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熊果酸对肝星状细胞NADPH 氧化酶-Hedgehog 信号通路的影响

《第三军医大学学报》[ISSN:1000-5404/CN:51-1095/R] 卷: 36 期数: 2014年第05期 页码: 427-431 栏目: 论著 出版日期: 2014-03-15

Title: Ursolic acid suppressed NADPH oxidase-Hedgehog signaling pathway in hepatic stellate cells *in vitro*

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关键词: 熊果酸; 肝星状细胞; Hedgehog信号通路; NADPH氧化酶; Rac1

Keywords: ursolic acid; hepatic stellate cells; Hedgehog signal pathway; NADPH oxidase; Rac1

分类号: R285.5; R322.47; R329.26

文献标志码: A

摘要: 目的 探讨熊果酸（ursolic acid，UA）对大鼠肝星状细胞（HSC-T6）的NADPH氧化酶（NOX）-Hedgehog（Hh）信号通路的影响。 方法 将处于对数生长期的HSC-T6细胞分为6组：正常对照组、瘦素组（100 ng/mL）、熊果酸自身对照组（50 μmol/L）、DPI自身对照组（20 μmol/L）、熊果酸干预组（瘦素+熊果酸）、DPI干预组（瘦素+DPI）。在药物作用12 h后，提取总RNA，采用RT-PCR法检测Shh、Smo、Gli1/2的表达；药物作用HSC-T6 细胞24 h后，提取总蛋白，采用Western blot分别检测Rac1和Gli2的表达；药物作用12、24、48 h后，采用MTT法检测HSC-T6细胞的增殖情况。 结果 RT-PCR分析显示，瘦素刺激HSC-T6细胞12 h后Smo mRNA表达较正常对照组升高（P<0.05）；Shh、Gli2 mRNA表达稍高于正常对照组，但差异无统计学意义（P>0.05）； 熊果酸干预后Shh、Smo和Gli2 mRNA表达明显低于瘦素组及正常对照组（均P<0.05）；瘦素对HSC-T6细胞Gli1 mRNA的表达无影响，而熊果酸及DPI干预也不影响HSC-T6细胞Gli1 mRNA 的表达。瘦素刺激HSC-T6细胞24 h后，Rac1和 Gli2蛋白的表达较正常对照组升高（P<0.01）；熊果酸干预后Rac1和Gli2蛋白的表达明显低于瘦素组（P<0.01）。MTT分析显示瘦素促进HSC-T6细胞增殖，熊果酸干预12 h后HSC-T6细胞的生长抑制率均显著高于瘦素组（P<0.01），随着作用时间延长，熊果酸对细胞生长的抑制作用进一步增强。 结论 熊果酸能抑制瘦素诱导的HSC-T6细胞Hh信号通路Shh、Smo、Gli2 mRNA和 Gli2蛋白表达。熊果酸通过抑制NOX亚基Rac1蛋白表达进而抑制Hh信号通路可能是它抑制肝星状细胞生长增殖的机制之一。

Abstract: Objective To determine the effect of ursolic acid (UA) on NADPH oxidase (NOX)- Hedgehog (Hh) signaling pathway in hepatic stellate cells（HSCs）. Methods Culture-activated HSC-T6 cells were divided into 6 groups: normal control group, leptin group (100 ng/mL), UA group (50 μmol/L), NOX inhibitor DPI (20 μmol/L) group, and the 2 intervention groups pretreated with UA or DPI followed by stimulation with leptin for different times. The mRNA expression of Shh, Smo and Gli1/2 was detected in above cells after 12 hours' treatment by RT-PCR. The protein expression of Rac1 and Gli2 were analyzed in the cells in 24 h of treatment by Western blotting. The proliferation of HSC-T6 cells was detected in 12, 24 and 48 h after treatment by MTT assay. Results RT-PCR analysis showed that Smo mRNA expression was increased when leptin stimulated HSC-T6 cells for 12 h (P<0.05). The expression of Shh and Gli2 mRNA was also increased compared with normal control group, but without significant difference. UA pretreatment significantly down-regulated the mRNA expression of Shh, Smo and Gli2

compared with control and leptin group (all $P<0.05$). Leptin, UA and DPI had no effect on Gli1 mRNA expression. The protein expression of Rac1 and Gli2 was increased when leptin stimulated HSC-T6 cells for 24 h ($P<0.01$). UA pretreatment significantly down-regulated Rac1 and Gli2 protein expression compared with leptin group (all $P<0.01$). MTT assay showed that leptin promoted the proliferation in HSC-T6 cells. After 12 hours' pretreatment with UA, the cell growth was inhibited significantly than in leptin treated cells ($P<0.01$) in a time-dependent manner. Conclusion UA inhibits the expression of Shh, Smo, Gli2 mRNA and down-regulates the expression of Gli2 protein in HSC-T6 cells. One mechanism of UA inhibiting cell proliferation is probably *via* its inhibiting NOX subunit Rac1 and then NOX-Hh signaling pathway.

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更新日期/Last Update: 2014-03-03