·XXXX·

慢性炎症在退行性视网膜病变中的作用机制及干预进展

李毛毛，岳昌武
(延安大学延安医学院 延安市微生物药物创新与转化重点实验室,陕西 延安 716000)

摘　要:退行性视网膜病变(如年龄相关性黄斑变性、糖尿病性视网膜病变、视网膜色素变性等)是全球范围内不可逆性视力损害的主要病因,现有抗血管内皮生长因子(VEGF)治疗、营养补充及光动力疗法等手段疗效有限,且难以逆转已受损的视功能。近年研究揭示,慢性炎症作为核心驱动因素贯穿于上述病变的发生与发展全过程。然而,当前针对慢性炎症的干预策略仍面临诸多瓶颈:炎症细胞异常活化的调控靶点虽已部分阐明,但多靶点协同干预的临床证据仍显不足;核因子-κB(NF-κB)/丝裂原活化蛋白激酶(MAPK)等信号通路及补体系统的联合调控策略尚未在临床层面系统建立;此外,血-视网膜屏障严重限制了药物的靶向递送效率,导致临床转化进展缓慢。靶向慢性炎症成为突破退行性视网膜病变治疗困境的重要方向。目前,针对该方向的干预研究涵盖传统抗炎药物(糖皮质激素、非甾体抗炎药)、补体靶向药物、细胞治疗、基因治疗及手术治疗等多种策略,部分药物已进入临床试验阶段。因此,本文就慢性炎症在退行性视网膜病变中的作用机制及干预策略的最新进展进行综述,以期为后续基础研究与临床转化提供参考。

关键词:退行性视网膜病变;慢性炎症;小胶质细胞;炎症干预;基因治疗
中图分类号:R774　　**文献标志码**:A　　**文章编号**:1672-3554(XXXX)XX-0001-12
DOI:10.11714/jsysu.med.YX20260109

Mechanisms and intervention progress of chronic inflammation in degenerative retinopathy

LI Maomao, YUE Changwu
(Yan'an Key Laboratory of Microbial Drug Innovation and Transformation, Yan'an Medical College, Yan'an University, Yan'an 716000, China)
Correspondence to: YUE Changwu; E-mail: changwuyue@126.com

Abstract: Degenerative retinopathy, including age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa, represents leading causes of irreversible visual impairment worldwide. Current therapeutic modalities, such as anti- vascular endothelial growth factor(VEGF) therapy, nutritional supplementation, and photodynamic therapy, offer limited efficacy and fail to reverse established visual loss. Accumulating evidence has established chronic inflammation as a core driving factor throughout the initiation and progression of these diseases. However, multiple barriers persist in the clinical translation of anti-inflammatory strategies. Although some regulatory targets involved in aberrant immune cell activation have been identified, clinical evidence supporting multi-target synergistic interventions remains insufficient. Furthermore, integrated combination strategies targeting nuclear factor (NF) - κB/mitogen activated protein kinases (MAPK) signaling pathways and the complement system have yet to be systematically established at the clinical level. The blood-retinal barrier also severely restricts targeted drug delivery, further impeding translational progress. Targeting chronic inflammation has thus emerged as a promising direction to overcome current therapeutic challenges in degenerative retinopathies. Current research in this field encompasses diverse strategies, including conventional anti-inflammatory

收稿日期:2026-07-16　　**录用日期**:2026-10-15
基金项目:延安大学科研计划(2023CGZH-001)
作者简介:李毛毛,第一作者,研究方向:慢性退行性视网膜病变的炎症机制,E-mail:limaomao227@163.com;岳昌武,通信作者,教授,硕士生导师,研究方向:药物开发,E-mail:changwuyue@126.com

agents (corticosteroids and non-steroidal anti-inflammatory drugs), complement-targeted therapies, cell-based therapies, gene therapy, and surgical interventions, with several candidates having progressed into clinical trials. This review summarizes recent advances in the mechanistic understanding and therapeutic targeting of chronic inflammation in degenerative retinopathies, aiming to inform future basic research and clinical translation.

Key words: Degenerative retinopathy; Chronic inflammation; Microglia; Inflammatory intervention; Gene therapy

[J SUN Yat-sen Univ(Med Sci)

退行性视网膜病变以视网膜神经元进行性丢失和感光细胞凋亡为主要特征,主要包括如年龄相关性黄斑变性(age-related macular degeneration, AMD)、糖尿病性视网膜病变(diabetic retinopathy, DR)、视网膜色素变性(retinitis pigmentosa, RP)[1]。全球范围内,这类疾病的患病率持续攀升:AMD是55岁以上人群首位致盲原因,预计2040年患者将达2.88亿;伴随糖尿病流行,DR患者2045年预计达1.61亿。这类疾病具有高致盲率与不可逆视力损害的特点,给患者生活质量及公共卫生系统带来沉重负担。

目前临床治疗仍有明显短板。湿性AMD常用抗血管内皮生长因子(vascular endothelial growth factor, VEGF)药物,虽能延缓视力下降,但需反复眼内注射,易引起眼压升高、眼内出血等并发症[2]。光动力疗法(photodynamic therapy, PDT)作为二线方案,疗效不及抗VEGF,操作繁琐,还存在视网膜损伤风险[3]。干性AMD至今缺乏有效药物,营养补充剂只能有限延缓病程,无法恢复已丧失的视力,也不能阻止黄斑萎缩[4]。因此,深入阐明退行性视网膜病变的炎症发病机制并探索新型干预策略,具有重要的临床转化意义与理论价值。

近年研究证实,慢性炎症在退行性视网膜病变的发生发展中扮演核心角色。病理状态下,视网膜免疫稳态失衡,小胶质细胞活化并极化为促炎表型,释放TNF-α、IL-1β、IL-6等炎症介质,进而招募巨噬细胞、中性粒细胞,形成持续的炎症微环境[5]。在DR中,高血糖诱导的氧化应激与晚期糖基化终末产物激活核因子-κB(nuclear factor-κB, NF-κB)等通路,促进白细胞黏附与血管内皮损伤[6];在AMD和RP中,小胶质细胞与Müller细胞、RPE细胞的相互作用进一步放大炎症反应并推动神经元凋亡[7]。大量动物实验证实,非甾体抗炎药、糖皮质激素及特异性抑制剂可减轻视网膜血管病变、改善血-视网膜屏障功能,提示靶向炎症通路是有效的治疗策略[8]。此外,将抗炎治疗与抗VEGF药物联用可产生协同效应,为克服现有治疗局限提供了新方向[9]。

1 退行性视网膜病变中的慢性炎症发生机制

慢性炎症是退行性视网膜病变的核心驱动环节,主要通过炎症细胞异常活化、核心炎症信号通路失控及补体系统失衡共同介导视网膜进行性损伤。

1.1 关键炎症细胞的活化与作用

炎症细胞在视网膜病变中不仅是被动反应者,更是主动驱动者,其活化、募集及功能改变共同影响视网膜损伤与修复[9]。

小胶质细胞是视网膜常驻免疫细胞,静息状态下监测微环境并维持突触稳态[10]。单细胞转录组学揭示,AMD患者病变视网膜中小胶质细胞特异性高表达*NFKBIA*(编码IκBα),其异常上调可能驱动AMD进展[10];小胶质细胞来源的BDNF对维持视网膜神经元稳态不可或缺,BDNF缺失可直接导致神经节细胞和光感受器变性[11]。受损伤或炎症刺激后,小胶质细胞迅速活化并极化为M1(促炎,释放TNF-α、IL-1β)或M2(抗炎,分泌IL-10、TGF-β)表型,其缺失可导致神经元存活率下降[5]。不同病变中小胶质细胞活化模式各异,AMD中,RPE内脂质A2E经内吞-溶酶体途径激活NLRP3炎症小体,促进IL-1β释放,补体系统协同驱动慢性损伤[12];RP中,活化小胶质细胞上调补体C3及其受体CR3,参与感光细胞清除[13],且常驻小胶质细胞与浸润性巨噬细胞协同作用,靶向CSF1R可同时抑制两类细胞增殖及促炎因子产生,延缓光感受器丢

