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Review Article

Role of Yes-associated Protein-1 in Gastrointestinal Cancers and Hepatocellular Carcinoma

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Abstract

Yes-associated protein-1 (YAP1) is a potent transcriptional co-activator and functions as an important downstream effector of the Hippo signaling pathway, which is key to regulating cell proliferation, apoptosis, and organ growth. YAP1 has been implicated as an oncogene for various human cancers including gastrointestinal cancers and hepatocellular carcinoma (HCC). YAP1 promotes tumorigenesis and cancer progression by multiple mechanisms, such as by promoting malignant phenotypes, expanding cancer stem cells, and inducing epithelial-mesenchymal transition. YAP1 overexpression or its activated forms are associated with advanced pathological grades and poor prognosis of cancer, and therefore targeting YAP1 may open a fertile avenue for cancer therapy. In this review, we summarize the recent evidence regarding the role of YAP1 in the carcinogenesis of gastrointestinal cancers and HCC.

Introduction

Gastrointestinal cancers involving the gastrointestinal tract and accessory organs of digestion are the most common malignancies worldwide.[1] Many of these cancers have poor prognoses although the combination of surgery, endoscopic therapy, chemotherapy, and radiation may improve the survival of some patients with gastrointestinal cancers and hepatocellular carcinoma (HCC).[2] The effectiveness of the treatments, however, depends on the cancer status which includes metastasis, resistance to radiation/chemotherapy, and recurrence. Given the high prevalence and mortality threat of these malignancies, further studies are needed to define prognostic, survival, and diagnostic markers for these cancers.

The Hippo signaling pathway is a critical regulator of cell proliferation, growth, and apoptosis. This pathway also provides important roles in tissue homeostasis, organ size and stem cell function.[3,4] Yes-associated protein-1 (YAP1) functions as an important downstream effector of the Hippo signaling pathway and is a potent transcriptional co-activator that interacts with multiple transcription factors, such as TEA domain (TEAD) and SMAD family members, to regulate the expression of target genes.[5,6] When the Hippo pathway is "on", YAP1 is phosphorylated on serine residues

Keywords: YAP1; Gastrointestinal cancers; Hepatocellular carcinomas; Carcinogenesis; Cancer therapy.

Abbreviations: APC, Adenomatous Polyposis Coli; BRD4, Bromodomain-Containing Protein 4; CCA, cholangiocarcinoma; CCL2, C-C Motif Chemokine Ligand 2; CRC, Colorectal Cancer; CREB, cAMP-response element binding protein; CSF1, Colony Stimulating Factor 1; CTGF, Connective Tissue Growth Factor; CYR61, Cysteine-rich angiogenic inducer 61; EAC, Esophageal Adenocarcinoma; EC, Esophageal Cancer; ECM, Extracellular Matrix; EMT, Epithelial-Mesenchymal Transition; EPCAM, Epithelial cell adhesion molecule; ERK, Extracellular Signal-Regulated Kinase; 5-FU, 5-Fluorouracil; H3K9me2, Histone H3K9 Dimethylation; HB, hepatoblastoma; HCC, Hepatocellular Carcinoma; HIF1a, Hypoxia Inducible Factor 1 Subunit Alpha; IGF1, Insulin Growth Factor 1; IL, Interleukin; IRS2, Insulin Related Substrate 2; ITGA, Integrin Subunit Alpha; ITGA3, Integrin A 3; JAG1, Jagged Canonical Notch Ligand 1; JAK-STAT, Janus Kinase-Signal Transducer and Activator of Transcription; JMJD1C, Jumonji Domain-Containing Protein 1C; lncRNA, long non-coding RNA; M, Metastasis; MAPK, mitogen-activated protein kinase; Mcp1, monocyte chemotactic protein 1; miR, MicroRNA; mTOR, mechanistic target of rapamycin; N, Node; NAFLD, nonalcoholic fatty liver disease; ncRNAs, Non-coding RNAs; NFkB, Nuclear Factor kappa-B; nYAP, nuclear YAP; PDAC, Pancreatic Ductal Adenocarcinoma; PD-L1, Programmed death-ligand 1; PI3K, Phosphatidylinositol-3-kinase; PPARD, Peroxisome Proliferator Activated Receptor Delta; PPARE, Peroxisome Proliferator-Activated Receptor Element; PTEN, Phosphatase and tensin homolog; RUNX, Runt-related transcription factor; SCC, Squamous Cell Carcinoma; SOX9, SRY-Box Transcription Factor 9; STAT3, Signal Transducer and Activator of Transcription 3; T, Tumor; TACE, transarterial chemoembolization; TAZ, Tafazzin; TEAD, TEA Domain; TGFBR2, Transforming Growth Factor Beta Receptor 2; Tregs, regulatory T cells; VGLL4, Vestigial Like Family Member 4; VP, Verteporfin; YAP1, Yes-Associated Protein-1; ZEB1, Zinc Finger E-Box Binding Homeobox 1.

