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糖尿病性黄斑水肿发病机制研究进展

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摘　要

随着全球糖尿病发病率的急剧上升，糖尿病性视网膜病变的患者在未来的几十年将继续增加。糖尿病性黄斑水肿(diabetic macular edema, DME)是导致糖尿病性视网膜病变患者视力下降的重要原因之一，其发生发展的机制复杂多样，但具体机制尚未明确。玻璃体腔内抗血管内皮生长因子(vascular endothelial growth factor, VEGF)治疗已成为DME的一线治疗方法，但临床中抗VEGF治疗对部分DME患者无效，这一发现表明除了VEGF还有其他因素参与DME的发生发展。故急需我们明确DME的发病机制，研究有效的治疗方法。本综述旨在归纳糖尿病性黄斑水肿发病机制的相关文献，对可能的发病机制进行总结。

关键词

糖尿病性视网膜病变，糖尿病性黄斑水肿，发病机制，综述

Advances in the Pathogenesis of Diabetic Macular Edema

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Abstract

With the global incidence of diabetes increasing dramatically, the number of cases of diabetic retinopathy will continue to increase in the coming decades. Diabetic Macular Edema is one of the most important causes of visual impairment in diabetic retinopathy, and its mechanisms are complex

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and varied, but the specific mechanisms are still unclear. Intravitreal anti-VEGF therapy has become the first-line treatment for DME, but it is ineffective for some patients in clinical practice. This finding suggests that other factors besides VEGF are involved in the occurrence and development of DME. Therefore, it is urgent for us to clarify the pathogenesis of DME and study effective treatment methods. The purpose of this review is to summarize the literature on the pathogenesis of diabetic macular edema and to summarize the possible pathogenesis.

Keywords

Diabetic Retinopathy, Diabetic Macular Edema, Pathogenesis, Review

1. 引言

由于社会老龄化发展，全球糖尿病的患病率，从 1980 年的 4.7%增加到 2019 年的 9.3%，预计到 2045 年将增加到世界人口的 10.9%，即达到 7 亿人口。截至 2019 年，中国作为世界上人口最多的国家，糖尿病患者数位居世界第一，为 1.164 亿，这一数据将在 2045 年达到 1.472 亿人[1] [2]。

糖尿病视网膜病变(diabetic retinopathy, DR)是糖尿病微血管的严重并发症之一，是一种慢性、进展性疾病，根据早期治疗糖尿病视网膜病变研究组，目前临床上将 DR 分为非增殖性糖尿病性视网膜病变(non proliferative diabetic retinopathy, NPDR)和增殖性糖尿病性视网膜病变(proliferative diabetic retinopathy, PDR)。糖尿病性黄斑水肿(diabetic macular edema, DME)在 DR 发展的任何阶段均可发生，其发生率随着病情的严重程度而增加。有文献报道，历经 10 年病程，1 型 DR [3]和 2 型 DR [4]患者 DME 的患病率分别为 11%和 14%，且其是 DR 患者视力严重下降的主要原因之一。故我们急需探寻 DME 的发病机制，研究治疗 DME 的有效方法，来预防 DME 的发生发展，改善 DME 患者的视力和生活质量，减轻患者家庭和社会的负担。

2. 发病机制

DME 发生发展的机制复杂多样，包括内部血－视网膜屏障的破坏、细胞因子、炎症反应、水通道蛋白改变、多元醇途径、晚期糖基化终末产物积累、甘油二酯/蛋白激酶 C 通路、激肽/激肽酶系统、醛固酮/盐皮质激素受体通路等，但具体机制尚未明确。

2.1. 内部血－视网膜屏障破坏

视网膜毛细血管内皮细胞间的闭合小带(zonula occludens)和壁内周细胞构成视网膜内屏障。内部血－视网膜屏障(blood retinal barrier, BRB)结构的完整及功能的正常在控制视网膜液体平衡中起着重要的作用，其是通过视网膜血管内皮细胞之间的紧密连接确保的。这种紧密连接是通过神经元、神经胶质和血管之间的相互微调来工作的[5]，以及周细胞和平滑肌细胞的相互作用动态调节[6]。导致内部 BRB 通透性增加的主要机制是：1) 通过下调细胞间连接蛋白质和磷酸化状态的改变；2) 增加跨内皮细胞转运；3) 构成屏障的细胞破坏(内皮细胞、周细胞、神经胶质细胞)。