失[14]；DR中，高糖经NF-κB及p38丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）通路激活小胶质细胞，促进VEGF介导的异常血管生成，同时小胶质细胞也清除异常血管，呈现损伤与保护的双重功能[15]。Petunidin可通过调节OGT/NF-κB/LCN2轴抑制小胶质细胞炎症反应，Parthenolide则通过阻断NF-κB核转位抑制小胶质细胞诱导的Müller细胞胶质增生[16-17]。

巨噬细胞主要来源于组织驻留巨噬细胞（tissue-resident macrophages，TRM）和骨髓来源巨噬细胞（bone marrow-derived macrophages，BDM），其中TRM起源于胚胎卵黄囊，通过自我更新维持，BDM由造血干细胞分化而来，在趋化因子（如CCL-2、SDF-1）驱动下迁移至视网膜[18]。在氧诱导视网膜病变（OIR）及DR模型中，巨噬细胞/小胶质细胞通过多种机制促进血管增殖与血-视网膜屏障破坏，包括分泌VEGF、通过迁移体递送VEGFA[19]；新募集的髓系细胞可极化为类小胶质细胞表型，进一步放大炎症[20]。巨噬细胞极化为M1型或M2型，在光诱导变性模型中早期以M1为主，慢性期M2上调[21]；rd1小鼠中还存在M1/M2中间表型（$CD86^+CD206^+$），可同时分泌IL-6和IL-10[22]。RPE来源外泌体携带的lncRNA CASC2可通过稳定SOCS6 mRNA诱导巨噬细胞向M2极化，减轻DR炎症损伤[23]。DR中M1加剧炎症，M2虽抗炎但分泌VEGF促进病理性血管新生[24]；与FEVR比较研究显示，DR中巨噬细胞/小胶质细胞显著增加且呈M2样极化与促炎分化并存[25]。巨噬细胞的吞噬功能具有双重性，RP中清除感光细胞碎片，功能异常加重氧化应激[26]；AMD中，巨噬细胞吞噬能力随年龄增长下降，影响RPE细胞存活[27]；DR中过度活化通过NF-κB释放过量炎症因子，加剧屏障破坏[28]。斑马鱼模型表明，IL-34在招募巨噬细胞/小胶质细胞至RPE损伤部位中发挥关键作用，其功能完整性直接影响RPE再生能力[29]。

除髓系细胞外，T细胞和B细胞等适应性免疫细胞亦参与退行性视网膜病变的慢性炎症调控[30]。在AMD中，患者脉络膜和视网膜可见$CD45RO^+$记忆T细胞聚集，其出现早于视网膜退行性改变，$IL-4^+$和$IL-17A^+$T细胞亚群与疾病分期及遗传风险相关[31]；在DR中，Th17/Treg失衡是关键的免疫病理特征，靶向RORγ恢复Treg数量或低剂量IL-2扩增Treg均可减轻视网膜血管病变[32]；在RP中，γδ T细胞升高而Treg减少，呈现免疫偏移[33]。在B细胞方面，AMD患者存在B细胞参与的体液免疫应答异常，表现为外周血B细胞端粒显著缩短，且玻璃体液中B细胞来源的自身抗体（如抗视黄醛结合蛋白抗体）水平在AMD患者中显著升高，可能通过形成免疫复合物激活补体经典途径，加剧RPE细胞损伤与炎症反应[34]。此外，糖尿病患者外周血B细胞组成亦发生偏移，其分泌的IgG型外泌体可通过激活补体经典途径参与DR微血管损伤[35]。与小胶质细胞和巨噬细胞相比，T/B细胞更多在慢性迁延期发挥免疫调节或加重损伤的双向作用[36-37]。

此外，中性粒细胞、自然杀伤（nature killer，NK）细胞、单核细胞及髓源性抑制细胞（myeloid-derived suppressor cell，MDSCs）等亦参与炎症调控。DR中，肠道来源的中性粒细胞胞外陷阱（neutrophil extracellular trap，NETs）可加剧全身性炎症而促进DR进展[38]；RP中循环炎症单核细胞（IMo）是介导视锥细胞死亡的关键效应细胞，其水平升高与疾病进展相关[39]；单核细胞来源的外泌体骨膜蛋白（POSTN）可促进DR视网膜新生血管形成[40]。AMD中，NK细胞是浸润脉络膜新生血管（CNV）病灶的主要淋巴细胞群之一[41]；增生性糖尿病视网膜病变（proliferative diabetic retinopathy，PDR）患者外周血MDSCs比例显著升高，与血糖水平正相关，可能是疾病进展的潜在生物标志物[42]。

1.2 核心炎症信号通路异常

NF-κB与MAPK通路是介导视网膜慢性炎症的核心信号轴，在AMD、DR、RP疾病中被持续激活，驱动炎症因子释放、血-视网膜屏障破坏及神经元损伤（附图1）。

NF-κB通路是炎症反应的“主开关”。静息状态下，NF-κB与抑制蛋白IκB结合呈无活性状态；在高糖、氧化应激或损伤相关分子模式（如A2E、晚期糖基化终末产物）刺激下，IκB激酶活化并降解IκB，使NF-κB入核调控靶基因转录，促进TNF-α、IL-1β、IL-6等促炎因子及趋化因子表达，放大炎症级联反应[43-44]。DR中，高糖通过糖基化终末产物受体/蛋白激酶C途径激活NF-κB，诱导视网膜血管内皮细胞黏附分子表达，促进白细胞黏附与血管渗

漏[45]；AMD中，RPE细胞内的A2E通过TLR4/MyD88轴激活NF-κB，协同NLRP3炎症小体促进IL-1β成熟释放，加速RPE细胞凋亡与视网膜损伤；RP中，活化小胶质细胞释放的促炎因子进一步激活NF-κB，推动神经元退行性变[46]。靶向NF-κB通路的抑制剂在视网膜炎症模型中展现出良好前景，如枸杞糖肽(LBGP)通过抑制NF-κB/MAPK通路介导的小胶质细胞M1极化减轻DR炎症损伤[47]；小白菊内酯(Parthenolide)通过阻断NF-κB核转位抑制小胶质细胞诱导的Müller细胞胶质增生[17]；Resolvin D1、JSH-23及姜黄素等NF-κB通路抑制剂可减轻DR病理改变，N-乙酰半胱氨酸等抗氧化剂亦可抑制ROS介导的NF-κB活化，提示该通路是潜在干预靶点[48]。

MAPK通路(p38、JNK、ERK亚家族)是炎症信号的关键调控节点。p38 MAPK主要介导小胶质细胞活化与促炎因子释放，在DR中，高糖及氧化应激可激活p38 MAPK，促进炎症因子释放与血管内皮损伤[49]；AMD中，p38 MAPK可被补体片段及氧化脂质激活，协同NF-κB促进炎症介质表达与脉络膜新生血管生成；JNK通路则主要参与氧化应激诱导的细胞凋亡；在DR中，JNK激活可促进内皮细胞凋亡与血-视网膜屏障破坏；RP中，JNK通路可被感光细胞碎片及ROS激活，放大炎症反应并加速神经元死亡[50]。

