

VEGF 和 PEDF 在增殖性糖尿病视网膜病变中的研究进展

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Recent progress in the investigation of VEGF and PEDF of proliferative diabetic retinopathy

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Abstract

• Proliferative diabetic retinopathy (PDR) is a group of disease characterized by neovascular disease complication of diabetes mellitus. Neovascular diseases of eye are one of the major causes of blindness of the world. Recent studies showed that vascular endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF) are now accepted as the key cytokine in the development of diabetic retinopathy. Recent progress in the investigation of VEGF and PEDF of PDR are summarized in this review.

• KEYWORDS: vascular endothelial growth factor; pigment epithelium - derived factor; proliferative diabetic retinopathy

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摘要

增殖性糖尿病视网膜病变 (proliferative diabetic retinopathy, PDR) 是一种以眼内新生血管形成为特征的糖尿病并发症。眼内新生血管的形成是当今世界主要致盲

原因之一。血管内皮生长因子 (vascular endothelial growth factor, VEGF) 与色素上皮衍生因子 (pigment epithelium-derived factor, PEDF) 作为眼内新生血管形成最主要的细胞因子,近年来成为研究热点。本文就 VEGF 和 PEDF 在 PDR 中的研究进展进行综述。

关键词:血管内皮生长因子;色素上皮生长因子;增殖性糖尿病视网膜病变

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0 引言

糖尿病视网膜病变 (diabetic retinopathy, DR) 是糖尿病常见的微血管并发症之一。在全球, DR 影响着大约 150 万人,世界卫生组织统计影响人数在 2025 年将翻倍^[1]。DR 分非增殖性 DR、增殖性 DR (proliferative diabetic retinopathy, PDR)。PDR 在美国是 20~74 岁人群最主要的新发致盲病因之一。糖尿病 20a 后,约 50% 的 1 型糖尿病、5%~10% 的非胰岛素依赖性 2 型糖尿病、30% 的胰岛素依赖性 2 型糖尿病并发 PDR。在 WESDR 报道中,有 3.6% 的 1 型糖尿病和 1.6% 的 2 型糖尿病患者是盲人^[2]。本文就血管内皮生长因子 (vascular endothelial growth factor, VEGF) 和色素上皮衍生因子 (pigment epithelium-derived factor, PEDF) 在 PDR 中的研究现状和进展综述如下。

1 VEGF 与 PDR

VEGF 是一种 48kDa 大小的同型二聚体糖蛋白,系由胎盘生长因子 (placenta growth factor, PLGF)、VEGF-A、VEGF-B、VEGF-C 和 VEGF-D 组成的分子家族^[1]。PLGF 功能尚未完全明确,但在 PDR、脉络膜新生血管疾病发展中起关键作用^[3,4]。它在新生血管生成、增加血管通透性方面,与 VEGF-A 起协同作用^[5]。VEGF-B 主要分布于血管内皮细胞,促进内皮细胞增殖,可诱导冠状血管生长和心脏肥大,使心脏免受缺血性损伤^[6]。VEGF-C 和 VEGF-D 促进淋巴管生成^[7]。VEGF-A 又称血管通透性因子,是 DR 发生发展中的关键者^[8]。人类 VEGF-A 基因通过选择性剪切至少可产生 6 种主要异构体 (VEGF121, 145, 165, 183, 189, 206)^[9] 和 8 种小型异构体。其中 VEGF165 的表达最丰富,是血管生成和通透性增加的主要活化因子^[1,7]。

VEGF 受体家族 (VEGF receptors, VEGFR) 包括 VEGFR-1 (flt-1), VEGFR-2 (flk-1), VEGFR-3 (flt-4)^[7]。VEGFR-1 分布于血管内皮细胞、周细胞; VEGFR-2 几乎仅存于血管内皮细胞,是 VEGF 发挥功能的主要受体; VEGFR-3 在胚胎时期表达于血管和淋巴内皮细胞,在成人仅表达淋巴细胞^[10]。

