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Review Article

Hippo-YAP signaling in digestive system tumors

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Abstract: The Hippo pathway is an evolutionally conserved pathway and plays an important role in regulating tissue hemostasis and organ size control. Deregulation of the Hippo pathway is implicated in various human digestive system tumors. The past two decades have witnessed the discovery and elucidation of key signaling components and molecular mechanisms of the Hippo pathway. Among these, the signaling transducers YAP/TAZ are in the center of this complex network to sense and respond to extracellular cues such as cell contact, matrix stiffness and growth factors. In this review, we summarize the biological and clinical significance of Hippo-YAP signaling in the digestive system tumors, and explore the novel therapeutic strategies for targeting Hippo-YAP signaling.

Keywords: Hippo pathway, YAP, esophagus, stomach, colon, pancreas, liver, tumorigenesis

Introduction

Originally discovered through *Drosophila* genetic screen for molecules regulating organ size, the Hippo-YAP pathway has emerged as an evolutionally conserved signaling pathway to regulate various biological functions including tissue homeostasis, regeneration and tumorigenesis [1, 2]. The first Hippo pathway gene identified was the NDR family protein kinase Warts (homologous to mammalian gene Large tumor suppressor kinase 1/2 [Lats1/2]) [3, 4]. Inactivation of Warts gene leads to dramatic tissue overgrowth in *Drosophila*. Subsequently, additional Hippo pathway components, including Salvador (homologous to mammalian gene Sav1, also known as WW45) [5, 6], Ste20-like protein kinase Hippo (homologous to mammalian gene MST1/2) [7-11], and Mats (homologous to mammalian gene Mob1) [12], were identified through similar genetic approaches. The identification of Yki (homologous to mammalian gene Yes-Associated Protein [YAP] and Transcriptional Co-activator with PDZ-binding Motif [TAZ]), published in a seminal article in 2005 [13], completed the missing link in the Hippo signaling kinase cascade. In mammals, the classical pathway proceeds as follows: Mst1/2 kinase binds its cofactor Sav1 (also known as WW domain containing adaptor 45, or WW45), and this complex phosphorylates and activates Lats1/2 kinase. Lats1/2 kinase then binds its cofactor Mob1, which phosphorylates and inactivates transcription coactivators YAP and TAZ. In the setting of signaling deregulation, YAP is dephosphorylated and translocate to nucleus. In conjunction with its transcription factor TEA domain family members (TEAD 1-4) [14-16], nuclear YAP functions as a potent transcription coactivator to promote target gene transcription (**Figure 1**). Besides transcription factor TEAD, the nuclear events for Hippo-YAP signaling also involve Vestigial-like family transcriptional coactivator VGLL 1-4. In the Hippo pathway, VGLL could compete with YAP/TAZ for TEAD binding [17]. The dramatic tissue overgrowth phonotype observed in Hippo pathway inactivation in *Drosophila* has been attributed to the ability of activated YAP to induce transcription of genes that promote cell growth and proliferation, as well as inhibition of apoptosis [7].

Multiple membrane-associated cytoskeletal proteins, including Merlin (homologous to mammalian gene NF2) and Expanded [18], Kibra

