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·综述·

辅助性T细胞17和白细胞介素17在口腔扁平苔藓中的研究进展

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【摘要】 口腔扁平苔藓（oral lichen planus，OLP）是发生于口腔黏膜的一种慢性炎症性疾病。临床上OLP出现不同的病损形态，被认为是宿主免疫反应差异所致。辅助性T细胞17（T-helper 17 cell，Th17）是细胞免疫应答的重要组成部分，它主要通过分泌白细胞介素17（interleukin 17，IL-17）发挥作用。IL-17在口腔黏膜中具有双重作用：一方面，它通过促进趋化因子驱动的中性粒细胞募集、增强抗菌肽的分泌以及增强黏膜的屏障功能等机制，发挥保护性作用；另一方面，它能与黏膜组织的靶细胞结合，激活核因子κB（nuclear factor kappa-B，NF-κB）、促分裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）等下游炎症信号通路，启动促炎级联反应，通过增加促炎因子的分泌并促进免疫细胞的募集与活化，从而加重炎症。目前有较多针对Th17/IL-17与OLP发生发展相关性的研究，本文旨在对这些研究进展进行综述，为进一步阐明OLP的免疫机制提供研究基础。文献复习结果显示，OLP患者口腔局部病损组织和外周血中Th17和IL-17表达上调可能是OLP发生发展的关键分子事件之一。与非糜烂型OLP相比，糜烂型OLP组织和外周血中Th17和IL-17表达水平更高，提示Th17/IL-17可能与疾病严重程度呈正相关。临床研究表明，针对Th17/IL-17轴的靶向药物通过直接阻断IL-17或抑制Th17细胞的产生发挥作用，能够有效改善OLP患者的黏膜损害，展现出其作为免疫治疗新靶点的潜力。然而，Th17和IL-17是否通过调节口腔微生物群落来影响OLP的发病过程，目前尚未有明确的研究结果。Th17/IL-17具有作为OLP免疫治疗新靶点的潜在价值，未来需进一步深入研究其在OLP炎性进程中的生物学功能和信号传导机制。

【关键词】 辅助性T细胞17；　白细胞介素17；　细胞因子；　口腔扁平苔藓；　免疫反应；　发病机制；　炎症；　口腔微生物；　靶向治疗

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Research progress on helper T cell-17 and interleukin-17 in oral lichen planus

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【Abstract】 Oral lichen planus (OLP) is a chronic inflammatory disease occurring in the oral mucosa. Clinically, OLP presents with various lesion morphologies, attributed to differences in host immune responses. T-helper 17 cells (Th17)

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are a crucial component of the cellular immune response, primarily functioning through the secretion of interleukin 17 (IL-17). IL-17 plays a dual role in the oral mucosa: on one hand, it exerts a protective effect by promoting the recruitment of neutrophils driven by chemokines, enhancing the secretion of antimicrobial peptides, and strengthening the mucosal barrier; on the other hand, it binds to target cells in the mucosal tissue, activating downstream inflammatory signaling pathways such as nuclear factor kappa-B(NF-κB) and mitogen-activated protein kinase(MAPK), thereby initiating a pro-inflammatory cascade. This process increases the secretion of pro-inflammatory factors and promotes the recruitment and activation of immune cells, exacerbating inflammation. Current research extensively explores the correlation between the Th17/IL-17 axis and the pathogenesis and progression of OLP. This paper aims to review these developments to provide a research foundation for further elucidating the immunological mechanisms of OLP. Literature review results indicate that upregulation of Th17 and IL-17 in local lesion tissues and peripheral blood of OLP patients may be a key molecular event in the development of OLP. Compared to non-erosive OLP, higher expression levels of Th17 and IL-17 in the tissues and blood of patients with erosive OLP suggest a positive correlation between Th17/IL-17 and disease severity. Clinical studies demonstrate that targeted drugs against the Th17/IL-17 axis, by directly blocking IL-17 or inhibiting the production of Th17 cells, can effectively improve mucosal damage in OLP patients, showcasing potential as a new target for immune therapy. However, whether Th17 and IL-17 influence the pathogenesis of OLP by regulating the oral microbiome remains unclear. In summary, the Th17/IL-17 axis holds potential value as a new target for the immune therapy of OLP, warranting further in-depth research into its biological functions and signaling mechanisms within the inflammatory process of OLP.

