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文献综述 REVIEW

胆管癌相关信号通路的研究进展

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Advances in research of signaling pathways in cholangiocarcinoma

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Abstract
Epidemiological data indicate that the incidence and mortality of cholangiocarcinoma (CC) show an increasing trend worldwide over the past several years. Many pathophysiologic aspects of this neoplasia are still unknown and need to be fully discovered. However, progress has been recently made in understanding molecular mechanisms involved in the transformation and growth of malignant cholangiocytes. It is found that cholangiocarcinogenesis is a multistep cellular process evolving from a normal condition of the epithelial biliary cells and ending with malignant transformation through a chronic inflammation status. The bad prognosis related to CC justifies why a better identification of the molecular mechanisms involved in the growth and progression of this cancer is required for the development of effective preventive measures and valid treatment regimens. Signaling pathways can regulate substance and energy metabolism in organisms and are closely related to biological growth and development. This paper mainly introduces signaling pathways which occur in cholangiocarcinoma and their roles in cholangiocarcinoma cells.

Key Words: Cholangiocarcinoma; Molecular mechanism; Signaling pathway

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摘要
过去几年的流行病学数据显示, 全世界胆管癌的发生率及致死率呈上升趋势. 对于这种疾病的病理学原因目前尚不明确. 然而, 最近对胆管癌的研究进展为我们从分子机制着手了解胆管癌发生和转化提供了一些思路. 这些研究结果至少可以总结为胆管癌发生是一个多步骤的细胞进程, 通常从正常状态的胆道上皮细胞经慢性炎症最终走向恶性胆管癌. 胆管癌的不良预后使得寻找与该肿瘤相关的分子机制及预防措施成为首要任务. 信号通路作为生物体内调节物质和能量代谢的信号系统与生物的生长、发育等密切相关. 本文主要以发生在胆管癌中的信号通路为重点, 介绍不同信号通路及其分子机制在胆管癌细胞中的生物学作用.

关键词: 胆管癌; 分子机制; 信号通路

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0 引言
胆管癌因其在世界范围内的高发生率及其易致死性而被认为是死亡性癌症, 他主要起源于分化的胆管上皮细胞[1], 部分也可起源于未分化的肝干细胞, 是仅次于肝细胞癌的肝胆恶性肿瘤,

■背景资料
目前国内外对胆管癌的研究较少, 胆管癌发生和发展中相关信号通路的分子机制仍不清晰. 因此, 介绍胆管癌发展进程中的信号通路将为今后的研究提供信息支持, 以便研究者了解目前的趋势和成果.

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■相关报道
胆管癌的发生是一个多步骤、多因素参与的过程, 国内外相关研究已经证实在胆管癌的发生中有大量信号通路被激活. 例如, 生长因子信号通路c-Met、ErbB2、Notch、TGF-β以及各类激酶信号系统, 这些信号通路系统大部分诱导胆管癌细胞抵抗凋亡, 从而逃脱死亡的命运, 最终导致不同程度的恶性侵袭胆管癌细胞的产生.

流行病学研究显示其在西方国家的发病率正逐年上升[2]. 由于胆管癌预后较差使其存活率一般<2年[3]. 治疗胆管癌唯一的方法是采用外科手术切除或肝移植. 由于大多数能检查出的胆管癌的患者已到癌症晚期, 即使能手术治疗, 预后也差, 效果不明显. 更严重的是, 传统的化学疗法和放射治疗对晚期胆管癌的治疗作用有限, 无法有效延长患者的生命[4]. 胆管癌的发生与胆道慢性感染、溃疡性结肠炎及胆汁积聚等关系密切, 是一个由多分子、多因素、多信号通路参与构成的多步骤疾病. 其发病机制十分复杂, 近年来对胆管癌的研究已日趋成熟. 胆管癌发生及进展过程中相关的信号通路也较为明朗. 本文以信号通路为切入点, 着重阐述胆管癌发生及发展中相关信号通路的研究进展.

