

肠道菌群在葡萄膜炎中的作用与研究进展

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摘要

葡萄膜炎是一种涉及眼部多个结构的致盲性炎症性疾病, 严重时威胁患者的视力和心理健康。目前, 针对葡萄膜炎的治疗以糖皮质激素以及免疫抑制剂为主, 其存在副作用较多、易复发且治疗费用高昂等问题。近年来的研究表明, 肠道菌群可通过肠-眼轴在葡萄膜炎的发展中起作用, 其相关代谢物也对该疾病的进展具有重要影响, 调节肠道菌群或相关代谢物可能成为治疗葡萄膜炎的新途径。文章综述了肠道菌群与各葡萄膜炎相关疾病如系统性结节病、Vogt-小柳原田病、白塞病、多发性硬化症、鸟枪弹样葡萄膜炎的联系, 介绍益生菌和益生元、抗生素、免疫调节剂、噬菌体疗法和粪便微生物移植等菌群相关治疗的研究进展, 旨在为推动针对葡萄膜炎特异菌群及相关基因标志物的新疗法发展提供参考, 促进精准医疗的实现。

关键词: 肠道菌群; 葡萄膜炎; 肠-眼轴; 鸟枪弹样葡萄膜炎; 噬菌体疗法; 粪便微生物移植

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Role and research progress of gut microbiota in uveitis

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Abstract

• Uveitis is a blinding inflammatory disease that affects multiple structures within the eye, posing significant risks to patients' vision and mental health. Current treatments mainly involve glucocorticoids and immunosuppressants, which are associated with significant side effects, high relapse rates, and substantial costs. Recent research suggests that the gut microbiota may play a role in the development of uveitis through the gut-eye axis, with related metabolites also influencing disease progression. Modulating the gut microbiota or its metabolites could offer new therapeutic avenues for uveitis. This review explores the relationship between gut microbiota and various uveitis-associated diseases, such as systemic sarcoidosis, Vogt-Koyanagi-Harada syndrome, Behcet's disease, multiple sclerosis, and birdshot chorioretinopathy. It also discusses advancements in microbiota-related therapies, including probiotics and prebiotics, antibiotics, immunomodulators, phage therapy, and fecal microbiota transplantation. The aim is to provide a reference for the development of new therapies targeting specific microbial communities and genetic markers associated with uveitis, thereby promoting the realization of precision medicine.

• KEYWORDS: gut microbiota; uveitis; gut-eye axis; birdshot chorioretinopathy; phage therapy; fecal microbial transplantation

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0 引言

葡萄膜炎是发生于葡萄膜、玻璃体、视网膜及视网膜血管的炎症疾病的总称, 是全球关注的致盲性眼病之一^[1]。未及时治愈的葡萄膜炎严重威胁患者的视力健康及心理状态, 据研究显示, 葡萄膜炎患者焦虑、抑郁的占比达 16.7% 和 26.5%^[2]。当前我国对葡萄膜炎的治疗有药物和手术两种方式, 其中药物治疗虽有一定疗效, 但副作用较多, 病情易反复, 且治疗费用高昂, 我国葡萄膜炎患者人均医疗总费用就高达 2179.03±3293.66 元, 人均住院总费用占 69.46%^[3]。近年来, 许多研究都强调了肠-眼轴的存在, 菌群失调已在青光眼^[4]、干眼^[5]、年龄相关性黄斑病变^[6]、眼眶病^[7]和葡萄膜炎^[8]等多种眼部疾病的发展中起重要作用, 相关代谢物^[9]对葡萄膜炎也有着至关重要的影响。肠道菌群可能成为葡萄膜炎新的潜在治疗方式, 本文就肠道菌群在葡萄膜炎中的作用及研究进展进行综述。

1 肠道菌群及其代谢产物

肠道菌群是由 38 万亿^[10]微生物组成的复杂生态系统,主要包括厚壁菌门、拟杆菌门、放线菌门和变形菌门。它们具有多种功能,如促进食物消化^[11]、保护免受病原体侵害^[12]、合成氨基酸和维生素^[13]、代谢口服药物^[14]以及调节宿主的免疫系统^[15]。肠道菌群失调可能由多种因素引起,包括生活方式^[16]、抗生素使用^[17]等,从而使有益微生物和致病微生物之间稳态失衡,进而引发一系列疾病。

肠道菌群产生的代谢物包括短链脂肪酸(SCFA)、胆汁酸等,通过它们对应的受体信号调节宿主的代谢,在宿主体内发挥重要作用。SCFA 通过与 G 蛋白偶联受体结合^[18],激活并调节免疫细胞,促进肠道稳态的维持。SCFA 家族的丙酸^[19]和丁酸^[20]已被证明可以抑制炎症反应,减轻葡萄膜炎的症状,同时促进肠道稳态的维持。胆汁酸则通过与 G 蛋白偶联受体和/或核受体结合调节胆汁酸代谢^[9],从而抑制胆汁酸敏感细菌的生长,塑造并改变肠道菌群,如在高脂饮食的小鼠中,通过胆汁酸代谢的调节,而使厚壁菌门相对丰度增加而拟杆菌门相对丰度减少^[21]。除了短链脂肪酸和胆汁酸,肠道菌群还能合成叶酸、维生素 K、色氨酸、生物素等多种营养物质^[22],促进宿主健康。

