·综　　述·

脉络膜新生血管的多通路病理机制及协同治疗新策略

姚牧笛　刘倩　颜标

上海交通大学医学院附属第一人民医院　眼和视光疾病国家临床医学研究中心，上海 200080

通信作者：颜标，Email：yanbiao@sjtu.edu.cn

【摘要】 脉络膜新生血管（CNV）是多种眼底疾病共同的致盲性终末病理改变。尽管抗血管内皮生长因子（VEGF）疗法已成为标准治疗，但长期临床实践表明其存在耐药、需频繁注射以及无法阻止视网膜萎缩等局限性。这主要源于CNV并非由单一通路驱动，而是血管生成、慢性炎症、免疫失衡、纤维化及细胞代谢重编程等多条通路相互作用的结果。因此，CNV的治疗思路正逐步从单一抑制血管生成转向多维稳态重建。本综述系统梳理了CNV的多通路病理机制，重点分析血管稳态（血管生成素/Tie2、血小板衍生生长因子）、炎症与免疫极化（补体、NOD样受体热蛋白结构域相关蛋白3炎症小体、免疫细胞表型转换）、纤维化（上皮-间质转化、内皮-间质转化、巨噬细胞-肌成纤维细胞转化）及代谢重编程的作用，并总结了新兴治疗策略，包括多靶点抗体、免疫调节剂、抗纤维化及代谢干预疗法，以及基因和细胞替代疗法。未来CNV治疗将依托精准分型，结合序贯或联合策略，并整合长效递送技术，实现从单纯抗VEGF转向主动修复视网膜-脉络膜稳态、延缓或逆转病变的治疗目标。

【关键词】 脉络膜新生血管；血管稳态；代谢重编程；纤维化；多靶点治疗

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Choroidal neovascularization: multipathway pathological mechanisms and novel synergistic therapeutic strategies

Yao Mudi, Liu Qian, Yan Biao

Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, National Clinical Research Center for Eye Diseases, Shanghai 200080, China

Corresponding author: Yan Biao, Email: yanbiao@sjtu.edu.cn

[Abstract] Choroidal neovascularization (CNV) represents a common blinding terminal pathological change across various fundus diseases. Although anti-vascular endothelial growth factor (VEGF) therapy has become the standard of care, long-term clinical practice has revealed significant limitations, including drug resistance, the burden of frequent injections, and the inability to prevent retinal atrophy. These challenges arise primarily due to the fact that CNV is not driven by a single pathway, but is the result of the interaction of multiple pathways involving angiogenesis, chronic inflammation, immune dysregulation, fibrosis, and cellular metabolic reprogramming. Consequently, the therapeutic paradigm is shifting from the sole inhibition of angiogenesis toward the multidimensional reconstruction of tissue homeostasis. This review systematically elucidates the multipathway pathological mechanisms of CNV, with a specific focus on vascular homeostasis (angiopoietin/Tie2, platelet-derived growth factor), inflammation and immune polarization (complement system, NOD-like receptor family pyrin domain containing 3 inflammasome, and immune cell phenotypic transition), fibrosis (epithelial-to-mesenchymal transition, endothelial-to-mesenchymal transition, and macrophage-to-myofibroblast transition), and metabolic reprogramming. Furthermore, emerging therapeutic strategies, including multi-target antibodies, immunomodulators, anti-fibrotic agents, and metabolic interventions, as well as gene and cell replacement therapies, are summarized. Future CNV management will rely on precision phenotyping combined with sequential or synergistic strategies and integrated long-acting delivery technologies. The ultimate goal is to transition from simple VEGF suppression to the active restoration of retinal and choroidal homeostasis, thereby delaying or reversing disease progression.

