·文献综述·

自身免疫性风湿病相关干眼的病理机制研究进展

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摘要

自身免疫性风湿病是一组由多种致病因素参与,发病机制与自身免疫功能紊乱有关的多系统疾病,眼部受累是其常见的表现,致病机制涉及系统性免疫失调与局部炎症微环境紊乱,导致泪膜功能障碍、角膜结膜上皮损伤及眼表炎症。文章系统综述干燥综合征、类风湿性关节炎、系统性红斑狼疮、强直性脊柱炎及 IgG4 相关疾病等自身免疫性风湿病相关干眼的特点及病理机制,为临床精准干预提供理论依据。

关键词:自身免疫性风湿病;病理机制;干眼
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Research progress on pathological mechanisms of dry eye disease associated with autoimmune rheumatic diseases

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Abstract

• Autoimmune rheumatic diseases are a group of multisystem disorders characterized by autoimmune dysfunction. Ocular involvement is common in these conditions, and the underlying pathogenic mechanisms involve systemic immune dysregulation and local inflammatory microenvironment disturbances, leading to tear film dysfunction, corneal and conjunctival epithelial damage, and ocular surface inflammation. This article systematically reviews the clinical characteristics and pathological mechanisms of dry eye disease associated with autoimmune rheumatic diseases, including Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and immunoglobulin-G4 related disease (IgG4-RD), aiming to provide a theoretical basis for precise clinical intervention.

• KEYWORDS: autoimmune rheumatic diseases; pathological mechanisms; dry eye disease

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0 引言

自身免疫性风湿病(autoimmune rheumatic diseases, ARDs)是一组由多种致病因素参与的,与自身免疫功能紊乱有关的多系统疾病,包括原发性干燥综合征(primary Sjögren's syndrome, pSS)、类风湿性关节炎(rheumatoid arthritis, RA)、系统性红斑狼疮(systemic lupus erythematosus, SLE)、强直性脊柱炎(ankylosing spondylitis, AS)和 IgG4 相关疾病(immunoglobulin-G4 related disease, IgG4-RD)等[1]。ARDs 患者中,约 20%-40%伴发眼表病变,干眼(dry eye disease, DED)是最常见的眼部并发症[2]。

DED 为多因素引起的慢性眼表疾病,严重影响患者的生活质量。全身因素是导致 DED 的危险因素之一。ARDs 作为一种系统性疾病与 DED 的发病密切相关。与不伴 ARDs 的 DED 患者相比,伴有 ARDs 的 DED 患者症状更明显,眼表细胞损伤和凋亡更严重,治疗也更复杂且预后不理想[3]。因此,深入理解 ARDs 相关干眼的发病机制具有重要临床意义。本文检索了 PubMed、Web of Science、CNKI 及万方数据库,时间范围为 2000 年 1 月至 2026 年 3 月,语种限定为中文及英文,以"自身免疫性风湿病""干眼""病理机制""干燥综合征""类风湿性关节炎""系统性红斑狼疮""强直性脊柱炎""IgG4 相关性疾病"及对应的英文检索词进行组合检索,就各类 ARDs 相关干眼的特点及病理机制作一综述,以期为临床精准干预提供理论依据。

1 ARDs 相关 DED 的共同病理机制

泪液的稳态是由泪液功能单位(lacrimal functional unit, LFU)动态维持,LFU 由眼表、分泌附属结构及神经三大组分构成[4]。DED 是炎症、代谢、神经、激素及物理等因素共同作用的结果。DEWS Ⅱ将 DED 分为水液缺乏型干眼(aqueous-deficient dry eye, ADDE)、蒸发过强型干眼(evaporative dry eye, EDE)及混合型干眼[4]。DEWS

Ⅲ[5]则进一步关注病因驱动模式,将其细分为泪膜缺陷、眼睑异常、眼表异常及系统性疾病四大领域。ARDs 相关 DED 即由系统性疾病所致。ARDs 相关干眼的病因及发病机制虽未完全阐明,但已明确其存在共同的免疫病理通路。目前认为与遗传易感性与环境暴露因素、先天免疫和适应性免疫系统激活、细胞因子失衡、微生物群改变有关。

