综述

Hippo通路与肿瘤相关性研究进展

史梦婕 邵松军 李洁媚 周艳芳* 黄培春*

(广东医学院病理生理教研室, 湛江 524023)

摘要 Hippo通路对控制组织器官大小以及细胞增殖、凋亡有着重要的调节作用。研究表明, Yes相关蛋白作为Hippo通路转录共激活因子, 参与了肿瘤的发生发展过程, 其过表达可促进细胞的恶性转化。研究Hippo通路在癌症发生发展中的作用及机制将为肿瘤的预防和治疗提供新的思路。

关键词 Hippo通路; YAP; 肝癌; 肺癌; 卵巢癌

The Advances in Hippo Pathway Association with Cancer

Shi Mengjie, Shao Songjun, Li Jiemei, Zhou Yanfang*, Huang Peichun*

(*Department of Pathophysiology, Guangdong Medical College, Zhanjiang 524023, China*)

Abstract The Hippo pathway is important for the regulation of organ size, cell proliferation and apoptosis. In recent studies, YAP (Yes-associated protein), as a transcription co-activator of the Hippo pathway, is involved in the development of tumor, and its overexpression promotes cell malignant transformation. Understanding the relationship between the Hippo pathway and cancer can provide a new perspective for the prevention and treatment of cancer.

Key words Hippo pathway; YAP; hepatocellular carcinoma; lung cancer; ovarian cancer

Hippo通路在果蝇功能遗传筛选的研究中被首次发现, 是一个高度保守的信号传导通路, 具有调节器官大小、维持细胞增殖凋亡的动态平衡等功能。Hippo通路异常, 细胞将过度增殖或凋亡不足, 器官过度增生, 最终导致肿瘤的发生发展[1]。

1 Hippo通路

KIBRA、WILLIN、神经纤维瘤蛋白2(neurofibromin2, NF2)[2]已确定为Hippo通路的上游信号分子, 调控Hippo信号通路, 肝脏条件性敲除NF2的小鼠发生肝癌、胆管癌及胆管错构瘤的几率大大增加[3]。此外, 上游信号分子非典型钙黏素FAT、DACHS也可影响哺乳动物Hippo信号通路, 但具体机制尚不清楚。最近发现, G蛋白偶联受体[4]也作为上游信号分子调控Hippo通路: 溶血磷脂酸(lysophosphatidic acid, LPA)作用G12/G13偶联受体抑制LATS1/2激酶, 从而激活YAP/TAZ, 促进细胞增殖和转移。

核心激酶链是人类Hippo信号通路的主要成分, 它包括MST1/2(mammalian STE20-like protein kinase)、LATS1/2(large tumor suppressor 1/2)、SAV1(human Salvador homology 1)及MOB(MOB kinase activator)。

Yes相关蛋白(Yes-associated protein, YAP)为Hippo通路的转录共激活因子, 定位于人类染色体11q22, 目

收稿日期: 2013-08-20 接受日期: 2013-12-23

广东省教育厅重点学科建设基金(批准号: GX9404)资助的课题

*通讯作者。Tel: 0769-22896332, Email: fangfang772003@163.com, huangpc@gdmc.edu.cn

Received: August 20, 2013 Accepted: December 23, 2013

This work was supported by the Fund for Key Discipline Construction, Guangdong Provincial Department of Education (Grant No.GX9404)

*Corresponding author. Tel: +86-769-22896332, Email: fangfang772003@163.com, huangpc@gdmc.edu.cn

网络出版时间: 2014-03-03 12:28 URL: http://www.cnki.net/kcms/doi/10.11844/cjcb.2014.03.0267.html

前被人们认定为候选癌基因[5], 通过增强转录因子的活性促进基因表达。YAP有两种表达亚型: YAP1及YAP2。另外, TAZ(transcriptional co-activator with PDZ-binding motif)与YAP同源, 其功能表达与YAP相似。

