世界华人消化杂志®
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世界华人消化杂志 2007年1月18日; 15(2): 151-156
ISSN 1009-3079 CN 14-1260/R

文献综述 REVIEW

整合素与胰腺癌

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收稿日期: 2006-08-07 接受日期: 2006-11-02

Roles of integrins in pancreatic adenocarcinoma

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Received: 2006-08-07 Accepted: 2006-11-02

Abstract
Integrins, serving as transmembrane proteins, play major roles in cell-extracellular matrix adhesions, and they can introduce extracellular signals into the cells, alter cellular morphology and influence cell motility as well as contribute to tumor invasion and metastasis. One of the major causes of low resection rates and extremely poor survival rates is its extraordinary local tumor progression and early systemic dissemination. Being a kind of adhesion molecules associating cells with extracellular matrix, integrins play a variety of roles in the process of invasion and metastasis in pancreatic adenocarcinoma.

Key Words: Integrin; Pancreatic adenocarcinoma; Invasion; Metastasis

He D, Zhang XH. Roles of integrins in pancreatic adenocarcinoma. Shijie Huaren Xiaohua Zazhi 2007;15(2):151-156

摘要
整合素为一类跨膜蛋白, 是介导细胞与细胞外基质黏附的主要黏附分子. 他将细胞外的信号传入细胞内调节细胞生长、改变细胞形态、影响细胞运动, 并在肿瘤侵袭和转移的过程中起重要作用. 胰腺癌手术切除率低死亡率高的重要原因之一是肿瘤早期即能发生局部浸润和远处器官转移, 整合素作为细胞与细胞外基质的黏附分子, 在胰腺癌侵袭及转移过程中发挥多重作用.

关键词: 整合素; 胰腺癌; 浸润; 转移

何度, 张秀辉. 整合素与胰腺癌. 世界华人消化杂志 2007;15(2):151-156
http://www.wjgnet.com/1009-3079/15/151.asp

■背景资料
胰腺癌是预后最差的恶性肿瘤之一, 原因之一是肿瘤极易浸润周围组织并发生远处器官转移, 整合素为一类重要的黏附分子, 主要介导细胞与细胞外基质的黏附, 在肿瘤的侵袭行为中发挥着重要作用.

0 引言
细胞外基质(extracellular matrix, ECM)是细胞生长的土壤, 在细胞的基本生命活动中起重要作用: 调控细胞存活或凋亡[1-4]、影响细胞形态[5]、调节细胞增殖[6]、控制细胞分化[7]、影响细胞迁移[8-10]等. 细胞通过自身整合素受体将细胞外的信号传导入细胞内, 参与白细胞黏附[11]、游出、趋化[12], 血液凝固[13], 受精卵植入[14-15], 创伤愈合[16], 细胞恶性转化[17-18], 肿瘤侵袭[19-23]等过程. 整合素(integrin)是一类表达于细胞膜上, 介导细胞与ECM黏附的主要受体, 在血细胞还可介导细胞与细胞之间的黏附. 整合素(或称整合素受体)由两条跨膜多肽链α和β以非共价方式结合而成的异二聚体. 现已发现, 哺乳动物细胞选择性表达18种α链和8种β链, 两者结合形成至少24种整合素的异二聚体[24]. 整合素的结构分为头部和腿部. 头部由两个结构域组成, 一个是位于α亚单位中由7个叶片组成的β片层结构域; 另一个位于β亚单位中的Ⅰ结构域, 他们并排分布于细胞膜外, 组成整合素的配体结合结构域. 整合素的两条“腿”, 一条由α亚单位中的"Thigh", "Calf1"和"Calf2" 3个结构域组成; 另一条由β亚单位中的"Hybrid", "PSI", 4个"EGF-like"和1个"β-尾部"结构域组成[25]. 当整合素黏附于ECM时, 整合素受体聚集成簇, 胞质内C-末端尾巴可与细胞内多种锚蛋白(anchor proteins), 如踝蛋白(talin)、桩蛋白(paxilin)等结合, 并诱导黏着斑(focal adhesion)的形成. ECM存在多种整合素配体, 一种整合素可与多种基

■应用要点
整合素将细胞外信号传入细胞内, 调节细胞的生命活动, 影响细胞运动, 并通过细胞内分子调节其与配体的亲和力. 整合素的研究对于认识肿瘤的侵袭机制具有重要意义, 有望成为提示预后的指标, 目前抗整合素的药物已经进行动物试验, 有助为胰腺癌等高度侵袭性肿瘤的治疗提供新的方法.

