·综述·

机械敏感离子通道在牙源性细胞中作用的研究进展

徐志清 杜宇
中山大学附属口腔医院,光华口腔医学院,广东省口腔医学重点实验室,广东省口腔疾病临床医学研究中心,广州 510055
通信作者:杜宇,Email:duyu3@mail.sysu.edu.cn

【摘要】 机械敏感离子通道(MS离子通道)是一类能感知机械应力的重要蛋白,将细胞外机械刺激信号转化为电化学信号,导致离子跨膜流通,继而传递至胞内调控下游靶基因。牙源性细胞胞膜表面有多种MS离子通道表达,但其如何调控细胞功能和具体机制仍不明确。本文就MS离子通道的分类及其在牙源性细胞的表达和功能作一综述。

【关键词】 机械敏感通道; 牙再生; 压电离子通道; 瞬时受体电位离子通道

基金项目:广东省自然科学基金(2021A1515010845);广东省医学科学技术研究基金(A2022126)

引用著录格式:徐志清,杜宇. 机械敏感离子通道在牙源性细胞中作用的研究进展[J/OL]. 中华口腔医学研究杂志(电子版), 2024,18(1):54-60.

DOI:10.3877/cma.j.issn.1674-1366.2024.01.009

Research advances on the role of mechanosensitive ion channels in odontogenic cells

Xu Zhiqing, Du Yu
Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University, Guangdong Provincial Key Laboratory of Stomatology, Guangdong Provincial Clinical Research Center of Oral Diseases, Guangzhou 510055, China
Corresponding author: Du Yu, Email: duyu3@mail.sysu.edu.cn

【Abstract】 As crucial proteins in sensing mechanical stress, mechanosensitive (MS) ion channels could transform external mechanical stimuli into electrochemical signals, enabling ion transmembrane movement. This movement signals the intracellular regulation of target genes. While various MS ion channels are present in odontogenic cell membranes, their roles in the cellular regulation and the exact mechanisms are still not fully understood. This review focused on the classification, expression, and functionality of MS ion channels in odontogenic cells.

【Key words】 Mechanosensitive channels; Tooth regeneration; PIEZO; TRP channels

Fund programs: Natural Science Foundation of Guangdong Province (2021A1515010845); Medical Scientific Research Foundation of Guangdong Province (A2022126)

DOI:10.3877/cma.j.issn.1674-1366.2024.01.009

机械微环境是构成细胞生存的周围力学微环境,可以对细胞产生力学刺激,在细胞的生长、发育和分化中都发挥重要作用。其依赖于细胞的机械信号转导感应外界产生的牵张力、压力、重力和渗透压等,转化为胞内生物信号,整合为细胞反应调控生物学功能[1]。既往研究发现机械信号转导与细胞膜分子相关,主要包括机械敏感离子通道[mechanosensitive (MS) ion channels]、特异性细胞骨架蛋白、细胞连接分子、G蛋白偶联受体和激酶等[2-3]。MS离子通道是一类快速响应外界机械压力引起Ca^{2+}、K^{+}和Mg^{2+}等离子跨膜流通的蛋白,广泛分布于各类生物器官,不仅参与牙胚发育[4-6],也影响牙源性细胞的增殖、迁移和分化[7-11],但其具体分子机制仍不清楚。本文就MS离子通道的分类、特点、调控牙源性细胞的生物学效应和分子机制作一综述。

一、机械敏感离子通道的分类及特点

MS离子通道是由跨膜蛋白组成的离子转导孔道,在机械应力刺激下激活,将应力转换为电、渗透压和化学细胞内信号后,调节细胞迁移、增殖和分化。MS离子通道感知的机械应力类型包括重力、渗透力、剪切力、弯曲力、扭转和压缩力[12-13],这些应力或直接通过通道附近的双层张力和曲率变化[14],或经由细胞外基质及细胞骨架间响应来打开离子通道[15-17]。通道开放时,带电离子沿电化学梯度被动扩散产生膜电流,刺激下游产生化学信号。迄今已经发现多种MS离子通道,包括压电离子通道(PIEZO)家族、瞬时受体电位(transient receptor potential,TRP)超家族、双孔结构域钾通道(two pore-domain potassium channels,TREKs/K2P)、钙激活的钾离子通道(Ca^{2+}-activated K^{+} channels,KCa)和酸敏感离子通道(acid-sensing ion channels,ASIC)等[18-19]。

PIEZO家族是哺乳动物细胞中首次发现的MS离子通道,包括PIEZO1和PIEZO2两种亚型。Coste等[20]率先在胶质瘤Neuro2A细胞株中筛选鉴定出PIEZO1,并通过序列同源性发现PIEZO2。两种蛋白的生理和生物特性相似,为四聚体(共120~160个预计的跨膜片段),是迄今为止确定的最大分子质量(>2 500个氨基酸)的膜离子通道复合物之一。PIEZO家族属于非选择性阳离子通道,对阳离子的选择通透性从Ca^{2+}、K^{+}、Na^{+}和Mg^{2+}依次降低,其差异受该孔道区域的氨基酸序列排序和空间结构的影响[21]。PIEZO1多表达于

受机械刺激的组织,如肺、肾脏和血管等,受压力调控后改变细胞体积或重塑组织[22]。PIEZO2则多表达于感觉系统,如本体感受器和表皮的默克尔细胞,受刺激后调控肢体运动和触觉[22]。

TRP家族是另一类广泛分布的MS离子通道,由28个TRP成员组成,均为6次跨膜蛋白,可分为7个亚群:TRPP、TRPC、TRPM、TRPML、TRPV、TRPN和TRPA。相比较PIEZO主要感知机械刺激,TRP家族还可响应其他刺激形式,例如温度、pH值等。目前,已鉴定出具有机械敏感功能的成员包括TRPV(2-4)、TRPA2、TRPM3/7/8和TRPC1/66等[23-27],其中TRPV4和TRPA1与机械刺激关系最为密切[28-29]。

