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Review Article

TGF-β and HIPPO Signaling Pathways Interplay in Distinct Hepatic Contexts

Victor M. Color-Aparicio[1], Angeles C. Tecalco-Cruz[2], Blanca Delgado-Coello[1], Marcela Sosa-Garrocho[1], Jaime Mas-Oliva[1], Genaro Vázquez-Victorio[3] and Marina Macías-Silva[1*]

[1]Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Mexico City, Mexico; [2]Programa en Ciencias Genómicas, Universidad Autónoma de la Ciudad de México, Mexico City, Mexico; [3]Facultad de Ciencias, Universidad Nacional Autónoma de México, Mexico City, Mexico

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Abstract

The liver plays a crucial role in maintaining whole-body homeostasis in both health and disease, engaging in important communication with other organs. The coordination of multiple signaling pathways is essential for facilitating such interorgan communication. Among these pathways, the transforming growth factor-β (TGF-β) and HIPPO signaling pathways serve critical functions as tumor suppressors, exerting pivotal control over liver development, size, and tissue regeneration. In the normal hepatic context, these pathways exhibit significant crosstalk through various molecular mechanisms. This interaction is context-dependent within the hepatic microenvironment, regulating diverse cellular processes from development to adulthood. Disruptions in the regulation of these pathways and their crosstalk contribute to the onset of liver diseases. This review delves into the intricate interplay between the canonical pathways of TGF-β and HIPPO, exploring their involvement in liver development and various pathologies such as fibrosis, cirrhosis, and tumorigenesis. Special attention is given to their impact on the epithelial-to-mesenchymal transition process, a crucial element associated with liver wound healing and cancer metastasis. By addressing these molecular interactions, the review aimed to provide insights into the underlying mechanisms that influence liver physiology and pathology, offering potential avenues for therapeutic interventions.

Introduction

Organ intercommunication occurs in multiple physiological and pathological contexts.[1] The liver is one of the main organs that establishes important crosstalk with other organs to maintain whole-body homeostasis, supported by the interplay of multiple signaling pathways.[1] Interestingly, the network of key signaling pathways responsible for orchestrating morphogenesis during embryonic development is reactivated during wound healing and tumorigenesis.[2]

The liver sustains active communication with other organs, which is crucial for the regulation of multiple cellular processes.[1] In liver regeneration, for instance, the liver communicates with other organs, such as the brain, pancreas, intestine, and heart, mainly through cell-cell communication using chemical messengers such as hormones, cytokines, and growth factors.[3] This cellular communication is crucial to restoring hepatic homeostasis after any damage. Among all these signals, the transforming growth factor-β (TGF-β) and HIPPO signaling pathways are particularly relevant, exerting critical functions as tumor suppressors and exhibiting important crosstalk to regulate liver development, size, and regeneration. This review focused on describing the interplay between the TGF-β and HIPPO signaling pathways in distinct hepatic contexts, including the maintenance of liver homeostasis in health, liver regeneration, and the progression of liver diseases such as hepatitis, fibrosis, cirrhosis, and cancer.

Liver physiology and the variety of hepatic contexts in health and disease

The liver stands as a multitasking organ, undertaking crucial functions essential for overall well-being. Among its vital roles, the liver manages the metabolism of nutrients, aids in digestion by producing bile for fat digestion, and actively participates in the detoxification of blood by processing toxins, drugs, and viruses. Additionally, the liver synthesizes proteins for blood plasma, regulates blood clotting, and serves as a frontline immune tissue, contributing significantly to the body's immune response.

Keywords: TGF-β; SMAD; HIPPO; TAZ; YAP; Liver.

***Correspondence to:** Marina Macías-Silva, Departamento de Biología Celular y Desarrollo, Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán, Ciudad de México, Mexico City, C.P. 04510, Mexico. ORCID: https://orcid.org/0000-0002-3972-0983. Tel: +52-55-56225729, E-mail: mmacias@ifc.unam.mx

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The hepatic lobules are the functional units of the liver, populated by different cell types that maintain constant intercellular communication through various signaling pathways in different contexts. Hepatocytes are the most abundant parenchymal cell type (80%) in the liver, whereas the non-parenchymal cells (20%) include hepatic stellate cells (HSCs), Kupffer cells, liver sinusoidal endothelial cells (LSECs), lymphocytes, and biliary epithelial cells (BECs) or cholangiocytes.[3] The hepatic tissue is crucial during all stages of organism development and shows relevant differences regarding hepatic cell proliferation and function in early embryonic stages compared to adulthood. For instance, in adulthood, the liver is an organ whose cells rarely divide, remaining quiescent most of the time; it is estimated that one cell among 20,000 cells undergoes mitosis.[3]

