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Hippo pathway: Regulation, Deregulation and Potential Therapeutic Targets in Cancer

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Abstract

Hippo pathway is a master regulator of development, cell proliferation, stem cell function, tissue regeneration, homeostasis, and organ size control. Hippo pathway relays signals from different extracellular and intracellular events to regulate cell behavior and functions. Hippo pathway is conserved from Protista to eukaryotes. Deregulation of the Hippo pathway is associated with numerous cancers. Alteration of the Hippo pathway results in cell invasion, migration, disease progression, and therapy resistance in cancers. However, the function of the various components of the mammalian Hippo pathway is yet to be elucidated in detail especially concerning tumor biology. In the present review, we focused on the Hippo pathway in different model organisms, its regulation and deregulation, and possible therapeutic targets for cancer treatment.

Keywords

Hippo pathway; Regulation; Cancer metabolism; Immunity; Epigenetics

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Introduction

It's really interesting to imagine the regulation of cell growth and division in a developing organism. During development, how a cell knows that it's the time to stop growth or to divide to attain a correct body size and shape, and how organ size is specified and maintained in adult life are still a mystery to biologists. Hippo pathway is one of the most important pathways that regulate organ size and maintain tissue homeostasis. Hippo pathway was first identified in *Drosophila melanogaster* through genetic mosaic screens for the tumor suppressor genes that are involved in the regulation of organ size [1]. The name of the Hippo pathway was coined based on the key component (Hippo kinase) of this pathway. Initially, the Hippo pathway was thought to be well-conserved in mammals [2]. Now, this pathway is also found to exist in other eukaryotes. The Hippo pathway plays a vital role in relaying various signals from upstream cues to regulate cell behavior, growth, proliferation, and tissue homeostasis [3]. Hippo pathway is also activated by contact inhibition when cells reach the highest confluency to inhibit cell growth and to regulate organ size [4].

Dysregulation of the Hippo pathway is apparent in many cancers. Mutations and alterations in the key components of this pathway result in tumorigenesis, aggressiveness, invasion, migration, metastasis, and resistance to treatments [5]. In this review, we envision giving a comparative outline of the Hippo pathway in *Drosophila*, mammals, *C. elegans,* and yeast, and its regulation, deregulation, role in different cancers, and possible therapeutic targets for cancer treatment.

Comparative study of Hippo pathway in different model organisms

The Hippo pathway is evolutionarily conserved in different organisms (Figure 1) (Table 1). The core components of the Hippo pathway are kinases, adaptor proteins, and transcription coactivators. The core kinase of this pathway is Hippo in *Drosophila* [6], mammalian STE20–like kinases (MST1/2)- (Hippo homolog) in mammals [7] and CST1/2 (Hippo homolog) in *C. elegans* [2]. The two adaptor proteins of the *Drosophila* Hippo pathway are Salvador (Sav) [8] and Mats (mob as tumor suppressor) [9]. In mammals, these two adaptors are Salvador-1 (Sav homolog of *Drosophila*) [10] and MOB1 (Mats homolog of Drosophila) [11]. In *C. elegans,* these are SAV-1 (Sav homolog of *Drosophila*) and F09A5.4 (Mats homolog of *Drosophila*) [2]. In *Drosophila*, the second kinase of the Hippo pathway is Warts (Wts) [12, 13]. In mammals, the Warts homolog is large tumor suppressor kinases 1/2 (LATS1/2) [14], and in *C. elegans* it is WTS-1 [2]. In *Drosophila* and *C. elegans*, the Hippo pathway has only one transcriptional coactivator, named Yorkie (in *Drosophila*) [15] and YAP-1 (in *C. elegans*) [2], whereas, mammalian Hippo pathway has two transcriptional coactivators, named YAP (yes-associated protein) and its paralog TAZ (Transcriptional activator with PDZ-binding domain) [16]. Both YAP and TAZ have TEAD binding domain, WW domain, and a transactivation domain (include coil-coil regions, phosphodegron motif, and PDZ binding motif). YAP also has a proline-rich region close to TEAD binding domain, PXXØP site in the TEAD binding domain, and SH3 binding motif [17] (Figure 2).

In *Drosophila*/mammals, along with the Sav/SAV1 and Mats/MOB1, Hippo/MST directly phosphorylates and activates Warts/LATS [6, 9, 11, 14, 18, 19] which in turn phosphorylates

and inactivates Yki/YAP/TAZ by either cytoplasmic retention or lysosomal/proteosomal degradation [15, 20–22]. Inactivation of the Hippo pathway leads to the activation and nuclear localization of Yki/YAP/TAZ where it interacts with Scalloped (Sd)/TEAD or other transcription factors that ultimately induce expression of target genes that are involved in proliferation, differentiation, and development [23–26]. In *C. elegans*, the role of core kinase CST1/2 on WTS-1 is still unknown. WTS-1 inhibits the nuclear localization of YAP-1. Inactivation of WTS-1 results in nuclear localization and interaction of YAP-1 with the EGL-44 and induces target gene expression [2].

Hippo pathway exists in budding yeast as well. In budding yeast, the mitotic exit network (MEN) is similar to the canonical LATS pathway (Salvador/warts/Hippo system), whereas the RAM network is similar to the non-canonical NDR pathway (furry/tricomered/Hippo system). In MEN, Cdc15 (Mst/Hippo-related kinase domain) phosphorylates the Nud1 (scaffold protein) and creates a docking site for Dbf2 and Dbf20 (Paralogous protein LATS-family kinases) to be activated [27]. Activated Dbf2 (Kinase)/Mob1(co-activator) activates Cdc14, Chs2 and Hof1 that ultimately regulate mitotic exit and cytokinesis [28–30]. The core components of the RAM network include Kic1 (Mst/Hippo-related protein kinase), Cbk1-Mob2 (Ndr/LATS kinase-Mob complex), Tao3 (scaffold protein), and Hym1 (activator) [31, 32]. Cbk1-Mob2 phosphorylates Ace2 and drives its nuclear localization [33]. Cbk1-Mob2 also allows bud wall expansion by inhibiting RNA binding protein Ssd1 [34].

Regulation of Hippo Signaling Pathway

Hippo signaling pathway is regulated by different intracellular, extracellular, and non-cellular events that modulate the subcellular localization and protein stability of its effector YAP/TAZ to regulate cell behavior, growth, and proliferation (Figure 3).

