

黏着斑激酶在结直肠癌中的研究进展

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Role of focal adhesion kinase in the pathogenesis of colorectal carcinoma

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Abstract

Focal adhesion kinase (FAK) was initially identified as a nonreceptor protein tyrosine kinase localized to the focal contact protein clusters. This enzyme has been shown to facilitate generation of integrin-stimulated signals to downstream targets. It has been reported that activation of FAK leads to a number of processes, including cell attachment, migration, proliferation, and survival. The expression of FAK in colon carcinoma is significantly higher than that in matched cancer-adjacent normal tissue, suggesting that FAK may be an important target for the therapy of colon carcinoma. The inhibition of FAK activation can interrupt many signal pathways involved in colon carcinogenesis and may represent a new therapy strategy for colon carcinoma.

Key Words: Focal adhesion kinase; Colorectal carcinoma; Signal pathway

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摘要

黏着斑激酶(focal adhesion kinase, FAK)是一种非受体酪氨酸激酶, 他作为整合素介导的信号传导过程中的中心分子与多个信号通路相交通, 参与细胞的生长、增殖、损伤修复及凋亡等多种生物学行为. FAK在结直肠癌中高表达, 在正常大肠组织中呈弱阳性或阴性. FAK可能成为结直肠癌治疗的一个重要靶点, 抑制FAK的功能可以阻断多条与肿瘤相关的信号通路.

关键词: 黏着斑激酶; 结直肠癌; 信号通路

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0 引言

结直肠癌占肿瘤发病率的第4位, 肿瘤相关疾病死亡率的第2位^[1], 对人类的健康和生命有着严重危害. 结直肠癌的侵袭和转移是影响疗效、预后和导致死亡的重要因素. 黏着斑激酶(focal adhesion kinase, FAK)在结直肠癌中高表达, 而在正常结肠组织中呈弱阳性或阴性, 与结直肠癌细胞的发生、侵袭、转移和增殖等生物学行为密切相关^[2-5]. FAK可能成为结直肠癌治疗的一个重要靶点, 抑制FAK的功能可以阻断多条与肿瘤相关的信号通路.

1 FAK简介及基本结构

FAK是Schaller等^[6]1992年从v-Src转染的鸡胚成纤维细胞中克隆鉴定出来, 因与细胞黏附关系密切, 故命名为FAK. 编码人FAK的基因定位于8q24, cDNA全长4 285 bp, 编码1 052个氨基酸, 分子量为125 000 Da.

FAK有3个结构域: 带有FERM区的氨基端(N端)、由富含脯氨酸和黏着斑定位区(focal adhesion targeting, FAT)组成的羧基端(C端)和激

■背景资料

FAK由Schaller等在1992年发现, 与细胞黏附关系密切, 作为整合素介导的信号传导过程中的中心分子与多个信号通路相交通, 其在结直肠癌中高表达, 有可能成为结直肠癌治疗的一个重要靶点.

■同行评议者

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■相关报道

Chen等运用RNA干扰技术构建了抑制FAK表达的载体pGenesil-1-FAK,成功干扰了FAK及磷酸化FAK pY397的表达,增加了癌细胞对化疗药物5-氟尿嘧啶的敏感性,促进了结直肠癌细胞的凋亡,进而有效地逆转结直肠癌细胞对化疗药物的耐药性。

酶区^[7]。氨基端FERM同源区结构域与激酶区相结合并抑制后者作用,占据位于FERM和激酶结构域间的Src募集反应位点,阻止了Tyr397位点的自体磷酸化,使FAK处于休眠状态^[7,8]。激酶区是指411-686位氨基酸残基区域,具有蛋白质酪氨酸激酶共有的底物结合位点和催化位点^[9,10]。FAK羧基端又称为黏着斑非激酶区(FAK related non kinase, FRNK),是FAK的选择性剪切产物,在某些因素作用下,FRNK与FAK竞争结合共有的细胞内受体,或与FAK形成FRNK/FAK异二聚体减弱FAK活性,是FAK的内源性抑制剂,可特异性阻断FAK磷酸化及下游信号通路的活化^[11,12]。

FAK有6个酪氨酸磷酸化位点: Tyr397、Tyr407、Tyr576、Tyr577、Tyr861、Tyr925。Tyr397是主要的自主磷酸化部位,可与Src家族的SH2结构域结合,随后激活其他磷酸化位点,促进FAK下游信号通路的活化^[13]。Tyr576和Tyr577位于激酶结构域的活化环内,是Src家族激酶磷酸化的主要部位。Tyr861和Tyr925位于羧基端结构域, Tyr861位点磷酸化后连接 α v β 5整合素与FAK结合,调节p130CAS与FAK的黏合。Tyr925磷酸化时,可以与含SH2结构域的蛋白质如接头蛋白鸟苷酸受体结合蛋白(growth receptor bound protein 2, Grb2)相结合,促进肿瘤相关的血管再生^[14,15]。

