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胰腺癌组织 MGMT, $hMLH_1$ 和 $hMSH_2$ 的表达意义

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Expression of MGMT, $hMLH_1$ and $hMSH_2$ and its clinopathological significance in pancreatic carcinoma tissues

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Abstract

AIM: To study the expression of MGMT, $hMLH_1$ and $hMSH_2$ and their clinicopathological significances in the tissues of chronic pancreatitis and pancreatic adenocarcinoma.

METHODS: The expressive levels of MGMT, $hMLH_1$ and $hMSH_2$ were assayed by immunohistochemical method of avidin-biotin complex on the formalin-fixed and routinely paraffin-embedded sections of surgical resected specimen with chronic pancreatitis (n =10) and pancreatic carcinoma (n =51).

RESULTS: The positive rates and the scores of MGMT, $hMLH_1$ and $hMSH_2$ were significantly higher in chroinic pancreatitis than those of pancreatic carcinoma (MGMT: 100.0% *vs* 39.2%,3.8±0.8 *vs* 1.8±1.4; hMLH1:100.0% *vs* 45.1%, 3.8±1.0 *vs* 1.7±1.6; $hMSH_2$: 90.0% *vs* 50.9%, 3.5±0.9 *vs* 1.9±1.7). The positive rates and the scores of MGMT, $hMLH_1$ and $hMSH_2$ were significantly higher in well-differentiated adenocarcinomas than those of poorly differentiated adenocarcinomas (P <0.05 or P <0.01). The positive rates and the scores of MGMT, $hMLH_1$ and $hMSH_2$ were higher in metastasis-free cases than those of ones with metastasis, but no statistic difference was found (P >0.05). There was also no difference among the expression of three proteins and the other clinicopathological characteristics of pancreatic carcinoma.

CONCLUSION: The expression of MGMT, $hMLH_1$ or $hMSH_2$ might be related to the carcinogenesis and progression, and they might have inhibiting effect on the carcinogenesis and progression of pancreatic carcinoma.

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摘要

目的: 研究 MGMT, $hMLH_1$ 和 $hMSH_2$ 在慢性胰腺炎和胰腺癌组织中表达特征及其临床病理意义.

方法: 胰腺癌(n =51)和慢性胰腺炎(n =10)手术切除标本经 40 g/L 中性甲醛固定后常规制作石蜡包埋切片, MGMT, $hMLH_1$ 和 $hMSH_2$ 表达均采用常规 ABC 免疫组化法.

结果: 胰腺癌 MGMT, $hMLH_1$ 和 $hMSH_2$ 表达阳性率(39.2%, 45.1% 和 50.9%)及其评分(1.8 ± 1.4, 1.7 ± 1.6 和 1.9 ± 1.7)明显低于慢性胰腺炎阳性率(100.0%, 100.0% 和 90.0%)及其评分(3.8 ± 0.8, 3.8 ± 1.0 和 3.5 ± 0.9), 均有显著或高度显著性差异(P<0.05或P<0.01); 转移病例三者表达阳性率及其评分较明显低于未转移病例, 但均无显著性差异(P<0.05); 三者表达与胰腺癌其他临床病理特征无明显关系.

结论: MGMT, $hMLH_1$ 或 $hMSH_2$ 表达与胰腺癌发生及进展密切相关, 均具有抑制胰腺癌发生及进展的作用.

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0 引言

烷化剂是环境中普通存在的致 DNA 损伤的一类物质, O^6-甲基鸟嘌呤-DNA 甲基转移酶(O^6-methylguanine-DNA methyltransferase, MGMT)是机体修复烷基化合物的关键酶, 对抗烷化剂造成的 DNA 损伤, 在肿瘤发生及化疗中有十分重要意义[1-11]. 错配修复是细胞复制后一种修复机制, 起着维持 DNA 复制保真度和控制基因突变的作用, 目前至少发现 6 个参与错配修复功能的基因, 其中最主要的有 $hMLH_1$ 和 $hMSH_2$, 该系统中任一基因突变都会导致细胞错配修复功能缺陷, 表现为复制错误或微卫星不稳定, 因而与肿瘤发生密切相关[4-8,12-23]. 我们应用免疫组化方法研究胰腺癌和慢性胰腺炎组织中 MGMT, $hMLH_1$ 和 $hMSH_2$ 表达特征及其临床病理意义.

