doi: 10.3978/j.issn.2095-6959.2017.07.034
View this article at: http://dx.doi.org/10.3978/j.issn.2095-6959.2017.07.034

Hippo信号通路与肾病

郑志煌[1] 综述 张志刚[2]，吴慧娟[2]，刘军[1] 审校

(1. 上海交通大学附属第一人民医院肾内科，上海 200080；2. 复旦大学基础医学院病理系，上海 200032)

[摘 要] Hippo信号通路是近年来备受关注的一条调节器官生长和组织大小的重要信号通路，其已被证实在肿瘤的发生、发展中发挥重要作用。目前Hippo信号通路与肾病的相关性研究仍处于起步阶段。在急性肾损伤(acute renal injury，AKI)方面，Hippo信号通路可能参与小管上皮细胞的凋亡、上皮–间质转化(epithelial-mesenchymal transition，EMT)以及AKI进展至慢性肾脏病(chronic kidney disease，CKD)等多个环节。此外，Hippo信号通路还参与多种慢性肾脏病，包括局灶节段性肾小球硬化症、糖尿病肾病、多囊肾等的发生和疾病进展。

[关键词] Hippo信号通路；YAP/TAZ；急性肾损伤；上皮–间质转化；慢性肾脏病

Hippo signaling pathway in kidney diseases

ZHENG Zhihuang[1], ZHANG Zhigang[2], WU Huijuan[2], LIU Jun[1]

*(1. Department of Nephrology, First Affiliated Hospital of Shanghai Jiao Tong University, Shanghai 200080;
2. Department of Pathology, School of Basic Medical Sciences, Fudan University, Shanghai 200032, China)*

Abstract Hippo signaling pathway is an important signaling pathway that regulates organ growth and tissue size, which has been received much concern recently and shown to play an important role in the development and progression of tumors. For now, researches about the relationship of Hippo signaling pathway and kidney diseases are still at the initial stage. In acute renal injury, Hippo signaling pathway may be involved in the apoptosis of tubule epithelial cells, epithelial-mesenchymal transition (EMT) and acute renal injury (AKI) progress to chronic kidney disease (CKD) and other processes. In addition, Hippo signaling pathway is also involved in the development and progression of a variety of chronic kidney diseases, including focal segmental glomerulosclerosis, diabetic nephropathy, polycystic kidney disease. Therefore, this review will briefly summarize the researches progress about Hippo signaling pathway in the field of kidney diseases, so as to provide new insights and strategies for the prevention and treatment of kidney diseases.

Keywords Hippo signaling pathway; YAP/TAZ; acute renal injury; epithelial-mesenchymal transition; chronic kidney disease

收稿日期 (Date of reception)：2017–04–24

通信作者 (Corresponding author)：刘军，Email: liujun-sgh@sjtu.edu.cn；吴慧娟，Email: hjwu@shmu.edu.cn

基金项目 (Foundation item)：上海市自然科学基金 (15ZR1433500)；上海市科委科创项目 (15140902900)。This work was supported by Natural Science Foundation of Shanghai (15ZR1433500) and Science and Technology Commission of Shanghai Municipality (15140902900), China.

Hippo信号通路是近年来备受关注的一条调节器官生长和组织大小的重要信号通路，其最初在果蝇体内发现，在哺乳动物中高度保守。Hippo信号通路通过对细胞增殖和凋亡的调控来影响组织器官的大小，近年来研究[1]发现其活性的异常与肿瘤的发生密不可分。哺乳动物Hippo信号通路是由Mst1/2激酶(mammalian sterile 20-like kinases 1/2)，Lats1/2激酶(large tumor suppressor kinases 1/2)和转录共激活因子YAP(Yes-associated protein)/TAZ(transcriptional coactivator with PDZ-binding motif)组成的三步激酶级联，其中TAZ是YAP的旁系同源物，YAP/TAZ是Hippo信号通路的重要下游效应分子[2]。Mst1/2与调节蛋白Sav1(Salvador homolog 1)复合，磷酸化和激活Lats1/2，其也与调节蛋白Mob1(Mps-one binder 1)形成复合物，这四种蛋白质目前被视为Hippo信号通路的核心组分[3]。活化的Lats1/2进一步磷酸化下游效应分子YAP/TAZ，使YAP/TAZ与胞浆骨架蛋白14-3-3等结合而滞留在细胞质内，从而抑制YAP/TAZ入核发挥其促转录增殖的功能[4]。滞留胞质内的YAP/TAZ大部分经泛素化途径降解，少部分经溶酶体途径降解[5]。因此，胞浆内磷酸化的YAP/TAZ无活性，只有去磷酸化时，YAP/TAZ才可被激活并进入到细胞核内，通过与TEAD家族转录因子结合发挥促增殖、抑凋亡的作用[6](图1)。

