·文献综述·

息肉状脉络膜血管病变相关分子生物标志物的研究进展

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摘要

息肉状脉络膜血管病变(PCV)自然病程的视力预后不佳,好发于亚洲人群。近年来光学相干断层扫描(OCT)及其血流成像技术(OCTA)显著提升了其诊断能力,但影像生物标志物存在滞后性,且无法解析血管生成、炎症、遗传因素、细胞外基质(ECM)重塑等分子机制。文章围绕 PCV 核心病理机制进行相关分子生物标志物研究现状的综述,作为影像生物标志物形态学局限的补充,揭示了 PCV 的病理机制线索,为精准防控、病情评估、预测治疗反应提供依据。文章提出可通过整合基因组学、蛋白质组学、影像组学等构建“多模态分层诊疗模型”,指导风险分层、动态评估和个体化诊疗,促进 PCV 精准诊疗体系的建立。

关键词:息肉状脉络膜血管病变;血管生成;炎症;遗传;细胞外基质;分子生物标志物
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Research progress on molecular biomarkers related to polypoid choroidal vasculopathy

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Abstract

• Polypoid choroidal vasculopathy (PCV) is associated with poor visual prognosis in its natural course and is more prevalent in Asian populations. Despite advancements in optical coherence tomography (OCT) and OCT angiography (OCTA) that have significantly improved morphological diagnostic capabilities, imaging biomarkers are limited by temporal resolution constraints and fail to elucidate molecular mechanisms underlying vascular angiogenesis, inflammation, genetic factors, and extracellular matrix (ECM) remodeling. This review synthesizes current research on molecular biomarkers associated with PCV, focusing on its core pathological mechanisms. These biomarkers provide crucial insights into disease pathogenesis to inform precision prevention, dynamic disease monitoring, and therapeutic response prediction. Furthermore, this article proposes the integration of multi-omics data (genomics, proteomics, and radiomics) to establish a multimodal hierarchical diagnostic-therapeutic model. This framework will guide risk stratification, real-time disease assessment, and personalized treatment strategies, advancing the development of a precision medicine framework for PCV management.

• KEYWORDS: polypoid choroidal vasculopathy; angiogenesis; inflammation; heredity; extracellular matrix; molecular biomarker

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0 引言

息肉状脉络膜血管病变(polypoid choroidal vasculopathy,PCV)是一种以视网膜下橘红色结节样病灶和异常分支的脉络膜血管网及末端息肉样病变为特征的慢性血管异常,好发于亚洲人群[1]。相比于典型的新生血管性年龄相关性黄斑变性(age-related macular degeneration,ARMD),其发病年龄更早、息肉样病变更明显、大量视网膜下出血的风险更高、对抗血管内皮生长因子(vascular endothelial growth factor,VEGF)治疗的反应更差[2-4]。近年来,光学相干断层扫描(optical coherence tomography, OCT)及其血流成像技术(OCT angiography, OCTA)通过高分辨率三维成像和血流可视化,显著提升了 PCV 的诊断准确性。例如,基于 OCTA 的深层脉络膜血管网定量分析可早期识别息肉样病灶,而人工智能辅助的 OCT 图像分割技术(如深度学习模型)进一步提高了对隐匿性病变的检出率[5-7]。然而,影像生物标志物存在形态学导向的固有局限,如仅反映结构改变难以揭示分子通路

异常、形态学改变有一定的滞后性、不同仪器的参数与成像质量存在差异。PCV 分子生物标志物的研究可作为影像生物标志物的补充,本文系统综述 PCV 分子生物标志物研究进展,聚焦其病理机制解析与临床价值,以期建立“多模态分层诊疗模型”,为风险评估和个体化诊疗提供新思路。

