Physiological and pathological roles of the Hippo-YAP/TAZ signaling pathway in liver formation, homeostasis, and tumorigenesis

Hiroshi Nishina

Department of Developmental and Regenerative Biology, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan

Correspondence
Hiroshi Nishina, Department of Developmental and Regenerative Biology, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan. Email: nishina.dbio@mri.tmd.ac.jp

Abstract
The liver plays central homeostatic roles in metabolism and detoxification, and has a remarkable capacity to fully recover from injuries caused by the various insults to which it is constantly exposed. To fulfill these functions, the liver must maintain a specific size and so must regulate its cell numbers. It must also remove senescent, transformed, and/or injured cells that impair liver function and can lead to diseases such as cirrhosis and liver cancer. Despite their importance, however, the mechanisms governing liver size control and homeostasis have resisted delineation. The discovery of the Hippo intracellular signaling pathway and its downstream effectors, the transcriptional coactivators Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), has provided partial elucidation of these mechanisms. The Hippo-YAP/TAZ pathway is considered to be a cell’s sensor of its immediate microenvironment and the cells that surround it, in that this pathway responds to changes in elements such as the ECM, cell–cell tension, and cell adhesion. Once triggered, Hippo signaling negatively regulates the binding of YAP/TAZ to transcription factors such as TEAD and Smad, controlling their ability to drive gene expression needed for cellular responses such as proliferation, survival, and stemness. Numerous KO mouse strains lacking YAP/TAZ, as well as transgenic mice showing YAP/TAZ hyperactivation, have been generated, and the effects of these mutations on liver development, size, regeneration, homeostasis, and tumorigenesis have been reported. In this review, I summarize the components and regulation of Hippo-YAP/TAZ signaling, and discuss this pathway in the context of liver physiology and pathology.

KEYWORDS
Hippo pathway, homeostasis, liver cancer, liver size, regeneration, YAP/TAZ

Abbreviations: AA, arachidonic acid; COL17A, collagen XVII; Dox, doxycycline; FLSPC, fetal liver stem/progenitor cell; LATS, large tumor suppressor homolog kinase; Hpo, Drosophila melanogaster kinase Hippo; Mob, Mps1 binder kinase activator; MST, mammalian STE20-like protein kinase; PGE\(_2\), prostaglandin E\(_2\); Sav1, Salvador homolog-1; TAZ, transcriptional coactivator with PDZ-binding motif; TEAD, transcriptional enhanced associate domain; TF, transcription factor; VGLL4, transcription cofactor vestigial-like protein 4; YAP, Yes-associated protein.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. Cancer Science published by John Wiley & Sons Australia, Ltd on behalf of Japanese Cancer Association.
1 | INTRODUCTION

During mammalian embryogenesis, the liver develops from the foregut derived from the endoderm and functions as a site of hematopoiesis (Figure 1). In the adult, this hematopoietic function is lost and the liver instead plays a central role in metabolism that involves the synthesis, storage, and redistribution of nutrients. The liver is also a major detoxifying organ, removing waste and xenobiotics through metabolic conversion and biliary excretion. Undesirable substances in the gastrointestinal tract enter the liver by way of the portal vein and diffuse through its structure through small blood vessels known as hepatic sinusoids. These sinusoids wind among the several different cell types composing the liver mass, including hepatocytes, which metabolize and detoxify substances, liver sinusoidal endothelial cells, which form the walls of sinusoids and cover the hepatocytes, and Kupffer cells, which are sinusoid-resident macrophages.

For the liver to properly function and maintain homeostasis, it must achieve and preserve a specific size. To this end, the liver must regulate its cell numbers while removing senescent, transformed, and/or damaged cells that can impair function and lead to liver diseases such as cirrhosis and cancer. The liver has a striking capacity to recover from injuries caused by various insults, such as surgical resection, viral infection, metabolic disorders, and chemical or toxic stresses. Interestingly, the processes underlying liver recovery differ depending on the type of injury. In the case of a partial hepatectomy in which 70% of the liver tissue is surgically removed, the remaining 30% returns the liver to near-original size through cell hypertrophy and cell proliferation. However, the precise mechanisms that the liver uses to control its size and maintain everyday homeostasis have been difficult to resolve.