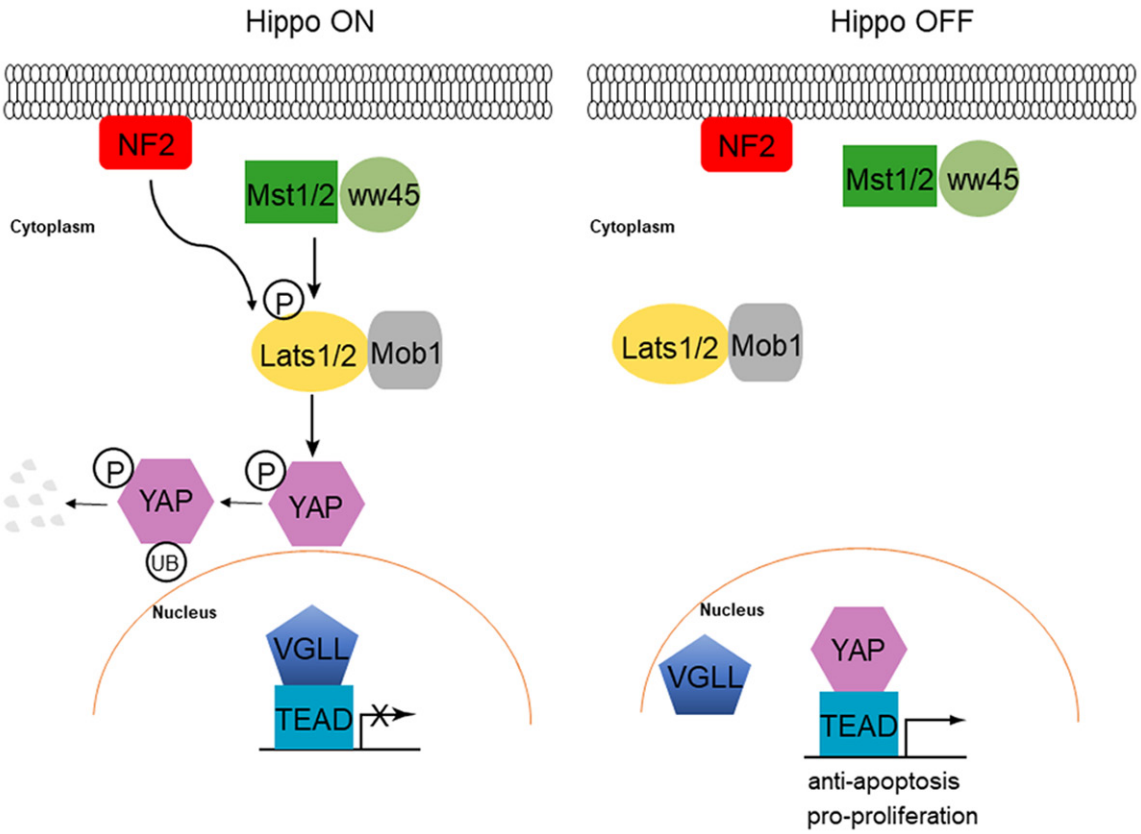

Figure 1. Schematic of Hippo-YAP signaling. When Hippo signaling is on, NF2 recruits Lats1/2 kinase to the membrane. Mst1/2 kinase will then phosphorylate Lats1/2 kinase, which leads to phosphorylation, cytoplasmic retention, and subsequent ubiquitination and degradation of YAP. When Hippo signaling is off, YAP translocates to the nucleus and competes with VGLL for TEAD binding to regulate target gene expression with resultant anti-apoptosis and pro-proliferation effects.

[19-21], and Fat [22-25], have been identified as upstream components and regulators of Hippo-YAP signaling pathway. These upstream components provide important clues to answering the ultimate question: how is Hippo-YAP signaling regulated by environmental cues for tumor initiation, progression and metastasis?

The first clue for this question comes from cell-cell contact inhibition, a well-known phenomenon in which cells cease proliferation once they contact another cell [26]. It is a common belief that cancer cells have the ability to escape from this barrier to achieve uncontrolled growth [27]. Phosphorylation and inactivation of YAP through the Hippo pathway plays an important role to control cell growth and proliferation upon cell contact [28]. At low cell density, YAP is active and predominantly localized in the nuclei to promote target gene transcription. High cell density, on the other hand, leads to Hippo pathway-dependent YAP phosphorylation and cytoplasmic translocation for its deactivation [28]. The interaction between YAP and alpha-catenin, a critical cell-cell junction component and cell density sensor in the skin, has been demonstrated in this process to control epidermal stem cell proliferation and tumorigenesis [29]. Cell density and NF2 could also control transcription factor TEAD activity through regulation of its palmitoylation status [30].

