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周细胞调控眼部新生血管的研究进展

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摘 要:病理性眼部新生血管(pathological ocular neovascularization)是多种致盲性眼病的共同病理特征,是在多种细胞成分和多种病理因素互相包含、交互影响下形成的。其发病率呈现持续增高的趋势,目前已成为威胁人群视觉健康的重要公共卫生问题。目前临床上以抗VEGF治疗为主,但是也存在应答率有限、依从性差等问题,因此迫切需要探究新的发病机制,寻找新的治疗靶点。近年来的研究发现,周细胞(pericytes,PCs)通过PDGF-B/PDGFR-β信号通路被招募,分泌TGF-β、Ang-1等因子来调控血管成熟、血流稳态以及血-组织屏障完整性。本文将深入探讨周细胞的生物学特性、新生血管生成的机制,以及周细胞在眼部新生血管生成过程中的作用,为治疗病理性眼部新生血管提供新的思路和方向。

关键词:周细胞;病理性新生血管形成;视网膜新生血管;脉络膜新生血管;角膜新生血管;虹膜新生血管
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Research advances on the regulation of ocular neovascularization by pericytes

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Abstract: Pathological ocular neovascularization is a universal pathological feature of various sight-threatening eye diseases, such as diabetic retinopathy, retinopathy of prematurity and age-related macular degeneration . Its global prevalence keeps rising, creating a mounting public health burden that severely impairs visual function and patients' quality of life. Current clinical interventions mainly rely on pan-retinal photocoagulation and anti-VEGF therapy. Despite partial therapeutic efficacy, these approaches are limited by insufficient response rates, transient curative effects, heavy treatment burden and unsatisfactory patient adherence. Accordingly, it is urgent to unravel the complex pathogenic mechanisms underlying ocular neovascularization and develop innovative therapeutic targets. Accumulating research evidence has validated that pericytes are central modulators of retinal vascular homeostasis and pathological angiogenesis. As mural cells closely encasing endothelial layers of capillaries, arterioles and venules, pericytes establish direct physical connections with endothelial cells and participate in reciprocal signal crosstalk to coordinate vascular maturation, hemodynamic stability and blood-tissue barrier integrity. The PDGF-B/PDGFR-β signaling cascade dominates the recruitment, migration and vascular coverage of pericytes throughout vascular development and remodeling. After recruitment, pericytes secrete key regulatory cytokines including TGF-β and Ang-1, which synergistically promote vessel maturation, stabilize microcirculation and sustain barrier function. Additionally, pericytes exhibit prominent functional plasticity. Under developmental or pathological stimuli, they may undergo dedifferentiation, proliferation or transdifferentiation into fibroblasts, smooth muscle cells and mesenchymal stem cells, thus dynamically regulating vascular remodeling, tissue repair and fibrotic progression. Recent studies have pinpointed pericyte dysfunction as a pivotal factor facilitating the progression of pathological ocular neovascularization. In retinopathy of prematurity, hyperoxia provokes intracellular Ca^{2+} overload and α-SMA-mediated vasoconstriction, leading to capillary obliteration. Subsequent retinal ischemia elevates HIF-1α expression to induce excessive VEGF secretion, while impaired Ang-2/Tie2 signaling further accelerates pericyte shedding and vascular destabilization. Early pericyte loss is acknowledged as the hallmark pathological alteration of diabetic