The discovery of the Hippo-YAP/TAZ pathway has provided clues that could solve some of the above mysteries. Genetic studies using KO and transgenic mice have revealed that the Hippo-YAP/TAZ pathway is a key regulator of organ size, regeneration, and homeostasis in many tissues, and that perturbations in the Hippo-YAP/TAZ pathway can lead to the development of various cancers. Many excellent review articles have been written about these strains and their phenotypes. So as not to repeat these outstanding efforts, I focus in this review on the roles of the Hippo-YAP/TAZ pathway in mammalian liver physiology and pathology, specifically with respect to this organ’s development, regeneration, mechanisms of size control and cell competition, and tumorigenesis.

2 | HIPPO-YAP/TAZ SIGNALING PATHWAY

2.1 Components of Hippo-YAP/TAZ signaling

The Hippo signaling pathway is an evolutionarily conserved regulator of cell proliferation and organ size control during embryogenesis, tissue regeneration, stem cell self-renewal, and tumorigenesis. In mammals, the core components of the Hippo pathway are MST1/2, which are mammalian homologues of Hpo, the MST adaptor protein Sav1, LATS1/2, and their adaptor proteins Mob1a/1b (Figure 2A). The major effectors downstream of the Hippo core are the transcriptional coactivators YAP and its paralog TAZ. Activation of the Hippo core components results in the phosphorylation of conserved serine residues in YAP/TAZ. Phosphorylated YAP/TAZ proteins either undergo proteasomal degradation in the cytoplasm, or are retained in the cytoplasm by binding to the phosphoserine/phosphothreonine-binding protein 14-3-3. Thus, Hippo activation negatively regulates YAP/TAZ activity. Conversely, a lack of triggering of Hippo signaling, or inactivation of a pathway element, allows unphosphorylated YAP/TAZ to translocate into the nucleus. These coactivators then bind to various TFs, including TEAD1/2/3/4, Smad1/2/3, p73, KLF5,
Runx1/2, ErbB4, TBX5, and FoxO1, and enable them to drive expression of their target genes. As a result, YAP/TAZ control a myriad of cellular responses such as cell proliferation, apoptosis, competition, and contact inhibition, as well as the epithelial–mesenchymal transition. In the liver, the dominant TFs binding to YAP/TAZ are the TEADs, and the main target genes activated by TEADs in the liver include Ctgf, Cyr 61, and Birc5, also known as Survivin. The expression of these TEAD target genes is balanced by VGLL4, which competes with YAP/TAZ for binding to the TEADs and represses TEAD target gene expression.16,17

2.2 | Regulation of Hippo-YAP/TAZ signaling

The Hippo-YAP/TAZ pathway is a sensor of the mechanical properties of the extracellular environment surrounding a cell and a
regulator of cellular integrity. Cellular stresses that impinge on the cell membrane, such as stiffness of the ECM, fluid shear stress, cell tension, cell stretching, altered cell shape, and cell–cell contact, initiate a chain of events that leads to activation or inactivation of Hippo signaling and thus inactivation or activation of YAP/TAZ, followed by specific effects on cell behavior (Figure 2B). In particular, cell stresses trigger the activation of intracellular Rho GTPases, which may also be stimulated (or inhibited) following the binding of soluble extracellular factors, such as lysophosphatidic acid and sphingosine-1 phosphate, to surface G protein-coupled receptors.18,19 Once activated, these Rho GTPases induce the remodeling of F-actin within the cell, which in turn can control the coactivation function of YAP/TAZ in both LATS1/2-dependent and -independent ways.20,21 When F-actin inactivates LATS1/2, YAP/TAZ avoid phosphorylation, translocate to the nucleus, and enable TEAD-mediated target gene expression. The functions of these genes then allow the cell to take action to alleviate the stress. For example, consider “cell contact inhibition”, which is a well-known phenomenon in which cells in monolayer culture stop proliferating when they reach confluence. In response to cell–cell contact, the angiomotin complex at the tight junction directly binds to YAP/TAZ. Angiomotin then stimulates LATS-dependent phosphorylation of YAP/TAZ that inhibits their activity.22 The cells can no longer transcribe the genes driving proliferation and culture overgrowth is prevented. Conversely, when Hippo signaling is inactivated by loss of function of a kinase or adaptor protein, YAP/TAZ activity in the nucleus is uncontrolled, cell proliferation is rampant, and tumorigenesis can initiate. Thus, although the Hippo-YAP/TAZ pathway has properties shared by many other existing signaling pathways, it also displays unique regulatory mechanisms.