【Key words】 T-helper 17 cell; interleukin-17; cytokine; oral lichen planus; immune response; pathogenesis; inflammation; oral microbiology; targeted therapy

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口腔扁平苔藓(oral lichen planus,OLP)是发生于口腔黏膜的一种由T细胞介导的慢性炎症性疾病[1]。有关OLP的病因尚不明确,可能与多种致病因素有关,如免疫因素、精神因素、药物因素、感染因素、遗传因素及口腔局部刺激因素等[2-4]。OLP的全球发病率为1.01%,其中印度的发病率最低为0.49%,欧洲的发病率最高,为1.43%[5]。患者以中年女性为主,多数患者有疼痛不适的症状,影响患者生活质量;部分病例有癌变风险,属于口腔潜在恶性疾患[6]。临床上OLP出现不同的病损形态,被认为是宿主免疫反应差异所致[7]。研究表明,OLP的主要发病机制是异常激活的细胞免疫应答破坏口腔黏膜结构[8]。辅助性T细胞17(T-helper 17 cell,Th17)是一种$CD4^+$辅助性T细胞亚型。Th17是口腔中最早参与抗感染的免疫效应细胞之一,在细胞免疫应答过程中发挥重要作用[9]。目前有较多针对Th17和白细胞介素17(interleukin 17,IL-17)与OLP发生发展相关性的研究,本文旨在对Th17及IL-17与OLP发生发展的相关性研究作综述。

1　OLP临床特征及免疫机制概述

OLP病损为小丘疹连成的线状白色、灰白色花纹,常为双侧对称分布,最常见于颊黏膜[10-11]。OLP的临床表现多种多样,其中网纹型OLP是最常见的类型,而糜烂型OLP被认为是病变最严重和最易恶变的类型[10,12]。目前,OLP的病因尚不明确,但一般认为其炎症过程主要由T细胞介导[13]。黏膜局部上皮基底细胞受始动因素影响分泌细胞因子,T细胞在细胞因子趋化作用下滞留于上皮与结缔组织交界的区域。上皮内和凋亡角质形成细胞附近的大多数是活化的$CD8^+$ T细胞,而固有层中的大多数是$CD4^+$ T细胞[8]。$CD8^+$细胞毒性T淋巴细胞(cytotoxic T lymphocyte,Tc)活化并启动Fas途径,最终导致患者口腔黏膜内角质形成细胞凋亡和基底膜结构破坏[7-8],而$CD4^+$辅助性T细胞辅助此过程。另外,T细胞介导的自身免疫反应被认为是导致OLP慢性炎症发生发展的另一机制[14]。

