·文献综述·

眼表菌群失调与翼状胬肉发病关系的研究现状

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摘要

翼状胬肉是一种与慢性眼表炎症相关的结膜增生性疾病,其发病机制尚未完全明确。既往聚焦人乳头瘤病毒(HPV)单一病原体致病的认知逐渐被转变,转而强调菌群失调的核心地位。近年研究表明,眼表菌群失调通过破坏眼表免疫稳态,在翼状胬肉的发生发展中发挥关键作用。研究发现环境因素(如紫外线辐射、高海拔、粉尘暴露)可导致菌群多样性降低、条件致病菌(如棒状杆菌等)丰度升高,进而激活模式识别受体,通过 NF-κB 等信号通路触发炎性细胞因子释放,诱发慢性眼表炎症。这一过程促进上皮异常增殖、血管形成及组织修复缺陷,最终驱动翼状胬肉的发生。文章旨在阐明眼表菌群-免疫-炎症轴在翼状胬肉发病中的关键作用,为探索更有效的防治策略提供了思路。
关键词:翼状胬肉;菌群失调;眼表炎症
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Current research status of the relationship between ocular surface dysbiosis and the pathogenesis of pterygium

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Abstract

• Pterygium is a proliferative disorder of the conjunctiva associated with chronic ocular surface inflammation, and the pathogenesis remains incompletely understood. The previous research focusing solely on single pathogens like human papillomavirus (HPV) has shifted towards emphasizing the central role of microbial dysbiosis. Recent studies indicate that ocular surface dysbiosis plays a critical role in the development and progression of pterygium by disrupting ocular surface immune homeostasis. Research has demonstrated that environmental factors (such as ultraviolet radiation, high altitude, and dust exposure) can induce a reduction in microbial diversity and an increased abundance of opportunistic pathogens (such as corynebacterium). This dysbiotic state activates pattern recognition receptors (PRRs), triggering the release of inflammatory cytokines *via* signaling pathways like NF-κB, thereby initiating chronic ocular surface inflammation. This inflammatory cascade promotes aberrant epithelial proliferation, angiogenesis, and impaired tissue repair, ultimately driving pterygium formation. This review aims to elucidate the pivotal role of the ocular surface microbiota-immune-inflammation axis in pterygium pathogenesis, providing a foundation for exploring more effective prevention and treatment strategies.
• KEYWORDS: pterygium; dysbiosis; ocular surface inflammation

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0 引言

翼状胬肉是发生于眼球表面的一种结膜组织异常增生性疾病,发病机制暂不明确,目前的研究认为翼状胬肉属于慢性炎症性眼表疾病[1]。近年的研究指出,眼表菌群失调与眼表的炎症状态显著相关[2-3],眼表菌群失调影响着翼状胬肉的发生与发展[4]。本文从眼表菌群失调的角度,通过对眼表菌群失调在翼状胬肉发病中的研究现状进行综述,以期为翼状胬肉的防治提供新的思路。

1 眼表菌群失调概述

人体体表和体腔中存在着种类繁多的微生物菌群,它们与周围的微生物环境共同构成人体微生态系统。随着人体菌群微生态系统相关研究的不断深入,研究的焦点聚集在人体不同部位的微生物群落研究,并于 2007 年启动了人体微生物组计划(human microbiome project, HMP)[5]。眼表微生物在维持眼表免疫稳态中发挥重要的作用,眼表是一个动态的微生态系统,年龄、性别、地理位置以及后天因素的影响可改变微生物与眼表屏障之间的关系,当微生物与眼表屏障之间的平衡被打破后,眼表的上皮细胞会应激产生多种促炎细胞因子,使眼表产生炎

症反应[6-7]。随着研究的不断进展,目前 HMP 已进入采用多组学研究策略来研究微生物在人类健康和疾病中的作用和功能。既往的研究指出健康眼球表面以革兰阳性菌为优势菌群,约占眼表菌落的 30%-70%[8];相对于周围的皮肤和黏膜,健康的眼球表面存在稳定、稀少的微生物组,而导致眼表微生物组稀少的因素可能与眼表黏膜分泌的抗菌肽、溶菌酶、眨眼机制、泪液引流引起的机械清除等因素有关[9]。尽管眼表始终存在微生物,但健康的眼表不会引起免疫炎症反应。研究表明眼表上皮细胞可以通过产生促炎性细胞因子及抗菌肽来选择性地对眼致病菌作出反应,而不对非致病菌作出反应,这表明眼表存在先天免疫反应,这种免疫反应允许共生微生物群定居[10]。健康眼表稳定的菌群定植对于维持眼表免疫状态具有重要意义,这些研究结论为未来进一步研究眼表菌群失调与眼部相关疾病的潜在联系提供了理论框架,为进一步探究眼表菌群失调与眼部疾病的发生提供了理论基础。