2 肠道菌群参与葡萄膜炎的致病机制

一直以来,研究者都认为眼内环境是无菌的,但通过定量 PCR、透射电子显微镜负染色技术、直接培养和高通量测序技术^[23]及从动物体液^[24]中,确定了眼内微生物群的存在,肠道菌群与眼部疾病之间的关联与作用就是肠-眼轴。肠-眼轴已在视网膜变性^[25]、干眼^[26]、葡萄膜炎^[27]等多种眼部疾病中被证实。肠-眼轴的稳态维持对葡萄膜等眼部结构的健康至关重要,而其失调可能导致眼部发生炎症或损伤:(1)菌群失调可能通过抗原模拟或分子模拟机制参与葡萄膜炎的发生。具体来说,肠道细菌抗原可以模仿自身抗原诱导交叉反应,激活外周的视网膜特异性 T 细胞^[28],从而引发炎症。R161H 小鼠模型就通过模仿自身 IRBP 激活特异性 T 细胞诱发葡萄膜炎^[29]。(2)肠-眼轴的失调也可能通过肠道免疫稳态失调机制^[30]诱发葡萄膜炎。肠道菌群紊乱可能降低免疫激活的阈值,打破 Th17/Treg 的平衡,导致炎症因子过度产生,从而诱发疾病。(3)肠-眼轴的失调还可能通过肠道屏障破坏机制^[31]参与葡萄膜炎的发生。菌群失调可能导致肠道通透性增加,允许一些细菌产物渗漏到血管,如若定植在葡萄膜组织,触发免疫反应就可能诱发葡萄膜炎。(4)肠道菌群失调可能导致有益微生物群和抗炎代谢物的减少,从而进一步促进葡萄膜炎的发生^[32]。除了菌群本身,其代谢物也会经过肠-眼轴相关途径影响葡萄膜炎^[33]。总之,肠-眼轴在葡萄膜炎的致病机制中扮演着重要的角色,其稳态的维持可能是治疗葡萄膜炎的一种可行策略。

3 肠道菌群与葡萄膜炎

3.1 系统性结节病 结节病是一种慢性肉芽肿性疾病,与 HLA-DRB1 相关^[34],大约 30%-50%的系统性结节病患者会发展为葡萄膜炎。结节病相关葡萄膜炎其病因尚不明确,可能跟遗传、表观遗传和环境因素与未知抗原触发因素相互作用有关,其致病机制涉及复杂的免疫反应,包括

TLR2 介导的巨噬细胞活化,IL-6、IL-12、IL-18 和 TNF- α 炎症细胞因子的产生,CD4⁺T 细胞的激活,INF- γ 和 IL-2 的产生并分化 Th1 细胞的过程以及 Th17 细胞分泌 IL-17 等。持久的 T 细胞反应可能导致肉芽肿的形成^[35]。

分枝杆菌^[36]和痤疮丙酸杆菌^[34]被认为是结节病最相关的病原体,有研究表明分枝杆菌可能引起 IV 型免疫反应,即 T 细胞对结核分枝杆菌特异性抗原产生免疫反应。Nagata 等^[34]从 11 例结节病患者的视网膜活检中发现 9 例患者痤疮丙酸杆菌染色阳性,阳性率高达 82%,而在非结节性葡萄膜炎等其余对照组中未发现痤疮丙酸杆菌,痤疮丙酸杆菌可能参与与眼结节病的发病机制,但具体机制仍需进一步研究。

3.2 Vogt-小柳原田病 Vogt-小柳原田病(Vogt-Koyanagi-Harada disease, VKHD)是一种以双侧肉芽肿性全葡萄膜炎为特征的疾病,与 HLA-DRA 相关。近期研究指出,肠道菌群在 VKHD 的发病机制中可能发挥着重要作用^[37]。VKHD 患者肠道菌群丰富,菌群转移已被证实能显著加剧实验性自身免疫性葡萄膜炎(experimental autoimmune uveitis, EAU)的严重程度。在活动性 VKHD 患者中,观察到丁酸、乳酸和产甲烷细菌减少,这可能与普雷沃氏菌属的革兰阴性菌等机会致病菌的增加有关。值得注意的是,经过免疫抑制治疗后, VKHD 患者的肠道菌群有所恢复。此外, Ye 等^[37]对 54 例活动性 VKHD 患者进行基因分型并进行 LEfSe 分析,结果显示 HLA-DRA 上的风险等位基因与 VKHD 富集种属 *Bacteroides* sp.2.1.33B、*Paraprevotella clara* 呈正相关,与耗竭种属 *Alistipes finegoldii* 和 *Eubacterium eligens* 呈负相关,且没有观察到其他易感基因型与肠道微生物组成之间存在可检测的相关性,这些特异性改变的菌群可能作为 VKHD 微生物标记,有望用于辅助 VKHD 的诊断和治疗,以及预测治疗的有效性。