Regulation by cell polarity and cell adhesion molecules

Hippo pathway is regulated by the apical-basal cell polarity and cell adhesion molecules. For example, Crumbs complex (CRB/PATJ/PALS1) that forms apical polarity of cells activates the Hippo pathway by interacting with Angiomotin (AMOTs) family of proteins, FERM domain-containing protein 6 (FRMD6), Kibra (WW domain-containing protein), and Merlin [35]. Scribble complex (SCRIB/DLG/LGL) that form basal polarity regulates Hippo pathway by interacting with the hippo pathway components [36]. E-cadherin, a transmembrane protein of adherens junction, interacts with the cytoskeleton through alpha-catenin and negatively regulates YAP/TAZ function [37]. Protein-tyrosine phosphatase type 14 (PTPN14), another adherens junction component, activates the Hippo pathway by sequestering YAP in the cytoplasm [38].

Regulation by mechanical cues

Hippo pathway is also regulated by different mechanical cues such as cell geometry, extracellular matrix stiffness, cell adhesiveness, mechanical strain, or distortion [39]. For example, ECM stiffness or mechanical stress induces nuclear localization of YAP/TAZ and

thus negatively regulates Hippo pathway [40, 41], whereas cell density positively regulates the Hippo pathway by preventing nuclear localization of YAP/TAZ [42].

Regulation by signaling pathways

Apart from cell polarity, mechanical cues, numerous extracellular ligands, and signaling pathways also regulate the Hippo pathway. For example, lysophosphatidic acid (LPA) and sphingosine1-phosphate (S1P) inactivate the Hippo pathway via activation of GPCR [43]. EGFR-Ras-Raf-Mitogen-activated protein kinases (MAPK) signaling axis also regulates Hippo signaling through activation of YAP/TAZ [44]. Amphiregulin (AREG) inhibits the Hippo pathway via EGFR mediated signaling pathway [45]. Integrin-linked kinase (ILK) inactivates the Hippo pathway via inactivation of the merlin through the phosphorylation of MYPT1-PP1 [46]. Integrin- Src signaling axis inactivates the Hippo pathway via triggering translocation of YAP/TAZ to the nucleus [47]. Mitogen-activated protein kinase kinase kinase kinase (MAP4K) activates the Hippo pathway by activating LATS1/LATS2 [48]. Thousand-and-one amino acid kinases (TAOK1/2/3) activate the Hippo pathway via phosphorylating core kinase MST1/MST2 [49]. Furthermore, autophosphorylation at the multiple sites on the MST linker also regulates the Hippo pathway [50] via MST1/2 activation.

Recently a study reported that STK25 suppresses Hippo pathway in human by phosphorylating SAV1 and in turn diminishes the inhibitory action of SAV1 to STRIPAK that ultimately blocks MST1/2 activation [51]. Recently another study reported that the TLK1-NEK1 signaling pathway can also regulate hippo pathway by phosphorylating and stabilizing YAP1, thereby promoting CRPC progression [52]. Our recent study shows that expression of Prostate-Derived ETS Factor (PDEF) in prostate cancer (PC3and DU145) cell lines resulted in increased phospho-YAP1 (Ser127) levels and inhibition of YAP1 activity [53]. To the best of our knowledge, this result provides the first demonstration of inhibiting YAP1 activity by PDEF in any system and suggests crosstalk between PDEF and the Hippo signaling pathway. However, the mechanism by which PDEF regulates the Hippo pathway is yet to be elucidated. Therefore, multiple cellular crosstalks and signaling pathways regulate the Hippo pathway to maintain homeostasis of cellular growth and proliferation.

Regulation by Endosomes

Several studies reported the role of endosomes in regulating the Hippo pathway. In *Drosophila*, the endosome regulates cytoplasmic Yki levels by concentrating Yki at the late endosome and subsequent lysosome-mediated degradation of Yki. Two endosomal adaptor proteins, Myopic (Mop) (co-localized with Rab7-positive endosomes) [54] and Leash (co-localized with Rab9 late endosome) [55] directly interact with the Yki and drive the endo-lysosomal pathway for Yki degradation [56].

In human, YAP activity is regulated by the phosphatidylserine in the recycling endosomes (REs) as evidenced by the suppression of YAP1 nuclear localization upon knockdown of ATP8A1 (an RE PS-flippase) or evectin-2 (a RE-resident protein) and masking of PS in the cytoplasmic leaflet of membranes [57]. Recycling endosome also regulates Hippo

pathway in the mature epithelia as evidence by the disruption of Rab11a directed recycling endosome that results in the activation of Yki/YAP [58]. Recently a study by Block et al. reported that late endosomal/lysosomal adaptor MAPK and mTOR activator (LAMTOR) complex promotes SRC- positive late endosome recycling and subsequent activation of YAP protein. Moreover, LAMTOR complex can also be activated by β1 integrin engagement and mechano-sensitive cues suggesting late endosomal recycling is an important regulator of YAP activity and YAP mechano-sensitivity [59]

Hippo pathway is also regulated by endosomal integral membrane protein, endotubin (EDTB) that binds to the AMOT in sub-confluent cells, and ultimately drives translocation of YAP into the nucleus. In the confluence cells, contact inhibition is mediated by the AMPT: YAP interaction because EDTB preferentially binds to occluding, suggesting a role of the endosomal membrane protein in regulating tight junction protein trafficking and hippo pathway [60].

Several studies reported that α-arrestins domain-containing protein 1 and 3 (ARRDC1 and ARRDC3), members of the α-arrestins family, also regulate Hippo pathway by directly interacting with YAP1, and E3 ubiquitin ligase Itch-mediated ubiquitination, followed by degradation of YAP [61, 62].

Hippo pathway and organ size regulation

Hippo signaling pathway plays an important role in regulating organ size and tissue homeostasis, as evidenced by the overgrowth of *Drosophila's* wings, eyes, or other appendages after mutation of Hippo pathway components and upstream regulators. A similar overgrowth phenotype was also observed by transgenic overexpression of Hippo downstream regulator *Yki* [63, 64]. In transgenic mice, liver-specific expression of *Yap* causes an increase in liver size and has long-term effects on liver cancer [23, 65]. Similar changes have been observed in liver-specific knockouts of *Mst1* and *Mst2*, *Sav1* or *Mer* [66–70]. Several studies showed enlargement of mouse embryos after the knockout of Hippo upstream regulators such as SAV1, MST1/2*, or* LATS1/2 [71–73]. Recently a study reported that O-GlcNAcylation on LATS2 disrupts the interaction with MOB1 and thereby activation of YAP/TAZ that promotes cell proliferation and tumor development [74]. Collectively, these compelling genetic studies and post-translational modification of Hippo components depict that the Hippo pathway is indubitably a key regulator of organ size.

