[DOI]10.12016/j.issn.2096-1456.202550267

·综述·

Piezo1在牙体组织及牙周组织中的作用研究进展

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【摘要】 Piezo1是一种Ca^{2+}渗透性机械敏感离子通道，在牙体组织及牙周组织中扮演着核心的机械力感受与信号转导角色。在牙体组织中，Piezo1是介导牙本质敏感疼痛的关键因子。外界刺激引发的牙本质小管液流动可激活成牙本质细胞上的Piezo1通道，通过泛连接蛋白-1-嘌呤能受体P2X3亚型(PANX-1-P2X3)受体轴触发神经元信号，导致疼痛感知。此外，Piezo1在牙髓炎症与修复过程中具有双重调控作用：一方面其表达在炎症环境下上调，可能加剧痛觉敏感；另一方面，通过介导Ca^{2+}内流、ATP释放及下游嘌呤受体P2X7亚型(P2X7R)、MEK/ERK等信号通路，激活牙髓干细胞的迁移、增殖及成牙本质向分化，从而促进修复性牙本质形成。在牙周组织中，Piezo1通过感知咬合力等机械刺激，在维持牙周组织稳态和调控牙槽骨改建中发挥核心作用。在正畸牙齿移动过程中，Piezo1在张力侧通过激活Wnt/Ca^{2+}、Notch等通路促进成骨分化；在压力侧通过调节核因子κB受体活化因子配体/骨保护素(RANKL/OPG)平衡影响破骨细胞活性。同时，Piezo1也是牙周免疫微环境的关键调节者，在巨噬细胞、中性粒细胞及树突状细胞等免疫细胞中表达，其激活可促进巨噬细胞向促炎M1型极化，增强促炎因子和基质金属蛋白酶的释放，从而加剧牙周组织的炎症破坏。鉴于其多重功能，Piezo1已成为极具潜力的治疗靶点，包括局部或全身应用针对其抑制剂，运用机械力干预、物理治疗以及基因治疗与干细胞治疗等手段，在口腔疾病治疗中展现出广阔的临床转化前景。本文对Piezo1的结构特性、信号转导机制及其在牙体组织与牙周组织中的表达分布、功能作用与调控网络的研究进展进行综述，为靶向Piezo1的口腔疾病治疗策略开发提供思路。

【关键词】 牙体组织；　牙周组织；　Piezo1；　牙本质敏感；　Ca^{2+}信号；　修复性牙本质；　巨噬细胞极化；　树突状细胞；　牙周膜干细胞；　正畸牙齿移动
【中图分类号】 R78　【文献标志码】 A　【文章编号】 2096-1456(2026)06-0595-11
【引用著录格式】 李文艳，莫朝伦，王亚静，等. Piezo1在牙体组织及牙周组织中的作用研究进展[J]. 口腔疾病防治, 2026, 34(6): 595-605. doi:10.12016/j.issn.2096-1456.202550267.

微信公众号

Research progress on the role of Piezo1 in dental and periodontal tissues

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【Abstract】 Piezo1 is a Ca^{2+}-permeable mechanosensitive ion channel that plays a central role in mechanosensing and signal transduction in dental and periodontal tissues. In tooth tissue, Piezo1 is a key factor mediating dentin sensitive pain. The flow of dentinal tubule fluid induced by external stimulation can activate the Piezo1 channel on odontoblasts, triggering neuronal signals through the pannexin-1-purinergic 2X3 receptor (PANX-1-P2X3) receptor axis, resulting in pain perception. In addition, Piezo1 has a dual regulatory role in the process of pulp inflammation and repair : on the one hand, its expression is up-regulated in an inflammatory environment, which may aggravate pain sensitivity ; on

【收稿日期】2025-06-20；　【修回日期】2025-10-27
【基金项目】贵州省科学技术基金项目(黔科合基础-ZK[2021]一般436)
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the other hand, it activates the migration, proliferation and odontogenic differentiation of dental pulp stem cells by mediating Ca^{2+} influx, ATP release and downstream purinergic 2X7 receptor (P2X7R), MEK / ERK signaling pathways, thereby promoting reparative dentin formation. In periodontal tissue, Piezo1 plays a central role in maintaining periodontal tissue homeostasis and regulating alveolar bone remodeling by sensing mechanical stimuli such as bite force. During orthodontic tooth movement, Piezo1 promotes osteogenic differentiation by activating Wnt / Ca^{2+}, Notch and other pathways on the tension side. It affects osteoclast activity by regulating receptor activator of nuclear factor-κB ligand/osteoprotegerin (RANKL/OPG) balance on the pressure side. At the same time, Piezo1 is also a key regulator of periodontal immune microenvironment. It is expressed in immune cells such as macrophages, neutrophils and dendritic cells. Its activation can promote the polarization of macrophages to pro-inflammatory M1 type, enhance the release of pro-inflammatory factors and matrix metalloproteinases, and thus aggravate the inflammatory destruction of periodontal tissue.In view of its multiple functions, Piezo1 has become a potential therapeutic target, including local or systemic application of its inhibitors, mechanical intervention, physical therapy, gene therapy and stem cell therapy, showing a broad clinical transformation prospect in the treatment of oral diseases. In this paper, the structural characteristics, signal transduction mechanism of Piezo1 and its expression distribution, function and regulatory network in tooth tissue and periodontal tissue are reviewed, so as to provide ideas for the development of oral disease treatment strategies targeting Piezo1.