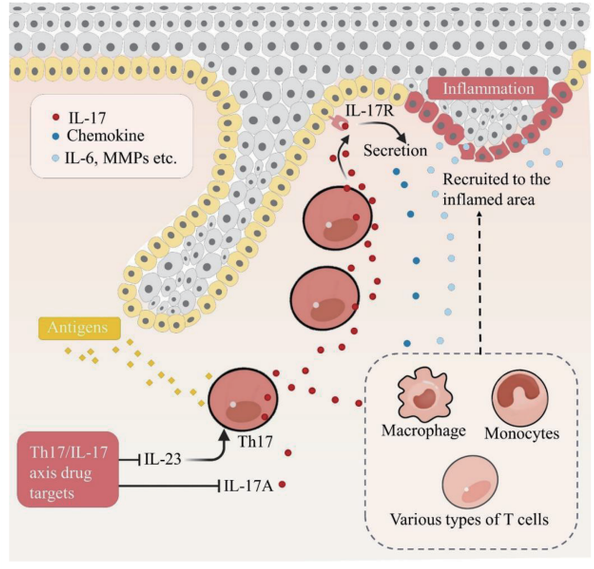
2　Th17细胞和IL-17

Th17是$CD4^+$辅助性T细胞的一个亚群,主要存在于皮肤和黏膜组织中[15]。$CD4^+$辅助性T细胞的分化主要在抗原提呈细胞和特异性细胞因子的刺激下进行,不同细胞因子对Th17分化的调控功能如下:①转化生长因子-β(transforming growth factor-β,TGF-β)和白细胞介素-6(interleukin-6,IL-6)介导的分化及激活作用[16];②白细胞介素-21(in-

terleukin-21，IL-21）介导的扩增作用[17]；③白细胞介素-23（interleukin-23，IL-23）介导的稳定作用[18]。其中IL-23虽不能直接启动Th17的分化，但确实是Th17细胞的维持、扩增和存活所必需。维A酸相关孤儿受体γt（retinoic acid receptor-related orphan receptor gamma，RORγt）是调节Th17分化的特异性关键转录因子[19]，由IL-6和IL-23通过激活信号转导及转录激活蛋白3（signal transducer and activator of transcription 3，STAT3）产生，可以调控Th17内特异性基因的表达，如IL-17A、IL-17F等[20]。Th17的分化也接受宿主局部环境的调控，在皮肤和胃肠道黏膜中Th17分化与共生定植细菌量正相关[21-22]。然而，在健康牙龈中，Th17的分化主要由生理性咀嚼刺激信号调控[21]。这种独特的调节方式能够积极应对咀嚼带来的生理损伤，激活口腔黏膜屏障保护功能[21]。因此，Th17的分化机制受到多重因素的调控，深入探究其分化机制有助于进一步理解免疫调节和炎症反应的本质。

Th17主要通过分泌促炎性的IL-17发挥免疫功能。IL-17家族包含6个成员（IL-17A、IL-17B、IL-17C、IL-17D、IL-17E和IL-17F），通过与之相应的IL-17受体结合参与调控生物学功能[23]。目前研究最多的IL-17家族成员是IL-17A，是Th17细胞发挥作用的主要执行者[24]。IL-17在宿主保护和致病过程中发挥着双重作用，既是促进保护性免疫的关键细胞因子，又在驱动炎症病理过程中发挥作用[25]。研究者在真菌和细菌感染的动物模型中证实了IL-17在黏膜中的关键保护作用，其主要作用机制为促进趋化因子驱动的中性粒细胞募集、促进抗微生物肽的分泌和增强黏膜的屏障功能[25]。然而，IL-17也具有致病性，IL-17分泌量的异常增加会损伤自身组织，特别是在慢性炎症性和自身免疫性疾病中[25-26]。在口腔黏膜组织中，IL-17的靶细胞主要包括两大类：一类为黏膜组织细胞，如上皮细胞、成纤维细胞及内皮细胞；另一类为黏膜内的免疫细胞群，如T细胞、巨噬细胞、单核细胞等[27]。IL-17一方面通过与黏膜组织细胞表面的相应受体结合，激活包括NF-κB、MAPK和C/EBP在内的下游炎症信号通路[27]，从而促进包括IL-6、IL-8、前列腺素E2和粒细胞-巨噬细胞集落刺激因子等促炎介质，趋化因子和基质金属蛋白酶（matrix metalloproteinases，MMPs）的产生，进而促进相关免疫细胞的募集和活化，加重炎症反应和组织损伤[28-29]；另一方面，IL-17也可直接参与调控免疫细胞的募集和活化（图1）。IL-17在牙周炎、OLP等其他口腔慢性炎症中的关键作用已被广泛报道[30-33]。此外，IL-17在多种自身免疫病的发病机制中的作用也已被广泛研究[29]。

除了Th17介导的炎症作用外，Th17和调节性T细胞（regulatory cell，Treg）的平衡在免疫反应中的作用也受到关注[34]。口腔黏膜中的Th17/Treg比率在正常情况下保持平衡，以维持免疫系统的正常功能[35]。当Th17/Treg比率增加时，免疫系统可