上游信号分子作用下激活MST1/2, 后者与调节蛋白SAV1结合, 磷酸化LATS1/2、MOB, 活化的LATS1/2直接磷酸化YAP/TAZ, 使之与14-3-3蛋白结合停滞于细胞质内, 抑制转录[6]。若信号通路被阻断或失活, 未磷酸化的YAP/TAZ则由细胞质转入胞核, 与TEADs(TEA domain family members)结合促进基因转录, 诱导上皮间质细胞转化, 增强细胞增殖、转移和侵袭能力。除了结合TEADs外, YAP /TAZ还可以与其他转录因子结合, 如Smad、Runx1/2、p63/p73、ErbB4、Omerovic等[7](图1), 最终参与细胞增殖与分化。研究发现, 结缔组织生长因子(connective tissue growth factor, CTGF)、脑源性神经营养因子、纤维母细胞生长因子1等多种细胞因子可作为Hippo通路的下游底物被YAP刺激上调。*CTGF*可作为YAP直接作用的靶基因, 促使细胞增殖和锚定非依赖性生长[8]。

2 Hippo通路的调节作用

正常机体环境下, 高细胞浓度诱导YAP磷酸化水平上升, 增强细胞间接触抑制[10]; 上游调控因子NF2缺失或YAP过度表达可促使细胞克服接触抑制, 促进增殖。近年研究显示, 14-3-3蛋白介导α-Catenin与YAP的WW结构域结合, YAP S127位点磷酸化影响细胞的黏附连接[11]。而细胞脱离通过细胞骨架重组激活LATS1/2, 导致YAP磷酸化, 诱导失巢凋亡[12]。

LATS1/2激酶负性调节细胞分裂: LATS2可抑制细胞G_1到S期的转换[14], LATS1/2过度表达导致细胞G_2/M期停滞[13]。MST2介导的NDR1(nuclear Dbf2-related protein kinase 1)对细胞有丝分裂染色体排列的保真度至关重要, MST2的缺失导致染色体错位[15]。MST1通过限制Aurora B激酶活性, 促进动粒–微管联接的稳定性, 确保染色体集合和正确分离[16]。