### Functions of Hippo-YAP/TAZ Signaling in the Liver

Tissues and organs undergo stress that can lead to damaged, senescent, and/or transformed cells requiring elimination. The loss of these cells must then be compensated for by cell proliferation, which maintains the size and functionality of the tissues and organs. The liver functions normally over a long period of time despite being exposed to more stress than most tissues, suggesting the existence of a variety of mechanisms that maintain liver homeostasis starting from birth. Some of these mechanisms involve Hippo signaling and YAP/TAZ regulation.23

#### 3.1 Early embryogenesis and liver development

Various animal-based methods of studying the Hippo-YAP/TAZ pathway have been reported (Table 1). Yap KO (Yap−/−) mouse embryos are lethal around embryonic day 8.5 (E8.5).24 Taz−/− mice are viable but develop glomerulocystic kidney disease and pulmonary disease.

| Mouse strain                  | Phenotype                                                                 | References |
|-------------------------------|---------------------------------------------------------------------------|------------|
| Yap−/− embryos                | Developmental arrest around E8.5                                           | 24         |
| Taz−/− mice                   | Viable; some adults develop kidney disease and pulmonary disease          | 25–27      |
| Yap−/− Taz−/− embryos         | Embryos die before the morula stage (16–32 cells)                        | 28         |
| ApoE/rtTA; TetO-Yap mice       | Massive hepatomegaly (5-fold increase), liver cancer                      | 32         |
| LAP/T; TetO- Yap (S127A) mice  | Greater than 4-fold increase in liver size                                | 33         |
| Mst1−/−; Mst2−/−, Albumin-Cre  | Increased liver size and liver cancer                                     | 15         |
| Mst1−/−; Mst2−/−, Adenovirus Cre mice | Increased liver size and liver cancer                               | 34         |
| Sav (WW45)−/−; Albumin-Cre mice | Increased liver size and liver cancer                                     | 35         |
| Lat1−/−; Lat2−/−, Albumin-Cre mice | Massive hepatomegaly                                                 | 36         |
| Mob1a−/− Mob1b−/− embryos      | Defective primitive endoderm formation                                   | 29         |
| Mob1a−/− Mob1b−/− mice         | Liver cancer, skin cancer, and exostosis                                  | 29         |
| Yap−/−, FoxA3-Cre mice         | Absence of intrahepatic biliary network                                   | 30         |
| siRNA against MST1/2           | Improved liver regeneration in aged WT mice                              | 38         |
| Plasmid Albumin-Yap (S127A) by HTVi | Enhanced elimination of injured hepatocytes                               | 54         |
| Yap−/− Taz−/−, AAV-Cre mice    | Liver cancer suppression due to peritumoral YAP/TAZ activation            | 39         |
| MST1/2 inhibitor, XMU-MP−1     | Promotion of liver repair and regeneration                               | 56         |
| siYAP-Lipid Nanoparticles      | Restoration of hepatocyte differentiation in liver cancer and tumor regression | 57         |
disease.\(^{25-27}\) Yap\(^{−/−}\)/Taz\(^{−/−}\) embryos die before the morula stage (16–32 cells).\(^{28}\) Mob1a\(^{−/−}\)/Mob1b\(^{−/−}\) blastocysts are normal at E3.5 but fail to form primitive endoderm.\(^{29}\) Thus, YAP/TAZ play essential roles in mouse early embryogenesis.

With respect to the liver, development of this organ in mice initiates around E9, when epithelial cells of the foregut endoderm interact with the cardiogenic mesoderm and commit to becoming the liver primordium. Around E14.5, bipotential hepatoblasts give rise to both hepatocytes and bile duct epithelial cells. The hepatocytes become major elements of the postnatal liver and this organ’s main function switches from hemopoiesis to metabolism.\(^{1,2}\) Deletion of YAP in bipotential hepatoblasts achieved in FoxA3-Cre mice led to a complete loss of the intrahepatic biliary tree in adult mutant mice but did not impair hepatoblast differentiation into hepatocytes.\(^{30}\) Thus, YAP is a key regulator of bile duct development. There are several pediatric diseases that affect the bile ducts, such as Alagille syndrome and biliary atresia. These mouse findings imply that perturbations in YAP function could contribute to the pathogenesis of these human disorders.\(^{31}\)

