四川大学学报（医学版） 2024，55（1）：31－38
J Sichuan Univ（Med Sci）

在线全文

牙槽骨修复重建分子调控机制的研究新进展*

魏洁雅，徐思群，周学东，谢 静△

口腔疾病防治全国重点实验室 国家口腔医学中心 国家口腔疾病临床医学研究中心 四川大学华西口腔医院 牙体牙髓病科（成都 610041）

【摘要】 牙槽骨是上下颌骨包绕牙根的突起部分，在牙发育、萌出和行使咀嚼功能等过程中发挥重要作用。在根尖周炎、牙周炎和种植体周围炎等口腔炎症性疾病中，牙槽骨缺损造成牙松动脱落和咀嚼功能障碍，危害患者身心健康。然而，由于口腔微环境中复杂的生物、机械和化学等因素综合作用，临床牙槽骨修复重建面临巨大挑战。深入了解牙槽骨修复重建分子调控机制，有助于探寻牙槽骨修复重建新靶点。新近研究表明，Notch、Wnt、Toll样受体（Toll-like receptor, TLR）和核因子-κB（nuclear factor-κB, NF-κB）等信号通路调控破骨细胞、成骨细胞、骨细胞、牙周韧带细胞、巨噬细胞和适应性免疫细胞等增殖、分化、凋亡和自噬等生命活动，调节炎症介质表达，影响核因子-κB受体活化因子配体（receptor activator for nuclear factor-κB ligand, RANKL）/核因子-κB受体活化因子（receptor activator for nuclear factor-κB, RANK）/护骨素（osteoprotegerin, OPG）系统平衡，参与牙槽骨修复重建。此外，牙槽骨修复重建也涉及腺苷酸激活蛋白激酶（AMP-activated protein kinase, AMPK）、磷脂酰肌醇3-激酶（phosphatidyl inositol 3-kinase, PI3K）/蛋白激酶B（protein kinase B, AKT）、Hippo/YAP、Janus 激酶（Janus kinase, JAK）/转录激活因子（signal transducer and activator of transcription, STAT）和转化生长因子-β（transforming growth factor β, TGF-β）等信号通路。然而，现有研究未能构建出成熟的牙槽骨修复重建分子调控网络，亟需利用单细胞转录组测序和空间转录组测序等新技术进一步加强对牙槽骨修复重建分子调控机制的探索。

【关键词】 牙槽骨 根尖周炎 牙周炎 种植体周围炎 信号通路 分子调控机制

Research Progress in the Molecular Regulatory Mechanisms of Alveolar Bone Restoration

WEI Jieya, XU Siqun, ZHOU Xuedong, XIE Jing△. *State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases, Department of Cariology and Endodontics, West China Hospital of Stomatology, Sichuan University*, Chengdu 610041, China

△ Corresponding author, E-mail: xiejing2012@scu.edu.cn

【**Abstract**】 Alveolar bone, the protruding portion of the maxilla and the mandible that surrounds the roots of teeth, plays an important role in tooth development, eruption, and masticatory performance. In oral inflammatory diseases, including apical periodontitis, periodontitis, and peri-implantitis, alveolar bone defects cause the loosening or loss of teeth, impair the masticatory function, and endanger the physical and mental health of patients. However, alveolar bone restoration is confronted with great clinical challenges due to the the complicated effect of the biological, mechanical, and chemical factors in the oral microenvironment. An in-depth understanding of the underlying molecular regulatory mechanisms will contribute to the exploration of new targets for alveolar bone restoration. Recent studies have shown that Notch, Wnt, Toll-like receptor (TLR), and nuclear factor-κB (NF-κB) signaling pathways regulate the proliferation, differentiation, apoptosis, and autophagy of osteoclasts, osteoblasts, osteocytes, periodontal ligament cells, macrophages, and adaptive immune cells, modulate the expression of inflammatory mediators, affect the balance of the receptor activator for nuclear factor-κB ligand/receptor activator for nuclear factor-κB/osteoprotegerin (RANKL/RANK/OPG) system, and ultimately participate in alveolar bone restoration. Additionally, alveolar bone restoration involves AMP-activated protein kinase (AMPK), phosphatidyl inositol 3-kinase/protein kinase B (PI3K/AKT), Hippo/YAP, Janus kinase/signal transducer and activator of transcription (JAK/STAT), and transforming growth factor β (TGF-β) signaling pathways. However, current studies have failed to construct mature molecular regulatory networks for alveolar bone restoration. There is an urgent need for further research on the molecular regulatory mechanisms of alveolar bone restoration by using new technologies such as single-cell transcriptome sequencing and spatial transcriptome sequencing.

【**Key words**】 Alveolar bone Apical periodontitis Periodontitis Peri-implantitis Signaling pathway Molecular regulatory mechanisms

牙槽骨是上颌骨下缘和下颌骨上缘包绕牙根的突起部分，通过牙周膜与牙根紧密联系，在牙发育、萌出和行使咀嚼功能等过程中发挥关键作用[1]。受口腔微环境中复杂的生物、机械和化学等因素综合影响，牙槽骨处于生理性吸收与形成的动态平衡中[2]。在口腔炎症性疾病（根尖周炎、牙周炎和种植体周围炎等）、创伤、肿瘤、遗传性疾病和系统性疾病等病理条件下，牙槽骨吸收与形成失衡，导致牙槽骨缺损，造成牙松动脱落，引发咀嚼功能

* 国家自然科学基金面上项目（No. 81771047）和四川省科技创新人才项目（No. 2022JDRC0044）资助

△ 通信作者，E-mail: xiejing2012@scu.edu.cn

出版日期：2024-01-20

障碍,危害患者身心健康[3]。在口腔炎症性疾病的临床诊疗过程中,针对性修复牙槽骨缺损仍面临着重大挑战。深入了解维持和恢复牙槽骨稳态的分子机制将有助于口腔炎症性疾病相关牙槽骨缺损的预防和治疗。本文对口腔炎症性疾病相关牙槽骨缺损特点与牙槽骨修复重建分子调控机制的研究新进展进行综述。

