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述评 EDITORIAL

VEGF与消化系肿瘤关系的研究新进展

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Progress in understanding the relationship between vascular endothelial growth factor and digestive tumors

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Abstract
Digestive tumors account for a large portion of human malignancies, and their incidence and mortality are on the rise. Neovascularization plays a critical role in the metastasis of tumors. Vascular endothelial growth factor (VEGF) is one of the best characterized angiogenic regulators. There is close relationship between VEGF and tumor growth, invasion and metastasis. VEGF has become a research hot for diagnosis, targeted therapy and prognosis of tumors. The purpose of this review is to review the recent progress in understanding the relationship between VEGF and digestive tumors.

Key Words: Vascular endothelial growth factor; Digestive tumors; Invasion

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摘要
消化系肿瘤在人类恶性肿瘤中占相当大的比例, 其发病率和死亡率呈逐年上升的趋势. 新生血管形成很大程度上决定了肿瘤细胞能否转移, 血管内皮生长因子(vascular endothelial growth factor, VEGF)是最具特征性的血管新生调节因子, 与肿瘤的生长、浸润、转移关系密切, 已成为肿瘤诊断、抗肿瘤血管生成靶向治疗以及预后判断的研究热点. 本文就VEGF与消化系肿瘤关系研究新进展做一综述.

关键词: 血管内皮生长因子; 消化系肿瘤; 浸润

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0 引言
血管内皮生长因子(vascular endothelial growth factor, VEGF)是1989年初Ferrara等[1]在体外培养牛垂体滤泡星状细胞时分离纯化出来的, 通过与血管内皮上的相应受体(vascular endothelial growth factor receptor, VEGFR)结合促进内皮细胞增殖, 同时可增加血管通透性使内皮细胞迁移, 诱导肿瘤血管生成, 维持肿瘤的继续生长. VEGF是目前发现的活性和专属性最强的血管生成因子[2].

1 VEGF概述
1.1 VEGF特征 VEGF是由2条相同多肽链通过二硫键组成的二聚体蛋白, 相对分子质量为46 000 Da. 人类VEGF基因由8个外显子和7个内含子构成, 可编码5种亚型: VEGF121、145、165、189、206, 人体内以VEGF165表达为主, 不同亚型在不同部位发挥不同的作用, 因为不同部位的微环境对他们有不同的影响[3]. 除VEGF外, 还发现一些与VEGF结构、功能相似的多肽, 包括VEGF-B、VEGF-C、VEGF-D、

■背景资料
消化系肿瘤在人类恶性肿瘤中占相当大的比例, 其发病率和死亡率呈逐年上升的趋势. 新生血管形成很大程度上决定了肿瘤细胞能否转移, 血管内皮生长因子(VEGF)是最具特征性的血管新生调节因子, 与肿瘤的生长、浸润、转移关系密切, 已成为肿瘤诊断、抗肿瘤血管生成靶向治疗及预后判断的研究热点.

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■研发前沿
本文主要研究VEGF与消化系肿瘤发生发展及治疗的关系，但是VEGF与其他血管形成相关的生长因子的关系及VEGF的具体信号传导通路尚不明确，亟待进一步研究.

VEGF-E及胎盘生长因子(placenta growth factor, PIGF), 组成了VEGF家族, 其中VEGF-C被认为与淋巴结转移密切相关[4].

1.2 VEGF受体 为受体型酪氨酸激酶,包括VEGFR-1(fms样酪氨酸激酶, Flt-1), VEGFR-2、KDR/FIR-1(激酶结构域受体/胎肝激酶受体-1)、Flt-4以及近年发现的内皮细胞表面球蛋白NRP-1[5]. VEGFR主要存在于血管内皮细胞(vascular endothelial cells, VEC), 在造血干细胞、巨噬细胞、单核细胞、血小板、卵巢癌细胞和黑色素瘤细胞上也有表达, 这些细胞中只有VEC对VEGF反应强烈[6]. Flt-1主要存在于人胎盘和血管内皮细胞, KDR/FIR-1可表达于所有内皮细胞, Flt-4在成人仅表达于淋巴管内皮细胞膜, 其中以KDR/FIR-1为主传递增殖信号[7]. VEGF与定位于血管内皮细胞表面的特异性受体结合后,促进内皮细胞增殖、游走、血管腔的形成及血管通透性的增加[8].

