

Hedgehog信号通路与胰腺癌关系的研究进展

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Relationship between Hedgehog signaling pathway and pancreatic cancer

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Abstract

Hedgehog (Hh) signaling pathway consists

of ligands such as Hh, receptor (patched), transmembrane protein Smo, nuclear transcription factor Gli, and downstream target genes. This pathway plays an important role in cell differentiation, tissue development and organ formation in the embryonic stage. In recent years, the Hh signaling pathway has been reported to play an important role in the development of pancreatic cancer. It can induce differentiation, proliferation and invasion of pancreatic cancer cells. Blocking the Hh signaling pathway in pancreatic cancer cells will provide a new and effective method for the treatment of pancreatic cancer. In this review, we will summarize the composition of the Hh signaling pathway and its relationship with the development of pancreatic cancer.

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Key Words: Hedgehog; Signaling pathway; Pancreatic cancer

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摘要

Hedgehog(Hh)信号通路主要是由配体蛋白Hh、蛋白受体蛋白Patched(Ptch)、跨膜蛋白Smo、核转录因子Gli蛋白及下游靶基因组成。该通路在胚胎时期的细胞分化、组织发育及器官形成中扮演重要角色,近年来其已被报道在胰腺癌发生和进展中发挥重要的作用,它能够诱导胰腺癌细胞的分化、增

背景资料

胰腺癌在世界范围内呈增多趋势,而他的侵袭性高,生存率低。目前的化疗和放疗治疗效果有限,因此,迫切需要对胰腺癌发病机制进行深入的基础研究,以提高早期诊断率、寻找新的治疗策略。

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■ 研究前沿

胰腺癌是一种恶性程度较高的消化系统肿瘤, 近年来发现Hedgehog(Hh)信号通路在胰腺癌发生发展中起重要的作用, 因此了解Hh信号通路在胰腺癌细胞中的作用以及当前的研究现状, 通过阻止此途径可能为胰腺癌的治疗提供新的方法。

殖和侵袭, 还与胰腺癌干细胞特性密切相关, 因此阻断胰腺癌细胞中Hh信号传导通路将为胰腺癌的治疗提供一个新的有效手段。在这篇综述中, 我们将总结Hh信号通路的组成、传导机制以及他与胰腺癌发生发展的关系。

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关键词: Hedgehog; 信号通路; 胰腺癌

核心提示: 本文较为详实地描述了Hedgehog信号通路传导机制及其在胰腺癌发生发展中的作用, 为胰腺癌的治疗提供新的思路。

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0 引言

胰腺癌在世界范围内呈增多趋势, 已成为癌症致死第4位病因, 且他将在2030上升到至癌症致死病因的第2位^[1]. 胰腺癌5年生存率<5%, 他的侵袭性生长和早期转移扩散使他成为最具有侵袭性的肿瘤之一, 约40%患者在确诊时已经发生局部或远处转移, 失去根治性手术的机会^[2]. 目前的化疗药物或放射治疗的效果是有限的, 因此, 我们迫切需要深入对胰腺癌发病机制的基础研究, 以提高早期诊断率、寻找新的治疗策略. Hedgehog(Hh)信号通路是几个主要调控胚胎生长发育重要步骤的信号途径之一^[3], 经研究发现Hh信号通路在胰腺发育过程中起重要作用, 但在成人胰腺组织中该信号通路处于失活状态, 异常的Hh信号通路会促进胰腺癌的发生并维持肿瘤生长的微环境^[4]. 了解Hh信号通路在胰腺癌细胞发生发展中的作用以及当前的研究现状, 通过阻止此途径可能为胰腺癌的治疗提供新的方法。

1 Hh信号通路传导机制

1.1 Hh配体的合成和释放 Hh基因最早是在果蝇里发现, 是由英文“刺猬”(hedgehog)简写而来的^[5]. 哺乳动物有3种Hh蛋白: Desert Hh(DHh)、Indian Hh(IHh)、Sonic Hh(SHh), 与其他两种亚型相比, SHh分布最广泛, 阳性表达率较高^[6]. Hh蛋白是一种高度保守的分泌性