2.1.1. 内皮细胞凋亡

视网膜毛细血管的内皮细胞由分子复合物连接，包括紧密连接、粘连连接和缝隙连接。这些分子复

合物不仅在细胞间的粘附中起作用，而且还参与内皮细胞分裂、细胞旁通透性的抑制[5]。视网膜和大脑的内皮细胞紧密连接链的数量最多，胞饮活性低，存在高度复杂的连续紧密连接，这为水和水溶性分子建立了物理屏障。高浓度的氧通过一氧化氮、过氧亚硝基阴离子和超氧阴离子诱导内皮细胞凋亡已经在氧诱导的视网膜病变模型中被描述[7]。在 DM 中，内皮细胞之间紧密连接结构完整性和功能的丧失，增加了对水、溶质和蛋白质的通透性。高糖能通过过氧亚硝基阴离子引起磷脂酰肌醇-3 激酶和 p38 丝裂原活化蛋白激酶的磷酸化，抑制 AKT-1 活性，从而加速内皮细胞凋亡[8]。此外，高糖诱导缝隙蛋白下调和 Müller 细胞间隙连接通讯活性降低，影响细胞增殖、细胞分化和触发凋亡，导致 DR 中胶质和血管细胞的丢失[9] [10]。研究指出，在链脲佐菌素(streptozotocin, STZ)诱导的糖尿病大鼠中，视网膜细胞间黏附分子 1 (intercellular adhesion molecule, ICAM-1)和中性粒细胞表面整合素增加，这些分子介导白细胞粘附，这一过程导致内皮细胞损伤和死亡，进而诱导了内部 BRB 的破坏[11]。

2.1.2. 周细胞丢失

周细胞在胚胎发育过程中起源于神经嵴，介导生理和病理修复过程[12]。在视网膜中[13]周细胞和内皮细胞的比例为 1:1，在视网膜中这一比例之所以如此之高，是因为视网膜本身需要极高的屏障功能，以防止多余的液体沉积导致视力丧失。周细胞的选择性脱落和凋亡是早期糖尿病视网膜病变的一个重要机制特征，其原因可能是由于基质蛋白的糖基化，使周细胞在细胞外基质上的粘附减少，周细胞在高糖环境中的变化比内皮细胞对微环境的改变更敏感[14]。在糖尿病患者中，缺氧、活性氧水平升高、血糖快速降低和晚期糖基化终末产物(advanced glycosylation end products, AGEs)的积累等因素破坏周细胞和内皮细胞的连接，引起周细胞凋亡，导致血管渗漏的增加。Kowluru [15]通过用视网膜微血管周细胞证明 AGEs 导致 Bcl-2/Bax 降低和半胱氨酸蛋白酶 3 (caspase-3)活性增加，诱导周细胞凋亡，而 caspase-3 抑制剂可显著减少凋亡的周细胞。越来越多的证据表明血管生成素 2 (Angiopoietin-2, Ang2)在周细胞丢失中起重要作用，在高血糖条件下，内皮细胞产生的 Ang-2 可以通过整合素 $\alpha 3$ 和 $\beta 1$ 对周细胞的脱离和凋亡产生影响[16]。此外，血小板源性生长因子信号通路的改变，不仅会使周细胞覆盖率降低，而且还会导致周细胞凋亡。高血糖持续激活蛋白激酶 δ (protein kinase, PKCδ)和 p38α 丝裂原活化蛋白激酶，增加 Src 同源 2 结构域磷酸酶-1 的表达，导致血小板源性生长因子受体 β 脱磷酸化，并增加周细胞凋亡[17]。最近，Betts-Obregon [18]采用末端标记法检测人视网膜周细胞凋亡时表明，在 DR 中，相关的巨噬细胞浸润到眼睛，其组成性地分泌转化生长因子 1 (transforming growth factor-β, TGF-$\beta 1$)，进而上调编码 TGF-β 诱导基因(TGFβ-Induced Gene Human Clone 3, BIGH3)的产生和分泌，BIGH3 以自分泌的方式引起视网膜周细胞的凋亡。毛细血管周细胞的丢失导致内皮细胞变性和视网膜灌注不稳定[19]，由此导致的视网膜缺血和缺氧促进 VEGF 和其他促炎症细胞因子的强烈表达。