Contrary to what is observed in the adult mammalian liver, where hepatic cells are typically quiescent, fetal hepatoblasts migrate together as cords while inserting between mesenchymal and epithelial cells to form the primitive liver. Hepatoblasts are bipotential cells that actively proliferate and differentiate into hepatocytes and cholangiocytes.[4] Once the hepatic vasculature is constructed, the fetal liver performs hematopoiesis around 10.5–12.5 days post-fertilization. Despite the technical issues involved in studying embryonic stages, we have a good understanding of the main phases involved in early liver development (progenitor specification, cell type-specific differentiation, and outgrowth) and the role of the placenta in providing oxygen, calcium, and possibly bile acids.[2,4]

An amazing property of the liver in adult vertebrates is its ability to regenerate. After exposure to stimuli provoking the loss of hepatic mass (e.g., the 70% partial hepatectomy (PH) model) or tissue damage, a phenomenon of rapid recovery of the original liver size occurs through a compensatory hyperplasia mechanism along with restoration of hepatic architecture and functions, known as liver regeneration (Fig. 1). Interestingly, other organs can undergo regeneration but not at the same scale as the liver, whose size is strictly regulated through an intricate signaling network. This molecular toolkit, evolutionarily acquired and improved in mammals,[3] includes pro-inflammatory and inhibitory cytokines, growth factors, members of different signaling pathways and transcription factors, as well as diverse epigenetic mechanisms. Together, they participate in the activation and deactivation of genes in a highly regulated manner.

It is important to note that all hepatic cell types contribute to recovering the liver mass and express outstanding functional and phenotypic changes. For instance, during the activation process of HSCs, these cells lose vitamin A storage, acquire a contractile myofibroblast-like phenotype, and synthesize distinct collagen types. Kupffer cells produce pro-inflammatory cytokines to promote changes in the hepatocytes that turn them responsive to growth factors. During liver regeneration after a 70% PH, all hepatic cells are activated by cytokines (e.g., interleukin-6 (IL-6) and tumor necrosis factor-alpha) and growth factors (e.g. hepatocyte growth factor and epidermal growth factor) that promote the overexpression of specific genes, allowing the cells to enter the cell cycle and go through each stage of regeneration (priming, proliferative, and termination phases). This process takes approximately seven days in rats until the mass, architecture and function of the liver are restored. All liver cells contribute to the process, with hepatocytes being the first to divide, followed by BECs, Kupffer cells, HSCs, and finally LSECs to complete the reconstruction of extracellular matrix (ECM) architecture and hepatic vasculature.[3]

Significantly, when the regenerative capabilities of the liver are surpassed, alternative scenarios unfold wherein liver cells manifest altered phenotypes in response to chemical or physical damage (Fig. 1). For instance, HSCs undergo prolonged activation with sustained exposure to damage from drugs, alcohol, or a high-fat diet. As a result, HSCs adopt a myofibroblast-like phenotype, leading to excessive production of ECM proteins, forming a perfect microenvironment for the development of fibrosis and cirrhosis, eventually leading to liver failure and, in some cases, hepatocarcinogenesis. The progression of fibrosis involves the gradual replacement of parenchymal tissue with scar tissue, altering the hepatic architecture and increasing stiffness. In the resolution stage of fibrosis, the liver returns to homeostasis, and the activated HSCs can be eliminated via apoptosis promoted by macrophages with pro-resolution properties.[5] However, if the liver damage is chronic, cirrhosis becomes a point of no return, characterized by severe scarring of the liver and significantly increasing the risk of developing hepatocellular carcinoma (HCC) (Fig. 1). Liver cancer, one of the deadliest cancers worldwide, primarily manifests as two types: HCC (malignant transformation of hepatocytes) and intrahepatic cholangiocarcinoma (ICC) (cancer of BECs).

In the aforementioned hepatic contexts, numerous signaling pathways assume pivotal roles. Therefore, understanding the intricate networks of signaling pathways contributing to the progression of liver disease is crucial for identifying potential therapeutic targets.[6] Given the significant impact chronic liver diseases have worldwide, we have recently reviewed various interdisciplinary efforts aimed at mitigating this trend.[7] In extreme cases of liver damage where patients may need a liver transplant, the situation is exacerbated by the low number of donors. Thus, options for patients with acute liver failure or severe chronic liver diseases include extracorporeal liver support devices that function while waiting for an organ donor. Another alternative provided by tissue engineering is the "recycling" of ECM obtained after liver decellularization for repopulation with healthy liver cells (bioengineered liver), which can eventually be transplanted.[7] Recently, Hans Clever's group has provided a promising alternative for personalized medicine, demonstrating that human and mouse hepatocytes can be cultured long-term as organoids with the potential to engraft and proliferate in a damaged liver.[8] Targeting key signaling pathways has been another important strategy to improve liver regeneration and restore homeostasis in hepatic diseases. Nevertheless, the main drawback of inhibiting key pathways is the potential cytotoxic side effects on normal cells.