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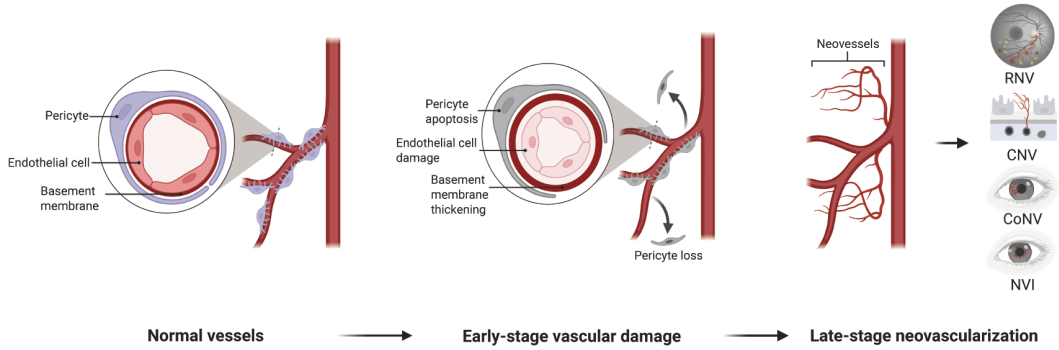
retinopathy; hyperglycemia triggers oxidative stress, mitochondrial damage and advanced glycation end-product deposition, jointly disrupting the pericyte microenvironment and triggering pericyte apoptosis and subsequent microvascular lesions. In age-related macular degeneration, early pericyte apoptosis causes choroidal capillary atrophy and Bruch's membrane rupture, and pericyte-myofibroblast transformation further drives subretinal fibrosis. During corneal neovascularization, PDGF-B/PDGFR-β signaling mediates pericyte recruitment to pathological vessels and aggravates abnormal angiogenesis. Chronic ischemia-induced pericyte dysfunction also reshapes iris vasculature and eventually induces neovascular glaucoma. In conclusion, pericytes are indispensable for maintaining ocular microvascular homeostasis. Pericyte depletion, phenotypic transformation and abnormal activation represent core mechanisms underlying the initiation and progression of pathological ocular neovascularization. This review systematically summarizes the regulatory roles of pericytes in multiple ocular neovascular disorders. Further investigations into pericyte-related signaling pathways in the ocular microenvironment will provide novel intervention strategies, offering theoretical support for developing long-term, effective and individualized therapies for blinding neovascular eye diseases.

Regulation of Pathological Ocular Neovascularization by Pericytes



Key words: pericyte cells; pathological neovascularization; retinal neovascularization; choroidal neovascularization; corneal neovascularization; iris neovascularization

人体内新血管的生成主要通过两种形式实现:血管发生(vasculogenesis)和血管生成(angiogenesis)。血管发生指的是由来自中胚层的成血管细胞逐步分化发育,在原本无血管的区域"从无到有"构建血管的过程;血管生成则是在血管生成因子的刺激下,新血管通过出芽式血管生成或套叠式血管生成方式进一步生长的过程[1]。一般来说,新生血管形成的过程主要包括促血管生成因子激活血管内皮细胞出芽,随后内皮细胞迁移与增殖,尖细胞与茎细胞分化,促进新生血管腔形成,最终血管趋于成熟与稳定[2]。当机体面临缺氧、炎症、组织损伤等病理刺激时,血管生成原有的调控平衡会被打破,促血管生成信号过度激活,最终导致结构异常、功能紊乱的病理性新生血管形成。本文将聚焦于眼部新生血管,通过研究周细胞与内皮细胞的信号互作、周细胞对血管稳态的维持机制,详细阐明周细胞对眼部新生血管生成的调控机制。

1　眼部新生血管

病理性新生血管是多种眼部疾病的共同病理特征,常发生于视网膜、脉络膜、虹膜及角膜等,会造成严重的视力损害[3],其中较常见的有早产儿视网膜病变(retinopathy of prematurity,ROP)、糖尿病视网膜病变(diabetic retinopathy,DR)、脉络膜新生血管(choroidal neovascularization,CNV)、新生血管性青光眼(neovascular glaucoma,NVG)等,在人的各个生命阶段都有可能发生[4]。

眼部新生血管生成是一个极其复杂的病理过程,可由多种因素共同造成。生理性眼部新生血管是在胚胎发育或组织修复等情况下,促血管与抑血管因子动态平衡,形成结构完整、功能成熟的血管。有研究表明,成熟血管通常保持静止状态,在生理条件下不会发生血管生成,然而,某些刺激会引发新生血管形成,例如早产儿在氧暴露/高血糖/损伤等情况下容易出现视网膜缺血、缺氧,导致缺氧诱导因子-1α(hypoxia inducible factor-1 alpha,HIF-1α)/血管内皮生长因子(vascular endothelial growth factor,VEGF)急剧上调,引发病理性新生血管和纤维增生,最终导致眼部病变[5]。