1 牙槽骨稳态

牙槽骨稳态是指牙槽骨吸收与形成的动态平衡状态。由于不断遭受着咬合力的冲击和病原微生物的侵袭,牙槽骨吸收与形成活跃,功能应变较其他骨组织高2~4倍,改建速度较其他骨组织高3~6倍[2]。破骨细胞和成骨细胞是牙槽骨吸收与形成的直接执行者,骨细胞、牙周韧带细胞、巨噬细胞、单核细胞、中性粒细胞和适应性免疫细胞等是牙槽骨稳态的其他细胞参与者[1, 4-5]。作为调节破骨细胞和成骨细胞相互作用的重要途径,核因子-κB受体活化因子配体(receptor activator for nuclear factor-κB ligand, RANKL)/核因子-κB受体活化因子(receptor activator for nuclear factor-κB, RANK)/护骨素(osteoprotegerin, OPG)系统是牙槽骨改建的最终环节。其中,RANKL与RANK结合诱导破骨细胞分化,促进骨吸收。OPG与RANKL竞争性结合RANK,促进骨形成[6]。此外,白介素(interleukin, IL)-1、IL-4、IL-6、IL-10、IL-12、IL-17、IL-37、肿瘤坏死因子-α(tumour necrosis factor-α, TNF-α)、干扰素-α(interferon-α, IFN-α)和干扰素-γ(interferon-γ, IFN-γ)等炎症细胞因子加剧着牙槽骨改建微环境的复杂性[7-8]。

2 口腔炎症性疾病与牙槽骨缺损

在根尖周炎、牙周炎和种植体周围炎等口腔炎症性疾病进程中,微生物侵入宿主组织细胞,通过表面致病物质、致病酶、毒素和代谢产物等直接破坏牙槽骨吸收与形成的动态平衡。同时,微生物通过与宿主免疫炎症反应相互作用间接破坏牙槽骨稳态,导致牙槽骨缺损,感染持续或扩散[1-2]。

2.1 根尖周炎与牙槽骨缺损

口腔环境中的微生物群落压力、机械压力和化学压力等可能引发牙齿硬组织损伤,导致微生物及其产物入侵牙髓,触发根尖周组织炎症免疫反应,破坏牙槽骨稳态,引发牙槽骨缺损,临床上表现为根尖周肉芽肿、根尖周囊肿和根尖周脓肿等慢性根尖周炎病损形式[9-10]。对健康和炎性牙槽骨细胞群的单细胞图谱研究发现,根尖周炎间充质干细胞自我支持网络和成骨潜能增强,骨结合素和I型胶原蛋白α等成骨相关标志物表达增加,对牙槽骨缺损具有一定保护作用[11]。在人和小鼠根尖周炎组织中,T细胞活化免疫球蛋白抑制V型结构域表达逐渐积累,伴随着CD3阳性T细胞、CD11b阳性髓系细胞和FOXP3阳性调节性T细胞等增加,维持免疫平衡,抑制根尖周炎牙槽骨进一步破坏[12]。De ROSSI等[13]通过将牙髓暴露于口腔环境诱导小鼠下颌第一磨牙根尖周炎发现,随着根尖周牙槽骨病损逐渐扩大,炎性细胞、破骨细胞和破牙骨质细胞等数量增加,RANK/RANKL/OPG、矮小相关转录因子2(Runt-related transcription factor 2, Runx2)和组织蛋白酶K(cathepsin K, CTSK)等基因表达增加。在健康根尖周组织无法检出的成纤维细胞生长因子受体2(fibroblast growth factor receptor 2, FGFR2)表达于根尖周炎组织的成骨细胞、成纤维细胞、巨噬细胞、浆细胞、中性粒细胞和增大的牙骨质细胞腔隙等部位,其表达量与根尖周病损大小相关。

2.2 牙周炎与牙槽骨缺损

牙周炎是一种以牙菌斑生物膜为始动因子,在牙石、牙齿解剖或位置异常、咬合创伤、食物嵌塞和口腔不良习惯等局部因素促进下,由宿主免疫炎症反应和全身促进因素共同参与的慢性感染性疾病[14]。在牙周炎发生发展过程中,牙菌斑生物膜微生物组成与数量变化触发牙周上皮和牙龈结缔组织的促炎免疫反应,并向邻近骨细胞发出旁分泌信号,破坏破骨细胞与成骨细胞耦合作用,导致牙槽骨损伤[15]。新近研究表明,牙周炎引发的氧化应激是牙槽骨稳态破坏的重要原因。在人牙周炎牙槽骨中,髓系细胞触发受体2显著上调,介导破骨细胞生成过程中活性氧信号的放大。牙周炎微环境积聚的可溶性Aβ42寡聚体通过与髓系细胞触发受体2直接相互作用进一步加剧氧化应激,促进牙槽骨破坏[16]。其中,氧化应激既可通过激活基质金属蛋白酶(matrix metalloproteinase, MMP)、触发脂质过氧化、介导线粒体损伤与呼吸爆发、破坏脱氧核糖核酸与蛋白质等直接造成牙槽骨组织细胞损伤;也可通过免疫炎症相关信号通路和转录因子发挥间接作用[17-18]。

2.3 种植体周围炎与牙槽骨缺损

种植体周围炎是发生于骨结合种植体周围软硬组织的炎症性疾病。与健康种植体周围组织相比,种植体周围炎病损部位出现牙龈卟啉单胞菌和福赛斯坦纳菌等19种细菌的较高计数、浆细胞和淋巴细胞的广泛浸润和牙槽骨的显著流失。IL-1α和TNF-α是种植体周围炎病损部位主要的破骨细胞激活因子[19]。随着种植体周围炎牙槽骨吸收加重,种植体龈沟液促炎因子表达水平发生时

序变化。当牙槽骨吸收达25%~50%时, 种植体龈沟液中IL-1α和IL-6表达减少; 当牙槽骨吸收超过50%时, 种植体龈沟液中IL-1α、IL-6和IL-17A表达减少[20]。

种植体周围炎与天然牙牙周炎的牙槽骨缺损存在显著差异。由于种植体周围软组织界面抵御细菌入侵能力弱于天然牙, 种植体周围炎牙槽骨缺损更易发生和进展。重复使用牙龈卟啉单胞菌对小鼠进行口腔灌洗后, 种植体和天然牙的支持牙槽骨均出现破坏; 然而, 单次灌洗牙龈卟啉单胞菌仅导致种植体周围牙槽骨流失[21]。与天然牙牙周炎相比, 种植体周围炎结缔组织中浆细胞、淋巴细胞、巨噬细胞、多形核白细胞和破骨细胞等浸润更密集、更广泛, 可延伸至牙槽嵴, 但炎性浸润区域血管密度较低。同时, 种植体周围炎病变组织IFN-α和IL-1β表达量更高, RANKL/OPG比率更高, 可见异物反应[21-22]。