VEGF是一种旁分泌和自分泌生长因子,与受体结合后产生相应生物学效应:促进内皮细胞迁移、增殖;提高血管通透性等^[11]。在眼内,色素上皮细胞(retinal pigment epithelium, RPE)、神经元、神经胶质细胞、睫状上皮细胞、Müller细胞、内皮细胞均有VEGF表达^[1]。周细胞缺失、内皮细胞及血流动力学异常是PDR的基本病理改变,造成血管通透性增加、黄斑水肿,进一步出现出血、渗出和血管闭塞等一系列变化。缺氧刺激低氧诱导因子(hypoxia inducible factor, HIF)转录增加,并进一步增加VEGF表达^[3]。VEGF的生物学效应在PDR发生发展中起重要作用。

2 PEDF与PDR

PEDF于1991年在人类胎儿RPE细胞的条件培养液中纯化分离出来,系一种分子质量为50kDa的分泌型蛋白,是丝氨酸蛋白酶抑制剂家族成员^[12,13]。PEDF在人体分布于大脑、眼、脊髓、肝脏、血液、肺脏^[13]。在眼内PEDF主要由RPE细胞和Müller胶质细胞产生^[14],旁分泌至光感受器间质,对视网膜的分化起重要作用。

糖尿病时,机体处于氧化应激,高血糖所致一系列糖代谢异常使视网膜内活性氧增加,同时抗氧化剂水平降低,加重内皮细胞核周细胞损伤;体内活性氧增加,亦可诱导细胞凋亡。PEDF作为眼内保护因子之一,在PDR中不仅能抗新生血管,更有对神经的营养和保护功能^[14,15]。PEDF通过启动的Fas-FasL所介导的凋亡作用与诱导剂所产生的生存信号之间的强弱,决定其是增殖形成新血管还是发生凋亡。PEDF通过Fas-FasL受体区别新生血管的内皮细胞和正常血管内皮细胞,使其在抑制新生血管形成的同时,不对已构建的视网膜血管产生明显的损害。同时PEDF能削弱VEGF的表达,从根源上阻断新生血管生成^[15]。此外,在PDR体内发生氧化应激损害时,PEDF能通过上调Bcl-2,阻止神经元细胞凋亡,从而保护神经^[15,16]。

3 VEGF抑制剂

多项研究证实,VEGF是促进新生血管生成和渗漏的重要因素,因此抑制VEGF成为抗新生血管的治疗热点。Pegaptanib(Macugen)系一种抗VEGF165适体,于2004-12成为第一个获得FDA批准的治疗老年性黄斑变性(age-related macular degeneration, AMD)的VEGF抑制剂。它能特异性与VEGF165结合,抑制其生物活性,阻碍其与受体结合,从而抑制新生血管形成,在治疗DR引起的黄斑水肿有一定的疗效^[17]。

Bevacizumab(Avastin)是由Genentech公司开发的一种单克隆抗体,美国FDA于2004-02批准其治疗转移性结直肠癌药品、非小细胞型肺癌^[18,19]。目前未批准用于眼内注射治疗^[16]。Avastin可以定向对抗VEGF-A所有亚型,间接阻断VEGF-A和其受体的结合,从而抑制新生血管形成^[1,19]。与Pegaptanib相比,它可结合所有VEGF-A亚型,而非仅仅是VEGF165。

Ranibizumab(Lucentis)是2006年美国FDA批准的、用来结合和抑制VEGF-A异构体及其活性降解产物的人源性抗原结合片段^[18,20,21]。它与VEGF-A亚型(即VEGF-110, VEGF-121, VEGF65)有较高亲和力,通过抑制VEGF-A与其受体VEGFR-1和VEGFR-2的结合,阻止新生血管形成。Bakri等^[22]和Gaudreault等^[23]报道,Ranibizumab在兔子房水中的半衰期分别是2.84d和3.0d,玻璃体腔中半衰期是2.88d和2.9d。Gaudreault等^[24]报道,在猴子体

