The Hippo pathway in normal development and cancer

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Abstract

The Hippo pathway is a central regulator of organ size and tissue homeostasis. Hippo kinases and adaptor proteins mediate the phosphorylation and inactivation of YAP and TAZ, two closely related transcription co-activators. The Hippo pathway responds to a variety of extracellular and intracellular signals, spanning from cell-cell contact and mechanical cues to ligands of G-protein-coupled receptors and metabolic avenues. In some instances, YAP/TAZ activation is tuned by forces that bypass the Hippo kinase module, adding further complexity to the biology of the pathway. Over the past two decades, the Hippo pathway has increasingly been connected with developmental processes and tissue repair, being intimately tied to the function of tissue-specific progenitor cells. Pervasive activation of YAP/TAZ has been recognized in a multitude of human tumors and connected with the acquisition of malignant traits, including resistance to anticancer therapies, distant dissemination and maintenance of cancer stem cells. On this ground, Hippo-related biomarkers are increasingly investigated in translational studies striving to identify prognostic and predictive factors. In addition, the dependency of many tumors on YAP/TAZ may be exploited for therapeutic purposes. Albeit no direct inhibitors are currently available, drug repositioning approaches provided hints that YAP/TAZ inhibition can be achieved with old drugs, such as cholesterol-lowering agents or compounds blocking bone resorption.

Keywords

Hippo pathway, TAZ, YAP, development, tissue regeneration, cancer

Table of Contents

Abbreviations

BC: breast cancer, CRC: colorectal cancer, CSCs: cancer stem cells, EMT: epithelial-mesenchymal transition, GPCRs: G-protein-coupled receptors, HCC: hepatocellular carcinoma, LATS1: large tumor suppressor 1, LATS2: large tumor suppressor 2, MOB1A: MOB kinase activator 1A, MOB1B: MOB kinase activator 1B, MST1: sterile 20-like kinase 1, MST2: sterile 20-like kinase 2, NF2: neurofibromin 2, NSCLC: non-small cell lung cancer, PC: prostate cancer, PDAC: pancreatic ductal adenocarcinoma, SAV1: Salvador homolog 1, SWH: Salvador-Warts-Hippo, TEADs: TEA domain-containing sequence-specific transcription factors, TAZ: transcriptional co-activator with PDZ-binding motif, YAP: Yes-associated protein.

1. Introduction

The interest surrounding the Hippo pathway in tissue development and cancer stemmed more than two decades ago from two studies in *Drosophila*, describing a remarkable tissue overgrowth upon loss of the *Warts* (*wts*) gene (Justice et al., 1995; Xu et al., 1995). Years later, a wave of studies showed that *Salvador* (*sav*) (Kango-Singh et al., 2002; Tapon et al., 2002), *Hippo* (*hpo*) (Harvey et al., 2003; Jia et al., 2003; Pantalacci et al., 2003; Udan et al., 2003; Wu et al., 2003) and *Mob as tumor suppressor* (*mats*) (Lai et al., 2005) mutations resulted in a similar outcome, leading to the functional and biochemical characterization of the "Salvador-Warts-Hippo" (SWH) pathway. Since inactivating mutations of the aforementioned genes promoted hyperproliferation and reduced apoptosis, with consequent tissue overgrowth and onset of tumors, the SWH pathway was designated as a tumor suppressor signaling in fly tissues. The transcriptional co-activator *Yorkie* (*yki*), the downstream effector of the pathway, was discovered in 2005 in a screen of Wts-interacting proteins (Huang et al., 2005). Yki was found to be phosphorylated and inactivated by Wts, and its overexpression phenocopied *hpo*, *sav*, and *wts* loss-of-function mutations. As Yki does not contain any DNA-binding domain, the final piece of the puzzle in the regulation of pathway-responsive genes was the identification of the TEA-domain transcription factor Scalloped (Sd) (Zhang et al., 2008; Wu et al., 2008).

Mammalian homologs of SWH pathway components, such as the transcriptional co-factor Yes-associated protein (YAP) (Sudol et al., 1994) and its paralog transcriptional co-activator with PDZ-binding motif (TAZ) (Kanai et al., 2000), were already known before the functional characterization of the pathway in *Drosophila*. Nevertheless, studies in flies have been instrumental in delineating the architecture and function of the mammalian Hippo pathway (Dong et al., 2007). Ever since, the Hippo pathway has gained increasing popularity, its deregulation was observed in a variety of tumors and linked to a number of tumor-promoting activities. Importantly, with the exception of *NF2*, Hippo pathway mutations have sporadically been detected in cancer genome studies,

indicating the functional nature of pathway perturbation in human tumors (Zanconato et al., 2016). Thus, aberrant YAP/TAZ activation in cancer is mainly driven by a combination of several inputs that physiologically regulate their function, but that are dysfunctional in tumors.

In this review, we first provide an overview of the Hippo pathway together with the complex molecular network that tunes its activation/inactivation, we then discuss its involvement in developmental processes, and finally summarize evidence on aberrant pathway activity in neoplastic diseases together with potential therapeutic opportunities.

2. Regulation of the Hippo pathway

The hearth of the mammalian Hippo signaling encompasses the serine/threonine kinases sterile 20-like kinase 1 and 2 (MST1 and MST2; Hpo in *Drosophila*) and large tumor suppressor 1 and 2 (LATS1 and LATS2, Wts in *Drosophila*). Hippo kinases, in cooperation with the scaffold proteins Salvador homolog 1 (SAV1; Sav in *Drosophila*) and MOB kinase activator 1A and 1B (MOB1A and MOB1B; Mats in *Drosophila*), phosphorylate and inhibit the Hippo transducers YAP and TAZ (Yki in *Drosophila*). In such a manner, the Hippo core module prevents YAP/TAZ nuclear accumulation and interaction with the TEA domain-containing sequence-specific transcription factors (TEAD1 to TEAD4, Sd in *Drosophila*). Beyond TEAD factors, YAP/TAZ also cooperate with other transcriptional partners including SMADs, T-box transcription factor 5 (TBX5) and RUNT-related transcription factors (RUNX1 and RUNX2) (Halder & Johnson, 2011). Thus, the phosphorylation cascade mediated by the Hippo core module refrains YAP/TAZ-driven gene transcription by promoting their nuclear exclusion, cytoplasmic retention and proteasomal degradation (Zhao et al., 2007; Dong et al., 2007; Lei et al., 2008; Liu et al., 2010; Zhao et al., 2010). When the regulatory module is inactivated, or in the presence of stimuli that activate YAP/TAZ independently on Hippo kinases, Hippo transducers accumulate into the nucleus where, upon interaction with transcriptional partners, mediate the transcription of target genes (i.e. *CTGF*, *CYR61*, *ANKRD1*, *BIRC5*, *AXL*) (Piccolo et al., 2014). Recently, it has been observed that

YAP/TAZ also function as transcriptional co-repressors in a process that requires TEAD factors and recruitment of the nucleosome-remodeling and histone deacetylase (NuRD) complex. This leads to transcriptional repression of tumor-suppressor genes, such as DNA-damage-inducible transcript 4 (DDIT4) and TNF-related apoptosis-inducing ligand (TRAIL), ultimately favoring the activity of mechanistic target of rapamycin complex 1 (mTORC1) (Kim et al., 2015).