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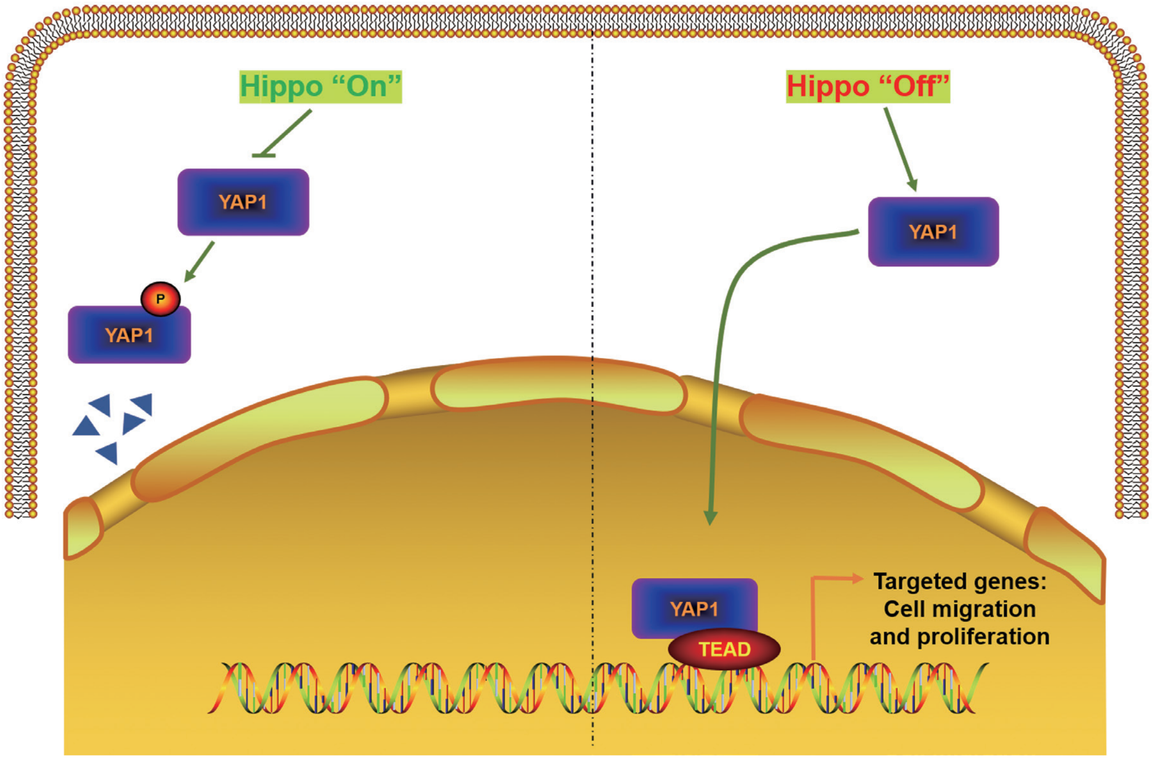

Fig. 1. The Hippo-Yes-Associated Protein-1 (YAP1) pathway. When the Hippo pathway is "on", YAP1 is phosphorylated and retained in the cytoplasm or degraded. When the Hippo pathway is "off," YAP1 translocates into the nucleus where it serves as a transcription co-regulator of TEA-Domain (TEAD), induces the expression of genes such as Survivin, Connective Tissue Growth Factor (CTGF), Jagged Canonical Notch Ligand 1 (JAG1), and Cysteine-rich angiogenic inducer 61 (CYR61), thus promoting the migration and proliferation of cancer cells.