3 Hippo通路与肿瘤

Hippo通路通过抑制细胞增殖和促进凋亡的方式限制组织器官的大小, 抑制肿瘤的形成。Hippo通

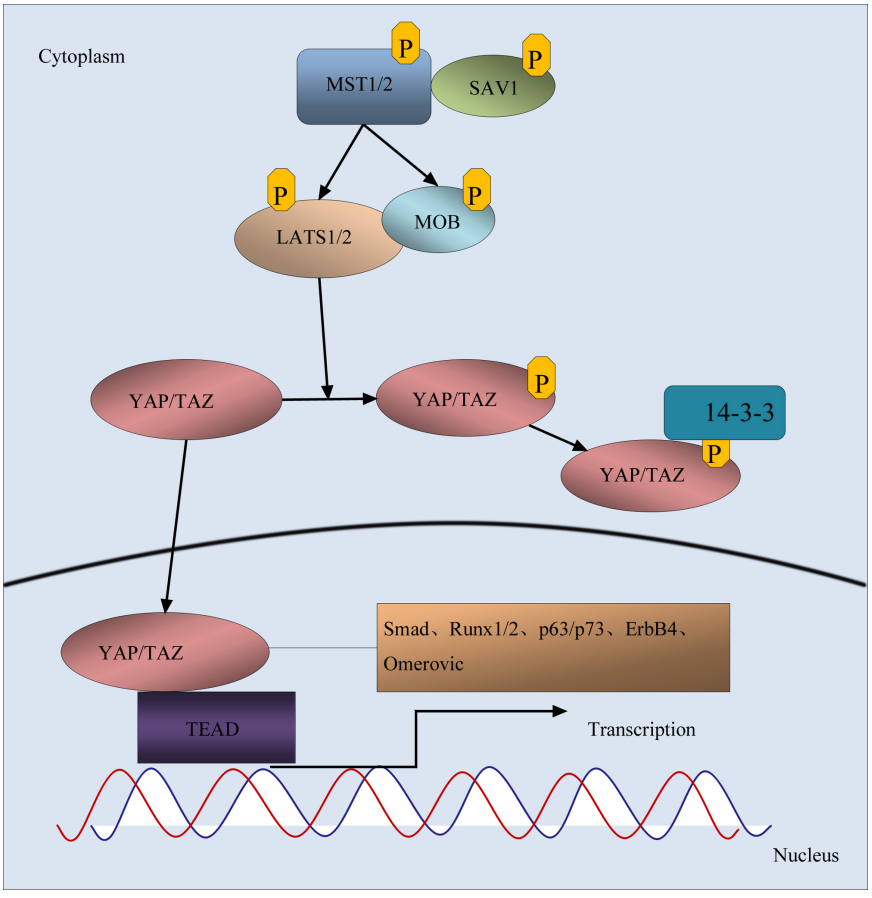

图1 Hippo通路的激酶级联反应(根据参考文献[9]修改)

Fig.1 Kinase cascade of Hippo pathway (modified from reference [9])

路的异常调节参与人类多种肿瘤的发生发展, 如乳腺癌、结肠癌、卵巢浆液性囊腺癌[17]、肺癌[18]、食管鳞状细胞癌[19]。

3.1 对细胞增殖的影响

Kim等[20]应用免疫组织化学方法检测非小细胞肺癌(non-small cell lung cancer, NSCLC)病例中YAP的表达情况。结果显示, 肺腺癌中胞核内YAP呈高表达, 并与cyclinA、丝裂原活化蛋白激酶(mitogen activated protein kinase, MAPK)表达正相关; 鳞癌病理TNM分期I期中, 胞质内YAP表达高于II~IV期。提示胞核内YAP高表达与细胞周期进程联系紧密, 促进肺腺癌细胞增殖, 而胞质内YAP高度表达可作为临床病理分期分级的一个独立预测指标, YAP的亚细胞定位可能通过不同途径影响肿瘤及其亚型的发生发展。肺腺癌A549细胞系转染*MST1*基因后, 细胞生长抑制, 其抗增殖能力与YAP磷酸化相关[21]。

Diep等[22]通过免疫组化等方法观察到, YAP1在胰腺癌BxPC-3、PANC-1细胞胞核内表达显著增加, 而在HPDE6细胞中其表达随着细胞密度增加而减少。用siRNA干扰*YAP1*基因表达后, BxPC-3、PANC-1细胞增殖被抑制。结果说明, YAP1参与胰腺癌发生发展, 在胰腺癌细胞的增殖和集落形成中起着重要作用。

胆汁淤积所致的肝损伤中, YAP高表达促进肝细胞及胆管上皮细胞增殖, 从而减轻机体损伤; 条件性敲除*YAP*基因后, 肝细胞增殖抑制, 甚至发生坏死[23]。Anakk等[24]进一步发现, 高浓度胆汁酸可作为Hippo通路上游激活物, 促进支架蛋白IQGAP1表达, 并激活YAP转录活性, 刺激肝脏增长及肿瘤的发生。

Hippo通路功能障碍同样也影响了胃癌的发生发展。在正常胃黏膜、胃黏膜肠上皮化生及胃癌组织中, MST1/2与LATS1的表达明显降低, 伴淋巴结转移的胃癌组织中LATS1表达明显低于无转移的胃癌组织, 提示Hippo通路功能障碍可能引发胃癌的增殖及转移[25]。*Mst1/2*基因敲除的转基因小鼠研究发现, YAP1在结肠组织中磷酸化水平降低, 核表达明显增加, 而且YAP表达的降低抑制Wnt/Notch信号通路、细胞增殖和存活。这证明MST1/2能抑制YAP的表达活性, 而YAP1过量表达将致使结肠癌的发生[26]。采用芯片检测及shRNA基因敲除等实验方法证明[27], β-连环蛋白/TCF4复合体与*YAP*基因增强子结合促进YAP在结肠癌细胞中的表达。Wierzbicki等[28]通过甲基化特异性PCR技术对140例大肠癌组织及40例正常肠组织分析显示, LATS1在癌组织中低表达, 并与其启动子甲基化相关。

