Balanced cell growth is crucial in animal development as well as tissue homeostasis. Concerted cross-regulation of multiple signaling pathways is essential for those purposes, and the dysregulation of signaling may lead to a variety of human diseases such as cancer. The time-honored Wnt/β-catenin and recently identified Hippo signaling pathways are evolutionarily conserved in both Drosophila and mammals, and are generally considered as having positive and negative roles in cell proliferation, respectively. While most mainstream regulators of the Wnt/β-catenin signaling pathway have been fairly well identified, the regulators of the Hippo pathway need to be more defined. The Hippo pathway controls organ size primarily by regulating cell contact inhibition. Recently, several cross-regulations occurring between the Wnt/β-catenin and Hippo signaling pathways were determined through biochemical and genetic approaches. In the present mini-review, we mainly discuss the signal transduction mechanism of the Hippo signaling pathway, along with cross-talk between the regulators of the Wnt/β-catenin and Hippo signaling pathways. [BMB Reports 2014; 47(10): 540-545]

INTRODUCTION

Understanding the mechanisms for controlling the size of animals and their organs has been a challenging issue in biology, and the molecular mechanisms remain poorly understood (1-3). It is obvious that cell growth, proliferation, differentiation, and death should be tightly controlled to attain organs of the proper size during development, and that tissue homeostasis should be maintained in adults. Relatively recent studies suggested that the Hippo signaling pathway is a key mechanism for the control of organ size (1-5). The upstream regulators and the list of genes regulated by the Hippo pathway suggest that it negatively regulates cell proliferation (5). Uncontrolled cell proliferation due to dysregulation of Hippo signaling is responsible for tumor formation (1, 4, 6). Therefore, Hippo signaling is under intense scrutiny because of its significant roles in both developmental and cancer biology.

Cell growth and proliferation are also controlled by other well-known signaling pathways, such as Wnt/β-catenin and TGFβ signaling (7-9). Recent studies have proven that multiple signaling pathways cross-regulate each other to attain fine regulation of certain biological phenomenon. Specifically, it has recently been suggested that diverse signaling pathways such as Wnt/β-catenin (10-12), Shh (13), BMP/TGFβ (14-16), and GPCR signaling (17) cooperate with the Hippo signaling pathway to control cell growth and proliferation.

In this mini-review, we mainly describe recent advances in the Hippo signaling pathway, along with a brief explanation of the Wnt/β-catenin signaling pathway. Several examples of the merging of the two signaling pathways by unexpected cross-talk between components of the Wnt/β-catenin and Hippo signaling pathways, which may provide novel therapeutic targets for cancer treatment, are also discussed.

Wnt/β-CATENIN SIGNALING PATHWAY

Wnt signaling plays critical roles during embryonic development as well as in homeostatic mechanisms in adult tissues (7, 8). Complexity inferred by the temporal and spatial expression of 19 different Wnts and 10 types of Frizzled receptors, in mice and human, enables the Wnt signaling pathway to be involved in the control of diverse biological processes such as cell proliferation, differentiation, fate determination, adipogenesis, aging, etc (18, 19). Therefore, dysregulation of Wnt signaling can lead to diverse human diseases including cancers, osteoporosis, and neurodegeneration.

Wnt signaling can be divided into canonical (β-catenin dependent) and non-canonical (β-catenin independent) pathways based on whether increase of and nuclear localization of β-catenin occur in the presence of Wnt ligands (19, 20). Combinations of certain types of Wnt and Wnt receptors leads to the stabilization of β-catenin, while other combinations transduce signals via small G-proteins such as Rho/Rac or through regulation of the intracellular calcium level. Since most of the known cross-talk occurring between Hippo and Wnt signaling, the main
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Fig. 1. Wnt/β-catenin signaling pathway. Schematic diagram for the core components and signal transduction of Wnt/β-catenin pathway. (A) In the absence of Wnt, GSK3β and CK1 phosphorylate β-catenin degradation complex which includes APC and Axin. The phosphorylated β-catenin is recognized by β-TrCP and subsequently degraded by proteasome-dependent manner to result in low cytoplasmic levels of β-catenin. The expression of genes regulated by Wnt/β-catenin signaling is thereby repressed due to the low levels of the transcriptional co-activator, β-catenin (Fig. 1A). However, in the presence of Wnt, binding of Wnt to its receptor Fz (frizzled) and co-receptor LRP5/6 leads to phosphorylation of the intracellular region of LRP5/6 by GSK3β and CK1γ. Axin interacts with the phosphorylated LRP5/6 resulting in elevation in the levels of cytoplasmic β-catenin in a Dvl (Dishevelled)-dependent manner, though it is still controversial whether Axin translocates to the phosphorylated LRP5/6 apart from the components of the β-catenin destruction complex or as a whole complex (26, 27). The accumulated cytoplasmic β-catenin then enters into the nucleus and interacts with TCF (T-cell factor)/LEF (lymphoid enhancer factor) to activate the expression of Wnt target genes, which control cell proliferation (for example, c-myc and cyclin D1) and developmental processes (for example, twin, brachyury etc.). Due to space limitations the basic frame of signal transduction of the Wnt/β-catenin pathway was explained only briefly; however, much more elaborated regulatory mechanisms can be found in recent reviews, including ours (7, 8, 19).

