[DOI]10.12016/j.issn.2096-1456.202550154

·综述·

# 牙龈成纤维细胞在牙周炎发病机制中的作用研究进展

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【摘要】 牙周炎是一种由牙周致病菌引发、免疫介导的慢性炎症性疾病。传统观念认为牙龈成纤维细胞（GFs）主要功能是维持牙周基质稳态。近年研究发现，GFs在牙周炎中具有显著免疫调控功能。GFs通过Toll样受体4（TLR4）等信号通路识别牙龈卟啉单胞菌等病原体的毒力因子，分泌多种炎症介质，驱动细胞外基质降解和破骨细胞分化，同时调控中性粒细胞、巨噬细胞等免疫细胞，放大炎症反应，形成慢性炎症微环境。高血糖、吸烟等危险因素通过氧化应激介导的核因子κB（NF-κB）通路等多种机制加剧GFs功能障碍，而炎症与细胞衰老形成恶性循环，衰老GFs通过激活哺乳动物雷帕霉素靶蛋白（mTOR）通路进一步加重牙槽骨破坏。调节GFs的干预策略，如抑制NF-κB通路、调控mTOR介导的衰老等，可阻断炎症与组织破坏的联系，展现出一定治疗潜力。未来需借空间多组学、单细胞蛋白组学等先进技术，深入解析GFs亚群的空间分布、功能互作网络及功能异质性，以深化对其参与牙周炎发生发展机制的理解。本文综述了GFs在牙周炎中的多重作用机制，并探讨了靶向调节GFs治疗牙周炎的潜在治疗策略，为牙周炎的防治提供新的思路。

【关键词】 牙周炎；　牙龈卟啉单胞菌；　牙龈成纤维细胞；　中性粒细胞；　巨噬细胞；　免疫调控；　细胞衰老；　Toll样受体4；　核因子κB；　哺乳动物雷帕霉素靶蛋白
【中图分类号】 R78　【文献标志码】 A　【文章编号】 2096-1456（2026）04-0395-10
【引用著录格式】 张永春，田艾. 牙龈成纤维细胞在牙周炎发病机制中的作用研究进展[J]. 口腔疾病防治，2026, 34(4): 395-404. doi:10.12016/j.issn.2096-1456.202550154.

微信公众号

**Research advances on the role of gingival fibroblasts in the pathogenesis of periodontitis**

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【Abstract】 Periodontitis is a chronic inflammatory disease triggered by periodontal pathogens and mediated by immune responses. Traditionally, gingival fibroblasts (GFs) were considered to be primarily responsible for maintaining periodontal matrix homeostasis. However, recent studies reveal that GFs play a significant immunoregulatory role in periodontitis. Through signaling pathways, such as the Toll-like receptor 4 (TLR4) pathway, GFs recognize virulence factors from pathogens, such as *Porphyromonas gingivalis*, and secrete various inflammatory mediators, thus driving extracellular matrix degradation and osteoclast differentiation. Simultaneously, GFs modulate immune cells, including neutrophils and macrophages, amplifying inflammatory responses and fostering a chronic inflammatory microenvironment. Risk factors, such as hyperglycemia and smoking, exacerbate GFs dysfunction via oxidative stress-mediated activation of the nuclear factor kappa B (NF-κB) pathway and other mechanisms, while inflammation and cellular senescence form a vicious cycle. Senescent GFs further aggravate alveolar bone destruction by activating the mechanistic target of the ra-

【收稿日期】2025-04-14；【修回日期】2025-08-06
【基金项目】国家自然科学基金项目（82260193）
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pamycin (mTOR) pathway. Therapeutic strategies targeting GFs, such as suppressing NF-κB signaling or modulating mTOR-mediated senescence, may disrupt the link between inflammation and tissue destruction, showing promising therapeutic potential. Future studies should employ advanced technologies such as spatial multi-omics and single-cell proteomics to elucidate the spatial distribution, functional interactomes, and heterogeneity of GFs subsets, in order to deepen our understanding of their roles in periodontitis progression. This review summarizes the multifaceted mechanisms of GFs in periodontitis and explores potential therapeutic strategies targeting GFs, offering novel insights for periodontitis prevention and treatment.

**【Key words】** periodontitis; *P*orphyromonas *gingivalis*; gingival fibroblasts; neutrophils; macrophages; immune regulation; cellular senescence; Toll-like receptor 4; nuclear factor kappa B; mammalian target of rapamycin

**J Prev Treat Stomatol Dis, 2026, 34(4): 395-404.**

**【Competing interests】** The authors declare no competing interests.

This study was supported by the grants from National Natural Science Foundation of China (No. 82260193).

