



## Emerging role of Hippo pathway in gastric and other gastrointestinal cancers

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### Abstract

More evidence has underscored the importance of Hippo signaling pathway in gastrointestinal tissue homeostasis, whereas its deregulation induces tumorigenesis. Yes-associated protein 1 (YAP1) and its close paralog TAZ, transcriptional co-activator with a PDZ-binding motif, function as key effectors negatively controlled by the Hippo pathway. YAP1/TAZ exerts oncogenic activities by transcriptional regulation *via* physical interaction with TEAD transcription factors. In various cancers, Hippo pathway cross-talks with pro- or anti-tumorigenic pathways such as GPCR, Wnt/ $\beta$ -catenin, Notch and TGF- $\beta$  signaling and is deregulated by multiple factors including cell density/junction and microRNAs. As YAP1 expression is significantly associated with poor prognosis of gastric and other gastrointestinal cancers, detailed delineation of Hippo regulation in tumorigenesis provides novel insight for therapeutic intervention. In current review, we summarized the recent research progresses on the deregulation of Hippo pathway in the gastrointestinal tract including stomach and discuss the molecular consequences leading to tumorigenesis.

**Key words:** Hippo signaling pathway; Yes-associated protein 1; MicroRNA; Oncogenic role; Tumor suppressor

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**Core tip:** Hippo signaling pathway is a gradually emerging pathway that plays a necessary role in homeostasis of gastrointestinal tissues, whereas its deregulation frequently induces the occurrence of cancers. In gastric and other gastrointestinal cancers, the upstream components of Hippo pathway often show decreased expression and their downregulation loses the inhibitory effect on yes-associated protein 1 (YAP1)/TAZ. Thus YAP1/TAZ is translocated into the nucleus and exerts oncogenic function by direct binding with TEAD transcription factors to activate the downstream targets transcriptionally. In this brief review, we summarize the deregulation of Hippo pathway in gastric and other gastrointestinal cancers.

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## INTRODUCTION

Gastric cancer (GC)<sup>[1]</sup> is still one of the most common malignancies worldwide. According to the World Health Organization statistics in 2012, GC counts for the 4<sup>th</sup> in men and 6<sup>th</sup> in women for the incidence and mortality. The incidence is exceptionally higher in eastern Asia countries and regions including China, South Korea and Japan than other countries. The potential risk factors of GC include *Helicobacter pylori* (*H. pylori*) infection, Epstein-Barr virus (EBV) infection, high-salty pickled food diet, low-vegetable diet, smoking, chronic gastritis with glandular atrophy, intestinal metaplasia, and the most important factor is genetic alterations<sup>[2]</sup>. The chronic *H. pylori* infection inducing GC appears to relate to the VacA virulence factor and Th17/Treg mechanisms<sup>[3]</sup>. Gastric adenocarcinoma is histologically classified as intestinal type and diffuse type. And it is also grouped by molecular classification that defines four major genomic subtypes of GC including EBV-infected tumors, microsatellite instability tumors, genomically stable tumors and chromosomally unstable tumors<sup>[4]</sup> in The Cancer Genome Atlas project. GC is a multistep carcinogenesis process with genetic and epigenetic alterations. The oncogenes, tumour suppressor genes, mismatch repair genes, cell adhesion molecules and cell cycle regulators showed altered from the DNA, RNA and protein level<sup>[5]</sup>. Multiple well-established oncogenic signaling pathways such as Wnt/ $\beta$ -catenin, nuclear factor- $\kappa$ B, Sonic Hedgehog (Shh), Notch and epidermal growth factor receptor (EGFR) signaling are involved in gastric carcinogenesis. Better revealing the biological significance of these signaling pathways will provide fundamental

knowledge for drug or small molecule screening<sup>[6]</sup>. Emerging evidence has underscore the Hippo signaling pathway in the developmental process and tumors<sup>[7]</sup>.