and retained in the cytoplasm, limiting its co-activator function in the nucleus. In contrast, when the Hippo pathway is "off," YAP1 translocates into the nucleus where it induces the expression of genes, such as *Survivin, CTGF, JAG1, and CYR61,* to promote the migration and proliferation of cancer cells (Fig. 1).[7,8] Elevated nuclear YAP1 has been detected in many cancers and the overexpression of YAP1 is associated with poor prognoses for gastrointestinal cancers such as esophageal cancer (EC), gastric cancer (GC), colorectal cancer (CRC), and HCC.[9] Pre-clinical studies have demonstrated that YAP1 inhibition led to the suppression of tumor progression and sensitized chemotherapy.[9,10] YAP1 also plays an important role in tumor immunity, which affects tumor progression, tumor prognosis and treatment response. YAP1 expression in T cells, myeloid-derived suppressor cells, and macrophages regulates the interaction between immune and tumor cells in the tumor microenvironment.[11] Therefore, YAP1 represents a potential target for anti-cancer therapy. In this review, we summarize the recent advances supporting the role of YAP1 in carcinogenesis of gastrointestinal cancers and HCC.

YAP1 in gastric cancer

Gastric cancer (GC) is the fifth most common and the third most life-threatening cancer worldwide. The risk factors of GC include infections with *Helicobacter pylori* (*H. pylori*) and Epstein-Barr virus (EBV), smoking, chronic atrophic gastritis, intestinal metaplasia, and genetic mutations. In the last several years, a set of tumor suppressor genes and microRNAs (*mi*R) were identified as having expression patterns associated with different GC stages and subtypes.[12,13] These genes were considered prognostic biomarkers and may serve as potential drug targets for interventional therapy. Among them, the genes encoding the Hippo-YAP1 signaling pathway emerged as important regulators for tumor formation and progression.

Clinical studies demonstrated that YAP1 overexpression in GC was related to high pathological grades, disorganized cellular differentiation, and a poor prognosis. *In vitro*, the inhibition of YAP1 suppressed cancer cell growth, migration, and invasion.[14] Studies in mice revealed that YAP1 mediated gastric adenocarcinoma peritoneal metastasis by promoting cancer stem cell (CSC) properties, and that inhibition of YAP1 significantly decreased the CSC properties and inhibited tumor growth in this aggressive phenotype.[14] With the oncogenic role of YAP1 revealed, molecular mechanisms by which YAP1 promotes GC have received attention and much progress has been made, as described below.

YAP1 promotes expression of various genes such as *MYC, CTGF* and *AXL*. It has been shown that deregulated *MYC* causes cell transformation and tumor progression,[15] and that *MYC* activation affects early-stage gastric carcinogenesis.[16] Additionally, *MYC* is a direct downstream mediator of YAP1,[17] which also regulates the initiation of gastric carcinogenesis by upregulating *MYC*.[18] YAP1 also promotes activation of the RAF/MEK/ERK pathway to enhance the expression of *c-Fos* in GC.[19] The overexpression of YAP1 in GC is also positively correlated with survivin expression, a known inhibitor of apoptosis.[20] Moreover, YAP1 interacts with RUNX2, a Runt box domain DNA-binding transcription factor, to promote oncogenic transformation through repressing the