1.1 遗传易感性与环境暴露因素作用 遗传易感性与环境暴露因素的相互作用,是 ARDs 相关干眼发病的核心驱动力[6]。ARDs 相关 DED 是全身免疫异常在眼部的具体表现。

1.1.1 遗传易感性 人类白细胞抗原(human leucocyte antigen, HLA)在免疫系统中负责将抗原片段呈递给 T 细胞,是迄今为止与 ARDs 关联最强的遗传易感因子[7-8]。不同 *HLA* 等位基因与特定疾病的风险紧密相关:*HLA*-Ⅱ类基因在 pSS 抗原递呈中起核心作用,其中 *HLA-DQB*1、*HLA-DRB*1 等位基因关联最强[9-10];*HLA-DRB*1 亦是 RA 的最强遗传风险因素[11],同时被鉴定为 IgG4-RD 的主要易感基因[12];*HLA-DR*2 和 *HLA-DR*3 等位基因与 SLE 发病相关[13];*HLA-B*27 与 AS 的发病有极强的关联[14]。上述 HLA 风险等位基因的存在,使得泪腺和眼表上皮在环境因素触发下更易成为自身免疫攻击的靶点。

非 *HLA* 基因也在 ARDs 易感性中发挥重要作用。*PTPN*22 编码的淋巴样酪氨酸磷酸酶参与 T 细胞受体信号的负向调节,其风险变异(rs2476601)可使 ARDs 的患病风险增加约 1.8 倍[15]。*STAT*4 是 IL-12 介导的 TH1 分化关键转录因子,也是多种 ARDs 共享的易感基因。*IRF*5 可驱动巨噬细胞向促炎的 M1 表型极化,与多种自身免疫疾病密切相关[16],目前也是 ARDs 靶向治疗的重要研究方向之一。

上述遗传易感基因的关联性由于种族遗传背景差异、样本量限制、疾病定义及亚表型差异等因素[17-19],部分研究结果尚不一致,因此未来研究应关注基因检测的种族适配性,并针对不同的疾病亚表型进行分层研究,以更精确地揭示 ARDs 相关 DED 的遗传基础。

1.1.2 环境暴露因素 环境因素作用于遗传易感个体,是触发和驱动疾病进程的关键。

1.1.2.1 空气污染 高浓度 CO、NO 和 CH4 能通过激活 IL-6等慢性炎症通路,显著增加 pSS 发病风险[20]。PM2.5/PM10 及 NO_2等直接接触眼表,通过氧化应激与炎症通路激活,导致角膜上皮凋亡,与 DED 发病显著相关[21]。

1.1.2.2 病毒感染 爱泼斯坦-巴尔病毒(Epstein-Barr virus,EBV)和巨细胞病毒(cytomegalovirus,CMV)与多种 ARDs 的发病相关,其他还有柯萨奇病毒、丙型肝炎病毒(hepatitis c virus, HCV)、细小病毒等[22-23]。病毒诱发 ARDs 并非单一途径,而是多种机制共同作用:(1)分子模拟,导致交叉免疫攻击[24-25]。这是目前最受关注的致病机制;(2)病毒直接感染泪腺和眼表上皮,启动局部自身免疫应答[26-27];(3)靶器官局部形成异位生发中心,持续产生致病性自身抗体[28];(4)激活固有免疫引发炎症风暴,直接抑制泪液分泌[29]。

1.1.2.3 吸烟及其他 吸烟是 RA 的明确风险因素,呈剂量依赖性[30-31]。但其与 DED 的关联尚存在争议[32-33]。另外,还存在其他共同的环境易感因素,包括维生素 D 缺乏、酒精和生活中的压力事件等[1,8,27]。

1.1.3 表观遗传修饰 表观遗传修饰是连接环境暴露与基因表达的“桥梁”[10],已成为近期研究的热点。在 ARDs 相关 DED 中,全基因组低甲基化与位点特异性高甲基化共存,如干扰素调节基因低甲基化,导致Ⅰ型干扰素(type Ⅰ interferons, IFN-Ⅰ)病理性高表达[34],而 FOXP3 启动子区域高甲基化导致调节性 T 细胞发育和功能缺陷[35]。METTL3 介导的 m6A 修饰可激活 STAT3/NLRP3 炎症小体,促进细胞焦亡和炎症反应[36-38]。m6A 阅读蛋白可激活 IFN-Ⅰ信号通路,启动自身免疫反应[39]。针对表观遗传和免疫代谢的干预正在兴起,如调节 m6A 修饰、抑制 M1 巨噬细胞极化等有望成为未来 ARDs 相关 DED 的精准治疗策略。

