COMMENTARY



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Diversity in function and regulation of the Hippo pathway

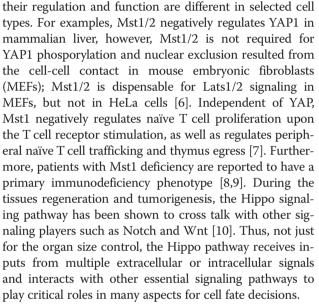
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The Hippo pathway is recognized as an important regulator of tissue growth and cell fate [1-3]. Originally indentified in Drosophila, the Hippo pathway, also known as the Salvador-Warts-Hippo pathway, contains core kinases cascade, Hippo and Warts(Wts) coupled by the scaffold protein Salvador (Sav), as well as Mats. The activation of the Hippo pathway kinases results in phosphorvlation and inactivation of the downstream transcriptional co-activator Yorkie which binds to the sequence-specific DNA-binding protein Scalloped and enhances the expression of proliferative and pro-survival genes. In general, the primary function of the Hippo signaling pathway is to inhibit the activation of Yorkie, inasmuch as deletion of Yki reverses the overgrowth phenotypes resulted from loss of Hippo, Warts, Salvador or Mats. Components of the Hippo pathway are highly conserved throughout evolution. The counterparts for the Hippo pathway in Drosophila can all be found in mammals, although they are more diverse and complex [4]. The Hippo orthologs Mst1 and Mst2 utilize the Salvador ortholog WW45/Sav1 to regulate the Warts orthologs Lats1/Lats2. Activated Lats kinases phosphorylate the transcriptional regulators TAZ/ YAP (Yorkie orthologs) which promotes 14-3-3 binding to YAP, causing YAP nuclear exit, hereby inhibiting its function. In recent years, increasing numbers of mammalian studies have expanded the large proteins network of the Hippo signaling pathway that controls tissues growth during development and regeneration, as well as in pathological states such as cancer [5].

The upstream regulator of the Hippo pathway and the downstream of Mst1/Mst2 have been diversified considerably in mammals compared with the Drosophila Hippo pathway. Multiple cellular stresses can trigger an adaptive response by activating the Hippo signaling pathway, which may, in turn, maintain the cellular homeostasis. The Hippo/Warts/Mats/Yorkie pathway predicated in Drosophila is not universal in all mammalian tissues in which

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In this issue of the Cell & Bioscience, we have provided some updates on the regulations beyond the canonical Hippo signaling, and their implications in pathological states. Qin et al. will review the recent updates of the roles of Mst1/2 on the cellular redox state regulation, the effects of Mst1/2 deficiency on the development process and tumorigenesis in multiple organs, and their involvement in the immune regulation. The review by Hergovich will summarize the current understanding of mammalian Lats1/2 kinases together with their closest relatives, the NDR1/2 kinases. He will focus on discussion about the regulation of the LATS/NDR family of kinases and their currently known substrates, as well as the biological roles of LATS/NDR kinases. Guo and Zhao follows with a discussion of the function of YAP and TAZ as effectors of cell responses to several extracellular signals including mechanical stress, GPCR signaling, and the Wnt signaling pathway, emphasizing that YAP and TAZ might have different role with cell-type specificity in the promotion of specific cancers. Collectively, these reviews have provided additional information to address the complexity of the



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hippo signaling pathway in response to physiological signals for regulating cellular and tissues homeostasis.

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