内,其房水中半衰期是2.54d,在玻璃体腔中半衰期是2.63d。

Aflibercept(眼用制剂VEGF Trap-Eye)分别于2011-11及2012-09被美国FDA批准用于湿性年龄相关性黄斑变性和视网膜中央静脉阻塞后视网膜水肿治疗。它系一种高亲和力的人源化的VEGF受体融合蛋白,由VEGFR-1和VEGFR-2细胞外段与人IgG₁Fc段融合蛋白^[7]。它与VEGF-A, VEGF-B, PLGF结合,阻断信号通路,抑制新生血管生成,降低血管通透性^[25,26]。通过建立数学模型计算VEGF Trap-Eye在人眼内半衰期为7.1d^[4],而Ranibizumab和Bevacizumab的半衰期分别为3.2d和5.6d^[27]。与其他抗VEGF药物相比,VEGF Trap-Eye半衰期较长,有望减少注射频次,减少不良反应。

康柏西普(Conbercept)是于2013-12获国家食品药品监督管理局批准的一种眼用注射液,系一种VEGF受体与人免疫球蛋白Fc段基因重组的融合蛋白,与VEGF有很高的亲和力,竞争性抑制VEGF与受体结合,抑制血管新生形成^[25]。与VEGF Trap-Eye结构相似,包含人IgG₁Fc片段、VEGFR-1和VEGFR-2^[28]。同时与VEGF-A高亲和力,也能结合VEGF-B和PLGF^[29]。研究显示玻璃体腔注射康柏西普是安全有效的^[25]。目前数据有限,有必要在更大规模人群中通过更长时间随访进一步评估该药的安全性。

4 VEGF和PEDF与PDR的相关性

4.1 PDR患者中VEGF和PEDF水平

PDR患者体内VEGF表达水平高,而PEDF表达水平报道存在差异性。2002年Ogata等^[30]报道PEDF在PDR眼内是低表达;2009年Matsuyama等^[18]报道了DR患者玻璃体腔中PEDF是低水平。2012年Mohan等^[31]报道PDR患者(56眼)玻璃体PEDF显著低于非糖尿病(49眼)。而2010年Matsuyama等^[20]发现11例11眼PDR血清PEDF含量(7.2μg/mL)高于对照组(30例非糖尿病,3.9μg/mL)。Ogata等^[32]和Matsuyama等^[33]同样报道:糖尿病患者血清PEDF水平显著高于对照组,合并有PDR的患者PEDF水平尤其高。PDR患者在血清高表达PEDF可能与肥胖有关^[12]。

4.2 VEGF与PEDF的相关性

2003年Ohno-Matsui等^[34]提出VEGF通过与VEGFR-1相结合,以自分泌的方式上调PEDF的表达,从而维持两者间平衡。2006年有学者^[35]反对Ohno-Matsui等的观点,同时提出在PDR中VEGF能下调PEDF表达。

4.3 抗VEGF与VEGF和PEDF

玻璃体腔注射抗VEGF药物,眼球局部和全身VEGF表达均有下调^[18,20,21,36]。关于PEDF, Matsuyama等领导的研究小组报道了Bevacizumab玻璃体腔注射治疗PDR,房水(10例11眼)^[18]、血清(11例11眼)^[20]中PEDF表达差异无统计学意义;2013年国内有报道^[37]PDR患者(13眼)玻璃体腔注射Avastin,视网膜增生膜中PEDF的表达率无明显变化。而Ahn等^[21]在湿性AMD患者(17例)玻璃体腔注射Ranibizumab,房水PEDF水平呈下降趋势;2010年报道了PDR患者(7例7眼)玻璃体腔注射Bevacizumab,房水PEDF呈上升趋势^[36];Chan等^[38]报道了AMD患者(34眼)玻璃体腔注射Bevacizumab,房水PEDF表达上升。

5 展望

糖尿病病程漫长,治疗费用高额,其并发症严重影响患者生活质量,其中PDR已成为一种严重影响人类健康

的疾病,故而降低其致残率、改善患者生活质量仍是当前医学界亟待攻破的难题之一。现有临床试验治疗表明, VEGF 和 PEDF 是 PDR 发生发展的关键性因子。但目前有限的证据并未完全阐明其相关病理生理作用机制,因此进一步明确 DR 与细胞因子间的相关联系,对指导临床有效的治疗有重大意义。

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