NF-κB与MAPK通路之间存在广泛的交叉对话。NF-κB可上调MAPK通路相关激酶的表达，MAPK则可通过磷酸化NF-κB亚基增强其转录活性，二者协同放大炎症信号，推动退行性视网膜病变进展[51]。Galectin-1过表达可通过抑制p38/MAPK-NF-κB通路保护视神经功能[52]。

1.3 补体系统失衡与炎症放大

补体系统作为固有免疫的关键组分，其过度激活与调控失衡是退行性视网膜病变中慢性炎症持续放大的重要机制，尤其在AMD、DR及RP的病理进程中发挥关键作用(附图2)。

补体系统通过经典、凝集素及旁路三条途径激活，最终形成膜攻击复合物(membrane attack complex，MAC)，介导细胞损伤与炎症介质释放[53]。生理状态下，补体激活受CD46、CD55、CD59等调控蛋白严格控制，维持免疫稳态[54]；病理条件下，调控失衡导致补体过度激活。多数AMD相关遗传变异位于补体基因中，CRISPR技术在ARPE-19细胞中靶向AMD相关SNP位点的研究表明，补体基因单核苷酸多态性可直接影响RPE细胞的补体调控能力和炎症易感性[55]。系统性补体激活的动态风险评估显示，补体通路持续失调显著增加中期AMD向进展期转化的风险，提示补体生物标志物可用于高危人群识别和个体化抗补体干预[56]。AMD中，RPE细胞及Bruch膜上的氧化脂质与淀粉样蛋白可激活旁路途径，生成大量C3a、C5a等过敏毒素，招募并活化小胶质细胞与巨噬细胞，同时MAC沉积于RPE细胞表面，诱导细胞凋亡与脉络膜新生血管生成[57]。不同疾病中补体失衡，在AMD中，*CFH*、*C3*等基因变异导致旁路途径过度激活，C1q经Wnt通路驱动补体异常[58-59]；NLRP3炎症小体在AMD早期病理中发挥关键作用，*Nlrp3*或*Casp1*基因敲除可显著减少年龄相关及*Efemp1*突变诱导的基底线性沉积物形成[60]；*IGF2BP2*在巨噬细胞中介导NLRP3炎症小体活化是干性AMD发病的关键机制之一，有望成为潜在生物标志物和治疗靶点[61]。氧化应激、线粒体功能障碍、炎症、异常补体激活与遗传易感性的动态交互共同驱动AMD进展[62]。DR中，高糖环境促使IgG外泌体激活经典途径，玻璃体C3a、C5a升高，C3bα′积累，CFH代偿性上调，提示替代途径亦参与[35,63]；环境因素与遗传易感性的“二次打击”交互作用在DR和RP中同样具有重要病理意义，为补体-炎症网络的多靶点联合干预提供了理论依据[62]。RP中，感光细胞碎片激活补体，C3片段沉积并被小胶质细胞CR3识别，伴随ROS释放，加剧氧化应激。*MERTK*相关RP中，功能障碍的RPE细胞释放细胞外囊泡，被小胶质细胞摄取后诱导其向促炎表型转化，形成“RPE-小胶质细胞”炎症偶联环路[64]；TSPO转运蛋白(translocator protein，TSPO)调控可通过调节神经炎症状态延缓光感受器退化[65]。

补体活化产物C3a与C5a通过结合其受体，激活NF-κB、MEK1/2-STAT3及PI3K-Akt等通路，促进TNF-α、IL-1β、IL-6释放，并诱导NLRP3炎症小体活化与Th17分化，趋化中性粒细胞及单核细胞浸润[66]。同时，C3a和C5a增加血管通透性，破坏血-视网膜屏障；MAC直接裂解RPE，促进VEGF-A

分泌，加速脉络膜新生血管形成[67]。三条补体途径在不同疾病中协同作用，最终导致视网膜结构破坏与功能丧失。

2 各型退行性视网膜病变的炎症特征

2.1 年龄相关性黄斑变性

干性AMD与氧化应激、遗传易感性及慢性炎症密切相关。视网膜的高氧、多不饱和脂肪酸和光照可促进ROS积累，而衰老、吸烟等则削弱抗氧化防御，加剧氧化损伤[68]。*CFH*基因Y402H变异使*CFH*与C3b结合力降低30%，导致补体替代途径过度激活，C3b在RPE表面沉积，激活小胶质细胞，驱动慢性炎症，显著增加AMD风险[69]。玻璃膜疣富含C3、C5b-9等补体成分及CRP、CEP等炎症介质，反映补体激活与脂质氧化的协同作用[70]。RPE内脂褐素沉积与自噬下降激活NLRP3炎症小体，促进IL-1β、IL-18释放，加剧局部炎症与细胞死亡[71]。

与干性AMD不同，湿性AMD以脉络膜新生血管（choroidal neovascularization，CNV）为特征。IL-6通过JAK-STAT和NF-κB通路上调HIF-1α，促进VEGF转录，驱动CNV形成[72]。补体产物C5a和C3a分别经巨噬细胞活化及NLRP3途径促进IL-6、IL-1β释放，并直接增强VEGF表达，形成炎症-血管生成恶性循环[72]。VEGF破坏内皮连接，TNF-α损伤内皮完整性，补体产物加重水肿，共同促进CNV进展[73]。

IL-6是AMD进展的关键标志物，其水平与疾病风险及地理性萎缩扩大率正相关，动物模型中IL-6缺失可显著抑制CNV[74]。IL-6诱导CRP合成，形成正反馈，增加湿性AMD风险[69]。综上，氧化应激、补体异常、炎症小体及细胞因子网络共同驱动AMD炎症反应，为靶向干预提供了理论基础（附图3）。

2.2 糖尿病视网膜病变

高血糖诱导的代谢紊乱、氧化应激及慢性炎症是DR发生发展的核心驱动力。高糖环境下，晚期糖基化终末产物（advanced glycation end products，AGEs）在视网膜血管基质沉积，直接损伤内皮功能通路，促进MCP-1、IL-6、TNF-α、ICAM-1，增加血管通透性[75]。AGEs与RAGE结合后激活NADPH氧化酶、MAPK及NF-κB 1等炎症因子表达，形成正反馈环路加剧血管损伤[76]。高血糖还通过PKC通路推动病变进展，PKCβ亚型磷酸化紧密连接蛋白occludin的Ser490位点，破坏血-视网膜屏障稳定性[77]。

TNF-α、IL-1β与IL-6在患者及动物模型中显著升高，不仅直接破坏血-视网膜屏障，还通过诱导神经元凋亡加重视网膜神经变性[78]。TNF-α与IL-1β激活NF-κB及JAK-2/STAT3通路，促进VEGF表达及白细胞黏附，导致血管通透性增加及病理性新生血管形成[79]。局部肾素-血管紧张素系统激活后，可与血脂异常协同加重炎症与氧化应激，进而推动DR的持续进展。

综上，高血糖通过AGE-RAGE轴、多元醇通路、PKC激活及氧化应激等多条途径持续放大视网膜炎症反应，形成恶性循环，也为代谢-炎症联合干预提供了理论依据。（附图4）

