

炎症与免疫反应在年龄相关性黄斑变性中的作用

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收稿日期: 2025年10月11日; 录用日期: 2025年11月4日; 发布日期: 2025年11月12日

摘 要

年龄相关性黄斑变性是一种常见且严重影响老年人中心视力的疾病, 其发病率随年龄增长显著升高。近年来, 多项独立研究均揭示炎症与免疫反应在年龄相关性黄斑变性的发生和发展中发挥关键作用。炎症介质在眼内微环境中的异常释放、免疫细胞的激活失调以及补体系统的过度活化均可诱导视网膜色素上皮细胞损伤和黄斑区域退化。然而, 对于这一复杂病理过程的具体分子机制的理解仍有待深入, 现有治疗方法在某些方面仍存在局限性。本文系统回顾并深入探讨了近年来国内外关于炎症和免疫在年龄相关性黄斑变性中的作用机制、生物标志物的研究进展以及潜在治疗策略, 旨在为未来研究和临床干预提供新的视角和参考。

关键词

年龄相关性黄斑变性, 炎症, 免疫反应, 生物标志物, 治疗策略

The Role of Inflammation and Immune Responses in Age-Related Macular Degeneration

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文章引用: 叶振伟, 赵恬, 杜汶泽, 钟紫露, 张艳莉. 炎症与免疫反应在年龄相关性黄斑变性中的作用[J]. 临床医学进展, 2025, 15(11): 1063-1072. DOI: 10.12677/acm.2025.15113192

Abstract

Age-related macular degeneration (AMD) is a prevalent ocular disorder that profoundly impairs central vision in the elderly, with incidence increasing markedly with advancing age. In recent years, multiple independent studies have demonstrated that inflammation and immune responses play pivotal roles in the onset and progression of AMD. Aberrant release of inflammatory mediators within the intraocular microenvironment, dysregulated activation of immune cells, and excessive complement system activation can collectively induce retinal pigment epithelium (RPE) injury and degeneration of the macular region. However, the precise molecular mechanisms underlying this complex pathological process remain incompletely understood, and current therapeutic approaches still exhibit notable limitations. This review provides a comprehensive and in-depth analysis of recent advances in elucidating the roles of inflammation and immunity in AMD, including mechanistic insights, emerging biomarkers, and potential therapeutic strategies, with the aim of offering new perspectives to guide future research and clinical interventions.

Keywords

Age-Related Macular Degeneration, Inflammation, Immune Response, Biomarkers, Therapeutic Strategies

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1. 引言

年龄相关性黄斑变性(AMD)是老年人群中导致不可逆性视力丧失的主要原因之一,严重影响患者的生活质量[1]。传统观点认为,AMD的发生主要与遗传、环境因素和氧化应激相关,但越来越多的证据表明,炎症反应和免疫调节失衡在疾病的发生和进展中扮演着关键角色[2]-[4]。炎症反应通常是机体对损伤或感染的一种保护机制,但在AMD中,慢性炎症可能导致视网膜色素上皮(RPE)细胞的损伤和功能障碍,加速疾病进展[1][5]。例如,研究已证实AMD患者的眼内环境中存在大量炎症因子和免疫细胞,且这些细胞的激活程度与疾病的严重程度密切相关[6]。

值得注意的是,干性AMD(以玻璃膜疣与地理性萎缩为特征)与湿性AMD(以脉络膜新生血管为特征)在炎症与免疫通路上存在重要差异[2][7]。干性AMD中补体旁路与慢性炎症驱动RPE退化更为突出[8][9];湿性AMD中新生血管形成与血管内皮生长因子(VEGF)信号、M2型巨噬细胞极化及免疫微环境重塑密切相关[10][11]。

在AMD的发病过程中,免疫系统失调被认为是一个关键因素[12]。其中,巨噬细胞在AMD的不同阶段均发挥重要作用,不仅参与局部炎症反应,还通过释放细胞因子调节免疫应答[3][4]。研究显示,巨噬细胞的激活与AMD的病理改变密切相关,尤其是在湿性AMD中,巨噬细胞的聚集和功能改变可能导致病情恶化[13]。此外,Toll样受体(TLR)的激活也被认为是RPE细胞炎症反应的重要途径,这些受体能够识别病原体和损伤相关分子模式(DAMPs),从而启动炎症反应[12]。

慢性炎症不仅影响 RPE 细胞的功能,还可能导致视网膜的进一步损伤[12]。例如,AMD 患者的补体系统激活与疾病进展密切相关,特别是补体因子 H (CFH)基因的变异被认为是 AMD 的重要易感因素之一[14]。这种补体系统失调可能导致局部免疫反应的过度激活,从而引发视网膜组织损伤和持续的炎症反应[15]。在干性 AMD 中,补体过度激活与玻璃膜疣形成及地理性萎缩扩展相关[8];在湿性 AMD 中,免疫驱动的促血管生成因子(如 VEGF)的上调及免疫细胞(如 M2 巨噬细胞)促新生血管作用更为关键[10]。

在治疗方面,针对炎症反应的干预措施日益受到重视。研究者正积极探索利用抗炎药物、免疫调节剂以及传统中药等多种方法,以期减轻 AMD 的炎症反应,从而减缓或逆转视力丧失的进程[16]。例如,已有研究发现某些中药成分能够抑制 RPE 细胞中的氧化应激和炎症反应,为 AMD 的治疗提供了新的思路[17]。此外,针对巨噬细胞的特异性治疗策略也显示出潜在的应用前景,有望为 AMD 的未来治疗提供新的方向[13]。本文旨在对炎症和免疫在 AMD 中的作用机制、生物标志物的研究进展以及潜在治疗策略进行系统回顾和深入分析,为未来的研究和临床实践提供参考。