牙周炎是一种慢性炎症性疾病，主要累及牙龈、牙周韧带以及牙槽骨等牙周组织，并且随着这些组织的炎症性破坏而不断进展[1]。牙周致病菌在牙周炎的发生发展中起着关键作用，它们通过分泌蛋白酶、内毒素等毒力因子刺激牙周组织中的中性粒细胞、单核巨噬细胞以及成纤维细胞，促使其分泌白细胞介素-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）、前列腺素E2（prostaglandin E2，PGE2）、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）以及基质金属蛋白酶（matrix metalloproteinases，MMPs）等多种炎症介质[2]。这些炎症介质通过复杂的细胞因子网络诱导炎症反应和细胞损伤，最终导致牙周组织的破坏。牙龈成纤维细胞（gingival fibroblasts，GFs）作为牙龈结缔组织中的主要细胞成分，在一定条件下具备增殖能力[3-5]及合成胶原纤维、弹性纤维和细胞外基质（extracellular matrix，ECM）的能力。传统观念将GFs视为“免疫中性”细胞，认为其主要功能是维持牙周基质稳态，然而近年研究揭示其在炎症微环境中可转化为促炎表型，通过驱动炎症放大、组织降解参与牙周炎进展，突破了对GFs的传统认知。这一发现并非孤立存在，已有研究证实成纤维细胞在免疫调节中发挥重要作用，是先天免疫系统的"非经典"分支[6-8]。牙周病原体如牙龈卟啉单胞菌的脂多糖可激活GFs中的Toll样受体4（Toll-like receptor 4，TLR4）信号通路，促使其分泌炎症因子，加剧炎症反应[9]；GFs受刺激后释放的炎症介质不仅损伤组织，还吸引炎症细胞聚集，放大炎症反应[10-12]。动物实验和临床研究均表明，牙周病原体感染可诱导GFs发生表型改变，加速牙周组织破坏，且GFs分泌炎症因子水平与牙周炎严重程度呈正相关[13-14]。本文就GFs与牙周炎发生发展的关系及靶向调节GFs治疗牙周炎策略进行综述，为揭示牙周炎的病理过程及开发新的治疗策略提供思路。

## 1　GFs的生物学特性与免疫调控功能

牙龈组织是抵御口腔微生物侵袭的首道防线，GFs作为其主要细胞成分，在牙周组织的生理稳态与病理演变中发挥关键作用。GFs具有强大的增殖潜能及基质重塑功能[3-5]，这些特性为其在创伤修复中的应用奠定了基础。研究表明，GFs在适当的实验条件下可获得成骨表型，具体表现为碱性磷酸酶活性显著升高，并形成矿化结节，展现出一定的成骨潜能[15]。此外，GFs通过调控MMPs及其基质金属蛋白酶抑制剂（tissue inhibitors of metalloproteinases，TIMPs）的平衡，维持牙周组织的完整性和稳态[16]。富血小板纤维蛋白（fibrinogen-depleted platelet-rich fibrin，FD-PRF）能显著促进GFs的增殖和迁移，加速组织修复过程[17]。然而，在炎症状态下，GFs的正常功能可能受到严重干扰，慢性牙周炎患者的GFs表现出细胞活性下降和凋亡增强，而高糖诱导的氧化应激则显著损害其增殖和迁移能力，进而阻碍组织修复[18-20]。

### 1.1　GFs与牙周致病菌的相互作用

在免疫调控方面，GFs扮演着至关重要的角色。牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*Pg*）作为牙周炎的关键致病菌，产生脂多糖（lipopolysaccharide，LPS）、菌毛、牙龈蛋白酶、荚膜等毒

