The Hippo Signaling Pathway: A Candidate New Drug Target for Malignant Tumors

Miki Nishio, Hiroki Goto, Miki Suzuki, Aya Fujimoto, Koshi Mimori, and Akira Suzuki

Abstract The Hippo pathway has the unique capacity to sense tissue architecture and the external forces that shape it, and dysregulation of this pathway leads to tumorigenesis. The study of mice bearing systemic or tissue-specific mutations of Hippo elements has driven huge progress in understanding this pathway's role in normal physiology and disease. Here, we summarize how disruption of Hippo signaling relates to cancer, and we highlight the importance of this pathway as a new drug target for malignant tumors.

Keywords Hippo • Cancer • Function • Mouse model

Introduction

The Hippo signaling pathway was first identified as a regulator of organ size in *Drosophila* [1]. In mammals, canonical Hippo signaling is mediated by mammalian sterile 20-like (MST) kinases, large tumor suppressor (LATS) kinases, the adaptor proteins Salvador homolog 1 (SAV1) and Mps one binder kinase activator protein (MOB1), and the downstream transcription cofactors Yes-associated protein 1 (YAP1) and its paralog, transcriptional coactivator with PDZ-binding motif (TAZ).

In a cell exposed to cell–cell contact, mechanical force, or a stress stimulus, MST phosphorylates LATS in a reaction facilitated by SAV1 and MOB1. LATS in turn phosphorylates YAP1 (S127)/TAZ (S89), which then binds to 14-3-3 protein. This binding prevents phosphorylated YAP1/TAZ from accessing the nucleus and

The authors declare that no conflicts of interest exist.

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K. Nakao et al. (eds.), *Innovative Medicine*, DOI 10.1007/978-4-431-55651-0_7