3　牙槽骨修复重建的分子调控机制

在根尖周炎、牙周炎和种植体周围炎等口腔炎症性疾病中, 牙槽骨缺损常常是标志性事件, 干扰牙发育、萌出和行使咀嚼功能。由于口腔微环境致病因素与宿主炎症免疫反应的相互作用复杂多变, 临床牙槽骨缺损修复面临巨大挑战[23]。为探寻口腔炎症性疾病防治新靶点, 亟需深入了解牙槽骨修复重建分子调控机制。新近研究表明, Notch、Wnt、Toll样受体(Toll like receptor, TLR)和核因子-κB(nuclear factor-κB, NF-κB)等信号通路通过调控破骨细胞、成骨细胞、骨细胞、牙周韧带细胞、巨噬细胞和适应性免疫细胞等增殖、分化、凋亡和自噬等生命活动, 调节炎症介质表达, 影响 RANKL/RANK/OPG系统平衡, 参与牙槽骨修复重建(图1)。此外, 牙槽骨修复重建也涉及腺苷酸激活蛋白激酶(AMP-activated protein kinase, AMPK)、磷脂酰肌醇3-激酶(phosphatidyl inositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, AKT)、Hippo/YAP、Janus 激酶(Janus kinase, JAK)/转录激活因子(signal transducer and activator of transcription, STAT)和转化生长因子-β(transforming growth factor β, TGF-β)等信号通路。

3.1　Notch信号通路

在Notch信号通路中, 相邻细胞通过膜蛋白受体Notch1-Notch4与膜蛋白配体Delta/Delta-like和Jagged/Serrate结合, 激活Notch蛋白。经过三步蛋白酶水解, Notch膜内区入核, 与CSL-DNA结合蛋白装配成转录激活复合体, 激活Hes、Hey和Herp等靶基因转录, 参与各种分化与发育事件[24]。

在牙槽骨修复重建中, Notch信号通路通过调控促炎细胞因子和骨吸收调控因子的复杂网络发挥作用。其中, Notch1信号可能促进牙槽骨修复。MIJAILOVIC等[25]通过分析侵袭性牙周炎患者、慢性牙周炎患者和牙周健康人群龈沟液总RNA发现, Notch1及其配体Jagged1的下调, 导致其骨保护功能丧失, 诱导破骨细胞过度形成, 加剧侵袭性牙周炎患者牙槽骨吸收。MILINKOVIC等[26]认为, Notch1下调与IL-1β、IL-6、IL-17和RANKL等关键炎症调节因子失调共同提高破骨细胞活性, 导致种植体周围炎牙槽骨严重破坏。

与Notch1信号作用相反, Notch2信号抑制牙槽骨修复。MIJAILOVIC等[25]通过分析龈沟液总RNA发现, Notch2过表达与侵袭性牙周炎和慢性牙周炎牙槽骨吸收的发病机制有关。种植体周围炎患者和种植体周围黏膜炎患者的种植体周围龈沟液总RNA分析结果表明, 在RANKL较OPG具有表达优势的种植体周围粘膜炎中, Notch2的上调可能是牙槽骨吸收的重要因素, 也是种植体周围黏膜炎向种植体周围炎转变的预测因子。Notch2的上调伴随着IL-1β和IL-6的上调, 为破骨细胞提供生成环境[27]。获取根尖切除术患者根尖周炎病变组织进行RNA检测发现, 在RANKL表达相对OPG表达占优势的根尖周炎病变中, Notch信号分子Notch2、Jagged1、Hey1和TNF-α等过表达且存在显著相关性, 共同参与广泛的牙槽骨吸收[28]。与Epstein-Barr病毒阴性根尖周病变相比, Epstein-Barr病毒阳性根尖周病变组织Notch2、Jagged1、RANKL和IL-1β等表达增加, 病损范围更大, 且常伴临床症状。其中, Notch2与Jagged1、Notch2与RANKL、Notch2与IL-6、Jagged1与RANKL、Jagged1与IL-1β、IL-1β与TNF-α、IL-6与OPG之间存在显著正相关性, OPG与Jagged1和IL-1β存在负相关性[29]。

3.2　Wnt信号通路

在经典Wnt信号通路中, Wnt1、Wnt2、Wnt3、Wnt3a、Wnt5b、Wnt7a、Wnt8、Wnt8b和Wnt10b等自分泌或旁分泌Wnts蛋白与跨膜受体Frizzled家族和共受体低密度脂蛋白受体相关蛋白5/6(LDL receptor related protein 5/6, LRP5/6)结合, 通过蛋白激酶磷酸化稳定β-catenin, 促进其入核并与T细胞因子/淋巴细胞样增强因子形成复合物, 调控基因转录, 影响细胞增殖、分化、极化、迁移、衰老、自噬和凋亡等行为, 决定细胞命运[30]。而Wnt4、Wnt5a、Wnt5b、Wnt6、Wnt7a和Wnt11等可激活非经典Wnt/Ca^{2+}、Wnt/JNK和Wnt/Rho等信号, 这一过程不依赖β-catenin, 甚至具有拮抗β-catenin的作用[31]。