Under the influence of endogenous or exogenous antigens and the adjunct action of IL-23, CD4+ T cells differentiate into Th17 cells. Once activated, Th17 cells secrete IL-17, which interacts with the IL-17 receptors on the basal cells of the oral mucosal tissue. Activation of these receptors prompts epithelial cells to initiate a pro-inflammatory cascade, enhancing the secretion of pro-inflammatory substances, chemokines, and matrix metalloproteinases (MMPs), leading to tissue damage and inflammation in the oral mucosa. Chemokines and pro-inflammatory cytokines derived from epithelial cells regulate various immune cells, including T cells, macrophages, and monocytes. These cells are activated and recruited to the site of inflammation, exacerbating the inflammatory response. Additionally, immune cells also serve as direct targets of IL-17, being regulated by it. Current targeted therapeutics against the Th17/IL-17 axis function by either directly blocking IL-17A or inhibiting the production of Th17 cells (i.e., blocking IL-23). IL-23: interleukin-23; IL-17: interleukin-17; Th17: T helper cell 17; IL-17R: interleukin-17 receptor; CXCL: chemokine; IL-6: interleukin-6; MMPs: matrix metalloproteinases

Figure 1　Mechanisms and therapeutic targets of the Th17/IL-17 axis in oral lichen planus

图1　Th17/IL-17轴在口腔扁平苔藓中的作用机制和药物靶点

能处于过度激活的状态，促进自身免疫疾病和炎症性疾病的发生。相反，Th17/Treg比率降低可能导致免疫系统对病原体和异常细胞的应答能力下降，增加感染和肿瘤发生的风险。Th17/Treg比率受多种因素的调节，其中细胞因子的调控是重要因素[36]。

3　Th17/IL-17在OLP中的临床研究进展

3.1　Th17/IL-17在OLP患者临床样本中的表达水平的研究

最近的一项Meta分析[37]总结了过去研究中OLP患者体内IL-17水平的变化情况，共纳入22篇文献，总计658例OLP患者和362例健康对照者。研究者分别合并了使用流式细胞术和酶联免疫吸附测定（enzyme linked immunosorbent assay，ELISA）检测OLP患者外周血中Th17/IL-17表达水平的研究，结果表明OLP组外周血中Th17/IL-17水平显著高于健康对照组，差异具有统计学意义[37]。然而，统计结果显示来源不同研究的OLP患者外周血Th17/IL-17表达水平异质性较大，且未能得到解释。此外，该研究以同样的方法合并了使用实时荧光定量聚合酶链反应（quantitative real-time polymerase chain reaction，qPCR）检测病损组织中IL-17基因表达水平的研究，结果表明OLP组病损组织中IL-17基因表达水平显著高于健康对照组[37]。随后，研究者合并了使用免疫组化染色检测病损组织中Th17细胞的研究，发现与对照组相比，OLP组病损组织中Th17细胞表达量差异无统计学意义。作者认为这是由于IL-17在局部组织中可能由多种免疫效应细胞分泌，因此对于IL-17基因转录水平的检测相比对于Th17细胞含量的检测更能直接、敏感、准确地反映IL-17的表达量[37]。综上，该研究认为相对于健康人群，OLP患者外周血中Th17/IL-17水平显著升高，OLP病损组织中IL-17表达显著升高。Aboud等[38]使用酶联免疫法评估了17例接受光生物调节（photobiomodulation，PBM）治疗和17例0.05%丙酸氯倍他索治疗前后OLP患者血清和唾液中IL-17表达水平的变化，结果显示治疗前后血清和唾液中IL-17表达差异无统计学意义。Gao等[39]指出已有文献中探究OLP治疗后细胞因子表达水平变化的机制的研究较少，仍需进一步探究IL-17能否作为生物指标反映OLP治疗效果。此外，有研究表明IL-17多态性（single nucleotide polymorphisms，SNP）与OLP易感性相关[40-41]。未来对IL-17等位基因位点的检测可能具有应用于OLP的大规模筛查和预防的潜能[40]。