Actions of TGF-β and HIPPO signaling pathways in the liver

The HIPPO and TGF-β pathways exert crucial functions in hepatic physiology by regulating essential cellular processes such as proliferation, differentiation, and apoptosis. These pathways control liver mass, architecture, and function from embryonic development through adulthood. The HIPPO and TGF-β signaling pathways have pleiotropic effects, and any gain or loss of their function, as well as aberrant actions, can lead to diseases such as chronic liver inflammation, fibrosis, and cancer.[9–11]

TGF-β is the prototype of a family of multifunctional polypeptides, including TGF-βs, ACTIVINs, INHIBINs, and BMPs (bone morphogenetic proteins). TGF-β initiates signaling through a complex of two types of transmembrane Ser/Thr kinase receptors, TβRII and TβRI (or activin-like kinase 5), which transduce signals via downstream effectors named (receptor-regulated SMADs) R-SMADs, such as SMAD2 and SMAD3. After phosphorylation by the type I receptor, these proteins form complexes with the common-SMAD4 for their translocation to the nucleus, where the SMAD2/3/4 complex binds to DNA sequences (tandem repeats of GTCT or AGAC), known as SMAD-binding elements (SBE) located on TGF-β target genes to tightly control their expression (Fig. 2).[12,13]

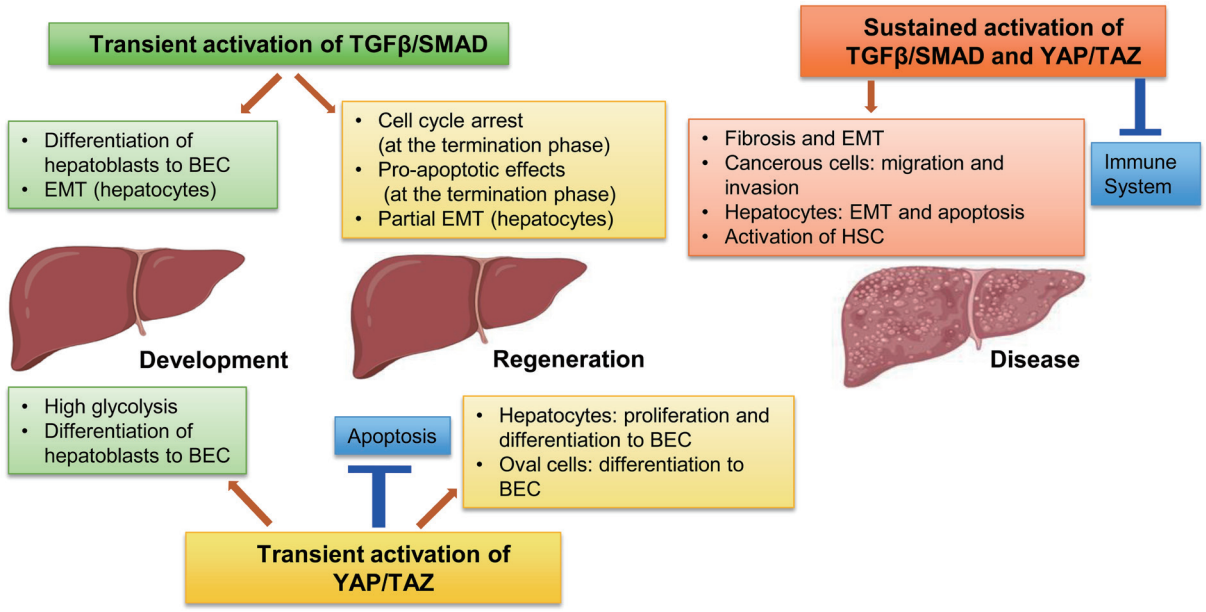

Fig. 1. The roles of HIPPO and TGF-β signaling pathways play in distinct hepatic contexts present in health and disease. BEC, biliary epithelial cells; EMT, epithelial-mesenchymal transition; HSC, hepatic stellate cells; TAZ, transcriptional co-activator with PDZ-binding motif; TGF-β, transforming growth factor-beta; YAP, Yes-associated protein.

