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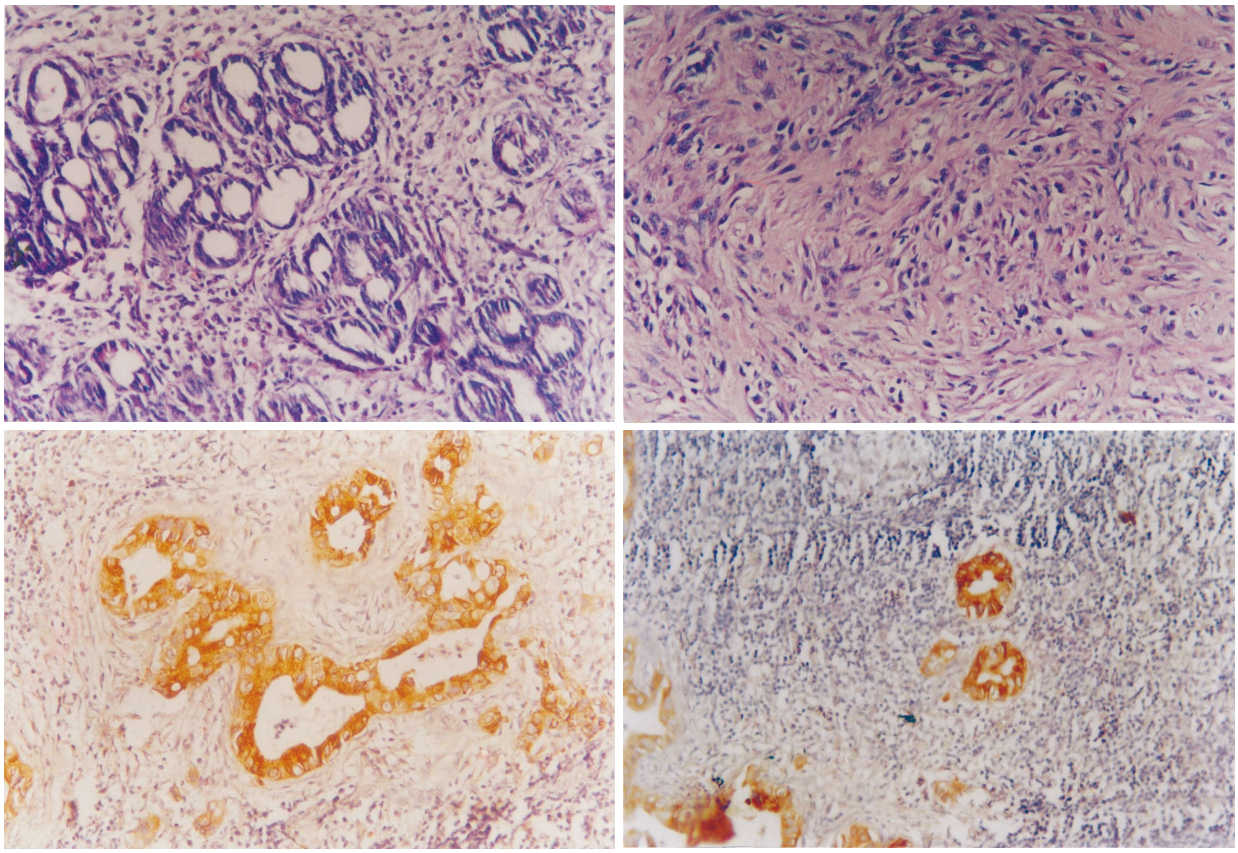

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SD 大鼠胰腺癌模型组神经生长因子 mRNA 表达

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Expression of nerve growth factor messenger RNA in pancreatic cancer tissues in Sprague Dawley rats

Zhu-Lin Yang, Xing-Hui Deng, Le-Ping Yang, Qing-Long Li, Wen-Tao Fan, Shan Liang, Xiong-Ying Miao

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Abstract

AIM: To establish a model of pancreatic cancer in Sprague-Dawley(SD)rats and to explore the expression and its significance of nerve growth factor(NGF)mRNA in pancreatic cancer and non-cancer tissues.