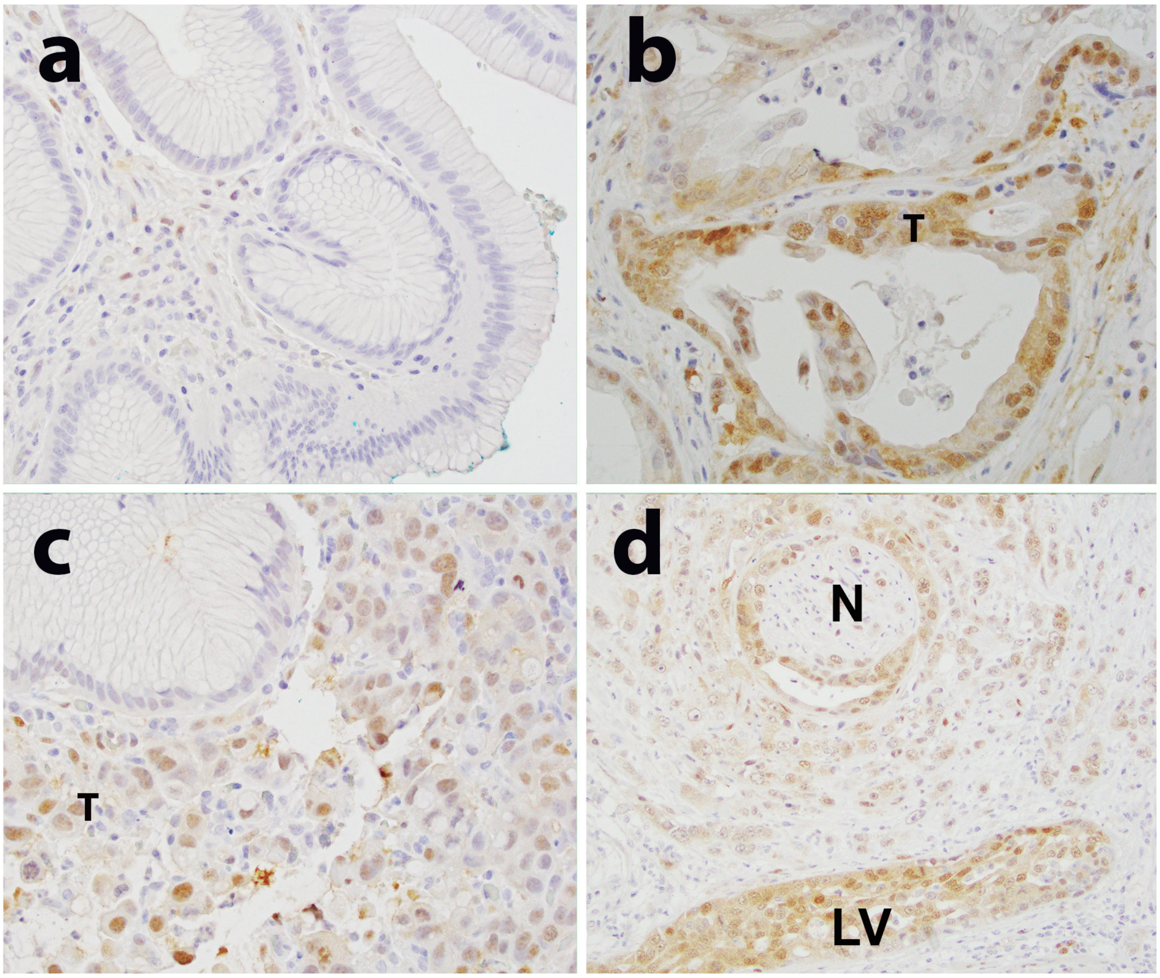

Fig. 2. YAP1 immuno-reactivity in a case of esophageal adenocarcinoma. (a) YAP1 is negative in the adjacent benign esophageal columnar epithelium; b–d: YAP1 is positive in the adenocarcinoma and the carcinoma with perineural invasion (N) and lympho-vascular invasion (LVI) (a–d, 400×).

expression of p21.[21] However, RUNX3, an important tumor suppressor, reduces YAP1 activity by decreasing the DNA-binding capacity of TEAD.[22] Furthermore, YAP1 directly promotes SOX9 transcription by interacting with TEAD proteins at the SOX9 promoter, which induces CSC properties in non-transformed cells of gastrointestinal origin. Oncogenic and CSC properties are also promoted by the peroxisome proliferator-activated receptors δ (PPARD) in GC cell lines in which PPARD forms a complex with YAP1. PPARD directly binds the YAP1 C-terminal transactivation domain, which then promotes SOX9 transcription. Inhibition of YAP1 significantly prohibited PPARD-induced oncogenic and CSC properties in GC.[23]

In terms of the regulation of YAP1, it has been reported that some miRNAs, such as miR15a, miR16-1 and miR375, negatively regulate YAP1 expression.[24,25] Deregulated function of these tumor suppressive miRNAs leads to YAP1 upregulation and subsequent tumorigenesis. In addition, VGLL4, a member of the Vestigial-like proteins, which directly interacts with TEAD through competing with YAP1 for binding TEADs, inhibits EMT in GC via suppressing the Wnt/β-catenin signaling pathway. A peptide mimicking VGLL4, and acting as a YAP1 antagonist, dramatically suppressed tumor formation, which suggests that inhibition of the YAP-TEADs interaction by this small molecule is a potential therapeutic method for GC.[26,27]

YAP1 in EC

EC has high incidence and is one of the most fatal malignancies worldwide. Targeted gene therapy is a promising prospect for improving the outcomes of EC.[28] Thus, it is crucial to find therapeutic target genes for the treatment of EC.

