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早产儿视网膜病变药物治疗新策略的应用与前景

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摘　要

早产儿视网膜病变(ROP)是导致儿童盲的主要原因之一，尽管激光光凝和抗VEGF药物注射等现有治疗方法取得了一定成效，但仍存在局限性。近年来，随着对ROP发病机制的深入理解，新型药物治疗策略不断涌现，为ROP的治疗带来了新的希望。文章综述了ROP药物治疗的最新进展，重点介绍了新型抗VEGF药物、生长因子抑制剂、靶向治疗药物及非VEGF靶向药物等策略的作用机制、临床研究进展及潜在优势，并探讨了未来研究方向。

关键词

早产儿视网膜病变，药物治疗，抗VEGF，生长因子抑制剂，靶向治疗

Emerging Pharmacotherapeutic Strategies and Clinical Prospects in Retinopathy of Prematurity (ROP): From Novel Applications to Future Directions

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Abstract

Retinopathy of Prematurity (ROP) remains one of the leading causes of childhood blindness worldwide.

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Although existing therapeutic approaches, including laser photocoagulation and anti-VEGF pharmacotherapy, have demonstrated clinical efficacy, they present inherent limitations. Recent advances in understanding the pathogenesis of ROP have facilitated the emergence of novel pharmaco-therapeutic strategies, offering promising alternatives for disease management. This comprehensive review summarizes contemporary progress in ROP pharmacotherapy, with particular emphasis on elucidating the mechanisms of action, clinical trial outcomes, and potential advantages of innovative therapeutic agents such as next-generation anti-VEGF biologics, growth factor inhibitors, targeted molecular therapies, and non-VEGF pathway antagonists. Furthermore, we critically analyze current challenges and propose future research directions to optimize therapeutic paradigms in ROP management.

Keywords

Retinopathy of Prematurity, Pharmacotherapy, Anti-VEGF, Growth Factor Inhibitor, Targeted Molecular Therapy

1. 引言

早产儿视网膜病变(Retinopathy of Prematurity, ROP)是低出生体重儿常见的视网膜血管发育障碍，以视网膜纤维血管异常增生和不完全血管化为特征[1] [2]。随着新生儿重症监护技术的进步，极低出生体重儿存活率显著提高，但 ROP 发病率也随之上升。据估计，全球每年约有 3.2 万例儿童因 ROP 失明，其中中低收入国家因医疗资源不足面临更严峻挑战[3]。在中国，ROP 已成为早产儿视力障碍的首要病因，2022 年一项多中心研究显示，极早产儿(23~27 周)中需接受 ROP 治疗的比例为 12.6%，且发病率未随医疗技术进步显著下降[4]。

ROP 的病理进程以“双阶段模型”为核心[5]：在血管闭塞期高氧环境下抑制血管内皮生长因子(VEGF)和胰岛素样生长因子-1 (IGF-1)表达，导致视网膜血管退化；在异常增殖期，缺氧诱导 VEGF、炎症因子(IL-6、TNF-α)及氧化应激信号过度激活，驱动病理性血管新生。此外，脉络膜为外层视网膜提供氧气和营养，其成熟障碍可能与 ROP 后的视力缺陷有关[6]。

目前临床主要采用激光光凝和抗 VEGF 药物治疗。激光光凝(LPC)通过破坏周边无血管区抑制血管增生，但可导致视网膜瘢痕、视野缺损及高度近视[7]。抗 VEGF 药物(如雷珠单抗、贝伐单抗)通过抑制 VEGF 信号通路快速消退新生血管，但存在全身吸收风险，可能影响肺、脑等器官发育，且长期疗效存在争议[8] [9]。2022 年 RAINBOW 临床试验显示，约 15%~17%患者需重复抗 VEGF 治疗以应对疾病复发[10]。此外，约 20%的患者对单一抗 VEGF 治疗无反应，因此这提示需探索其他机制干预来参与 ROP 的治疗[11]。本文综述近年来 ROP 药物治疗的新进展，旨在为临床转化提供理论依据，推动更安全、精准的干预方案。

2. 治疗策略

2.1. 抗 VEGF 药物

2.1.1. 经典抗 VEGF 药物的临床证据

贝伐单抗和雷珠单抗作为临床应用最广泛的抗 VEGF 药物，其疗效已通过多项研究验证。Mintz-

Hittner [12]及 RAINBOW [7]多中心研究显示，玻璃体腔注射贝伐单抗(IVB)和雷珠单抗(IVR)在 ROP 治疗中的解剖学成功率显著优于 LPC。Ortiz-Seller [13]的系统评价进一步指出，尽管抗 VEGF 治疗的再干预率与 LPC 相当，但 IVB 和 IVR 在屈光结果方面更具优势。