Hippo信号通路的研究主要集中于肿瘤领域。最近其与肾病发生发展的相关性开始受到关注，已有研究[7]观察到Hippo信号通路与肾小球滤过屏障的破坏、肾小管细胞上皮–间质转化(epithelial-mesenchymal transition，EMT)以及间质纤维化、肾囊肿和糖尿病肾病(diabetic nephropathy，DN)的发生等密切相关。因此，探索Hippo信号通路在肾病发生发展中的作用机制，将为肾病的防治提供新靶点和新策略。

1 Hippo 信号通路与急性肾损伤

已有研究[8-10]证实：Hippo信号通路可参与大脑和心脏的缺血–再灌注损伤(ischemia reperfusion injury，IRI)，其中包括缺血–再灌注引起的炎症反应和氧化应激。而缺血–再灌注是引起急性肾损伤(acute renal injury，AKI)的一个常见病因，在缺血性AKI中，因缺血的严重程度不同，肾小管细胞的病理改变不同，包括细胞极性的丧失，坏死、凋亡、残留细胞的去分化和再生等[11]。Hippo信号通路的活化或抑制可以调节细胞增殖、凋亡、细胞接触和细胞极性等众多细胞生物学行为[12]。近年来随着Hippo信号通路研究的深入，其与AKI的关系也逐步得到揭示。在IRI诱导的AKI大鼠模型中发现，肾小管上皮细胞的胞质和胞核中均有YAP蛋白的高度表达，提示Hippo信号通路极有可能参与AKI的发生发展[13]，因此，本部分将综述Hippo信号通路在AKI中作用机制方面的研究进展。

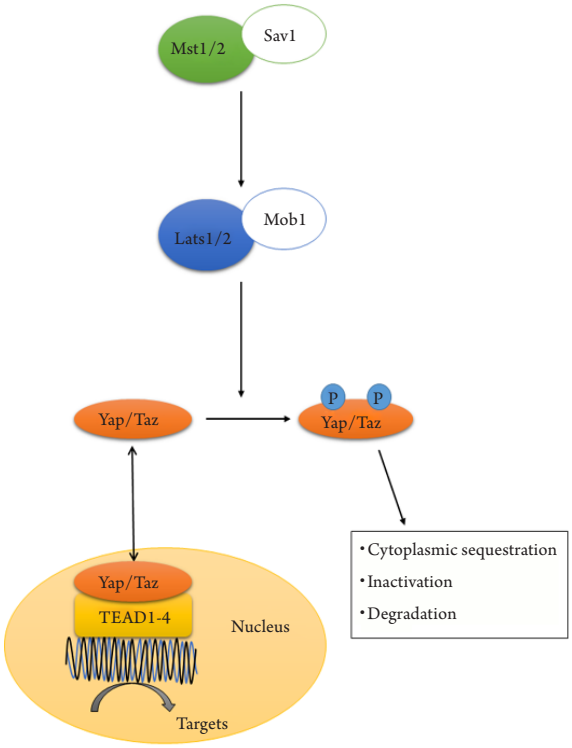

图1 Hippo信号通路示意图

Figure 1 Schematic diagram of Hippo pathway

刺激因子磷酸化和活化Mst1/2和Sav1，而后活化的Mst1/2磷酸化Lats1/2和Mob1。Lats1/2磷酸化YAP/TAZ，导致其滞留在胞浆中，失活和降解。当YAP/TAZ去磷酸化时，它们进入细胞核与TEAD1-4转录因子相互作用而诱导基因转录。

Firstly, upstream molecules promote phosphorylation and activation of Mst1/2 and Sav1. And then Lats1/2 and Mob1 are phosphorylated by Mst 1/2. Further YAP/TAZ are phosphorylated by Lats1/2 on multiple sites, resulting in its cytoplasmic sequestration, inactivation, and degradation. When Hippo signaling is off, YAP/TAZ are dephosphorylated and enter the nucleus to induce gene transcription by interacting with TEAD1-4 transcription factors.