1 材料和方法

1.1 材料 我院及湘雅医院胰腺癌手术切除标本 51 例,

男 38 例，女 13 例，年龄 21-73(51 ± 17 岁)；均为胰腺导管上皮癌，包括高分化腺癌 20 例，中分化腺癌 12例和低分化腺癌19例；临床和(或)病理证实发生胰腺外转移(包括区域淋巴结、网膜、邻近组织器官等) 35 例(68.6%). 另慢性胰腺炎手术切除标本 10 例，男 7 例，女 3 例，年龄 35-55(44 ± 10 岁). 标本经固定后常规制作石蜡包埋切片，切片厚4 μm. HE染色复述病理组织学特征，其他切片行免疫组化染色. 兔抗人MGMT，$hMLH_1$ 和 $hMSH_2$ 多克隆抗体，生物素标记羊抗兔 lGg，ABC 试剂及 DAB-Hcl 显色试剂盒均购自武汉博士德公司.

1.2 方法 MGMT，$hMLH_1$ 和 $hMSH_2$ 表达均为常规 ABC 免疫组化法，胞质内出现明显棕黄色颗粒者为阳性细胞. 参照三者评分标准[6, 8, 11, 23, 25]将细胞染色强度评分(无，0 分；弱，1 分；中度，2 分；强度，3 分)和阳性细胞率评分(小于 5%，0 分；5-10%，1 分；10-20%，2 分；20-50%，3 分；大于 50%，4 分)之和为该病例评分值，将评分值小于或等于 2 分定为阴性病例，大于 2 分定为阳性病例. 以博士德公司提供的阳性切片作为染色的阳性对照，以 0.01 mol/L PBS 液(pH7.4)替代 - 抗作为每次染色的阴性或替代对照.

统计学处理 采用 SPSSS10.0 统计软件包进行 *t* 检验，χ^2 检验或 Fischer 精确概率法，检验水准 α=0.05.

2 结果

MGMT，$hMLH_1$ 和 $hMSH_2$ 免疫反应阳性物质主要定位于胞质，部分病例偶见胞核着色(图 1-3). 三者在癌组织中分布呈较明显异质性，同一切片不同视野阳性细胞率及着色程度可有较明显不同. 胰腺癌 51 例 MGMT，$hMLH_1$ 和 $hMSH_2$ 阳性病例分别为 20(39.2%)、23(45.1%)和 26(50.9%)例，其评分值分别 1.8 ± 1.4，1.7 ± 1.6 和 1.9 ± 1.7；慢性胰腺炎 10 例仅 $hMSH_2$ 1 例阴性表达，其评分值分别为 3.8 ± 0.8、3.8 ± 1.0 和 3.5 ± 0.9，胰腺癌三者表达阳性率及其评分均明显低于慢性胰腺炎 (P <0.05 或 P <0.01). 高分化腺癌三者表达阳性率及其评分明显高于低分化腺癌(P <0.05 或 P <0.01)；未转移胰腺癌病例三者表达阳性率及其评分较明显高于转移病例，但均无统计学差异(P >0.05，表 1). 胰腺癌其他临床病理特征与三者表达均无明显关系(P >0.05).

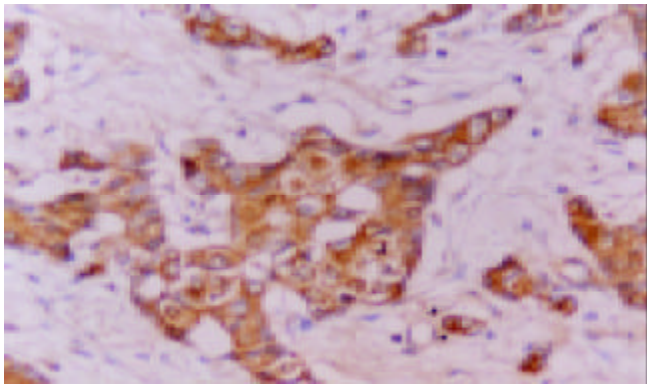

图 1 胰中分化腺癌，MGMT 阳性，评分 6 分，ABC × 200.