METHODS: Ninety rats were randomly divided into A (*n* = 40), B (*n* = 40) and C (*n* = 10) group. For group A and B, dimethylbenzanthrancene (DMBA) was directly implanted into the parenchyma of the rat pancreas to establish pancreatic cancer model. The rats in group B were treated with trichostatin(TSA). The rats in group C served as the controls. The rats were executed within 3-5 mo, and the carcinogenesis of the rats was observed by pathological methods. *In situ* hybridization was used to detect the expression of NGF mRNA in the formalin-fixed and routinely paraffin-embedded sections of pancreatic cancer and non-cancer tissues.

RESULTS: The prevalence rate of pancreatic cancer in group A was 48.7%(18/37) within 3-5 mo, 28.6%(2/7) at mo, 40.0%(4/10) at 4 mo and 60%(12/20) at 5 mo (*P* >0.05), and that in group B was 33.3%(12/36), 16.7%(1/6), 30.0%(3/10) and (40.0%)8/20, respectively (*P* >0.05). The prevalence rate in group A was higher than that of group B (*P* >0.05). The diameters of tumor mass in group A were significantly larger than those in group B (group A: 0.5-1.0 cm 7 cases, 1.0-2.0 cm 10 cases, >2 cm 1 case *vs* group B: 0.5-1.0 cm 9 case, 1.0-2.0 cm 2 cases, >2.0 cm 1 case, *P* <0.05). No tumor formed in the pancreas of the rats in group C or in other main organs of the rats in group A and B. The positive rate of NGF mRNA expression in the pancreatic ductal cancer tissues was significantly higher than that in non-cancer tissues (67.9% *vs* 18.6%, *P* <0.01), and severely atypical hyperplasia was observed in the positive non-cancer pancreatic tissues of ductal epithelium. The positive rate of NGF mRNA expression in ductal adenocarcinoma was markedly higher in group A than that in group B (*P* = 0.052). The positive rate of NGF mRNA in the rats with tumor maximal diameter ≤1.0 cm was lower than that in the ones with tumor maximal diameter >1.0 cm (*P* >0.05) .

CONCLUSION: Direct implantation of DMBA in the parenchyma of pancreas can induce pancreatic cancer with a high occurrence rate in a short time. NGF may play an important role in the carcinogenesis of pancreatic cancer. TSA can inhibit the occurrence and progression of pancreatic cancer by inhibiting NGF expression.

Key Words: Nerve growth factor; Dimethylbenzanthrancene; Trichostatin

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摘要

目的：建立SD鼠胰腺癌模型并探讨胰腺癌和非癌胰腺组织神经生长因子(NGF)mRNA表达及其意义.

方法：90只SD大鼠随机分为模型组(A，*n* = 40)、DMBA干预组(B，*n* = 40)和对照组(C，*n* = 10). 将二甲基苯并蒽(DMBA)置入A、B组大鼠胰腺实质内建立胰腺癌模型，B组大鼠以曲古霉素(TSA)干预，3-5 mo内处死观察胰腺癌发生情况，标本经40 g/L中性甲

醛固定后常规制作石蜡包埋切片，原位杂交行NGF mRNA表达研究.

结果：A组(实验组)3-5 mo发癌率48.7%，5 mo(60%)高于4 mo组(40.0%)和3 mo组(28.6%)；B组发癌率为33.3%，5 mo组(40.0%)高于4 mo组(30.0%)和3 mo组(16.7%)；A和B组胰腺导管癌分别为17例和11例，余为纤维肉瘤；A组发癌率高于B组(P>0.05)，A组肿块最大径明显大于B组(A组：0.5-1.0 cm 7例，1.0-2.0 cm 10例，>2.0 cm 1例；B组：0.5-1.0 cm 9例，1.0-2.0 cm 2例，>2.0 cm 1例，P<0.05)；C组(对照组)胰腺及A、B两组胰腺外主要脏器均无明显病理改变. SD大鼠胰腺导管癌NGF mRNA表达阳性率明显高于非癌胰腺组织(67.9% *vs* 18.6%，P<0.01)，且非癌胰腺组织阳性表达者导管上皮均呈重度不典型增生；A组胰腺导管癌NGF mRNA表达阳性率高于B组(P = 0.052)；肿块最大径≤1.0 cm者NGF mRNA表达阳性率低于肿块最大径≥1.0 cm者(P>0.05).