TREKs/K2P是哺乳动物K^+通道家族的一个结构不同的亚群,具有4个跨膜片段和2个孔道结构域[30]。其中具有MS离子通道特征的亚型包括TRAAK(K2P4.1)和TREK-1(K2P2.1)。K2P被机械激活,可以感知负向膜压(如静水压力)和剪应力[12,31]。当应力施加于膜时,TREK和TRAAK通过调节K^+,选择性释放电流,超极化静息膜电位,调节细胞的兴奋性[32]。

KCa通道具有6个跨膜片段和1个孔道结构域,根据电导大小和药理特性,可将其分为3个亚型,分别为大电导KCa通道(large-conductance calcium-activated K^+ channels, BKCa)、中电导KCa通道(intermediate-conductance Ca^{2+}-activated potassium channels, IKCa)和小电导KCa通道(small-conductance Ca^{2+}-activated potassium channels, SKCa)[33]。BKCa通道属于其中特殊的一组,特点是电导率大,能感知细胞内Ca^{2+},使细胞膜超极化,并控制各种组织的兴奋性和功能[34-35]。不仅如此,BKCa中还存在可以参与应力调节的结构域,提示其具有机械敏感性[36]。KCa通道开放时,K^+外流,细胞膜电位下降,细胞内Ca^{2+}浓度增加。细胞内Ca^{2+}作为第二信使,参与细胞骨架蛋白解聚及重组装、骨架收缩、迁移及相关蛋白的转录等,进而参与细胞的增殖、凋亡及其他行为改变。

ASIC是退化蛋白/上皮钠通道(degenerin/epithelial sodium channel, DEG/ENaC)超家族成员之一,优先渗透Na^+、Ca^{2+}、K^+和H^+,在感受pH值和调控痛觉等多方面扮演着重要角色[37]。ASIC由4个相同或不同的亚基构成,即ASIC1~4,其中ASIC1a、ASIC1b、ASIC2a和ASIC3均可能产生机械响应作用,然而由于常以复合体形式存在,这些蛋白是否能直接响应机械应力仍存在争议[38]。

二、机械敏感离子通道在牙源性细胞中的表达及分布

1. MS离子通道在成牙本质细胞(odontoblasts, OD)及牙髓干细胞(dental pulp stem cell, DPSC)中的表达及分布:OD是具有极性的细胞,参与牙本质的形成,并在痛觉传导中发挥重要作用。每个OD有1个突起延伸至牙本质小管内并浸泡于牙本质液中,受机械刺激时可发生改变,提示OD具有机械敏感性[39-40],研究表明可能与MS离子通道有关[8,41-44]。

组织切片染色实验发现PIEZO1/2、TRPV1-4、TRPM8、TREK-1、TRPC1/5/6和KCa均在人OD中表达[8,27,41-42,45-46]。从牙髓中的定位观察,发现TREK-1在冠髓中的OD中表达较高,而在根髓OD不表达[8],TRPV3在人冠部OD的表达明显高于根部[41],KCa通道则主要分布于神经或小动脉周围的OD中[41]。从OD中的定位分析,发现PIEZO1及TRPC5多在人OD胞突上表达[45-46]。

有关MS离子通道的动物实验与人类研究结果存在差异。组织染色观察到大鼠OD上有TRPV1/2/4、TRPV4、TRPC1/6及TRPM7的表达[10,47-49],并且TRPV1多在成年大鼠OD细胞膜和细胞突中表达[48]。新生小鼠的OD中有TRPM3表达,TRPM8不表达[50]。而成年C57小鼠的OD中则出现TRPC5、TRPM8的表达[46,51],并且TRPM8在髓角及OD的胞突中表达较高[51]。

除切片染色外,部分学者使用酶消化法将大鼠OD从牙髓中急性分离,以便能更好地观察活体组织中的OD[52]。对成年大鼠牙髓中的OD进行急性分离后未观察到TRPV1的表达,即使用热温度(42 ℃)或TRPV1激动剂辣椒素刺激后均未增加OD中的细胞内Ca^{2+}浓度,也没有检测到OD中的TRPV1或TRPV2的mRNA[50]。

此外,体外培养的DPSC及其矿化诱导后形成的OD样细胞胞膜上有PIEZO1/2、TRPV1/2/3、TRPM8、TRPA1及TREK-1的表达[7-9,27,53-55],透射电镜亚细胞定位发现TRPV1/2/3还可在胞质、线粒体和内质网表达[9],TRPC1则主要分布在细胞质中[8]。

2. MS离子通道在其他牙源性细胞的表达及分布:牙周膜是连接牙根及牙槽骨的纤维结缔组织,具有传导、感觉、缓冲咀嚼力及形成功能。既往研究证实牙周膜细胞(periodontal ligament cell, PDLC)存在机械敏感性[56-57],体内及体外研究发现PIEZO1/2、TRPM3/4和TREK-1在人PDLC胞膜中均有表达[58-61]。

此外,组织染色发现PIEZO2在C57小鼠成牙骨质细胞中存在表达[62]。在体外培养的人牙囊干细胞(dental follicle stem cell, DFSC)和脱落乳牙干细胞(stem cells from human exfoliated deciduous teeth, SHED)上也发现有PIEZO1的表达[6]。

三、机械敏感离子通道在牙源性细胞中的功能

1. MS离子通道介导牙源性细胞的迁移:体外研究表明,PIEZO1小分子激动剂Yoda1激活人间充质干细胞中的PIEZO1可以促进三磷酸腺苷(adenosine triphosphate, ATP)释放并激活嘌呤能受体(P2X3, ATP受体),诱导富含脯氨酸的活化酪氨酸激酶2(PYK2)和促分裂原活化蛋白激酶/细胞外信号调节激酶(MEK/ERK)的改变以影响细胞迁移[63]。