质成分结合, 一种基质成分也可与多种整合素结合[26], 这使得整合素的黏附网络更加复杂. 整合素的信号调节为双向变构调节, 即胞内信号外传(inside out signaling)和胞外信号内传(outside in signaling)[27]. Inside-out信号即从细胞内控制整合素与配体的相互作用[28], 主要通过细胞内分子对整合素进行变构调节从而控制整合素受体与其配体的亲和力; outside-in信号途径与常规信号途径相似, 即细胞外配体激活整合素受体引起细胞的全球性反应, 触发细胞增生[29]、变形、迁移[30]、生物活性物质分泌[31]等效应. 胰腺癌占美国癌症死亡原因的第4位[32], 一旦胰腺癌的诊断成立即预示所有恶性肿瘤中最高的死亡率. 近10 a来, 我国胰腺癌5 a生存率<10%, 手术切除率虽有所提高, 但也仅达27.1%[33]. 其中一个重要的原因是肿瘤极容易早期浸润周围结构并出现远处转移[34-35], 整合素作为ECM黏附分子在胰腺癌恶性行为中起着重要作用.

1 整合素在胰腺癌中的表达

在正常人胰腺组织中, 导管、腺泡、泡心细胞及胰岛的整合素表达分布有所不同. 整合素α3, α5在泡心细胞呈中-强阳性表达; 整合素α2, α6在导管细胞呈中-强阳性表达, 在泡心细胞不表达[36-38]. 人胰腺癌组织中, 整合素α1, α2, α3, α5, α6, αV, β1, β3, β4, β5, β6表达程度不同. 胰腺癌整合素α2和α6呈中-强阳性表达[36-37], 与正常组织相比表达强度相似[36]或增强[39-41], 整合素α2, α6表达部位由正常时的局限细胞基底膜侧转变成在细胞表面弥散分布[36]. Weinel *et al*[36]研究发现, 整合素α3, α5在胰腺癌组织和胰腺癌细胞株中均呈异质性表达, 并指出假设胰腺癌是起源于胰腺导管的恶性肿瘤, 由于整合素α3在正常胰腺组织中仅在泡心细胞表达, 而在胰腺癌组织中约半数肿瘤细胞呈弱-中等强度表达, 因此胰腺癌整合素α3表达是增强的; 对于整合素α5来讲, 正常胰腺组织中, 除泡心细胞强阳性表达外, 还在多数导管上皮细胞中呈弱阳性表达, 因此在胰腺癌中整合素α5表达呈不同程度减弱. 整合素β4在92%胰腺癌病例中呈中-强阳性, 表达较正常胰腺和慢性胰腺炎明显增强[42]. Hosotani *et al*[43]用LM609(抗整合素αVβ3的mAb)检测50例胰腺导管癌, 发现58%的病例呈阳性表达, 并发现整合素αVβ3表达与MMP-2的活化率有关. Sipos *et al*[44]用抗整合素β6的mAb检测了多种来自消化道和肺的恶性肿瘤, 其中包括34例胰腺导管癌病例, 结果显示, 整合素αVβ6在胰腺癌中表达最强. 整合素α4和β2无论在正常胰腺、慢性胰腺炎还是在胰腺癌中均不表达[45].

