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文献综述 REVIEW

VEGF –634G/C基因多态性与疾病相关性的研究进展

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Association between VEGF -634G/C polymorphism and diseases

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Abstract

Vascular endothelial growth factor (VEGF) is a special heparin-binding growth factor, and can significantly stimulate vasculogenesis and angiogenesis in both cancer and healthy tissues. There have been many studies confirming that the single nucleotide polymorphisms (SNP) of VEGF have a close relationship with the occurrence, development, and prognosis of diseases. According to statistics, the human VEGF gene has at least 30 SNP loci, among which VEGF -634C/G, -936C/T and -2578C/A mutations have been proved to regulate the VEGF plasma levels. Here we review the recent advances in understanding the association between VEGF -634G/C polymorphism and diseases.

Key Words: Vascular endothelial growth factor; -634G/C; Single nucleotide polymorphism

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摘要

血管内皮生长因子(vascular endothelial growth factor, VEGF)是对血管内皮细胞具有特异性的肝素结合生长因子, 可在体内刺激血管新生, 在正常组织以及肿瘤组织中都发挥着强大的促进血管生成的作用. 现已有较多研究证实VEGF的基因多态性与多种疾病的发生、发展、预后都有着密切的关系. 据统计人类的VEGF基因至少包含30多个单核苷酸多态性(single nucleotide polymorphisms, SNP)位点, 其中VEGF -634C/G、-936C/T和-2578C/A突变位点已被证明可改变VEGF的血浆水平, 现本文选取VEGF -634G/C位点对其多态性与疾病的相关性进行综述.

关键词: 血管内皮生长因子; –634G/C; 单核苷酸多态性

核心提示: 血管内皮生长因子(vascular endothelial growth factor)634G/C基因多态性几乎与全身各个系统的疾病相关, 多国学者都在积极努力的研究, 但更多的挑战需要我们共同迎接.

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0 引言

血管内皮生长因子(vascular endothelial growth factor, VEGF)是由细胞产生的能刺激新生血管形成的化学因子[1], 是目前发现的活性和特异性最强的血管生成因子[2], 在多种疾病的发生发展过程中发挥着强大的调节作用, 并能维持血管内皮细胞分化状态、提高微血管通透性. VEGF

■背景资料
血管内皮生长因子(vascular endothelial growth factor, VEGF)是人体最重要的促血管生成因子, 对新生血管的形成起到了重要作用. 近几年的研究发现单核苷酸基因位点的突变影响了血管内皮生长因子的血浆水平, 与疾病的发生、发展和预后有着密切的关系. 对其与疾病相关性的研究将为今后医疗事业的发展提供新思路.

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■研发前沿
*VEGF*基因至少包含30多个单核苷酸多态性(single nucleotide polymorphisms, SNP)位点, 目前研究较多的有-460C/T、-634G/C、+936C/T、-2578C/A、-1154G/A等. VEGF的SNP位点与多种疾病不同预后的相关性研究已经越来越引起人们的重视, 类于此项的研究将为未来疾病的基因诊疗起到重要的推动作用.

蛋白家族共有6个成员, 分别是VEGF(亦称VEGFA)、VEGFB、VEGFC、VEGFD、VEGFE和胎盘生长因子(placenta growth factor, PLGF)[3], 分子量从35 kDa到45 kDa不等. VEGF蛋白质结构具有高度保守性, 是通过两对链间二硫键共价连接的反平行同型二聚体[4]. 编码VEGF的基因定位于6p21.3, 全长约14 kb, 由8个外显子和7个内含子交替组成[5]. VEGF具有两大重要功能: 促进血管内皮细胞分裂增生和增加血管通透性, 主要是通过与血管内皮细胞表面特异性受体结合而发挥生物学效用[6]. VEGF因能特异性的促进血管内皮分裂、增殖及迁移, 被公认为是血管生成的"中心调节者", 是最为有力的血管生成因子[7].

1 *VEGF*的基因多态性

单核苷酸多态性(single nucleotide polymorphisms, SNP), 即散在的单个碱基的不同, 包括单个碱基的缺失和插入, 但更多的是单个碱基的置换, 使同一基因位点可存在两种以上的基因型, 他是人类可遗传变异中最常见的一种, 占所有已知多态性的90%以上. SNPs是人与人之间基因差异的主要表现形式, 也就是这些SNPs位点的不同决定了人在寿命、体质、外形、性格、疾病的转归等方面的差异. 人类的*VEGF*基因至少有30多个SNP位点, 仅在其启动子区就有10种多态性, 目前研究比较多的SNP位点有-460C/T(rs833061)、-634G/C(rs2010963)、+936C/T(rs3025039)、-2578C/A(rs699947)、-1154G/A(rs1570360)等[8,9]. 基于近几年的研究, VEGF -634C/G、-936C/T和-2578C/A突变位点已被证明可改变VEGF的血浆水平[10-12], 现本文对-634G/C(rs2010963)位点与近年研究较多的与之相关的疾病进行综述.

