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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α2β1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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The role and research progress of bacteria in nifedipine-induced gingival hyperplasia

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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 α2β1 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-1β（interleukin-1β，IL-1β）、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-1β和NIF具有协同作用，可通过IL-6-STAT3-Colα1（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-β1（transforming growth factor-β1，TGF-β1）、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-β1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-β1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-β1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-β1为核心的复杂复杂调控网络中，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-β1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-β1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-β1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-β1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-β1分泌来源广泛，绝大多数免疫细胞均可分泌TGF-β1[66-68]。尽管以上实验证明细菌感染可升高TGF-β1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-β1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、口腔粘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α2β1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α2β1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α2β1和整合素β3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α2β1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α2β1的表达或通过竞争性结合整合素α2β1受体，从而减少胶原降解。整合素α2β1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-1β、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-β1的重要来源。因此，纤维化也可能是牙周组织的应激反应。TGF-β1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.

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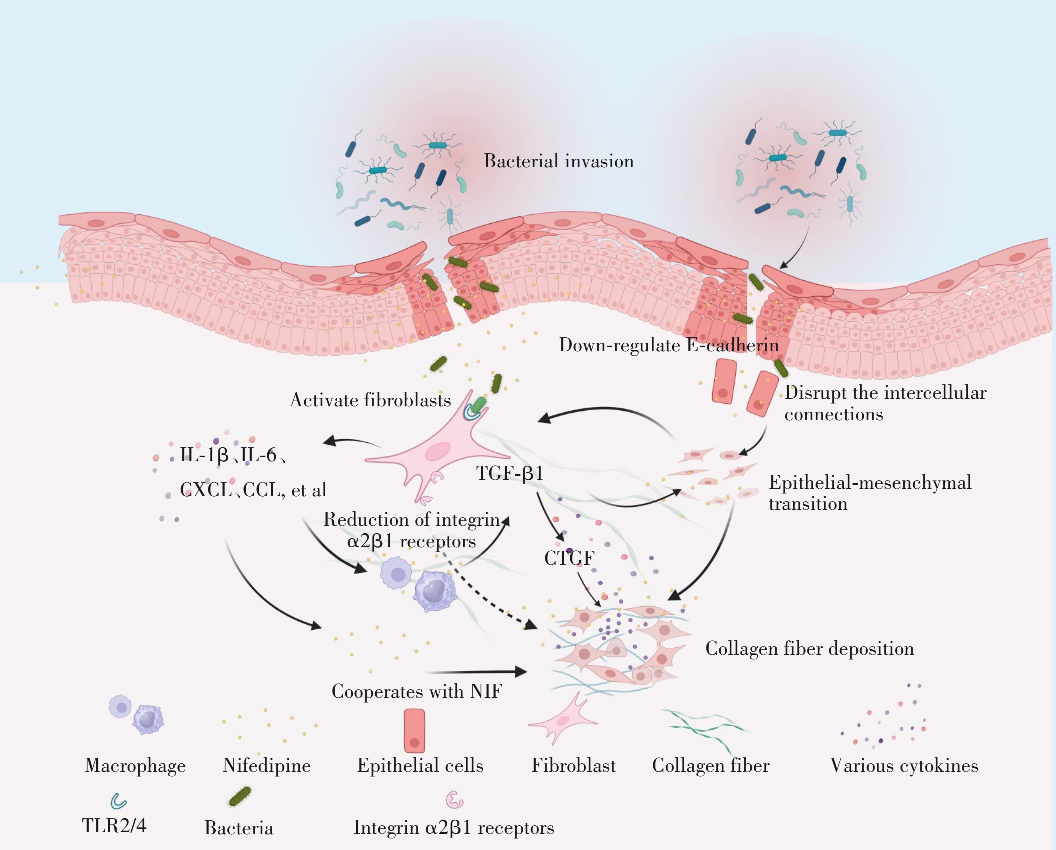

Bacteria promote drug-induced gingival overgrowth through multiple mechanisms. GFs express pattern recognition receptors such as TLR. After recognizing periodontal pathogens, they activate pro-inflammatory signaling pathways (such as IL-6-STAT3) and, in synergy with nifedipine, up-regulate collagen synthesis. 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.

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