·文献综述·

小胶质细胞在糖尿病视网膜病变视网膜神经血管单元中的作用

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摘要

糖尿病视网膜病变(DR)是工作年龄人群主要致盲眼病,血-视网膜屏障破坏是关键环节。近年研究显示,DR 不再是单纯微血管病变,而是视网膜胶质细胞与神经退行性变、微血管病变的共同发展结果。DR 病程早期视网膜神经血管单元(RNVU)中神经元的损伤可能早于血管内皮的变化,胶质细胞的激活加重血管屏障功能障碍。视网膜小胶质细胞是常驻视网膜的局部免疫细胞,参与长期高糖诱导的慢性炎症反应、高糖诱导其分泌多种炎症因子,破坏血-视网膜屏障结构、增加神经元凋亡、改变 Müller 细胞胶质化等,影响视网膜局部稳态平衡。RNVU 作为一个单元结构研究,近年来受到越来越多的关注,本文将针对小胶质细胞在 RNVU 中的作用机制、研究进展进行综述。

关键词:小胶质细胞;视网膜神经血管单元;糖尿病视网膜病变;炎症;综述
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Role of microglia in retinal neurovascular unit of diabetic retinopathy

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Abstract

• Diabetic retinopathy (DR) represents the primary cause of blindness among the global working-age population, and the disruption of the blood-retinal barrier is a crucial factor. Research in recent years has elucidated that DR transcends the scope of a mere microvascular disorder into a complex interplay of retinal glial cells and neurodegeneration microvascular pathology. Neuronal damage may precede vascular endothelial changes in the retinal neurovascular unit (RNVU) in the early stage of DR, and glial cell activation further exacerbates vascular barrier dysfunction. Retinal microglia are immune cells that reside in the retina and are involved in chronic inflammatory responses induced by long-term exposure to high glucose levels. Microglia secrete various inflammatory factors in response to high glucose levels, which can lead to the destruction of the blood-retinal barrier structure, increased neuronal apoptosis, and altered gliosis of Muller cells, thus affecting the retina's homeostatic balance. The RNVU has received increasing attention in recent years as a unitary structural study, and the mechanism of microglia in the RNVU and the progress of the study are reviewed.

• KEYWORDS: microglia; retinal neurovascular unit; diabetic retinopathy; inflammation; review

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0 引言

糖尿病视网膜病变(diabetic retinopathy,DR)是糖尿病引起的可致盲眼部疾病,主要影响工作年龄人群。DR 的基本病理改变主要为微血管病变相关的血-视网膜屏障(blood-retina barrier,BRB)破坏以及新生血管的形成[1]。但是,近年来越来越多的研究支持以神经元、胶质细胞与血管系统组合形成的视网膜神经血管单元(retinal neurovascular unit,RNVU)功能失调全程参与 DR 的发生

发展。RNVU 中小胶质细胞失衡影响单元结构中其他细胞功能障碍,调整小胶质细胞对维持 RNVU 正常功能至关重要[2]。本文将对 DR 视网膜神经血管单元中小胶质细胞的作用机制及研究进展进行综述。

1 视网膜小胶质细胞

1.1 生理功能 小胶质细胞起源于卵黄囊并且能够自我更新,在视网膜和中枢神经系统(central nervous system,CNS)监测局部周围环境、参与主动免疫防御第一线[3]。正常情况下,视网膜小胶质细胞分布在视神经纤维层(nerve fiber layer,NFL)、神经节细胞层(ganglion cell layer,GCL)、内丛状层(inner plexiform layer,IPL)和外丛状层(outer plexiform layer,OPL)[4]。主要功能:(1)清除视网膜中的细胞废物[5];(2)抵抗感染性物质的过程中参与抗原呈递、炎症反应和补体激活,并促进视网膜的组织修复和免疫调节[6];(3)调节祖细胞增殖、分化和神经元存活[7];(4)维持基于突触结构和视网膜正常视觉功能的突触传递[8];(5)参与血管生成;(6)维持视网膜稳态[9]。总体上小胶质细胞在哺乳动物类进化过程中发挥着基本相似的功能,与周围的神经元之间存在相互作用,维持视网膜正常生长、发挥免疫监视、突触修剪等作用。