研究还发现, LATS1可由泛素连接酶E3 WWP1多聚泛素化修饰后降解[29], WWP1介导的LATS低表达可促使乳腺癌细胞的增殖。肾结核蛋白4(nephrocystin protein 4, NPHP4)与LATS结合负性调控TAZ磷酸化[30], 而同一NPH家族的NPHP9表现了相反的作用, 其直接结合TAZ, 诱导TAZ/NPHP9复合体核易位, 表现TAZ癌基因的特性, 下调NPHP9可抑制正常上皮细胞和乳腺癌细胞增殖。

Li等[31]确立了LATS2下调的一个新机制: 前列腺癌细胞中, FOXP3识别基序与LATS2启动子结合促进LATS2转录, 而FOXP3缺失造成了LATS2缺陷表达, 成为前列腺癌细胞YAP蛋白升高的主要决定因素。

3.2 对细胞凋亡的影响

Bai等[32]发现肝细胞癌(hepatocellular carcinoma, HCC)及肝内胆管细胞癌(intrahepatic cholangiocarcinoma, ICC)细胞核内富含YAP及凋亡蛋白抑制因子survivin呈高表达, 且*survivin* mRNA表达依赖于YAP蛋白。MST1转染HepG2细胞后, MST1过表达及YAP磷酸化, *ETGF*、双调蛋白(amphiregulin, *AREG*)、*survivin*等mRNA表达下调, 细胞增殖抑制, 并发生凋亡[33]。Wang等[34]发现, TAZ在肺腺癌A549细胞系内过表达, 敲除*TAZ*基因后, cyclinA、CTGF表达明显下降, 细胞周期停滞在G_0~G_1期, 细胞增殖受到抑制, 紫杉醇诱导的凋亡、caspase3表达显著增加; 而*TAZ*基因转染后的表达结果与之相反, 显示TAZ促进细胞增殖、抑制其凋亡的能力。

3.3 对细胞迁移侵袭的影响

YAP/TAZ活性增强可促进肿瘤细胞迁移。Hall等[35]发现, 卵巢癌患者的YAP表达水平与生存期相关; 胞核YAP过表达及胞质磷酸化YAP低表达的患者中, 约50%的患者生存期少于5年。此外, 卵巢癌上皮细胞YAP2表达于卵巢表面上皮细胞和卵巢癌上皮细胞。YAP2过表达和YAP2-5SA位点去磷酸化使其永久性增生, 抵抗顺铂介导的细胞凋亡, 促进细胞迁移; *YAP*基因敲除则增加了细胞对顺铂介导凋亡的敏感性。Cai等[36]发现一个新的信号传导通路与LPA介导卵巢癌细胞迁移相关。这个信号通路依赖多个调节因子的参与: LPA3、G13、Rho/Rock、

PP1A、AREG、表皮生长因子。LPA诱导YAP去磷酸化, 使其在细胞核积聚, 参与卵巢癌细胞迁移和侵袭。siRNA干扰*YAP*基因表达后, YAP蛋白表达下降, LPA诱导的卵巢癌细胞转移和侵袭能力也显著下降。

Lamar等[37]基于Luminex技术的多重检测方法证实, TEAD结合域在YAP介导肿瘤生长和转移中必不可少, 而非WW结构域或PDZ结合基序。转移性乳腺癌的侵袭能力与TEAD转录活性密切相关。YAP/TEAD转录活性增强, 导致非转移性NMuMG细胞、67NR细胞、A375细胞原发部位转移。TAZ在乳腺癌过表达, 调节细胞增殖、迁移及上皮间充质转化。Lai等[38]利用野生型*TAZ*基因转染MCF10A细胞发现, TAZ/TEAD可增加BMP4(bone morphogenetic protein 4)启动子活性, 活化的BMP4亦同时提高TAZ表达活性。通过Western blot及伤口愈合分析, TAZ过表达可诱导细胞迁移及pSmad1/5表达活性的增加, 而敲除*BMP4*基因后, 细胞迁移能力显著降低。

3.4 Hippo通路与多通路间的作用

多信号通路的相互联系、相互作用构建了极为复杂的细胞信号传递网络, 其维持并影响正常机体的生长发育及生命活动。

Wnt经典途径中, β-catenin突变或稳定性增加与恶性肿瘤发病密切相关。磷酸化YAP的TEAD结合域可与β-catenin的N端直接结合, 调控β-catenin核转位, 提示Hippo通路可拮抗Wnt通路信号传导[39]。