经典与非经典Wnt信号是骨发育、骨代谢和骨修复等的重要调控通路。新近研究表明, 激活经典Wnt信号

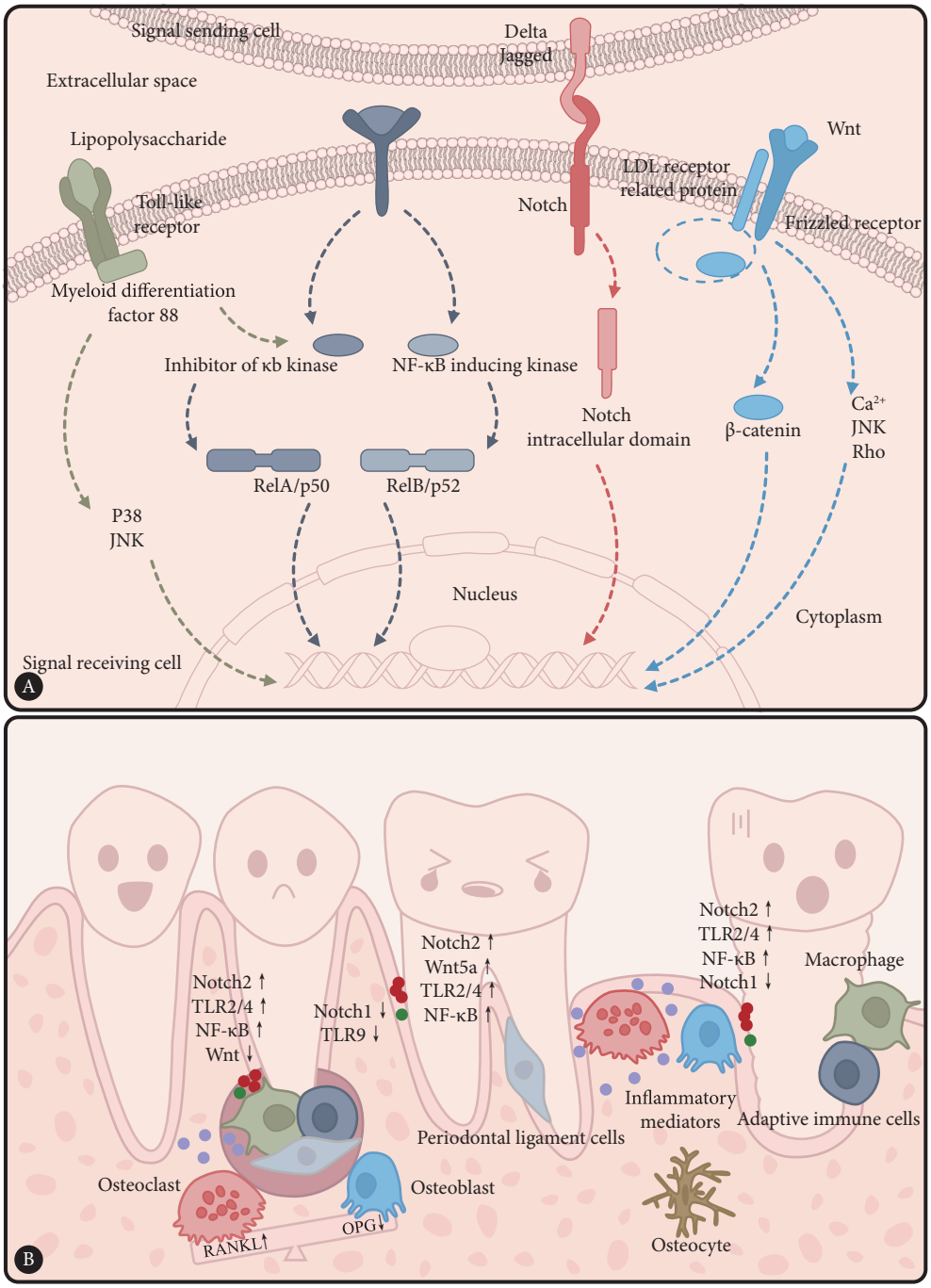

图 1 口腔炎症性疾病牙槽骨修复重建的分子机制

Fig 1 Molecular mechanisms involved in alveolar bone restoration in oral inflammatory diseases

A, Schematic diagram of pathways involved in molecular mechanisms in alveolar bone restoration. B, Changes in molecular signals involved in alveolar bone destruction in oral inflammatory diseases. NF-κB:nuclear factor-κB; TLR: Toll-like receptor; RANK: receptor activator for nuclear factor-κB; OPG: osteoprotegerin.

有助于口腔炎症性疾病相关牙槽骨修复。对根尖周炎患者颊黏膜细胞基因组DNA进行单核苷酸多态性基因表达分析发现，经典Wnt信号共受体LRP5的单核苷酸多态性与根尖周炎病变有显著的基因型关联。在小鼠根尖周炎模型中，通过尾静脉注射经典Wnt信号通路抑制剂IWR-1将扩大牙槽骨损伤病灶；使用经典Wnt信号通路激活剂氯化锂进行根管封药可提高Ⅰ型胶原蛋白α1和Runx2表达水平，增加CD45R阳性细胞数量，通过诱导骨形成和免疫反应加速根尖周炎牙槽骨损伤的愈合[32]。此外，雌激素能够通过与雌激素受体结合激活Wnt信号，刺激成骨细胞分化，抑制RANKL诱导的破骨细胞活性，促进骨细胞自噬，阻止骨细胞凋亡，直接参与牙槽骨重建；也能够通过抑制氧化应激和炎症反应间接调控牙槽骨代谢稳态[33-34]。然而，LEI等[35]发现，健康人群牙周韧带干细胞外

泌体通过抑制经典Wnt信号过度激活促进牙周炎患者炎性牙周韧带干细胞表达成骨标志物并形成矿化结节, 利用基底膜基质或β-磷酸三钙负载健康人群牙周韧带干细胞外泌体可加速修复牙周炎大鼠模型的牙槽骨缺损。经典Wnt信号通路在口腔炎症性疾病相关牙槽骨修复重建中的作用仍存在争议, 这可能与实验模型、组织定位、细胞类型、炎症分期和检测指标等差异有关。因此, 未来研究需进一步精准把握经典Wnt信号在炎性牙槽骨损伤修复过程的时空表达特征。

非经典Wnt信号也参与口腔炎症性疾病相关牙槽骨修复重建。据报道, 广泛型中重度牙周炎患者病变部位龈沟液非经典Wnt家族配体Wnt5a水平显著高于健康部位, 具有较高的诊断价值[36]。NAKAO等[37]发现, TNF-α刺激能够促进牙龈间充质干细胞分泌外泌体, 增加外泌体微小核糖核酸-1260b含量, 抑制非经典的Wnt5a和JNK信号, 介导RANKL下调与OPG上调, 减少破骨细胞形成, 诱导抗炎M2巨噬细胞极化, 最终促进小鼠牙周炎的牙槽骨修复。PURWANINGRUM等[38]则发现, IL-6既能通过Wnt2b或Wnt10b激活经典Wnt信号, 又能通过Wnt5a激活非经典Wnt信号, 共同诱导人牙周韧带干细胞成骨分化, 有利于牙槽骨再生。