2. MS离子通道介导牙源性细胞的分化:MS离子通道调控牙源性细胞分化作用的报道不一。在人DFSC中加入0.5 μm的Yoda1可以增强细胞增殖并促进成骨分化,同时经典Wnt通路中的Wnt3a和β-Catenin的表达也显著上调,提示PIEZO1可能通过Wnt/β-Catenin通路促进人DFSC的增殖和成骨分化[6]。静水压力(hydrostatic pressure, HP)也可通过PIEZO1增强Wnt/β-catenin信号促进骨和牙本质形成,Yoda1能激活PIEZO1并显著诱导WNT16表达,加强人SHED的分

化、成熟和矿化[5]。然而,加入1 μm的Yoda1显著抑制了人DPSC的成牙本质向分化,而shRNA敲低PIEZO1增强了成牙本质向分化,推测PIEZO1介导的细胞内Ca^{2+}信号通路参与牙本质的形成[11]。对人DPSC进行矿化诱导发现TRPC6的表达随时间增加,对敲除TRPC1/6的人DPSC进行矿化诱导,发现TRPC1/6的下调抑制了分化,证实TRPC1/6在成牙本质向分化过程中起着关键作用[62,64]。

除了成牙本质向分化,MS离子通道也可参与牙本质矿化。Ca^{2+}和KCa通道在人OD顶端存在共定位,此处OD可主动将Ca^{2+}转运到前期牙本质,推测KCa通道与牙本质矿化密切相关[43]。单细胞RT-PCR(Single-cell RT-PCR)分析发现约87%的大鼠OD中可观察到TRPM7的表达[65],由于TRPM7主要负责转运Mg^{2+},并且Mg^{2+}又是牙本质矿化的关键金属[66],推测OD中广泛表达的TRPM7可能参与继发性牙本质形成。

局部微环境改变也会影响牙源性细胞的MS离子通道表达并调节功能。低强度脉冲超声(low-intensity pulsed ultrasound,LIPUS)被认为是一种有效的非侵入性治疗工具,可以增强硬组织修复[67]。对人DPSC进行LIPUS处理发现PIEZO1和PIEZO2在DPSC表达显著增加,施加LIPUS可激活ERK1/2和MAPK信号通路促进增殖,而该作用可以被PIEZO通道抑制剂钌红(ruthenium red,RR)抑制[7]。LIPUS处理人DPSC后还可引起TRPM7和成骨标志物OPN、OCN、RUNX2的表达水平升高[68]。

四、机械敏感离子通道介导牙损伤修复

1. MS离子通道促进修复性牙本质形成:牙在发挥功能时会遭遇外界刺激,此时会有修复性牙本质的生成来应对损伤并进行修复。对SD大鼠分别建立牙本质缺损组和穿髓组模型以模拟深龋和牙髓炎,同时给予硬食作为机械刺激并持续1个月,免疫组化染色发现牙本质缺损组第21天时才可在修复性牙本质中检测到PIEZO1的低表达,第28天在牙髓、牙本质甚至在牙槽骨中均有PIEZO1表达,而PIEZO2在所有时间点均有表达并随时间依赖性增加。在穿髓模型中,PIEZO2从修复早期即有表达,在第14天达到高峰,主要存在于牙本质、前期牙本质和靠近牙髓牙本质交界处的牙髓细胞中,随后表达降低。随着修复时间的增加,PIEZO2又开始在远离髓角和牙体缺损区域的牙本质中表达,直至28 d才可再次检测到PIEZO1,提示PIEZO2的早期表达与牙髓的伤害性感受有关,而后期PIEZO1和PIEZO2均有表达提示共同参与了牙髓牙本质复合体的损伤修复过程[69]。

2. MS离子通道介导牙周组织修复和正畸牙移动:将人PDLC施加拉伸力8 h后PIEZO1和TRPV4表达显著增加,且PIEZO1可以通过ERK信号通路传导机械信号[60]。低渗带来的低张力通过激活人PDLC中的TRPM3和TRPV4,介导细胞外Ca^{2+}内流,促进核因子κB受体活化因子配体(receptor activator of nuclear factor-kappa B ligand,RANKL)的表达,可能导致破骨细胞分化和骨吸收活动活化,刺激成骨细胞的骨合成,参与牙槽骨的骨重塑[70]。在压应力作用下,人PDLC中PIEZO1和破骨细胞生成相关标志物的表达显著增加。使用PIEZO抑制剂Gsmtx4可以减弱核转录因子κB(nuclear transcription factor-kappa B,NF-κB)信号通路的活性,进而减弱PDLC诱导破骨细胞生成的能力,表明机械应力通过PIEZO1转导并由NF-κB信号传导,参与牙槽骨吸收[59]。

3. MS离子通道介导正畸牙力学转导:对成年SD大鼠的第一磨牙施加正畸力进行正畸牙移动(orthodontic tooth movement,OTM)后,发现PDLC中的PIEZO1被激活,并且第3天开始表达增加,在第7天达到峰值,在第14天才开始下降;每隔1天在皮下注射20 μL浓度为10 μmol/L的GsMTx4抑制PIEZO1后,Mirco CT检测第7~14天正畸牙移动速率减慢,牙槽骨张力区域的骨量减少,抗酒石酸酸性磷酸酶(tartrate-resistant acid phosphase,TRAP)染色发现牙槽骨张力侧的破骨细胞活性下降,提示PIEZO1参与OTM过程中的力转导作用[71]。但对$PIEZO1^{floxed/floxed}$、$DMP1^{cre}$小鼠进行OTM,发现与未处理组相比,牙槽骨中破骨细胞活性明显增加,骨体积减小,但是牙齿移动的距离没有明显区别,推测PIEZO1的力学转导作用在OTM过程中作用不大[72]。