In EC, overexpression of YAP1 has been reported in both esophageal adenocarcinoma (EAC) and squamous cell carcinoma (SCC).[29,30] Recently, we also found increased expression of YAP1 in EAC, perineural invasion (N) and lymphovascular invasion (LVI) (Fig. 2). Studies have shown that the expression level of YAP1 is correlated with EC progression and that the knockdown of YAP1 suppresses esophageal tumor growth and metastasis in mice.[31] The role of YAP1 in esophageal carcinogenesis and metastasis is mediated by cooperation with multiple factors. YAP1 upregulates the expression of EGFR through binding to a TEAD-binding site at the EGFR promoter in EC cells. YAP1 also promotes sustained EGFR overexpression to increase cell proliferation and confer resistance in therapy. Verteporfin (VP), a small molecular YAP1 inhibitor, significantly decreases the expression of YAP1 and EGFR, and sensitizes esophageal cancer cells to 5-fluorouracil and docetaxcel.[32] YAP1 also directly promotes SOX9 transcription to confer EC cells with CSC properties including tumorsphere formation, propagation, and tumorigenicity. The YAP1 inhibitor, VP, suppresses SOX9 expression, CSC phenotypes and tumor growth.[33] Moreover, YAP1 mediates histone demethylase Jumonji Domain Containing 1C (JMJD1C)-induced EC growth. JMJD1C, which is upregulated in EC, enhances the transcription of YAP1 by its activity on H3K9me2.[34]

YAP1 represents a novel therapeutic target for EC with high YAP1 expression; however, targeting YAP1 in the clinical setting remains challenging. VP is the first small molecule identified as an inhibitor that targets YAP1/TEAD association and oncogenic activity of YAP1. Song *et al.* reported recently that the bromodomain-containing protein 4 (BRD4), a chromatin remodeling protein, significantly promotes YAP1 transcription through binding to its promoter. This work also found that the BRD4 inhibitor JQ1 effectively decreased the expression of YAP1 and YAP1 transcriptional targets (CTGF, SOX9, and Cyr61) in EAC cells. JQ1 represents a new YAP1 inhibitor, mainly targeting YAP1, which is a prevalent and therapeutic resistant tumor cell with CSC properties.[35]

YAP1 in PC

Pancreatic cancer (PC) is one of the most common gastrointestinal cancers and is projected to be the second most life-threatening cancer globally by 2030.[36] Although many new clinical techniques have been used for the treatment of PC, the prognosis remains unsatisfactory due to limited clinical significance of the therapeutic targets.[37] This makes it crucial to identify more promising therapeutic targets for PC treatment.

KRAS is a crucial oncogene for PC initiation and progression. YAP1 replaces the function of KRAS in KRAS-mutant PC cells.[38] YAP1 depletion abolishes PC development that is driven by oncogenic KRAS.[39,40] YAP1 activation enables the bypass of KRAS dependency to maintain PC growth.[41] These insights strengthen the notion that YAP1 maintains its oncogenic roles through a pathway-independent mechanism of KRAS. Recent studies have shown that WNT5A, a prototypical non-canonical WNT ligand, enhances tumor proliferation and recurrence in a YAP1-dependent manner, which enables the bypass of KRAS dependency.[42] KRAS facilitates acinar-to-ductal metaplasia and thereby generates cells for tumor initiation. This involves YAP1 activation in acinar cells and YAP1-induced transcription of genes in the JAK-STAT3 signaling pathway, leading to the development of pancreatic ductal adenocarcinoma, as seen in mice.[39]

PC is characterized by frequent metastasis, in which the ZEB1, a zinc-dependent EMT transcriptional factor, plays a crucial role. A recent study demonstrated that YAP1 formed a complex with ZEB1 to activate integrin alpha3 (ITGA3) transcription in human PC cells. Furthermore, the cancer-promoting zinc transporter (ZIP4) induces PC cell adhesion to ECM, EMT plasticity and metastasis through a ZEB1/YAP1-ITGA3 signaling axis.[43]

Increasing clinical data also shows that YAP1 is overexpressed in PC and its high expression is correlated with poor patient survival. This implies that inhibiting nuclear accumulation of YAP1 is a potential therapeutic strategy to manage PC. The combination of metformin and LW6 significantly inhibits PC cell proliferation, migration, and viability via increased YAP1 phosphorylation and reduced nuclear localization of YAP1.[44] In addition, miR141 and miR375 have been reported to negatively regulate YAP1 in PC, thereby inhibiting cancer cell growth.[45,46]

