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Intersection of Hippo/YAP and Wnt/β-catenin signaling pathways

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Traditionally, signaling pathways have been perceived to act in an autonomous manner to regulate tissue morphology, size, differentiation, and development. Recent evidence suggests that these pathways often intersect and regulate one another to elicit an appropriate response to a complex set of stimuli. Two pathways known to be important for development, growth, and homeostasis are the Wnt/β-catenin and the Hippo/YAP pathways. Growing data indicate that these two pathways influence each other in a number of ways to properly regulate tissue growth and repair. Deregulation of these pathways often contributes to tumorigenesis. In this review, we will discuss the points of intersection between the Wnt/β-catenin and Hippo/YAP pathways and how these interactions contribute to homeostasis, organ repair, and tumorigenesis.

Keywords Wnt/β-catenin signaling; Hippo signaling; cancer; tissue repair

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Introduction

Historically signal transduction pathways have been studied as separate and independent cascades that transmit an extracellular signal through a series of phosphorylation-dependent events that ultimately change the genetic program of a cell. Signaling pathways alter gene expression profiles by controlling the subcellular localization of key regulatory transcription factors. Recent work has led to the realization that these simple linear pathways are really part of an interconnected web that feeds multiple signals through the cell to elicit the appropriate response to an external stimulus.

The Wnt and Hippo signaling pathways are critical for tissue development, growth, and homeostasis [1–4]. While the Wnt pathway has been studied for the past 30 years, the Hippo pathway is a relative newcomer to the signaling field and has only received intense study within the past decade. This review will first provide a brief introduction to the Wnt/β-catenin and the Hippo/YAP signaling pathways. We will next focus on the intersection points between these two pathways and mechanisms of cross-regulation. Finally, we will discuss the roles that both pathways play in organ regeneration and tumorigenesis.

Wnt/β-Catenin Signaling Pathway

A viable mutation in *Drosophila melanogaster* that lacked wings was described in the 1970s and this phenotype was attributed to a mutation in the *wingless (wg)* gene [5,6]. Subsequent work in 1980 identified an embryonic lethal mutation in *wg* that effected segment polarity [7]. In 1982, work by Nusse and Varmus [8] identified *int-1*, or integration 1, as a gene required for tumorigenesis induced by mouse mammary tumor virus (MMTV). It was not until 1987 that *wingless* was identified as the homolog of *int-1*, and the name 'Wnt' was derived from the merging *wingless* and int-1 [9,10]. Wnts are cysteine-rich and secreted glycoproteins that mediate short-range paracrine signaling. In humans, 19 different Wnt genes have been identified [11]. Wnt signaling can be divided into three classes: the canonical or Wnt/β-catenin pathway, the noncanonical or planar cell polarity pathway, and the Wnt/Ca^{2+} pathway. This review will focus on the canonical pathway, as this pathway has been described to intersect with the Hippo pathway most frequently in the literature. The canonical pathway requires the β-catenin transcriptional co-activator and as the key effector of Wnt/β-catenin signaling, the subcellular localization and levels of β-catenin are tightly regulated.

In the absence of Wnt signal, cytoplasmic β-catenin associates with a multiprotein destruction complex. This destruction complex contains the adenomatous polyposis coli (APC), Axis inhibition protein 1 or 2 (Axin1/2), casein kinase 1α (CK1α), and glycogen synthase kinase 3β (GSK3β) proteins [12–18]. APC and Axin act as scaffolds that coordinate β-catenin phosphorylation by GSK3β and CK1α. CK1α phosphorylates β-catenin on Ser45 and this primes β-catenin for further phosphorylations on Ser33, Ser37, and Thr41 [19,20]. Phosphorylated β-catenin is then ubiquitinated by the β–transductin-repeat-containing protein (β-TrCP) E3 ubiquitin ligase and targeted for

proteasomal degradation [21,22]. This process keeps levels of free β-catenin in the cytoplasm low. β-Catenin also interacts with E-cadherin at adherens junctions. Here, it serves as a bridging factor that links the cell membrane, via E-cadherin, to the actin cytoskeleton, via α-catenin. The binding of α-catenin to β-catenin enhances the ability of β-catenin to bind E-cadherin [23]. In the absence of Wnt, Groucho/TLE co-repressors silence expression of Wnt/β-catenin target genes [24,25]. These co-repressors are tethered to DNA via interactions with members of the T-cell factor/lymphoid enhancer factor (TCF/Lef) family of sequence-specific transcription factors. TCF/Lef (hereafter TCF) complexes assemble on Wnt responsive DNA elements to control underlying gene expression.