五、机械敏感离子通道参与牙的感觉功能

1. MS离子通道与温度觉:牙的感觉包括温度觉、疼痛觉及本体感觉。既往研究发现温度可以激活TRP通道,如超过43 ℃可以激活TRPV1,超过52 ℃可以激活TRPV2,33~39 ℃可以激活TRPV3,小于25 ℃可以激活TRPM8[26]。OD中也有这类MS离子通道表达,提示MS离子通道可能参与牙对温度的感知。小鼠OD受到32 ℃以上的热刺激或TRP通道激动剂辣椒素时,细胞内Ca^{2+}浓度明显增加,表明TRPV1/2/3在热刺激转导中发挥功能[50]。通过冷刺激(22±1) ℃成年大鼠OD增加了胞内Ca^{2+}水平,并且这些变化可以通过TRPM8的拮抗剂来削弱[27],然而大鼠OD中未检测到TRPM8的mRNA[73]。此外,TRPV3在人冠部OD的表达明显高于根部,提示牙的不同部位对温度感觉存在差异[40]。

2. MS离子通道与牙本质过敏:MS离子通道与牙本质过敏的关系是目前的研究热点。牙本质过敏是不能解释为由任何其他牙齿缺陷或疾病引起的,由暴露的牙本质对化学、热触觉或渗透刺激的反应引起的疼痛[74]。流体动力学理论是最广泛接受的发病机制,认为机械、热或化学变化引起牙本质小管内液体的运动,诱导机械感觉转导,刺激牙髓神经纤维末梢,产生短暂的急性疼痛[75]。

通过模拟牙本质液体运动,发现机械刺激引发膜变形,可以激活大鼠OD膜上的TRPV1/2/4和TRPA1通道,诱导Ca^{2+}跨膜内流。激活的TRP通道通过泛连接蛋白1(pannexin-1,PANX-1)介导ATP的释放,经OD-三叉神经节(trigeminal ganglion,TG)神经元通讯激活离子型ATP受体3型(ionotropic ATP receptor,$P2X_3$)受体,传递细胞-神经元信号;也可以采取自分泌或旁分泌的方式激活周围OD上的$P2Y_1$和$P2Y_{12}$受体,形成OD间信号传导[76]。一项电生理学研究发现,大鼠OD通过PIEZO1响应机械刺激并与三叉神经节的神经元建立神经传导。通过流体动力的改变激活OD胞膜上的PIEZO,诱导ATP的释放并激活有髓Aδ神经元上的$P2X_3$受

体,诱导Aδ神经元的动作电位,产生疼痛[44]。进一步研究提出,PIEZO1介导的牙齿机械传导主要发生在外周牙髓的轴突中,并且PIEZO1主要参与介导由高阈值机械刺激引起的急性疼痛[45]。PIEZO2在大多数牙髓细胞的轴突中表达,其在OD层下的外周牙髓中广泛分支并形成轴突网络。这些在外周牙髓和牙本质小管中的PIEZO2和轴突一起可以作为低阈值机械感受器起作用,以响应弱的机械刺激而引起疼痛[77]。除了将信号传递给TG神经元,激活PIEZO1也可以诱发快速向内电流释放ATP,传递给邻近细胞引起三叉神经冲动导致疼痛[78]。

3. MS离子通道与炎症疼痛:炎症等化学变化引发的疼痛也可能与MS离子通道相关。通过切片染色发现与健康牙髓相比,人炎症牙髓中TRPV4、TRPC5表达增加,TRPM8表达减少,推测TRPV4、TRPC5级TRPM8可能与牙髓炎引发的痛觉有关[46,79]。体外使用10 ng/mL肿瘤坏死因子α(tumor necrosis factor-α,TNF-α)10 min即可增强人成牙本质细胞样细胞(odontoblast-like cells,OLC)中TRPV4对化学激动剂和低渗溶液诱导的膜拉伸的反应,表明炎症增加TRPV4通道的活化[80]。有学者将SD大鼠的第一磨牙用球钻穿髓后进行分析,发现穿髓后第3天TRPA1开始在支配该牙的三叉神经节中表达,7 d后表达降低,推测三叉神经元中TRPA1表达的增加可能与牙损伤后的痛觉过敏和异常疼痛有关[81]。对敲除TRPC5的小鼠的第一磨牙用球钻穿髓制造牙髓损伤,发现其疼痛程度与未受伤的野生型无明显差异,表明TRPC5与炎症性牙痛有关[46]。

另外,对成年SD雄性大鼠进行OTM后进行疼痛评分,发现PDLC中ASIC3的上调与口颌面疼痛的增加有关,而使用拮抗剂可减轻疼痛,使用激动剂可以重现牙齿疼痛,推测正畸移动会引起局部牙周膜缺血,造成乳酸及H^+堆积,形成局部酸性微环境,激活MS离子通道引起牙及口颌面疼痛[82-83]。

4. MS离子通道与牙本体感觉:牙的本体感觉也是其发挥正常功能的重要部分。牙周韧带是牙齿和牙槽骨之间的致密结缔组织,含有丰富的机械感受器。Ruffini末梢是牙周韧带中的主要机械感受器,多为低阈值和慢适应性,可参与本体感觉及痛觉的传导。免疫荧光发现ENaC蛋白的主要成分β-ENa亚基在大鼠切牙牙周的Ruffini末梢的轴突末端分布,提示该分子可能参与机械感应的转导和调节[84]。ASIC3在小鼠切牙牙周Ruffini末梢呈树突状分布且存在于轴突中,提示ASIC3可能是牙周膜末梢本体感觉的受体[85]。

外界刺激既可启动MS离子通道介导牙源性细胞的迁移分化及组织修复,又可参与感觉功能的调控,提示MS离子通道作用的多样性。深入阐明MS离子通道调控牙源性细胞的具体机制将为调控全功能牙再生与修复提供新的分子依据。

利益冲突 所有作者均声明不存在利益冲突

参 考 文 献

[1] Huang H, Kamm RD, Lee RT. Cell mechanics and mechanotransduction: Pathways, probes, and physiology [J]. 2004, 287(1): C1-C11. DOI: 10.1152/ajpcell.00559.2003.