表 1 胰腺癌分化程度和是否转移与 MGMT、$hMLH_1$ 和 $hMSH_2$ 表达的关系

病理特征	n	MGMT		$hMLH_1$		$hMSH_2$	
		阳性(%)	评分	阳性(%)	评分	阳性(%)	评分
高分化	20	65.0	2.4 ± 1.5	80.0	2.6 ± 1.2	75.0	2.6 ± 1.4
中分化	12	25.0[b]	1.6 ± 1.2[a]	25.0[a]	1.3 ± 1.7[a]	58.3[a]	2.4 ± 1.8
低分化	19	21.0[b]	1.2 ± 1.3[b]	21.0[b]	0.9 ± 1.4[a]	21.0[b]	1.0 ± 1.4[a]
无转移	16	50.0	2.3 ± 1.1	62.5	2.2 ± 1.6	62.5	2.3 ± 1.8
有转移	35	34.3	1.5 ± 1.5	37.1	1.4 ± 1.5	45.7	1.8 ± 1.6

[a]P <0.05, [b]P <0.01 *vs* 高分化或无转移.

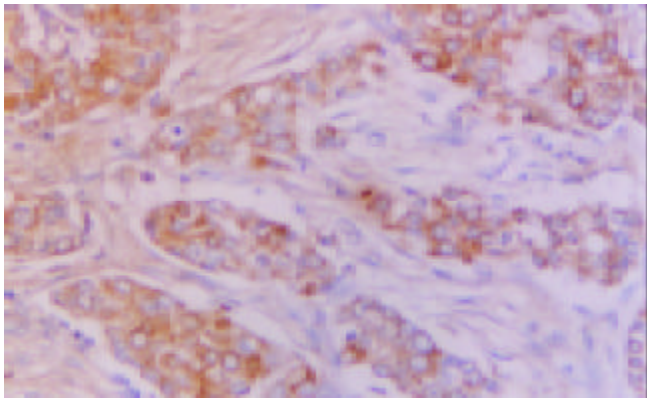

图 2 胰低分化腺癌，$hMLH_1$ 阳性，评分 5 分，ABC × 200.

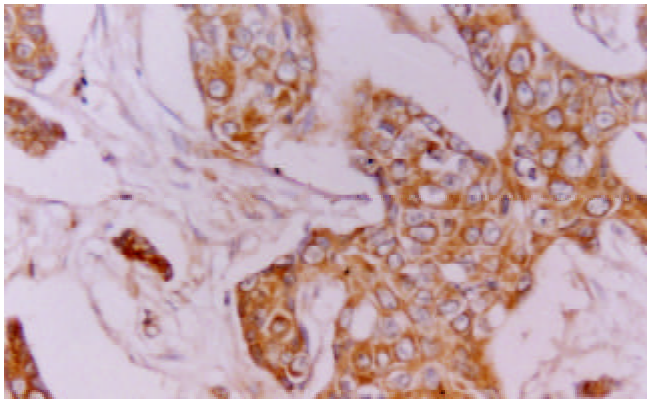

图 3 胰中分化腺癌，$hMSH_2$ 阳性，评分 6 分，ABC × 200.

