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• 综 述 •

视网膜星形胶质细胞在视网膜血管生成中的研究进展

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文章亮点

1. 关键发现

• 视网膜星形胶质细胞在病理性视网膜新生血管形成中发挥着促进和抑制的双重复杂作用，其极化表型（A1/A2）和网络完整性是调控血管异常生长的核心。

2. 已知与发现

• 星形胶质细胞是哺乳动物视网膜特有的胶质细胞，起源于视盘祖细胞。在生理上通过形成“蜂窝”模板并进行代谢清除和营养供应来维持视网膜稳态和血管有序发育。

3. 意义与改变

• 对视网膜星形胶质细胞功能进行精准干预，包括保护其网络完整性、重编程其反应性表型，以及利用其释放的外泌体作为药物载体，有望开发出治疗视网膜新生血管形成的新型疗法。

[摘　要]　视网膜星形胶质细胞作为神经血管单元的关键组成部分，在维持视网膜稳态中发挥着结构支持、营养供应、代谢清除和免疫调控等多重功能。本综述系统阐述其胚胎起源、分子标志物及与 Müller 细胞在发育来源、空间分布和功能耦合上的本质差异。生理条件下，星形胶质细胞迁出形成"蜂窝"模板，通过分泌 N-钙黏蛋白、纤维连接蛋白及层粘连蛋白引导血管内皮细胞有序迁移并建立浅层血管丛，其终足广泛覆盖毛细血管基底膜，参与构成血-视网膜屏障。营养供应方面，通过葡萄糖转运体 1 (glucose transporter type 1, GLUT1) 摄取葡萄糖，经有氧糖酵解产生乳酸，供给神经元，并储存糖原作为应急能源。代谢清除层面，作为视网膜主要的谷胱甘肽合成者，清除活性氧并转化谷氨酸为无毒谷氨酰胺，保护神经元免受氧化应激与兴奋性毒性。而在缺氧、炎症等病理条件下，星形胶质细胞表现出促进和抑制病理性视网膜新生血管形成 (retinal neovascularization, RNV) 的双重作用：缺氧时低氧诱导因子-1α (hypoxia-inducible factor-1α, HIF-1α) 稳定并激活核因子 κB (nuclear factor kappa-B, NF-κB) 通

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电子全文

路，促进血管内皮生长因子-A（vascular endothelial growth factor-A, VEGF-A）、成纤维细胞生长因子 2 (fibroblast growth factor 2, FGF2)、白细胞介素-6 (interleukin-6, IL-6)、基质金属蛋白酶-2/9 (matrix metalloproteinase-2/9, MMP-2/9) 等因子释放导致病理性 RNV；同时可极化为 A2 型反应性星形胶质细胞，分泌血小板反应蛋白-1(thrombospondin-1, TSP-1)、色素上皮衍生因子 (pigment epithelium-derived factor, PEDF) 及携带抗血管生成蛋白的外泌体，抑制血管过度增生并促进有序修复。深入理解其精细调控机制，有望为开发保护星形胶质细胞网络完整性、重编程反应性表型及应用外泌体递送等靶向 RNV 治疗策略提供新的方向。

[关键词] 视网膜星形胶质细胞；视网膜血管生成；生理；病理

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Research progress on retinal astrocytes in retinal angiogenesis

