hippo pathway. (A) The oxidation states regulate the hydroxylation rate of HIFA, which dictates the fate of HIFA: degradation or transcriptional activation. The HIFA indicates HIF1A and/or HIF2A. (B) Hypoxia counteracts the inhibitory effects of Hippo core kinases on YAP/TAZ, which accelerates nuclear translocation and promotes the transcriptional activation of YAP/TAZ. YAP/TAZ indicates YAP and/or TAZ.

numerous physiological functions, including hepatic lipid metabolism[42], nervous system development[43], and the inflammatory response[44]. Recently, a growing number of studies have been directed at the relationship between tumors and GPCRs[45,46].

Several canonical tumor-related pathways, including the Ras−ERK pathway[47], the phosphoinositide 3-kinase (PI3K)−serine/threonine kinase (AKT) pathway[48] and the Rho-dependent pathway[49] have been found to contribute to GPCR-mediated tumorigenesis and tumor development. Interestingly, the Hippo pathway also plays critical roles in GPCR-mediated malignancy[50]. Mechanically, upon ligand-binding, G12/13-, Gq/11-, and Gi/o-coupled receptors trigger the remodeling of the actin cytoskeleton through the activation of Rho guanosine triphosphatases (Rho GTPases) and then suppress the MST1/2−LATS1/2 kinase cascade, which promotes the nuclear translocation and transcriptional activity of YAP/TAZ[50]. Recent evidence has shown that several GPCRs, including the β-adrenergic receptor[51], lysophosphatidic acid (LPA) receptor[52], chemokine receptor US28[53], and C−X−C chemokine receptor type 4 (CXCR4)[54] interact with HIF1A in the hypoxic microenvironment so as to promote tumor metabolic reprogramming, cell motility, and cell proliferation. Given the above-mentioned effects, it's possible that GPCR signaling aids in bridging the gap between HIFs and YAP/TAZ.

Particularly, GPRC5A, an orphan GPCR, is reported to be a direct transcriptional target of HIFs[55] and would be upregulated under hypoxia. The overexpression of GPRC5A inhibits both the phosphorylated and the total protein levels of LATS, which is mediated by the small GTPase RhoA, a positive upstream regulator of YAP activity (Fig. 2B)[56]. Consequently, the phosphorylation (S397) of YAP decreases while nuclear YAP is enhanced, accompanied by the transactivation of YAP target genes such as *AREG*, *CYR61*, *CTGF*, and BCL2 like 1 (*BCL2L1*). Notably, the observation that RhoA promotes the overexpression of GPRC5A indicates that activated YAP might regulate the expression of GPRC5A *via* a positive feedback loop (Fig. 2B). Therefore, the activation of the HIFs−GPRC5A−YAP axis significantly promotes hypoxic cell growth and survival in colorectal cancer, and the higher mRNA levels of *GPRC5A* reduce the event-free survival period of patients with tumors[55]. However, the association between TAZ and the HIFs−GPCRs axis has not been revealed fully.

2.1.3. *The mevalonate (MVA) pathway regulates phosphorylation of YAP under hypoxia*

The MVA pathway is a complex biochemical pathway which uses acetyl-CoA, adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide phosphate (NADPH) to produce isoprenoids and sterols[57]. The close crosstalk between the MVA pathway and other tumor-promoting signaling such as YAP/TAZ signaling, the Hedgehog pathway and steroid hormone signaling highlights the importance of the MVA pathway in cancer[57,58].

