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慢性鼻窦炎的发病机制研究进展

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摘　要

慢性鼻窦炎(Chronic Rhinosinusitis, CRS)是一种病程超过12周的鼻窦黏膜慢性炎症性疾病，主要表现为鼻塞、流涕、嗅觉减退及头面部闷胀感，严重影响患者生活质量，并带来沉重的社会经济负担。其确切病因至今尚未完全阐明，本文通过系统梳理国内外最新研究进展，深入探讨CRS的发病机制，以期为临床诊疗策略的优化提供理论依据。

关键词

慢性鼻窦炎，病因，发病机制

Research Progress on the Pathogenesis of Chronic Rhinosinusitis

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Abstract

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of the sinus mucosa with a duration of more than 12 weeks, which is characterized by nasal congestion, runny nose, decreased sense of smell, and stuffiness in the head and face, which seriously affects the quality of life of patients and brings a heavy socioeconomic burden. Its exact etiology has not been fully elucidated so far. In this

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paper, the pathogenesis of CRS is explored in depth by systematically combing the latest research progresses at home and abroad, in order to provide theoretical basis for the optimization of clinical diagnosis and treatment strategies.

Keywords

Chronic Rhinosinusitis, Etiology, Pathogenesis

1. 引言

CRS 根据有无鼻息肉可分为伴息肉的慢性鼻窦炎(Chronic Rhinosinusitis with Nasal Polyps, CRSwNP)和不伴息肉的慢性鼻窦炎(Chronic Rhinosinusitis without Nasal Polyps, CRSsNP)，流行病学数据显示，我国CRS 患病率为 4.8%~9.7% [1]，EPOS 2020 报告指出，人群中基于症状的 CRS 的总体患病率在 5.5%至 28%之间[2]。该疾病不仅发病率高，还造成沉重的经济负担，仅在美国，CRS 的管理直接费用每年高达 100~130 亿美元，人均年支出约 2609 美元[3]，由于 85%的患者处于 18~65 岁的工作年龄段，因疾病导致的缺勤和生产力下降等间接成本甚至超过直接医疗支出，使得 CRS 已成为一个全球性的重大公共卫生问题。大多数患者在接受规范化治疗后症状得到显著改善，但仍有约 30%的患者出现术后复发或治疗抵抗[4]，这一临床难题的出现，很大程度上归因于目前对 CRS 的病因学和发病机制认识仍不够全面，导致现有的治疗策略存在一定的局限性。因此，深入理解 CRS 的发病机制，对临床诊疗具有重要意义。

2. 发病机制研究进展

2.1. 解剖异常

解剖因素在 CRS 的发病中起重要作用，尤其是鼻腔和鼻窦的结构异常可能阻塞鼻窦开口，影响黏液引流，导致炎症慢性化。常见的解剖因素包括鼻中隔偏曲(Deviated Nasal Septum, DNS)、鼻甲肥大、鼻息肉、筛窦解剖变异等。

DNS 是一种以鼻中隔从中线移位为特征的常见解剖变异，可导致鼻腔对称性破坏。其患病率在不同人群和研究中存在显著差异，受种族、年龄及诊断方法等多种因素影响。全球范围内，DNS 的患病率介于 20%至 92.5%之间[5] [6]，约 48.8%的慢性或复发性鼻窦炎患者存在 DNS [7]。DNS 可能引发多种并发症，尤其在严重且未得到治疗的情况下，CRS 是最常见的并发症之一，DNS 导致 CRS 主要有三大机制[8]-[11]：1) 鼻窦通气和前鼻腔压力变化理论：鼻中隔后位偏曲引起前鼻腔压力及气流改变，进而影响副鼻窦通气；2) 机械理论：OMC 狭窄导致分泌物在副鼻窦内积聚，淤积的粘液分泌物继发感染，最终引发CRS；3) 空气动力学理论：副鼻窦内气压流动改变及粘液纤毛功能破坏是 CRS 形成的关键因素。然而，也有研究表明鼻中隔在 CRS 的发展过程中可能并不具有显著作用或促成效应[12]。

窦口鼻道复合体(Ostiomeatal Complex, OMC)由中鼻甲、钩突、筛泡、眶下筛窦气房等结构组成，任何一部分的解剖变异都可能影响鼻窦引流，导致 CRS 的发生[13]。钩突作为 OMC 的重要组成部分，其附着点变异与额窦炎的发生密切相关，研究表明，钩突附着于眶纸板时，额窦炎的发生率较高[14]，钩突的偏曲、气化或肥大等变异可能阻碍鼻窦通气引流，从而引发炎症。中鼻甲气化是鼻外侧壁常见解剖变

