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· 综述 ·

细菌在硝苯地平诱导的药物性牙龈增生中的作用及研究进展

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【摘要】 硝苯地平诱导的药物性牙龈增生(nifedipine-induced gingival overgrowth, NIGO)是指由长期服用高血压药物硝苯地平(nifedipine, NIF)引起的牙龈增生,是一种药物不良反应。NIGO具有发病率高,患者基数大的特点,是临床上最为常见的牙龈增生类型之一。既往关于NIGO病因的研究多聚焦于NIF的直接药理作用,但近年来的研究表明,炎症亦是NIGO的关键风险因素。菌斑是牙周炎症的核心始动因素,然而细菌在NIGO发病机制中的具体作用尚不明确。本文对相关研究进行综述,探讨细菌参与NIGO发病的潜在途径:①以NIF为代表的高血压药物可引起口腔菌群失调,导致牙周致病菌相对丰度增加。在宿主对细菌的免疫应答中,牙龈成纤维细胞释放的炎症趋化因子可与NIF产生协同效应,促进胶原过度生成或募集免疫细胞参与组织纤维化进程;②转化生长因子- β (transforming growth factor- β , TGF- β)在纤维化疾病中具有重要作用,细菌感染可显著上调TGF- β 水平,进而促进上皮-间充质转化,或通过激活其下游信号通路直接参与牙龈纤维化;③细菌还可通过激活Wnt/ β -catenin通路、干扰整合素 α 2 β 1表达、抑制miR-200调控细胞周期等多种途径,导致牙龈成纤维细胞增殖异常、胶原合成增多而降解减少,最终加剧NIGO。综上,细菌是NIGO发生发展中的重要因素,对接受NIF治疗的高血压患者进行口腔菌斑控制和健康管理,对预防和缓解NIGO具有重要临床意义。未来研究可聚焦NIGO患者口腔菌群与宿主免疫细胞间的相互作用,为NIGO的预防和治疗提供新的策略。

【关键词】 药物性牙龈增生; 硝苯地平; 口腔细菌; 炎症; 上皮间充质转化; 细胞外基质; 纤维化; 口腔疾病

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【Abstract】 Nifedipine-induced gingival overgrowth (NIGO) refers to gingival hyperplasia caused by long-term use of the hypertensive drug nifedipine (NIF), and it is a drug adverse reaction. NIGO is characterized by a high incidence rate and a large patient base, and it is one of the most common types of gingival hyperplasia in clinical practice. Previous studies on the etiology of NIGO mainly focused on the pharmacological effects of NIF, while in recent years, it has been proposed that inflammation may also be a major risk factor for NIGO. Plaque is the initiating factor of periodontal inflammation. However, the role and mechanism of bacteria in the pathogenesis of NIGO remain unclear at present.

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Therefore, this article reviews relevant research and finds that bacteria may be involved in the pathogenesis of NIGO through the following pathways: ① Hypertensive drugs represented by NIF can cause dysbiosis of the oral flora, increasing the relative abundance of periodontal pathogenic bacteria. The inflammatory chemokines released by fibroblasts in the immune response to bacteria can work in synergy with NIF to promote excessive collagen production or recruit immune cells to participate in tissue fibrosis. ② Transforming growth factor- β (TGF- β) plays a significant role in fibrotic diseases. Bacterial infections can significantly increase the level of TGF- β , promoting epithelial-mesenchymal transition or allowing TGF- β and its downstream substances to directly participate in gingival fibrosis. ③ Bacteria can also cause massive proliferation of gingival fibroblasts, increased collagen synthesis and reduced degradation by activating the Wnt/ β -catenin pathway, interfering with integrin $\alpha 2 \beta 1$ expression, and inhibiting miR-200 to alter the cell cycle, ultimately exacerbating NIGO. In conclusion, bacteria may be an important factor in aggravating NIGO, and oral health management for patients with hypertension should be given due attention. Future research can focus on the interaction between the oral microbiota and immune cells in NIGO patients, providing new strategies for their prevention and treatment.

[Key words] drug-induced gingival overgrowth; nifedipine; oral bacteria; inflammation; epithelial-mesenchymal transition; extracellular matrix; fibrosis; oral diseases

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药物性牙龈增生(drug-induced gingival overgrowth, DIGO)是指长期服用特定药物引发的牙龈增生,是一种药物不良反应,主要致病药物包括抗癫痫药物、钙通道阻滞剂(calcium channel blockers, CCBs)、免疫抑制剂等。在上述药物中,CCBs所引起的DIGO因其庞大的用药群体而备受关注。CCBs作为我国治疗高血压的一线用药,其临床使用率高达46.5%^[1]。硝苯地平(nifedipine, NIF)是其中最具代表性的药物,常用于治疗高血压和心血管类疾病^[1-2],但其诱导的牙龈增生(nifedipine-induced gingival overgrowth, NIGO)发病率可高达20%~83%^[3-4]。尽管新一代CCBs(如氨氯地平)在药效和安全性上均优于NIF^[5],且在国外市场已成为心血管疾病主流用药,但DIGO发病率仍可达3.3%~31.4%^[6-7]。因此,相较于抗癫痫药物和免疫抑制剂,CCBs所致的DIGO因其患者基数更大,其公共健康影响更为显著。而在CCBs类别中,NIF因其较高的NIGO发病率和广泛的临床使用,使得其诱导的NIGO疾病模型更具有代表性。临床上,重度NIGO常伴随牙周炎症,不仅损害患者的口腔功能与美观,亦严重影响其生活质量。在我国,高血压发病率高达31.6%且呈持续上升趋势^[8],NIF作为其常用药物无疑加重了庞大高血压患者群体的牙周健康负担。

目前研究认为,NIGO的发病机制主要与NIF

的药理作用直接相关,涉及胶原合成—降解失衡、上皮间充质转化、细胞外基质过度沉积、细胞增殖与凋亡异常等多种因素^[9-12]。然而近来的证据表明,菌斑控制水平可能是影响NIGO的主要风险因素^[13-15]。研究发现,NIGO患者龈下菌斑中,牙周致病性微生物的相对丰度显著高于无增生者^[16-17];此外,动物实验表明,口腔链球菌感染可加重NIGO增生程度^[18]。上述发现提示,口腔微生物可能与DIGO的发病过程间存在密切关联。因此,深入研究菌斑微生物在NIGO发生发展中的作用及机制,对指导高血压患者的口腔菌斑控制,实现NIGO的有效预防和治疗具有重要意义。

1 细菌在药物性牙龈增生中的作用基础

1.1 菌斑生物膜的形成、作用与失衡

口腔作为与外界相连的器官,有着涵盖1 000余种微生物的复杂微生态系统,其中细菌种类可多达700余种^[19]。在口腔环境中,细菌主要以生物膜的形式存在于牙齿及其他组织表面,即菌斑生物膜。菌斑生物膜的形成始于唾液糖蛋白和龈沟液形成获得性膜,随后细菌经黏附、共聚集、成熟等阶段,逐步形成结构复杂的成熟生物膜,存在于牙齿表面、龈沟等部位。在健康个体中,口腔菌斑生物膜主要由早期定植菌(如链球菌、放线菌等)组成^[20-21]。这些共生菌与宿主之间维持着稳定的

共生关系,它们通过产生碱性代谢产物、细菌素和过氧化氢等物质,共同维持口腔环境的稳定,并抑制潜在的致病菌^[22-23]。当宿主的健康状况发生改变时,例如宿主免疫功能受损、口腔卫生状况不佳或唾液分泌减少等,口腔微生物平衡可被打破。这种口腔微生态失调可导致牙周致病菌,如牙龈卟啉单胞菌(*Porphyromonas gingivalis*, *P.g*)、福赛坦氏菌(*Tannerella forsythia*, *T.f*)等厌氧菌的相对丰度显著增加,逐渐在生物膜中占据主导地位^[24-25]。这些病原菌可通过代谢活动改变口腔环境^[26],促进牙菌斑的积累和结构变化,进而引起牙周炎症^[27-28]。