[Key words] Choroidal neovascularization; Vascular homeostasis; Metabolic reprogramming; Fibrosis; Multi-target therapy

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脉络膜新生血管(choroidal neovascularization, CNV)是湿性年龄相关性黄斑变性(wet age-related macular degeneration, wAMD)、病理性近视等眼部疾病的共同终末病理改变,其核心在于视网膜-Bruch膜-脉络膜复合体稳态的破坏[1]。抗血管内皮生长因子(vascular endothelial growth factor, VEGF)疗法虽显著改善了CNV的治疗效果,但长期临床实践表明其存在局限性:部分患者应答不足或耐药,需频繁注射,且无法阻断视网膜萎缩与纤维化[2-3]。这提示CNV并非由单一通路驱动,而是血管生成、炎症免疫、纤维化及代谢重编程等通路相互交织、形成恶性循环的结果[4-5]。此外,遗传易感性与累积的氧化应激往往是这些级联反应的关键因素。

随着对CNV发生和发展机制认识的深入,研究者们对是否应完全抑制新生血管也有了新的认识。缺氧驱动的新生血管本是机体为改善组织供氧产生的代偿反应,但在Bruch膜破裂及炎性微环境的共同作用下,这些新生血管结构异常、功能失调,反而加重组织损伤与病理进程。这一认识催生了"血管正常化"的治疗理念,其目标不再仅仅是抑制血管生长,而是通过干预促进新生血管成熟、减少血管渗漏以及恢复微环境稳态[6]。为实现这一目标,需深入解析各病理通路间的交叉对话机制;并探索能够实现协同干预、长效作用且重塑稳态的新型治疗策略。本文就CNV的多通路病理机制及协同治疗新策略进行综述。

1　CNV的复杂病理机制

CNV的发生和发展是一个多阶段、多细胞参与的动态过程。其核心机制是由血管失衡、免疫应答、纤维化及代谢应激构成的交互网络,各通路相互作用、互为因果,共同推动病程进展。

1.1　血管生成与稳态失衡:超越VEGF的核心驱动

VEGF-A/VEGF受体2(VEGF receptor-2, VEGFR-2)轴驱动早期内皮细胞增殖与迁移,是CNV形成的核心机制[7]。然而,病变的稳定性更依赖血管生成素(angiopoietin, Ang)/Tie2、血小板衍生生长因子(platelet-derived growth factor, PDGF)等通路的调控。针对难治性CNV(如光学相干断层扫描血管成像所示的动脉性CNV)的研究表明,这类病灶对VEGF信号的依赖性较低[8-9],其耐药机制主要包括:(1)周细胞紧密覆盖形成药物屏障[10];(2)碱性成纤维细胞生长因子、肝细胞生长因子等促血管生成因子表达代偿性上调[11];(3)内皮细胞通过代谢重编程(如增强脂肪酸氧化)获得生存优势[12]。早期研究还指出,在新生血管性疾病的动脉化阶段,血管生成对Ang-1的依赖更强[13],这进一步解释了抗VEGF治疗抵抗现象。

Ang/Tie2通路与血管失稳密切相关。Ang-2是关键的血管失稳因子,通过拮抗Tie2增加血管通透性,并协同VEGF促进异常出芽[14],这也解释了VEGF/Ang-2双靶点抑制(如法瑞西单抗)能更有效地恢复血管稳定性[15]。PDGF-BB/PDGF受体β(PDGFR-β)信号对周细胞募集和覆盖至关重要,是血管成熟的必需机制,但其过度激活可能促使周细胞向肌成纤维细胞转化,进而参与纤维化过程[16]。此外,Notch/Delta样配体4通路调控血管尖端细胞与茎细胞的平衡[17],Wnt/β-连环蛋白信号通路影响内皮屏障功能[18],而缺氧诱导因子作为上游调控中心,在氧化应激条件下持续激活,整合并放大多种促血管生成因子的表达[19]。