TGF-β signaling is negatively regulated by multiple factors. For instance, the Sloan Kettering Institute (SKI) and SKI-novel (SNON) proteins are transcriptional cofactors that function as negative regulators of TGF-β signaling by associating with SMAD proteins to actively turn off the TGF-β canonical pathway through negative feedback mechanisms.[6,14] The TGF-β/SMAD signaling pathway becomes activated during murine liver regeneration, with SKI and SNON proteins being upregulated to modulate the magnitude and

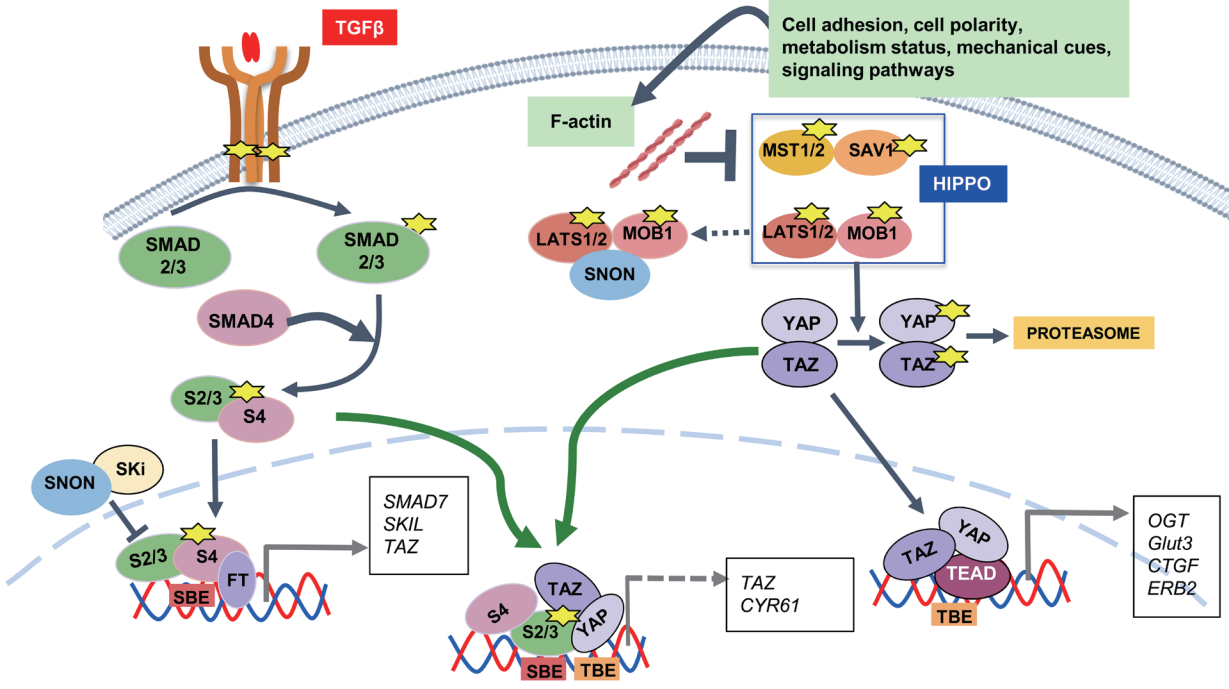

Fig. 2. The canonical HIPPO and TGF-β signaling pathways. CYR61, cysteine-rich angiogenic inducer 61; FT, factors of transcription; LATS, large tumor suppressor; MOB, mob kinase activator; MST, mammalian sterile 20-like kinase; SBE, SMAD-binding elements; SKI, Sloan Kettering Insitute; SKIL, SKI-like; SNON, SKI-novel; TAZ , transcriptional co-activator with PDZ-binding motif; TBE, TEAD-binding elements; TEAD, transcriptional enhanced associate domain; TGF-β, transforming growth factor-beta; YAP, Yes-associated protein.

duration of the TGF-β/SMAD pathway functions in this context (Fig. 2).[15–17] Additionally, evidence shows that SNON/SKI protein stability is differentially regulated by actin cytoskeleton dynamics in hepatic cells, similar to how YAP/TAZ (Yes-associated protein 1/transcriptional co-activator with PDZ-binding motif) stability is controlled by F-ACTIN cytoskeleton rearrangements. Intriguingly, there is evidence that SNON promotes TAZ protein stabilization and signaling in human breast cancer by sequestering LATS kinase.[18] Given the relevance of HIPPO/TGF-β crosstalk in liver regeneration, this positive regulation of TAZ by SNON deserves investigation in the hepatic context.

