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· 综述 ·

NLRP3炎症小体调节正畸牙移动过程中组织改建的研究进展

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【摘要】 核苷酸结合寡聚化结构域样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)炎症小体通过其下游的半胱氨酸蛋白酶1(Caspase-1)依赖性促炎细胞因子白细胞介素1 β (interleukin-1 β , IL-1 β)和白细胞介素18(interleukin-18, IL-18)的成熟和分泌,介导炎症并诱导细胞焦亡,调节牙周组织改建。正畸力通过介导牙周组织无菌性炎症引发牙周组织适应性改建,进而促进正畸牙移动与稳定。NLRP3炎症小体在正畸牙移动过程中发挥重要作用,但同时也是导致正畸患者牙周组织炎症和正畸炎性牙根吸收的原因之一。文献复习结果表明,NLRP3炎症小体参与正畸牙移动组织改建中牙周膜成纤维细胞、牙周膜干细胞、巨噬细胞、成骨细胞和破骨细胞的活化与分化过程,并且靶向NLRP3炎症小体上游NF- κ B信号通路、下游Caspase-1、IL-1 β 和IL-18等效应分子及NLRP3炎症小体组成蛋白本身在调节牙移动以及治疗和预防正畸伴发牙周组织炎症、正畸炎性牙根吸收等方面具有重要意义。未来研究可重点关注NLRP3炎症小体在正畸牙移动过程中组织改建的具体作用机制。本文就NLRP3炎症小体信号通路在正畸牙移动过程中相应组织改建的影响及其调控机制进行综述。

【关键词】 NLRP3炎症小体; 正畸牙移动; 白细胞介素1 β ; 白细胞介素18; 细胞焦亡; 牙槽骨; 牙周炎; 牙根吸收

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Research progress on NLRP3 inflammasome-mediated regulation of tissue remodeling during orthodontic tooth movement WANG Jiajia, ZHANG Jiangtao, ZENG Fulei. Affiliated Stomatological Hospital of Zunyi Medical University, Zunyi 563000, China

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【Abstract】 NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome mediates inflammation, induces pyroptosis, and regulates periodontal tissue remodeling through the maturation and secretion of its downstream cysteine protease 1 (Caspase-1)-dependent pro-inflammatory cytokines, interleukin (IL)-1 β and IL-18. Orthodontic force mediates the aseptic inflammation of periodontal tissues and triggers adaptive alteration of periodontal tissues, thereby promoting the movement and stability of orthodontic teeth. NLRP3 inflammasome plays an important role in orthodontic tooth movement and causes periodontal tissue inflammation and orthodontic inflammatory root resorption in orthodontic patients. Literature review suggests that NLRP3 inflammasome is involved in the activation and differentiation of periodontal ligament fibroblasts, periodontal ligament stem cells, macrophages, osteoblasts, and osteoclasts in orthodontic tooth mobile tissue remodeling. Additionally, it targets the upstream nuclear factor kappa-B signaling pathway; down-

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stream effectors, such as Caspase-1, IL-1 β , and IL-18; and the NLRP3 inflammasome components for regulating tooth movement as well as treating and preventing orthodontics-associated periodontitis and orthodontic-induced inflammatory root resorption. Future studies can be focused on the specific mechanism of NLRP3 inflammasome tissue modification during orthodontic tooth movement. This article reviews the effects and regulatory mechanisms of the NLRP3 inflammasome signaling pathway on the corresponding tissue remodeling during orthodontic tooth movement.

【Key words】 NLRP3 inflammasome; orthodontic tooth movement; interleukin-1 β ; interleukin-18; pyroptosis; alveolar bone; periodontitis; root resorption

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正畸治疗时,正畸应力造成了牙周组织无菌性炎症的发生,炎症因子和介质释放,促使牙周组织细胞活化,导致骨吸收、骨沉积以及细胞外基质的合成与分解^[1],通过上述作用,牙周组织发生改建,牙齿随之移动。正畸牙移动有赖于牙周组织的适应性改建,然而牙齿受到过度正畸力会放大炎症级联反应导致牙及牙周组织损害^[2]。因此,探究正畸牙移动过程中牙周组织无菌性炎症的调控机制具有关键作用。

