Review Article
The HIPPO pathway in gynecological malignancies

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Abstract: The Hippo pathway has been initially discovered by screening genes that regulate organ size in *Drosophila*. Recent studies have highlighted the role of the Hippo pathway in controlling organ size, tissue homeostasis and regeneration, and signaling dysregulation, especially the overactivation of the transcriptional coactivator YAP/TAZ, which leads to uncontrolled cell growth and malignant transformation. The core components of the Hippo pathway may initiate tumorigenesis by inducing tumor stem cells and proliferation, ultimately leading to metastasis and drug resistance, which occurs extensively in gynecological malignancies, including cervical cancer, ovarian cancer, and endometrial cancer. In this review, we attempt to systematically summarize recent progress in our understanding of the mechanism of Hippo pathway regulation in tumorigenesis and the mechanisms that underlie alterations during gynecological malignancies, as well as new therapeutic strategies.

Keywords: Hippo pathway, YAP/TAZ, tumorigenesis, cervical cancer, ovarian cancer, endometrial cancer, therapeutic strategies

Background

The Hippo pathway is a highly conserved signaling pathway in *Drosophila* and mammals that controls organ size and tumor growth [1, 2]. All the Hippo pathway core components have direct homologs in *Drosophila* compared to mammals (**Table 1**). In addition to the core components of the Hippo pathway, many regulators and other signaling pathways have been identified to interact with the Hippo pathway. Loss of Hippo pathway-encoded proteins leads to cell proliferation and tumorigenesis and has been observed in multiple types of human cancers [3-6]. To date, there are no reviews on the role of the Hippo pathway in gynecological malignancies. In this review, we outline the Hippo pathway and discuss its various roles in tumorigenesis. We further discuss the mechanism of Hippo signaling in gynecological malignancies and describe opportunities and challenges for therapeutic interventions. The Hippo pathway has also been identified to be associated with Loeys-Dietz syndrome [7], Sveinsson chorioretinal atrophy (SCRA) [8], Rienhoff syndrome [9] and Neurofibromatosis type 2 [10], but these are beyond the scope of this review.

The Hippo pathway

The Hippo pathway consists of a set of conserved kinases that can be divided into three interrelated parts: upstream regulatory proteins, intermediary core kinases, and downstream transcriptional mechanisms. [11]. More than 30 proteins (including those in *Drosophila* and mammals) have been identified in the Hippo pathway. Upstream membrane protein receptors of the Hippo pathway receive growth inhibition signals from the extracellular environment and then undergo a series of kinase phosphorylation reactions, which ultimately act on downstream effector factors YAP and TAZ. Subsequently, YAP and TAZ interact with cytoskeletal proteins and remain in the cytoplasm, unable to enter the nucleus to perform transcriptional activation, thereby regulating the size and voume of organs. In addition, dysregulation of the Hippo pathway leads to abnormal cell growth and tumors, and these processes are regulated by intrinsic cell machinery. The description of the Hippo pathway in *Drosophila* and mammals is shown in **Figures 1** and **2**, respectively.

Table 1. The Hippo pathway components in Drosophila and mammals

Drosophila gene	Mammal gene	Function
Upstream modulators		
four-jointed box protein 1 (Fj)	FJX1	Golgi resident Ser/Thr kinase
Dachsous (Ds)	Dchs1, Dchs2	Transmembrane cadherin repeat domain
FAT(Ft)	FAT1-4	Transmembrane cadherin repeat domain
Discs overgrown (Dco)	CSNK1E	Casein kinase Ser/Thr kinase
dRASFF	RASSF1-6	Ras association and SARAH domains adaptor
aPKC	PRKCI	PKC kinase, PB1, and C1 domains
dSTRIPAK PP2A	STRIPAK PP2A	PP2A Ser/Thr phosphatase complex
Lethal giant larvae (Ljl)	LJL1, LJL2	WD40 scaffold protein
Expanded (Ex)	Ex1/FRMD6/Willin	FERM domain adaptor protein
Crumbs (Crb)	CRB1-3	Transmembrane receptor
Merlin (Mer)	NF1-2	FERM domain adaptor protein
Kibra	WWC1/WWC2	WW and C2 domain adaptor protein
dJub	AJUBA, LIMD1, WTIP	LIM-domain adaptor protein
Stardust (Sdt)	MPP5, PALS1	L27/PDZ/SH3 domain and guanylate kinase-like domain
Par6	PARD6	PDZ domains
Intermediate core kinase components		
Hippo (Hpo)	MST1, MST2	Ste20 family Ser/Thr kinase
Salvador (Sav)	SAV1/WW45/WWP4	WW domain adaptor protein
Warts (Wts)	LATS1, LATS2	NDR Ser/Thr kinase domain
Mats	MOB1A, MOB1B	Cys2-His2 zinc-binding site/Mob1/phocein domain
Yorkie (Yki)	YAP/TAZ	WW/PDZ transcriptional coactivator
Downstream mediators		
Scalloped (Sd)	TEAD1-4	TEA-domain transcription factor
Teashirt (Tsh)	TSHZ1-3	Zn-finger transcription factor
Homothorax (Hth)	MEIS1	HM (Homothorax-Meis) domain and homeodomain

The core kinase cassette of the mammalian Hippo pathway is composed of macrophage stimulating 1 (MST1) and MST2 [12], together with the adaptor proteins salvador family WW domain containing protein 1 (SAV1) [13, 14] and large tumor suppressor kinase 1 (LATS1) and LATS2, together with MOB kinase activator 1A (MOB1A) and MOB1B [15]. These proteins in turn phosphorylate and inactivate yes associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ)/WW domain containing transcription regulator 1 (WWTR1), which are downstream nuclear effectors of the Hippo pathway that restrict proliferation and promote apoptosis [16-18]. YAP and TAZ and their *Drosophila* homolog Yorkie (YKI) regulate the activity of different transcription factors, including TEADs and SMADs. The presence of TEAD transcription factors is required to promote tissue growth, cell viability, anchorage-independent growth, and epithelial-mesenchymal transition (EMT) induction [19]. TEADs direct the transactivation of YAP, TAZ, and YKI, but their full-length sequences have not been experimentally verified [20]. In *Drosophila*, Hippo, Salvador, Warts and Mats (corresponding to MST1/2, SAV1, LATS1/2, and MOB1 in mammals, respectively) are important tumor suppressors of the Hippo pathway, which regulate tissue growth by controlling cell proliferation and apoptosis [1, 12, 21-24].