1.2 先天免疫和适应性免疫系统失调 环境触发因素激活 Toll 样受体(Toll-like receptors, TLRs),启动 IFN-Ⅰ/JAK-STAT 通路[40],上调趋化因子(CXCL9、CXCL10、CXCL13)表达,招募 CD4+ T 细胞和 B 细胞浸润外分泌腺诱导腺上皮细胞的初始失调[27]。IFN-Ⅰ通路的激活使 B 细胞活化因子(B cell activating factor, BAFF)基因表达升高。BAFF 作为先天性免疫和适应性免疫反应的交叉点[41],促进了自身反应性 B 细胞的存活和自身抗体的产生[42]。

Th17/Treg 免疫失衡是 ARDs 相关 DED 免疫失调的关键。在 TGF-β 和 IL-6 的作用下初始 T 细胞向 Th17 分化,Treg 细胞则存在功能受损甚至向促炎表型转化的争议[43]。IL-17 不仅促进中性粒细胞募集,还诱导基质金属蛋白酶(matrix metalloproteinase, MMP)表达,破坏腺体基质与导管结构,影响泪腺功能[44]。

此外,机械敏感离子通道 Piezo1/Piezo2 功能异常可导致白细胞过度表达细胞因子,可能参与 ARDs 免疫系统激活的初始环节[45-46]。

1.3 细胞因子失衡 ARDs 相关 DED 患者的泪液因子谱呈现复杂的失衡状态。IL-17、TNF-α、IL-1β、IL-6、IL-8 及 IL-21 等促炎因子普遍升高,IL-2、IL-4、IFN-γ 及表皮生长因子(epidermal growth factor, EGF)水平较低[47-49]。

这些细胞因子中,TNF-α、IL-1 等通过激活 NF-κB 通路,诱导 MMP-9 表达,破坏角膜上皮紧密连接和泪腺腺泡基底膜[50];IFN-γ 通过激活 JAK-STAT 通路促进泪腺上皮细胞凋亡[51];EGF 降低削弱 MAPK/ERK 通路介导的上皮修复能力;TNF-α 激活 MAPK/JNK 及 MAPK/p38 通路促进凋亡,导致泪腺分泌单位丢失[52-53]。上述细胞因子网络失衡共同构成 ARDs 相关 DED 的分子枢纽。

1.4 微生物群改变 眼表微生物群失调可引发持续炎症和泪膜不稳定而导致 DED 发病[54]。SS 患者存在肠道-眼-泪腺微生物组轴[55],共生细菌稳态遭到破坏后[56],机会致病菌的脂多糖可激活 TLR4/NF-κB 通路,上调 IL-1β、TNF-α 及 MMP-9,溶解角膜上皮,破坏泪膜稳定性[57-58]。另外,肠道菌群失调也参与 ARDs 相关 DED[56]:产丁酸菌耗竭导致外周 Treg 功能下降[59];促炎菌富集诱导 IL-1β、IL-6 及 IL-23 的产生,促使 CD4+T 细胞向 Th17 分化,导致 Th17/Treg 失衡[60]。然而,菌群失调在 ARDs 相关 DED 中是“因”还是“果”,现有的横断面研究尚无法推断,仍待进一步研究。