## HIPPO SIGNALING PATHWAY AND ITS ROLE IN SOLID TUMORS

### *The main components of Hippo kinase cascade*

The mammalian Hippo signaling pathway, short for MST1/2-WW45-LATS1/2 signaling, is a critical pathway that determines cell growth rate and organ size<sup>[8-9]</sup>. MST1/2 (short for mammalian Ste20-like kinase 1 and 2) phosphorylates LATS1/2 (large tumor suppressor 1 and 2) and Mob1 (Mobk1a/b), leading to their activation<sup>[10,11]</sup>. LATS1/2 phosphorylates YAP1 (Yes-associated protein 1)<sup>[9]</sup> and TAZ (WW domain-containing transcription regulator 1)<sup>[12]</sup> and promotes 14-3-3 binding to phosphorylated YAP1/TAZ, causing YAP1/TAZ cytoplasmic accumulation and sequestering its oncogenic function. The unphosphorylated YAP1 and TAZ are translocated to the nucleus and bind with TEAD1-4 (TEA domain DNA-binding transcription factors 1-4), inducing transcriptional activity for cell proliferation and differentiation<sup>[13-15]</sup>.

As the most important negative regulator of YAP1/TAZ, much studies have provided new findings into the Hippo signaling pathway<sup>[9]</sup>, elucidating novel phosphorylation-dependent<sup>[16]</sup> and independent mechanisms of YAP1/TAZ inhibition by the Hippo pathway. The key components of Hippo pathways form a phosphokinase cascade and play a crucial role to inhibit the downstream effectors, YAP1 and TAZ. Meanwhile, the Hippo pathway is the same important for homeostasis control and dysregulation of Hippo pathway contributes to carcinogenesis<sup>[17]</sup>.

### *Upstream regulators of Hippo pathway and signal crosstalks*

The tumor suppressor function of Hippo pathway is enhanced by E-cadherin/catenin complex<sup>[18,19]</sup>, AMOT family proteins<sup>[20]</sup> and LKB1-MARK signaling<sup>[21]</sup>, but is negatively regulated by GPCR (G-protein-coupled receptor) signaling<sup>[22]</sup>. The protease activated receptors<sup>[23]</sup> inhibits the LATS1/2 kinase activity *via* Rho GTPase and G12/13-coupled receptors<sup>[24]</sup>.

The tight junction (TJ)<sup>[25]</sup> and adherens junction (AJ) components contact with YAP1 and quench its oncogenic function.  $\alpha$ -catenin, a component of AJ, binds with 14-3-3 to form complex and phosphorylates YAP1, promoting YAP1 inhibition<sup>[19]</sup>. AMOT proteins restrict YAP1 activity in a LAST1/2 dependent and LATS1/2 independent manners<sup>[20,26]</sup>. As YAP1/TAZ is also a mechanotransduction sensor<sup>[27]</sup>, the cell spreading, tension, attachment and detachment modulate YAP1/TAZ activity which is associated with Rho GTPase activity and reorganization of actin cytoskeleton<sup>[28]</sup>. YAP1/TAZ is also positively or negatively regulated by GPCR signaling pathway

through RhoGTPases/actin/LATS1/2 cascade, which is determined by different GPCR ligands.  $G_{\alpha 12/13}$ -,  $G_{\alpha q/11}$ -, and  $G_{\alpha i/o}$ -coupled ligands activate YAP1/TAZ but  $G_{\alpha s}$ -coupled ligands suppress YAP1/TAZ activity<sup>[22,29]</sup>.