Hippo pathway and regulation of stem cell behavior

Hippo pathway regulates stem cell renewal, proliferation, and differentiation. For example, activation of YAP results in reprogramming of the somatic cells into induced pluripotent stem cells, whereas knockdown of YAP causes loss of stem cell pluripotency. Inactivation of YAP triggers Embryonic Stem Cells (ESCs) differentiation [75]. A recent study reported that YAP plays an important role in maintaining trophoblast stemness of the developing placenta in human [76]. An *in-vitro* study showed that knockdown of TAZ (paralog of YAP) results in the differentiation of human CA1 stem cells [77].

Overexpression of YAP in mouse intestine expands undifferentiated progenitor cells [65]. A similar expansion of neural progenitor cells is also observed when YAP and TEAD are activated in the chicken neural tube model [78]. Higher expression of YAP is also observed in the perivascular cancer stem cell compartment in the subtypes of medulloblastomas indicating that YAP plays an important role in the proliferation and maintenance of cancer stem cells [79]. The role of the Hippo pathway in regulating cancer stem cell proliferation is also shown by the knockout of upstream hippo components such as Merlin, or double knockout of *Mst1* and *Mst2*, or knockout of *Sav1* in mice liver which results in accumulation of oval cells and adult liver stem cells that subsequently induce tumor formation [66, 67, 70]. These pieces of evidence support the role of the Hippo pathway in regulating stem cell behavior.

Hippo pathway and cancer metabolism

Energy metabolism is significantly different in cancer cells than the normal cells. Cancer cells have a high demand for glucose, amino acid, and fatty acid for their unrestricted growth and proliferation. This phenomenon is more apparent in the Warburg effect where cancer cells rely on aerobic glycolysis to obtain more energy by converting the glucose to lactate synthesis; whereas, normal tissues depend on mitochondrial oxidative phosphorylation [80].

Hippo pathway is regulated by glucose metabolism and energy levels. Cellular energy stress activates the Hippo pathway by AMP-activated protein kinase (AMPK) (an energy sensor) mediated LATS activation that leads to YAP phosphorylation and inactivation. AMPK can also inactivate YAP, independent of Hippo activation, by disrupting the interaction between YAP and TEAD through direct phosphorylation of YAP at ser 89 that are necessary for their interaction [81]. Glucose metabolism also regulates YAP/TAZ transcriptional activity, as evidenced by the study conducted by Enzo et al. where the main rate-limiting enzyme of glycolysis, phosphofructokinase-1 (PFK-1) was shown to bind to TEAD and enhance the interaction between TEAD and YAP/TAZ which in turn increases the gene transcription [82]. In liver cancer, the high glucose level activates YAP through O-GlcNAcylation at T241 by O-GlcNAC transferase (OGT) [83].

Fat metabolism also regulates YAP/TAZ activity. Mevalonate pathway regulates YAP/TAZ by activating Rho GTPase mediated inhibition of YAP/TAZ phosphorylation and promoting nuclear localization of YAP/TAZ. In Breast cancer, the mevalonate/YAP/TAZ axis stimulates the proliferation and self-renewal of breast cancer cells [84]. During development and tumorigenesis, YAP reprograms glutamine metabolism by inducing glutamine synthase expression and subsequent increase in glutamine levels for nucleotide biosynthesis that acts as the building block for liver growth and tumorigenesis [85]. A recent study suggests that YAP/TAZ coordinates the interplay between metastasis and metabolic alternation [86]. Therefore, understanding the interplay between the Hippo pathway and metabolism in cancer could open a new avenue for cancer treatment.

Hippo pathway and cancer immunity

Several studies have demonstrated the role of the Hippo pathway in regulating host immune response and tumor immunity. Tumor initiating cells utilize Hippo effector YAP to escape from immune clearance by recruiting M2 macrophages [87]. A previous study showed that Hippo signaling impairs tumor progression by infiltrating polymorphonuclear myeloid-derived suppressor cells (MDSC) through up-regulation of TEAD dependent CXCL5 expression [88]. However, an *in-vivo* study by Moroishi et al. showed that depletion of LATS1/2 induces antitumor immunity by stimulating the host TLRs-IFN pathway through the secretion of nucleic-acid-rich extracellular vesicles [89].

Recently, immunotherapy against programmed cell death protein 1 ligand (PD-L1) opened a new avenue for treating metastatic cancer. A recent study showed that YAP upregulates the PD-L1 expression in many solid tumors. In EGFR-TKI-resistant lung adenocarcinoma, YAP induces expression of PD-L1 at the transcription level and thus stimulates cell proliferation and migration [90]. TAZ activation is known to up-regulate PD-L1 expression through the GPR81 receptor in human lung cancer cells. Moreover, activation of GPR81 induces TAZ activation by inhibiting protein kinase A activity by decreasing intracellular cAMP levels [91]. These studies suggest an interplay between YAP/TAZ and programmed cell death protein 1 ligand in the regulation of cancer immunity.

Hippo pathway also plays an important role in regulating inflammation and T cell differentiation. Contact-dependent activation of the Hippo pathway by Cytotoxic T lymphocyte antigen 4 (CTLA-4) and CD80 ligand drives terminal differentiation of the CD8 T cells via regulating Blimp-1 expression through degradation of YAP in the CD8+ T cells [92]. Hippo pathway effector, TAZ, reciprocally regulates the differentiation of inflammatory Th17, subset of T helper cells and Treg cells, immunosuppressive regulatory T cell [93]. A recent study reported that YAP attenuates activated cytotoxic T cell (CD8 T cell) mediated anti-tumor immunity in the tumor microenvironment [94]. Therefore, future research will help to understand the role of YAP/TAZ and the Hippo pathway in cancer immunity and to identify new targets for cancer treatment.

Hippo pathway and cancer biology

The deregulation of the Hippo pathway results in an overgrowth of cells and organs, thus highlighting the significance of the Hippo pathway in cancer biology. Numerous studies have revealed the connection of YAP/TAZ/TEAD overexpression with cell proliferation, invasion and migration, metastasis, cancer stem cell characteristics, and drug resistance [95, 96].

An *In-vivo* study showed that knockdown of upstream Hippo regulators or overexpression of YAP in mouse liver leads to the abnormal growth of liver tissue and enlargement of the liver that subsequently developed into liver cancer [23, 65]. Another study reported that knockdown of MST1/2 or SAV1 increased cryptic hyperplasia and tumorigenesis by up-regulation of YAP [18]. Hippo-independent inactivation of YAP/TAZ is also observed

by the APC tumor suppressor, as evidenced by the deletion of APC results in activation of YAP/TAZ in colon cancer [97].