力因子，通过多种途径激发GFs的免疫应答[21]。LPS可通过激活GFs的TLR4信号通路，刺激PGE2的产生，引发GFs介导的促炎反应和骨吸收[22]。此外，LPS还可诱导GFs线粒体DNA损伤和氧化应激，加剧慢性牙周炎患者的线粒体功能障碍[23]，这种异常可能在牙周炎的发病机制中起着重要作用[24]。*Pg*的菌毛通过其核心结构蛋白Mfa1与GFs表面的TLR4特异性结合，激活下游核因子κB（nuclear factor-κB，NF-κB）和丝裂原活化蛋白激酶（mitogen-activated protein kinase，MAPK）信号通路，诱导IL-6、IL-8、PGE2及TNF-α等促炎因子的表达，其中TLR4依赖的免疫信号可触发中性粒细胞趋化与局部炎症放大，同时通过上调核因子κB受体活化因子配体（receptor activator of nuclear factor-κB ligand，RANKL）等破骨细胞分化因子间接促进牙槽骨吸收[25]。*Pg*还可通过分泌含有蛋白酶的细胞外膜泡调节宿主的炎症反应并促进GFs衰老[26]，牙龈炎症期间，牙龈蛋白酶通过降解E-钙黏蛋白等细胞连接蛋白，导致细胞间隙扩大，促进致病菌向组织深层侵袭，扩大病变范围[27-28]。赖氨酸特异性牙龈蛋白酶（lysine-specific gingipain，Kgp）可将牙龈上皮细胞的细胞角蛋白6降解为特定片段，诱导GFs迁移并分泌IL-6、IL-8和单核细胞趋化蛋白-1（monocyte chemoattractant protein-1，MCP-1），其中IL-6通过激活破骨细胞分化直接破坏牙槽骨，IL-8通过趋化中性粒细胞浸润引发局部氧化应激损伤，而MCP-1通过招募单核/巨噬细胞形成慢性炎症反馈环路，三者协同作用加速牙周组织破坏[29]。

### 1.2　GFs对免疫细胞的调控作用

1.2.1　中性粒细胞　GFs不仅分泌大量促炎因子来应答宿主的免疫反应，还通过调控中性粒细胞、巨噬细胞以及B细胞等免疫细胞的功能，进一步增强炎症级联反应[10]。中性粒细胞是牙周组织中占比最高的先天免疫细胞，适度的浸润水平可抵御牙周致病菌入侵，但过度浸润则会导致免疫失衡。中性粒细胞胞外陷阱（neutrophil extracellular traps，NETs）是中性粒细胞活化后释放的一种由染色质和多种蛋白质组成的细胞外网状结构，可加剧重度牙周炎患者的牙龈炎症和牙槽骨吸收。NETs通过弹性蛋白酶直接破坏牙周胶原，同时捕获的病原菌加剧局部炎症，形成恶性循环。GFs对中性粒细胞的趋化性和免疫浸润具有重要调节作用。GFs分泌的细胞因子可显著增强中性粒细胞的迁移，并诱导NETs形成，从而加剧炎症反应[30-31]。研究表明，GFs分泌的IL-8和C-X-C基序趋化因子配体1（C-X-C motif chemokine ligand 1，CXCL1）等趋化因子通过激活中性粒细胞表面C-X-C趋化因子受体2（C-X-C chemokine receptor type 2，CXCR2）及其下游磷脂酰肌醇3激酶/蛋白激酶B（phosphatidylinositol 3-kinase/protein kinase B，PI3K/Akt）信号通路，显著增强中性粒细胞的跨内皮迁移能力，促进其向炎症部位的定向聚集[12, 32-33]。同时，GFs产生的活性氧（reactive oxygen species，ROS）激活NADPH氧化酶复合体（NADPH oxidase 2，NOX2），导致线粒体DNA（mitochondrial DNA，mtDNA）泄漏并触发环磷酸鸟苷-腺苷酸合成酶/干扰素基因刺激蛋白（cyclic GMP-AMP synthase/stimulator of interferon genes，cGAS-STING）通路，诱导NETs的过度形成[30-31]。此外，GFs通过TNF-α/NF-κB通路上调钙卫蛋白（calprotectin，S100A8/A9）的表达，该蛋白通过结合中性粒细胞表面的TLR4，激活肽酰精氨酸脱亚胺酶4（peptidylarginine deiminase 4，PAD4），诱导组蛋白瓜氨酸化，从而促进NETs释放[30-31, 34]。单细胞测序数据进一步证实GFs与高表达NETs标志物的中性粒细胞亚群存在密切互作，凸显其在牙周炎病理进展中的核心调控作用[30-31]。近期研究利用单细胞测序技术首次鉴定了牙龈组织中一个与NETs相关的中性粒细胞亚群，该亚群受成纤维细胞的影响最为显著，细胞通讯分析证实GFs促进NETs产生[35]。