除了VEGF以外,血小板衍生生长因子(platelet-

derived growth factor,PDGF)-B、成纤维细胞生长因子(fibroblast growth factor,FGF)等多种细胞因子也参与其中[6]。PDGF-B主要是由血管内皮细胞分泌,并富集于血管周边的细胞外基质上,与周细胞表面的血小板衍生生长因子受体(platelet-derived growth factor receptor,PDGFR)-β结合,并将周细胞募集到内皮细胞周围,促进血管的成熟[7]。FGF通过依赖性的代谢调控,为内皮细胞的快速增殖与迁移创造必要的能量和物质条件,从而有力地促进新生血管生成[8]。新生血管的形成受多种机制的调控,当VEGF、血管生成素-2(angiopoietin-2,Ang2)和FGF等促血管生成因子上调并刺激静息状态下的内皮细胞转变为血管生成表型时,新生血管就会发生,这些因子水平的增高促使内皮细胞向"尖端"细胞分化[9]。值得注意的是,不同细胞因子之间存在着复杂的相互作用,它们共同调节新生血管的生成。

针对眼部新生血管性疾病,目前临床上主要以视网膜激光光凝术(pan-retinal photocoagulation,PRP)、抗血管内皮生长因子(anti-vascular endothelial growth factor,Anti-VEGF)治疗、玻璃体切除为主,虽有一定疗效,但仍有部分患者的病情控制不佳[9]。此外,频繁眼内操作会产生不良反应如眼内感染、眼压升高或由操作带来的晶体或视网膜损伤等,同时这也给患者带来了不小的经济负担[10]。因此,我们需要更加深入地探究眼部新生血管形成的原因,寻找新的治疗方法。

2 周细胞

2.1 周细胞的位置与形态

周细胞(pericytes,PCs)是广泛分布于微血管的壁细胞[11],其细胞突起紧贴内皮,嵌入微血管的基底膜中,位于内皮细胞与基底膜之间,诱导紧密连接和基底膜成熟[12]。周细胞与毛细血管、小动脉和小静脉的内皮细胞的腔内表面相互作用,维持屏障通透性、血-组织屏障解剖成熟与功能稳态[13]。周细胞形态多样,与其定位和功能有关,例如:分支点和最靠近小动脉的周细胞往往具有鞘状或网状形态;沿着更远端的毛细血管和没有分支的毛细血管段的周细胞具有更多的细链形态,下层脉管系统的突起较少[14]。不同器官中周细胞的形态、可塑性和功能同样也存在着差异,即使在同一个器官内,周细胞之间也存在区别:大脑中周细胞存在两种功能异质性亚群,分别是通过激活Hedgehog信号通路促进紧密连接形成的1型周细胞和高表达吞噬及免疫细胞浸润相关基因的2型周细胞,两者之间会相互转化[15]。

2.2 周细胞的功能

周细胞是维系微血管功能的关键细胞枢纽:在生理状态下,它们能够调控血管成熟、血流稳态以及血-组织屏障的完整性;在发育或病理情况下,周细胞能够去分化、增殖或转分化为成纤维细胞、平滑肌细胞,甚至间充质干细胞,动态地响应血管重塑、组织修复及纤维化等进程[16]。为了适应不同器官的微环境,周细胞功能存在差异性。大脑和视网膜是周细胞分布较密集的器官,周细胞通过诱导紧密连接来形成和维持血-脑屏障(blood-brain barrier,BBB)和血-视网膜屏障(blood-retinal barrier,BRB)[12,17]。除此之外,像心、肺这类需要微循环精密调控的器官中周细胞含量也很丰富,已有研究报道:心周细胞独特的"桥接型"亚型结构使其能同时调控多个毛细血管节段,响应心肌代谢需求[18];肺损伤通过Smad2和Smad3上调TGF-β表达,进而诱导周细胞增殖、分化为产生胶原蛋白的肌成纤维细胞,促进瘢痕形成和纤维化进展[19]。