结论：DMBA置入胰实质可在短期内获得较高的SD鼠胰腺癌发生率，NGF在SD鼠胰腺癌发生过程中可能起重要作用. TSA能抑制胰腺癌的发生和生长，其作用可能与抑制NGF表达有关.

关键词：神经生长因子；二甲基苯并蒽；曲古霉素

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0 引言

胰腺癌早期诊断和手术切除极为困难[1-4]，动物模型为探讨癌变机制及肿瘤防治的重要手段[5-8]. 目前，仍缺乏理想的胰腺癌动物模型. 我们应用二甲基苯并蒽(dimethylbenzanthrancene，DBMA)置入SD大鼠胰腺实质内建立胰腺癌模型及设立曲古霉素(trichostatin，TSA)干预组[9-11]. 应用原位杂交方法研究胰腺癌和非癌胰腺组织内神经生长因子(nerve growth factor，NGF)mRNA表达水平，探讨模型优劣、TSA干预机制及胰腺癌发生发展过程中NGF的作用.

1 材料和方法

1.1 动物模型 由湘雅二医院实验动物中心提供的SD大鼠90只，体质量为150-200 g，雌雄不限，随机分成A，B，C3组，A组40只(DMBA组)，B组40只(DMBA+TSA组)和C组10只(空白对照组). 术前禁食24 h，不禁水，20 g/L戊巴比妥钠(1.5 mL/kg)ip麻醉，经上腹正中切口进腹，暴露胰腺后于胰体尾部切开胰腺被膜及部分胰实质，深1 mm，A，B两组置入9 mg DMBA，缝合胰腺被膜后关腹. C组除不置DMBA外，余同A组. 在普通环境中喂养，自由饮净化水及全价营养颗粒饮食. B组鼠每周ip 1 mg/L TSA 1 mL. 除自然死亡外，分别于3，4，5 mo随机处死A组(7，10和20只)和B组(6，10和20只)，C组鼠于5 mo全部处死. 行病理学观察.

1.2 NGF mRNA表达 NGF mRNA原位杂交试剂盒及DAB-HCL显色试剂盒均购自武汉博士德公司. SD大鼠胰腺及非癌胰腺组织NGF mRNA染色方法为分子原位杂交染色法，严格按试剂盒说明书操作(具体步骤略). 细胞质内含棕黄色颗粒者为阳性细胞，以切片中阳性细胞≥25%为阳性，<25%为阴性[12-13]. 以试剂盒阳性切片作为染色的阳性对照，以0.5 mol/L磷酸盐缓冲液(PBS，pH7.4)替代杂交液作为阴性对照.

统计学处理 采用SPSS10.0软件包进行χ^2检验、秩和检验或Fishers精确概率法，检验水准α = 0.05.

2 结果

2.1 建模情况 A组37只(2只在术后1 mo和1只在术后2 mo内自然死亡)发生胰腺癌18只(48.7%)，其中5 mo组(60.0%)较明显高于4 mo组(40.0%)和3 mo组(28.6%)，但差异无统计学意义(P>0.05)；病理组织学类型包括胰腺导管癌17例(高分化6例、中分化7例和低分化4例)和纤维肉瘤1例. B组36只(3只在术后1 mo和1只在术后2 mo内自然死亡)发生胰腺癌12只(33.3%)，其中5 mo组(40.0%)高于4 mo(30.0%)和3 mo组(16.7%)，但差异无统计学意义(P>0.05)；病理组织学类型包括胰腺导管癌11例(高分化6例，中分化4例和低分化1例)和纤维肉瘤1例. A组发癌率高于B组，但差异无统计学意义(P>0.05). A组肿块最大径(0.5-1.0 cm 7例，1.0-2.0 cm 10例和>2.0 cm 1例)明显大于B组(0.5-1.0 cm 9例，1.0-2.0 cm 2例和>2.0 cm 1例)，经秩和检验差异有统计学意义(P<0.05). A组和B组胰腺导管癌组织学结构完全相同于人类胰腺导管癌(图1A)，无1例腺泡细胞癌. A组和B组纤维肉瘤(图1B)分别发生肝转移和网膜脂肪组织转移. C组胰腺组织均无明显病理学变化. 胰腺外主要脏器(包括肝、胆囊、胆总管、胃、肠、肺、脑等)均无肿瘤发生及病理组织学改变. 3-5 mo处死大鼠非癌胰腺组织可见腺泡细胞形态改变，导管上皮细胞乳头状增生及不典型增生等病理改变，其中导管上皮中至重度不典型增生者A组(52.6%)高于B组(33.3%)，但差异无统计学意义(P>0.05).

