PO Box 2345 Beijing 100023, China
Fax: +86-10-85381893
Email: wcjd@wjgnet.com www.wjgnet.com

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转化生长因子βII型受体在胃癌组织中表达的研究

张朋彬, 李宜辉, 徐采朴

张朋彬, 李宜辉, 中国人民解放军第三军医大学新桥医院消化内科 重庆市 400037
徐采朴, 中国人民解放军第三军医大学西南医院消化内科 重庆市 400038
张朋彬, 男, 1966-04-13生, 汉族, 河北省宁晋县人. 1999年第三军医大学新桥医院消化内科博士毕业, 主要从事消化道疾病的诊治.
项目负责人: 张朋彬, 40037, 重庆市新桥, 中国人民解放军第三军医大学新桥医院消化内科. zpb666@sina.com
电话: 023-68774665
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Expression of transforming growth factor β type II receptor in gastric carcinoma tissue

Peng-Bin Zhang, Yi-Hui Li, Cai-Pu Xu

Peng-Bin Zhang, Yi-Hui Li, Department of Gastroenterololgy, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, China
Cai-Pu Xu, Department of Gastroenterololgy, Southwest Hospital, Third Military Medical University, Chongqing 400038, China
Correspondence to: Peng-Bin Zhang, Department of Gastroenterololgy, Xinqiao Hospital, Third Military Medical University, Chongqing 400037, China. zpb666@sina.com
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Abstract

AIM: To investigate the expression of transforming growth factor β type II receptor (TGFβIIR) in the gastric carcinoma tissue.

METHODS: Expression of TGFβIIR was studied in 20 cases of normal gastric tissues and 74 gastric carcinoma tissues by immunohistochemical method.

RESULTS: In normal gastric tissue, TGFβIIR was mainly expressed in the lower part of the gland, especially in the cytoplasm, and the expresssion was significantly decreased in well and moderately differentiated adenocarcinoma tissues (P <0.05), and in poorly differeantiated and mucinous or signet ring cell carcinoma tissues (P <0.01) as compared with normal mucosa.

CONCLUSION: Decreased expression of TGFβIIR may play a role in the development of gastric cancer.

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摘要

目的: 研究转化生长因子β(TGFβ)II型受体在胃癌组织中的表达及其意义.

方法: 应用免疫组织化学方法, 对20例正常胃粘组织及74例胃癌组织(高中分化腺癌32例, 低分化腺癌23例, 黏液腺癌14例, 印戒细胞癌5例) TGFβII型受体的表达情况进行了研究.

结果: 在正常胃黏膜组织, TGFβII型受体主要表达于腺体的体底部; 在胃高中分化腺癌组织中, TGFβII型受体表达减少(P <0.05, vs 正常胃黏膜); 在低分化腺癌及黏液印戒细胞癌中, 其表达明显减少(P 均<0.01, vs 正常胃黏膜).

结论: TGFβII型受体表达的减少可能在胃癌的发生发展中起了一定的作用.

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0 引言

转化生长因子β(transforming growth factor β, TGFβ)是一具有多功能的细胞因子[1-4], 对细胞的生长分化具有重要的调节作用. 他可抑制多种细胞的生长, 并对一些肿瘤细胞具有生长抑制作用[5-6]. 我们利用免疫组织化学方法, 对TGFβII型受体(TGFβII receptor, TGFβIIR)在胃癌组织中的表达进行了研究如下.

1 材料和方法

1.1 材料 我院1999/2001年手术切除胃癌石蜡标本74例, 高分化腺癌32例, 低分化腺癌23例, 黏液腺癌14例, 印戒细胞癌5例. 男54例, 女20例, 平均年龄57.4岁. 以癌旁正常胃黏膜组织20例作为正常对照. 标本连续切5 μm厚切片, 供HE染色及免疫组织化学用.

1.2 方法 免疫组织化学采用ABC法, TGFβIIR抗体(兔抗人, 即用型)及ABC试剂盒均购自武汉博士德公司. 切片常规脱蜡水化, 30 mL/L H_2O_2封闭内源性过氧化物酶, 胰酶消化, 正常血清封闭, 加入TGFβIIR 4 ℃过夜, 生物素化羊抗兔IgG 37 ℃孵化20 min, ABC 37 ℃孵育20 min, DAB显色, 苏木素复染, 常规脱水、透明、封片. 以细胞质和/或细胞膜有棕黄色沉淀者为表达阳性细胞. 随机计数100个细胞, 观察其表达阳性率, 结果表示为无表达(-), 1-33%阳性为(+), 34-66%阳性为(++), >67%阳性为(+++).

统计学处理 计数资料, 采用χ^2检验.