Hippo pathway effector YAP also promotes resistance of cancer cells with BRAF, KRAS, and NRAS mutations to anticancer drugs such as RAF and MEK inhibitors [98]. Overexpression of YAP/TAZ is detected in many solid tumors [3, 99–101] and positively associated with the poor survival rate of cancer patients [95]. Here, we describe the role of YAP/TAZ in the top five cancers according to Global cancer incidence in both sexes (Table 2).

Non-small cell lung cancer (NSCLC)

A deregulated Hippo pathway is observed in NSCLC. Overexpression of YAP/TAZ is associated with the development, progression, and poor prognosis of the disease. In NSCLC, YAP is frequently mutated which leads to the formation and progression of lung cancer [102]. Knockdown of YAP/TAZ is shown to decrease the tumor cell mass, migration, and metastasis of lung cancer cells [103]. Recently, a study reported that in NSCLC, YAP/TAZ and EZH2 act together to suppress tumor suppressor activity of TGFBR2 [104]. In their previous study, they also reported that many signaling molecules that induce YAP/TAZ nuclear translocation are increased and those are involved in cytoplasmic retention and degradation of YAP/TAZ are mostly suppressed in NSCLC. [105]. For example, several studies reported upregulation of oncogenic ABL1/2 kinases and downregulation of LATS1/2 in NSCLC [103, 105]. *In vitro* and *in vivo* experiments showed that expression of the MST1, upstream regulator of YAP/TAZ, inhibits the NSCLC growth [106]. During DNA damage response or other cellular stress, RASSF1A (Ras-association domain family 1 isoform A), an upstream regulator of the Hippo pathway, activates MST1/2 and LATS1 in NSCLC [107]. Other signaling pathway components, such as TGF-β and ERK1/2 can interplay with the Hippo pathway in NSCLC affecting the development and progression of lung cancer [108, 109].

Breast cancer

Deregulated Hippo pathway is also observed in breast cancer [110, 111]. The two effectors of the Hippo pathway, YAP/TAZ commonly overexpressed in breast cancer and could be used as therapeutic targets [112, 113]. YAP overexpression in mammary epithelia causes a defect in the terminal differentiation; whereas, loss of YAP suppresses the growth of oncogenic mammary tumors [114]. Recently it is reported that RING finger protein RNF181 regulates Hippo pathway and induces triple-negative breast cancer progression, as evidenced by the depletion of RNF181 that results in decreased level of YAP, suggesting the role of YAP in TNBC [110].

In highly invasive breast cancer, TAZ is overexpressed and induces migration, metastasis, and chemo-resistance of breast cancer cells. In a hypoxic microenvironment, TAZ interacts with hypoxic-inducing factor (HIF)-1α and stimulates bone metastasis in breast cancer [115, 116]. Overexpressed TAZ also reduces disease-free survival, overall survival, and increases the recurrence of cancer in breast cancer patients; while the loss of TAZ has opposite effects

[112, 117]. Moreover, in triple-negative breast cancer (TNBC), TAZ is highly overexpressed in both the cytoplasmic and nuclear compartments [118, 119]. Generally, the nuclear expression of TAZ was reported in triple-negative breast cancer (60.5%), basal-like subtype (70.8%), and metaplastic breast carcinomas (90%) [112].

Measurement of the YAP/TAZ expression has a predictive and prognostic value to assess the effectiveness of chemotherapy on triple-negative breast cancer [120]. For example, In paclitaxel-treated breast cancer cells, overexpression of TAZ, Cyr61, and CTGF- the Hippo pathway downstream targets, is a good indication of paclitaxel-resistant breast cancer cells [121]. Furthermore, downregulation of YAP/TAZ expression by siRNA or small molecule inhibitors increases the sensitivity of breast cancer cells to drug lapatinib in mice [122].

Colorectal cancer

Deregulation of the Hippo pathway is associated with the progression and metastasis of colorectal cancer (CRC) [123, 124]. Progression of CRC from colorectal adenomas is associated with suppression of the Hippo pathway and the increased expression of YAP, TAZ, TEAD, and OCT4 [125]. In CRC patients, expression of YAP and TAZ is highly associated with lymph node metastasis [126]. Higher expression of YAP and TAZ is also positively correlated with their downstream target genes AXL and CTGF in the CRC patients [127].

Recently it is reported that in human CRC, YAP drives epithelial-mesenchymal transition (EMT) by inducing *Slug* expression that subsequently inhibits E-cadherin expression [128]. In human CRC liver metastases, a higher expression of YAP is correlated with CRC relapse [123]. Also, in the familial adenomatous polyposis (FAP), activation of YAP is confirmed to be related to the development of Adenomatous polyposis coli-deficient adenomas [97]. In CRC patients, nuclear localization of YAP and positive expression of β-catenin are indicators of shorter overall survival and progression-free survival [126]. YAP/TAZ is also highly expressed in chemo-resistance liver metastasis in colon cancer. YAP inactivation increases the sensitivity to cetuximab monotherapy in colorectal patients and longer progression-free survival [129].

Prostate cancer

Both YAP and TAZ are believed to be involved in tumorigenesis and metastasis of prostate cancer [130, 131]. However, the exact contribution of each of these orthologues to prostate cancer progression is not clearly understood. Our analysis of the TCGA prostate cancer data set revealed that YAP1 expression is lower in high-grade prostate cancer [53]. Overexpressed TAZ is involved in EMT transition, cell migration, anchorage-independent growth, and metastasis in prostate cancer with a high Gleason score [132]. TAZ can regulate epigenetic changes by interacting with other transcription factors such as NURD that can recruit HDAC and reduce chromatin accessibility. This leads to the suppression of gene expression [133–135], which plays an important role in prostate cancer progression [136]. Our studies for over the last decade have shown an inverse relationship of PDEF with prostate cancer progression and a complete loss of PDEF in NEPC [137–140]. Moreover,

we demonstrated that PDEF expression suppresses genes associated with tumor progression and metastasis [139, 140] and that PDEF serves as a negative regulator of YAP1/TAZ transcriptional networks in prostate cancer is quite exciting [53].

Gastric cancer

Hippo pathway associates with the development, progression, and metastasis of gastric cancer as evidenced by the upregulation of YAP/TAZ/TEAD and the downregulation of MST1 and LATS1 in gastric cancer. All of these Hippo components are found to closely correlate with lymphatic metastasis and tumor TNM stage in gastric cancer [141]. YAP1 is also highly activated in dysplasia, gastric adenocarcinoma, and metastatic stomach disease [142], and is associated with the poor outcome of the early stages in gastric carcinoma.