2.3 周细胞的免疫标志物

周细胞的免疫标志物并非单一的,不同的标志物代表的含义也不同。PDGFR-β是周细胞核心的标志物和受体之一,介导周细胞与内皮细胞间的信号传递,PDGF-B/PDGFR-β信号通路调控周细胞在血管发育过程中的招募与增殖,促进微血管的稳定、毛细血管血流的调节和血管生成[20];神经胶质抗原2(neuron-glial antigen 2,NG2)又称硫酸软骨素蛋白聚糖4(chondroitin sulfate proteoglycan 4,CSPG4),已被广泛用作中枢神经系统周细胞标志物,与PDGFR-β协同,介导周细胞迁移、生存与血管成熟[21],常用PDGFR-β^+/$NG2^+$组合标记周细胞。α-平滑肌肌动蛋白(α-smooth muscle actin,α-SMA)是收缩蛋白,标志着周细胞具有收缩功能,在微循环的调节中起着至关重要的作用,有研究发现视网膜毛细血管上周细胞表达α-SMA,但是并非所有周细胞都表达[22]。α-SMA并非周细胞特异性标记,鉴于平滑肌细胞不表达PDGFR-β和NG2,联合PDGFR-β^+/$NG2^+$/α-SMA^+共同标记可代表具有收缩功能的

周细胞。其他辅助标志物还有黑色素瘤细胞黏附分子(melanoma cell adhesion molecule,MCAM,又称CD146),在缺氧的条件下,CD146上调以多种方式来促进PDGF-B/PDGFR-β信号转导,涉及CD146-PDGFRβ结合、CD146二聚化、PI3K募集和CD146-细胞骨架结合[23],因此CD146$^+$/PDGFR-β$^+$/NG2$^+$ 可富集"活化型"周细胞;其他还包括G蛋白信号调节因子5(regulator of G protein signaling 5,RGS-5)、氨肽酶N (aminopeptidase N,APN,又称CD13、结蛋白(Desmin)) [24]等。

2.4 周细胞丢失或功能异常易引发疾病

已经有相关研究报道证明,周细胞作为维持微血管结构稳定与功能正常的关键细胞,它的丢失或功能障碍会破坏血管稳态,进而引发多系统的疾病,比如Li等[25]发现转录因子Fli-1会导致周细胞丢失、炎症反应、Aβ沉积、血管功能障碍和认知能力下降,最终导致阿尔茨海默病;肺部微血管的周细胞丢失和功能障碍破坏了肺泡的正常结构和血供,周细胞被异常激活,在PDGFR-β/TGF-β/Wnt驱动下转化为成纤维细胞,并分泌大量胶原蛋白,最终导致特发性肺纤维化[26];Wang等[27]发现周细胞中CCM3的缺失会诱导整合素表达增加,并且上调Ang2/Tie2的表达,破坏内皮细胞与周细胞的结合,产生脑海绵状血管畸形。诸多其他报道相继证明周细胞丢失或功能异常会引发包括糖尿病视网膜病变[28]、肌萎缩侧索硬化症[29]、心力衰竭[30]或者某些家族遗传性疾病,如肥厚型及扩张型心肌病[31]、脑小血管病伴白质病变[32]等。由此可见,周细胞丢失或功能异常是多种疾病发生发展的共同特征,其核心危害在于破坏血管稳态,引发组织缺血、屏障功能异常、新生血管形成,最终导致器官功能的损伤。因此,抑制周细胞丢失和保持周细胞功能不受破坏已受到广泛关注,有望成为治疗相关疾病的重要潜在靶点。

3 周细胞调控眼部新生血管

周细胞在血管生成中起着关键作用,有助于血管形成、重塑和稳定。血管的形成、成熟和稳定需要周细胞-内皮细胞相互作用[28]。周细胞主要通过三种类型的细胞间连接与内皮细胞相互作用,分别是间隙连接(gap junctions)、黏着斑(adhesive plaques)和栓-窝连接/嵌合连接(peg-and-socket junctions)[12]。周细胞与内皮细胞的相互作用通过以下方式调节血管成熟和稳定:(1)刺激血管基底膜形成,调节血管成熟和稳定;(2)诱导识别新沉积基质的整合素;(3)通过抑制蛋白水解来稳定该基质[33]。其中,PDGF-B/PDGFR-β信号通路通过促进周细胞的增殖、存活与附着,有效介导了周细胞向新生血管的招募,并确保其实现稳定的血管壁覆盖[34]。报道表明,PDGFR-β或PDGF-B的基因缺失会阻断体内周细胞募集,导致壁细胞与毛细血管的结合减少,从而导致血管扩张和不稳定、通透性增加和血管基底膜沉积减少[35]。此外,周细胞与内皮细胞之间的通讯还可由血管生成素1(angiopoietin-1,Ang-1)、转化生长因子-β(transforming growth factor-β,TGF-β)等介导,以此促进血管内皮的成熟与稳定[36]。