1.2 病理改变 小胶质细胞被认为是糖尿病患者高血糖信号的第一个检测器[10],高糖环境下小胶质细胞数量增多,移行至视网膜外核层(external nuclear layer,ONL)[11],部分学者认为颅内高糖导致脑神经血管单元(neurovascular unit,NVU)结构耦合失调,血-脑屏障破坏,小胶质细胞活化增生并向下移行至视网膜[12]。DR 早期小胶质细胞激活态 M1 型(促炎型)和 M2 型(抗炎型)均升高,随着病情发展,M1/M2 比例升高,M1 型比例显著高于 M2 型[13]。M1 型是神经炎症的重要神经毒性介质之一,分泌促炎因子,如白细胞介素(IL)-1β、IL-6、肿瘤坏死因子(TNF-α)、趋化因子,导致神经元死亡或损伤[14],参与视网膜无灌注区的定位与新生血管形成[15],加剧 BRB 功能障碍,促进血管渗漏和内皮周细胞凋亡[16]。M2 型主要分泌多种抗炎因子和神经营养因子,抑制视网膜炎症反应、保护神经节细胞和光感受器细胞,减少新生血管形成[17],M1/M2 比例异常诱导局部小胶质细胞参与各种炎症通路,加速 DR 进程。

2 视网膜神经血管单元

2.1 RNVU 生理功能 RNVU 由神经元(神经节细胞、双极细胞、水平细胞、无长突细胞及光感受器)、胶质细胞(Müller 胶质细胞、小胶质细胞及星形胶质细胞)、血管细胞(内皮细胞和周细胞)共同耦合。小胶质细胞分支接触视网膜血管,分泌营养因子和血管生成因子,控制周细胞和内皮细胞的凋亡,及时清除多余的血管碎片[18-20];Müller 细胞、星形胶质细胞为神经元提供代谢支持,维持突触传递[21]。与其他中枢神经系统比较,RNVU 的微血管系统线粒体相对较少,视网膜血管密度较低[22]且以分层的方式组成,深血管丛位于内核层(inner nuclear layer,INL)的外表面,中间血管丛位于 IPL 与 INL 之间的边界和 NFL 中的浅表血管丛[23]。光信号传导时,RNVU 中小动脉和毛细血管会随着神经元活动而扩张,以增加血流量,并提供足够的营养来满足神经元的代谢需求[24-25]。RNVU 各类细胞和细胞间紧密连接组成 BRB,维护屏障功能;神经元和血管间紧密配合实现光信号及时快速的传递。

2.2 糖尿病视网膜小胶质细胞激活与 RNVU 改变

2.2.1 视网膜血管细胞变化 高糖、缺血缺氧激活小胶质细胞,通过 PI3K/STAT3/NF-κB 信号通路释放过量的促炎介质、细胞因子、趋化因子、补体、半胱天冬酶以及谷氨酸等诱导视网膜血管内皮细胞凋亡;活化的小胶质细胞穿透内层血-视网膜屏障(inner blood-retinal barrier,iBRB)的基底膜并吞噬 iBRB 内皮细胞,或诱导视网膜血管周细胞产生活性氧基团(reactive oxygen species,ROS),上调 NF-κB-p65蛋白和 Caspase-3 蛋白,加速周细胞凋亡,重塑血管[26-29];小胶质细胞来源的旁分泌途径产生的血管内皮生长因子(vascular endothelial growth factor,VEGF)与 VEGF/VEGFR-2 结合介导视网膜血管内皮细胞生成反应,改变新生血管管壁完整性,促进 DR 中视网膜新生血管长出及血管渗漏[30];在 DR 的缺血缺氧条件下因 BRB 中的连接蛋白半通道开放促进 ATP 从细胞内流出,ATP 过度刺激、激活 P2X7 受体诱导视网膜小胶质细胞活化,分泌 IL-1β、TNF-α 等细胞因子增加,刺激 NLRP3 炎症小体自分泌激活,局部上调的炎症因子导致血管周细胞损伤,钙信号、钾离子通道失调,促进 DR 中的炎症反应,引发微血管细胞、神经元死亡[31-33]。