糖蛋白, 需经过翻译后的修饰才具有活性. Hh的前体肽(45 kDa)进入内质网后首先经历一个胆固醇依赖性催化裂解产生19 kDa的N-端肽片段和一个25 kDa的C-端肽片段^[7], 而所有的Hh蛋白信号驻留在N-末端片段^[8]. 随后其N端片段的N末端在酰基转移酶(Hh acyltransferase, HHAT)的作用下发生棕榈酰化, C末端与胆固醇结合从而变成具有信号功能的蛋白^[7], 最后以旁分泌或自分泌的方式释放出去^[9].

1.2 Hh信号的传导 Hh信号的转导始于Hh配体与其受体Patched蛋白(Ptch)的结合. 受体Ptch是一种12跨膜蛋白, 其有两个亚型, 分为Ptch1和Ptch2, 两者与Hh的亲合力大致相同, 但Ptch1是更为适合Hh的受体, 这可能与他们的表达模式有关^[6]. 近年来研究^[10]表明, 细胞表面蛋白GAS1、CDO及BOC也能够与Hh配体结合并促进Ptch与Hh结合, 且有研究^[11]发现, 在一些小鼠的组织中, 如果缺乏这3种小分子, Hh信号将会失活. 尽管GAS1、CDO及BOC形成的多分子复合物与Ptch都能与Hh信号结合, 但前者主要是促进Hh信号, 而后者主要是抑制Hh信号^[12]. 然而, 这些细胞表面蛋白的具体作用机制仍然不清楚, 未来我们可以通过这方面的研究寻求抑制Hh通路的靶点. 除了担任Hh受体, PTC通过抑制七次跨膜蛋白Smo的功能而对Hh通路发挥负性调节的作用, 即当无Hh配体存在时, Ptch对Smo起抑制作用, 从而抑制下游信号的传导. 由于Smo不直接与Ptch1接触, 一般认为是受Ptch1调节的小分子介导于Ptch和Smo之间来调节他们之间的作用, 但Ptch1分子调节Smo的活性的具体机制仍然不明确^[13].

Smo是一种7次跨膜蛋白, 属于G蛋白偶联受体超家族成员(G protein coupled receptor, GPCR), 结构与Wnt信号受体Frizzled(Fz)家族相似. 他的C端位于细胞内, 而N端位于细胞外, 且N端有一个富含半胱氨酸结构域(cysteine rich domain, CRD)和一个跨膜片段(7TM)^[14]. 以前研究的重点主要在含有环靶明(Smo抑制剂)结合位点的7TM结构域上^[15], 但近几年研究推测Smo的CRD的功能可能与Fz的CRD功能相似, 分泌型配体Wnt结合到Fz的CRD区域触发信号穿过膜进入细胞核, 而内源性脂质如氧化胆固醇结合于CDR部位后使得Smo能够响应Hh信号, 提示CDR区是Smo活化的重要调控区

域^[14,16]. Smo激活的机制提醒我们通过药物干扰这些内源性脂质的合成也许能够阻止Hh信号的传导.