1.2 高血压药物对口腔微生态的影响及NIGO龈下菌斑特征

高血压药物可间接或直接地影响口腔微生态:其间接作用体现在通过影响口腔物理化学环境进而影响口腔菌群,如高血压药物可降低唾液腺分泌功能、增加唾液粘度和促使局部微环境酸化^[28-30],而以上改变可影响细菌代谢,从而诱导微生态紊乱^[30-32]。药物的直接作用则表现为对口腔菌群的选择性调控,如Silveira等^[33]发现高血压个体中*P.g*、中间普氏菌(*Prevotella intermedia*, *P.i*)和具核梭杆菌(*Fusobacterium nucleatum*, *F.n*)的检出水平更高;而Zhang等^[34]、Kim等^[35]则通过宏基因组测序、16S rRNA测序发现,抗高血压药物的使用与牙周致病菌*T.f*、齿垢密螺旋体(*Treponema denticola*, *T.d*)、龈沟产线菌(*Filifactor alocis*, *F.a*)的相对丰度显著升高相关,这可能与硝酸盐还原菌丰度降低有关。这种由药物驱动的微生态紊乱,在NIGO患者的龈下微环境中尤为显著。在NIGO病变区域,异常增生的牙龈组织导致牙周袋加深,不仅造成了菌斑的机械性滞留,也形成了局部缺氧的微环境,这为厌氧菌的生长创造了有利条件。已有研究通过PCR技术检测DIGO患者的龈下菌斑,结果显示在牙龈增生的患者龈下菌斑中,*P.g*、*P.i*、*T.d*和*T.f*的相对丰度显著高于服用NIF但未出现牙龈增生的高血压患者^[16-17],表明特定的牙周致病菌可能在NIGO的病理生理过程中起重要作用。

2 细菌促进牙龈增生的分子机制

2.1 牙龈成纤维细胞的免疫识别与胶原生成作用

牙龈成纤维细胞(gingival fibroblasts, GFs)作为牙龈结缔组织最丰富的细胞之一,其主要功能为合成与重塑胶原蛋白等细胞外基质(extracellular

matrix, ECM),从而维持组织结构完整。虽然已有研究表明,DIGO相关药物能上调GFs炎症相关基因的表达、促进牙龈的炎症反应^[36-37],但细菌感染仍然是驱动牙周炎发生发展的始动因素。GFs可表达多种模式识别受体,在炎症过程中发挥重要作用^[38],包括Toll样受体(Toll-like receptors, TLRs)家族的TLR1-9、蛋白酶激活受体-1等^[39-40]。其中,TLRs在细菌识别中占主要作用,例如,TLR2可识别*P.g*的菌毛和*F.a*的脂磷壁酸、TLR4可识别革兰氏阴性菌的脂多糖(lipopolysaccharides, LPS)等^[41]。这些细菌可激活不同的通路分泌白细胞介素-1 β (interleukin-1 β , IL-1 β)、白细胞介素-6(interleukin-6, IL-6)、白细胞介素-8(interleukin-8, IL-8)等促炎细胞因子和趋化因子,招募免疫细胞清除病原体^[42]。Lu等^[43]的研究证明了IL-1 β 和NIF具有协同作用,可通过IL-6-STAT3-Col α 1(I)级联反应加剧胶原的过度合成,为炎症在NIGO发病中的作用提供了重要证据。

2.2 细菌的促上皮-间充质转化反应

牙龈上皮是牙周组织的第一道屏障,在抵抗细菌的侵袭中具有重要作用^[44]。研究表明^[3],DIGO患者牙龈组织中,常观察到细胞间黏附减少、基底膜降解和组织纤维化,提示上皮-间充质转化(epithelial-mesenchymal transition, EMT)在DIGO发病中有重要作用。EMT是指上皮细胞失去自身特性而转化为具有迁移能力的间充质干细胞的过程,如E-钙黏蛋白是维持上皮细胞间连接的关键分子,其表达下调被视为EMT启动的重要标志。在组织纤维化过程中,EMT被认为是成纤维细胞的重要来源之一。DIGO相关药物可通过上调转化生长因子- β 1(transforming growth factor- β 1, TGF- β 1)、锌指E盒结合同源异形框蛋白1(zinc finger E-box binding homeobox 1, ZEB1)、锌指E盒结合同源异形框蛋白2(zinc finger E-box binding homeobox 2, ZEB2)、Snail、Slug、睾丸蛋白聚糖1(sparc/osteonectin, cwcv, and kazal-like domains proteoglycan 1, SPOCK1)等多种EMT相关因子,促进EMT的发生^[3, 45]。其中,TGF- β 1被视为最强EMT调控诱导分子,经TGF- β /Smad轴可驱动多个转录因子的表达,从而调控EMT进程^[46];如Snail是TGF- β 1诱导EMT的首要驱动因子,与Slug在抑制E-钙黏蛋白过程中具有协同和补充作用^[47];ZEB1、ZEB2则可抑制上皮标志物并激活间充质基因来推动细胞表型转化,其表达不仅受TGF- β /Smad通路

调控还受 MAPK、Wnt/ β -catenin 等信号通路的共同调控^[48-50]；而 SPOCK1^[45, 51] 作为纤维化模型中的 EMT 促进因子，其表达可被 TGF- β 1 通过 Smad 与磷脂酰肌醇 3-激酶 (phosphatidylinositol 3-kinase, PI3K)/蛋白激酶 B (protein kinase B, AKT) 信号通路上调，进而增强 Snail 和 ZEB1 等转录因子的作用，最终促进细胞黏附的降解与基质重塑。在以 TGF- β 1 为核心的复杂调控网络中，牙周病原菌也可通过其致病物质来促进 EMT。例如，*F.n* 可通过 TLR4 信号通路激活 Akt 直接影响 E-钙黏蛋白的表达^[52-53]；张升华等^[54] 证明 *P.g* 可通过 TGF- β /Smad 轴诱导 Snail 和 Slug 等转录因子；Zhang 等^[55] 发现 *F.n* 可促进 Snail 1 表达；Abdulkareem 等^[56]、Saliem 等^[57] 则证明 *P.g*、*F.n* 可通过不同途径诱导 Snail、Slug 和 N-钙黏蛋白的表达，从而下调 E-钙黏蛋白。因此，EMT 可能是牙龈上皮组织对牙周病原菌的应激反应。在 NIF 等药物与局部菌群的协同作用下，EMT 进程被异常激活，导致上皮细胞向间充质细胞转化，为细胞外基质的异常沉积提供条件，最终共同驱动了 DIGO 的纤维化病理进程。

