REVIEW

Hippo vs. Crab: tissue-specific functions of the mammalian Hippo pathway

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The Hippo signaling pathway is a vital suppressor of tumorigenesis that is often inactivated in human cancers. In normal cells, the Hippo pathway is triggered by external forces such as cell crowding, or changes to the extracellular matrix or cell polarity. Once activated, Hippo signaling down-regulates transcription supported by the paralogous cofactors YAP1 and TAZ. The Hippo pathway’s functions in normal and cancer biology have been dissected by studies of mutant mice with null or conditional tissue-specific mutations of Hippo signaling elements. In this review, we attempt to systematically summarize results that have been gleaned from detailed in vivo characterizations of these mutants. Our goal is to describe the physiological roles of Hippo signaling in several normal organ systems, as well as to emphasize how disruption of the Hippo pathway, and particularly hyperactivation of YAP1/TAZ, can be oncogenic.

Introduction

Components of the Hippo pathway are often altered in aggressive human malignancies. In normal cells, Hippo signaling is triggered by changes to the immediate microenvironment that affect cell crowding, cell size or polarity, or the extracellular matrix. Dysregulation of the Hippo pathway can result in abnormal embryogenesis and/or organogenesis and may eventually lead to tumorigenesis (Nakatani et al. 2016). Hippo signaling in normal cells is triggered when upstream mammalian STE20-like protein kinase (MST)/mitogen-activated protein kinase kinase kinase (MAP4K) phosphorylates and activates downstream large tumor suppressor kinase (LATS)/nuclear Dbf2-related kinase (NDR), which then interact with the adaptor proteins Mps one binder kinase activator-like 1 (MOB1) and saldor family WW domain containing protein 1 (SAV1) and phosphorylate the paralogous transcriptional cofactors Yes-associated protein 1 (YAP1) and transcriptional coactivator with PDZ-binding motif (TAZ). Phosphorylated YAP1/TAZ binds to 14–3–3 protein, forcing their retention in the cytoplasm (Zhao et al. 2007) such that they cannot support nuclear transcription mediated by their main binding partners, the TEA domain (TEAD) family of transcription factors (Fig. 1). The TEADs regulate many genes involved in cell migration, growth, reprogramming, self-renewal, EMT and anti-apoptosis. All of these factors are known to play key roles in tumor initiation and cancer progression. Phosphorylation of YAP1/TAZ by active LATS/NDR also allows their binding to SCFβ-TrCP E3 ligase complexes, which promote proteasomal degradation of YAP1/TAZ (Liu et al. 2010; Zhao et al. 2010). Thus, the interaction between YAP1/TAZ and LATS/NDR works in two ways to suppress the activities of

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transcription factors dependent on YAP1/TAZ as cofactors. This sequence of events constitutes canonical Hippo signaling. A noncanonical Hippo pathway also exists that involves angiomotin (AMOT) in the crumb complex (Chan et al. 2011), zona occludens 2 (ZO-2) in the tight junction (Oka et al. 2010) and α-catenin (Schlegelmilch et al. 2011; Silvis et al. 2011), protein tyrosine phosphatase, non-receptor type 14 (PTPN14) (Wang et al. 2012) and scribble (Cordenonsi et al. 2011) in the adherens junction. When phosphorylated YAP1 binds to any of these molecules, YAP1 is confined to the cytoplasm and cannot influence transcription.

With respect to Hippo pathway activation, the exact sequence of upstream events is unclear. Extracellular triggers that have been implicated in the regulation of neurofibromin 2 (NF2), LATS or YAP1/TAZ activation include engagement of CD44 or E-cadherin (CDH1), and signals mediated by axes such as G protein-coupled receptors (GPCRs)-cAMP-PKA; β1-integrin (ITGB1)-ILK-MYPT1-PP1; and protease-activated receptors (F2Rs)-RhoGTPases-F-actin

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**Figure 1** Mammalian canonical and noncanonical Hippo signaling pathways. Hippo signaling, which is triggered by high cell density, GPCR agonists/antagonists and other stress stimuli, inhibits cell proliferation and other processes promoting tumorigenesis. The core components of the mammalian canonical Hippo pathway are MST kinases, LATS/NDR kinases, SAV1 adaptor and MOB adaptor. Upstream sensory components such as FAT4, DCHS1 and others activate MST, which binds to SAV1 and phosphorylates MOB1. Phospho-MOB1 binds to LATS/NDR, triggering self- or MST-mediated phosphorylation. Phospho-LATS phosphorylates and inactivates YAP1/TAZ, promoting binding to 14-3-3 and cytoplasmic retention. LATS-phosphorylated YAP1/TAZ is also degraded so that transcription factors (such as the TEADs) promoting cell survival are not activated. The noncanonical Hippo pathway operates with tight and adherens junction components. AMOT, ZO-1/2 and others bind to phospho-YAP1/TAZ to control their localization and activity. Solid black lines indicate known direct interactions; dashed black lines, unknown mechanisms.
Hippo elements also interact with components of pathways involved in organ morphogenesis, with mutual reinforcement of their activities. These components include phosphoinositide-3-kinase (PI3K)/AKT, WNT/b-catenin, bone morphogenetic protein (BMP), transforming growth factor (TGF)-b, NOTCH and sonic hedgehog (SHH) (Nishio et al. 2013). Many of these molecules have been linked to tumorigenic signaling.

This review focuses on results derived from the successful use of conditional gene targeting to create tissue-specific mouse models. Null mutation of most Hippo components, including YAP1/TAZ, leads to early embryonic lethality, precluding any analysis of Hippo signaling functions in adult tissues. Studies of these conditional mutants showed much about the Hippo pathway’s roles in normal physiology and development, as well as the tumorigenic effects of Hippo pathway dysregulation in various tissues and organ systems. Knowledge of this kind can only help to advance the generation of new, more effective, targeted anticancer therapies.

Digestive tissues
Liver

Human hepatocellular carcinomas (HCCs) frequently exhibit loss of YAP1(Ser127) phosphorylation (Zhou et al. 2009), increased nuclear YAP1 and impaired MOB1 phosphorylation (Zhou et al. 2009). YAP1 amplification occurs in 5%–10% of HCCs (Zender et al. 2006) such that increased YAP1 is now an independent prognostic marker for this malignancy (Xu et al. 2009). Interestingly, YAP1 levels are higher in HCCs showing ‘stemness’ (EpCAM+, keratin19+) than in HCCs lacking this property (Kim et al. 2013). Increased YAP1 is also observed in intrahepatic cholangiocellular carcinoma (ICC) and combined hepatocellular cholangiocarcinoma (cHC-CC) (Nishio et al. 2016).

In mice, liver-specific deletion of Mob1a/1b (Nishio et al. 2016), Nf2 (Benhamouche et al. 2010; Zhang et al. 2010; Liu-Chittenden et al. 2012), Mst1/2 (Zhou et al. 2009; Lu et al. 2010; Song et al. 2010), Lats1/2 (Chen et al. 2015b) or Sav1 (Lu et al. 2010) results in tumors with both ICC and HCC characteristics, as well as expansion/transformation of a mixed pool of liver progenitor cells (Song et al. 2010; Nishio et al. 2016). In addition, these mutants show hepatomegaly, increased oval cells (liver stem/progenitor cells) and hepatocyte dedifferentiation (Yimlamai et al. 2014). These latter abnormalities are reversible in the short term but lead to irreversible hepatocarcinogenesis in the long term (Zender et al. 2006). Similar liver phenotypes result from transgenic (Tg) expression of Yap1 (Camargo et al. 2007; Dong et al. 2007; Yimlamai et al. 2014). Further analysis of Hippo core component mutants has shown that these effects are strongly dependent on YAP1 but also partially dependent on TAZ (Nishio et al. 2016). In contrast, mice lacking Yap1 show a profound deficit in hepatocytes and cholangiocytes and resist HCC formation induced by NF2 mutation (Zhang et al. 2010).