The Hippo pathways limit the function of YAP and TAZ by regulating their cellular sublocalization and protein levels [20]. Multiple upstream kinases in the Hippo pathway control the activity of YAP, TAZ and YKI: First, Kibra, Expanded, and Merlin in *Drosophila*; the mammalian orthologs of these proteins are KIBRA, FRMD, and NF2 [25]. Second, CRB (Crumbs) and SCRIB (Scribble) are polarity complexes that can promote the activation of the core kinase box, and CRB can bind and isolate YAP and TAZ [26-28]. Third, the Hippo pathway is regulated by G-protein-coupled receptor (GPCR) signaling, which bypasses MST1 and MST2 to activate LATS1/2 kinase activity, thereby inhibiting YAP function [29]. Fourth, protocadherin,
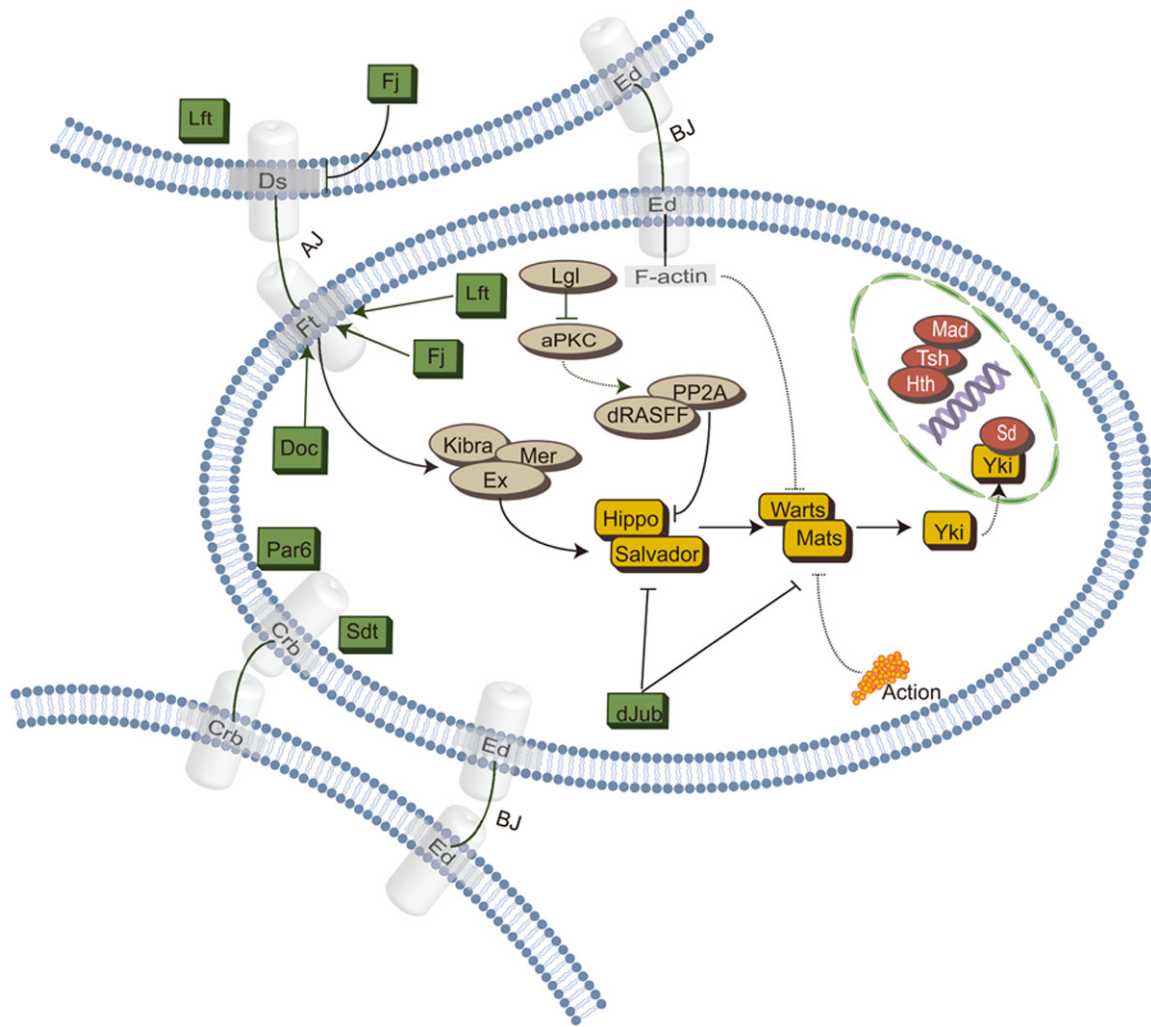
Figure 1. Schematic diagram of the Hippo pathway in *Drosophila*. Cells are shown with a blue outline, upstream regulatory proteins are shown in green/gray, intermediate core kinases are shown in yellow and downstream transcriptional proteins are shown in red, with sharp arrows and blunt arrows indicating activation and inhibition interactions, respectively. Continuous lines indicate direct communication, while dashed lines indicate indirect communication. Abbreviations: AJ, adherens junctions; BJ, basolateral junctions; Fj, four-jointed box protein 1; Ds, Dachsous; Ed, echinoid; Ft, FAT; Dco, Discs overgrown; aPKC, atypical protein kinase C; Ljl, Lethal giant larvae; Rassf, Ras-associated factor; PP2A, protein phosphatase 2A; Ex, Expanded; Crb, Crumbs; Mer, Merlin; dJub, *Drosophila* Ajuba; Sdt, Stardust; Sd, Scalloped; Tsh, Teashirt; Hth, Homothorax.

Dachsous (Ds) and FAT (Ft) are well-defined upstream branches in *Drosophila* that promote the abundance of the Kibra-Expanded-Merlin complex [30-32]. In *Drosophila,* the Hpo-Sav complex phosphorylates and activates the Wts-Mats complex [13, 23, 24, 33, 34], which negatively regulates yki-sd interaction and sd-mediated gene expression by sequestering Yki in the cytoplasm for phosphorylation and inactivation of Yki [35]. In mammals, mitogen-activated protein kinase family members (MAP4K 1-7, the Hppy and the Msn homologs) phosphorylate the hydrophobic motifs of LATS1 and LATS2 in parallel with MST1 and MST2, resulting in their

activation [36, 37]. Activated LATS1 and LATS2 successively phosphorylate YAP and TAZ, resulting in 14-3-3 family proteins retaining YAP and TAZ in the cytoplasm. Cytoplasmic YAP and TAZ can be further phosphorylated and degraded after ubiquitylation, preventing them from interacting with transcriptional enhancer factor TEA domain family members (TEAD1-4), which are homologous to Sd in Drosophila [16, 38].