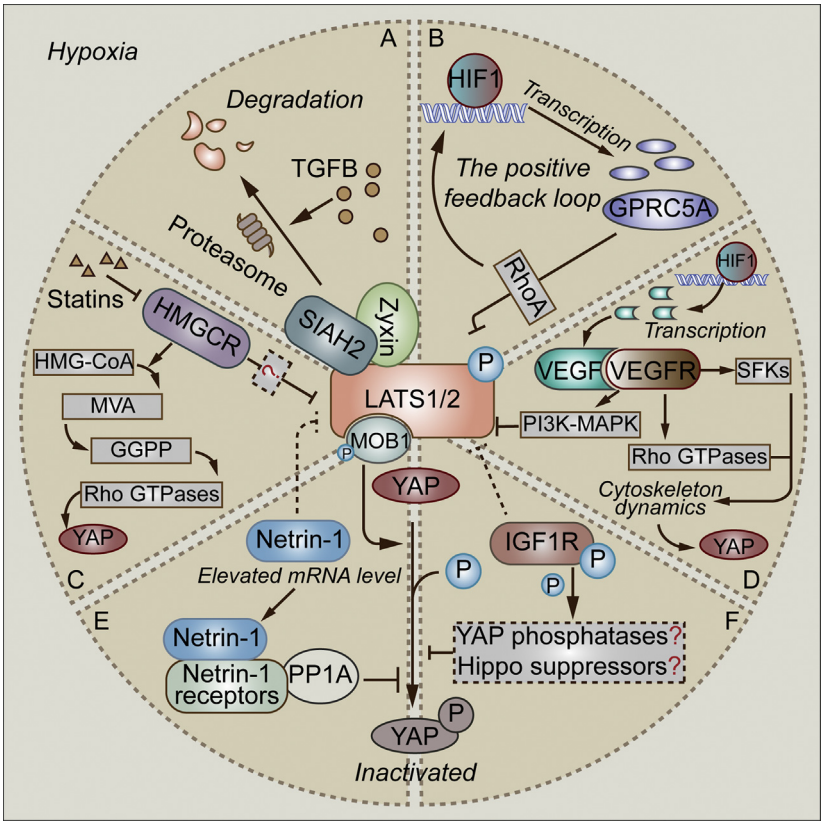


Figure 2 LATS-mediated signaling crosstalk between hypoxia and YAP. (A) The E3 ubiquitin ligase SIAH2 and the scaffold protein zyxin direct LATS to be degraded *via* the ubiquitin−proteasome system, while TGFB strengthens this process. (B) Hypoxia-induced HIF1 transactivates *GPRC5A*, which inhibits the phosphorylation of LATS by activating RhoA. (C) Hypoxia-activated HMGCR inhibits LATS and activates YAP, and this effect can be reversed by statins. (D) Hypoxia-induced overexpression of VEGFs triggers its receptors and activates YAP by SFKs, Rho GTPases, and PI3K−MAPK axis. (E) and (F) Hypoxia elevates the mRNA level of netrin-1 (E) or activates IGF1R (F), then induces dephosphorylation and activation of YAP. Dashed lines and dashed arrows indicate unknown molecular mechanisms and question marks denote unknown components.

In the MVA pathway 3-hydroxymethylglutaryl-CoA reductase (HMGCR) is the rate-limiting enzyme, which catalyzes 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) conversion to MVA. The MVA serves as a precursor of geranylgeranyl pyrophosphate (GGPP). GGPP directs Rho GTPases to the membrane so that the Rho GTPases are activated, which inhibits the phosphorylation of YAP/TAZ and promotes the nuclear translocation and activation of YAP/TAZ[58]. Sorrentino et al.[58] have shown that statins, as inhibitors of HMGCR, could potently hinder nuclear translocation of YAP/TAZ under normoxia. Notably, compared to normoxia, both mRNA and protein levels of HMGCR are upregulated under hypoxia while the protein level of phosphorylated LATS is downregulated[59], which indicates that hypoxia-induced overexpression of HMGCR might inhibit phosphorylation of LATS (Fig. 2C). However, the mechanisms of the HMGCR−LATS axis are unclear under hypoxia. Further studies have shown that HMGCR mediates the nuclear translocation of dephosphorylated YAP and subsequently induces the transcription of target genes (*BCL2L1*, *CTGF*, and *CYR61*). This series of events consequently leads to chemotherapy resistance to SN38 and sorafenib in hepatocellular carcinoma (HCC) cells[59,60]. Fortunately, statins ameliorate hypoxia-induced chemotherapy resistance by blocking the MVA pathway (Fig. 2C)[61]. Based on this mechanism, statins could ameliorate the hypoxia-induced resistance towards sorafenib, the first clinical drug for HCC treatment[60]. Although no evidence has revealed the relationship between the MVA pathway and TAZ under hypoxia so far, the studies mentioned above have established the link between the hypoxia−HMGCR−YAP axis and HCC malignancy.

2.1.4. *Vascular endothelial growth factor (VEGF)-mediated changes in phosphorylation of YAP/TAZ*

VEGFs and their receptors (VEGFRs) are critical drivers of angiogenesis in tumors[62−65]. Numerous studies have revealed that *VEGF* is a canonical target gene of HIFs[66−69] and is closely related to hypoxia-induced tumorigenesis and tumor development[70−72]; thus blockade of this signaling has been developed as an anti-cancer strategy and has been successfully applied in clinical treatment[73−76].

Notably, the causal link between VEGFs/VEGFRs and aberrant activation of YAP/TAZ has been validated by two independent studies[77,78]. The mechanisms of VEGFs-mediated activation of YAP/TAZ are two-fold: LATS-dependent pathways and actin cytoskeleton-mediated signaling[77,78]. Some studies have suggested that VEGFRs activation primed by VEGFs triggers PI3K-mitogen-activated protein kinase (MAPK) signaling to inhibit the phosphorylation of MST1/2 and subsequent LATS1/2, which induces the nuclear translocation of YAP/TAZ and ultimately transactivates target genes regulating blood vessel formation (Fig. 2D)[78]. In addition, activated VEGFR2 could also modulate the actin cytoskeleton through the activation of SRC family kinases (SFKs) and Rho GTPases, which promotes YAP-dependent transcription of target genes contributing to the migration and angiogenesis of endothelial cells (Fig. 2D)[77]. Although VEGFR2 is considered a positive regulator of YAP/TAZ, another study has shown that the activation of VEGFR2 inhibits YAP-mediated EMT in retinal pigment epithelial cells[79]. Further mechanisms have shown that the novel ligand VEGFC rather than the primary ligand VEGFA induces the activation of VEGFR2. Therefore, the biological functions of VEGR2 might be distinct when bound by different ligands.