2 结果

在正常胃黏膜组织, 以腺体的颈部为界, TGFβIIR基

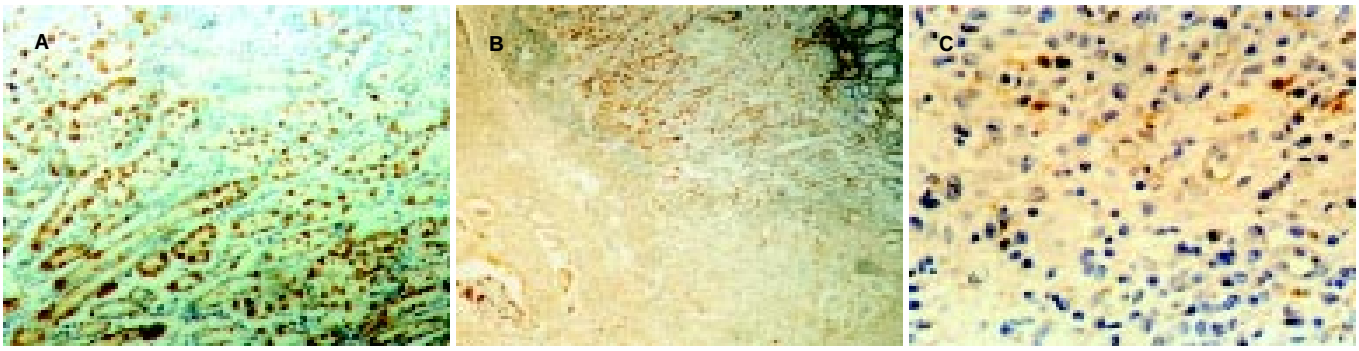

图1 A:正常胃黏膜组织，ABC × 100; 图B:高分化胃癌组织，ABC × 100; 图C: 低分化腺癌组织，ABC × 200.

本集中表达于腺体的中下部，尤以壁细胞表达最为明显. 而在腺体表面的黏液细胞则几乎无表达(图1A). 在表达细胞中，TGFβIIR 表达于细胞质及细胞膜上，与TGFβ的表达非常相似. 在胃癌组织中，TGFβIIR的表达明显减少，与正常胃黏膜组织相差非常显著(高中分化腺癌 $P<0.05$，低分化腺癌与黏液印戒细胞癌均 $P<0.01$，表1)，但与组织分化无关($P>0.05$，图1B，图1C).

表1 TGFβIIR 在正常胃黏膜组织及胃癌组织中的表达

组织学类型	*n*	TGFβIIR 表达		
		+	++	+++
正常胃黏膜组织	20		13	7
高中分化腺癌[a]	32	10	18	4
低分化腺癌[b]	23	8	15	
黏液印戒细胞癌[b]	19	11	8	

[a]$P<0.05$, [b]$P<0.01$, vs 正常胃黏膜.

3 讨论

在信号传导时TGFβ首先与细胞膜上TGFβIIR结合，后者使I型受体加入这一复合体并被活化. 活化的受体通过激活细胞内Smad蛋白而将TGFβ信号传到细胞核. 在信号传导中，I型或II型受体的异常表达均可使TGFβ的信号传递中断或减弱[7-9]. TGFβ除对正常细胞具有生长抑制作用外，对癌细胞的生长也具有抑制作用，并可引起癌细胞发生凋亡[10-16]. 在肿瘤治疗中，一些药物的部分疗效是通过诱导产生TGFβ而达到治疗目的的[17-18]. 动物实验证明，TGFβ可阻抗化学诱癌剂的诱癌作用[19]. 当TGFβIIR表达异常，造成TGFβ信号传递中断时，则癌细胞就逃脱了TGFβ的抑制作用，修复TGFβ信号后，癌细胞又受到了TGFβ的抑制[20-21].

表达异常的TGFβIIR多是由于其基因709-718区的多聚腺苷酸 $Poly(A)_{10}$ 中的腺苷酸的插入或缺失所造成. 该区域腺苷酸的插入或缺失，使TGFβIIR基因发生框架移动，产生异常的II型受体或使其转录中断[22-29]. 这种现象与微卫星不稳定性(microsatellite instability，MI)有关. 微卫星是指基因组中散在的较短的重复序列，他在DNA复制时容易产生错配现象，即易发生碱基的插入或缺失，这种错配可由体内的错配修复系统(mismatch repair，MMR)来纠正. 当该系统有缺陷，不能纠正DNA的复制错误时，便出现MI，使相关基因自发突变率升高[30-33]. Johannsdottir et al [34]发现，在高MI患者TGFβIIR突变率高达62%，但该突变与肿瘤类型无关. 但也有研究发现，TGFβIIR异常表达更多见于低分化腺癌及印戒细胞癌[28]. Yang et al [35]发现TGFβIIR表达异常的胃癌细胞不受TGFβ抑制，当对该细胞进行TGFβIIR基因转染后，TGFβ又重新能够抑制该细胞的生长.

我们通过免疫组织化学方法，发现在胃癌组织中，TGFβIIR的表达明显减少($P<0.01$)，说明TGFβ的信号传导出现了障碍，阻断或减弱了TGFβ对胃癌细胞的生长抑制作用. 但TGFβIIR的表达与胃癌组织分化程度无明显关系. TGFβIIR表达的减少，使胃细胞逃脱TGFβ的生长抑制作用，对胃癌的发生发展起了一定的促进作用.

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