Hippo pathway in tumorigenesis

The Hippo pathway regulates YAP/TAZ through a series of upstream alteration mechanisms.
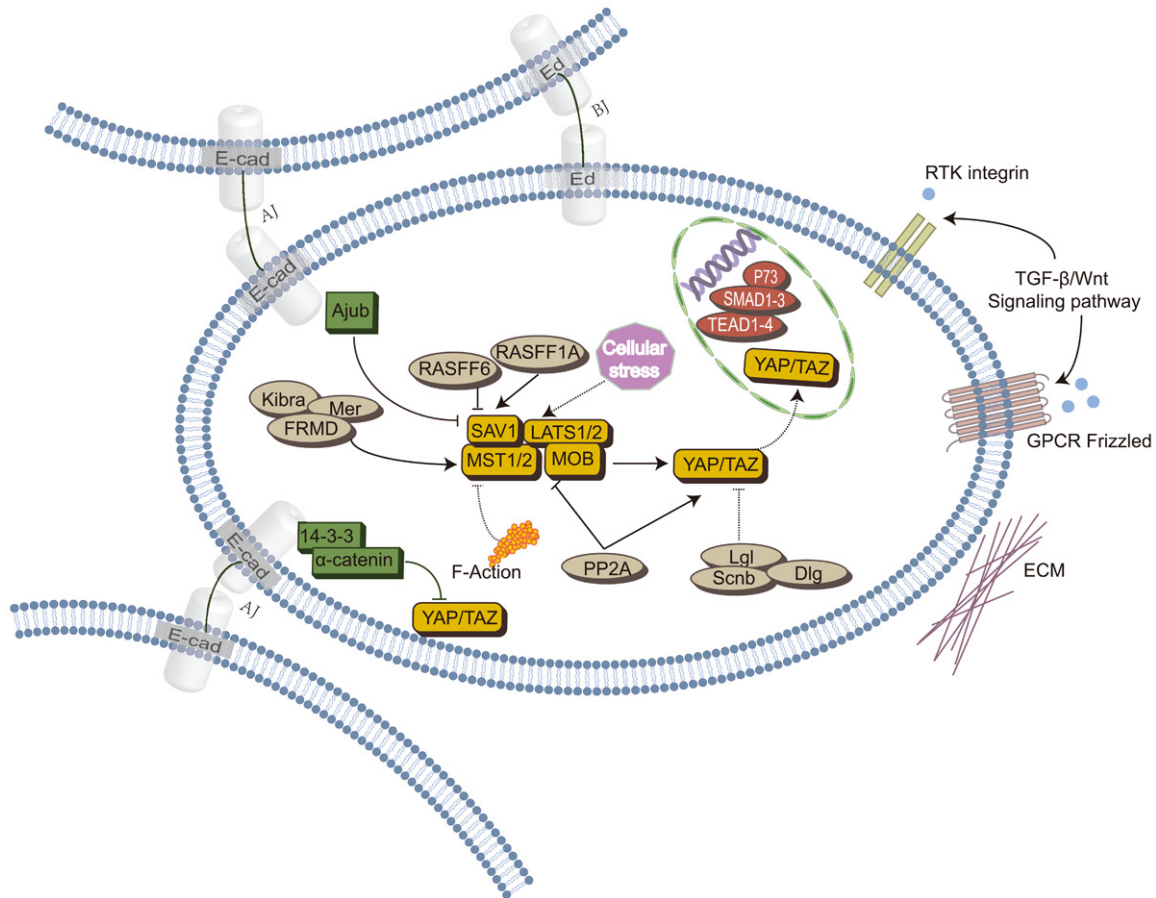
Figure 2. Schematic diagram of the Hippo pathway in mammals. Cells are shown with a blue outline, upstream regulatory proteins are shown in green/gray, intermediate core kinases are shown in yellow and downstream transcriptional proteins are shown in red, with sharp arrows and blunt arrows indicating activation and inhibition interactions, respectively. Continuous lines indicate direct communication, while dashed lines indicate indirect communication. Abbreviations: AJ, adherens junctions; BJ, basolateral junctions; Ed, echinoid; E-cad, E-cadherin; Ajub, Ajuba LIM Protein; FRMD, FERM Domain Containing; Mer, merlin; Rassf, Ras-associated factor; PP2A, protein phosphatase 2A; Ljl, Lethal giant larvae; Dlg, disks large protein; Scnb, Scribble Planar Cell Polarity Protein; MST1/2, Macrophage Stimulating 1/2; SAV1, Salvador Family WW Domain Containing Protein 1; MOB, MOB kinase activator; LAT1/2, large tumour suppressor 1/2; YAP, Yes-associated protein; TAZ, Tafazzin; RTK, receptor tyrosine kinase; GPCR, G-protein coupled receptor; ECM, extracellular matrix.

YAP and TAZ are homologous genes of the Yorkie gene of *Drosophila*, which are critical conduits for the regulation and output of the homologous Hippo pathway. Dysregulation of the Hippo pathway leads to abnormal activation of YAP/TAZ, which further leads to tumorigenesis and confers cancer stem cell characteristics.

Cell proliferation and apoptosis

Uncontrolled cell proliferation is a key characteristic of tumorigenesis. Overexpression of upstream kinases that lead to YAP or TAZ hyperactivation increases proliferation and tissue

overgrowth and impairs apoptosis [39, 40]. Similarly, overexpression or hyperactivation of YAP leads to hyperplasia and tumorigenesis in mouse tissues [41-43]. P53 and RB tumor suppressor genes cause oncogene-induced senescence in cancer cells, block cell cycle progression and promote apoptosis [44]. Homoplastically, the interaction between human E2F1 and TEADs affects the activity of YAP, and the RB tumor suppressor gene modifies these effects by inhibiting the E2F1/TEADs interaction [45]. LATS2 stabilizes p53 by altering small G protein signaling and inhibits the transcriptional regulators YAP and TAZ, which is an important tumor suppression mechanism [46].

In the process of tissue or cell injury, inhibition of apoptosis and regeneration of progenitor and stem cells may be attributed to optimal regulation of upstream kinases in the Hippo signaling pathway [47]. In conclusion, unrestricted activation of YAP and TAZ can counteract classical tumor inhibition pathways.

Cancer stem cells

The Hippo pathway regulates the differentiation of progenitor cells in healthy organ development and cancer environments. Activation of YAP and TAZ can induce tumor stem cell (CSC) properties, including anoikis resistance, EMT, drug resistance, and metastasis, in a variety of human cancers [48]. In follicle stem cells (FSCs) of the *Drosophila* ovary, YKI maintains the integrity of the follicular epithelium, and the Hippo pathway is indispensable for FSC maintenance [49, 50]. Concretely, in the reproductive system, YAP expression can be used to regulate the proliferation and differentiation of ovarian germline stem cells and ovarian function [51, 52]. YAP knockdown leads to a loss of pluripotency in embryonic stem (ES) cells, while YAP protein levels decrease and phosphorylation increases, leading to YAP inactivation during ES cell differentiation [53]. Therefore, an ample amount of evidence suggests that YAP/TAZ play critical roles in the determination of tumorigenic potential by enhancing stem cell properties.

Cell-cell junctions and cell polarity

Cell-cell junctions, such as adherens junctions and basolateral junctions, serve as platforms for Hippo signaling [54]. The components of apical-basal polarity proteins (such as Crumbs, F-actin, PATJ, α-catenin, Ajub, and E-cadherin) can localize and regulate scaffolding proteins that interact with YAP/TAZ [55]. In *Drosophila*, the accumulation of F-actin may increase the activity of Yki [56]. In addition, epithelial cells are mechanically coupled to each other under tension, which promotes Yki activity by activating Ajub and α-catenin [57]. This also occurs in mammalian cells-as all three components are downregulated to increase Yap activity, it has been determined that they are a vital link between F-actin and Hippo pathway regulation [58, 59]. These cell-cell junction proteins are thought to maintain tissue integrity and polarity, and compromised function of these proteins

results in YAP and TAZ hyperactivation, which might drive proliferation in cancer. Some tumor suppressor genes in Drosophila, whose mutations disrupt apical-basal polarization, have been shown to induce YKI-dependent growth [60]. The changes in YAP/TAZ activity in mammalian cells are also related to changes in cellular polarization [61]. A recent study showed that Dlg5, an evolutionarily conserved scaffold and a regulator of cell polarity, interacts with YAP/TAZ mechanistically, which inhibits the association between MST1/2 and LATS1/2, connects MST1/2 to MARK3 using its scaffolding function, and inhibits MST1/2 kinase activity [62].