2.3 细菌与细胞外间质沉积

2.3.1 细菌与细胞因子的促纤维化作用 TGF- β 1 是 DIGO 发病的关键调控因子，除诱导 EMT 外，还具有刺激胶原蛋白合成、诱导结缔组织生长因子 (connective tissue growth factor, CTGF) 表达的作用^[58-59]。研究证实，NIF 可上调牙龈组织中的 TGF- β 1 水平^[45, 60]。而 Schweizer 等^[61] 使用细菌来源的 LPS 干预正常人真皮成纤维细胞 8 h 后，TGF- β 1 的表达显著上调，说明细菌或其致病物质感染也可能是 NIGO 发病中 TGF- β 1 的重要诱因之一。CTGF 作为 TGF- β 的关键下游介质，在介导成纤维细胞增殖和胶原过度生成中发挥重要作用^[62-63]。Wiedmaier 等^[64]、Situmorang 等^[65] 通过细胞实验证明，细菌感染可诱导 CTGF 的表达上调。然而 TGF- β 1 分泌来源广泛，绝大多数免疫细胞均可分泌 TGF- β 1^[66-68]。尽管以上实验证明细菌感染可升高 TGF- β 1 水平及其下游介质，但其主要来源却不明确。GFs 在对牙周病原菌的免疫应答中可产生炎症趋化因子以募集免疫细胞到炎症组织^[38]；且体外研究证明 NIF 可诱导 M0 巨噬细胞向 M1 极化，而该过程可能进一步募集能大量分泌 TGF- β 1 的 M2 巨噬细胞^[69]。因此，GFs 与巨噬细胞的互作可能在 NIF 存在时更为显著，纤维化可能是 GFs 对细菌感染的应激反应，参与组织修复或免疫调节。

2.3.2 细菌激活 Wnt / β -catenin 信号通路 Wnt / β -catenin 在多种组织器官纤维化中发挥重要作用，该信号通路的激活能诱导 GFs 增殖并活化为肌成纤维细胞，从而促进 ECM 大量沉积^[70-73]。研究表明，在 NIGO 患者的牙龈组织中，Wnt / β -catenin 信号通路相关蛋白表达显著高于正常牙龈^[74]。此外，多种病原细菌也可通过不同的机制激活 Wnt/ β -catenin 信号通路，从而影响宿主细胞的增殖和炎症反应^[75]。例如，*F.n* 可凭借其毒力因子结合宿主细胞 E-钙粘蛋白等分子，激活 Wnt/ β -catenin 通路或通过其黏附蛋白 FadA 激活 β -catenin 来上调 Wnt 信号^[76]；*P.g* 通过其牙龈蛋白酶降解 E-钙粘蛋白，破坏其与 β -catenin 的膜结合复合体，使 β -catenin 释放并进入细胞核，或通过维持 β -catenin 磷酸化状态以保持转录活性^[77]；而肺炎克雷伯菌通过其产生的 LPS 可激活 Wnt/ β -catenin 通路^[78]。这些证据表明，牙周致病菌是 NIGO 中 Wnt/ β -catenin 通路异常激活的重要因素。

2.3.3 细菌对细胞周期相关 miRNA 的调控 miR-200 是一类非编码小 RNA 分子，属于微小-RNA (microRNA, miRNA) 家族，可以通过多种机制影响细胞周期的不同阶段，从而影响细胞的增殖和分化。其在牙龈增生、口腔黏膜纤维化疾病中显著下调，可能是疾病的关键分子^[79]。在 DIGO 中，环孢素 A 通过作用于 miR-200 / ZEB2 轴，抑制 miR-200a、上调 ZEB2 表达，从而促进细胞增殖^[80]。牙周病原菌同样表现出对 miR-200 家族的调控能力，Krongbaramee 等^[81] 在肥胖合并牙周炎小鼠模型中，注射 *P.g* 来源的 LPS 可显著降低小鼠牙周组织中 miR-200c 表达水平。尽管有研究显示，miR-4651 在 NIGO 中可抑制牙龈间充质干细胞增殖^[4]，可能成为治疗 NIGO 的靶点，但目前没有直接证据表明牙周病原菌可直接影响 miR-4651 的表达。

2.4 细菌与胶原降解失衡

胶原降解减少是 NIGO 组织纤维化的核心病理环节。生理条件下，胶原的降解途径可分为整合素 α 2 β 1 受体介导的细胞内吞噬和基质金属蛋白酶 (matrix metalloproteinases, MMPs) 介导的细胞外吞噬过程，两条途径相互协同，共同维持着 ECM 的动态平衡。整合素 α 2 β 1 是一种金属蛋白，其功能依赖 Mg^{2+} 和 Ca^{2+} 的相互作用。该受体与 I 型胶原具有高度亲和力，二者结合可使 Ca^{2+} 内流，进而触发一系列细胞内信号传导途径，促进胶原在细胞内吞噬和降解^[82]。NIF 作为钙通道阻滞剂可能

干扰这一过程,降低整合素的结合力,从而抑制胶原的内吞降解^[83]。在NIGO中,除了药物的直接作用,牙周病原菌亦可通过多种机制干扰整合素介导的降解通路。Baba等^[84]的研究指出,*P.g*与成纤维细胞共培养后,整合素 $\alpha 2\beta 1$ 和整合素 $\beta 3$ 显著减少;Liu等^[85]则通过实验发现厌氧消化链球菌(*Peptostreptococcus anaerobius*, *P.a*)可与结直肠癌细胞的整合素 $\alpha 2\beta 1$ 受体直接结合发挥作用。由此推断细菌的入侵可能抑制整合素 $\alpha 2\beta 1$ 的表达或通过竞争性结合整合素 $\alpha 2\beta 1$ 受体,从而减少胶原降解。整合素 $\alpha 2\beta 1$ 与I型胶原的结合不仅影响细胞内吞噬,还影响MMP1基因的表达^[86-87],其编码产物MMP1在细胞外降解胶原蛋白和弹性蛋白中发挥重要作用^[88-89]。尽管在常规炎症反应中,MMPs的表达通常会被上调以促进组织重塑^[90],但在NIGO的复杂环境中,情况并非如此。有研究指出,细菌对MMPs表达的上调作用具有细胞特异性,仅黏膜上皮细胞(如结肠、膀胱、肺上皮细胞)被诱导,成纤维细胞、单核细胞、角质形成细胞等无响应^[91]。此外,TGF- β 也可调控MMP1的表达,抑制胶原降解过程。因此在NIGO患者中^[92],在NIF和细菌的共同作用下MMPs的表达受到抑制,但具体的作用机制,还需进一步验证。

3 总结与展望

中老年群体是高血压和牙周病的高发病群体^[8, 93],高血压与牙周炎之间可相互影响^[94-95]。抗高血压药物可通过改变唾液性质和选择性调控口腔菌群,促进口腔微生态紊乱,导致牙周病原菌丰度增高^[35],反之,牙周病原菌亦可加重高血压^[34]。牙周病原菌的协同作用可增强其入侵能力与致病性^[96-97]。既往研究认为,牙周病原菌主要通过降解ECM破坏牙周组织^[89],但在NIGO患者中研究者却发现牙龈增生与炎症反应并存且相互加剧的现象。据此推测在NIF的参与下,细菌可能在牙龈纤维性增生中可能起到重要作用。

牙龈上皮是牙周组织非特异性免疫的第一道防线,在与牙周病原菌相互作用的过程中,GFs释放的炎症因子和趋化因子可参与纤维化过程。如IL-1 β 、IL-6可与NIF协同促进胶原过度生成;而趋化因子招募的免疫细胞如巨噬细胞可能是TGF- $\beta 1$ 的重要来源。因此,纤维化也可能是牙周组织的应激反应。TGF- $\beta 1$ 不仅可促进EMT,还直接参与组织纤维化。牙周病原菌如*P.g*、*F.n*等也可通过