2. 主体

2.1. 炎症反应的机制

2.1.1. 炎症因子的释放

炎症因子是机体在遭受感染、损伤或其他刺激时释放的生物活性分子,主要包括细胞因子、趋化因子和急性期蛋白等[18]。这些因子的释放是炎症反应的起始环节,能够募集免疫细胞至损伤部位并启动局部免疫应答[19]。例如,肿瘤坏死因子 α (TNF- α)和白细胞介素-1 β (IL-1 β)是两种关键的促炎因子,它们通过激活下游信号通路,促进其他炎症因子的产生,进而加剧局部炎症应答[16]。在 AMD 的病理背景下,炎症因子的过度释放可能导致视网膜细胞损伤和死亡,进一步加速疾病进展[3]。干性 AMD 中,低水平的慢性促炎因子与 RPE 功能障碍和玻璃膜疣积累相关[20];湿性 AMD 中,促炎因子与促血管生成介质相互放大,促进脉络膜新生血管(CNV)形成[21] [22]。

2.1.2. 细胞因子的作用

细胞因子的平衡在维持组织稳态中发挥着至关重要的作用。多种促炎和抗炎细胞因子在炎症过程中协同作用,既能促进炎症进程,也能在适当的时机抑制反应,以防止过度损伤[23]。以白细胞介素 6 (IL-6)为例,其在炎症反应中具有双重功能,在炎症初期能够增强免疫应答,而在恢复期则有助于抑制炎症扩散[24]。在 AMD 中,细胞因子的异常表达与疾病的发生发展密切相关,尤其是在老年患者中,慢性炎症可能导致细胞因子的持续释放,进而加剧视网膜损伤和功能障碍[25]。干性 AMD 倾向于出现慢性低度炎症及抗炎因子补偿不足,导致 RPE-小体吞噬障碍与线粒体功能下调[9] [26];湿性 AMD 中,IL-6、IL-8 及 VEGF 等上调,与 M2 型巨噬细胞分泌的抗炎/促修复因子(如 IL-10)共同构建“促血管生成”的免疫微环境,推动 CNV 形成[2] [10]。

2.1.3. 炎症信号通路的激活

炎症信号通路的激活是炎症反应的关键环节,涉及多种信号转导途径,如核因子 κ B (NF- κ B)、丝裂原活化蛋白激酶(MAPK)和 Janus 激酶 - 信号转导及转录激活因子通路(JAK-STAT)等[27]。以 NF- κ B 信号通路为例,其在炎症反应中发挥核心调控作用,能够调节多种促炎因子的表达[28]。在 AMD 的病理过程中,NF- κ B 信号通路的过度激活可能导致 RPE 细胞凋亡和视网膜神经节细胞损伤,从而影响患者的视功能[29]。MAPK 通路则调控细胞因子的释放和免疫细胞活化,进一步加剧 AMD 的病理进程[30]。干扰素- γ (IFN- γ)通过 Janus 激酶 1-2 (JAK1-2)/信号转导和转录激活因子 1 (STAT1)/溶质载体家族 7 成员 11 (SLC7A11)信号通路诱导 RPE 细胞铁死亡,而铁死亡与玻璃膜疣形成、炎症反应密切相关,抑制铁死亡

或减少 IFN- γ 可能作为 AMD 的一种治疗策略[31]。

除传统通路外, 环鸟苷酸-腺苷酸合成酶-干扰素基因刺激因子(cGAS-STING)在 RPE 中因线粒体 DNA 泄露或核酸应激被激活, 驱动 I 型干扰素与炎症反应, 加速组织退化, 在干性 AMD 中更为显著[32]; 补体旁路的失衡与 CFH 变异可放大局部炎症与吞噬压力, 促进 RPE 功能障碍与玻璃膜疣形成[8]; 免疫细胞代谢重编程(糖酵解/氧化代谢切换)影响小胶质细胞与巨噬细胞的促炎/修复表型, 进而改变 AMD 的炎症与血管生成[33] [34]。

2.2. 免疫系统在 AMD 中的角色

2.2.1. 先天性免疫与适应性免疫

先天性免疫与适应性免疫系统在 AMD 的病理生理机制中均具有重要的调控作用[2]。先天性免疫是机体的第一道防线, 主要由巨噬细胞、树突状细胞和其他免疫细胞组成, 并通过识别病原体和清除细胞碎片来维持眼部稳态[1]。研究表明, AMD 患者的眼内环境中存在显著的炎症反应, 特别是巨噬细胞和小胶质细胞的活化, 这些细胞通过分泌细胞因子和趋化因子促进局部炎症[35]。而适应性免疫则依赖于 B 细胞和 T 细胞, 其中 T 细胞在调节免疫反应和维持免疫耐受方面起着至关重要的作用[36]。近年来的研究指出, AMD 的发生与免疫系统失调密切相关, 特别是适应性免疫的异常激活可能导致自身免疫反应, 进而加剧视网膜损伤[37]。干性 AMD 更体现为先天性免疫的慢性、低度激活(补体/小胶质细胞) [20] [38]; 湿性 AMD 中适应性免疫与先天免疫交织, T 细胞与 B 细胞介导的细胞因子网络与 VEGF 通路协同促进 CNV [2] [10]。

2.2.2. B 细胞与 T 细胞的相互作用

B 细胞与 T 细胞之间的相互作用在 AMD 的免疫反应中至关重要。B 细胞主要通过产生抗体发挥其功能, 而 T 细胞则通过分泌多种细胞因子来调节 B 细胞的增殖与活性[39]。研究发现, AMD 患者 B 细胞和 T 细胞之间的相互作用受到显著影响, 尤其是在慢性炎症背景下, 这种相互作用可能导致 B 细胞异常激活和抗体产生, 进而加剧视网膜损伤[40]。例如, T 细胞分泌的 IL-21 等细胞因子促进 B 细胞的增殖和抗体产生, 在 AMD 中, T 细胞功能失调可能导致 B 细胞产生自身抗体, 进而引发自身免疫反应[37]。因此, 针对这种相互作用的调控可能为未来 AMD 的治疗提供新的思路。