研究者使用流式细胞术检测33例OLP患者和17例健康对照组的外周血Th17、Treg细胞的表达水平，结果表明OLP组外周血中Th17/Treg比率显著高于健康对照组[42]。OLP是一种炎症性疾病，Th17更具有分化优势，既往有关OLP中Th17/Treg水平的研究也证实了这一点[42]。然而，在Javvadi等[43]报道的一项组织病理学研究中，研究者使用免疫组化染色发现OLP组织基底层细胞浸润的Th17数量较对照组减少而Treg细胞较之增多，这与以往的文献不同。作者认为这可能是因为Treg细胞在OLP局部炎症组织中发挥着上调的免疫抑制作用[43]。OLP患者机体循环系统的Th17/Treg平衡是否与局部组织中有差异，仍需进一步探究。

3.2　Th17/IL-17与不同类型OLP相关性的研究

临床上OLP出现不同的病损形态，被认为是宿主免疫反应差异所致。Pouralibaba等[44]通过ELISA法对比糜烂型OLP（24例）、非糜烂型OLP（24例）和健康对照组（24例）血清IL-17表达水平，发现糜烂型OLP组IL-17表达水平较非糜烂型OLP组和健康对照组显著增高。研究者使用流式细胞分选技术分别获得糜烂型和非糜烂型OLP组织中CD8+组织驻留记忆T细胞，并通过ELISA法检测上清液中IL-17的表达量，结果显示糜烂型OLP组织内IL-17含量显著上升[23]。Piccinni等[45]采用qPCR检测取自同一患者的网纹或糜烂型病损和健康口腔黏膜组织中的$CD4^+$T细胞相关的细胞因子和转录因子mRNA表达量进行研究，结果显示，糜烂型OLP病损组织中IL-17的mRNA水平升高，且Th17和Th0的mRNA水平较高，而网纹型OLP病损组织中Th2 mRNA水平较高，这进一步提示了Th17、Th0和Th2细胞可能分别在糜烂型和网纹型口腔扁平苔藓的发病机制中发挥作用。研究者使用流式细胞技术检测不同类型OLP外周血中Th17和Treg细胞的百分比，发现较非糜烂型OLP组相比，糜烂型OLP组外周血中Th17/Treg比率增加[42]。综上，Th17/IL-17在糜烂型OLP中上调比在非糜烂型OLP中更显著，提示Th17/IL-17水平与疾病严重程度可能正相关。

4　Th17/IL-17与口腔微生物相互作用在OLP中的研究

在健康的牙龈中，共生微生物群并不参与对Th17分化的调控[21]。相反，在特定的病理情况下（如牙周炎），Th17的分化依赖于共生微生物群的调控，需要IL-6和IL-23的诱导和协助[46]。

目前，口腔微生物在OLP发生发展中的作用机

制尚不清楚。Wang等[47]通过16S rDNA基因测序对OLP患者和健康对照组的唾液（n = 60）和组织（n = 24）样本进行了检测，结果表明OLP患者病损组织微生物群和唾液微生物群的群落构成有差异。与健康对照组相比，二氧化碳噬纤维菌属和孪生球菌属在OLP唾液中含量较高，而埃希氏菌-志贺氏菌和巨球形菌属在OLP组织中含量较高，而包括二氧化碳噬纤维菌属、解黄酮菌属和巨球形菌属在内的7个分类群在OLP患者的唾液和组织中均有富集。此外，该研究提到当前研究主要集中于探究OLP患者唾液微生物的组成，而对OLP病损组织处微生物组成研究较少[48-49]。这可能是对OLP发病相关微生物种属仍存争议的原因之一。目前还没有一种微生物确定与OLP的发展存在因果关系[49]。Li等[50]发现IL-17唾液表达水平与OLP疾病相关的18种口腔真菌属丰度之间呈显著正相关。此外，微生物还能够影响口腔黏膜内Th17/Treg的平衡。Zhang等[51]发现大肠杆菌在OLP病损中显著增加，将大肠杆菌脂多糖（lipopolysaccharide，LPS）与OLP患者和健康对照组外周血的T细胞共培养，并使用流式细胞术比较处理后两组T细胞的分化情况。结果表明，大肠杆菌LPS可引起OLP组织中Th17/Treg比率升高，而不会引起健康对照组中Th17/Treg比率升高。因此，该研究认为大肠杆菌能够通过促进Th17/Treg失衡参与OLP的发生发展[51-52]。综上，既往研究主要集中在探究OLP患者唾液中Th17/IL-17表达水平与微生物群落的细菌构成和多样性之间的相关性，而Th17/IL-17表达水平的改变如何影响微生物参与OLP发生发展的具体机制尚未查明。