The Hippo-YAP signaling also plays an important role in matrix stiffening-associated mechanotransduction. Frequently, tumors are stiffer than the surrounding benign tissue, largely due to increased fibrosis, interstitial pressure and angiogenic blood flow shear stress [31, 32]. Mechanotransduction is the concept that the cancer and stromal cells can sense matrix stiffening and transduce this mechanical force to promote tumorigenic biochemical pathways for cell cycle progression, epithelial-mesenchymal transition, cell motility and metastasis. YAP is

essential for tissue tension and morphogenesis during development [33]. Activation of the YAP is also a signature feature of cancer-associated fibroblasts (CAFs), and YAP-dependent matrix remodeling is required for CAFs to promote cancer cell invasion and angiogenesis [34].

In the past decade, the combined efforts of genetics and biochemistry have furthered our understanding of this important signaling pathway. With the advances in sequencing technology, it has become evident that the Hippo-YAP signaling pathway is frequently deregulated in different human cancers. In this review, we will focus on its role in gastrointestinal, pancreatic and hepatic tumorigenesis.

Hippo-YAP signaling in esophageal cancer

Esophageal cancer is the seventh most common cancer worldwide. It is also the sixth most common cause for cancer-associated death [35]. Esophageal squamous cell carcinoma is the most prevalent esophageal cancer worldwide, with a high incidence in developing countries. In the United States, even with decreasing incidence of esophageal squamous cell carcinoma, the prevalence, incidence and associated mortality of esophageal cancer (adenocarcinoma) have been increasing over the past several decades, largely due to the pandemic of obesity and associated acid reflux [36].

Frequent inactivating mutations of the Hippo-YAP signaling, including mutations in AJUBA, FAT1-4, STK3, LATS1 and YAP, have been identified and validated in roughly half of the esophageal squamous cell carcinoma cases [37, 38], supporting the critical role of the Hippo-YAP signaling in the tumorigenesis of esophageal squamous cell carcinoma. The Cancer Genome Atlas (TCGA) Research Network detected higher rates of YAP (11q22.1) amplification and deletion of VGLL4, a negative regulator of Hippo-YAP signaling, in esophageal squamous cell carcinoma [39]. This study also demonstrated the strong resemblance of esophageal adenocarcinoma with the chromosomally unstable variant of gastric adenocarcinoma [39].

Unlike esophageal squamous cell carcinoma, the involvement of the Hippo-YAP pathway in the development of esophageal adenocarcinoma is less clear. One study reported increased cytoplasmic and nuclear YAP expression in esophageal high-grade dysplasia and adenocarcinoma [40]. Preliminary data from our investigations also suggests that Hippo signaling effector YAP plays critical roles in the progression of neoplasia associated with Barrett's esophagus (BE), a precursor lesion of esophageal adenocarcinoma that is more commonly seen in patients with longstanding gastroesophageal reflux disease. YAP expression is absent on the surface of benign esophageal columnar epithelium (**Figure 2A**), and is only weakly expressed in the deep crypts of benign esophageal mucus glands and non-dysplastic BE glands. In contrast, BE with high-grade dysplasia (**Figure 2B**) and esophageal adenocarcinoma show significantly increased YAP expression (**Figure 2C**). These data support a potential role of Hippo-YAP signaling in the tumorigenesis of esophageal adenocarcinoma.

Hippo-YAP signaling in gastric cancer

Gastric cancer is the fifth most common cancer and the fourth most common cause of cancer-associated death worldwide [35]. With adenocarcinoma being the most common cancer type, gastric cancer has a clear relationship with long-standing chronic inflammation [41]. The common environmental factors include infectious agents such as *Helicobacter pylori* (HP) and Epstein-Barr virus (EBV), tobacco use, and dietary factors. HP eradication could reduce the risk of gastric adenocarcinoma [42]. Based on TCGA database, Hippo-YAP pathway is positively associated with HP infection [43]. Infection with cytotoxin-associated gene A (CagA) positive HP is the strongest risk factor for the development of gastric adenocarcinoma [44, 45]. CagA+ HP infection significantly increased YAP expression in gastric epithelial cells, as compared with CagA- HP strain. Furthermore, CagA promotes epithelial mesenchymal transition in gastric carcinogenesis through Hippo-YAP pathway [46].