2.3 视网膜色素变性

RP是一组以进行性感光细胞丧失为特征的遗传性视网膜疾病。视紫红质（rhodopsin，Rho）基因突变（如P23H）是常染色体显性RP的常见原因，导致蛋白错误折叠与功能丧失[80]。此外，*RPE65*、*PDE6A/B*、*RPGR*等基因突变也参与发病，引起光感受器功能障碍与视网膜萎缩，错误折叠蛋白积累可诱发内质网应激并激活炎症反应[81]。炎症机制在RP进展中发挥关键作用。在视网膜脱离及遗传模型中，浸润的巨噬细胞与激活的小胶质细胞通过释放IL-1β、TNF-α、IL-6直接促进光感受器死亡[82]。RIP3介导的坏死性凋亡及C3补体通路上调参与感光细胞退化，抑制这些通路可延缓视网膜结构损伤[83]。

临床研究显示，RP患者房水与玻璃体中单核细胞、淋巴细胞浸润，IL-6、IL-8、MCP-1水平显著升高，提示先天与获得性免疫系统均参与疾病[84]。高敏C反应蛋白（hs-CRP）在RP患者中明显上升，其水平与中央视网膜功能下降速度正相关，可作为疾病分期与治疗评估的潜在生物标志物[84]。

综上，RP的发病源于基因突变导致的蛋白质功能异常及后续神经炎症反应，靶向调控小胶质细

胞活化、补体通路及关键炎症因子可能为延缓RP进展提供新策略(附图5)。

3 基于炎症调控的干预策略

慢性炎症是退行性视网膜病变的关键驱动因素,针对炎症环节的干预策略成为治疗研究的重要方向。

3.1 抗炎药物

糖皮质激素通过激活受体抑制NF-κB等转录因子,下调IL-1β、TNF-α、VEGF,增强血-视网膜屏障稳定性,临床用于糖尿病黄斑水肿、视网膜静脉阻塞及AMD[8,85]。临床研究显示,玻璃体内注射曲安奈德、地塞米松及缓释植入物可有效改善黄斑水肿患者视力与视网膜形态,部分患者视力提升达42%[86]。然而,其应用伴随眼压升高、白内障进展并可引发眼内炎、玻璃体出血等注射相关并发症。非甾体抗炎药抑制COX减少前列腺素,减轻炎症与渗漏,但眼部渗透性差,长期使用有角膜不良反应。新型生物制剂如抗TNF-α抗体、抗IL-6受体抗体通过阻断相应通路,在动物模型中显示保护效果,但存在免疫原性与高成本问题。小分子NF-κB、MAPK抑制剂在实验中亦有抗炎神经保护作用,但特异性和安全性仍需提升[75]。

近年来,靶向补体、炎症小体及血管生成相关通路的多种新型抗炎与基因治疗药物已进入临床试验或获批上市,代表性药物的临床研究进展(附表1)。其中,补体靶向治疗在地图样萎缩(geographic atrophy, GA)中取得了里程碑式突破——Pegcetacoplan作为首个获FDA批准的GA治疗药物,其Ⅲ期OAKS和DERBY试验证实可显著延缓GA病灶生长[87];进一步显示,Pegcetacoplan与Avacincaptad Pegol在12个月时具有相似的视力和解剖学结局[88]。在新型抗炎靶点方面,AAV介导的斯钙素-1(STC-1)过表达可通过减轻神经炎症保护退行性视网膜病变中的视功能[89];TLR2信号通路也被证实在AMD和DR中发挥重要作用,TLR2抑制可能成为潜在治疗策略[90]。此外,NLRP3炎症小体抑制剂在临床前和临床研究中均显示出减缓视网膜退行性变的潜力[60]。

附表
Appendix table

3.2 细胞治疗

间充质干细胞(MSC)具有多向分化与免疫调节功能,通过分泌TGF-β、IL-10、PGE2等因子抑制T细胞、B细胞及巨噬细胞活化,并诱导调节性T细胞生成。不同来源MSC的免疫调节能力存在差异:脐带MSC的IL-10分泌量(250 pg/mL)显著高于骨髓MSC(120 pg/mL);在链脲佐菌素诱导的DR大鼠模型中,脐带MSC干预组视网膜血管渗漏率降低52%,效果优于骨髓MSC组[91]。MSC来源的外泌体免疫原性低、生物安全性高,近年受到关注。这些外泌体携带的非编码RNA,在多种视网膜疾病中发挥调控作用。例如在DR中,外泌体miR-377-3p可抑制VEGF,影响RPE增殖;circPWWP2A则能上调血管生成素1和occludin等保护因子。在AMD中,miR-486-5p通过IGF1/AKT/mTOR通路,参与调控血管生成和炎症[92]。MSC主要通过玻璃体腔注射递送,操作简便但细胞迁移受限;视网膜下注射更常用于于RP等外层视网膜疾病,但存在视网膜脱离风险;全身给药因血-视网膜屏障靶向效率低[93]。RPE细胞移植方面,RPESC-RPE-4W(成体RPE干细胞来源祖细胞)在干性AMD早期临床试验中展现安全性和有效性[94];OpCT-001作为首个iPSC来源的光感受器前体细胞疗法,已获FDA快速通道资格和孤儿药资格认定。

调节性T细胞(Treg)通过分泌IL-10、TGF-β等抑制性细胞因子调控免疫反应。在早产儿视网膜病变模型中,Treg浸润可减轻血管渗漏与新生血管形成。采用CD3/CD28微球体外扩增、IL-2/抗IL-2复合物过继转移等策略可增强Treg治疗效果[95]。最新研究表明,在2型糖尿病小鼠模型中系统性扩增Treg可有效保护视网膜免受神经退行性改变、胶质增生和血管渗漏,提示Treg调控是预防DR早期阶段的有前景的治疗策略[37]。巨噬细胞极化调控是另一重要方向:小分子化合物(如咪康唑)、细胞因子(如IL-4)及纳米材料可诱导巨噬细胞向抗炎M2表型极化,通过STAT3、NF-κB等通路抑制炎症并促进组织修复[96]。

一项纳入355例RP患者的Meta分析显示,MSC疗法可短期改善最佳矫正视力及视网膜功能,视网膜下及脉络膜上腔给药优于全身输注,不良反应轻微[97]。然而,MSC临床转化仍面临细胞存活率低、归巢效率不足、静脉输注易滞留肺部、致瘤及纤

维化等风险，异质性及体外扩增标准化亦是亟待解决的问题。

3.3 基因治疗

RNA干扰（RNAi）通过siRNA或shRNA降解靶mRNA，可精准沉默补体因子、炎症细胞因子等关键分子[98]。腺相关病毒（AAV）是常用递送载体，但存在载荷容量有限及免疫原性等局限[99-100]。非病毒载体如脂质体及化学修饰siRNA（如cp-asiRNA）可突破血-视网膜屏障，安全性更高[101-102]。玻璃体腔注射为主要递送方式[103]。动物实验中，靶向PRR/ATP6AP2或PDGFR-α的RNAi干预可抑制炎症因子表达、延缓纤维化，改善视网膜结构与功能[104-105]。在新型基因治疗策略方面，AAV介导的STC-1过表达在退行性视网膜病变模型中展现出缓解神经炎症和保护视功能的潜力[89]。光遗传学作为一种新兴的基因治疗策略，通过向存活的视网膜内层神经元导入光敏感蛋白以重建视觉信号传导，为晚期RP患者提供了恢复部分视功能的可能[106]。CRISPR/Cas9系统已用于修复Rho、RPGR等基因突变，并在AMD模型中调控VEGFA、Hif1a抑制新生血管[107]。碱基编辑不产生DNA双链断裂，可避免插入缺失和基因组整合异常风险。在Rho-E150K突变RP模型中，腺嘌呤碱基编辑器成功恢复野生型视紫红质表达，部分挽救视网膜功能[108]。

