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食管鳞状细胞癌中Smad4基因CpG岛甲基化状态分析 点此下载全文

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摘要：

目的：探讨食管鳞状细胞癌（esophageal squamous cell carcinoma，ESCC）中Smad4 （mothers against decapentaplegic homolog 4）基因启动子区及第一外显子区的CpG岛甲基化状态及其与Smad4蛋白、TGF-β1蛋白表达之间的相关性。方法：128例ESCC组织标本采集自河北医科大学第四医院2004-2008年的手术病例，每例患者均取癌旁正常黏膜组织作对照。分别应用甲基化特异性PCR（methylmion specific PCR，MSP）、RT-PCR和免疫组织化学法检测ESCC组织及相应癌旁组织中Smad4基因CpG岛的甲基化情况、Smad4 mRNA和Smad4蛋白表达情况，应用免疫组织化学法检测TGF-β1的蛋白表达情况。结果：ESCC组织中Smad4基因启动子区CpG岛甲基化率为5.5%（7/128），第一外显子5′非翻译区CpG岛甲基化率为30 5%（ 39/128 ）；相应癌旁正常黏膜组织均未检测到这两个位点的甲基化（ P <0.05）；ESCC组织中 Smad4 甲基化率显著高于癌旁正常组织（ P <0 05）。ESCC组织中Smad4 mRNA及蛋白表达显著低于癌旁正常组织（ P <0.05），且与 Smad4 甲基化相关。TGF-β1蛋白在ESCC组织中的表达率（66.4%）显著高于相应癌旁正常组织（21.9%，P <0.01），且随ESCC分期的增高和分化程度的降低而升高（ P <0.05）。Smad4和TGF-β1蛋白在ESCC中的表达呈明显的负相关（ P <0.01)。结论: Smad4基因CpG岛甲基化及TGF-β1的过表达可能是ESCC发生机制之一，其中Smad4基因第一外显子5′非翻译区CpG岛比启动子区CpG岛更易发生甲基化,从而导致Smad4基因沉默。

关键词：食管鳞状细胞癌 Smad4 DNA甲基化 TGF-β1 CpG岛

Methylation status of CpG island of Smad4 gene in esophageal squamous cell carcinoma Download Fulltext

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Abstract:

Objective : To investigate the methylation status in promoter and exon1 CpG island of Smad4 (mothers against decapentaplegic homolog 4) gene and its correlation with protein expressions of Smad4 and TGF-β1 in esophageal squamous cell carcinoma (ESCC). Methods: Totally 128 ESCC samples and the corresponding adjacent normal tissues were obtained from Fourth Hospital of Hebei Medical University (2004-2008) in the present study. Methylation specific PCR (MSP), RT-PCR and immunohistochemistry assays were used to examine the methylation status of 5′ CpG island, mRNA and protein expression of Smad4 in ESCC and the corresponding adjacent normal tissues. Immunohistochemistry method was used to detect the protein expression of TGF-β1 in ESCC and the corresponding adjacent normal tissues. Results: For the CpG island of promoter site, Smad4 was methylated in 7/128 (5.5%) ESCC tissues; for the CpG island of 5′ UTR of exon1, Smad4 was methylated in 39/128 (30.5%) ESCC tissues; the numbers were all significantly higher than those in the corresponding adjacent normal tissues (P <0.05). Smad4 mRNA and protein expressions in ESCC tissues were significantly lower than those in the corresponding adjacent normal tissues (P <0.05) and were correlated with Smad4 methylation status. TGF-β1 expression rate was 66.4% in ESCC tissues, which was significantly higher than that in the corresponding adjacent normal tissues (P <0.01), and TGF-β1 expression rate was increased with the increase of MNT stage and the decrease of differentiation stage of ESCC (P <0.05). The protein expression of Smad4 was inversely correlated with TGF-β1 expression in ESCC. Conclusion: Methylation of CpG island in Smad4 gene and TGF-β1 overexpression might play important roles in the development of ESCC, and CpG island in 5′ UTR of exon1 in Smad4 gene is more likely to be hypermethylated than the promoter region and results in Smad4 gene silence.

Keywords:esophageal squamous cell carcinoma DNA methylation Smad4 gene TGF-β1 CpG island

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