1.3 VEGF功能

1.3.1 促进血管内皮细胞增殖: VEGF作为特异性的血管内皮细胞分裂素, 能够刺激体外的血管内皮细胞发生有丝分裂和迁移, 以及体内血管的形成, 目前已经确定的能促进内皮细胞增殖的主要是VEGF-A121和VEGF-A165. Moreira等[9]对结直肠癌的研究过程中发现, VEGF高水平表达, 并与其受体结合,促进血管内皮细胞的有丝分裂, 从而促进肿瘤血管的新生.

1.3.2 增加血管通透性: VEGF可以增加血管的通透性,尤其是微小血管的通透性, 引起血浆蛋白渗漏到细胞外基质, 为肿瘤细胞的生长和新生毛细血管网的建立提供营养.

1.3.3 促进血管支持物的生成: VEGF能诱导内皮细胞表达尿激酶型纤溶酶原激活因子(uPA)、组织型纤溶酶原激活因子(tPA)及尿激酶型纤溶酶原激活因子受体(u PAR)等, 从而促使渗透到血管外区域的血浆蛋白形成血浆蛋白凝块, 作为血管新生的支持物.

1.3.4 抑制肿瘤细胞凋亡: 有实验证明[10]VEGF阳性肿瘤细胞的增生与对照组差异无统计学意义, 但凋亡细胞的数目明显下降, 而且NOS(一氧化氮合酶)活性也增强[11].

2 VEGF与消化系肿瘤

2.1 食管癌 中国是食管癌的高发国家, 食管癌具有早期浸润和转移的特点. Cavazzola等[12]用免疫组织化学法检测到食管腺癌标本VEGF阳性率是46.8%, Verbeke等[13]用相同的方法检测到食管鳞癌标本VEGF阳性率为69%, Takala等[14]也证实食管腺癌和鳞癌中VEGF阳性表达率不同, 并证实VEGF与食管癌的浸润深度有关; Lu等[15]曾报道VEGF的表达情况与食管癌的分化程度、浸润深度及TNM分期有关; Yang等[16]研究发现VEGF高度表达导致CD80表达下降, 导致免疫系统功能障碍, 从而使食管癌细胞逃离免疫监视, 促进食管癌的进展; Nakatani等[17]用RT-PCR法测定食管梭形细胞癌HN-Eso-1细胞系VEGF-A、VEGF-C、VEGF-D 和VEGFR-1, VEGFR-2的表达情况, 结果发现VEGF-A、VEGF-C、VEGF -D和VEGFR-1, VEGFR-2表达与细胞自分泌有关, 并且VEGF高度表达使食管癌细胞在抗肿瘤治疗中脱逃; 后一观点同样得到Gholamin等[18]的证实; Naumnik等[19]用免疫组织化学法检测食管癌标本VEGF-C、VEGF-D的表达情况, 结果发现VEGF-C和VEGF-D高度表达与淋巴转移有关, 尤其VEGF-C表达水平可作为预测食管癌淋巴结转移独立的危险因子, 对局限性进展期食管癌患者, 即使曾行食管切除术, VEGF-C和VEGF-D过表达也提示预后不良. 有学者[20]应用分子成像技术, 对胃镜检查提示为食管不典型增生者的表皮生长因子(epidermal growth factor, EGF)、人表皮生长因子-2(human epidermal growth factor receptor 2, HER-2)和VEGF进行探查, 以评估不同患者的基因表达谱, 实时监控患者对治疗的反映性, 这种技术突破了目前检测手段的限制, 为食管癌的个性化治疗奠定了基础.

