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·综述·

牙周炎与炎症性肠病相关研究进展

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【摘要】 炎症性肠病(inflammatory bowel disease，IBD)是一组受多种因素影响的慢性非特异性胃肠道炎症性疾病，主要包括克罗恩病和溃疡性结肠炎。牙周炎是一类以牙菌斑生物膜为始动因子，牙槽骨慢性吸收破坏为表现的疾病。近年来越来越多的研究表明牙周炎与炎症性肠病二者之间存在相关性，但两者间的关系仍不明确。本综述从流行病学证据、生物学证据、关联治疗证据三个维度探究了两种疾病的内在关系：从流行病学证据来看，牙周炎与IBD患病风险增加相关，反过来IBD也影响牙周健康，其双向关联还需要进一步扩大数据源研究；从生物学证据来看，无论临床研究还是动物实验均说明IBD和牙周炎相互影响；从关联治疗证据来看，对IBD治疗有益的药物用于牙周炎的防治同样有效，对牙周炎改善有利的药物也可明显缓解IBD。IBD与牙周炎的相互作用机制包括微生物途径和免疫途径。微生物途径是指由于牙周炎患者口腔内机会致病菌的比例增加以及IBD影响了胃液分泌以及肠道菌群平衡，口腔细菌通过口腔肠道轴或血行传播异位定植于肠道的几率增大，这些微生物会通过释放毒力因子，破坏肠道黏膜屏障，引发炎症反应等方式进一步加重IBD炎症。免疫途径是指牙周炎激活口腔内适应性免疫，产生大量免疫细胞，特别是Th17细胞，其表面存在肠道归巢标记物α4β7整合素，IBD患者肠道黏膜上的α4β7整合素的配体表达增加，使得口腔Th17细胞加速转移至肠道从而加剧肠道炎症。研究表明，IBD患者口腔内细胞因子的表达量异常，如肿瘤坏死因子-α、白细胞介素-1β、白细胞介素-10、白细胞介素-6、白细胞介素-21、可溶性CD40配体(soluble CD40 ligand，sCD40L)、白细胞介素-23和干扰素-γ，提示IBD通过免疫途径影响牙周炎，以上细胞因子是治疗两种疾病的靶点所在，可为未来两种疾病的防治提供研究方向。

【关键词】 牙周炎；　牙菌斑；　口腔-肠轴；　微生物；　免疫途径；　Th17细胞；　整合素；　白细胞介素；　炎症性肠病；　克罗恩病；　溃疡性结肠炎
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Research progress on association between periodontitis and inflammatory bowel disease

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【Abstract】 Inflammatory bowel disease (IBD) is a group of chronic, non-specific inflammatory diseases of the gastrointestinal tract including primarily Crohn's disease and ulcerative colitis, which are affected by multiple factors. Periodontitis is a type of disease characterized by plaque biofilm as the initiating factor and chronic destruction of alveolar bone via resorption. An increasing number of studies have reported a correlation between periodontitis and IBD, but the relationship between the two remains unclear. In this study, we explore the internal relationships between the two diseases from three dimensions, including epidemiological, biological, and associated treatment evidence. Based on epidemio-

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logical evidence, periodontitis was found to be associated with an increased risk of IBD, which also affects periodontal health, although the bidirectional correlation needs to be further studied by expanding the number of data sources. From the biological evidence, both clinical studies and animal experiments show that IBD and periodontitis are interconnected. Based on evidence from association therapy, drugs that are beneficial for the treatment of IBD are also effective in the prevention and treatment of periodontitis. In addition, drugs that are good for improving periodontitis can also significantly alleviate IBD. The interaction mechanism between IBD and periodontitis includes the microbial pathway and the immunization route. The microbial pathway refers to the increase in the probability of intestinal tract ectopic colonization by oral bacteria transmitted through the mouth-gut axis or blood, resulting from the increase in the proportion of opportunistic pathogens in the oral cavity of patients with periodontitis and the influence of IBD on the secretion of gastric juice and the balance of intestinal flora. These microorganisms further aggravate IBD inflammation by releasing virulence factors, destroying the intestinal mucosal barrier, and triggering inflammatory responses. In periodontitis, adaptive immunity is activated in the mouth, leading to the production of a large number of immune cells, including Th17 containing the intestinal homing marker α4β7 integrin on their surface. Increased ligand expression of α4β7 integrin in the intestinal mucosa of patients with IBD accelerates oral Th17 cell transfer to the intestine, thereby worsening intestinal inflammation. In parallel, the abnormal expression of cytokines, such as TNF-α, IL-1β, IL-10, IL-6, IL-21, soluble CD40 ligand (sCD40L), IL-23, and INF-γ, in the oral cavity of patients with IBD was observed, suggesting that IBD may affect periodontitis through immunity. These cytokines represent targets for the treatment of both diseases and provide a research direction for their prevention and treatment in the future.