2 FAK在肿瘤细胞生物学行为中的功能及机制

2.1 FAK介导肿瘤细胞的增殖与存活 Zouq等^[15]总结了10年来FAK在肿瘤细胞中的研究进展,发现FAK在细胞的生存与死亡上起着决定性作用。FAK在整合蛋白的介导下与细胞外基质(extracellular matrix, ECM)黏附是细胞生长、增殖的必要条件^[16,17]。FAK-Ras-丝裂酶原活化蛋白激酶(mitogen activated proteinase, MAPK)通路负责锚定机制。MAPK属于丝/苏氨酸蛋白激酶,在细胞周期调控中发挥重要作用^[18,19]。FAK的Tyr925磷酸化后,为Grb2提供了泊点,Grb2再通过结合鸟苷酸交换因子sos激活Ras蛋白,活化MAPK^[15,20]。另一方面,FAK/Src结合后,可以磷酸化Cas(Crk associated substrate)和桩蛋白(Paxillin)^[21,22],二者酪氨酸磷酸化后,除可以调节细胞骨架外,还产生其他含SH2结构域蛋白如Crk的结合部位与C3G结合, C3G是公认的Ras鸟苷酸交换因子,因此, Cas和桩蛋白酪氨酸磷酸化后可以通过Crk激活Ras/MAPK途径,进一步作用于DNA转录因子,启动细胞的增殖、转化和分化^[12,23]。

FAK-PI3K-Akt通路对肿瘤细胞的存活和增殖也有影响, Akt能通过磷酸化Bcl-2家族成员BAD和蛋白水解酶Caspase-9阻止细胞凋亡,促进细胞存活^[24]; Akt可磷酸化P53结合蛋白MDM2,磷酸化的MDM2转位到细胞核与P53结合,增加P53的泛素化而促进细胞的存活^[25-27]。

2.2 抑制肿瘤细胞的凋亡 在癌细胞中FAK的过度表达可以使细胞超越凋亡这种生长抑制机制,甚至在缺乏细胞黏附的条件下,转为非锚定生长,使癌细胞不断增生。Bcl-2蛋白家族在细胞的存活和凋亡中起主要作用^[28], FAK介导的PI3K/Akt和MEK/Erk通路都与多种Bcl-2同源染色体的表达和作用有关^[12,27,28]。磷脂酰肌醇3-激酶(phosphoinositide 3-kinase, PI3K)是一种脂类激酶,催化磷脂酰肌醇242磷酸和磷脂酰肌醇24, 52二磷酸的肌醇环D3位磷酸化,分别生成磷脂酰肌醇23, 42二磷酸和磷脂酰肌醇23, 4, 52三磷酸,这2种产物均与细胞骨架重组有关^[29,30]。FAK在Tyr397位点磷酸化后, PI3Kp85亚基的SH2结构域与其结合,在Ras的参与下, PI3K被激活,进而通过蛋白激酶B(protein kinase B, PKB)成员Akt磷酸化一系列下游分子如促凋亡蛋白Bad、核转录因子- κ B、cAMP反应元件结合蛋白、生存素(survivin)以及Forkhead转录因子家族成员FKHRL1等导致Bcl-2转录增强, FAK-PI3K-AKT通路通过增加Bcl-2的转录等方式抑制细胞凋亡^[2,31]。

2.3 介导肿瘤细胞的迁移和侵袭 FAK信号通路可促进细胞能动性的获得,剔除FAK的裸鼠细胞有能动力缺陷,重组野生型FAK可补救这一缺陷。细胞运动是复杂的过程,包括质膜伸出前突,形成黏着斑,稳定前缘,产生收缩力,黏着翻转,细胞后部的松解等。这些活动紧密协调,主要被调节肌动蛋白细胞骨架动力的Rho家族的GTP酶类控制。FAK/Src信号通路与Rac1和RhoA协调调控细胞的黏附和迁移。RhoA活化促进了有收缩能力的肌动蛋白-肌球蛋白丝的形成。Rho家族GTP酶类失去调节和缺乏FAK一样,都会引起成纤维细胞样细胞失去定向黏着^[14,28]。FAK/Src复合物主要通过两个下游底物调节Rac1活性: Cas和桩蛋白^[9,13,32],活化的Rac1主要作用是通过Arp2/3复合物激活肌动蛋白磷酸化,肌动蛋白可诱导质膜伸出前突,层形足板伸展。Crk可与DOCK180/ELMO相互作用,进而对Rac1起GEF活性作用。在黏着斑上, Crk/DOCK180/ELMO与Cas的募集反应对调控Rac1下游的质膜前突起重

要作用, 调节细胞骨架, 进而影响细胞迁移^[32,33].