在口腔炎症性疾病相关牙槽骨修复重建中, Wnt信号通路也可与其他信号通路相互作用。例如, GUAN等[39]提出, 在人和大鼠根尖周炎病变组织中, 随着牙槽骨缺损扩大和炎性细胞浸润增加, 经典Wnt信号与NF-κB信号均被激活, 二者之间存在更为显著的串扰。抑制经典Wnt信号通路, 可减少脂多糖诱导的人牙周韧带细胞NF-κB和IL-1β表达, 减轻根尖周炎症。抑制NF-κB信号通路, 也可阻断经典Wnt信号通路, 导致脂多糖诱导的人牙周韧带细胞炎症反应减弱。PIELES等[40]发现, 抑制蛋白激酶C信号能够促进地塞米松诱导的人牙囊细胞经典Wnt通路关键效应分子β-catenin核表达, 促进人牙囊细胞成骨分化。然而, 抑制蛋白激酶C信号对骨形态发生蛋白2(bone morphogenetic protein 2, BMP2)诱导的人牙囊细胞β-catenin定位无显著影响, 这可能是因为BMP2本身足以激活牙囊细胞β-catenin, 无需进一步诱导Wnt信号。过度激活经典Wnt信号甚至可能干扰BMP2诱导的成骨分化, 阻碍牙槽骨修复重建。

3.3　TLR信号通路

人类含10种TLRs(TLR1-TLR10)。FAWZY El-SAYED等[41]通过对TLRs表达谱进行基因和蛋白水平的鉴定, 首次发现牙槽骨间充质干细胞高表达TLR2, 其次是TLR4、TLR5、TLR7、TLR1、TLR10、TLR8、TLR3和TLR6; 而牙槽骨成骨细胞高表达TLR2, 其次是TLR10、TLR4、TLR7、TLR5、TLR1、TLR8和TLR6。各型TLRs位于不同细胞的不同区室, 识别脂多糖、脂磷壁酸、脂蛋白、肽聚糖、葡聚糖、甘露糖和核酸等不同病原相关分子模式或损伤相关分子模式, 通过接头蛋白髓样分化因子88依赖或非依赖的方式激活NF-κB和MAPK等不同信号级联反应, 调控细胞因子和趋化因子合成与分泌, 介导一氧化氮相关杀菌途径与呼吸爆发, 诱导细胞募集、增殖、分化、活化与凋亡, 在感染与炎症免疫反应不同阶段产生不同生物学效应。

TLR信号通路在炎症损伤牙槽骨的修复重建中扮演着重要角色。据报道, MMP9能够抑制TLR2/4表达, 从而抑制IL-1β、TNF-α、RANK和RANKL等表达, 促进OPG和骨钙素表达, 在脂多糖诱导的炎症中对小鼠胚胎成骨细胞MC3T3-E1具有保护作用, 支持牙槽骨重建。基因敲除MMP9将加剧小鼠根尖周炎牙槽骨破坏[42]。在小鼠丝线结扎种植体周围炎模型中, 抗炎微小核糖核酸-146a可通过下调TLR2/4信号, 抑制TNF-α表达, 减少牙龈炎症细胞浸润, 增强抗RANKL诱导种植体周围牙槽骨吸收的作用[43]。除响应局部刺激因素作用外, TLR信号通路还参与了全身因素对口腔炎症性疾病相关牙槽骨缺损修复的调控。例如, 与持续高血糖相比, 血糖波动导致小鼠种植体周围炎模型出现更显著的牙槽骨流失、炎症细胞浸润和破骨细胞生成, 这可能与种植体周围微生物群失调及TLR2/4-白介素-1受体相关激酶1-肿瘤坏死因子受体相关因子6信号激活有关[44]。

尽管在多数根尖周炎、牙周炎和种植体周围炎相关研究中, 以TLR2/4为代表的TLR信号能够通过RANKL依赖性和非依赖性机制诱导破骨细胞分化, 阻碍牙槽骨修复重建, 其他TLR信号可能具有不同效应。例如, 唾液样本基因分型结果显示, 在唾液牙龈卟啉单胞菌阳性成人中, TLR4多态性似乎会导致牙槽骨流失; 但在唾液牙龈卟啉单胞菌阴性成人中, TLR9多态性对牙槽骨流失具有保护作用[45]。激活早期破骨细胞前体TLRs, 尤其是TLR4/9, 能够增加IL-12合成与释放, 下调巨噬细胞集落刺激因子受体的细胞膜表达, 抑制RANK表达, 抑制RANKL诱导的破骨细胞分化。这反映出TLR信号参与骨免疫与骨代谢稳态的复杂性, 提示可能存在未知的反馈机制[46]。

3.4　NF-κB信号通路

NF-κB信号通路是宿主响应外界刺激、产生炎症反应或免疫应答的信号通路。在经典NF-κB信号通路中, 多种刺激因素与模式识别受体、B细胞受体、T细胞受体或

促炎细胞因子受体等结合，激活κB抑制因子激酶，促进NF-κB异二聚体RelA/p50瞬时核易位，调控促炎基因转录；在非经典NF-κB信号通路中，TNF与其受体结合，稳定NF-κB诱导激酶，导致RelB/p52复合物入核，缓慢而持久地调控蛋白质表达，参与免疫系统发育、免疫稳态维持和免疫应答等过程[47-48]。

经典或非经典NF-κB信号通过调节炎症细胞因子和介质表达直接影响炎性牙槽骨损伤修复。例如，在通过丝线结扎和大肠杆菌脂多糖接种建立的小鼠牙周炎模型中，二甲基草酰甘氨酸增加缺氧诱导因子-1α表达与积聚，抑制NF-κB通路磷酸化，下调TNF-α和IL-6等促炎细胞因子，上调IL-4和IL-10等抗炎细胞因子，降低M1/M2巨噬细胞比例，抑制破骨细胞分化，减少牙槽骨吸收，增加牙槽骨体积和密度[49]。腹腔注射吡非尼酮通过抑制骨髓来源巨噬细胞NF-κB信号通路，抑制脂多糖诱导的促炎细胞因子IL-1β、IL-6和TNF-α等表达，抑制RANKL诱导的破骨细胞生成，明显减轻实验性小鼠牙周炎的牙槽骨损失[50]。在大鼠种植体周围炎模型中，车叶草苷通过抑制NF-κB激活和细胞外信号调节激酶1/2磷酸化，下调转录因子活化T细胞核因子1，降低促炎细胞因子水平，抑制破骨细胞形成，减轻种植体周围炎牙槽骨吸收[51]。此外，NF-κB信号还可通过调节炎性小体组装，介导促炎因子成熟和细胞焦亡，间接影响炎性牙槽骨损伤修复。据报道，IL-37通过抑制NF-κB途径，抑制NOD样受体热蛋白结构域相关蛋白3炎性小体表达，减少破骨细胞数量，减少降钙素受体、CTSK、RANKL和IL-10表达，增加OPG、IL-1β、IL-6和TNF-α表达，缓解实验性牙周炎小鼠牙槽骨吸收[52-53]。

