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文献综述 REVIEW

肝激酶B1基因在胰腺癌中的作用及研究进展

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背景资料
肝激酶B1(liver kinase B1, *LKB1*)基因首先发现于Peutz-Jeghers综合征患者, 其下游包括了14种腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)相关性激酶, LKB1功能失活与包含胰腺癌在内的多种肿瘤形成、发展有关.

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Update on the roles of liver kinase B1 in pancreatic cancer

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Abstract

Germline mutations of the liver kinase B1 (*STK11/LKB1*) gene which encodes a serine/threonine kinase is responsible for Peutz-Jeghers syndrome. There are 14 AMP-activated protein kinase (AMPK)-related kinases in pathways downstream of LKB1, which are involved in many physiological and pathological processes such as regulation of energy metabolism, cell polarity and apoptosis in cells. *LKB1* gene mutation has been investigated extensively in a variety of cancers, including pancreatic cancer. Pancreatic cancer is commonly recognized as a disease with extremely poor prognosis. Therefore, a full understanding of its molecular pathology is critical. This review aims to elucidate the structure, distribution, and function of LKB1, and the relationship with pancreatic cancer. In addition, we also point out that in some scenarios, LKB1 may play a role as a tumor protector.

Key Words: Pancreatic cancer; Pancreatic ductal adenocarcinoma; Liver kinase B1; AMP-activated protein kinase

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摘要

Peutz-Jeghers综合征相关基因丝氨酸/苏氨酸激酶11(serine/threonine kinase 11, *STK11*), 也被称为肝激酶B1(liver kinase B1, *LKB1*)编码一种丝氨酸/苏氨酸激酶, 其下游信号通路包含14种腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)相关性激酶, 参与细胞能量调节、细胞极性调节和细胞凋亡等多种生理、病理生理学过程. 目前主流观点认为*LKB1*是一种重要的肿瘤抑制基

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因, 其功能失活与包含胰腺癌在内的多种肿瘤形成、发展有关. 胰腺癌是预后较差的一种恶性肿瘤, 全面了解其分子生物学知识对诊断治疗都尤为重要. 本文就LKB1结构、分布、功能及其与胰腺癌之间关系作一综述, 并指出其在某些情况下可能具有的肿瘤保护作用.

关键词: 胰腺癌; 胰腺导管腺癌; 肝激酶B1; 腺苷酸活化蛋白激酶

核心提示: 目前认为肝激酶B1(liver kinase B1, *LKB1*)是一种重要的肿瘤抑制基因, 其对胰腺癌的发生发展也非常重要, 另外LKB1还可以具有肿瘤保护作用.

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0 引言

尽管近年来联合手术、放疗、化疗等多种手段治疗胰腺癌, 其5年生存率已有所提高, 但是胰腺癌患者确诊后的平均生存期仅1年左右, 且发病率及总死亡人数呈逐年升高的趋势[1]. 胰腺癌相对肺癌、胃肠癌等其他肿瘤发生率并不高, 故对人群进行大规模筛查显然并不实际, 但由于其病死率相对较高使得在诊治胰腺癌过程中有两点极其重要: 一是早期诊断; 二是有效杀伤手术无法切除的瘤细胞. 因此, 通过基因技术侦测胰腺癌高风险人群和研究有效的靶向治疗药物就变得尤其重要. 胰腺癌中已发现存在多种基因改变, 其中家族性黑斑息肉病(Peutz-Jeghers syndrome, PJS)相关基因肝激酶B1(liver kinase B1, *LKB1*)是一种目前大多数研究认为比较重要的肿瘤抑制基因, 本文将通过综述该基因的研究进展及其与胰腺癌的关系, 来阐明这一家族性遗传基因在胰腺癌发生、发展过程中的作用.

1 LKB1的表达、调控及功能

1.1 LKB1与PJS *LKB1*也称为丝氨酸/苏氨酸激酶11(serine/threonine kinase 11, STK11), 在染色体上定位于19p13.3, 基因所编码的激酶大小约50 kDa, 该基因的突变首先发现于PJS中[2]. PJS是一种罕见的常染色体显性遗传病, 发病人口约占出生人口的1/200000-1/8300. 1921年由荷兰医师Jan Peutz首次报道, 随后于1949年由美国医师Harold Jeghers将该病归纳为一类综合征, 并最终定名Peutz-Jeghers综合征, 其特有表现包括肠道错构性息肉及口唇、颊黏膜及指趾端斑点状色素沉着. 虽然PJS息肉最常见于小肠, 但在包括胆囊的整个消化系, 以及甚至在泌尿系中也都有可能发生. PJS患者拥有较高的肿瘤(肠道或肠道外)发生风险. PJS患者消化系肿瘤好发部位包括胃、小肠、结肠、胰腺, 非消化系肿瘤则多见于乳腺、子宫内膜、卵巢、睾丸、肺及皮肤等处[3-7].