1.2　炎症与免疫动态极化

慢性低度炎症是CNV持续发展的重要驱动力,先天与适应性免疫系统均深度参与其中,且其激活状态与遗传背景密切相关。wAMD风险基因(如CFH、ARMS2)的变异削弱了补体抑制功能,导致C3a、C5a过度产生,它们不仅募集中性粒细胞,还直接损伤视网膜色素上皮(retinal pigment epithelium, RPE)并诱导VEGF表达[20]。氧化应激产生的活性氧可激活NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor family pyrin domain containing 3, NLRP3)炎症小体,引发caspase-1介导的白细胞介素(interleukin, IL)-1β、IL-18释放,并通过消皮素D导致细胞焦亡,进一步放大局部炎症反应[21]。免疫微环境表现出动态极化特征:早期M1型巨噬细胞参与组织清除过程,而后期M2型巨噬细胞则在几丁质酶3样蛋白1等因子驱动下分泌转化生长因子-β(transforming growth factor-β, TGF-β)和PDGF,促进血管生成与组织重塑[22]。适应性免疫细胞(如辅助性T细胞1/17)[23]、免疫检查点(如程序性死亡配体1)[24]、趋化因子轴[如趋化因子(C-X-C基序)配体12-趋化因子(C-X-C基序)受体4)][25]及信号素4D-PlexinB1[26]亦深度参与其中,为免疫干预提供了潜在靶点。

1.3　纤维化瘢痕:炎症与血管病变的终末结局

CNV向纤维血管膜转化是导致视力不可逆丧失的关键[27]。TGF-β是纤维化的核心驱动因子,诱导RPE发生上皮-间质转化和内皮细胞发生内皮-间质转化[28-29]。炎症信号在此过程中起到催化剂作用:浸润的巨噬细胞可通过巨噬细胞-肌成纤维细胞转化为相当比例的肌成纤维细胞池[30-31]。结缔组织生长因子(connective tissue growth factor, CTGF)作为TGF-β的下游关键效应分子,是维持纤维化的"开关",长期抗VEGF治疗可能导致VEGF/CTGF平衡失调,相对升高的CTGF加速细胞外基质(extracellular matrix, ECM)沉积[32]。此外,补体激活产物(C3a、C5a)也可通过RPE细胞诱导上皮-间质转化和胶原分泌,将炎症信号与纤维化过程紧密偶联[33]。

1.4　细胞应激与代谢重编程

细胞应激与代谢重编程不仅是适应性反应,更是病理性改变恶化的核心驱动因素。氧化应激通常作为病理级联反应的始动因素,在遗传易感性(如ARMS2变异导致线粒体功能障碍)背景下,持续的氧化损伤首先累及作为视网膜代谢支持中心的RPE细胞,引发严重的线粒体功能衰竭与内质网应激,并

触发未折叠蛋白反应及NLRP3炎症小体的激活。代谢组学研究显示，这种应激状态可直接导致RPE脂质代谢紊乱，促使其由稳态向促炎/凋亡表型转变，为CNV的发生奠定病理微环境基础[34-36]。

与此同时，增殖中的血管内皮细胞表现出显著的代谢重编程特征，即高度依赖6-磷酸果糖激酶/果糖-2，6-二磷酸酶3驱动的高糖酵解（Warburg效应）供能。这种代谢偏移通过免疫代谢及代谢-表观遗传双重机制重塑病理进程：一方面，代谢状态决定了免疫表型，即高糖酵解环境促使巨噬细胞向促炎M1型极化[37]；另一方面，乳酸脱氢酶A驱动的乳酸产生可促进组蛋白乳酰化修饰，进而调控促血管生成基因的转录表达[38-39]。此外，非编码RNA（如tRNA衍生小RNA、微小RNA）也被证实能通过靶向关键代谢酶（如己糖激酶2）精细调节内皮细胞的代谢状态与血管生成能力[40]。这种氧化应激-代谢重塑-免疫极化回路揭示了多通路协同参与相关深层病理机制。

2 基于多通路干预的新型治疗策略

基于对上述复杂病理网络的深入理解，CNV的治疗策略正从单点突破转向多靶点协同与稳态重建。下文围绕不同病理环节的新兴药物及联合治疗方案展开论述。

2.1 靶向血管生成与稳态

传统抗VEGF制剂主要依赖于VEGF-A的高亲和力结合发挥作用，但当前治疗策略正从单一VEGF抑制向双重机制协同与长效给药发展。法瑞西单抗作为首个获批用于眼科的双特异性抗体，可同时中和VEGF-A与Ang-2，在抑制血管生成的同时恢复血管稳定性，临床数据显示，超过60%的患者可实现每16周1次的给药间隔[41]。国产创新药IBI324亦采用双靶点设计，在早期临床试验（Ⅰ/Ⅱ期）中显示出良好的视力改善和积液消退效果[42-43]；此外，酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI）如vorolanib和axitinib可同时靶向VEGFR、PDGFR等多个受体酪氨酸激酶，并可结合长效眼内递送系统，以延长药物作用时间并降低重复玻璃体腔注射负担[44-45]；AXT107则通过调控整合素信号促进血管正常化（Ⅰ/Ⅱa期）[46]。这些策略的核心在于抑制新生血管增生的同时促进其成熟稳定，为CNV的长效管理提供了新方向[47]。