【Key words】 dental tissues;　periodontal tissues;　Piezo1;　dentin hypersensitivity;　Ca^{2+} signal;　reparative dentin;　macrophage polarization;　dendritic cells;　periodontal ligament stem cells;　orthodontic tooth movement

J Prev Treat Stomatol Dis, 2026, 34(6): 595-605.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from Science and Technology Foundation of Guizhou Province [No. Qian Ke He Ji Chu-ZK [2021] General 436)].

Piezo1作为机械敏感离子通道的核心成员，通过感知机械刺激调控细胞内Ca^{2+}信号，在组织稳态和病理过程中发挥关键的机械转导作用[1-2]。近年来，其在口腔医学领域的研究迅速扩展，已成为极具潜力的新型治疗靶点。Piezo1不仅被证实在牙本质小管液流动引发的疼痛信号传递（牙本质敏感）[3]中扮演重要角色，还广泛参与牙髓炎症反应的调控[4]以及牙髓干细胞介导的再生修复过程[5]。Piezo1在牙周组织中的功能更为多元化，其通过调控成骨-破骨细胞平衡[6]、影响巨噬细胞极化状态[7]以及介导牙周膜干细胞分化[8]等途径，影响正畸牙齿移动[9]、种植体骨结合[10]以及牙周炎的进展。笔者对Piezo1的结构特性、信号转导机制及其在牙体和牙周组织中的研究进展进行综述，为未来靶向Piezo1的口腔疾病治疗策略提供思路。