1.2 LKB1的表达与分布形式 *LKB1*基因由10个外显子构成, 跨度约23 kb[8]. mRNA全长为1302 nt, 同时还存在长度仅为444 nt的剪接体变异以及保留内含子4等的多种变异形式. LKB1的常见突变包括如K78I、D17GN、W308C以及L67P等, 这些突变均可致激酶活性的丧失[9,10]. LKB1广泛表达于多种人体组织中, 胎儿较成人组织中LKB1表达量高, 而成人则主要在睾丸的上皮细胞及生精小管中存在较高的表达量. 另外, LKB1在肿瘤中也并非均呈失活状态, 甚至在一些恶性程度较高的肿瘤中也有其过表达发生[11]. 在细胞内LKB1可在不同情况出现分布差异, 野生型LKB1在正常细胞的核及细胞质中均有分布, 而在凋亡细胞中, LKB1主要分布于线粒体. LKB1与相关结合蛋白相互作用时, 可出现核内聚集或膜定位障碍, 而其突变后, 也可因结构域的改变而产生类似现象.

1.3 LKB1蛋白复合体 内源性LKB1主要与假激酶STE20相关适配蛋白(STE20 related adapter, STRAD)和支架蛋白鼠蛋白25(mouse protein 25, MO25)形成异源三聚复合体[12], 这种LKB1-STRAD-MO25复合体形成加强了LKB1的稳定性, 并可激活LKB1[13]. 另外, LKB1还可与热休克蛋白90(heat shock protein 90, HSP90)和CDC37分子组成复合体, 也增强了其在细胞质中的稳定性[14,15], 但LKB1-HSP90-CDC37复合体形成将抑制LKB1激酶活性, 同时该复合体分解后可引起HSP/HSC70及E3泛素连接酶介导的LKB1降解. 故上述两种复合体虽然均有利于保持LKB1分子稳定, 但对LKB1激酶活性, 二者则呈现出相互拮抗关系[16].

研发前沿
有关LKB1在胰腺癌发生、发展相关机制的研究目前还不多, 虽然目前公认其为一种肿瘤抑制基因, 但是也要警惕其可能具有的保护肿瘤的作用.

相关报道
Reznik等概述了目前胰腺癌相关基因研究的热点和重点. Jeon等阐述了一种重要的通过LKB1-AMPK通路产生的肿瘤保护机制.

1.4 LKB1表达的调控

1.4.1 转录调节: *LKB1*基因启动子区域长约2.5 kb, 其上已发现存在雌激素受体α(estrogen receptor α, ERα)的结合位点, 研究[17]也显示雌激素可通过影响转录过程调节LKB1的表达, 但作用关系并不十分明确, 如在MCF-7乳腺癌细胞中, 17β-雌二醇可通过抑制*LKB1*启动子活性下调LKB1的mRNA及蛋白表达水平, 而另一组试验则发现通过敲除或使用17β-雌二醇处理降低ERα表达, 可增强LKB1的表达[18]. 虽然在*LKB1*启动子区域并未发现雄激素受体(androgen receptor, AR)原件, 但研究[19]发现在小鼠3T3-L1细胞及人SGBS脂肪细胞中, 睾酮和双氢睾酮可以显著降低LKB1 mRNA水平, 以其拮抗剂氟他胺预处理则可阻断这一过程, 提示雄激素也可间接调节LKB1表达. 另外在某些细胞的*LKB1*启动子上还发现4个可能的p53结合位点, 其中(-164--1)位点结合p53后可极大增强LKB1的表达[20], 还有研究[21]结果则提示这可能与NKX2-1/p53轴的调节有关.

1.4.2 转录后修饰: LKB1蛋白可通过磷酸化、异戊烯化、去乙酰化和泛素化等进行转录后修饰. 研究[22,23]显示LKB1的Thr366、Ser431、Ser428位点可分别被ATM、ERK1/2、PKCζ磷酸化并激活, 另外在HEK293细胞中发现LKB1的Ser31、Ser325位点也可被磷酸化, 但并不影响LKB1的核定位以及激酶活性[24]. LKB1的羧基端异戊烯化由PKA介导, 在HEK293细胞中LKB1还可在Cys433位点新增一个法尼基基团后发生异戊烯化[23]. 在293T细胞中过表达的去乙酰化酶(sirtuin 1, SIRT1)可以通过减少赖氨酸的乙酰化以增强LKB1活性并激活下游AMPK通路[25]. 另外上文提及的LKB1-HSP90-CDC37复合体可在裂解后通过泛素-蛋白酶体途径发生降解[16].

