

VEGF与肝脏疾病的关系

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Relationship between vascular endothelial growth factors and liver diseases

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Abstract

Vascular endothelial growth factors play an important role in the processes of cell differentiation and maturation. As a kind of multi-functional factor, they are closely related to the occurrence and progression of liver diseases. They can not only promote postoperative liver regeneration but also repress the propagation of chronic hepatitis B and liver cirrhosis. In addition, they have a role in cancer diagnosis and treatment and graft rejection in liver transplantation. In this paper, we will give a brief introduction of vascular growth factors and their role in liver regeneration, cirrhosis, liver cancer and liver transplantation.

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Key Words: Vascular endothelial growth factors; Liver regeneration; Liver cirrhosis; Liver neoplasms; Liver transplantation

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摘要

血管内皮生长因子(vascular endothelial growth factor, VEGF), 作为一种多功能因子, 在组织细胞分化成熟的过程中, 发挥着很大的作用。不论是在术后促进肝细胞再生, 还是抑制慢性乙型肝炎、肝硬化的发展、肿瘤的诊治与治疗、肝脏移植的排斥反应等方面, VEGF通过与各自组织细胞之间的相互作用, 与肝脏疾病的发生、进展和结局密切相关。本文就以肝脏为对象, 简要介绍血管内皮生长因子及其在肝脏的再生、硬化、肿瘤及移植等方面的进展情况。

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关键词: 血管内皮生长因子; 肝再生; 肝硬化; 肝肿瘤; 肝移植

核心提示: 不论是在术后促进肝细胞再生, 还是抑制慢性乙型肝炎、肝硬化的发展、肿瘤的诊治与治疗、肝脏移植的排斥反应等方面, 血管内皮生长因子(vascular endothelial growth factor)通过与各自组织细胞之间的相互作用, 与肝脏疾病的发生、发展和结局密切相关。

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0 引言

血管内皮生长因子(vascular endothelial growth factor, VEGF)又称为血管渗透因子(vascular permeability factor, VPF), 最初是从牛的垂体滤泡星状细胞的条件培养基中纯化出来的, 随后在鼠垂体前叶源性肿瘤细胞系AtT20、人单核细胞、鼠神经胶质瘤细胞系也纯化出了VEGF^[1]. 在人类, VEGF包括主要5种类型, 分别

■背景资料

随着诊断治疗水平的进步, 肝切除的适应证和能够切除的范围不断扩大, 过去认为不能切除的巨大肝癌可以安全的切除, 这导致扩大性肝切除术在临床上的应用逐年增加. 如何提高肝脏术后的抗损伤修复能力, 一直是我们要关注的重点。

■同行评议者

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■应用要点

本文阐述血管因子多功能作用及与疾病的基本关系, 引发人们对疾病认识的进一步思考. 在组织细胞生长发育, 变性坏死方面意义重大.

为VEGF-A、VEGF-B、VEGF-C、VEGF-D和placental growth factor(PGF). 其中, VEGF-A为刺激血管生成最有效的类型, 至少存在6个亚型, 各自对应着不同亲和力的受体, 起着不同功能作用^[2]. 在正常细胞中也存在, 但其表达的数量是相当小的, 一般不参与新生血管合成, 仅维持正常的血管密度和通透性. 只有在生理需要或病理情况下才出现其过度表达, 促使血管生成作用急剧增加^[3]. 目前, 综合资料显示, VEGF虽然研究比较多, 但是在肝脏基础研究与临床衔接方面的综合性还是较少的, 本文就VEGF与肝脏疾病的关系做一综述.

1 血管内皮生长因子与肝再生

1.1 肝再生的机制 肝再生过程虽然早就被Higgins和Anderson^[4]描述过, 但是关于肝脏再生能力的分子及细胞研究机制还不是很透彻. 肝部分切除后, 在起步阶段, 剩余成熟细胞通过旁分泌, 自分泌, 补体C3a, C5a激活巨噬细胞, 细菌内毒素, 分泌肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α), 白介素6(interleukin-6, IL-6)等细胞因子, 激活JAK/STAT和MAPK通路启动肝细胞的再生^[5]. 肝细胞快速由静止状态G₀期开始肝细胞的再生, 一直持续到原肝质量的基本恢复.