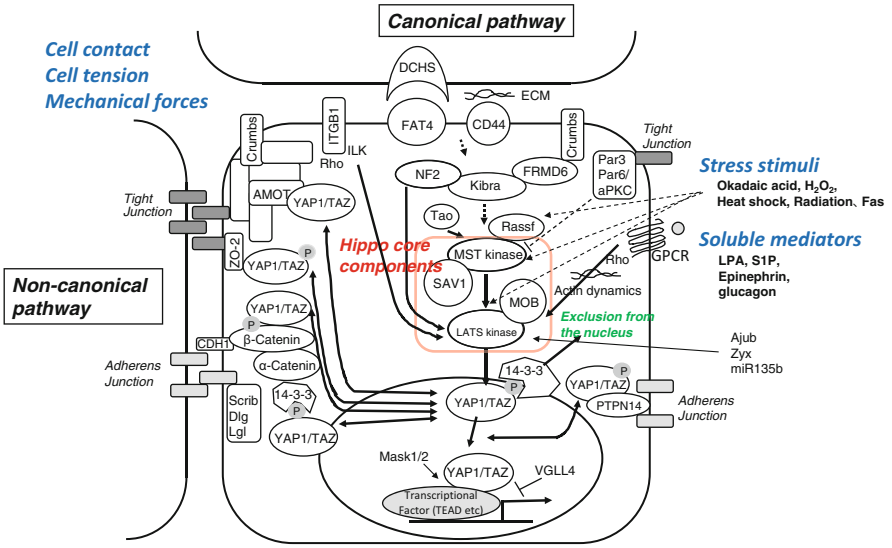

Fig. 1 Mammalian canonical and non-canonical Hippo signaling pathways. The core components of the mammalian Hippo pathway are the MST and LATS kinases, and the SAV1 and MOB adaptor proteins. The Hippo pathway is activated in response to increased cell density, cell tension, mechanical forces, stress stimuli, or G-protein-coupled receptor (GPCR) antagonists, and inhibits cell proliferation and other processes potentially contributing to tumorigenesis. Candidate sensory components upstream of the Hippo core include FAT4, DCHS1, ITGB1, CD44, NF2, FRMD6, KIBRA, TAO, and RASSF. Upon Hippo core activation, SAV1 binding to MST allows this kinase to phosphorylate MOB1. Phospho-MOB1 binding to LATS both enhances LATS catalytic activity and allows it to be phosphorylated by MST. Phospho-LATS then phosphorylates and inactivates YAP (or its paralog, TAZ), promoting their cytoplasmic retention through binding to 14-3-3 protein. LATS-phosphorylated YAP1 (or TAZ) is also degraded so transcription factors (such as the TEADs) promoting cell survival are not activated. In contrast, under conditions of low cell density or minimal stress, YAP dissociates from 14-3-3, translocates into the nucleus, and activates transcription factors that induce the expression of pro-survival genes. *Solid lines* indicate known direct interactions; *dashed lines* indicate unknown mechanisms. The non-canonical Hippo pathway operates in the tight and adherens junction complexes and involves AMOT in the Crumb complex in the tight junction, ZO-2 in the tight junction, and α-catenin, β-catenin and PTPN14 in the adherence junction. Each of these molecules can bind to phosphorylated YAP1 to control its localization and activity

activating the transcription of a broad range of growth factors and anti-apoptotic genes (Fig. 1). Additional control is exerted by the binding of phosphorylated YAP1(S397)/TAZ(S311) to the E3 ligase complex $SCF^{\beta\text{-}TrCP}$, which facilitates YAP1/TAZ ubiquitination and proteasomal degradation [2–5] (Fig. 2). Thus, the promotion of cell proliferation by YAP1/TAZ is negatively regulated by Hippo signaling.

The upstream sensors activating Hippo signaling in mammals are not clearly understood. With respect to extracellular triggers, E-cadherin (CDH1), CD44, β1-integrin (ITGB1)–Rho–GTPase, β1-integrin–ILK–MYPT1–PP1, G-protein-coupled receptors (GPCRs), and protease-activated receptors (F2Rs) Rho–GTPases–ROCK have all been linked to control of NF2, LATS, or YAP1/TAZ activation, as illustrated in Figs. 1 and 2 [2, 6–15], but the precise sequence of events remains

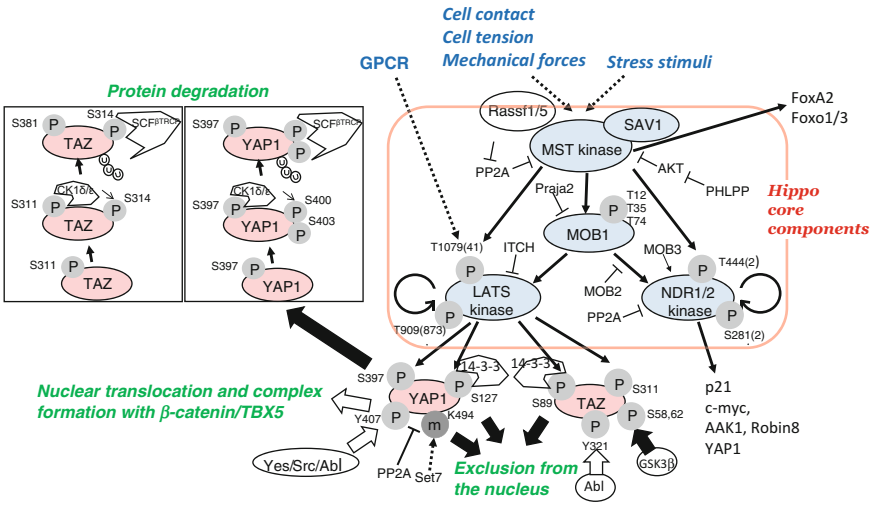

Fig. 2 Mechanisms of YAP1/TAZ inactivation. Activation of the Hippo core, as described in Fig. 1, leads to LATS-mediated phosphorylation of YAP1 (S127) and TAZ (S89) and the cytoplasmic retention of these proteins via 14-3-3 binding. Alternatively, LATS-mediated phosphorylation of YAP1 (S397)/TAZ (S311) triggers the binding of the E3 ligase complex SCFβ-TRCP, which facilitates YAP1/TAZ ubiquitination and proteasomal degradation. Phosphorylation of YAP1 (Y407)/TAZ (Y321) by SRC family kinases (YES1, SRC, ABL) excludes YAP1/TAZ from the nucleus, whereas methylation of YAP1(K494) by SET7 promotes its nuclear localization. Phosphorylation of TAZ (Ser58 and Ser62) by glycogen synthase kinase 3β (GSK3β) recruits β-TrCP to target TAZ for degradation. RASSF1A activates MST1 by preventing PP2A-mediated dephosphorylation of MST1/2 and YAP1. NDR1/2 are alternative MST substrates

obscure. The roles of intracellular triggers are even less well defined but include KIBRA binding to NF2 and FRMD6 and the activities of TAOK1, PP2A, and RASSFs [16–23].