在Hippo通路及TGF-β通路对肿瘤发生发展的作用研究中发现, Smad3/YAP/TEAD/p300可形成复合体[40], 提高CTGF表达活性, 促进恶性间质细胞瘤细胞增殖及细胞外基质分泌。研究还发现, EGFR通路激活促进肝癌细胞内CTGF表达的过程亦通过YAP/TEAD介导[41]。

另外, Tschaharganeh等[42]发现肝癌内Notch配体Jagged-1可被YAP正性调节。YAP S127位点突变可促使TEAD4过表达, Jag-1表达上调, 激活Notch信号通路, 促进肝癌细胞增殖。同时, 在肝癌、胰腺癌及大肠癌中YAP/Jagged-1表达与β-catenin的表达并无相关性, 提示YAP及Notch抑制剂可为胃肠道肿瘤提供新的临床治疗手段。

4 Hippo通路作为治疗靶点的介绍和展望

Hippo通路核心成分LATS、MST低表达及YAP的高表达, 已在多种肿瘤的相关研究中得以证实。YAP表达与HCC低分化及血清甲胎蛋白水平相关[43], 可作为肝癌潜在的临床治疗靶点和独立预后指标, 对预测HCC复发及生存率都具有指示性意义。抑癌因子MST1在NSCLC[21]、HCC[33]中过表达增加顺铂的化疗敏感性, 表明MST1可作为临床抗肿瘤药物应用的新靶点。因此, 深入了解Hippo通路的调控机制, 将为临床新靶点治疗药物的设计提供新的思路和方法, 对肿瘤的诊断及防治有着重要意义。

参考文献 (References)

1 Huang J, Wu S, Barrera J, Matthews K, Pan D. The Hippo signaling pathway coordinately regulates cell proliferation and apoptosis by inactivating Yorkie, the *Drosophila* Homolog of YAP. Cell 2005; 122(3): 421-34.

2 Harvey KF, Zhang X, Thomas DM. The Hippo pathway and human cancer. Nat Rev Cancer 2013; 13(4): 246-57.

3 Zhang N, Bai H, David KK, Dong J, Zheng Y, Cai J, *et al*. The Merlin/NF2 tumor suppressor functions through the YAP oncoprotein to regulate tissue homeostasis in mammals. Dev Cell 2010; 19(1): 27-38.

4 Yu FX, Zhao B, Panupinthu N, Jewell JL, Lian I, Wang LH, *et al*. Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. Cell 2012; 150(4): 780-91.

5 Overholtzer M, Zhang J, Smolen GA, Muir B, Li W, Sgroi DC, *et al*. Transforming properties of YAP, a candidate oncogene on the chromosome 11q22 amplicon. Proc Natl Acad Sci USA 2006; 103(33): 12405-10.

6 Dong J, Feldmann G, Huang J, Wu S, Zhang N, Comerford SA, *et al*. Elucidation of a universal size-control mechanism in Drosophila and mammals. Cell 2007; 130(6): 1120-33.

7 Yu FX, Guan KL. The Hippo pathway: Regulators and regulations. Genes Dev 2013; 27(4): 355-71.

8 Zhao B, Li L, Lei Q, Guan KL. The Hippo-YAP pathway in organ size control and tumorigenesis: An updated version. Genes Dev 2010; 24(9): 862-74.

9 Zhao B, Lei QY, Guan KL. The Hippo-YAP pathway: New connections between regulation of organ size and cancer. Curr Opin Cell Biol 2008; 20(6): 638-46.

10 Zhao B, Wei X, Li W, Udan RS, Yang Q, Kim J, *et al*. Inactivation of YAP oncoprotein by the Hippo pathway is involved in cell contact inhibition and tissue growth control. Genes Dev 2007; 21(21): 2747-61.

11 Schlegelmilch K, Mohseni M, Kirak O, Pruszak J, Rodriguez JR, Zhou D, *et al*. Yap1 acts downstream of alpha-catenin to control epidermal proliferation. Cell 2011; 144(5): 782-95.