A complex network regulates Hippo signaling. A variety of different molecular inputs, spanning from cell polarity and cell adhesion mechanisms to mechanical cues, metabolic pathways and soluble factors modulate YAP/TAZ activation (Piccolo et al., 2014). In turn, regulation of the Hippo signaling is controlled by a negative-feedback loop, since YAP/TAZ mediate the transcription of Hippo kinases and other negative pathway regulators (Chen et al, 2015a; Dai et al., 2015; Moroishi et al., 2015; Mohseni et al., 2014). In addition, YAP/TAZ modulate the expression of ligands controlling the activity of a number of pathways, such as sonic hedgehog (SHH), Wnt, transforming growth factor β (TGF-β) and Notch, delineating their involvement in an extensive crosstalk governing cell fate via both autocrine and paracrine mechanisms (Yu et al., 2015).

Stimuli regulating the Hippo signaling in mammals can be schematically grouped in: i) determinants of cell polarity and cell-cell junctions. These include apicobasal cell polarity (ABCP) proteins, such as Scribble (SCRIB), which promote the activation of Hippo kinases (Cordenonsi et al., 2011; Mohseni et al., 2014), and factors that sequester YAP/TAZ including the apical crumbs complex (CRB) (Varelas et al., 2010), angiomotin family (AMOTs), which can either sequester YAP/TAZ (Chan et al., 2011; Wang et al., 2011; Zhao et al., 2011) or activate the Hippo pathway (Adler et al., 2013; Hirate et al., 2013), and protein tyrosine phosphatase non-receptor type 14 (PTPN14) (Wang et al., 2012; Liu et al., 2013); ii) factors mediating the activation of Hippo kinases, such as KIBRA, neurofibromin 2 (NF2, also known as Merlin), and TAO (thousand and one amino acid protein) kinases (Genevet et al., 2010; Xiao et al., 2011; Yin et al., 2013; Yu et al., 2010; Boggiano et al., 2011; Poon et al., 2011); iii) mechanical cues (mechanotransduction), such

as extracellular matrix stiffness and changes in cell geometry, attachment status and density (Dupont et al., 2011; Aragona et al., 2013; Wada et al., 2011). These mechanical forces regulate the Hippo pathway by modulating Rho GTPases and remodeling of the actin cytoskeleton; iv) soluble factors that act through G-protein-coupled receptors (GPCRs) and Rho GTPases. Hormones and growth factors can either activate (lysophosphatidic acid, thrombin, angiotensin II and estrogen) or inhibit (epinephrine and glucagon) YAP/TAZ (Kim et al., 2013a; Miller et al., 2012; Mo et al., 2012; Wennmann et al., 2014; Yu et al., 2013a; Yu et al., 2012; Zhou et al., 2015). Another level of ligand-dependent regulation of YAP/TAZ refers to the Hippo-Wnt pathway cooperation. This model envisions the incorporation of YAP/TAZ into the β-catenin destruction complex (Azzolin et al., 2014). In the absence of Wnt signaling, YAP/TAZ participate in β-catenin degradation. Conversely, stimulation by Wnt ligands disassembles the destruction complex, promoting both YAP/TAZ- and β-catenin-mediated gene transcription; v) metabolic pathways promoting YAP/TAZ nuclear localization (mevalonate pathway) or their binding to TEAD factors (glucose metabolism and aerobic glycolysis) (Sorrentino et al., 2014; Enzo et al., 2015; DeRan et al., 2014; Wang et al., 2015; Mo et al., 2015). Control of YAP/TAZ operated by the mevalonate pathway involves Rho GTPases, as geranylgeranyl pyrophosphate, produced in the mevalonate cascade, is required for correct membrane anchoring of Rho GTPases. Figure 1 illustrates the Hippo cascade and its regulatory branches.

3. The Hippo pathway in organ development

The idea that the Hippo pathway plays a central role in organ development is rooted in pioneering studies in *Drosophila*, unveiling how mutations of Hippo pathway kinases or Yki overexpression led to the overgrowth of various organs and appendages (Justice et al., 1995; Xu et al., 1995; Kango-Singh et al., 2002; Tapon et al., 2002; Harvey et al., 2003; Jia et al., 2003; Pantalacci et al., 2003; Udan et al., 2003; Wu et al., 2003; Lai et al., 2005; Huang et al., 2005). A wave of studies exploiting conditional knockout alleles and inducible transgenic mice later revealed that the effects

of the Hippo pathway on cell proliferation and stem cell fate, and ultimately tissue overgrowth and tumorigenesis, are conserved in mammals.

3.1 Digestive system

The first clues that Hippo-mediated organ size control is conserved in mammals date back to 2007, when two independent reports described an increase in liver mass upon transgenic *Yap* expression (Camargo et al., 2007; Dong et al., 2007). This process was related to proliferation of mature hepatocyte, and molecularly tied to the transcription of genes promoting hepatocyte proliferation together with negative regulators of apoptosis. Hepatomegaly was a reversible phenomenon, as the liver returned to its original size when *Yap* overexpression was turned off. Prolonged YAP overexpression resulted in the onset of liver nodules with characteristics of hepatocellular carcinoma (HCC), a finding consistent with the imbalance in proliferation/apoptosis. YAP-induced liver overgrowth and tumorigenesis was later found to be dependent on TEAD-mediated gene responses, as hepatomegaly and tumorigenesis were suppressed by a small molecule inhibiting TEAD-YAP association (verteporfin), or by a dominant-negative TEAD2 molecule (Liu-Chittenden et al., 2012). Liver enlargement and tumorigenesis were also observed with liver-specific knockout of *Mst1* and *Mst2*, *Lats1* and Lats*2*, *Sav1*, *Nf2* and *Mob1A/1b* (Zhou et al., 2009; Lu et al., 2010; Song et al., 2010; Zhang et al., 2010; Lee et al., 2010; Benhamouche et al., 2010; Yin et al., 2013; Nishio et al., 2016). The observed phenotype was connected, at the cellular level, with an increased proliferative capacity of oval cells, a population of bipotential progenitors capable of differentiating into either hepatocytes or ductal cholangiocytes. This is in line with the observations that mice developed, in some instances, both HCC and cholangiocarcinoma (or bile duct hamartoma). Alternatively, the onset of both HCC and cholangiocarcinoma in Hippo mutant mice was reconnected with the dedifferentiation of hepatocytes into cells carrying progenitor characteristics (Yimlamai et al., 2014). In addition, it has been recently proposed that activation of YAP/TAZ induced by loss of *Lats*1/2 triggers the differentiation of hepatoblasts and hepatocytes into biliary

epithelial cells (Lee et al., 2016a). Overall, it is plausible that cell fate determination in the liver depends on a precise spatiotemporal regulation of the Hippo pathway and YAP/TAZ. The YAP-mediated proliferative transcriptional program is involved in liver repair after injury (i.e. partial hepatectomy or cholestatic liver injury) (Grijalva et al., 2014; Su et al., 2015; Yimlamai et al., 2014; Herr et al., 2014; Bai et al., 2012). Consistently, the pharmacological inhibition of MST1/2 was proposed for enabling liver repair and regeneration (Fan et al., 2016). Prolonged YAP activity also fuels activation of hepatic stellate cells, leading to liver fibrosis (Mannaerts et al., 2015).