2.2.2 大胶质细胞变化 RNVU 中包含两类大胶质细胞,即 Müller 细胞和星形胶质细胞。Müller 细胞主要调节视网膜代谢以及调节神经元和血管功能,正常情况下,Müller 细胞可作为细胞外 ATP 的一个潜在来源,介导小胶质细胞的动态变化调节[34]。星形胶质细胞位于 NFL,包围血管和神经节细胞,具有提供营养和调节支持的功能[35]。长期高糖环境,活化的视网膜小胶质细胞向 Müller 细胞发出信号,直接影响 Müller 细胞形态变化和功能反应。小胶质细胞激活后上调 TNF-α、IL-1β 等炎症因子表达,促进 Müller 细胞胶质化、VEGF 表达增加[36]。反之,Müller 细胞可通过趋化性和黏附性细胞接触增加小胶质细胞诱导的视网膜炎症反应[37]。Müller 细胞通过激活 CD40-ATP-P2X7/NLRP3 信号通路协同小胶质细胞形成促炎反应,并使 RNVU 形成炎症级联反应,造成视网膜炎症环境、影响视网膜内皮细胞死亡与毛细血管变性[38]。星形胶质细胞和小胶质细胞之间以层黏连蛋白依赖的方式相互作用,星形胶质细胞增生引起小胶质细胞活化,调节视网膜血管分支和内皮细胞增殖,DR 进程中小胶质细胞和星形胶质细胞均发生胶质增生、转运蛋白上调[39]。

2.2.3 神经元变化 DR 发生发展过程中小胶质细胞对神经元有双重作用。DR 早期,激活的小胶质细胞释放神经保护类因子,保护神经元免受 Müller 细胞胶质化增加引起的谷氨酸毒性作用,但随着 DR 病程的进展小胶质细胞分泌过多炎症因子加速神经元凋亡。小胶质细胞激活后上调谷氨酰胺合成酶,促进谷氨酸转化为谷氨酰胺,降低谷氨酸毒性,增强小胶质细胞中胰岛素介导的葡萄糖摄取,缓解小胶质细胞的炎症反应,下调 NO 的生成[40];与此同时,作为信号分子的 ROS 发挥了相互矛盾的作用,包括下调减少 ROS 参与神经元极性的建立、生长锥延伸、突触连

接和神经网络的形成等过程;但也增加 ROS 对蛋白质、脂质和 DNA 的有害的氧化应激作用,导致神经元死亡[41]。视网膜神经元分泌的单核趋化蛋白(monocyte chemoattractant proteins,MCP-1)刺激小胶质细胞活化,并通过 p38-MAPK、ERK 和 NF-κB 信号通路诱导小胶质细胞释放 TNF-α,分泌促炎因子(如 IL-1β、IL-6、IL-12、TNF-α 等),引起凋亡蛋白 Caspase-3 活化,促进视网膜神经元死亡。谷氨酸、Caspase-3、ROS 等神经毒性介质的产生可导致神经细胞功能障碍,损伤视网膜血管周细胞和内皮细胞[42-44]。

总之,高糖环境可引起视网膜 RNVU 各个组成成分发生变化,小胶质细胞与 RNVU 中其他细胞相互作用,共同参与 DR 的发生发展,因此针对小胶质细胞作为靶向治疗 DR 在近年的研究中备受重视。

3 DR 治疗方案对小胶质细胞和 RNVU 的影响

小胶质细胞可通过免疫防御受体(Toll 样受体、主要组织相容性复合体Ⅰ类和Ⅱ类等)、免疫监视相关受体、细胞因子受体等发挥抗原提呈功能、分泌功能、吞噬功能及与神经系统其他细胞相互作用等功能,发挥神经元的保护作用[45-46],也可通过 Wnt-Fll 途径抑制深层血管丛产生过度分支。深层视网膜血管丛旁聚集的小胶质细胞可特异性表达 Wnt5a 和 Wnt11 配体等 Wnt 信号成分,表达 VEGF 抑制蛋白可溶性 Fll,从而抑制视网膜深层血管丛的血管分支[47]。因此,激活小胶质细胞 Wnt 信号通路,有望成为抑制 DR 中视网膜产生新生血管的重要靶点,保护血管细胞及血管完整性。