2.2 NGF mRNA表达 A，B组胰腺导管癌28例NGF mRNA表达阳性19例(67.9%)，明显高于非癌胰腺组织(8/43，18.6%)，差异有高度统计学意义(P<0.01)；A、B两组纤维肉瘤均呈NGF mRNA阳性表达. A组胰腺导管癌NGF mRNA表达阳性率(14/17，82.4%)明显高于A组

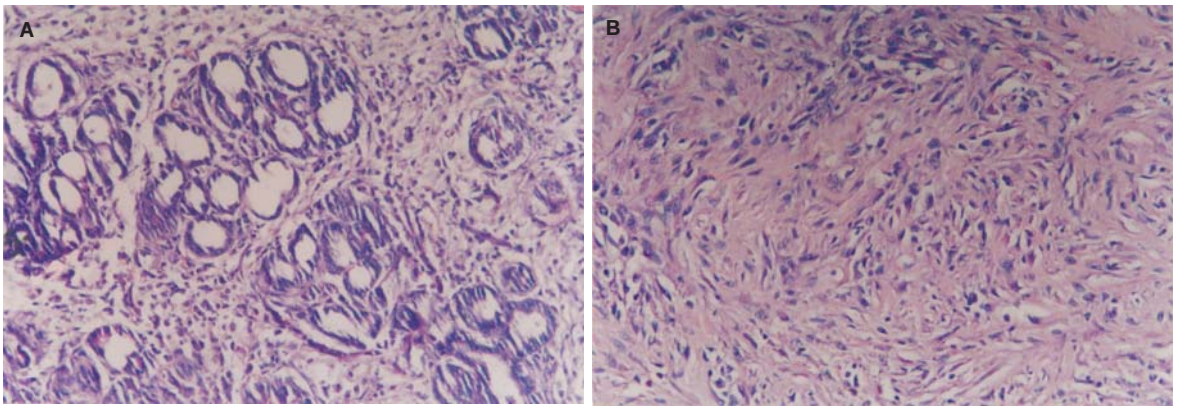

图1 SD大鼠实验胰腺肿瘤HE×200. A：高化导管腺癌；B：纤维肉瘤.

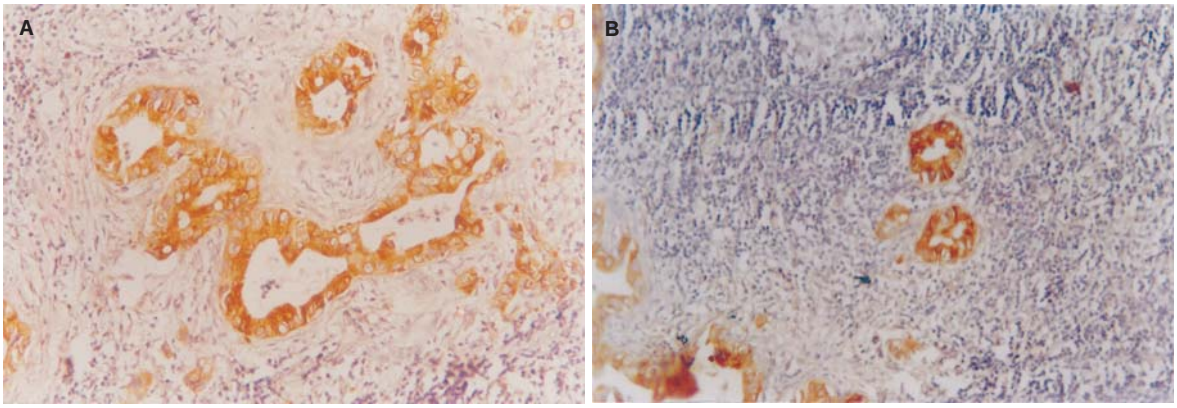

图2 大鼠胰腺NGF mRNA阳性表达, 原位杂交×200. A：中分化导管癌；B：非癌胰腺组织.