Down-regulation of YAP1 expression correlates with the reduced cell proliferation, invasion, migration, and single layer colony formation in gastric cancer cell lines. Ectopic expression of YAP1 in MKN45 cells, which have low endogenous YAP1 expression, showed increased cell proliferation and colony formation [143]. In gastric adenocarcinoma cells, YAP1 activates the receptor tyrosine kinase AXL, and thus promotes the growth and metastasis of adenocarcinoma [144]. A recent study reported that YAP1 drives gastric adenocarcinoma peritoneal metastases, as evidenced by the attenuation of peritoneal carcinomatosis upon inhibition of YAP1, suggesting YAP1 could be a good target for treating gastric adenocarcinoma patients [145]

In gastric carcinoma, YAP1 also induces the expression of survivin, an inhibitor of apoptosis. Both YAP1 and Survivin markers together could help in the early diagnosis of gastric carcinoma [146]. YAP1 is used as a biomarker for the diagnosis and prediction of the disease progression in patients with gastric cancers. Increased expression of YAP1 positively correlated with progression, lymph node metastasis, and lower survival in gastric carcinoma [147]. TAZ is positively associated with the abnormal expression of β-catenin, a critical component of the Wnt pathway. Both are positive regulators of tumor development and progression in the adenocarcinoma of the esophagogastric junction (AEG) and could be potential therapeutic targets for the treatment of AEG [148].

Epigenetic regulation of Hippo pathway in cancer

Cancer development follows a multi-stage process in which epigenetic modifications play decisive roles. The connection between epigenetic hallmarks (DNA methylation and histone modifications, as well as non-coding RNAs) and the gene expression regulation is shown in most of the proteins involved in the cancer hallmarks (proliferation, apoptosis resistance, immune checkpoint bypassing, etc.). The Hippo signaling, as a well-defined functional pathway controlling cancer initiation and progression, is also a subject of the epigenetic machinery.

Our recent bioinformatics analysis revealed that the promoter of YAP/TAZ, as the final targets of the Hippo pathway in the nucleus, is highly enriched in binding sites for various transcription factors (TFs). Interestingly, most of these TFs were shown to be either the direct members of the epigenetic machine (e.g. P300 acts as a histone acetyl-transferase

(HAT) at YAP1 promoter) or act indirectly by recruiting chromatin remodelers of other DNA or histone-modifying components (e.g. CTCF that recruits HDAC and HAT enzymes at the TAZ promoter) in human cancer cells. In this *in-silico* study, a long list of more than 2000 different binding sites analyzed and confirmed to be mostly associated with active epigenetic components regulating the YAP/TAZ transcriptional activity as the functional outcomes of the Hippo pathway (unpublished data). On the other hand, YAP/TAZ affects the activity of their target genes through epigenetic modifications exerted by chromatin-remodeling complex proteins [149].

Other contributors of the Hippo pathway (from the ligand-receptor interaction to the TFs in the nucleus), show a tight regulation of these proteins by various epigenetic signatures that ultimately change the cancer phenotypes [150, 151]. Specifically, the DNA methylation-based regulation of RASSF1A, a Hippo pathway scaffold protein that enhances the tumor-suppressive function of YAP/p73, in multiple human cancer types is well known [152, 153]. RASSF1A has been frequently silenced epigenetically in cancer, leading to numerous phenotypic consequences including cancer cell migration and chemo-resistance [154]. The reactivation of the silenced RASSF1A using a combination of chemotherapeutic agents with decitabine, a demethylase compound, was shown to be beneficial in bladder cancer. This treatment restores the RASSF1A and Hippo pathway activity and suppresses the oncogenic activity of its downstream targets [155].

The WW-domain containing protein KIBRA, an upstream of the Hippo pathway, is deregulated in response to aberrant DNA methylation in various cancer cell lines. As reported by Hill et al., while the cell lines representing common epithelial cancers showed an un-methylated pattern for KIBRA, those representing acute lymphoblastic leukemia (ALL) undergo frequent silencing of KIBRA by DNA hypermethylation, suggesting a dynamic DNA methylation pattern governing Hippo signaling in various cancers [156]. A genome-wide CRISPR screen revealed that the transcriptional repressor protein Trichorhinophalangeal Syndrome 1 (TRPS1) serves as an epigenetic modulator of YAP activity in breast cancer. TRPS1 binds to a large set of enhancer regions and represses the transcriptional activity of its targets including YAP. This was shown to be associated with suppressed tumor-infiltrating immune cells in breast cancer [157].

Interestingly, the C4–2 cells, a human prostate carcinoma cell line, harbor a silenced MST1 kinase signaling. MST is epigenetically down-regulated in castration-resistant prostate carcinoma (CRPC) patients [158]. Cellular myelocytomatosis (c-MYC), a well-described tumor initiator, is highly expressed in prostate cancer. Mechanistically, the c-MYC regulates the enhancer of EZH2, a histone methyltransferase that catalyzes H3K27 trimethylation (H3K27me3) [159], and result in the MST1 promoter silencing via suppressing microRNA - miR-26a/b, which leads to increased survival in human prostate cancer cells [158].

A large effort has also been undertaken to dissect the impact of small non-coding RNAs in the Hippo signaling and their tumorigenic potentials. Using the microarray technology, Pinto et al. evaluated miRNA profiling in familial breast cancer and revealed 287 differentially expressed miRNA molecules that are associated mostly with MAPK and Hippo signaling pathways. Among these, miR-152 and miR-497 up-regulation showed an indirect interaction

with RASSF1A and NORE1A gene expressions [160]. In the esophageal squamous cell carcinoma (ESCC) cells, low promoter methylation of miR-373-3p correlated with ESCC development. A bioinformatics analysis detected LATS2 and OXRI genes as the main targets of this miRNA [161]. Besides, MicroRNA-135b targets Hippo signaling components, thereby accelerating lung cancer metastasis [162].

The role of long- noncoding RNAs (lncRNAs) via Hippo signaling was also verified in cancer development. Using an integrative Bioinformatics assessment, James et al. reported 1235 deregulated lncRNAs and proposed a strong correlation between their promoter methylation pattern with the TGF-β and Hippo signaling-related genes in certain subtypes of acute lymphoblastic leukemia (ALL) cells [163]. Furthermore, long intergenic non-coding RNA 673 (LINC00673) was shown to accelerate the proliferation of breast cancer cells via miR-515-5p/MARK4/Hippo signaling pathway [164].

Collectively, not only the role of epigenetic mechanisms in controlling various layers of the Hippo signaling pathway has been clearly defined, but also, it is considered as a potential therapeutic target for the cancers in which Hippo signaling plays a decisive role.