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Abstract Retinal astrocytes, as key elements of the neurovascular unit, fulfill a multitude of roles in preserving retinal homeostasis. These roles include providing structural support, supplying nutrients, facilitating metabolic waste clearance, and regulating immune responses. This review presents a systematic and in-depth exploration of their embryonic origin, molecular markers, as well as the fundamental disparities between them and Müller cells in terms of developmental origin, spatial distribution, and functional coupling. Under physiological conditions, astrocytes migrate outward to form a "honeycomb" - like template. This template acts as a guiding framework for the orderly migration of vascular endothelial cells, facilitating the establishment of the superficial vascular plexus. This is achieved through the secretion of N-cadherin, fibronectin, and laminin. The end-feet of astrocytes extensively wrap around the capillary basement membrane and are actively involved in the formation of the blood-retinal barrier. When it comes to nutrient supply, astrocytes take up glucose *via* glucose transporter type 1 (GLUT1). Subsequently, they generate lactate through aerobic glycolysis and store glycogen as an emergency energy reserve to meet potential demands. In terms of metabolic waste clearance, as the primary producers of glutathione in the retina, astrocytes are capable of eliminating reactive oxygen species and converting glutamate into non-toxic glutamine. This process effectively shields neurons from oxidative stress and excitotoxicity, thereby maintaining the normal function of the retinal neural network. Under pathological conditions, such as hypoxia and inflammation, astrocytes exhibit a dual role in either promoting or inhibiting retinal neovascularization (RNV). Hypoxia leads to the stabilization of hypoxia-inducible factor-1α (HIF-1α) and activates the nuclear factor kappa-B (NF-κB) pathway. This activation, in turn, promotes the release of factors like vascular endothelial growth factor-A (VEGF-A), fibroblast growth factor 2 (FGF2), interleukin-6 (IL-6), and matrixmetalloproteinase-2/9 (MMP-2/9), ultimately resulting in pathological RNV. On the contrary,

astrocytes can also polarize into A2-type reactive astrocytes. These reactive astrocytes secrete thrombospondin-1 (TSP-1), pigment epithelium-derived factor (PEDF), and exosomes loaded with anti-angiogenic proteins. These secretions inhibit excessive vascular proliferation and facilitate orderly repair, thereby counteracting the pathological process of RNV. A more profound understanding of their precise regulatory mechanisms of retinal astrocytes may pave the way for the development of targeted RNV therapies. These potential therapies could involve strategies such as safeguarding the integrity of astrocyte network, reprogramming the phenotypes of reactive astrocyte, and utilizing exosome-based delivery systems to precisely modulate the biological functions of astrocytes and achieve effective treatment of RNV.

Keywords retinal astrocytes; retinal angiogenesis; physiology; pathology

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视网膜作为中枢神经系统的一部分，是体内代谢最活跃的组织，对氧气和营养物质有着极高的需求[1]。因此，组织良好、功能完善的血管系统对于维持视网膜的正常结构和视觉功能至关重要。视网膜内的神经胶质细胞，主要包括星形胶质细胞、Müller 细胞和小胶质细胞，它们共同协作，维持局部微环境的稳态[2]。视网膜血管生成不仅是视网膜发育的关键环节，也与多种主要的致盲性眼病密切相关，如糖尿病视网膜病变、早产儿视网膜病变等[3]。

在视网膜的多种胶质细胞中，星形胶质细胞虽然在数量上远少于 Müller 细胞，并且主要存在于哺乳动物视网膜的神经纤维层[4]，但其在视网膜血管发育中扮演着不可或缺且多方面的角色。它们不仅为血管生长提供物理支架，还通过分泌关键信号分子来精确调控血管网络的构建[5]。本综述旨在基于当前的研究进展，系统阐述视网膜星形胶质细胞的起源、生物学特性、生理功能及其与 Müller 细胞的异同，并聚焦于星形胶质细胞在生理性和病理性视网膜血管生成中的复杂作用，详细解析其涉及的关键分子机制。

1　视网膜星形胶质细胞的起源

星形胶质细胞起源于神经上皮衍生的放射状胶质细胞[6]，其前体细胞通过神经组织迁移、增殖并最终转化为星形胶质细胞。在出生后，已分化的星形胶质细胞仍保留有部分增殖能力[7]。早期发育过程中，神经管通过形态因子如音猬因子 (sonic hedgehog, Shh)、骨形态发生蛋白 (bone morphogenetic protein, BMP)、无翅相关整合位点 (wingless-related integration site, Wnt) 的浓度梯度分布，组成性地诱导神经管背-腹图式的形成[8]。这些形态因子调节同源结构域转录因子如配对盒基因 2 (paired box gene 2, Pax2) 和 Pax6 的表达，通过腹侧同源盒基因 (ventral anterior homeobox, Vax) 和鸡卵清蛋白上游启动子转录因子 (chicken ovalbumin upstream promoter-transcription factor, Coup-TF) 家族转录因子的正反馈作用以及锌指蛋白 2a (zinc finger protein 2a, Zia2a) 的负反馈作用，在视杯和视柄之间形成了一个神经上皮细胞环 (视盘祖细胞区)[9]。在这个区域，细胞表达着视柄的特定标记物 (如 Pax2) 以及腹侧神经视网膜特异性标记物如 Vax2 和视黄醇脱氢酶 3 (retinaldehyde dehydrogenase 3, Raldh3)[10]。视盘祖细胞是视网膜星形胶质细胞的来源，而紧密的视杯和视柄边界是形成视网膜星形胶质细胞的关键[11]。