肝窦内皮细胞(liver sinusoidal endothelial cells, LSECs)的活化与肝脏再生密切相关. Ding等和Wang等^[6,7]的研究表明, LSEC具有一种特殊VEGFR2⁺ VEGFR3⁺ CD34⁺ VE_cadherin⁺ FactorVIII⁺ CD4⁺表型, 在激活启动肝细胞再生过程中具有重要作用. 肝脏切除后, 在LSECs细胞的诱导下, VEGFR2激活, 启动Id1上调及HGF, Wnt2细胞外因子的释放并直接与肝窦内皮细胞、肝细胞联系. 随后, 通过VEGFR2-Id1途经, 毛细血管血管出芽增生, 用来保障肝脏不断增长所需的营养血液供养.

对于肝细胞及肝窦内皮细胞的再生, 适当的条件也是重要的. 当切除大鼠70%到90%的肝脏术后, 如果通路被ERK/MEK阻滞剂阻断, 会导致肝脏再生速度下降^[8]. 若肝切除术后突然出现大量再生反应, 则会使肝窦细胞窒息, 肝实质细胞大量沉积, 导致肝细胞及肝窦内皮细胞缺血缺氧, 引起肝功能损害.

1.2 肝再生的调节 (1)来源于脾、小肠的肝再生因子对肝实质细胞再生可能产生积极影响^[9,10]. Yamamoto等^[9]通过建立70%肝部分切除模型, 分别检测血液中VEGF蛋白、HIF-1 α 、肝细胞生

长因子(hepatocyte growth factor, HGF)、HGFA mRNA及在脾脏、小肠、门静脉的表达水平, 结果显示: 术后VEGF mRNA、HIF-1 α 、HGF和HGFA mRNA的表达明显上升; (2)血小板能促进LSECs的增殖并诱导IL-6及VEGF的产生, 而LSECs又能产生HGF、IL-6、NO等生长因子和细胞因子, 当这些因子激活细胞膜上各自的受体, 转录因子和信号转导通路后, 肝脏产生有丝分裂反应, 肝细胞增殖. 其中Kupffer细胞, 肝星状细胞等均参与肝细胞的再生过程^[11,12]; (3)NO在调节VEGF的表达方面发挥着重要作用. 当阻滞NO合成时, VEGF蛋白的表达下降, 且具有与VEGF协调调节肝窦内皮细胞分裂增殖的作用^[13,14].

1.3 肝细胞替代治疗 基于肝脏再生的特点, 有些学者曾设想将肝细胞替代治疗来取代原位肝移植, 但目前, 这种技术治疗在治疗急性肝功能衰竭的疗效方面, 效果还不确定. 据研究, 要确切提高治疗效果, 联合使用肝内皮细胞、内皮干细胞和模拟支架, 应用肝实质细胞嫁接到脱细胞肝支架中, 再放入功能完好的内皮细胞, 比直接移植更有效^[15]. 显然, 血管生长因子对肝窦内皮细胞分裂的促进作用是不可或缺的.

在处理肝脏外伤及其他肝脏手术中, 我们经常因为无法修补或不能彻底止血而必须采用肝脏部分切除术. 因此, 不管是术后, 外伤, 还是慢性炎症, 中毒性损伤等, 对肝细胞再生的深入研究, 均具有重大的意义.

2 血管内皮生长因子与肝硬化

2.1 肝硬化形成的血管机制 肝硬化形成的分子机制目前尚未彻底阐明. 一方面, 肝硬化是一系列生长因子, 细胞因子及金属蛋白酶等在组织慢性修复中过表达的结果, 尤以血小板源性生长因子(platelet derived growth factor, PDGF), 转化生长因子- β 1(transforming growth factor- β 1, TGF- β 1), 纤维母细胞生长因子(fibroblast growth factor, FGF), VEGF对肝脏纤维化及血管生成的影响大^[16,17]. 在病理上, 主要表现为肝细胞的变性坏死, 慢性炎细胞的浸润, 纤维结缔组织的增生及肝细胞的结节状再生. 此外, integrins、 β -catenin、ephrins及其他黏附分子, 细胞外基质也参与此过程^[18]; 另一方面, 在持续的炎症反应中, 组织逐渐发生纤维化, 血管阻力增加, 对血液灌注产生影响, 降低组织间氧含量, 进而刺激VEGF的表达, 促进肝窦内皮细胞的有丝分裂,

细胞基质增加和新生血管生成. 随着肝硬化的进展, 肝细胞破坏, 纤维化加重, 血液灌注得不到有效缓解, HIF-1 α 再次被迅速活化, 进一步诱导下游靶基因VEGF、PDGF-J3、血管紧张素-II表达, VEGF通过与其受体VEGF-R2结合, 再通过蛋白激酶C途径激活细胞外信号调节激酶通路, 从而促进内皮细胞增殖, 使肝纤维化进一步加重^[19,20].