2.2 胃癌 胃癌是我国最常见的恶性肿瘤之一, 在癌症病死率中排列第2位, 如何通过检测胃癌患者某些体液因子的表达来早期诊断、评估预后并制订个体化治疗方案尤为重要. Lieto等[21]发现胃癌组织中VEGF阳性率为48%, 且发现经手术治疗的患者VEGF的含量与患者生存时间高度相关, 比肿瘤TNM分级更能准确地反映患者预后; Yang等[22]研究结果表明处于T3-T4期、有血管浸润、淋巴结转移、肝脏和腹膜转移的胃癌患者VEGF阳性率显著高于T1-T2期、无血管浸润、淋巴结、肝脏和腹膜转移者, VEGF高度表达者肿瘤血管形成更活跃, 5年生存率更低, 同时提出VEGF可作为判断胃癌的预后生物学指标, 并可作为治疗胃癌的新靶点. Deguchi等[23]证实VEGF-C和VEGF-D在胃癌组织中阳性表达率分别是88%和63%, VEGF-C表达在淋巴结转移分期Ly+N-期显著高于Ly-N+期, 并指出VEGF-C

和VEGF-D在胃癌早期的淋巴道转移有重要作用, VEGF-D主要通过自分泌和旁分泌机制促进肿瘤血管、淋巴管的形成, 并促进肿瘤细胞增殖, 抑制肿瘤细胞凋亡[25]; Han等[24]也证实胃癌组织中VEGF-C表达高于正常组织, 阳性率是54.9%, 其中淋巴结转移患者VEGF-C表达显著高于无淋巴结转移者; Zhou等[26]用PCR-PFLP法分析VEGF的基因多态性, (包括VEGF-634G/C, VEGF+936C/T和VEGF+1612 G/A), 发现在胃癌患者中VEGF+1612AA基因型表达显著高于对照组, 而贲门癌患者VEGF+1612AA基因型表达低于非贲门癌者, Laurens分型为弥漫型的胃癌者1612AA基因型表达显著高于肠型者, 而VEGF-634G/C, VEGF+936C/T基因多形性与胃癌的发生、发展无关, 从而证实VEGF +1612 G/A基因多形性可能是汉族中国人胃癌发生的高危因素, 并提出基因型的差异与地域和胃癌的Lauren's分型关系密切. 有学者[27]证实抗血管内皮生长因子受体-2抗体“ IMC-1121B” 在胃癌治疗中将有广泛的前景, 还有研究指出[28], VEGF-A在弥漫性胃癌中的促进血管形成作用更显著, 并提出以VEGF-A为靶点的治疗方法对弥漫性胃癌更有效, 而对局限性胃癌效果甚微.

2.3 肝癌 原发性肝癌是我国常见的恶性肿瘤之一, 其病死率在消化系统肿瘤中居第3位, 仅次于胃癌和食管癌, 近年来其发病率有上升趋势, 肝癌为血管丰富的肿瘤, 而VEGF在肿瘤血管生成中具有极其关键的作用, 因此VEGF在肝癌的研究中日益受到重视. Hu等[29]研究发现在AFP阴性的肝癌组织中VEGF的阳性率是59.9%, VEGF对预测AFP阴性的肝癌根治术后者的生存和复发有重要意义. Gadelhak等[30]用ELISA法检测血清p53 Abs(p53抗体)和VEGF表达水平, 并研究他们与AFP的关系, 发现肝癌患者和肝硬化患者血清VEGF的表达显著高于健康人, 但肝癌和肝硬化患者之间VEGF的表达无明显差异, P53 Abs或VEGF与AFP浓度之间无任何相关性, 但是在AFP阳性病例中VEGF的表达率达85.3%, P53抗体的累积表达为83.3%. 此外, P53基因抗体阳性的患者VEGF表达水平高, 因此两者联合检测可用于肝癌患者的筛选. 还有学者[31]认为, VEGF、缺氧诱导因子-1α(hypoxia inducible factor-1α, HIF-1α)、基质金属蛋白酶-2(matrix metalloproteinase-2, MMP-2)是进展期肝癌淋巴结转移的3个独立危险因素, 三者联合检测可作为肝癌是否发生淋巴结转移的预测因子; Kemik等[8]发现肝癌患者血清VEGF-A 及VEGFR-1表达显著高于健康人, VEGF-A阳性表达见于肝癌晚期或已发生转移者, VEGFR-1与肝癌转移、分化程度及分期有关, 提示VEGF-A及其受体VEGFR-1参与肝癌的进展、转移; Treska等[32]用ELISA法检测经导管静脉化疗栓塞后肝癌患者血清中VEGF的浓度, 发现在接受化疗栓塞1-2 d后血清VEGF浓度呈短暂性升高, 且上升程度与肿瘤大小、分期及血管与淋巴的浸润能力高度相关, 说明VEGF短暂上升的程度越高, 远处转移可能性越大, 预后越差. 有研究表明[33]VEGF基因多态性是肝癌预后不良的独立危险因素, 该研究用生物快照和Taq Man技术分析接受肝移植治疗的肝癌患者VEGF的7种基因型(rs699947, rs1570360, rs2010963, rs3024997, rs3025010, rs3025035, rs3025039)发现: rs3025030和肝移植后复发显著相关, 可作为预测肝移植复发的遗传标记. 在治疗上, 联合应用VEGF受体选择性抑制剂PTK/ZK和干扰素(interferon, IFN)以及5-氟尿嘧啶(5-FU)能显著地抑制体内肝癌细胞的生长, 并且PTK/ZK能促进IFN/5-FU诱导肝癌细胞凋亡, 从而使其的抗肿瘤效果增强[34]; 有学者[35]分析肝上皮样血管内皮瘤(epithelioid hemangioendothelioma, EHE)细胞中VEGF及其受体的表达发现, 抗VEGF的化疗药物能够减小肿瘤体积, 对不能切除和转移性肿瘤有效, 并可作为肝移植术后的辅助治疗.