[2] Matthews BD, Thodeti CK, Tytell JD, et al. Ultra-rapid activation of TRPV4 ion channels by mechanical forces applied to cell surface beta1 integrins [J]. Integr Biol (Camb), 2010, 2(9): 435-442. DOI: 10.1039/c0ib00034e.

[3] Anishkin A, Kung C. Stiffened lipid platforms at molecular force foci [J]. Proc Natl Acad Sci U S A, 2013, 110(13): 4886-4892. DOI: 10.1073/pnas.1302018110.

[4] Sugimoto A, Miyazaki A, Kawarabayashi K, et al. Piezo type mechanosensitive ion channel component 1 functions as a regulator of the cell fate determination of mesenchymal stem cells [J]. Sci Rep, 2017, 7(1): 17696. DOI: 10.1038/s41598-017-18089-0.

[5] Miyazaki A, Sugimoto A, Yoshizaki K, et al. Coordination of WNT signaling and ciliogenesis during odontogenesis by piezo type mechanosensitive ion channel component 1 [J]. Sci Rep, 2019, 9(1): 14762. DOI: 10.1038/s41598-019-51381-9.

[6] Xing Y, Yang B, He Y, et al. Effects of mechanosensitive ion channel Piezo1 on proliferation and osteogenic differentiation of human dental follicle cells [J]. Ann Anat, 2022, 239: 151847. DOI: 10.1016/j.aanat.2021.151847.

[7] Gao Q, Cooper PR, Walmsley AD, et al. Role of Piezo channels in ultrasound-stimulated dental stem cells [J]. J Endod, 2017, 43(7): 1130-1136. DOI: 10.1016/j.joen.2017.02.022.

[8] Magloire H, Lesage F, Couble ML, et al. Expression and localization of TREK-1 K^+ channels in human odontoblasts [J]. J Dent Res, 2003, 82(7): 542-545. DOI: 10.1177/154405910308200711.

[9] Wen W, Que K, Zang C, et al. Expression and distribution of three transient receptor potential vanilloid (TRPV) channel proteins in human odontoblast-like cells [J]. J Mol Histol, 2017, 48(5-6): 367-377. DOI: 10.1007/s10735-017-9735-2.

[10] Won J, Vang H, Kim JH, et al. TRPM7 mediates mechanosensitivity in adult rat odontoblasts [J]. J Dent Res, 2018, 97(9): 1039-1046. DOI: 10.1177/0022034518759947.

[11] Matsunaga M, Kimura M, Ouchi T, et al. Mechanical stimulation-induced calcium signaling by Piezo1 channel activation in human odontoblast reduces dentin mineralization [J]. Front Physiol, 2021, 12: 704518. DOI: 10.3389/fphys.2021.704518.

[12] Cox CD, Bavi N, Martinac B. Biophysical principles of ion-channel-mediated mechanosensory transduction [J]. Cell reports, 2019, 29(1): 1-12. DOI: 10.1016/j.celrep.2019.08.075.

[13] Syeda R, Florendo MN, Cox CD, et al. Piezo1 channels are inherently mechanosensitive [J]. Cell reports, 2016, 17(7): 1739-1746. DOI: 10.1016/j.celrep.2016.10.033.

[14] Suchyna TM. Piezo channels and GsMTx4: Two milestones in our understanding of excitatory mechanosensitive channels and their role in pathology [J]. Prog Biophys Mol Biol, 2017, 130(Pt B): 244-253. DOI: 10.1016/j.pbiomolbio.2017.07.011.

[15] Cox CD, Bae C, Ziegler L, et al. Removal of the mechanoprotec-

tive influence of the cytoskeleton reveals PIEZO1 is gated by bilayer tension [J]. Nat Commun, 2016,7:10366. DOI:10.1038/ncomms10366.

[16] Retailleau K, Duprat F, Arhatte M, et al. Piezo1 in smooth muscle cells is involved in hypertension-dependent arterial remodeling [J]. Cell Rep, 2015,13(6):1161-1171. DOI:10.1016/j.celrep.2015.09.072.

[17] Gottlieb PA, Bae C, Sachs F. Gating the mechanical channel Piezo1: A comparison between whole-cell and patch recording [J]. Channels (Austin), 2012,6(4):282-289. DOI:10.4161/chan.21064.

[18] Douguet D, Honoré E. Mammalian mechanoelectrical transduction: Structure and function of force-gated ion channels [J]. Cell, 2019,179(2):340-354. DOI:10.1016/j.cell.2019.08.049.

[19] Ranade SS, Syeda R, Patapoutian A. Mechanically activated ion channels [J]. Neuron, 2015,87(6):1162-1179. DOI:10.1016/j.neuron.2015.08.032.

[20] Coste B, Mathur J, Schmidt M, et al. Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels [J]. Science, 2010,330(6000):55-60. DOI:10.1126/science.1193270.

[21] Lee W, Leddy HA, Chen Y, et al. Synergy between Piezo1 and Piezo2 channels confers high-strain mechanosensitivity to articular cartilage [J]. Proc Natl Acad Sci U S A, 2014,111(47):E5114-E5122. DOI:10.1073/pnas.1414298111.