随着发育的进行，视网膜星形细胞的前体细胞 (astrocyte precursor cell, APC) 从视神经出现、扩散，并分化为未成熟围产期星形胶质细胞 (immature perinatal astrocyte, IPA)[12]。两种细胞以 APC 在外，IPA 在内的形式组成细胞盘进行迁移、增殖、分化并最终定位于视网膜的内层核层和神经节层之间[13-14]。随着血管从视盘呈放射状发育，星形胶质细胞从 IPA 向成熟围产期星形胶质细胞过渡，其轴突与大量的血管和神经元连接，对维持视网膜神经细胞功能、促进内皮细胞网络形成有重要作用[15-17]。尽管目前对视网膜星形胶质细

胞的发育的认识已经取得了一些进展，但是对其发育和分化的详细机制以及确切前体细胞起源，仍然有待更深入的探索。

2 视网膜星形胶质细胞与 Müller 细胞的差异

视网膜包含两类大胶质细胞：Müller 细胞和星形胶质细胞[18]。Müller 细胞是放射状胶质细胞和星形胶质细胞的分子和功能同源物[19]。二者的差异如下：1) 物种差异，Müller 胶质细胞存在于所有脊椎动物物种中，而视网膜星形胶质细胞是哺乳动物独有的[20]。2) 位置差异，Müller 细胞普遍存在于视网膜中，而星形胶质细胞分布与视网膜血管的存在和分布显著相关，视网膜血管化区域富含星形胶质细胞，无血管区例如中央凹不含星形胶质细胞[21-22]。此外，Müller 细胞横跨视网膜的整个厚度，而视网膜星形胶质细胞明显局限于神经纤维层和神经节细胞层[23]。3) 细胞来源差异，Müller 细胞及各种类型的视网膜神经元均来源于视杯祖细胞，而星形胶质细胞则来源于视盘祖细胞[24-25]。4) 细胞标志物差异分析，单细胞测序结果显示，波形蛋白 (vimentin, VIM)、谷氨酰胺合成酶 (glutamine synthetase, GS) 和 S100 钙结合蛋白 A1 (S100 calcium binding protein A1, S100A1) 在 Müller 胶质细胞和视网膜星形胶质细胞中均呈现高表达。在 Müller 胶质细胞和视网膜星形胶质细胞中均有高表达水平的标志[26]。胶质纤维酸性蛋白 (glial fibrillary acidic protein, GFAP) 是视网膜星形胶质细胞的可靠标志，但 Müller 胶质中却没有，然而，在视网膜变性中，Müller 细胞开始增加 GFAP 表达，使星形胶质细胞难以区分[27]。相反，Müller 胶质可通过谷氨酰胺合成酶和视黄醇结合蛋白的特异性表达与视网膜星形胶质细胞区分开来[28-29]。5) 功能差异，星形胶质细胞和 Müller 细胞具有一些相似的细胞功能，如钾离子稳态、谷氨酸摄取、细胞外 pH 调节、突触发生控制、血液视网膜屏障等[30-32]。不同的是，星形胶质细胞与视网膜血管内皮细胞网络的形成更为紧密，而 Müller 胶质细胞更多与感光细胞耦合，并在视网膜的玻璃体表面充当集光器以及单细胞光纤将光直接传输到光感受器[16, 33]。