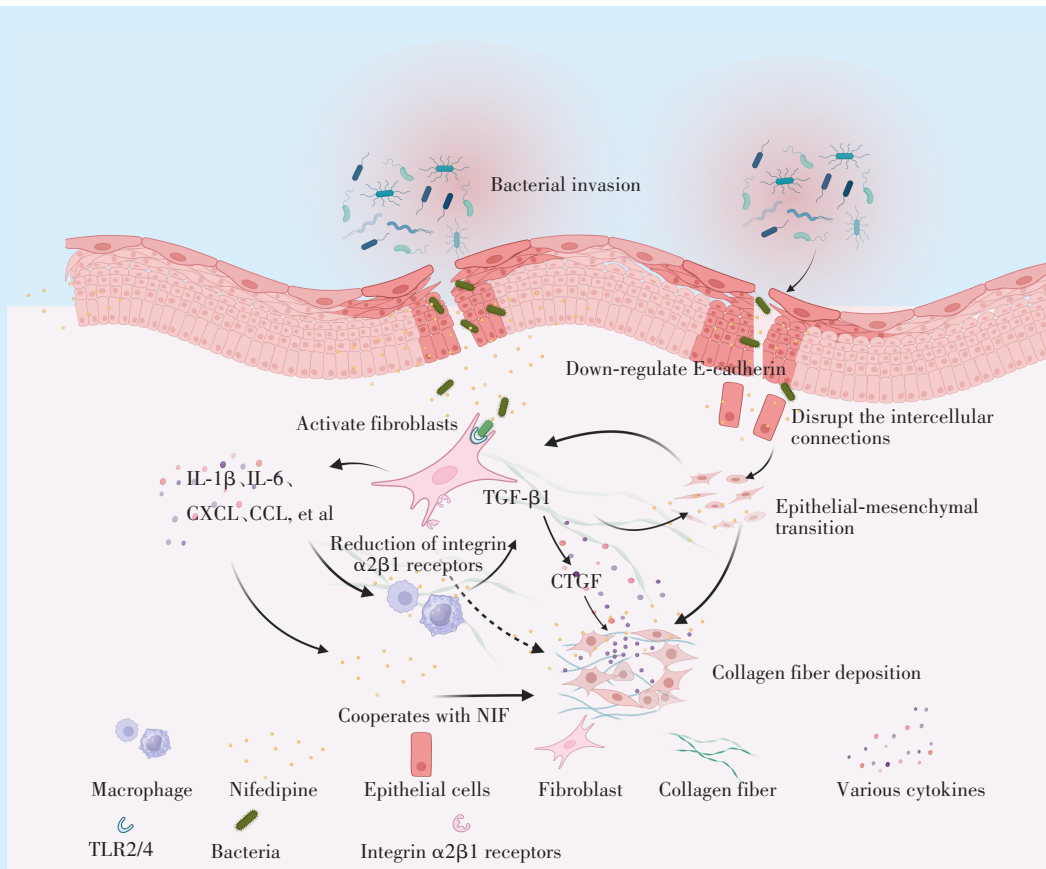
不同途径下调E-钙黏蛋白来破坏细胞间连接,该过程不仅促进上皮-间充质转化,还有利于细菌的进一步侵袭^[98]。此外,细菌还可通过激活Wnt/ β -catenin通路、干扰整合素 $\alpha_2\beta_1$ 表达、抑制miR-200表达而改变细胞周期等作用,使GFs大量增殖、胶原合成增多而降解减少,最终加重NIGO的病理进程(图1)。

目前,NIGO中细菌感染与NIF的相互作用机制尚不完全清楚。临床研究表明,对于轻度增生患者,在不更换抗高血压药物的情况下,通过牙周基础治疗彻底去除牙石即可显著改善症状^[99];对于牙龈增生显著者,则需更换抗高血压药物,联合牙周基础治疗和抗生素^[100](如阿奇霉素、米诺环素),以取得更好的疗效。然而,长期使用广谱抗生素有引发口腔菌群失调及继发念珠菌感染的风险。若牙龈严重增生,保守治疗效果不佳时则应考虑手术治疗,如牙龈切除术、牙龈成形术等;术后需加强口腔卫生管理,以防止复发。因此,NIGO的早期预防和治疗显得更为重要,在高血压患者的用药初期,即应由内科医生和口腔医生共同指导,进行相关的健康教育,并采取措施预防NIGO。然而目前对高血压患者的口腔健康管理以及NIGO的预防和早期治疗仍然缺乏重视。深入阐明细菌在NIGO发病中的具体作用,可为其治疗提供新的理论依据与方案,如针对差异菌群使用窄谱抗生素减少副作用,或根据多因素构建风险预测模型以制定个性化治疗方案,有利于高血压患者的口腔健康和血压控制。展望未来,可利用高通量测序等先进技术,深入探究牙周病原菌、GFs、免疫细胞三者互作网络,为NIGO的发病机制提供新的视角。

[Author contributions] Ma XR reviewed the literature, wrote and revised the article. Zhang XM contributed to the conception and review of the article. All authors read and approved the final manuscript as submitted.

参考文献

- [1] 陈源源. 硝苯地平不同制剂临床应用的中国专家共识[J]. 中华老年心脑血管病杂志, 2022, 24(11): 1143-1148. doi: 10.3969/j.issn.1009-0126.2022.11.007.
Chen YY. Consensus of Chinese experts on clinical application of different nifedipine preparations[J]. Chin J Geriatr Heart Brain Vessel Dis, 2022, 24(11): 1143-1148. doi: 10.3969/j.issn.1009-0126.2022.11.007.
- [2] Cui B, Dong Z, Zhao M, et al. Analysis of adherence to antihypertensive drugs in Chinese patients with hypertension: a retrospec-



Bacteria promote drug-induced gingival overgrowth through multiple mechanisms. GFs express pattern recognition receptors such as TLR. After recognizing periodontal pathogens, they activate pro-inflammatory signaling pathways (such as IL-6-STAT3) and, in synergy with nifedipine, up-regulate collagen synthesis. Meanwhile, bacteria and their products can induce EMT and further stimulate GF activation and extracellular matrix deposition by up-regulating TGF-β1 and activating the Wnt/β-catenin pathway. In addition, bacterial infection may inhibit the expression of integrin α2β1 and the activity of matrix metalloproteinases (MMPs), thereby reducing collagen degradation. In conclusion, bacterial infections jointly lead to abnormal proliferation of gingival tissue by intensifying inflammation, promoting fibrosis and hindering matrix degradation. NIF: nifedipine; IL-1β: interleukin-1β; IL-6: interleukin-6; TGF-β1: Transforming growth factor; CTGF: Connective tissue growth factor; TLR: Toll-Like Receptor; GFs: gingival fibroblasts; EMT: epithelial-mesenchymal transition; CXCL: C-X-C Chemokine Ligand; CCL: C-C Chemokine Ligand

Figure 1 The mechanism by which bacteria aggravate nifedipine-induced gingival overgrowth