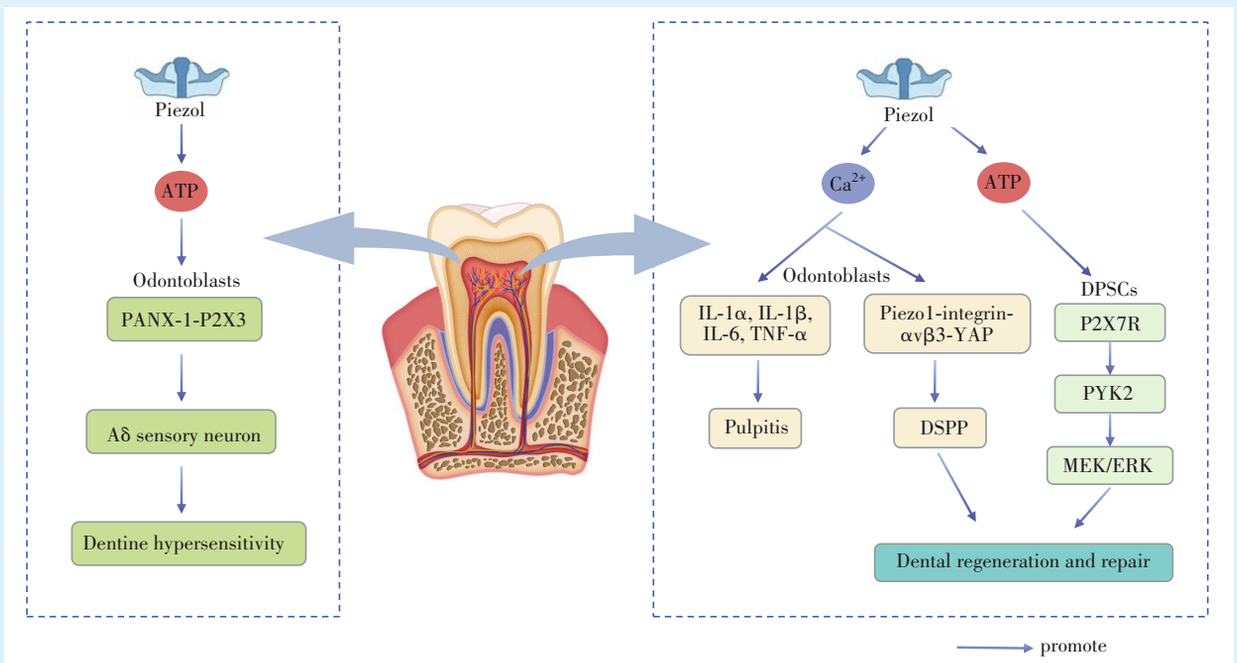
1　Piezo1结构与特性

2010年，Coste等[1]鉴定了一个机械敏感通道小家族Piezo1（Fam38A）和Piezo2（Fam38B），这两种通道在脊椎动物的机械转导中发挥着重要作用。Piezo1以一个类似于三个远端叶片和一个中央帽的三聚体螺旋桨状结构存在[1,11-13]，细胞外阳离子可以沿着帽结构域进入通道，实现跨膜转运并激活细胞内的生物化学信号以传递信息。Piezo1通道是一种非选择性的阳离子通道，对碱金属离子、K^+、Na^+、Cs^+、Ba^{2+}、Ca^{2+}、Mg^{2+}、Mn^{2+}和几种有机阳离子（四甲基铵、四乙基铵）具有渗透性[14-16]。

Piezo1通道的激活受到机械刺激和蛋白质相互作用的双重调控[17]。Piezo1的激活会导致Ca^{2+}内流和细胞骨架重构[18]。矿化的细胞外基质（extracellular matrix，ECM）是骨组织的力学微环境[19]，可能通过自身或机械刺激激活Piezo1通道[20]。已知的激活剂包括Yoda1、Jedi1/2和Yoda2，其中Yoda1是Piezo1的选择性激活剂[21]，降低Piezo1的机械激活阈值，从而增强其对机械刺激的敏感性[22-23]。Jedi1/2通过与上游叶片结合激活Piezo1[21]，而Yoda2是含有4-苯甲酸的Yoda1类似物，能更有效地激活Piezo1通道[24]。Piezo1抑制剂有钌红、钆、链霉素、Dooku1和狼蛛毒液肽（grammostola spatulata mechanotoxin 4，GsMTx4）等，其中GsMTx4能可逆抑制Piezo1全细胞电流，并减少由其引起的钙内流现象[25-27]。

2　Piezo1在牙体组织中的作用

Piezo1作为机械敏感离子通道，在牙体组织中具有双相调控特性：一方面参与机械性疼痛的传导，另一方面调控牙髓干细胞的再生修复功能（图1）。



PANX-1-P2X3: pannexin-1-P2X3; IL: interleukin; DPSCs: dental pulp stem cells; DSPP: dentin sialophosphoprotein; P2X7R: purinergic 2X7 receptor; PYK2: proline-rich tyrosine kinase 2; MEK: mitogen-activated protein kinase kinase; ERK: extracellular signal-regulated kinase; YAP: Yes-associated protein

Figure 1　Role of Piezo1 in dental tissues

图1　Piezo1在牙体组织中的作用

2.1　Piezo1介导牙本质敏感与疼痛信号传递

牙本质敏感作为常见的口腔健康问题[28-29]，其发生机制与Piezo1介导的力学-疼痛信号转导密切相关[30]。流体动力学理论表明，当牙本质表面受到温度、机械、化学和渗透刺激时，牙本质小管内的液体从牙髓侧到牙本质表面向外运动[3]，通过激活瞬时受体电位香草素亚型1（transient receptor potential vanilloid 1，TRPV1）、TRPV2、TRPV4，瞬时受体电位锚蛋白亚型1（transient receptor potential ankyrin 1，TRPA1）[31]以及Piezo1通道[32]，转化机械信号为胞内生物化学信号并引发疼痛反应。机械刺激激活Piezo1通道，成牙本质细胞释放的ATP诱导泛连接蛋白-1（pannexin-1，PANX-1）-嘌呤能受体P2X3亚型（purinergic 2X3 receptor，P2X3）受体轴，在牙髓内Aδ传入神经元中产生和传播动作电位，产生牙本质敏感症状[25,32-33]。

2.2　Piezo1介导牙髓炎症与再生修复

在牙髓感觉神经调控方面，研究显示Piezo1在外周牙髓的有髓鞘轴突中高表达，参与介导机械刺激引起的急性疼痛[34]。然而，感觉神经元中广泛表达Piezo1反而会减少机械性疼痛反应[35]，这种看似矛盾的现象可能与Piezo1在不同神经元亚群中的差异性分布有关。在炎症调控方面，人不可逆性牙髓炎组织中牙本质细胞的Piezo1 mRNA表达水平显著升高，随之白细胞介素（interleukin，IL）-1α、IL-1β、IL-6及肿瘤坏死因子（tumor necrosis factor-alpha，TNF）-α等炎症标志物表达增加，炎症加重[36-37]，进一步证实了Piezo1在牙髓炎症过程中的重要作用。