Contact inhibition

Contact inhibition is a phenomenon in which dispersed cells stop growing once they come into contact with neighboring cells. A lack of restriction by contact inhibition is a common feature of tumor cells [63]. The Hippo pathway has been demonstrated to regulate contact inhibition; isolated mammalian cells usually have higher YAP activity, whereas high-density cultured cells have lower YAP activity [64]. The Hippo pathway components are integral components of the E-cadherin/catenin complex-dependent contact inhibition of proliferation [65]. In addition, CRB3 which activates the Hippo pathway, also regulates contact inhibition by recruiting Kibra and FRMD in mammary epithelial cells [66]. In vitro, YAP and TAZ are inhibited by intercellular contact through the Hippo pathway [67], and the DNA binding transcription factor TEAD is downregulated by high cell density in an NF2/Merlin-dependent manner [68].

Extracellular matrix (ECM) attachment

Tumor cells are surrounded by ECM, and the remodeling and hardening of ECM are essential features of tumors [69]. The ECM plays important biological functions by interacting with the Hippo pathway and is involved in the development of various diseases, especially cancer. The detachment of ECM can result in cell death by activating the Hippo pathway. Integrin-linked kinase (ILK) mediates extracellular matrix (ECM) signaling, which can inhibit Merlin activation either by inhibiting phosphatase MYPT1 or through activation of RAC and PAK [70, 71]. Integrins that bind to fibronectin can stimulate

focal adhesion kinase (FAK), which activates PI3K through Src. PDK1, located downstream of PI3K, disrupts the core kinase cassette and inhibits Hippo signaling [72, 73].

Mechanotransduction

The behavior of tumor cells is related to the mechanical properties of the surrounding environment [74]. Tumor microenvironment signals, including cell geometry, cell attachment or detachment, cytoskeletal tension, and ECM stiffness, are active regulators of YAP/TAZ [75, 76]. Integrin is an important mediator that can sense the chemical composition and physical properties of ECM. FAK is also involved in integrin-mediated regulation of Hippo signaling [77]. Integrin and focal adhesion complexes have been shown to modulate YAP/TAZ, and mechanical elasticity or ECM stiffness can strongly influence cellular behavior [78]. The interface between F-actin and the adhesion junction is a vital mechanotransduction hub, and the force exerted by the adhesion junctions is essential for the morphogenesis of epithelial cells [79]. The Hippo pathway receives mechanical signals, such as stretch and compression signals, which to some extent control the size of the organ [79].

Metastasis

Recent studies have confirmed that inactivation of the Hippo pathway plays an important role in tumor invasion and metastasis. Metastasis is an important feature of malignant tumors and the cause of most cancer-related deaths. Tumor cells metastasize from the primary tumor site to the circulatory or lymphatic system and then grow into secondary tumor masses. Overexpression of YAP does not only promote EMT in cultured cells but also suppresses anoikis [80] and promotes migration via dynamic changes in F-actin, leading to cytoskeletal rearrangement [81]. In addition, the YAP domain interacts with the TEAD family of transcription factors, which are critical for YAP-mediated tumor growth and metastasis, and TEAD transcriptional activity increases the metastatic potential of cancer cells [82]. Hippo pathway regulation in the metastasis of breast cancer has been proposed: long noncoding RNA-dependent methylation leads to inactivation of MST1 and activation of YAP target genes in tumor cells, which in turn leads to osteoclast differentiation and bone metastasis [83].

Tumor immune microenvironment

The Hippo pathway also plays critical immune-regulatory roles. PD-1 is an important immune checkpoint that inhibits T cell and cytokine activation by interacting with its two ligands, PD-L1 and PD-L2 [84]. YAP/TAZ may directly regulate the transcription of PD-L1 in tumor cells thereby inhibiting T-cell-mediated tumor cell killing [85-87]. Activation of YAP/TAZ triggers p53-mediated senescence and/or apoptosis processes, leading to immune recognition, rejection and clearance [88-91]. The Hippo pathway is thus a crucial bridge between tumor cells and the immune system, regulating the inherent function of various types of immune cells, as well as the interaction between tumor cells and T cells. The application of therapies regulating tumor immunity will be an essential direction of Hippo pathway therapy in the future [92].