The deregulated Hippo pathway shares crosstalks with Wnt/ $\beta$ -catenin<sup>[30]</sup>, Notch<sup>[31]</sup> and TGF- $\beta$  (transforming growth factor beta)<sup>[32]</sup> signaling pathways to promote tumorigenesis coordinately. Many studies have highlighted the regulation of Hippo pathway on Wnt/ $\beta$ -catenin pathway. The cytoplasmic accumulation of YAP1/TAZ directly interacts with  $\beta$ -catenin and inhibits  $\beta$ -catenin nuclear translocation<sup>[33]</sup>, whereas in the nuclei YAP1 binds with  $\beta$ -catenin to enhance the tumorigenicity<sup>[34]</sup>. The subcellular localization and phosphorylation status of YAP1/TAZ also determine the effect of Hippo signaling on TGF- $\beta$  signaling. In the cytoplasm, YAP1/TAZ binds with Smad protein to suppress the TGF- $\beta$  induced transcription, but in the nuclei, YAP1/TAZ retains Smad protein and enhances transcription under the TGF- $\beta$  stimulation<sup>[35,36]</sup>. The interplay of Hippo pathway and Notch pathway was also demonstrated in mouse intestine. YAP1 induces the expression Notch ligand Jagged-1 and activates Notch signaling<sup>[37]</sup>. Meanwhile in MST1/2-deficient intestinal epithelium,  $\beta$ -catenin and Notch signaling are strongly activated<sup>[38]</sup>. In addition, the EGFR ligand amphiregulin (AREG) is another transcriptional target of YAP1, which functions as a contributor for YAP1-mediated proliferation and invasion<sup>[39]</sup>, suggesting that the Hippo pathway also regulates the growth factor receptor tyrosine kinase signaling.

Some other studies focus on findings of new Hippo pathway components and crosstalks, novel YAP1/TAZ target genes and the three-dimensional structure of the YAP1-TEAD complex<sup>[40,41]</sup>. This provides further evidence and insight for the involvement of the deregulated Hippo pathway and YAP1/TAZ activation in tumorigenesis<sup>[42]</sup>.

### **Key Hippo pathway effector, YAP1, and its role in solid tumors**

YAP1 is located at Chromosome 11q22, a recurrent amplicon region in esophageal squamous cell carcinoma and liver cancer<sup>[43,44]</sup>. The amplification within this region is also identified in a subset of cervical and lung cancers<sup>[45,46]</sup>. The modular structure of YAP1 contains a WW domain, TEAD-binding domain, SH3-binding motif and PDZ-binding motif<sup>[47]</sup>. YAP1 is a modular adaptor protein with multiple protein interaction domains and it was first identified by its affinity to bind the SH3 domain of nonreceptor tyrosine kinase c-Yes, a Src protein kinase<sup>[48]</sup>. The majority of the interactions are mediated by the WW domain of YAP1. Through WW domain, YAP1, PPxY motif-containing LATS1 kinase, and AMOTL1 protein form functional complex<sup>[49,50]</sup>. YAP1 binds to the ERBB4 and functions as a transcription co-activator for the