2.4 胰腺癌 胰腺癌近年来发病率明显上升, 恶性程度高, 发展快, 早期诊断十分困难, 治疗效果不理想, 死亡率很高. Talar-Wojnarowska等[36]指出, VEGF是胰腺癌微血管形成所必需的, 其在胰腺癌的生长和浸润中有重要作用, 胰腺癌患者血清中VEGF的浓度显著高于慢性胰腺炎者, 并且VEGF基因型+405C/C有致胰腺癌的作用, 但是血清VEGF浓度与VEGF基因多态性无关. Koch等[37]证实了VEGF-D促进胰腺癌淋巴结转移; Chang等[38]用ELISA法测定血清VEGF、可溶性血管内皮生长因子受体-1(sVEGFR-1), 发现胰腺癌患者血清VEGF和sVEGFR-1水平显著高于正常对照组, 且sVEGFR-1与胰腺癌分期有关, 并发现VEGF与sVEGFR-1的比值越高, 胰腺癌预后越不良; 对转移性胰腺癌患者VEGF高度表达者无进展生存率和总生存率低于低度表达者[39]; 治疗上, Hotz等[40]报道, 抗VEGF受体制剂如SLT-VEGF融合蛋白(由VEGF和志贺样毒素A亚型组成)可以抑制胰腺癌生长和扩散, 提高14

■相关报道

Bendardaf等研究发现, VEGF在结直肠癌中阳性率达50%, 而在正常结直肠黏膜和腺瘤中几乎无表达, 还发现Ⅱ、Ⅲ、Ⅳ期结直肠癌患者VEGF阳性率分别是47%、50%、70%, VEGF在左半结肠和直肠的表达率高于右半结肠, VEGF的阳性表达与结直肠癌的分化程度、浸润深度、淋巴结转移、Dukes分期、远处转移、淋巴/脉管肿瘤栓子形成有关.

■同行评价
本文立题新颖, 思路清晰, 语言表述流利, 研究具有一定的科学价值.

周生存率, 联合应用抗VEGF受体制剂与吉西他滨治疗胰腺癌比单用吉西他滨显著延长生存时间, 提高治疗效果.