Based on the findings on HIFs−VEGFs signaling and the VEGFs−YAP/TAZ axis mentioned above, it is plausible that VEGFs are critical for the interplay between HIFs and YAP/TAZ. Interestingly, studies have shown that TEADs interact with transcription coactivator vestigial-like family member (VGLL) and promote the transcription of *VEGF*[80]. Furthermore, hypoxia-induced nuclear translocation of YAP promotes the accumulation of HIF1A and subsequently increases the transcription of *VEGFA*[81]. These lines of evidence suggest the possibility of a positive feedback loop where hypoxia-induced overexpression of VEGFs activates YAP/TAZ, which in turn elevates the stability of HIFs and promotes transcription of *VEGF*.

2.1.5. *Other hypoxia-related factors/pathways controlling the dephosphorylation and activation of YAP*

In addition to those mentioned above, some other signal transduction pathways, particularly those primed by cell surface receptors are also involved in hypoxia-regulated YAP/TAZ signaling.

Laminin-related secreted protein netrin-1, an important member of the netrin family, promotes cell proliferation, invasion, and cell morphogenesis[82−84] through its interaction with cell surface netrin-1 receptors, including deleted in colorectal cancer netrin 1 receptor (DCC), UNC-5 netrin receptor B (UNC5B), neogenin, and down syndrome cell adhesion molecule (DSCAM)[85−87]. Recent studies identified YAP as a potential mediator of netrin-1-mediated tumorigenesis and tumor development[85,88,89], while the interaction between netrin-1 and TAZ is unclear. Qi et al.[88] revealed that netrin-1 enhances the binding of protein phosphatase 1A (PP1A) to UNC5B/DCC receptors. Activated PP1A then binds to YAP and stabilizes YAP by dephosphorylating YAP (S127 and S397), which induces the nuclear translocation of YAP and promotes the transcription of *CTGF* to accelerate cell proliferation and migration[88]. Another study has shown that netrin-1 activates the canonical receptor neogenin and contributes to the metastasis of gastric cancer in a YAP-dependent manner[85]. Notably, the association between YAP and netrin-1 is further strengthened under hypoxia as a recent study has shown that hypoxia elevates the mRNA level of netrin-1, which induces the dephosphorylation and activation of YAP, and then accelerates EMT and cell migration of PC3 and DU145 cells (Fig. 2E)[90].

Another cell surface receptor insulin-like growth factor 1 receptor (IGF1R), a member of the tyrosine kinase growth factor receptor family, is also engaged in YAP signaling under hypoxia[18]. A large amount of evidence shows that IGF1R plays a key role in cancer cell proliferation and tumor growth by interacting with IGF1[91−93]. These tumor-promoting roles of IGF1R are mediated by the Ras−MAPK pathway, which results in E2F transcription factor-dependent gene transcription and cell proliferation[94−96], and PI3K−AKT signaling, which prevents cells from undergoing apoptosis[97] and promotes the EMT[98]. The connection between IGF/IGF1R and the Hippo pathway is indicated by several recent studies. In *Drosophila*, insulin/IGF signaling activates AKT as well as downstream pyruvate dehydrogenase kinase 1 (PDK1), which inhibits Warts (Wts)-Mob as tumor suppressor (Mats). Subsequently, yorkie (the homologues of YAP) translocates into the nucleus and transactivates target genes to promote cell proliferation[99]. In mammals, IGF1 or insulin is used to mimic intracellular upregulation of phosphorylation in order to phosphorylate and activate IGF1R, which significantly inhibits phosphorylation of

YAP (S127; Fig. 2F). Subsequently, dephosphorylated YAP translocates into the nucleus and induces transcription of downstream genes related to carcinogenesis, such as *CTGF*, *CYR61*, and *AREG* in HCC. Further studies have found that hypoxia induces the activation of IGF1R in this HCC model, which contributes to the elevated transcriptional activity of YAP[18]. However, there is no evidence to show a direct interaction between YAP/TAZ and IGF1R. It is possible that phosphorylated IGF1R activates phosphatases of YAP (such as PP1A) or activates upstream suppressors of MST1/2 or LATS1/2 in the Hippo pathway, which promotes the nuclear translocation and activation of YAP.