基因治疗仍面临脱靶效应、免疫反应及长期安全性问题，生殖系编辑等伦理问题亦有待规范。

3.4 手术治疗

对于晚期退行性视网膜病变或出现严重并发症的患者，手术干预是重要的治疗手段。玻璃体切除术是治疗增生性DR所致玻璃体积血和牵拉性视网膜脱离的核心术式，术前辅助抗VEGF药物可降低术中出血及术后再出血风险[109]。在RP等遗传性视网膜变性中，玻璃体切除术可用于处理黄斑前膜和黄斑裂孔等继发性改变，但术后视力改善程度通常有限[110]。视网膜假体植入通过将微电极阵列植入视网膜特定位置，以电刺激替代受损光感受器的信号转导功能，主要适用于晚期RP及干性AMD患者[111]。第三代PRIMA系统（无线光伏视网膜下植入物）在干性AMD患者中展现出良好的安全性和有效性，植入12个月后81%的患者最佳矫正视力获得≥0.2 logMAR的改善[112]；第二代44通道脉络膜上腔视网膜假体在晚期RP患者中亦显示植入2.7年后无设备相关严重不良事件，患者在功能性视力测试中均有改善[113]。细胞移植与组织替代疗法是通过手术将干细胞来源的RPE细胞或光感受器前体细胞移植至病变部位，以重建受损的视网膜结构，目前正处于临床转化阶段[114]。iPSC来源的RPE补片在动物模型中证实可支持光感受器存活并促进脉络膜毛细血管再生[115]；人胚胎干细胞来源RPE细胞移植在湿性AMD患者中亦展现出结构改善和安全性[116]。此外，黄斑转位术因操作复杂、风险较高，临床应用已逐渐减少[117]。总体而言，手术治疗的定位因病变类型和阶段而异——PPV侧重于并发症处理，视网膜假体和细胞移植则分别从功能替代和结构修复两个方向为难治性晚期患者提供潜在获益，与抗炎药物、基因治疗形成互补。

4 总结与展望

慢性炎症作为AMD、DR、RP退行性视网膜病变的共同通路，其核心作用已得到充分证实。本综述围绕炎症细胞（含小胶质细胞、巨噬细胞、T/B细胞及中性粒细胞）、NF-κB与MAPK信号通路以及补体系统三个层面，梳理了慢性炎症的网络化调控机制，并总结了现阶段基于炎症干预的主要策略及部分临床在研药物。尽管临床前研究取得了积极进展，但向临床转化仍面临多重挑战。

当前转化瓶颈主要体现在四方面，一是疾病异质性强，缺乏可靠生物标志物用于患者分层，导致“一刀切”治疗模式效果有限；二是血-视网膜屏障限制靶向递送效率，现有给药方式存在分布不均、频繁注射等问题；三是干预策略的长期安全性存疑，广谱抗炎药副作用明显，靶向药物及基因编辑可能干扰正常免疫稳态，干细胞治疗的存活率与致瘤风险仍需解决；未来要取得突破，需要多学科协作，包括整合多组学与影像数据建立分子分型体系，开发能穿透视网膜的智能递送系统（如响应微环境的纳米载体或工程化外泌体），推进抗VEGF与抗炎药的联合使用，以及借助类器官、器官芯片和人源化动物模型提高临床预测的准确性，并结合表观遗传编辑与人工智能实时监测实现精准调控。

总之,靶向慢性炎症为退行性视网膜病变的治疗开辟了新方向。未来的突破将不再依赖单一“神药”,而在于精准、多靶点、跨学科的系统性策略,通过技术创新克服递送与安全壁垒,最终实现个体化的炎症干预。

参考文献

[1] An W, Zhang W, Qi J, et al. Mesenchymal stem cells and mesenchymal stem cell-derived exosomes: a promising strategy for treating retinal degenerative diseases[J]. Mol Med, 2025, 31(1): 75.

[2] Ayachit A, Rao S, Eqbal S, et al. Neovascular age-related macular degeneration management - beyond anti-VEGF[J]. Indian J Ophthalmol, 2026, 74(5): 653-660.

[3] Funatsu R, Terasaki H, Mihara N, et al. Evaluating photodynamic therapy versus brolucizumab as a second-line treatment for polypoidal choroidal vasculopathy[J]. Int J Retina Vitreous, 2024, 10(1): 32.

[4] Ciszewski P, Drelichowska A, Pikor D, et al. Innovative technologies for the treatment of dry age-related macular degeneration (AMD) - modern therapeutic perspectives and their future[J]. Rom J Ophthalmol, 2025, 69(1): 10-16.

[5] Sun Y, Li F, Liu Y, et al. Targeting inflammasomes and pyroptosis in retinal diseases-molecular mechanisms and future perspectives[J]. Prog Retin Eye Res, 2024, 101: 101263.

[6] Brownlee M. Biochemistry and molecular cell biology of diabetic complications[J]. Nature, 2001, 414(6865): 813-820.

[7] Kaur G, Singh NK. The role of inflammation in retinal neurodegeneration and degenerative diseases[J]. Int J Mol Sci, 2021, 23(1):386.

[8] Hata M, Hata M, Dejda A, et al. Corticosteroids reduce pathological angiogenesis yet compromise reparative vascular remodeling in a model of retinopathy[J]. Proc Natl Acad Sci U S A, 2024, 121(52): e2411640121.

[9] Forrester JV, Kuffova L, Delibegovic M. The role of inflammation in diabetic retinopathy[J]. Front Immunol, 2020, 11: 583687.

[10] Lei S, Liu Y. Identifying microglia-derived NFKBIA as a potential contributor to the pathogenesis of alzheimer's disease and age-related macular degeneration[J]. J Alzheimers Dis, 2025, 105(1): 134-146.

[11] Zhang D, Hu F, Li T, et al. Platelet factor 4 attenuates inflammation of microglia and protects retinal ganglion cells in retinal excitotoxicity[J]. Exp Eye Res, 2025, 255: 110352.

[12] Anderson OA, Finkelstein A, Shima DT. A2E induces IL-1ß production in retinal pigment epithelial cells via the NLRP3 inflammasome[J]. PLoS One, 2013, 8(6): e67263.

[13] Silverman SM, Ma W, Wang X, et al. C3- and CR3-dependent microglial clearance protects photoreceptors in retinitis pigmentosa[J]. J Exp Med, 2019, 216(8): 1925-1943.

[14] Wu J, Zhang J, Lin B. Dual-targeting CSF1R signaling attenuates neurotoxic myeloid activation and preserves photoreceptors in retinitis pigmentosa[J]. J Neuroinflammation, 2025, 22(1): 193.

[15] Carpi-Santos R, De Melo Reis RA, Gomes FCA, et al. Contribution of müller cells in the diabetic retinopathy development: focus on oxidative stress and inflammation[J]. Antioxidants (Basel), 2022, 11(4):617.

[16] Yu M. Petunidin attenuates lipopolysaccharide-induced retinal microglia inflammatory response in diabetic retinopathy by targeting OGT/NF-κB/LCN2 axis[J]. Open Med (Wars), 2025, 20(1): 20251274.

[17] Li Z, Xiong Q, Li Q, et al. Parthenolide ameliorates diabetic retinopathy by suppressing microglia-induced müller cell gliosis and inflammation via the NF-κB signalling[J]. Int Immunopharmacol, 2025, 151: 114219.

[18] Gao ML, Ju YY, Zhang J. Exploring retinal microglia: development, degeneration, and iPSC-derived model systems[J]. Brain Struct Funct, 2026, 231(1): 11.

[19] Li B, Chen J, Zhu J, et al. M2 macrophage-derived migrasomes mediate ischaemia-induced retinal neovascularization by targeting TREM2[J]. J Extracell Vesicles, 2025, 14(11): e70180.