Non-core components of Hippo-YAP1 signaling have also been implicated in liver cancer. F-box and WD repeat domain containing 7 (FBXW7), one of the E3 ligases acting on YAP1, regulate the abundance of YAP1 protein in human HCC (Tu et al. 2014). FBXW7 is generally reduced in HCC tissues in a manner correlating with unfavorable clinicopathological features. In contrast, sirtuin 1 (SIRT1) is markedly up-regulated in human HCC samples. Because SIRT1 deacetylates YAP1 protein in HCC cells, YAP1/TEAD4 interaction is increased, promoting YAP1/TEAD4 transcriptional activation that stimulates HCC growth (Mao et al. 2014).

Intestine

The Hippo pathway has been implicated in human intestinal stem cell (ISC) expansion and regeneration because endogenous YAP1 is expressed in the base of normal intestinal crypts (Camargo et al. 2007). In most human colon cancer cells, YAP1 is over-expressed and localized in the nucleus. However, YAP1 expression is lost in a subset of undifferentiated and highly aggressive human colorectal carcinomas (Barry et al. 2013).

In mice, reports conflict on the roles of Hippo elements in ISC expansion and regeneration. In one study, Yap1 deficiency in intestinal epithelial cells did not affect intestinal development but did inhibit intestinal regeneration induced by dextran sodium sulfate (DSS) treatment (Cai et al. 2010). In addition, inducible YAP1 activation caused undifferentiated dysplastic intestinal intestinal progenitors to expand in a Notch-dependent manner (Camargo et al. 2007). In contrast, a different group found that loss of YAP1 in the intestine led to WNT hypersensitivity followed by ISC expansion, hyperplasia and the appearance of microadenomas and ectopic crypts (Barry et al. 2013). In agreement with this finding, Tg Yap1 expression
in the intestine reduced the size of the small intestine and colon and decreased WNT target gene expression, triggering a loss of crypts. In this latter case, cytoplasmic YAP1 may have bound to dishevelled (DVL) to dampen WNT signaling (Barry et al. 2013). The stark differences between these reports should be investigated since both decreased cytoplasmic YAP1 and increased nuclear YAP1 have been linked to an increased risk of colon cancer in humans.

Mice with loss of Sarrl in the intestine show accelerated crypt regeneration and formation of DSS-induced colonic polyps (Cai et al. 2010). Intestine-specific Mst1/2-deficient mice show YAP1-mediated NOTCH and β-catenin activation in addition to ISC expansion associated with intestinal adenomagenesis (Zhou et al. 2010). Similarly, mice lacking Nhr1/2 in the intestine show intestinal hyperplasia and quickly develop adenocarcinomas after azoxymethane/DSS treatment (Zhang et al. 2015).

Finally, phosphorylation of YAP1(Y407) by YES1 allowed YAP1 to access the nucleus and form a complex with β-catenin and T-box 5 (TBX5) that stimulated transcription of the anti-apoptotic genes baculoviral IAP Repeat-containing 5 (BIRC5) and BCL2-like 1 (BCL2L1) (Rosenbluh et al. 2012). It may be that a SRC-YAP1-β-catenin-TBX5 complex is essential for the transformation and survival of β-catenin-driven cancer cells such as those present in the above mouse mutants.

**Stomach and esophagus**

YAP1 is frequently hyperactivated in human gastric and esophageal cancers (Lam-Himlin et al. 2006) in a manner correlating with poor patient survival (Song et al. 2012). In gastric cancer cell lines, LATS1 overexpression or YAP1 inhibition decreases cell proliferation and metastasis (Zhou et al. 2011b; Zhang et al. 2012, 2016). To date, mice with stomach– or esophageal-specific mutations of Hippo elements have not been reported.

**Pancreas**

In humans, key pancreatic signaling elements are activated by YAP1/TEAD interaction, which also regulates the proliferation of embryonic pancreatic progenitors (Cebola et al. 2015). Pancreatic ductal adenocarcinoma (PDAC) is often caused by oncogenic KRAS mutation. A mouse PDAC model driven by inducible KRASG12D develops pancreatic tumors in which KRASG12D and MAPK activation disappears but Yap1 DNA amplification and/or mRNA overexpression are induced. Increased YAP1 may therefore be a major driver of PDAC (Kapoor et al. 2014; Zhang et al. 2014).

Pancreas-specific Mst1/2 double-knockout (DKO) mice have a small pancreas with an exocrine compartment that shows heightened cell proliferation but is disorganized and subject to autodigestion (George et al. 2012). Pancreatic Mst1/2 loss also induces acinar cells to de-differentiate postnatally into duct-like cells, reducing total acinar cell numbers (Gao et al. 2013). However, neither these mutants nor any other mice lacking Hippo elements in the pancreas develop pancreatic cancers. Interestingly, inducible Yap1 overexpression in mouse pancreas enlarges this organ and results in ductal metaplasia (Camargo et al. 2007). These data suggest that the abnormalities of pancreas-specific Mst1/2 DKO mice may be independent of YAP1.

The pancreas is home to the pool of all-important beta cells, whose apoptotic death is observed in diabetes mellitus. Constitutive MST1-MOB1-LATS2 signaling strongly induces human beta cell apoptosis (Ardestani et al. 2014). MST1 is vigorously activated under diabetogenic conditions and phosphorylates and destabilizes pancreatic and duodenal homeobox1 (PDX1) to trigger its degradation. Apoptosis is then induced through BCL-like 11 (BIM) up-regulation. Conversely, overexpression of constitutively active YAP1 increases the proliferation of beta cells without impairing their differentiation or function (George et al. 2015). Thus, manipulation that activates YAP1 or inhibits Hippo signaling might represent a novel approach to expanding beta cells for regenerative therapy of diabetes.

**Salivary gland**

In mice, TAZ phosphorylation increases during the development of the normal salivary submandibular gland (SMG) (Enger et al. 2013). In human Sjogren’s syndrome (SS) patients, TAZ is hyperactivated and found in the nuclei of SMG cells rather than in the junctional areas of these glands. As a result, the SMG cells of SS patients show abnormal accumulation of TAZ targets such as CTGF, fibronectin and extracellular matrix components. Similarly, inhibition of Lats1 expression by siRNA in a murine organ culture system leads to defective SMG morphogenesis and a decrease in junction-localized TAZ (Enger et al. 2013). Finally, 5% of mice partially deficient for MOB1 develop salivary gland dysplasia (Nishio et al. 2013).
Thus, some SS cases may be due to impaired Hippo signaling rather than autoimmunity.