异，Rahman 等人[15]研究发现，中鼻甲气化与上颌窦炎之间存在统计学上的相关性，尤其是中鼻甲前端的气化，这可能归因于 OMC 阻塞导致上颌窦引流受阻，但未发现中鼻甲气化与慢性额窦炎和筛窦炎之间存在显著关联。而鼻丘气房过度气化或异常发育可能影响额窦引流，是额窦炎的重要解剖因素[16]。眶下筛窦气房又称 Haller 气房，位于眶下壁下方，靠近上颌窦自然开口和筛漏斗的区域，发生率为 3.62%至 36% [17]，Haller 气房若过度发育或气化程度较高，可能压迫上颌窦自然开口、筛漏斗或中鼻道，阻塞 OMC，进而导致上颌窦、前组筛窦甚至额窦的黏液潴留，增加感染和炎症的风险，从而诱发或加重 CRS。

2.2. 纤毛功能障碍

纤毛上皮细胞的功能在于清除被气道表面液体和粘液捕获的各类病原体及吸入性刺激物，CRS 与鼻窦粘膜纤毛清除功能受损密切相关，其受损程度与 CRS 的严重程度呈正相关[18]。纤毛功能障碍可分为原发性和继发性两类，二者均可导致黏液纤毛清除能力下降，进而引发鼻窦黏膜黏液分泌过多和清除功能障碍。原发性纤毛运动障碍是一种罕见的常染色体隐性遗传疾病，其发病机制主要与纤毛结构或功能异常有关，导致黏液运输延迟和慢性炎症反应。研究表明，编码纤毛运动蛋白的多个基因(如 DNAI1、DNAH5、DNAH11 和 DNAH5)的突变是原发性纤毛运动障碍的重要病因[19]。继发性纤毛功能障碍则由多种因素引起，包括生化、环境和机械刺激等[20] [21]，流感嗜血杆菌、肺炎链球菌、金黄色葡萄球菌、烟曲霉菌和铜绿假单胞菌等病原菌释放的多种毒素可显著破坏纤毛上皮细胞的结构与功能[22]。纤毛功能障碍会削弱鼻黏膜的天然防御机制，促进细菌定植、生物膜形成以及黏膜炎症的发生，而黏膜炎症在 CRS 的发病机制中扮演着不可忽视的角色。

2.3. 上皮屏障破坏

鼻窦上皮在先天免疫和适应性免疫中均发挥关键作用，其功能异常对 CRS 的发生和发展具有重要影响。上皮细胞是鼻黏膜的第一道防线，其通过黏膜纤毛清除系统和上皮细胞层共同构成了鼻黏膜的机械屏障。研究表明，尘螨能够通过降低紧密连接蛋白的表达，显著破坏上皮屏障功能[23]。此外，香烟烟雾提取物的刺激也被证实会导致上皮连接蛋白的整体结构破坏，并伴随跨上皮电阻水平的下降[24]。人类活动产生的颗粒物(PM)对呼吸道黏膜健康具有潜在危害。体外实验显示，人鼻上皮细胞暴露于直径小于 2.5 微米的颗粒物(PM2.5)后，多种紧密连接蛋白的表达显著降低，细胞旁通透性增加，跨上皮电阻水平下降，同时促炎细胞因子 IL-8 和胸腺基质淋巴细胞生成素(Thymic Stromal Lymphopoietin, TSLP)的分泌增加，这些变化严重损害了上皮屏障的完整性和功能[25] [26]。此外，PM2.5 暴露还会增加细胞内活性氧水平，促进核因子 E2 相关因子 2 (Nrf2)的核转位，诱导氧化应激和炎症反应，从而进一步加重对鼻上皮屏障的损伤[27]。

2.4. 组织重塑

CRS 组织重塑主要表现为上皮损伤、基底膜增厚、上皮杯状细胞化生、黏液腺增生、细胞外基质胶原沉积等。黏膜重塑不仅见于 CRSwNP，也见于 CRSsNP。有证据表明，嗜酸性粒细胞增多和嗜酸性粒细胞活化可能与 CRS 重塑和黏膜损伤密切相关[28]。体外研究发现，IL-5 刺激嗜酸粒细胞产生的嗜酸性粒细胞源性神经毒素可有效诱导鼻上皮分泌基质金属蛋白酶 9，从而影响上皮再生和细胞外基质分解，最终导致鼻腔组织重塑[29]。骨膜蛋白是一种细胞外基质蛋白，由 IL-4 和 IL-13 诱导，由气道上皮细胞分泌，涉及 CRS 鼻黏膜活检的研究表明，骨膜蛋白可引起嗜酸性粒细胞浸润并介导纤维化，从而参与黏膜重塑[30]。TGF-β 是一种多效、多功能的生长因子，可诱导成纤维细胞增殖、分化和纤维化，它还能刺激组织金属蛋白酶 1 抑制剂的产生，从而阻止细胞外基质的酶促分解，有文献报道，CRSsNP 与 CRSwNP