3.3 白塞病 白塞病(behcet disease, BD)是涉及复发性葡萄膜炎的多器官炎症,无葡萄膜炎 BD 患者和发生葡萄膜炎的 BD 患者的肠道菌群组成存在显著差异^[38]。BD 相关葡萄膜炎患者中, *Blautia*、*Coprococcus*、*Dorea* 和 *Lachnospiraceae* 这四种亚群减少, *Succinivibrionaceae*、*Bilophila* 和 *Stenotrophomonas* 增加^[39-40]。此外,不同疾病表型具有不同的分类群,其中 *Lachnospiraceae* NK4A136 在 BD 葡萄膜炎中具有特异性,该研究还在葡萄膜炎组中检测出 2.5%的密螺旋体,而在皮肤黏膜和血管中并未发现^[38]。将活动期 BD 患者的粪便移植到 EAU 小鼠体内会导致疾病加重、肠上皮屏障损伤以及促炎细胞因子 IFN- γ 和 IL-17 表达增加^[41]。此外,短链脂肪酸中丁酸、戊酸和丙酸减少^[41-42],丁酸对 Treg 的分化起促进作用,其减少可导致 Treg 相应减少,从而激活免疫病理 T 效应反应。

3.4 多发性硬化症 在一项来自 IMSMS^[43]联盟的研究中,多发性硬化症(multiple sclerosis, MS)和健康人的肠道细菌图谱之间存在显著差异,接受不同药物治疗的 MS 患者之间也存在差异。他们还发现了这些细菌可能潜在影响疾病产生和治疗反应的新机制。在 MS 相关的前葡萄膜炎或中葡萄膜炎中,也发现肠道菌群失调,促进 Treg 分化的梭状芽胞杆菌簇 IV 和 XIVa 减少^[44]。不过 MS 相关的葡萄膜炎的研究较少,且肠道菌群与 MS 存在联系的大多

数实验证据都来自小鼠研究,而临床试验与小鼠实验的结果并不完全一致,故其中的联系还需进一步研究验证。

3.5 HLA-B27 相关性急性前葡萄膜炎 HLA-B27 与急性前葡萄膜炎(acute anterior uveitis, AAU)的显著相关性已被证实,约有1/3的HLA-B27阳性AS患者发生AAU,其发病机制可能涉及HLA-B27依赖性生态失调、肠道通透性改变和分子模拟^[31]。有研究测试AAU患者和健康人的粪便样本,结果显示肠道菌群的组成没有明显差异,但其代谢表型存在显著的差异性^[45]。在其他HLA相关疾病中,基因型已被发现会影响肠道菌群的组成,比如HLA-DQ2基因型改变了肠道微生物组,使婴儿易患乳糜泻^[46]。因此,根据代谢表型差异,我们可以进一步研究微生物与HLA的关系,这可能有助于推测HLA相关AAU的发病机制。

也有研究表明微生物肽结合HLA-B27分子可能在眼睛和关节等靶器官中诱导免疫反应^[47],HLA-B27也明显影响肠道菌群,在生态失调之前,动物结肠中的抗菌肽Reg III和S100A8可能就已上调^[48],钙结合蛋白在内源性后葡萄膜炎中升高。血清钙结合蛋白已被建议作为幼年特发性关节伴有葡萄膜炎的生物标志物^[49]。

3.6 鸟枪弹样葡萄膜炎 鸟枪弹样视网膜脉络膜病变(birdshot retinochoroidopathy, BSRC)也称为鸟枪弹样或玻璃质状脉络膜视网膜炎^[50],是一种罕见的葡萄膜炎,与HLA-A29基因相关,BSRC还与Th17细胞分泌IL-17有关,不过这种自身免疫的触发因素还有待研究。肠道菌群在动物模型中被证实能直接激活Th17^[51],在BSRC患者的血液中,也被发现Th17细胞数量和Th17细胞因子水平升高^[52]。由白色念珠菌^[53]感染诱导的Th17细胞会持续存在并加重自身免疫性疾病,也会通过破坏血-视网膜屏障引起内源性眼内炎^[54]。