**Skin**

In mice, YAP1 is critical for skin morphogenesis. Nuclear YAP1 in normal basal epidermal progenitors drives them to proliferate, whereas progenitors with cytoplasmic YAP1 differentiate into hair follicles. When Yap1 is overexpressed in mouse skin, epidermal stem cells and progenitors expand, leading to hyperkeratosis, hair follicle evagination, epidermal thickening, and squamous cell carcinomas (SCC) (Zhang et al. 2011a; Beverdam et al. 2013). In contrast, Yap1 deficiency in mouse skin, or loss of YAP1–TEAD interaction, reduces epidermal stem/progenitor cells and decreases keratinocyte proliferation (Schlegelmilch et al. 2011).

At least one wild-type (WT) Mob1a or Mob1b allele is also required for normal mouse skin formation. Loss of all Mob1 alleles leads mainly to trichilemmal skin carcinomas with some basal cell carcinomas (Nishio et al. 2012). Mob1a/1b-deficient keratinocytes cultured in vitro show abnormalities in contact inhibition, proliferation, apoptosis, progenitor self-renewal and centrosome numbers. LATS1/2 inhibition and YAP1 activation occur in these mutant cells, similar to the YAP1 activation seen in human basal cell carcinomas and trichilemmal carcinomas (Nishio et al. 2012).

Mice lacking Sav1 (Lee et al. 2008) or Gnas (the gene encoding Gα, subunit of heterotrimeric G protein) also show skin phenotypes, with the abnormalities in Gnas KO mice dependent on a cAMP-PKA–LATS–YAP1 pathway (Iglesias-Bartolome et al. 2015). Surprisingly, keratinocyte-specific Mst1/2 DKO mice are healthy, have no skin phenotypes and show normal YAP1 phosphorylation and activation (Schlegelmilch et al. 2011). YAP1 phosphorylation in normal keratinocytes may thus be mediated routinely by an alternative mechanism such as GPCR signaling or NDR1/2 kinase activity. Loss of z-catenin specifically in keratinocytes disrupts noncanonical Hippo signaling and leads to hyperplasia and SCC (Schlegelmilch et al. 2011).

**Reproductive systems**

**Mammary gland**

Studies of KO mice showed the role of Hippo signaling in both mammary gland development and breast cancer. Although mammary gland development in virgin mammary gland–specific Sav1 KO Tg mice is not affected, terminal differentiation of this gland is impaired in late pregnancy in these mutants (Chen et al. 2014a). In vitro, forced TAZ overexpression in mammary luminal cells induces them to take on basal cell characteristics. Prepubescent virgin Taz−deficient mice appear to have normal mammary glands, but duct branching and luminal differentiation are impaired in the postpubertal stage (Skibinski et al. 2014). Null Lats1 KO mice unexpectedly show a perplexing defect in nipple formation accompanied by altered formation of ductal components. However, this phenotype may be an indirect effect of hormonal changes affecting mammary gland development (St John et al. 1999).

TAZ overexpression occurs in 20% of human breast cancers, particularly invasive ductal carcinomas, and drives tumor cell transformation, migration and invasion (Chen et al. 2008). TAZ overexpression alone, or combined YAP1/TAZ overexpression, correlates with breast cancer grade, recurrence and poor patient survival (Vici et al. 2014, 2016). LATS1/2 mRNA levels in human breast cancers are down-regulated due to promoter methylation, and this deficit is associated with tumor growth and metastasis. Interestingly, decreased expression of LATS1, but not LATS2, is linked to poor patient prognosis (Takahashi et al. 2005).

The involvement of YAP1 in human breast cancer is puzzling, as both tumor-suppressive and tumor-promoting functions have been proposed. When endogenous YAP1 is inhibited in MCF-7 cells, cisplatin-induced apoptosis is attenuated (Basu et al. 2003). Nevertheless, Yap1 deficiency slows the growth of PyMT-induced tumors in mice, and human breast cancer cell lines treated with a small molecule inhibitor of YAP1/TAZ show decreased proliferation (Chen et al. 2014a). Conversely, YAP1/TAZ overexpression promotes TGFβ-induced tumorigenic characteristics (Hiemer et al. 2014). Notably, estrogen can engage the G protein–coupled estrogen receptor (GPER; also known as GPR30), which activates YAP1/TAZ via a Gαq/11–Rho/ROCK–LATS signaling pathway that has been linked to breast cancer (Zhou et al. 2015).

**Ovary**

In mouse ovary, inhibition of MST or LATS, or activation of YAP1, influences the size of the primordial follicle pool. Therefore, activation of YAP1 induced
by either ovary fragmentation or the addition of YAP1 activators can promote follicle growth and oocyte maturation. Indeed, treatment of patients suffering from primary ovarian insufficiency with YAP1 activators has produced oocytes suitable for therapeutic in vitro fertilization (Kawamura et al. 2013; Cheng et al. 2015). In addition, recent genomewide association analyses of DNA from patients with polycystic ovarian syndrome (PCOS) showed two candidate single nucleotide polymorphisms (SNPs) in YAP1 introns, implying that YAP1 may be a new susceptibility gene for this disorder (Li et al. 2012).

With respect to ovarian cancer, null Lats1 KO mice show impaired fertility and develop ovarian stromal cell tumors within 3 months of birth (St John et al. 1999). In humans, YAP1 is often highly expressed in ovarian cancer samples and, in vitro, constitutively activated YAP1 increases human ovarian cancer cell proliferation, migration, resistance to chemotherapy, EMT and anchorage-independent growth (Xia et al. 2014). In ovarian clear cell tumors, high levels of YAP1 correlate with poor patient survival (Zhang et al. 2011b). Thus, YAP1 is a potential future target for ovarian cancer therapy.

**Prostate**

In human metastatic prostate cancers, YAP1 is often up-regulated (Zhao et al. 2007), whereas MST1/2 (Cinar et al. 2007) and LATS1/2 (Zhao et al. 2012) are down-regulated. Among radical prostatectomy patients, many possess MST2 SNPs linked to better recurrence-free survival (Huang et al. 2015). Rearrangements of the ETS gene family have been identified in 20%–50% of human prostate adenocarcinomas, and ETS-related gene (ERG) may be a key driver of prostate carcinogenesis. In prostate cancer cells, ERG binds to regions of chromatin occupied by YAP1-TEAD and activates target genes. ERG also binds to the YAP1 promoter and drives its expression in human luminal-type prostate cancer cells. In mice, prostate-specific activation of either YAP1 or ERG triggers transcriptional changes leading to eventual prostate tumorigenesis (Nguyen et al. 2015). In prostate adenocarcinomas cells with phosphatase and tensin homologue (PTEN) or SMAD4 deficiency, YAP1 is hyperactivated such that the cells secrete excessive C-X-C motif ligand 5 (CXCL5). As a result, C-X-C motif receptor 2 (CXCR2)-expressing myeloid-derived suppressor cells infiltrate these malignancies, spurring tumor progression (Wang et al. 2016). Finally, YAP1 can interact with the androgen receptor (AR) in nuclei of incipient prostate cancer cells, an event that may be central to the development of advanced prostate cancer. The small molecule inhibitor verteporfin disrupts this interaction, blocking AR-dependent gene expression and prostate cancer cell growth (Kuser-Abali et al. 2015).