【Key words】 periodontitis; plaque; oral-intestinal axis; microorganism; immune ways; Th17 cells; intergrin; interleukins; inflammatory bowel disease; Crohn's disease; ulcerative colitis

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炎症性肠病(inflammatory bowel disease,IBD)是一种受到包括遗传、免疫、微生物等多种因素影响的胃肠道慢性炎症,主要包括克罗恩病(Crohn's disease,CD)和溃疡性结肠炎(ulcerative colitis,UC)两种疾病类型,其特点是肠道黏膜免疫系统的异常激活,表现为腹痛、腹泻、便血等[1]。除了上述肠道症状外,约15%~40%的IBD患者被报道有全身表现,包括口腔、关节、眼部疾病等[2]。牙周炎是一种影响牙周支持组织的慢性炎症性疾病,来自17个国家(包含发达国家和发展中国家)的最新数据显示,成人牙周炎患病率高达62%,其中重度牙周炎患病率为23.6%[3]。其典型特征是牙龈炎症、牙周袋形成、牙槽骨吸收、牙齿松动移位等。治疗不及时将导致牙齿缺失,严重影响患者的身心健康。近年来,大量研究表明牙周炎与全身健康密切相关,与包括IBD在内的多种疾病(如心血管疾病[4]、糖尿病[5]、不良妊娠结局[6]、痴呆[7]、多囊卵巢综合征[8]等)呈双向关系。本文从流行病学、生物学、关联治疗等多种证据出发,对牙周炎和IBD的相关性进行回顾分析,并深入探讨二者相互影响的作用机制,为防治相关疾病提供参考。

1　流行病学证据

1.1　牙周炎与IBD患病风险增加相关

牙周炎患者发生IBD的风险较高,并在一定程度上影响着IBD的预后。一项对995 048人的长达8年的随访队列研究指出,牙周炎患者相比于非牙周炎患者IBD患病率更高。其中,在牙周炎合并有吸烟、高龄(>65岁)的情况下,患IBD的风险高达1.9倍[9]。此外,2023年的一项研究指出,失牙的患者和自我报告患有严重牙周炎的患者在IBD患病指数上得分更高,同时与IBD发作次数之间存在微弱关联[10]。She等[11]对以往的研究进行了Meta分析,最终纳入了六项符合条件的研究,涉及599名受试者和448名对照者。牙周炎和IBD之间的比值比(odds ratio,*OR*)为3.17,95% 置信区间(95% confidence interval,95%*CI*)为2.09~4.8,其中与克罗恩病和溃疡性结肠炎之间的关联*OR*分别为3.64(95%*CI*:2.33~5.67)和5.37(95% *CI*:3.30~8.74),上述结果表明牙周炎与IBD患病风险增加显著相

关。但也有研究指出没有观察到牙周病与克罗恩病或溃疡性结肠炎风险之间的关联[12]。因此需要更长期的、更广泛的数据集，剔除混杂因素的影响，以探究牙周炎与IBD风险之间的关联。

1.2　IBD影响牙周健康

IBD患者的牙周情况较健康人群更令人担忧。Baima等[13]比较了180例IBD患者和180名健康对照者的牙周炎诊断和全口牙周参数。结果发现，IBD患者相比于健康人群，患有中度/重度牙周炎（85.6% *vs*. 65.6%）和重度牙周炎（36.7% *vs*. 25.6%）的比例明显更多。牙周筛查评分是准确衡量牙周状况的指标之一，评分≥5提示重度牙周炎。一项包含了4 537例患者的病例对照研究结果显示，与对照组（19.9%）相比，IBD患者牙周筛查评分≥5的比例明显更高（31.8%）[14]。针对我国IBD患者的研究同样显示，牙周探诊深度≥5 mm和临床附着丧失≥4 mm的部位相比于健康人群显著更高[15]。Domokos等[16]通过Meta分析进一步证实，IBD患者患牙周炎的几率较高，是牙科的高危人群。Bertl等[17]进行的队列研究也表明，IBD患者牙周健康更差，克罗恩病比溃疡性结肠炎患者受到的影响更明显。近来另一项研究发现，和健康对照组相比，IBD患者的牙周炎患病率明显更高，进一步亚组分析表明，在36～65岁人群中，IBD患者和健康人的牙周炎患病率有显著差异，这提示IBD和牙周炎在中年人群中的相关性更显著[18]。上述结果说明IBD在一定程度上影响牙周健康，并使牙周炎风险增加。