2.2 调节炎症与免疫微环境

针对炎症这一核心放大器，抗炎联合抗血管生成的策略正在成为新的治疗方向。IBI302是一种同时靶向VEGF与补体通路的双靶点融合蛋白。其Ⅲ期STAR研究已达到52周主要终点，在维持视力获益的同时显示出延长给药间隔的潜力[48-49]。C3抑制剂Pegcetacoplan和C5抑制剂Avacincaptad pegol虽主要用于地图样萎缩，但其改善局部炎症微环境、保护RPE的潜力正在wAMD联合治疗中被探索（Ⅱ期）[50-51]。临床前研究显示，针对NLRP3炎症小体以及CCR2/CCR5趋化因子轴的小分子抑制剂能有效调节免疫微环境、减轻纤维血管膜形成（临床前研究阶段）[52-54]。这些策略旨在从源头上控制炎症，为突破现有抗VEGF治疗的局限提供了可能。

2.3 抗纤维化与延缓组织重塑

为防止疾病进入不可逆的终末阶段，干预纤维化进程至关重要。具体策略包括：（1）多因子阻断 ①RC-28E作为VEGF/FGF-2双诱饵受体，可同时高亲和力结合两者，阻断内皮增殖与纤维化转型（Ⅲ期）[55]；②GB-102利用Sunitinib长效制剂同时抑制VEGF-A和PDGF-BB，切断周细胞募集及纤维化支架构建的信号流（Ⅱb期）[56-57]；（2）靶向细胞-基质相互作用 例如整合素拮抗剂Risuteganib（ALG-1001）通过干扰细胞与ECM的黏附及下游信号来抑制纤维化进程（Ⅱb/Ⅲ期）[58]；（3）抑制ECM交联 如赖氨酰氧化酶抑制剂，通过减少胶原交联软化瘢痕，改善药物渗透性（临床前研究阶段）[59]。这些探索为干预CNV晚期结构性损伤提供了新方向。

2.4 靶向代谢异常与细胞保护

针对代谢这一底层驱动因素，具有疾病修饰潜力的策略正在兴起。线粒体保护剂如Elamipretide通过稳定线粒体膜结构改善RPE能量代谢和抗氧化能力，Ⅱ期临床试验（ReCLAIM-2）显示其能改善干性AMD患者视功能[60]。补充烟酰胺腺嘌呤二核苷酸前体（如烟酰胺单核苷酸，临床前研究阶段）或使用衰老细胞清除剂（如UBX-1325，Ⅱ期）可改善细胞代谢功能、抑制异常血管生成，已证实其潜在应用价值[61]。同时，靶向糖酵解关键酶6-磷酸果糖激酶/果糖-2，6-二磷酸酶3可纠正内皮细胞Warburg效应，抑制过度血管生成（临床前研究阶段）[62]。这些策略为实现CNV的长期组织保护与功能维持提供了多维度框架。

3 治疗技术的革新：长效递送与“治本”探索

依托眼球的相对免疫豁免特性，基因与细胞疗法为CNV治疗提供了从延缓病程向功能重塑转变的可能。此外，长效递送技术的改进也为减轻患者治疗负担奠定了基础。目前，以重组腺相关病毒（adeno-associated virus，AAV）载体为基础的基因疗法进展较快，部分项目已进入后期临床试验；而诱导多能干细胞衍生细胞移植及基因编辑技术仍处于早期探索阶段，临床转化尚需时间。