1.4.3 表观遗传修饰: 虽然在多种散发性癌肿中发现存在*LKB1*基因突变, 但对应的体细胞内却极少见到对应的突变形式, 提示*LKB1*基因的失活还可能与表观遗传学改变有关, 试验也在包括胰腺癌等多种原发性肿瘤标本或癌症细胞系中检测到*LKB1*启动子CpG岛的高甲基化状态, 而*LKB1*转录子相对应处于较低水平[26], 其他还包括在原发性结肠癌及部分PJS患者的肠息肉中发现了*LKB1*启动子的甲基化, 而相对应的正常组织中未见到类似的改变[27], 总之, 可以认为*LKB1*启动子甲基化是其在肿瘤等细胞中基因沉默的原因之一.

1.5 LKB1及其下游激酶 LKB1是14种AMPK相关蛋白激酶(AMPK-related kinases, AMPK-RKs)的关键激酶. LKB1可以磷酸化AMPK-RKs上与AMPK T172位点等位的T-环结构位点, 并显著增加其激酶活性. 另外在新激酶(novel/nua kinase, NUAK)、盐诱导激酶(salt-inducible kinase, SIK)、微管蛋白黏附调节激酶(microtubule affinity-regulating kinase, MARK)等AMPK-RKs的结构域中还存在不止一个可被LKB1磷酸化激活的位点[28]. 另外, 虽然AMPK还可以被钙调蛋白激酶激酶(calmodulin-dependent kinase kinase, CaMKKs)激活, 且其他AMPK-RKs的磷酸化位点结构与AMPK的十分接近, 但目前大部分研究[29]认为CaMKKs并不能磷酸化并激活这些AMPK-RKs.

2 LKB1与胰腺癌

2.1 LKB1缺失与胰腺癌高风险有关 *LKB1*基因的失活与胰腺癌尤其是胰腺导管腺癌(pancreatic ductal adenocarcinoma, PDAC)的发生有关, 既往研究[30,31]发现约36%的PJS患者有发生胰腺癌的风险, 并且相对风险是正常人群的40倍以上, 约5%的散发性PDAC患者发现具有体细胞*LKB1*基因突变. 另外还有约25%的胰腺导管内乳头状黏液瘤(intraductal papillary mucinous neoplasm, IPMN)患者具有*LKB1*基因的杂合性缺失, 但这些患者并未表现有PJS的特征性症状[32,33], 另外部分胆管癌患者也存在LKB1表达缺失[34]. 荷兰研究组进行的大规模队列研究[35]显示来自61个家族的共144例PJS患者(男性70例, 女性74例)中7例(5%)患者确诊胰腺癌(中位年龄54岁), 4例患者(3%)确诊远端胆管(2例)或壶腹部(2例)肿瘤(中位年龄55岁). 70岁胰腺癌累积风险为26%(4%-47%, 95%置信区间), 相对风险76(36-160, 95%置信区间). 另一个意大利研究组进行的多中心研究[36]回顾性分析显示, 119例PJS患者中有31人发生36例恶性肿瘤, 其中29例携带*LKB1*基因突变, 胰腺肿瘤发病相对风险为139.7, 累积风险为71%(中位年龄60岁). 这些研究认为具有*LKB1*基因缺失背景的PJS患者同时罹患胰胆管肿瘤的风险较高.

创新盘点

开始关注于*LKB1*基因与胰腺癌之间存在的相互作用关系, 并指出LKB1对肿瘤可能存在的双向作用.