3.5 其他信号通路

牙槽骨修复重建的分子调控网络十分复杂。除Notch、Wnt、TLR和NF-κB等信号通路外，AMPK[54]、PI3K/AKT[55]、Hippo/YAP[56]、JAK/STAT[57]和TGF-β[58]等信号通路也涉及其中。例如，人脱落乳牙牙髓干细胞外泌体可通过激活AMPK信号通路上调人脐静脉内皮细胞血管生成相关基因表达，上调大鼠骨髓间充质干细胞骨生成相关基因表达，协同β-磷酸三钙促进大鼠牙周炎牙槽骨再生[54]。低强度脉冲式超声波通过空化效应和机械效应发挥作用，上调PI3K/AKT通路，激活核因子-红细胞2相关因子2，减轻氧化应激，促进牙周韧带细胞成骨分化，有利于小鼠牙周炎牙槽骨修复[55]。过表达α-降钙素基因相关肽可通过上调Hippo/YAP信号通路介导人牙周韧带细胞成骨分化，促进牙周炎牙槽骨再生[56]。白花丹素通过抑制JAK/STAT信号通路，抑制大鼠慢性牙周炎牙龈TNF-α、IL-1β和IL-6等表达，减缓牙周炎牙槽骨流失[57]。在牙周炎小鼠和患者牙周组织中，B细胞表达高水平TGF-β1，并通过上调p-Smad2/3表达和下调Runx2表达，抑制间充质干细胞成骨分化，促进牙槽骨流失。特异性敲除B细胞TGF-β1或耗竭B细胞可显著增加成骨细胞活性和牙槽骨体积[58]。

4 总结与展望

在以根尖周炎、牙周炎和种植体周围炎为代表的口腔炎症性疾病中，牙槽骨吸收与形成失衡，导致牙槽骨缺损。修复牙槽骨缺损是治愈口腔炎症性疾病的关键环节。Notch、Wnt、TLR和NF-κB等信号通路在调控牙槽骨修复重建中发挥重要作用。构建成熟的牙槽骨修复重建分子调控网络，有望为实现口腔炎症性疾病的分子靶向治疗提供新方案，有望为深入认识口腔病灶与全身系统性疾病关联提供新思路。

* * *

作者贡献声明 魏洁雅负责调查研究、研究方法、研究项目管理和初稿写作，徐思群负责调查研究和初稿写作，周学东和谢静负责论文构思、经费获取、研究项目管理、提供资源、监督指导和审读与编辑写作。所有作者已经同意将文章提交给本刊，且对将要发表的版本进行最终定稿，并同意对工作的所有方面负责。

Author Contribution WEI Jieya is resposible for the investigation, methodology, project administration, and writing original draft. XU Siqun is resposible for the investigation and writing original draft. ZHOU Xuedong and XIE Jing are resposible for the conceptualization, funding acquisition, project administration, resources, supervision, and writing review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

利益冲突 所有作者均声明不存在利益冲突

Declaration of Conflicting Interests All authors declare no competing interests.

参 考 文 献

[1] LI Y, LING J, JIANG Q. Inflammasomes in alveolar bone loss. Front Immunol, 2021, 12: 691013. doi: 10.3389/fimmu.2021.691013.

[2] HATHAWAY-SCHRADER J D, NOVINCE C M. Maintaining homeostatic control of periodontal bone tissue. Periodontol 2000, 2021, 86(1): 157–187. doi: 10.1111/prd.12368.

[3] YU B, WANG C Y. Osteoporosis and periodontal diseases--An update on their association and mechanistic links. Periodontol 2000, 2022, 89(1): 99–113. doi: 10.1111/prd.12422.

[4] WANG Q, XIE J, ZHOU C, *et al*. Substrate stiffness regulates the differentiation profile and functions of osteoclasts via cytoskeletal arrangement. Cell Prolif, 2022, 55(1): e13172. doi: 10.1111/cpr.13172.

[5] LIU Y, PU X, DUAN M, *et al*. Biomimetic fibers derived from an equidistant micropillar platform dictate osteocyte fate via

mechanoreception. Nano Lett, 2023, 23(17): 7950–7960. doi: 10.1021/acs.nanolett.3c01739.

[6] ZAIDI M, KIM S M, MATHEW M, *et al*. Bone circuitry and interorgan skeletal crosstalk. Elife, 2023, 12: e83142. doi: 10.7554/eLife.83142.

[7] LUO X, WAN Q, CHENG L, *et al*. Mechanisms of bone remodeling and therapeutic strategies in chronic apical periodontitis. Front Cell Infect Microbiol, 2022, 12: 908859. doi: 10.3389/fcimb.2022.908859.

[8] GUO D, KAN S, ZHANG L, *et al*. IL-10 enhances cell-to-cell communication in chondrocytes via STAT3 signaling pathway. Cell Signal, 2023, 105: 110605. doi: 10.1016/j.cellsig.2023.110605.

[9] GALLER K M, WEBER M, KORKMAZ Y, *et al*. Inflammatory response mechanisms of the dentine-pulp complex and the periapical tissues. Int J Mol Sci, 2021, 22(3): 1480. doi: 10.3390/ijms22031480.

[10] CUI Y, XIE J, CAI L, *et al*. Berberine regulates bone metabolism in apical periodontitis by remodelling the extracellular matrix. Oral Dis, 2023, 29(3): 1184–1196. doi: 10.1111/odi.14094.

[11] FAN Y, LYU P, BI R, *et al*. Creating an atlas of the bone microenvironment during oral inflammatory-related bone disease using single-cell profiling. Elife, 2023, 12: e82537. doi: 10.7554/eLife.82537.

[12] YANG F, ZHANG Y, CHEN Z, *et al*. VISTA blockade aggravates bone loss in experimental murine apical periodontitis. Front Immunol, 2021, 12: 738586. doi: 10.3389/fimmu.2021.738586.

[13] De ROSSI A, HUAMÁN S D, LEÓN J E, *et al*. Fibroblast growth factor receptor 2 expression in apical periodontitis in mice. Int Endod J, 2020, 53(8): 1111–1119. doi: 10.1111/iej.13315.

[14] TRINDADE D, CARVALHO R, MACHADO V, *et al*. Prevalence of periodontitis in dentate people between 2011 and 2020: a systematic review and meta-analysis of epidemiological studies. J Clin Periodontol, 2023, 50(5): 604–626. doi: 10.1111/jcpe.13769.