In liver cancer, the tumor microenvironment dictates that TGF-β functions as a tumor suppressor in early stages but becomes a tumor promoter in advanced stages.[19] Snorri Thorgeirson's group reported two main TGF-β-dependent gene expression signatures in mouse hepatocytes that are useful for predicting clinical outcomes in human liver cancer and distinguishing between subgroups of HCC.[20] An early TGF-β signature (high expression of anti-proliferative and anti-apoptotic genes) correlated with a good prognosis for patients with liver cancer, whereas a late TGF-β signature (high expression of invasion-related, epithelial-mesenchymal-transition (EMT), and anti-apoptotic genes) was associated with tumor recurrence and metastasis.[20,21]

The HIPPO signaling pathway is regulated by diverse upstream signals such as cell polarity, cell adhesions, mechanical forces, cytoskeleton dynamics, G protein coupled receptors (GPCR) ligands, and some stress signals.[22] The HIPPO pathway comprises two core kinases, mammalian sterile 20-like kinase 1 (MST1) and MST2, which activate large tumor suppressor 1 (LATS1) and LATS2 kinases through phosphorylation.[10,23,24] A cytoskeletal protein named NF2/moesin-ezrin-radixin like (MERLIN) regulates MST1/2 kinases and their adaptor protein SAV1/WW45, while activators MOB kinase activator 1A (MOB1A) and MOB1B regulate LATS1/2. The main effectors of the HIPPO signaling pathway are the transcriptional co-regulators TAZ/WW domain-containing transcription regulator 1 (WWTR1) and YAP, which are negatively regulated by HIPPO signaling (Fig. 2). In the liver, signals like mechanical forces generated by the F-ACTIN cytoskeleton and high energy levels may negatively regulate HIPPO signaling. When the HIPPO pathway is active, the LATS1 and LATS2 kinases phosphorylate YAP and TAZ, leading to their inactivation. Other post-transcriptional modifications can modulate YAP/TAZ protein stability and activity, such as ubiquitination, methylation, acetylation, and O-GlcNAcylation.[25] YAP/TAZ inactivation might occur through several mechanisms, such as their phosphorylation resulting in exclusion from the nucleus, or their ubiquitination promoting degradation via the proteasome.[10,26] When the HIPPO pathway is inactive, MST1/2 and LATS1/2 kinases are inactivated, allowing YAP and TAZ to become active and translocate to the nucleus to regulate gene expression. YAP and TAZ are ubiquitously expressed transcriptional cofactors that share similar structures and functions and may be regulated by similar mechanisms, although they have different roles from development to adulthood. Notably, YAP/TAZ co-regulators can interact with many other transcription factors besides transcriptional enhanced associate domain (TEADs), such as RUNX2 (runt-related transcription factor 2), TBX5 (T-box transcription factor 5), P73, and SMADs, allowing for the control of specific context-dependent gene expression (Fig. 2).[10] Thus, they can regulate the expression of target genes related to several cellular processes, such as proliferation, differentiation, and EMT.[10,27–29]

In the liver, the HIPPO pathway is one of the main signaling pathways sustaining hepatic physiology. It plays a crucial role in maintaining the quiescence of hepatic cells and contributes to proper metabolic zonation of the liver.[30,31] Consequently, deregulation of the HIPPO pathway, along with other factors, has been associated with metabolic diseases such as type 2 diabetes, and non-alcoholic fatty liver disease. Moreover, overexpression of YAP and TAZ in the liver promotes cell proliferation that may lead to hepatomegaly and eventually hepatocarcinogenesis, revealing an outstanding role in regulating organ size in various scenarios.[27,32] For instance, during liver regeneration, HIPPO signaling becomes relevant for controlling mouse liver size, as shown in the conditional liver double knockout of *YAP* and *TAZ*, where regeneration is impaired, causing a longer restoration period for liver mass.[27,33] In contrast, studies in young mice show a redundancy of other pathways that permit liver regeneration to take place but at a slower rate.[34] When mice livers are exposed to chronic damage, liver repair is associated with fibrosis, and in this context, HSCs are activated for extended periods, producing excess ECM proteins. YAP is activated during HSC activation triggered by different stimuli and is associated with increased ECM protein deposition in the long term. Meanwhile, other non-parenchymal cells, such as LSEC, also show YAP activation, promoting angiogenesis and thereby increasing mice liver damage.[35] In these hepatic contexts, TGF-β and HIPPO pathways converge to regulate organ size, regeneration, and fibrosis, but the mechanisms involved require further studies.