图1 细菌加重硝苯地平诱导的药物性牙龈增生的相关机制

- tive analysis using the China health insurance association database [J]. Patient Prefer Adherence, 2020, 14: 1195-1204. doi: 10.2147/PPA.S243665.
- [3] Drożdżik A, Drożdżik M. Drug-induced gingival overgrowth: molecular aspects of drug actions[J]. Int J Mol Sci, 2023, 24(6): 5448. doi: 10.3390/ijms24065448.
- [4] Han X, Yang R, Yang H, et al. miR-4651 inhibits cell proliferation of gingival mesenchymal stem cells by inhibiting HMGA2 under nifedipine treatment[J]. J Clin Oral Sci, 2020, 12(1): 10. doi: 10.1038/s41368-020-0076-8.
- [5] Lee HW, Huang CC, Leu HB, et al. Comparative efficacy of generic nifedipine versus brand-name amlodipine for hypertension management in Taiwan[J]. J Clin Hypertens (Greenwich), 2022, 24(7): 870-877. doi: 10.1111/jch.14521.
- [6] Wojda M, Świstowska M, Wielgosz A, et al. Gingival overgrowth during hypertension therapy. A case report and literature review [J]. Qual Sport, 2024, 16: 52604. doi: 10.12775/qs.2024.16.52604.
- [7] Desnica J, Vujovic S, Stevanovic M, et al. Gingival enlargement caused by calcium channel blockers[J]. Exp Appl Biomed Res EABR, 2024. doi: 10.2478/sjccr-2021-0061.
- [8] 刘明波, 何新叶, 杨晓红, 等. 《中国心血管健康与疾病报告 2024》要点解读[J]. 实用医学杂志, 2025, 41(14): 2111-2131. doi: 10.3969/j.issn.1006-5725.2025.14.001.
- Liu MB, He XY, Yang XH, et al. Interpretation of annual report on cardiovascular health and diseases in China 2024[J]. J Pract Med, 2025, 41(14): 2111-2131. doi: 10.3969/j.issn.1006-5725.2025.14.001.
- [9] Liu Y, Peng Q, Liu B, et al. Er, Cr: YSGG laser therapy for drug-induced gingival overgrowth: a report of two case series[J]. Front Surg, 2022, 9: 922649. doi: 10.3389/fsurg.2022.922649.
- [10] Wan M, Wan M, Syamimi IMZ, et al. Assessment of gingival status and gingival overgrowth among immunosuppressed patients in uni-

- versiti sains Malaysia hospital[J]. J Dent Indones, 2021, 28(1): 27-32. doi: 10.14693/jdi.v28i1.1172.
- [11] Imagawa M, Shinjo T, Sato K, et al. Epithelial-to-mesenchymal transition, inflammation, subsequent collagen production, and reduced proteinase expression cooperatively contribute to cyclosporin-A-induced gingival overgrowth development[J]. Front Physiol, 2023, 14: 1298813. doi: 10.3389/fphys.2023.1298813.
- [12] Kaliyaperumal R, Appusamy K, Gokulraj S, et al. Laser-assisted gingivectomy in amlodipine-induced gingival enlargement: a case report[J]. Cureus, 2024, 16(12): e75761. doi: 10.7759/cureus.75761.
- [13] Tungare S, Paranjpe AG. Drug-induced gingival overgrowth[M/OL]. Treasure Island: StatPearls Publishing (2022-09-19)[2025-07-31]. <https://www.ncbi.nlm.nih.gov/books/NBK538518/>.
- [14] Manjunatha VA, Wodeyar VB, Pandey L, et al. Nifedipine induced gingival overgrowth - a detailed histopathological and clinical analysis: a case series[J]. Oral Maxillofac Path, 2023, 14(2): 233-237.
- [15] Gaur S, Agnihotri R. Is dental plaque the only etiological factor in amlodipine induced gingival overgrowth? A systematic review of evidence[J]. J Clin Exp Dent, 2018, 10(6): e610-e619. doi: 10.4317/jced.54715.
- [16] 龚逸明, 曹凌峰, 杨毅, 等. 五种牙周致病菌与药物性牙龈增生的关系[J]. 中华口腔医学杂志, 2008, 43(6): 347-351. doi: 10.3321/j.issn:1002-0098.2008.06.007.
- Gong YM, Cao LF, Yang Y, et al. Relationship of putative periodontopathogenic bacteria and drug-induced gingival overgrowth [J]. Chin J Stomatol, 2008, 43(6): 347-351. doi: 10.3321/j.issn: 1002-0098.2008.06.007.
- [17] 刘海杰, 潘亚萍. 牙周致病微生物与药物性牙龈肥大的关系[J]. 口腔医学研究, 2015, 31(4): 370-372, 376. doi: 10.13701/j.cnki.kqxyj.2015.04.015.
- Liu HJ, Pan YP. Relationship between periodontal pathogens and drug-induced gingival enlargement[J]. J Oral Sci Res, 2015, 31(4): 370-372, 376. doi: 10.13701/j.cnki.kqxyj.2015.04.015.
- [18] Morisaki I, Kato K, Loyola-Rodriguez JP, et al. Nifedipine-induced gingival overgrowth in the presence or absence of gingival inflammation in rats[J]. J Periodontol Res, 1993, 28(6 Pt 1): 396-403.
- [19] Radaic A, Kapila YL. The oralome and its dysbiosis: new insights into oral microbiome-host interactions[J]. Comput Struct Biotechnol J, 2021, 19: 1335-1360. doi: 10.1016/j.csbj.2021.02.010.
- [20] Esberg A, Barone A, Eriksson L, et al. *Corynebacterium matruchotii* demography and adhesion determinants in the oral cavity of healthy individuals[J]. Microorganisms, 2020, 8(11): 1780. doi: 10.3390/microorganisms8111780.
- [21] Scheithauer TPM, Fernandes de Oliveira IM, Ossendrijver M, et al. Yeast cell wall derivatives as a potential strategy for modulating oral microbiota and dental plaque biofilm[J]. Front Oral Health, 2025, 6: 1543667. doi: 10.3389/froh.2025.1543667.
- [22] Tian J, Utter DR, Cen L, et al. Acquisition of the arginine deiminase system benefits epiparasitic saccharibacteria and their host bacteria in a mammalian niche environment[J]. Proc Natl Acad Sci USA, 2022, 119(2): e2114909119. doi: 10.1073/pnas.2114909119.
- [23] Franco EM, Alves LA, Naveed H, et al. Amyloid fibrils produced by *Streptococcus sanguinis* contribute to biofilm formation and immune evasion[J]. Int J Mol Sci, 2023, 24(21): 15686. doi: 10.3390/ijms242115686.
- [24] Arce M, Endo N, Dutzan N, et al. A reappraisal of microbiome dysbiosis during experimental periodontitis[J]. Mol Oral Microbiol, 2022, 37(5): 180-195. doi: 10.1111/omi.12382.
- [25] Diao J, Yuan C, Tong P, et al. Potential roles of the free salivary microbiome dysbiosis in periodontal diseases[J]. Front Cell Infect Microbiol, 2021, 11: 711282. doi: 10.3389/fcimb.2021.711282.
- [26] Wei F, Wu Z, Li G, et al. Ensemble learning for microbiome-based caries diagnosis: multi-group modeling and biological interpretation from salivary and plaque metagenomic data[J]. BMC Oral Health, 2025, 25(1): 1188. doi: 10.1186/s12903-025-06590-2.
- [27] Tan HC, Cheung GSP, Chang JWW, et al. *Enterococcus faecalis* shields *Porphyromonas gingivalis* in dual-species biofilm in oxic condition[J]. Microorganisms, 2022, 10(9): 1729. doi: 10.3390/microorganisms10091729.
- [28] Santi-Rocca J, Martín-García DF, Lorca-Alonso I, et al. Microbial complexes in subgingival plaque: a bacterial meta-taxonomic study [J]. J Clin Periodontol, 2025, 52(7): 983-998. doi: 10.1111/jcpe.14138.
- [29] Ramírez Martínez-Acitores L, Hernández Ruiz de Azcárate F, Casañas E, et al. Xerostomia and salivary flow in patients taking antihypertensive drugs[J]. Int J Environ Res Public Health, 2020, 17(7): 2478. doi: 10.3390/ijerph17072478.
- [30] Mohiti A, Eslami F, Dehestani MR. Does hypertension affect your saliva properties[J]. J Dent (Shiraz), 2020, 21(3): 190-194. doi: 10.30476/DENTJODS.2019.80992.0.
- [31] du Toit L, Sundqvist ML, Redondo-Rio A, et al. The effect of dietary nitrate on the oral microbiome and salivary biomarkers in individuals with high blood pressure[J]. J Nutr, 2024, 154(9): 2696-2706. doi: 10.1016/j.tjnut.2024.07.002.
- [32] Alam J, Lee A, Lee J, et al. Dysbiotic oral microbiota and infected salivary glands in Sjögren's syndrome[J]. PLoS One, 2020, 15(3): e0230667. doi: 10.1371/journal.pone.0230667.
- [33] Silveira TMD, Silva CFE, Vaucher RA, et al. Higher frequency of specific periodontopathogens in hypertensive patients. A pilot study[J]. Braz Dent J, 2022, 33(5): 64-73. doi: 10.1590/0103-6440202204914.
- [34] Zhang J, Chen BY, Zhi MF, et al. Linking oral microbiota to periodontitis and hypertension unveils that *Filifactor alocis* aggravates hypertension via infiltration of interferon- γ ⁺ T cells[J]. mSystems, 2025, 10(6): e0008425. doi: 10.1128/msystems.00084-25.
- [35] Kim HJ, Shim KW, Na HS, et al. Assessing the effect of antihypertensives on plaque microbiota in patients with periodontitis and hypertension using 16S rRNA sequencing: a cross-sectional study[J]. J Periodontol, 2023, 94(4): 529-541. doi: 10.1002/JPER.22-0204.
- [36] Rapone B, Ferrara E, Santacroce L, et al. Periodontal microbiological status influences the occurrence of cyclosporine-A and tacrolimus-induced gingival overgrowth[J]. Antibiotics (Basel),