然而, 也有人认为肝内血管增生与纤维化之间的变化关系, 能为治疗肝硬化提供新的方法, 肝内血管增生和肝窦重建可作为慢性肝脏疾病门脉高压新的治疗靶标^[21]. 这可能与VEGF表达降低, 内脏和肝内炎症渗透减少, 肝星状细胞激活的减少密切相关.

2.2 血管内皮生长因子与门脉高压关系 数据显示门体静脉侧枝循环的建立及高压状态跟VEGF有较大关联. 在大鼠肝硬化模型中, 门静脉结扎后, VEGF、VEGFR-2、FLK-1及CD31的表达都不断增加. 同样, 在四氯化碳诱导的模型中, 在缺氧条件下, 肝细胞内血管不断生成, 同时伴有VEGF、angiopoietin-1、angiopoietin-2及PGF的过表达^[22].

2.3 肝硬化的治疗 根据肝硬化的发病机制, 很多分子靶向治疗方法正在研究之中. (1)主要针对纤维化发生及纤维化溶解方面的研究. 如金属蛋白酶组织抑制因子anti-TIMP-1, 抗血小板衍生生长因子anti-PDGF-b受体等阻断抑制性抗体; (2)对肝内起关键作用的细胞, 针对性地使用靶向药物, 如肝星状细胞, 通过维生素A的修饰后的脂质体等. 已有实验证明抗血管生成因子治疗, 如索拉菲尼、舒尼替尼能改善门体侧枝循环, 内脏血管机械力, 降低门静脉压力等. 其中血管紧张素-2、VEGF-A受体阻断剂及拉格唑拉等, 在抗纤维化动物模型, 及临床试验中, 证明有着很好的运用前景^[23-26]; (3)针对并发症的研究治疗, 如Sakamoto等和Kaur等^[27,28]将内皮祖细胞注射到肝硬化老鼠的静脉后, 不管是在门静脉压力的变化还是微循环的改变, 都得到了很大的改善. 干细胞的治疗, 将来不失为一种有效治疗肝硬化门脉高压的手段^[29].

3 血管内皮生长因子与肝癌关系

3.1 血管内皮生长因子与肿瘤的关系 原发性肝癌是肝脏的一种主要恶性肿瘤, 在肿瘤的进展, 侵袭及转移过程中, 对血管依赖性很强. 肝癌细胞的快速生长需要一个高营养的环境支持供

应. 而高度血管化则能适应肿瘤生长的需要. 这与血管生成表型的转换与血管生成正反方面的调节紊乱有关. 在肿瘤进展过程中, 当肿瘤逐渐缺血缺氧时, 肿瘤细胞分泌大量的促血管生成因子, 如VEGF、PDGF、PIGF及TGF- β 1, 而内源性表达抑制因子如TSP-1、endostatin和angiostatin的表达则下调, 激活内皮祖细胞干细胞从骨髓释放, 促进细胞外间隙和基底膜重建形成新的血管. 然而, 这些新生血管的功能结构并不完善, 时有渗出, 出血等, 并导致血流的方向混乱. 由于结构功能并不完善, 也为肿瘤细胞进入血液循环提供了一个通道, 因此极易转移^[30].

VEGF的表达水平与血管的侵袭及转移, 复发, 血管密度, 分化, 肿瘤的分期和预后等息息相关^[31-34]. Zhong等^[35]通过原发性肝癌术前术后血液及组织标本, 采用ELISA及免疫组织化学方法测定VEGF的表达量, 结果得出血液中的表达量明显高于正常组. 复发组明显高于未复发组. 在细胞质中, 复发组明显高于未复发组. 1, 2, 3年生生存率明显VEGF(-)比VEGF(+)高.