The Hippo pathway is continually dysregulated in gynecological malignancies

We analyzed genomic data from 308 cervical cancer patients, 594 ovarian cancer patients and 547 endometrial cancer patients in The Cancer Genome Atlas (TCGA) to investigate the role of the Hippo pathway in the development of gynecologic malignancies (**Figure 3**) [93]. Data were analyzed using cBioPortal online tools (http://www.cbioportal.org/) [94] and GEPIA online tools (http://gepia.cancer-pku.cn/). The results showed that YAP/TAZ and WWTR1, oncogenic factors of the Hippo pathway, were continually amplified in patients with cervical cancer, while upstream tumor suppressors of the Hippo pathway (LATS1/2, MST1, and FATs) were often deleted, mutated or highly expressed at the mRNA level (**Figure 3A**). YAP/TAZ, WWTR1, and STK3 were frequently amplified in patients with endometrial cancer (**Figure 3B**), and FATs were often displayed missense mutations. YAP/TAZ, WWTR1, FATs, and STK3 were frequently highly expressed at the mRNA level in patients with ovarian cancer (**Figure 3C**). Moreover, we found that the core components of the Hippo pathway were differently expressed in gynecological malignancies compared with paired normal tissues. YAP/TAZ was highly expressed in tumor tissues, while negative regulatory components of the Hippo pathway were underexpressed in tumor tissues (**Figure 3D**). Mutations, copy number changes (CNAs) and network analysis of HIPPO pathway-related genetic alterations in gynecologic
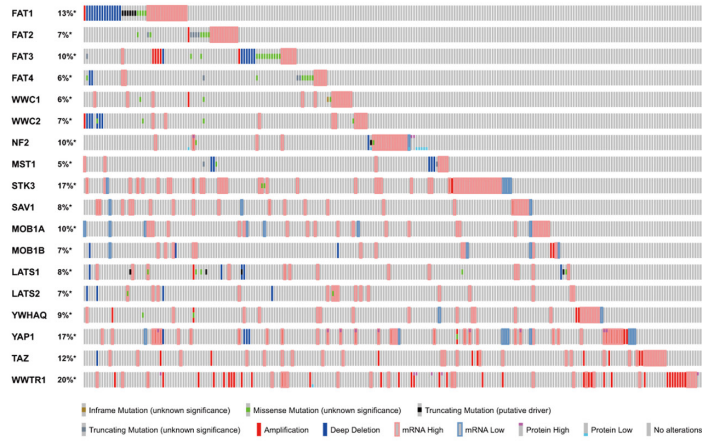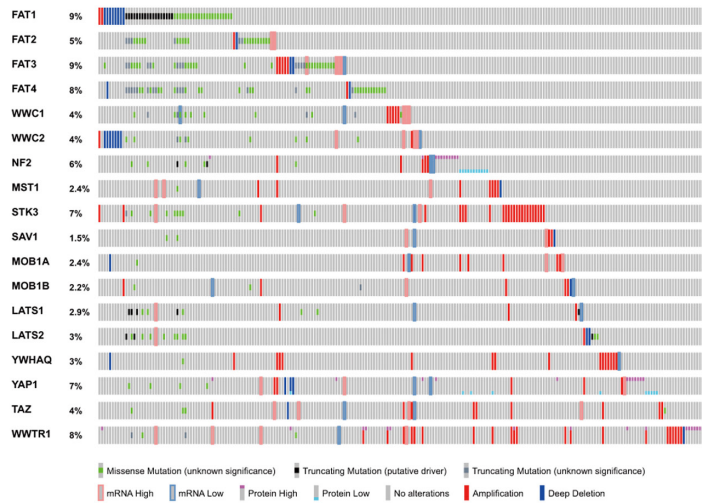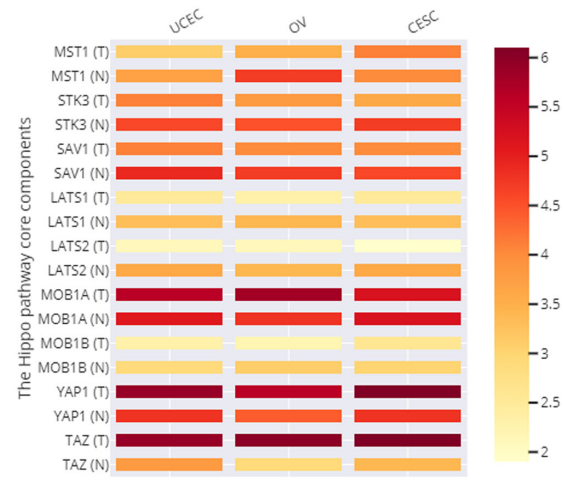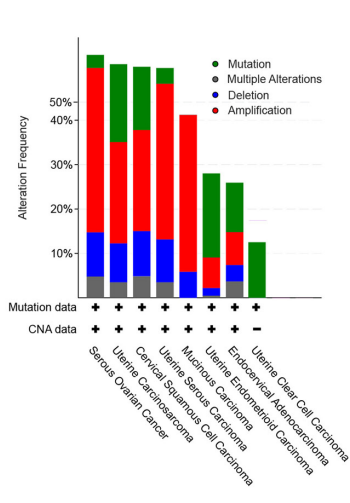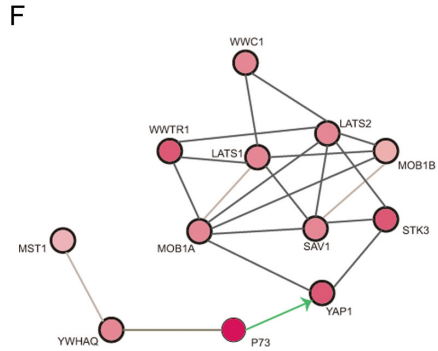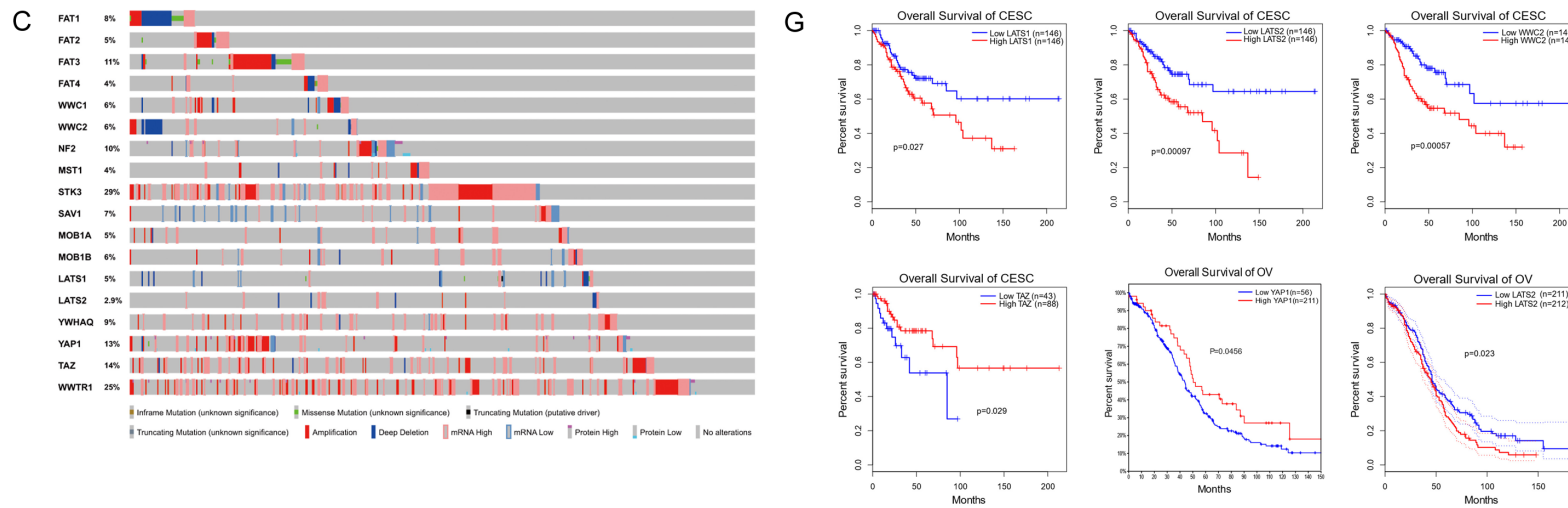
Figure 3. Gene-related changes in critical components of the Hippo pathway in patients with gynecological tumors. The genomic profiles examined included the upstream tumor suppressive genes (MST1, LATS1/2, and FAT1/2/3/4, etc.), the downstream tumorigenic effectors (YAP/TAZ & WWTR1), and the mRNA and protein expression of these genes. Genetic alterations of the Hippo pathway occurred in 79% of examined patients with CESE (308 total, A), 38% with UCEC (547 total, B), and 73% with OV (594 total, C). (D) Expression matrix plots of the Hippo pathway in gynecological malignancies and normal tissues deposited in TCGA and GTEx databases. The density of color in each block represents the median expression value of a gene in a specific tissue. (E) The composition of mutations and copy number alterations (CNAs) of gynecologic tumors is presented in the form of stacked histograms. Different colors represent amplification, deletion, mutation, and multiple alterations, among which 3 data sets have the most significant proportion of mutations, and 5 data sets have the most significant portion of amplification. (F) Network view of alterations of HIPPO pathway linker genes in gynecologic malignancies. We analyzed the genomic data of 308 cervical cancer patients, 594 ovarian cancer patients and 547 endometrial cancer patients, which were deposited in TCGA, and the seed genes are indicated by the thick border. (G) Kaplan-Meier curves showed a correlation between overall survival in cervical and ovarian cancer patients and genetic alterations in the Hippo pathway. Patients with TCGA survival information were divided into two groups: patients with high gene expression levels (red line) and patients with low gene expression levels (blue line). Abbreviations: CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; OV, ovarian serous cystadenocarcinoma; UCEC, uterine corpus endometrial carcinoma.

malignancies are shown in **Figure 3E** and **3F**. We also found that dysregulation of the Hippo pathway could be an important factor in the poor prognosis of ovarian cancer and cervical cancer but not in endometrial cancer. Cervical cancer patients with high genetic expression levels of TAZ and low genetic expression levels of LATS1/2 and WWC2 had poor prognosis. Ovarian cancer patients with high genetic expression levels of YAP1 and low genetic expression levels of LATS2 and WWC2 had also poor prognosis (**Figure 3G**).