- 2019, 8(3): 124. doi: 10.3390/antibiotics8030124.
- [37] Lauritano D, Lucchese A, Di Stasio D, et al. Molecular aspects of drug-induced gingival overgrowth: an *in vitro* study on amlodipine and gingival fibroblasts[J]. Int J Mol Sci, 2019, 20(8): 2047. doi: 10.3390/ijms20082047.
- [38] Schuster R, Rockel JS, Kapoor M, et al. The inflammatory speech of fibroblasts[J]. Immunol Rev, 2021, 302(1): 126-146. doi: 10.1111/imr.12971.
- [39] Wielento A, Lagosz-Cwik KB, Potempa J, et al. The role of gingival fibroblasts in the pathogenesis of periodontitis[J]. J Dent Res, 2023, 102(5): 489-496. doi: 10.1177/00220345231151921.
- [40] Vashishta A, Li L, Srivastava S, et al. *Filifactor alocis* pathogenicity requires TLR2 and the oral microbiome[J]. J Dent Res, 2025, 104(11): 1248-1256. doi: 10.1177/00220345251331959.
- [41] Nieboga E, Schuster A, Drapala DM, et al. Synergistic induction of PGE2 by oral pathogens and TNF promotes gingival fibroblast-driven stromal-immune cross-talk in periodontitis[J]. mBio, 2025, 16(5): e0004625. doi: 10.1128/mbio.00046-25.
- [42] Aral K, Milward MR, Cooper PR. Inflammasome dysregulation in human gingival fibroblasts in response to periodontal pathogens[J]. Oral Dis, 2022, 28(1): 216-224. doi: 10.1111/odi.13760.
- [43] Lu SL, Huang CF, Li CL, et al. Role of IL-6 and STAT3 signaling in dihydropyridine-induced gingival overgrowth fibroblasts[J]. Oral Dis, 2021, 27(7): 1796-1805. doi: 10.1111/odi.13724.
- [44] 王晓, 吴雅洁, 苏志飞, 等. 牙龈上皮细胞在牙周稳态维持中的作用及机制[J]. 口腔疾病防治, 2025, 33(8): 672-679. doi: 10.12016/j.issn.2096-1456.202550044.
- Wang X, Wu YJ, Su ZF, et al. The role and mechanisms of gingival epithelial cells in maintaining periodontal homeostasis[J]. J Prev Treat Stomatol Dis, 2025, 33(8): 672-679. doi: 10.12016/j.issn.2096-1456.202550044.
- [45] Alshargabi R, Sano T, Yamashita A, et al. SPOCK1 is a novel inducer of epithelial to mesenchymal transition in drug-induced gingival overgrowth[J]. Sci Rep, 2020, 10(1): 9785. doi: 10.1038/s41598-020-66660-z.
- [46] 付晓洁, 杨佳, 刘凯乐, 等. 肺岩宁方通过TGF- β 1/Smad信号通路调控EMT抑制非小细胞肺癌侵袭转移[J]. 中国实验方剂学杂志, 2025, 31(12): 110-120. doi: 10.13422/j.cnki.syfjx.20242421.
- Fu XJ, Yang J, Liu KL, et al. Feiyanning inhibits invasion and metastasis of non-small cell lung cancer by regulating EMT *via* TGF- β 1/Smad signaling pathway[J]. Chin J Exp Tradit Med Formulae, 2025, 31(12): 110-120. doi: 10.13422/j.cnki.syfjx.20242421.
- [47] Fan C, Wang Q, Krijger PHL, et al. Identification of a SNAI1 enhancer RNA that drives cancer cell plasticity[J]. Nat Commun, 2025, 16(1): 2890. doi: 10.1038/s41467-025-58032-w.
- [48] Park MK, Lee HJ, Sung JY, et al. ERK2-mediated phosphorylation of ZEB1 at S322 enhances PD-L1 expression and EMT, leading to pancreatic cancer progression[J]. Cell Commun Signal, 2025, 23(1): 204. doi: 10.1186/s12964-025-02182-3.
- [49] Li Y, Kong Y, An M, et al. ZEB1-mediated biogenesis of circ-NIPBL sustains the metastasis of bladder cancer *via* Wnt/ β -catenin pathway[J]. J Exp Clin Cancer Res, 2023, 42(1): 191. doi: 10.1186/s13046-023-02757-3.
- [50] Huang L, Liu Z, Hu J, et al. miR-377-3p suppresses colorectal cancer through negative regulation on Wnt/ β -catenin signaling by targeting XIAP and ZEB2[J]. Pharmacol Res, 2020, 156: 104774. doi: 10.1016/j.phrs.2020.104774.
- [51] Lin YW, Wen YC, Hsiao CH, et al. Proteoglycan SPOCK1 as a poor prognostic marker promotes malignant progression of clear cell renal cell carcinoma *via* triggering the snail/slug-MMP-2 axis-mediated epithelial-to-mesenchymal transition[J]. Cells, 2023, 12(3): 352. doi: 10.3390/cells12030352.
- [52] Kong C, Yan X, Zhu Y, et al. *Fusobacterium nucleatum* promotes the development of colorectal cancer by activating a cytochrome P450/epoxyoctadecenoic acid axis *via* TLR4/Keap1/NRF2 signaling[J]. Cancer Res, 2021, 81(17): 4485-4498. doi: 10.1158/0008-5472.CAN-21-0453.
- [53] Yan X, Qu X, Wang J, et al. *Fusobacterium nucleatum* promotes the growth and metastasis of colorectal cancer by activating E-cadherin/Krtippel-like factor 4/integrin α 5 signaling in a calcium-dependent manner[J]. MedComm (2020), 2025, 6(3): e70137. doi: 10.1002/mco2.70137.
- [54] 张升华, 杨静怡, 祁春晖, 等. 牙龈卟啉单胞菌通过GARP促进TGF- β /Smad轴介导食管鳞状细胞癌细胞的上皮间质转化[J]. 中国肿瘤生物治疗杂志, 2024, 31(8): 769-776. doi: 10.3872/j.issn.1007-385x.2024.08.004.
- Zhang SH, Yang JY, Qi CH, et al. *Porphyromonas gingivalis* promotes epithelial-mesenchymal transition of esophageal squamous cell carcinoma cells mediated by TGF- β /Smad signaling *via* GARP[J]. Chin J Cancer Biother, 2024, 31(8): 769-776. doi: 10.3872/j.issn.1007-385x.2024.08.004.
- [55] Zhang S, Li C, Liu J, et al. *Fusobacterium nucleatum* promotes epithelial-mesenchymal transition through regulation of the lncRNA MIR4435-2HG/miR-296-5p/Akt2/SNAI1 signaling pathway[J]. FEBS J, 2020, 287(18): 4032-4047. doi: 10.1111/febs.15233.
- [56] Abdulkareem AA, Shelton RM, Landini G, et al. Periodontal pathogens promote epithelial-mesenchymal transition in oral squamous carcinoma cells *in vitro*[J]. Cell Adhes Migr, 2018, 12(2): 127-137. doi: 10.1080/19336918.2017.1322253.
- [57] Saliem SS, Bede SY, Cooper PR, et al. Pathogenesis of periodontitis - a potential role for epithelial-mesenchymal transition[J]. Jpn Dent Sci Rev, 2022, 58: 268-278. doi: 10.1016/j.jdsr.2022.09.001.
- [58] Marconi GD, Fonticoli L, Rajan TS, et al. Transforming growth factor-Beta1 and human gingival fibroblast-to-myofibroblast differentiation: molecular and morphological modifications[J]. Front Physiol, 2021, 12: 676512. doi: 10.3389/fphys.2021.676512.
- [59] Yanagihara T, Tsubouchi K, Gholfiof M, et al. Connective-tissue growth factor contributes to TGF- β 1-induced lung fibrosis[J]. Am J Respir Cell Mol Biol, 2022, 66(3): 260-270. doi: 10.1165/rcmb.2020-05040C.
- [60] 朱婷婷, 李楠楠, 陈志慧, 等. 硝苯地平与环孢素A诱导的牙龈增生大鼠模型中血清TGF- β 1的表达[J]. 牙体牙髓牙周病学杂志, 2018, 28(12): 689-694. doi: 10.15956/j.cnki.chin.j.conserv.dent.2018.012.002.
- Zhu TT, Li NN, Chen ZH, et al. Expression of serum TGF- β 1 in