FAK-Ras-MAPK信号通路可参与基质金属蛋白酶(matrix metallo proteinases, MMPs)表达的调节. MMPs能降解基底膜, 其活性与肿瘤的迁移侵袭密切相关^[34,35].

2.4 促进肿瘤血管的生成 肿瘤血管发生是肿瘤转移的一个重要基础. FAK与肿瘤细胞和胞外基质成分的黏附及其信号转导关系密切, VEGF可通过诱导FAK磷酸化介导内皮细胞迁移并抑制其凋亡而促进肿瘤血管生成及入侵转移^[29,30]. 侵袭性垂体腺瘤组织内FAK过度表达可激活VEGF/VEGFR而加速血管生成, 使瘤体内微血管密度(microvessel density, MVD)值显著增高, 进而促进垂体腺瘤侵袭性生长^[36].

3 FAK在结直肠癌中的研究进展

3.1 FAK与结直肠肿瘤相关基因间的关系 在结直肠癌中, 发现了多种基因包括结肠腺瘤性息肉(adenomatous polyposis coli, APC)、错配修复(mismatch repair, MMR)、受体型酪氨酸激酶磷酸酶R(protein-tyrosine phosphatase receptor type R, PTPRR)、*p53*等基因的改变^[37]. 这些基因相互作用, 产生多条信号通路致结直肠癌形成.

3.1.1 参与FAP向结肠癌的转化: 家族性腺瘤样息肉(familial adenomatous polyposis, FAP)是一种迟发的常染色体显性遗传病, 患者表现为大肠广泛而密集分布的腺瘤性息肉, 如不治疗, 患者在40岁前几乎无一例外的转化为结直肠癌^[38], FAP的致病基因是APC基因^[39], APC突变后, 造成APC蛋白功能失活, 活化FAK-Wnt- β -catenin信号通路, Wnt/ β -catenin连环蛋白功能增强, 结合微管能力下降, 影响细胞分裂和迁移, 引起细胞增殖和细胞分化之间的平衡失调, 细胞过度增殖, 导致结直肠癌发生^[40].

3.1.2 参与RAF突变致结肠癌发生的信号通路: RAF突变则可活化Src/FAK/Ras/Raf/ERK通路, 该通路活化后可增强*c-fos*, *c-jun*基因的表达, 进一步作用于DNA转录因子启动细胞增殖、转化和分化^[41,42]. Seon等研究发现, RAF的突变只在结肠癌中发现, 而Ras突变在直肠癌中明显比在结肠癌中少见, APC/Wnt和MMR/RAF致肿瘤形成及其交联作用在结肠癌中比在直肠癌中常见^[37]. 这些发现也许可以解释结肠和直肠在肿瘤形成中尚未经确认的差别.

3.1.3 促进P53的降解: FAK以一种非激酶依赖性形式, 通过提高MDM2依赖性的泛素化, 促进

P53降解, 具体机制为: 整合素黏着减少和有细胞外压力的情况下, FAK离开其黏着位点, 使细胞质中FAK增加, 也通过FAK-FERM介导的靶向作用增加FAK在细胞核中的含量, 核内FAK是P53-MDM2复合体的支架分子, 其FERM结构域作为提高依赖于MDM2的P53泛素化的平台, FERM结构域中F1亚结构域与P53相结合, FERM F2亚结构域将FAK定位于核内, FERM F3亚结构域与MDM2以及蛋白酶体降解相连接, 引起P53多聚泛素化, 随后P53被细胞质或细胞核内蛋白酶体降解. FAK和P53间的这种调节关系由FAK FERM结构域参与, 并不需要FAK激酶的活性作用^[25,27].