Establishment of epithelial apical–basal polarity requires the Crumbs, Par, and Scribble complexes [24, 25]. In addition to the canonical Hippo signaling pathway, a non-canonical Hippo pathway exists that involves AMOT in the Crumb complex in the tight junction, ZO-2 in the tight junction, and α-catenin, β-catenin, and PTPN14 in the adherence junction [26–32]. These molecules all bind to phosphorylated YAP1 to control its localization and activity. The Scribble and Par3 polarity complexes also influence Hippo signaling.

The localization and activity of YAP1/TAZ are also regulated by several other non-Hippo molecular events. For example, the phosphorylation of YAP1 (Y407)/TAZ (Y321) by SRC family kinases (YES1, SRC, ABL) [33] induces nuclear localization of YAP1, while methylation of YAP1 (K494) by SET7 excludes YAP1 from the nucleus [34]. Like Hippo-mediated phosphorylation, phosphorylation of TAZ (Ser58 and Ser62) by glycogen synthase kinase 3β (GSK3β) recruits β-TrCP, driving TAZ degradation [35].

The main transcription factors regulated by YAP1/TAZ are the TEADs, but, as illustrated in Fig. 3, many other transcription factors are affected by

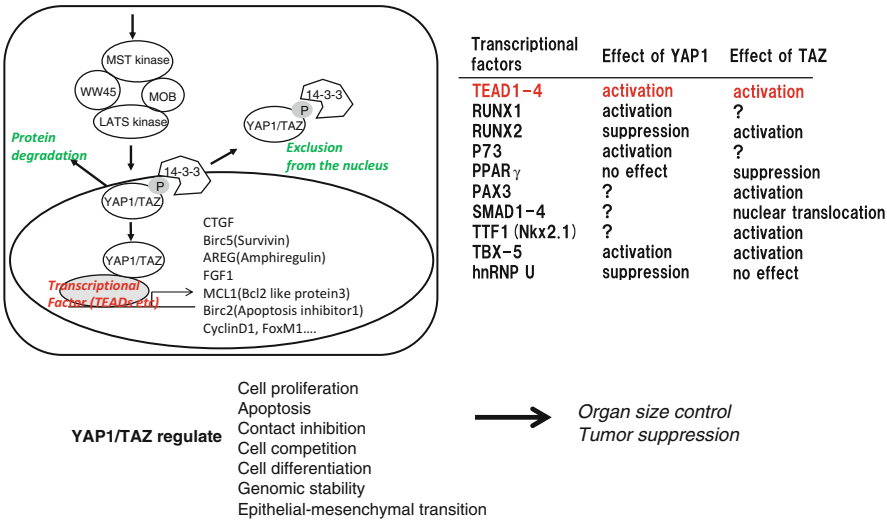

Fig. 3 Transcription factors and downstream target genes activated by Hippo signaling. *Left*: the main transcription factors regulated by YAP1/TAZ are the TEADs. Following interaction with nuclear YAP1/TAZ, TEADs enhance the transcription of anti-apoptotic genes such as CTGF and BIRC5 (survivin). *Right*: list of other transcription factors controlled either positively or negatively by YAP1 or TAZ. *Bottom:* cellular processes regulated by YAP1/TAZ

YAP1/TAZ. Accordingly, the Hippo pathway regulates cell proliferation, organ size, and tumor suppression. As shown in Fig. 4, the Hippo pathway also engages in crosstalk with several morphogenetic signaling pathways whose disruption is linked to morphogenesis and carcinogenesis [36]. While YAP1 and TAZ share most structural features, TAZ lacks two sequences present in YAP1: a PxxφP motif and an SH3-binding motif. The effect of these differences on specific transcriptional activation patterns is under investigation.