1.3　IBD与牙周炎的双向关联

尽管从上述流行病学的观察性研究来看，IBD与牙周炎之间存在相关性，但两者是否存在因果关系目前还不明确。横断面研究和病例对照研究具有回忆偏差，队列研究报告也存在混杂因素的干扰，因此需要孟德尔随机化研究从遗传学层面证实IBD与牙周炎的因果关联。Wang等[19]进行了双向双样本孟德尔随机化研究，结果说明IBD作为一个整体以及溃疡性结肠炎亚型和牙周炎有因果关系，同样，牙周炎与IBD存在提示性的因果关系。齐兆岩等[20]研究表明，IBD在整体上会增加急性牙周炎的风险，反之急性牙周炎会增加克罗恩病的风险。然而Yu等[21]进行的双向双样本孟德尔随机化研究表明，IBD与牙周炎之间不存在因果关系。以上研究结果的不同主要源于数据源选择的差别。同时，目前相关研究所纳入的研究对象均为欧洲人种，能否进一步推广到所有人种有待商榷。因此需要进一步扩大数据源，以便更好地得出真实数据。

2　生物学证据

2.1　临床研究

正常情况下，肠道拥有其独特的微生态，肠道特有的菌群在其中保持着动态平衡。健康人体肠道中的微生物群主要由厚壁菌门、拟杆菌门、变形菌门和放线菌门组成，其中厚壁菌门占比49%～76%。然而，IBD患者肠道微生物的组成明显改变，厚壁菌门相对丰度降低，而变形菌门、拟杆菌门相对丰度增加[22-23]。丰度增加的细菌中可发现来自口腔的常驻菌，如链球菌、牙龈卟啉单胞菌、弯曲杆菌、肺炎克雷伯菌等。一项临床研究招募了60例IBD患者和45名无IBD的健康人群，发现与健康人群相比，IBD患者的肠道微生物组与口腔微生物组更加相似[24]。另外一项大型多中心微生物组研究从粪便和直肠、回肠多个胃肠道部位收集了超过400个未经治疗的儿科IBD样本，结果清楚地表明，直肠和回肠黏膜的微生物变化与疾病状态之间存在显著相关性，作为牙周炎致病菌之一的梭杆菌科的丰度明显增加[25]。此外，牙周炎的主要致病菌牙龈卟啉单胞菌也在IBD患者的粪便样本中被发现，并且丰度值和非IBD患者粪便样本中的牙龈卟啉单胞菌丰度值具有统计学差异[26]。上述结果意味着牙周炎致病菌可能在IBD的发病机制中发挥作用。

来自IBD患者肠道的微生物同样影响着口腔微生态的变化。Qi等[27]通过高通量基因测序检测发现，IBD患者出现明显的唾液微生物群失调，糖杆菌、潜伏杆菌、纤毛菌、普氏菌、布雷德菌等显著增加，而普氏菌、纤毛菌是慢性牙周炎的优势菌群。在未服用抗生素的IBD患者的龈下微生物群中，梭杆菌的水平也显著增加[28]，此外，有研究发现肠道菌群代谢物与重度牙周炎之间存在密切关系[29]，这同样支持了牙周炎和IBD之间存在相互影响的假设。

2.2　动物实验

目前大多数在人群中进行的牙周炎与IBD相关性的研究属于观察性研究，结果受到机体、环境等多方面因素影响。而利用诱导产生的IBD和牙周炎动物模型，包括口服葡聚糖硫酸钠（dextran sulfate sodium，DSS）、基因敲除、结扎栓丝等方式，

被广泛用作替代模型，以更深入地了解IBD与牙周炎之间的相互关系[30]。

Qian等[31]探讨了牙周炎唾液微生物群对结肠炎的可能影响。研究者从健康个体和患有牙周炎的个体中收集唾液微生物群，并将其灌胃给C57BL/6小鼠。同时用DSS诱导结肠炎5 d，结扎1周诱导牙周炎。结果显示DSS诱导后，牙周炎唾液微生物群加剧了结肠炎的发生发展。IL-10基因缺乏小鼠通常会发展为自发性结肠炎。一项研究显示，与正常小鼠相比，IL-10敲除小鼠的牙槽骨丧失增加了30%～40%，相关分析还显示，牙槽骨丧失程度与肠道炎症呈正相关[32]。此外，Pietropaoli等[33]在SAMP1/YitFc小鼠（自发性克罗恩病样回肠炎模型）中同样报道了牙周病的自发性发生，牙槽骨丧失比对照小鼠更严重。