### 3.2 Liver size control and regeneration

The Hippo-YAP pathway controls liver size, as evidenced by studies showing that YAP overexpression in mouse liver induced hepatomegaly.\(^{32,33}\) Interestingly, this increase in liver mass was completely reversible since cessation of YAP hyperactivation resulted in a normal-sized liver without any gross abnormalities. To explore YAP’s role in this process in detail, Dong et al. generated transgenic mice carrying a tetracycline (Tet)-On system that induced conditional YAP activation.\(^{32}\) When provided with Dox-containing drinking water, these transgenic mice developed massive hepatomegaly and showed YAP hyperactivation in hepatocytes. The elevation in liver mass was detectable as early as 3 days after induction, and whereas a normal liver constitutes approximately 5% of body weight, livers in these mutants reached 25% of total body weight after 4 weeks of Dox treatment. The increase in liver mass was caused by an expansion in cell numbers (hyperplasia) as opposed to an increase in cell size (hypertrophy). Strikingly, by 2 weeks after Dox withdrawal, the enlarged livers had returned to near-normal size due largely to hepatocyte apoptosis. However, when the mice were exposed to Dox for over 8 weeks, they developed hepatocellular carcinoma. This study dramatically demonstrated the tight regulation of liver size. In addition to YAP mutants, mice with liver-specific deficiencies of Mst1/2, Sav1, Lats1/2, or Mob1a/1b all show sustained YAP activation leading to hepatomegaly.\(^{15,29,34-36}\) These results reveal a direct link between dysregulation of Hippo-YAP/TAZ signaling in liver size control, and hepatomegaly and tumorigenesis.

In Yap\(^{−/−}\)/Taz\(^{−/−}\)/Albumin-Cre mutant mice, YAP and TAZ are specifically depleted in the liver, and consequently liver mass was increased in neonates and adults.\(^{37}\) However, hepatocytes of these YAP/TAZ-deficient livers showed profound defects in processes needed to support liver regeneration, including the coordination of cell cycle entry. This apparent discrepancy could be due to the loss of suppression of other cell proliferation signals caused by inactivation of the Hippo-YAP/TAZ pathway, which could result in an increase in mass of YAP/TAZ-deficient livers. A similar link exists for liver regeneration, in that YAP/TAZ activation induced by siRNA-mediated inactivation of MST1/2 provoked hepatocyte proliferation in quiescent livers of aged WT mice subjected to two-thirds partial hepatectomy.\(^{38}\) Thus, YAP/TAZ are required in more than one way in the mouse liver, with their regulatory roles in liver formation during fetal development differing from their multiple influences on liver regeneration in the adult.

### 3.3 Liver cancer formation and suppression

There is now much evidence that dysregulation of the Hippo-YAP pathway promotes liver cancer formation. The overexpression of YAP in mouse liver caused by any one of numerous defects in the Hippo pathway induced not only hepatomegaly but also eventually liver cancer.\(^{15,29,32-36}\) Liver-specific Mob1a/1b double-deficient mice also developed liver cancer, which could be suppressed by inactivation of the YAP gene in these animals.\(^{29}\) In general, the liver phenotypes arising from impairment of any step of the Hippo pathway are strongly dependent on YAP. Thus, hyperactive YAP functions as an oncogene, promoting liver overgrowth and liver cancer formation.

Although hyperactivated YAP/TAZ are most often function as drivers of tumor growth, there are some reports of YAP/TAZ also exerting a tumor-suppressive function. In one study of mouse liver cancer development, some normal hepatocytes surrounding a liver tumor were found to exhibit activated YAP/TAZ, and deletion of YAP/TAZ in these peritumoral hepatocytes accelerated tumor growth.\(^{39}\) Conversely, hyperactivation of YAP in peritumoral hepatocytes triggered the regression of primary liver cancers. In this model, the survival of the tumor cells clearly depended on the relative levels of YAP/TAZ activity in the tumor cells compared to the surrounding normal hepatocytes. These results indicate that, when YAP/TAZ act to eliminate tumor cells, they do so through a mechanism of cell competition and not by direct regulation of target genes in cancer cells.

### 3.4 Cell competition

“Cell competition” is a type of cell–cell interaction that was originally discovered in the imaginal wing disc of Drosophila melanogaster.\(^{40}\) During cell competition, a cell compares its fitness to that of its neighboring cells. Cells that are less fit than their neighbors are “losers” and are eliminated by either apoptosis or apical extrusion; cells that are more fit are the “winners” and survive. For example, within the Drosophila wing disc, cells that were heterozygous for the Minute gene, which encodes a ribosomal protein, underwent apoptosis as losers when they were confronted with WT cells (Figure 3A).\(^{41,42}\) Activation of the Src oncogene also turns Drosophila cells into losers,
whereas increased activity of the Myc oncogene or the YAP ortholog Yki turns Drosophila cells into winners. These studies set the stage for the study of Hippo-YAP/TAZ signaling in the mammalian context.