3 视网膜星形胶质细胞的功能特点

3.1 结构支持

星形胶质细胞、血管内皮细胞、周细胞以及它们共享的基底膜共同构成了神经血管单元[34]。神经血管单元各组成部分之间的协调作用对于维持血管稳态和屏障功能至关重要。星形胶质细胞通过其广泛分布的突起网络和与其他细胞的相互作用，对维持视网膜分层结构以及神经血管单元的稳定性有关键作用[35]。在啮齿动物的视网膜中，星形胶质细胞广泛重叠，它们的突起垂直于视神经的长轴，与少突胶质细胞规律间隔排列于轴突之间[36-37]，通过径向排列形成胶质细胞隔膜，大量的神经胶质细胞隔膜以及弹性纤维和胶原纤维将神经分成界限分明的神经束[38]，维护了神经元的排列和定位。星形胶质细胞另一个最显著的结构特征之一是其特化的末端突起，称为终足。这些终足广泛地覆盖在视网膜毛细血管和微动脉的基底膜外表面 (管腔外侧)，参与构成和维持血-视网膜屏障[39]。更重要的是，视网膜星形胶质细胞在血管与神经组织之间建立了一个关键的生理界面，它们分泌了层粘连蛋白等基底膜成分，积极参与血管基底膜的构建[40]，同时它们通过释放谷氨酸、一氧化氮等信号分子，参与神经血管单位的信号传递，耦合神经活动和血流调节[41]。

3.2 营养供应

视网膜具有独特的代谢特征，其有氧糖酵解率远高于大脑[42]。视网膜星形胶质细胞还作为神经元与血液循环之间的桥梁，负责摄取、代谢、储存和转运多种关键营养物质，以满足视网膜的高能量需求[43]。星形胶质细胞通过其血管终足 (endfeet) 上的葡萄糖转运蛋白 1，从血液中高效摄取葡萄糖[44]。即使在有氧条件下，星形胶质细胞也能够表现出高糖酵解速率 (有氧糖酵解)，产生的大量的丙酮酸被乳酸脱氢酶转化为乳酸，这些乳酸通过单羧酸盐转运蛋白 (monocarboxylate transporter, MCT) 的两种亚型 MCT1 和 MCT4 输出到细胞外间隙，并通过 MCT2 进入神经元轴突中作为三羧酸循环的主要底物[45]。近期研究表明，水通道蛋白 9 (aquaporin-9, AQP9) 参与乳酸运输，通过蛋白质-蛋白质相互作用，与 MCT 协同驱动星形胶质细胞-神经元乳酸穿梭器，在神经元的代

谢中发挥着关键作用[46]。此外，视网膜星形胶质细胞还能够储存大量糖原，这些糖原构成了重要的能量储备。在能量需求增加 (如神经元活动增强) 或葡萄糖供应不足 (如短暂缺血或低血糖) 时，星形胶质细胞内的糖原可以被迅速分解，产生葡萄糖-6-磷酸，进入糖酵解途径生成乳酸，作为替代能量来源[47]。

3.3　代谢清除

视网膜星形胶质细胞参与清除代谢废物和毒性物质，有助于维持视网膜的健康。视网膜是一个高耗氧组织，容易产生大量活性氧 (reactive oxygen species, ROS)[48]。氧化应激 (ROS 产生与清除失衡) 是导致血管内皮细胞损伤、周细胞凋亡和血-视网膜屏障 (blood-retinal barrier, BRB) 破坏的关键因素，尤其在糖尿病视网膜病变等疾病中[45]。星形胶质细胞是视网膜主要的谷胱甘肽 (glutathione, GSH) 合成者和供应者[49]。它们不仅利用自身高水平的 GSH 直接清除 ROS，还向邻近神经细胞提供 GSH 或其合成前体，如 N-乙酰半胱氨酸 (N-acetylcysteine, NAC)，NAC 作为 GSH 的限速前体，加快神经元自身合成 GSH 的速度，增强抵抗氧化损伤的能力[50-51]。星形胶质细胞还通过产生其他抗氧化分子如血红素加氧酶-1 产生的 CO 或激活抗氧化信号通路 (如核因子 E2 相关因子 2 通路) 来对抗氧化应激，从而保护神经和血管免受损伤[52-54]。此外，过量的兴奋性神经递质谷氨酸具有神经毒性，可导致神经元损伤或死亡。星形胶质细胞通过高亲和力转运体高效清除突触间隙中的谷氨酸，并通过谷氨酰胺合成酶将其转化为无毒的谷氨酰胺，保护神经元免受兴奋性毒性[55]。