The Hippo pathway in cervical cancer

The viewpoint that cervical cancer is caused by high-risk human papillomavirus (hr-HPV) infection has been widely confirmed [95]. HPV infection is common in healthy women, but only a small portion develop cervical cancer [96, 97]. In addition to hr-HPV infection, multiple regulatory pathways are involved in the malignant transformation of cervical epithelial cells. Recently, a study showed that YAP oncogenes increase putative HPV receptor molecules and disrupt host cell innate immunity, and the differential activation and expression of YAP oncogenes determine individual susceptibility to HPV infection [98]. Immunohistochemical analysis showed that YAP expression in cervical cancer tissues was significantly higher than that in normal control tissues.

Moreover, the expression of YAP is related to the tumor stage. YAP protein levels in tissues of patients with advanced cervical carcinoma were significantly higher than those of early-stage patients [99, 100]. The TCGA Research Network published comprehensive molecular characteristics of 228 cases of primary cervical cancer. The expanded TCGA dataset shows that squamous tumors mainly contained high copy number altered gene clusters and amplification events involving YAP, BIRC2/3 and EGFR [93]. The YAP protein interacts with the HPV16 E6 oncoprotein to promote the development of cervical cancer. Overexpression of YAP can also make cervical cancer cells overcome contact inhibition and induce cancer cell proliferation. In addition, the EGFR pathway interacts with the YAP-Hippo pathway to induce cervical cancer cell proliferation and migration [100], and Ajuba LIM Protein (AJUBA) negatively regulates the Hippo signaling pathway and antagonizes

YAP phosphorylation. High AJUBA levels increase the resistance of cervical cancer cells to cisplatin, which is also associated with reduced survival time [101].

Furthermore, TAZ protein levels in normal tissues are significantly higher than those in cervical squamous cell carcinoma (SCC) tissues, and β1 integrin signaling supports the function of the Hippo pathway through Src kinases. TAZ expression and cellular localization are inversely related to SCC development, nuclear TAZ accumulation is associated with lymph node involvement [102], and TAZ expression is associated with a reduced pathological complete response rate [103]. Protein tyrosine phosphatase 14 (PTPN14) is an evolutionarily conserved and important YAP/TAZ upstream regulator [104] that binds to HPV18 E7, resists degradation via the proteasome and negatively regulates the proliferation, migration, and invasion of cervical cancer cells by attenuating the activity of downstream effectors of Hippo signaling [105]. The underlying mechanism by which Hippo signaling regulates cervical cancer progression is shown in **Figure 4**.

The Hippo pathway in ovarian cancer

Ovarian cancer (OC) has the highest mortality rate in gynecological malignancies [106]. At present, the development of ovarian cancer is still poorly understood [107]. The YAP/TAZ oncogene plays a role in promoting tumorigenesis in human ovarian cancer by promoting cell proliferation and apoptosis resistance, reducing contact inhibition, and improving motility and anchorage-independent growth [108-111]. Lysophosphatidic acid (LPA) induces YAP/TAZ dephosphorylation in ovarian cancer cells, which leads to cell migration and proliferation. These processes include LPA3-G12/13 coupled signaling, the upstream regulator RhoA-ROCK, and the major regulator PP1A [112-114]. YAP interacts with the EGFR signaling pathway to regulate AREG secretion and EGFR-dependent cell migration [113, 115]. Current evidence indicates that ovarian high-grade serous carcinoma (HGSC) may originate from fallopian tube umbilical epithelial cells (mainly the secretory epithelial cells of fallopian tubes) [116]. YAP is overexpressed in inflammatory and cancerous fallopian tube tissues, and the YAP-Hippo pathway interacts with the FGF-
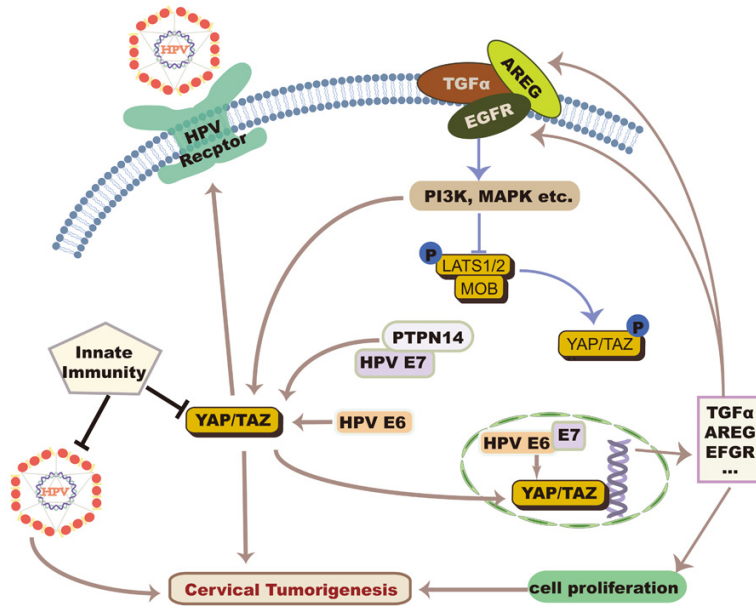
Figure 4. A schematic diagram shows the proposed mechanism by which the Hippo pathway regulates cervical cancer. In cervical cancer cells, nuclear accumulation of YAP protein stimulates the expression of EGF-like ligands, such as TGF-α and AREG, which in turn activates EGFR and inhibits LATS 1/2 and MOB1 binding and further phosphorylation. Activated YAP activates transcription factors and induces the expression of growth factors, such as TGF-α and AREG, thereby promoting the growth of cervical cancer. HPV E6/ E7 oncoproteins maintain YAP protein levels in cervical cancer cells by preventing the degradation of proteasome-dependent YAP. Accordingly, the high expression of YAP further promotes persistent HPV infection by upregulating putative HPV membrane receptor molecules and suppressing innate immunity in host cells.

FGFR pathway, which regulates fallopian tube umbilical epithelial cell activity, suggesting that the Hippo pathway may be involved in the occurrence and development of HGSC [115]. Neuron-restrictive silencer factor (NRSF) can activate the transcription of the Hippo pathway to enhance the proliferation of ovarian cancer cells, which promotes the dephosphorylation of MST1, LATS1, and YAP [117]. MicroRNAs (miR-NAs) are noncoding RNAs encoded by endogenous genes with a length of approximately 22 nucleotides and are involved in the regulation of posttranscriptional gene expression [126]. The function of miRNAs and their exosomes in ovarian cancer cells has recently been revealed with the discovery that miRNA-129-5p and miR-NA-149-5p are tumor suppressor miRNAs that inhibit the expression of YAP/TAZ, leading to the inactivation of TEAD transcription, which in turn has suppressive effects on the proliferation and tumorigenicity of ovarian cancer cells [118-120].