3.1 AAV介导的基因疗法：一次治疗，长期表达

基因疗法利用AAV载体将编码抗血管生成因子（如抗VEGF蛋白）的基因导入视网膜细胞，使其持续分泌治疗蛋白，从而实现一次治疗、长期获益的效果。针对wAMD的多项AAV基因疗法正在临床验证中，例如RGX-314已进入Ⅲ期临床试验[63-64]，Ixo-vec（Ⅲ期）和4D-150（Ⅲ期，双靶向VEGF/Ang-2）也在积极推进[64]。该治疗策略不仅有望替代频繁注射，还能维持眼内药物浓度稳定，避免传统注射的峰谷效应。此外，递送血管稳态调节因子（如Tie2激动剂）或补体调控蛋白的多靶点策略也处于临床前研究阶段。尽管前景广阔，AAV基因疗法的长期安全性、免疫原性及高成本仍是其推广应用需解决的关键问题[64]。

3.2 细胞替代与基因编辑：修复与根治疗法的探索

诱导多能干细胞衍生RPE细胞移植旨在通过手术植入健康功能性RPE细胞片，修复受损的血-视网膜外屏障并支持光感受器生存。针对wAMD的早期临床试验已初步验证其安全性，但移植细胞在眼内的长期存活、功能整合以及避免过度增

殖仍是目前面临的主要挑战[65]。另一方面，成簇规律间隔短回文重复序列相关蛋白9等基因编辑技术理论上可通过敲除病理性高表达的*VEGFA*基因，从源头抑制新生血管生成[66]。然而，该类技术目前仍处于临床前研究阶段，其递送效率、编辑精准度及长期安全性均有待进一步验证。

3.3　长效递送技术与给药途径革新

频繁眼内注射是wAMD长期管理的重大负担。在长效递送技术方面，高剂量抗VEGF制剂如阿柏西普8 mg已获批应用于临床，将半数患者的给药间隔延长至12周[67]；雷珠单抗植入式递送系统通过手术植入可补充药物的眼内储药装置，实现雷珠单抗持续释放[68]；可生物降解的长效TKI眼内递送制剂，如vorolanib玻璃体内植入剂EYP-1901（DURAVYU）和axitinib水凝胶植入剂OTX-TKI（AXPAXLI），均已进入wAMD Ⅲ期临床开发，可通过持续释放药物延长给药间隔并降低重复玻璃体腔注射负担[44]。在给药途径革新方面，除脉络膜上腔微创注射可提高靶向性外，非侵入性的局部滴眼给药亦是重要的探索方向。传统的滴眼液受限于眼表解剖屏障，难以在视网膜和脉络膜达到有效治疗浓度，但新型小分子药物及纳米递送系统的应用为其带来转机。例如，PAN-90806（VEGFR-2抑制剂滴眼液，Ⅱ期）[56]旨在通过增强跨巩膜或角膜的渗透性实现无创治疗。尽管目前点眼给药的疗效尚难以完全替代玻璃体腔注射，但有望成为维持期治疗的重要补充。然而，这些新技术仍面临诸多挑战与局限性：植入装置存在眼内炎风险，基因疗法需解决长期表达调控及免疫原性问题，细胞治疗则受限于工艺与成本。但总体而言，这些进展为CNV的长效管理提供了极具潜力的可行方案[69]。

4　总结与展望

CNV的发病机制已超越单纯血管异常范畴，涉及炎症免疫、纤维化和代谢网络的多维交互。这一认识推动治疗从单一抗VEGF注射，向多靶点联合干预及稳态修复发展。未来治疗将更趋个体化：早期病变可采用VEGF/Ang-2双抗或基因疗法控制进展，高炎症或纤维化风险患者可加入补体抑制或抗纤维化策略，晚期结构损伤则可考虑细胞替代修复技术。治疗的核心在于整合多靶点药物、长效缓释技术、基因疗法及微创干预手段，以提升疗效并降低患者治疗负担。最终目标不仅是控制血管渗漏，更在于恢复并维持视网膜-Bruch膜-脉络膜复合体功能稳态。面对精准分型、联合治疗时机选择和长期安全性等挑战，多学科协作有望推动CNV治疗由被动控制向主动干预与长期功能修复转变，为防治CNV相关致盲眼病开辟新路径。

利益冲突　所有作者均声明不存在利益冲突

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