In the intestine, *Yap* overexpression generated intestinal dysplasia without affecting the size of the organ. Expression of endogenous YAP was restricted to the progenitor/stem cell compartment residing at the bottom of the intestinal crypts (Camargo et al., 2007; Cai et al., 2010). Consequently, its activation expanded multipotent undifferentiated progenitors that replaced differentiated cell types (i.e. enterocytes, mature goblet cells and Paneth cells). The conditional knockout of *Sav1* and *Mst1/2* also resulted in the expansion of progenitor cells in a YAP-dependent manner (Lee et al., 2008; Cai et al., 2010; Zhou et al., 2011a). Interestingly, while the YAP/TAZ-TEADs cooperation was required for the proliferation of intestinal stem/progenitor cells, the interaction of YAP/TAZ with the transcription factor KLF4 promoted differentiation into goblet cells, plausibly operating at the level of secretory progenitors (Imajo et al., 2015). Unpredictably, in 2013 Barry and colleagues reported an unexpected growth-suppressive function of YAP. Transgenic expression of *Yap* provoked a rapid loss of intestinal crypts by repressing the Wnt signalling, whereas *Yap* loss promoted Wnt hypersensitivity after irradiation, leading to crypt cell proliferation (Barry et al., 2013). These conflicting results may derive from differences in the experimental models, YAP-mediated negative feedback regulation (Moroishi et al., 2015; Chen et al., 2015a; Dai et al., 2015), and the complex connection between YAP/TAZ and the Wnt pathway. Indeed, two recent studies described YAP/TAZ-dependent intestinal crypt overgrowth in a background of adenomatous polyposis coli (APC) deficiency, albeit via different molecular mechanisms. The first model

proposed the incorporation of YAP/TAZ in the β-catenin destruction complex (Azzolin et al., 2014). When the Wnt pathway is inactive, YAP/TAZ participate in β-catenin degradation. Conversely, Wnt ligand stimulation releases YAP/TAZ from the complex favoring nuclear accumulation of both β-catenin and YAP/TAZ. On this ground, it has been hypothesized that YAP/TAZ may act as both mediators and inhibitors of the Wnt pathway. The second model envisions that APC, a key negative regulator of β-catenin, functions as a scaffold protein facilitating YAP/TAZ phosphorylation and inhibition via Hippo kinases (Cai et al., 2015). Overall, these lines of evidence pointed to an intricate Hippo-Wnt crosstalk in intestinal development and regeneration, and bring to light the need for further investigations to better delineate this relationship. Further highlighting the role of YAP in intestinal homeostasis and regulation of stem cell fate, YAP activity was found to be essential for intestinal regeneration after injury (Cai et al., 2010; Taniguchi et al., 2015; Gregorieff et al., 2015; Kim et al., 2017). Given the close connection between uncontrolled tissue regeneration and malignant transformation, YAP activation promoted the development of *Apc*-deficient adenomas (Camargo et al., 2007; Cai et al., 2015; Gregorieff et al., 2015), and constitutive YAP activity induced by the inflammatory mediator prostaglandin E2 (PGE2) led to formation of polyps and colon cancers (Kim et al., 2017).

The Hippo signalling in pancreatic development and homeostasis deserves a final mention. *Mst1/2* deletion unexpectedly resulted in a reduction of the pancreas size, a phenotype related to pancreatitis-like autodigestion consequent to defective formation of ductal structures (George et al., 2012; Gao et al., 2013). Defects in the Hippo pathway mainly affected the exocrine compartment.

3.2 Heart, lung and kidney

Heart enlargement was reported with inactivation of *Sav1, Mst1* and *Mst2,* and *Lats2* (Song et al., 2010; Heallen et al., 2011). Likewise, cardiomyocytes hyperproliferation with consequent enlargement of the heart was observed with *Yap* overexpression (von Gise et al., 2012; Xin et al., 2011; Del Re et al., 2013), whereas its inactivation resulted in lethal heart hypoplasia (von Gise et

al., 2012; Xin et al., 2011) similar to earlier reports with *Tead1* knockouts (Chen et al., 1994; Sawada et al., 2008). Genetic ablation of Hippo pathway components determined an increased expression of nuclear β-catenin and up-regulation of Wnt target genes, determining cardiomyocytes proliferation via YAP/β-catenin interaction (Heallen et al., 2011). In the adult heart, inactivation of Hippo kinases/adaptors (Heallen et al., 2013) or forced *Yap* expression (Xin et al., 2013; Lin et al., 2014a; Del Re et al., 2013) promoted heart regeneration and improved cardiac function in myocardial infarction models. YAP-mediated activation of the PI3K-AKT pathway and cytoskeletal remodeling were described as mechanisms promoting heart regeneration (Lin et al., 2015a; Morikawa et al., 2015). Of note, *Yap* overexpression promotes proliferation of satellite cells, the resident stem cells of skeletal muscle, promoting muscle hypertrophy (Judson et al., 2012; Watt et al., 2015). YAP activity increases after degeneration of motor nerves as a mechanism to mitigate neurogenic muscle atrophy (Watt et al., 2015).

The first line of evidence highlighting the involvement of the Hippo pathway in lung development and function stemmed from studies investigating the effects of *Taz* inactivation (Makita et al., 2008; Mitani et al., 2009). Adult mice displayed abnormal alveolar structures with an emphysema-like phenotype. This morphological picture seemed independent of TTF1, a crucial factor in branching morphogenesis requiring TAZ for the production of the surfactant protein C (Park et al., 2004). It was later revealed that loss of *Mst1/2* disrupted lung structures resulting in neonatal lethality (Chung et al., 2013; Lin et al., 2015b; Lange et al., 2015), and that conditional deletion of *Mst*1/2 from bronchiolar epithelial cells in the mature lung induced progressive airway hyperplasia (Lange et al., 2015). Moreover, YAP emerged as a crucial factor in airway stem cell biology (Mahoney et al., 2014; Zhao et al., 2014). Zhao et al. reported that, after *Yap* deletion, the adult basal stem cell pool was markedly reduced due to an uncontrolled differentiation and, at the histological level, the normal pseudostratified airway epithelium was simplified into a columnar epithelium (Zhao et al., 2014). Conversely, *Yap* overexpression induced stem cell self-renewal and inhibited terminal

differentiation, promoting epithelial stratification and hyperplasia. Moreover, YAP regulates proximal-distal patterning of the lung and proper airway morphogenesis by inducing Sox2 expression and enabling epithelial progenitors to properly respond to TGF-β stimulation (Mahoney et al., 2014).

Inactivation of *Yap* or *Taz* in the kidney resulted in different phenotypes: while *Taz* inactivation determined polycystic kidney disease (Hossain et al., 2007; Makita et al., 2008; Tian et al., 2007), YAP was found to be required for nephron morphogenesis (Reginensi et al., 2013). This process was linked to the Rho GTPase Cdc42, which controls YAP activity. Indeed, defects in nephrogenesis observed upon *Cdc42* ablation phenocopied *Yap* loss. At the molecular level, *Cdc42* ablation decreased nuclear localization of YAP and reduced the expression of YAP-responsive genes (Reginensi et al., 2013). YAP and TAZ are also essential for the development of the lower urinary tract (Reginensi et al., 2015) and in branching morphogenesis (Reginensi et al., 2016). Moreover, podocyte-specific *Yap* deletion resulted in podocyte apoptosis with consequent proteinuria and histological features of focal segmental glomerulosclerosis (Schwartzman et al., 2016). Even though *Sav1* and *Mst1/2* knockout kidneys appeared unaffected (Reginensi et al., 2013; Song et al., 2010), more recent studies showed that *Sav1* deficiency promoted YAP-dependent proliferation of renal tubular epithelial cells with formation of both glomerular and tubular cysts (Kai et al., 2016), and that dual deletion of *Lats1* and *Lats2* disrupted nephrogenesis by impairing maintenance and differentiation of nephron progenitor cells (McNeill & Reginensi, 2017). Finally, increased transcriptional activity of YAP was implicated in renal compensatory hypertrophy in a rat model of uninephrectomy, and in kidney regeneration after acute injury (Domínguez-Calderón et al., 2016; Xu et al., 2016). On the other hand, constant activation of YAP and TAZ was tied to kidney fibrosis, raising the hypothesis that their activation should be finely modulated for therapeutic purposes (Xu et al., 2016; Seo et al., 2016; Szeto et al., 2016).