在牙髓再生方面，静水压力通过Piezo1通道协调Wnt16表达和纤毛生成，促进人脱落乳牙干细胞（stem cells from human exfoliated deciduous teeth，SHED）多能干细胞的前成牙本质细胞扩散和矿

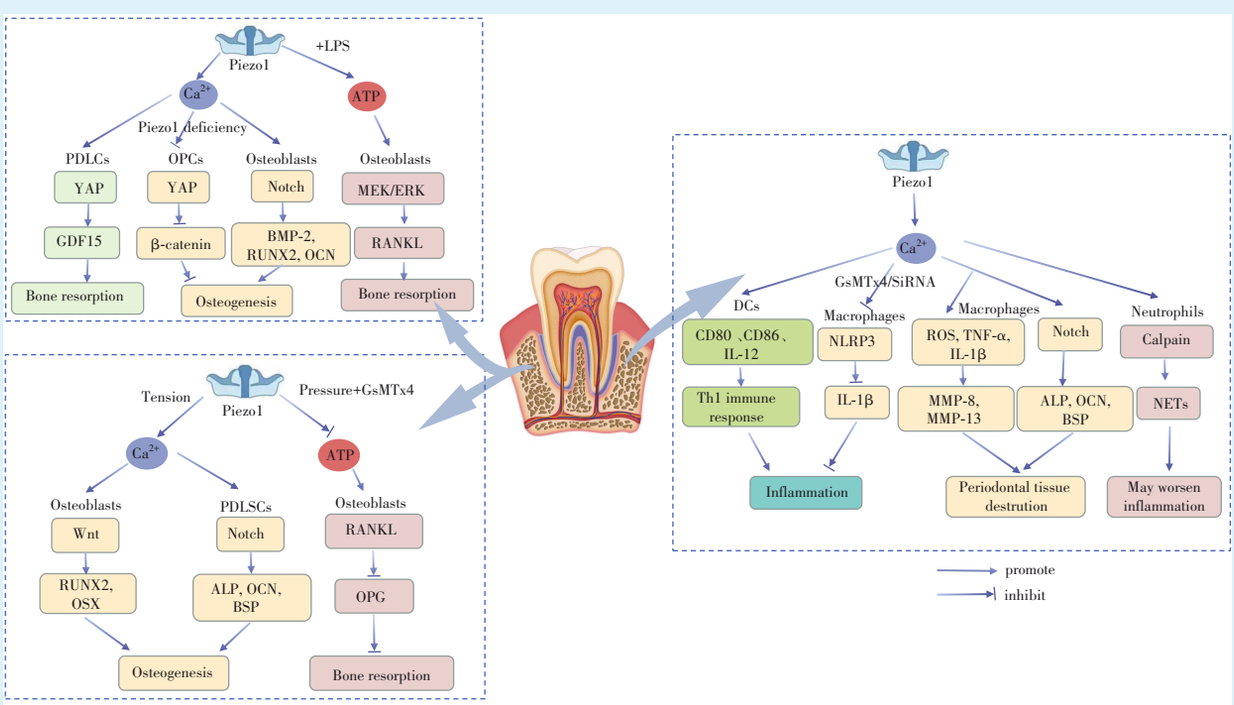
化[4]。值得注意的是，Gaite等[38]、Wang等[39]研究发现人牙髓组织存在大量Piezo1/2阳性细胞，Piezo1通过将机械信号转化为生物化学信号来调控干细胞[40]。具体表现为，激活Piezo1通道可诱导ATP释放，通过激活P2受体嘌呤（purinergic 2X7 receptor，P2X7R）信号传导以及下游PYK2和MEK/ERK信号通路来激活牙髓间充质干细胞的迁移[41]，在牙齿再生修复[5]、牙根发育[42]和多功能分化中发挥关键作用。

在修复性牙本质形成过程中，Xu等[5]研究发现Piezo1/2在终末期广泛表达于成牙本质细胞层和牙髓中，可能参与调节流体剪切应力（fluid shear stress，FSS）对成牙本质细胞功能的调控[43]。近期研究揭示了Piezo1-integrinαvβ3-YAP这一全新的机械转导途径：适当的FSS通过该途径不仅能增强牙本质涎磷蛋白（dentin sialophosphoprotein，DSPP）等成牙本质细胞中相关因子的表达，还能抑制牙本质小管中水动力诱导的细胞变形，促进生理性/反应性牙本质形成[39,44-45]，为临床促进牙本质修复提供了潜在靶点。Piezo1还可能参与成釉细胞发育过程中的牙齿形态发生[46]。