Upon Wnt binding to frizzled (Fzd) and low-density lipoprotein receptor-related protein 5 or 6 (LRP5/6) co-receptors, the cytoplasmic destruction complex disassembles. The formation of a Wnt/Fzd/LRP5/6 receptor co-complex recruits the scaffold protein, Dishevelled (Dvl), to the plasma membrane [26,27]. The binding of Dvl to Fzd promotes the formation of LRP5/6 aggregates that enhance the phosphorylation of the LRP5/6 cytoplasmic tail by CK1γ [28]. These phosphorylation events, and the multimerization of Dvl, lead to the recruitment of Axin from the destruction complex to the plasma membrane [26,27]. Recruitment of Axin to the plasma membrane prevents the formation of the destruction complex and this event stabilizes newly synthesized β-catenin [29]. β-Catenin then translocates to the nucleus, binds TCF family members and displaces Groucho/TLE co-repressor complexes. In addition, β-catenin recruits transcriptional co-activators including CBP/p300 and BRG1 which then remodel Wnt/β-catenin target genes into a transcriptionally permissive state [30,31]. The genetic program activated by Wnt/β-catenin signaling ultimately promotes cell proliferation. A summary of the Wnt/β-catenin pathway is diagrammed in **Fig. 1**.

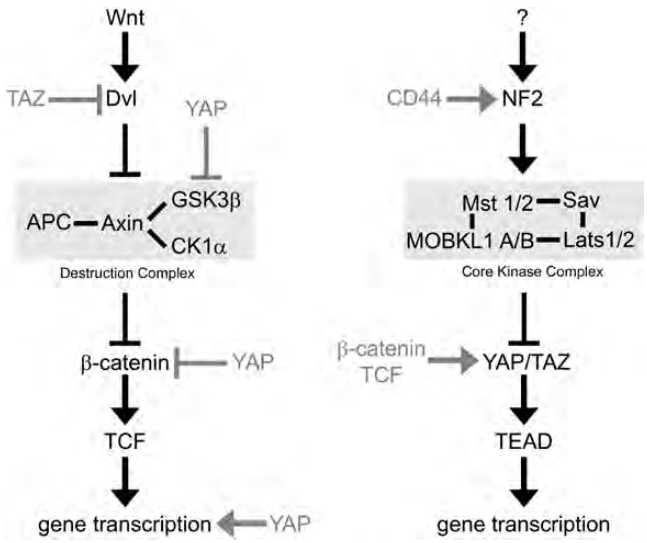

Figure 1 Cross-regulation of the Wnt/β-catenin and Hippo/YAP signaling pathways The canonical Wnt/β-catenin pathway is diagrammed on the left, in black. Parts of the Wnt/β-catenin pathway impacted by Hippo signaling are shown in gray. The Hippo effector protein TAZ interacts with Dishevelled to prevent the dissociation of the β-catenin destruction complex and this interaction inhibits the Wnt response. YAP limits the Wnt response by sequestering β-catenin in the cytoplasm and preventing activation of Wnt/β-catenin target genes. Interestingly, YAP activates the Wnt/β-catenin response by inhibiting GSK3β and blocking β-catenin degradation. YAP can also enhance β-catenin-mediated transactivation of gene expression, and the two co-activators can co-regulate a set of target genes. The Hippo/YAP pathway is depicted on the right. Shown in gray are points where Wnt/β-catenin signaling influences Hippo signaling. The Wnt/β-catenin target gene CD44 interacts with NF2 and activates the Hippo pathway. YAP is also a Wnt/β-catenin target gene and its expression can drive proliferation of human colon cancer cells.