Multiple studies also confirm that the expression of YAP is significantly increased in gastric adenocarcinoma [47-49] (**Figure 2D**), with higher levels of cytoplasmic YAP in the early tumor stages and higher levels of nuclear YAP in the advanced tumor stages. Nuclear YAP accumulation is associated with poor survival, especially in patients with early-stage gastric cancer

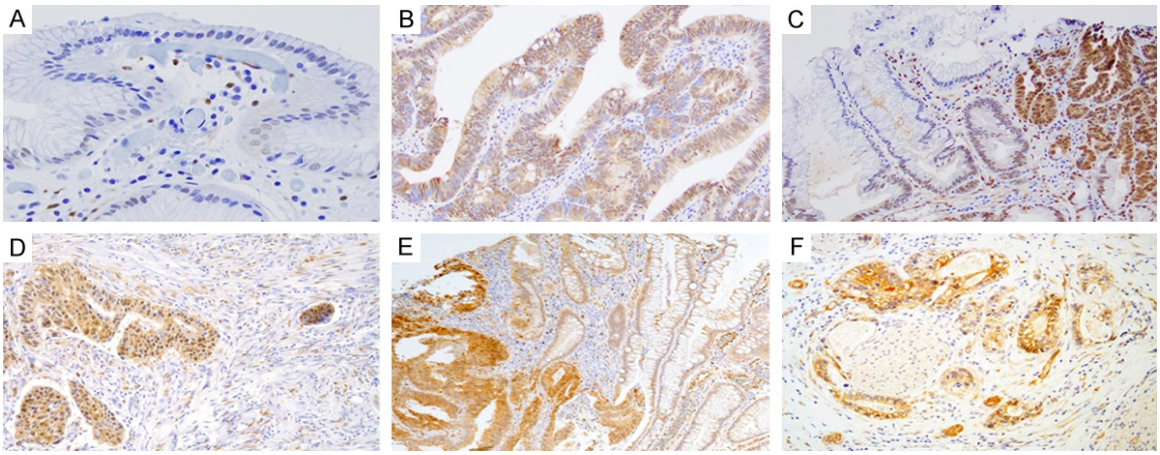

Figure 2. YAP expression in various digestive system tumors. (A-C) YAP expression in Barrett's esophagus and esophageal adenocarcinoma. A. Negative YAP expression in benign esophageal columnar epithelium (×200); B. YAP expression in Barrett's esophagus with high-grade dysplasia, note the increased YAP expression extending to surface epithelium (×200); C. YAP expression in esophageal adenocarcinoma, note the sharp transition between non-dysplastic mucosa and carcinoma (×200); D. YAP expression in gastric adenocarcinoma (×100); E. YAP expression in colorectal adenocarcinoma (×100); F. YAP expression in pancreatic ductal adenocarcinoma (×100).

[50]. YAP mediates peritoneal carcinomatosis in advanced gastric adenocarcinoma patients [51]. Oncoprotein Myc has been identified as a key downstream target of YAP to initiate gastric tumorigenesis [52]. Up-regulation of YAP significantly correlates with HP infection status and gastric cancer progression including tumor size and tumor stage. On the contrary, the transcription levels of VGLL4, a negative regulator of Hippo signaling, were downregulated in 61% of gastric cancer samples, with inverse correlation with gastric cancer progression (tumor size, tumor stage and lymph node metastasis) [53]. The YAP/VGLL4 ratio has the potential to serve as a biomarker for gastric cancer.

In a study of 86 patients with advanced gastric cancer who received first-line chemotherapy, a significant association between nuclear TAZ expression and Wnt mutations was noted. The patients with tumors harboring a signature of combined nuclear TAZ expression and Wnt mutations had significantly increased risk of disease progression and poor overall survival [54]. Interestingly, the patients with tumors harboring a different signature (combined YAP expression and *TP53* mutations) had favorable survival outcomes that is linked to the administration of first-line chemotherapy [55].

