

细胞因子在糖尿病视网膜病变中的研究进展

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Study progress of cytokine in diabetic retinopathy

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Abstract

• Diabetic retinopathy (DR) is one of the most serious and common microvascular complications of diabetes, it is a major cause of blindness all over the world. The pathogenesis of DR is very complex and are still being elucidated at present. The classic theory includes abnormal metabolism of polyol, increased advanced glycation end products, activation of protein kinase C, oxidative stress, etc. Recently, with the rapid development of molecular biology, the research of molecular basis has become the focus and hot topic. Cytokines have been shown to involve in the progress of DR such as VEGF, IGF-1, bFGF, etc. A variety of cytokines can induce intraocular angiogenesis through complex signal transduction system, break down blood retinal barrier, and finally result in the development of DR. This article reviews the relationship between cytokine and the progress of DR.

• **KEYWORDS:** diabetic retinopathy; pathogenesis; cytokine; research progress

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摘要

糖尿病视网膜病变 (diabetic retinopathy, DR) 是糖尿病最严重和最常见的微血管并发症之一, 也是一种世界范围内

主要的致盲性眼病。其发病机制相当复杂, 目前尚未完全明确。经典理论包括多元醇代谢异常、糖基化终产物的形成增加、蛋白激酶 C 的活化、氧化应激等。近年来, 随着分子生物学的发展, 分子基础研究已成为目前 DR 发病机制研究的焦点和热点。目前已知与 DR 有关的细胞因子有 VEGF, IGF-1, bFGF, TNF 等。多种细胞因子通过信号转导系统形成复杂的网络系统, 引起新生血管生成, 破坏血-视网膜屏障等多种改变, 从而导致 DR 的发生发展。本文就细胞因子表达异常与 DR 的关系进行综述。

关键词: 糖尿病视网膜病变; 发病机制; 细胞因子; 研究进展

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0 引言

糖尿病视网膜病变 (diabetic retinopathy, DR) 是糖尿病最严重和最常见的微血管并发症之一, 也是一种世界范围内主要的致盲性眼病^[1]。最新研究发现: 在全世界, DR 患者约 9300 万, 其中影响视力者约 2800 万^[2]。近年来, 随着分子生物学的发展, 分子基础研究已成为目前 DR 发病机制研究的焦点和热点, 本文就细胞因子表达异常与 DR 的关系进行综述。

1 血管内皮细胞生长因子

血管内皮细胞生长因子 (vascular endothelial growth factor, VEGF) 是一种从牛垂体滤泡星状细胞体外培养液中分离纯化的, 具有血管内皮细胞特异的促有丝分裂素^[3]。包括 VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F 和 PGF。人 VEGF 基因位于染色体 6p21.3, 长为 14kb, 含有 8 个外显子、7 个内含子, 编码产物为 34~45kD 的同源二聚体糖蛋白。在眼内, 视网膜血管内皮细胞、周细胞、视网膜色素上皮细胞、神经节细胞、Müller 细胞以及感光细胞均可表达 VEGF。VEGF 是 DR 新生血管形成的主要刺激因子^[4,5]。

VEGF 是一种旁分泌和自分泌生长因子, 通过与受体结合后产生多种生物学效应。(1) 增加血管通透性: 研究表明 VEGF 可诱导紧密连接蛋白和 Zonula Occluden-1 的快速磷酸化, 还增加活性氧的产生, 引起血-视网膜屏障损害, 导致视网膜血管通透性增加, 从而引起血浆蛋白外渗, 形成纤维蛋白凝胶, 构成维持新生血管形成及基质细胞内向生长的临时基质, 促进新生血管形成^[6];(2) 促进内皮细胞迁移、增殖和新生血管形成: VEGF 是一种内皮细胞的特异性有丝分裂原, 通过旁分泌途径与内皮细胞内受体结合, 在体外可促进内皮细胞分裂生长, 在体内可诱导血管形成^[7];(3) 改变细胞外基质: VEGF 能改变内皮细胞基因的激活状态, 使组织型纤溶酶原激活物、尿纤溶酶

原激活物、纤溶酶原激活物抑制剂-1 以及间质胶原酶表达上调,导致细胞外基质变性,诱导血管形成^[8]; (4) 增加细胞间黏附分子-1 (intercellular adhesion molecule-1, ICAM-1) 的表达: VEGF 可以增加 ICAM-1 的表达,促成视网膜的白细胞瘀滞,形成白细胞栓子,导致视网膜局部缺血、缺氧及新生血管形成^[9]; (5) 增加内皮细胞对葡萄糖的转运: 葡萄糖转运载体 (glucose transporter-1, GLUT-1) 特异性表达在视网膜内皮细胞、色素上皮细胞。糖尿病患者细胞内葡萄糖水平增高,可能通过激活多元醇代谢途径、蛋白激酶 C 等调节 GLUT-1 使内皮细胞葡萄糖转运增加,进一步导致糖尿病视网膜病变。