2.2.3. 免疫调节与炎症

随着年龄的增长, 机体的免疫功能逐渐下降, 容易出现慢性低级别炎症, 即所谓的“炎症老化”[41]。在 AMD 患者中, 免疫调节机制失衡使得局部炎症持续存在, 对视网膜细胞产生长期的慢性刺激, 进而导致视网膜细胞损伤和死亡[42]。研究显示, 补体系统激活和小胶质细胞过度活化是 AMD 中炎症反应的主要驱动因素, 这些因素不仅促进病变进展, 而且可能导致视网膜进一步损伤[43]。巨噬细胞是 AMD 病变中的关键炎症细胞, 可调节免疫反应并影响疾病进展[13]。各种免疫细胞, 包括小胶质细胞、巨噬细胞和髓系抑制细胞(MDSCs), 通过视网膜黄斑硬化症形成、视网膜变性和脉络膜新生血管等过程促进 AMD 的发展[35] [44]。因此, 针对炎症反应的干预措施, 例如使用抗炎药物或调节免疫反应的治疗, 有望减缓 AMD 进展并改善患者视功能[45]。

2.3. 生物标志物的研究进展

2.3.1. 炎症相关生物标志物

基于近期研究, 炎症相关生物标志物在 AMD 的诊断和预后评估中具有潜在应用价值[46]。例如, 炎症小体蛋白(包括 ASC 和 IL-18)、C 反应蛋白(CRP)和肿瘤坏死因子 α (TNF- α) 等标志物水平的升高与 AMD

的发生和进展密切相关[35][47]。此外,补体系统特别是旁路途径的过度激活也被认为是 AMD 病理生理的重要组成部分。CFH 的遗传多态性是 AMD 最重要的遗传风险因素之一,这种变异会影响补体因子 H 的功能,使其对补体系统的调节能力下降,从而导致慢性炎症和氧化应激加剧,加速 AMD 的发展[14][15][48]。在干性 AMD(尤其是地理性萎缩)中,ASC、IL-18、C3 裂解产物及 CFH 相关标志物与病灶扩展密切相关[8][49];湿性 AMD 中,炎症标志物常与 VEGF 水平、基质金属蛋白酶(MMP)与内皮激活指标(如细胞间粘附分子-1 (ICAM-1))共同评估 CNV 活动度[50][51]。这些炎症相关生物标志物不仅可以作为疾病活动的指示,而且可能为新型抗炎治疗提供靶点。

2.3.2. 免疫相关生物标志物

除炎症因子外,免疫细胞及其分泌的细胞因子变化同样具有指示作用。近年来,研究发现,特定免疫细胞及其分泌的细胞因子在 AMD 的不同阶段呈现出不同的表达模式[52]。例如,巨噬细胞和小胶质细胞在 AMD 的病理过程中发挥重要作用,它们通过释放促炎因子和调节局部免疫反应影响视网膜稳态[53]。与此同时,近期研究发现,补体 C1s (C1S)、肾上腺髓质素(ADM)和早期生长反应蛋白 5 样分子(IER5L)等有望成为 AMD 的诊断生物标志物,它们与 AMD 组织中的免疫细胞浸润呈现相关性[54]。微小 RNA (miRNA)作为新兴的生物标志物,已被证实在 AMD 的炎症和免疫应答中起重要作用,特定 miRNA 的表达变化可能与 AMD 进展相关[55]。

干性 AMD 中 miRNA 谱更偏向炎症、代谢通路与 RPE 稳态调控,例如 miR-34a、miR-146a 等被发现与炎症小体、氧化应激及线粒体功能障碍密切相关[56][57];湿性 AMD 中,miRNA 表达更集中于血管生成、内皮细胞迁移及免疫极化相关通路,如 miR-126 和 miR-505 等可调控 VEGF、MMP9 及 M2 型巨噬细胞极化,参与 CNV 形成[58][59]。这些免疫相关标志物的研究为理解 AMD 的复杂病理机制提供了新的视角,并有望为个体化治疗策略的制定奠定基础。

2.3.3. 生物标志物在 AMD 早期诊断中的应用

通过检测血清中的炎症和免疫相关生物标志物,研究者能够在临床症状出现之前识别出高风险个体[60]。例如,某些特定 miRNA 与炎症因子组合检测方法在区分正常老年人与 AMD 患者方面已显示出较高的敏感性和特异性[45]。研究通过质谱蛋白质组学技术识别了 AMD 的潜在生物标志物:血清转铁蛋白(TF)、载脂蛋白 A1 (APOA1)、补体 C3 (C3)和脂质运载蛋白-1 (LCN1),这些生物标志物有助于了解疾病机制并有助于早期诊断[61]。随着技术进步,液体活检等新兴检测方法的应用使得生物标志物检测更为便捷高效[61]。这些进展不仅提高了 AMD 的早期诊断能力,也为临床治疗策略制定提供新的思路,未来有望通过整合多种生物标志物,建立更精准的 AMD 早期筛查体系[62]。在应用层面,可分别构建干性 AMD 风险评分(偏重补体与炎症小体组合),如 CFH、C3 裂解产物、ASC 与 IL-18 等标志物已被证实与地理性萎缩扩展密切相关[8][49];湿性 AMD 活动度评分可整合 VEGF 水平、炎症标志物(如 IL-6、TNF- α)与内皮功能指标(如 ICAM-1),用于评估 CNV 活性与治疗反应[2][10],从而提升分型与分层管理的准确度。

2.4. 潜在的治疗策略

2.4.1. 抗炎药物

鉴于慢性炎症在 AMD 中的关键作用,抗炎药物的应用成为当前重要的探索方向之一。已有研究指出,通过抑制炎症介质的释放可以有效减轻视网膜内炎症水平,从而延缓 RPE 细胞的退化[55]。例如,长链多不饱和脂肪酸(LCPUFA)已被发现可调节 AMD 中的炎症反应,其通过代谢成促炎和抗炎代谢物影响免疫应答[62]。此外,cGAS-STING 信号通路激活与 RPE 细胞退化有关,抑制该通路的药物,如溴结构域蛋白 4 (BRD4)抑制剂 JQ1,已显示出减轻氧化应激引起的视网膜炎症和退化的潜力[32]。研究表明,

补体系统抑制剂 Pegcetacoplan (APL-2)、Avacincaptad pegol (Zimura®)可以减少炎症引起的补体级联反应,从而减缓干性年龄相关性黄斑变性中地理萎缩病灶的发展[43] [63]。因此,抗炎药物的应用不仅可减轻AMD症状,而且可能在疾病早期发挥预防作用。抗炎策略在干性AMD中的核心目标为减炎、护RPE与延缓GA扩展;在湿性AMD中,抗炎治疗作为抗VEGF的辅助手段,用于降低复发活动度与免疫驱动的血管生成。