周细胞是微血管血流的动态调控者:一方面,周细胞因α-SMA赋予其收缩功能[16],同时周细胞覆盖了毛细血管表面积的90%,可以对神经元刺激做出快速的反应[12];另一方面,ATP、CO_2及代谢信号可迅速改变其张力,能够通过其收缩功能,实现毛细血管血流的快速调节,精确控制不同微血管区域的血流分布,从而及时满足所需能量需求与血液供应,以此能够调节液体和细胞的灌注,维持血流稳态[37]。

3.1 周细胞与视网膜新生血管

3.1.1 早产儿视网膜病变

早产儿视网膜病变(retinopathy of prematurity,ROP)的主要病因是早产导致的视网膜血管发育不全与出生后异常氧暴露的相互作用。视网膜血管系统在胎儿16周开始形成,并持续发育至妊娠40周,早产会造成视网膜脉管系统发育不成熟[38]。出生后相对高氧引起血管生长抑制与闭塞;随后,发育不全的血管无法满足日益增长的视网膜代谢需求,组织陷入相对缺氧状态,进而驱动病理性新生血管形成[39],而周细胞亦参与其中。一方面,高氧诱导周细胞内钙离子(Ca^{2+})浓度迅速升高,激活肌球蛋白轻链激酶,上调周细胞内α-SMA表达,引起血管收缩和闭塞[40];另一方面,HIF-1α被脯氨酸羟化酶(prolyl hydroxylase domain-containing enzymes,PHD)迅速羟化降解,促使VEGF、EPO、Ang-2转录下调,同时周细胞因PDGF-B的减少而逐渐凋亡,毛细血管失去支撑出现闭塞[41]。随后,视网膜代谢需求增加,但已闭塞的血管无法供氧,干扰Ang-2转录及Tie2信号的缺乏会通过周细胞脱落、新生血管形成、血管渗漏、炎

症和纤维化导致血管不稳定[42]，同时HIF-1α大量累积，引发VEGF的过度和持续表达[43]，最终导致视网膜新生血管(retinal neovascularization，RNV)生成。Xia等[44]发现ROP和DR患者的房水中Col1a1表达上升，并且抑制Col1a1可保护视网膜血管，抑制周细胞向内皮细胞的募集，抑制周细胞-肌成纤维细胞转化。沉默Col1a1可抑制毛细血管重塑过程中眼部血管生成，对病理性血管生成和纤维化反应具有拮抗作用，为抗新生血管治疗提供了新靶点。

3.1.2 糖尿病视网膜病变

糖尿病视网膜病变(diabetic retinopathy，DR)是糖尿病最常见且严重的微血管并发症之一，发病机制复杂，病程呈现出从早期无症状微血管异常到不可逆视力丧失的渐进性、阶段性发展特征。其中，毛细血管壁周细胞丢失是DR的标志，同时周细胞丢失也是糖尿病视网膜血管异常的最早形态学特征[45]。在高血糖状态下，视网膜组织内的多元醇通路会被异常激活，诱发代谢紊乱，进而加剧氧化应激反应[46]。Trudeau等[47]发现高糖暴露可诱发视网膜周细胞碎裂，造成线粒体膜电位下降、氧消耗减少，并伴随胞外酸化程度降低，提示线粒体功能障碍可能是视网膜周细胞凋亡增加的驱动因素。另一方面，持续高糖会促使蛋白质、脂质等生物大分子发生非酶促糖基化反应，引起晚期糖基化产物(advanced glycation end products，AGEs)积聚，诱导NADPH氧化酶产生更多的ROS[48]。这些病理过程会共同破坏视网膜周细胞的微环境，最终导致视网膜周细胞的凋亡。周细胞损伤与视网膜血管张力失调共同导致微动脉瘤[45]。