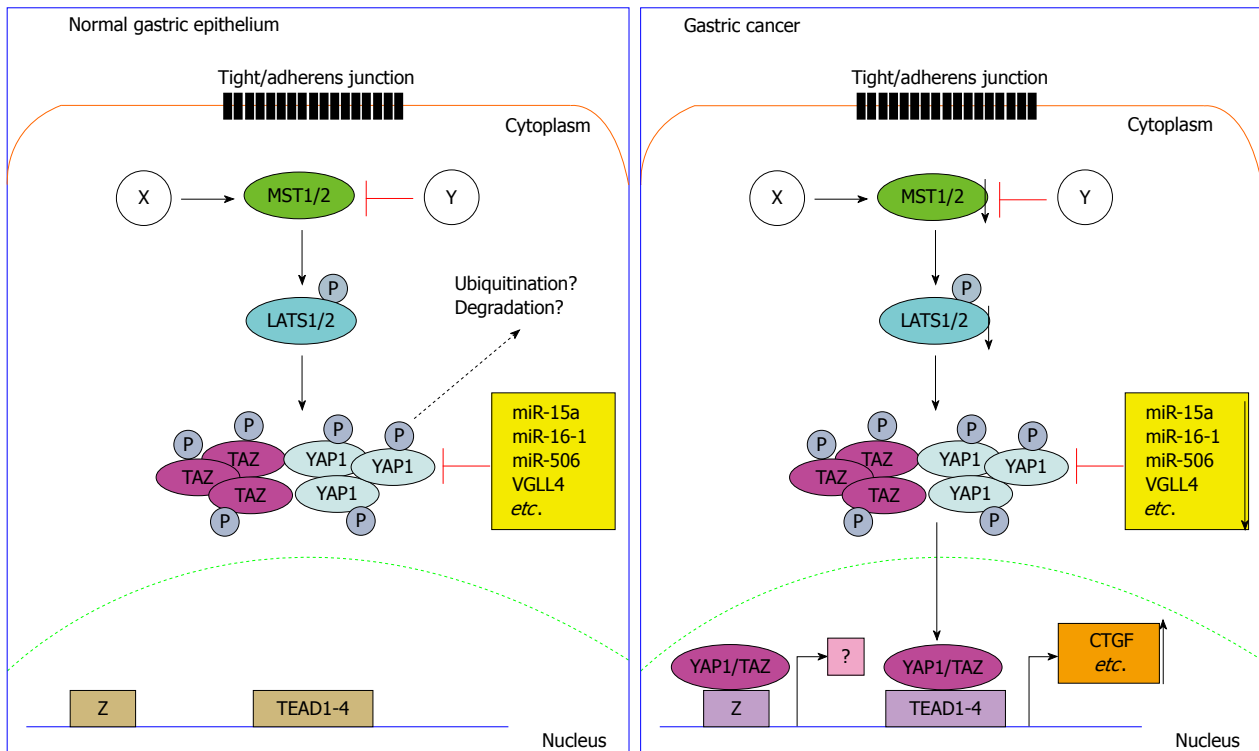
cytoplasmic fragment of ERBB4 which is translocated to the nucleus<sup>[51]</sup>. TEAD family is one of the most important binding partners of YAP1<sup>[40]</sup> through TEAD-binding domain which is responsible for promoting oncogenic transformation<sup>[52]</sup> and metastasis<sup>[53]</sup>. PDZ-binding motif of YAP1 is a critical region for its cytoplasmic-nuclear translocation<sup>[54]</sup> and accumulation thus to exert its oncogenic function in tumorigenesis.

YAP1 has been concordantly identified as a candidate oncogene that promotes tumorigenesis in many different types of solid tumor<sup>[55-59]</sup>. In non-transformed mammary epithelial cells, the upregulation and activation of YAP1 promotes epithelial-mesenchymal transition (EMT) and induces growth factor independent growth and anchorage independent proliferation in soft agar<sup>[60]</sup>. In non-small cell lung cancer, YAP1 binds with Oct4 through its WW domain and transcriptionally induces Sox2 activation thus to endow the stem-like properties<sup>[61]</sup>. In medulloblastoma, Shh signaling induces YAP1 expression and promotes YAP1 nuclear localization to promote tumorigenesis<sup>[62]</sup>. In uveal melanoma,  $G_{\alpha q}$  promotes the YAP-dependent growth *via* a Trio-Rho/Rac signaling circuitry which promotes actin re-polymerization. This process is independent of phospholipase C $\beta$  and the canonical Hippo pathway<sup>[63]</sup>. In ovarian cancer cell lines, YAP1 can enhance the transformed phenotype and confers drug resistance to chemotherapeutic agents, which are commonly used in clinical ovarian cancer<sup>[64]</sup>.

On the contrary, other studies identify that YAP1 stabilizes p73 and prevents its ubiquitination<sup>[65]</sup> thus selectively activating the transcription of proapoptotic genes as a consequence of damage to the DNA<sup>[66]</sup>. Therefore the function of YAP1 in favoring tumor suppression is thought to through apoptosis induction. Promyelocytic leukemia, a tumor suppressor gene and direct transcriptional target of p73/YAP1, directly binds with YAP1 physically *via* the PVPVY domain and WW domain thus to stabilize YAP1 from degradation<sup>[67]</sup>. The binding affinity of protein-protein interaction domains is thought to be critical in directing the biological function of YAP1<sup>[68]</sup>. O'Neill and his colleagues pointed out the molecular background such as loss of RASFF1A expression switches YAP1 from a tumor suppressor to an oncogene<sup>[69]</sup>.