尽管BSRC患者肠道菌群相关的研究尚少,但针对HLA-A29阳性个体的研究表明^[55],他们的肠道菌群与HLA-B27阳性或HLA-DRB1^[56]阳性对照组相似,肠道菌群与HLA-A29抗原呈递中的相互作用在炎症性肺病和肠病中也起着重要作用。因此,我们可以进一步研究HLA-A29在BSRC疾病机制中抗原呈递相互作用,将HLA-A29与BSRC中的Th17反应联系起来也是一个值得深入研究的问题。未来,靶向IL-17治疗BSRC可能是一个潜在的治疗方向。

4 葡萄膜炎的肠道菌群治疗

4.1 益生菌和益生元 益生菌是活的微生物,可以改善宿主微生态平衡,抵抗肠道病原体,保护宿主肠道免受外源性病原体感染,并增加SCFA的产生^[57]。它们主要通过调节肠道上皮细胞中JAK/STAT和NF- κ B通路^[58]发挥抗炎作用,促进组织愈合,改善细胞对应激的反应,以及调节T细胞、树突状细胞、NK细胞、B淋巴细胞和巨噬细胞的活性^[59]。益生菌预防EAU可能需要活性微生物体^[60],研究发现,给予定植大肠杆菌Nissle 1917(EcN)的小鼠可防止EAU的发展,而高压灭菌的EcN治疗效果不明显,这表明菌株选择对治疗成功至关重要。此外,联合使用益生菌与类固醇可提高视力并限制眼部炎症^[61]。而IRT5益生菌可以通过降低致病性CD4⁺T细胞的百分比来调

节EAU^[62]。

益生元是一组被肠道菌群降解的营养素,其降解产物是对宿主有益的脂肪酸。益生元包括低聚半乳糖、果聚糖、菊粉、葡萄糖衍生的低聚糖和淀粉等^[63]。可以选择性地促进有益抗炎细菌生长,但在眼部疾病中单独使用益生元效果不明显,联合使用益生菌和益生元则有明显的疗效,能够减轻葡萄膜炎患者的症状和炎症参数^[64]。

益生菌和益生元对葡萄膜炎菌群稳态的维持具有潜在的治疗作用,虽然目前相关研究尚不充分,但已有的结果为进一步临床试验提供了支持。

4.2 抗生素 抗生素在EAU中的治疗效果和影响值得关注。抗生素如米诺环素^[65]和小檗碱^[66]能够通过抑制视网膜小胶质细胞活化、调整肠道微环境等方式,显著改善EAU。然而,单用抗生素治疗^[67]存在局限性,可能因细菌来源的多样性导致效果不明显,但广谱抗生素的使用也可能导致耐药菌株增加。因此,有必要寻找更窄谱的药物以消除目标细菌群落。

4.3 免疫调节剂 免疫调节剂作为治疗EAU的一种选择,具有抑制不同微生物生长的功能。例如柳氮磺吡啶可降低血管通透性,并改善关节疾病和HLA-B27相关葡萄膜炎^[68]。环孢素等免疫抑制剂的使用可以减少活动性VKHD患者的生态失调,降低眼内炎症^[37]。此外,甲氨蝶呤和吗替麦考酚酯^[69]可能通过影响肠道细菌变化,从而消除EAU。因此,免疫抑制剂的使用对肠道菌群具有一定影响,靶向生物制剂为调控菌群治疗葡萄膜炎提供了新的前景。

4.4 噬菌体疗法 近年来,噬菌体疗法作为抗生素治疗的替代物备受关注。噬菌体介导的菌群调节已被证明可消除耐药性感染^[70]。研究人员还发现,噬菌体可以作为治疗溃疡性角膜炎的潜在候选者^[71],具有很高的治疗潜力。噬菌体芽孢杆菌溶酶在细菌性眼内炎和角膜炎中的治疗潜力也得到了验证^[72]。噬菌体不仅能去除敏感细菌,还能对菌株整体产生影响。噬菌体对微生物群的精准调节显示出治疗菌群相关疾病的潜力,与传统的抗生素相比,噬菌体对靶向细菌具有极高的选择性和良好的人体生物安全性,为眼内药物递送提供一种新的途径。

尽管与葡萄膜炎相关的噬菌体研究较少,但随着葡萄膜炎相关的特定微生物群标志物的深入研究,靶向特定菌群标志物的噬菌体治疗势不可挡,噬菌体、肠道菌群和葡萄膜炎之间的关联治疗可以在未来进一步证实。

4.5 粪便微生物移植 粪便微生物移植(fecal microbial transplants, FMT)是一种潜在的治疗方法,通过替换肠道菌群来治疗肠外疾病。已有研究表明FMT在治疗干眼等疾病具有一定疗效^[73],尽管该研究受限较多且症状改善主要依赖于患者的主观报告,但它们也为FMT治疗自身免疫性眼病的进展提供了一定的依据。有研究通过将年轻小鼠菌群转移到老年小鼠中,使老年小鼠视网膜的健康状况得到改善^[25]。该实验发现,FMT可以降低炎症性补体C3水平,并恢复关键蛋白RPE65的表达水平,这表明FMT可以通过改善肠道菌群来减轻相关炎症反应。尽管FMT尚未广泛应用于葡萄膜炎的治疗,但其在该领域的应用仍值得深入研究,在临床治疗中,FMT的普及还有待

