

胰岛素/胰岛素样生长因子与肝再生的关系

褚延魁, 王胜智, 刘育蕾, 康志龙

褚延魁, 王胜智, 刘育蕾, 康志龙, 中国人民解放军第302医院普通外科 北京市100039

褚延魁, 副主任医师, 主要从事肝胆外科与腹腔镜微创外科的研究。

作者贡献分布: 褚延魁、王胜智、刘育蕾及康志龙对此文所做贡献均等; 设计方案由褚延魁提供; 文献检索由王胜智与刘育蕾共同完成; 此论文写作由褚延魁与康志龙完成。

通讯作者: 康志龙, 100039, 北京市西四环中路100号, 中国人民解放军第302医院普通外科, bjjoan008@126.com

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Relationship between insulin/insulin-like growth factor and liver regeneration

Yan-Kui Chu, Sheng-Zhi Wang, Yu-Lei Liu, Zhi-Long Kang

Yan-Kui Chu, Sheng-Zhi Wang, Yu-Lei Liu, Zhi-Long Kang, Department of General Surgery, 302nd Hospital of the Chinese People's Liberation Army, Beijing 100039, China
Correspondence to: Zhi-Long Kang, Department of General Surgery, 302nd Hospital of the Chinese People's Liberation Army, 100 Xisihuan Middle Road, Beijing 100039, China. bjjoan008@126.com

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Abstract

Hepatocellular carcinoma is one of the most common cancers, and the main treatments include intervention, radiofrequency ablation, surgical resection and liver transplantation. Metastasis and recurrence contribute greatly to the high mortality rate of hepatocellular carcinoma. Currently, many efforts have been taken to find the ways to promote liver regeneration after liver resection. This article will discuss the relationship between liver regeneration and insulin/insulin-like growth factor.

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Key Words: Insulin; Insulin-like growth factor; Liver regeneration

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摘要

原发性肝癌(hepatocellular carcinoma)是目前最常见的癌症之一, 其主要治疗方法包括介入、射频消融、手术切除、肝移植等, 但是复发转移快, 病死率高是个不容忽视的问题。因此寻找肝切除术后剩余肝脏的再生方法逐渐引起了大家的广泛关注。本文将就肝再生与胰岛素及胰岛素生长因子之间的关系进行阐述。

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关键词: 胰岛素; 胰岛素样生长因子; 肝再生

核心提示: 胰岛素家族的研究不仅是肝再生研究的新方向, 也是肝癌机制深入研究的一个切入点。

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0 引言

原发性肝癌(hepatocellular carcinoma)在我国发病率极高, 目前治疗肝癌的方法很多, 虽然手术切除部分肝脏后, 机体释放的促进肝脏再生的因子, 能改善患者肝功能, 提高其生活质量, 但是大量肝癌术后患者由于肝脏损伤严重, 肝细胞坏死能力远远超过肝再生的能力。

1 肝再生的意义

众所周知肝移植是治疗肝脏衰竭最终解决途径^[1,2], 但是在我国由于肝源短缺, 受体供体配型、找到适合受体的肝脏供体需要等待的时间长, 许多患者往往没有等到供体肝脏时, 病情就已经恶化, 导致死亡。另外, 移植手术后长期应用免疫抑制剂带来的不良反应使其应用也受到了限制。

于是肝干细胞的研究逐渐成为了热点, 肝干细胞是具有无限增殖能力和多向分化潜能的细

■背景资料

原发性肝癌是目前最常见的癌症之一, 其复发转移快, 病死率高已成为不容忽视的问题, 因此寻找肝切除术后剩余肝脏的再生方法逐渐引起了大家的广泛关注。

■同行评议者

刘宝林, 教授, 中国医科大学附属盛京医院

■ 研发前沿

肝再生是一个复杂的过程,其发生机制至今也未阐明,肝再生的研究对于探讨肝癌的发病机制有重要意义。

胞^[3,4]。体内有许多细胞都符合肝干细胞的特征,如肝脏胚胎发育过程中的胎肝干细胞及成肝细胞、成年肝内存在的兼性肝干细胞及其子代细胞卵圆细胞,表达CD133的肝星状细胞等,此外,骨髓间充质干细胞、胰腺干细胞等可能也参与了肝再生^[5-7]。肝干细胞目前在移植领域、遗传性及慢性肝病治疗、肝肿瘤预防和肝病药物筛选等方面应用广泛^[8-10]。

目前寻求除了肝脏器官及肝干细胞移植以外的促进肝再生的方法逐渐成为了研究的热点,近年来肝再生的研究已经有了十分重大的成果,但其分子机制尚未达成共识^[11]。肝脏损伤或部分肝叶切除后,其他肝细胞可快速从G₀期进入S期,实现肝细胞的再生,并且这种肝细胞完成2-3次细胞分裂,刺激机体分泌一系列促进肝再生的细胞因子,从而激发一系列的生物效应,最终达到肝再生的目的^[12]。