1 PCV 的发病机制

PCV 的发病机制尚未完全明确,目前认为主要与血管生成、炎症反应、遗传因素、细胞外基质(extracellular matrix,ECM)重塑等相关。

1.1 新生血管形成 新生血管的形成在 PCV 发病过程中占据核心地位。VEGF 是病理性新生血管形成的关键介质,其在 PCV 患者房水中表达显著增加[8-9];血管生成素-2(angiopoietin-2,Ang-2)与具有免疫球蛋白和表皮生长因子同源结构的酪氨酸激酶受体 2(tyrosine kinase with immunoglobulin and epidermal growth factor homology domains 2,Tie2)结合、表皮生长因子(epidermal growth factor,EGF)同样参与新生血管形成[10-11]。

1.2 炎症反应 炎症反应在 PCV 发病过程中起着重要作用。Yanagi 等[12]提出补体激活、白细胞募集和炎症介质可引发脉络膜毛细血管变薄和 Bruch 膜降解,驱动 PCV 进展。某些炎症因子如白细胞介素-6(interleukin-6,IL-6)、肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)等在眼内表达增加,提示局部处于炎症激活状态[9,13-15]。

1.3 遗传因素 多种遗传因素参与 PCV 发病机制,如表 1[16-20]所示为部分 PCV 相关基因的多态性。补体因子 H(complement factor H,CFH)基因、丝氨酸蛋白酶 A1(high-temperature requirement factor A1,HTRA1)基因、年龄相关性黄斑病变易感性 2(age-related maculopathy susceptibility 2,ARMS2)基因与 PCV 关联性最强,可增强 PCV 的易感性[21-23]。

1.4 细胞外基质重塑 目前研究表明脉络膜-Bruch 膜区域的 ECM 降解为 PCV 的始动阶段,当 ECM 代谢异常,会诱导脉络膜血管破坏性重塑、Bruch 膜降解,最终导致 PCV 典型病理特征[12,24]。ECM 降解过程中自身抗原的暴露提供了补体激活的平台,引发慢性局部炎症反应推动 PCV 疾病进展。

2 PCV 相关分子生物标志物

2.1 血管生成相关分子生物标志物

2.1.1 VEGF PCV 患者眼内 VEGF 水平升高[8-9],Sato 等[25]研究结果显示房水基线 VEGF 浓度>150.4 pg/mL(灵敏度为 0.667,特异度为 0.818)可作为抗 VEGF 药物治疗第 2 a 时黄斑萎缩的预测因子,曲线下面积(area under the curve,AUC)= 0.818;基线 VEGF 浓度<43.9 pg/mL 也预示着抗 VEGF 药物的治疗反应欠佳(灵敏度为 71.1%,特异度为 78.6%,AUC=0.805)[26]。此外,VEGF 不同亚型的重要性也得到了关注。VEGF-A 是影响新生血管形成的主要因素,VEGF-C、VEGF-D 也可刺激新生血管形成、损害光感受器层[27]。目前,临床常用的抗 VEGF 药物如贝伐单抗主要靶向 VEGF-A,然而 VEGF-A 的抑制会使 VEGF-C 和 VEGF-D 代偿性上调,导致抗 VEGF 治疗反应不佳[28]。Sozinicept(OPT-302)是 VEGF-C 和 VEGF-D 的生物抑制剂,联合靶向 VEGF-A 的药物可更广泛阻断血管生成,临床试验成效满意[29-30]。然而 VEGF-C/D 是调节眼淋巴管生成的关键因子,长期被抑制可能加重眼部炎症[31]。因此,有必要基于房水 VEGF-C/D 水平进行亚组分析,优化获益人群。

2.1.2 Ang-2 Ang-2 是 Tie2 受体的竞争性拮抗剂,可破坏内皮细胞间连接、导致周细胞脱落,并与 VEGF 协同作用增加血管通透性,促进新生血管形成[10]。法瑞西单抗作为 Ang-2/VEGF-A 双重抑制剂展现出持久的治疗效果。Todoroki 等[32]评估了 54 例渗出性 ARMD 患者(含 40.7% PCV 亚型)从阿柏西普转换为法瑞西单抗的短期疗效,治疗后房水 Ang-2 浓度显著降低(P<0.001),52.1%患者疾病活动度下降,其中转换间隔为 7-12 wk 组较高的基线 Ang-2 水平预示着更好的治疗反应(P = 0.02)。Nonogaki 等[33]在 32 例初治渗出性 ARMD 患者(含 40.6% PCV 亚型)中发现,法瑞西单抗治疗 1 mo 后房水 Ang-2 浓度从 6.35±6.39 pg/mL 降至 2.94±5.04 pg/mL(P<0.01),基线房水 Ang-2 浓度较高与疗效改善显著相关(P=0.019)。因此,房水中基线 Ang-2 浓度可作为预测 PCV 患者对法瑞西单抗治疗反应的生物标志物。