Moreover, the upregulation of miRNA-149-5p increases ovarian cancer cell resistance to cisplatin [118]. A type of long noncoding RNA (lncRNA), urothelial cancer associated 1 (UCA1), is a driving factor of ovarian cancer carcinogenesis. AMOT, the HIPPO pathway upstream regulator, enhances the interaction between AMOT and YAP through UCA1, which mediates YAP activation and promotes the dephosphorylation and nuclear translocation of YAP [121]. The underlying mechanism by which Hippo signals regulate the progression of ovarian cancer is shown in **Figure 5**.

The Hippo pathway in endometrial cancer

Endometrial cancer (EC) is a malignant epithelial tumor that occurs in the endometrium, with an estimated annual incidence of 3-11/100,000 women [106]. In addition to traditional clinical and pathological classification, it is also essential to identify new molecular mechanisms for the development of endometrial cancer therapies. As mentioned above, the Hippo pathway transcriptional regulators YAP and TAZ are reported to be overexpressed in various cancers, and overexpression of TAZ/YAP has been also shown to increase proliferation, migration, and invasion in endometrial cancer cell lines [122-124]. Furthermore, TAZ/YAP interacts with the PI3K/AKT pathway at multiple pathophysiological levels in endometrial cancer. In endometrial cancer cell lines, the synergistic downregulation of YAP/TAZ activates the Hippo pathway, which reduces the activation of the PI3K/AKT pathway by reducing the level of GAB2 linker molecules [122, 125]. In addition, the YAP gene in the nucleus can directly bind to the promoter of interleukin-6 (IL-6) and induce its transcription. IL-6 and IL-11 are essential for YAP-induced tumorigenesis of endometrial cancer cell lines [123]. MIR31 overexpression and FAT4 silencing reduce the
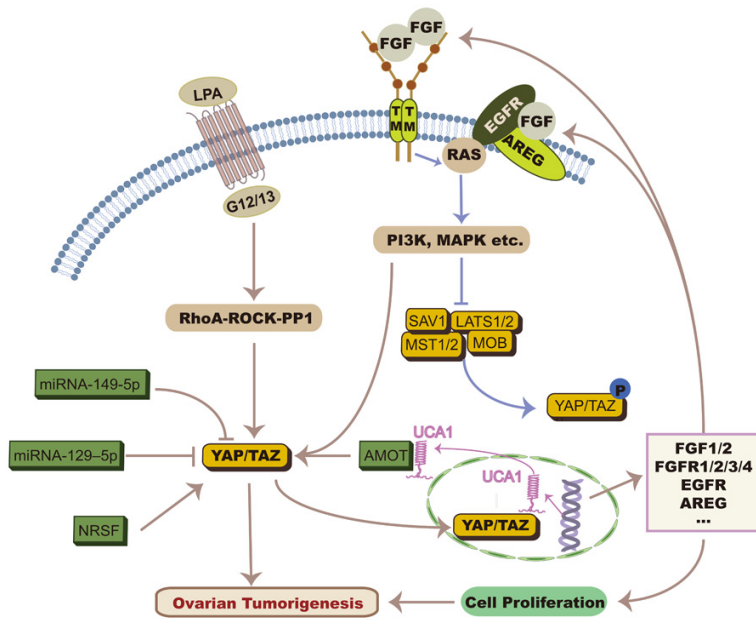
Figure 5. A schematic diagram showing the proposed mechanism by which the Hippo signaling pathway regulates ovarian cancer. In normal ovarian tissues, deactivated FGF ligands, such as FGFRs, are insufficient to activate YAP, leading to ubiquitin-dependent degradation of YAP proteins. In ovarian cancer tissues, the nuclear accumulation of YAP protein stimulates the expression of FGFs, FGFRs and AREG, thereby activating FGF receptors and EGFR, which in turn interact with downstream signaling pathways, such as the PI3K and MAPK pathways, inhibiting the Hippo pathway and activating the YAP protein. Moreover, the NRSF, UCA1, and LPA-G12/13-RhoA-ROCK-PP1A-YAP signaling pathways can stimulate the expression of YAP, miRNA-129-5p, and miRNA-149-5p and inhibit the expression of YAP, which affects the occurrence and development of ovarian cancer.
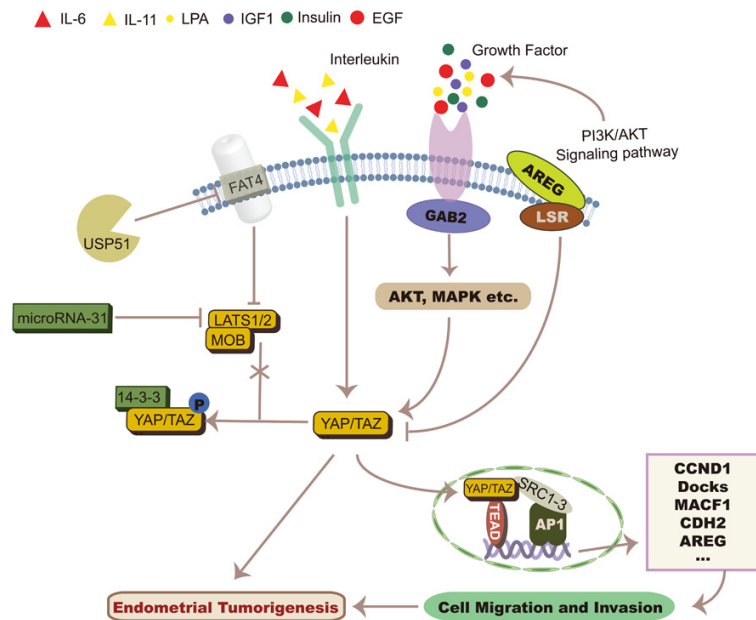
YAP and TAZ dephosphorylation, leading to nuclear translocation and TEAD transcriptional activation. MIR31 significantly inhibits the luciferase activity of mRNA binding to the LATS2 3'-UTR, and the downregulation of LATS2 leads to the dephosphorylation of YAP, promotes the translocation of YAP into the nucleus, and increases the transcription of CCND1. Inactivation of deubiquitinating enzyme USP51 inhibits FAT4, resulting in decreased phosphorylation of LATS1/2 and YAP, while increased YAP nuclear translocation and loss of LSR up-regulate TEAD/AREG in EC cells, which promote proliferation and invasion. YAP/TEAD-AP1 cooperation engages SRC1-3 coactivators and drives downstream gene expression to regulate endometrial cancer cell migration and invasion. Verteporfin induces YAP retention in the cytoplasm through increasing levels of 14-3-3 and blocks the transcriptional activation of targets downstream of YAP.

protein levels of LATS1/2 by inhibiting phosphorylation [127, 128], and downregulation of LSR results in AREG upregulation [129], which promotes YAP/TAZ translocation into the nucleus; an important link in promoting endometrial cancer tumorigenesis. In endometrial cancer cell lines, the TEAD family and the AP1 transcription factors act closely in the active enhancer or promoter regions and bind to the SRC1-3 coactivator to promote downstream transcription, thereby promoting cell migration and invasion [130]. Theunderlyingmechanismbywhich Hippo signals regulate the progression of endometrial cancer is shown in **Figure 6**.