2.2 LKB1缺失引发胰腺肿瘤的可能机制

2.2.1 抑制瘤细胞生长: LKB1可以抑制瘤细胞生长, 但不会影响正常细胞, 这可能与瘤细胞所处生长环境存在诸多应激因素有关, 如代谢应激及缺氧等. 代谢应激如能量匮乏, 可导致LKB1-AMPK信号在肿瘤细胞中的激活[28], AMPK激活可使瘤细胞同化作用减少、细胞周期停滞并最终抑制细胞生长. LKB1-AMPK信号可以通过分别抑制乙酰辅酶A羧化酶1(acetyl-CoA carboxylase 1, ACC1)、3-羟基-3-甲基戊二酸单酰辅酶A还原酶(HMG-CoA reductase, HMGCR)、哺乳动物类雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1, mTORC1)的活性, 从而减少脂肪酸、胆固醇以及蛋白质等生物大分子的合成[28,37]. 在瘤细胞中, 使用AMPK激动剂如二甲双胍, 可阻滞细胞周期进行从而显著抑制细胞生长, 这一效应的发生可能与磷酸化结节性硬化蛋白2(tuberous sclerosis complex 2, TSC2)导致的mTOR抑制作用有关[38]. LKB1对瘤细胞的细胞周期影响还依赖于p21和p53. LKB1可上调细胞周期蛋白依赖性激酶(cyclin dependent kinase, CDK)抑制子p21WAF1/CIP1从而介导G_1细胞周期阻滞[39], 并且可以被G_1细胞周期蛋白如细胞周期蛋白CyclinD1和CyclinE共表达所拮抗[40,41]. LKB1与p53的作用主要表现为细胞核内直接相互结合并使p53保持稳定, 同时通过直接或间接磷酸化p53上的Ser15及Ser392等位点以阻滞细胞周期进行. 并且AMPK也可以持续磷酸化激活p53从而加速细胞凋亡[42]. 大部分肿瘤存在缺氧现象, 这种状态下可刺激细胞上调的缺氧诱导因子1(hypoxia-inducible factor 1, HIF-1), 有利于细胞在缺氧环境中的存活[43]. 如前所述, LKB1-AMPK通路可负性调节mTORC1, 而mTORC1可上调HIF-1[44]. 在LKB1缺陷的瘤细胞中, mTORC1和HIF-1表达均明显增加[45]. 另外, 在某些癌细胞中, LKB1-AMPK可以通过降低环氧化酶2(cyclooxygenase 2, COX-2)信号以阻滞细胞生长[46], 而COX-2的过表达又可抑制LKB1的活性[47], 提示LKB1-AMPK-COX-2信号通路存在某种反馈环路调节细胞生长. LKB1还可与Brahma相关基因1(Brahma related gene 1, BRG1)蛋白相互作用并抑制瘤细胞生长, 而这种蛋白的编码基因*SMARCA4*也是一种胰腺癌相关的肿瘤抑制基因[48].

2.2.2 介导瘤细胞死亡: LKB1可通过多种途径介导细胞凋亡. 既往研究证实LKB1可通过p53依赖的信号通路诱导细胞死亡. 其他研究[26]还发现如在胰腺癌细胞株AsPC-1中, LKB1介导的细胞凋亡并不依赖p53, 但需要p73参与. 在某些瘤细胞中, 当LKB1发生K78M突变导致酶活性丧失后, 死亡相关蛋白3(death associated protein 3, DAP3)介导的细胞凋亡也会受到抑制, 同时LKB1也可经DAP3和肿瘤坏死因子相关的凋亡诱导配体(TNF-related apoptosis inducing ligand, TRAIL)介导细胞凋亡[49]. 除介导凋亡外, LKB1还参与细胞自噬过程, 在代谢应激如缺氧、能量剥夺等情况下, 激活的LKB1-AMPK信号将进一步磷酸化并激活TSC2, 从而抑制mTOR和mTORC1, 最终诱发细胞自噬[50]. 但值得注意的是, 细胞自噬对肿瘤细胞而言作用具有双重性, 一方面细胞自噬可导致瘤细胞的死亡; 但同时也可能有利于维持肿瘤在无法正常凋亡的情况下持续生长[51]. 因此LKB1调控的细胞自噬是否能抑制肿瘤细胞生长, 还与肿瘤细胞的类型及所处微环境情况等有关.

2.2.3 阻滞瘤细胞转移: 研究发现LKB1与瘤细胞的浸润和转移关系密切. *LKB1*是调节细胞极性的一个关键基因, 激活的LKB1可以使细胞在即使没有细胞间连接的情况下发生自发性极化. LKB1/AMPK可以通过维持上皮细胞极化状态防止细胞发生上皮间质化(epithelial-to-mesenchymal transition, EMT)转变[52]. 除瘤细胞自身变化外, 其转移还与细胞及基质间的分离、黏附有关, 其中局部黏附激酶(focal adhesion kinase, FAK)发挥了重要作用, LKB1则可以通过抑制FAK-src途径阻滞这一过程[53,54]. 此外, 在LKB1天然缺失的MDA-MB-435细胞中, 过表达LKB1可显著抑制该细胞的浸润和转移能力, 同时伴随有基质金属蛋白酶(matrix metalloproteinase, MMP)-2和MMP-9以及血管内皮生长因子(vascular endothelial growth factor, VEGF)等转移相关基因的表达下调[55]. 对于已发生转移的癌细胞而言, LKB1/SIK1途径的失活还有助于其避免发生p53介导的失巢凋亡, 提示了LKB1缺失不仅能让癌细胞获得脱离基质的能力, 同时也为其在与基质脱离后保持存活提供了帮助[56].