尽管存在上述共性,但不同 ARDs 相关 DED 的主导病理机制各有侧重。以下分述各病的特征性病理机制。

2 不同自身免疫性风湿病相关 DED 的特征性机制

ARDs 相关 DED 机制比较见表 1。

表 1 ARDs 相关 DED 机制比较

疾病	核心免疫特征	主要攻击靶点	DED 主导亚型	关键生物标志物	潜在治疗靶点
pSS	B 细胞过度活化、抗 SSA/SSB	泪腺	ADDE→混合型	抗 SSA/SSB、BAFF	BAFF、JAK
RA-SS	与 pSS 重叠	泪腺	ADDE	抗 SSA/SSB、RF	BAFF、TNF-α
RA-nonSS	Th1/Th17、TNF-α	睑板腺、角膜神经	混合型(EDE 为主)	RF、抗 CCP	TNF-α、IL-6
SLE	免疫复合物、抗 dsDNA	睑板腺、结膜	混合型	抗 dsDNA、C3	IFN、JAK
AS	IL-17/IL-23 轴、亚临床炎症	结膜杯状细胞	混合型	HLA-B27、CRP	IL-17
IgG4-ROD	纤维化、$IgG4^+$浆细胞	泪腺、睑板腺	混合型	血清 IgG4	TGF-β、JAK

2.1 pSS 相关 DED pSS 的特征是淋巴细胞增殖及进行性外分泌腺体损伤[61]。全球患病率为 0.5%-1%,我国为 0.3%-0.7%,在常见全身性自身免疫性疾病中位居前列[61]。约 95%的 pSS 患者有干眼症状[62]。

pSS 相关 DED 发病分为四个阶段[27,63]:遗传易感个体在环境因素触发下启动自身免疫,继而破坏泪腺导致水液缺乏,最终 LFU 受损进入 DED 恶性循环。其特异性机制包括:(1)BAFF 促进 B 细胞分化为浆细胞,产生特征性自身抗体:抗 SSA/Ro 和抗 SSB/La,分别见于 50%-70%和 25%-40%患者,可在临床症状出现前 18-20 a 检出[27]。CXCL13 等趋化因子促进 B 细胞在腺体内形成异位生发中心[64];(2)腺体上皮细胞异常高表达 MHC-Ⅱ类分子及 CD80/CD86、CD40,获得抗原递呈功能[65-66],激活 $CD4^+$ T 细胞并招募淋巴细胞向腺体归巢[66],形成"自身免疫性上皮炎";(3)抗 M3R 抗体通过补体介导细胞毒性诱导腺体细胞凋亡及竞争性阻断乙酰胆碱信号,导致腺体分泌衰竭[67]。诊断特异性高达 85%-97.5%[68]。

上述机制导致淋巴细胞浸润破坏泪腺组织,泪液分泌功能丧失,形成 ADDE[69]。高渗环境继发睑板腺功能障碍(meibomian gland dysfunction, MGD)和角膜神经损伤,形成 DED 的"恶性循环"。pSS 患者泪液中的 IL-1β、TNF-α 水平可达非 SS 干眼患者的 2-3 倍,且与角膜神经密度呈显著负相关[70],但尚无明确体征能清晰区分两者。腺体上皮细胞是免疫的启动者还是被动受累的靶细胞、B 细胞过度活化是主要驱动还是上游副产物,仍有待阐明。生物制剂在控制全身症状上有效,但对眼表炎症的改善作用有限[71],提示 pSS-DED 的治疗需全身及局部抗炎协同治疗。

2.2 RA 相关 DED RA 的主要表现是侵蚀性关节炎。在发达国家,RA 发病率为 0.5%-1%,我国约为 0.2%-0.4%[72]。RA 中 DED 患病率为 16%[2]。DED 严重程度与 RA 的疾病活动度无显著相关,而与病程相关[73-74]。RA 患者可分为继发 SS(RA-SS)与未继发 SS(RA-nonSS)[75],且两者发病机制不完全相同。

RA-SS 约占 RA 患者的 1%-31%[49],其眼部炎症与全身炎症活动密切相关,机制与 pSS 相关 DED 高度重叠。系统治疗 RA 后,DED 症状和角膜染色可得到改善[76]。RA-nonSS 患者出现 DED 与局部因素更相关,表现为混合型 DED:(1)RA 患者 MGD 发生率增高,且 MGD 与疾病活动参数相关。其自身免疫反应会攻击睑板腺组织,导致腺管阻塞和腺泡萎缩,而 RA 女性雄激素缺乏进一步增加 MGD 的风险[77];(2)RA 活动期患者泪液中 IL-1β、IL-6、TNF-α 及趋化因子(CCL3/4/5)水平显著高于单纯干眼患者[78]。TNF-α 和 IFN-γ 诱导结膜杯状细胞凋亡,泪膜黏蛋白层破坏[79]。TNF 抑制剂治疗可增加结膜杯状细胞的数量,缓解 DED[79]。此外,RA 疾病活动度增加与角膜神经纤维的丢失以及角膜敏感度的降低显著相关[80]。可导致不完全眨眼、MGD 以及 EDE。