2.1.2. 安全性研究进展

短期安全性数据显示，玻璃体腔内注射抗 VEGF 药物局部并发症包括眼内炎、医源性白内障和视网膜脱离[9]，而脉络膜缺血、破裂和视网膜牵拉恶化等罕见事件发生率低于 0.1% [14] [15]。长期全身效应仍存争议，部分研究[16]提示 IVB 可能影响神经发育以及降低认知和语言评分。Lee [17]的回顾性分析报道称雷珠单抗治疗与全身 VEGF 抑制无关，RAINBOW [7] [18]扩展研究进行了一项前瞻性观察性研究，分别收集了雷珠单抗 0.2 mg 组、雷珠单抗 0.1 mg 组、激光治疗组三组患儿治疗 24 周及 2 年后的治疗成功率、眼部不良事件(眼内炎、白内障、视网膜脱离等)及全身不良反应，发现三组全身性不良事件的发生均与早产基础疾病相关，雷珠单抗 0.2 mg 组出现眼部结构性损害(1.4% vs 10.3%)和高度近视(≤−5.00 D)的发生率均低于激光组(5% vs 20%)，这表明 IVR 治疗可能减少远期眼部不良事件的发生。

2.1.3. 新型药物临床应用

阿柏西普于 2023 年获 FDA 批准用于严重 ROP，其疗效与现有药物相当[19]，但缺乏大量的安全性研究来探究不良事件的发生情况[20]。全球多中心研究[21] (N = 118)显示其 5 年随访数据具有视力保护优势，且可能降低高度近视发生率。中国自主研发的康柏西普在 Cheng [22]的研究中表现出与 IVR 相当的血管化效果(P = 0.441)，且再治疗率降低，未观察到晶状体混浊、玻璃体出血、眼内膜炎或视网膜脱离等不良反应[23]，但需关注其潜在的眼压升高风险[24]。

2.1.4. 药代动力学特征与潜在风险

新一代药物(阿柏西普[19]、康柏西普[25]-[27])较传统药物具有更强的 VEGF 结合力和更长半衰期，这可能降低病变复发风险。但需注意其导致的血清 VEGF 抑制持续时间延长(>8 周 vs 2~4 周) [28]，目前尚未发现神经发育相关不良事件[29]，仍需大规模长期随访验证(推荐研究周期 ≥ 5 年)。

2.2. 生长因子抑制剂

ROP 特征性病理改变为视网膜新生血管(Retinal Neovascularization, RNV)的形成，视网膜血管异常增生与缺氧诱导的细胞因子级联反应密切相关[5]。研究证实，视网膜缺氧可刺激视网膜色素上皮过度分泌碱性成纤维细胞生长因子(bFGF) [30]，同时激活血管内皮细胞产生血小板源性生长因子(PDGF)，二者协同破坏视网膜抗血管化微环境[31]。Fang 团队通过氧诱导视网膜病变(OIR)小鼠模型发现，bFGF 在血管消退期的表达显著上调，提示其可能通过维持神经视网膜功能参与病理代偿过程[32]。此外，PDGF 通过调控星形胶质细胞增殖分化，在视网膜血管发育中发挥双重作用：一方面促进生理性血管生成，另一方面加剧病理性新生血管形成[33]。Kaito 等进一步验证，PDGF 信号通路激活可显著减少 OIR 模型鼠视网膜无血管区面积，证实其在血管重塑中的关键地位[34]。

索拉菲尼和舒尼替尼作为多激酶抑制剂，已获 FDA 批准并用于实体瘤治疗[35]-[37]。近期研究显示其在 ROP 治疗中具有潜在价值。索拉菲尼通过抑制 VEGF、PDGF 等多条促血管生成信号通路，阻断病理性新生血管的形成，这与 ROP 的核心病理机制(缺氧诱导的血管异常增殖)高度相关。并且索拉菲尼在大鼠 OIR 模型中呈现剂量依赖性抑制效应，高剂量组(80 μg)可使新生血管面积减少(vs 对照组，P < 0.001) [38]。舒尼替尼则通过抑制 VEGF 受体，有效控制视网膜新生血管，在治疗糖尿病视网膜病变中显示出与抗 VEGF 药物贝伐单抗相当的疗效，且短期内未观察到眼内炎、出血和视网膜功能损伤[39]。目前，上述药物尚处于临床前研究阶段，需进一步通过类器官模型与灵长类动物实验评估其视网膜毒性(如光感受器