3.3 Other organs and systems

Activation of YAP or *Sav1* deletion lead to skin thickening, as a result of the expansion of basal progenitor cells (Camargo 2007; Lee et al., 2008; Schlegelmilch et al., 2011; Zhang et al., 2011a). However, neither *Mst1/2* nor *Lats1/2* inactivation influenced YAP activation, suggesting the existence of a yet unappreciated control mechanism (Schlegelmilch et al., 2011; Silvis et al., 2011). Long-term activation of YAP, or *Mob1a/1b* deletion, resulted in skin cancers (Nishio et al., 2012; Silvis et al., 2011; Schlegelmilch et al., 2011; Iglesias-Bartolome et al., 2015), and deletion of *Yap* and *Taz* impaired regeneration after wounding (Elbediwy et al., 2016; Lee et al., 2014). Evidence supporting the involvement of YAP in brain development stemmed from studies investigating the effects of *Nf2* inactivation. Absence of *Nf2* determined an overexpansion of neural progenitor cells, resulting in severe malformation of the hippocampus in mice. This process was mediated by YAP activation in a Hippo pathway-independent manner (Lavado et al., 2013). NF2-YAP signaling is also involved in the development of the corpus callosum and dorsal root ganglia (Lavado et al., 2014; Serinagaoglu et al., 2015). Regarding the breast, *Yap, Taz* and *Sav1* seemed dispensable in mammary gland development but, rather, are implicated in post-natal changes such as those occurring during pregnancy or in the post-pubertal period (Chen et al., 2014; Skibinski et al., 2014). A final mention deserves the immune-related, non-canonical Hippo/MST pathway. In this field, MST1/2 kinases operate via different downstream effectors, and their activity is essential for immune homeostasis and immunological self-tolerance. The Hippo/MST pathway controls a number of T cell functions including development, activation, survival, trafficking, and homing (Du et al., 2014).

4. The Hippo pathway in cancer

Aberrant activation of YAP/TAZ has been reported in various human tumors and linked to a plethora of tumor-promoting functions, spanning from invasion and metastasis to therapeutic resistance and maintenance of the cancer stem cell (CSCs) pool. Remarkably, activated YAP/TAZ confers resistance to both chemotherapeutics (Cordenonsi et al., 2011; Bartucci et al., 2015) and molecular targeted agents such as BRAF-, MEK- and HER2-directed agents (Lin et al., 2015c; Kim et al., 2016a; Lin et al., 2015d). Activation of YAP via mechanotransduction is also required for maintaining cancer-associated fibroblasts (CAF) and their tumor-enhancing functions, indicating that YAP/TAZ promote oncogenic functions even by controlling the tumor-stroma interplay (Calvo et al., 2013). Consistently with the widespread deregulation of YAP/TAZ observed in functional studies, increased expression of YAP/TAZ and signature denoting their activation have been associated with adverse clinical outcomes in cancer patients.

4.1 Breast cancer

TAZ expression has frequently been reported in different breast cancer (BC) subtypes, where its expression is associated with aggressive clinical, pathological and molecular features (triple-negative tumors, elevated Ki-67 levels, high grade, stem cell signatures), inferior survival outcomes and decreased efficacy of neoadjuvant (presurgical) therapy (Bartucci et al., 2015; Cordenonsi et al., 2011; Vici et al., 2014; Skibinski et al., 2014; Vici et al., 2016; Diaz-Martin et al., 2015). Increased TAZ expression in basal-like BC compared with other subtypes may be related to a TAZ-induced luminal to basal lineage switch, which requires an interaction with components of the SWI/SNF chromatin-remodeling complex (Skibinski et al., 2014). Expression of Hippo transducers, together with their targets (CTGF and AXL) and regulators (HMG-CoA reductase), was also observed in male BC, one of the rarest tumors arising in men (Di Benedetto et al., 2016a; Di Benedetto et al., 2016b; Di Benedetto et al., 2017).

Mechanistically, overexpression of TAZ induced oncogenic transformation of non-neoplastic mammary cells via the interaction with TEAD factors and the disruption of Hippo kinase-mediated control (Chan et al., 2008; Chan et al., 2009; Zhao et al., 2012). Moreover, an oncogenic program requiring YAP/TAZ, TEADs and SMAD2/3 was described as a way BC cells use to overcome the tumor-suppressive effect of TGF-β in early oncogenic phases (Hiemer et al., 2014). Overexpression of TAZ in BC cell lines also promotes invasive and migratory properties (Chan et al., 2008; Yang et al., 2012), and drives the establishment and progression of bone metastases (Bendinelli et al., 2013; Matteucci et al., 2013). Novel insights into the multifaceted tumor-promoting role of TAZ have been provided by investigations specifically looking for molecular factors governing the BC stem cell (BCSC) compartment. TAZ promotes self-renewal and tumor-forming ability of BCSCs, enabling them to withstand chemotherapy and to distantly disseminate (Cordenonsi et al., 2011; Bartucci et al., 2015). Different molecular circuits account for the TAZ-mediated acquisition/retention of CSCs features, including EMT-mediated delocalization of Scribble with the consequent alleviation of TAZ inhibition (Cordenonsi et al., 2011), the cooperation between TAZ and hypoxia-inducible factor 1 (HIF-1) (Xiang et al., 2014; Xiang et al., 2015), and the interaction between laminin 511 matrix and α6Bβ1 integrin that promotes TAZ nuclear localization (Chang et al., 2015).

While both experimental and clinical evidence converge in assigning oncogenic functions to TAZ, some discrepancies exist regarding YAP. On the one hand, YAP overexpression in non-transformed mammary epithelial cells or BC cell lines induced EMT, proliferation, anchorage-independent growth and metastatic proclivity (Overholtzer et al., 2006; Zhang et al., 2009; Wang et al., 2014; Lamar et al., 2012; Chen et al., 2012). Moreover, in a mouse model of oncogene-induced BC, *Yap* knockout delayed the onset of mammary tumors, reducing metastasis formation (Chen et al., 2014). On the other hand, different lines of evidence point to YAP as a tumor-suppressive factor: i) YAP stabilizes p73 inducing the transcription of pro-apoptotic genes (Strano et al, 2001; Strano et al.,

2005; Danovi et al., 2008; Levy et al., 2007), ii) YAP is phosphorylated and inhibited by oncogenic Akt (Basu et al., 2003), iii) YAP is located at 11q22.2, a site of frequent loss of heterozygosity in BC (Carter et al., 1994; Gudmundsson et al., 1995), iv) functional studies described increased malignant features upon YAP knockdown in BC cell lines (Yuan et al., 2008; Yu et al., 2013b), and v) some inconsistencies exist when comparing studies investigating the clinical significance of YAP expression in BC (Kim et al., 2014; Sheen-Chen et al., 2012; Lehn et al., 2014; Vici et al., 2016). Speculatively, it is possible that YAP elicits different functions in relation to the underlying genetic background of BC, and consequently in the different intrinsic subtypes. For instance, YAP interacts with mutant p53 inducing a transcriptional program that accelerates cell cycle progression (Di Agostino et al., 2016). Moreover, YAP expression should be analyzed in the different cellular compartments (e.g. tumor and stromal cells), in order to consider its involvement in the tumor-stroma crosstalk (Calvo et al., 2013; Vici et al., 2016).