[15] ZHOU M, GRAVES D T. Impact of the host response and osteoblast lineage cells on periodontal disease. Front Immunol, 2022, 13: 998244. doi: 10.3389/fimmu.2022.998244.

[16] WENG Y, WANG H, LI L, *et al*. Trem2 mediated Syk-dependent ROS amplification is essential for osteoclastogenesis in periodontitis microenvironment. Redox Biol, 2021, 40: 101849. doi: 10.1016/j.redox.2020.101849.

[17] CHEN E, WANG T, TU Y, *et al*. ROS-scavenging biomaterials for periodontitis. J Mater Chem B, 2023, 11(3): 482–499. doi: 10.1039/d2tb02319a.

[18] XIN L, ZHOU F, ZHANG C, *et al*. Four-octyl itaconate ameliorates periodontal destruction via Nrf2-dependent antioxidant system. Int J Oral Sci, 2022, 14(1): 27. doi: 10.1038/s41368-022-00177-1.

[19] SCHWARZ F, DERKS J, MONJE A, *et al*. Peri-implantitis. J Periodontol, 2018, 89(Suppl 1): S267–S290. doi: 10.1002/jper.16-0350.

[20] 冷春涛, 李婷, 高晓蔚. 4种白细胞介素在种植体周围炎分期模型中的表达分析. 上海口腔医学, 2020, 29(2): 162–167. doi: 10.19439/j.sjos.2020.02.010.

LENG C T, LI T, GAO X W. Study on the expression level of four kinds of interleukins in mice model with peri-implantitis. Shanghai J Stomatol, 2020, 29(2): 162–167. doi: 10.19439/j.sjos.2020.02.010.

[21] HEYMAN O, HOREV Y, MIZRAJI G, *et al*. Excessive inflammatory response to infection in experimental peri-implantitis: resolution by Resolvin D2. J Clin Periodontol, 2022, 49(11): 1217–1228. doi: 10.1111/jcpe.13631.

[22] 李悦, 冯向辉, 胡文杰. 种植体周炎的组织病理学特点. 中华口腔医学杂志, 2023, 58(3): 281–286. doi: 10.3760/cma.j.cn112144-20220702-00362.

LI Y, FENG X H, HU W J. Histopathological characteristics of peri-implantitis. Chin J Stomatol, 2023, 58(3): 281–286. doi: 10.3760/cma.j.cn112144-20220702-00362.

[23] GRUBER R. Osteoimmunology: Inflammatory osteolysis and regeneration of the alveolar bone. J Clin Periodontol, 2019, 46(Suppl 21): 52–69. doi: 10.1111/jcpe.13056.

[24] ZHOU B, LIN W, LONG Y, *et al*. Notch signaling pathway: architecture, disease, and therapeutics. Signal Transduct Target Ther, 2022, 7(1): 95. doi: 10.1038/s41392-022-00934-y.

[25] MIJAILOVIC I, NIKOLIC N, DJINIC A, *et al*. The down-regulation of Notch 1 signaling contributes to the severity of bone loss in aggressive periodontitis. J Periodontol, 2020, 91(4): 554–561. doi: 10.1002/jper.18-0755.

[26] MILINKOVIC I, DJINIC KRASAVCEVIC A, NIKOLIC N, *et al*. Notch down-regulation and inflammatory cytokines and RANKL overexpression involvement in peri-implant mucositis and peri-implantitis: a cross-sectional study. Clin Oral Implants Res, 2021, 32(12): 1496–1505. doi: 10.1111/clr.13850.

[27] DJINIC KRASAVCEVIC A, NIKOLIC N, MILINKOVIC I, *et al*. Notch signalling cascade and proinflammatory mediators in peri-implant lesions with different RANKL/OPG ratios-an observational study. J Periodontal Res, 2023, 58(2): 360–368. doi: 10.1111/jre.13096.

[28] NIKOLIC N, JAKOVLJEVIC A, CARKIC J, *et al*. Notch signaling pathway in apical periodontitis: correlation with bone resorption regulators and proinflammatory cytokines. J Endod, 2019, 45(2): 123–128. doi: 10.1016/j.joen.2018.10.015.

[29] JAKOVLJEVIC A, NIKOLIC N, CARKIC J, *et al*. Notch-a possible mediator between Epstein-Barr virus infection and bone resorption in apical periodontitis. Acta Odontol Scand, 2020, 78(2): 126–131. doi: 10.1080/00016357.2019.1658896.

[30] ZHOU C, YANG Y, DUAN M, *et al*. Biomimetic fibers based on equidistant micropillar arrays determines chondrocyte fate via mechanoadaptability. Adv Healthc Mater, 2023, 12(30): e2301685. doi: 10.1002/adhm.202301685.

[31] RIM E Y, CLEVERS H, NUSSE R. The Wnt pathway: from signaling mechanisms to synthetic modulators. Annu Rev Biochem, 2022, 91: 571–598. doi: 10.1146/annurev-biochem-040320-103615.

[32] NARUSE H, ITOH S, ITOH Y, *et al*. The Wnt/β-catenin signaling pathway has a healing ability for periapical periodontitis. Sci Rep, 2021, 11(1): 19673. doi: 10.1038/s41598-021-99231-x.

[33] JAYUSMAN P A, NASRUDDIN N S, BAHARIN B, *et al*. Overview on postmenopausal osteoporosis and periodontitis: the therapeutic potential of phytoestrogens against alveolar bone loss. Front Pharmacol, 2023, 14: 1120457. doi: 10.3389/fphar.2023.1120457.

[34] CHENG C H, CHEN L R, CHEN K H. Osteoporosis due to hormone

imbalance: an overview of the effects of estrogen deficiency and glucocorticoid overuse on bone turnover. Int J Mol Sci, 2022, 23(3): 1376. doi: 10.3390/ijms23031376.

[35] LEI F, LI M, LIN T, *et al*. Treatment of inflammatory bone loss in periodontitis by stem cell-derived exosomes. Acta Biomater, 2022, 141: 333–343. doi: 10.1016/j.actbio.2021.12.035.

[36] CHATZOPOULOS G S, MANSKY K C, LUNOS S, *et al*. Sclerostin and WNT-5a gingival protein levels in chronic periodontitis and health. J Periodontal Res, 2019, 54(5): 555–565. doi: 10.1111/jre.12659.

[37] NAKAO Y, FUKUDA T, ZHANG Q, *et al*. Exosomes from TNF-α-treated human gingiva-derived MSCs enhance M2 macrophage polarization and inhibit periodontal bone loss. Acta Biomater, 2021, 122: 306–324. doi: 10.1016/j.actbio.2020.12.046.