Hippo/YAP Signaling Pathway

The Hippo signaling pathway was discovered in *D. melanogaster* through genetic mosaic screens that were designed to uncover novel tumor suppressor genes. The first component discovered was the NDR-like kinase, *Warts* (*wts*), and loss of function mutations in this gene resulted in strong tissue overgrowth [32,33]. Subsequently, three additional components of the core kinase complex were identified using similar screens: the Ste20-like kinase Hippo (Hpo), the adaptor protein Salvador (Sav), and the activating protein Mob as tumor suppressor (Mats) [34–41]. Because loss of function mutations in each of these four proteins gave a similar phenotype, it was hypothesized that they functioned as part of a signaling pathway. It was not until the discovery of Yorkie (Yki) that a mechanism for how this pathway could regulate tissue growth was appreciated [42]. Yki acts as a transcriptional co-activator protein, and it interacts with the transcription factor Scalloped to drive the expression of genes that promote cell growth and inhibit apoptosis [43–45]. Homologs of these five core components have been identified in mammals. The warts homologs are Large tumor suppressor 1 and 2 (Lats1/2), the Hippo homologs are the Mammalian ste20 kinases 1 and 2 (Mst1/2), the Salvador homolog is WW45 (or Salvador), the Mats homologs are Mps one binder kinase activator-like A and B (MOBKL1A/B), and the Yorkie homologs are Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). As in flies, these core proteins have been shown to regulate tissue growth in mammals. However, studies in mammalian systems have revealed that not all components of the Hippo complex appear necessary in all tissues; for example, Mst1/2 is not required for Hippo signaling in skin [46]. For the purposes

of this review mammalian gene names will be used, unless referring to signaling events in *Drosophila*.

Unlike the Wnt/β-catenin pathway that is inactive in differentiated cells, the Hippo/YAP pathway is active in differentiated cells and it serves to limit growth. When the Hippo/YAP pathway is engaged, Mst1/2 kinases are activated and these kinases phosphorylate the other members of the core Hippo kinase complex. The phosphorylation of Lats1/2 by Mst1/2 activates the Lats1/2 kinases [47]. The interaction between Lats1/2 and MOBKL1A/B is necessary for Lats activation, and the phosphorylation of MOBKL1A/B by Mst1/2 enhances this interaction and further promotes Lats activity [48,49]. The function of Salvador phosphorylation by Mst1/2 remains unclear [50]. Lats1/2 phosphorylates YAP/TAZ on multiple serine residues. Phosphorylation of YAP on Ser127 creates a binding site for 14-3-3 proteins, and p-S127 YAP/14-3-3 complexes are sequestered in the cytoplasm [51,52]. In addition, phosphorylation of YAP on Ser381 by Lats can act as a priming event and triggers additional residues to be phosphorylated by CK1ε [53,54]. Phosphorylation of these additional residues creates a 'phospho-degron' that allows YAP to be degraded in a β-TRCP-mediated manner. In the absence of a Hippo signal, YAP translocates into the nucleus where it interacts with a variety of transcription factors, most commonly with members of the TEA domain-containing transcription factor family (TEAD) [55].

The upstream signals that lead to the activation of the Hippo/YAP pathway have yet to be fully defined. In *Drosophila*, a number of potential mediators have been identified. The protocadherin Fat is thought to 'sense' cell–cell contacts by binding the protocadherin Dachsous [56]. How signaling between these two proteins occurs is not fully understood; however, the gradient of Dachsous seems to regulate the activity of Fat [57]. Fat has been shown to interact with Expanded, and in conjunction with Kibra and Merlin, this complex phosphorylates and activates Hippo [58–61]. While mutations of Fat, Merlin, and Expanded all lead to tissue overgrowth, the observed phenotype is not as robust as mutations in core Hippo components, suggesting additional pathways or regulators act upon Hippo. While most of these components have mammalian homologs, the roles of these proteins in mammalian tissues are not as well defined. One exception is neurofibromatosis type two (NF2), the mammalian homolog of Merlin, which has been shown to be an upstream mediator of Hippo signaling in some mammalian tissues [62]. A summary of the Hippo signaling pathway is diagrammed in **Fig. 1**.