## **DEREGULATION OF HIPPO PATHWAY IN GC**

The deregulated Hippo signaling pathway is strongly associated with initiation, development and distant metastasis of human GC<sup>[70]</sup> (Figure 1). The most upstream of Hippo pathway, MST1/2 and LATS1, is frequently showing downregulation in GC compared with its expression in normal gastric epithelium or adenoma<sup>[71,72]</sup>. The tumor suppressor RUNX3 is an evolutionarily conserved component of the Hippo pathway. RUNX3 is capable to induce cell apoptosis



**Figure 1 Deregulation of Hippo pathway in gastric cancer.** The schematic representation of Hippo signaling deregulation in gastric carcinogenesis. In normal gastric epithelium, YAP1/TAZ is strongly negatively regulated and quenched in the cytoplasm by the activated Hippo signaling pathway. miR-15a/16-1/506 also exerts its tumor suppressor function by targeting YAP1. In gastric cancer (GC) cells, the upstream of Hippo pathway, MST1/2 and LATS1/2 are down-regulated and fail to phosphorylate YAP1/TAZ. YAP1/TAZ is then translocated to the nucleus and binds with TEAD transcription factors to transcriptionally activate the downstream targets. Meanwhile, downregulation of miR-15a/16-1/506 and VGLL4, an antagonist of YAP1, are partially responsible for the activation of YAP1 in GC. YAP1: Yes-associated protein 1; MST1/2: Mammalian Ste20-like kinase 1 and 2; LATS1/2: Large tumor suppressor 1 and 2.

through cooperation with MST2 and SAV1. It is a very complex circuit. SAV1/WW45 facilitates the tight association of MST2 and RUNX3. In turn, MST2 stimulates the interaction of SAV1 and RUNX3<sup>[73]</sup>. 3,3-diindolylmethane<sup>[74]</sup> stimulates RASSF1 binding to the MST1/2-LATS1-Mob1 complex, which will further promote the activation of Hippo signaling pathway and inactivate cell proliferation<sup>[75]</sup>.

As the core downstream effector of Hippo pathway, the expression of YAP1 both in the cytoplasm and nucleus was first described to be dramatically upregulated in high-grade dysplasia, gastric adenocarcinoma, and metastatic gastric disease<sup>[76]</sup>. The YAP1 nuclear accumulation was correlated with shorter disease specific survival. In early stage GC, the result is more stringent, suggesting the activation of YAP1 is correlated with poor outcome. As YAP1 is up-regulated in GC, siRNA-mediated YAP1 knockdown exhibited suppressive phenotype, such as decreased cell proliferation, inhibited anchorage-dependent monolayer colony formation, reduced cell invasion and migration. In MKN45 cells which show negative YAP1 expression due to the homozygous deletion, ectopic expression of YAP1 promoted anchorage-dependent or -independent colony formation. The upregulation of YAP1 in MKN45 cells also induced more invasive phenotype change and promoted cell

proliferation both *in vitro* and *in vivo*. The signaling pathway analysis revealed that RAF/MEK/ERK pathway is constitutively activated in cells stably expressing YAP1. YAP1 was further demonstrated to enhance the serum/EGF-inducing c-Fos expression in GC cells<sup>[72]</sup>. The upregulation of YAP1 in GC exhibits positive expression correlation with survivin<sup>[77]</sup>. The interaction of YAP1 and RUNX2, a Runt box domain DNA-binding transcription factor, increases oncogenic transformation by repression of p21 protein expression<sup>[78]</sup>. In gastric and lung adenocarcinoma, receptor tyrosine kinase AXL is the direct functional target of YAP1<sup>[79]</sup>. The similar oncogenic role of YAP1 in gastric tumorigenesis and metastasis was also comprehensively illustrated by several research groups<sup>[80-84]</sup>.