2.4.2. 免疫调节疗法

当前关于免疫调控的研究不断深入,针对免疫系统功能异常的治疗方法也越发被重视。随着对AMD病理机制的深入理解,研究者开始探索如何通过调节免疫反应以改善患者视功能[64]。研究指出,MDSCs在AMD进展中可能发挥双重作用:在某些情况下,它们可以抑制过度免疫反应,从而减轻炎症;但在其他情况下,则可能促进疾病进展[45]。因此,针对MDSCs的免疫调节策略有望为AMD治疗提供新的思路。干扰素和其他免疫调节剂在调节视网膜免疫微环境中亦可能发挥作用,进而影响AMD进展[65]。基因疗法GT005将补体因子I(CFI)基因递送至视网膜,以调节补体级联反应,减少炎症,并潜在减缓地理性萎缩进展[66]。基因疗法同样对湿性AMD有用,如RGX-314让视网膜细胞持续产生抗VEGF蛋白,减少新生血管形成;ADVM-022用于引入阿柏西普的编码序列,旨在长期减少病变区域的新生血管[67]。干性AMD免疫调节优先靶向补体、炎症小体与RPE代谢稳态;湿性AMD免疫调节需与抗VEGF协同,抑制M2极化与促血管免疫通路。

2.4.3. 生物制剂的应用

近年来,新型生物制剂的开发为AMD治疗带来了新的希望。这些生物制剂包括针对特定炎症介质的单克隆抗体及其他生物制剂,能够精确靶向与AMD相关的病理过程[16]。例如,针对IL-6和TNF- α 等炎症因子的抗体已在多种炎症性疾病中表现出良好疗效,未来亦可能应用于AMD治疗[68]。随着制药技术的发展,利用纳米技术增强生物制剂的靶向性和生物相容性,可以提高治疗效果并减少不良反应[69]。共组装和缓释的天然药用纳米粒子可以抑制血管生成、减少炎症和抵消氧化应激,从而治疗年龄相关性黄斑变性[70]。此外,双特异性融合蛋白同步靶向VEGF与补体C3b/C4b,有望在湿性AMD中同时抑制血管生成与炎症放大环路[71];在干性AMD中,前瞻性生物制剂聚焦补体关键节点与炎症小体抑制[49]。

抗VEGF治疗在湿性AMD中已证实显著改善视力与解剖学指标,但复发与耐受问题提示需要免疫调控与抗炎联合策略[72] [73];在干性AMD的地理萎缩中,补体抑制剂如Pegcetacoplan和Avacincaptad pegol显示出减缓病灶扩展的潜力[74] [75]。面向转化实践,建议:①按干/湿分型建立治疗组合(干性:补体/炎症小体 $\pm$ 代谢稳态[76];湿性:抗VEGF $\pm$ 免疫表型重塑[10]);②将生物标志物用于疗效监测与复发预警(湿性:VEGF/炎症组合[2];干性:补体/炎症小体组合[49])。

3. 结论

近年来,炎症与免疫反应在AMD研究中的重要性日益凸显。随着对其机制认识的不断深入,越来越多的证据表明,炎症和免疫反应不仅是病理变化的结果,更是推动疾病进程的关键动力。炎症反应的激活与免疫系统功能失调相互作用,共同引发视网膜细胞的损伤,最终导致视力下降。这一认识为开发新型治疗策略提供了新的视角,特别是在探索针对炎症和免疫调控的干预方法上具有重要意义。

然而,不同研究之间关于炎症和免疫在AMD中作用的结果和观点仍存在一定分歧,这需要我们在评价相关研究时保持批判性与开放性的态度。一方面,部分研究侧重于强调特定炎症因子在病理过程中的作用;另一方面,也有研究指出其他因素在疾病进展中可能具有同等或更为重要的影响。为了更全面深入理解AMD的复杂性,未来的研究应重点开展多中心、大规模的临床试验,以验证潜在生物标志物

的临床价值和治疗靶点。同时,通过跨学科合作,整合基础研究与临床实践,将有助于进一步推动新疗法的探索和应用。

在这一基础上,未来的工作应着力于验证这些生物标志物在临床中的应用效果,以便能够在疾病早期就识别出高风险患者并及时进行干预,进而改善患者的预后和生活质量。随着个体化医疗的逐步推进,根据患者具体情况调整治疗方案也将成为未来研究的一个重要方向。

总之,炎症与免疫反应在 AMD 的发展过程中发挥着举足轻重的作用。通过对这些机制的持续探讨,我们不仅能够为 AMD 的防治提供坚实的理论依据,还将为临床实践中制定更合理的干预方案提供指导。唯有不断深入研究与探索,才能最终找到更为有效的治疗策略,从而提高患者的视功能和生活质量。