Hippo-YAP signaling in colorectal cancer

Colorectal cancer is the third most common cancer and the second leading cause of cancer death in the United States [35]. Colorectal cancers can be divided into 3 major categories based on their unique molecular signatures: chromosomal instability pathway (84%) involving molecular alterations of APC, TP53, KRAS, SMAD and PIK3CA; microsatellite instability (MSI) hypermutant pathway (13%) involving the mismatch repair genes MLH1 and MSH2; ultramutant pathway (3%) involving POLE gene [56].

Adenomatous polyposis coli (APC) alterations are the most common molecular events for the colorectal cancer, mostly through conventional adenoma-carcinoma sequence [57]. APC is one of the key players in the Wnt pathway, a critical signaling pathway in regulating intestinal stem cell proliferation, differentiation and cell-fate decisions. Loss-of-function APC gene mutations lead to activation of Wnt pathway through accumulation of nuclear β-catenin. The cross-talk between Hippo and Wnt pathway plays important roles during intestinal regeneration, homeostasis and tumorigenesis [58]. The interactions of these two important pathways appear complex, multi-layered, and context-dependent. In the nucleus, a β-catenin YAP complex is essential to the transformation and survival of β-catenin-dependent colon cancers [59]. However, in the cytoplasm, YAP/TAZ can function as negative regulators of Wnt/β-catenin signaling [60-62]. On the other hand, Wnt-APC pathway negatively regulates YAP function through β-catenin destruction com-

plex [61]. Additionally, APC can function as a scaffold protein to promote Hippo signaling and to restrict YAP activity [63]. Upon APC deficiency, YAP/TAZ and β-catenin are required for intestinal crypt overgrowth and adenoma formation [61, 63].

In the normal colon tissue, YAP is predominantly expressed in the basal crypt zones where the intestinal progenitor cells are located. YAP is critical for intestinal regeneration and tumorigenesis [64, 65]. Colonic adenocarcinoma tissues have significantly elevated YAP protein expression in both the cytoplasm and nucleus [66] (**Figure 2E**). Elevated protein expression levels of YAP and TAZ are independent predictors of poor prognosis and are positively correlated with tumor stage, nodal status, and metastasis [66-69]. Elevated YAP protein expression, together with high plasma carcinoembryonic antigen (CEA) level, are potential prognostic biomarkers in patients with early-stage colorectal cancer [68]. Consistently, positive expression of VGLL4, combined with low YAP expression, is an independent good prognostic factor in colorectal cancers [70].

Although YAP has well been accepted as a potent oncoprotein, dual roles of YAP in colorectal cancer have been proposed, and there are multiple lines of evidence that YAP may also function as tumor suppressor, presumably in a context-dependent manner [71]. One example is its negative regulation of Wnt signaling. During intestinal regeneration, loss of YAP causes Wnt pathway hyperactivation, resulting in intestinal stem cell expansion, as well as ectopic crypt and microadenoma formation [62]. Alternatively, YAP is able to induce DNA damage-associated apoptosis through p73 transcription factor [72-74]. Complete loss of YAP expression was correlated with aggressive clinical behaviors, including larger tumor size, higher tumor stage, and worse overall survival, and therefore represented an aggressive subtype of colorectal cancer [75]. The proposed tumor suppressor function of YAP might also play an important role in chronic colitis-associated colorectal cancer (CAC). In a recent study, our group has identified a subgroup of CAC with double negative expression of YAP and CDX2 that is more frequently seen in younger patients (mean age of 45.3 years) with higher pathological tumor stage and nodal metastasis [76].

Hippo-YAP signaling in pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC), the most common form of pancreatic cancer, is one of the most aggressive cancers and ranks the seventh of all cancer-associated death [35]. Through next-generation sequencing, recurrent molecular alterations have been found in PDAC, with the oncogenic mutations of KRAS and loss-of-function mutation/deletion of tumor suppressor genes TP53, SMAD4 and CDKN2A (P16) being the most common [77]. Oncogenic mutations of KRAS are present in the majority of human PDAC cases, and targeting KRAS pharmacologically has a great clinical potential for the treatment of pancreatic cancer. Two elegant studies have independently identified YAP as a central driver to compensate for the loss of KRAS signaling and to sustain tumor maintenance in an advanced PDAC mouse model [78, 79]. In a KRAS-mutant mouse model, YAP is also required for pancreatitis-induced acinar-to-ductal metaplasia, a precursor of pancreatic intraepithelial neoplasia that can progress to PDAC [80].