2.1.3. 神经胶质细胞异常

神经胶质细胞位于视网膜血管和神经元之间，其在调节视网膜微环境的分子组成中起关键作用。视网膜中主要存在的神经胶质细胞包括星形胶质细胞、Müller 细胞(RMG)和常驻小胶质细胞。它们不仅保持视网膜的完整结构，而且还通过调节新陈代谢、吞噬神经元碎片、释放神经递质和营养因子来维持视网膜的复杂稳态。视网膜病理改变与神经胶质细胞功能异常有关，包括神经功能障碍和死亡、视网膜水肿和 BRB 破裂[20]。持续的高血糖、AGEs 的积累和复杂的全身炎症反应导致星形胶质细胞活化，并发生一系列变化：增殖、迁移、肥大、胶质纤维酸性蛋白、白介素 6 (interleukin, IL-6)和单核细胞趋化蛋白 1 (monocyte chemoattractant protein, MCP-1)过度表达[21]。研究指出，Ang2 能通过整合素 αv、$\beta 5$ 介导星形胶质细胞的凋亡[22]。小胶质细胞在视网膜神经组织的扰动下被激活并开始产生促炎介质和 VEGF，促进内部 BRB 的破坏[23]。例如，在高糖环境中，小胶质细胞来源的 IL-6 下调了内皮细胞紧密连接蛋白(zona occludens-1,

ZO-1)和闭塞蛋白(occludin)的水平，诱导视网膜内皮细胞产生 VEGF，从而增加了内皮细胞的通透性和血管的渗漏[24]。在 STZ 糖尿病大鼠模型中，视网膜中所有 Müller 细胞的胶质纤维酸性蛋白的表达发生强烈的改变，同时伴有内皮细胞中闭塞蛋白的减少和重新分布[25]。

2.2. 细胞因子

2.2.1. VEGF

血管内皮生长因子家族包括 VEGF-A、-B、-C、-D、-E 和胎盘生长因子(placental growth factor, PLGF)，其中，VEGF-A 是生理和病理血管生成的主要调节因子[26]，能够增加血管通透性，促进细胞生长和内皮细胞增殖、迁移等[27]。目前主要发现有 VEGF121，VEGF165，VEGF189 和 VEGF206 等亚型，VEGF165 是促血管活性最强的亚型[28]。高血糖、AGEs [29]、各种生长因子和促炎细胞因子可以上调 VEGF mRNA 的表达[30]，导致通透性增加，影响 DME 的发生和发展。在 DR 患者眼内测得 VEGF 水平显著高于正常眼[31]。VEGF 通过以下几种途径诱导血管通透性增加，从而引起黄斑水肿。在内皮细胞中，VEGF-A 通过激活 PKC-β 诱导 occludin 磷酸化和泛素化，改变 TJ 蛋白的分布，增加视网膜内皮细胞的血管通透性[32]。Behzadian [33]用 VEGF 和尿激酶纤溶酶原激活剂(urokinase plasminogen activator, uPA)处理牛视网膜微血管内皮细胞，结果显示，VEGF 处理后细胞内游离 β-连环蛋白(β-catenin)增加，引起 uPAR 上调和 occludin 的下调，从而导致细胞通透性增加。VEGF 也可以通过血管内皮生长因子受体 2 (vascular endothelial growth factor receptor, VEGFR-2)和磷脂酰肌醇 3 激酶激活基质金属蛋白酶 2，上调 uPAR，增加内皮钙黏素的降解而增加通透性[34]。此外，最新研究表明，VEGF/VEGFR-2 通路增加视网膜内皮细胞的跨细胞通透性涉及小窝蛋白和质膜囊泡相关蛋白的胞饮机制[35]。除 VEGF 直接导致闭合蛋白发生磷酸化外，还可以刺激 ICAM-1 产生间接破坏增加血管通透性，引发黄斑水肿。