12 Zhao B, Li L, Wang L, Wang CY, Yu J, Guan KL. Cell detachment activates the Hippo pathway via cytoskeleton reorganization to induce anoikis. Genes Dev 2012; 26(1): 54-68.

13 Yabuta N, Okada N, Ito A, Hosomi T, Nishihara S, Sasayama Y, *et al*. Lats2 is an essential mitotic regulator required for the coordination of cell devision. J Biol Chem 2007; 282(26): 19259-71.

14 Li Y, Pei J, Xia H, Ke H, Wang H, TaoW. Lats2, a putative tumor suppressor, inhibits G_1/S transition. Oncogene 2003; 22(28): 4398-405.

15 Chiba S, Ikeda M, Katsunuma K, Ohashi K, Mizuno K. MST2- and Furry-mediated activation of NDR1 kinase is critical for precise alignment of mitotic chromosomes. Curr Biol 2009; 19(8): 675-81.
16 Oh HJ, Kim MJ, Song SJ, Kim T, Lee D, Kwon SH, *et al*. MST1 limits the kinase activity of aurora B to promote stable kinetochore-microtubule attachment. Curr Biol 2010; 20(5): 416-22.
17 Steinhardt AA, Gayyed MF, Klein AP, Dong J, Maitra A, Pan D, *et al*. Expression of Yes-associated protein in common solid tumors. Hum Pathol 2008; 39(11): 1582-9.
18 Wang Y, Dong Q, Zhang Q, Li Z, Wang E, Qiu X. Overexpression of yes-associated protein contributes to progression and poor prognosis of non-small-cell lung cancer. Cancer Sci 2010; 101(5): 1279-85.
19 Muramatsu T, Imoto I, Matsui T, Kozaki K, Haruki S, Sudol M, *et al*. YAP is a candidate oncogene for esophageal squamous cell carcinoma. Carcinogenesis 2011; 32(3): 389-98.
20 Kim JM, Kang DW, Long LZ, Huang SM, Yeo MK, Yi ES, *et al*. Differential expression of Yes-associated protein is correlated with expression of cell cycle markers and pathologic TNM staging in non-small-cell lung carcinoma. Hum Pathol 2011; 42(3): 315-23.
21 Xu CM, Liu WW, Liu CJ, Wen C, Lu HF, Wan FS. Mst1 overexpression inhibited the growth of human non-small cell lung cancer *in vitro* and *in vivo*. Cancer Gene Ther 2013; 20(8): 453-60.
22 Diep CH, Zucker KM, Hostetter G, Watanabe A, Hu C, Munoz RM, *et al*. Down-regulation of Yes associated protein 1 expression reduces cell proliferation and clonogenicity of pancreatic cancer cells. PLoS One 2012; 7(3): e32783.
23 Bai H, Zhang N, Xu Y, Chen Q, Khan M, Potter JJ, *et al*. Yes-associated protein regulates the hepatic response after bile duct ligation. Hepatology 2012; 56(3): 1097-107.
24 Anakk S, Bhosale M, Schmidt VA, Johnson RL, Finegold MJ, Moore DD. Bile acids activate YAP to promote liver carcinogenesis. Cell Rep 2013; 5(4): 1060-9.
25 Xu ZP, Zhu JS, Zhang Q, Wang XY. A breakdown of the Hippo pathway in gastric cancer. Hepatogastroenterology 2011; 58(110/111): 1611-7.
26 Zhou D, Zhang Y, Wu H, Barry E, Yin Y, Lawrence E, *et al*. Mst1 and Mst2 protein kinases restrain intestinal stem cell proliferation and colonic tumorigenesis by inhibition of Yes-associated protein (Yap) overabundance. Proc Natl Acad Sci USA 2012; 108(49): 1312-20.
27 Konsavage WM Jr, Kyler SL, Rennoll SA, Jin G, Yochum GS. Wnt/beta-catenin signaling regulates Yes-associated protein (YAP) gene expression in colorectal carcinoma cells. J Biol Chem 2012; 287(15): 11730-9.