1.2.2　巨噬细胞与B细胞　巨噬细胞是牙周局部重要的免疫细胞，GFs通过多种机制调控巨噬细胞功能，多个GFs亚群参与这一调控过程。ICAM1$^+$成纤维细胞是一类高表达细胞间粘附分子1（intercellular adhesion molecule 1，ICAM1）的牙龈成纤维细胞亚群，可通过C-C基序趋化因子配体2（C-C motif chemokine ligand 2，CCL2）调节巨噬细胞的募集与吞噬活性，抑制过度骨质吸收，在牙周病早期发挥保护作用[32]；SAA1$^+$成纤维细胞是一类高表达血清淀粉样蛋白A1（serum amyloid A1，SAA1）的牙龈成纤维细胞亚群，其分泌的C-X-C基序趋化因子配体12（C-X-C motif chemokine ligand 12，CXCL12）、集落刺激因子1（colony-stimulating factor 1，CSF1）可招募巨噬细胞，同时释放的SAA1能结合巨噬细胞表面TLR4，诱导其向促炎的M1型极化并分泌促炎因子与基质降解酶，且活化的M1型巨噬细胞会反向上调该细胞SAA1表达，形成促炎

正反馈[36]。此外，炎性GFs的培养上清液可显著诱导更多NETs形成，并驱动巨噬细胞极化为M1型[37]。GFs分泌的PGE2通过旁分泌作用促进巨噬细胞IL-8生成及活化[10]。巨噬细胞免疫代谢调节因子（macrophage immunometabolism regulator，MACIR）是调控巨噬细胞功能的关键分子，在调节免疫反应中发挥关键作用。GFs中MACIR基因的表达受IL-1β、TNF-α等促炎介质刺激而下调，这会减弱其对巨噬细胞炎症活性的抑制作用，导致巨噬细胞活化并分泌促炎介质，而这些介质又会反向抑制MACIR表达，形成恶性循环[38]。GFs在TNF-α刺激下可上调B细胞活化因子的表达，为B细胞的存活创造有利条件[11]。B细胞在牙周炎病变中大量富集，特定B细胞亚群与炎症程度和骨吸收密切相关，为后续牙周组织破坏埋下隐患[39]。

## 2　牙周炎危险因素对GFs功能的影响

高血糖和吸烟是牙周炎的重要危险因素，它们通过多种机制影响GFs的功能。糖尿病与牙周炎之间存在显著的双向关系，血糖控制不佳会加重牙周炎的严重程度，而牙周炎也可能反过来影响血糖控制[40]。在高糖环境下，GFs的TNF-α、IL-1β、IL-6、IL-8和CXCL1、CCL2等促炎因子的分泌显著增加，而抗炎细胞因子IL-10的产生则减少[41]。高糖还诱导GFs增加MMP-1、MMP-13的基因表达[42]，抑制GFs的增殖能力[43]。吸烟同样显著损害GFs功能，刺激炎症反应，加速HGF细胞衰老。长期暴露于尼古丁或香烟烟雾冷凝物（cigarette smoke condensate，CSC）的GFs，其细胞增殖和迁移能力受到显著抑制，并上调IL-6、IL-8、p16、p21、p53的表达[44]。CSC通过激活MMP-2和MMP-9的表达，降解Ⅰ型和Ⅳ型胶原，同时抑制其内源性抑制剂TIMP-1的活性，破坏胶原代谢平衡，加剧ECM的破坏，这一过程与氧化应激介导的NF-κB信号通路激活密切相关[45]。在细胞凋亡方面，CSC通过诱导Bax/ B细胞淋巴瘤-2（B-cell lymphoma-2，Bcl-2）比例失衡（促凋亡蛋白Bax的线粒体转位增加、抗凋亡蛋白Bcl-2表达下调）及半胱天冬酶-3（caspase-3）激活，触发线粒体依赖性凋亡[46]。同时，CSC通过活性氧（ROS）积累引发线粒体DNA损伤，而抗氧化干预可部分恢复GFs功能[47]。因此，高血糖和吸烟通过多种机制共同加剧GFs的功能失调，促进牙周炎进展。