Hippo pathway regulation mediated by exosomes

Tumor-derived exosomes (TDEs) engage in the initiation and progression of tumors, and associate with different cancer hallmarks including the modulation of tumor immunity, promoting angiogenesis, invasion, metastasis, as well as drug-resistance [165] [166]. Numerous regulatory mechanisms are identified in the oncogenic generation of exosomes involved in tumor progression. By carrying different biological molecules including lipids, DNA, mRNA, miRNA, and lncRNA, exosomes can regulate different signaling pathways including the Hippo pathway in stromal and cancer cells [167] [168]. For instance, Moroishi et al. showed that the nucleic acid-rich extracellular vesicles from tumor cells depleted for LATS1/2 improves the immunogenicity by inducing the interferon response and Toll-like receptors-MYD88/TRIF pathway. Consistent with this, the anti-tumor response leads to tumor suppression by targeting LATS1/2 [169]. In addition, the miR-145 in exosomes generated by the ovarian cancer cells targets connective tissue growth factor (CTGF) as a downstream target of the Hippo pathway. Therefore, the down-regulation of miR-145 in ovarian cancer cells might accelerate further phenotypic development [170]. Interestingly, exosomes from stromal cells can regulate the Hippo pathway in tumor cells. For example, adipocyte exosomes could activate the Hippo pathway in MCF7 breast cancer cells to promote the malignant phenotypes including proliferation, migration, and resistance to apoptosis [171]. In contrast, tumor-derived exosomes can regulate stromal cells by modulating the Hippo pathway. In a recent study, Yoshida et al. showed that exosomal miR-7977 released by AML can regulate the Hippo-YAP signaling pathway in bone marrow mesenchymal stromal cells (BM-MSCs) and this might exert leukemia-favoring stromal phenotypes [172], [173]. Together these studies suggest that the components of exosomes mediate a path to regulate the Hippo pathway in supporting cancer cells in the tumor microenvironment. However, this topic warrants further investigation in addition to elucidation of the underlying mechanisms.

Hippo pathway as a therapeutic target

Considering the roles of the Hippo signaling pathway in diverse pathophysiological processes, targeting different components of this pathway could open a new window for cancer treatment. Core components of the Hippo pathway are kinases, thus different therapeutics might target these kinases, such as XMU-MP-1 an inhibitor of MST1/2 kinases [174]. Inhibitors of serine-threonine kinases, MST1/2 or LATS1/2 may up-regulate the transcriptional co-activator YAP/TAZ that facilitates tissue repair in regenerative medicine.

As most cancers have elevated YAP/TAZ expression, inhibitors of these two transcriptional activators may be used as cancer therapeutics. Recently, Wu et al. showed that peptide inhibitors that disrupt the interaction between TEAD and YAP/TAZ could be used as a potential therapeutic option for gastric cancer [175]. Hippo effector Yki/YAP promotes transcription by modifying chromatin through recruitment of the Trr/MLL H3K4 methyltransferase complex [176]. It is possible to develop Inhibitors against these downstream components of Yki/YAP as a therapeutic intervention.

In addition to targeting the downstream regulators of the Hippo pathway, activating upstream regulators may also be beneficial in cancer therapy. For example, Tankyrase inhibitors stabilize Hippo upstream regulator angiomotin family proteins (AMOT) and thus suppress Yap activity [177]. Statins inhibit the mevalonate cascade that is necessary for the activation of Rho GTPase and thereby suppress YAP/TAZ activity [84]. Simvastatin negatively modulates transcription of the receptor for hyaluronan-mediated motility (RHAMM), a downstream effector of the mevalonate pathway, by regulating YAP phosphorylation and cytoplasmic localization and subseconsequently inhibit breast cancer cell migration and invasion [84, 178]. Moreover, rolipram and ibudilast inhibit the phosphodiesterase, thus activate cAMP-dependent protein kinase A signaling that ultimately suppresses Yap activity [179]. It is also reported that metformin activates Hippo upstream regulator AMPK [180]. Activated AMPK then phosphorylates and inactivates YAP. Recently Slemmons et al reported that YAP is highly expressed in Rhabdosarcoma. DNA methyltransferase inhibitor (DNMTi) can be used to activates Hippo pathway upstream regulators RASSF1 and RASSF5 by demethylating their promoter sequence that lead to the activation of Hippo pathway and reduction of tumor growth [181]. Very recently, another study reported that inhibition of the YAP/TAZ/YEAD complex by Verteporfin may prevent Ewing sarcoma cell migration and metastasis [182]. These reports highlight the importance of having better insights into the regulation of the Hippo pathway to open the new therapeutic window that will maximize the effects of anticancer agents and minimize unwanted side effects.

Summary and future directions:

Hippo pathway is one of the most conserved pathways among the different species from Protista to eukaryotes and plays an important role in the regulation of cell growth/proliferation, cellular homeostasis, and by extension in cancer. Different intracellular and extracellular signaling events regulate the Hippo pathway. Much information regarding the mechanism of regulation of the Hippo signaling pathway and the deregulation of this pathway in cancers remains to be fully elucidated. In mammalian systems, Hippo signaling

regulates YAP and TAZ transcriptional networks. We discovered that PDEF, a tumor metastasis suppressor, positively regulates Hippo signaling as evidenced by downregulation of YAP1/TAZ transcriptional output. These findings could open a new window for prostate cancer therapy, but the molecular mechanisms are far from understood. Insights learned from the Hippo pathway will likely pave the way toward better therapeutic targets for many human cancers. Targeting the YAP/TAZ transcriptional network with small molecule inhibitors might bring much needed promising advances in overcoming cancer therapeutic resistance.

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Highlights:

- Hippo pathway is a master regulator of development, cell proliferation, stem cell function, tissue regeneration, homeostasis, and organ size.
- Deregulation of the Hippo pathway is associated with numerous cancers.
- Alteration of the Hippo pathway results in cell invasion, migration, disease progression, and therapy resistance in cancers.
- Ttargeting Hippo pathway offers a new paradigm in therapeutic intervention in cancer.