参考文献

- [1] Fleckenstein, M., Keenan, T.D.L., Guymer, R.H., Chakravarthy, U., Schmitz-Valckenberg, S., Klaver, C.C., *et al.* (2021) Age-Related Macular Degeneration. *Nature Reviews Disease Primers*, 7, Article No. 31. <https://doi.org/10.1038/s41572-021-00265-2>
- [2] Tan, W., Zou, J., Yoshida, S., Jiang, B. and Zhou, Y. (2020) The Role of Inflammation in Age-Related Macular Degeneration. *International Journal of Biological Sciences*, 16, 2989-3001. <https://doi.org/10.7150/ijbs.49890>
- [3] Garcia-Garcia, J., Usategui-Martin, R., Sanabria, M.R., Fernandez-Perez, E., Telleria, J.J. and Coco-Martin, R.M. (2022) Pathophysiology of Age-Related Macular Degeneration: Implications for Treatment. *Ophthalmic Research*, 65, 615-636. <https://doi.org/10.1159/000524942>
- [4] Wong, J.H.C., Ma, J.Y.W., Jobling, A.I., Brandli, A., Greferath, U., Fletcher, E.L., *et al.* (2022) Exploring the Pathogenesis of Age-Related Macular Degeneration: A Review of the Interplay between Retinal Pigment Epithelium Dysfunction and the Innate Immune System. *Frontiers in Neuroscience*, 16, Article 1009599. <https://doi.org/10.3389/fnins.2022.1009599>
- [5] Stepp, M.A. and Menko, A.S. (2021) Immune Responses to Injury and Their Links to Eye Disease. *Translational Research*, 236, 52-71. <https://doi.org/10.1016/j.trsl.2021.05.005>
- [6] Fursova, A.Z., Derbeneva, A.S., Vasilyeva, M.S., Niculich, I.F., Tarasov, M.S., Gamza, Y.A., *et al.* (2022) New Findings on Pathogenetic Mechanisms in the Development of Age-Related Macular Degeneration. *Vestnik oftal'mologii*, 138, 120-130. <https://doi.org/10.17116/oftalma2022138021120>
- [7] Tang, S., Yang, J., Xiao, B., Wang, Y., Lei, Y., Lai, D., *et al.* (2024) Aberrant Lipid Metabolism and Complement Activation in Age-Related Macular Degeneration. *Investigative Ophthalmology & Visual Science*, 65, 20. <https://doi.org/10.1167/iovs.65.12.20>
- [8] Wilke, G.A. and Apte, R.S. (2024) Complement Regulation in the Eye: Implications for Age-Related Macular Degeneration. *Journal of Clinical Investigation*, 134, e178296. <https://doi.org/10.1172/jci178296>
- [9] Datta, S., Cano, M., Ebrahimi, K., Wang, L. and Handa, J.T. (2017) The Impact of Oxidative Stress and Inflammation on RPE Degeneration in Non-Neovascular AMD. *Progress in Retinal and Eye Research*, 60, 201-218. <https://doi.org/10.1016/j.preteyeres.2017.03.002>
- [10] Zhan, P., Cui, Y., Cao, Y., Bao, X., Wu, M., Yang, Q., *et al.* (2022) PGE2 Promotes Macrophage Recruitment and Neovascularization in Murine Wet-Type AMD Models. *Cell Communication and Signaling*, 20, Article No. 155. <https://doi.org/10.1186/s12964-022-00973-6>
- [11] Liu, X., Guo, A., Tu, Y., Li, W., Li, L., Liu, W., *et al.* (2020) Fruquintinib Inhibits VEGF/VEGFR2 Axis of Choroidal Endothelial Cells and M1-Type Macrophages to Protect against Mouse Laser-Induced Choroidal Neovascularization. *Cell Death & Disease*, 11, Article No. 1016. <https://doi.org/10.1038/s41419-020-03222-1>
- [12] Klettner, A. and Roeder, J. (2021) Retinal Pigment Epithelium Expressed Toll-Like Receptors and Their Potential Role in Age-Related Macular Degeneration. *International Journal of Molecular Sciences*, 22, Article 8387. <https://doi.org/10.3390/ijms22168387>
- [13] Zhao, Q. and Lai, K. (2024) Role of Immune Inflammation Regulated by Macrophage in the Pathogenesis of Age-Related Macular Degeneration. *Experimental Eye Research*, 239, Article ID: 109770. <https://doi.org/10.1016/j.exer.2023.109770>
- [14] Nielsen, M.K., Subhi, Y., Falk, M., Singh, A., Sørensen, T.L., Nissen, M.H., *et al.* (2023) Complement Factor H Y402H Polymorphism Results in Diminishing CD4⁺ T Cells and Increasing C-Reactive Protein in Plasma. *Scientific Reports*, 13, Article No. 19414. <https://doi.org/10.1038/s41598-023-46827-0>
- [15] Ermakova, N.A. (2018) The Role of Inflammation in Age-Related Macular Degeneration. *Vestnik oftal'mologii*, 134, 116-123. <https://doi.org/10.17116/oftalma2018134061116>