2.2.2. HIF-1a

缺氧也是引起 DME 不可缺少的因素，近年来 Arjamaa 等[36]认为缺氧在人视网膜色素上皮细胞可以引起炎症反应，这些细胞分泌的 VEGF 受低氧的直接调节。缺氧诱导因子(hypoxia inducible factors, HIF)是缺氧适应性反应的主要调节因子，是在缺氧环境下培养的哺乳动物细胞中发现的一种转录因子，是由一个 HIF-1a 亚基和一个 HIF-1β 亚基[37]组成的异源二聚体。Lin [38]证明 HIF-1a 是 DR 主要病理变化的关键介质，包括血管炎症、血管渗漏和视网膜新血管生成。多种受 HIF-1α 调节的蛋白质参与了 DR 的发展，包括 VEGF、PLGF、Ang2、血小板衍生生长因子和促红细胞生成素。VEGF 信号的过度激活是 BRB 破裂和病理新生血管形成的关键，在 PDR 中形成的新血管是不成熟的，具有高渗透性，容易破裂[39]，抑制 HIF-1 确实会导致血管通透性降低[40]。此外，HIF-1 激活胶质细胞中诱导型一氧化氮合酶的产生[41]，增加血管通透性。既往研究表明 DR 患者血清和玻璃体液中 HIF-1α 表达显著增加[42]，且发现 HIF-1 值似乎与 Ang-2 水平高度相关[43]。新出现的证据表明，HIF-1α 在神经退行性变中发挥了重要作用[44]，受损的神经胶质细胞功能异常导致血管渗漏[45]。同时，它还会导致促炎症因子的分泌，损害 BRB 的完整性[46]。综上所述，这些研究表明 HIF-1α 在 DME 缺血及损伤反应的发生发展中起着关键作用。

2.3. 炎症反应

炎症是 DME 的另一个主要病理特征，越来越多的证据表明免疫机制在 DR 和 DME 的发病机制中发挥基本作用。胶质细胞(Müller 细胞和小胶质细胞)、视网膜素色上皮细胞(retinal pigment epithelium, RPE)和巨噬细胞分泌的 VEGF 和促炎细胞因子 IL-1β、IL-6、IL-8、MCP-1 和肿瘤坏死因子(tumor necrosis factor，TNF-α)，引起白细胞活化、淤滞，BRB 封闭功能的改变[47]，导致血管通透性增加。TNF-α 是起始的具有渗透性的促炎细胞因子，可以通过 PKCζ/NF-κB 信号通路降低 ZO-1 和紧密连接蛋白(claudin-5)的表达，

增加细胞旁通透性[48]。IL-6 是一种多功能细胞因子，来源于单核巨噬细胞、淋巴细胞和非淋巴细胞，主要参与免疫和炎症反应过程。它可以直接破坏 BRB 使内皮通透性增加，还可以通过间接作用诱导 VEGF 表达增加，从而加重 BRB 破坏的发生发展[49]。人血管内皮细胞的 IL-8 浓度增加表现出紧密连接蛋白下调，包括 occludin，claudin-5 和 ZO-1 [50]。研究表明，在 DME 患者的视网膜中表现出炎症因子调节失调，如 lL-1β、lL-6、lL-8、MCP-1 和 TNF-α [51]，这些细胞因子的水平与对照组相比显著增加，且其表达水平与 DME 的严重程度相关[52]。