2.2. *The formation of HIF1-YAP/TAZ complexes*

Compared with hypoxia-induced dephosphorylation and nuclear translocation of YAP mentioned above, direct protein−protein binding is a more straightforward means to demonstrate interactive signaling transduction.

2.2.1. *YAP/TAZ function as transcriptional activators of HIF1*

HIF1 is well known as a transcription factor. HIF1A, rather than HIF1B, plays a key role in the formation of HIF1−YAP/TAZ complexes[17]. Therefore, the established structure of HIF1A contributes to understanding the interaction between HIF1 and YAP/TAZ. HIF1A consists of two regions, including a DNA binding/dimerization region and a regulatory region. The N-terminal includes a basic helix−loop−helix (bHLH) motif and PERARNT-SIM (PAS) domain, which contribute to dimerization and interaction between HIF1 and DNA. Following PAS, there is an oxygen-dependent degradation domain (ODDD), which is hydroxylated by PHDs and dictates HIF1A to degradation. The regulatory region contains two transactivation domains (TAD), including N-TAD and C-TAD, which are separated by inhibitory domain (ID) (Fig. 3)[100,101]. As is well known, both P300 and CBP, two canonical coactivators of HIF1, interact with HIF1A by binding to the C-TAD[100]. What is the binding site between HIF1 and YAP/TAZ?

A study has shown that TAZ, as a coactivator of HIF1, could be pulled down by GST-HIF1A (531−826) (Fig. 3), which indicates that TAZ directly interacts with the TAD of HIF1A. In the complex, TAZ directs HIF1 to the HRE, which contributes to the transcription of downstream genes (*PDK1*; lactate dehydrogenase A, *LDHA*; BCL2 interacting protein 3, *BNIP3*, and prolyl 4-hydroxylase subunit alpha 2, *P4HA2*) (Fig. 4A). Consequently, the TAZ−HIF1 complex accelerates the migration of breast cancer cells to the lungs and the lymph nodes[17]. Further studies have revealed that WW domain-containing oxidoreductase (WWOX) directs HIF1A to translocate into the nucleus and conjugate with TAZ[102]. Therefore, WWOX plays a key role in the regulation of the TAZ-HIF1 complex and is a potential therapeutic target. In addition, the TAZ-HIF1 complex contributes to the transcription of *SIAH1*[17] and SIAH1 induces TAZ nuclear localization by mediating the degradation of LATS2 (Fig. 4A)[38].

YAP, as a paralog of TAZ, also serves as a transcription coactivator of HIF1. On one hand, the YAP−HIF1 complex binds together with HRE to induce transcription of *VEGF* and consequently accelerates cell growth and promotes angiogenesis. However, no study has uncovered the binding sites on HIF1. On the other hand, YAP has the ability to inhibit VHL-dependent degradation of hydroxylated HIF1A (Fig. 4B). These two aspects indicate that the LATS−YAP pathway could regulate the VHL−HIF1A axis, which is a strategy to interfere the stability of HIF1A[39].

2.2.2. *HIF1 induces transcription activation of YAP/TAZ*

Recent evidence has revealed that HIF1 is not only a transcription activator but also an important transcription coactivator[17]. Lots of genes have been proven to be regulated by the HIF1−TAZ complex, including *CTGF*, *PAI1*, and *BIRC5* (Fig. 4C)[17,38], which play key roles in tumorigenesis and tumor development. Similarly, Ma et al.[39] have revealed that the HIF1−YAP complex promotes the transcription of target genes of TEADs (Fig. 4D).

YAP consists of several motifs and domains. The N-terminal includes a proline-rich region (P-rich) followed by TEAD binding region. In the middle there are two tandem WW domains that bind to PPXY-motif-containing transcription factors, a Src homology domain 3 binding motif (SH3 BM), and a coiled-coil domain (CC). The C-terminal is made up of the activation region and a PDZ domain ligand called the TWL sequence (Fig. 3)[27]. The structure of TAZ is similar to that of YAP (Fig. 3). Although the protein structures of YAP and TAZ are clear, no direct evidence has shown that the activation regions of YAP/TAZ interact with HIF1. Notably, The PDZ domain ligand, which has the ability to bind to PDZ domain-containing proteins, is highly conserved in C-terminal of YAP/TAZ[103]. Furthermore, the PDZ domain ligand in TAZ has