YAP1 in CRC

CRC remains the third most common cancer and the second most life-threatening cancer worldwide. Many studies have reported increased YAP1 expression in CRC, with the activation of YAP1 being correlated with poor prognosis of CRC.[47–49] Wang *et al.* proved the association between high YAP1 expression and shorter patient survival, and a positive association of high YAP1 expression with TNM stage.[50] Immunohistochemistry showed that nuclear YAP1 level is positively correlated with the expression of Ki67 and phosphorylated ERK, which induces CRC cell growth and progression.[51] In CRC samples, the activated YAP1 level is positively correlated with the expression level of EMT markers, including vimentin and N-cadherin, as well as EMT-inducing transcription factors, including Snail1, Slug and zinc finger E-box binding homeobox 1 and 2.[52] Recent studies have revealed a novel role of YAP1 in regulating non-coding RNAs (*nc*RNAs) in CRC, including microRNAs (miR130a and miR29) and long non-coding RNAs (*lnc*RNAs) (RMRP, BCAR4, MALAT1, and *lnc*ARSR). LINC00152 is one of the known YAP1 target *Inc*RNAs, which is highly expressed in human CRC tissues and induces CRC cell proliferation, invasion, and metastasis.[53] In addition, YAP1 exhibits cross-talk with the Wnt/β-catenin signaling pathway, which plays an important role in CSC self-renewal and tumorigenesis in CRC.[54]

YAP1 has also been reported to be upregulated in 5-Flourouracil (5FU)-resistant cancer cells and correlated with colon cancer relapse.[55] YAP1 activation is also correlated with resistance to cetuximab therapy, and only patients without YAP1 activation benefited from cetuximab treatment.[56]

In CRC, YAP1 transcription is positively regulated by β-catenin, HIF1α, NFkB, TEAD or CREB.[57] Inactivation of tumor suppressor adenomatous polyposis coli (APC) initiates carcinogenesis of CRC through activating β-catenin. A recent study reported that APC inactivation leads to up-regulation of interleukin 6 (IL6) signal transducer (IL6ST/gp130), thereby activating Src family kinases (SFKs), which induce nuclear activation of YAP1 in human CRC cells. On the other hand, activated YAP1 promotes IL6ST transcription. This YAP1-IL6ST auto-regulatory loop, which is induced by APC inactivation, has been shown to regulate CRC tumorigenesis.[58]

YAP1 in HCC

HCC is the sixth most frequent cancer and the third leading cause of cancer-related death globally.[59] The majority of HCC cases present at advanced stages due to most patients with underlying chronic liver disease or cirrhosis. Despite recent improvement in the treatment methods for advanced HCC, the prognosis remains unsatisfactory.

Overexpression of YAP1 in HCC is reported to be correlated with advanced pathological grades, poor prognosis and chemoresistance.[60] Xu *et al.* reported that YAP1 can serve as an independent prognostic marker for HCC, and that increased YAP1 expression is associated with decreased survival.[61] It is reported that in transgenic mice with YAP1 overexpression, the liver size is expanded and ultimately progresses to HCC, which implies a vital role of YAP1 in hepatocarcinogenesis.[62,63] As a transcriptional coactivator, YAP1 is involved in several important tumorigenic signaling pathways in HCC. YAP1 up-regulates Jagged-1 to activate

