[1]陈柯宏,李兴森,何江,等.LATS1基因去甲基化对人肾癌细胞生物学功能及其Hippo-YAP信号通路的影响[J].第三军医大学学报,2014,36(12):1249-1254.

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《第三军医大学学报》[ISSN:1000-5404/CN:51-1095/R] 卷：36 期数：2014年第12期 页码：1249-1254 栏目：论著 出版日期：2014-06-30

Title: Effects of LATS1 gene demethylation on biological function and Hippo-YAP signaling pathway in human renal cell carcinoma cell line

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关键词：肾细胞癌；去甲基化；Hippo-YAP；大肿瘤抑制基因1；Yes-相关蛋白

Keywords: renal cell carcinoma; demethylation; Hippo-YAP; ; large tumor suppressor gene 1; YAP

分类号：R394.3，R730.23，R737.11

文献标志码：A

摘要：目的 探讨LATS1基因去甲基化对人肾癌细胞生物学功能及其Hippo-YAP信号通路的影响。 方法 利用RT-PCR检测人肾透明细胞癌细胞系786-O和人胚肾细胞系HEK-293中Hippo-YAP信号通路大肿瘤抑制基因1（large tumor suppressor gene 1，LATS1）mRNA和下游癌基因Yes-相关蛋白（yes-associated protein，YAP）mRNA的表达水平，用亚硫酸氢盐测序法(bisulfite sequence-PCR，BSP)对LATS1低表达细胞786-O进行甲基化分析，5-氮杂-2脱氧胞苷(5-aza-2′-deoxycytidine，DAC)处理786-O和HEK-293后，用RT-PCR、Western blot检测各组细胞LATS1和YAP的mRNA和蛋白表达水平，流式细胞术检测各组细胞凋亡和周期，CCK-8检测各组细胞增殖抑制情况。 结果 786-O较HEK-293 LATS1 mRNA 表达水平显著降低（$P<0.05$），YAP mRNA表达水

更新日期/Last Update: 2014-06-20

平显著升高（P<0.05），BSP显示LATS1在人肾癌细胞系786-O中高度甲基化；DAC处理786-O后，LATS1 mRNA和蛋白表达水平显著升高（P<0.05），YAP mRNA和蛋白表达水平显著降低（P<0.05），周期停滞在G_0/G_1期（P<0.05）、细胞增殖受到明显抑制（P<0.05）、细胞凋亡显著增加（P<0.05），而HEK-293组均无明显变化（P>0.05）。 结论 LATS1基因去甲基化后下调YAP基因表达，抑制786-O细胞增殖并诱导其凋亡。LATS1基因甲基化在肾癌发生中起重要作用。

Abstract: Objective To investigate the effects of large tumor suppressor gene 1 (LATS1) demethylation on the biological function and Hippo-YAP signaling pathway in human renal cell carcinoma (RCC) cells. Methods The mRNA expression levels of LATS1 and downstream gene YAP of Hippo-YAP signaling pathway were detected by RT-PCR in human clear cell RCC cell line 786-O and human embryonic kidney cell line HEK-293. The methylation of 786-O cells with low LATS1 expression was analyzed by bisulfite sequence-PCR (BSP). After 786-O and HEK-293 cells were treated by 5-aza-2′-deoxycytidine (DAC), the mRNA and protein levels of LATS1 and YAP were detected by RT-PCR and Western blotting in each group. Cell apoptosis and cell cycle were detected by flow cytometry (FCM). The cell proliferation inhibition was detected by cell proliferation and toxicity detection reagent (CCK-8). Results Compared with the HEK-293 cells, the mRNA expression level of LATS1 was significantly decreased (P<0.05), while that of YAP was markedly increased (P<0.05) in the 786-O cells. LATS1 was highly methylated in the 786-O cells as proven by BSP. After DAC treatment in the 786-O cells, the mRNA and protein expression levels of LATS1 were dramatically increased (P<0.05), but those of YAP were significantly decreased (P<0.05). Cell cycle was arrested in G_0/G_1 phase (P<0.05) and cell proliferation was obviously inhibited (P<0.05). Cell apoptosis was increased significantly (P<0.05). In the HEK-293 cells, however, those above-mentioned changes were insignificant (P>0.05). Conclusion The demethylation of LATS1 gene down- regulates the expression of YAP gene, inhibits the cell proliferation of 786-O cells and induces apoptosis. The methylation of LATS1 gene may contribute greatly to the occurrence of RCC.

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