3.4.1 | Mammalian tissue studies

Mammalian cell competition has been reasonably well studied in mice and rats. Mouse epiblasts are a pluripotent cell population first formed in preimplantation embryos, and the normal function of these cells is important for proper embryonic development. It was shown that YAP-TEAD signaling regulated the expression of pluripotency factors and eliminated any cells lacking these factors through cell competition (Figure 3B).

Mouse embryonic stem cells or epiblasts showing low Myc levels also underwent apoptosis and were eliminated (Figure 3C). In mouse intestinal epithelium, metabolic changes mediated by pyruvate dehydrogenase kinase 4 promoted the elimination of active Ras-transformed cells. In mouse epidermal stem cells, protein levels of the skin hemidesmosome component COL17A1 fluctuated in response to genomic or oxidative stress. This stress induced COL17A1 proteolysis, and the resulting differing levels of COL17A1 in individual stem cells were a driving force for cell competition. In adult rats, the liver can be repopulated by highly proliferative rat FLSPCs through cell competition. A four- to five-fold increase in liver repopulation occurred when FLSPCs were transplanted into older rats compared with younger rats. Thus, cell competition phenomena have been reported across vertebrate and invertebrate species, and in many tissues. However, the underlying molecular mechanisms remain a mystery in many cases and a better understanding of these phenomena is needed.

3.4.2 | Mammalian cultured cell studies

Madin–Darby canine kidney epithelial cells are useful for studying cell competition in culture and have revealed much about mammalian genes involved in this process. When MDCK cells expressing an oncogene, such as Ras (G12V) or v-Src, and were surrounded by normal MDCK cells, the oncogene-expressing cells were “losers” in cell competitions and underwent apical extrusion. The MDCK cells expressing a constitutively active form of YAP also underwent apical extrusion in the presence of normal MDCK cells through a mechanism that involved TEAD-dependent gene expression (Figure 4A). This apical extrusion was regulated by multiple signaling pathways, including those involving PI3K, mTOR, and p70S6 kinase. Also important was the AA cascade, which is related to choline metabolism. Cyclooxygenase-2 catalyzes the conversion of AA to PGE2. In the presence of active YAP, PGE2 induced internalization of E-cadherin, leading to apical extrusion of the oncogene-expressing cell. These studies demonstrate that, in vitro, experimental systems
of cell competition can be highly useful for elucidating molecular mechanisms that are difficult to track in vivo.

### 3.4.3 | Injured hepatocyte elimination studies

Yes-associated protein functions in mouse hepatocytes have been explored using the HTVi method, which introduces foreign genes into cells by hydraulic pressure. The acquisition of plasmids encoding constitutively active YAP creates a mosaic condition in which the liver contains a population of active YAP-expressing hepatocytes among normal YAP-quiescent hepatocytes. Studies of these livers have revealed the dynamics of how the abnormal hepatocytes are dealt with in vivo. It was shown that the YAP-overexpressing hepatocytes were eliminated from the livers of injected mice within 7 days in a manner independent of adaptive immunity. Tracking demonstrated that active YAP-expressing hepatocytes migrated to the hepatic sinusoids where they were engulfed by Kupffer cells (Figure 4B). Clodronate liposome-mediated depletion of Kupffer cells from these mice suppressed the elimination of active YAP-expressing hepatocytes from the liver and increased the presence of TUNEL-positive apoptotic cells. The molecular mechanism underlying this YAP-mediated elimination of abnormal hepatocytes was proposed to proceed as follows: (a) active YAP and TEAD induce Ect2 and Fgd3 mRNA expression, (b) Ect2 and Fgd3 proteins activate Cdc42 and Rac, and (c) active Cdc42 and Rac regulate cytoskeletal reorganization and stimulate cell migration. This work concluded that a change in hepatocyte fate from proliferation to migration/apoptosis depended on a mechanism of stress detection involving YAP. In other words, YAP acts as a stress sensor that induces elimination of injured hepatocytes to maintain tissue and liver homeostasis.

### 4 | THERAPEUTIC PERSPECTIVE

The studies described above raise the tempting possibility of manipulating the Hippo-YAP/TAZ pathway for preventing the development and progression of liver diseases and cancers. Indeed, three groups of drugs and methods manipulating the Hippo-YAP/TAZ pathway are under development. Group I drugs target Hippo components acting upstream of YAP/TAZ, whereas Group II methods target YAP/TAZ or TEAD family molecules, and Group III drugs target downstream targets of YAP/TAZ.