Piezo1在牙髓组织损伤修复中具有功能双相性。急性期：作为痛觉传感器，介导急性疼痛；修复期：炎症微环境下可上调Piezo1表达，既增强痛觉神经元敏感性，又通过Ca^{2+}-ATP信号轴激活牙髓干细胞迁移与成牙本质分化。Piezo1既是牙本质敏感的"触发器"，又是组织修复的"促进剂"，靶向调控其活性需遵循"急性期抑制、修复期激活"的时序策略。

3　Piezo1在牙周组织中的作用

Piezo1作为机械-化学信号转导的核心分子，在牙周组织中发挥多重作用机制，包括牙周重塑、正畸牙齿移动及免疫调控等过程（图2）。



LPS: lipopolysaccharide; IL: interleukin; PDLSCs: periodontal ligament stem cells; RANKL: receptor activator of nuclear factor-κB ligand; BMP-2: bone morphogenetic protein 2; RUNX2: runt-related transcription factor 2; OCN: osteocalcin; OPN: osteopontin; OPG: osteoprotegerin; ALP: alkaline phosphatase; BSP: bone sialoprotein; OSX: osterix; TNF-α: tumor necrosis factor-α; MMP: matrix metalloproteinases; NETs: neutrophil extracellular traps; OTM: orthodontic tooth movement; DCs: dendritic cells; ALP: alkaline phosphatase; DFCs: dental follicle cells; PDLCs: periodontal ligament cells; GsMTx4: grammostola spatulata mechanotoxin 4; OPCs: osteoblast progenitor cells; YAP: Yes-associated protein

Figure 2　Role of Piezo1 in periodontal tissues

图2　Piezo1在牙周组织中的作用

3.1　Piezo1介导牙周组织的力学调控

3.1.1　Piezo1介导咬合力与牙周组织稳态维持　机械力在维持牙周组织稳态中发挥着关键作用，而Piezo1作为重要的力学感受器在这一过程中扮演

着核心角色。

对牙周膜施加机械力，激活Piezo1可诱导ATP释放，并通过ERK、Yes相关蛋白（Yes-associated protein，YAP）等信号通路参与牙周膜细胞（periodontal ligament cells，PDLCs）的机械转导[47-49]。牙周膜干细胞（periodontal ligament stem cells，PDLSCs）具有强大的增殖能力和多向分化潜能[50]。Lepr$^+$ PDLSCs位于血管周围，具有多谱系潜力及组织修复能力。Piezo1缺失会导致Lepr$^+$ PDLSCs的数量减少、牙骨质形成和牙槽骨骨量减少，牙骨质ECM质量降低，胶原纤维排列紊乱。这表明Lepr$^+$ PDLSCs通过Piezo1通道的机械转导作用有助于维持牙周稳态[8]。机械力通过激活Piezo1促进PDLSCs的成骨及成牙骨质分化[51-53]，并通过Ca^{2+}、Wnt/β-catenin通路促进人牙囊细胞（human dental follicle cells，DFCs）增殖和成骨分化[54]。同时，PDLSCs中，Piezo1通过Notch信号通路上调骨形态发生蛋白2（bone morphogenetic protein 2，BMP-2）、Runt相关转录因子2（runt-related transcription factor 2，RUNX2）、骨钙素（osteocalcin，OCN）等关键成骨因子的表达，并通过YAP依赖性机制促进Ⅰ型胶原蛋白的合成[6]。使用低强度脉冲超声（low-intensity pulsed ultrasound，LIPUS）可促进干细胞分化并调节其生物学功能，通过激活Piezo1的表达，增强PDLSCs的内皮分化和血管生成[55]。在压力下激活Piezo1通道对成骨细胞分化具有抑制作用，通过LIPUS下调Piezo1可以促进PDLCs的成骨分化，减轻牙槽骨吸收[56-57]及降低正畸过程的炎症性牙根吸收[58]。研究显示，YAP是人PDLCs中生长分化因子15（growth differentiation factor 15，GDF15）的上游调节因子，机械力可能通过YAP-GDF15轴，上调炎症因子的表达，从而促进破骨细胞生成[59]。这些发现为理解机械力促进骨形成[60]的分子机制提供了重要线索。