YAP is highly expressed in PDAC [79, 81-83] (**Figure 2F**). In fact, YAP is the top upregulated protein in PDAC samples on mass spectrometry-based proteomics [84]. Expression level of YAP is an independent predictor of poor overall survival (OS), disease-free survival (DFS) and liver metastasis [83-85], partially through its ability to promote transcription of target genes involved in the remodeling of pancreatic tumor microenvironment. YAP can also modulate the tumor immune microenvironment in PDAC by promoting the expression of cytokines/chemokines that recruit and differentiate myeloid-derived suppressor cells [86]. Therefore, YAP/TAZ is at the center of a signaling network that is crucial for the development and progression of PDAC [87].

Hippo-YAP signaling in liver cancer

Liver cancer is the sixth most common cancer and the third leading cause of cancer-related death worldwide [35]. Hepatocellular carcinoma (HCC) is the most common primary liver cancer, and its major risk factors include viral infection (hepatitis B or C virus), alcohol abuse, obesity and iron overload, among others [88]. Due to its high degree of heterogeneity, HCC

remains a challenge for actionable molecular subtyping.

During the past decade, Hippo-YAP signaling has emerged as a key pathway for the normal liver homeostasis maintenance, as well as the initiation and progression of liver cancer. In mouse model, liver-specific deletion of Hippo pathway tumor suppressor components NF2 [89], Mst1/2 [90-92], Sav1 [92, 93], Mob1 [94] and Lats1/2 [95], or conditional overexpression of YAP in the liver [96] all leads to hepatomegaly and liver cancer formation. The liver tumors developed in these mouse model include hepatic adenoma, HCC and intrahepatic cholangiocarcinoma (iCC). Interesting, heterozygosity of YAP is sufficient to suppress hepatomegaly and HCC formation in those mouse models, supporting YAP/TAZ as potential therapeutic targets for HCC. Besides its function to regulate cellular proliferation and organ size, Hippo-YAP signaling also plays a critical role by influencing cell fates in the liver. YAP could induce a ductal fate in hepatocytes by dedifferentiating hepatocytes into progenitor cells [97]. These findings lay the groundwork for regenerative medicine of liver disease and liver cancer through the manipulation of Hippo-YAP signaling.

The role of Hippo-YAP signaling in liver tumorigenesis is quite complex, even with multiple lines of evidence demonstrating the potent oncogenic activity of YAP/TAZ. In a recent Science article, Moya et al. have revealed an unexpected non-autonomous tumor suppressor function of YAP/TAZ in liver cancer [98]. Overexpression of YAP in peritumoral hepatocytes triggered regression of primary liver tumors and melanoma-derived liver metastases, and deletion of YAP/TAZ in peritumoral hepatocytes accelerated liver tumor growth. These interesting findings support a “cell competition” theory originally proposed in a *Drosophila* study [99], that during interaction between tumor cells and their surrounding tissue, the cell with low YAP/TAZ level will become the “loser” and be eliminated through cell-cell competition by the “winner”, the cell with high YAP/TAZ level.

In human HCC, YAP overexpression is significantly associated with poor tumor differentiation and high serum alpha-fetoprotein (AFP) level and is an independent predictor for HCC-specific OS and DFS [100, 101]. The serum level of Amphiregulin, a member of the epidermal growth factor family and one of the direct target genes of YAP/TAZ, is frequently elevated in HCC patients and may be used as a serological biomarker of HCC [100]. Besides Amphiregulin, it is now evident that YAP overexpression can induce the expression and secretion of many paracrine-acting factors including plasminogen activator inhibitor-1 (PAI-1), C-X-C motif chemokine ligand 13 (CXCL13), CXCL16 during liver tumorigenesis. Amphiregulin and PAI-1 may play unique roles in liver tumorigenesis and therefore could serve as novel targets in HCC therapy [102-105]. Sohn et al. further extended these findings and identified a unique subgroup of HCC with silence of Hippo (SOH) signature. The SOH subgroup consists approximately 21% in the National Cancer Institute cohort, has a significantly poorer prognosis than non-SOH HCC patients. The SOH signature was an independent predictor of DFS on multivariate analysis [106].