3.1 视网膜激光光凝 视网膜激光光凝目前仍为经典的 DR 治疗手段,激光可破坏无灌注区视网膜色素上皮(retinal pigment epithelial,RPE)层,减少视网膜需氧量,增加脉络膜与视网膜血流沟通。动物实验显示,视网膜激光光凝后早期周围视网膜以及下方脉络膜和巩膜中出现 CD11b、F4/80 和 iba1 等小胶质细胞标志物呈阳性的细胞增殖。激光术后炎症主要由小胶质细胞触发,通过释放促炎细胞因子介导视网膜炎症反应,通常导致原发性神经元损伤的加重[48-51]。研究显示,视网膜疾病进行局灶性激光治疗后,视网膜小胶质细胞可能以各种活动状态存在,并且在局部损伤后可能从“静息”状态转变为“激活”状态[52]。“激活”的小胶质细胞可能会释放神经营养因子和炎症介质,神经营养因子发挥血管保护和神经保护作用,这也是糖尿病性黄斑水肿(DME)局灶性激光获益的基础[53],而小胶质细胞释放的炎症因子则加重局部视网膜及神经损伤。因此,虽然视网膜激光光凝可能加重小胶质细胞的激活,但通过改变视网膜激光光凝方式,减少曝光时间可抑制炎症反应,并促使激活的小胶质细胞发挥神经保护作用[54],进而保护 RNVU 中的神经元,达到延缓 DR 进展的治疗效果。

3.2 药物治疗 针对 DR 小胶质细胞被激活后出现促炎型 M1 及抗炎型 M2 两种极化状态,通过药物调节 M1/M2 比例有望成为以小胶质细胞为靶点治疗 DR 的一种方案。目前,临床上治疗 DR 使用的抗 VEGF 药物及口服药物均在一定程度上促进小胶质细胞向 M2 型转化。DR 中视网膜 VEGF 表达上调,并与 VEGFR-1 结合激活小胶质细胞,促进炎症介质及促新生血管生成介质的产生[55-58],抗 VEGF 药物通过抑制 VEGF 受体改善视网膜缺氧区域的新生血管形成,减轻视网膜水肿及出血[59-61]。此外,抗 VEGF 治疗可显著降低相关细胞因子和趋化因子、细胞间黏附分子(intercellular adhesion molecules,ICAM-1)的表达、紧密连接蛋白 ZO-1 的异常定位和变性及细胞黏附蛋白血管内皮钙黏蛋白的表达,抑制糖尿病相关的血管渗漏、白细胞淤积和血管内皮细胞增生[58]。抗 VEGF 药物可通过抑制新生血管产生、改善视网膜炎症环境保护 RNVU 中血管内皮细胞。

糖皮质激素(glucocorticoids,GCs)常用于治疗抗 VEGF 治疗疗效差或特殊类型的 DME,GCs 通过小胶质细胞上糖皮质激素受体(glucocorticoid receptors,GCR)能够抑制炎症反应,是 GCs 发挥抗炎作用的重要靶点[62]。研究显示,低剂量的地塞米松(DEX)、曲安奈德(triamcinolone acetonide,TA)可能会使小胶质细胞向 M2 型转化,从而增强神经保护作用并抑制促炎小胶质细胞的活化及浸润,保护视网膜感光细胞及视神经[63-64]。类固醇激素可以通过抑制小胶质细胞 M1 型的炎症反应、增强 M2 型的神经保护作用,进而保护 RNVU 神经元、减轻光感受器细胞损伤,但需密切监测用药过程中眼压变化及白内障发生情况。