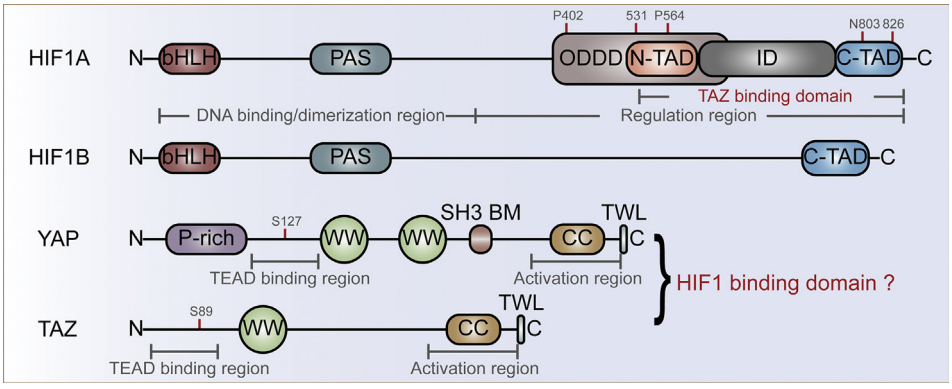


Figure 3 A schematic drawing of HIF1A, HIF1B, YAP, and TAZ.

the ability to localize TAZ into discrete nuclear foci and is essential for transcriptional activation of TAZ[104]. Whether the PDZ domain ligand plays a role in the formation of HIF1-YAP/TAZ complex needs to be elucidated.

2.3. *Other crosstalk between hypoxia and YAP/TAZ*

In addition to the regulatory mechanisms that promote the nuclear translocation of YAP/TAZ and the formation of HIF1−YAP/TAZ complexes mentioned above, other signaling pathways are also implicated in the crosstalk between hypoxia and YAP/TAZ. However, although the malignant phenotypes related to a variety of crosstalk pathways are clear, the detailed mechanisms are yet to be elucidated.

The correlation between HIF1A and YAP has been demonstrated in several independent studies[105–107]. As the paralogue for YAP, TAZ is also implicated in hypoxia. Interestingly, Yan et al.[108] have shown that HIF1A elevates the level of total TAZ and phosphorylated TAZ (S69) in a time-dependent manner in ovarian cancer. However, detailed mechanisms should be explored, because according to this study, neither LATS nor AKT mediates this regulation.

In addition to HIF1A, HIF2A, another member of HIFs family, could also form the heterodimeric complexes with HIF1B and induce the transcription of target genes related to anaerobic metabolism and angiogenesis[109,110]. A recent study has revealed that HIF2A is also responsible for the hypoxia-induced elevation of YAP protein level, which subsequently leads to the transcription of YAP target genes (*CYR61*, *CTGF*, and transforming growth factor beta receptor 2, *TGFBR2*) related to the abnormal growth of colorectal tumors. However, this study has shown that neither the protein−protein interaction nor canonical kinase signaling contributes to the overexpression of YAP[111]. Moreover, it remains unknown whether HIF2A can regulate TAZ and *vice versa*. Therefore, the regulatory mechanisms of the HIF2A−YAP axis and the relationship between HIF2A and TAZ need to be further explored.

LPA, an extracellular phospholipid ligand of GPCRs, plays a key role in numerous biological processes by activating GPCRs and initiating downstream pathways[112]. Notably, the Hippo pathway is an important downstream signaling target of LPA. Studies have shown that LPA activates the G protein (G12/13) followed by Rho GTPase-mediated regulation of actin cytoskeleton dynamics, which inhibits phosphorylation of LATS at the activation loop (S909) and the hydrophobic motif (T1079). Consequently, the dephosphorylated LATS fails to phosphorylate YAP/TAZ, thus resulting in the activation of YAP/TAZ and the transactivation of target genes, ultimately leading to increased cell migration and cell proliferation[50,113]. These clues indicate that LPA is closely related to the YAP/TAZ pathway, at least under normoxia. Notably, recent findings have also highlighted the important roles of LPA under hypoxia, as Kim and colleagues[114] have found that LPA stimulates cytosolic phospholipase A2 (PLA2) phosphorylation in a HIF1A-dependent manner under hypoxia, which is required in LPA-induced cell migration. Taken together, these observations raise the possibility that LPA also contributes to the hypoxia-YAP/TAZ crosstalk.

3. Hypoxia-targeting therapeutic strategies based on YAP/TAZ

In the past few years the main approach developed to treat the hypoxia-mediated malignancy is to design hypoxia-activated prodrugs which are activated by enzymatic reduction in hypoxic tissue, such as tirapazamine (TPZ)[115,116]. However, these bioreductive prodrugs have been limited by poor tissue penetration and high toxicity. Therefore, exploration of the agents targeting factors overactivated under hypoxia (for instance, YAP/TAZ) may provide an opportunity to improve treatment outcomes. Herein we introduce current compounds that target the hypoxia−YAP/TAZ axis in preclinical research and clinical trials (Table 1).