2.4. 水通道蛋白改变

水通道蛋白(aquaporin, AQP)是形成跨膜通道的一种完整膜蛋白，在渗透梯度下促进水在质膜上的运输，有助于细胞内和细胞外的水离子调节，因此也被称为“渗透传感器”。在哺乳动物中，AQP1 除了大脑和视网膜外的所有组织的微血管内皮中均有表达，视网膜中的主要是 AQP4，它由 Müller 胶质细胞表达，在血管周围和突触周围膜结构域的密度最高[53]。研究报告称，糖尿病导致大鼠视网膜表面血管周围的 AQP4 被 AQP1 所替代[54]，离子和其他渗透性物质在视网膜上的分布也发生改变，导致 ME。在正常的生理条件下，Müller 细胞从视网膜组织吸收液体，并通过 AQP4 水通道和内向整流钾通道(Kir4.1)的共同运输将其输送到血液中。在 STZ 大鼠模型[55]中，这一离子通道很早就被破坏了。综上所述，在糖尿病病理条件下，通过 Müller 细胞的液体运输受到干扰，提示 Müller 细胞大量肿胀导致细胞内水肿。

2.5. 多元醇途径

多元醇途径是基于醛酮还原酶家族，这种酶可以作为底物利用多种羰基化合物，并通过还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate, NADPH)将这些羰基化合物还原为它们各自的糖醇(多元醇) [56]。多元醇的增加是视网膜神经退行性疾病的一个牵连通路。葡萄糖在醛糖还原酶的作用下转化为山梨醇，山梨醇进一步转化为果糖。山梨醇不会直接进入细胞膜产生渗透胁迫，而是诱导蛋白质的氮糖基化，促进 AGEs 的积累[57]。同时，醛糖还原酶的活化使 NADPH 过度消耗，从而诱导下调抗氧化剂谷胱甘肽，随后加剧氧化应激反应[58]。这两种机制(山梨醇和醛糖还原酶途径)进入线粒体，增加多元醇途径诱导的氧化应激，从而损伤视网膜细胞并诱导 DR 和 DME。

2.6. AGEs 通路

AGEs 是葡萄糖和其他糖基化合物反应形成的一组不可逆的分子化合物[59]。在 DM 中，随着年龄的增长，AGEs 在视网膜血管中的积累比正常人增加，并且参与了微血管并发症[60]。AGEs 不仅直接增加纤维化，而且刺激 AGEs 的内皮细胞膜受体，引发 RMG 细胞的炎症反应[61]。实验表明，在体外和体内的糖尿病条件下，AGEs 可诱导视网膜周细胞凋亡[62]，并在 RMG 细胞中积累。AGEs 也可以通过 NF-kB 和 JAK-STAT 途径激活 RPE 细胞炎症反应[63]。这些过程导致水离子通道功能障碍、氧化应激和胶质纤维酸性蛋白被激活[64]，增加细胞通透性，引起 DME 的发生。

2.7. DAG/PKC 通路

蛋白激酶 C (protein kinase C, PKC)是一个多功能同工酶家族。常规的 PKCs (PKC-α, -β1, -β2 和-γ)被磷脂酰丝氨酸、钙和甘油二酯(diacylglycerol, DAG)激活。新型 PKCs (PKC-δ, -ε, -θ 和-η)被磷脂酰丝氨酸和 DAG 激活，非典型的 PKCs (如 PKC-ζ)主要由磷脂酰肌醇(PI)-3,4,5-三磷酸酯激活[65]。由于糖酵解和葡萄糖超载受损，细胞中 DAG 合成增加，激活传统和新型 PKC，特别是异构体 β、δ、ε 和 γ。研究表明，

在糖尿病患者中，总 DAG 水平在血管组织如视网膜[66]、主动脉[67]、心脏中升高[68]。DAG/PKC 通路的激活与内皮细胞功能障碍、通透性增加、血管收缩、血管生成、白细胞黏附和炎症有关[69] [70]。在高血糖条件下，PKC-δ 的激活诱导视网膜血管细胞死亡[71]。非典型 PKCζ，激活内皮细胞和 RPE 细胞的 TNF-α 反应，使紧密连接不稳定和细胞极性发生改变[72] [73]。

2.8. 激肽/激肽酶系统(KKS)