[20] Sterling JK, Rajesh A, Droho S, et al. Retinal perivascular macrophages regulate immune cell infiltration during neuroinflammation in mouse models of ocular disease[J]. J Clin Invest, 2024, 134(20):e180904.

[21] Tang X, Liu W, Liang J, et al. Correction to: triamcinolone acetonide protects against light-induced retinal degeneration by activating anti-inflammatory STAT6/Arg1 signaling in microglia[J]. Inflammation, 2025, 48(4): 2837-2838.

[22] Zhou T, Huang Z, Sun X, et al. Microglia polarization with M1/M2 phenotype changes in rd1 mouse model of retinal degeneration[J]. Front Neuroanat, 2017, 11: 77.

[23] Xiao F, Wu F, Zhong P, et al. LncRNA CASC2 mediates SOCS6 mRNA stabilization via U2AF2 recruitment to

modulate macrophage polarisation in diabetic retinopathy[J]. Diabet Med, 2025, 42(8): e70014.

[24] 徐雯鑫，韦俏燕，周顺，等.视网膜新生血管中的小胶质细胞极化:敌友之争?(英文)[J].中南大学学报(医学版)，2026，51(3)：544-568.
Xu WX, Wei QY, Zhou S, et al. Microglial polarization in retinal neovascularization: friend or foe? [J]. J Cent South Univ (Med Sci), 2026, 51(3): 544-568.

[25] Li J, Fei P, Zhang X, et al. Comparative analysis of activation of macrophages/microglia in diabetic retinopathy and familial exudative vitreoretinopathy[J]. Biochem Biophys Rep, 2026, 45: 102396.

[26] Morales M, Mitchell DM. Microglia maintain retinal redox homeostasis following ablation of rod photoreceptors in zebrafish[J]. J Biol Chem, 2026, 302(7): 113169.

[27] Li W. Phagocyte dysfunction, tissue aging and degeneration [J]. Ageing Res Rev, 2013, 12(4): 1005-1012.

[28] Zhang H, Zhang X, Li H, et al. The roles of macrophage migration inhibitory factor in retinal diseases [J]. Neural Regen Res, 2024, 19(2): 309-315.

[29] Leach LL, Gonzalez RG, Jayawardena SU, et al. Macrophage/microglia-dependent mechanisms drive retinal pigment epithelium regeneration in zebrafish[J]. Cell Rep, 2025, 44(10): 116325.

[30] Fan Q, Li Z. Breach and restoration of retinal immune privilege: barrier failure, innate dysregulation, and adaptive autoimmunity[J]. Front Immunol, 2025, 16: 1703382.

[31] Rijken R, Pameijer EM, Gerritsen B, et al. Blood integrin- and cytokine-producing T cells are associated with stage and genetic risk score in age-related macular degeneration [J]. Exp Eye Res, 2025, 250: 110154.

[32] Deliyanti D, Suphapimol V, Ang P, et al. Targeting RORγ to boost regulatory T cells and ameliorate diabetic retinopathy in mice[J]. Am J Pathol, 2026, 196(2): 562-574.

[33] Liang J, Wu B, Hei X, et al. Linking mitochondrial gene dysregulation to immune cell shifts in retinitis pigmentosa[J]. Mol Neurobiol, 2025, 63(1): 164.

[34] Khalatyan AS, Shishparenok AN, Avetisov KS, et al. Association of telomere length in T lymphocytes, B lymphocytes, NK cells and monocytes with different forms of age-related macular degeneration [J]. Biomedicines, 2024, 12(8):1893..

[35] Huang C, Fisher KP, Hammer SS, et al. Plasma exosomes contribute to microvascular damage in diabetic retinopathy by activating the classical complement pathway [J]. Diabetes, 2018, 67(8): 1639-1649.

[36] Bu S, Ling JY, Wu X, et al. Downregulation of MerTK in circulating T cells of patients with non-proliferative diabetic retinopathy [J]. Front Endocrinol (Lausanne), 2024, 15: 1509445.

[37] Llorián-Salvador M, Pérez-Martínez D, Tang M, et al. Regulatory T cell expansion prevents retinal degeneration in type 2 diabetes[J]. J Neuroinflammation, 2024, 21(1): 328.

[38] Floyd JL, Prasad R, Dupont MD, et al. Intestinal neutrophil extracellular traps promote gut barrier damage exacerbating endotoxaemia, systemic inflammation and progression of diabetic retinopathy in type 2 diabetes [J]. Diabetologia, 2025, 68(4): 866-889.

[39] Funatsu J, Murakami Y, Shimokawa S, et al. Circulating inflammatory monocytes oppose microglia and contribute to cone cell death in retinitis pigmentosa [J]. PNAS Nexus, 2022, 1(1):pgac003.

[40] Shen W, Nie Z, Wang M, et al. Monocyte-derived exosomal periostin driven by histone lactylation contributes to retinal neovascularization[J]. Proc Natl Acad Sci U S A, 2025, 122(44): e2501704122.

[41] Dong X, Song Y, Liu Y, et al. Natural killer cells promote neutrophil extracellular traps and restrain macular degeneration in mice[J]. Sci Transl Med, 2024, 16(760): eadi6626.

[42] Xiang X, Zhang Z, Xu W, et al. Role of myeloid-derived suppressor cells (MDSCs), specifically monocyte-derived MDSCs, in type 2 diabetes-related diabetic retinopathy [J]. Diabetes Metab Syndr Obes, 2025, 18: 2213-2220.

[43] Eidet JR, Reppe S, Pasovic L, et al. The silk-protein sericin induces rapid melanization of cultured primary human retinal pigment epithelial cells by activating the NF-κB pathway[J]. Sci Rep, 2016, 6: 22671.

[44] Pan S, Liu M, Xu H, et al. Lipopolysaccharide activating NF-kB signaling by regulates HTRA1 expression in human retinal pigment epithelial cells[J]. Molecules, 2023, 28(5): 2236.

[45] Wang W, Zhao H, Chen B. DJ-1 protects retinal pericytes against high glucose-induced oxidative stress through the Nrf2 signaling pathway[J]. Sci Rep, 2020, 10(1): 2477.

[46] Almalki WH, Almujri SS. The impact of NF- κB on inflammatory and angiogenic processes in age-related macular degeneration[J]. Exp Eye Res, 2024, 248: 110111.

[47] Ou Y, Huang Y, Yang X, et al. Lycium barbarum glycopeptide alleviates retinal inflammation by suppressing microglial M1 polarization via NF-κB/MAPK pathways [J]. Exp Eye Res, 2025, 257: 110452.