Identifying the roles of mammalian Hippo signaling elements has been a challenge because multiple homologs exist for almost all components. Each isoform's function has required separate clarification via the use of specific knockout (KO) mice. Strikingly, mutants lacking NF2, MST1/2, or LATS1, as well as YAP1 transgenic animals, all develop some type of tumor. In human cancers, inactivation of the Hippo pathway due to either genetic (NF2, SAV1, MOB1A, LATS2, or YAP1) or epigenetic changes has been documented [37–40]. Indeed, for a variety of tumors, loss of Hippo signaling can predict patient sensitivity to chemotherapy as well as disease-free survival and overall survival [41]. This function of Hippo components as potent tumor suppressors makes them attractive targets for new anti-cancer therapies. To date, certain porphyrin derivatives, such as verteporfin (VP) and protoporphyrin IX (PPIX), have been reported to inhibit YAP1–TEAD association [42]. GPCR (Gα12/13, Gαq/11, Gαi/o) antagonists, GPCR (Gαs) agonists [8], and Src family antagonists (dasatinib) [33] have also been proposed as candidate Hippo modulators for tumor therapy.

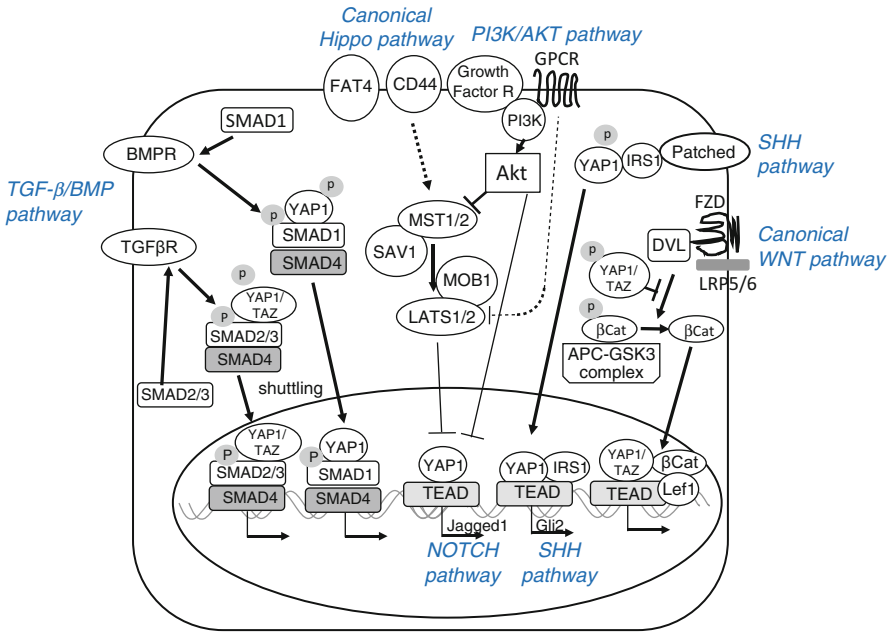

Fig. 4 Crosstalk between the Hippo pathway and other signaling pathways. The Hippo pathway is influenced by and interacts with components of the indicated morphogenetic pathways whose dysregulation is related to tumorigenesis

In this chapter, we describe gene-targeted mouse models that have been useful in characterizing the physiological and tumor-suppressive properties of the Hippo pathway in various tissues, and relate these models to human cancers.

Loss of Hippo Signaling in the Liver

YAP1 transgenic mice show hepatomegaly due to an increase in liver cell numbers rather than cell size. This hyperplasia was completely reversible in the short term but led to irreversible liver tumorigenesis in the long term [37]. YAP1 hyperactivation caused adult hepatocytes to dedifferentiate into liver progenitor cells that exhibited enhanced self-renewal and engraftment capacities as well as increased Notch2 transcription promoting the cholangiocyte lineage [43]. In contrast, mice deficient for YAP1 specifically showed loss of hepatocytes and cholangiocytes, and resisted the induction of hepatocarcinoma (HCC) [38, 42, 44].