On the flip side, there is the possibility of manipulating the Hippo-YAP/TAZ pathway to boost liver regeneration. Indeed, some such approaches have already been reported. For example, the MST1/2 inhibitor XMU-MP-1 (4-((5,10-dimethyl-6-oxo-6,10-dihydro-5H-pyrimido[5,4-b]thieno[3,2-e][1,4]diazepin-2-yl)amino)benzenesulfonamide) augments mouse liver repair and regeneration in both acute and chronic liver injury mouse models. Conversely, treatment with siRNA-lipid nanoparticles targeting YAP restored hepatocyte differentiation and induced pronounced tumor regression in a genetically engineered mouse model of liver cancer. Although this latter approach might seem to offer proof-of-concept that differentiation
therapy might be used to treat an epithelial tumor, the therapeutic activation of YAP/TAZ for regenerative purposes has significant risks. YAP/TAZ hyperactivation is well established as promoting cancer development, making it imperative to continue detailed research of the Hippo-YAP/TAZ pathway to discover all its functions and regulatory mechanisms before applying any such knowledge to human therapy.

5 | CONCLUSION

The Hippo-YAP/TAZ pathway is a very attractive target of exploration from the point of view of liver physiology and pathology. Tellingly, Hippo pathway mutations are extremely rare in human liver cancers. This observation suggests that nongenetic factors, such as the status of elements in the surrounding microenvironment (e.g., stiff ECM), are vital for the activation of YAP/TAZ linked to cancer initiation. Multifaceted investigation of these issues is sure to yield much helpful information on Hippo-YAP/TAZ signaling in liver biology.

ACKNOWLEDGMENTS

This work was supported by a Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research 20H03381, a grant from AMED under Grant Number 18fk0210042h0001–20fk0210042h0003, a grant from the SECOM Science and Technology Foundation, and a Nanken-Kyoten grant from Tokyo Medical and Dental University.

CONFLICT OF INTEREST

The author declares no conflicts of interest.