Wnt Regulation of the Hippo Pathway

The wingless (Wg), Fat-Dachsous and Hippo signaling pathways intersect to control wing development in *D. melanogaster* [63,64]. Border cells in the fly imaginal disc express Wg and Vestigial (Vg). Vestigial is a transcription factor that specifies wing cells. Border cells provide a feed-forward signal, that involves Wg, and this signal recruits non-wing cells from surrounding tissue and instructs them to become wing cells [65,66]. Zecca and Struhl found that Fat-Dachsous and Hippo signaling pathways are integral to the Vg-dependent feed-forward signal [63]. As non-wing cells are recruited, the feed-forward signal is transduced in part by the atypical myosin Dachs. Dachs represses the Hippo pathway and this leads to nuclear accumulation of Yorkie. Scalloped/Yorkie complexes directly activate *Vg*, which results in the conversion of non-wing cells to wing cells. Interestingly, as Vg accumulates, it can substitute for Yorkie as a Scalloped cofactor to drive *Vg* gene expression. Thus, by coordinating the expression of *Vg*; Wg, Fat-Dachsous and Hippo signaling pathways control growth of wing cells in the wing primordium. Whether this relationship governs the development of mammalian tissues has yet to be tested.

The CD44 cell surface glycoprotein also connects the Wnt/β-catenin and Hippo/YAP signaling pathways. CD44 binds hyaluronic acid (HA) that is expressed by the extracellular matrix and this interaction elicits a signaling cascade that restricts cell growth [67]. The *CD44* gene is a direct target of β-catenin/TCF complexes [68]. An interaction between CD44 and the Hippo component NF2 was identified [69]. The binding of HA to CD44 receptors lead to recruitment and activation of the NF2 kinase. Active NF2 kinase was found to inhibit the Ras/Raf pathway and prevent cell growth. It has since been appreciated that NF2 is a Hippo component and thus NF2 connects Hippo and CD44 signaling pathways [61]. Therefore, the up-regulation of CD44 by Wnt/β-catenin signaling may serve as a rheostat to limit cell growth by activating the Hippo pathway.

Several studies have reported increased nuclear accumulation of YAP in colorectal tumors compared with levels in normal colonic mucosa, but the underlying mechanisms that account for this accumulation have yet to be fully defined [70,71]. Our lab identified a β-catenin/TCF-binding site within the first intron of the *YAP* gene by mapping β-catenin-binding regions in colon cancer cells using ChIP-Seq [72]. This binding site demarcated an enhancer element that functioned to mediate β-catenin/TCF-dependent activation of *YAP* gene expression [73]. These results demonstrate that *YAP* is a bona fide and direct Wnt/β-catenin target gene. We also found that the reduction of YAP protein levels decreased colorectal cancer cell growth and xenograft tumor formation. Furthermore, both YAP and β-catenin are nuclear in the majority (85%) of primary human colonic tumors, suggesting that these two transcriptional co-activators may synergize to promote tumorigenesis in the colon. **Figure 1** summarizes the effects of Wnt/β-catenin on Hippo signaling.

Hippo Regulation of the Wnt Pathway

The Hippo pathway intersects with the Wnt pathway at many levels. The first identified point of regulation was that the Hippo effector protein TAZ could interact with Dishevelled [74]. TAZ binding to Dvl impaired the dissociation of the β-catenin destruction complex, and this interaction dampened the Wnt response. The phosphorylation of TAZ by the Hippo kinases Lats1/2 is required for the TAZ/Dvl interaction. When TAZ expression levels were reduced by siRNA, Wnt-stimulated β-catenin transcriptional activity was induced. This increase in transcriptional activity was phenocopied when either Mst1/2 or Lats1/2 kinases were depleted via siRNA. *TAZ* knockout mice develop severe renal cysts that are similar to the polycystic kidney disease phenotype that is associated with hyperactivation of the Wnt/β-catenin signaling pathway [74]. In addition, β-catenin transcriptional activity was elevated in the kidneys and cysts of *TAZ* knockout mice. Taken together, these data demonstrate that the Hippo signaling pathway inhibits the Wnt/β-catenin signaling pathway through TAZ.