HIPPO SIGNALING PATHWAY

Recent studies have shown that the Hippo signaling pathway is a conserved regulator of organ size. The Hippo signaling pathway is composed of a core kinase cascade initiating from Hippo (Mst1 and Mst2 in mammals) to the phosphorylation of a Yki (YAP and TAZ in mammals), which leads to change of the subcellular localization of Yki from the nucleus, where it acts as a transcriptional activator, to the cytoplasm (4, 28, 29). The Hippo signaling pathway does not have specifically allo-
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Fig. 2. Hippo signaling pathway. Schematic diagram for the core components and signal transduction of Hippo pathway. (A) When Hippo signaling is Off (in low cell density): The kinases MST1/2 and LATS are inactive, which results in inhibition of phosphorylation of YAP and TAZ. The stabilized YAP/TAZ in nuclei interacts with TEAD and enhances the transcription of target genes related to anti-apoptosis and proliferation. (B) When Hippo signaling is On (in high cell density): Activation of KIBRA and NF2 via unknown upstream signaling leads to activation of MST1/2. Activated MST1/2 phosphorylate SAV1 which in turn phosphorylate LATS and MOB1. The activated LATS/MOB phosphorylates YAP/TAZ which results in cytoplasmic retention by 14-3-3 protein and proteasomal degradation of YAP/TAZ. As a result, TEAD interacts with VGL4 and suppresses the expression of target genes.

The core kinase cascade for the inactivation of YAP/TAZ
Hippo signaling is composed of a highly conserved kinase cascade module that relays signals in a similar fashion in both mammals and Drosophila (1, 4). Mutations of the genes composing the core kinase complex, which were discovered in genetic screens in Drosophila for tumor suppressor genes, lead to a phenotype similar to hippopotamus in Drosophila due to increased cell proliferation and diminished cell death. As such, this signaling was named the Hippo pathway. The identified genes encode the following serine/threonine protein kinases and scaffolding proteins: (1) Hippo (MST1 and MST2 in mammals), which interacts with Salvador (SAV1 or also known as WW45 in mammals); and (2) Warts (LATS1 and LATS2 in mammals), which interacts with Mats (MOB1A and MOB1B in mammals) (1, 5). The transcriptional co-activator Yorkie (YAP and TAZ in mammals) forms a complex with the transcription factor Scalloped (TEAD 1-4 in mammals) to finally control the expression of genes regulated by the Hippo signaling pathway (Fig. 2).

Hippo signaling is regulated in a cell-density-dependent manner. When the MST1/2 and LATS1/2 kinases are activated at high cell density, Hippo signaling is considered to be in the active state. Although the biochemical mechanism is not yet known, MST1/2 are phosphorylated and activated in response to upstream signals (30, 34). The activated MST1/2, in complex with SAV1, activates LATS1/2 and MOB1 by phosphorylation, which in turn phosphorylate the major targets of the Hippo pathway: YAP, at Ser127, and TAZ, at Ser89 (34). The phosphorylated YAP and TAZ are then translocated to the cytoplasm. As a result, the expression of genes mediated by YAP/TAZ and TEAD ceases, and the YAP/TAZ is sequestered by 14-3-3 protein and degraded via the ubiquitin/proteosomal pathway (34, 35).

It has also been shown that the PPxY motifs of Ex (Expanded), Wart, and Hippo directly bind to the WW domain of Yorkie, se-

icated extracellular ligands or receptors, but instead appears to be regulated by a network of upstream components which are mainly involved in the regulation of cell adhesion and cell polarity (1, 30-33). It is evident that the core kinase cascade is strictly conserved, while the upstream signals influencing the kinase activity are much more diverse, for which the biochemical mechanisms of regulation are still obscure. The Hippo signaling pathway was also found to cross-talk with multiple signaling pathways in a tissue or context-dependent manner; therefore, it may be reasonable to consider Hippo signaling as a complex network rather than a single linear pathway.