[38] PURWANINGRUM M, GIACHELLI C M, OSATHANON T, *et al*. Dissecting specific Wnt components governing osteogenic differentiation potential by human periodontal ligament stem cells through interleukin-6. Sci Rep, 2023, 13(1): 9055. doi: 10.1038/s41598-023-35569-8.

[39] GUAN X, HE Y, WEI Z, *et al*. Crosstalk between Wnt/β-catenin signaling and NF-κB signaling contributes to apical periodontitis. Int Immunopharmacol, 2021, 98: 107843. doi: 10.1016/j.intimp.2021.107843.

[40] PIELES O, REICHERT T E, MORSCZECK C. Classical isoforms of protein kinase C (PKC) and Akt regulate the osteogenic differentiation of human dental follicle cells via both β-catenin and NF-κB. Stem Cell Res Ther, 2021, 12(1): 242. doi: 10.1186/s13287-021-02313-w.

[41] FAWZY El-SAYED K M, BOECKLER J, DÖRFER C E. TLR expression profile of human alveolar bone proper-derived stem/progenitor cells and osteoblasts. J Craniomaxillofac Surg, 2017, 45(12): 2054–2060. doi: 10.1016/j.jcms.2017.09.007.

[42] ZHANG H, LIU L, JIANG C, *et al*. MMP9 protects against LPS-induced inflammation in osteoblasts. Innate Immun, 2020, 26(4): 259–269. doi: 10.1177/1753425919887236.

[43] PAN K, HU Y, WANG Y, *et al*. RANKL blockade alleviates peri-implant bone loss and is enhanced by anti-inflammatory microRNA-146a through TLR2/4 signaling. Int J Implant Dent, 2020, 6(1): 15. doi: 10.1186/s40729-020-00210-0.

[44] LI H, WANG Y, ZHANG D, *et al*. Glycemic fluctuation exacerbates inflammation and bone loss and alters microbiota profile around implants in diabetic mice with experimental peri-implantitis. Int J Implant Dent, 2021, 7(1): 79. doi: 10.1186/s40729-021-00360-9.

[45] GURSOY U K, HE Q, PUSSINEN P, *et al*. Alveolar bone loss in relation to toll-like receptor 4 and 9 genotypes and porphyromonas gingivalis carriage. Eur J Clin Microbiol Infect Dis, 2016, 35(11): 1871–1876. doi: 10.1007/s10096-016-2741-6.

[46] GU Y, HAN X. Toll-like receptor signaling and immune regulatory lymphocytes in periodontal disease. Int J Mol Sci, 2020, 21(9): 3329. doi: 10.3390/ijms21093329.

[47] CAPECE D, VERZELLA D, FLATI I, *et al*. NF-κB: blending metabolism, immunity, and inflammation. Trends Immunol, 2022, 43(9): 757–775. doi: 10.1016/j.it.2022.07.004.

[48] CHEN S, WU Z, HE Y, *et al*. Cyclic di-adenosine monophosphate regulates the osteogenic and adipogenic differentiation of hPDLSCs via MAPK and NF-κB signaling. Acta Biochim Biophys Sin (Shanghai), 2023, 55(3): 426–437. doi: 10.3724/abbs.2023018.

[49] CHEN M H, WANG Y H, SUN B J, *et al*. HIF-1α activator DMOG inhibits alveolar bone resorption in murine periodontitis by regulating macrophage polarization. Int Immunopharmacol, 2021, 99: 107901. doi: 10.1016/j.intimp.2021.107901.

[50] ZHANG Z, SONG J, KWON S H, *et al*. Pirfenidone inhibits alveolar bone loss in ligature-induced periodontitis by suppressing the NF-κB signaling pathway in mice. Int J Mol Sci, 2023, 24(10): 8682. doi: 10.3390/ijms24108682.

[51] WANG X, CHEN X, ZHANG Z, *et al*. Asperuloside prevents peri-implantitis via suppression of NF-κB and ERK1/2 on rats. Pharmaceuticals (Basel), 2022, 15(8): 1027. doi: 10.3390/ph15081027.

[52] LI L, LI J, LI S, *et al*. IL-37 alleviates alveolar bone resorption and inflammatory response through the NF-κB/NLRP3 signaling pathway in male mice with periodontitis. Arch Oral Biol, 2023, 147: 105629. doi: 10.1016/j.archoralbio.2023.105629.

[53] 王甲河, 邹淑娟, 谢静, 等. NLRP3炎性小体与骨及关节疾病发生的研究进展. 四川大学学报(医学版), 2023, 54(3): 679–684. doi: 10.12182/20230560105.

WANG J H, ZOU S J, XIE J, *et al*. Latest findings on NOD-Like receptor family pyrin domain containing protein 3 inflammasome and bone and articular diseases. J Sichuan Univ (Med Sci), 2023, 54(3): 679–684. doi: 10.12182/20230560105.

[54] WU J, CHEN L, WANG R, *et al*. Exosomes secreted by stem cells from human exfoliated deciduous teeth promote alveolar bone defect repair through the regulation of angiogenesis and osteogenesis. ACS Biomater Sci Eng, 2019, 5(7): 3561–3571. doi: 10.1021/acsbiomaterials.9b00607.

[55] YING S, TAN M, FENG G, *et al*. Low-intensity pulsed ultrasound regulates alveolar bone homeostasis in experimental periodontitis by diminishing oxidative stress. Theranostics, 2020, 10(21): 9789–9807. doi: 10.7150/thno.42508.

[56] CHEN J, CHENG J, ZHAO C, *et al*. The Hippo pathway: a renewed insight in the craniofacial diseases and hard tissue remodeling. Int J Biol Sci, 2021, 17(14): 4060–4072. doi: 10.7150/ijbs.63305.

[57] ZHENG X Y, MAO C Y, QIAO H, *et al*. Plumbagin suppresses chronic periodontitis in rats via down-regulation of TNF-α, IL-1β and IL-6 expression. Acta Pharmacol Sin, 2017, 38(8): 1150–1160. doi: 10.1038/aps.2017.19.

[58] CHEN Y, WANG H, NI Q, *et al*. B-cell-derived TGF-β1 inhibits osteogenesis and contributes to bone loss in periodontitis. J Dent Res, 2023, 102(7): 767–776. doi: 10.1177/00220345231161005.

（2023－12－15收稿, 2024－01－02修回）

编辑 汤 洁