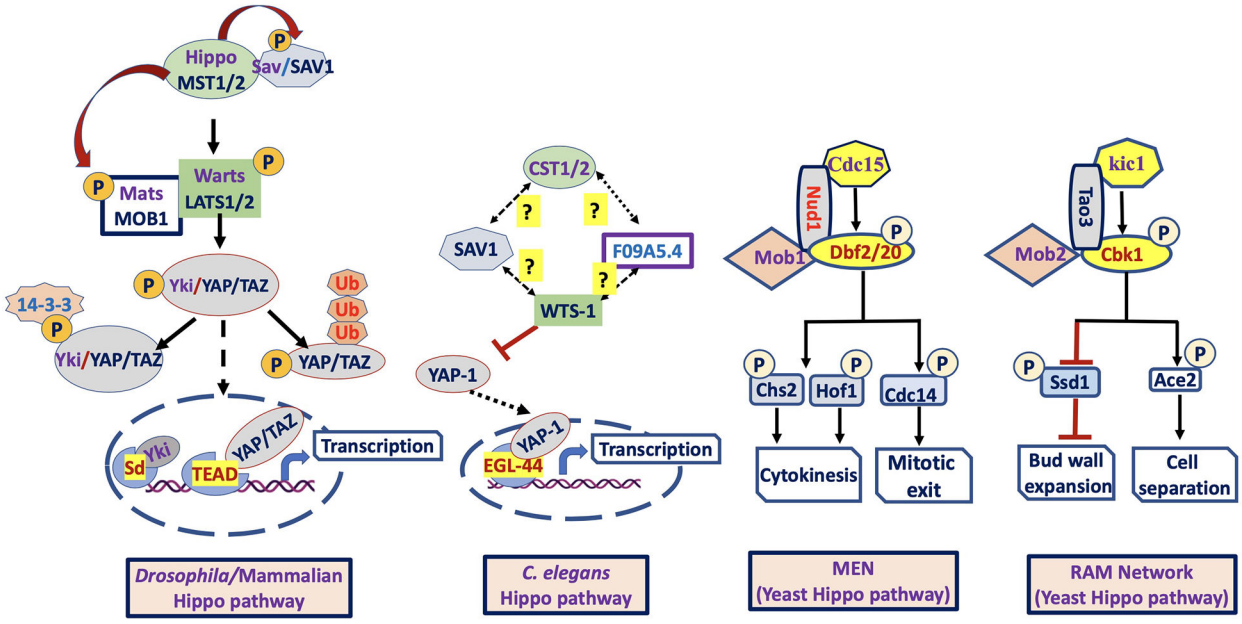

Figure 1: Components of the Hippo pathway in Drosophila/Mammals, *C. elegans* and Yeast (*S. cerevisiae*):

In *Drosophila*/Mammals (left figure), together with Sav/SAV1 and Mats/MOB1, the Hippo/MST1/2 (kinase) phosphorylates and activates Warts/LATS1/2 (kinase) that in turn phosphorylates and inactivates Yki/YAP/TAZ (downstream effector). Inactivation of hippo pathway results in Yki/YAP/TAZ nuclear translocation and interaction with Sd/TEAD or other transcription factors to induce target gene expression. In *C. elegans* (middle figure), the role of upstream regulator CST1/2 (Hippo homolog) on the activation of F09A5.4 (Putative Mats homolog), SAV1 (Salvador homolog) and WTS-1 (Warts homolog) is unknown. However, the WTS-1_YAP-1_EGL-44 axis is conserved, supported by the same role as Warts_Yorkie_Scalloped or LATS_YAP_TEAD axis of Hippo pathway. In Yeast (*S. cerevisiae*), mitotic exit network (MEN) is similar to canonical LATS pathway (Salvador/warts/Hippo system), whereas RAM network is similar to non-canonical NDR pathway (furry/tricomered/Hippo system). The core components of MEN include, Cdc15 (MST/Hippo -related kinase domain), and the protein kinases Dbf2 and Dbf20 (Paralogous protein LATS-family kinases) and Mob1 (co-activator). The core components of RAM network include Kic1 (MST/Hippo related protein kinase), Cbk1 (Ndr/LATS family-related protein kinase), Tao3 (scaffold protein), Mob2, and Hym1 (activator), Ace2 and Ssd1 (downstream effectors).