1.1 Hippo 信号通路与肾小管上皮细胞的凋亡

细胞凋亡是IRI后损伤细胞的早期重要表现[14]。Hippo信号通路可能受到神经纤维瘤蛋白2(neurofibromin2，NF2)的调控或与TGF-β信号通路相互作用，进而调控缺血-再灌注组织细胞的凋亡[15-16]。Matsuda等[17]的研究显示：NF2是Hippo信号通路的调节蛋白，可抑制各种细胞生长并促进凋亡，在心脏IR损伤的过程中，NF2是氧化应激的关键因子，活化后进而激活Mst1和抑制YAP入核来促进心肌细胞凋亡，从而加剧IRI。Del等[9]研究又发现YAP能够促进心肌细胞的生长和提高心肌细胞生存能力，从而在一定程度上抵抗心肌的IRI，以上一系列研究对AKI具有一定的借鉴意义。另一方面，Gewin等[18]发现：在缺血-再灌注引起的AKI中，近端小管细胞中TGF-β信号通路的异常激活和TTGF-β受体I型(type I receptors of TGF-β，TβRI)的高表达可促进近端小管上皮细胞的损伤和凋亡，而Hippo信号通路可通过其下游磷酸化的YAP/TAZ与胞质中磷酸化活化的Smad复合物(TGF-β信号通路下游效应分子)螯合，阻止其进入细胞核参与转录[19]，这说明Hippo信号通路的激活可能干扰并抑制TGF-β/Smad信号通路。因而我们猜想在AKI中的某个阶段，Hippo信号通路可能失活，致使下游的YAP/TAZ去磷酸化活化，增强了TGF-β/Smad信号通路，进一步加剧肾小管上皮细胞的凋亡，但是这一猜想与上述心肌IRI中Hippo通路对凋亡的调控作用不一致，故在IRI引起的AKI中，Hippo信号通路是否能通过介导TGF-β/Smad信号通路调控肾小管上皮细胞的凋亡还有待进一步探索。

1.2 Hippo 信号通路与肾小管上皮细胞 EMT 的发生

肾小管上皮细胞EMT指的是肾小管上皮细胞丧失其细胞极性和细胞黏附的上皮表型，并获得间充质干细胞特有的迁移和侵入性能力的过程，而小管上皮细胞极性的丢失和TGF-β/Smad信号通路的过度激活则可导致EMT的发生[20]。细胞极性决定因子CRB(Crumbs)复合物及其组分pals1蛋白是维持细胞极性的重要成分之一，有研究[21]表明其具有调节Hippo信号通路的作用，研究[22]表明CRB复合物是一个抑癌基因，其功能缺失将引起Hippo信号通路的靶基因表达上调，组织过度生长[23]。有趣的是：CRB复合物的破坏还可以增强TGF-β信号通路的功能，促进EMT的发生[19]，而上文已提及Hippo信号通路不仅能调控TGF-β/Smad信号通路，其本身还受到CRB及其组分pals1的调节。因此我们假设，在AKI发生阶段，肾小管上皮中CRB复合物受到影响而下调，引起Hippo信号通路的失活，YAP/TAZ去磷酸化，入细胞核发挥促进转录的功能，同时，在CRB下调和Hippo信号通路失活的双重叠加效应下TGF-β/Smad信号通路激活，最终造成肾小管上皮细胞的极性消失和EMT(图2)。此外，有研究[24]表明：小管上皮细胞Sav1的特异性缺失会促进单侧输尿管阻塞(unilateral ureteral obstruction，UUO)后小管上皮细胞EMT样表型的出现，其也可能通过TGF-β/Smad信号通路介导参与EMT。