**Brain and nervous system**

In normal mouse brain, YAP1 acts downstream of the SHH pathway and enhances neural stem cell proliferation (Fernandez et al. 2009; Kagey et al. 2012). In addition, GLI family zinc finger 2 (GLI2), an SHH signaling mediator, functions downstream of YAP1 to regulate neuronal differentiation (Lin et al. 2012). In both human and mouse, YAP1 is frequently up-regulated in PATCHED1-mutated or SHH-dependent medulloblastomas (Fernandez et al. 2009; Kagey et al. 2012). Overexpression of YAP1 or TEAD promotes cell cycle progression and migration, blocks neuronal differentiation by triggering cyclin D1 and PAX3 expression and mediates resistance to cisplatin-induced apoptosis in vitro (Milewski et al. 2004; Cao et al. 2008; Baia et al. 2012). YAP1 hyperactivation is also observed in human glioblastoma and ependymoma patients with poor prognoses (Modena et al. 2006; Verhaak et al. 2010; Orr et al. 2011).

Mutations that inactivate human NF2 are linked to hereditary neurofibromatosis type 2, as well as to sporadic schwannomas, ependymomas and meningiomas (Giovannini et al. 2000). In mice, complete loss of NF2 is embryonic lethal. Mice heterozygous for mutated NF2 do not develop neuronal malignancies, but homozygous NF2 loss only in Schwann cells leads to their hyperplasia and eventually schwannomas (Giovannini et al. 2000). Double loss of NF2 plus one p53 allele drives the development of peripheral nerve sheath tumors (Robanus-Maandag et al. 2004), whereas telencephalon-specific NF2 KO embryos show expansion of neural progenitors with increased nuclear YAP1/TAZ (Lavado et al. 2013, 2014).

Humans with mutations of the Hippo non-core components DCHS1 or FAT4 develop Van Maldergem syndrome. This disorder is characterized by mislocalized cortical neuron progenitors, craniofacial, limb and skeletal malformations, and renal and auditory deficits (Cappello et al. 2013). DCHS1 or FAT4 depletion in murine embryonic neuroepithelium leads to expansion of neuronal progenitors but decreases their differentiation. These mutant progenitors then mislocalize in the neocortex in a YAP1-dependent
fashion (Cappello et al. 2013), generating a phenotype resembling human Van Maldergem syndrome.

Finally, endogenous overexpression of the cancer stem cell marker CD44 in glioblastoma promotes NF2 phosphorylation/inactivation as well as YAP1 up-regulation. These tumor cells are markedly resistant to oxidative stress and cytotoxic drugs (Xu et al. 2010).

Mesenchymal cells

Bone

The differentiation of mesenchymal stem cells (MSCs) into osteogenic cells depends on YAP1/TAZ activity because TAZ is a transcriptional co-activator of the master regulator runt-related transcription factor 2 (RUNX2), which drives the expression of osteogenesis genes such as osteocalcin (Cui et al. 2003; Hong et al. 2005; Dupont et al. 2011). Taz Tg mice show significantly greater bone mineral density and enhanced bone formation (Yang et al. 2013). TAZ nuclear localization leading to osteogenic differentiation is triggered by WNT3A/PP1A-mediated TAZ dephosphorylation (Byun et al. 2014). However, the function of YAP1 in osteogenesis is less clear. Unlike TAZ, YAP1 is a transcriptional repressor of RUNX2 (Zaidi et al. 2004) and also a direct target of SOX2, the transcription factor crucial for deciding MSC cell fate. High levels of YAP1 or SOX2 block osteogenesis, whereas depletion of either YAP1 or SOX2 stimulates this process (Seo et al. 2013). Why TAZ and YAP1 functions differ in this context has yet to be elucidated.

Heterozygous mutations of Nf2, Sav1 or Mob1a/1b in mice result in osteosarcoma development (McClatchey et al. 1998; Lee et al. 2008; Nishio et al. 2012). Similarly, tumor cells of human osteosarcoma patients show increased nuclear YAP1, and YAP1 knockdown in osteosarcoma cell lines decreases expression levels of cyclin D1 and C-MYC, resulting in reduced proliferation and invasion (Chan et al. 2014; Yang et al. 2014). In human tissue microarray analyses, high YAP1 expression correlated with staging in osteosarcoma (Zhang et al. 2013). Up-regulated Hedgehog signaling induces osteosarcoma through activation of Yap1 and long non-coding RNA H19 (Chan et al. 2014).

Chondrocytes

YAP1 function in chondrocytes is also a conundrum. In vivo, Col2a1-Yap1 Tg mice show premature chondrocyte proliferation but defective chondrocyte maturation (Deng et al. 2016). In vitro, YAP1 over-expression in murine C3H10T1/2 cells reduces inhibitor of DNA binding (ID) 1-3 expression and the SMAD-1, SMAD-5 and SMAD-8 phosphorylation induced by BMP-2, resulting in impaired chondrogenic differentiation (Karystinou et al. 2015).

Adipose cells

Although little is known about YAP1 functions in adipocytes, TAZ is a transcriptional corepressor of PPARγ, the master controller of adipogenesis. TAZ inhibition allows MSCs to differentiate into adipocytes (Hong et al. 2005). Activated MST1/2 interacts with SAV1 such that SAV1 binds to PPARγ and stabilizes it, promoting adipogenic differentiation. Although inhibition of MST1/2 or SAV1 blocks adipogenesis in vitro (Park et al. 2012), it is not known whether this effect depends on canonical Hippo-YAP1/TAZ signaling or on an alternative pathway (Park et al. 2012).

Myocytes

TAZ physically interacts with myogenic differentiation (MYOD) and co-activates MYOD-dependent transcription accelerating myogenic differentiation (Jeong et al. 2010), whereas YAP1 promotes the proliferation of myocytes and satellite cells and blocks their differentiation (Watt et al. 2010; Tremblay et al. 2014). Satellite cells that sustain injury overexpress YAP1 such that inhibitors of MYOD and MEF2 are up-regulated and myogenic transcription factors are suppressed, eventually inducing rhabdomyosarcoma (Tremblay et al. 2014). In alveolar rhabdomyosarcoma, expression of the PAX3-FOXO1 fusion gene increases RASSF4 which inhibits MST1 (Crose et al. 2014). In one immunohistochemical study of patients with embryonal rhabdomyosarcoma, 171 of 196 cases (87.2%) showed tissue positivity for YAP1. In 143 of these 171 cases (83.6%), this YAP1 expression was nuclear (Tremblay et al. 2014).

Hematopoietic cells

T lymphocytes

In humans, mutations that inactivate MST1 are frequent in families with T-cell immunodeficiency and autoimmune disorders (Abdollahpour et al. 2012;
Hematopoietic stem cells

Curiously, Hippo signaling appears to be of little relevance in hematopoietic stem cells (HSCs). YAP1 is detected at only low levels in human and murine HSCs, and YAP1 overexpression does not alter HSC number and functions in vivo (Jansson & Larsson 2012).