- rat model of gingival overgrowth induced by nifedipine and cyclosporine A[J]. *Chin J Conserv Dent*, 2018, 28(12): 689-694. doi: 10.15956/j.cnki.chin.j.conserv.dent.2018.012.002.
- [61] Schweizer M, Adwent I, Grabarek BO, et al. Analysis of the influence of adalimumab to the expression pattern of mRNA and protein of TGF- β 1-3 in dermal fibroblast exposed to lipopolysaccharide[J]. *Postepy Dermatol Alergol*, 2021, 38(4): 597-602. doi: 10.5114/ada.2020.94181.
- [62] Deng YT, Wu KJ, Kuo MY. Phenytoin induces connective tissue growth factor (CTGF/CCN2) production through NADPH oxidase 4-mediated latent TGF β 1 activation in human gingiva fibroblasts: suppression by curcumin[J]. *J Periodontal Res*, 2022, 57(6): 1219-1226. doi: 10.1111/jre.13058.
- [63] Gebril SM, El Din M, Lasheen F, Khalaf M, et al. Cold atmospheric plasma enhances TGF- β 1, CTGF protein expression, and healing in full-thickness skin burns: an animal study[J]. *Biomolecules*, 2025, 15(7): 924. doi: 10.3390/biom15070924.
- [64] Wiedmaier N, Müller S, Köberle M, et al. Bacteria induce CTGF and CYR61 expression in epithelial cells in a lysophosphatidic acid receptor-dependent manner[J]. *Int J Med Microbiol*, 2008, 298(3/4): 231-243. doi: 10.1016/j.ijmm.2007.06.001.
- [65] Situmorang JH, Chen MC, Kuo WW, et al. 9-POHSA prevents NF- κ B activation and ameliorates LPS-induced inflammation in rat hepatocytes[J]. *Lipids*, 2023, 58(5): 241-249. doi: 10.1002/lipd.12380.
- [66] Mathews JA, Borovsky DT, Reid KT, et al. Single cell profiling of hematopoietic stem cell transplant recipients reveals TGF- β 1 and IL-2 confer immunoregulatory functions to NK cells[J]. *iScience*, 2024, 27(12): 111416. doi: 10.1016/j.isci.2024.111416.
- [67] Deng R, Li C, Wang X, et al. Periosteal CD68⁺ F4/80⁺ macrophages are mechanosensitive for cortical bone formation by secretion and activation of TGF- β 1[J]. *Adv Sci (Weinh)*, 2022, 9(3): e2103343. doi: 10.1002/adv.202103343.
- [68] Lindstedt KA, Wang Y, Shiota N, et al. Activation of paracrine TGF- β 1 signaling upon stimulation and degranulation of rat serosal mast cells: a novel function for chymase[J]. *FASEB J*, 2001, 15(8): 1377-1388. doi: 10.1096/fj.00-0273com.
- [69] Palmieri A, Pellati A, Lauritano D, et al. Drugs that induce gingival overgrowth drive the pro-inflammatory polarization of macrophages *in vitro*[J]. *Int J Mol Sci*, 2024, 25(21): 11441. doi: 10.3390/ijms252111441.
- [70] Wang F, Zhang Y, Ren J, et al. HIPK2 attenuates bleomycin-induced pulmonary fibrosis by suppressing the Wnt/ β -catenin signaling pathway[J]. *Folia Histochem Cytobiol*, 2022, 60(3): 247-259. doi: 10.5603/FHC.a2022.0022.
- [71] Liang L, Huang K, Yuan W, et al. Dysregulations of miR-503-5p and Wnt/ β -catenin pathway coordinate in mediating cadmium-induced kidney fibrosis[J]. *Ecotoxicol Environ Saf*, 2021, 224: 112667. doi: 10.1016/j.ecoenv.2021.112667.
- [72] Działo E, Czepiel M, Tkacz K, et al. WNT/ β -catenin signaling promotes TGF- β -mediated activation of human cardiac fibroblasts by enhancing IL-11 production[J]. *Int J Mol Sci*, 2021, 22(18): 10072. doi: 10.3390/ijms221810072.
- [73] Li M, Liu Q, He S, et al. Icaritin inhibits skin fibrosis through regulating AMPK and Wnt/ β -catenin signaling[J]. *Cell Biochem Biophys*, 2021, 79(2): 231-238. doi: 10.1007/s12013-020-00952-z.
- [74] 崔硕, 王鹏, 高秀秋. Wnt1、 β -catenin在硝苯地平引起的药物性牙龈增生中的表达[J]. *实用口腔医学杂志*, 2017, 33(1): 78-82. doi: 10.3969/j.issn.1001-3733.2017.01.017.
- Cui S, Wang P, Gao XQ. Expression of Wnt1 and β -catenin in the gingival tissue with gingival overgrowth induced by nifedipine[J]. *J Pract Stomatol*, 2017, 33(1): 78-82. doi: 10.3969/j.issn.1001-3733.2017.01.017.
- [75] Silva-García O, Valdez-Alarcón JJ, Baizabal-Aguirre VM. Wnt/ β -catenin signaling as a molecular target by pathogenic bacteria[J]. *Front Immunol*, 2019, 10: 2135. doi: 10.3389/fimmu.2019.02135.
- [76] Rubinstein MR, Baik JE, Lagana SM, et al. *Fusobacterium nucleatum* promotes colorectal cancer by inducing Wnt/ β -catenin modulator annexin A1[J]. *EMBO Rep*, 2019, 20(4): e47638. doi: 10.15252/embr.201847638.
- [77] Reyes M, Urrea H, Peña-Oyarzún D. Evaluating the link between periodontitis and oral squamous cell carcinoma through Wnt/ β -catenin pathway: a critical review[J]. *Front Oral Health*, 2025, 6: 1575721. doi: 10.3389/froh.2025.1575721.
- [78] Jang J, Song J, Lee H, et al. LGK974 suppresses lipopolysaccharide-induced endotoxemia in mice by modulating the crosstalk between the Wnt/ β -catenin and NF- κ B pathways[J]. *Exp Mol Med*, 2021, 53(3): 407-421. doi: 10.1038/s12276-021-00577-z.
- [79] Lin T, Yu CC, Liao YW, et al. miR-200a inhibits proliferation rate in drug-induced gingival overgrowth through targeting ZEB2[J]. *J Formos Med Assoc*, 2020, 119(8): 1299-1305. doi: 10.1016/j.jfma.2020.04.031.
- [80] Hsieh PL, Huang CC, Yu CC. Emerging role of microRNA-200 family in dentistry[J]. *Noncoding RNA*, 2021, 7(2): 35. doi: 10.3390/nrna7020035.
- [81] Krongbamee T, Zhu M, Qian Q, et al. Plasmid encoding microRNA-200c ameliorates periodontitis and systemic inflammation in obese mice[J]. *Mol Ther Nucleic Acids*, 2021, 23: 1204-1216. doi: 10.1016/j.omtn.2021.01.030.
- [82] Madamanchi A, Santoro SA, Zutter MM. α 2 β 1 integrin [J]. *Adv Exp Med Biol*, 2014, 819: 41-60. doi: 10.1007/978-94-017-9153-3_3.
- [83] 康颖竹, 郭淑娟, 刘程程, 等. 整合素 α 2 β 1 与药物性牙龈增生相关性的研究进展[J]. *华西口腔医学杂志*, 2017, 35(1): 99-103. doi: 10.7518/hxkq.2017.01.016.
- Kang YZ, Guo SJ, Liu CC, et al. Research progression of the relationship between integrin α 2 β 1 and drug-induced gingival overgrowth[J]. *West Chin J Stomatol*, 2017, 35(1): 99-103. doi: 10.7518/hxkq.2017.01.016.
- [84] Baba A, Abe N, Kadowaki T, et al. Arg-gingipain is responsible for the degradation of cell adhesion molecules of human gingival fibroblasts and their death induced by *Porphyromonas gingivalis*[J]. *Biol Chem*, 2001, 382(5): 817-824. doi: 10.1515/BC.2001.099.
- [85] Liu Y, Wong CC, Ding Y, et al. *Peptostreptococcus anaerobius* mediates anti-PD1 therapy resistance and exacerbates colorectal can-