4.2 Gastrointestinal tumors

YAP/TAZ knockdown in human colorectal cancer (CRC) cell lines suppressed growth, hindered tumor-forming ability and limited metastatic dissemination after injection in mice (Azzolin et al., 2012; Pan et al., 2012; Rosenbluh et al., 2012; Yuen et al., 2013; Wang et al., 2013). YAP depletion decreased proliferation and survival in CRC cells in a process accompanied by reduced β-catenin and Notch signaling (Zhou et al., 2011a). In turn, YAP expression in CRC cells is driven by β-catenin/TCF4, and a YAP-TBX5-β-catenin transcriptional complex promotes the transcription of anti-apoptotic genes in β-catenin-dependent CRC cells (Konsavage et al., 2012; Rosenbluh et al., 2012; Avruch et al., 2012). Overall, these findings point to a reciprocal interaction between YAP and the Wnt pathway in CRC. Further increasing the complexity of pathway crosstalk mediating YAP/TAZ function in CRC, endothelin receptor A (ETAR) was found to trigger proliferation and tumorigenicity of CRC cells via GPCRs and Rho GTPases, with consequent suppression of the

Hippo pathway and transcriptional activation of YAP/TAZ (Wang et al., 2017). Moreover, YAP overexpression rescued cell viability of KRAS-dependent CRC (and lung cancer) cells after KRAS suppression, and KRAS and YAP establish an oncogenic cooperation that converges on the transcription factor FOS to induce EMT (Shao et al., 2014). Finally, attenuation of malignant features in CRC cells were reported with miR-195-5p-mediated YAP repression (Sun et al., 2017). Elevated expression of YAP/TAZ in biological samples from CRC patients was associated with poor survival outcomes and reduced efficacy of chemotherapy in retrospective case series (Kim et al., 2013b; Wang et al., 2013; Touil et al., 2014; Yuen et al., 2013). Interestingly, a signature denoting YAP activation confers inferior progression-free survival in advanced CRC patients with KRAS wild-type disease treated with cetuximab monotherapy (Lee et al., 2015).

In esophageal cancer cells, YAP over-activation installs CSC features by up-regulating SOX9, and feeds chemoresistance through increased EGFR expression (Song et al., 2014; Song et al., 2015). YAP expression was associated with more aggressive clinical-pathological characteristics (e.g. Ki-67 levels, histological grade, stage) and adverse clinical outcomes (Muramatsu et al., 2011; Yeo et al., 2012; Zhao et al., 2016). YAP-mediated oncogenic functions were also described in gastric cancer (GC), both in functional assays and in biological specimens (Kang et al., 2011). YAP knockdown hindered cell proliferation, invasion, and motility of GC cells, and nuclear YAP expression conferred inferior disease-specific survival (Kang et al., 2011). Disruption of the YAP-TEAD interaction with a Vgl-like-4- (VGLL4) mimicking peptide suppressed tumor growth both *in vitro* and *in vivo* (Jiao et al., 2014).

In pancreatic ductal adenocarcinoma (PDAC), YAP promotes the proliferation of mutant *KRAS* cells and induces the expression of genes encoding secretory factors, ultimately promoting the pro-tumorigenic stromal response that characterizes PDAC (Zhang et al., 2014a). In addition, the YAP/TEAD2 complex drives an oncogenic program essential for the maintenance of *KRAS*-independent PDAC (Kapoor et al., 2014). The idea that YAP functions as a central oncogenic force

in non-*KRAS*-driven PDAC has been further confirmed in a mouse model of chronic inflammation (Swidnicka-Siergiejko et al., 2016). Consistently with the oncogenic role of YAP in PDAC, disruption of the YAP-TEAD interaction hindered tumor growth, promoted apoptosis, and inhibited angiogenesis and vasculogenic mimicry (Wei et al., 2017), whereas its hyper-activation confers chemoresistance (Chen et al., 2015b). Finally, activation of TAZ induces proliferative and migratory properties to pancreatic cancer cells (Xie et al., 2015).

The connection between deregulated Hippo signaling and human liver tumorigenesis has widely been documented with genetically engineered mouse models (Camargo et al., 2007; Dong et al., 2007; Liu-Chittenden et al., 2012; Zhou et al., 2009; Lu et al., 2010; Song et al., 2010; Zhang et al., 2010; Lee et al., 2010; Benhamouche et al., 2010; Yin et al., 2013; Yimlamai et al., 2014). A number of factors plausibly account for the increased YAP activity and the consequent onset of HCC and bile duct cancer, including YAP amplification (Zender et al., 2006), carcinogenic compounds (Kowalik et al., 2011), interaction with hepatitis B virus proteins (Zhang et al., 2012), and defects in bile acid homeostasis (Anakk et al., 2013). Mechanistically, tumor-enhancing functions of YAP/TAZ in liver cancer have been connected with activation of Notch signaling, together with an up-regulation of amino acid transporters, increased uptake of amino acids and ultimately mTORC1 activation (Tschaharganeh et al., 2013; Park et al., 2015). Moreover, the YAP-TEAD complex mediates a positive feedback loop by inducing the expression of miR-130a that, in turn, represses the YAP antagonist VGLL4 (Shen et al., 2015). Therapeutically, blocking the YAP-TEAD interaction hinders YAP-mediated HCC (Liu-Chittenden et al., 2012), and YAP inhibition achieved with a small interfering RNA-lipid nanoparticles was proposed as a differentiation-inducing therapy (Fitamant et al., 2015). More recently, Hippo signal deficiency and YAP activation were connected with polyploid cell division and genomic instability via Akt signaling (Zhang et al., 2017a). From a clinical perspective, YAP and TAZ expression have been associated with inferior survival outcomes in HCC patients (Xu et al., 2009; Kim et al., 2013c; Guo et al.,

2015). Likewise, signatures denoting inactivation of the Hippo pathway and YAP-induced chromosome instability seem to confer adverse survival outcomes (Sohn et al., 2016; Weiler et al., 2017).