Furthermore, genetic alterations of some HIPPO signaling components, such as knockouts (*NF2*, *SAV1*/*WW45*, or *MST1*/*2*) or overexpressions (*YAP* or *TAZ*), promote liver overgrowth and tumorigenesis.[30,36–41] Although DNA mutations in the main HIPPO pathway components are rare, irregular activation of YAP/TAZ in liver cancer has been described, although the molecular mechanisms involved remain uncertain.[10,41–46] In liver cancer, YAP/TAZ activation can also be regulated by many extrinsic signals, such as growth factors, cytokines, stress signals, altered metabolic conditions, autophagy, and mechanical forces.[47–55] Intriguingly, YAP/TAZ also cooperate with different signaling pathways in a context-dependent manner, such as TGF-β, RTK/PI3K, WNT, and NOTCH signaling.[56–60]

Crosstalk between TGF-β and HIPPO signaling pathways in distinct hepatic contexts

A major crosstalk between the HIPPO and TGF-β pathways occurs to control liver size and regeneration, while their deregulation promotes fibrosis and hepatocarcinogenesis. It is well known that both pathways inhibit cell proliferation and maintain hepatocyte homeostasis, acting primarily as tumor suppressors.[19,57,61] HIPPO downstream effectors, such as TEAD and TAZ/YAP, can function as cofactors of the TGF-β/SMAD canonical pathway, since some gene promoters contain both SBE and TBE (TEAD-binding elements) (Fig. 3). When HIPPO signaling is inactive, dephosphorylated YAP and TAZ proteins translocate to the nucleus, where they associate with members of the TEAD transcription factor family to bind target gene promoters, inducing the expression of genes involved in cell proliferation and inhibition of apoptosis.[62] In the context of low cell density, the HIPPO pathway is likewise inactive, allowing YAP/TAZ to facilitate the accumulation of SMAD proteins in the nucleus in response to TGF-β. Consequently, SMAD/YAP/TAZ complexes can synergize transcriptionally (Fig. 3).[57,60,61,63–65] In contexts such as breast cancer cells, where TGF-β/SMAD signaling is active, this pathway may cooperate with YAP/

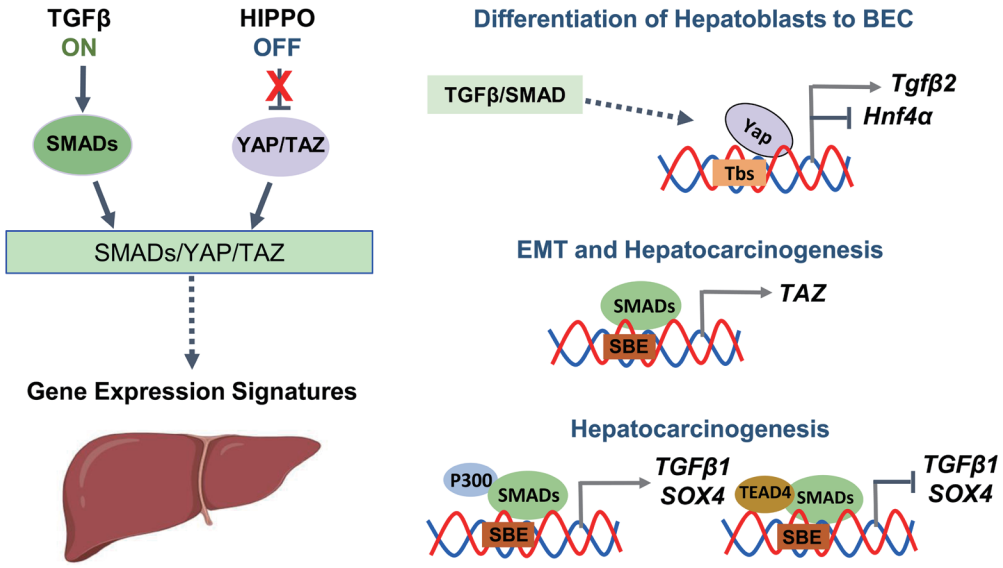

Fig. 3. Gene expression is regulated by the HIPPO/YAP/TAZ and TGF-β/SMAD crosstalk in the liver. BEC, biliary epithelial cells; EMT, Epithelial-Mesenchymal Transition; HNF4α, hepatocyte nuclear factor alpha; SBE, SMAD-binding elements; TAZ, transcriptional co-activator with PDZ-binding motif; Tbs, TEAD binding sites; TGF-β, transforming growth factor-beta; YAP, Yes-associated protein.

TAZ to induce fibrogenic factors, such as *CTGF*, *NEGR1*, and *UCA1*, as well as genes encoding ECM proteins.[66] Therefore, the close relationship between TGF-β and HIPPO pathways in the development of fibrosis and cirrhosis merits further studies.