YAP1 is reported to be negatively regulated by tumor suppressor microRNAs (miRNAs) including miR-15a, miR-16-1<sup>[85]</sup> and miR-506<sup>[86]</sup> in GC. VGLL4 is a family member of the Vestigial-like proteins which have been reported to function as tumor suppressors. By competing with YAP1 for the TEADs binding, VGLL4 directly interacts with TEAD transcription factors in GC and inhibits EMT through Wnt/ $\beta$ -catenin signaling pathway<sup>[87]</sup>. A peptide mimicking this function of VGLL4 potentially suppressed tumor proliferation *in vitro* and *in vivo*<sup>[88]</sup>, which sheds light on the therapeutic potential of this small molecule.



Several YAP1 related genes exhibit mutation or epigenic modification in gastric carcinogenesis. RhoA, an upstream and activator of YAP1, is found to have recurrent mutations in diffuse type GC<sup>[89,90]</sup>. TEAD4 transcription factor, the binding partner of YAP1 and a linker between Hippo pathway upstream components and the downstream targets, is significantly hypomethylated in the CpG site cg21637033 and overexpressed in GC tissues compared with the adjacent normal gastric epithelium<sup>[91]</sup>. TAZ, another key effector of Hippo pathway and transcriptional coactivator with PDZ binding motif, is associated with abnormal overexpression of  $\beta$ -catenin, which correlates with poor prognosis of patients with adenocarcinoma of the esophagogastric junction<sup>[92]</sup>.

## HIPPO PATHWAY IN OTHER GASTROINTESTINAL CANCERS

The Hippo signaling pathway also plays an important role in other gastrointestinal cancers which was recently comprehensively summarized in a review by Yu *et al.*<sup>[93]</sup>.

### **Deregulation of Hippo pathway in hepatocellular carcinoma**

In hepatic oval cells, the mammalian Hippo pathway controls the proliferation rate and thereby restricts liver size and prevents the initiation of hepatocellular carcinoma (HCC)<sup>[94]</sup>. Overexpression of MST1/2 inhibits cell proliferation<sup>[95]</sup>, promotes YAP1 phosphorylation<sup>[96]</sup> and downregulates the mRNA expression of CTGF, AREG and Survivin<sup>[97]</sup>. YAP1 plays an oncogenic even cancer-driven role in HCC development<sup>[98,99]</sup>. YAP1 knockdown by siRNA-lipid nanoparticles (siRNA-LNPs) dramatically restores hepatocyte differentiation in advanced HCC and leads to tumor regression<sup>[100]</sup>. The activation of YAP1 is an early event<sup>[101]</sup> in HCC and serves as an independent prognostic factor<sup>[102,103]</sup>. The PDZ binding motif in YAP1 is crucial for its activation of CTGF, a cell proliferation gene and TEAD-dependent transcription target<sup>[104]</sup>. CREB (cyclic adenosine monophosphate response element-binding protein) promotes YAP1 transcriptional output through binding to -608/-439, a novel region from the YAP promoter<sup>[105,106]</sup>.

Several binding partners were identified to enhance the oncogenic property exerted by YAP1. YAP1 and PI3K exerts oncogenic cooperation in HCC<sup>[107]</sup>. The interaction of MEK1-YAP1 is critical for cell proliferation and transformed phenotype maintenance of HCC cells<sup>[108]</sup>. Amot-p130 was associated with the YAP1-TEAD transcriptional complex and contributed to the regulation of a bunch of YAP1 targeting genes. These targeted genes are associated with liver tumorigenesis<sup>[109]</sup>. SIRT1 was reported to deacetylate YAP1 protein in HCC cells and SIRT1-mediated deacetylation strengthened the YAP1-TEAD4 interaction, leading to the activation of

YAP1/TEAD4 transcriptional ability and stimulating tumor growth in HCC cells<sup>[110]</sup>. YAP1 up-regulates Jag-1 to activate Notch signaling in HCC cells<sup>[37]</sup> and it also activates PI3K-mTOR signaling pathway<sup>[111]</sup>, indicating the crosstalks of Hippo pathway and oncogenic pathways. As the same with GC, AXL is a target for YAP1-dependent oncogenic transcription in HCC and has been reported to be a potential therapeutic target<sup>[112]</sup>.