进一步探索和发展。

4.6 其他治疗 其他疗法包括饮食干预和菌群代谢物调节等。一些研究表明, 高脂饮食可增加拟杆菌丰度, 而高纤维摄入能使普氏菌丰度增加^[74-75], 根据个体肠道菌群的特点, 积极调整饮食结构可能有助于缓解葡萄膜炎^[76]。虽然饮食调整不是针对特定靶点的疗法, 但基于饮食和生活方式的支持治疗有助于恢复免疫系统稳态, 然而, 肠道菌群的复杂性, 使饮食调整仍然面临挑战, 因为很难确定需要添加或减少的成分, 以及如何持续获益。代谢物也是一个重要的治疗靶点, 一些药物如非诺贝特^[77] 被发现可以减轻高脂肪饮食诱导小鼠的视网膜炎, 并逆转代谢产物下降。其他如腹腔内注射的 SCFA^[78] 通过血眼屏障可在眼睛中被检测到, 达到减轻眼部炎症的效果。丙酸的口服可以抑制效应 T 细胞迁移, 减轻 EAU 的严重程度^[19]。然而, 肠道菌群产生数千种代谢物, 因此我们需要鉴定葡萄膜炎特异性代谢物, 以实现精准调节和治疗。

5 结论

总体而言, 这些研究强调了肠道菌群在调节葡萄膜炎发病机制和治疗方面的潜在贡献, 在宿主基因组中鉴定并干预与葡萄膜炎的易感性、治疗反应性有关的基因多态性是实现葡萄膜炎精准医疗的核心, 如结节病与 HLD-DRB1、VKHD 与 HLA-DRA、BSRC 与 HLA-A29、AS 相关的葡萄膜炎与 HLA-B27 等, 了解葡萄膜炎、基因型、肠道菌群之间的联系可能推进新疗法的发展。然而, 靶向肠道菌群的治疗方法仍处于初步阶段, 在葡萄膜炎领域的研究较少, 存在一定的局限性。由于肠道菌群的多样性, 我们难以精确靶向特定的葡萄膜炎相关菌群。此外, 单独使用抗生素的效果不明显, 而广谱抗生素易增加耐药性, 饮食调整也难以确定具体应添加或减少的成分, 以及如何持续获益。不过, 噬菌体疗法因其高选择性和生物安全性显示出巨大的潜力, FMT、免疫调节剂、益生菌等菌群疗法也在减轻葡萄膜炎炎症反应和防止疾病进展方面展示了疗效, 在未来的研究中我们也可寻找更窄谱的抗生素以消除目标细菌群落, 各类葡萄膜炎都有其特异相关的菌群, 随着对肠道菌群与葡萄膜炎的深入了解与技术的进步, 未来有望研发出基于葡萄膜炎相关特异菌群标志物的高效疗法, 推进精准医疗的实现。

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参考文献

[1] Bonnet C, Brézin A. Uvéites, éléments d'orientation diagnostique. *J Français D'ophtalmologie*, 2020,43(2):145-151.
[2] Jin YY, Lin D, Dai ML, et al. Economic hardship, ocular complications, and poor self-reported visual function are predictors of mental problems in patients with uveitis. *Ocul Immunol Inflamm*, 2021, 29(6):1045-1055.
[3] 陈莉莉, 范长生. 我国葡萄膜炎患者治疗费用及疾病负担分析. *中国卫生经济*, 2022,41(6):72-74.
[4] Zhang YL, Zhou XJ, Lu Y. Gut microbiota and derived metabolomic