[22] Xu BY, Jin Y, Ma XH, et al. The potential role of mechanically sensitive ion channels in the physiology, injury, and repair of articular cartilage [J]. J Orthop Surg (Hong Kong), 2020,28(3):2309499020950262. DOI:10.1177/2309499020950262.

[23] Corey DP, García-Añoveros J, Holt JR, et al. TRPA1 is a candidate for the mechanosensitive transduction channel of vertebrate hair cells [J]. Nature, 2004,432(7018):723-730. DOI:10.1038/nature03066.

[24] Suzuki M, Mizuno A, Kodaira K, et al. Impaired pressure sensation in mice lacking TRPV4 [J]. J Biol Chem, 2003,278(25):22664-22668. DOI:10.1074/jbc.M302561200.

[25] Kamkin AG, Kiseleva IS, Iarygin VN. Mechanosensitive ion channels [J]. Usp Fiziol Nauk, 2002,33(3):3-37.

[26] Venkatachalam K, Montell C. TRP channels [J]. Annu Rev Biochem, 2007,76:387-417. DOI:10.1146/annurev.biochem.75.103004.142819.

[27] Tazawa K, Ikeda H, Kawashima N, et al. Transient receptor potential melastatin (TRPM) 8 is expressed in freshly isolated native human odontoblasts [J]. Arch Oral Biol, 2017,75:55-61. DOI:10.1016/j.archoralbio.2016.12.007.

[28] Kärki T, Tojkander S. TRPV protein family-from mechanosensing to cancer invasion [J]. Biomolecules, 2021,11(7):1019. DOI:10.3390/biom11071019.

[29] Talavera K, Startek JB, Alvarez-Collazo J, et al. Mammalian transient receptor potential TRPA1 channels: From structure to disease [J]. Physiol Rev, 2020,100(2):725-803. DOI:10.1152/physrev.00005.2019.

[30] Enyedi P, Czirják G. Molecular background of leak K^+ currents: Two-pore domain potassium channels [J]. Physiol Rev, 2010,90(2):559-605. DOI:10.1152/physrev.00029.2009.

[31] Lengyel M, Enyedi P, Czirják G. Negative influence by the force: Mechanically induced hyperpolarization via K2P background potassium channels [J]. Int J Mol Sci, 2021,22(16):9062. DOI:10.3390/ijms22169062.

[32] Brohawn SG, Su Z, MacKinnon R. Mechanosensitivity is mediated directly by the lipid membrane in TRAAK and TREK1 K^+ channels [J]. Proc Natl Acad Sci U S A, 2014,111(9):3614-3619. DOI:10.1073/pnas.1320768111.

[33] Aguan DW, George AG, Richard A, et al. International union of pharmacology. LII. nomenclature and molecular relationships of calcium-activated potassium channels [J]. Pharmacol Rev, 2005,57(4):463. DOI:10.1124/pr.57.4.9.

[34] Koh SD, Sanders KM. Stretch-dependent potassium channels in murine colonic smooth muscle cells [J]. J Physiol, 2001,533(Pt 1):155-163. DOI:10.1111/j.1469-7793.2001.0155b.x.

[35] Balemans D, Boeckxstaens GE, Talavera K, et al. Transient receptor potential ion channel function in sensory transduction and cellular signaling cascades underlying visceral hypersensitivity [J]. Am J Physiol Gastrointest Liver Physiol, 2017,312(6):G635-G648. DOI:10.1152/ajpgi.00401.2016.

[36] Wang W, Huang H, Hou D, et al. Mechanosensitivity of STREX-lacking BKCa channels in the colonic smooth muscle of the mouse [J]. Am J Physiol Gastrointest Liver Physiol, 2010,299(6):G1231-G1240. DOI:10.1152/ajpgi.00268.2010.

[37] MacLean DM, Soto E. Editorial: ASICs: Structure, function, and pharmacology [J]. Front Physiol, 2022,13:831830. DOI:10.3389/fphys.2022.831830.

[38] Ruan N, Tribble J, Peterson AM, et al. Acid-sensing ion channels and mechanosensation [J]. Int J Mol Sci, 2021,22(9):4810. DOI:10.3390/ijms22094810.

[39] Magloire H, Couble ML, Thivichon-Prince B, et al. Odontoblast: A mechano-sensory cell [J]. J Exp Zool B Mol Dev Evol, 2009,312b(5):416-424. DOI:10.1002/jez.b.21264.

[40] Shibukawa Y, Sato M, Kimura M, et al. Odontoblasts as sensory receptors: Transient receptor potential channels, pannexin-1, and ionotropic ATP receptors mediate intercellular odontoblast-neuron signal transduction [J]. Pflugers Arch, 2015,467(4):843-863. DOI:10.1007/s00424-014-1551-x.

[41] 梁春云,吴声,胡德渝,等.瞬时感受器电位香草酸受体3离子通道蛋白在人成牙本质细胞中的表达[J].中华口腔医学杂志,2013,48(11):679-682. DOI:10.3760/cma.j.issn.1002-0098.2013.11.009.

[42] Seux D, Joffre A, Fosset M, et al. Immunohistochemical localization of L-type calcium channels in the developing first molar of the rat during odontoblast differentiation [J]. Arch Oral Biol, 1994,39(2):167-170. DOI:10.1016/0003-9969(94)90113-9.

[43] Allard B, Couble ML, Magloire H, et al. Characterization and gene expression of high conductance calcium-activated potassium channels displaying mechanosensitivity in human odontoblasts [J]. J Biol Chem, 2000, 275(33): 25556-25561. DOI: 10.1074/jbc.M002327200.

[44] Sato M, Ogura K, Kimura M, et al. Activation of mechanosensitive transient receptor potential/Piezo channels in odontoblasts generates action potentials in cocultured isolectin B4-negative medium-sized trigeminal ganglion neurons [J]. J Endod, 2018, 44(6): 984-991.e2. DOI: 10.1016/j.joen.2018.02.020.