## 3　牙周炎病理进程中GFs的功能失调机制

### 3.1　炎症微环境对GFs的调控作用

在外部危险因素（如高血糖、吸烟）的影响基础上，牙周炎性微环境通过炎性介质（如TNF-α、IL-1β）进一步加剧GFs的功能失调。这些关键促炎因子主要来源于两种途径：一是中性粒细胞、单核/巨噬细胞等免疫细胞的分泌；二是细菌毒力因子直接刺激牙周组织细胞（如GFs）后，由这些细胞诱导产生。*Pg*等致病菌通过Toll样受体2（Toll-like receptor 2，TLR2）激活中性粒细胞和巨噬细胞[48]，诱导释放TNF-α和IL-1β，其中单核/巨噬细胞是IL-1β的主要来源，牙周炎患者龈沟液中IL-1β水平显著升高[49]。此外，菌毛和LPS通过GFs表面的TLR2受体触发自分泌，促使GFs自身产生TNF-α和IL-1β[50-51]。这些变化导致GFs分泌更多的促炎细胞因子和MMPs，加剧炎症反应和ECM降解，为后续牙周组织破坏奠定基础[51]。此外，炎症微环境促使GFs产生免疫记忆，使其在LPS刺激下，经PI3K/AKT通路发生代谢和表观遗传改变，促炎因子如IL-6和TNF-α的分泌显著增加，同时这些因子基因的增强子区域出现组蛋白H3第4位赖氨酸单甲基化修饰富集，推动牙周炎的复发和持续[52]。

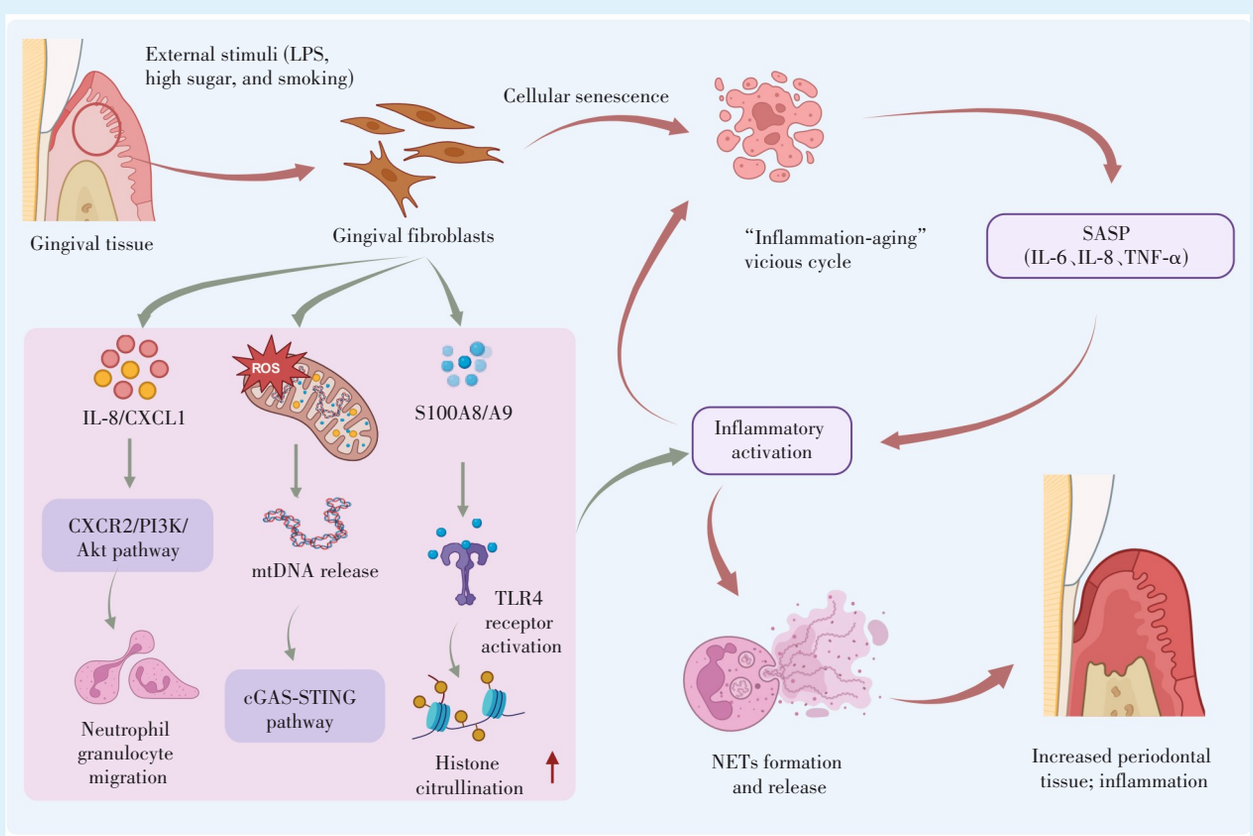
牙周炎性微环境的炎性介质在GFs促炎表型诱导中发挥重要作用。TNF-α通过激活MAPK通路和上调NADPH氧化酶2（NADPH oxidase 2，NOX-2）表达，促进GFs分泌IL-1β、IL-6和IL-8等促炎因子，并调节核因子κB受体活化因子配体/骨保护素（receptor activator of nuclear factor-κB ligand/osteoprotegerin，RANKL/OPG）比值，加剧牙槽骨破坏[53-55]。在炎症微环境中，口腔病原体与TNF产生协同效应，通过激活TLR2和p38 MAPK激酶信号通路，特异性诱导GFs中环氧合酶-2的表达，促使PGE2大量分泌，激活巨噬细胞，诱导中性粒细胞浸润，进而推动牙周炎的发展进程[10]。IL-1β刺激人GFs时，促炎因子IL-1β、IL-2、IL-6、IL-17、IL-8、IL-12、TNF-α和PGE2的产生显著增加[56-57]。研究表明IL-1β刺激GFS可通过上调细胞间黏附分子-1的表达促进其对活化淋巴细胞的粘附作用[58]。IL-1β与LPS协同作用，激活MyD88依赖的MAPK和NF-κB信号通路，增加IL-6的表达[59]。瘦素与IL-1协同上调MMP-8和MMP-12，参与GFs介导的ECM重塑[60]。此外，IL-1β与IL-22或IL-17A的共同刺激可增加GFs中CCL20产生，参与辅助性