De Rossi等[49]发现在高糖环境下，视网膜中LRG1的表达上调早于VEGFA，并且通过改变周细胞中TGF-β信号转导来驱动其转分化为更具收缩性的纤维化表型，导致毛细血管变窄和基底膜增厚，引发视网膜微血管功能障碍，形成早期视网膜血管病变，这为治疗新生血管病提供了新的靶点。周细胞持续丢失，致使毛细血管壁丧失结构性支撑与密封性，最终引发管腔塌陷与闭塞，导致视网膜严重缺血和缺氧，随后根据病情的发展，可出现视网膜出血点、硬性渗出、棉绒斑等出血性改变；继而发生新生血管、纤维增殖，最终导致牵拉性视网膜脱离。有研究发现，周细胞在缺氧条件下大量释放circEhmt1，并且通过外泌体转运到内皮细胞，上调转录因子NFIA，抑制NLRP3介导的炎性小体形成来防止高糖诱导的内皮损伤。这可能有助于制定治疗DR的新临床策略[50]。

3.2 周细胞与脉络膜新生血管

脉络膜新生血管(choroidal neovascularization，CNV)常见于年龄相关性黄斑变性(age-related macular degeneration，AMD)、病理性近视、Vogt-小柳原田综合征(Vogt-Koyanagi-Harada syndrome，VKH)、特发性CNV等。CNV是AMD最常见、最主要的病因，主要是随着年龄的增长，加上环境、代谢、遗传等因素，导致视网膜外层(视网膜色素上皮-脉络膜-Bruch膜)慢性损伤与修复失衡[51]，最终导致玻璃膜疣、地图样萎缩或CNV，其中氧化应激、炎症、脂质代谢紊乱和免疫失调是核心机制。脉络膜周细胞维持脉络膜毛细血管结构和功能的完整性[52]。由于各种因素，早期周细胞的凋亡直接导致毛细血管萎缩和Bruch膜结构崩解[53]。最后，周细胞通过表达α-SMA和分泌胶原转化为肌成纤维细胞，导致纤维化[54]。在吸烟等因素影响下，周细胞会因$CD8^+$T细胞表面的Sema4D与其自身的PlexinB1结合而激活RhoA通路，进而出现收缩迁移能力增强、表型转化为肌成纤维细胞的变化，最终参与构建并稳定结构异常的新生血管[55]，这也解释了抗VEGF治疗效果不佳的原因。Shen等[7]发现新型维甲酸药物EYE-502主要与视黄酸受体结合，通过影响Wnt/β-catenin和PDGF/PDGFR/PI3K/Akt信号的激活，靶向内皮细胞和周细胞发挥抗血管生成作用，是一种治疗CNV的新型双通路、双靶点药物。

3.3 周细胞与角膜新生血管

角膜新生血管(corneal neovascularization，CoNV)可由多种病因引起，包括长时间佩戴隐形眼镜、角膜感染和外伤性损伤等[56]，导致角膜干细胞丢失，引发角膜混浊和视力显著下降，直至失明。健康角膜凭借无血管、无淋巴管的结构特点，维持着平日视力所需的高度透明清晰。而当角膜受到外伤、感染、营养不良等病理刺激时，血管内皮细胞增殖和迁移到角膜基质中，新血管从角膜基质生长，并从角膜缘向角膜中央区域异常生长，破坏角膜原有的透明性[57]。多项研究表明，在缺氧、炎症等刺激下，角膜缘干细胞释放大量炎症因子[58]，激活下游促血管信号通路，促进VEGF等促血管因子的表达，促进新生血管的形成[59]。例如，Xia等[58]

发现,在碱烧伤(alkali burn,AB)小鼠角膜中Toll样受体4 (Toll-like receptor 4,TLR4)过表达,减少TLR4可抑制MyD88、NF-κB、VEGF和炎症因子的表达,从而减轻碱烧伤诱导的角膜新生血管的形成。角膜碱烧伤后,周细胞通过PDGF-B/PDGFR-β通路被募集并逐渐包裹这些新生血管,同时诱导VEGF-A、MMP-2、MMP-9等促血管生成因子的表达,并抑制TSP-1、TSP-2、ADAMTS-1、ADAMTS-2等抗血管生成因子的表达,从而打破血管生成的平衡,最终导致病理性新生血管生成[60]。近来,Liu等[61]开发了一种基于中性粒细胞纳米囊泡的滴眼液,通过靶向炎症病变、结合VEGF,抑制血管内皮细胞活化和增殖,同时联合化学激发光动力疗法消除已形成的角膜血管,破坏血管的形成和周细胞募集,从而诱导新生血管细胞凋亡,为CoNV治疗提供了一种新颖有效的策略。