2 翼状胬肉的发病机制

目前对于翼状胬肉的发病机制尚不完全明确,现有的研究表明翼状胬肉的发病与地理位置、紫外线照射、粉尘刺激等环境因素以及病毒感染等多种因素有关,其发病机制涉及炎症、新生血管、异常增殖和细胞凋亡等[11]。主流的研究认为翼状胬肉属于眼表慢性炎症性疾病,多种炎性细胞因子参与了翼状胬肉的发生和进展,炎性细胞因子通过激活诱导细胞增殖和抗体分泌的多种信号通路发挥关键作用[12-13],同时介导炎症反应导致组织损伤,并伴随细胞外基质沉积、纤维增生和血管形成过程,促进翼状胬肉的形成和进展[14-15]。这些研究表明炎症在翼状胬肉的发病过程中起到了至关重要的作用。

3 眼表菌群失调与翼状胬肉发病的关系

近年来,越来越多的研究表明眼表菌群失调与翼状胬肉的发病密切相关,有学者对眼表菌群与翼状胬肉的关系进行了研究,发现翼状胬肉患者的眼表菌群多样性减少,菌群的种类和数量也发生了变化[4,16],包括某些有益菌的减少和潜在致病菌的增加。目前,眼表菌群失调对翼状胬肉发病的影响机制尚不完全清楚,现有的研究认为,眼表菌群失调打破了眼部组织的正常代谢和修复功能,通过影响眼表免疫炎症反应、促进上皮细胞增殖和迁移等途径参与翼状胬肉的发病过程[17],这些研究证实了眼表菌群失调在翼状胬肉发病中的重要作用。

3.1 环境因素与眼表菌群失调 一项针对高海拔地区人群翼状胬肉患病率的调查报告显示,长期居住高海拔地区的人群,其翼状胬肉患病率升高了 1.524 倍[18];研究发现高海拔地区与低海拔地区健康人群眼表微生物组的组成具有较大的差异,高海拔地区人群眼表棒状杆菌等菌属的丰度较低海拔地区人群显著升高[19],而居住于低海拔地区不同纬度的健康人群,其眼表也具有不同的菌群分布[6],这可能与高海拔、低纬度地区阳光中紫外线强度较大有关[18,20]。研究表明暴露于阳光下,紫外线辐射可以调节眼表微生物群,并改变眼表的抗菌肽,破坏微生物组与眼表免疫之间的健康平衡,导致慢性眼表炎症[21],促进翼状胬肉发生[22]。空气中的粉尘颗粒不仅是空气污染的重要组成部分,也是翼状胬肉的致病因素之一。研究表明粉尘颗粒会改变人体菌群群落的组成[23],通过诱发眼表氧化应激反应[24]及细胞凋亡等途径[25],造成眼表组织损伤[26],引发慢性眼表炎症[27],进而促进翼状胬肉发生[28-29]。这些研究表明,地理环境的变化通过引发眼表菌群失调诱发眼表慢性炎症而导致翼状胬肉发病。

3.2 眼表菌群失调与眼表炎症 健康的眼表具有稳定而稀疏的微生物种群,越来越多的证据表明眼表菌群失调是诱发眼部疾病的一个重要因素[30]。Janeway 等[31]于 1989 年提出了模式识别受体(pattern recognition receptors, PRRs)的概念,并发现 PRRs 会受到菌群变化的影响,从而影响眼睛的生理功能。进一步的研究发现,PRRs 触发转录因子上调,引导眼表黏膜释放多种炎性细胞因子和趋化因子,诱导眼表产生先天性和适应性免疫反应[32]。在正常情况下,人体微生物群与组织黏膜免疫系统处于稳态中,微生物相关的分子模式能够被黏膜上皮细胞的模式识别受体所识别,从而使机体保持一个健康稳定的状态,当这种稳态被打破时,会导致多种疾病的发生[10,33]。

眼表泪膜中含有生长因子、抗菌肽、分泌型 IgA 和维生素等多种物质,它们通过促进免疫稳态和宿主防御等机制维持着眼表的健康[34-35]。研究发现,眼表菌群作用于眼表产生中间代谢物直接激活 PRRs,通过 NF-κB、TBet/GATA3 等多种信号通路刺激免疫细胞产生炎性细胞因子[3],调节泪液中多种蛋白质组分的表达,维持眼表免疫防御的稳态[36]。Wang 等[37]观查了无菌和常规 C57BL/6J 小鼠的眼和泪腺,研究发现无菌小鼠的眼表屏障功能异常,杯状细胞丢失,炎症细胞和 $CD4^+$T 细胞浸润增加;Zaheer 等[38]将 CD25 基因敲除的无菌小鼠与正常环境生长的小鼠进行比较,发现无菌小鼠眼表屏障功能严重受损,杯状细胞密度明显降低,淋巴细胞浸润增加,γ-干扰素和白细胞介素-12 表达增加,$CD4^+$T 细胞数量增加。此外,近年的研究发现,在慢性眼表疾病患者的眼部存在非常驻菌的持续定植[39]。这些研究表明,眼表菌群失调打破了眼表的免疫稳态,改变了眼表的免疫功能,诱发慢性眼表炎症,进而导致眼部疾病的发生。