在病理状态下，Piezo1的调控作用呈现出更为复杂的特征。研究表明，牙齿缺失导致的咬合力丧失会显著影响骨代谢平衡，这种影响主要通过Piezo1介导的复杂信号网络实现。在成骨细胞祖细胞中，Piezo1缺失会中断YAP信号通路，β-catenin活性降低，抑制成骨细胞分化和增加骨吸收[61-62]。在承受过大咬合力（>2 N/cm^2）时，Piezo1介导的机械应力会与牙龈卟啉单胞菌（*Porphyromonas gingivalis*，*Pg*）的脂多糖（lipopolysaccharides，LPS）产生协同效应，诱导成骨细胞中MEK/ERK磷酸化，使成骨细胞中破骨细胞分化因子（receptor activator of nuclear factor-κ B ligand，RANKL）的表达增加，显著加速破骨细胞分化和骨吸收过程[63-66]，这些发现为牙周炎患者牙槽骨快速丧失的机制研究提供了新视角。研究发现，机械力通过Piezo1能够促进小鼠牙周膜中一种与成骨作用紧密偶联的新型毛细血管亚型——H型血管的生成[67]，有望为预防牙槽骨废用性骨质疏松（alveolar bone disuse osteoporosis，ABDO）提供了潜在的治疗靶点[68-69]。在雌激素缺乏的骨质疏松模型中，Piezo1的功能状态与骨代谢紊乱密切相关。研究表明，骨质疏松的老年女性使用Piezo1特异性激动剂Yoda1干预后，可显著改善骨质疏松症[68,70]，这一结果不仅证实了Piezo1在骨代谢调控中[71-72]的关键作用，更提示其作为治疗代谢性骨疾病潜在靶点的重要价值。

3.1.2　Piezo1介导正畸牙齿移动的力学调控　Piezo1在正畸牙齿移动过程中发挥着关键的力学调控作用[73]。作为机械敏感离子通道，Piezo1能够将正畸力转化为生物化学信号，从而协调牙周组织的适应性改建[9,74]。在张力侧，机械力通过激活Piezo1显著提升Wnt/Ca^{2+}信号通路活性，促进成骨相关转录因子RUNX2、成骨细胞特异基因（osterix，OSX）的表达，同时优化RANKL/骨保护素（osteoprotegerin，OPG）比值，有效调控破骨细胞活性[75]。此外，Piezo1介导的Ca^{2+}内流还能激活Notch1信号通路，上调PDLSCs中碱性磷酸酶（alkaline phosphatase，ALP）、骨钙素（OCN）和骨涎蛋白（bone sialoprotein，BSP）等成骨标志物的表达，显著增强其成骨分化能力[76]。有学者发现Piezo1通道激动剂Yoda1可以促进正畸牙齿移动，促进张力侧血管生成及成骨改建[77-78]。这些发现为理解正畸力促进骨形成的分子机制提供了重要依据。

在压力侧，Piezo1则呈现出更为复杂的调控特征。研究表明，在正畸牙齿移动过程中，GsMTx4抑制Piezo1的表达，下调Wnt/β-catenin信号通路活性，并打破RANKL（促破骨）和OPG（抗破骨）的平衡，增强了压力侧RANKL水平，抑制OPG的表达，促进破骨细胞分化，导致牙槽骨改建过程迟缓，从而减慢牙齿的移动速度[74,79-82]。Piezo1还参与调控OPG、骨桥蛋白（osteopontin，OPN）等牙骨质活性标志物的表达，这可能与压力诱导的牙根吸收现象密切相关[81-83]。这种区域特异性的调控模式提示了Piezo1在协调正畸牙齿移动过程中骨吸收与骨形成动态平衡的重要作用。