应用要点
胰腺癌研究中有关LKB1的研究并不多, 尤其是其可能存在的抑瘤效应之外, 其他可能影响胰腺肿瘤发生发展的作用是进一步研究的重点.

2.2.4 LKB1/AMPK通路为靶向的胰腺癌治疗: 目前大部分研究认为LKB1及其下游信号通路具有肿瘤抑制效应, 故以此为靶点进行抗癌药物开发前景广泛. 已有研究[57-59]报道某些针对LKB1下游信号通路分子的药物, 如AMPK激活剂, mTOR抑制剂等对某些类型肿瘤或病变具有杀伤、抑制效力. 研究[60,61]发现二甲双胍可促进AMPK磷酸化肿瘤抑制基因*TSC2*从而负性调节mTOR, 并且在临床上也观察到使用二甲双胍治疗的患者, 其发生包括胰腺癌在内的肿瘤的风险相对较低. 目前使用二甲双胍与吉西他滨、厄洛替尼对比治疗进展期胰腺癌患者的研究已完成了二期临床试验(NCT01210911). 这种通过干扰肿瘤细胞葡萄糖及谷氨酰胺代谢的方法成为治疗胰腺肿瘤的一条新路[62], 并且根据这一思路, 许多新药也正在试验性用于治疗转移性胰腺癌的患者(NCT01196247). mTOR不仅是LKB1/AMPK通路下游的重要组成, 同时也是PI3K/AKT信号通路效应子, mTOR受体抑制剂理论上具有双重作用, 是非常值得期待的一类药物, 以依维莫司(Everolimus, RAD001)为代表, 目前已完成了二期临床研究(NCT00560963)并显示其可能对吉西他滨抵抗的转移胰腺癌患者具有一定的疗效[63], 而使用依维莫司单药与卡培他滨、妥西单抗等对比的研究也已完成二期临床试验(NCT01077986).

3 LKB1: 护癌基因?

尽管目前主流观点认为*LKB1*是一种抑癌基因, 但也有研究观察到一些矛盾的结果, 提示在某些环境下LKB1也可以是一种护癌因子. 除前文所述LKB1介导的细胞自噬可能在某些情况反而维护了瘤细胞的持续生长外. 在如能量剥夺等应激情况下, 相较于LKB1野生型成纤维细胞, LKB1缺陷细胞发生更多的细胞死亡[64]. 而作为AMPK激动剂的二甲双胍, 对LKB1-AMPK通路缺陷的非小细胞肺癌NSCLC治疗效果反而更好[65]. 在LKB1缺陷的肺腺癌细胞A549中, 过表达LKB1可激活AMPK抑制脂肪酸合成, 从而更利于瘤细胞抵抗葡萄糖饥饿诱发的细胞死亡[66]. 另外在肺癌EKVX细胞中还发现过表达LKB1还与多重耐药基因1(multiple-drug resistance 1, MDR1)介导的紫杉醇耐药有关[67]. 总之, 在某些应激状态下, 癌细胞存活可受到LKB1或其下游信号的保护, 因此以LKB1本身作为靶点进行肿瘤药物设计仍需谨慎.

4 结论

目前大部分研究支持LKB1以及下游信号可以抑制肿瘤细胞生长、诱发肿瘤细胞死亡或阻滞肿瘤细胞转移, *LKB1*可被认为是一种肿瘤抑制基因. 对胰腺癌而言, LKB1也可能具有相似的效应, 从流行病学研究结果到体内外试验均支持这一结论. 不过在某些情况下, LKB1还可能帮助瘤细胞躲避能量剥夺或药物引起的细胞杀伤, 这也是在今后研究LKB1对胰腺癌作用的研究中值得注意的问题.

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名词解释

Peutz-Jeghers综合征：是一种与生殖系*LKB1*基因缺失密切相关遗传综合征，其特有表现包括肠道错构性息肉及口唇、颊黏膜及指趾端斑点状色素沉着.

同行评价

既往研究中已经证实了LKB1在胰腺癌的发生发展中所起的作用, 本文对*LKB1*基因在胰腺癌的作用作了较为完整的综述.

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