2.1.3 EGF EGF 与 VEGF 有共同的下游信号通路,参与血管生成[11],也可促进视网膜 Muller 细胞的增殖和迁移、增强抗氧化作用,影响抗 VEGF 药物的功效[34]。研究发现,PCV 患者血浆 EGF 水平增加[13],且 Gorenjak 等[35]发现外周血单核细胞中 EGF 水平显著正向影响 VEGF 蛋白水平(β=0.017,P<0.0001)。Wang 等[36]基于 PCV 患者房水蛋白组学的研究表明,房水中高 EGF 水平的患者接受抗 VEGF 治疗有更显著的解剖学结构改善,可作为预测 PCV 患者抗 VEGF 治疗反应的生物标志物(AUC = 0.939)。

2.2 炎症反应相关分子生物标志物

2.2.1 炎症因子

(1)IL-6:IL-6 由巨噬细胞产生,具有促炎和促进血管生成的能力[37]。临床研究显示,PCV 患者房水中 IL-6 水平显著升高并与眼内炎症程度相关[8,36,38-39],且 Wang 等[36]进一步发现抗 VEGF 治疗反应差的患眼 IL-6 浓度更高(P<0.01),提示 IL-6 可能通过增强炎症反应参与治疗抵抗。Sato 等[25]分析了 28 例湿性 ARMD 患者(含 18 例 PCV 亚型)接受阿柏西普注射 2 a 后黄斑萎缩的情况及房水炎症因子,结果表明第三针注射后房水 IL-6 浓度>7.01 pg/mL(AUC=0.758,P=0.013)预示 2 a 病程后黄斑萎缩发病风险显著增加。白血病抑制因子(leukemia inhibitory factor,LIF)是 IL-6 家族的成员,在炎症期间表达,可保护血管系统和视网膜完整性[40]。Zhou 等[9,13]发

表 1 与 PCV 相关基因

基因	单核苷酸多态性	人群
CFH	rs1061170(Y402H)、rs800292(I62V)	欧裔美国[16]、新加坡[17]、日本[18]
ARMS2	rs10490924(A69S)	日本[18]
HTRA1	rs2293870	中国[19]
TIE2	rs2273717、rs625767	亚洲[20]

现 PCV 患者房水与血浆 LIF 浓度显著增加,并且血浆 LIF 可作为区分其与典型的新生血管性 ARMD 的生物标志物。

(2)TNF-α:TNF-α 是由巨噬细胞和 T 细胞产生的重要促炎因子。研究表明,PCV 患者房水中 TNF-α 水平显著升高[15],且 Dong 等[26]对 PCV 患者房水细胞因子与抗 VEGF 反应关系的回顾性研究发现,TNF-α>8.45 pg/mL 是抗 VEGF 治疗反应不佳的独立危险因素(AUC=0.897,敏感度 84.2%,特异度 90.5%),提示其与难治性 PCV 密切相关。目前研究发现,TNF-α 可直接介导脉络膜新生血管形成以及增加 VEGF 的表达、激活烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate,NADPH)氧化酶产生活性氧(reactive oxygen species,ROS)从而升高氧化应激水平[41],一定程度上解释了难治性 PCV 的机制,需要在临床试验和体外研究中进一步验证。