1.3 Hh信号的效应分子: Gli转录因子 Gli蛋白属于Kruppel样因子家族, 为含有结合DNA的锌指结构域的核转录因子, 他即是Hh信号的家族成员之一, 又是其转录目的基因之一, 因此*Gli*可作为Hh信号通路激活的标记基因^[17]. Gli在人类存在3种亚型: 分别为Gli1、Gli2和Gli3, 其中Gli1主要是转录激活剂, Gli2具有激活和抑制的双重功能, 而Gli3主要起转录抑制作用^[18]. 因此我们可以认为Gli2是Hh通路的主要感应器^[17]. 在没有Hh配体时, Ptch抑制Smo, 使得下游信号分子Gli2、Gli3的C-末端依次被PKA、糖原合成酶激酶3 β (glycogen synthesis kinase 3 β , GSK3 β)及CK1磷酸化, 随后招募具有F-box亚基的泛素连接酶E3, 这种泛素连接酶能够水解Gli2、Gli3, 形成C-端肽小片段, 这个小片段含有阻遏N-端肽片段的结构域和锌指结构域, 而缺乏C-端肽片段的激活结构域, 能够抑制信号的传导^[19]. 相反的, 当Hh配体存在时, Hh配体与Ptch结合, Ptch失去了对Smo的抑制, Smo被激活, 从而抑制了Gli2、Gli3的降解, 使得他们能够以全长形式进入细胞激活靶基因^[20].

1.4 Hh信号的抑制因子: Sufu Sufu在1999年被提出, 他能够抑制Gli转录因子的活性, 是Hh信号通路下游的一个关键负性调节因子^[21]. 近年来研究发现在配体受体结合的情况下, Sufu可直接和Gli蛋白结合从而抑制Gli在细胞核内聚集, 或者直接在核内抑制Gli的转录活性^[22]. Sufu与Gli结合后能够促进Gli的降解从而抑制Hh信号通路^[23]. 且利用*Sufu*基因敲除的小鼠实验表明, Sufu参与Gli2、Gli3活性调节的多个过程, 但具体机制仍有待阐明^[24]. 进一步研究Sufu的功能及其作用机制也许能让我们更加了解Hh信号的调控机制.

2 Hh信号与胰腺癌

Hh信号通路在胰腺发育过程中起重要作用, 但在成人胰腺组织中该信号通路处于失活状态, 炎症修复或肿瘤形成时才会重新激活. 胰腺癌早期及癌前病变阶段即可检测到Hh信号通路的激活, 且实验研究发现, 通过环靶明或其他方式阻断Hh通路能够诱导肿瘤

细胞的凋亡和阻止肿瘤细胞的分裂^[25]. 此通路在胰腺癌的发生中起着重要作用, 能通过以下几点来证明: (1)在小鼠发育的过程中强制表达SHh能够诱导类似于胰腺上皮类瘤变(PanINs)的病变^[26]; (2)激活*Gli2*基因能够诱导未分化的胰腺肿瘤^[27]; (3)Smo抑制剂环靶明能够诱导细胞凋亡和减少肿瘤组织的形成^[28]; (4)在表型为CD44⁺CD24⁺ESA⁺的胰腺癌干细胞中, SHh的表达量比正常的胰腺导管上皮细胞高出46倍^[29]. 最后, SHh信号通路的激活, 在放疗后胰腺肿瘤增殖中起着重要的作用, 且SHh和Gli1蛋白的表达水平与细胞的生长呈正相关^[30]. 此外, Hh通路抑制剂联合胰腺癌化疗药物如吉西他滨等治疗胰腺癌的模式表明, Hh通路抑制剂能够增加个体对化疗药物的耐药性^[31].

在胰腺和胰腺导管癌(pancreatic ductal adenocarcinoma, PDAC)中, SHh以旁分泌的方式表达于上皮和间质^[32,33]. Yauch等^[34]利用特异性表达分析表明, Hh信号通路的拮抗剂导致下游靶基因下调仅发生在间质而不是在上皮性癌细胞. Hwang等^[35]也经实验表明Hh靶向治疗主要影响肿瘤相关的间质, 而不是上皮细胞. 此外, Lee等^[32]通过PDAC的小鼠模型发现Hh信号通路的激活引起的间质增生而抑制上皮生长, 相反的通路抑制剂能促进上皮细胞的生长, 可以推测Hh信号可能通过控制上皮和间质生长之间的平衡来影响肿瘤的发生.