Kidney

Development

In normal murine glomerulus, the injury sensor dendrin binds to the non-core Hippo element WW and C2 domain containing 1 (KIBRA), activating LATS (Wennmann et al. 2014). YAP1 is then inhibited, resulting in a podocyte apoptosis (Campbell et al. 2013; Wennmann et al. 2014). Podocyte-specific Yap1 deficiency in mice leads to proteinuria and a
disease with the histological features of human focal segmental glomerulosclerosis (FSGS) (Schwartzman et al. 2016). Patients suffering from FSGS show up-regulated KIBRA expression in glomeruli, indicating that KIBRA is crucial for normal kidney physiology (Bennett et al. 2007). KIBRA also binds to the cell polarity protein PATJ and the actin-bundling protein synaptopodin, such that cultured human podocytes lacking KIBRA expression migrate faster than normal podocytes but show reduced directed migration and decreased wound healing (Duning et al. 2008).

Mice depleted of Yap1 in the kidney cap mesenchyme show hypoplastic, abnormal kidneys and die within 48 h of birth (Reginensi et al. 2013). Yap1 depletion in the murine nephric duct (ND) leads to excessive signaling of the RET tyrosine kinase receptor, with death occurring soon after birth due to severe kidney and urinary tract abnormalities (Reginensi et al. 2015). Humans with congenital anomalies of the kidney or urinary tract often have RET mutations. Surprisingly, mice lacking Taz in the ND develop normally. Nevertheless, Yap1/Taz double deficiency in murine ND greatly exacerbates the abnormal kidney phenotypes (Reginensi et al. 2015).

Kidney diseases

Altered Hippo signaling is frequently observed in patients with polycystic kidney disease (PKD), and adult Taz KO mice develop PKD-like disease (Hossain et al. 2007; Makita et al. 2008). TAZ is a transcriptional co-activator of Glis3, which suppresses renal cysts and ciliary defects (Beak et al. 2008; Kang et al. 2009). In mice, epithelial cell-specific deletion of Pkd1 results in renal cysts associated with aberrations in four-jointed (Fix1), a polarity and Hippo pathway regulator (Willecke et al. 2008; Happe et al. 2009). When Pkd1-deficient kidneys become cystic, Fix1 increases significantly. Kidneys of patients with autosomal dominant PKD (ADPKD) also show enhanced WNT/β-catenin signaling (Lal et al. 2008), as do kidneys of Taz KO mice (Varelas et al. 2010) and those of mice overexpressing activated mutant β-catenin (Saadi-Kheddouci et al. 2001). Thus, enhanced WNT/β-catenin signaling may explain kidney cyst formation in the absence of cytoplasmic TAZ.

In diabetic animals, prolonged EGFR activation leads to renal injury, whereas inhibition of EGFR signaling is protective (Sayed-Ahmed et al. 1996; Saad et al. 2005; Chen et al. 2012; Reddy & Irvine 2013). EGFR-triggered YAP1 activation is enhanced in kidney cells of animal models of type 1 and type 2 diabetes, as well as in proximal tubule-like epithelial cells cultured in high glucose (Reddy & Irvine 2013; Chen & Harris 2016). In renal fibrosis, YAP1/TAZ mediates the process by which a stiff extracellular matrix promotes TGFβ-induced SMAD signaling as well as TEAD-induced connective tissue growth factor (CTGF) transcription (Szeto et al. 2016). YAP1/TAZ activation is also involved in the unilateral ureteral obstruction model of renal fibrosis (Szeto et al. 2016).

Cancer

Some patients with clear cell renal cell carcinoma (ccRCC) show YAP1 activation in their tumor cells (Schütte et al. 2014). YAP1 silencing in human ccRCC cells reduces their proliferation, migration, and anchorage-independent growth while increasing their apoptosis (Cao et al. 2014; Schütte et al. 2014). In mice, because NF2 inhibits EGFR internalization and signaling, targeted deletion of Nf2 in proximal convoluted epithelium leads to intratubular neoplasia and invasive carcinomas (Morris & McClatchey 2009).

Cardiovascular system

Heart

In humans, arrhythmogenic cardiomyopathy is associated with impaired desmosome formation due to altered plakoglobin distribution. This change in plakoglobin distribution promotes cytoplasmic YAP1 retention and repression of WNT/β-catenin signaling, leading to fibroadipogenesis and increased myocyte death (Chen et al. 2014b; Asimaki et al. 2015).

In mice, heart-specific inactivation of Yap1 is embryonic lethal. The mutant heart shows decreased cardiomyocyte proliferation and thin myocardium but normal chamber formation and cardiac looping (Xin et al. 2011; von Gise et al. 2012). Conversely, constitutively active YAP1 expression (Xin et al. 2011, 2013; von Gise et al. 2012) or heart-specific KO of Lats2, Mst1/2 or Sav1 (Heallen et al. 2011) thickens the myocardium and stimulates cardiomyocyte proliferation (without hypertrophy) that is driven by a nuclear complex of YAP1 and β-catenin. Loss of WNT/β-catenin activity can rescue all these phenotypes (Heallen et al. 2011). Cardiomyocyte proliferation is also stimulated when the microRNA cluster
| Conditional promotor | Targeted gene | Phenotype | Reference |
|---------------------|--------------|-----------|-----------|
| Liver (Straight KO) | Sav/−/−       | Partially embryonic lethal poor placental vascularization Immature lung cell differentiation Defective enterocyte differentiation Loss of apical–basal polarity | Lee et al. (2008) |
| (Conditional KO)    | Nf2/−/−       | Hepatomegaly ICC, HCC Biliary hamartoma Cataract | Zhang et al. (2010); Benhamouche et al. (2010); Liu-Chittenden et al. (2012); Yimlamai et al. (2014) |
| AlbCre              | Mst1/−/−;Mst2/− | Hepatomegaly Oval cell hyperplasia HCC, ICC | Lu et al. (2010); Song et al. (2010); Zhou et al. (2009) |
| AdenoCre            | Sav/−/−       | Hepatomegaly, HCC | Lu et al. (2010) |
| AdenoCre            | Lats1/−/−;Lats2/− | Hepatomegaly Biliary epithelial hyperplasia | Chen et al. (2015b) |
| AlbCreER            | Mob1a/−/−;Mob1b/− | Oval cell hyperplasia cHC-CC, ICC | Nishio et al. (2016) |
| AlbCreER            | Yap1/−/−      | Loss of hepatocytes and biliary epithelial cells | Zhang et al. (2010) |
| (Transgenic)        | Yap1 S127A OE (overexpression) | Biliary epithelial hyperplasia due to hepatocyte dedifferentiation | Yimlamai et al. (2014) |
| ApoE-rTA/TetO-Yap   | Yap1 OE       | Hepatomegaly, HCC | Dong et al. (2007); Liu-Chittenden et al. (2012) |
| LAP-rTA/TetO-YapS127A | Yap1 S127A OE | Reversible hepatomegaly Intestinal dysplasia with expanded progenitors | Camargo et al. (2007) |
| (Knock-In)          | Yap1 S112A KI | Prone to carcinogen (DEN)-induced HCC | Chen et al. (2015b) |
| Intestine (Conditional KO) | Yap1/−/− | Reduced DSS-induced intestinal regeneration | Cai et al. (2010) |
| VillinCre           | Yap1/−/−      | Intestinal stem cell expansion Ectopic crypts and microadenomas | Barry et al. (2013) |
| VillinCre           | Sav1/−/−      | Crypt hyperplasia DSS-induced colonic polyps | Cai et al. (2010) |