2 VEGF –634G/C基因多态性与相关性疾病

2.1 VEGF -634G/C基因多态性与眼部疾病 经多年研究发现VEGF -634G/C SNPs与2型糖尿病视网膜病变关系密切. Awata等[13]对来自日本的378例2型糖尿病患者进行研究, 其中203例无视网膜病变, 93例为非增殖性糖尿病视网膜病变(non-proliferative diabetic retinopathy, NPDR), 82例为增殖性糖尿病视网膜病变(proliferative diabetic retinopathy, PDR), 其中黄斑水肿在NPDR、PDR中分别为16例和47例. 研究结果显示, 在*VEGF*基因启动区(5p-UTR、3p-UTR), 5p-UTR的-634G/C基因多态性与糖尿病视网膜病变(diabetic retinopathy, DR)关系最为密切, DR患者的-624C等位基因频率明显高于不伴DR患者. 由此得出, -634CC基因型是黄斑水肿的遗传危险因素, 并与2型糖尿病的黄斑部视网膜厚度明显相关. 另一项于2012年对巴西53例视网膜样本的分析[14]显示在-634G/C位点多态性中C等位基因的频率与VEGFA的表达率呈正相关, 而目前的研究表明VEGFA与糖尿病视网膜病变关系密切. Errera等[15]对501例欧洲2型糖尿病患者的研究中发现, VEGF -634C等位基因是PDR的独立危险因素之一(OR = 1.9, 95%CI: 1.01-3.79, P = 0.04). 2012年Liu等[16]对VEGF基因多态性与早产儿视网膜病变(retinopathy of prematurity, ROP)关系的大样本Meta分析显示VEGF -634G/C多态性与进展期ROP无相关性.

2.2 VEGF -634G/C基因多态性与消化系统疾病 Kim等[17]对来自韩国的864例人群进行了研究, 其中148例为患有胃十二指肠溃疡病组、716例为对照组, 研究人员对他们的*VEGF*基因多态性进行了检测, 结果显示-634G/C位点与胃十二指肠溃疡易感性无明显关联. Guan等[18]对美国德克萨斯大学MD安德森癌症中心(德克萨斯·休斯顿)病理证实为胃癌的171例患者, 以及从人群中招募的353例对照者进行VEGF SNPs检测, 统计结果显示杂合子-634CG以及-634CG+CC合并的基因型携带者患胃癌的风险与-634GG基因型相比明显增加. 然而来自韩国的研究表明-634CC基因型明显降低胃癌的发病风险[19]. 一项对韩国350例大肠癌患者的研究[20]表明虽然在韩国患有大肠癌的人群中血管内皮生长因子基因多态性的调查未被发现是独立的预后标志物, 但携带-634GG单倍型的患者在总的大肠癌患者中存活率较低.

2.3 VEGF -634G/C基因多态性与泌尿生殖系统疾病 2010年Sfar等[21]研究发现VEGF -634GG/CC单倍体基因型可显著降低前列腺癌的发病风险(OR = 0.14, P = 0.00005). Hefler等[22]对来自欧洲的563例卵巢癌患者的研究发现, 同时携带VEGF -634CC, VEGF -1154GG, VEGF -2578CC三个纯合子基因型是降低卵巢癌整体存活率的独立因素, 为VEGF SNPs与卵巢癌的研究提供了第一手数据. Jeon等[23]对韩国118例孕期小于20 wk的自发性流产(spontaneously aborted fetuses, SAFs)患者和380例正常对照者的研究发现, VEGF -2578CA+AA/-634CC和-1154GA+AA/-

634CC联合基因型显著增加SAFs的发病率. 但2012年一篇关于基因多态性能否作为妇科肿瘤的预测生物学指标的系统评价提示*VEGF*基因多态性与妇产科肿瘤的总生存率以及治疗毒性均无相关性[24], 然而该评价没有详细的描述妇科肿瘤与VEGF基因多态性的关系且纳入病例仅有140例.