5　Th17/IL-17作为OLP的潜在治疗靶点的研究

针对OLP的临床治疗仍面临较大的挑战，尤其是对于顽固性OLP的治疗亟需开发新的手段。Th17/IL-17与口腔念珠菌病、复发性阿弗他溃疡等多种口腔黏膜疾病的发病机制密切相关，被认为是治疗多种口腔黏膜疾病的潜在靶标[9]。由于IL-23参与Th17的分化，因此目前临床上针对Th17/IL-17轴的靶向药物主要为IL-17和IL-23拮抗剂[18]。针对IL-17、IL-23靶点的单克隆抗体已被美国食品药品监督管理局（Food And Drug Administration，FDA）批准在银屑病的治疗中使用[53]。针对IL-17靶点司库奇尤单抗（Secukinumab）可通过阻断IL-17A来抑制Th17/IL-17轴[54]，而针对IL-23靶点的乌司奴单抗（Ustekinumab）、古塞奇尤单抗（Guselkumab）和替拉珠单抗（Tildrakizumab）则可通过阻止$CD4^+$细胞向Th17细胞的分化抑制该轴[55]。

虽然既往研究表明Th17及其分泌的细胞因子在OLP的发病中有重要作用，但使用IL-17靶向抑制药物治疗OLP的临床研究较少。Solimani等[56]报道了5例接受IL-17靶向治疗的OLP患者疗效，其中3例顽固性口腔黏膜和皮肤扁平苔藓（lichen planus，LP）患者接受了司库奇尤单抗的治疗，1例顽固性OLP患者接受了乌司奴单抗的治疗，另有1名顽固性OLP患者接受了古塞奇尤单抗的治疗。研究者使用免疫组织化学染色分析治疗前后皮肤和黏膜的炎细胞浸润情况，并使用流式细胞术和ELISpot试验评估治疗前后患者的外周血T细胞的细胞因子谱。在12周的随访过程中发现，受试者病损处炎症减弱、黏膜白色网纹消退、病损糜烂愈合；且外周血和病变部位Th17/IL-17表达量下降[56]。Ismail等[57]报道了一例使用替拉珠单抗治疗顽固性糜烂型OLP患者的临床疗效，结果显示在3剂替拉珠单抗治疗后患者黏膜糜烂完全消失，仅残留细小网状条纹，临床症状显著改善。Th17/IL-17有望作为OLP治疗的新靶点，尤其是为顽固性糜烂型OLP患者提供新的治疗途径。

6　总结与展望

目前较多研究显示OLP患者口腔局部病损组织和血清中Th17和IL-17表达的上调可能是OLP发生发展的关键分子事件之一，且临床研究证实以Th17/IL-17为靶点的药物对OLP的治疗具有潜在临床应用价值，但Th17和IL-17是否通过口腔微生物群落影响OLP的发生发展尚不明确。未来进一步深入研究Th17/IL-17在OLP炎性进程中的生物学功能和信号传导机制，探究其与微生物作用的因果联系，可为明确OLP发病机制及OLP的免疫治疗提供更多科学的依据。

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