(continued)
### Table 1 (continued)

| Conditional promotor | Targeted gene | Phenotype | Reference |
|----------------------|---------------|-----------|-----------|
| VillinCre Mst1 −/−;Mst2 f/f | Intestinal stem cell expansion<br>Colon adenoma | Zhou et al. (2010) |
| VillinCre Ndr1 −/−;Ndr2 f/f | Intestinal hyperplasia<br>Adenocarcinomas after azoxymethane/DSS treatment | Zhang et al. (2015) |
| (Transgenic) Rosa26-rTA/TetO-YapS127A | Yap1 S127A OE | Expansion of undifferentiated dysplastic progenitors | Camargo et al. (2007) |
| Villin-rTA/TetO-YapS127A | Yap1 S127A OE | Reduced size of intestine and colon<br>Loss of proliferative crypts | Barry et al. (2013) |
| Pancreas (Straight KO) Mst1 −/− | Reduced β-cell apoptosis, restoration of β-cell function under diabetogenic conditions | Ardestani et al. (2014) |
| (Conditional KO) Pdx1Cre Mst1 f/f;Mst2 f/f | Disorganized pancreas of reduced size due to autodigestion | George et al. (2012) |
| | Mst1 −/−;Mst2 f/f | Increased β-cell proliferation<br>Dedifferentiation of acinar cells into duct-like cells | Gao et al. (2013) |
| RIPCre | Mst1 f/f;Mst2 f/f | Resistance to β-cell apoptosis<br>Protected from diabetes | Ardestani et al. (2014) |
| (Transgenic) LAP-rTA/TetO-YapS127A | Yap1 S127A OE | Enlarged pancreas<br>Ductal metaplasia | Camargo et al. (2007) |
| Salivary gland (Straight KO) Mob1a Δ/Δ;Mob1b +/− | Salivary gland dysplasia | Nishio et al. (2012) |
| Skin (Straight KO) Sav −/− | Increased immature keratinocytes<br>Premature hair follicles of reduced size | Lee et al. (2008) |
| (Conditional KO) K14CreER Mob1a f/f;Mob1b −/− | Progenitor hyperplasia<br>Parakeratosis<br>Trichilemmal carcinomas | Nishio et al. (2012) |
| K14Cre Yap f/f | Reduced epidermal stem/progenitor cells | Schlegelmilch et al. (2011) |
| | Yap S79A/f<br>(unable to interact with TEADs) | Decreased keratinocyte proliferation | |
| Conditional promotor | Targeted gene         | Phenotype                                         | Reference                   |
|----------------------|-----------------------|--------------------------------------------------|-----------------------------|
| **(Transgenic)**     |                       |                                                  |                             |
| K14-rtTA/TetO-YapS127A | Yap1 S127A OE        | Progenitor hyperplasia Hyperkeratosis            | Schlegelmilch et al. (2011); Zhang et al. (2011a) |
| K14Cre/inducible     |                       |                                                  |                             |
| rtTA/tetO-YapS127A   |                       |                                                  |                             |
| K5 promoter          | Yap2-5SA-D OE         | Expansion of epidermal stem/progenitor cells     | Beverdam et al. (2013)      |
| Mammary gland        |                       |                                                  |                             |
| **(Straight KO)**    |                       |                                                  |                             |
| –                    | Lats1 −/−             | Lack of nipple formation                         | St John et al. (1999)       |
| –                    | Taz −/−               | Impaired duct branching and luminal differentiation at postpubertal virgin stage | Skibinski et al. (2014)    |
| **(Conditional KO)** |                       |                                                  |                             |
| MMTVCre              | Sav1 flox             | Impaired terminal differentiation of epithelial cells at late pregnancy | Chen et al. (2014a)        |
| MMTVCre              | Yap flox              | Reduced alveolar structure at pregnancy stage    | Chen et al. (2014a)        |
| **(Transgenic)**     |                       |                                                  |                             |
| MMTV-rtTA/TER-Yap    | Yap1 OE              | Impaired terminal differentiation of epithelial cells at late pregnancy | Chen et al. (2014a)        |
| **Ovary**            |                       |                                                  |                             |
| **(Straight KO)**    |                       |                                                  |                             |
| –                    | Lats1 −/−             | Subfertile                                       | St John et al. (1999)       |
| **Prostate**         |                       |                                                  |                             |
| **(Transgenic)**     |                       |                                                  |                             |
| PbsnCre              | Yap1 S127A OE        | Age-related prostate tumors                      | Nguyen et al. (2015)        |
| LSL-rtTA/TetO-YapS127A |                |                                                  |                             |
| **Brain and nervous system** |               |                                                  |                             |
| **(Straight KO)**    |                       |                                                  |                             |
| Dchs1 −/−            |                       | Van Maldergem syndrome                           | Cappello et al. (2013)     |
| Fat4 −/−             |                       | Expanded neuronal progenitors with poor differentiation YAP1-dependent mislocalization of progenitors in neocortex |                             |
| **(Conditional KO)** |                       |                                                  |                             |
| POCre (Schwann cells)| Nf2 f/f               | Schwannomas Neurofibrosarcomas                    | Giovannini et al. (2000)   |
| –                    |                       | Schwann cell hyperplasia cataracts Osseous metaplasia |                             |
| −                    | Nf2 −/−;p53 +/−      | Malignant peripheral nerve sheath tumors         | Robanus-Maandag et al. (2004) |

(continued)
Table 1 (continued)

| Conditional promotor | Targeted gene | Phenotype | Reference |
|----------------------|---------------|-----------|-----------|
| Emx1-IRES-Cre        | Nf2 f/f       | Neural progenitor cell expansion Malformation of midline guideposts, resulting in callosal agenesis | Lavado et al. (2013, 2014) |
| **Bone** (Straight KO) |               |           |           |
|                      | Nf2 +/+      | Osteosarcoma | McClatchey et al. (1998) |
|                      | Sav --/--    | Osteosarcoma | Lee et al. (2008) |
|                      | Mob1a f/+/Mob1b --/-- | Osteosarcoma | Nishio et al. (2012) |
| (Transgenic) Col1 promotor | Taz OE       | Increased whole-body bone mineral density and bone formation | Yang et al. (2013) |
| Chondrocytes (Transgene) Col2a1 promotor | Yap1 OE       | Increased early chondrocyte proliferation Decreased chondrocyte maturation | Deng et al. (2016) |
| Myocytes (Transgene) Myf5Cre | TetO-hYAP1 S127A OE | Gait defect Increased muscle regeneration Embryonal rhabdomyosarcoma | Tremblay et al. (2014) |
| Rosa26-LSL-rTA Myod1Cre | Rosa26-LSL-rTA Pax7CreERT2 Rosa26-LSL-rTA | | |
| Lymphocytes (Straight KO) | Mst1 --/-- | Increased SP thymocytes Decreased peripheral naïve T and B cells Decreased proliferation and IL-2 secretion Increased activation-induced cell death Impaired LFA-1 clustering Reduced thymocyte emigration, migration and homing Mst1/2-Foxo1/3-dependent decrease in SOD2 and catalase Increased ROS Suppressed Th1 response Reduced severity of EAE or collagen-induced arthritis Decreased Treg numbers Splenomegaly Lymphadenopathy Age-related autoimmune disease Decreased MZB cells Decreased antigen-specific IgG production | Zhou et al. (2008); Choi et al. (2009); Dong et al. (2009); Du et al. (2014); Salojin et al. (2014) |
|                      | Mst1 --/--;p53 --/-- | Spontaneous lymphoma Increased susceptibility to ENU-induced T-ALL | Kim et al. (2012) |