3.1. *Compounds targeting YAP/TAZ under preclinical research and clinical trials*

YAP and TAZ play key roles in the development of liver cancer[118,119], which is considered the third leading cause of cancer-related death worldwide[120]. Due to unique anatomical and functional roles, liver cancer often displays severe intratumoral

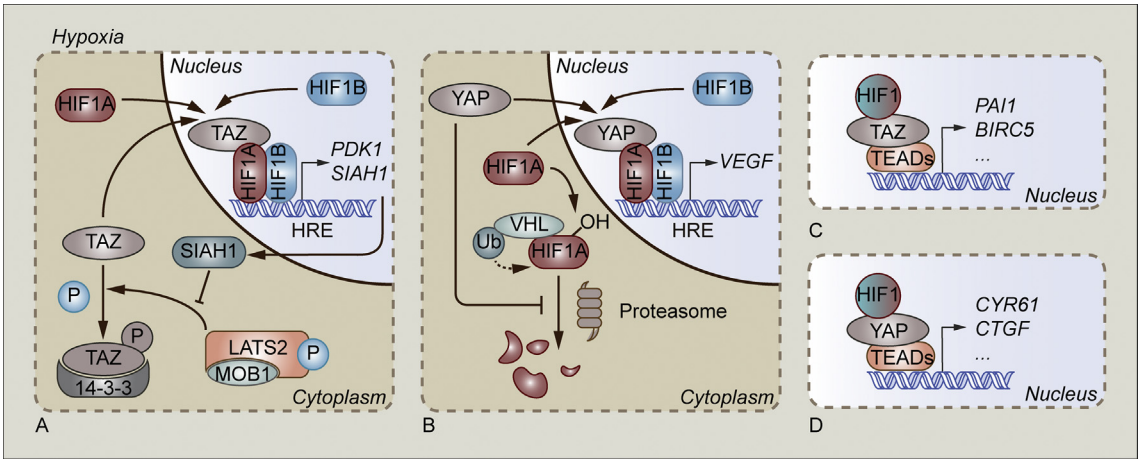


Figure 4 A schematic view of HIF1−YAP/TAZ complexes. (A) Hypoxia-induced nuclear translocation of TAZ promotes transcription of HIF1 target genes such as *PDK1* and *SIAH1*. SIAH1 inhibits phosphorylation of TAZ, which forms a positive feedback loop. (B) Hypoxia induces nuclear translocation of YAP and HIF1A, which enhances the transactivation of HIF1 target genes. (C) and (D) Serving as a coactivator, HIF1 binds to TAZ (C) and YAP (D) in the promoter region to induce target gene transcription.

hypoxia[121], which results in the poor therapeutic outcomes. Therefore, therapeutic strategies targeting hypoxic activation of YAP/TAZ in liver cancer have attracted great interest.

Verteporfin, an FDA-approved benzoporphyrin-like drug used as a photosensitizer for photodynamic therapy, has been suggested to inhibit YAP by targeting the interface between YAP and TEADs[122]. Interestingly, Chen et al.[117] have found that verteporfin also blocks the formation of the HIF1A-YAP complex induced by high mobility group box 1 (HMGB1), which reduces excessive glycolysis in HCC.

Utilizing a cell-based YAP-TEAD luciferase reporter assay and functional analyses, Zhu et al.[18] screened a new compound, named CT-707 [a NMPA (National Medical Products Admininstration) approved multi-kinase inhibitor under clinical trial, NCT02695550]. CT-707 is capable of inhibiting hypoxia-induced activation of IGF1R and subsequently restrains the nuclear translocation of YAP, and consequently suppresses the proliferation and survival of hypoxic HCC cells. Intriguingly, on one hand, the multi-kinase inhibitor CT-707 possesses the remarkable inhibitory ability of focal adhesion kinase (FAK). On the other hand, HIF1 is a well-recognized hallmark of hypoxia. However, neither FAK nor HIF1 is related to the hypoxic anti-tumor activity of CT-707.

Notably, HCC cells generally develop hypoxia-induced resistance to a variety of anti-cancer drugs, including sorafenib and SN38[59]. Zhou et al.[60] found that statins are able to elevate the anti-tumor effects of sorafenib by blocking the hypoxia-activated HMGCR-MVA pathway, thus significantly attenuating the hypoxic resistance to sorafenib.

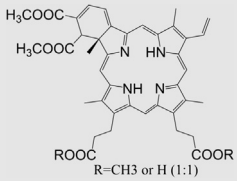
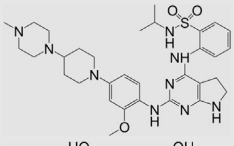
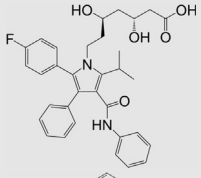
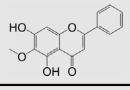
In addition to synthetic compounds, Zhang et al.[81] have shown that oroxylin A, a natural active component extracted from *Scutellariae radix*, inhibits hypoxia-induced angiogenesis during liver fibrosis. Notably, the detailed mechanism includes suppression of hypoxia-induced nuclear translocation and subsequent transcriptional activation of YAP, which restricts the accumulation of HIF1 and inhibits transcription of HIF1 downstream genes such as *VEGFA*, angiopoietin 2 (*ANGPT2*), and platelet and endothelial cell adhesion molecule 1 (*PECAM1*)[81]. Interestingly, VEGFA, a major inducer of angiogenesis, is secreted in response to hypoxia and elicits autocrine effects on tumor progression and metastasis[123]. Therefore, oroxylin A might exert anti-tumor effects through the YAP−HIFs axis while blocking the hypoxic autocrine effects of VEGFA.