激肽/激肽酶系统(Kinin/kallikrein system, KKS)是一个复杂的多酶和肽能系统，不但在人体生理中起关键作用，而且在疼痛和炎症中也起关键作用[74]。激肽包括缓激肽和激肽，是具有天然血管扩张和内皮保护特性的多肽。激肽酶有组织激肽酶(tissue kallikrein, TK)和血浆激肽酶(plasma kallikrein, PK) [75]。激肽的作用是由两个相关的 G 蛋白偶联受体介导的，即缓激肽受体 B1R 和 B2R。B2R 主要在血管内皮细胞、神经节细胞层、内核层和外核层中表达[76]，血管舒张可能由 B2R 介导[77]。B1R 在正常组织中几乎不存在，但是，在 2 型糖尿病大鼠模型中[78]以及 1 型或 2 型糖尿病患者死后的眼睛中，PK [79]和 B1R [80]在中枢神经系统氧化应激反应中过度表达。研究表明，KKS 系统在糖尿病视网膜病变中被激活，并促进视网膜水肿和炎症的发生[81] [82]。在动物模型中，玻璃体内注射 PK 或缓激肽可增加视网膜血管通透性，使用 KKS 拮抗剂可降低视网膜血管通透性[83]。缓激肽通过 B2R 激活内皮型一氧化氮合酶和前列环素诱导血管舒张，通过 B1R 上调诱导型一氧化氮合酶诱导血管舒张和通透性[84]，特异性 B1R 拮抗剂已被开发出来，并发现能有效降低视网膜增厚和血管通透性[85]。B2R 活化也可以通过 Src 活化途径诱导渗透性[86]。

2.9. 醛固酮/MR 通路

盐皮质激素受体(mineralocorticoid receptors, MR)在 RMG 细胞和内皮细胞中表达。醛固酮是一种特异性 MR 激活剂，调节 RMG 细胞中离子和水通道(如 AQP4、Kir4.1、αENac)的表达及分布，来控制视网膜的水合作用，并通过改变神经胶质的引流机制使视网膜厚度增加[87]。另一方面，脉络膜血管中的 MR 激活，通过上调钙活化的 K+通道(KCa2.3)诱导血管舒张和通透性，该通道在视网膜血管中不表达[88]。在血管内皮细胞中，MR 通过激活 RhoA/Rho 激酶，调节了肌动蛋白细胞骨架的重排和紧密粘附的连接，加剧了细胞旁通透性的增加[89]。此外，醛固酮通过增加视网膜血管内皮细胞炎症介质、ICAM-1 和环氧化酶 2 的表达，进而诱导血管通透性[90]。研究表明，使用 MR 拮抗剂能降低 2 型糖尿病患者的 MCP-1 水平[91]。MR 过度激活能引发中心性浆液性脉络膜视网膜病变已被证明[92]。

3. 展望

DR 是工作年龄成年人失明的主要原因，DME 和病理性新生血管生成是 DR 患者视力下降最常见、最重要的原因，大约一半的 DME 患者将在 2 年内失去 2 行视力。因此，了解 DME 和 DR 的发病机制对于预防糖尿病并发症和开发新的治疗方法以及保护糖尿病患者的视力非常重要。目前 DME 的治疗方法多种多样，有内科药物治疗、激光光凝术、玻璃体腔内注射抗 VEGF 药物和类固醇激素、玻璃体切除手术等方法。虽然眼部抗 VEGF 治疗糖尿病性黄斑水肿的发展和广泛应用在改善视力方面具有革命性意义，但是，仍有患者对抗 VEGF 治疗无效，持续的黄斑水肿会导致黄斑结构发生不可逆的损害，使患者视力永久下降。此外，频繁注射抗 VEGF 药物给患者和医疗系统带来了巨大的治疗负担和成本，故当务之急是明确 DME 的具体发病机制，从源头上阻断疾病的发生、发展。未来的前瞻性研究应该更加深入地探索发病机制及损伤更小、更加优化的临床治疗方法，相信随着科学技术的发展，临床基础研究的深入和治疗方法的探索，更加有效、安全的治疗手段与方案将会出现。

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