(continued)
Table 1 (continued)

| Conditional promotor | Targeted gene | Phenotype | Reference |
|----------------------|---------------|-----------|-----------|
| –                    | Ndr1 −/−      | Age-related spontaneous T-cell lymphomas | Cornils et al. (2010) |
|                      | Ndr1 +/-     | Increased susceptibility to carcinogen-induced T-cell lymphomas | |
| (Conditional KO)     |               |           |           |
| CAGCre               | Mst1 f/f      | As for Mst1−/− mice | Katagiri et al. (2009); Ueda et al. (2012) |
| LckCre               | Mst1 f/f      | As for Mst1−/− mice | Dong et al. (2009); Mou et al. (2012); Ueda et al. (2012) |
|                      | Mst1 −/−;Mst2 f/f | Impaired thymocyte emigration | Tang et al. (2015) |
|                      | Ndr1 −/−;Ndr2 f/f | Increased SP thymocytes Decreased peripheral naïve T cells Similar to MST1/2 KO | |
| Myeloid cells        |               |           |           |
| (Conditional KO)     |               |           |           |
| Lys2Cre              | Mst1 f/f;Mst2 f/f | Decreased neutrophils and macrophages Recurrent bacterial infections Impaired autophagosomal maturation | |
| VavCre               | Mst1 −/−;Mst2 f/f | Reduced ROS production Impaired mitochondrion–phagosome juxtaposition | Geng et al. (2015) |
| Hematopoietic stem cells |             |           |           |
| (Transgenic)         |               |           |           |
| Rosa26-rTA/TetO-YapS127A | Yap1 S127A OE | No abnormalities | Jansson & Larsson (2012) |
| Kidney               |               |           |           |
| (Straight KO)        |               |           |           |
| –                    | Taz −/−       | Polycystic kidney disease with dilatation of Bowman’s spaces Atrophy of glomerular tufts | Hossain et al. (2007); Makita et al. (2008); Varelas et al. (2010) |
| (Conditional KO)     |               |           |           |
| Six2Cre (cap mesenchyme) | Yap1 f/f     | Hypoplastic kidneys | Regnensni et al. (2013) |
| Hoxb7Cre (nephric duct) | Yap1 f/f     | Hydronephrotic kidneys with blind-ending megaureters | Regnensni et al. (2015) |
| PodocinCre (podocytes) | Yap1 f/f     | Focal segmental glomerulosclerosis Proteinuria | Schwartzman et al. (2016) |
| VillinCre (proximal convoluted epithelium) | Nf2 f/f | Renal intratubular neoplasia | Morris & McClatchey (2009) |
| Cardiovascular system |               |           |           |
| (Straight KO)        |               |           |           |
| –                    | Yap −/−       | Defective yolk sac vasculogenesis | Morin-Kensicki et al. (2006) |

(continued)
| Conditional promoter | Targeted gene | Phenotype | Reference |
|----------------------|--------------|-----------|-----------|
| **(Conditional KO)** |             |           |           |
| Nkx2.5Cre | Yap1 f/f | Embryonic lethality (E10.5) Decreased cardiomyocyte proliferation Thin myocardium | Xin et al. (2011) |
| Tnnt2Cre | Yap1 f/f | Embryonic lethality (E16.5) Reduced cardiomyocyte proliferation Hypoplastic ventricles | von Gise et al. (2012) |
| αMHCCre | Yap1 f/f, Yap1 f/+ | Dilated cardiomyopathy Increased apoptosis and fibrosis Decreased proliferation and hypertrophy after chronic myocardial infarction | Del Re et al. (2013) |
| Nkx2.5Cre | Sav1 f/f Mst1 f/f; Mst2 f/f Lats2 f/f | β-catenin-dependent myocardial expansion | Heallen et al. (2011) |
| Myh6CreERT2 | Sav1 f/f Lats1 f/f; Lats2 f/f | Increased renewal of adult cardiomyocytes Increased regeneration after apex resection and myocardial infarction | Heallen et al. (2013) |
| Nkx2.5Cre | LSL-miR302-367 TG | Enlarged heart Thickened ventricular myocardium Ventricular septal defects | Tian et al. (2015) |
| SM22αCre | Yap1 f/f | Perinatal lethality Hypoplastic arterial wall, short/absent brachiocephalic artery Retroesophageal right subclavian artery Membranous ventricular septal defect Double outlet right ventricle | Wang et al. (2014) |
| **(Transgenic)** |             |           |           |
| βMHC promotor | mYap1 S112A (active) OE | Enhanced cardiomyocyte proliferation Thickened myocardium Expanded trabecular layer Increased cardiac regeneration | Xin et al. (2011, 2013) |
| αMHC promotor | LSL- rTA/TRE-Yap (Yap1 OE) | Increased myocardocyte proliferation Thickened myocardium Cardiomegaly Induction at E8.5 leads to embryonic lethality by E15.5 Induction at P5 increases heart weight | von Gise et al. (2012) |
| **Lung** |             |           |           |
| **(Straight KO)** |             |           |           |
| Taz --/-- | Airspace enlargement mimicking emphysema | Makita et al. (2008) |
| Taz +/+-- | Resistance to lung fibrosis induced by bleomycin | Mitani et al. (2009) |
| Nf2 +/+-- | Accelerated malignant mesotheliomagenesis upon asbestos exposure | Altomare et al. (2005) |

(continued)
miR302–367 represses the expression of Mst1, Lats and Mob1b mRNAs (Tian et al. 2015).

Heart injury or myocardial infarction in mice activates YAP1 in surrounding cardiomyocytes (Del Re et al. 2013). Constitutively active YAP1-S112A, or deficiency of Sav1 or Lats1/2 specifically in cardiomyocytes, induces cardiac regeneration and reduces fibrosis (Heallen et al. 2013; Xin et al. 2013). In contrast, Yap1 deletion in murine cardiomyocytes exacerbates cardiac injury and cardiomyocyte proliferation is reduced (Del Re et al. 2013).

Vascular system

Many human malignancies arising from vascular endothelial cells contain gene fusions such as YAP1-TEF3, TAZ-FOSB or TAZ-CAMTA1 (Tanas et al. 2011; Antonescu et al. 2013, 2014; Patel et al. 2015; Stockman 2015). Yap1 KO mice show defective yolk sac vasculogenesis (Morin-Kensicki et al. 2006), and Yap1 deletion specifically in cardiac and smooth muscle cells generates severe arterial anomalies (Wang et al. 2014).