profiling in glaucoma with progressive neurodegeneration. *Front Cell Infect Microbiol*, 2022,12:968992.
[5] Lee K, Gwon H, Shim JJ, et al. Consumption of *Limosilactobacillus fermentum* inhibits corneal damage and inflammation in dry eye disease mouse model through regulating the gut microbiome. *Int J Mol Sci*, 2024, 25(6):3528.
[6] Xiao J, Zhang JY, Luo W, et al. The emerging role of gut microbiota in age-related macular degeneration. *Am J Pathol*, 2023,193(11):1627-1637.
[7] Biscarini F, Masetti G, Muller I, et al. Gut microbiome associated with Graves disease and Graves orbitopathy: the INDIGO multicenter European study. *J Clin Endocrinol Metab*, 2023,108(8):2065-2077.
[8] Zysset-Burri DC, Morandi S, Herzog EL, et al. The role of the gut microbiome in eye diseases. *Prog Retin Eye Res*, 2023,92:101117.
[9] Hu JP, Wang CK, Huang XY, et al. Gut microbiota-mediated secondary bile acids regulate dendritic cells to attenuate autoimmune uveitis through TGR5 signaling. *Cell Rep*, 2021,36(12):109726.
[10] Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biol*, 2016, 14(8):e1002533.
[11] Fang J, Yu CH, Li XJ, et al. Gut dysbiosis in nonalcoholic fatty liver disease: pathogenesis, diagnosis, and therapeutic implications. *Front Cell Infect Microbiol*, 2022,12:997018.
[12] Shayya NW, Foote MS, Langfeld LQ, et al. Human microbiota associated IL-10^{-/-} mice: A valuable enterocolitis model to dissect the interactions of *Campylobacter jejuni* with host immunity and gut microbiota. *Eur J Microbiol Immunol (Bp)*, 2023,12(4):107-122.
[13] Rowland I, Gibson G, Heinken A, et al. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr*, 2018,57(1):1-24.
[14] Kumar K, Dhoke GV, Sharma AK, et al. Mechanistic elucidation of amphetamine metabolism by tyramine oxidase from human gut microbiota using molecular dynamics simulations. *J Cell Biochem*, 2019, 120(7):11206-11215.
[15] Guo YL, Liu YJ, Rui BQ, et al. Crosstalk between the gut microbiota and innate lymphoid cells in intestinal mucosal immunity. *Front Immunol*, 2023,14:1171680.
[16] Liu JH, He ZY, Ma N, et al. Beneficial effects of dietary polyphenols on high-fat diet-induced obesity linking with modulation of gut microbiota. *J Agric Food Chem*, 2020,68(1):33-47.
[17] Andremont A, Cervesi J, Bandinelli PA, et al. Spare and repair the gut microbiota from antibiotic-induced dysbiosis: state-of-the-art. *Drug Discov Today*, 2021,26(9):2159-2163.
[18] Ratajczak W, Rył A, Mizerski A, et al. Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). *Acta Biochim Pol*, 2019,66(1):1-12.
[19] Nakamura YK, Janowitz C, Metea C, et al. Short chain fatty acids ameliorate immune-mediated uveitis partially by altering migration of lymphocytes from the intestine. *Sci Rep*, 2017,7(1):11745.
[20] Chen XQ, Su WR, Wan TS, et al. Sodium butyrate regulates Th17/Treg cell balance to ameliorate uveitis via the Nrf2/HO-1 pathway. *Biochem Pharmacol*, 2017,142:111-119.
[21] Wahlström A, Sayin SI, Marschall HU, et al. Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism. *Cell Metab*, 2016,24(1):41-50.
[22] Bäckhed F, Roswall J, Peng YQ, et al. Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe*, 2015,17(5):690-703.