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It has also been shown that the PPxY motifs of Ex (Expanded), Wart, and Hippo directly bind to the WW domain of Yorkie, se-
showed that TAZ blocks the interaction of Ck1 δ/ε to Dvl, inhibiting the Wnt3a-induced phosphorylation of Dvl2, and thereby inhibiting Wnt/β-catenin signaling. They also demonstrated ectopic expression of MST or LATS, which leads to cytoplasmic localization of TAZ, to inhibit Wnt3a-mediated reporter activity. However, whether or not endogenous Wnt/β-catenin signaling is inhibited by the activation of the Hippo signaling pathway at the endogenous level still needs to be examined. The fact that the kidneys of TAZ conditional knockout mice showed very little increase of nuclear β-catenin raised questions about the functional relevance of their model in in vivo situations (46).

Moreover, an inhibitory role of Hippo signaling in the Wnt/β-catenin signaling pathway in developing heart was suggested by heart-specific Salvador knockout mice (SAV cKO) (47). Increased heart size as well as increased cardiomyocyte proliferation and nuclear β-catenin was found in SAV cKO (47). In microarray analysis on SAV cKO, it was also discovered that the expressions of important genes in heart development or anti-apoptosis were increased, and that the expressions of these genes were dependent on β-catenin. Finally, results from ChIP and reporter assay suggested that YAP-TEAD and β-catenin-TCF/Lef act cooperatively to induce some of their target genes, sox2 and snail2, when SAV is deleted in developing heart. However, it is still unknown whether similar results would be obtained when other Hippo core components, such as MST and LATS, are conditionally deleted, and whether this inhibitory role of SAV is applicable to all tissues rather than being restricted to the heart.

Later, an additional cross-talk mechanism was suggested (48). Imajo et al. found that YAP2 strongly blocks the constitutively active form of β-catenin (β-catenin S33Y, S37A)-mediated Topflash activity. This would be unexplainable if the inhibitory mechanism of Hippo signaling on Wnt signaling were restricted to the inhibition of Dvl, as constitutively active β-catenin is independent from Dvl activation status. YAP and TAZ interact with β-catenin to block its nuclear localization, inhibiting Wnt/β-catenin signaling. The E66A mutant of YAP, which does not bind to β-catenin, showed much reduced inhibitory activity on Wnt/β-catenin signaling. YAP(S127D), which mimics the phosphorylated-form of YAP and is mainly localized in the cytoplasm, but not YAP(S127A), which mimics the unphosphorylated-form of YAP and is mainly localized in the nucleus, inhibits the nuclear localization of β-catenin. These results suggested that YAP or TAZ inhibit Wnt signaling in two ways: by blocking the activation of Dvl and/or the cytoplasmic sequestration of β-catenin (48).

So far, we have described how Hippo signaling inhibits Wnt/β-catenin signaling. However, Piccolo and colleagues identified a mechanism by which the level of YAP/TAZ is regulated by β-catenin (11, 12). It is a truly provocative idea that TAZ is an integral mediator of Wnt/β-catenin signaling. It was shown that the level of TAZ is regulated in the β-catenin destruction complex, which is composed of APC, Axin, and GSK3β. In the absence of Wnt signaling, β-catenin phosphorylated by GSK3β serves as a scaffold for the association of TAZ with the β-TrCP E3 ligase complex. However, in the presence of Wnt, blocking the phos-
phorylation of β-catenin leads to escape of both β-catenin and TAZ from the destruction complex, subsequently enhancing expression of the target genes mediated by the β-catenin/Tcf and TAZ/TEAD complexes. Extended from these results, the same group showed YAP/TAZ to be essential for β-TrCP recruitment to the β-catenin destruction complex and subsequent β-catenin degradation. Overall, these data suggest that the Hippo signaling transcription factors YAP and TAZ are integral components of the β-catenin destruction complex, orchestrating the Wnt responses.

CONCLUSION

It is just the beginning to understand how animals control their organ size. Hippo signaling and cross-talk of Hippo and other signaling pathways including Wnt, Shh, and BMP/TGFβ signaling is known to be involved in the regulation of cell growth, proliferation, and death. Since Hippo signaling is a new concept compared to the other well-defined signaling pathways, the identification and characterization of more Hippo signaling components is expected. More specifically, excavation of the upstream regulators of the Hippo signaling pathway and discovery of mechanisms for the regulation of the core kinase cascade are imminent. Discovery of the cross-talk between Hippo and other well-known signaling pathways will deepen our understanding of signaling pathways as a whole network, which may lead to the development of valuable therapeutic targets for curing human diseases such as cancer.

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