目前, 肝脏肿瘤诊断运用比较多的是甲胎蛋白(alpha-fetoprotein, AFP), 为进一步研究评价AFP阴性肝癌患者治疗后的复发风险, Hu等^[36]收集了162例肝癌AFP阴性患者标本, 通过统计VEGF和PDGF在各组中表达的分析, 联合2项指标能够分别提高术后等治疗的复发率及生存时间的估计. 实践证明, 血清VEGF水平明显高于健康人, 有腹水转移者VEGF表达水平明显高于无腹水转移者. Jia等^[37]通过原发性肝癌患者血液术前术后HIF-1 α 和VEGF对比及相关性研究. 结果显示2因子高度相关, 数据显示两者血液量可能与门静脉血栓及转移成正相关性. 另外, HCC患者VEGF水平明显高于慢性肝炎和肝硬化患者, 也说明VEGF与肝癌早期血管增生密切相关.

可见VEGF水平有助于肝癌的诊断和转移监测, 与AFP联检可提高肝癌检出的阳性率. 不仅可以作为监测肿瘤转移的重要指标^[38], 而且可以作为术后及生物治疗疗效和预后判断提供依据^[39,40]. 临床上我们可以通过测定血清中VEGF浓度来了解肝细胞损伤程度及再生能力, 为判断肝硬化, 肝癌患者的病情和预后提供参考.

3.2 肿瘤的治疗 通过VEGF与肿瘤之间复杂关系的了解, 我们发现: VEGF高表达是肝癌的一个共性, 直接导致肿瘤血管增生和较差的预后. 针对肿瘤血管生成, 抗血管生长因子及通路阻断

■同行评价

血管内皮生长因子在多领域都有研究及应用, 本文就其在肝再生、肝硬化、肝癌、移植等近期研究进行了综述, 为临床及相关研究者提供了有价值的信息.

剂的研究应用,目前在临床上已取得不错的效果.如索拉菲尼、贝伐单抗等多酶抑制剂,能够显著地提高肿瘤患者的生存质量预后^[41-44],另外,Chan等^[45]通过抑制(HIF-1 α)表达试验,也证明了下调VEGF蛋白能减少肿瘤的血管生成和生长,提高患者生存率.

4 血管内皮生长因子与肝移植的关系

组织器官移植的成功与否,后期疗效好坏,并发症的发生.主要决定性因素还在于排斥反应的强弱及免疫耐受的产生.目前,有关VEGF在同种异体移植免疫反应的研究不多.肝移植术后急性排斥反应的发生主要是由于同种异体抗原识别捐赠者的淋巴细胞,导致T淋巴细胞激活,增值和分化,引发一系列的免疫反应,最终破坏移植肝脏.Aharinejad等^[46]注意到,在人体心脏移植反应中,VEGF与器官移植的急慢性排斥反应相关联.Berberat等^[47]发现在自体移植术中,VEGF对于白细胞的运输有着重要作用;当使用anti-VEGF则能有效地阻止急性排斥反应的进程,但是并不能防止人体T淋巴细胞的激活,只能阻止内皮细胞黏附分子及细胞因子如IP-10的表达.

通过对炎症介质的研究,也发现VEGF在移植反应中发挥着重要作用.如移植脂肪组织来源的干细胞后,能减少肝细胞的损伤,特别是肝窦内皮细胞凋亡,能保护小体积移植肝脏的微环境不受干扰,易于肝实质及内皮细胞的再生,提高患者的生存率^[48,49].包括介导IP-10,单核细胞趋化因子MCP-1、IL-8、E-selectin、ICAM-1、VCAM-1在体内体外的表达,所有这些分子都与急性排斥反应有关.大鼠实验证明,当阻断这些分子或者他们各自的配体后,能延长移植的生存率^[48].在减轻移植急性排斥反应中,VEGF可能成为一种靶向干扰治疗的方法^[3].近年来发现,肥胖,高脂血症,脂肪肝的发生也与VEGF有着密切的联系^[50].

5 结论

VEGF在肝硬化、肝癌、移植等方面已有了较多研究进展及应用.有理由相信,随着VEGF在人体中作用机制的深入研究,正确利用有利因素,避其不利,不论在术后促进肝脏再生,还是抑制慢性乙型肝炎、肝硬化、肝癌的发展,肿瘤的诊断和治疗,肝脏移植的排斥反应等方面

将提供多种全方位性、崭新的治疗方案.

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