引起上皮肿瘤分泌的Hh信号运输至间质后, 为肿瘤的生长提供了一个有利的环境, 且Hh信号模型的建立表明了胰腺癌中, Hh信号通路的激活是肿瘤的生长所必需的^[36]. 最近的证据表明, Hh信号通路通过影响上皮间质转化(epithelial mesenchymal transition, EMT)来影响不同类型癌症的发生^[37], 而实验发现Hh通路的异常的激活能够增加胰腺癌细胞中与EMT相关基因*N-cadherin*、*vimentin*、*fibronectin*、*Snail*和*Slug*的表达^[38], 且有研究者认为Hh信号通过增加Snail蛋白表达和减少E-cadherin表达来促进肿瘤的转移, 同时也增加血管生成因子与细胞周期蛋白, 减少血管生成素的抗凋亡基因来促进肿瘤的生长^[39,40]. 有报道^[41]发现, Hh信号通路通过介导磷脂酰肌醇-3-激酶(phosphatidylinositol 3-kinase, PI3K)/Akt通路在胰腺转移和耐药中起着重要作用.

■ 相关报道

近年来不断有研究发现该通路的异常调控对多种人类恶性肿瘤的发生、发展极为重要, 如基底细胞癌、成神经管细胞瘤、前列腺癌、胃癌、乳腺癌、膀胱癌、肺癌、硬脑膜肉瘤以及横纹肌肉瘤等.

应用要点

针对Hh信号的特异性靶向治疗必然会成为临床上的一项有效的治疗肿瘤的新措施, 有望用于治疗Hh信号通路中各种信号分子异常激活引起的胰腺癌, 应用前景广阔。

胰腺癌干细胞(cancer stem cell, CSC)假说认为由于其表达抗凋亡和多药耐药相关蛋白, 干细胞可能是负责胰腺肿瘤发病, 突变、迁移, 从而维持肿瘤的生长^[42,43]。体外实验发现, 胰腺癌干细胞中SHh的表达量显著高于一般的胰腺癌细胞, 而体内实验也观察到用Smo抑制剂作用于胰腺癌细胞后, 发现其干细胞的量减少^[38]。此外, 肿瘤干细胞与肿瘤的耐药密切相关, 而Gli的表达也与胰腺癌的耐药性有关^[44]。Gu等^[45]经研究证实, 胰腺癌肿瘤的转移伴随着胰腺癌干细胞表明标志及Hh信号通路的靶基因的表达增加, 且Hh通路抑制剂能够有效抑制胰腺癌肿瘤的转移。这些都说明Hh信号通路在维持胰腺癌干细胞的生物学特性中起着重要的作用。

3 结论

由于Hh信号通路在大多数胰腺癌细胞中处于激活状态, 因此针对此通路的靶向治疗具有潜在的治疗效益。一些体外的细胞实验已经证实环靶明和小分子SHh拮抗剂具有降低肿瘤负荷和诱导肿瘤细胞凋亡的疗效^[46], 然而在临床上验证Hh通路抑制剂的疗效仍然难度较大, 可能是因为该通路中的各个分子机制仍不太明了^[47]。Gli即是转录因子也是靶基因, 他还能通过不同的信号转导通路诸如转化生长因子- β (transforming growth factor β , TGF- β)^[48]、MAP3K^[49]、CXCR4^[50]等信号而激活, 因此, Gli可能是胰腺癌治疗的更好的靶向治疗目标。另外由于这些信号分子之间的协同作用, 我们可以通过了解胰腺患者个体中各通路的活化状态, 进而进行分子分型, 确定个体化的治疗方案, 这也将有可能成为未来胰腺癌治疗的关键。

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同行评价

该综述对近几年国内外关于Hh信号通路传导机制及其在胰腺癌发生发展中的作用的研究成果以及研究意义进行了较为系统的归纳和总结, 内容严谨, 具有重要的理论意义和应用价值。

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