非癌胰腺组织(5/19，26.3%)，差异有高度统计学意义(P<0.01)，且非癌胰腺组织阳性者导管上皮均呈重度不典型增生. B组胰腺导管癌NGFmRNA表达阳性率(5/11，45.5%)明显高于B组非癌胰腺组织(3/24，12.5%)，差异有统计学意义(P<0.05)，且非癌胰腺组织阳性者导管上皮均呈重度不典型增生. A组胰腺导管癌NGFmRNA阳性率(82.4%)高于B组胰腺导管癌(45.5%)，但差异无统计学意义(P = 0.052). 肿块最大径≤1.0 cm的胰腺导管癌NGFmRNA阳性率(8/15，53.3%)明显低于肿块最大径>1.0 cm胰腺导管癌(11/13，84.6%)，但差异无统计学意义(P>0.05，图2).

3 讨论

我们应用较大剂量DMBA置入SD大鼠胰腺组织内3-5 mo内总发癌率A组达48.7%，B组总发癌率为33.3%，病理学类型除2例纤维肉瘤外，均与人类胰腺导管腺癌组织学结构相同. B组肿块直径明显低于A组，非癌病变胰腺组织可观察到导管上皮从增生至不典型增生等癌前病理改变；且两组大鼠除2例胰腺纤维肉瘤分别发生肝脏和网膜脂肪组织转移外，均未见胰腺外主要脏器发生肿瘤及其他病理改变. 我们制作的SD大鼠模型具有以下优点[1-8,11,14-21]：(1)成瘤周期短；(2)能在短期内观察胰腺癌发生发展的病变过程；(3)组织学特征更接近人类胰腺导管癌；(4)胰腺外其他脏器均未见恶性肿瘤出现；(5)TSA抑癌作用及抑癌生长效果较明显；(6)制作成本低廉. NGF是一种M_r为26 000多肽，属神经生长因子家族的成员. TrKA是NGF的高亲和力受体，M_r14 000的跨膜糖蛋白，NGF与TrKA结合后使胞质内区的酪氨酸激酶活性增高，进而引起生物学效应[22-25]. NGF在神经嵴来源肿瘤呈高表达，部分非神经嵴来源的肿瘤NGF及其受体TrKA也呈高表达，其作用与神经嵴来源肿瘤相反，认为是促进恶性细胞增生和使其向更“恶性”表型转化[12,13,26-29]. NGF及其受体TrKA表达与乳腺癌、涎腺囊性腺癌、胰腺癌等非神经嵴来源肿瘤发生、进展、侵袭潜力、转移及预后密切相关，阳性表达者多进展快、侵袭潜力强、易发生嗜神经侵袭、易发生转移和预后差[12,13,20,22,24-30]. 胰腺癌为嗜神经侵袭的恶性肿瘤，嗜神经侵袭是影响胰腺癌预后的重要因素，神经侵袭患者预后明显比神经未侵袭者差[12,23,24]. 我们应用原位杂交方法研究SD大鼠胰腺癌模型中胰腺癌和非癌胰腺组织NGF mRNA表达水平，发现胰腺导管癌NGF mRNA表达水平明显高于非癌胰腺组织，非癌胰腺组织NGF mRNA阳性者导管上皮均呈重度不典型增生；A组胰腺导管癌NGF mRNA阳性率高于B组，以及肿瘤最大径≤1.0 cm者NGF mRNA阳性率低于肿块最大径>1.0 cm者，但差异均无统计学

意义($P>0.05$). 结果提示NGF在SD大鼠胰腺癌发生及生长速率方面有重要作用，TSA可能通过抑制NGF表达发挥抑瘤和抑瘤生长作用，其作用机制有待更深入研究.

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