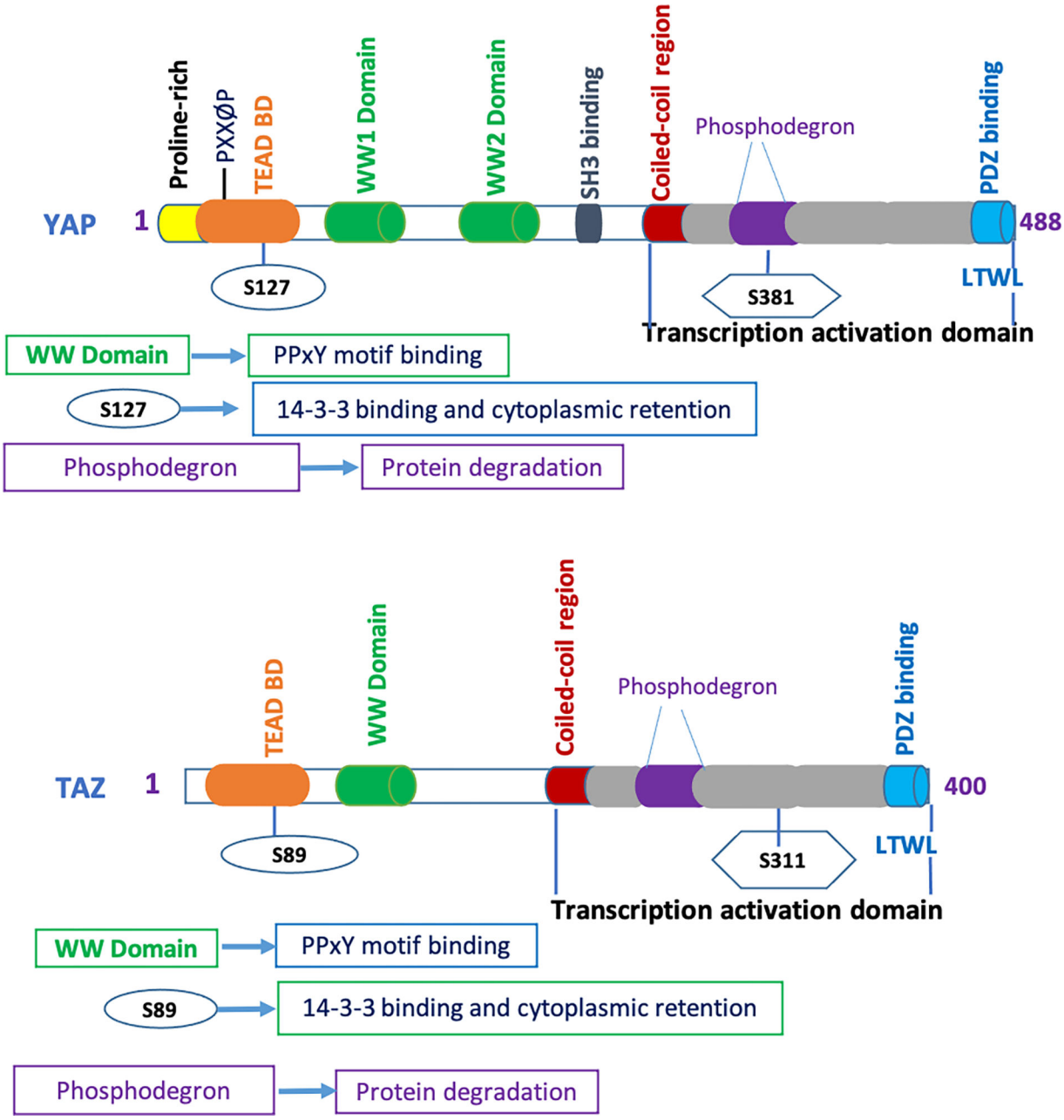

Figure 2: Regulatory domains of YAP/TAZ (Hippo pathway effector proteins):
Domains of YAP effector include the Proline-rich domain (P-rich), TEAD binding domain (TEAD BD), two WW domain, SH3-binding domain, coiled-coil domain (CC), transcriptional activation domain (TAD) and PDZ-binding motif. TAZ has TEAD binding domain (TEAD BD), one WW domain, coiled-coil domain (CC), transcriptional activation domain (TAD), and PDZ-binding motif.

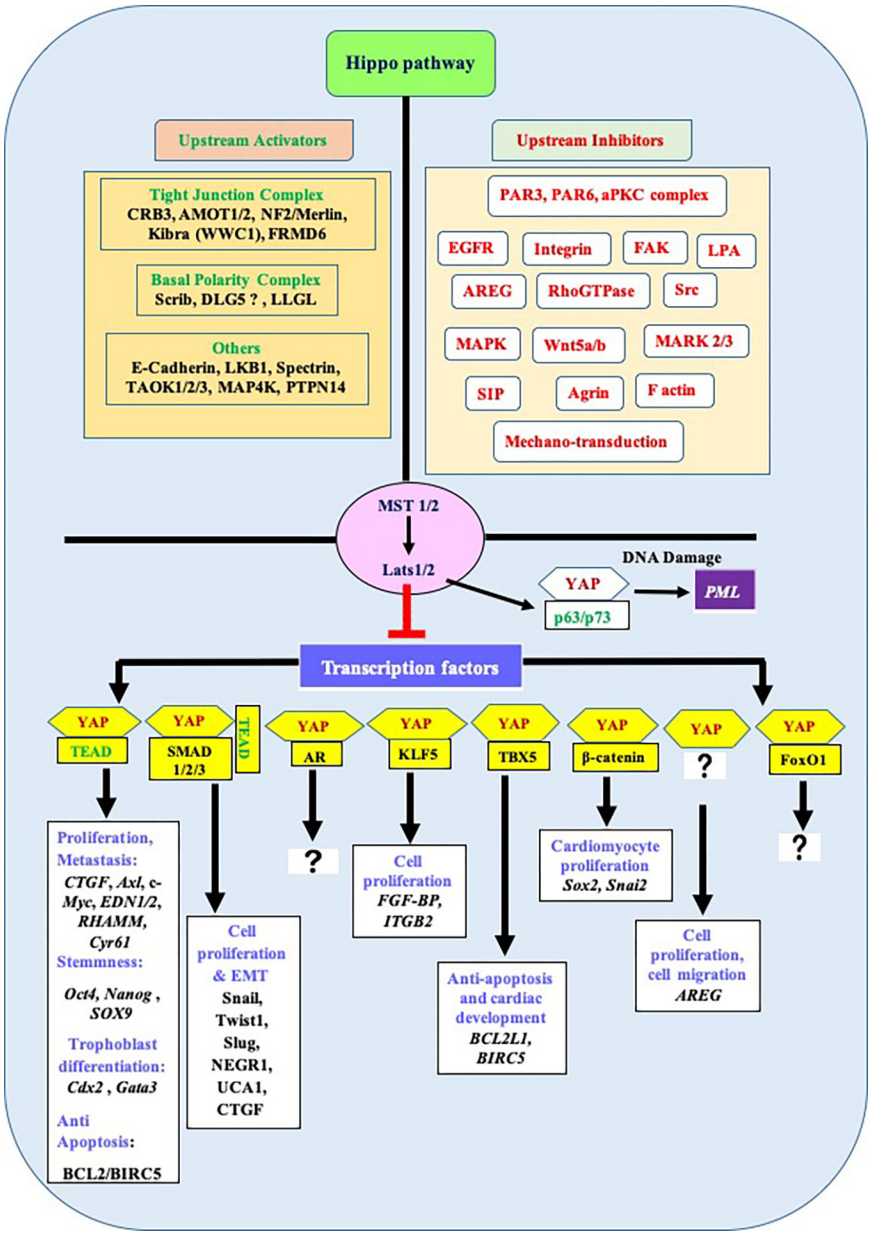

Figure 3: Regulators and downstream targets of the Hippo pathway:

The figure shows upstream activators and inhibitors of the Mammalian Hippo pathway, their binding partners and downstream target genes. Apical polarity complex (Crumbs complex) and basal polarity complex (Scribble complex) as well as cell adhesion molecules such as E-cadherin and signaling molecules positively regulate Hippo pathway (Left side of the figure), whereas, PAR complex and various signaling molecules negatively regulate Hippo pathway (Right side of the figure). These upstream regulators regulate nuclear translocation and binding of YAP/TAZ with different transcription factors that induce expression of genes involved in cell proliferation and migration, stemness, differentiation, apoptosis, DNA damages response etc.

Table 1:

Core components of the Hippo pathway are conserved in various organisms

Hippo pathway components in different species				
Drosophila	**Mammals**	***S. cerevisiae***		***C. elegans***
		MEN network	**RAN network**	
Hippo	MST1/2	Cdc15	Kic1	CST1/2
Sav	SAV1	Nud1	Tao3 (not well defined)	SAV-1
Mob	MOB1A/B	Mob1	Mob2	F09A5.4
Warts	LATS1/2	Dbf2/20	Cbk1	WTS-1
Yorkie	YAP/TAZ	?	?	YAP-1
Scalloped	TEAD	?	?	EGL-44

*Same row-wise components represent functional similarity

Table 2:

Deregulation of YAP/TAZ in top 5 cancers

Cancers	Hippo pathway components	References
NSCLC	⬆Yap/Taz ⬇Lats1/2	[103, 105]
Breast Cancer	⬆Yap/Taz	[112, 113, 118, 119, 132]
Colorectal Cancer	⬆Yap/Taz, ⬆TEAD	[123, 125, 127]
Prostate Cancer	⬆Yap/Taz	[132, 183]
Gastric Cancer	⬆Yap/Taz, ⬆TEAD ⬇MST,⬇Lats	[141, 142, 147]