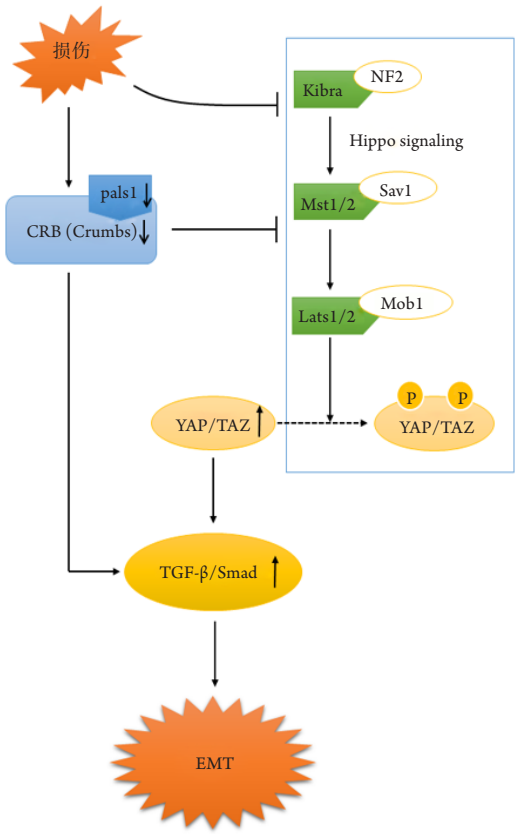

图2 肾小管细胞的EMT

Figure 2 EMT of renal tubular epithelial cells

小管上皮细胞损伤引起CRB复合物的下调和Hippo信号通路的失活，共同激活TGF-β/Smad信号通路，从而促进EMT的发生

Injury of tubular epithelial cell causes downregulation of CRB complex and inactivation of Hippo signaling pathway, which activate TGF-β/Smad signaling pathway together, thus promoting the occurrence of EMT.

1.3 Hippo 信号通路在 AKI 进展至慢性肾病中的作用

通常认为，AKI是慢性肾脏病(chronic kidney disease，CKD)发生发展的一个独立危险因素[25]，需要透析治疗的AKI患者更容易发展为CKD和终末期肾病(end-stage renal disease，ESRD)[26]。Xu等[13]通过检测AKI大鼠模型的肾脏以及AKI患者肾穿刺活检标本中Hippo信号通路组分的表达，发现在AKI修复阶段，肾小管上皮细胞的胞浆和胞核中YAP蛋白水平明显增加，且YAP的表达变化不仅与YAP的下游靶标TEAD2和TEAD3的表达变化正相关，也与结缔组织生长因子(connective tissue growth factor，CTGF)的表达变化正相关。而众所周知，CTGF是肾纤维化发生发展的关键调节因子之一[27]。结果提示，Hippo信号通路参与缺血性AKI肾修复和纤维化的过程，其中YAP是关键的效应器，其可促进损伤的肾小管上皮细胞修复，但持续过度的活化和增加则可能引起间质纤维化的发生。

已有研究[18]证实TGF-β在肾纤维化发生发展中起重要作用，且YAP/TAZ通过对TGF-β信号通路的调控来参与这一过程[28]。在Seo等[24,29]的研究中：肾小管上皮细胞Sav1特异性敲除的小鼠进行UUO处理后，不仅出现肾小管上皮细胞EMT，更直接表现出间质纤维化的加重。不仅如此，Sav1基因敲除后，YAP1/TAZ显著激活，诱导TGF-β和TβRII的高表达，而体外实验更是发现TAZ可直接调节TGF-β信号通路，通过与TβRII的结合后引起一系列激活效应，活化Smad信号通路，调节参与纤维化的多个靶基因转录。上述研究提示Hippo信号通路很可能从多方位参与到肾纤维化的发生发展。

2 Hippo 信号通路与其他肾病的相关性

2.1 Hippo 信号通路与局灶节段性肾小球硬化症

目前我们普遍认为，局灶节段性肾小球硬化症(focal segmental glomerulosclerosis，FSGS)的病理机制主要是肾小球足细胞的损伤和减少[30]，且已有研究[31]表明：Hippo信号通路的关键效应分子YAP的活性和定位对于足细胞的存活和稳定相当重要，在足细胞中，Hippo信号通路的激活包括引起Lats1/2的磷酸化，进而引起下游YAP的磷酸化并滞留在胞浆中，无法进入细胞核调控转录、参与细胞增殖，最终导致足细胞细胞凋亡水平的增加。Schwartzman等[32]在人类原发性FSGS中，观察到肾小球中YAP的表达降低。将YAP基因在足细胞中特异性敲除后会导致足细胞凋亡，肾小球逐渐出现局灶节段性硬化灶，小鼠出现蛋白尿和血肌酐水平的升高，结果提示，YAP具有抗足细胞凋亡的保护作用，而YAP缺失可能与FSGS的发生相关。国内有课题组[33-34]使用体外培养的足细胞观察到了与骨架蛋白密切相关的RhoA及Cdc42的缺失可通过抑制Hippo信号通路中YAP的活化及入核，进一步促进足细胞凋亡。综合以上的研究，基本可以得出如下结论，Hippo信号通路中YAP的活化和表达增多可能对足细胞产生抗凋亡的保护作用。