- [16] Fabre, M., Mateo, L., Lamaa, D., Baillif, S., Pagès, G., Demange, L., *et al.* (2022) Recent Advances in Age-Related Macular Degeneration Therapies. *Molecules*, **27**, Article 5089. <https://doi.org/10.3390/molecules27165089>
- [17] Cao, Y., Li, X., Tchiveleket, G.M., Li, X., Zhou, X., He, Z., *et al.* (2022) Bioinformatical and Biochemical Analyses on the Protective Role of Traditional Chinese Medicine against Age-Related Macular Degeneration. *Current Eye Research*, **47**, 1450-1462. <https://doi.org/10.1080/02713683.2022.2108456>
- [18] Gauldie, J. (2020) Acute and Chronic Inflammation. In: Snape, J. and Collins, S.M., Eds., *Effects of Immune Cells and Inflammation on Smooth Muscle and Enteric Nerves*, CRC Press, 1-9. <https://doi.org/10.1201/9780367813024-1>
- [19] Sierawska, O., Małkowska, P., Taskin, C., Hryniewicz, R., Mertowska, P., Grywalska, E., *et al.* (2022) Innate Immune System Response to Burn Damage—Focus on Cytokine Alteration. *International Journal of Molecular Sciences*, **23**, Article 716. <https://doi.org/10.3390/ijms23020716>
- [20] Keenan, T.D.L., Toso, M., Pappas, C., Nichols, L., Bishop, P.N. and Hageman, G.S. (2015) Assessment of Proteins Associated with Complement Activation and Inflammation in Maculae of Human Donors Homozygous Risk at Chromosome 1 *CFH*-to-*F13B*. *Investigative Ophthalmology & Visual Science*, **56**, 4870-4879. <https://doi.org/10.1167/iovs.15-17009>
- [21] Lurier, E.B., Dalton, D., Dampier, W., Raman, P., Nassiri, S., Ferraro, N.M., *et al.* (2017) Transcriptome Analysis of IL-10-Stimulated (M2c) Macrophages by Next-Generation Sequencing. *Immunobiology*, **222**, 847-856. <https://doi.org/10.1016/j.imbio.2017.02.006>
- [22] Sasaki, F., Koga, T., Ohba, M., Sacki, K., Okuno, T., Ishikawa, K., *et al.* (2018) Leukotriene B4 Promotes Neovascularization and Macrophage Recruitment in Murine Wet-Type AMD Models. *JCI Insight*, **3**, e96902. <https://doi.org/10.1172/jci.insight.96902>
- [23] Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., *et al.* (2021) Inflammation and Tumor Progression: Signaling Pathways and Targeted Intervention. *Signal Transduction and Targeted Therapy*, **6**, Article No. 263. <https://doi.org/10.1038/s41392-021-00658-5>
- [24] Yang, Y., Zhou, H., Huang, X., Wu, C., Zheng, K., Deng, J., *et al.* (2024) Innate Immune and Proinflammatory Signals Activate the Hippo Pathway via a Tak1-Stripak-Tao Axis. *Nature Communications*, **15**, Article No. 145. <https://doi.org/10.1038/s41467-023-44542-y>
- [25] Bhumika, Bora, N.S. and Bora, P.S. (2024) Genetic Insights into Age-Related Macular Degeneration. *Biomedicines*, **12**, Article 1479. <https://doi.org/10.3390/biomedicines12071479>
- [26] Ochoa Hernández, M.E., Lewis-Luján, L.M., Burboa Zazueta, M.G., Del Castillo Castro, T., De La Re Vega, E., Gálvez-Ruiz, J.C., *et al.* (2025) Role of Oxidative Stress and Inflammation in Age Related Macular Degeneration: Insights into the Retinal Pigment Epithelium (RPE). *International Journal of Molecular Sciences*, **26**, Article 3463. <https://doi.org/10.3390/ijms26083463>
- [27] Chen, Y., Fang, Z., Yi, X., Wei, X. and Jiang, D. (2023) The Interaction between Ferroptosis and Inflammatory Signaling Pathways. *Cell Death & Disease*, **14**, Article No. 205. <https://doi.org/10.1038/s41419-023-05716-0>
- [28] Cao, B., Zhao, Y., Luo, Q., Chen, Y., Xu, T. and Sun, Y. (2023) Vinculin B Inhibits NF- κ B Signaling Pathway by Targeting MyD88 in Miiuy Croaker, *Miichthys miiuy*. *Fish & Shellfish Immunology*, **135**, Article ID: 108683. <https://doi.org/10.1016/j.fsi.2023.108683>
- [29] Kureshi, C.T. and Dougan, S.K. (2025) Cytokines in Cancer. *Cancer Cell*, **43**, 15-35. <https://doi.org/10.1016/j.ccell.2024.11.011>
- [30] Li, J., Zhai, Y. and Tang, M. (2024) Integrative Function of Histone Deacetylase 3 in Inflammation. *Molecular Biology Reports*, **51**, Article No. 83. <https://doi.org/10.1007/s11033-023-09077-x>
- [31] Wei, T., Zhang, M., Zheng, X., Xie, T., Wang, W., Zou, J., *et al.* (2021) Interferon- γ Induces Retinal Pigment Epithelial Cell Ferroptosis by a JAK1-2/STAT1/SLC7A11 Signaling Pathway in Age-Related Macular Degeneration. *The FEBS Journal*, **289**, 1968-1983. <https://doi.org/10.1111/febs.16272>
- [32] Zou, M., Ke, Q., Nie, Q., Qi, R., Zhu, X., Liu, W., *et al.* (2022) Inhibition of cGAS-STING by JQ1 Alleviates Oxidative Stress-Induced Retina Inflammation and Degeneration. *Cell Death & Differentiation*, **29**, 1816-1833. <https://doi.org/10.1038/s41418-022-00967-4>
- [33] Liu, Y., Xu, R., Gu, H., Zhang, E., Qu, J., Cao, W., *et al.* (2021) Metabolic Reprogramming in Macrophage Responses. *Biomarker Research*, **9**, Article No. 1. <https://doi.org/10.1186/s40364-020-00251-y>
- [34] Viola, A., Munari, F., Sánchez-Rodríguez, R., Scolaro, T. and Castegna, A. (2019) The Metabolic Signature of Macrophage Responses. *Frontiers in Immunology*, **10**, Article 1462. <https://doi.org/10.3389/fimmu.2019.01462>
- [35] Zhang, Y. and Wong, W.T. (2021) Innate Immunity in Age-Related Macular Degeneration. In: Chew, E.Y. and Swaroop, A., Eds., *Age-Related Macular Degeneration: From Clinic to Genes and Back to Patient Management*, Springer, 121-141. https://doi.org/10.1007/978-3-030-66014-7_5