2.4 VEGF -634G/C基因多态性与心脑血管疾病 VEGF是目前已知最强的促有丝分裂因子和血管生成因子, 能特异性的刺激血管内皮细胞增殖, 参与新生血管的形成, 其与心血管系统疾病的产生及预后关系十分密切. 据相关资料显示, 室间隔缺损(ventricular septal defect, VSD)是最常见的先天性心脏缺陷, 2007年Xie等[25]对中国222例单纯性室间隔缺损的儿童和352例健康对照者的研究发现-634C等位基因在患病组(OR = 0.39, 95%CI: 0.25-0.62, χ^2 = 8.11, P = 0.004)的频率明显低于健康对照组(OR = 0.76, 95%CI: 0.59-0.97, χ^2 = 5.06, P = 0.024), 提示-634C等位基因对VSD来说是重要的保护因素, 其可通过维持VEGF的稳定表达来防止VSD的发生. 然而, 与之相反的是另一项对匈牙利儿童的研究[26]表明-634C等位基因在先天性心脏病组出现的频率更高, 因此更多的探讨需要我们进行. 2012年Park等[27]对韩国烟雾病患者的对照研究发现, -634CC基因型较少出现在小儿烟雾病组(P = 0.040)且携带-634CC基因型的患者手术后呈现出更好的侧支血管构建, 此研究表明-634G等位基因与小儿烟雾病和侧支血管构建不良有相关性.

2.5 VEGF -634G/C基因多态性与骨关节运动疾病 2008年Kim等[28]首次报道了在*VEGF*基因启动区的-634G/C多态性与韩国人口股骨头坏死的易感性增加相关. 随后, 2012年Liu等[29]的一项研究同样验证了血管内皮生长因子基因rs2010963位点(-634G/C)多态性与中国地区非创伤性股骨头坏死(osteonecrosis of the femoral head, ONFH)相关. Liu等[29]将220例ONFH患者与同样数量的健康人用PCR-RFLP方法对比研究, 分析显示病例组该位点CC基因型(OR = 1.64, 95%CI: 1.03-2.60, P = 0.04)的频率高于对照组, 基因型与病因(激素、酒精、自发)无明显相关. 此外, 欧洲一项研究[30]发现VEGF SNPs与女性双磷酸盐相关的颌骨坏死(bisphosphonate-related osteonecrosis of the jaws, BRONJ)相关. 其将实验分为3组: A组为30例来自意大利患有BRONJ的女性, B组为30例曾静脉注射双磷酸盐但不伴有骨坏死的阴性对照组, C组为125例健康对照者. 结果显示: A组-634CC基因型的频率高于C组, 表明VEGF的表达可能与意大利女性BRONJ的易感性相关, 但此结果需要大样本实验的进一步证明. Lambrechts等[31]研究发现-634GG基因型可通过降低血管内皮生长因子的表达、加速运动神经元损伤和死亡增加肌萎缩性侧索硬化症的患病风险. 综上研究显示VEGF -634G/C位点多态性与运动关节疾病的关系值得我们进一步探究.

2.6 VEGF -634G/C基因多态性与其他恶性肿瘤 乳腺癌是最常诊断出的癌症和女性癌症死亡的首要原因, 占癌症病例总数的23%和癌症死亡人数的14%[32]. 2013年Luo等[33]对中国汉族乳腺癌患者的研究发现, -634CC基因型与乳腺癌肿瘤的高侵袭性明显相关[肿瘤体积大(OR = 2.63, 95%CI: 1.15-6.02, P = 0.02); 组织学分级高(OR = 1.47, 95%CI: 1.06-2.03, P = 0.02), 但与区域性或远处转移、诊断分期、雌激素或孕激素受体状态等其他肿瘤特性无关联. 此外, VEGF -634G/C基因多态性还可能与其他恶性肿瘤存在相关性. 2012年一项关于261例根治性放射治疗非小细胞肺癌(non-small cell lung cancer, NSCLC)患者的研究[34]发现, -460T/-634C/-936T单倍体型发生严重放射性肺炎(radiation pneumonitis, RP)的风险较高, 所以可能是用来预测RP易感性的重要生物学标志物.

3 结论

VEGF -634G/C基因多态性几乎与全身各个系统的疾病相关, 因-634CC基因型可通过增加VEGF的表达影响疾病的进展而成为多国研究的热点. 虽然VEGF -634G/C基因多态性几乎与全身各个系统的疾病相关, 随着, 靶向治疗药物的发明、疾病诊断基因分型等需求的不断进展, *VEGF*基因多态性的研究也越来越有助于新位点的确立. 希望, 今后多领域、大样本、多种族的研究能通过更多的国际间的合作来进行.

■相关报道
VEGF是目前已知的作用最强的促血管生成因子. VEGF -634C/G、-936C/T和-2578C/A突变位点已被证明可改变VEGF的血浆水平, -634CC等位基因型可通过增加VEGF的表达影响疾病发展.

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■创新盘点

本文综述了二十年以内多地区关于VEGF -634G/C基因多态性与多种疾病相关性的研究, 具有一定的参考价值, 并探讨了该项研究所能起到的重要作用. 为今后科研的进一步发展提供了新的思路.

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