T细胞17(T helper 17,Th17)细胞的募集,从而加剧牙周病[61-62]。

### 3.2　细胞衰老对GFs功能的影响

细胞衰老是GFs在牙周炎中的另一个重要特征,与炎症微环境形成“炎症-衰老”恶性循环。近期研究发现,*Pg*细胞外膜泡通过IL21R-AS1促进GFs衰老,使其炎症因子分泌增加,加剧牙周炎症[26]。单细胞RNA测序显示,炎性牙龈组织中的GFs衰老程度显著升高;牙周病患者GFs表现出明显的衰老特征,如衰老相关β-半乳糖苷酶(senescence-associated β-galactosidase,SA-β-gal)阳性率增加、细胞形态增大以及p16表达上调[37,63]。衰老GFs通过激活雷帕霉素靶蛋白(mechanistic target of rapamycin,mTOR)通路,导致成纤维细胞激活蛋白(fibroblast activation protein,FAP)与骨连接蛋白(osteolineage nectin,OLN)的失衡,加剧局部炎症和骨吸收[8]。此外,衰老GFs释放的衰老相关分泌表型(senescence-associated secretory phenotype,SASP)组分(如IL-1β、IL-6、TNF-α)不仅影响周围细胞功能,还通过旁分泌作用募集免疫细胞,扩大炎症反应[37,64]。组织微环境中的有害影响可在机体早期诱发细胞衰老,加速生物衰老进程,推动疾病发生进展。这种“炎症-衰老”恶性循环可能是牙周炎慢性进展的重要机制。

最新研究发现,牙周炎微环境中存在一个独特的CD81高表达GFs亚群,该亚群表现出更高的ROS积累和衰老基因富集,通过分泌SASP相关因子(如IL-6)直接促进牙周炎的进展,并通过补体途径(特别是C3)募集中性粒细胞间接放大炎症[65-66]。此外,衰老GFs的积累还导致ECM分泌减少,胶原蛋白和纤维连接蛋白的降解增加,削弱牙龈屏障功能[67]。这种功能障碍不仅影响组织修复能力,还使牙周组织更容易受到细菌侵袭,形成炎症与衰老相互促进的病理循环(图1)。




SASP: senescence-associated secretory phenotype; LPS: lipopolysaccharide; IL-6: interleukin-6; IL-8: interleukin-8; TNF-α: tumor necrosis factor-α; NETs: neutrophil extracellular traps; CXCL1: C-X-C motif chemokine ligand 1; ROS: reactive oxygen species; CXCR2: C-X-C chemokine receptor type 2; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; TLR4: toll-like receptor 4; mtDNA: mitochondrial DNA

Figure 1　Regulatory mechanisms of gingival fibroblasts on neutrophils and the inflammation-aging vicious cycle