[48] Homme RP, Sandhu HS, George AK, et al. Sustained inhibition of NF-κB activity mitigates retinal vasculopathy in

diabetes[J]. Am J Pathol, 2021, 191(5): 947-964.
[49] Barone V, Surico PL, Cutrupi F, et al. The role of immune cells and signaling pathways in diabetic eye disease: a comprehensive review [J]. Biomedicines, 2024, 12(10): 2346.
[50] Liao C, Chen S, Chen X, et al. Inhibition of JNK ameliorates rod photoreceptor degeneration in a mouse model of retinitis pigmentosa[J]. FEBS Lett, 2024, 598(21):2683-2701.
[51] Ding W, Sun Y, Tuohudaali W, et al. Isostrictiniin alleviates LPS-induced acute lung injury via the regulation of the keap1-Nrf2/HO-1 and MAPK/NF-κB signaling pathways[J]. Int J Mol Sci, 2025, 26(12):5912.
[52] He X, Yang N, Zhang N, et al. Galectin-1 overexpression protects damaged optic nerve and visual function in mice by inhibiting the p38/ MAPK-NF-κB signaling pathway[J]. Exp Eye Res, 2025, 261: 110689.
[53] Wilke GA, Apte RS. Complement regulation in the eye: implications for age-related macular degeneration[J]. J Clin Invest, 2024, 134(9):e178296.
[54] Borucki DM, Toutonji A, Couch C, et al. Complement-mediated microglial phagocytosis and pathological changes in the development and degeneration of the visual system [J]. Front Immunol, 2020, 11: 566892.
[55] Salman A, Song WK, Storm T, et al. CRISPR targeting of SNPs associated with age-related macular degeneration in ARPE-19 cells: a potential model for manipulating the complement system[J]. Gene Ther, 2025, 32(2): 132-141.
[56] Lynch AM, Grove NC, Wagner BD, et al. Dynamic risk of systemic complement activation with time to progression to advanced age-related macular degeneration [J]. JAMA Ophthalmol, 2025, 143(8): 634-642.
[57] Navneet S, Rohrer B. CR2-fH. A targeted inhibitor of alternative complement pathway reduces dry AMD-like phenotype in AMD patient iPSC-derived RPE cells[J]. Invest Ophthalmol Vis Sci, 2026, 67(2): 9.
[58] Ma Y, Ding X, Shao M, et al. Association of serum complement C1q and C3 level with age-related macular degeneration in women [J]. J Inflamm Res, 2022, 15: 285-294.
[59] Rodríguez De Córdoba S. Genetic variability shapes the alternative pathway complement activity and predisposition to complement-related diseases[J]. Immunol Rev, 2023, 313(1): 71-90.
[60] Ortega AJ, Daniel S, Renwick M, et al. Genetic removal of Nlrp3 protects against age-related and R345W efemp1-induced basal laminar deposit formation[J]. Cell Death Dis, 2025, 16(1): 803.
[61] Zhao Y, Zhang Y, Li J, et al. The role of IGF2BP2 in macrophage-mediated NLRP3 inflammasome activation in the pathogenesis of dry AMD[J]. Biol Direct, 2025, 20(1): 57.
[62] Delrue C, Speeckaert R, Speeckaert MM. Molecular crosstalk in age-related macular degeneration: integrating oxidative stress, inflammation, microRNAs, and genetic susceptibility toward precision therapeutics [J]. Biomolecules, 2026, 16(2):234.
[63] Shahulhameed S, Vishwakarma S, Chhablani J, et al. A systematic investigation on complement pathway activation in diabetic retinopathy[J]. Front Immunol, 2020, 11: 154.
[64] Zhang H, Liu ZY, Wu L, et al. Retinal pigment epithelium extracellular vesicles induce microglia polarization in MERTK-associated retinal degeneration [J]. Invest Ophthalmol Vis Sci, 2025, 66(15): 1.
[65] Corsi F, Castagnoli J, Galante A, et al. TSPO modulation prevents photoreceptor degeneration and produces neuroprotective effects in an animal model of retinitis pigmentosa[J]. Cells, 2025, 14(22):1778.
[66] Luo S, Xu H, Gong X, et al. The complement C3a-C3aR and C5a-C5aR pathways promote viability and inflammation of human retinal pigment epithelium cells by targeting NF-κB signaling[J]. Exp Ther Med, 2022, 24(2): 493.
[67] Bai Y, Wang R, Jin C, et al. Impacts of sulfate polysaccharide JCS1S2 on retinal neovascularization in oxygen-induced retinopathy rats[J]. Front Pharmacol, 2025, 16: 1499420.
[68] Kushwah N, Bora K, Maurya M, et al. Oxidative stress and antioxidants in age-related macular degeneration [J]. Antioxidants (Basel), 2023, 12(7):1379.
[69] Borodi PG, Slevin M. Exploring the role of inflammation in age-related macular degeneration: new insights and implications for future therapies[J]. Rom J Morphol Embryol, 2025, 66(1): 51-59.
[70] Vienne-Jumeau A, Bousquet E, Behar-Cohen F. Complement system modulation in age-related macular degeneration: navigating failures, building future successes [J]. Curr Opin Immunol, 2025, 96: 102616.
[71] Garcia-Garcia J, Usategui-Martin R, Sanabria MR, et al. Pathophysiology of age-related macular degeneration: implications for treatment [J]. Ophthalmic Res, 2022, 65(6): 615-636.
[72] Zong Y, Miyagaki M, Yang M, et al. Ophthalmic use of targeted biologics in the management of intraocular diseases: current and emerging therapies [J]. Antibodies (Basel), 2024, 13(4):86.
[73] Kayembe-Mulumba B, Leffondré K, Merle BMJ, et al. Long-

term blood pressure variability and risk of age-related macular degeneration in older adults: the ALIENOR study [J]. Ophthalmol Sci, 2025, 5(6): 100878.

[74] Krogh Nielsen M, Subhi Y, Molbech CR, et al. Systemic levels of interleukin-6 correlate with progression rate of geographic atrophy secondary to age-related macular degeneration[J]. Invest Ophthalmol Vis Sci, 2019, 60(1): 202-208.

[75] Ramadass V, Vaiyapuri T, Tergaonkar V. Small molecule NF-κB pathway inhibitors in clinic[J]. Int J Mol Sci, 2020, 21(14):5164.

[76] Yamashita AS, Belchior T, Lira FS, et al. Regulation of metabolic disease-associated inflammation by nutrient sensors [J]. Mediators Inflamm, 2018, 2018: 8261432.

[77] Murakami T, Frey T, Lin C, et al. Protein kinase cβ phosphorylates occludin regulating tight junction trafficking in vascular endothelial growth factor-induced permeability in vivo[J]. Diabetes, 2012, 61(6): 1573-1583.

[78] Yue T, Shi Y, Luo S, et al. The role of inflammation in immune system of diabetic retinopathy: molecular mechanisms, pathogenetic role and therapeutic implications [J]. Front Immunol, 2022, 13: 1055087.

[79] Tang L, Xu GT, Zhang JF. Inflammation in diabetic retinopathy: possible roles in pathogenesis and potential implications for therapy[J]. Neural Regen Res, 2023, 18 (5): 976-982.

[80] Athanasiou D, Aguila M, Bellingham J, et al. The molecular and cellular basis of rhodopsin retinitis pigmentosa reveals potential strategies for therapy [J]. Prog Retin Eye Res, 2018, 62: 1-23.

[81] Audo I, Nassisi M, Zeitz C, et al. The extraordinary phenotypic and genetic variability of retinal and macular degenerations: the relevance to therapeutic developments[J]. Cold Spring Harb Perspect Med, 2024, 14(6):a041652.

[82] Cai L, Xia M, Zhang F. Redox regulation of immunometabolism in microglia underpinning diabetic retinopathy[J]. Antioxidants (Basel), 2024, 13(4):423.

[83] Moekotte L, De Boer JH, Hiddingh S, et al. Elevated plasma complement factors in CRB1-associated inherited retinal dystrophies[J]. Invest Ophthalmol Vis Sci, 2025, 66(2): 55.

[84] Takeda A, Yanai R, Murakami Y, et al. New insights into immunological therapy for retinal disorders [J]. Front Immunol, 2020, 11: 1431.

[85] Jampol LM, Glassman AR, Sun J. Evaluation and care of patients with diabetic retinopathy[J]. N Engl J Med, 2020, 382(17): 1629-1637.