3.2　Piezo1介导牙周组织的免疫调控

研究发现，Piezo1在巨噬细胞、中性粒细胞、树突状细胞（dendritic cells，DCs）等免疫细胞中均有表达，参与调节免疫细胞的迁移、吞噬、细胞因子分泌等功能[84-88]。在牙周组织中，Piezo1不仅在免疫细胞中表达，还在牙周膜细胞、成骨细胞等组织细胞中表达，通过整合机械信号和免疫信号，共同维持牙周组织的稳态[48,89-90]。在牙周炎模型中，Zhao等[91]发现，LPS可激活巨噬细胞中的Piezo1，刺激Ca^{2+}内流，M1型巨噬细胞极化增加，产生活性氧（ROS），促进促炎因子（如TNF-α和IL-1β），基质金属蛋白酶（matrix metalloproteinases，MMP）（如MMP-8、MMP-13）分泌，从而加剧牙龈胶原纤维的降解和组织破坏。相反，抑制Piezo1可减少M1型巨噬细胞的浸润和炎症因子的释放，减轻牙周组织的损伤。这些结果提示，Piezo1可能通过促进巨噬细胞向M1型极化，参与牙周炎的病理进程。在牙周炎环境中，机械刺激和炎症共同激活巨噬细胞上的Piezo1。Xu等[89]在正畸牙移动模型中发现，机械力可通过激活Piezo1促进牙周组织中巨噬细胞的增殖，其机制涉及Akt/GSK3β信号通路的激活，潜在下游靶因子细胞周期蛋白D1（Cyclin D1，Ccnd1）显著扩增，巨噬细胞过度增殖，可能导致炎症反应的放大，从而加速牙槽骨的吸收。使用GsMTx4或siRNA抑制Piezo1能显著减少NLRP3炎性小体的组装和活化，进而抑制促炎因子IL-1β的成熟和释放，以及细胞焦亡的发生，最终减轻牙周组织的炎症破坏[92]。有学者发现在种植体部位的炎症微环境中会增加Piezo1的表达，并随后会激活机械传导信号效应物YAP，从而促进巨噬细胞M1极化，同时抑制M2极化，使用YAP抑制剂可以诱导巨噬细胞向M2型极化，从而促进种植体的骨结合[10,93]。将种植体植后施加即刻载荷，发现种植体周围骨中Piezo1的表达在压缩侧显著升高，与骨细胞外基质与种植体的接触率的趋势一致，提示了即刻加载的方向性可能对种植体周围骨的早期愈合过程产生不同的影响[94]。因此，靶向Piezo1可能通过抑制巨噬细胞的异常增殖和促炎极化，达到治疗牙周炎及促进种植体骨结合的目的。

中性粒细胞的迁移依赖于趋化因子梯度和细胞外基质的机械特性。Piezo1作为机械力感受器，可能感知血管内皮细胞或细胞外基质的机械信号，调节中性粒细胞的黏附和渗出。例如，Piezo1的激活可通过Ca^{2+}内流促进中性粒细胞整合素的激活，增强其与内皮细胞的黏附[73]。此外，中性粒细胞在吞噬病原体后，可通过Piezo1感知细胞内的机械应力变化，激活介导钙蛋白酶活性和细胞骨架重塑，从而诱导中性粒细胞细胞外陷阱（neutrophil extracellular traps，NETs）的释放。NETs由DNA、组蛋白和抗菌肽组成，能够捕获和杀死病原体，但也可能导致组织炎症和破坏[95]。在牙周炎患者中，NETs的清除障碍可能加剧炎症反应，而Piezo1是否参与这一过程尚不清楚，有待进一步研究。

Piezo1在树突状细胞（dendritic cells，DCs）中的表达和功能调节是近年来的研究热点。Zhou等[96]总结了离子通道在DCs功能调节中的作用，指出Ca^{2+}通道（包括Piezo1）通过调节细胞内Ca^{2+}浓度，影响DCs的成熟、迁移、细胞因子分泌和抗原提呈能力。机械信号（如细胞外基质刚度、剪切力）可通过Piezo1调节DCs的表型和功能。例如，在高刚度基质上培养的DCs可能通过Piezo1的激活表达更高水平的共刺激分子（如CD80、CD86）和促炎因子（如IL-12），从而促进Th1型免疫应答；而在低刚度基质上，DCs可能倾向于诱导免疫耐受[84,96]。在牙周组织中，DCs通过感知口腔微生物和机械力的变化，调节局部免疫微环境。Piezo1可能作为机械信号和免疫信号的整合者，参与DCs介导的牙周免疫平衡调节。例如，牙周炎时，牙龈组织细胞外基质刚度增加可能通过Piezo1激活DCs，促进其成熟和促炎因子的释放，加剧炎症反应；而在健康状态下，Piezo1可能维持DCs的未成熟状态，诱导免疫耐受[96-97]。

4　Piezo1的临床转化

Piezo1的临床转化可主要分为3个方面：Piezo1抑制剂的开发、机械干预与物理治疗、基因治疗与干细胞治疗。

目前常用的Piezo1抑制剂包括GsMTx4和Dooku1等。GsMTx4是一种从蜘蛛毒液中提取的多肽，能够特异性抑制Piezo1通道的活性，而不影响其他离子通道[89]。在实验性牙周炎模型中，局部或全身应用GsMTx4可显著抑制Piezo1的激活，减少巨噬细胞向M1型极化，降低促炎因子（如IL-1β、TNF-α）和MMPs的释放，从而减轻牙龈炎症和牙槽骨吸收[98-99]。此外，Xu等[89]发现，GsMTx4可通过抑制Piezo1/Akt/Cyclin D1信号通路，减少机械力诱导的巨噬细胞增殖，进而减缓正畸牙移动过