(3)干扰素诱导蛋白-10(interferon-induced protein-10,IP-10):IP-10 是一种与炎症反应相关的细胞因子,能够抑制视网膜和脉络膜新生血管的形成[42],其在 PCV 中的病理意义呈现矛盾性。临床研究显示 PCV 患者眼内 IP-10水平显著升高,血浆水平无明显变化,提示 IP-10 与 PCV 的联系限于眼局部[13,43]。Sakurada 等[44]发现房水 IP-10的浓度与病变大小显著相关($P=0.002$,$\beta=0.568$),并提出眼内 IP-10 水平增加可能是对 VEGF 过度表达的一种代偿机制,但其浓度不足以有效遏制新生血管形成,反而可能通过募集炎症细胞促进 PCV 的发病。因此未来需要明确 IP-10 在 PCV 中抑制血管生成与促炎效应的平衡阈值,探索增强 IP-10 抑制血管生成或阻断其促炎效应的治疗潜力,尤其针对难治性 PCV 患者。

2.2.2 趋化因子 单核细胞趋化蛋白-1(monocyte chemoattractant protein-1,MCP-1)是调节单核细胞和淋巴细胞浸润的关键趋化因子。PCV 患者眼内 MCP-1 浓度显著升高[44-45],卜倩等[46]发现血清 MCP-1 水平增加($P=0.005$)是 PCV 的独立危险因素。此外,MCP-1 可被 VEGF 诱导表达,同时通过上调缺氧诱导因子 1α 增强 VEGF 的生成,造成恶性循环[47],这可能是难治性 PCV 的潜在机制。Arai 等[48]发现房水基线时较高的 MCP-1 与初治湿性 ARMD 患者(含 56.25% PCV 亚型)抗 VEGF 治疗 12 mo 更好的视力改善显著相关($\beta=-0.20$,$P=0.015$)。Sato 等[25]通过受试者工作特征(receiver operating characteristic,ROC)曲线分析和 Kaplan-Meier 生存曲线分析发现,接受阿柏西普治疗的患者房水中基线 MCP-1 浓度>120.8 pg/mL(AUC=0.841,$P<0.001$)、注射 3 针后的 MCP-1 浓度>152.8 pg/mL(AUC=0.780,$P=0.006$)均提示第 2 a 病程时具有黄斑萎缩的高发病风险。因此,MCP-1可作为预测抗 VEGF 治疗疗效和病情评估的生物标志物。

2.2.3 其他炎症反应相关分子生物标志物 除炎症因子(IL-6、TNF-α、IP-10)、趋化因子 MCP-1 外,参与炎症过程中的其他分子也与 PCV 密切相关[26,49-56](表 2)。

2.3 遗传相关分子生物标志物

2.3.1 CFH 基因 CFH 基因位于染色体 1q31,是补体替代通路的关键负调控因子,通过抑制补体过度激活保护组织免受炎症损伤[57],其功能缺陷削弱补体途径抑制能力,显著增加 PCV 发病风险[21-22]。CFH 基因多态性存在种族差异,Jordan-Yu 等[17]对东亚人群和高加索人群 PCV 眼进行比较,CFH rs800292 G 等位基因使东亚人群中 PCV 发病风险增加 1.7 倍($P=0.010$),高加索人群中则无显著相关性($P=0.487$);CFH rs1061170(Y402H)风险等位基因(C)在欧洲人群高发,但在亚洲 PCV 中频率极低[22]。此外吸烟与 CFH rs1061170(Y402H)存在显著的协同效应[58],进一步加剧发病风险。

2.3.2 HTRA1 基因 HTRA1 基因位于染色体 10q26,编码一种具有蛋白酶活性的分泌蛋白,其过度表达可通过降解 Bruch 膜的关键 ECM,使得脉络膜新生血管更容易突破 Bruch 膜[59]。Kumar 等[60]整合转基因小鼠与人类 PCV 标本分析证实 HTRA1 过表达是 PCV 的始动因素,进展阶段则由炎性级联反应驱动,最终导致血管异常增生[24]。Luo 等[19]研究了 PCV 基因型与临床表型关联,HTRA1 rs2293870 TT 型比 GG 型更可能表现为单侧 PCV($P=0.021$),与更厚的中心凹下脉络膜厚度($P=0.022$)相关。