[45] Cho YS, Han HM, Jeong SY, et al. Expression of Piezo1 in the trigeminal neurons and in the axons that innervate the dental pulp [J]. Front Cell Neurosci, 2022, 16: 945948. DOI: 10.3389/fncel.2022.945948.

[46] Bernal L, Sotelo-Hitschfeld P, König C, et al. Odontoblast TRPC5 channels signal cold pain in teeth [J]. Science advances, 2021, 7(13): eabf5567. DOI: 10.1126/sciadv.abf5567.

[47] Okumura R, Shima K, Muramatsu T, et al. The odontoblast as a sensory receptor cell? The expression of TRPV1 (VR-1) channels [J]. Arch Histol Cytol, 2005, 68(4): 251-257. DOI: 10.1679/aohc.68.251.

[48] Tsumura M, Sobhan U, Muramatsu T, et al. TRPV1-mediated calcium signal couples with cannabinoid receptors and sodium-calcium exchangers in rat odontoblasts [J]. Cell calcium, 2012, 52(2): 124-136. DOI: 10.1016/j.ceca.2012.05.002.

[49] Sato M, Sobhan U, Tsumura M, et al. Hypotonic-induced stretching of plasma membrane activates transient receptor potential vanilloid channels and sodium-calcium exchangers in mouse odontoblasts [J]. J Endod, 2013, 39(6): 779-787. DOI: 10.1016/j.joen.2013.01.012.

[50] Son AR, Yang YM, Hong JH, et al. Odontoblast TRP channels and thermo/mechanical transmission [J]. J Dent Res, 2009, 88(11): 1014-1019. DOI: 10.1177/0022034509343413.

[51] Kim YS, Kim TH, McKemy DD, et al. Expression of vesicular glutamate transporters in transient receptor potential melastatin 8 (TRPM8)-positive dental afferents in the mouse [J]. Neuroscience, 2015, 303: 378-388. DOI: 10.1016/j.neuroscience.2015.07.013.

[52] Guo L, Berry JE, Somerman MJ, et al. A novel method to isolate odontoblasts from rat incisor [J]. Calcif Tissue Int, 2000, 66(3): 212-216. DOI: 10.1007/pl00005837.

[53] Sun X, Dong S, Kato H, et al. Mitochondrial calcium-triggered oxidative stress and developmental defects in dopaminergic neurons differentiated from deciduous teeth-derived dental pulp stem cells with MFF insufficiency [J]. Antioxidants (Basel), 2022, 11(7): 1361. DOI: 10.3390/antiox11071361.

[54] El Karim IA, Linden GJ, Curtis TM, et al. Human odontoblasts express functional thermo-sensitive TRP channels: Implications for dentin sensitivity [J]. Pain, 2011, 152(10): 2211-2223. DOI: 10.1016/j.pain.2010.10.016.

[55] Egbuniwe O, Grover S, Duggal AK, et al. TRPA1 and TRPV4 activation in human odontoblasts stimulates ATP release [J]. J Dent Res, 2014, 93(9): 911-917. DOI: 10.1177/0022034514544507.

[56] Lin Y, Cheng T, Zhu S, et al. mRNA and long non-coding RNA expression profiling of human periodontal ligament cells under tension loading [J]. Eur J Orthod, 2021, 43(6): 698-707. DOI: 10.1093/ejo/cjab043.

[57] de Jong T, Bakker AD, Everts V, et al. The intricate anatomy of the periodontal ligament and its development: Lessons for periodontal regeneration [J]. J Periodontal Res, 2017, 52(6): 965-974. DOI: 10.1111/jre.12477.

[58] 康婷,黄世友,李鹏,等. Piezos离子通道在大鼠牙周组织中表达的实验研究[J]. 牙体牙髓牙周病学杂志, 2014, 24(5): 269-273. DOI: 10.15956/j.cnki.chin.j.conserv.dent.2014.05.006.

[59] Jin Y, Li J, Wang Y, et al. Functional role of mechanosensitive ion channel Piezo1 in human periodontal ligament cells [J]. Angle Orthod, 2015, 85(1): 87-94. DOI: 10.2319/123113-955.1.

[60] Shen Y, Pan Y, Guo S, et al. The roles of mechanosensitive ion channels and associated downstream MAPK signaling pathways in PDLC mechanotransduction [J]. Mol Med Rep, 2020, 21(5): 2113-2122. DOI: 10.3892/mmr.2020.11006.

[61] Ohara A, Saeki Y, Nishikawa M, et al. Single-channel recordings of TREK-1 K^+ channels in periodontal ligament fibroblasts [J]. J Dent Res, 2006, 85(7): 664-669. DOI: 10.1177/154405910608500716.

[62] Song Z, Chen L, Guo J, et al. The role of transient receptor potential cation channel, subfamily C, member 1 in the odontoblast-like differentiation of human dental pulp cells [J]. J Endod, 2017, 43(2): 315-320. DOI: 10.1016/j.joen.2016.10.021.

[63] Mousawi F, Peng H, Li J, et al. Chemical activation of the Piezo1 channel drives mesenchymal stem cell migration via inducing ATP release and activation of P2 receptor purinergic signaling [J]. Stem Cells, 2020, 38(3): 410-421. DOI: 10.1002/stem.3114.

[64] Yang X, Song Z, Chen L, et al. Role of transient receptor potential channel 6 in the odontogenic differentiation of human dental pulp cells [J]. Exp Ther Med, 2017, 14(1): 73-78. DOI: 10.3892/etm.2017.4471.

[65] Kwon M, Baek SH, Park CK, et al. Single-cell RT-PCR and immunocytochemical detection of mechanosensitive transient receptor potential channels in acutely isolated rat odontoblasts [J]. Arch Oral Biol, 2014, 59(12): 1266-1271. DOI: 10.1016/j.archoralbio.2014.07.016.