程中的牙槽骨吸收。除了多肽类抑制剂，小分子化合物也在开发中。Dooku1是一种新型小分子Piezo1抑制剂，具有更高的选择性和口服生物利用度[100]。虽然Dooku1在牙周炎中的应用尚未见报道，但其在其他炎症性疾病中的潜力提示其可能成为牙周炎治疗的候选药物。

Piezo1是机械力感受器，调节牙周组织的机械微环境可能成为间接靶向Piezo1的治疗策略。正畸治疗中的机械力控制、低强度脉冲超声（LIPUS）、高压氧治疗等物理疗法可能通过调节Piezo1的活性影响牙周组织的修复。LIPUS是一种常用的物理治疗手段，已被证实可促进骨愈合和组织修复。Zheng等[56]在正畸牙移动模型中发现，LIPUS通过下调Piezo1的表达，可促进PDLCs的成骨分化，同时抑制破骨细胞的活性，从而减轻牙槽骨吸收。其机制可能与LIPUS抑制Piezo1介导的Ca^{2+}内流，进而调节YAP/TAZ等下游信号通路有关。因此，优化超声参数可能成为精准调控Piezo1活性、促进组织修复的有效方法。

在基因治疗方面，通过局部递送Piezo1 siRNA或shRNA，特异性下调Piezo1在牙周组织中的表达，可能减轻炎症反应和组织破坏。例如，Zhao等[91]在巨噬细胞中通过siRNA沉默Piezo1，可显著抑制LPS诱导的M1型极化和促炎因子释放。在干细胞治疗方面，将Piezo1修饰的牙周膜干细胞或间充质干细胞移植到牙周缺损部位，可能促进组织再生。Xie等[53]发现，过表达Piezo1的人牙囊干细胞在机械刺激下具有更强的成骨分化潜能。相反，在炎症微环境中，抑制Piezo1的干细胞可能有利于存活和发挥修复功能。Cui等[101]发现，褪黑素工程化的M2巨噬细胞外泌体通过调节内质网应激和免疫重编程，促进牙周炎的治疗。结合Piezo1抑制，可能进一步增强干细胞的抗炎和修复能力。

5　小　结

Piezo1在口腔疾病治疗中展现出多方面的潜力：在牙本质敏感中，局部使用抑制剂缓解疼痛；在牙髓修复和正畸牙移动中，适时使用激活剂促进组织再生与改建；在牙周炎和种植体周围炎中，调控Piezo1活性抑制炎症并促进骨结合（表1）。

表1　Piezo 1在牙体组织及牙周组织中的靶向干预价值

Table 1　Targeted intervention value of Piezo1 in dental and periodontal tissues

Tissues/cells	Pathological/physiological processes	Piezo1 functional mechanism	Value of targeted intervention
Dentinal tubule	Dentin hypersensitivity[67]	Mediator fluid flow→ activation of Aδneuron pain signal[33]	Local inhibitor relieves sensitivity
Dental pulp	Pulpitis	Inflammation upregulates Piezo1 → promotion of SHED migration and mineralization[4]	Timing regulation: first inhibiting pain, then promoting regeneration
Periodontal membrane	OTM	Activation of Piezo1 → Wnt/Ca^{2+} pathway promotes bone remodeling.[65]	The agonist accelerates movement, and the inhibitor reduces absorption
Macrophages, neutrophils, dendritic cells	OTM/periodontitis	Regulate immune cell migration, phagocytosis, cytokine secretion, and other functions[73-75]	YAP inhibitors improve osseointegration
Osteoblast	Bite force lost	Piezo1 deletion → reduced bone formation, activation of Yoda1 to save bone mass[56]	Agonists prevent and treat disuse osteoporosis

OTM: orthodontic tooth movement; YAP: Yes-associated protein; SHED: stem cells from human exfoliated deciduous teeth

Piezo1在牙体牙周组织中的研究仍存在很多挑战，包括Piezo1蛋白抑制剂和激活剂对其在体内环境中的调控方式尚需深入阐明；现有的研究还只存在于动物模型，无法反映复杂的体内微环境；此外，Piezo1在牙体牙髓病及牙周病进展及正畸牙齿移动过程中的作用机制仍需进一步探讨。

【Author contributions】 Li WY wrote the article. Mo CL, Wang YJ revised the article. Fu XF conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

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