2.3.3 ARMS2 基因 ARMS2 是一种灵长类特异性基因,编码 11.4 kDa 分泌蛋白,眼部表达水平较低[61]。目前认为 ARMS2 风险基因与 ARMS2 蛋白无明显关联,其与 HTRA1 基因在染色体 10q26 的同一连锁不平衡区中相隔

表 2 其他炎症反应相关分子生物标志物

分子生物标志物	关键机制	临床意义
C 反应蛋白(c-reactive protein,CRP)	炎症激活 mCRP 亚型,破坏视网膜色素上皮(retinal pigment epithelium,RPE)紧密连接及血-视网膜屏障[49]。	血清及房水 CRP 水平与病情严重程度相关[50-51]。
血清淀粉样蛋白 A(serum amyloid A,SAA)	上调 VEGFR2 表达,诱导炎性因子及趋化因子[52]。	房水 SAA4 是 PCV 持续性炎症的标志物[53]。
细胞间黏附分子-1(intercellular adhesion molecule-1,ICAM-1)	促进内皮细胞黏附及免疫细胞活化,驱动炎症反应及纤维化进程[54]。	眼内 ICAM-1 水平升高与黄斑纤维化显著相关($P<0.01$)[55]。
血管细胞黏附分子-1(vascular cell adhesion molecule 1,VCAM-1)	调控巨噬细胞的迁移、向促纤维化的表型极化[55]。	眼内 VCAM-1 水平<862.00 pg/mL 是抗 VEGF 治疗反应不佳的独立危险因素(AUC=0.846,敏感度 65.8%,特异性 88.1%)[26];眼内 VCAM-1 水平与黄斑纤维化显著相关($P<0.01$)[55]。
CD11b+单核细胞	促进炎症细胞黏附和迁移;有助于 VEGF 介导的脉络膜新生血管形成。	基线时 CD11b+单核细胞的比例可预测 PCV 患者 12 mo($\beta=0.77$,$P=0.004$)、24 mo($\beta=0.94$,$P<0.001$)和 36 mo($\beta=0.78$,$P=0.005$)时所需抗 VEGF 药物的次数[56]。

仅约4 kbp,更倾向于通过HTRA1蛋白发挥作用[62]。此外,一项META分析显示ARMS2和CFH基因之间存在协同作用[63],在PCV发病机制中二者存在共同途径。ARMS2 A69S基因多态性与PCV的表型特征及治疗反应密切相关,ARMS2 A69S TT基因型患者黄斑下出血面积更大[64]、对侧眼发生PCV风险更高[65]、对光动力治疗(photodynamic therapy,PDT)、抗VEGF治疗反应差[66-68]。近期研究揭示,ARMS2风险单倍型(rs10490924)可通过调控线粒体功能紊乱加剧氧化应激,进而促进Bruch膜损伤[69]。此外,基因编辑技术(如CRISPR-Cas9)在ARMS2敲除模型中证实其通过补体旁路途径调控炎症微环境[70]。未来研究需聚焦ARMS2在补体通路中的分子机制,探索基因分型指导下的个体化治疗策略。

多基因风险评分(polygenic risk scores,PRS)也称为遗传风险评分,是一种整合多个基因变异信息从而量化疾病遗传易感性的常用工具,已显示出在眼科领域如ARMD中的巨大潜力[71]。日本一项研究通过PRS预测261例渗出性ARMD患者(含132例PCV患者)对阿柏西普的治疗反应,结果显示包含ARMS2 A69S和CFH I62V的PRS与再次治疗(比值比=2.09,$P=1.6\times10^{-4}$)和额外注射次数($\beta=0.75$,$P=2.42\times10^{-6}$)显著相关[72]。Sendecki等[73]首次使用深度学习方法初步建立ARMD患者PRS与OCT图像关联的模型($R^2=0.42$),后续研究中将进一步验证模型性能。PRS可帮助疾病风险分层、改善疾病筛查和临床决策,仍然需要前瞻性研究验证临床实践中的有效性和实用性。