目前临床上有多项小样本药物研究显示,在 DR 或 DME 治疗中,抗生素类(沙星类)和四环素类药物可通过 TLR4/NF-κB 途径减弱小胶质细胞炎症反应,抑制小胶质细胞活化,减少炎症因子、细胞毒性物质释放及 Caspase-3 活性,抑制视网膜炎症反应及神经元损伤,进而保护 RNVU 各细胞单元结构[65-66]。常用的降糖药二甲双胍可通过下调血清胱抑素 C(cystatin C,CysC)介导炎症和氧化应激反应[67-68],褪黑素可增加小胶质细胞中磷酸化信号转导和转录激活因子-3(STAT3)的表达[69],姜黄素和白藜芦醇可减少髓细胞触发受体 2(TREM2)和 Toll 样受体 4(TLR4)的失衡并平衡下游 NF-κB 的激活[70-71],高选择性 α2-肾上腺素能激动剂右美托咪定可通过 MAPK/ERK 途径[72],非选择性 ATP 敏感性钾(KATP)通道开放剂 Pinacidil[73]可通过直接调节改变小胶质细胞极化 M1/M2 比例,将 M1 促炎表型转变为 M2 抗炎表型,促进小胶质细胞向 M2 抗炎表型极化,同时下调 M1 促炎表型比例,抑制 TNF-α 和 IL-1β 的产生,减少视网膜炎症,下调高糖环境中 Müller 细胞胶质增生。总之,通过药物改善高糖诱导的视网膜小胶质细胞 M1/M2 比例,能够促进神经保护、抑制炎症通路、减少炎症介质,改善局部炎症反应,保护 RNVU 各结构完整性。但上述药物转化小胶质细胞表型在治疗 DR 中的疗效及安全性仍需进行长期、多中心研究证实。

3.3 基因治疗 miRNA 能够调节 DR 基因转录及其相关信号通路,其中 miR-124 可调节神经元分化和小胶质细胞发育,使巨噬细胞和小胶质细胞向 M2 型分化,促进小胶质细胞的静止,并与视网膜小胶质细胞中 MCP-1 mRNA 的 3'-UTR 结合抑制天冬氨酰氨基葡萄糖苷酶(aspartylglucosaminidase,AGA)诱导的 MCP-1 表达[74-77]。Dong 等[78]通过敲低人肺腺癌转移相关转录本 1 基因(metastasis associated in lung denocarcinoma transcript 1,

MALAT1)抑制 amadori 糖化白蛋白诱导的 MCP-1 在视网膜小胶质细胞中的积聚,并证明 MALAT1 可通过直接与 miR-124 结合调节小胶质细胞中 AGA 诱导的 MCP-1 表达,从而作为竞争性内源性 RNA 发挥作用。MALAT1 通过增加髓细胞分化因子-88 衔接蛋白(MyD88)启动子的 H3 组蛋白乙酰化上调 MyD88 的表达,然后激活 IL-1 受体相关激酶(IRAK1)/肿瘤坏死因子受体相关因子 6(TRAF6)轴传导促进小胶质细胞激活引起的炎症级联反应[79-80]。虽然 MALAT1 还有许多调节小胶质细胞的方式未被探索,但 MALAT1 有望成为抑制 DR 中小胶质细胞过度激活的靶点[81]。miR-124 在 DR 炎症的发展中起着重要作用,MALAT1-miR-124-MCP-1 信号通路可能参与 AGA 诱导的小胶质细胞 MCP-1 的表达,这可能为治疗 DR 提供一种新的途径[78]。上述研究表明,在糖尿病环境中基因疗法调节视网膜和其他组织中的小胶质细胞激活、转化及炎症介导并预防 RNVU 中神经胶质细胞功能障碍可能是治疗 DR 炎症的有效手段[82]。

4 小结

小胶质细胞作为 RNVU 组成结构之一,对于维持神经血管单元各结构之间的相互关联、保障视网膜稳态环境具有重要意义。在 DR 中小胶质细胞参与炎症反应影响 RNVU 中神经元、胶质细胞和血管细胞之间正常的结构与生理功能,同时也影响视网膜稳态平衡。药物、激光治疗可通过改变小胶质细胞 M1/M2 极化转换,影响 RNVU 功能结构的完整性,改善高糖对视网膜血管、胶质细胞及神经元的作用。基因疗法以 RNVU 中小胶质细胞为靶点调节 DR 炎症反应,达到保护 RNVU 结构与生理功能的目的,更加精准的基因水平调控小胶质细胞向抗炎型转换或许是未来维护 DR 发生发展过程中视网膜 RNVU 功能新的方向。

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