Therapeutic strategies targeting the Hippo pathway

As mentioned above, YAP/TAZ may play an oncogenic role in gynecological malignancies. Therefore, current therapeutic

Figure 6. A schematic diagram showing the proposed mechanism by which the Hippo signaling pathway regulates endometrial cancer. The Hippo pathway activates the PI3K/AKT pathway via growth factors, including 1-oleoyl-2-hydroxy-sn-glycerol-3-phosphate (LPA), EGF, insulin, and IGF1, resulting in
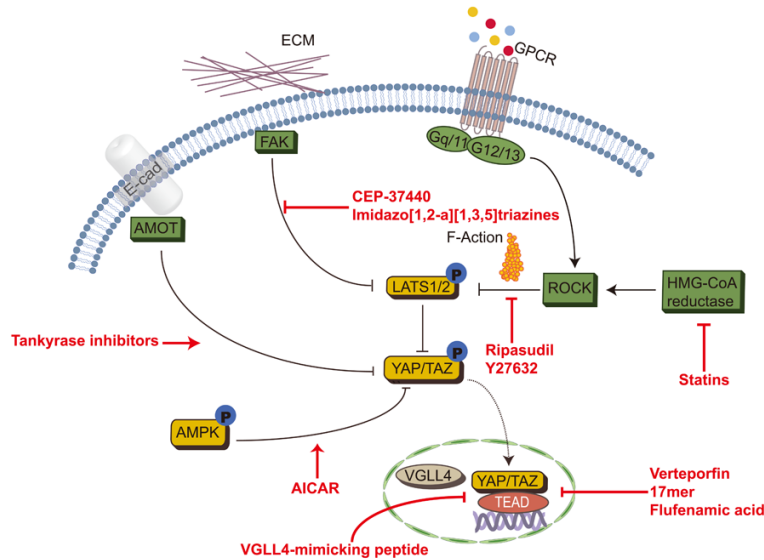
Figure 7. A schematic diagram showing putative targets and small molecules specific to the Hippo pathway. Cells are shown with a blue outline, upstream regulatory proteins are shown in green, and core kinases are shown in yellow, with sharp arrows and blunt arrows indicating activation and inhibition interactions, respectively. Continuous lines indicate direct communication, while dashed lines indicate indirect communication.

strategies primarily target the carcinogenic activity of YAP/TAZ. In addition, activating the negative regulatory components of the Hippo pathway can also play a role in tumor inhibition. Here, we introduce some small molecules or drugs that target the Hippo pathway core components (**Figure 7**).

Targeting YAP/TAZ-TEAD interactions

Recent research demonstrateds that blocking YAP/TAZ-TEAD complex formation could be a potential anticancer therapy. Further, verteporfin, an inhibitor of YAP-TEAD interactions [131], significantly inhibits the proliferation of endometrial cancer cells in a concentration-dependent manner and decreases tumor size and weight *in vivo*, suggesting that verteporfin can be used as a new treatment for endometrial cancer [122, 123, 132].

Vestigial-like family member 4 (VGLL4) has two tondu (TDU) motifs in its carboxyl-terminal domain, which modulate the activity of TEAD-1. VGLL4 was first reported to have counteracted α1-adrenergic activation of TEAD-1-dependent gene expression in cardiac myocytes [133]. Recent reports indicate that VGLL4 directly interacts with TEAD through its TDU domain and inhibits YAP/TAZ-TEAD transcriptional activ-

ity [134]. In addition, VGLL4 is downregulated in endometrial cancer [135]. VGLL4 deficiency reduces the expression of PD-L1 in tumor cells, and VGLL4 and YAP play a central role in regulating tumor immunity [136]. Therefore, VGLL4 is considered a therapeutic and tumor suppressor marker. YAP-like peptides (17mers) target TEAD to disrupt the YAP-TEAD interaction, which is an effective strategy for combating YAP-induced tumorigenesis [137]. Flufenamic acid binds to a central pocket in the YAP-binding domain of TEAD, and inhibits TEAD-YAP-dependent malignant biological properties [138].

Targeting upstream components of the Hippo pathway

YAP/TAZ is widely regulated by upstream signals of the Hippo pathway. Therefore, the main goals for small therapeutic molecules are to regulate YAP/TAZ activity and subcellular localization. Metabolic pathways, such as the mevalonate pathway and energy stress, can regulate YAP/TAZ activity [139]. Inhibitors of the rate-limiting enzymes of these pathways, such as HMG-CoA reductase inhibitors (statins), facilitate YAP/TAZ cytoplasm localization and inhibit transcriptional responses [139]. Recent studies have confirmed that statins have antitumor effects on cervical, endometrial, and ovarian cancer [140]. Energy stress induces YAP phosphorylation through AMPK. On the one hand, it depends on LATS1/2 activation to promote YAP cytoplasmic retention; on the other hand, it directly phosphorylates YAP at Ser 94, thus disrupting the YAP-TEAD interaction. AMPK-induced YAP phosphorylation can inhibit YAP-mediated carcinogenesis [141, 142]. Specifically, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) inhibits YAP activity by activating AMPK [143]. Metabolic pathways play an important role in the tumorigenesis of gynecological malignancies, and small molecules that target metabolic pathways can exert partial antitumor effects by inhibiting YAP/TAZ [144, 145].

As mentioned above, the Hippo pathway is a downstream branch of GPCR signaling. The GPCR-G-protein-cytoskeleton axis can regulate the phosphorylation status of LATS1/2, thereby regulating YAP/TAZ activity. Specifically, YAP/TAZ is regulated through G12/13, Gi/o, Gq/11 or Gs-coupled GPCR ligands via actin dynamics, Rho GTPases and their downstream effector ROCK [29, 146]. Recent reports have verified that G12/13-ROCK signaling promotes ovarian and cervical cancer invasion. Therefore, ROCK inhibitors, such as ripasudil and Y27632, may inhibit YAP/TAZ activity [147, 148]. The ECM is considered a potential therapeutic target; specifically, FAK-AKT signaling regulates the malignant biological properties of gynecological malignancies [149-151]. Thus, some FAK inhibitors, such as compound 2 (CEP-37440) and imidazo[1,2-a][1,3,5]triazines, may suppress YAP by promoting nuclear translocation [152-154]. In addition, tankyrase inhibitors stabilize AMOT family proteins, thereby suppressing YAP activity [155].

Conclusion

The Hippo pathway is a critical regulatory pathway in mammalian tissue growth and development. Recent advances have supported the role of Hippo pathway deregulation in tumorigenesis, especially in gynecologic oncology. Increasing evidence shows that the disturbance of YAP/TAZ activity has a profound effect on malignancies. In addition, the interaction of the Hippo pathway with other oncogenic signaling pathways may provide valuable therapeutic targets. Notably, the core components of the Hippo pathway are continually dysregulated in multiple human cancers, and it is essential that we identify multiple upstream regulators and downstream targets of the Hippo pathway. Therefore, the development of anticancer therapies targeting the Hippo pathway is critical, and we expect many new insights into this pathway in the near future.

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Disclosure of conflict of interest

None.

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