3.1.4 与促进结直肠癌发生的激素相关: 促胃泌素释放肽(gastrin releasing peptide, GRP)及其受体GRPR在正常大肠表皮细胞中不表达, 在结直肠癌细胞中异常表达. 通过调控细胞骨架重组中的细胞能动性, 增加细胞基质的黏附, 减少细胞侵袭, 降低肿瘤细胞的恶性程度, 使肿瘤细胞有更好的分化表型^[43], 对剔除GRPR基因的小鼠研究发现, GRPR对形态改变的调节作用是由FAK介导的. FAK与GRP的联系提示FAK在结直肠癌中所起的作用也许并非全部有害^[44,45]. 作为促胃泌素释放肽调控的下游激素, 胃泌素起着与之相反的作用, 胃泌素是一种肽类激素, 也是一种营养因子, 可调节胃酸分泌, 肿瘤发生时, 可促进肿瘤细胞的生长^[46-48]. 曹俊等发现胃泌素能够促进转染胃泌素受体(CCK-B受体)人结肠癌细胞株Colo320的FAK、桩蛋白和p130CAS酪氨酸磷酸化, 进而通过磷酸化FAK Tyr397, 激活FAK/Src-RAF-RAF-MEK-ERK1/2通路, 影响结直肠癌中E-钙黏蛋白和 β -catenin分布, 促进结直肠癌细胞侵袭和转移^[47,49-51].

3.1.5 调控结直肠癌干细胞生物学行为: 结直肠癌干细胞引起肿瘤形成^[46], FAK/Wnt和转化生长因子 β (transforming growth factor, TGF- β)通路可调控干细胞的自我更新、增殖、分化^[45,46,52,53]. 结直肠癌干细胞在结直肠癌中的发病机制已阐明, 为结直肠癌的治疗提供了新的治疗靶点, 干细胞生物标记剂, 如CD44、CD45和Lgr5, 均以结直肠癌干细胞为靶点破坏相关信号通路, 有可能在不久的将来彻底治愈结直肠癌晚期患者^[54,55].

3.2 外科手术的影响 大部分结直肠癌患者都需要接受手术治疗^[56], 手术一方面可以切除肿瘤组织及周围淋巴结, 是较为彻底的肿瘤治疗方法, 但另一方面, 外科手术操作后, 残余的肿瘤细胞

■创新盘点

FAK自1992年发现以来, 对其进行了大量研究, 但多是针对其信号通路, 少有其与结直肠癌关系的详细论述, 笔者在阅读了大量文献后, 系统详尽地总结了FAK与结直肠癌基因, 相关激素以及手术、放疗和化疗间的关系.

■应用要点

本文简略介绍了FAK相关的多个信号通路及其作用,与结直肠癌细胞生物学行为、基因、相关激素及手术和放化疗的关系,增加了读者对FAK的了解,避免重复性研究,为FAK在结直肠癌中的研究提供思路 and 方向。

从淋巴系统和血管通过时,都会受到压力和切应力,术后脱落到腹腔的细胞也会受到术后腹腔内组织水肿增加的压力^[57-59]。Thamilselvam等的研究表明机械性刺激如增加的细胞外压和非层流切应力可激活经典的Src/FAK/PI3K/Akt信号通路,增加结直肠癌细胞对细胞外基质的黏附,促进结直肠癌细胞存活,抑制其凋亡^[1,60-62]。

3.3 与结直肠癌化疗的关系 术前化疗可使结直肠癌细胞FAK的表达下降,原因有两方面:(1)FAK的激活需要整合蛋白和ECM配体结合,整合蛋白的表达量影响着FAK的表达,化疗使肿瘤组织中整合蛋白 $\beta 1$ 的表达减少,从而使FAK的表达量减少;(2)化疗可以使部分肿瘤细胞缺血坏死、凋亡,肿瘤表达FAK减少。术前化疗可通过引起FAK表达的减少,降低术后肿瘤的侵袭转移,改善患者预后^[63]。

Chen等^[64]运用RNA干扰技术构建了抑制FAK表达的载体pGenesil-1-FAK,成功干扰了FAK及磷酸化FAK pY397的表达,增加了癌细胞对化疗药物5-氟尿嘧啶的敏感性,促进了结直肠癌细胞的凋亡,进而有效地逆转结直肠癌细胞对化疗药物的耐药性。

4 结论

FAK与结直肠癌基因、肿瘤形成相关激素以及手术治疗和化疗关系密切。FAK可通过多条信号通路促进结直肠癌发生。术前化疗可使FAK表达量下降。RNA干扰技术可抑制FAK表达,促进结直肠癌细胞的凋亡。FAK有望成为结直肠癌治疗的一种新的靶向分子,具有广阔的临床应用前景。

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同行评价

本文具有一定的科学性和学术价值, 对结直肠癌的研究提供了一定的价值。

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