1 胆管癌发生及发展中的信号通路

1.1 Ras信号通路 许多研究证实Ras信号转导通路在真核细胞的生长过程中处于中枢地位. 在人类的许多癌症中都有*ras*基因的突变, 其突变后持续活化的生长信号导致细胞的恶性增殖. 研究表明, 激活Ras的表达能增强血管生长因子[例如血管内皮生长因子(vascular endothelial growth factor, VEGF)/(vascular permeability factor, VPF)]的表达提示Ras在血管生成中发挥作用. 抑制Ras活性能抑制依赖Ras的肿瘤细胞的增生, 并且也能干扰血管生成[5]. 而在胆管肿瘤发生中有*k-ras*基因的点突变的报道. 这种点突变主要是编码*ras*的基因序列上12号密码子甘氨酸突变成天冬氨酸, 也有少许突变为缬氨酸[6-8]. 另外, 突变还会发生在密码子13上和密码子61上. 这些在*k-ras*上的不同突变主要是由肿瘤类型、人种以及地域差异, 或者采取不同的分析技术造成的[6]. 另外, Ras信号通路还有多个磷酸激酶信号通路偶联, 如Raf激酶磷酸化有丝分裂原活化蛋白激酶激酶(mitogen-activated protein kinase kinase, MAPKK, 也称MEK), MAPKK激活有丝分裂原激活蛋白激酶(mitogen-activated protein kinase, MAPK, 也称ERK)等. 这些激酶被激活后, 转至细胞核内, 可直接激活转录因子的转录和表达, 从而诱导一系列极限反应, 最终发生细胞信号通路的异常激活或紊乱.

1.2 IL-6信号通路 白介素-6(interleukin-6, IL-6)是参与调节胆管癌细胞生长的一个主要的细胞因子. Meng等[9]的研究显示IL-6能促进胆管癌细胞的增殖并诱导其抵抗化疗进而存活. IL-6是肝细胞在不同病理状态如胆管细胞发生炎症状态时分泌的细胞因子. 这种细胞因子有2种功能: (1)免疫应答; (2)刺激正常细胞及肿瘤细胞的生长能力. 有研究证实IL-6对胆管癌细胞的发病和生长具有根本性作用[9]. 许多数据显示炎症介导的IL-6可作为在胆管癌细胞抗凋亡的直接信号机制, 并指出激活转录因子-3(signal transducers and activators of transcription, STAT-3)在胆管癌恶性转化过程中有重要功能, 并且在胆管癌患者中其胆汁和血清中可检测到高水平的IL-6[10]. 说明IL-6或许可作为检测胆管癌疾病的指标之一. IL-6可通过旁分泌/自分泌机制及特殊的促进子P44/P42和P38 MAPK通路刺激细胞的增殖[11].

另外, IL-6已被证实在胆管癌以及其他癌症的发生中扮演着促进因子和存活因子的作用[12-14]. IL-6促进胆管癌细胞的增殖和分化[15]是通过激活Akt信号通路上调Mcl-1(抗凋亡Bcl-2家族的一员)抵抗TRAIL诱导的细胞凋亡作用而发生[14,16-18]. 当抑制IL-6诱导Mcl-1的表达可恢复癌细胞对TRAIL的敏感性[14]. 还有研究发现在胆管癌细胞内IL-6通过磷酸化信号转导途径和STAT-3诱导抗凋亡蛋白Mcl-1的表达, 从而增强胆管癌细胞抵抗凋亡的能力. 也有研究发现IL-6还可通过激活MAPK信号通路上调Mcl-1的表达[19]. 并且, 这种效应也依赖于IL-6诱导激活STAT-3(特别是在侵袭性高的恶性胆管癌中)[16]. 也有研究发现细胞因子信号抑制物-3(suppressor of cytokine signaling, SOCS-3)可通过经典的反馈环控制IL-6/STAT-3信号通路实现对胆管癌细胞的负调节作用[19]. 也许, SOCS-3可作为这一信号通路的靶点治疗胆管癌.

1.3 NF-κB信号通路 大量研究表明NF-κB信号通路在多种人类癌症中存在异常表达的现象[20]. 在一些癌症中, NF-κB信号通路主要存在于细胞核内[21-23]. NF-κB的激活不仅可保护肿瘤细胞免受凋亡, 还能增强肿瘤细胞的生存能力[24]. 抑制NF-κB的激活能诱导肿瘤细胞的凋亡, 暗示肿瘤细胞的生存与死亡之间的对抗平衡与NF-κB信号水平相关. 在胆管癌的NF-κB信号通路研究中, 有结果显示咖啡酸苯乙烯酯(caffeic acid phenethyl ester, CAPE)能作为NF-κB信号通路的抑制剂, 抑制胆管癌细胞的生长[25].