因此对于 RA-nonSS 相关 DED 更需关注眼表免疫调节及 MGD 相关的治疗。MGD 是系统性炎症的波及还是局部病理主导尚存在争议。提示眼科医师除关注患者全身状况外,还需建立独立的眼表随访体系。

2.3 SLE 相关 DED SLE 主要特点是多系统受累及大量自身抗体[81]。全球发病率为(1.4-11.0)/10 万,我国约 14.09/10 万[82]。SLE 患者 DED 患病率为 16%,发病风险是健康人群的 4 倍以上[83]。

SLE 相关 DED 的特异性病理机制包括:(1)独立于继发性 SS:SLE 患者抗 SSA 抗体阳性率为 65.3%,其中 29.3% 的患者有 SS 症状[84]。SLE 相关 DED 症状并非完全由继发性 SS 引起。无 SS 的 SLE 患者,DED 的严重程度与抗双链 DNA(antidouble-stranded DNA, anti-dsDNA)抗体和补体 C3 显著相关,与 C4、红细胞沉降量(erythrocyte sedimentation rate, ESR)和抗核抗体(antinuclear antibody, ANA)无关[84];(2)SLEDAI-2K 评分和皮肤皮疹:两者是 SLE 相关 DED 的风险因素[85]。伴皮疹者风险为无皮疹者的 7 倍[85],提示皮肤与睑板腺可能共享免疫攻击靶点。即使 SLE 疾病活动指数不严重,患者仍可能有较为常见的眼睑异常[86]、睑板腺萎缩、腺周血管增生及淋巴结样炎症细胞浸润[87];(3)免疫复合物/补体介导的微血管损伤:抗心磷脂抗体(anticardiolipin antibody, ACL)等激活补体经典途径,导致眼表及睑板腺微血管内皮损伤、微血栓形成,引起腺泡细胞缺血性坏死和纤维化[88]。同时,泪腺及眼表沉积的免疫复合物启动补体级联反应,C5b-9 直接导致上皮细胞溶解,C3a/C5a 招募中性粒细胞释放 MMP-9,降解角膜上皮基底膜[89]。

综上,SLE 相关 DED 可由泪腺、睑板腺、结膜及角膜多结构受累引起,呈现混合型 DED 表现。临床上需警惕的是,SLE 患者的 DED 症状有时可能是神经精神系统性红斑狼疮累及视神经或脑干自主神经核团的早期表现[90]。对于伴有顽固性干眼且合并神经系统症状的 SLE 患者,眼科医师应及时建议其至风湿免疫科排查神经系统病因,避免延误病情。

2.4 AS 相关 DED AS 主要侵犯骶髂关节、脊柱、脊柱旁软组织及外周关节。HLA-B27 阳性率约 85%-90%[91]。AS 患病率初步调查为 0.3%左右,国内 AS 并发 DED 的相关报道较少,我国台湾地区调查显示,AS 组 DED 发病风险为非 AS 组的 1.947 倍[92]。

AS 相关 DED 特异性病理机制包括:(1)IL-17/IL-23 轴:Th17 细胞及其效应因子 IL-17 过度活化,驱动骶髂关节炎症,也是眼表破坏的核心[93]。IL-17 直接破坏角膜上皮紧密连接[44];TNF-α、IFN-γ 诱导结膜杯状细胞凋亡,结膜鳞状化生,并介导泪腺功能衰竭[79];(2)神经-免疫交