In human HCC, amplification of the YAP1 gene is uncommon (~5–10 %) [37], but loss of YAP1 (Ser127) phosphorylation and elevated nuclear YAP1 are frequently observed [38, 39]. Increased YAP1 is now considered an independent prognostic marker for HCC [41]. Among human liver tumor subtypes, YAP1 elevation is most

frequent in combined hepatocellular cholangiocarcinomas (cHC-CC; 67%). YAP1 is also higher in more HCCs exhibiting "stemness" (EpCAM$^+$ and keratin 19$^+$; 56%) than in HCCs lacking "stemness" (17%). In addition, impaired phosphorylation of MOB1 occurs in 81% of human HCCs [40].

Complete knockout of both MST1 and MST2 (DKO) in mice results in embryonic lethality, whereas retention of a single functional copy of either MST1 or MST2 is sufficient for normal embryogenesis. These mutants show enhanced proliferation of liver stem cells and progenitor cells (such as oval cells) that give rise to both hepatocytes and cholangiocytes. Eventually these mutants develop liver tumors due to loss of function of the single MST1 or MST2 allele. These tumors display characteristics of both HCC and CC, and feature the expansion and transformation of a mixed liver progenitor cell population [45]. Liver-specific MST1/2 DKO mice develop similar hepatomegaly and HCC/CC tumors by 5–6 months after birth [46].

It is still unclear whether LATS function is essential for tumor suppression in the liver. One study showed that loss of MST1/2 decreased MOB1 and YAP1 phosphorylation but had no effect on LATS1/2 phosphorylation [45]. However, another study demonstrated reduced levels of phosphorylated YAP1 and LATS1/2 but unexpectedly decreased TAZ protein levels in MST1/2 DKO liver and tumors [40]. These data suggest that LATS1/2 and TAZ may be unlikely to play a major role in this liver phenotype.

Liver-specific deletion of Sav1 in mice enhances oval cell proliferation such that the mutants eventually develop HCC/CC liver tumors. However, levels of phospho-YAP1 and phospho-LATS1/2 are normal in SAV1 KO livers, suggesting that Sav1 promotes oval cell expansion and tumorigenesis in this model but acts independently of LATS1/2 and YAP1 [46, 47].

Liver-specific deletion of NF2 in mice also results in hepatocyte and cholangiocyte proliferation, leading to HCC/CC [42, 48, 49]. In one study, YAP1 and LATS1/2 phosphorylation were reduced in NF2-deficient liver and nuclear YAP1 was increased. Deletion of one copy of YAP1 was sufficient to reverse tumorigenesis in this model, indicating that NF2-mediated tumor suppression is achieved by inactivating YAP1 [48]. However, another group reported that liver-specific deletion of NF2 led to dramatic progenitor cell expansion without altering YAP1 localization or phosphorylation. EGFR inhibition blocked tumorigenesis triggered by NF2 deletion in this model, arguing against a role for YAP1 [49].

Loss of Hippo Signaling in the Pancreas

Pancreas-specific MST1/2 DKO mice (using PDX1-Cre Tg) exhibit a small pancreas in which the exocrine compartment shows increased cell proliferation but also extensive disorganization and pancreatitis-like autodigestion [50]. Pancreatic MST1/2 deficiency also induces postnatal de-differentiation of acinar cells into duct-like cells and thus reduces the total number of acinar cells [51]. However, neither

these nor any other pancreas-specific Hippo mutants examined to date develop tumors. Interestingly, doxycycline-dependent YAP1 activation in the mouse pancreas expands its size and increases the number of acinar cells, leading to ductal metaplasia [44]. Thus, the phenotype observed in pancreas-specific MST DKO mice may be YAP1 independent.

In humans, pancreatic ductal adenocarcinoma (PDAC) frequently carries an oncogenic Kras mutation. In an inducible KrasG12D-driven mouse PDAC model, the mutants can develop malignancies in which KrasG12D and downstream MAPK activation are lost, but DNA amplification and/or mRNA overexpression of YAP1 are acquired [52, 53]. Excessive YAP1 may thus be the major driver of invasive and recurrent PDAC.