3.3 眼表菌群失调与翼状胬肉发病 既往关于翼状胬肉与眼表菌群失调的研究焦点主要集中在人乳头瘤病毒(human papillomavirus, HPV)感染,认为 HPV 感染诱导了翼状胬肉的发生[40-41],但进一步的研究表明 HPV 感染这一孤立因素并不足以促使翼状胬肉的发生[42],它可能只是作为一个辅助因素[43-44],为条件致病菌的增殖创造了条件,通过改变眼表的菌群分布,打破了眼表的免疫稳态,从而促进了翼状胬肉的发病。

近年的研究指出,眼表棒状杆菌的丰度增高可能参与了眼表免疫状态调节,并影响翼状胬肉的发病[4,19]。既往普遍认为棒状杆菌是人类皮肤和黏膜的正常寄生菌[45],一般无致病性,但近年的多项研究表明,棒状杆菌是一种与自身免疫性炎症相关的重要潜在病原菌[46-47],通过刺激巨噬细胞引起眼表免疫性炎症状态的变化[48-49],进而引起免疫性干眼等多种炎症性眼病[30,50]。进一步的研究发现,免疫炎症微环境通过诱导眼表组织修复缺陷[51],引起眼表组织中的白细胞迁移,Th2 细胞、M1 巨噬细胞和静止树突状细胞的浸润增加,通过白细胞介素信号传导等关键信号通路机制,促使翼状胬肉发生[52-53]。

4 小结与展望

随着 HMP 研究的不断深入,我们越来越深入地了解微生物的特性及其在眼部疾病中的作用,这为预防和治疗疾病提供了新的思路和手段。既往的研究长期聚焦于 HPV 感染诱发翼状胬肉,随着研究的不断扩大与深入,

HPV 单一病原体致病的认知逐渐被转变[44],并逐渐认识到眼表常驻菌棒状杆菌的双面性,即低丰度时参与维持眼表免疫稳态[54]、高丰度时持续激活免疫促进炎症[55],这些阶梯性的研究结论将微生物与翼状胬肉之间的关系从感染逐步过渡到菌群失调。而环境因素与菌群失调的深入研究为翼状胬肉的发病提出了“环境因素-菌群失调-免疫炎症-翼状胬肉发病”的新视角。这些研究将翼状胬肉的病因学研究提升到一个新的层面,即眼表菌群失调改变了眼表的免疫炎症状态,从而促进了翼状胬肉的发生。

眼表菌群失调参与翼状胬肉发病的研究现状表明,这一领域的研究正在不断深入和拓展;探索翼状胬肉发病过程中发挥主要作用的关键菌种以及针对眼表菌群失调的防治策略将是未来的重要研究方向。目前对于眼表菌群失调已经提出了使用益生菌来调节眼表的免疫[56],缓解眼部的慢性炎症[57],但是关于该主题的研究较少,其有效性和安全性尚有待进一步的观察与研究[58]。未来的研究或可以聚焦局部应用噬菌体选择性清除条件致病菌,或应用抗菌肽滴眼剂抑制条件致病菌增殖,改善眼表菌群分布、缓解眼表免疫性炎症,以期起到防治翼状胬肉等眼表免疫炎症性疾病的目的。

眼表菌群失调与翼状胬肉发病的相关研究是一个充满挑战与机遇的领域,目前关于眼表菌群失调参与翼状胬肉发病的研究还存在诸多的挑战与限制。有研究指出眼表菌群的组成和变化受到年龄、性别、环境等多种因素的影响[59];也有观点认为,翼状胬肉的发生加剧眼表微环境的改变,也可能会加剧眼表菌群失衡[60]。这种相互关系表明,眼表菌群失调和翼状胬肉之间可能存在一种复杂的相互作用,翼状胬肉的发病机制也可能涉及多个因素之间的相互作用。为了进一步理解这种关系,未来的研究应综合考虑这些因素,以揭示其潜在机制,通过不断深化眼表菌群失调参与翼状胬肉发病的认识,深入揭示眼表菌群失调与翼状胬肉发病之间的复杂关系,探索更加有效的防治策略。

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