The Hippo pathway has been shown to impact the transcription of Wnt target genes by altering the ability of β-catenin to activate gene transcription [75,76]. This relationship was first identified in neonatal hearts in conditional *Salvador* (*Sav*) knockout mice [75]. *Sav* is required for Hippo signaling, and its deletion leads to nuclear accumulation of YAP. A microarray analysis revealed that several canonical Wnt target genes were up-regulated in $Sav^{-/-}$ versus wild-type cardiomyocytes. Subsequent analysis revealed that this effect was likely due to a 4-fold increase in the nuclear levels of β-catenin in $Sav^{-/-}$ cardiac tissue. Moreover, in $Sav^{-/-}$ cardiomyocytes, β-catenin/TCF and YAP/TEAD complexes were shown to directly co-regulate expression of *Sox2* and *Snai2*. A second study found that deletion of Mst1/2 kinases in the intestines lead to an increase in Wnt/β-catenin activity [76]. As a consequence of *Mst1/2* deletion, stabilized YAP enhanced the transcriptional efficacy of β-catenin. While these studies demonstrated that active Hippo signaling could negatively impact β-catenin transcriptional activity, the mechanism for how this occurred requires further investigation.

Imajo *et al*. [77] have recently shown that phosphorylated YAP/TAZ can reduce β-catenin-mediated transcriptional activation of reporter constructs and Wnt responsive genes. Using a model of Wnt/β-catenin signaling in HEK 293T cells, β-catenin was shown to directly bind YAP/TAZ and this association retained β-catenin in the cytoplasm. Truncated forms of β-catenin that were incapable of interacting with YAP retained the ability to trans-activate gene expression. Therefore, while active Hippo signaling inhibits the Wnt/β-catenin pathway, cessation of Hippo signaling may act to enhance Wnt/β-catenin-dependent gene expression. It is tempting to speculate that as phosphorylated YAP can retain β-catenin in the cytoplasm, unphosporylated YAP may facilitate β-catenin transport into the nucleus.

Another point of intersection between the Hippo/YAP pathway and the canonical Wnt/β-catenin signaling pathway centres on the kinase GSK3β. Xin *et al.* [78] found that YAP could induce the insulin-like growth factor (IGF) pathway. Overexpression of a constitutively active form of YAP (S112A) in mice increased the transcription of genes involved in IGF signaling, such as IGF1, IGF-binding protein, and β-catenin. Activation of the IGF pathway in embryonic hearts leads to the inactivation of GSK3β. The inactivation of GSK3β resulted in the stabilization and subsequent nuclear translocation of cytosolic β-catenin. Consistent with this premise, the authors observed increased expression of β-catenin target genes in cardiomyocytes expressing YAP (S112A). Therefore, YAP can induce a β-catenin transcriptional program through the IGF pathway and independently of a Wnt signal. **Figure 1** summarizes the effects of Hippo/YAP signaling on the Wnt/β-catenin pathway.

Other Points of Intersection

While the above examples demonstrate ways in which the two pathways are able to regulate each other's activities, a number of studies have shown that there are several shared co-regulators in the Wnt/β-catenin and Hippo/YAP signaling pathways. These include, but are not limited to, α-catenin, E-cadherin, and β-TrCP. The functional importance of such mutual interactions in regulating Wnt/β-catenin and Hippo/YAP signaling is currently not fully appreciated. In murine skin, YAP is not regulated in the usual manner, as deletion of *Mst1/2* does not affect the localization of YAP [46]. Interactions with α-catenin are critical in regulating the localization of YAP within this tissue. Phosphorylated YAP interacts with α-catenin via 14-3-3 proteins, and this complex is localized to the membrane [46,79]. The binding of α-catenin to YAP/14-3-3 complexes prevents the association of PP2A with YAP, thereby keeping YAP in an inactive state [46]. The deletion of α-catenin is sufficient to cause the localization of YAP to the nucleus and induce tumor formation [46,79]. At adherens junctions, β-catenin serves as a bridge that directly links α-catenin to E-cadherin [23,80]. This interaction links the actin cytoskeleton to the cell membrane and also serves to limit the amount of free β-catenin in the cytoplasm, which therefore acts to limit Wnt/β-catenin signaling. It is well established that in a variety of cancers there is reduced expression of α-catenin and this could increase the available pools of both β-catenin and YAP [79,81].