3.4　免疫调控

视网膜星形胶质细胞可以参与视网膜免疫反应，帮助抵御感染和炎症，保护视网膜组织。星形胶质细胞通过紧密连接蛋白[56]，稳定内皮血管细胞之间的紧密连接，参与维持视网膜毛细血管屏障，限制了血源性免疫效应细胞和分子的进入，确保免疫特权[57-58]。此外，星形胶质细胞在局部免疫反应中起着重要作用。在视网膜损伤或疾病状态下，视网膜星形胶质细胞被诱导活化成为反应性星形胶质细胞。近年来，研究发现反应性星形胶质细胞并非单一状态，而是表现出显著的异质性，可以极化为不同的表型。其中，A1 和 A2 表型是研究最为广泛的两种极化状态[59]。A1 型星形胶质细胞的活化通常由促炎信号[如小胶质细胞释放的白细胞介素-1α (interleukin-1 alpha, IL-1α)，肿瘤坏死因子-α (tumor necrosis factor-alpha, TNF-α)，补体 1q (complement component 1q, C1q)]诱导[60]，能够加剧局部炎症反应或直接释放促血管生成介质，可能促进病理性 RNV[61-64]。相反，A2 型星形胶质细胞通常在缺血等损伤后出现，具有抗炎和修复特性，可能通过抑制炎症、分泌血管生成抑制因子或促进有序的血管修复来抑制病理性 RNV[65-71]。

4　星形胶质细胞影响生理性视网膜血管生成

视网膜星形胶质细胞在生理性视网膜血管发育过程中扮演着不可或缺的角色，汇总于表 1。

它们首先迁移进入视网膜，形成一个空间有序的细胞网络或模板，通常呈蜂窝状结构，为后续迁移的血管内皮细胞提供引导和支架，从而决定了表层血管丛的形态和模式[72-73]。视网膜血管的发育完全依赖于这个预先形成的星形胶质细胞模板。如果星形胶质细胞的数量或空间排布受到干扰，会导致血管模式紊乱，损害血管的完整性[72]。视网膜星形胶质细胞分泌的多种细胞黏附分子介导血管生成支架的形成。1) 钙黏蛋白，星形胶质细胞表达的 N-钙黏蛋白介导的细胞相互作用对细胞迁移有负面影响，在血管稳定中发挥作用[74]。同时 R-粘连蛋白、非典型 Fat1 钙黏蛋白等促进视网膜血管生成[75-76]。2) 纤维连接蛋白，在无血管区域受到生理性较低氧气水平的刺激，星形胶质细胞通过低氧诱导因子 (hypoxia-inducible factor, HIF) 和孤儿核受体 Tlx 信号转导途径和 (或) 依赖血管生成素-1(angiopoietin-1, Ang-1) 的方式，上调纤维连接蛋白的表达并促进其细胞外沉积。这些星形胶质细胞生成的纤维连接蛋白与内皮细胞上的 α5β1 和 αvβ3 整合素识别、结合，促进星形胶质细胞与血管内皮细胞的黏附，并激活血管内皮生长因子 (vascular endothelial growth factor, VEGF) 信号传导通路，诱导内皮细胞的迁移[16]。3) 层粘连蛋白，层粘连蛋白-β1 整合素信号传导和层粘连蛋白-蛋白多糖相互作用促进星形

表 1 视网膜星形胶质细胞在生理性与病理性血管生成中的作用比较

Table 1 Comparison of the roles of retinal astrocytes in physiological and pathological angiogenesis