2 整合素在胰腺癌中的作用

2.1 对胰腺癌细胞系形态、分化及增生的影响 在层黏连蛋白5培养基中整合素α6β4介导胰腺癌FG细胞系上皮细胞形态的形成[46]. 整合素αVβ6过表达与胰腺癌细胞系扁球形构造有关[44]. 整合素β1在纤黏蛋白培养基中使Mia PaCa细胞系铺展[47]. Stagge *et al*[48]用层黏连蛋白1诱导胰腺癌低分化细胞系PaTu-Ⅱ微绒毛和假腺腔形成, 用JB1a(抗整合素β1抗体)及ASC3(抗整合素β4抗体)作用5 d后细胞系导管结构消失. 但Lohr *et al*[49]检测多种分化不同的胰腺癌细胞系及异种移植肿瘤的整合素表达强度, 认为整合素表达与肿瘤细胞的分化无关. 整合素β1和α5可介导纤连蛋白诱导的胰腺癌Mia PaCa细胞系增生[47].

2.2 介导胰腺癌细胞与ECM黏附 Arao *et al*[50]将5种整合素mAb加入胶原、纤黏蛋白和层黏连蛋白培养基中, 证实整合素α2β1, α5β1和α6β1主要分别是胰腺癌细胞胶原、纤黏蛋白及层黏连蛋白的受体. 整合素α3β1[41,46,51]和α6β4[41]为层黏连蛋白5的受体; 整合素αVβ5为玻璃黏连蛋白受体[52], 整合素αVβ6为纤黏蛋白受体[53].

2.3 介导细胞侵袭行为 在众多整合素中, 整合素β1与多种肿瘤细胞侵袭性密切相连[54-55]. 在含ECM的培养基中加入多种整合素mAb的试验已经证明, 整合素β1介导胰腺癌细胞系在层黏连蛋白中迁移, 并通过基底膜重建证明整合素β1, α6在肿瘤细胞侵袭中的重要作用[38]; Tani *et al*[51]研究分化不同的3个胰腺癌细胞系BxPC-3(高分化)、CFPAN-1(中分化)和PANC-1(低分化)的体外黏附机制以及BxPC-3在ECM中的迁移情况, 并将3个细胞系植入裸鼠体内检测3系层黏连蛋白分泌情况, 发现胰腺癌细胞将合成的层黏连蛋白5异常沉积于基底膜, 细胞通过整合素α3β1识别层黏连蛋白5, 并在上面迁移; Vogelmann *et al*[56]将胰腺癌PaTu8988s细胞系(来自转移灶)和PaTu8988t细胞系(非转移系)做了黏附和转移分析, 发现PaTu8988s经抗整合素α6β1抗体预处理后再注入裸鼠尾部静脉内可抑制转移灶的形成. Arao *et al*[50]发现, 不同胰腺癌细胞系, TS2/16(一种激活型抗整合素β1抗体)需求度不一, 侵袭性越高的细胞系对TS2/16需求度越低,

说明整合素β1持续性活化状态越高细胞侵袭性越强.

2.4 整合素表达的调节 Plath *et al*[57]用流式细胞术检测了$p16^{INK4a}$对Capan-1细胞系整合素α1, α2, α3, α5, α6, αV, β1, β4和β5表达的影响, 除整合素α5外, 几乎所有的整合素与$p16^{INK4a}$状态无关, 为进一步确定整合素α5表达水平, Plath *et al*还运用免疫沉淀、Northern杂交等方法证明, $p16^{INK4a}$能上调整合素α5的表达. Sawai *et al*[58]发现, IL-1α通过与IL-1R结合, 使SW1990细胞系的整合素α6和β1表达增加, AsPC-1细胞系的整合素α2, α6和β1表达增加, BxPC-3细胞系的整合素α2, α3, α6和β1表达增加; 在后续的试验中, 还证明IL-1α不仅增强整合素α6β1与相应ECM的黏附, 而且增强人胰腺癌细胞的转移能力[59]. Funahashi *et al*[60]在Mia PaCa-2和BxPC-3细胞系中加入胶质细胞源性神经营养因子(glial cell line-derived neurotrophic factor, GDNF)24 h后, BxPC-3细胞系整合素α5及α6的表达增加, Mia PaCa-2细胞系还伴随整合素β1表达上升, 并且两系与相应ECM黏附力和侵袭性增强.