### **Dysregulated Hippo pathway in colorectal cancer**

In colorectal cancer (CRC), decreased expression of LATS1 in CRC was associated with promoter hypermethylation and such reduced expression promotes progression of CRC<sup>[113]</sup>. The Hippo pathway is suppressed by a critical regulator named integrin-linked kinase (ILK) *via* phosphorylation of MYPT1-PP1, leading to the Merlin inactivation<sup>[114]</sup>. MST1 and MST2 significantly repress the abundance and activation of YAP1 in normal intestinal epithelium. As tumor suppressors, MST1 and MST2 have an anti-proliferative function, however this function is often overcome by the over-abundance of YAP1 in CRC<sup>[38]</sup>. YAP1 overexpression in CRC cells is partly due to the activation of  $\beta$ -catenin pathway. The  $\beta$ -catenin/TCF4 complexes bind to a DNA enhancer element within the first intron of the YAP1 gene to promote the transcription of YAP1<sup>[115]</sup>. The interplay between overexpressed YAP1 and  $\beta$ -catenin drives proliferation of colon cancer cells<sup>[116]</sup>. In KRAS-dependent cells when KRAS was suppressed, overexpression of YAP1 could rescue cell viability, suggesting that YAP1 was required for KRAS-induced cell transformation like EMT in CRC<sup>[117]</sup>. YAP1 transcription levels positively correlates with 5-fluorouracil resistance<sup>[118]</sup>, relapse and shorter patient survival<sup>[119]</sup>. TAZ, the paralog of YAP1, regulates AXL in CRC and also plays a critical role in clonogenicity and non-adherent growth<sup>[120]</sup>. However, YAP1 is negatively regulated by E2A, which encodes two bHLH (basic helix-loop-helix) transcription factors E12 and E47<sup>[121]</sup>.

### **Hippo pathway deregulation in pancreatic ductal adenocarcinoma**

In pancreatic ductal adenocarcinoma (PDAC), YAP1 was identified as a critical and functional downstream which plays a role in the oncogenic switch between KRAS pathway and MAPK (mitogen-activated protein kinase) pathway. YAP1 promotes the expression of genes which encode secretory factors. These factors accumulatively sustained the neoplastic proliferation, a stromal tumorigenic response from the tumor microenvironment<sup>[122]</sup>. The recent findings reveal that YAP1 and TEAD2, a TEAD transcriptional factor, interact and function cooperatively with E2F transcription factors to drive KRAS(G12D)-independent tumor initiation. In PDAC, this complex activates cell cycle progression and DNA synthesis program and finally escapes from the oncogenic KRAS addiction<sup>[123]</sup>. AGR2

up-regulates the expression of AREG, a EGFR ligand with growth-promoting potential, which is mediated by activation of YAP1 in PDAC<sup>[124]</sup>. YAP1 is negatively regulated by miR-141<sup>[125]</sup> and miR-375<sup>[126]</sup>, which serves an independent prognostic factor for PDAC patients and exerts tumor suppressor functions.

## CONCLUSION

In conclusion, the activation of Hippo signaling pathway is necessary for the homeostasis maintenance of gastric and other gastrointestinal organs. However, its deregulation causes tumorigenesis in digestive system through loss of control on YAP1/TAZ. The YAP1/TAZ hyperactivation in gastrointestinal cancers seems to drive tumorigenesis and take over carcinogenesis in a RAS-independent manner. Thus it provides a therapeutic target for clinical intervention.

However several issues should be addressed in the following study on Hippo pathway in GC as indicated in Figure 1. First, the detailed regulation mechanism on Hippo pathway in GC is not understood, thus the cell tight/adherens junction, cytoskeleton changes and other factors linked with Hippo pathway need to be addressed. Second, the left regulatory mechanisms on YAP1/TAZ should be addressed including miRNA/lncRNA regulation to facilitate our understanding on the regulation of YAP1/TAZ in tumorigenesis. Third but not the last, exploring novel transcription factors which are required for YAP1/TAZ to exert its function will be helpful to fully understand the oncogenic role of YAP1/TAZ in GC.

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