YAP/TAZ has also played a critical role for epithelioid hemangioendothelioma (EHE), a rare form of primary liver sarcoma. The chromosomal translocations involving 1p36.3 and 3q25, with formation of TAZ (WWTR1) - CAMTA1 (calmodulin-binding transcription activator 1) gene fusion, has been identified in about 90% of EHE cases [107, 108]. The remaining 10% of EHE cases harbor YAP-TFE3 gene fusion [109]. CAMTA1 nuclear expression by immunohistochemistry has been proven to be highly sensitive and specific for the diagnosis of hepatic EHE, and could be used to differentiate hepatic EHE from its close mimic angiosarcoma [110]. In two recent studies, TAZ-CAMTA1 gene fusion is sufficient to drive EHE tumorigenesis by dysregulating YAP/TAZ signaling in a mouse model [111, 112].

Therapeutic perspective

Given its important role in tumorigenesis, targeting Hippo-YAP signaling is a novel and attractive approach for cancer therapy. As the signaling transducer and nexus of Hippo pathway, YAP/TAZ has been in the center for such development. Few experimental prototype molecules have been discovered due to their ability to suppress YAP/TAZ activity. Verteporfin, the first photosensitizer approved for the treatment of age-related macular degeneration, was identi-

fied as a potent inhibitor of the physical interaction between YAP with transcription factor TEAD. In a mouse model, Verteporfin significantly suppressed YAP-induced hepatomegaly [113]. Song et al. identified CA3 through a small molecular screen that could potently inhibit YAP/TEAD transcriptional activity. CA3 inhibits esophageal adenocarcinoma cell growth both *in vitro* and *in vivo* [114]. Jiao et al. designed a VGLL4-mimicking peptide that could suppress gastric cancer growth through competing with YAP for TEAD interaction [53]. Drugs targeting the cellular receptors including G-protein-coupled receptor (GPCR) [115, 116], epidermal growth factor receptor (EGFR) [117, 118] and vascular endothelial growth factor receptor (VEGFR) [119, 120] could also inhibit YAP/TAZ activity through an indirect manner.

Moroishi et al. revealed an unexpected function of Hippo pathway in modulating tumor immunogenicity. In tumor cells, deletion of LATS1/2 leads to enhanced tumor-specific humoral and cellular immune responses, resulting in immune-mediated tumor cell elimination. Deletion of LATS1/2 also enhances tumor vaccine efficacy through adaptive immunity. These interesting findings raise the possibility of targeting LATS1/2 kinase in cancer immunotherapy [121]. Meanwhile, pharmacological targeting of MST1/2 kinase has resulted in the discovery of XMU-MP-1, a potent and selective inhibitor of MST1/2 kinase. XMU-MP-1 has demonstrated its *in vivo* efficacy to promotes liver and intestinal regeneration and to attenuate acetaminophen-induced liver injury [122]. Searching for potent and specific small molecule kinase inhibitor targeting Mst1/2 and Lats1/2 kinases is therefore of great clinical relevance.

Conclusions

As an evolutionally conserved pathway, Hippo-YAP signaling has played an important role in regulating cell proliferation, apoptosis and differentiation from *Drosophila* to human. Hippo-YAP signaling has been shown to extensively involve in intestinal stem cell reprogramming, intestinal and liver regeneration, and digestive system tumorigenesis. YAP/TAZ may function either as oncogene or tumor suppressor depending on the cellular context. Current studies have begun to reveal its complex multifaceted nature, as well as its complicated interplay with other conserved signaling pathways, such as the Wnt/β-catenin/APC pathway. It is of great clinical interest to develop pharmacological molecules targeting Hippo-YAP signaling for personalized medicine on digestive system tumors.

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Disclosure of conflict of interest

None.

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