Loss of Hippo Signaling in the Intestine

The role of Hippo signaling in the intestine is complex. YAP1 is overexpressed and localized in the nucleus in most human colon cancers, but silenced in a subset of highly aggressive and undifferentiated human colorectal carcinomas [54]. In mice, reports differ regarding Hippo element functions in intestinal stem cell (ISC) expansion and intestinal regeneration. In one study, loss of YAP1 in intestinal epithelial cells (Villin-Cre) had little effect on intestinal development but severely impaired DSS-induced intestinal regeneration. In the same study, doxycycline-dependent YAP1 activation expanded multipotent undifferentiated dysplastic progenitor cells in the intestine in a manner partly dependent on Notch activation [44]. However, another study found that intestinal YAP1 deficiency (Villin-Cre) resulted in WNT hypersensitivity leading to hyperplasia, ISC expansion, and formation of ectopic crypts and microadenomas. This report also showed that transgenic YAP1 expression reduced WNT target gene expression and induced rapid loss of intestinal crypts. In this latter case, the authors speculated that cytoplasmic YAP1 can bind to DVL and dampen WNT signaling [54]. The discrepancies between these reports require resolution because both increased nuclear YAP1 and decreased cytoplasmic YAP1 are associated with an increased risk of colon cancer in humans.

Intestine-specific Sav1-deficient mice show accelerated crypt regeneration and DSS-induced colonic polyp formation dependent on nuclear YAP1 but independent of β-catenin [55]. In contrast, intestine-specific MST1/2-deficient mice (Villin-Cre) display YAP1-dependent activation of Notch and β-catenin, as well as ISC expansion associated with colonic adenoma formation [56]. Recent work has shown that phosphorylation of YAP1(Y407) by the SRC family tyrosine kinase YES1 allows YAP1 to enter the nucleus and form a complex with the transcription factor TBX5 and β-catenin. This complex then promotes the transcription of anti-apoptotic genes such as BCL2L1 and BIRC5 [33]. Thus, a SRC–YAP1–β catenin–TBX5 complex may be essential to the transformation and survival of β-catenin-driven cancers.

Loss of Hippo Signaling in the Lung

Lung-specific MST1/2 DKO mice (TTF1(NKX2.1)-Cre) exhibit perinatal mortality due to respiratory failure [57]. The lungs appear immature, with reduced type I pneumocytes and increased immature type II pneumocytes lacking microvilli, lamellar bodies, and surfactant protein expression. These features are reminiscent of human infant respiratory distress syndrome (IRDS). MST normally phosphorylates and stabilizes the transcription factor FOXA2, which regulates alveolar epithelial cell maturation and surfactant protein expression. The IRDS phenotype of MST1/2 DKO mice is independent of YAP1 hyperactivation but dependent on FOXA2 [57].

Whether MST1/2 deficiency in the adult mouse lung would trigger lung tumorigenesis remains unknown. In $Sca1^+$ murine lung tumor–propagating cells (TPC), TAZ is overexpressed by more than twofold and NF2 is downregulated by more than 15-fold compared with non-TPC [58]. Knockdown of YAP1 or TAZ in lung cancer cell lines decreases their cellular migration capacity and ability to metastasize. Conversely, expression of doxycycline-inducible constitutively active YAP1 in *Kras* Tg mice results in lung tumor progression in vivo [58].

TAZ KO mice display alveolarization defects similar to those seen in human emphysema patients [59–62]. However, although TAZ activates TTF1, a transcription factor essential for lung formation, TAZ KO lungs show a normal pattern of TTF1 target gene expression [63]. Mutant mice heterozygous for TAZ deficiency are resistant to bleomycin-induced lung fibrosis, suggesting that TAZ regulates fibrotic responses in this tissue [61].

Humans exposed to asbestos often develop malignant mesothelioma (MM). Mutation of NF2 occurs in 50 % of human MM and YAP1 activation is frequent [64]. However, no statistically significant MM development has been reported to date in mice bearing mutations of Hippo elements.