1.4 生长因子信号通路 多类生长因子如肝细胞生长因子(hepatocyte growth factor, HGF)、c-Met以及ErbB2已被证实参与胆管癌细胞的生命进程[26]. c-Met的含量与胆管癌细胞的分化程度相

关, 高分化的胆管癌细胞中c-Met的水平比低分化的胆管癌细胞高[27,28]. 研究发现c-Met作为一个酪氨酸激酶受体在许多癌症中有过量表达或调控紊乱的现象, 并证实c-Met与胆管癌的生长相关[27-30]. 特别是与侵袭性和迁移性肿瘤的生长密切相关[31]. c-Met是定位在7号染色体上的原癌基因, 能在胆管癌细胞表面的高表达酪氨酸激酶生长因子受体[32,33]. c-Met的亚基为HGF/SF. HGF/SF-Met通路可参与胚胎发育进程. 然而相关研究结果也显示胆管癌细胞中的HGF的表达水平升高, 同时有c-Met(HGF的细胞表面受体)的上调和过度磷酸化, 并存在调节恶性胆管癌生长的自分泌环[34]. 胆管癌细胞过表达c-Met与其增强细胞迁移和侵袭有关. 相反的, 抑制c-Met的表达伴随着细胞生长和侵袭的减缓[35]. HGF与c-Met结合诱导细胞内酪氨酸激酶在受体β-亚基的自磷酸化[33]. 这一过程伴随一系列信号网络如Src、PI3K、Gab1、SOS、Grb2和MEK1/2的激活, 所有这些信号网络都参与调节细胞侵袭, 血管形成, 肿瘤分化及增殖[36,37]. HGF/Met信号通路通过调节如细胞分布、侵袭、增殖和细胞存活等参与多种生物学进程[37-39]. 已有研究证实HGF/Met是通过激活胆管癌细胞中的ERK1/2, 以及PI3K/Akt等信号通路调节细胞的侵袭和迁移[40].

1.5 JAK/STAT信号通路 JAK/STAT信号通路是调节胆管癌细胞抵抗凋亡的一条关键信号通路. 在最近的一项研究中, Blechacz等[41]表明JAK/STAT信号通路能被多重激酶抑制剂-索拉菲尼抑制, 这可以作为降低胆管癌生长的治疗物. 索拉菲尼通过刺激磷酸激酶SHP-2的激活诱导STAT-3去磷酸化, 最终导致胆管癌细胞对TRAIL介导的凋亡敏感而发生细胞凋亡.

1.6 Fas凋亡信号通路 Fas/Fas L信号通路最早证明在细胞凋亡中起着重要的作用. Fas介导的肿瘤细胞凋亡被认为是一个潜在的肿瘤治疗靶点, 包括胆管癌. Chen等[42]的研究发现有Fas抗性的胆管癌细胞比Fas敏感性细胞展示出更高的Akt的磷酸化作用. 而过高的Akt磷酸化已被证实正与胆管癌的形成有关. 蛋白激酶B/Akt信号通路在调节胆管癌凋亡进程中发挥重要的作用[4,43]. 研究人员还发现3, 3'-二吲哚甲烷可促进Fas介导的胆管癌细胞凋亡, 原因是二吲哚甲烷可抑制Akt的磷酸化并激活FLICE-类似的-抑制蛋白抑制磷脂酰肌醇3-激酶/Akt从而减少FLICE-类似的-抑制蛋白的活性最终促进Fas介导的凋亡[42]. 这一系列结果提示Akt和FLICE-类似的-抑制蛋白也许可作为治疗胆管癌潜在的分子靶点, 而二吲哚甲烷可作为在胆管癌治疗中的有效药物.

1.7 TGF-β信号通路 转化生长因子-β(transforming growth factor-β, TGF-β)信号通路是一个由细胞因子参与的与细胞生长, 分化, 迁移, 凋亡, 黏附, 存活和免疫等细胞学作用相关的信号因子. TGF-β大部分由肝细胞合成, 而胆管细胞只有在病理状态如胆汁郁积时才合成TGF-β[44]. 一般来说, TGF-β的作用是抑制效应. 例如, 他通过调节细胞周期蛋白P21依赖性激酶抑制子而降低胆管癌细胞增殖[45]. 然而, 由于TGF-β的受体(TβR1)突变以及细胞内信号介质改变(如Smad4), 或者细胞内周期蛋白CyclinD1的过表达使得在胆管癌细胞中这种抗增殖作用被隐藏[46,47]. 另外, TGF-β信号通路通过下游分子Smads家族介导胆管癌细胞的上皮-间质转化(epithelial–mesenchymal transitions, EMT)进程. Sato等[48]的研究还发现TGF-β可通过降低上皮标记基因E-钙粘蛋白(E-cadherin)和细胞角蛋白19, 并增加间质标记基因*vimentin*和*s100a4*, 通过下游分子Snail激活胆管癌细胞的上皮-间质转化进程. 即TGF-β信号能刺激胆管癌细胞纤维化[49]. 总之, 在胆管癌中TGF-β信号的异常激活可导致细胞增殖, 形成纤维样并发EMT[47]. 将TGF-β信号通路作为抑制靶点也许可以作为治疗侵袭性胆管癌或其他侵袭性癌症的方法.