3　关联治疗证据

牙周炎与IBD的相关性在治疗方面也有所体现，控制两种疾病其中之一往往对另一项疾病的改善也有帮助。乳酸菌等益生菌对治疗IBD等胃肠道疾病具有益活性，多项临床研究表明，牙周基础治疗后辅助口服肠道益生菌（罗伊氏乳杆菌等）可显著改善牙周临床症状，并且灌胃益生菌可显著减少牙槽骨中破骨细胞的数量[34-35]。Yuan等[36]发现，采用粪便微生物群移植可修复肠道微生物群和屏障，降低口腔微生物群的致病性，缓解牙槽骨的流失。一些用于IBD治疗的药物如类固醇、补骨脂素、维生素D等也被证明可以通过修复肠道炎症损伤屏障来实现牙周炎的防治[37-39]。此外，Zhang等[40]证明随着牙周炎经外泌体治疗改善后，IBD也明显缓解。总体而言，一些研究表明牙周炎和IBD治疗之间存在关联，但此方面的数据仍然有限，仍需要更高水平的纵向研究来考虑二者治疗之间的关联性。

4　相互作用机制

上述内容从流行病学证据、生物学证据和关联治疗证据三个维度证明了牙周炎与IBD之间存在双向影响关系，然而对于二者具体的相互作用机制仍然是未知的。现有研究表明，微生物途径和免疫途径可能在二者相互作用机制方面发挥了作用。

4.1　微生物途径

人体内存在着上亿共生微生物，与人体健康息息相关，其中口腔和肠道是微生物的主要聚集地之一，二者通过微生物建立了复杂的联系。口腔细菌可通过直接异位定植影响IBD的发生发展[41]。细菌一般通过口腔肠道轴和血行方式实现肠道异位定植。口腔和肠道属于消化道的起点和终点，日常吞咽过程中，大量口腔细菌随着口腔-肠轴进入肠道[42]。IBD的异常炎症状态改变了肠道固有的微生态平衡，使得口腔细菌更容易定植。异位定植的另一种可能途径是通过口腔的血行传播。研究表明，日常牙科活动（例如用力咀嚼、刷牙）和牙科手术（例如正畸、拔牙）引起的口腔机械损伤会使口腔细菌扩散到体循环中，并通过体循环进入肠道。而牙周炎患者血液中口腔细菌的含量会更高[43]。

异位定植于肠道的口腔微生物会通过释放毒力因子、破坏肠道黏膜屏障、引发炎症反应等方式使IBD炎症进一步加重。有学者通过研究具核梭杆菌在溃疡性结肠炎发病机制中的作用得出，具核梭杆菌使炎症因子水平进一步升高，进一步加重了微生物群失调和上皮屏障损伤。具核梭杆菌的毒力因子梭杆菌粘附素A（*Fusobacterium nucleatum* adhesin A，FadA）可能在其中发挥重要作用[44]。Tsuzuno等[45]发现，在小鼠结肠炎模型中，口服牙龈卟啉单胞菌显著降低了体内紧密连接蛋白的表达，结肠炎严重程度增加，可能与其表达的牙龈蛋白酶有关。其他的口腔致病菌如肠杆菌、白色念珠菌等也通过类似的机制加重IBD[46]。

总体而言，牙周炎的存在使口腔微生物中机会致病菌的比例大大增加，相应提高了其成功进入肠道的几率。另一方面，IBD的存在影响了胃液分泌以及肠道菌群平衡，使得来自口腔的细菌更容易定植，进而通过多种作用机制影响IBD的发生发展。

4.2　免疫途径

免疫细胞可以在肠道和其他器官之间进行双向运输，并促进肠道或远处部位的疾病发展。据报道，口腔引流淋巴结中的白细胞在正常条件下也可以进入肠道，表明全身免疫细胞循环在口腔与肠道疾病中的潜在作用[47]。此外，IBD和牙周炎都属于慢性炎症性疾病，这也提示二者可能通过免疫途径进行相互作用[48]。