- [36] Chapman, N.M. and Chi, H. (2022) Metabolic Adaptation of Lymphocytes in Immunity and Disease. *Immunity*, **55**, 14-30. <https://doi.org/10.1016/j.immuni.2021.12.012>
- [37] Thomas, C.J., Mirza, R.G. and Gill, M.K. (2021) Age-Related Macular Degeneration. *Medical Clinics of North America*, **105**, 473-491. <https://doi.org/10.1016/j.mcna.2021.01.003>
- [38] Vecino, E., Rodriguez, F.D., Ruzafa, N., Pereiro, X. and Sharma, S.C. (2016) Glia-Neuron Interactions in the Mammalian Retina. *Progress in Retinal and Eye Research*, **51**, 1-40. <https://doi.org/10.1016/j.preteyeres.2015.06.003>
- [39] Wang, W., Lin, P., Wang, S., Zhang, G., Chen, C., Lu, X., *et al.* (2023) In-Depth Mining of Single-Cell Transcriptome Reveals the Key Immune-Regulated Loops in Age-Related Macular Degeneration. *Frontiers in Molecular Neuroscience*, **16**, Article 1173123. <https://doi.org/10.3389/fnmol.2023.1173123>
- [40] Behnke, V., Wolf, A. and Langmann, T. (2020) The Role of Lymphocytes and Phagocytes in Age-Related Macular Degeneration (AMD). *Cellular and Molecular Life Sciences*, **77**, 781-788. <https://doi.org/10.1007/s00018-019-03419-4>
- [41] Lee, K., Flores, R.R., Jang, I.H., Saathoff, A. and Robbins, P.D. (2022) Immune Senescence, Immunosenescence and Aging. *Frontiers in Aging*, **3**, Article 900028. <https://doi.org/10.3389/fragi.2022.900028>
- [42] Heloterä, H. and Kaarniranta, K. (2022) A Linkage between Angiogenesis and Inflammation in Neovascular Age-Related Macular Degeneration. *Cells*, **11**, Article 3453. <https://doi.org/10.3390/cells11213453>
- [43] Park, Y.G., Park, Y.S. and Kim, I. (2021) Complement System and Potential Therapeutics in Age-Related Macular Degeneration. *International Journal of Molecular Sciences*, **22**, Article 6851. <https://doi.org/10.3390/ijms22136851>
- [44] Kauppinen, A., Kaarniranta, K. and Salminen, A. (2020) Potential Role of Myeloid-Derived Suppressor Cells (MDSCs) in Age-Related Macular Degeneration (AMD). *Frontiers in Immunology*, **11**, Article 384. <https://doi.org/10.3389/fimmu.2020.00384>
- [45] Allingham, M.J., Lokszejn, A., Cousins, S.W. and Mettu, P.S. (2021) Immunological Aspects of Age-Related Macular Degeneration. In: Chew, E.Y. and Swaroop, A., Eds., *Age-Related Macular Degeneration*, Springer, 143-189. https://doi.org/10.1007/978-3-030-66014-7_6
- [46] Chaudhuri, M., Hassan, Y., Bakka Vemana, P.P.S., Bellary Pattanashetty, M.S., Abdin, Z.U. and Siddiqui, H.F. (2023) Age-related Macular Degeneration: An Exponentially Emerging Imminent Threat of Visual Impairment and Irreversible Blindness. *Cureus*, **15**, e39624. <https://doi.org/10.7759/cureus.39624>
- [47] Weaver, C., Cyr, B., de Rivero Vaccari, J.C. and de Rivero Vaccari, J.P. (2020) Inflammasome Proteins as Inflammatory Biomarkers of Age-Related Macular Degeneration. *Translational Vision Science & Technology*, **9**, 27. <https://doi.org/10.1167/tvst.9.13.27>
- [48] Romero-Vazquez, S., Llorens, V., Soler-Boronat, A., Figueras-Roca, M., Adan, A. and Molins, B. (2021) Interlink between Inflammation and Oxidative Stress in Age-Related Macular Degeneration: Role of Complement Factor H. *Biomedicines*, **9**, Article 763. <https://doi.org/10.3390/biomedicines9070763>
- [49] Marnaros, A.G. (2013) NLRP3 Inflammasome Blockade Inhibits VEGF-A-Induced Age-Related Macular Degeneration. *Cell Reports*, **4**, 945-958. <https://doi.org/10.1016/j.celrep.2013.08.002>
- [50] Ilhan, N., Daglioglu, M.C., Ilhan, O., Coskun, M., Tuzcu, E.A., Kahraman, H., *et al.* (2014) Assessment of Neutrophil/Lymphocyte Ratio in Patients with Age-Related Macular Degeneration. *Ocular Immunology and Inflammation*, **23**, 287-290. <https://doi.org/10.3109/09273948.2014.921715>
- [51] Zhang, B., Wang, D., Ji, T., Shi, L. and Yu, J. (2016) Overexpression of LncRNA ANRIL Up-Regulates VEGF Expression and Promotes Angiogenesis of Diabetes Mellitus Combined with Cerebral Infarction by Activating NF- κ B Signaling Pathway in a Rat Model. *Oncotarget*, **8**, 17347-17359. <https://doi.org/10.18632/oncotarget.14468>
- [52] Khan, A.H., Chowder, I. and Lotery, A.J. (2023) Beyond the Complement Cascade: Insights into Systemic Immunosenescence and Inflammation in Age-Related Macular Degeneration and Current Barriers to Treatment. *Cells*, **12**, Article 1708. <https://doi.org/10.3390/cells12131708>
- [53] Armento, A., Ueffing, M. and Clark, S.J. (2021) The Complement System in Age-Related Macular Degeneration. *Cellular and Molecular Life Sciences*, **78**, 4487-4505. <https://doi.org/10.1007/s00018-021-03796-9>
- [54] Zeng, Y., Yin, X., Chen, C. and Xing, Y. (2021) Identification of Diagnostic Biomarkers and Their Correlation with Immune Infiltration in Age-Related Macular Degeneration. *Diagnostics*, **11**, Article 1079. <https://doi.org/10.3390/diagnostics11061079>
- [55] Xu, G., Zhang, J. and Tang, L. (2023) Inflammation in Diabetic Retinopathy: Possible Roles in Pathogenesis and Potential Implications for Therapy. *Neural Regeneration Research*, **18**, 976-982. <https://doi.org/10.4103/1673-5374.355743>
- [56] Jun, S., Datta, S., Wang, L., Pegany, R., Cano, M. and Handa, J.T. (2019) The Impact of Lipids, Lipid Oxidation, and Inflammation on AMD, and the Potential Role of miRNAs on Lipid Metabolism in the RPE. *Experimental Eye Research*, **181**, 346-355. <https://doi.org/10.1016/j.exer.2018.09.023>
- [57] Urbańska, K., Stępień, P.W., Nowakowska, K.N., Stefaniak, M., Osial, N., Chorągiewicz, T., *et al.* (2022) The Role of Dysregulated miRNAs in the Pathogenesis, Diagnosis and Treatment of Age-Related Macular Degeneration. *International*