| Conditional promotor | Targeted gene | Phenotype                                                                 | Reference               |
|----------------------|---------------|---------------------------------------------------------------------------|-------------------------|
| (Conditional KO)     |               |                                                                           |                         |
| ShhCre               | Yap1 f/f      | Highly hypoplastic lung                                                    | Mahoney et al. (2014)   |
|                      |               | Disrupted branching morphogenesis                                          |                         |
|                      |               | Dilated cyst-like structures                                              |                         |
|                      |               | Defective alveolar epithelial cell differentiation                        |                         |
| K5-rtTA/TetO-Cre     | Yap f/f       | Loss of adult airway basal stem cells through unrestrained differentiation  | Zhao et al. (2014)      |
| Nkx2.1Cre            | Mst1 f/f;Mst2 −/− | Perinatal mortality                                                        | Chung et al. (2013)     |
|                      |               | Decreased type I and immature type II pneumocytes lacking surfactant protein |                         |
|                      |               | RDS-like disease dependent on regulation of Foxa2 rather than YAP          |                         |
| ShhCre               | Mst1 f/f;Mst2 f/f | RDS-like disease with airway hyperplasia dependent on YAP/TAZ             | Lange et al. (2015)     |
| Nkx2.1Cre            | Mst1 −/−;Mst2 f/f | RDS-like disease with airway hyperplasia dependent on YAP/TAZ             | Lin et al. (2015)       |
| (Transgenic)         |               |                                                                           |                         |
| K5-rtTA/TetO-Yap1    | Yap1 S127A OE | Increased stem cell self-renewal without terminal differentiation          | Zhao et al. (2014)      |
| (S127A)              |               | Epithelial hyperplasia and stratification                                  |                         |

Lung

Development

Hippo signaling is vital for normal lung development and homeostasis in mice. SOX2 expression is decreased in mice with Yap1-deficient lung epithelium, and these animals show hypoplastic lungs with cystic structure (Mahoney et al. 2014). YAP1 also maintains p63+ airway basal stem cells, supporting their self-renewal and resistance to differentiation (Zhao et al. 2014). Surviving adult Taz KO mice show abnormal alveoli with expanded airspaces similar to those in human emphysema patients (Tian et al. 2007; Makita et al. 2008; Mitani et al. 2009). Heterozygous Taz mutant mice are resistant to lung fibrosis induced by bleomycin, indicating that TAZ controls fibrotic responses in this tissue (Mitani et al. 2009).

Surfactants

In murine lung epithelial cells, TAZ promotes NKX2.1-mediated transcription of surfactant protein.
However, a lack of Mst1/2 in murine lung epithelial cells results in perinatal lethality associated with an increase in immature pneumocytes that cannot express SP-C, similar to human respiratory distress syndrome (RDS) (Chung et al. 2013; Lange et al. 2015; Lin et al. 2015). However, exactly how MST1/2 and YAP1/TAZ achieve their effects in the lung is controversial. On the one hand, MST1/2 phosphorylates and stabilizes the FOXA2-mediated transcription responsible for pneumocyte maturation and SP-C production, such that the lung defect in Mst1/2-deficient mice appears to be FOXA2 dependent but YAP1 independent (Chung et al. 2013). In contrast, YAP1 is activated in Mst1/2-depleted lungs, and loss of one Yap1 allele counteracts the lung defects induced by Mst1/2 deficiency (Lin et al. 2015). These data suggest that Mst1/2 loss has effects on mouse lung that are YAP1 dependent but FOXA2 independent. These differences remain to be explained.

Cancer

Hippo signaling appears to be important for the tumorigenicity of human nonsmall cell lung cancer (NSCLC) cells (Wang et al. 2010; Zhou et al. 2011a; Noguchi et al. 2014). Liver kinase B1 (LKB1) is a tumor suppressor that is frequently inactivated in NSCLC (Gao et al. 2011). When LKB1 activity is lost, activation of YAP1/TAZ ensues and stimulates alveolar cell proliferation (Nguyen et al. 2013; Mohseni et al. 2014). High levels of YAP1 correlate with shorter survival of NSCLC patients (Wang et al. 2010). NSCLC cells also show a dramatic decrease in MOB1 (Sasaki et al. 2007). A germ-line mutation of YAP1 (R331W) that leads to constitutive activation is linked to lung adenocarcinomagenesis (Chen et al. 2015a).

Malignant mesothelioma (MM) in humans exposed to asbestos may also be associated with aberrant Hippo signaling. NF2 mutations occur in half of human MM patients and these tumors often show YAP1 hyperactivation (Sekido 2013). Heterozygous Nf2 mutant mice exposed to asbestos develop MM faster than WT Nf2 controls (Alto Mare et al. 2005).

It is not yet clear whether Mst1/2 deficiency in adult mouse lung triggers lung tumorigenesis. TAZ overexpression accompanied by NF2 down-regulation has been observed in murine SCA1+ lung tumor-propagating cells, and constitutively active YAP1 expression in Kras Tg mice accelerates lung tumor progression (Lau et al. 2014). Finally, depletion of YAP1/TAZ in human lung cancer cell lines reduces their capacity for migration and metastasis (Lau et al. 2014).

Figure 2 Acquired and hereditary human disorders linked to Hippo pathway abnormalities. Diseases in which the Hippo pathway is inactivated appear in blue, whereas those characterized by Hippo hyperactivation are in red.
Stem cells

In mice, YAP1/TAZ is crucial for the maintenance of embryonic stem (ES) cells, adult stem cells, induced pluripotent stem (iPS) cells and cancer stem cells. In normal mouse tissues, YAP1/TEAD are highly expressed in ES cells and mesenchymal stem/progenitor cells and are required for their ‘stemness’. In response to TGFβ or BMP, YAP1/TAZ binds to SMADs and modulates the induction of pluripotency factors important for ES cell survival and function (Varelas et al. 2008; Alarcón et al. 2009). In addition, activated YAP1 promotes the expression of many genes involved in iPS induction (Lian et al. 2010). In human malignancies, activated YAP1/TAZ supports cancer stem cell survival and tumorigenicity (Fernandez et al. 2009; Bhat et al. 2011; Cordenonsi et al. 2011).

Discussion

Suppression of the transcriptional cofactors YAP1/TAZ by effective Hippo signaling is now recognized as a major tumor-suppressive mechanism. In the absence of a normal Hippo pathway, YAP1/TAZ becomes hyperactivated and functions as formidable oncogenes in a wide range of mammalian tissues.

In humans, the Hippo pathway has been studied extensively in primary tumors to identify the many ways in which Hippo signaling can be inactivated and that YAP1/TAZ can become hyperactivated. The effects of these changes on the clinical features and prognoses of various cancer patients have been examined in detail. Remarkably, these clinical observations are in general firmly supported by the findings of much research dissecting the consequences of Hippo pathway alterations in mutant mice. Because homozygosity for mutation of a Hippo pathway component is usually embryonic lethal, it has been difficult to analyze the functions of Hippo signaling in adult mouse organs and tissues. To overcome this hurdle, many groups have generated tissue-specific conditional mutants in which one or more Hippo components have been deleted in a particular tissue (Table 1). Detailed analyses of these mutants have yielded both expected and unexpected phenotypes, all pointing toward the indisputable importance of proper Hippo signaling not only for protection against tumorigenesis but also for regulating a broad range of physiological and pathophysiological phenomena.

The close correlation between findings in human disorders and the phenotypes of Hippo-disrupted mutant strains shows the use of these mouse models. In addition, because of their similarities to the human situation, these mutants will be of great value for finding means to modify the features or course of a human disease as well as to assess the efficacy of novel experimental therapies (Fig. 2). Such work is already under way, as summarized in our recent review on the potential for therapeutic activation or inhibition of the Hippo pathway to treat human afflictions, especially cancers (Nakatani et al. 2016). Future discoveries of drugs able to molecularly target Hippo signaling elements may yield even more useful and effective therapies.

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