ORCID

Hiroshi Nishina © https://orcid.org/0000-0002-6647-7480

REFERENCES

1. Nakamura T, Nishina H. Liver development: Lessons from knockout mice and mutant fish. Hepatol Res. 2009;39:633-644.
2. Miyajima A, Tanaka M, Itoh T. Stem/progenitor cells in liver development, homeostasis, regeneration, and reprogramming. Cell Stem Cell. 2014;14:561-574.
3. Anderson RM, Higgins GM. Experimental pathology of the liver. I. Restoration of the liver of the white rat following partial surgical removal. Arch Pathol. 1931;12:186-202.
4. Miyaoa Y, Ebato K, Kato H, et al. Hypertrophy and unconventional cell division of hepatocytes underlie liver regeneration. Curr Biol. 2012;22:1166-1175.
5. Halder G, Dupont S, Piccolo S. Transduction of mechanical and cytoskeletal cues by YAP and TAZ. Nat Rev Mol Cell Biol. 2012;13:591-600.
6. Meng Z, Muroishi T, Guan K-L. Mechanisms of Hippo pathway regulation. Genes Dev. 2016;30:1-17.
7. Zanconato F, Cordenonsi M, Piccolo S. YAP/TAZ at the roots of cancer. Cancer Cell. 2016;29:783-803.
8. Fu V, Plouffe SW, Guan K-L. The Hippo pathway in organ development, homeostasis, and regeneration. Curr Opin Cell Biol. 2017;49:99-107.
9. Moya IM, Halder G. Hippo–YAP/TAZ signalling in organ regeneration and regenerative medicine. Nat Rev Mol Cell Biol. 2018;20:211-226.
10. Ma S, Meng Z, Chen R, et al. The Hippo pathway: Biology and pathophysiology. Annu Rev Biochem. 2019;88:577-604.
11. Zheng Y, Pan D. The Hippo signaling pathway in development and disease. Dev Cell. 2019;50:264-282. doi:10.1016/j.devcel.2019.06.003
12. Vassilev A, Kaneko KJ, Shu H, Zhao Y, DePamphilis ML. TEAD transcription factors utilize the activation domain of YAP65, a Src/Yes-associated protein localized in the cytoplasm. Genes Dev. 2001;15:1229-1241.
13. Zhao B, Ye X, Yu J, et al. TEAD mediates YAP-dependent gene induction and growth control. Genes Dev. 2008;22:1962-1971.
14. Pepe-Mooney BJ, Dill MT, Alemany A, et al. Single-cell analysis of the liver epithelium reveals dynamic heterogeneity and an essential role for YAP in homeostasis and regeneration. Cell Stem Cell. 2019;25:33-38.e8.
15. Lu L, Li Y, Kim SM, et al. Hippo signaling is a potent in vivo growth and tumor suppressor pathway in the mammalian liver. Proc Natl Acad Sci U S A. 2010;107:1437-1442.
16. Guo T, Lu Y, Li P, et al. A novel partner of Scalloped regulates Hippo signaling via antagonizing Scalloped-Yorkie activity. Cell Res. 2013;23:1201-1214.
17. Koontz LM, Liu-Chittenden Y, Yin F, et al. The Hippo effector Yorkie controls normal tissue growth by antagonizing scolloped-mediated default repression. Dev Cell. 2013;25:388-401.
18. Miller E, Yang J, DeRan M, et al. Identification of serum-derived sphingosine-1-phosphate as a small molecule regulator of YAP. Chem Biol. 2012;19:955-962. doi:10.1016/j.chembiol.2012.07.005
19. Yu FX, Zhao B, Panupinthu N, et al. Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. Cell. 2012;150:780-791.
20. Panciera T, Azzolin L, Cordenonsi M, et al. Mechanobiology of YAP and TAZ in physiology and disease. Nat Rev Mol Cell Biol. 2017;18:758-770. doi:10.1038/nrm.2017.87
21. Dupont S, Morsut L, Aragona M, et al. Role of YAP/TAZ in melanotransduction. Nature. 2011;474:179-183.
22. Li Y, Zhou H, Li F, et al. Angiomotin binding-induced activation of Merlin/NF2 in the Hippo pathway. Cell Res. 2015;25:801-817.
23. Driskill JH, Pan D. The Hippo Pathway in Liver Homeostasis and Pathophysiology. Annu Rev Pathol. 2021;16:299-322.
24. Morin-Kensicki EM, Boone BN, Howell M, et al. Defects in Yolk sac vasculogenesis, chorioallantoic fusion, and embryonic axis elongation in mice with targeted disruption of Yap65. Mol Cell Biol. 2006;26:77-87.
25. Hossain Z, Ali SM, Ko HL, et al. Glomerulocystic kidney disease in mice with a targeted inactivation of Wwtr1. Proc Natl Acad Sci U S A. 2007;104:1631-1636.
26. Makita R, Uchiyama Y, Nishiyama K, et al. Multiple renal cysts, urinary concentration defects, and pulmonary emphysema in mice lacking Taz. Genes Dev. 2009;23:1631-1636.
27. Mitani A, Nagase T, Fukushima T, et al. Transcriptomic coactivator with PDZ-binding motif is essential for normal alveolarization in mice. Am J Respir Crit Care Med. 2009;180:326-338.
28. Nishioka N, Inoue K-I, Adachi K, et al. The Hippo signaling pathway components Lats and Yap pattern Tead4 activity to distinguish mouse trophoderm from inner cell mass. Dev Cell. 2009;16:398-410.
29. Nishio H, Kamada K, Kawahara K, et al. Cancer susceptibility and embryonic lethality in Mob1a/1b double-mutant mice. J Clin Invest. 2012;122:4505-4518.
30. Molina LM, Zhu J, Li Q, et al. Compensatory hepatic adaptation accompanies permanent absence of intrahepatic biliary network due to Yap1 loss in liver progenitors. Cell Rep. 2021;36:109310.

31. Molina L, Nejak-Bowen K, Monga SP. Role of YAP1 signaling in biliary development, repair, and disease. Semin Liver Dis. 2022;42:17-33.

32. Dong J, Feldmann G, Huang J, et al. Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell. 2007;130:1120-1133.

33. Camargo FD, Gokhale S, Johnnidis JB, et al. YAP1 increases organ size and expands undifferentiated progenitor cells. Curr Biol. 2007;17:2054-2060.

34. Zhou D, Conrad C, Xia F, et al. Mst1 and Mst2 maintain hepatocyte quiescence and suppress hepatocellular carcinoma development through inactivation of the Yap1 oncogene. Cancer Cell. 2009;16:425-430.

35. Lee K-P, Lee J-H, Kim T-S, et al. The Hippo-Salvador pathway regulates the size and function of Drosophila imaginal discs. Development. 2010;137:3589-3600.

36. Chen Q, Zhang N, Xie R, et al. Homeostatic control of Hippo signaling activity revealed by a endogenous activating mutation in YAP. Genes Dev. 2015;29:1285-1297.

37. Lu L, Finegold MJ, Johnson RL. Hippo pathway coactivators Yap and Taz are required to coordinate mammalian liver regeneration. Exp Mol Med. 2018;50:e423.