4.3 Thoracic tumors

The Hippo pathway has been implicated in the biology of non-small cell lung cancer (NSCLC), which accounts for approximately 85% of lung cancers. Inhibition of YAP/TAZ in NSCLC cells suppresses cell proliferation, induces cell cycle arrest, reduces tumorigenicity and increases sensitivity to EGFR-directed therapies (Zhou et al., 2011b; Noguchi et al., 2014; Lau et al., 2014; Hsu et al., 2016; Lee et al., 2016b; Xu et al., 2015; Lo Sardo et al., 2017; Xu et al., 2013; Dubois et al., 2016; Zhang et al., 2014b; Lin et al., 2013). YAP/TAZ also sustain self-renewal of NSCLC stem cells, partly through a metabolic control operated by stearoyl-CoA-desaturase 1 (SCD1), an enzyme involved in monounsaturated fatty acids synthesis (Bora-Singhal et al., 2015; Noto et al., 2017). YAP was found to inhibit squamous transdifferentiation of LAC (Gao et al., 2014), and its overexpression accelerates the progression of lung adenocarcinoma (LAC) in the *Kras*^{G12D} lung cancer mouse model (Zhang et al., 2015a). Furthermore, a screening of synthetic-lethal genetic interaction in *KRAS*-mutant NSCLC cells revealed a selective sensitivity of these cells to the inhibition of the nuclear transport receptor XPO1 (Kim et al., 2016b). Nevertheless, a subset of *KRAS*-mutant cell lines was intrinsically resistant to XPO1 inhibition as a consequence of YAP activation, further highlighting the YAP-dependent resistance mechanism to *KRAS* inhibition. Functional studies are complemented by clinical data suggesting that increased protein-level expression of YAP/TAZ, gene signatures mirroring their activity, and decreased expression of LATS1/2 are associated with poor clinical outcomes (Noguchi et al., 2014; Wang et al., 2010; Xie et al., 2012; Lau et al., 2014; Lin et al., 2014b). While deregulated Hippo pathway also promotes malignant pleural mesothelioma (Mizuno et al., 2012; Fujii et al., 2012; Tranchant et al., 2016;

Zhang et al., 2017b; Tanaka et al., 2017), YAP/TAZ activation defines a subset of small cell lung cancer (SCLC) with atypical features such as adherent cell morphology, lower expression of neuroendocrine markers, increased chemosensitivity and better prognosis (Horie et al., 2016; Ito et al., 2016). Thus, YAP/TAZ supposedly play an opposite role in NSCLC and SCLC.

4.4 Genitourinary and gynecologic tumors

YAP activation induces age-related prostate cancer (PC) in mice (Nguyen et al., 2015). YAP interacts with the androgen receptor (AR) and positively regulates AR signaling, mediating a switch from an androgen-sensitive to an androgen-insensitive state (Zhang et al., 2015b; Kuser-Abali et al., 2015). These findings are supported by YAP analysis in tissue samples, conveying the message that increased YAP activity may represent a mechanism conferring resistance to androgen-deprivation therapy (Zhang et al., 2015b; Sheng et al., 2015). Moreover, YAP contributes to the establishment of a tumor-supportive microenvironment by inducing the production of the chemokine CXCL5 that, in turn, attracts CXCR2-expressing myeloid-derived suppressor cells (Wang et al., 2016). Likewise, in PC cells TAZ promotes cell migration, EMT and induces CSC features (Liu et al., 2016; Liu et al., 2017). Recent studies also suggested a central role of Hippo kinases in refraining YAP/TAZ activation in PC. For instance, α3β1 integrin was found to restrain Rho GTPase activity, thereby supporting tumor-suppressive functions of the Hippo pathway (Varzavand et al., 2016), whereas the molecular chaperone heat shock protein 27 accelerates proteasomal degradation of MST1, leading to nuclear accumulation of YAP (Vahid et al., 2016).

The contribution of deregulated Hippo pathway in the pathobiology of renal cancer is less clear, owing to the paucity of functional studies. Nevertheless, molecular characterization efforts revealed that *NF2* mutations, and deregulation of the Hippo pathway, are fairly common in mucinous tubular and spindle cell carcinoma, and in renal cell carcinomas with unclassified histology (Mehra et al., 2016; Chen et al., 2016a). YAP activation confers cisplatin resistance in urothelial cell carcinoma,

and its nuclear expression is associated with inferior survival outcomes in patients with urothelial cell carcinoma treated with perioperative chemotherapy (Ciamporcero et al., 2016).

As mentioned for liver cancer, emerging evidence points to the role of viral oncoproteins in mediating YAP activation. Human papilloma virus (HPV) infection is the leading cause of cervical cancer, owing to the ubiquitin-mediated degradation of p53 and pRb mediated by the HPV proteins E6 and E7. HPV E6 protein has also been found to prevent proteasome-dependent YAP degradation, fuelling cervical cancer cell proliferation. (He et al., 2015a). Clinically, nuclear TAZ expression was associated with reduced pathological complete response rate in cervical cancer patients treated with neoadjuvant chemotherapy (Buglioni et al., 2016).

YAP and TAZ overexpression in ovarian cancer (OC) cell lines increases cell proliferation, induces EMT and confers chemoresistant features (Zhang et al., 2011b; Hall et al., 2010; Chen et al., 2016b; Xia et al., 2014; Yagi et al., 2016). Constitutive YAP activation induces malignant transformation through increased secretion of fibroblast growth factor1/2 and epidermal growth factor (EGF)-like ligands, and thereby stimulation of their cognate receptors (Hua et al., 2016; He et al., 2015b). Two studies recently described miR-mediated control of YAP/TAZ. In particular, two miRs, namely miR-129-5p and miR-509-3p, were found to repress YAP/TAZ and attenuate malignant features (Tan et al., 2015; Pan et al., 2016). Elevated nuclear YAP expression, increased expression of TAZ mRNA, and a gene expression signature reflecting YAP activation have consistently been correlated with poor clinical outcomes in OC patients (Zhang et al., 2011b; Hall et al., 2010; Chen et al., 2016b; Jeong et al., 2014; Cho et al., 2017). Of note, YAP seems implicated in the biology of granulosa cell tumors, which accounts for ~70% of all malignant sex-cord stromal tumors. YAP overexpression promotes proliferation, migration and steroidogenesis in granulosa cell tumor cell lines, and nuclear YAP expression was more frequently observed in tumor tissues compared with their normal counterparts (Fu et al., 2014).

4.5 Melanoma, primary brain tumors and sarcomas

YAP-dependent growth of uveal melanoma cells has been reported as a consequence of mutations in the *GNAQ* oncogene (Yu et al., 2014; Feng et al., 2014). According to this model, *GNAQ*-induced tumorigenesis and YAP activation was reconnected to the regulation of the actin cytoskeleton by Rho GTPases. Importantly, inhibition of the YAP-TEAD4 interaction by verteporfin efficiently targeted uveal melanoma cells carrying gain-of-function *GNAQ* mutations. From a therapeutic perspective, it is important to note that some discrepancies exist regarding YAP/TAZ activation in relation to *BRAF* mutations. Indeed, while Yu et al. reported that YAP is suppressed in *BRAF*-mutant cells (Yu et al., 2014), Nallet-Staub and colleagues suggested that in cutaneous melanoma YAP/TAZ oncogenic functions are independent of the underlying *BRAF* mutational status (Nallet-Staub et al., 2014). Moreover, remodeling of the actin cytoskeleton and YAP/TAZ activation have been recently connected with resistance to pharmacological inhibition of BRAF in *BRAF*- mutant melanoma cells (Kim, et al., 2016a). Further supporting this argument, a genetic screen in *BRAF*-mutant tumor cells revealed that YAP mediates resistance to BRAF and MEK inhibitor therapy, whereas YAP silencing enhanced the antitumor efficacy of vemurafenib (BRAF inhibitor) and trametinib (MEK inhibitor) in melanoma xenografts (Lin et al., 2015d). Unexpectedly, it has recently been reported that inactivation of LATS1/2 in melanoma cells induced an host anti-tumor immune response that suppresses tumor growth (Moroishi et al., 2016). LATS1/2 deletion in tumor cells stimulates the secretion of nucleic-acid-rich extracellular vesicles that elicit a type I interferon response. This, in turn, stimulates multiple cellular components involved in the immune-mediated elimination of cancer cells.