作为先天性免疫系统的重要成员,炎症小体在感知外界病原体或自身损伤后诱发机体炎症反应^[3]。适当的炎症小体活性是组织稳态所必需的,但过度的炎性小体活性可促进与骨破坏相关的各种疾病的发生和发展。核苷酸结合寡聚化结构域样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)炎症小体是组织细胞暴露于病原相关分子模式(pathogen-associated molecular patterns, PAMPs)或损伤相关分子模式(damage-associated molecular patterns, DAMPs)之后在细胞质中组装形成的多蛋白复合体,并且后续裂解活化促炎细胞因子白细胞介素1(interleukin-1 β , IL-1 β)和白细胞介素18(interleukin-18, IL-18),参与机体固有免疫防御反应^[4]。多项研究表明NLRP3炎症小体的激活及其相关分子调控信号通路 with 口腔多种疾病的发生、发展密切相关。

正畸应力的加载导致牙周组织内血管受压,组织缺氧,细胞坏死,DAMPs刺激NLRP3炎症小体的活化与释放,触发NLRP3/Caspase-1/IL-1 β 信号通路级联反应,影响牙周膜及牙槽骨的代谢平衡,调节正畸牙移动^[5-6]。本文从NLRP3炎症小体的基

本结构与功能、活化途径等方面进行阐述整理,对NLRP3炎症小体参与正畸牙移动过程中的组织改建以及相关作用机制进行归纳分析,以期为正畸科学研究、临床治疗提供参考。

1 NLRP3炎症小体的结构及其活化机制

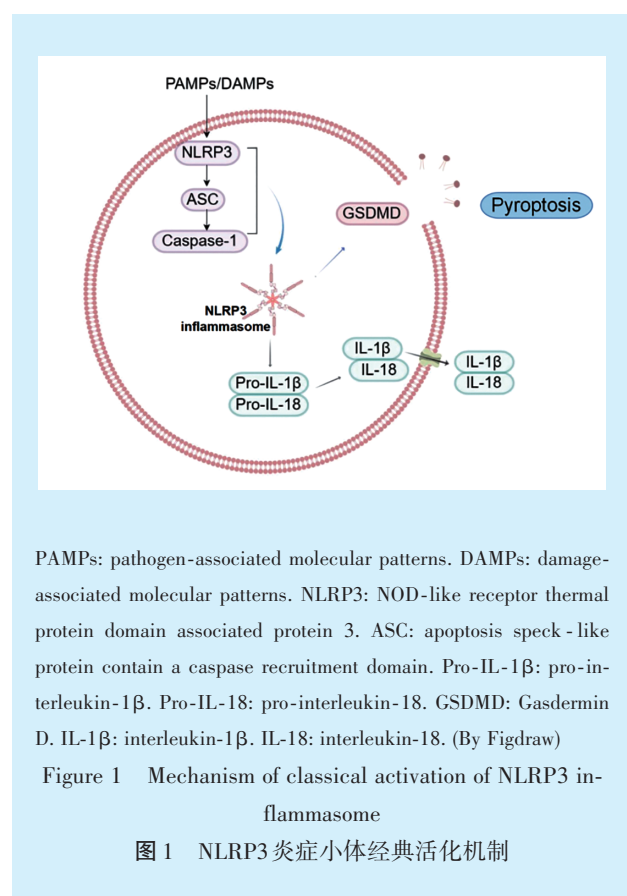
1.1 NLRP3炎症小体的结构

NLRP3炎症小体在调控口腔组织炎症发生发展过程方面具有重要作用^[7]。NLRP3炎症小体主要由核心蛋白NLRP3、含胱天蛋白酶募集域(caspase recruitment domain protein, CARD)的凋亡相关斑点样蛋白(apoptosis speck-like protein contain a caspase recruitment domain, ASC)和效应分子半胱氨酸蛋白酶-1(Caspase-1)组成。这三种蛋白质之间的相互作用严格调节炎性小体功能,进而调节炎症和免疫反应。核心蛋白NLRP3是具有模式识别功能的蛋白复合物,由三个部分组成:能够与ASC相互作用的氨基端PYRIN结构域(PYD),具有水解ATP作用的中间核苷酸寡聚化结构域(NACHT),负责识别配体的包含12个亮氨酸重复序列羧基端结构域(LRR)^[8]。