E-cadherin has also been demonstrated to impact Hippo signaling. It has been known for some time that E-cadherin expression is lost during the progression and metastasis of

tumors [82]. E-cadherin mediates contact inhibition of cell growth; however, mechanisms for the anti-growth properties of E-cadherin have only recently been elucidated [83]. E-cadherin homophilic ligation has been shown to relocalize YAP to the cytoplasm in breast cancer cells [84]. This process requires β-catenin, NF2, and Lats1/2, but not Mst1/2. E-cadherin was proposed to mediate the phosphorylation of YAP through the adapter protein NA^+/H^+ exchanger regulatory factor (NHERF). NHERF binds NF2, β-catenin, and YAP/TAZ, and potentially mediates the activation of NF2. The role that β-catenin plays in mediating YAP phosphorylation remains to be determined. These studies suggest that the reduction of E-cadherin that occurs during tumorigenesis may act to promote cell growth by increasing the levels of free β-catenin and YAP within the cytoplasm.

As mentioned previously, both β-catenin and YAP can be degraded in a ubiquitin-dependent manner. Both proteins are ubiquitinated after the phosphorylation of key serine/threonine residues that create a phosphodegron, which is recognized by the E3 ubiquitin ligase β-TrCP [21,22,53,54]. Ultimately this leads to the degradation of β-catenin and YAP by the proteasome, which helps maintain low levels of both proteins in the cytoplasm.

Hippo and Wnt Signaling in Organ Regeneration

Monga and colleagues [85,86] have demonstrated a requirement for Wnt/β-catenin signaling in the repair of liver tissue after hepatectomy. Following hepatectomy, there is a rapid increase of β-catenin protein, and nuclear levels of β-catenin remain high for up to 48 h after surgery [87]. The knockdown or deletion of β-catenin after hepatectomy dramatically decreases the rate of recovery by decreasing cellular proliferation [86]. A number of studies have shown that the Hippo pathway plays a vital role in regulating liver size and proliferation. Most notably, liver-specific deletion of *Mst1/2* and *Sav* or overexpression of YAP results in increased cellular proliferation and development of hepatocellular carcinomas [71,88–90]. Moreover, a separate study found that two days after hepatectomy, YAP protein levels are induced and then return to pre-hepatectomy levels by day 3 [91]. These fluctuations are similar to those observed with β-catenin levels during a similar procedure. The requirement for YAP in liver regeneration is unresolved; however, it is likely that *YAP* deletion would decrease the ability of animals to recovery after hepatectomy.

Wnt signaling plays a critical role in the proliferation and maintenance of intestinal stem cells. YAP has been found within the nuclei of intestinal stem cells, suggesting that YAP may also be important for the proliferation and maintenance of the intestinal lining [71]. However, studies in *YAP* conditional knockout mice revealed that *YAP* is dispensable for the intestinal homeostasis [92]. Despite this, an increase in YAP protein was noted during the repair of the intestine following injury induced by treatment with dextran sodium sulfate (DSS). Furthermore, $YAP^{-/-}$ intestines did not fully recover from DSS-induced colitis demonstrating that YAP is required for intestinal regeneration in response to injury. An increase in apoptosis and fewer proliferative cells were observed in knockout intestines after injury compared with wild-type controls. Enhanced Wnt/β-catenin signaling has also been implicated in improving the recovery of mice after DSS treatment. Mice with a hypomorphic allele of the Wnt inhibitor DKK1 have improved health during DSS treatment and recover faster from DSS-induced colitis [93]. Treatment of mice with the Wnt agonist R-spondin greatly enhanced recovery of mice after DSS treatment, as measured by disease activity index [94]. These studies suggest that both the Hippo/YAP and Wnt/β-catenin pathways play key roles in the repair of intestinal tissue after injury. Future studies are needed to determine whether the pathways synergize to co-activate a set of target genes or whether each pathway activates a distinct set of targets that promotes intestinal regeneration.