DR 的基本病理改变包括视网膜毛细血管周细胞减少或消失、内皮细胞及血流动力学异常导致血管通透性增加、血-视网膜屏障破坏,进一步引起视网膜出血、棉絮斑、硬性渗出、黄斑水肿及新生血管形成等一系列病变。多项研究结果显示: 血清 VEGF 水平与 DR 特别是增殖性糖尿病视网膜病变 (proliferative diabetic retinopathy, PDR) 的发生具有显著相关性, PDR 患者血清 VEGF 水平明显增高^[10]。Lee 等^[11]报道玻璃体切割术后的 PDR 患者玻璃体 VEGF 水平显著降低^[12]。

2 胰岛素样生长因子-1

胰岛素样生长因子-1 (insulin-like growth factor-1, IGF-1) 是一种与胰岛素作用相似的多肽类生长因子,通过与 IGF 受体结合发挥生物学效应。IGF 结合蛋白 (insulin-like growth factor binding protein, IGFBP) 参与调节 IGF-1 与受体结合。研究发现 IGF-1 水平增高与 DR 的发生发展有密切关系^[13, 14]。其引起 DR 的机制包括: (1) 刺激 VEGF 表达: IGF-1 通过激活丝裂酶原活化蛋白激酶途径,增加 VEGF 表达从而促进新生血管形成^[15]; (2) 促进细胞增生、分化,抑制视网膜内皮细胞凋亡^[16, 17]; (3) 诱导周细胞凋亡,促进新生血管形成。

3 碱性成纤维细胞生长因子

碱性成纤维细胞生长因子 (basic fibroblast growth factor, bFGF) 是一种具有强烈的促进细胞增殖和分化能力的生长因子。bFGF 可由多种视网膜细胞如色素上皮细胞、光感受器细胞合成。bFGF 参与 DR 新生血管形成及纤维化的机制可能有: (1) 促进毛细血管内皮细胞、成纤维细胞的有丝分裂,同时诱发分泌多种纤溶酶原激活物及胶原酶,加重 DR 的血液循环障碍,最终导致新生血管生成; (2) bFGF 也可能协同 VEGF 刺激新生血管形成; (3) 调节产生胶原蛋白、纤维连接蛋白等细胞外基质,在 DR 纤维化的过程中起重要作用^[18]。

4 肿瘤坏死因子- α

肿瘤坏死因子 (tumor necrosis factor, TNF)- α 是一种多功能炎症性细胞因子,主要由活化的单核细胞或巨噬细胞产生。研究发现 TNF- α 增高与 DR 病程进展有密切关系^[19]。TNF- α 参与 DR 形成可能有以下几种机制: (1) 损伤血-视网膜屏障,引起血管通透性增加,使 DR 从非增殖期向增殖期转变^[20]。 (2) 增高视网膜血管通透性,刺激血管外基质过量产生和血管内皮细胞的增殖,导致眼内新生血管形成。 (3) 直接杀伤细胞,促发细胞凋亡^[21]。 (4) TNF- α 是一种炎症前细胞因子,促使血管内皮细胞表达黏附分子异常,使小胶质细胞活化,从而刺激炎症循环而使白细胞增加黏附、聚集,增强视网膜局部炎症反应^[22]。

5 间质衍生因子

间质衍生因子 (stromal cell-derived factor, SDF)-1 是新发现的一种分泌型炎症性细胞因子。SDF-1 广泛分布在组织干细胞、血管内皮细胞、视网膜色素上皮细胞中。SDF-1 可以促进新生血管形成,其与 DR 关系密切,可能的作用机制有: (1) SDF-1 是一种促使造血干细胞和血管内皮细胞增殖的趋化因子,从而促进新生血管形成^[23-25]。 (2) 在 DR 患者中 SDF-1 和 VEGF 均为明显的高表达。研究表明: SDF-1 可以刺激 VEGF 在血管内皮细胞中表达, VEGF 能加强 SDF-1 表达。两者之间具有协同促进新生血管生成的作用^[26, 27]。 (3) SDF-1 还可以破坏血-视网膜屏障,造成 DR 新生血管形成、视网膜渗出、黄斑水肿等。它还可能聚集视网膜星形胶质细胞,其作为新生血管的支架,促使新生血管生成。

6 色素上皮衍生因子

色素上皮衍生因子 (pigment epithelium-derived factor, PEDF) 是一种天然血管抑制因子,具有保护神经、抑制新生血管生成、降低血管通透性等作用,还可以阻止 DR 发生发展^[28, 29]。在视网膜内皮细胞及 Müller 细胞中, PEDF 可以抑制 VEGF 与 VEGF-2 结合,从而降低 VEGF 的表达^[30]。Nam 等^[31]发现: DR 患者的 PEDF 水平比正常者低, VEGF 与 PEDF 的比率较正常者高,说明血管刺激因子 VEGF 与血管抑制因子 PEDF 之间的平衡破坏在 DR 的发生发展过程中起着重要作用。

7 小结

总之, DR 的病因及发病机制相当复杂,至今对其具体机制尚未完全阐明。多数学者认为多种细胞因子表达异常、相互之间平衡被破坏,通过复杂的信号转导系统,诱导新生血管生成,引起炎症反应,破坏血-视网膜屏障,从而导致 DR 的发生发展。相信通过对细胞因子与 DR 关系的不断深入研究,能够为临床治疗 DR 提供合理、有效的方法。

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