Loss of Hippo Signaling in the Skin

YAP1 plays a key role in murine skin morphogenesis. Normal basal epidermal progenitors with nuclear YAP1 localization are driven to proliferate, whereas those with cytoplasmic YAP1 localization differentiate into hair follicles. YAP1 overexpression in mouse skin causes expansion of epidermal stem cells and progenitors, resulting in epidermal thickening, hyperkeratosis, hair follicle evagination, and the development of squamous cell-like carcinomas in skin grafts [65, 66]. Conversely, YAP1 deficiency in mouse epidermis, or disruption of YAP1–TEAD interaction, leads to epidermal hypoplasia and decreased keratinocyte proliferation due to loss of epidermal stem/progenitor cells.

At least one wild-type (WT) MOB1A or MOB1B allele is essential for murine embryogenesis, and any loss of this remaining allele results in trichilemmal carcinomas of the skin [67]. YAP1 activation and MOB1A/1B inactivation are also frequently observed in human trichilemmal carcinomas. Newborn MOB1A/1B DKO mice

show hyperplastic keratinocyte progenitors and defective keratinocyte terminal differentiation, and rapidly die of malnutrition. MOB1A/1B-deficient keratinocytes exhibit hyperproliferation, apoptotic resistance, impaired contact inhibition, enhanced progenitor self-renewal, and increased centrosomes. LATS1/2 and YAP1 activities are altered in these cells [67].

SAV1-deficient mice exhibit a thick epidermal skin layer and succumb to early embryonic lethality [68]. SAV1-deficient primary keratinocytes show hyperproliferation, progenitor expansion, decreased apoptosis, and inhibition of terminal differentiation.

Surprisingly, keratinocyte-specific MST1/2 DKO mice are healthy and show normal YAP1 phosphorylation and activation. YAP1 is therefore likely phosphorylated by an alternative mechanism in keratinocytes [22], perhaps by NDR1/2 kinases or GPCR signaling [8].

As noted above, cell adhesion and junction complex proteins can also regulate YAP1. Keratinocyte-specific loss of α-catenin results in keratinocyte hyperplasia and squamous cell carcinomagenesis similar to that observed in YAP1 transgenic mice [22]. In normal keratinocytes, α-catenin interacts directly with YAP1 and restricts it to the cytoplasm [39]. YAP1 localization in the skin is also influenced by β-catenin, PTPN14, AMOT, and ZO-2 [69, 70].

Loss of Hippo Signaling in T Lymphocytes

In humans, inactivating MST1 mutations occur in families with T cell immunodeficiency or autoimmune disorders [71, 72]. In MST1 KO mice, naïve T cells show impaired CCL19/21-induced LFA-1 clustering and reduced cell migration [73–75]. In addition, MST1-deficient T cells exhibit defective FOXO1–IL-7R–BCL2 signaling, FAS upregulation, and a FOXO1/3-dependent decrease in SOD2 and catalase. As a result, these mutant T cells possess increased ROS and undergo apoptosis [76], a mechanism that may also underlie the observed immunodeficiency in humans with MST1 mutations. MOB1 phosphorylation is decreased in MST1 KO T cells but LATS1/2 and YAP1 phosphorylation are essentially normal, suggesting that LATS1/2 and YAP1 are not downstream effectors of MST1 and MOB1 in naïve T cells.

Despite their T cell deficiency, aged MST1 KO mice develop autoimmune disease because MST1 normally enhances FOXP3 expression and thus sustains regulatory T cell development through stabilizing FOXO1/3 [75]. These mutants are also susceptible to chemical induction of T-ALL and undergo accelerated spontaneous lymphomagenesis in a p53-deficient background [77].

The chemokines CCL19/21 normally induce the binding of DOCK8 to phosphorylated MOB1, promoting actin polarization and thymocyte migration from the wild-type thymus. MST1/2 DKO thymocytes show a loss of DOCK8 binding to MOB1 [78]. As a result, T cell–specific MST1/2 DKO thymocytes develop normally but undergo apoptosis before they can exit the thymus, leading to an absence of mature T cells in the circulation and lymphoid tissues [78].