因此,肝再生的研究意义十分重大,这将会大大提高肝癌患者肝切除术后的生存质量,延长患者寿命,除此之外,肝再生的研究对于探讨肝癌的发病机制有重要意义。

2 肝再生与胰岛素及胰岛素生长因子

肝脏的再生的启动及快速增值阶段主要是通过成熟肝细胞的有丝分裂或当肝组织巨大损伤后激活肝干/祖细胞来实现^[13]。近年来的研究表明,除了上皮生长因子(epidermal growth factor, EGF)、胰岛素、肾上腺素等因素外,肝特异性的生长因子(augmenter of liver regeneration, ALR)和抑素也参与了肝组织生长和再生的调节^[14]。1994年, Hagiya等从乳鼠肝脏中分离出一种促进肝脏再生的物质,并成功克隆了他的cDNA,即肝再生增强因子(augmenter of liver regeneration, ALR)^[15-17]。Takahashi等^[18]最近的研究表明:血小板对于抑制肝脏纤维化及肝损害有着很重要的作用,主要是通过3种途径来实现,直接作用于肝细胞、与肝窦状内皮细胞的协同作用及与Kupffer细胞的系统效应。因此,输注血小板及促血小板生成素将是除了肝脏移植外治疗肝脏疾病的新方向。

有研究表明,在人肝癌组织中,胰岛素生长因子-1(insulin-like growth factor-1, IGF-1)的mRNAs的表达较正常组织低^[19-21]。在动物模型和人肝癌中,胰岛素生长因子-2(insulin-like growth factor-2, IGF-2)已经有报道是高表达的^[22,23]。Zhou等^[24]用了多种肝癌细胞系进行检

测,包括(PLC、HCC细胞系)全部测得IGF-1R mRNA的表达低于正常对照,而IGF-2的表达却高于对照组。且在正常人、肝硬化患者及肝癌患者3组中,肝癌患者肝组织的IGFBP-3 mRNA水平显著降低。肝癌患者血清中IGFBP-2的水平显著增加,该研究小组首次采用了抗体芯片对25对肝癌与正常组织进行高通量检测,结果提示IGF-2R和IGFBP-2蛋白在肝癌组织中提高^[25,26]。这也提示了IGF家族蛋白也将成为今后肝脏疾病研究的热点。

部分肝切除术后,迅速进入了增殖阶段,当其增殖乏力时即进入肝再生终止阶段。在肝再生末期,肝重相对精确地被调整以与原肝重相适应;同时,通过TUNEL标记分析发现在小鼠肝再生的末期会出现一小部分肝细胞凋亡^[27,28]。

有报道发现肝再生终止阶段与转换生长因子-1(transforming growth factor, TGF-1)、激活素A(activin A)、整合素连接激酶(integrin-linked kinase, ILK)、磷脂酰肌醇3(glypican-3)、白介素1(interleukin-1, IL-1)等因子有关。可能是通过再生的肝细胞对TGF-1的分子进行分解,来发挥其抑制肝细胞增殖的作用^[29-32]。

研究人员通过*Nrf2*基因敲除小鼠的体外和体内的实验发现,部分肝脏切除后,胰岛素/胰岛生长因子氧化应激^[33-35],从而致使p38激酶和AKT激酶通路下游的靶点因子激活受损,进一步抑制了肝脏再生^[36-38]。由此说明,胰岛素/胰岛生长因子系统对于肝脏的再生的终止也发挥了非常重要的作用^[39]。

IGFs的蛋白质序列与胰岛素有极高的相似性,IGFs家族主要由两种低分子多肽(IGF-I、IGF-II)、两类特异性表面受体(IGF1R和IGF2R)组成^[40-44]。除此以外,还包含高亲和性IGF结合蛋白(IGFBP-1至IGFBP-6)以及相关IGFBP降解酶。IGF是一类细胞增殖调控因子,在细胞的增殖、分化及个体的生长发育过程中具有重要的促进作用^[45]。

IGF-I通过与IGF-I受体结合发挥生物学效应,然而IGF-II却具有双重结合力,不仅能与IGF-I受体结合,还能与IGF-II受体结合而起作用^[46]。IGF-I、IGF-II及其受体在肝细胞癌变过程中发挥重要作用,肝癌的发生发展与IGF-I、IGF-I R、IGF-II、IGF-II R的协同作用有密切相关性,IGF-I受体及IGF-II在HCC进展过程中过量表达,IGF-I受体通过与IGF-II结合导致自身酪氨酸激酶磷酸化,从而激活下游信号通路,

使肝细胞恶性分化能力增强^[47,48]。

IGF-2在肝癌的发生过程中具有极为重要的意义, 他不仅通过内分泌参与机体代谢过程中, 而且还通过自分泌/旁分泌的途径促进了肝癌细胞的增殖和分化^[49,50], 由于HCC中肿瘤细胞生长迅速导致局部缺氧, 大大增加人肝癌血管内皮因子(vascular endothelial growth factor, VEGF)mRNA和蛋白水平^[51], VEGF通过与窦状内皮细胞表面表达的受体Flt-1、Flk-1的结合, 在体内和体外均可促进内皮细胞的增殖分化, 从而进一步诱导IGF-2基因的表达。

3 结论

肝再生的过程是一个复杂的过程, 主要包括再生启动、快速增值及再生终止3个阶段, 其机制至今也尚未阐明, 许多的细胞因子都参与了这一过程, 除了胰岛素/胰岛素生长因子家族外, 肝再生增强因子, 上皮生长因子、肾上腺素、转化因子等也参与了肝再生的调节, 本文不再赘述。我们认为, 胰岛素生长因子家族的研究不仅是肝再生研究的新方向, 也是肝癌机制深入研究的一个切入点。

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■相关报道

相关报道提示患者血清中IGF-1R及IGF-2的表达与原发肝癌的发生密切相关。

■同行评价

本文结合临床,文献合理,结论客观可信,具有一定指导意义。

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