3.4 周细胞与虹膜新生血管

虹膜新生血管(iris neovascularization,NVI)的本质是眼内缺血缺氧微环境打破虹膜血管稳态[62]。严重缺血缺氧会触发VEGF的爆发式释放,同时导致周细胞的丢失和功能障碍[63]。虹膜新生血管向房角生长并造成堵塞后,房水引流功能受阻,眼内压力升高,对视神经产生不可逆损伤,最终发展为新生血管性青光眼 (neovascular glaucoma,NVG)。当长时间持续释放大量VEGF时,会增加白细胞对内皮细胞的黏附,从而导致血-视网膜屏障(BRB)的破坏[64]。有研究报道,周细胞受炎症刺激分泌TGF-β,激活下游的Smad3进而诱导星形胶质细胞转化,同时炎症因子的分泌增加,促使星形胶质细胞激活迁移,导致视神经基质重塑;同时星形胶质细胞又会通过分泌细胞因子,招募、稳定和促进周细胞分化成熟[53],这种相互作用的破坏导致周细胞功能障碍。

综上所述,目前有不少关于周细胞与病理性新生血管的研究,系统探究了周细胞缺失、表型转化如何导致病理性新生血管的结构、功能异常,揭示了周细胞功能异常是驱动病理性RNV形成的重要病理环节,为理解眼部血管稳态调控及眼部新生血管相关疾病的发生发展提供了丰富且深入的理论依据(表1)。

4 总结与展望

周细胞是血管系统的重要组成部分,在视网膜血管发育、稳定及功能维持中起关键作用:生理状态下,周细胞通过与内皮细胞交互(如PDGF-B/PDGFR-β通路)、调节收缩,把控局部组织血流灌注与物质交换,维持血管生成及稳态;在不同病理情况下,周细胞的作用机制存在差异,例如:在ROP中,缺氧条件下周细胞异常招募促使病理性新生血管生成;在DR中,早期周细胞丢失是重要标志;在AMD中,周细胞驱动视网膜下纤维化形成。目前,越来越多的研究表明,周细胞在调控病理性新生血管的形成中扮演重要角色,这将为临床治疗病理性眼部新生血管提供新的方向。近年来,仍有患者抗VEGF治疗后效果不佳,且长期使用产生的耐药性日益凸显,而周细胞作为新靶点不仅可改善抗VEGF治疗的耐药性问题,还能保护视网膜结构完整,并能在早期抑制病理性眼部新生血管的生成。

表1　周细胞调控眼部新生血管汇总

眼部新生血管疾病	作用机制	临床表现
早产儿视网膜病变(ROP)	•高氧PDGF-B下调,抑制周细胞募集 •缺氧期病理性新生血管生成 •周细胞覆盖不全	•视网膜周边无血管区 •视网膜新生血管生成 •牵拉性视网膜脱离
糖尿病视网膜病变(DR)	•早期高血糖诱导周细胞凋亡 •血-视网膜屏障破坏 •PDGF-B、VEGF等通路失调导致微血管异常	•微动脉瘤 •视网膜出血、渗出 •视网膜新生血管、视网膜脱离
年龄相关性黄斑变性(AMD)	•脉络膜毛细血管萎缩:周细胞丢失 •血管通透性增加:血-视网膜屏障破坏 •纤维化:周细胞表达α-SMA、分泌胶原	•玻璃膜疣、地图状萎缩 •脉络膜新生血管生成 •黄斑水肿
角膜新生血管(CoNV)	•周细胞活化分泌PDGF-B •VEGF过度表达:促进血管生长	•角膜混浊 •角膜新生血管生成
新生血管性青光眼(NVG)	•长期慢性缺血缺氧:周细胞进行性丢失 •血管重塑:周细胞分泌TGF-β表型转化 •瘢痕牵拉虹膜与房角黏连,房水排出通道受阻	•眼压急剧升高 •混合充血、角膜水肿 •虹膜新生血管、房角关闭

但是,目前直接靶向周细胞的治疗药物及临床研究较少,现阶段研究多集中在调控细胞相关信号通路,如通过抑制PDGFR-β干预周细胞增殖与迁移等。有研究表明,法瑞西单抗(Faricimab)作为双特异性抗体,通过靶向Ang-2和VEGF,减少周细胞丢失、维持BRB的完整性[65],并抑制病理性血管生成与血管渗漏。

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