**图1**　牙龈成纤维细胞对中性粒细胞的调控及炎症-衰老恶性循环机制

## 4　GFs介导的牙周组织破坏机制

### 4.1　软组织降解机制

GFs作为牙龈组织中最丰富的细胞类型之一，负责维持组织结构的完整性。在健康状态下，GFs通过分泌细胞ECM成分（如胶原蛋白和纤维连接蛋白）维持牙周软组织的稳态。然而牙周炎时，GFs功能发生显著改变，从维持稳态转变为促进炎症和组织破坏。研究表明，牙周炎患者中GFs的数量减少，且细胞凋亡率增加，可能与牙龈退缩有关[41, 68]。福赛坦氏菌分泌的甲基乙二醛通过诱导GFs凋亡、激活RAGE通路及破坏内皮功能加剧牙周炎[69]。长期暴露于LPS的GFs发生细胞凋亡和DNA损伤，而短期暴露则表现抗凋亡特性[70]，这表明GFs在炎症早期具有一定的保护作用，但随着炎症的持续，其功能逐渐受损，这也部分解释了牙龈炎阶段时牙周组织损害趋于可逆，可以被治愈；而进入牙周炎阶段后组织受到不可逆性损害，临床治疗只能起到控制作用。在炎症条件下GFs会分泌大量促炎细胞因子（如IL-1β、IL-6、TNF-α）和ECM降解酶（如MMPs、弹性蛋白酶等），这些因子不仅加剧炎症反应，还破坏牙周组织的完整性，导致牙齿松动。此外，GFs的功能失衡不仅破坏软组织稳态，还通过调控骨代谢加速牙槽骨吸收。

### 4.2　骨稳态失衡机制

牙槽骨吸收是牙周炎进展中的关键事件，GFs在其中发挥重要作用。研究发现GFs通过分化为成骨细胞样细胞及诱导破骨细胞前体分化影响骨稳态，其成骨分化程度越高，破骨细胞诱导能力越低[15]。健康牙龈中的GFs分泌IL-4和OPG，抑制破骨细胞的生成，维持骨稳态[71]。然而，在炎症微环境中，GFs的促炎表型会被激活，分泌IL-1β、TNF-α等促炎细胞因子[72]和巨噬细胞集落刺激因子（macrophage colony-stimulating factor，M-CSF）和RANKL等破骨细胞分化相关分子，促进破骨细胞的分化和活化[73-74]。同时，GFs在LPS刺激下能够持续产生炎性因子，这种长期炎症反应可能是牙周炎慢性进展的重要机制。GFs的这种分泌特性使其成为牙周病中负责产生炎性细胞因子的主要细胞，与传统观点中仅能短暂产生炎症因子的单核细胞/巨噬细胞等相比，GFs在维持炎症并推动骨稳态失衡方面发挥着更持久的作用[75]。炎性因子对GFs的影响可持续数周，导致GFs的功能发生长期改变，进一步加剧骨稳态的破坏，推动牙周炎进展期间牙槽骨的逐步吸收[37, 72]。此外，衰老GFs通过分泌SASP因子（如IL-6、IL-8）和溶骨因子（如IL-17），进一步加剧骨吸收进程[76]（图2）。