Th17细胞是一种致病性T细胞，被认为在免疫途径中发挥着重要作用。牙周炎期间，受到细菌毒力因子刺激，口腔内的适应性免疫被激活，从而

产生大量Th17细胞。这些口腔Th17细胞表面存在肠道归巢标记物α4β7整合素，表明它们具有肠道趋向性[49]。值得注意的是，IBD条件下，肠道黏膜上的α4β7整合素的配体表达增加，这将加速口腔Th17细胞转移至处于炎症状态的肠道[50]。当在健康肠道中时，口腔Th17细胞不会被肠道内原有的微生物激活。但在IBD条件下，来自口腔内的病原体可以激活Th17细胞并导致结肠炎的发展[51]。因此，口腔炎症（例如牙周炎）会向肠道提供致结肠炎病原体和致病性T细胞，从而加剧肠道炎症。

此外，一些研究通过评估细胞因子的表达来探究IBD是否通过免疫影响牙周炎。据报道，IBD患者口腔分泌物中TNF-α、IL-1β和IL-10的表达水平与非IBD患者不同[52]。Figueredo等[53]收集了21例IBD患者的肠道及牙龈组织，发现牙龈组织中的IL-1β、IL-6、IL-21、sCD40L、IL-23和INF-γ含量随肠道炎症水平的提高而显著增加。这些研究强调了IBD有可能通过共同的免疫炎症机制促进牙周炎，提示上述分子可能是未来治疗的潜在靶点。

5　结　语

综上，本文从流行病学证据、生物学证据、关联治疗证据三个维度概述了关于牙周炎与IBD相关性的最新研究进展，提示牙周炎与IBD之间可能存在一定的双向影响关系（图1）。同时讨论了牙周炎与IBD通过微生物途径和免疫途径进行相互作用的可能机制。未来期待有更多的关于牙周炎和IBD相关性的循证研究，并在动物疾病模型上进行针对性的干预治疗，以获得更多的直接证据，深入探究两者间的相互作用机制，以期为临床上牙周炎和IBD的预防和治疗提供理论基础。

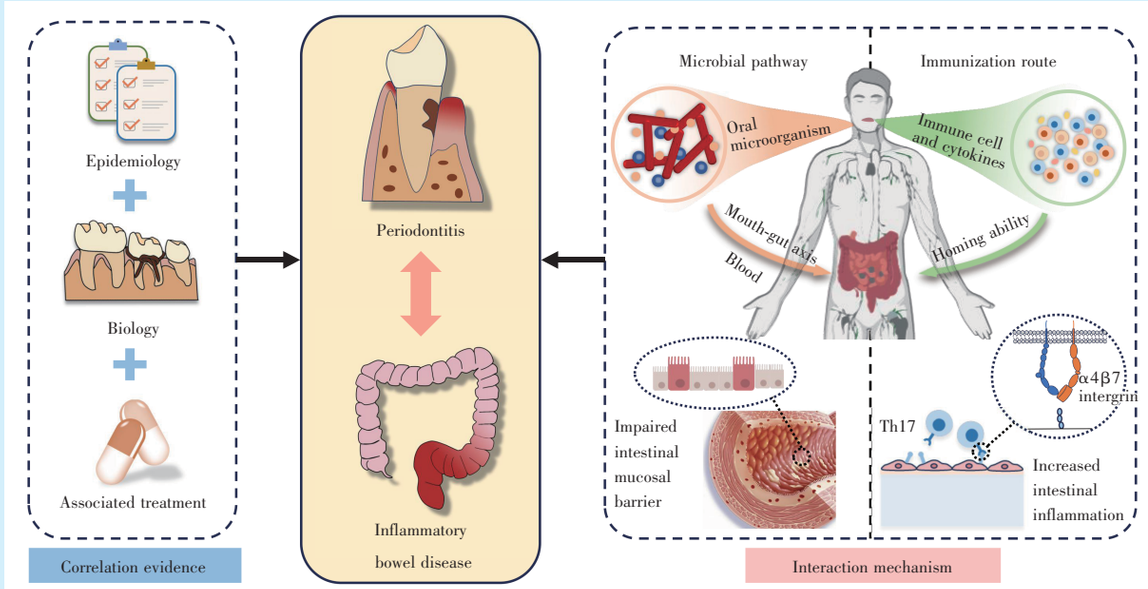

Figure 1　Periodontitis is associated with inflammatory bowel disease

图1　牙周炎和炎症性肠病具有相关性

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