2.5 胆管癌 胆管癌是一种恶性程度高, 难于早期诊断的恶性肿瘤, 迄今为止, 大多数胆管癌患者在确诊时肿块已经无法切除, 其病程平均少于12 mo, 5年生存率仅5%. Yoshikawa等[41]用免疫组织化学法检测胆管癌标本中VEGF的表达水平, 发现VEGF在肝内胆管癌的阳性率为53.8%, 在肝外胆管癌的阳性率为59.2%, 并发现VEGF过表达与胆管癌肝内转移和血行转移有关; Aishima等[42]研究表明VEGF-C促进肝内胆管癌边缘淋巴管形成, 与胆管癌淋巴道浸润关系密切, 有淋巴结转移的胆管癌者VEGF-C阳性率是80%, 因此VEGF-C表达可作为判断胆管癌预后的生物学指标; 最近一项研究发现[43], 多激酶抑制剂“索拉菲尼”可以通过抑制RAF激酶、VEGF和血小板衍生生长因子(platelet-derived growth factor, PDGF)的活性而抑制胆管癌细胞增殖并诱导其凋亡, 在胆管癌治疗中发挥了强大的抗肿瘤活性.

2.6 结直肠癌 结直肠癌包括结肠癌与直肠癌, 易发生淋巴结转移和肝转移. 近年来由于饮食结构和生活习惯的改变, 其发病率和死亡率呈逐年增高的趋势. VEGF对结直肠癌的浸润和转移起极为重要的作用. Bendardaf等[44]研究发现, VEGF在结直肠癌中阳性率达50%, 而在正常结直肠黏膜和腺瘤中几乎无表达, 还发现Ⅱ、Ⅲ、Ⅳ期结直肠癌患者VEGF阳性率分别是47%、50%、70%, VEGF在左半结肠和直肠的表达率高于右半结肠, VEGF的阳性表达与结直肠癌的分化程度、浸润深度、淋巴结转移、Dukes分期、远处转移、淋巴/脉管肿瘤栓子形成有关, Dukes分期愈晚者VEGF的阳性率愈高, 这提示VEGF是一个有助于判断预后的指标, 也表明对VEGF高度表达者应加强术后的辅助治疗[45]; Toiyama等[46]等研究也证实了分析直肠癌VEGF表达水平有助于判断直肠癌术后患者放化疗的疗效, 预测全身性并发症的发生; Morales-Gutiérre等[47]用ELIAS法检测结直肠癌组织和结直肠癌周围组织VEGF的表达水平, 发现癌组织VEGF的表达显著高于癌的周围组织, 癌肿中心组织与癌肿周围组织VEGF含量的比值大于2的结直肠癌患者生存时间更长. 有研究表明[48], VEGF基因型+936C/T与结直肠癌发生部位有关, 其杂合子10.7%位于近端结肠, 35.2%位于远端结肠, 54.1%位于直肠, 具有+936T/T基因型结直肠癌者生存率高, 总生存率可达100%, VEGF的基因型可作为结直肠癌患者随访和治疗效果的监测指标. Huang等[49]研究含有VEGF和组织因子(TF)的融合蛋白(rVEGF-TF)在结肠癌模型中抑制肿瘤生长能力中发现, 注入rVEGF-TF的肿瘤组织能够形成血栓和坏死, 并指出rVEGF-TF肿瘤血管闭塞是治疗肿瘤潜在的有效方法.

3 结论

异常活跃的血管生成是恶性肿瘤生长、增殖、转移及扩散的一个重要条件. 近年来, VEGF及其家族成员被认为在调节肿瘤血管生成中起极其重要作用, 在临床治疗中的应用亦受到越来越多的关注. 检测肿瘤组织中VEGF含量不仅有利于了解肿瘤的生物学行为, 对评估手术时机及选择合理治疗方案判断预后都有重要意义. VEGF现已成为癌症治疗的新靶点, 抗VEGF药物作为肿瘤治疗的一种重要的新手段, 显示出了广阔的应用前景, 将在肿瘤的综合治疗中发挥越来越重要的作用. 但目前还有许多问题尚未解决, 如VEGF家族是影响新生血管生成的主要因子但不是唯一因子, 临床发现成纤维细胞生长因子、转化生长因子、肿瘤坏死因子等也与血管生成有关, 而VEGF家族与其他生长因子的关系有待进一步的研究. 另外, VEGF家族中的部分成员的特性, 如作用机制、信号传导等仍然不十分清楚, 在未来的一段时间, VEGF及其家族成员仍将是多个学科研究的热点问题之一.

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