1.8 ErbB-2信号通路 许多研究表明胆管癌细胞表达大量的ErbB-2蛋白. 这个分子参与胆管癌的发生和发展[29], 且其过表达能维持胆管癌细胞的生长和存活. 另外, 其对肿瘤细胞的直接作用还与其刺激环氧酶-2(cyclo oxyge nase, COX-2)的形成有关. COX-2形成的复合物又可作为IL-6受体的亚基[50]. 这一作用暗示IL-6和ErbB-2信号之间的密切联系[48,50]. Lai等[51]在正常胆管细胞中转染大鼠同源的ErbB-2后细胞经历类似人类胆管癌细胞的恶性转化过程, 暗示ErbB-2对胆管细胞成癌的密切作用. Treekitkarnmongkol等[52]证实ErbB2能通过PI3K/AKT/p70S6K途径诱导胆管癌细胞的侵袭和增殖. 在ErbB2高表达的胆管癌细胞中, ErbB2及其作用的效应分子或许可作为今后在胆管癌诊断和治疗的靶位点.

1.9 Notch信号通路 在哺乳类动物中Notch信号通路包含4个Notch受体(Notch1-4)和5个亚基(Jagged1、Jagged2、DLL1、DLL3和DLL4). 从生理学方向看, Notch信号通路在多细胞生物发育

■创新盘点

此文章的主要创新之处在于将目前对胆管癌分子机制的研究成果进行总结, 是目前国内首篇关于胆管癌信号通路的综述性文章. 这篇文章可为胆管癌的进一步研究提供信息参考.

■名词解释
胆管癌: 是指原发于左右肝管汇合部至胆总管下端的肝外胆管恶性肿瘤.

过程中发挥着调节细胞的分化、增殖、凋亡、干细胞形态的维持以及决定多种细胞命运[53]的作用. 许多研究发现, *notch*基因紊乱与血液系统恶性肿瘤有关[54,55]. 另外, Notch信号通路异常与大多数实体瘤形成, 如乳腺癌、肾癌、前列腺癌、胰腺癌、宫颈癌、脑癌、肺癌、肝癌和皮肤癌等相关[56]. DLL4是Notch信号通路的内皮细胞特异性亚基, 在血管发生及血管再生时表达升高[57,58], 可由VEGF诱导产生并作为VEGF的下游调节分子, 使VEGF失活, 最终导致微血管的成熟和稳定[57]. 最近一项研究发现, Notch信号通路的受体(notch1-4)及其亚基DLL4与人类肝外胆管癌进程有关, 在不同分化程度的胆管癌组织中存在Notch蛋白1-4的较高表达, 而DLL4在细胞质中水平较高. 在肝外胆管癌上调DLL4与组织的低分化相关, 而DLL4定位于细胞质中也与胆管肿瘤发生有一定的联系[59].

另外, γ-分泌酶素(γ-secretase)能在多种肿瘤中激活Notch信号通路. 当Notch与其亚基DLL或Jagged结合后在特殊的位点进行两个连贯的分裂. 第一个分裂发生在细胞膜外, 由ADAM-类似蛋白酶介导[60]; 另一个则由γ-分泌酶素复合物[含有早衰蛋白增强子-2(Pen-2), APH-1等]介导, 最终导致细胞核内靶基因的转录和表达. Frampton等[61]研究发现内源性大麻素(anandamide, AEA)能够促进早衰蛋白1的表达从而募集γ-分泌酶素复合物调节Notch1的活性; 而2-花生酰甘油基增强早衰蛋白-2的表达募集γ-分泌酶素复合物激活Notch2的活性, 最终抑制胆管癌细胞的增殖和分化. 这些研究结果表明Notch信号通路也许也可以作为潜在的治疗胆管癌的靶点, 反转其对肿瘤的正向活性而导致肿瘤凋亡.

