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摘要:

目的: 观察人胃癌、癌旁组织与胃癌AGS细胞中人音猬因子相互作用蛋白(human hedgehog interacting protein, HHIP)基因启动子区域CpG岛的甲基化水平, 探索其与胃癌发生的关系。方法: RT-PCR检测30例人胃癌组织、癌旁组织及AGS细胞中HHIP mRNA的表达, 免疫组织化学方法和甲基化特异性PCR(methylation specific PCR, MSP)分别检测胃癌组织和癌旁组织的HHIP表达和HHIP基因启动子区域甲基化状态。AGS细胞予甲基化转移酶抑制剂5-氮杂-2'-脱氧胞苷(5-Aza-2'-deoxycytidine, 5-Aza-dc)处理前后, RT-PCR、MSP和硫化测序PCR(bisulfite sequencing PCR, BSP)分别检测AGS细胞中HHIP mRNA表达、启动子区域甲基化水平变化、CpG岛甲基化位点数量的变化; 分析HHIP基因启动子区CpG岛甲基化水平变化与HHIP mRNA表达水平变化之间的相关性。结果: 胃癌组织中的HHIP mRNA ( $0.82 \pm 0.38$  vs  $1.60 \pm 0.26$ ,  $P=0.000$ )和蛋白 ( $0.51 \pm 0.03$  vs  $0.83 \pm 0.27$ ,  $P<0.05$ )的表达均低于癌旁组织, 并且与年龄、性别、TNM分期、分化程度、淋巴结转移均无显著相关性(均 $P>0.05$ )。癌旁组织中HHIP基因启动子区甲基化水平显著低于胃癌和AGS细胞[( $17.7 \pm 3.59$ )% vs ( $62.9 \pm 6.14$ )%、( $99.7 \pm 0.67$ )%], 均 $P<0.05$ 。AGS细胞在5-Aza-dc干预后HHIP mRNA表达明显增高( $4.68 \pm 0.22$  vs  $0.21 \pm 0.12$ ,  $P<0.01$ ), HHIP基因启动子区甲基化水平明显下降[( $10.1 \pm 0.21$ )% vs ( $90.2 \pm 0.67$ )%],  $P<0.01$ 。CpG岛甲基化位点明显减少, 并且HHIP基因启动子区甲基化水平与mRNA表达呈负相关( $r=-0.693$ ,  $P=0.00$ )。结论: HHIP基因启动子区CpG岛的高甲基化水平可能通过抑制HHIP基因表达参与胃癌的发生。

关键词: [人音猬因子相互作用蛋白基因](#) [胃癌](#) [甲基化](#)

High methylation level of CpG island in HHIP gene participates in the occurrence of gastric cancer [Download Fulltext](#)

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Abstract:

Objective : To Observe the methylation level of CpG island in human hedgehog interacting protein (HHIP) gene in gastric cancer tissues, peritumoral tissues and AGS cells, and to explore the relationship between the methylation level of CpG island and the tumorigenesis of gastric cancer. Methods: The expressions of HHIP mRNA in 30 human gastric carcinnoma tissues, peritumoral tissues and gastric carcinoma AGS cells were detected by RT-PCR. The expressions of HHIP and the methylation level of promoter region of HHIP gene in gastric carcinoma tissues and peritumoral tissues were detected by immunohistochemical staining and methylation specific PCR (MSP), respectively. Before and after the treatment of methyl transferase inhibitor 5-Aza-2'-deoxycytidine (5-Aza-dc), the HHIP mRNA expression, methylation level of promoter region and methylation sites locus on CpG island in AGS cells were detected by RT-PCR, MSP and bisulfite sequencing PCR(BSP), respectively. The correlation between the methylation status of CpG island at HHIP promoter region and HHIP mRNA expression level was analyzed. Results: The expression of HHIP mRNA ( $0.82 \pm 0.38$  vs  $1.60 \pm 0.26$ ,  $P=0.000$ ) and HHIP ( $0.5 \pm 0.03$  vs  $0.8 \pm 0.27$ ,  $P<0.05$ ) in gastric carcinoma was significantly lower than that in the peritumoral tissues. No significant correlation was observed between the expression of HHIP mRNA or protein and age, sex, TNM stage, differentiation degree and lymph node metastasis ( $P>0.05$ ). The methylation level of HHIP gene promtor in the peritumoral tissues was significantly higher than that in the gastric cancer tissues and AGS cells [( $17.7 \pm 3.59$ )% vs ( $62.9 \pm 6.14$ )%, ( $99.7 \pm 0.67$ )%]; all  $P<0.05$ ). Compared with that before 5-Aza-dc treatment, the HHIP mRNA expression in AGS cells was significantly increased after treatment ( $4.68 \pm 0.22$  vs  $0.21 \pm 0.12$ ,  $P<0.01$ ), while the methylation level of AGS cells decreased significantly [( $10.1 \pm 0.21$ )% vs ( $90.2 \pm 0.67$ )%],  $P<0.01$ , and the methylation sites in CpG islands were significantly reduced. The degree of HHIP methylation showed a negative correlation with the mRNA expression( $r=-0.693$ ,  $P=0.00$ ). Conclusion: High methylation level of CpG island in HHIP gene promoter may increase the expression of HHIP gene, and then be involved in the carcinogenesis of gastric cancer.

Keywords: [human hedgehog interacting protein \(HHIP\) gene](#) [gastric cancer](#) [methylation](#)

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