- [23] Xue W, Li JJ, Zou Y, et al. Microbiota and ocular diseases. *Front Cell Infect Microbiol*, 2021,11:759333.
- [24] Deng YH, Ge XF, Li Y, et al. Identification of an intraocular microbiota. *Cell Discov*, 2021,7:13.
- [25] Parker A, Romano S, Ansoorge R, et al. Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain. *Microbiome*, 2022,10(1):68.
- [26] Bai XD, Xu Q, Zhang WN, et al. The gut-eye axis: correlation between the gut microbiota and autoimmune dry eye in individuals with sjögren syndrome. *Eye Contact Lens*, 2023,49(1):1-7.
- [27] Alfuzai R. The link between gastrointestinal microbiome and ocular disorders. *Clin Ophthalmol*, 2023,17:2133-2140.
- [28] Avni O, Koren O. Molecular (me) micry? *Cell Host Microbe*, 2018,23(5):576-578.
- [29] Horai R, Zúrate-Bladés CR, Dillenburg-Pilla P, et al. Microbiota-dependent activation of an autoreactive T cell receptor provokes autoimmunity in an immunologically privileged site. *Immunity*, 2015,43(2):343-353.
- [30] Zhuang ZC, Wang YQ, Zhu GJ, et al. Imbalance of Th17/Treg cells in pathogenesis of patients with human leukocyte antigen B27 associated acute anterior uveitis. *Sci Rep*, 2017,7:40414.
- [31] Parthasarathy R, Santiago F, McCluskey P, et al. The microbiome in HLA-B27-associated disease: implications for acute anterior uveitis and recommendations for future studies. *Trends Microbiol*, 2023,31(2):142-158.
- [32] Fu X, Chen Y, Chen D. The role of gut microbiome in autoimmune uveitis. *Ophthalmic Res*, 2021,64(2):168-177.
- [33] Scuderi G, Troiani E, Minnella AM. Gut microbiome in retina health: the crucial role of the gut-retina axis. *Front Microbiol*, 2021,12:726792.
- [34] Nagata K, Eishi Y, Uchida K, et al. Immunohistochemical detection of *Propionibacterium acnes* in the retinal granulomas in patients with ocular sarcoidosis. *Sci Rep*, 2017,7(1):15226.
- [35] Allegri P, Olivari S, Rissotto F, et al. Sarcoid uveitis: an intriguing challenger. *Medicina (Kaunas)*, 2022,58(7):898.
- [36] Fang CL, Huang H, Xu ZJ. Immunological evidence for the role of mycobacteria in sarcoidosis: a meta-analysis. *PLoS One*, 2016,11(8):e0154716.
- [37] Ye Z, Wu CY, Zhang N, et al. Altered gut microbiome composition in patients with Vogt-Koyanagi-Harada disease. *Gut Microbes*, 2020,11(3):539-555.
- [38] Yasar Bilge NS, Pérez Brocal V, Kasifoglu T, et al. Intestinal microbiota composition of patients with behçet's disease: differences between eye, mucocutaneous and vascular involvement. the rheuma-BIOTA study. *Clin Exp Rheumatol*, 2020,38(5):60-68.
- [39] Tecer D, Gogus F, Kalkançi A, et al. Succinivibrionaceae is dominant family in fecal microbiota of Behçet's Syndrome patients with uveitis. *PLoS One*, 2020,15(10):e0241691.
- [40] Wang QF, Wu S, Ye XS, et al. Gut microbial signatures and their functions in Behçet's uveitis and Vogt-Koyanagi-Harada disease. *J Autoimmun*, 2023,137:103055.
- [41] Wang QF, Yi SL, Su GN, et al. Changes in the gut microbiome contribute to the development of behçet's disease *via* adjuvant effects. *Front Cell Dev Biol*, 2021,9:716760.
- [42] Ye Z, Zhang N, Wu C, et al. A metagenomic study of the gut microbiome in Behçet's disease. *Microbiome*, 2018,6(1):135.
- [43] iMSMS Consortium Electronic address: sergio baranzini@ucsf.edu, iMSMS Consortium. Gut microbiome of multiple sclerosis patients and paired household healthy controls reveal associations with disease risk and course. *Cell*, 2022,185(19):3467-3486.e16.
- [44] Miyake S, Kim S, Suda W, et al. Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to clostridia XIVa and IV clusters. *PLoS One*, 2015,10(9):e0137429.
- [45] Huang XY, Ye Z, Cao QF, et al. Gut microbiota composition and fecal metabolic phenotype in patients with acute anterior uveitis. *Invest Ophthalmol Vis Sci*, 2018,59(3):1523-1531.
- [46] Olivares M, Neef A, Castillejo G, et al. The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. *Gut*, 2015,64(3):406-417.
- [47] Bodis G, Toth V, Schwarting A. Role of human leukocyte antigens (HLA) in autoimmune diseases. *Methods Mol Biol*, 2018,1802:11-29.
- [48] Asquith MJ, Stauffer P, Davin S, et al. Perturbed mucosal immunity and dysbiosis accompany clinical disease in a rat model of spondyloarthritis. *Arthritis Rheumatol*, 2016,68(9):2151-2162.
- [49] Walscheid K, Heiligenhaus A, Holzinger D, et al. Elevated S100A8/A9 and S100A12 serum levels reflect intraocular inflammation in juvenile idiopathic arthritis-associated uveitis: results from a pilot study. *Invest Ophthalmol Vis Sci*, 2015,56(13):7653-7660.
- [50] Pham BH, Uludag G, Hien DL, et al. Birdshot chorioretinopathy in early adulthood: review of current literature and case report. *Int Med Case Rep J*, 2023,16:815-831.
- [51] Horai R, Caspi RR. Microbiome and autoimmune uveitis. *Front Immunol*, 2019,10:232.
- [52] Kuiper JJ, Mutis T, de Jager W, et al. Intraocular interleukin-17 and proinflammatory cytokines in HLA-A29-associated birdshot chorioretinopathy. *Am J Ophthalmol*, 2011,152(2):177-182.e1.
- [53] Krebs CF, Reimers D, Zhao Y, et al. Pathogen-induced tissue-resident memory T_H17 (T_{RM}17) cells amplify autoimmune kidney disease. *Sci Immunol*, 2020,5(50):eaba4163.
- [54] Singh S, Singh S, Kumar A. Systemic *Candida albicans* infection in mice causes endogenous endophthalmitis via breaching the outer blood-retinal barrier. *Microbiol Spectr*, 2022,10(4):e0165822.
- [55] Sternes PR, Martin TM, Paley M, et al. HLA-a alleles including HLA-A29 affect the composition of the gut microbiome: a potential clue to the pathogenesis of birdshot retinochoroidopathy. *Sci Rep*, 2020,10:17636.
- [56] Asquith M, Sternes PR, Costello ME, et al. HLA alleles associated with risk of ankylosing spondylitis and rheumatoid arthritis influence the gut microbiome. *Arthritis Rheumatol*, 2019,71(10):1642-1650.
- [57] Liu Y, Wang JQ, Wu CX. Modulation of gut microbiota and immune system by probiotics, pre-biotics, and post-biotics. *Front Nutr*, 2021,8:634897.
- [58] Aghamohammad S, Sepehr A, Miri ST, et al. The effects of the probiotic cocktail on modulation of the NF-κB and JAK/STAT signaling pathways involved in the inflammatory response in bowel disease model. *BMC Immunol*, 2022,23(1):8.
- [59] Mazziotta C, Tognon M, Martini F, et al. Probiotics mechanism of action on immune cells and beneficial effects on human health. *Cells*, 2023,12(1):184.
- [60] Dusek O, Fajstova A, Klimova A, et al. Severity of experimental autoimmune uveitis is reduced by pretreatment with live probiotic *Escherichia coli* nissle 1917. *Cells*, 2020,10(1):23.
- [61] Napolitano P, Filippelli M, D'Andrea L, et al. Probiotic supplementation improved acute anterior uveitis of 3-year duration: a