[66] Wiesmann HP, Tkotz T, Joos U, et al. Magnesium in newly formed dentin mineral of rat incisor [J]. J Bone Miner Res, 1997, 12(3): 380-383. DOI: 10.1359/jbmr.1997.12.3.380.

[67] Harrison A, Lin S, Pounder N, et al. Mode & mechanism of low intensity pulsed ultrasound (LIPUS) in fracture repair [J]. Ultrasonics, 2016, 70: 45-52. DOI: 10.1016/j.ultras.2016.03.016.

[68] 姚欢,潘华锋,郑妍,等. 机械敏感离子通道Trpm7在LIPUS促进牙髓间充质干细胞成骨分化中的作用机制的研究[J]. 中国

细胞生物学学报, 2018,40(9):1518-1525. DOI:10.11844/cjcb.2018.09.0129.

[69] 刘瑞瑞,徐小桥,洪珊珊,等. 机械敏感离子通道Piezo在大鼠牙体缺损模型中的时空表达[C]//中华口腔医学会口腔生物医学专业委员会. 2019第九次全国口腔生物医学学术年会论文汇编, 2019:29. DOI:10.26914/c.cnkihy.2019.024951.

[70] Son GY, Yang YM, Park WS, et al. Hypotonic stress induces RANKL via transient receptor potential melastatin 3 (TRPM3) and vaniloid 4 (TRPV4) in human PDL cells [J]. J Dent Res, 2015,94(3):473-481. DOI:10.1177/0022034514567196.

[71] Jiang Y, Guan Y, Lan Y, et al. Mechanosensitive Piezo1 in periodontal ligament cells promotes alveolar bone remodeling during orthodontic tooth movement [J]. Front Physiol, 2021,12:767136. DOI:10.3389/fphys.2021.767136.

[72] Nottmeier C, Lavicky J, Gonzalez Lopez M, et al. Mechanical-induced bone remodeling does not depend on Piezo1 in dentoalveolar hard tissue [J]. Sci Rep, 2023,13(1):9563. DOI:10.1038/s41598-023-36699-9.

[73] Yeon KY, Chung G, Shin MS, et al. Adult rat odontoblasts lack noxious thermal sensitivity [J]. J Dent Res, 2009,88(4):328-332. DOI:10.1177/0022034509334100.

[74] Addy M, Urquhart E. Dentine hypersensitivity: Its prevalence, aetiology and clinical management [J]. Dent Update, 1992,19(10):407-408,410-402.

[75] Lee K, Lee BM, Park CK, et al. Ion channels involved in tooth pain [J]. Int J Mol Sci, 2019,20(9):2266. DOI:10.3390/ijms20092266.

[76] Shibukawa Y, Sato M, Kimura M, et al. Odontoblasts as sensory receptors: Transient receptor potential channels, pannexin-1, and ionotropic ATP receptors mediate intercellular odontoblast-neuron signal transduction[J]. Pflugers Archiv, 2015,467(4):843-863. DOI:10.1007/s00424-014-1551-x.

[77] Han HM, Jeong SY, Cho YS, et al. Expression of Piezo2 in the dental pulp, sensory root, and trigeminal ganglion and its coexpression with vesicular glutamate transporters [J]. J Endod, 2022,48(11):1407-1413. DOI:10.1016/j.joen.2022.07.012.

[78] Sun XF, Qiao WW, Meng LY, et al. PIEZO1 Ion Channels Mediate Mechanotransduction in Odontoblasts [J]. J Endod, 2022,48(6):749-758. DOI:10.1016/j.joen.2022.02.005.

[79] Bakri MM, Yahya F, Munawar KMM, et al. Transient receptor potential vanilloid 4(TRPV4) expression on the nerve fibers of human dental pulp is upregulated under inflammatory condition [J]. Arch Oral Biol, 2018,89:94-98. DOI:10.1016/j.archoralbio.2018.02.011.

[80] El Karim I, McCrudden MT, Linden GJ, et al. TNF-α-induced p38MAPK activation regulates TRPA1 and TRPV4 activity in odontoblast-like cells [J]. Am J Pathol, 2015,185(11):2994-3002. DOI:10.1016/j.ajpath.2015.07.020.

[81] Haas ET, Rowland K, Gautam M. Tooth injury increases expression of the cold sensitive TRP channel TRPA1 in trigeminal neurons [J]. Arch Oral Biol, 2011,56(12):1604-1609. DOI:10.1016/j.archoralbio.2011.06.014.

[82] Gao M, Long H, Ma W, et al. The role of periodontal ASIC3 in orofacial pain induced by experimental tooth movement in rats [J]. Eur J Orthod, 2016,38(6):577-583. DOI:10.1093/ejo/cjv082.

[83] Gao M, Yan X, Lu Y, et al. Retrograde nerve growth factor signaling modulates tooth mechanical hyperalgesia induced by orthodontic tooth movement via acid-sensing ion channel 3 [J]. Int J Oral Sci, 2021,13(1):18. DOI:10.1038/s41368-021-00124-6.

[84] Hitomi Y, Suzuki A, Kawano Y, et al. Immunohistochemical detection of ENaCbeta in the terminal Schwann cells associated with the periodontal Ruffini endings of the rat incisor [J]. Biomed Res, 2009,30(2):113-119. DOI:10.2220/biomedres.30.113.

[85] Rahman F, Harada F, Saito I, et al. Detection of acid-sensing ion channel 3 (ASIC3) in periodontal Ruffini endings of mouse incisors [J]. Neurosci Lett, 2011,488(2):173-177. DOI:10.1016/j.neulet.2010.11.023.

(收稿日期:2023-07-20)

(本文编辑:王嫚)