2.4 细胞外基质重塑相关分子生物标志物 基质金属蛋白酶(matrix metalloproteinases,MMPs)是一类依赖锌离子的内肽酶,通过降解ECM调控血管生成与炎症反应。研究显示PCV病变脉络膜血管[24]中MMP-9水平显著增加。PCV患者血液中MMP-9水平的研究存在争议,Zeng等[68]发现中国汉族PCV患者血清MMP-9水平为健康人群的两倍($P<0.001$),Sørensen等[74]基于高加索PCV人群的前瞻性研究显示高加索PCV患者血浆MMP-9水平与健康人群无显著差异,鉴于血清与血浆MMP-9水平密切相关,提示可能存在种族差异。Arai等[48]分析了48例初治湿性ARMD患者(含56.25% PCV亚型)基线和治疗期间的房水蛋白与抗VEGF治疗效果,研究结果表明基线较高的MMP-9浓度与12 mo内的注射次数增加显著相关($\beta=0.56$,$P=0.01$)。

3 PCV相关分子生物标志物的应用前景

3.1 精准防控 PCV病程复杂,建立"风险分层、早期预警、个体化干预"的精准防控体系至关重要。无创影像学技术(如OCT显示的RPE脱离、视网膜下高反射物质)是PCV诊断的核心工具,但难以预见发病风险、实现早期预警。近年来PRS在ARMD中显示出疾病预测和风险分层的优越性能[75],可量化个体的遗传风险分层采取预防措施。目前PCV的PRS研究仍处于探索阶段,未来应继续完善PCV的基因组学构建PRS模型,推动PCV的精准防控。

3.2 病情评估 发展到中晚期的PCV,其视网膜神经上皮以及RPE细胞已明显受损,因此对病情进行评估、监测疾病的活动性至关重要。目前基于OCT的影像学标志物为临床病情评估主要指标,但形态学改变相较于分子水平的变化具有一定滞后性。分子标志物能够反应病情严重程度,如眼内VEGF[25]、ICAM-1[55]、VCAM-1[55]水平与黄斑纤维化显著相关,房水IL-6、MCP-1可作为预测接受阿柏西普治疗患者发生黄斑萎缩的生物标志物[25],房水IP-10水平反应病变大小[44],与影像学标志物的多模式联合分析,有助于动态评估PCV活动性,指导治疗间隔调整。

3.3 治疗 目前PCV的临床治疗以抗VEGF药物为主,但患者常面临治疗抵抗、病灶复发及频繁的注射负担。分子生物标志物的研究为优化PCV治疗方案提供了契机,如房水中VEGF[26]、Ang-2[32-33]、EGF[36]、TNF-α[26]、MCP-1[48]可作为抗VEGF药物的治疗反应的生物标志物,房水中MMP-9[48]、循环中CD11b+单核细胞的比例[56]可预测抗VEGF药物的次数。但单一组学数据难以解析PCV的复杂病理机制以及实现精准治疗,Bobadilla等[76]提出整合基因组学、蛋白质组学与影像学特征等有助于识别抗VEGF治疗反应差的潜在分子机制,建立个性化治疗方案。

4 总结与不足

PCV是一种病因未明的复杂脉络膜血管疾病,探究相关分子生物标志物对全面理解深层机制、病情评估和个体化治疗具有重大意义。目前临床更为关注难治性PCV患者眼内液的分子变化及其深层的分子机制,并发现了可预测治疗反应和病情评估的生物标志物,此外人工智能在PCV诊疗中的应用也展现出广阔前景[77]。但PCV分子生物标志物的临床应用仍存在挑战:眼内液检测的有创性和高成本限制了大规模的临床应用,需探索人工智能与多组学的整合,推动病理机制线索的无创解析;PCV基因组学的研究仍需深入,基于此的PRS效能和实用性需要前瞻性研究进行验证。未来依托多中心协作、跨学科技术融合,有望推动PCV"多模态分层诊疗模型"的建立,实现疾病的精准诊疗。

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