3 讨论

人 MGMT 基因定位于 $10q^{26}$，编码由 207 个氨基酸组成的蛋白质，活性位点在 145 位半胱氨酸残基. 生理条件下 MGMT 是一种含磷蛋白，磷酸化可抑制其活性，蛋白激酶C、酪氨酸激酶Ⅱ等可使其磷酸化，影响其功能，但该酶磷酸化后可抵抗蛋白酶对他的消化而得以保存活性，碱性磷酸酶可使其去磷酸化而恢复活性[5-11, 25]. MGMT 在正常及大多数肿瘤组织中均有表达(称为 Mer^+ 表型)，约 5% 肿瘤组织和 20% 肿瘤细胞株检测不到 MGMT 活性(称为 Mer^- 表型)[1-2]. MGMT 表达与许多肿瘤的发生及肿瘤耐药性密切相关，如食管癌，乳腺癌、胃癌、肝癌等[4-11]. MGMT 表达具有组织及细胞类型特异性，Mer^- 细胞内 MGMT 基因本身极少发生突变、缺失、重排等改变，其 mRNA 水平和蛋白水平是一致的. 但关于其在转录水平的精确调控机制尚不清楚，可能与启动子区域CpG岛甲基化有关[1-3]. MGMT基因调节失活增加了靶细胞对烷化剂损伤的易感性，在早期肿瘤发生中起重要作用[1, 3, 11]. 烷化剂与胸腺嘧啶错配，发生 G：C → A：T 突变，可导致癌基因激活和抑癌基因失活，进一步发展为肿瘤[4-11]. 我们发现胰腺癌 MGMT 表达阳性率及其评分明显地低于慢性胰腺炎，高分化腺癌 MGMT 表达阳性率及其评分也明显地高于低分化腺癌，与国外文献[4-11]报道较一致. 说明 MGMT 在抑制胰腺癌发生和进展方面可能起重要作用，其机制除与 MGMT 本身生物学作用有关外仍需进一步研究.

$hMLH_1$ 基因位于染色体 $3p^{21}$，与酿酒酵母 MLH_1 高度同源. 已证实约 30%HNPCC(遗传性非息肉性大肠癌)病因与 hMLH1 突变有关[13]. 研究发现 HCT_{116} 细胞(结肠肿瘤细胞)中有 $hMLH_1$ 缺陷，表现为错配修复功能缺陷和微卫星序列不稳定，且对 MNNG 耐受. 微细胞融合技术将 3 号染色体上野生型 $hMLH_1$ 基因导入 HCT_{116} 细胞中，该细胞株恢复了错配. $hMLH_1$ 高度甲基化是引转微卫星不稳定的重要原因，在散发性大肠癌、子宫内膜癌和胃癌等肿瘤中均有发现[5, 7, 13-24]. $hMSH_2$ 是第一个被分离的人类错配修复基因，位于染色体 $2p^{22-22}$ 或 $2p^{16}$ 上. 研究发现约 60% HNPCC 与 $hMSH_2$ 突变有关，突变无明显热点，但相当多突变为缺失性突变和移码突变形成新的终止密码，产生载短蛋白[13]. 在其他家族性结肠癌综合征中也发现有 $hMSH_2$ 突变(如 Muir-Totte 综合征)，在散发性结肠癌、子宫内膜癌、胃癌、肝癌、胆管癌、膀胱癌、黑色素瘤等恶性肿瘤中发现错配修复蛋白功能的缺陷，证实有 $hMSH_2$ 突变[5, 7, 13-24]. 现已证实 $hMSH_2$ 以复合蛋白质的形式与错配因子进行结合，这种错配结合因子是由两种不同蛋白质组成的二聚体，能特异性地识别并结合错配的 DNA 序列[5, 7]. 故 DNA 错配修复系统缺陷在许多肿瘤的发生及进展过程中起重要作用，对大肠癌发生发展的影响作用研究尤为深入[5,7]. 我们发现胰腺癌 $hMLH_1$，$hMSH_2$ 表达阳性率及其评分明显低于慢性胰腺炎，高分化腺癌二者表达阳性率及其评分也明显高于低分化腺癌. 说明 $hMLH_1$ 和 $hMSH_2$ 表达水平与胰腺癌发生和分化程度有关，二者表达可抑制胰腺癌发生和进展. 目前，胰腺癌发病在增加[26-27]，早期诊断困难[28-33]，临床治疗仍不满意[34-38]，受到关注.

我们发现未转移癌 MGMT，$hMLH_1$ 和 $hMSH_2$ 表达阳性率及其评分较明显高于转移癌，但均无显著性差异，可能与病例数少有关，如要确证三者表达与抑制胰腺癌转移发生有关仍需积累研究病例和进行更深入研究. 研究发现 MGMT，$hMLH_1$ 和 $hMSH_2$ 表达与一些恶性肿瘤预后有关，绝大多数文献显示 $MGMT_1$ 和 $hMSH_2$ 低表达的恶性肿瘤预后明显差于高表达者，而 $hMLH_1$ 低表达者预后较高表达者好[5, 7, 9, 12, 19, 22-23].

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