38. Loforese G, Malinka T, Keogh A, et al. Impaired liver regeneration in aged mice can be rescued by silencing Hippo core kinases MST1 and MST2. EMBO Mol Med. 2017;9:46-60.

39. Moya IM, Castaldo SA, Van den Mooter L, et al. Peritumoral activation of the Hippo pathway effectors YAP and TAZ suppresses liver cancer in mice. Science. 2019;366:1029-1034.

40. Morata G, Ripoll P. Minutes: Mutants of drosophila autonomously affecting cell division rate. Dev Biol. 1975;42:211-221. doi:10.1016/0012-1606(75)90330-9

41. Martin FA, Herrera SC, Morata G. Cell competition, growth and size control in the Drosophila wing imaginal disc. Development. 2009;136:3747-3756.

42. Moreno E, Basler K, Morata G. Cells compete for Decapentaplegic survival factor to prevent apoptosis in Drosophila wing development. Nature. 2002;416:755-759. doi:10.1038/416755a

43. Hashimoto M, Sasaki H. Epiblast formation by TEAD-YAP-dependent expression of pluripotency factors and competitive elimination of unspecified cells. Dev Cell. 2019;50:139-154.e5.

44. Claveria C, Giovinazzo G, Sierra R, et al. Myc-driven endogenous cell competition in the early mammalian embryo. Nature. 2013;500:39-44.

45. Kon S, Ishibashi K, Katoh H, et al. Cell competition with normal epithelial cells promotes apical extrusion of transformed cells through metabolic changes. Nat Cell Biol. 2017;19:530-541.

46. Liu N, Matsumura H, Kato T, et al. Stem cell competition orchestrates skin homeostasis and ageing. Nature. 2019;568:344-350.

47. Oertel M, Menthena A, Dabeva MD, et al. Cell competition leads to a high level of normal liver reconstitution by transplanted Fetal liver stem/progenitor cells. Gastroenterology. 2006;130:507-520. doi:10.1053/j.gastro.2005.10.049

48. Menthena A, Koehler CI, Sandhu JS, et al. Activin A, p15INK4b signaling, and cell competition promote stem/progenitor cell repopulation of livers in aging rats. Gastroenterology. 2011;140:1009-1020. doi:10.1053/j.gastro.2010.12.003

49. Hogan C, Dupré-Crochet S, Norman M, et al. Characterization of the interface between normal and transformed epithelial cells. Nat Cell Biol. 2009;11:460-467.

50. Kajita M, Hagan C, Harris AR, et al. Interaction with surrounding normal epithelial cells influences signalling pathways and behaviour of Src-transformed cells. J Cell Sci. 2010;123:171-180.

51. Chiba T, Ishihara E, Miyamura N, et al. MDCK cells expressing constitutively active Yes-associated protein (YAP) undergo apical extrusion depending on neighboring cell status. Sci Rep. 2016;6: doi:10.1038/srep28383

52. Ishihara E, Nagaoka Y, Okuno T, et al. Prostaglandin E2 and its receptor EP2 trigger signaling that contributes to YAP-mediated cell competition. Genes Cells. 2020;25:197-214. doi:10.1111/gtc.12750

53. Sunaga S, Kofuji S, Nishina H. YAP drives cell competition by activating choline metabolism. Biochim Biophys Res Comm. 2021;572:178-184. doi:10.1016/j.bbrc.2021.07.101

54. Miyamura N, Hata S, Itoh T, et al. YAP determines the cell fate of injured mouse hepatocytes in vivo. Nat Commun. 2017;8:16017.

55. Pobbell A, Hong W. A combat with the YAP/TAZ-TEAD oncogenes for cancer therapy. Theranostics. 2020;10:3622-3635.

56. Fan F, He Z, Kong L-L, et al. Pharmacological targeting of kinases for cancer therapy. Theranostics. 2020;10:3622-3635.

57. Fitamant J, Kottakis F, Benhamouche S, et al. YAP inhibition restores hepatocyte differentiation in advanced HCC, leading to Tumor regression. Cell Rep. 2015;10:1692-1707.

58. Fujimoto A, Furuta M, Totoki Y, et al. Whole-genome mutational landscape and characterization of noncoding and structural mutations in liver cancer. Nat Genet. 2016;48:500-509.

How to cite this article: Nishina H. Physiological and pathological roles of the Hippo-YAP/TAZ signaling pathway in liver formation, homeostasis, and tumorigenesis. Cancer Sci. 2022;113:1900-1908. doi:10.1111/cas.15352