特征	生理性视网膜血管生成	病理性视网膜新生血管
状态	生理发育状态	反应性星形胶质细胞增生
形态学	正常，突起界限清晰	肥大，突起形态改变
分子标记	GFAP (+), Vimentin (-)	GFAP (+++), Vimentin (+)
主要功能	引导支架网络形成，受控地促进生长，促进血管成熟，参与iBRB的形成与维持[72]	损伤：缺血区星形胶质细胞死亡和支架网络破坏，促进杂乱RNV，引发炎症，降解细胞外基质，导致iBRB破坏。修复：其存活及其网络完整性，能够促进正常化的血管再通并减少病理性RNV[73]
ECM相互作用	衍生的或与之相互作用的ECM成分主动调节星形胶质细胞迁移及后续血管新生	ECM产生及相互作用的改变，损害正常的血管引导，促进病理信号传导
分泌因子	在新生血管前端的缺氧区分泌促血管生成因子，其释放受到严格管制，以确保血管的有序发育和模式化	星形胶质细胞大量分泌促血管生成因子，其释放不受控制，导致血管过度、无序增生。也可携带抗血管生成成分具有治疗潜力[74]
炎症调节	主要起维持稳态和支持作用，炎症反应较少，受到严格控制	A1型，释放促炎细胞因子，促进病理性RNV；A2型，具有抗炎/修复作用，抑制病理性RNV
最终结果	有序、稳定、功能性的血管网络	紊乱、渗漏、脆弱、无功能的新生血管

胶质细胞迁移和形成血管生成的模板[77-78]。综上，星形胶质细胞通过结构性模板功能，为生理性血管生成奠定空间基础。

除结构性作用外，星形胶质细胞还通过多分子协同调控血管生成的动态过程。传统的观点认为，星形胶质细胞通过分泌 VEGF 形成化学梯度，在血管内皮生长因子受体 2 (vascular endothelial growth factor receptor 2, VEGFR2) 介导下内皮细胞的丝状伪足生长和扩展并定向迁移形成血管[79-81]。然而，近年来的研究对星形胶质细胞来源的 VEGF 在生理性血管发育中的必要性提出了挑战。利用 Cre/loxP 位点特异性重组系统 RNV 在星形胶质细胞中特异性敲除 VEGF 基因的小鼠模型研究发现，虽然 VEGF 的缺失导致某些病理条件下的血管不稳定或异常发育，但在正常的生理条件下，视网膜血管的发育没有受到显著影响[82]。星形胶质细胞在生理性血管发育中的主要贡献可能更多地体现在其结构性作用，即提供精确的空间模板和引导线索，而非仅仅依赖其分泌的 VEGF。在生理条件下，其分泌的 VEGF 的功能可以通过内皮细胞、视网膜色素上皮细胞和周细胞分泌的 VEGF，独立于 VEGF 参与生理性视网膜血管生成的磷酸烯醇丙酮酸激酶 (phosphoenolpyruvate kinase, PEPK)、血管生成因子 1 (angiogenic factor 1, AGGF1)、成纤维细胞生长因子/血小板衍生生长因子 (fibroblast growth factor/platelet-derived growth factor, FGF/PDGF) 通路及血管生成素/Tie2 受体 (angiopoietin/Tie2 receptor, Ang/Tie2) 信号网络等调控机制[83-87]。由此可见，生理性血管生成中，星形胶质细胞的结构性引导作用可能比分泌功能更为关键，而病理条件下的角色则截然不同。

5 星形胶质细胞影响病理性视网膜血管生成

病理性血管生成是多种致盲性眼底疾病的共同特征[1]。这种病理性新生血管通常结构异常、脆弱、易渗漏和出血，最终导致视网膜结构破坏

和视力丧失[88]。综合现有研究证据，视网膜星形胶质细胞在病理性 RNV 的调控中扮演着复杂且具有双重性的角色，汇总于表 1。

5.1　星形胶质细胞促进病理性 RNV

在病理条件下，如视网膜缺血、缺氧或慢性高血糖环境，部分视网膜星形胶质细胞的功能会发生显著改变，从生理性的支持者转变为病理性视网膜新生血管的驱动者。这一功能转变主要通过 3 条相互关联的分子通路实现：缺氧应答通路、炎症信号通路和细胞外基质重塑通路。