Finally, attenuation of the Hippo signaling and YAP/TAZ-mediated gene transcription confer aggressive molecular features in glioblastoma multiforme (Xu et al., 2010; Orr et al., 2011; Lignitto et al., 2013; Artinian et al., 2015; Yang et al., 2016), and YAP has been designated as an oncogene

in osteosarcoma (Chan et al., 2014; Basu-Roy et al., 2015), embryonal rhabdomyosarcoma (Tremblay et al., 2014) and soft-tissue sarcomas (Eisinger-Mathason et al., 2015)

4.6. Targeting the Hippo pathway for anticancer therapy

Functional studies conveyed the message that blocking YAP/TAZ-mediated transcription may be an effective treatment for various tumors. Even though no specific inhibitors are currently available, screening of approved drugs revealed that compounds already in use for various medical conditions may target YAP/TAZ (Figure 2). In a screening of more than 3300 Food and Drug Administration (FDA)-approved drugs, porphyrin molecules, which are used as photodynamic therapy in macular degeneration, emerged as the most potent compounds inhibiting TEAD-YAP association, thus efficiently counteracting YAP-induced liver overgrowth (Liu-Chittenden et al., 2012). Verteporfin treatment also effectively killed uveal melanoma cells carrying Gq/11 mutations (Yu et al., 2014). Next, the G protein-coupled β-adrenergic receptor agonist dobutamine, an inotropic agent used for acute heart failure, was found to promote the recruitment of YAP to the cytosol, thus hindering YAP-dependent gene transcription (Bao et al., 2011). These effects were unrelated to the activation of Hippo kinases, as knocking down *LATS1* and *LATS2* did not affect dobutamine-induced YAP phosphorylation. Also the BCR-ABL inhibitor dasatinib inhibits YAP (Rosenbluh et al., 2012). Again, inhibitory effects on YAP occurred independently on Hippo kinases, but were rather due to dasatinib-mediated inhibition of YES1. This, in turn, interfered with the assembly of a YAP-β-catenin-TBX5 complex mediating the proliferation of β-catenin-dependent CRC cells. Statins, the popular cholesterol-lowering medications, inhibit YAP/TAZ in a LATS1/2-independent manner (Sorrentino et al., 2014). At the biochemical level, statin-mediated inhibition of YAP/TAZ is related to the inhibition of HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway. HMG-CoA reductase inhibition causes a reduction of geranylgeranyl pyrophosphate, with the consequent altered membrane tethering of Rho GTPases (protein prenylation). Similar effects were reported with nitrogen-containing bisphosphonates (N-BPs), compounds administered for the

treatment of osteoporosis and the prevention of skeletal-related events in cancer patients. N-BPs (i.e. zoledronic acid) act on the mevalonate pathway by inhibiting farnesyl pyrophosphate synthase, thus interfering with protein prenylation. Finally, the antidiabetic agent metformin was found to inhibit YAP. At the molecular level, metformin activates AMP-activated protein kinase (AMPK) that, in turn, inhibits YAP via both LATS activation and direct YAP phosphorylation (Mo et al., 2015).

5. Conclusions

Research over the past decade provided considerable insights into the way the Hippo signaling govern organ development and tissue regeneration. Moreover, overwhelming functional evidence shed light on the multifaceted way through which YAP/TAZ promote oncogenic transformation and boost tumor progression. In spite of this, a number of questions still remain unanswered. Since the earliest evidence emerged that Hippo-mediated size control is not an universal mechanism, as not all organs are equally affected by pathway manipulation. Specific tissue contexts, requirements of signals acting upstream the Hippo cascade, Hippo-independent control of YAP/TAZ and/or mechanical inputs may account for these differences. On this ground, further tailored investigations are needed to elucidate the different molecular networks that converge on the Hippo pathway for regulating the development of various organs. In the field of regenerative medicine, YAP/TAZ activation was advocated as essential for tissue repair after acute, and in some instances chronic, tissue damage. In most cases, YAP/TAZ-driven regeneration was connected to the activation of tissue-resident adult stem/progenitor cells. However, prolonged YAP/TAZ activity culminated into fibrosis, as observed in liver and kidney (Mannaerts et al., 2015; Xu et al., 2016; Seo et al., 2016; Szeto et al., 2016). Paradoxically, signaling pathways inducing stem cell proliferation may also provoke stem cell exhaustion and depletion, if persistently activated. This implies that therapeutic exploitation of YAP/TAZ manipulation for regenerative purposes might necessitate from an alternation of activatory and inhibitory stimuli in order to enable tissue repair while avoiding

fibrotic degeneration. Regarding tumors, a number of intertwined factors deserve attention to accelerate the preclinical-clinical transition of Hippo biomarkers and YAP/TAZ-targeting agents. While YAP/TAZ activation seems to be a shared trait across a constellation of tumor types, differences plausibly exist in the forces that drive their activity, and in the way they interact with and respond to genetically defective pathways. From a clinical prospective, achieving a deeper understanding of this inter-tumor variability is instrumental for the development of both Hippo biomarkers predicting the efficacy of anticancer therapies (and/or survival outcomes), and YAP/TAZ-directed therapeutics. In the first case, namely the identification of prognostic/predictive markers, attempts which have been carried out so far relied on the assessment of individual molecular endpoints in retrospective case series. We envision that this process may be streamlined with the generation of more sophisticated assays that, for instance, also take into account upstream and "lateral" pathway regulators, constitutively activated signals that intersect the Hippo cascade (e.g. mutated Wnt pathway components, *KRAS* mutations), together with the molecular output of YAP/TAZ transcription (i.e. target genes). Obtaining a more exhaustive picture of the processes underlying improper YAP/TAZ activation may increase the chances to successfully validate Hippo signatures in prospective and adequately powered studies. Similar considerations can be extended when considering YAP/TAZ as therapeutic targets. In this case, two critical factors deserve consideration: i) YAP/TAZ modulation has been obtained only indirectly, as aforementioned in the previous section, and ii) YAP/TAZ inhibition does not probably configure the targeting of an oncogenic addiction, as mutations in key pathway components have uncommonly been reported. Trial designs specifically ideated for assessing pathway modulation upon exposure to a given treatment may help overcome these hurdles. For example, window-of-opportunity trials rely on the administration of a given compound in the period elapsing between diagnosis and surgical resection (Maugeri-Saccà et al., 2016), thus offering the advantage of pre- and post-therapy tissue collection for extensive molecular analysis. Testing putative YAP/TAZ inhibitors (e.g. statins, bisphosphonates, metformin) in window-of-opportunity trials may provide a wealth of information,

including efficient YAP/TAZ targeting (e.g. decreased expression, increased phosphorylation, decreased expression levels of target genes), together with an estimate of anti-tumoral effects elicited by their inhibition (e.g. down-staging, anti-proliferative activity as assessed by Ki-67 reduction). In conclusion, over the past years considerable steps forward have been made in understanding Hippo pathway biology; how to transfer these notions to the clinical setting is the challenge ahead.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Figure legends

Figure 1: Regulation of the Hippo pathway: 1) Cell polarity and cell-cell junction factors that activate Hippo kinases or sequester YAP/TAZ, 2) Upstream positive regulators of the Hippo pathway, that activate MST1/2 or LATS1/2, 3) Soluble factors binding GPCRs: soluble factors and hormones can either activate or inhibit YAP/TAZ (via RHO GTPases), 4) mechanical cues, such as extracellular matrix stiffness and cell density, which activate YAP/TAZ independently on Hippo kinases, via RHO GTPases and the actin cytoskeleton, and 5) metabolic factors including the energy sensor AMPK that inhibits YAP/TAZ both directly and by activating LATS1/2, and HMG-CoA reductase, the central enzyme of the mevalonate pathway, that activates YAP/TAZ via prenylation of RHO GTPases.