No evidence has demonstrated that verteporfin, CT-707, statins, or oroxylin A exert hypoxia-targeting anti-tumor abilities in a TAZ-dependent manner. Notably, a study focused on HCC has revealed that the overexpression of YAP/TAZ is positively associated with HIF1A in tumor tissues and only simultaneous knockdown of YAP and TAZ increases the apoptosis of HCC cells[124]. Although the mechanisms remain unclear, these clues indicate that some compensatory mechanisms between YAP and TAZ might exist in HCC and highlight the importance of TAZ. Therefore, it is urgent to discover agents and strategies that target YAP and TAZ simultaneously in order to fight against HCC with synergistic effects.

Unfortunately, following the development of therapeutic strategies against liver cancer, few compounds targeting YAP/TAZ have been discovered for other types of cancer. Very limited evidence indicates that dimethyloxyallylglycine (DMOG), a PHD inhibitor, stabilizes HIFs and regulates the translocation of SMAD family member 2 (SMAD2), YAP, and TAZ in renal tubular cells[125]. In addition, verteporfin has also been found to increase hypoxic glioma cell death[126]. Although YAP is not involved in this process, the relationship between hypoxia and verteporfin will provide clues about hypoxia-targeting therapies based on YAP/TAZ.

The results mentioned above show that current compounds targeting YAP/TAZ mainly focus on liver cancer in a YAP-dependent manner. It is urgent to explore more potential inhibitors against both YAP and TAZ, and approaches toward other types of cancer should also be investigated.

Table 1 Agents targeting Hypoxia−YAP/TAZ axis.

Target	Drug	Structure	Major mechanism	Ref.
YAP	Verteporfin		Blocks the formation of HIF1α −YAP complex	117
IGF-1R	CT-707		Inhibits hypoxia-induced activation of IGF-1R and thus restrains the nuclear translocation of YAP	18
HMGCR	Statins (*e.g.*, atorvastatin)		Blocks the MVA pathway and activates LATS	60
Unclear	Oroxylin A		Suppresses nuclear translocation of YAP and inhibits transcription of HIF1	81

3.2. *HIF inhibitors that impede the YAP/TAZ pathway*

As mentioned above, IGF1R and HMGCR are crucial mediators of YAP/TAZ. Interestingly, a growing number of clinical and preclinical studies have focused on HIFs, which are canonical targets in hypoxia-targeting therapy[127−130]. Notably, the close interaction between HIFs and YAP/TAZ provides the possibility that HIFs might be another key regulators in hypoxia-targeting therapy based on YAP/TAZ. Notably, due to the rapid development of HIF inhibitors, it's valuable to explore the effects of HIF inhibitors against YAP/TAZ.

According to several clinical studies, the HIF inhibitor panzem inhibits protein synthesis and transcriptional activity of HIF1A[131] while 17-AAG and vorinostat promote the degradation of HIF1A[132,133]. PT2385 and PT2977 impede HIF2 dimerization and the DNA binding ability of HIFs[134,135], EZN-2208 decreases the mRNA level of HIF1[136], and CRLX101 inhibits the expression of HIF1A[137]. Among these compounds, 17-AAG might mediate the crosstalk between the inhibition of HIFs and interference of YAP due to its functions in YAP signaling. A study has revealed that 17-AAG elevates the total protein and the phosphorylated level of LATS1 in a dose-dependent manner, which promotes the phosphorylation of YAP and inhibits the transcription of *CTGF* in lung adenocarcinoma cells[138]. These results raise the possibility that 17-AAG has the ability to block both HIFs signaling and the YAP signaling.

In preclinical studies a number of agents can attenuate HIF expression (EZN-2968[139] and cetuximab[140]), impede its nuclear translocation (benzophenone-1B[141]), obstruct dimerization (acriflavine[142]) and promote its degradation (bisphenol A[143]). In addition to these compounds, topotecan, which suppresses the transactivation of HIF1A/HIF2A and then inhibits VEGF expression and angiogenic activity[144], might have a relationship with YAP/TAZ because a study has shown that small cell lung cancer cell lines with high YAP/TAZ level are more sensitive to topotecan[145]. Therefore, these results provide the possibility that topotecan inhibits HIFs and simultaneously targets YAP/TAZ in hypoxic tumor tissues, which might contribute to synergistic anti-tumor effects.