2.2 Hippo 信号通路与 DN

有研究[35]发现：DN小鼠模型中YAP的活性增加，YAP下游靶信号分子CTGF在肾小球疾病患者的肾活检中高度表达。此外，Chen等[36]课题组于2015年发表的文章中，报道了在DN方面，YAP的核转位及TEAD的结合可受到上游EGFR-PI3K-Akt-CREB信号通路调控，该研究也首次在DN中证明了表皮生长因子受体(Epidermal growth factor receptor，EGFR)信号通路和Hippo信号通路之间的串扰，并表明EGFR介导的YAP信号可能是DN病情进展的重要基础机制。药物干预Hippo信号通路可能减缓DN的进展。

2.3 Hippo 信号通路与多囊肾

Hippo信号通路和囊性肾脏疾病的发生发展也存在相关性，TAZ缺失可导致多囊肾(polycystic kidney disease，PKD)的发生[37]。Hossain等[38]观察到：TAZ基因敲除后的小鼠在8周龄时开始出现肾囊肿，4~6个月龄内相继出现进行性肾功能不全。Wnt/β-catenin信号通路很大程度参与了PKD中囊肿的形成[39]。在TAZ基因敲除所致PKD的小鼠中可检测到Wnt/β-catenin信号通路的显著激活[40]，提示Hippo信号通路极有可能是Wnt/β-catenin信号通路的上游，并通过调控Wnt/β-catenin信号通路参与囊肿形成。此外，YAP表达的下调可抑制肾囊肿内衬上皮细胞的增生，YAP去磷酸化后，进入细胞核增加，转录活性增强可能是导致PKD发生、发展的重要原因之一[41]。

3 结语

近年来的大量研究[42]表明：Hippo信号通路调节细胞增殖和凋亡，与器官结构功能以及肿瘤发生密切相关。而在肾病领域，虽然目前已有证

据显示Hippo通路参与了部分肾病的发生和发展，但Hippo信号通路在AKI所致肾小管上皮细胞的凋亡、再生、EMT及间质纤维化中的具体分子机制，其与TGF-β/Smad和Wnt/β-catenin等信号通路间的相互作用等仍需进一步阐明，Hippo信号通路干预的时机和分子靶点等问题仍需要进一步研究，从而为肾病的预防和治疗提供新的方案，开拓新的策略。