互:角膜 Piezo2 功能受损致其与朗格汉斯细胞(langerhans cell, LC)上的 Piezo1 串扰中断,使 LC 异常活化并放大下游 Th17 反应;同时,脊髓神经免疫交互可能将全身炎症信号传递至眼表,导致干眼症状的急性发作[46]。AS 患者角膜 LC 密度增加且形态异常,导致局部 Th17/Treg 失衡,加速了杯状细胞丢失和泪膜不稳定[46];(3)HLA-B27 介导的分子模拟:HLA-B27 不仅是 AS 的遗传标志,其重链错误折叠可激活未折叠蛋白反应,使角膜上皮细胞处于前炎状态。同时,HLA-B27 呈递的微生物肽可能被交叉反应性 T 细胞识别,导致眼表局部免疫攻击,引起急性前葡萄膜炎及隐匿的角膜上皮损伤[46]。

综上,AS 相关 DED 是由泪腺腺泡细胞受损、杯状细胞凋亡及角膜神经微环境失衡共同导致,表现为混合型 DED。然而,AS 患者常表现为"症状体征分离",这引发了神经感觉障碍是源于炎症直接损伤还是神经适应性重塑的争议,提示 AS 的眼表神经微环境损伤具有一定的独立性,单纯的抗炎治疗可能无法完全逆转已发生的角膜神经病变。

2.5 IgG4-RD 相关 DED IgG4-RD 特征为血清 IgG4 升高,受累组织中可见大量 $IgG4^+$浆细胞浸润、席纹状纤维化和闭塞性静脉炎。亚洲国家年发病率为(0.28-1.08)/10 万[94],泪腺受累占比 88%-98%[95]。22%的 IgG4 相关眼病(immunoglobulin-G4 related ophthalmic disease, IgG4-ROD)患者出现 DED 症状[96]。纤维化主导的组织破坏是其区别于其他 ARDs 相关 DED 的显著特征。

其特异性病理机制包括:(1)泪腺纤维化与 TGF-β/Smad 信号通路:IgG4-ROD 早期以淋巴细胞浸润为主,随着病程进展,席纹状纤维化和闭塞性静脉炎成为主导[97]。核心驱动因子 TGF-β1 通过结合 TGF-βⅡ型受体,磷酸化 Smad2/3,导致泪腺组织进行性纤维化替代[98],闭塞性静脉炎加重泪腺组织缺血性损伤[98]。最终泪腺腺泡结构被纤维组织取代,分泌功能不可逆性丧失,形成 ADDE;(2)MGD 与泪腺肿大:IgG4-ROD 患者睑板腺缺失率与发病年龄呈正相关,NITBUT 与发病年龄呈负相关,眼外器官受累越多泪液分泌越差,提示多系统受累加剧泪腺功能障碍[99]。另外,泪腺肿大导致患眼 NITBUT 更低[99],这可能与机械性压迫、泪液排出受阻以及局部炎症负荷加重有关。

综上,IgG4-ROD 相关 DED 是由泪腺纤维化和 MGD 共同导致的混合型 DED。目前研究尚处起步阶段,从炎症主导到纤维化主导的转变机制尚不清楚,其反映全身性疾病活动度还是局部组织不可逆损伤的结果,目前亦无定论。

3 结论与展望

上述五种 ARDs 相关 DED 虽各具特征,但共同的病理机制为"免疫-炎症"驱动的 LFU 损伤。然而,当前研究多聚焦于共同的炎症通路,对不同 ARDs 靶向攻击泪腺、睑板腺及角膜神经的特异性分子开关仍知之甚少。

与朱笑莹等[100]既往综述相比,本文聚焦于自身免疫性风湿病这一特定疾病群,深入剖析五种疾病相关 DED 的特异性免疫病理机制,并首次系统阐述 AS 和 IgG4-RD 相关 DED 的特征性机制,为临床精准干预提供更清晰的策略依据。

未来研究应聚焦于:(1)寻找不同 ARDs 中眼部的特异性趋化因子信号;(2)开发基于泪液生物标志物的无创分型诊断工具;(3)开展针对共同上游通路或疾病特异性靶点的临床试验。治疗应突破单纯"抗炎"思维,向"靶向特异性通路"和"阻断组织纤维化"转变。另外,眼科应与风湿免疫科紧密协作,在疾病不同阶段采取个体化治疗策略,以实现视觉功能保护与患者生活质量提升的双重目标。

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