首先，在缺氧相关通路方面，在病理状态下，星形胶质细胞通过异常激活原有的血管生成通路，增加病理性 RNV 生成。当氧气充足时，HIF-1 α 中的关键脯氨酸残基被羟基化并被希佩尔-林道蛋白 (Von Hippel Lindau, VHL) 蛋白 E3 连接酶识别，从而促进蛋白酶体降解。在缺氧条件下，HIF-1α 在视网膜星形胶质细胞中稳定存在，进入细胞核与 HIF-1β 结合后形成 HIF-1。HIF-1 与缺氧靶基因启动子中的缺氧反应元件结合，启动促血管生成靶基因的转录，从而上调 VEGF、FGF2 的分泌[89-91]。同时在细胞外炎症、缺氧环境刺激下，核因子 κB (nuclear factor kappa-B, NF-κB) 通路被激活，NF-κB 进入细胞核后结合到有 κB 元件的缺氧靶基因启动子上，促进 VEGF、FGF2、胰岛素样生长因子分泌[92], 血管生成因子的爆发破坏原有的时间和空间梯度，触发紊乱的脉管系统即病理性 RNV [93]。治疗方面，考虑到 HIF-1α 在缺氧条件下驱动星形胶质细胞表达 VEGF，HIF 抑制剂可能间接减少星形胶质细胞的 VEGF 产出[86]。有学者使用 Salubrinal 在氧诱导视网膜病变 (oxygen-induced retinopathy, OIR) 小鼠模型中，通过抑制 CCAAT/增强子结合蛋白同源蛋白 (CCAAT/enhancer-binding protein homologous protein, CHOP)-HIF1α-VEGF 通路减轻 RNV，这可能与间接调控星形胶质细胞 VEGF 产生有关[94]。

除了缺氧应答通路以外，视网膜星形胶质细胞在病理状态下可分泌多种促炎细胞因子，包括 IL-6、TNF-α、IL-1β 等[95]，这些因子通过激活特定信号通路，增强新生血管的形成。病理情况下，星形胶质细胞中的 NF-κB 激活导致白细胞 IL-6 的释放，IL-6 与 IL-6 受体相互作用并激活信号转导与转录激活因子 3 (signal transducer and activator of transcription 3, STAT3) 信号通路[22, 67]，STAT3 是 HIF1α-VEGF 通路的已知上游因子，直接参与病理性 RNV 的发病机制[81]。STAT3 的持续活化可导致血管过度生长及血-视网膜屏障破坏[96]。成熟的 IL-1β 通过一系列信号通路激活 TGF-β 活化激酶 1，然后启动丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 级联反应和 NF-κB 转录，促进 IL-6、IL-8 和 TNF-α 等炎症介质募集，过度激活炎症反应，并且激活小胶质细胞，其分泌的因子 (如单核细胞趋化蛋白-1、IL-1β 等) 具有潜在的血管生成作用[97-98]。

在细胞外基质重塑方面，星形胶质细胞参与细胞外基质 (extracellular matrix, ECM) 成分 (如纤连蛋白、层粘连蛋白、蛋白聚糖) 的合成以及基质金属蛋白酶 (matrix metalloproteinase, MMP) 等 ECM 重塑酶的产生[99]。在青光眼和糖尿病视网膜病变等疾病状态下，星形胶质细胞产生蛋白质蛋白酶、MMP 来重塑 ECM 促进 RNV 生成。例如，在青光眼视网膜中观察到纤连蛋白和层粘连蛋白水平升高，被证实与新生血管和炎症相关[100]。

5.2　星形胶质细胞减少病理性 RNV

与促进病理性 RNV 的作用相反，星形胶质细胞在特定条件下能够发挥抑制异常血管生成和促进有序修复的双重保护作用。这种功能的发挥主要依赖于其结构的完整性和分泌调控的平衡。