参考文献

1. Zhao B, Lei QY, Guan KL. The hippo-yap pathway: New connections between regulation of organ size and cancer[J]. Curr Opin Cell Biol, 2008, 20(6): 638-646.
2. Zhao B, Tumaneng K, Guan KL. The hippo pathway in organ size control, tissue regeneration and stem cell self-renewal[J]. Nat Cell Biol, 2011, 13(8): 877-883.
3. Zhao B, Li L, Lei Q, et al. The hippo-yap pathway in organ size control and tumorigenesis: An updated version[J]. Genes Dev, 2010, 24(9): 862-874.
4. Zhao B, Wei X, Li W, et al. Inactivation of yap oncoprotein by the hippo pathway is involved in cell contact inhibition and tissue growth control[J]. Genes & Development, 2007, 21(21): 2747-2761.
5. Zhao B, Li L, Tumaneng K, et al. A coordinated phosphorylation by lats and ck1 regulates yap stability through scf(beta-trcp)[J]. Genes Dev, 2010, 24(1): 72-85.
6. Zhao B, Ye X, Yu J, et al. Tead mediates yap-dependent gene induction and growth control[J]. Genes Dev, 2008, 22(14): 1962-1971.
7. Wong JS, Meliambro K, Ray J, et al. Hippo signaling in the kidney: The good and the bad[J]. Am J Physiol Renal Physiol, 2016, 311(2): F241-F248.
8. Shao D, Zhai P, Del Re DP, et al. A functional interaction between hippo-yap signalling and foxo1 mediates the oxidative stress response[J]. Nat Commun, 2014, 5: 3315.
9. Del Re DP, Yang Y, Nakano N, et al. Yes-associated protein isoform 1 (yap1) promotes cardiomyocyte survival and growth to protect against myocardial ischemic injury[J]. J Biol Chem, 2013, 288(6): 3977-3988.
10. Zhao S, Yin J, Zhou L, et al. Hippo/mst1 signaling mediates microglial activation following acute cerebral ischemia-reperfusion injury[J]. Brain Behav Immun, 2016, 55: 236-248.
11. Devarajan P. Update on mechanisms of ischemic acute kidney injury[J]. J Am Soc Nephrol, 2006, 17(6): 1503-1520.
12. Yu FX, Zhao B, Guan KL. Hippo pathway in organ size control, tissue homeostasis, and cancer[J]. Cell, 2015, 163(4): 811-828.
13. Xu J, Li PX, Wu J, et al. Involvement of the hippo pathway in regeneration and fibrogenesis after ischaemic acute kidney injury: Yap is the key effector[J]. Clin Sci (Lond), 2016, 130(5): 349-363.
14. Supavekin S, Zhang W, Kucherlapati R, et al. Differential gene expression following early renal ischemia/reperfusion[J]. Kidney Int, 2003, 63(5): 1714-1724.
15. Grannas K, Arngarden L, Lonn P, et al. Crosstalk between hippo and tgfbeta: Subcellular localization of yap/taz/smad complexes[J]. J Mol Biol, 2015, 427(21): 3407-3415.
16. Nallet-Staub F, Yin X, Gilbert C, et al. Cell density sensing alters tgf-beta signaling in a cell-type-specific manner, independent from hippo pathway activation[J]. Dev Cell, 2015, 32(5): 640-651.
17. Matsuda T, Zhai P, Sciarretta S, et al. Nf2 activates hippo signaling and promotes ischemia/reperfusion injury in the heart[J]. Circ Res, 2016, 119(5): 596-606.
18. Gewin L, Vadivelu S, Neelisetty S, et al. Deleting the tgf-beta receptor attenuates acute proximal tubule injury[J]. J Am Soc Nephrol, 2012, 23(12): 2001-2011.
19. Varelas X, Samavarchi-Tehrani P, Narimatsu M, et al. The crumbs complex couples cell density sensing to hippo-dependent control of the tgf-beta-smad pathway[J]. Dev Cell, 2010, 19(6): 831-844.
20. Liu Y. Epithelial to mesenchymal transition in renal fibrogenesis: Pathologic significance, molecular mechanism, and therapeutic intervention[J]. J Am Soc Nephrol, 2004, 15(1): 1-12.
21. Weide T, Vollenbröker B, Schulze U, et al. Pals1 haploinsufficiency results in proteinuria and cyst formation[J]. J Am Soc Nephrol, 2017, 28(7): 2093-2107.
22. Ling C, Zheng Y, Yin F, et al. The apical transmembrane protein crumbs functions as a tumor suppressor that regulates hippo signaling by binding to expanded[J]. Proc Natl Acad Sci U S A, 2010, 107(23): 10532-10537.
23. Chen CL, Gajewski KM, Hamaratoglu F, et al. The apical-basal cell polarity determinant crumbs regulates hippo signaling in drosophila[J]. Proc Natl Acad Sci U S A, 2010, 107(36): 15810-15815.
24. Seo E, Kim WY, Hur J, et al. The hippo-salvador signaling pathway regulates renal tubulointerstitial fibrosis[J]. Sci Rep, 2016, 6(31931.
25. Rifkin DE, Coca SG, Kalantar-Zadeh K. Does aki truly lead to ckd?[J]. J Am Soc Nephrol, 2012, 23(6): 979-984.
26. Chawla LS, Amdur RL, Amodeo S, et al. The severity of acute kidney injury predicts progression to chronic kidney disease[J]. Kidney Int, 2011, 79(12): 1361-1369.
27. Phanish MK, Winn SK, Dockrell ME. Connective tissue growth factor-(ctgf, ccn2)—a marker, mediator and therapeutic target for renal fibrosis[J]. Nephron Exp Nephrol, 2010, 114(3): e83-92.
28. Szeto SG, Narimatsu M, Lu M, et al. Yap/taz are mechanoregulators of tgf-β-smad signaling and renal fibrogenesis[J]. Journal of the American Society of Nephrology, 2016, 27(10): 3117-3128.