The involvement of the HIPPO and TGF-β pathways in tumorigenesis has been extensively investigated. It is well-established that the interplay between these pathways can induce the EMT process.[67] EMT is a key hallmark of cancer related to metastasis, although it also becomes activated during development and wound healing. In this process, epithelial cells can completely or partially transdifferentiate (partial EMT), losing epithelial markers and acquiring characteristics similar to mesenchymal cells. This is crucial for cancerous cells, as EMT confers features such as resistance to apoptosis, drug resistance, cancer stem cell characteristics, and invasive abilities.[68,69] Recently, it was shown that the *TGFB1* gene is overexpressed in the murine AS-30D hepatocarcinoma, and more importantly, treatment of these cells with TGF-β increased the levels of phospho-SMAD2 and the expression of several mesenchymal markers.[70] Given the potential of AS-30D cells to undergo EMT, the plausible interplay between the TGF-β and HIPPO signaling pathways in this HCC model is evident.

EMT is regulated by different signals depending on the context. For instance, TGF-β signaling may cooperate with YAP/TAZ to induce EMT in liver cancer.[67,70] The expression of *TAZ* is enhanced in cancer cells from brain, breast, pancreas, and liver tumors,[42,71–74] and appears to mediate cancer stem cell characteristics promoted by TGF-β/SMADs.[60,63,64] In liver cancer, YAP and TAZ promote cellular proliferation, stem cell marker expression, and EMT.[73,75–77] In fact, EMT may serve as a self-sustaining mechanism for TAZ expression and activation.[74] The molecular mechanisms regulating *TAZ/WWTR1* gene expression are poorly studied. Thus far, the *TAZ/WWTR1* gene is regulated by several transcriptional factors such as STAT3, SMAD3, MRTF, and HIF1, whereas different miRNAs regulate *TAZ* mRNA translation. Recent evidence shows that TGF-β cytokine uses distinct molecular mechanisms to control *TAZ/WWTR1* gene expression in a context-dependent manner: Firstly, a non-canonical TGF-β pathway can increase TAZ levels in murine fibroblasts and some pig epithelial cells in a P38/MRTF-dependent and SMAD3-independent manner.[78] Secondly, the synergistic action of IL-6 and TGF-β pathways is essential for inducing *TAZ/WWTR1* gene expression in mouse CD4+ lymphocytes, leading to their differentiation into Th17 cells. This phenomenon is intriguing given that TAZ deficiency promotes the differentiation of lymphocytes toward regulatory T cells (Treg).[79] Notably, the TGF-β pathway regulates *TAZ/WWTR1* gene expression depending on the cellular context and species-specific gene promoter. This evidence suggests that TGF-β predominantly controls *TAZ/WWTR1* gene expression through Smad-independent pathways or in collaboration with other signaling pathways such as IL-6/STAT3.[78,79]

There is evidence in human HCC samples of a correlation between the upregulation of TGF-β and HIPPO pathway components with increased levels of EMT markers, as shown by analyzing LIHC public datasets.[80,81] In contrast to previous reports, we recently described that the TGF-β/SMAD pathway promotes human *TAZ/WWTR1* gene expression and enhances TAZ protein levels in human cancer hepatic cells. Thus, TAZ is a primary target of TGF-β signaling, a major pathway in hepatic cancer development.[80] Moreover, our investigation revealed that the human *TAZ/WWTR1* gene promoter encompasses both canonical and non-canonical SBEs. Particularly noteworthy is the identification of a TRE (TGF-β-response element) within the *TAZ/WWTR1* gene promoter, formed by canonical SBEs.[80] Consequently, our findings indicate that the TGF-β/SMAD canonical pathway plays a regulatory role in TAZ expression within human hepatic cancer cells by amplifying *TAZ/WWTR1* gene transcription and enhancing TAZ protein stability (Fig. 3). Our findings suggest that TGF-β/SMAD signaling might cooperate with TAZ in liver cancer progression, probably through the regulation of a specific gene signature. Furthermore, the conflicting evidence suggesting that TGF-β regulates *TAZ/WWTR1* gene expression through SMAD or non-SMAD signaling needs further investigation to elucidate the relevance of the differential regulation of *TAZ/WWTR1* gene expression depending on the cellular context and species-specific gene promoter.