- case report. Am J Case Rep, 2021,22:e931321.
- [62] Kim J, Choi SH, Kim YJ, et al. Clinical effect of IRT-5 probiotics on immune modulation of autoimmunity or alloimmunity in the eye. Nutrients, 2017,9(11):1166.
- [63] Davani - Davari D, Negahdaripour M, Karimzadeh I, et al. Prebiotics: definition, types, sources, mechanisms, and clinical applications. Foods, 2019,8(3):92.
- [64] Askari G, Moravejolahkami AR. Synbiotic supplementation may relieve anterior uveitis, an ocular manifestation in behcet's syndrome. Am J Case Rep, 2019,20:548-550.
- [65] Zhou JH, Yang JJ, Dai ML, et al. A combination of inhibiting microglia activity and remodeling gut microenvironment suppresses the development and progression of experimental autoimmune uveitis. Biochem Pharmacol, 2020,180:114108.
- [66] Du ZY, Wang QF, Huang XY, et al. Effect of berberine on spleen transcriptome and gut microbiota composition in experimental autoimmune uveitis. Int Immunopharmacol, 2020,81:106270.
- [67] Zárata-Bladés CR, Horai R, Mattapallil MJ, et al. Gut microbiota as a source of a surrogate antigen that triggers autoimmunity in an immune privileged site. Gut Microbes, 2017,8(1):59-66.
- [68] Deshpande G, Sonawale A, Mulkalwar A, et al. Short-term efficacy and adverse effects of sulfasalazine in the management of axial spondyloarthritis. Cureus, 2023,15(12):e49978.
- [69] Llorenç V, Nakamura Y, Metea C, et al. Antimetabolite drugs exhibit distinctive immunomodulatory mechanisms and effects on the intestinal microbiota in experimental autoimmune uveitis. Invest Ophthalmol Vis Sci, 2022,63(3):30.
- [70] Zhang Y, Li CX, Zhang XZ. Bacteriophage-mediated modulation of microbiota for diseases treatment. Adv Drug Deliv Rev, 2021,176:113856.
- [71] Santos TM, Ledbetter EC, Caixeta LS, et al. Isolation and characterization of two bacteriophages with strong *in vitro* antimicrobial activity against *Pseudomonas aeruginosa* isolated from dogs with ocular infections. Am J Vet Res, 2011,72(8):1079-1086.
- [72] Mursalin MH, Astley R, Coburn PS, et al. Therapeutic potential of Bacillus phage lysin PlyB in ocular infections. mSphere, 2023, 8(4):e0004423.
- [73] Watane A, Cavuoto KM, Rojas M, et al. Fecal microbial transplant in individuals with immune-mediated dry eye. Am J Ophthalmol, 2022,233:90-100.
- [74] Kovatcheva-Datchary P, Nilsson A, Akrami R, et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of *Prevotella*. Cell Metab, 2015,22(6):971-982.
- [75] Wang K, Liao MF, Zhou N, et al. Parabacteroides distasonis alleviates obesity and metabolic dysfunctions via production of succinate and secondary bile acids. Cell Rep, 2019,26(1):222-235.e5.
- [76] Pagliai G, Dinu M, Fiorillo C, et al. Modulation of gut microbiota through nutritional interventions in behcet's syndrome patients (the MAMBA study): study protocol for a randomized controlled trial. Trials, 2020,21(1):511.
- [77] Wang X, Yu CF, Liu XM, et al. Fenofibrate ameliorated systemic and retinal inflammation and modulated gut microbiota in high-fat diet-induced mice. Front Cell Infect Microbiol, 2022,12:839592.
- [78] Chen N, Wu J, Wang JR, et al. Short chain fatty acids inhibit endotoxin-induced uveitis and inflammatory responses of retinal astrocytes. Exp Eye Res, 2021,206:108520.