中 TGF-β 含量存在明显差异，CRSsNP 中 TGF-β 含量较高，且细胞外基质胶原纤维较粗，导致组织过度修复，形成纤维化；而 CRSwNP 中 TGF-β 缺失，组织修复受阻，表现为严重炎症组织中出现疏松结缔组织和水肿形成[31]。

2.5. 病原微生物

2.5.1. 细菌

细菌在 CRS 发病中暂无定论，CRS 患者鼻腔中已发现多种类型的细菌，包括金黄色葡萄球菌、凝固酶阴性葡萄球菌、肺炎链球菌、流感嗜血杆菌和铜绿假单胞菌等[32]，假单胞菌属或耐甲氧西林金黄色葡萄球菌在内的耐药病原体引起的感染极难治疗，会导致慢性炎症。细菌生物膜在 CRS 发病中也可能发挥作用，生物膜是指微生物附着于鼻黏膜表面并嵌入自身分泌的保护性细胞外基质中形成的群落结构[33]。该基质主要由多糖、蛋白质、脂质和核酸等多种生物聚合物组成，这些生物膜成分促进细胞凝聚性和细胞表面附着。由于细胞外基质的保护作用，生物膜中的细菌能够有效抵御抗体、吞噬作用、抗生素渗透以及补体结合等外部威胁，使其对抗生素的抵抗力提升高达 1000 倍[34]。生物膜不仅可以发挥致病作用，这些细菌不断定植和释放，对鼻黏膜纤毛上皮造成持续损害，从而破坏正常鼻黏膜纤毛运输系统的功能[35]，鼻窦腔内的黏液淤滞容易导致进一步的生物膜形成。

2.5.2. 病毒

CRS 患者中最常分离出的四种病毒是鼻病毒、副流感病毒、流感病毒和呼吸道合胞病毒[36]。当这些病毒感染鼻黏膜上皮时，它们会触发免疫反应，诱导释放细胞因子和趋化因子，导致感染区域出现炎症，再加上病毒感染本身造成的损伤以及淋巴细胞(如 Th1 细胞、细胞毒性 T 细胞)消除病毒造成的损伤，导致上皮损伤[37]。持续的病毒感染和炎症会导致鼻上皮气道重塑以及紧密连接退化，机械屏障被破坏以及先天和获得性免疫系统的缺陷使鼻窦粘膜更容易受到抗原暴露和刺激，这导致上皮对病毒的易感性增加，使病情进一步恶化，并更容易发生细菌感染。随着上皮退化，持续的感染和免疫反应会导致 CRS 恶化[38]。

2.5.3. 真菌

真菌在 CRS 中的作用仍存在争议，有研究表明，真菌成分可诱导气道上皮屏障功能障碍，导致细胞内活性氧水平升高、上皮通透性增加及连接复合物的结构和功能改变[39] [40]。真菌蛋白酶可干扰先天免疫系统，引发组织损伤和免疫激活，还能通过蛋白质降解、抑制真菌蛋白活性或灭活补体系统，削弱先天粘膜防御功能[41]。TLR 广泛表达于各种免疫细胞、非免疫上皮细胞、内皮细胞以及成纤维细胞表面，TLR 在病原体识别以及先天性和适应性免疫反应的诱导与调控中发挥关键作用[42]。研究表明，CRS 患者的鼻上皮细胞中 TLR2 和 TLR4 的 mRNA 表达水平显著升高，其中，TLR2 能够与真菌分生孢子和菌丝中的 β-葡聚糖和磷脂甘露聚糖相互作用，而 TLR4 则通过与 O-连接甘露聚糖和树突状细胞相关 C 型凝集素-1 结合而被激活[43] [44]。但是，在随机双盲安慰剂对照研究显示，使用抗真菌药物两性霉素 B 滴鼻 3 个月并不能减轻 CRS 的临床体征或症状[45]，这可能与真菌在 CRS 病因中作用有限、患者群体特性以及研究设计的限制导致治疗效果不显等因素有关。未来仍需进一步优化研究设计，以更深入地探讨真菌在 CRS 发病机制中的潜在作用。

2.6. 免疫因素

免疫缺陷是 CRS 的危险因素，研究发现，原发性抗体缺乏症患者更易复发 CRS [46]，自身免疫病与慢性鼻窦炎具有相关性，尤其是肉芽肿性多血管炎，有证据表明，自身免疫性疾病是 CRS 症状复发性急性加重的预测因素[47]。