Hippo and Wnt Signaling in Cancer

The proper regulation of Wnt/β-catenin signaling is crucial for mammalian development as well as tissue homeostasis. Mutations in components of this pathway that lead to its constitutive activation are found in numerous cancers [95–97]. Approximately 80% of colorectal cancers have inactivation of both *APC* alleles. Inactivation of Axin has been implicated in colorectal cancer, esophageal squamous cell carcinoma, hepatocellular cancer, and medulloblastomas. Activating mutations of β-catenin are found in colorectal cancers, hepatocellular carcinomas, endometrial ovarian cancer, melanoma, and hepatoblastomas. These findings highlight the importance of keeping the Wnt/β-catenin signaling pathway in check.

Given the role of the Hippo pathway in regulating cell growth it is perhaps not surprising that the most common diseases in which aberrant Hippo signaling has been implicated are various cancers [98,99]. NF2 mutations are the cause of the autosomal-dominant disorder, neurofibromatosis type II. Individuals afflicted with this disorder have multiple tumors of the nervous system. It is interesting to note that, unlike in Wnt/β-catenin signaling, mutations in the Hippo pathway components are relatively rare in cancers. However, there is a decrease in Hippo signaling activity in most cancers. Decreased activity of the Hippo pathway has been linked to epigenetic changes that alter expression of key components. Decreased expression of Mst1/2 has been implicated in colorectal and prostate cancers, while MOBKL1A/B is decreased in colorectal and lung

cancers [100–103]. Additionally, microRNAs have been implicated in the down-regulation of Lats 2 [104,105]. YAP has been implicated as an oncogene on chromosome 11q22 that is frequently duplicated in medulloblastomas, oral squamous-cell carcinomas, lung, pancreas, liver, and breast cancers [106]. The levels of nuclear YAP are elevated in a variety of tumors across many tissues; although the underlying causes of these elevated levels of YAP have yet to be fully uncovered.

β-Catenin is nuclear in a moderate percentage of hepatocellular carcinomas, but the target genes activated by β-catenin in these cancers have not been well characterized. The *c-MYC* proto-oncogene is a well-established target of Wnt/β-catenin signaling, and *c-MYC* is required for Wnt/β-catenin-induced intestinal tumors [107]. Interestingly, *c-MYC* is dispensable for Wnt/β-catenin-induced tumors in the liver [108]. The overexpression of YAP or reduction of Hippo function in the liver is sufficient to drive proliferation and tumorigenesis [71,88,89]. It is therefore possible that YAP is a key factor in the development of hepatocellular carcinomas that arise from deregulated Wnt/β-catenin signaling.

It has been realized for a number of years that the majority of colorectal cancers have increased Wnt signaling, resulting in the aberrant expression of Wnt/β-catenin target genes [109]. It has also become apparent that 85% of colorectal tumors have increased levels of nuclear YAP and increased YAP transcriptional activity in addition to heightened levels of Wnt/β-catenin activity [70,71,73]. Designing small molecule inhibitors that target the Wnt/β-catenin signaling pathway for the treatment of colorectal tumors has thus far been challenging [110]. Our recent findings in human CRC cells demonstrate that YAP plays a critical role in cell growth and proliferation [73]. These data suggest that targeting YAP may provide a novel target for combating this disease. Liu-Chittenden *et al.* [111] have identified small molecule inhibitors that disrupt the association of YAP with TEAD. These inhibitors reduced liver tumorigenesis in both YAP-overexpressing and *NF2* knockout mice. These findings clearly demonstrate the feasibility of targeting the Hippo/YAP pathway as a therapeutic strategy for the treatment of cancers. It remains to be determined whether these inhibitors are effective in reducing colorectal and other tumors with deregulated Hippo signaling; however, as Hippo signaling is dispensable for homeostasis, these inhibitors could represent the long awaited silver bullets that are needed to eradicate epithelial cancers.

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