- Journal of Molecular Sciences*, **23**, Article 7761. <https://doi.org/10.3390/ijms23147761>
- [58] Wang, L., Lee, A., Wigg, J., Peshavariya, H., Liu, P. and Zhang, H. (2016) miR-126 Regulation of Angiogenesis in Age-Related Macular Degeneration in CNV Mouse Model. *International Journal of Molecular Sciences*, **17**, Article 895. <https://doi.org/10.3390/ijms17060895>
- [59] Zhao, S., Lu, L., Liu, Q., Chen, J., Yuan, Q., Qiu, S., *et al.* (2019) miR-505 Promotes M2 Polarization in Choroidal Neovascularization Model Mice by Targeting Transmembrane Protein 229B. *Scandinavian Journal of Immunology*, **90**, e12832. <https://doi.org/10.1111/sji.12832>
- [60] Han, D. and He, X. (2023) Screening for Biomarkers in Age-Related Macular Degeneration. *Heliyon*, **9**, e16981. <https://doi.org/10.1016/j.heliyon.2023.e16981>
- [61] Guo, H., Li, J. and Lu, P. (2023) Systematic Review and Meta-Analysis of Mass Spectrometry Proteomics Applied to Ocular Fluids to Assess Potential Biomarkers of Age-Related Macular Degeneration. *BMC Ophthalmology*, **23**, Article No. 507. <https://doi.org/10.1186/s12886-023-03237-0>
- [62] Ren, J., Ren, A., Deng, X., Huang, Z., Jiang, Z., Li, Z., *et al.* (2022) Long-Chain Polyunsaturated Fatty Acids and Their Metabolites Regulate Inflammation in Age-Related Macular Degeneration. *Journal of Inflammation Research*, **15**, 865-880. <https://doi.org/10.2147/jir.s347231>
- [63] Jaffe, G.J., Westby, K., Csaky, K.G., Monés, J., Pearlman, J.A., Patel, S.S., *et al.* (2021) C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration: A Randomized Pivotal Phase 2/3 Trial. *Ophthalmology*, **128**, 576-586. <https://doi.org/10.1016/j.ophtha.2020.08.027>
- [64] Potilinski, M.C., Tate, P.S., Lorenc, V.E. and Gallo, J.E. (2021) New Insights into Oxidative Stress and Immune Mechanisms Involved in Age-Related Macular Degeneration Tackled by Novel Therapies. *Neuropharmacology*, **188**, Article ID: 108513. <https://doi.org/10.1016/j.neuropharm.2021.108513>
- [65] Wang, Y., Gao, S., Cao, F., Yang, H., Lei, F. and Hou, S. (2024) Ocular Immune-related Diseases: Molecular Mechanisms and Therapy. *MedComm*, **5**, e70021. <https://doi.org/10.1002/mco2.70021>
- [66] Nielsen, J., MacLaren, R.E., Heier, J.S., Steel, D., Ivanova, T., Sivaprasad, S., *et al.* (2022) Preliminary Results from a First-In-Human Phase I/II Gene Therapy Study (FOCUS) of Subretinally Delivered GT005, an Investigational AAV2 Vector, in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration. *Investigative Ophthalmology & Visual Science*, **63**, 1504.
- [67] Guimaraes, T.A.C.D., Georgiou, M., Bainbridge, J.W.B. and Michaelides, M. (2020) Gene Therapy for Neovascular Age-Related Macular Degeneration: Rationale, Clinical Trials and Future Directions. *British Journal of Ophthalmology*, **105**, 151-157. <https://doi.org/10.1136/bjophthalmol-2020-316195>
- [68] Wang, X., Wang, T., Lam, E., Alvarez, D. and Sun, Y. (2023) Ocular Vascular Diseases: From Retinal Immune Privilege to Inflammation. *International Journal of Molecular Sciences*, **24**, Article 12090. <https://doi.org/10.3390/ijms241512090>
- [69] Placha, D. and Jampilek, J. (2021) Chronic Inflammatory Diseases, Anti-Inflammatory Agents and Their Delivery Nanosystems. *Pharmaceutics*, **13**, Article 64. <https://doi.org/10.3390/pharmaceutics13010064>
- [70] Shen, J., Chen, L., Lv, X., Liu, N., Miao, Y., Zhang, Q., *et al.* (2024) Emerging Co-Assembled and Sustained Released Natural Medicinal Nanoparticles for Multitarget Therapy of Choroidal Neovascularization. *Advanced Materials*, **36**, Article ID: 2314095. <https://doi.org/10.1002/adma.202314095>
- [71] Ke, X., Wu, Y., Yu, X., Yang, S., Luo, S., Qing, X., *et al.* (2024) Combined Complement Inhibitors and Anti-VEGF Therapy for the Treatment of Dry Age-Related Macular Degeneration (AMD). *Investigative Ophthalmology & Visual Science*, **65**, 5317.
- [72] Heier, J.S., Brown, D.M., Chong, V., Korobelnik, J., Kaiser, P.K., Nguyen, Q.D., *et al.* (2012) Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-Related Macular Degeneration. *Ophthalmology*, **119**, 2537-2548. <https://doi.org/10.1016/j.ophtha.2012.09.006>
- [73] Holz, F.G., Tadayoni, R., Beatty, S., Berger, A., Cereda, M.G., Cortez, R., *et al.* (2014) Multi-Country Real-Life Experience of Anti-Vascular Endothelial Growth Factor Therapy for Wet Age-Related Macular Degeneration. *British Journal of Ophthalmology*, **99**, 220-226. <https://doi.org/10.1136/bjophthalmol-2014-305327>
- [74] Liao, D.S., Grossi, F.V., El Mehdi, D., Gerber, M.R., Brown, D.M., Heier, J.S., *et al.* (2020) Complement C3 Inhibitor Pegcetacoplan for Geographic Atrophy Secondary to Age-Related Macular Degeneration: A Randomized Phase 2 Trial. *Ophthalmology*, **127**, 186-195. <https://doi.org/10.1016/j.ophtha.2019.07.011>
- [75] Patel, S.S., Lally, D.R., Hsu, J., Wykoff, C.C., Eichenbaum, D., Heier, J.S., *et al.* (2023) Avacincaptad Pegol for Geographic Atrophy Secondary to Age-Related Macular Degeneration: 18-Month Findings from the GATHER1 Trial. *Eye*, **37**, 3551-3557. <https://doi.org/10.1038/s41433-023-02497-w>
- [76] Lin, J.B., Serghiou, S., Miller, J.W. and Vavvas, D.G. (2022) Systemic Complement Activation Profiles in Nonexudative Age-Related Macular Degeneration: A Systematic Review. *Ophthalmology Science*, **2**, Article ID: 100118. <https://doi.org/10.1016/j.xops.2022.100118>