鼻黏膜上皮细胞在应对多种环境刺激(如病毒和细菌感染、过敏原、化学刺激物及物理损伤)时，会释放 TSLP、IL-25 和 IL-33 等细胞因子[48]。TSLP 作为关键的免疫启动因子，触发下游炎症反应[49]，不仅参与 T2 型炎症，还涉及非 T2 型免疫过程。多种细胞(如嗜酸性粒细胞、肥大细胞和 2 型固有淋巴细胞)表达 TSLP 受体[50]。TSLP 通过抑制凋亡增强嗜酸性粒细胞活性，并诱导 IL-6、CXCL8、CXCL1 和 CCL2 等炎症介质产生[51]。此外，TSLP 刺激 CD34+祖细胞释放 IL-5、IL-13、GM-CSF 及趋化因子[52]，发挥促炎作用，还驱动嗜酸性粒细胞祖细胞成熟并促进其迁移。TSLP 与 IL-25、IL-33 协同激活 2 型固有淋巴细胞，促进 IL-5、IL-13 产生[53]，并延长 2 型固有淋巴细胞存活。临床研究表明，重度哮喘和 CRS 患者鼻腔组织中 2 型固有淋巴细胞数量与 TSLP 水平呈正相关[54]，进一步强调了 TSLP 在炎症性疾病中的重要作用。IL-5 和 IL-13 在息肉形成中具有重要作用，Bachert 等人发现，针对 IL-5 或 IL-4/IL-13 受体 α 链的抗体会使息肉缩小[55] [56]。

2.7. 遗传因素

CRS 的发病与遗传因素存在一定关联。研究表明，有 CRS 家族史的人群患病风险显著升高。美国犹他州人口数据库的一项研究分析了超过 25,000 名 CRS 患者的家庭数据，发现 CRSwNP 患者的一级亲属患 CRS 的风险增加了 4.1 倍，CRSsNP 患者的一级亲属风险增加了 2.4 倍，而 CRSwNP 和 CRSsNP 患者的二级亲属患病风险分别增加了 3.3 倍和 1.4 倍[57]。某些基因变异可能在 CRS 的发病机制中起重要作用，囊性纤维化基因 CFTR 被确定为 CRS 的风险基因，研究发现，7%的 CRS 患者携带 CFTR 突变，而在普通人群中这一比例仅为 2%，这一结果在 Hutterite 人群的连锁研究中得到了进一步验证[58] [59]。此外，Adappa [60]等人发现，苦味受体基因 T2R38 的多态性对 CRS 易感性具有显著的遗传影响。两项基于混合样本的全基因组关联研究还揭示了 CRS 与基质蛋白(如层粘连蛋白 α2、层粘连蛋白 β)以及 AOAH 基因的关联[61]，在一项我国 CRS 患者和对照人群的研究中，AOAH 的关联性得到了进一步验证[62]。多项研究还表明，CRS 与 HLA 基因、先天免疫基因显著相关[63]。

3. 总结与展望

CRS 作为一种常见的慢性炎症性疾病，严重影响患者生活质量，给社会带来沉重经济负担。目前临床治疗仍面临不少患者术后复发或疗效不佳的困境，这反映出我们对 CRS 的发病机制认识仍存在不足。当前研究已从解剖变异、纤毛功能障碍、上皮屏障损伤、组织重塑、微生物感染、免疫异常及遗传易感性等多角度揭示了 CRS 复杂的发病网络。然而值得注意的是，现有证据多基于欧美人群数据，其结论在中国人群中的适用性亟待验证，例如中国人群与欧美人群在 CRS 的炎症类型存在差异，CRSsNP 在欧美人群中 33%~55%表现为 T2 型炎症，而在中国则以非 T2 型炎症为主；CRSwNP 在欧美人群中 T2 型炎症占比高达 73%~87%，而中国患者则更多表现为混合型炎症[1]；且研究方法以横断面调查为主，缺乏高质量的纵向研究证据，难以建立确切的因果关系。因此，直接套用欧美诊疗策略可能难以满足中国患者的实际需求。未来，我们应立足中国人群特点，开展全国多中心、大样本前瞻性队列研究，深入探讨地域性环境暴露、生活方式及遗传背景等因素对 CRS 发生发展的影响，针对中国人群特有的发病机制开发精准干预手段，如靶向纤毛功能、非 T2 型炎症、上皮屏障、微生物群及组织重塑等治疗手段。通过优化诊疗策略，有望突破当前 CRS 诊疗的瓶颈，提高 CRS 的长期控制率，最终实现改善患者预后和减轻社会疾病负担的双重目标。

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