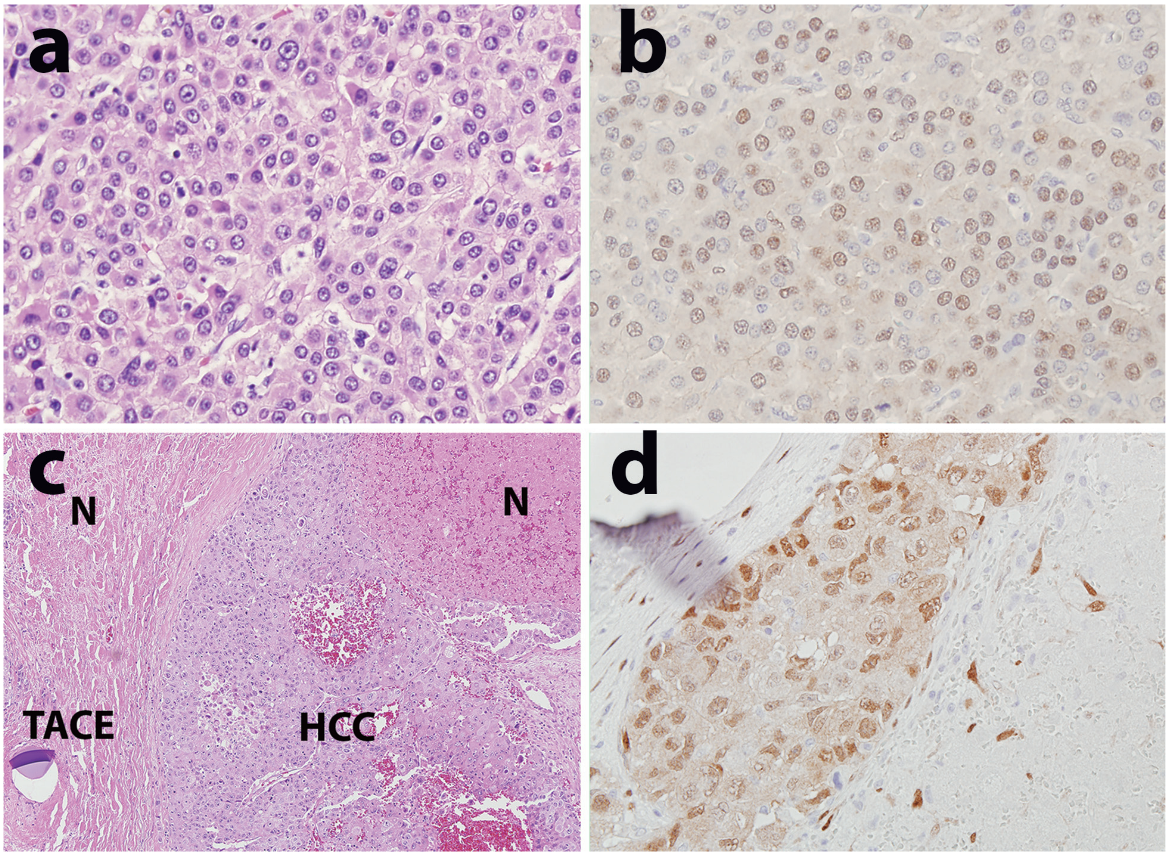

Fig. 3. YAP1 immuno-reactivity in a case of primary hepatocellular carcinoma (HCC) (a, b) and the residual HCC after trans-arterial chemoembolization (TACE) treatment (c, d) with background of TACE-caused tumor necrosis (N) (a and c, H&E stain; a, 400×; c, 100×;) YAP1 is weakly positive in the primary HCC (b) but increased expression in the residual HCC (d) (b–d, YAP IHC, 400×).

Notch signaling for an oncogenic effect.[64] YAP1 also regulates PI3K-mTOR pathways via suppressing PTEN.[65] YAP1 activates the AKT/mTOR, ERK/MAPK and Notch pathways through concomitant action with PI3K for carcinogenesis in the liver.[66] CSCs have been reported to be responsible for chemoresistance and the recurrence of HCC.[67,68] YAP1 has been reported to be expressed concurrently with two stem cell markers, EPCAM and keratin 19, in HCC.[69] Microarray-based transcriptome data showed that YAP1 promoted liver CSCs self-renewal activity via regulating long *nc*RNAs expression.[70] Additional work demonstrates that the adriamycin treatment significantly amplified the oncogenic effects of YAP1, and that YAP1 induced the expression of various stem-cell markers and ATP-binding cassette transporters in adriamycin-resistant HCC cells. Moreover, miR590-5p decreases HCC chemoresistance through modulating YAP1 expression, and YAP1 is dramatically upregulated in the residual/recurrent HCC after transarterial chemoembolization (TACE) treatment.[70] In addition, we also found that YAP1 expression was weakly positive in the primary HCC but was significantly increased in the residual HCC after TACE treatment (Fig. 3).

In recent years, different immunotherapies have been used to treat HCC.[71] YAP1 has been reported to play important roles in tumor cell immune escape. YAP1 contributes to the immune escape by directly binding to the enhancer to induce PD-L1 expression.[72] In HCC, the expression of YAP1 in peripheral blood mononuclear cells is positively associated with the enrichment of regulatory T cells in the tumor tissue, and is negatively associated with patient survival.[73] YAP1 exerts this effect by directly promoting TGFBR2 transcription. YAP1 also facilitates the recruitment of M2 macrophages via activating the release of the chemokines CCL2 and CSF1 for liver tumorigenesis.[74] YAP1 also upregulates CCL2 expression in hepatocytes to induce macrophage infiltration and promote HCC development.[75] A recent study also showed that through regulating monocyte chemotactic protein 1 (Mcp1), the activated YAP1 promotes macrophage infiltration, which impairs immune clearance of transforms hepatocytes, leading to HCC development.[76]