凋亡风险)及全身安全性(肝肾功能影响)。

2.3. 靶向药物

尽管血管内皮生长因子(VEGF)在维持正常血管内皮细胞增殖和血管稳态中发挥重要作用[40]，但广谱抗 VEGF 药物的使用可能对生理性血管发育造成不可逆损害，如视网膜无血管区扩大及周边视网膜缺血等[41]。近年来，分泌粒蛋白 III (Secretogranin III, Scg3)作为一种新型限制性血管生成因子受到广泛关注。研究表明，Scg3 通过激活 MEK/ERK 信号通路选择性促进病理性血管生成[42]。在 OIR 小鼠模型中，Scg3 基因敲除可使病理性新生血管面积减少 68% ± 5% (vs 野生型，$P < 0.001$)，而不影响生理性血管生成[43]。这一发现揭示了 Scg3 在病理性血管生成中的特异性调控作用。基于 Scg3 的选择性作用机制，抗 Scg3 抗体疗法展现出显著的治疗潜力。临床前研究显示，与阿柏西普相比，抗 Scg3 抗体治疗 OIR 小鼠具有以下优势：病理性 RNV 面积减少 75% ± 6% (vs 阿柏西普组 52% ± 7%，$P < 0.05$)；周边视网膜血管密度维持正常(92.3% ± 3.1% vs 阿柏西普组 78.5% ± 4.2%，$P < 0.01$) [44]；未观察到体重减轻(Δ 体重 < 5%)、视网膜发育异常及肾脏毒性(血清肌酐水平：(15.2 ± 1.8) μmol/L vs (18.6 ± 2.1) μmol/L，$P > 0.05$) [45]。鉴于 Scg3 的高度选择性，其抑制剂可能成为一类新型选择性血管生成阻滞剂。但 Scg3 阻滞剂目前仅在小鼠模型中被证实有效，还需要进行临床研究来确定其安全性和有效性。

乙酰肝素酶(Heparanase, HPAE)是一种内-β-D-葡萄糖醛酸酶，通过降解硫酸乙酰肝素(HS)参与细胞外基质重塑，其过表达与肿瘤血管生成及转移密切相关[46] [47]。在视网膜缺氧病理模型中，HPAE 通过激活 NF-κB 信号通路，显著上调 VEGF 表达(mRNA 升高 2.3 倍，$P < 0.001$)，进而驱动病理性新生血管形成[48]。Liang 团队[49]针对 HPAE 的抑制作用开展了系统性研究：在 OIR 小鼠模型中，玻璃体腔注射 HPAE 特异性抑制剂 PI-88 可显著降低视网膜 HPAE 活性并同步减少 VEGF 蛋白表达($P < 0.001$)，且未观察到视网膜内层神经元凋亡增加。因此，乙酰肝素酶可能是以视网膜缺氧缺血为特征的视网膜疾病的新治疗靶点。

2.4. 非 VEGF 靶向药物

ROP 的血管闭塞期以氧化应激为核心驱动因素。高氧暴露通过 NADPH 氧化酶激活，诱导活性氧(ROS)水平升高，进而持续激活 HIF-1α/VEGF 轴及 JAK2/STAT3 通路，形成促炎微环境并加速病理性血管生成[50]。值得注意的是，高氧还可特异性激活视网膜小胶质细胞，促进白细胞介素-1β (IL-1β)释放，导致血视网膜屏障破坏及微血管内皮细胞凋亡[51]。早期抑制 IL-1β 受体可保留脉络膜，减少视网膜下缺氧，从而改善 OIR 动物的视觉功能[52]。新型抗 IL-1β 药物 rytvela 在小鼠模型中有效保护了视网膜的完整性，是 ROP 治疗潜在药物[53]。

TLR4 作为固有免疫关键受体，其感染性激活在 ROP 进展中发挥重要作用。实验证据表明在没有氧化应激的情况下，炎症也会导致 ROP 的血管特征[54] [55]。报道证实[56] TLR4 拮抗剂可以有效阻断异体角膜移植和糖尿病视网膜病变等疾病的炎症反应。这表明 TLR4 拮抗剂可能在治疗 ROP 中发挥潜在疗效。

黄芪作为传统中药，其活性成分(芒柄花素，FMN)通过多机制发挥视网膜保护作用[57]。FMN 抑制 ROS 生成、降低促凋亡因子 Bax 表达、上调抗凋亡因子 Bcl-2，保护视网膜细胞免受氧化应激损伤，减少细胞凋亡；同时也可以通过抑制 HIF-1α/VEGF 信号通路，减少缺氧条件下视网膜色素上皮细胞(ARPE-19)的 VEGF 分泌，并下调 PHD-2 (脯氨酰羟化酶 2)的表达，阻断病理性血管生成[58]；在 OIR 模型中，黄芪可以修复视网膜血管形态，维持视网膜屏障完整性[59]。

3. 结论

综上所述，ROP 是一种多因素疾病，且病因尚不完全明确。自 1940 年以来，治疗和预防 ROP 的药

物及干预措施主要针对氧化激活和 VEGF，但其治疗的有效性及远期预后存在争议。除了 VEGF 抑制剂外，其他针对 ROP 发展和进展关键介质的治疗方法正在研究中，但是否抑制正常血管发育(如生理性视网膜血管化)，未来需进一步开展多中心临床试验，评估其在早产儿中的长期安全性及有效性，以推动其临床应用转化。

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