1.10 Wnt信号通路 Wnt信号转导途径参与细胞多种复杂的生化反应过程. Wnt信通路中关键作用的分子即β-连环蛋白(β-catenin). Wnt信号通路通过下游多个信号通路控制细胞行为. 主要包含3种途径: β-catenin依赖的Wnt级联反应、β-catenin非依赖的平面细胞极性Wnt/PCP(planar cell polarity pathway)和Wnt/Ca^{2+}信号通路[62-64]. Wnt信号通路的异常激活与多种肿瘤发生有关. DeMorrow等[65]在研究AEA对胆管癌生长的调节中发现AEA能通过活化非经典的Wnt/Ca^{2+}信号通路抑制体外培养的胆管癌细胞的生长. 相反, Abuetabh等[66]的研究发现经典Wnt信号通路能参与激活胆管癌细胞的生长进程. 他们的研究发现经典Wnt信号通路关键因子β-catenin的表达与侵袭程度不同的胆管癌细胞相关, 且其表达后在细胞内的定位根据胆管癌侵袭程度不同而不同. 另外, Tokumoto等[67]对24例肝内胆管癌患者样品进行分析后发现Wnt靶基因β-catenin过表达且可分布在细胞膜和细胞核内, Wnt信号通路下游靶基因*c-myc*、*cyclind1*等也发生明显的过表达现象, 而CyclinD1的表达量出现不同程度的升高; 序列分析结果显示腺瘤息肉病毒(adenomatous polyposis coli, APC), *axin1*等基因发生不同程度的突变. 这些结果都暗示经典Wnt信号通路靶基因的过量表达在胆管癌的发生中发挥重要的作用.

系统研究Wnt信号通路在胆管癌中的相关分子机制的信息相对较少, 这也可能是由于Wnt信号通路在其他肿瘤的研究中投入过多, 另外, 在胆管癌内的预后低, 造成发现该病症时已是癌症晚期, 因此较难发现早期的治病机制, 而Wnt信号的激活一般发生于早期.

1.11 PTEN和mTOR信号通路 作为在多种恶性肿瘤中起着关键调控作用的信号通路, PI3K/PTEN/Akt/mTOR信号通路可介导肿瘤细胞的增殖、分化和凋亡等. *pten*是一个抑癌基因, 在多种肿瘤中具有较高的突变率, 是PI3K/Akt/PTEN信号通路的重要调节因子[68]. mTOR是一种蛋白激酶, 能被PI3K/Akt磷酸化而激活, 从而通过下游分子影响细胞周期, 调节细胞凋亡[69]. Chung等[70]在对221例肝外胆管癌的研究中发现在胆管癌细胞内PTEN的表达明显低于正常胆管组织, 而mTOR和Akt的表达明显增高. PTEN的表达降低同样导致PTEN/p-AKT和PTEN/p-mTOR信号减弱, 导致患者的存活率下降. 这一结果提示这条信号通路在介导胆管癌的发生及凋亡进程中可能发挥着重要的作用. 最近还有发现Smad4能与PTEN结合调节细胞周期. 当Smad4和PTEN在胆管癌模型老鼠体内被敲除后, 小鼠胆道出现大规模增生. 另外, 研究人员还发现胆管癌的形成还伴随着多步骤与多个信号通路转变的组织病理学变化, 包括Akt的磷酸化、FOXO1、GSK-3B、mTOR和ERK信号水平增加, 以及细胞核内的CyclinD1的水平升高[71].

2 结论

尽管现阶段对肿瘤发生和发展的的研究已越来越深入, 对其发生和发展的机制也越来越明确, 但是参与胆管癌发生和发展的分子机制仍未阐

明. 并且, 由于胆管癌发病机制难以明细, 且预后差, 因此明确胆管癌发病相关信号通路之间的关系尤为重要. 多细胞生物体细胞内的信号传递是高度复杂的网络过程. 不同的外界或内在刺激会引发不同的信号传导和信号偶联, 从而对生物的生命活动进程进行调控. 信号通路的异常往往与肿瘤发生相关. 由于胆管癌发生率呈现世界范围内的递增又缺乏有效的治疗手段, 因此找到治疗胆管癌的关键靶位点以及靶向药物成为目前研究热点之一. 由于信号通路的网络效应, 在众多的信号通路中发现他们的关联分子也许可为胆管癌的治疗提供新的视点. 现阶段对信号通路的研究已经取得了不少的进展, 但还有许多路要走. 通过对胆管癌内信号通路的分析, 可以知道胆管癌的各种信号通路之间有一定相似性, 单一分子作用可能会被信号偶联作用放大, 如蛋白激酶信号系统(AKE/MAPK/JAK/PI3K), 以及细胞因子信号系统等, 也有许多信号系统通过激活抗凋亡基因Mcl-1等而使胆管癌细胞逃脱衰老与凋亡的程序而继续增殖分化、侵袭和迁移. 由于胆管癌预后较差, 找到引发胆管癌发生和发展中的关键调节子并将其作为治疗胆管癌的有效靶分子, 或找出诊断胆管癌发生的关键因子都将为胆管癌的治疗提供新的思路.

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■同行评价
本文较全面的总结了信号通路在胆管癌发生、发展中的作用.

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