Figure 2: Strategies for targeting YAP/TAZ: 1) agents inhibiting key enzymes of the mevalonate pathway, including statins and nitrogen-containing bisphosphonates (N-BPs). These agents prevent protein prenylation, hindering proper membrane anchoring of Rho GTPases, 2) compounds interfering with the interaction between YAP/TAZ and their transcriptional partners (verteporfin, dasatinib, VGLL4-mimicking peptides), and 3) drugs that activate AMP-activated protein kinase (AMPK), such as metformin. Once activated, AMPK inhibits YAP both directly and by activating LATS kinases.

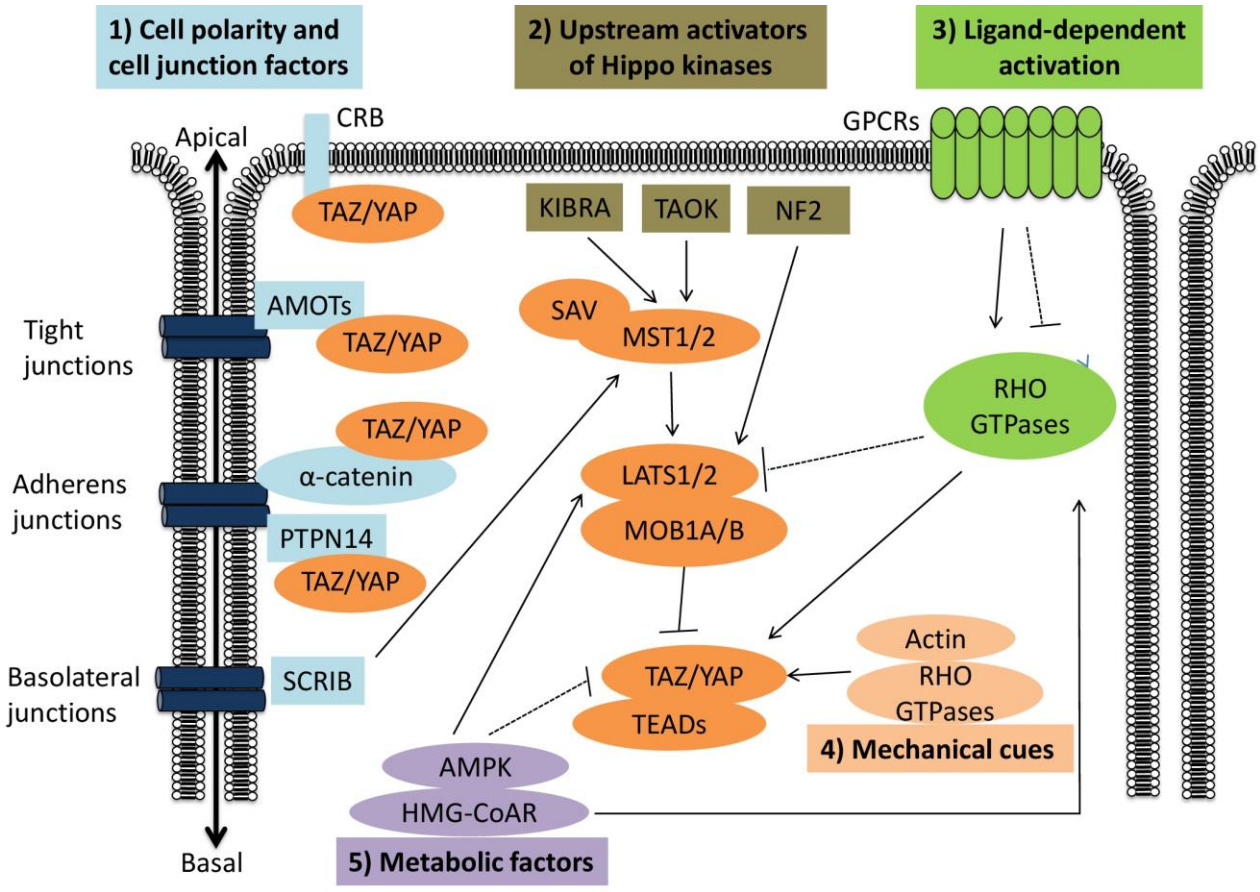

Figure 1

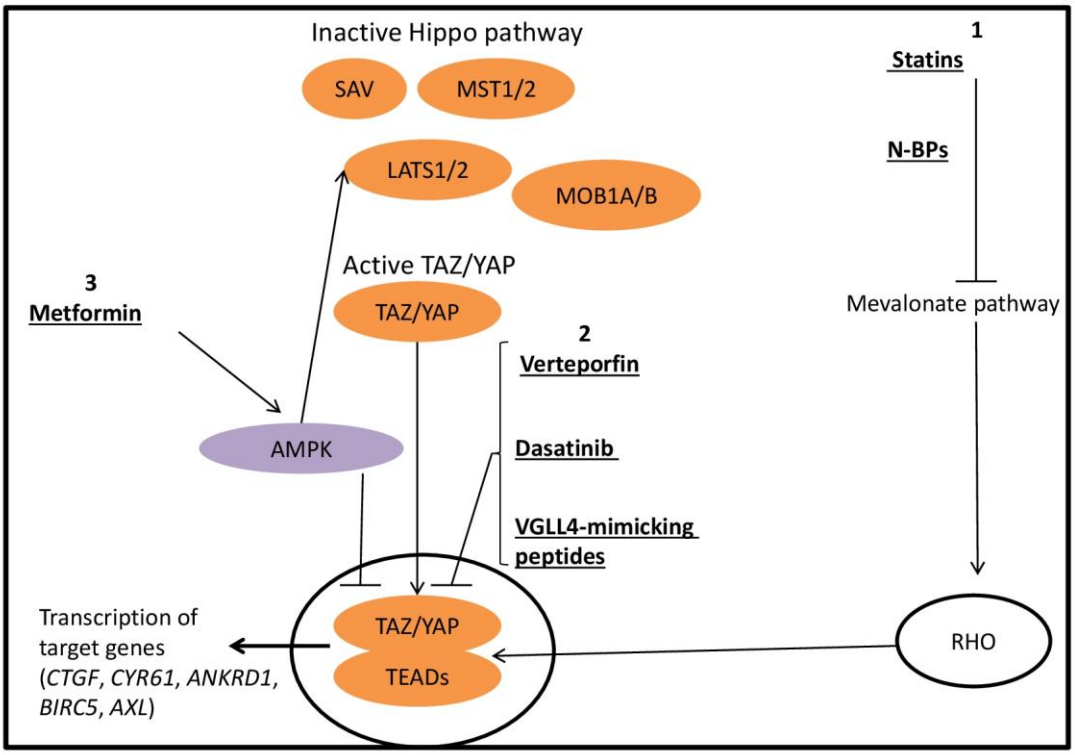

Figure 2