29. Loeffler I, Wolf G. Transforming growth factor-beta and the progression of renal disease[J]. Nephrol Dial Transplant, 2014, 29(Suppl 1): i37-i45.
30. Schiffer M, Bitzer M, Roberts ISD, et al. Apoptosis in podocytes induced by tgf-beta and smad7[J]. J Clin Invest, 2001, 108(6): 807-816.
31. Wennmann DO, Vollenbroeker B, Eckart AK, et al. The hippo pathway is controlled by angiotensin ii signaling and its reactivation induces apoptosis in podocytes[J]. Cell Death Dis, 2014, 5: e1519.
32. Schwartzman M, Reginensi A, Wong JS, et al. Podocyte-specific deletion of yes-associated protein causes fsgs and progressive renal failure[J]. J Am Soc Nephrol, 2016, 27(1): 216-226.
33. Huang Z, Zhang L, Chen Y, et al. Cdc42 deficiency induces podocyte apoptosis by inhibiting the nwasp/stress fibers/yap pathway[J]. Cell Death Dis, 2016, 7: e2142.
34. Huang Z, Zhang L, Chen Y, et al. Rhoa deficiency disrupts podocyte cytoskeleton and induces podocyte apoptosis by inhibiting yap/dendrin signal[J]. BMC Nephrol, 2016, 17(1): 66.
35. Rinschen MM, Grahammer F, Hoppe AK, et al. Yap-mediated mechanotransduction determines the podocyte's response to damage[J]. Sci Signal, 2017, 10(474): eaaf8165.
36. Chen J, Harris RC. Interaction of the egf receptor and the hippo pathway in the diabetic kidney[J]. J Am Soc Nephrol, 2016, 27(6): 1689-1700.
37. Makita R, Uchijima Y, Nishiyama K, et al. Multiple renal cysts, urinary concentration defects, and pulmonary emphysematous changes in mice lacking taz[J]. Am J Physiol Renal Physiol, 2008, 294(3): F542-553.
38. Hossain Z, Ali SM, Ko HL, et al. Glomerulocystic kidney disease in mice with a targeted inactivation of wwtr1[J]. Proc Natl Acad Sci U S A, 2007, 104(5): 1631-1636.
39. Saadi-Kheddouci S, Berrebi D, Romagnolo B, et al. Early development of polycystic kidney disease in transgenic mice expressing an activated mutant of the beta-catenin gene[J]. Oncogene, 2001, 20(42): 5972-5981.
40. Varelas X, Miller BW, Sopko R, et al. The hippo pathway regulates wnt/beta-catenin signaling[J]. Developmental Cell, 2010, 18(4): 579-591.
41. 贺靓靓, 胡文娟, 梅长林, 等. Hippo通路在常染色体显性多囊肾病中的作用[J]. 中华肾脏病杂志, 2015, 31(3): 227-232.
HE Liangliang, HU Wenjuan, MEI Changlin, et al. Role of Hippo pathway in autosomal dominant polycystic kidney disease[J]. Chinese Journal of Nephrology, 2015, 31(3): 227-232.
42. Yu FX, Zhao B, Guan KL. Hippo pathway in organ size control, tissue homeostasis, and cancer[J]. Cell, 2015, 163(4): 811-828.

本文引用： 郑志煌, 张志刚, 吴慧娟, 刘军. Hippo信号通路与肾病[J]. 临床与病理杂志, 2017, 37(7): 1518-1523. doi: 10.3978/j.issn.2095-6959.2017.07.034

Cite this article as: ZHENG Zhihuang, ZHANG Zhigang, WU Huijuan, LIU Jun. Hippo signaling pathway in kidney diseases[J]. Journal of Clinical and Pathological Research, 2017, 37(7): 1518-1523. doi: 10.3978/j.issn.2095-6959.2017.07.034