Loss of Hippo Signaling in Salivary Glands

TAZ phosphorylation increases during salivary submandibular gland (SMG) development in mice [79]. In human Sjogren's syndrome (SS) patients, TAZ is localized in the nucleus rather than in the junctional regions of the SMGs, causing an abnormal accumulation of TAZ downstream targets such as extracellular matrix components, fibronectin, and CTGF [79]. LATS2 deficiency also results in defective SMG morphogenesis and a reduction in junction-localized TAZ in mice. Lastly, 5 % of MOB1 partially deficient mice develop salivary gland adenomas and carcinomas [67].

Loss of Hippo Signaling in Neurons

In humans, mutations of DCHS1 or FAT4 cause Van Maldergem syndrome, which is characterized by a periventricular neuronal heterotopia (the mislocalization of cortical neuron progenitors) accompanied by auditory and renal deficits as well as craniofacial, skeletal, and limb malformations [80]. In mice, reduction of DCHS1 or FAT4 in embryonic neuroepithelium increases neuronal progenitors but reduces their differentiation. These cells are then mislocalized in the neocortex in a YAP1-dependent manner [80], producing a phenotype similar to human Van Maldergem syndrome.

Inactivating mutations of NF2 in humans are associated with sporadic schwannomas, meningiomas, and ependymomas [81]. Heterozygous NF2 mutant mice do not develop neuronal tumors, but homozygous loss of NF2 specifically in Schwann cells results in their hyperplasia and eventually schwannomas [81]. Additional loss of one p53 allele results in the appearance of malignant peripheral nerve sheath tumors [82]. Complete loss of NF2 in mice is embryonic lethal. Telencephalon-specific NF2 KO embryos show neural progenitor expansion associated with increased nuclear YAP1/TAZ [83]. YAP1 or TEAD overexpression promotes cell cycle progression and inhibits neuronal differentiation by inducing the expression of downstream targets such as cyclin D1 and Pax3 [84, 85].

In normal brain, YAP1 is a downstream effector of the SHH pathway and increases neural stem cell proliferation [86, 87]. YAP1 and SHH signaling engage in crosstalk, since GLI2, which participates in SHH signaling, also acts downstream of YAP1 to control neuronal differentiation [88]. YAP1 is often upregulated in both human and mouse SHH-dependent or *PATCHED1*-mutated medulloblastomas [86, 87].

Loss of Hippo Signaling in Bone

Several Hippo elements have been implicated in controlling tumor suppression in bone. Many human osteosarcoma patients show high levels of nuclear YAP1 in their tumor cells [89], and aged mice bearing heterozygous mutations of NF2 develop osteosarcomas [90]. Some SAV1 heterozygous mouse mutants also develop osteosarcomas [68], as do some MOB1A/1B partially deficient mice [67].

Concluding Remarks

This chapter has summarized evidence showing that heterozygous inactivation of Hippo components leads to tumorigenesis in a wide range of tissues. For more detail on the in vivo functions of the Hippo pathway, please refer to several excellent recent reviews [36, 91, 92]. In general, loss of Hippo signaling or abnormal activation of YAP1/TAZ leads to impaired cell contact inhibition and eventually malignant transformation. Hippo components also control the differentiation/de-differentiation of many stem/progenitor cells. Thus, proper Hippo signaling not only protects against tumor formation but also regulates a vast array of physiological and pathological phenomena.

The studies we have cited demonstrate a strong correlation between findings in human diseases and the phenotypes of Hippo mutant mouse strains. These animals may therefore be of great value for studying the mechanisms underlying various pathological conditions and for determining the efficacy of new therapeutic strategies. Manipulation of Hippo signaling could spur stem cell expansion for regenerative medicine or halt tumor progression to benefit cancer patients. As noted above, porphyrin derivatives [42], GPCR agonists and antagonists [8], and Src family antagonists [33] have already been proposed as candidate Hippo regulators for cancer therapy. Future work will no doubt uncover other Hippo-based approaches worth exploring for their anticancer potential.

Acknowledgments We gratefully acknowledge the support of the Uehara Memorial Foundation and the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT).

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