2.5 整合素功能的调节 胰腺癌细胞并非都通过改变整合素表达数量来调节自身与ECM的黏附, 还可通过改变整合素与其配体亲和力来调节自身与ECM的黏附, 影响细胞的侵袭能力. Duxbury *et al*[61]发现, 通过整合素αVβ3介导, CEACAM6交联后能增强BxPC-3细胞系与ECM的黏附, 这一过程中整合素αVβ3表达仅临界上升, 说明整合素αVβ3亲和力增强是促进细胞与ECM的黏附的重要因素. Shirk *et al*[62]发现, 表皮生长因子(epidermal growth factor, EGF)调节Capan-1细胞与Ⅰ型胶原脱离, 并促进细胞在Ⅰ型胶原和基质胶中侵袭, 此过程中Ⅰ型胶原受体整合素α2β1的表达并未受到EGF影响, 提示某些整合素功能的激活比单独的表达变化更为重要.

2.6 整合素与细胞因子 肿瘤的生长, 演进与异常的生存环境密切相关, 环境中细胞因子的改变参与肿瘤的发生、发展. 在胰腺癌中, IL-1α通过上调整合素α6β1的表达增强肿瘤细胞的黏附及侵袭行为[59,63]. 另一方面, 整合素还参与肿瘤细胞因子的分泌和表达. Lowrie *et al*[47]进行整合素阻滞实验发现, 整合素α5β1具有限制Mia PaCa-2细胞分泌IL-8的作用, 与之相反, 整合素αVβ5具有刺激IL-8分泌的效应, 正常情况下整合素αVβ5的刺激作用被整合素α5β1的抑制效应所掩盖. 与Lowrie *et al*的试验结果部分相反, Grzesiak *et al*[64]运用免疫荧光及细胞迁移分析证明整合素α2β1和α5β1分别介导FG细胞与Ⅰ型胶原和纤连蛋白黏附、调节细胞生长, 同时通过ELIAS证实整合素α2β1导致IL-6, IL-8表达减少, 而整合素α5β1导致IL-6, IL-8表达增加. 这可能与同一整合素在不同胰腺癌细胞系所起作用不同有关.

3 整合素表达与预后

Bottger *et al*[65]对19例十二指肠壶腹部癌和42例胰腺导管癌术后切除标本做整合素β1免疫组化分析, 结果显示, 整合素β1表达强度与胰腺导管癌预后无关, 该作者认为与样本含量较小有关. 虽然整合素β1是胰腺癌细胞侵袭的重要黏附分子, 但由于整合素β1链可与10多种α链相结合组成多种整合素异二聚体, 在胰腺癌中某些含β1的整合素异二聚体表达增加, 如整合素α3β1, α6β1等, 但另一方面整合素α5β1却表达下降, 并且不同的整合素异二聚体对胰腺癌预后提示意义不尽相同甚至相反, 故单独分析整合素β1与胰腺癌临床病理的联系很难得出正确结论. Hosotani *et al*[43]对50例胰腺导管癌术后标本进行整合素αVβ3免疫组化染色, 发现整合素αVβ3表达与胰腺癌分期及淋巴结转移有关. Sawai *et al*[63]对42例浸润型胰腺导管癌手术标本做免疫组化发现整合素α6强阳性表达与uPAR具有明显的相关性, 并且整合素α6和uPAR强阳性表达是提示胰腺癌患者预后差的独立因素.

目前, 对胰腺癌整合素表达的研究较多, 但是对正常人胰腺组织整合素的表达情况缺少较大样本的研究, 因此对于某些整合素在胰腺癌中是否增强或减弱还存在争议. 整合素存在3种构象: 高亲和力状态、中间亲和力状态和低亲和力状态[66]. 在分化不同或生物学特征不同的肿瘤中, 某些整合素的表达虽然无明显差异, 但由于多种分子可调节整合素亲和力, 改变其功能, 因此研究整合素亲和力改变在这些肿瘤中的作用尤为重要. 由于整合素可触发多种效应, 并且已经发现整合素与其他分子如生长因子等信号之间相互联系[67-70], 因此研究整合素与其他侵袭相关分子及相应调节通路的关系, 有利于为治疗胰腺癌等高侵袭性肿瘤提供新的靶点.

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■同行评价
本文综述了整合素与胰腺癌的关系, 有一定参考价值.

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