在 OIR 模型的血管增殖期，缺血区域的星形胶质细胞因缺氧而大量死亡或网络结构被破坏，内皮细胞将失去引导，导致血管再生缓慢、杂乱无章[90, 101]，并倾向于向玻璃体内异常生长，形成病理性 RNV[91]。在血管重建期，存活于缺血区域的星形胶质细胞网络扮演着至关重要的“模板”角色，引导内皮细胞以有序的方式重新生长，形成功能性的毛细血管丛[9, 101-103]。因此，保护星形胶质细胞免受缺氧损伤，维持其网络结构的完整性，是促进正常血管修复、抑制病理性 RNV 的一个重要策略。多种干预措施，如移植星形胶质细胞、注射星形胶质细胞条件培养基、给予特定剂量的生长因子 (如低剂量 VEGF 或 bFGF)、移植髓系祖细胞或使用药物干预，包括组织金属蛋白酶抑制剂 (tissue inhibitor of metalloproteinases, TIMP)、蛋白激酶 R 样内质网激酶抑制剂 (PKR-like ER kinase inhibitor, PERK inhibitor) 及缝隙连接蛋白 43 抑制

剂 (connexin 43 inhibitor, Cx43 inhibitor) 等治疗策略均被证明可以通过保护内源性星形胶质细胞来促进正常再血管化并减少病理性 RNV[21, 87, 104]。

星形胶质细胞还能分泌多种内源性血管生成抑制因子，直接对抗病理性 RNV。研究表明，星形胶质细胞来源的血小板反应蛋白 (thrombospondin, TSP) 在维持血管稳态和抑制血管生成中发挥作用[105-106]。高糖环境会减少星形胶质细胞 TSP-1 的分泌，这可能促进糖尿病视网膜病变中的血管病理变化[107]。同时，星形胶质细胞分泌的色素上皮衍生因子 (pigment epithelium-derived factor, PEDF) 在高血糖条件下通过抑制氧化应激、炎症和谷氨酸兴奋性毒性表现出神经保护和抗血管生成作用[108]。此外，视网膜星形胶质细胞能够释放外泌体。这些纳米级的囊泡携带有多种生物活性分子，包括抗血管生成蛋白如 PEDF、内皮抑素和 TIMP 等[109-110]。体外实验显示，星形胶质细胞来源的外泌体能够抑制巨噬细胞迁移和内皮细胞的管腔形成能力[111]。在激光诱导的脉络膜新生血管 (choroidal neovascularization, CNV) 模型中，注射星形胶质细胞外泌体能够抑制 CNV 的形成并减少血管渗漏[112-113]。

6 针对视网膜星形胶质细胞的潜在干预措施

针对视网膜星形胶质细胞的干预策略，其核心目标在于维护视网膜细胞的正常生理功能，并有效调控其在眼部病理发展中的复杂行为。这些策略涵盖了多个层面：首先，通过药理学干预维持星形胶质细胞的存活状态及网络结构的完整性，进而促进受损血管的正常化与再通，为组织修复创造有利条件。其次，通过对关键信号通路的精准调控，致力于将病理状态下激活的反应性星形胶质细胞从可能有害的表型，重编程为有益或至少是中性的状态，从而减轻其对视网膜的潜在损伤。此外，新兴的治疗方法还包括应用星形胶质细胞来源的外泌体，利用其作为天然载体递送具有抗血管生成或神经保护作用的分子。最后，基因治疗策略也展现出巨大潜力，通过采用星形胶质细胞特异性启动子驱动，并结合腺相关病毒等高效安全的载体系统，以实现保护性因子的靶向过表达或特异性沉默致病分子，为视网膜疾病的治疗开辟了新的途径。

7 总结和展望

星形胶质细胞作为神经血管单元的关键成员，对维持视网膜结构、稳态及血管网络至关重要。它们不仅负责能量代谢与抗氧化/免疫调节，更在生理性和病理性视网膜血管生成中扮演核心角色。深入理解这种复杂调控是开发靶向治疗的关键，尽管已有进展，仍有许多问题亟待探索。未来的研究仍需进一步阐明其与 Müller 细胞在 RNV 中的协同或拮抗关系。同时，基于星形胶质细胞外泌体开发新型抗 RNV 疗法的潜力，以及人为精准调控 A1/A2 等反应性星形胶质细胞亚型转化的可能性，也是亟待探索的关键方向。解决这些核心问题，不仅将深化我们对视网膜疾病病理生理的认识，更有望开发有效的新治疗策略。

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