[86] Tariq F, Wang Y, Ma B, et al. Efficacy of intravitreal injection of filtered modified low-dose triamcinolone acetonide and ranibizumab on pseudophakic cystoid macular edema[J]. Front Med (Lausanne), 2022, 9: 777549.

[87] Heier JS, Lad EM, Holz FG, et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials[J]. Lancet, 2023, 402(10411): 1434-1448.

[88] Rush RB, Klein W, Reinauer RM. Real-world outcomes with complement inhibitors for geographic atrophy: a comparative study of pegacetacoplan versus avacincaptad pegol[J]. Clin Ophthalmol, 2025, 19: 1167-1174.

[89] Wang Y, Li S, Zhang C, et al. AAV-mediated STC-1 expression mitigates neuroinflammation and preserves visual function in degenerative retinopathy[J]. J Transl Med, 2025, 23(1): 924.

[90] Dalton R, Doyle S. Current perspectives of TLR2 signalling in the retina[J]. Adv Exp Med Biol, 2025, 1468: 127-131.

[91] Holan V, Palacka K, Hermankova B. Mesenchymal stem cell-based therapy for retinal degenerative diseases: experimental models and clinical trials[J]. Cells, 2021, 10 (3):588.

[92] Heo JI, Ryu J. Exosomal noncoding RNA: a potential therapy for retinal vascular diseases [J]. Mol Ther Nucleic Acids, 2024, 35(1): 102128.

[93] Ezquer M, Urzua CA, Montecino S, et al. Intravitreal administration of multipotent mesenchymal stromal cells triggers a cytoprotective microenvironment in the retina of diabetic mice[J]. Stem Cell Res Ther, 2016, 7: 42.

[94] Rao RC, Arduini BL, Borden S, et al. Safety and tolerability of RPESC-RPE transplantation in patients with dry age-related macular degeneration: low-dose clinical outcomes[J]. Cell Stem Cell, 2025, 32(11): 1659-1670.e1654.

[95] Hanna BS, Yaghi OK, Langston PK, et al. The potential for treg-enhancing therapies in tissue, in particular skeletal muscle, regeneration[J]. Clin Exp Immunol, 2023, 211(2): 138-148.

[96] Wu Y, Li X, Fu X, et al. Innovative nanotechnology in drug delivery systems for advanced treatment of posterior segment ocular diseases [J]. Adv Sci (Weinh), 2024, 11(32): e2403399.

[97] Krungkraipetch L, Supajitgulchai D, Assawaboonyadech A, et al. Efficacy and safety of mesenchymal stem cell therapies in retinitis pigmentosa: a systematic review and meta-analysis [J]. Int Ophthalmol, 2025, 45(1): 85.

[98] Cui ZT, Mao ZT, Yang R, et al. Spinocerebellar ataxias: from pathogenesis to recent therapeutic advances[J]. Front

Neurosci, 2024, 18: 1422442.

[99] Kulbay M, Tuli N, Akdag A, et al. Optogenetics and targeted gene therapy for retinal diseases: unravelling the fundamentals, applications, and future perspectives[J]. J Clin Med, 2024, 13(14):4224.

[100] Vitry S, Mendia C, Maudoux A, et al. Advancing precision ear medicine: leveraging animal models for disease insights and therapeutic innovations[J]. Mamm Genome, 2025, 36(2): 417-443.

[101] Lohia A, Sahel DK, Salman M, et al. Delivery strategies for CRISPR/Cas genome editing tool for retinal dystrophies: challenges and opportunities[J]. Asian J Pharm Sci, 2022, 17(2): 153-176.

[102] Lee H, Jang H, Chae JB, et al. In vivo efficacy of NRL knockdown with cell-penetrating siRNA in retinal degeneration[J]. Sci Rep, 2025, 15(1): 27176.

[103] Wu W, Mcrae J, Brown A, et al. Tropism and retinal transduction efficiency of adeno-associated virus serotypes in mice[J]. Invest Ophthalmol Vis Sci, 2025, 66(12): 18.

[104] Wang J, Zhao P, Chen Z, et al. Non-viral gene therapy using RNA interference with PDGFR-α mediated epithelial-mesenchymal transformation for proliferative vitreoretinopathy[J]. Mater Today Bio, 2023, 20: 100632.

[105] Sun R, Wang Y, Zhou W, et al. Novel compound heterozygous CNGA3 mutation associated with retinal cone dystrophy[J]. Exp Ther Med, 2025, 30(2): 155.

[106] Freise J. Regulatory aspects of optogenetic research and therapy for retinitis pigmentosa under EU law[J]. Front Med Technol, 2025, 7: 1548927.

[107] Fenner BJ, Tan TE, Barathi AV, et al. Gene-based therapeutics for inherited retinal diseases[J]. Front Genet, 2021, 12: 794805.

[108] Du SW, Newby GA, Salom D, et al. In vivo photoreceptor base editing ameliorates rhodopsin-E150K autosomal-recessive retinitis pigmentosa in mice[J]. Proc Natl Acad Sci U S A, 2024, 121(48): e2416827121.

[109] 中华医学会眼科学分会眼底病学组, 中国医师协会眼科医师分会眼底病专委会,《玻璃体切割手术治疗2型糖尿病视网膜病变专家共识》专家组. 玻璃体切割手术治疗2型糖尿病视网膜病变专家共识[J]. 中华眼底病杂志, 2024, 40(9): 663-686.
Fundus Disease Group of Ophthalmological Society of Chinese Medical Association, Fundus Disease Committee of Ophthalmologist Branch of Chinese Medical Doctor Association, Expert Group of Expert Consensus for Pars Plana Vitrectomy Treatment of Type 2 Diabetic Retinopathy. Expert consensus for pars plana vitrectomy treatment of type 2 diabetic retinopathy[J]. Chin J Ocul Fundus Dis, 2024, 40(9): 663-686.

[110] Al-Moujahed A, Lu ES, Zhou HW, et al. Outcomes of pars plana vitrectomy in inherited retinal degenerations[J]. Ophthalmol Retina, 2026, 10(5): 521-531.

[111] Alqahtani HB, Votruba M, Regini J. Do retinal implants provide long-term efficacy, safety and improve quality of life? A systematic review[J]. Ther Adv Ophthalmol, 2025, 17: 25158414251385884.

[112] Holz FG, Le Mer Y, Muqit MMK, et al. Subretinal photovoltaic implant to restore vision in geographic atrophy due to AMD[J]. N Engl J Med, 2026, 394(3): 232-242.

[113] Allen PJ, Kolic M, Baglin EK, et al. Second-generation (44-Channel) suprachoroidal retinal prosthesis: surgical stability and safety during a 2-year clinical trial[J]. Clin Exp Ophthalmol, 2025, 53(5): 529-541.

[114] Pearson RA. Photoreceptor replacement: a disease-agnostic approach for the treatment of advanced retinal degeneration[J]. Eye (Lond), 2026, 40(14):2145-2151.

[115] Gupta R, Bunea I, Alvisio B, et al. IPSC-RPE patch restores photoreceptors and regenerates choriocapillaris in a pig retinal degeneration model[J]. JCI Insight, 2025, 10(10):e179246.

[116] Lv YX, Li QY, Duan P, et al. Safe CNV removal is crucial for successful hESC-RPE transplantation in wet age-related macular degeneration[J]. Stem Cell Reports, 2025, 20(3): 102424.

[117] Terasaki H, Ishikawa K, Suzuki T, et al. Morphologic and angiographic assessment of the macula after macular translocation surgery with 360 degrees retinotomy[J]. Ophthalmology, 2003, 110(12): 2403-2408.

(编辑 孙慧兰)