- cer *via* myeloid-derived suppressor cells in mice[J]. *Nat Microbiol*, 2024, 9(6): 1467-1482. doi: 10.1038/s41564-024-01695-w.
- [86] Kanamoto T, Hikida M, Sato S, et al. Integrin $\alpha 2\beta 1$ plays an important role in the interaction between human articular cartilage-derived chondrocytes and atelocollagen gel[J]. *Sci Rep*, 2021, 11(1): 1757. doi: 10.1038/s41598-021-81378-2.
- [87] Galdyszyńska M, Radwańska P, Szymański J, et al. The stiffness of cardiac fibroblast substrates exerts a regulatory influence on collagen metabolism *via* $\alpha 2\beta 1$ integrin, FAK and src kinases[J]. *Cells*, 2021, 10(12): 3506. doi: 10.3390/cells10123506.
- [88] Rattanaprukskul K, Xia XJ, Jiang M, et al. Molecular signatures of senescence in periodontitis: clinical insights[J]. *J Dent Res*, 2024, 103(8): 800-808. doi: 10.1177/00220345241255325.
- [89] Luchian I, Goriuc A, Sandu D, et al. The role of matrix metalloproteinases (MMP-8, MMP-9, MMP-13) in periodontal and peri-implant pathological processes[J]. *Int J Mol Sci*, 2022, 23(3): 1806. doi: 10.3390/ijms23031806.
- [90] Boynes SG, Sofiyeva N, Saw T, et al. Assessment of salivary matrix metalloproteinase (MMP8) and activated salivary matrix metalloproteinase (aMMP8) in periodontitis patients: a systematic review and meta-analysis[J]. *Front Oral Health*, 2025, 6: 1444399. doi: 10.3389/froh.2025.1444399.
- [91] López-Boado YS, Wilson CL, Hooper LV, et al. Bacterial exposure induces and activates matrilysin in mucosal epithelial cells[J]. *J Cell Biol*, 2000, 148(6): 1305-1315. doi: 10.2307/1619734.
- [92] 陈龙杰, 杨俊, 李午丽, 等. 硝苯地平对人牙龈成纤维细胞 MMP-1 和 MMP-2 mRNA 表达的影响[J]. *同济大学学报(医学版)*, 2015, 36(4): 33-37. doi: 10.16118/j.1008-0392.2015.04.007.
- Chen LJ, Yang J, Li WL, et al. Effects of nifedipine on expression of matrix metalloproteinase-1 and matrix metalloproteinase-2 in human gingival fibroblasts[J]. *J Tongji Univ Med Sci*, 2015, 36(4): 33-37. doi: 10.16118/j.1008-0392.2015.04.007.
- [93] Huang Q, Dong X. Prevalence of periodontal disease in middle-aged and elderly patients and its influencing factors[J]. *Am J Transl Res*, 2022, 14(8): 5677-5684.
- [94] Zhang Z, Zhao X, Gao S, et al. Biological aging mediates the association between periodontitis and cardiovascular disease: results from a national population study and Mendelian randomization analysis[J]. *Clin Epigenetics*, 2024, 16(1): 116. doi: 10.1186/s13148-024-01732-9.
- [95] Muñoz Aguilera E, Suvan J, Orlandi M, et al. Association between periodontitis and blood pressure highlighted in systemically healthy individuals: results from a nested case-control study[J]. *Hypertension*, 2021, 77(5): 1765-1774. doi: 10.1161/HYPERTENSIONAHA.120.16790.
- [96] Song X, Wang J, Gu Z, et al. *Porphyromonas gingivalis* and *Fusobacterium nucleatum* synergistically strengthen the effect of promoting oral squamous cell carcinoma progression[J]. *Infect Agent Cancer*, 2025, 20(1): 60. doi: 10.1186/s13027-025-00689-5.
- [97] Sakanaka A, Kuboniwa M, Shimma S, et al. *Fusobacterium nucleatum* metabolically integrates commensals and pathogens in oral biofilms[J]. *mSystems*, 2022, 7(4): e0017022. doi: 10.1128/msystems.00170-22.
- [98] Shao W, Fujiwara N, Mouri Y, et al. Conversion from epithelial to partial-EMT phenotype by *Fusobacterium nucleatum* infection promotes invasion of oral cancer cells[J]. *Sci Rep*, 2021, 11(1): 14943. doi: 10.1038/s41598-021-94384-1.
- [99] Fang L, Tan BC. Clinical presentation and management of drug-induced gingival overgrowth: a case series[J]. *World J Clin Cases*, 2021, 9(32): 9926-9934. doi: 10.12998/wjcc.v9.i32.9926.
- [100] Dalal R, Garg S, Gupta A. Nonsurgical management of drug-induced gingival overgrowth in a young patient[J]. *Int J Clin Pediatr Dent*, 2023, 16(Suppl 3): 331-334. doi: 10.5005/jp-journals-10005-2482.

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