The crosstalk between TGF-β and HIPPO pathways is crucial in various hepatic contexts, from embryonic development to homeostasis and disease in adulthood. The interplay between these pathways may generate a TGF-β/SMAD/YAP/TAZ axis that likely controls specific gene expression networks depending on the different hepatic contexts present in liver health or disease (Fig. 3). Studies on mouse embryo development show that TGF-β and HIPPO pathways cooperate to promote mesoderm to endoderm differentiation during liver formation and maturation; in this context, YAP activation in hepatoblasts promotes increased TGF-β signaling, leading to hepatoblast differentiation into BECs.[2,11,31] Moreover, some murine models, such as mice liver-conditional KO of *LATS1/2* kinases are used to study the fate of hepatic progenitors.[82] In BECs obtained from these livers, the loss of *LATS1/2* promotes SMAD2/3 nuclear localization and the binding of YAP to the mouse *TGFB2* gene promoter, resulting in the upregulation of genes such as *TGFB2*, *CK7/KRT7*, and *CK9/KRT9*. YAP also promotes the downregulation of HNF4α (Hepatocyte Nuclear Factor 4 alpha) by binding to the mouse *HNF4a* gene promoter, influencing cells fate determination by inducing hepatoblast differentiation into BECs.[82] This model demonstrates the crosstalk between HIPPO and TGF-β signaling pathways in the differentiation of mouse hepatoblasts into BECs.[82–84]

Liver regeneration is a primary context where the interplay between TGF-β and HIPPO pathways is evident. After PH in mice, the nuclear localization of SMAD2 and YAP increases in proliferating hepatocytes undergoing partial EMT, correlating with the upregulation of *SNAI1*, *ZEB1*, *aSMA*, *COL1a1*, *VIM*, *MMP9,* and *QSOX1* genes, and the downregulation of *CDH1* (E-cadherin) and *ALB* genes. In this model, TGF-β and YAP1 cooperate to induce partial EMT in hepatocytes, which acquire fibroblast-like characteristics, allowing hepatocytes to proliferate and manage anti-proliferative signals present in the microenvironment.[67] In a human cell line of HSCs, *TAZ* overexpression induces the upregulation of genes associated with fibrosis, such as *TGFB1* and *SNAI1*.[85] In a rat model of hepatic fibrosis induced by diethyl-nitrosamine, the nuclear co-localization of SMAD2/3 and YAP/TAZ increases, along with the upregulation of MMP2, MMP9, and TIMP1 proteins, and the downregulation of MMP1 protein.[86] Additionally, in human hepatic fibrosis, TGF-β can promote the activation of PYK2 (proline-rich tyrosine kinase 2), while SRC (Sarcoma kinase) activates the RHOA/ROCK axis, increasing YAP nuclear localization in an HSC cell line. Together, TGF-β and HIPPO pathways cooperate to upregulate genes such as *CTGF* and *CYR61* in activated human HSC cell line.[87] Intriguingly, SIRT6, a NAD-dependent deacetylase, has therapeutic potential as it protects against liver fibrosis by deacetylating key lysine residues on SMAD2, SMAD3, YAP, and TAZ, causing their inactivation.[88–90] Thus, liver regeneration benefits from the interplay between TGF-β and HIPPO pathways.

The main types of liver cancer, ICC and HCC, are induced in the *MOB1a*/*MOB1b*-deficient mouse model. In this liver cancer model, there is an observed increase in the nuclear co-localization of SMAD2 and YAP/TAZ, along with increased levels of CTGF, TGF-β2, and TGF-β3 protein levels.[91] Moreover, the upregulation of YAP, SMAD2/3, and TGF-β2, combined with the downregulation of MOB1, may serve as a prognostic indicator of poor survival for ICC patients.[92] In human HCC cells, TGF-β promotes an increase in the nuclear localization of the SMAD2/3 complex, which can recruit P300 to promote the expression of *TGFB1* and *SOX4* genes, associated with increased proliferation, migration, and invasion of HCC cells. Intriguingly, the ectopic expression of TEAD4 in these HCC cells allows TEAD4 to associate with SMAD2/3/4, competing with P300 to repress *TGFB1* and *SOX4* gene expression, through a YAP/TAZ-independent mechanism. This crosstalk between TGF-β/SMADs and HIPPO/TEAD4 in cancer is relevant as it inhibits specific gene expression signatures related to HCC progression.[93]

Conclusions

The interplay between the HIPPO and TGF-β canonical pathways plays a significant role in various hepatic contexts. In certain scenarios, the inactivation of the HIPPO pathway leads to the activation of its principal downstream effectors, the transcriptional cofactors YAP and TAZ. The activation of these cofactors can intersect with the activation of the TGF-β/SMAD pathway, forming an axis termed SMAD/YAP/TAZ. This axis effectively governs specific gene expression signatures that may contribute to diverse physiological or pathological processes in the liver. Therefore, it is imperative to identify these genetic signatures to delineate potential targets for therapeutic interventions.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Conceptualization of the review (MMS); collection of information (VMCA, ACTC, BDC, MSG, JMO, GVV, MMS); writing of original draft (VMCA, ACTC, BDC, MMS); figures (VMCA, MSG); intellectual input, critical manuscript revisions, and final draft approval (all authors).

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