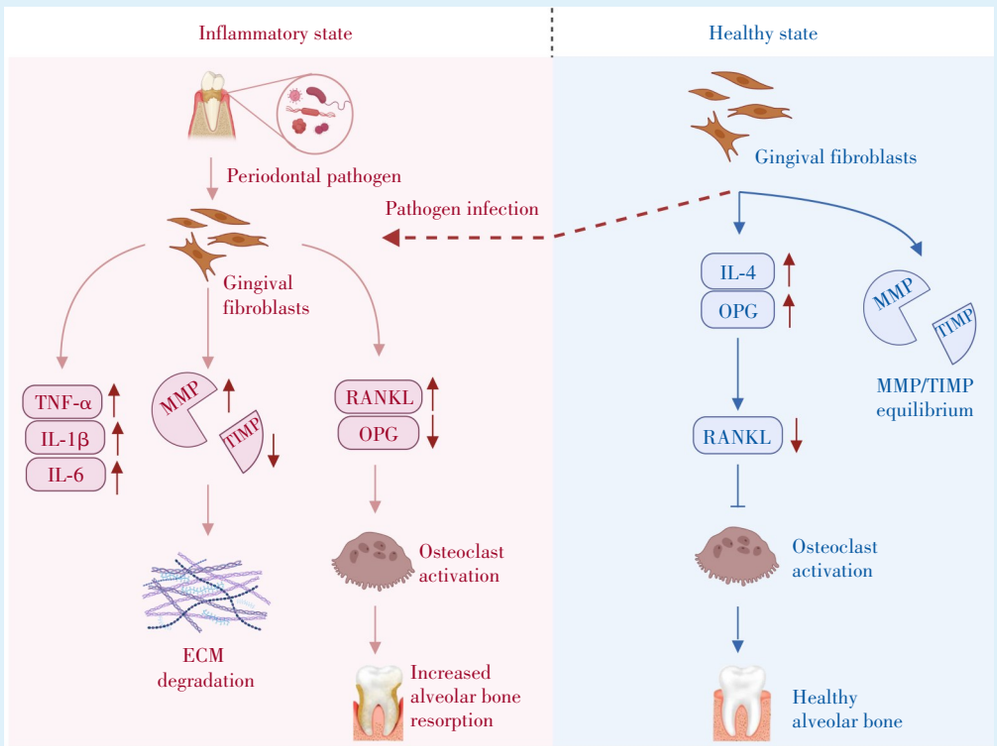
## 5　调节GFs改善牙周炎的治疗策略

基于GFs在牙周炎中的多重作用机制，调节GFs的干预措施，如抗炎药物和抗衰老治疗，为牙周炎的治疗提供了新思路。研究表明，抑制GFs的炎症反应能够显著减轻牙周炎的症状。例如，西格列汀能够通过干预NF-κB信号通路，从而抑制GFs中LPS诱导的炎症反应[77]；二甲双胍通过调节GFs中MMPs和促炎因子IL-8的表达，抑制其在炎症刺激下的过度释放，发挥抗炎作用，为牙周病治疗提供潜在辅助价值[78]。

此外，鉴于GFs衰老与牙周组织破坏密切相关，因此抗衰老治疗可能成为牙周炎的有效干预策略。沉默信息调节因子6（sirtuin 6，SIRT6）激活剂通过增强核因子E2相关因子2/血红素加氧酶-1（nuclear factor erythroid 2-related factor 2/heme oxygenase-1，Nrf2-HO-1）抗氧化通路，有效减轻*Pg*来源LPS诱导的GFs衰老[63]；白藜芦醇能够调节NF-κB信号通路，缓解晚期糖基化终末产物（advanced glycation end products，AGEs）诱导的炎症反应以及细胞衰老[79]；苯妥英钠通过增强自噬通路，改善GFs的衰老进程[80]。mTOR通路的激活与牙周炎中的炎症反应和骨吸收密切相关，而雷帕霉素作为一种mTOR抑制剂，能抑制衰老细胞的积累，并减少SASP因子产生，缓解慢性炎症[8]。在牙周炎模型中，短期雷帕霉素治疗可显著改善老年小鼠的口腔健康，表现为牙槽骨的再生、牙龈炎症减轻以及口腔微生物组趋于年轻化[81]。此外，赤藓糖醇通过增强糖酵解代谢，抑制细胞衰老，改善牙龈组织的病理状态[82]。

## 6　小　结

综上所述，GFs作为牙龈结缔组织中的主体细胞，不仅参与牙周基质稳态的维持，还通过免疫调控、ECM降解、骨吸收及衰老表型驱动牙周炎进展。调节其促炎通路（如NF-κB）或衰老机制（如mTOR）为牙周炎治疗提供新的研究方向。单细胞转录组测序和空间转录组学已成功应用于成纤维细胞亚群鉴定。近期单细胞研究发现了一种在牙周炎早期发挥保护性免疫功能的ICAM1$^+$炎性牙龈成纤维细胞[32]。Gao等[83]通过跨组织单细胞图谱发现肌成纤维细胞亚群（如LRRC15$^+$亚群）在免疫




TNF-α: tumor necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6; MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinase; RANKL: receptor activator of nuclear factor-κB ligand; OPG: osteoprotegerin; IL-4: interleukin-4; ECM: extracellular matrix

Figure 2　Regulatory mechanisms of gingival fibroblasts on periodontal tissues in healthy and inflammatory states

**图2**　健康与炎症状态下牙龈成纤维细胞介导的牙周组织调控机制

抑制微环境中的核心作用，而口腔鳞癌研究中也鉴定出mCAF1和mCAF2亚群，分别调控免疫抑制与ECM重构[84]。未来对GFs的研究应充分利用空间多组学和单细胞蛋白组学等手段，深入解析GFs亚群的空间分布与功能互作网络，剖析其功能异质性，从而更好地理解GFs参与牙周炎发生和进展的机制。这将为开发针对性的干预措施提供科学依据，推动牙周炎治疗策略的创新。

**【Author contributions】** Zhang YC wrote the article. Tian A conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

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