Although most of the HIF inhibitors mentioned above haven't been reported to have a direct interaction with YAP/TAZ, it's still worth exploring their functions in the HIFs−YAP/TAZ axis due to the rapid development of HIF inhibitors in clinical trials.

4. Conclusions

Therapeutic strategies targeting YAP/TAZ in hypoxia have a bright future. On one hand, not only direct inhibitors against YAP/TAZ but also compounds targeting upstream regulatory factors, such as SIAH2, IGF1R, and netrin-1 mentioned above, are expected to be further developed. On the other hand, current targets are indeed not enough for us to fully understand the hypoxia−YAP/TAZ axis. In addition to HIFs and its inhibitors, a growing number of targets and agents have been shown to have a close relationship with hypoxia and YAP/TAZ, such as the SWI/SNF complex[146−150] and the PI3K-mTOR pathway[109,151,152]. It's urgent to find novel targets and agents in order to develop a hypoxia-targeting therapy based on YAP/TAZ.

5. Discussion

TAZ shares approximately 50% sequence identity with YAP[27]. However, hypoxia-induced regulation of YAP is different from that of TAZ. As mentioned above, the total protein and phosphorylated protein (S69) level of TAZ is upregulated in epithelial ovarian cancer, which is dependent on HIF1A[108], while there is HIF2A-induced overexpression of YAP in colorectal cancer[111]. Therefore, we must determine the root cause of the regulatory diversity of YAP/TAZ, including possibilities such as differences in upstream pathways.

Although the hypoxia-induced regulation of YAP and TAZ is not identical, LATS, which is the core component of the Hippo pathway, plays a key role in both regulatory processes. As mentioned above, it is obvious that both SIAH-mediated and HMGCR-mediated signaling under hypoxia are integrated into the core component LATS[41,59], which suggests that LATS is a critical nexus in the crosstalk between hypoxia and YAP/TAZ. Indeed, dysfunction of LATS leads to tumorigenesis and tumor development in various types of cancer in spite of low mutation rates of LATS[153−155]. Therefore, it is urgent to develop direct agonists of LATS, which would have great prospects in the field of hypoxia-targeting therapy against cancer. In addition, whether LATS is also a precise nexus in IGF1R-mediated or netrin-1-mediated regulation of YAP under hypoxia remains unknown.

In the field of hypoxia−YAP/TAZ axis, the research imbalance is a critical problem. Firstly, hypoxia activates YAP mainly by dephosphorylation-mediated nuclear translocation. However, hypoxia mainly alters the abundance of TAZ or interacts with TAZ through HIFs-TAZ complexes. Secondly, HIFs[2,3], UPR[5], and the mTOR pathway[6−9] are three main signaling pathways that are key targets in hypoxia-targeting therapy. Unfortunately, the interaction between the three pathways and hypoxia has not been fully elucidated. Notably, eukaryotic translation initiation factor 2A (EIF2A) is phosphorylated by PKR-like endoplasmic reticulum kinase (PERK) and then increases the protein level of activating transcription factor 4 (ATF4) during endoplasmic reticulum stress-induced UPR, which triggers the transcription activation of YAP and protects cells from death. However, excessive UPR activates the Hippo pathway, subsequently inhibiting the activation of YAP, and consequently accelerates apoptosis[156]. In addition, some studies have indicated that YAP/TAZ could be degraded *via* the autophagy pathway[157,158]. Therefore, whether mTOR and UPR are bridges to connect hypoxia and YAP/TAZ in addition to HIFs is worthy of in-depth discussions and further studies. Thirdly, current research on the mechanisms of interaction between hypoxia and YAP/TAZ has mainly focused on breast cancer[17,38,39,41]. However, the development of drugs and the exploration of therapeutic strategies based on YAP/TAZ have been directed against liver cancer[59,60,81]. Therefore, we must consider how to keep a balance between mechanistic research and clinical applications.

In summary, hypoxia is a critical factor in tumorigenesis and tumor development, and YAP/TAZ is a key nexus between hypoxia and malignant tumor phenotypes. In addition to HIF1, UPR, and the mTOR pathway, YAP/TAZ signaling is expected to offer potential targets for intervention in malignant cancers displaying intratumoral hypoxia.

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Author contributions

Chenxi Zhao was responsible for the conception and design of the review. Chenming Zeng, Song Ye and Xiaoyang Dai collected literatures. Qiaojun He, Bo Yang, Hong Zhu and Chenxi Zhao analyzed literatures and summarized results. Chenxi Zhao drafted the manuscript and drew the figures. Hong Zhu and Chenxi Zhao revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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