YAP1 is also overexpressed in other hepatic malignancies, such as hepatoblastoma (HB) and cholangiocarcinoma (CCA).[77] We also found high expression of YAP1 in the hepatoblastoma, especially in the embryonal component (Fig. 4). YAP1 interacts with β-catenin in hepatoblastoma, which is increased in most human hepatoblatomas. Overexpression of the activated forms of YAP1 and β-catenin in hepatocytes also promotes rapid tumor development.[78] Pei *et al*. reports that the nuclear YAP1 level is positively correlated with TNM stage and poor prognosis of CCA. YAP1 induces EMT and promotes the progression of CCA through forming a regulatory circuit with miR29c, IGF1, AKT and gankyrin.[79]

YAP1 is also correlated with situations pre-disposed to HCC development, such as nonalcoholic fatty liver disease (NAFLD). YAP1 activation increases the insulin receptor substrate IRS2, which subsequently leads to AKT activation and disease progression of NAFLD, and eventually HCC.[80] It has also been reported that the long non-coding RNA *lnc*ARSR activates the IRS2/AKT

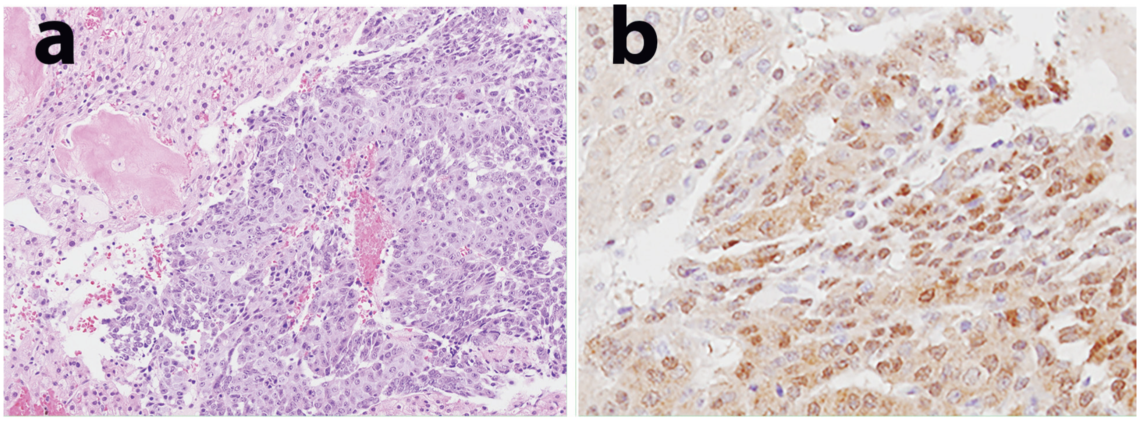

Fig. 4. YAP1 immuno-reactivity in a case of hepatoblastoma (HB). (a) Histology of HB with fetal (left) and embryonal (right) components in the background of osteoid; (b) YAP1 is weakly positive in the fetal component (left) and increased expression in the embryonal component (right) (a, H&E stain; 200×; b, YAP1, 400×).

signaling pathway by binding to YAP1 and that this binding inhibits YAP1 phosphorylation and promotes YAP1 nuclear translocation, which in turn accelerates NAFLD progression.[81]

Future directions

YAP1 functions as an important downstream effector of the Hippo signaling pathway and is a potent transcriptional co-activator that interacts with multiple transcription factors to regulate the expression of target genes. When the Hippo pathway is "on", YAP1 is phosphorylated on serine residues and retained in the cytoplasm, limiting its co-activator function in the nucleus. In contrast, when the Hippo pathway is "off," YAP1 translocates into the nucleus where it induces the expression of genes to promote the migration and proliferation of cancer cells. Elevated nuclear YAP1 has been detected in many cancers and the overexpression of YAP1 is associated with poor prognoses for gastrointestinal cancers and HCC. We hypothesize that YAP1 may serve as a treatment target for some gastrointestinal and liver cancers.

Conclusions

In conclusion, accumulating evidence reveals that YAP1 plays a crucial role in tumorigenesis, metastasis and chemoresistance in gastrointestinal cancer and HCC. This support strengthens the notion that YAP1 is a potential therapeutic target; however, further studies are required to explore novel transcription factors that mediate the function of YAP1 and additional regulatory mechanisms of YAP1 in cancer cells. These studies will greatly advance our understanding of the role of YAP1 in carcinogenesis.

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Conflict of interest

The authors declare that they have no conflict of interest regarding this article

Author contributions

XQ and WZ wrote the manuscript; HY, LZ and NK critically reviewed the manuscript; JL collected and analyzed the data and finalized the manuscript. All authors have made a significant contribution and have approved the final manuscript.

Data sharing statement

No additional data are available.

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