28 Wierzbicki PM, Adrych K, Kartanowicz D, Stanislawowski M, Kowalczyk A, Godlewski J, *et al*. Underexpression of LATS1 TSG in colorectal cancer is associated with promoter hypermethylation. World J Gastroentero 2013; 19(27): 4363-73.
29 Yeung B, Ho KC, Yang X. WWP1 E3 ligase targets LATS1 for ubiquitin-mediated degradation in breast cancer cells. PLoS One 2013; 8(4): e61027.
30 Habbig S, Bartram MP, Sagmuller JG, Griessmann A, Franke M, Muller RU, *et al*. The ciliopathy disease protein NPHP9 promotes nuclear delivery and activation of the oncogenic transcriptional regulator TAZ. Hum Mol Genet 2012; 21(26): 5528-38.
31 Li W, Wang L, Katoh H, Liu R, Zheng P, Liu Y. Identification of a tumor suppressor relay between the FOXP3 and the Hippo pathways in breast and prostate cancers. Cancer Res 2011; 71(6): 2162-71.
32 Bai H, Gayyed MF, Lam-Himlin DM, Klein AP, Nayar SK, Xu Y, *et al*. Expression of Yes-associated protein modulates Survivin expression in primary liver malignancies. Hum Pathol 2012; 43(9): 1376-85.
33 Xu C, Liu C, Huang W, Tu S, Wan F. Effect of Mst1 overexpression on the growth of human hepatocellular carcinoma HepG2 cells and the sensitivity to cisplatin *in vitro*. Acta Biochim Biophys Sin 2013; 45(4): 268-79.
34 Wang L, Chen Z, Wang Y, Chang D, Su L, Guo Y, *et al*. WWTR1 promotes cell proliferation and inhibits apoptosis through cyclin A and CTGF regulation in non-small cell lung cancer. Tumour Biol 2013; 35(1): 463-8.
35 Hall CA, Wang R, Miao J, Oliva E, Shen X, Wheeler T, *et al*. Hippo pathway effector Yap is an ovarian cancer oncogene. Cancer Res 2010; 70(21): 8517-25.
36 Cai H, Xu Y. The role of LPA and YAP signaling in long-term migration of human ovarian cancer cells. Cell Commun Signal 2013; 11(1): 31.
37 Lamar JM, Stern P, Liu H, Schindler JW, Jiang ZG, Hynes RO. The Hippo pathway target, YAP, promotes metastasis through its TEAD-interaction domain. Proc Natl Acad Sci USA 2012; 109(37): 2441-50.
38 Lai D, Yang X. BMP4 is a novel transcriptional target and mediator of mammary cell migration downstream of the Hippo pathway component TAZ. Cell Signal 2013; 25(8): 1720-8.
39 Imajo M, Miyatake K, Iimura A, Miyamoto A, Nishida E. A molecular mechanism that links Hippo signalling to the inhibition of Wnt/beta-catenin signalling. EMBO J 2012; 31(5): 1109-22.
40 Fujii M, Toyoda T, Nakanishi H, Yatabe Y, Sato A, Matsudaira Y, *et al*. TGF- synergizes with defects in the Hippo pathway to stimulate human malignant mesothelioma growth. J Exp Med 2012; 209(3): 479-94.
41 Urtasun R, Latasa MU, Demartis MI, Balzani S, Goni S, Garcia-Irigoyen O, *et al*. Connective tissue growth factor autocriny in human hepatocellular carcinoma: Oncogenic role and regulation by epidermal growth factor receptor/yes-associated protein-mediated activation. Hepatology 2011; 54(6): 2149-58.
42 Tschaharganeh DF, Chen X, Latzko P, Malz M, Gaida MM, Felix K, *et al*. Yes-associated protein up-regulates Jagged-1 and activates the Notch pathway in human hepatocellular carcinoma. Gastroenterology 2013; 144(7): 1530-42.
43 Xu MZ, Yao TJ, Lee NP, Ng IO, Chan YT, Zender L, *et al*. Yes-associated protein is an independent prognostic marker in hepatocellular carcinoma. Cancer 2009; 115(19): 4576-85.