1.2 NLRP3炎症小体活化途径

现有研究认为,NLRP3炎症小体活化有经典、非经典及替代活化途径三种活化方式。NLRP3炎性小体的经典活化途径包括两个关键步骤,启动和激活^[9]。在启动步骤中,特定的模式识别受体(pattern recognition receptors, PPRs)识别PAMPs和DAMPs,导致NF- κ B信号通路随后激活,NLRP3、pro-IL-1 β 和pro-IL-18转录水平上调。在激活步骤中,NLRP3通过NACHT结构域发生寡聚后招募ASC,并进一步活化Caspase-1后剪切IL-1 β 前体和

IL-18前体形成IL-1 β 、IL-18,介导细胞炎症及组织损伤^[10]。激活的Caspase-1也会裂解消皮素D(gasdermin D, GSDMD), GSDMD最终导致细胞穿孔、肿胀,从而引发一种特定形式的程序性细胞死亡,焦亡^[11](图1)。Caspase-11、Caspase-4、Caspase-5等被脂多糖(lipopolysaccharide, LPS)激活后裂解GSDMD导致细胞焦亡的途径被称为NLRP3炎症小体非经典活化途径,且有研究表明非经典活化途径在革兰氏阴性菌感染引起的炎症性反应中起关键作用^[12]。NLRP3炎症小体替代活化途径主要是LPS通过TLR4直接触发NLRP3炎症小体激活及IL-1 β 成熟,但是无法介导ASC斑点形成及细胞焦亡^[13],而正畸牙移动期间牙周组织反应主要为无菌性炎症,与LPS诱导的炎症小体非经典途径及替代途径联系不大。



1.3 影响NLRP3炎症小体活化的因素

多种因素影响NLRP3炎症小体活化及功能作用的发挥,如K⁺外流^[14]、Cl⁻外流^[15]、溶酶体损伤^[16]、线粒体功能障碍和活性氧产生^[17]等上游信号的产生可触发NLRP3炎症小体的激活。翻译后修饰(post-translation modification, PTM)如磷酸化^[18]、泛素

化^[19]、苏莫酰化^[20]和S-亚硝基化^[21]等能够严密调控NLRP3炎症小体的激活。适当的NLRP3炎症小体活性是正畸牙移动过程所必须的,而NLRP3炎症小体激活过量,则会导致炎症反应和自身免疫反应紊乱,导致正畸过程中并发症的发生。因此,探究NLRP3炎症小体对正畸患者牙周组织无菌性炎症反应的调节机制对临床工作中调节正畸牙移动具有重要意义。

2 NLRP3炎症小体与正畸牙移动

正畸牙移动是牙周组织适应性改建的结果,与牙周组织中多种成分密切相关。在适当的正畸力作用下,体内各种细胞因子通过多通路调控NLRP3炎症小体的表达,而NLRP3通过其下游的Caspase-1依赖性促炎细胞因子IL-1 β 和IL-18的成熟和分泌,介导炎症并诱导细胞焦亡,调节成骨细胞和破骨细胞的平衡状态,引起牙周组织反应性结构变化,牙齿发生位移,外力去除后牙周组织在新的位置上发生改建使牙齿重新获得稳定。

2.1 NLRP3炎症小体影响牙周膜纤维组织改建

适当正畸力使牙周膜纤维发生适应性改建,而当牙周组织接受过度的咬合力或正畸力的时候会诱导炎症细胞因子的过量表达,破坏牙周组织内的生理稳态^[22]。多项研究表明,NLRP3炎症小体可以通过调节牙周膜成纤维细胞、牙周膜干细胞及巨噬细胞等影响牙周膜纤维组织改建。

2.1.1 牙周膜成纤维细胞 成纤维细胞是牙周膜的主要组成细胞,在正畸牙移动过程中的牙周组织改建发挥重要作用。在拉力刺激下牙周膜成纤维细胞(periodontal ligament cells, PDLFs)通过Runt相关转录因子2(runt-related transcription factor 2, RUNX-2)、骨钙素(osteocalcin, OCN)上调诱导成骨分化,并加速沿牙周组织和牙槽骨界面的新骨沉积^[23]。研究表明PDLFs中NLRP3炎症小体激活诱导产生IL-1 β 刺激前列腺素E2的表达上调会增加RANKL并促进破骨细胞生成,从而调节骨重塑^[24]。有研究发现,受到过度正畸力的大鼠PDLFs中NLRP3裂解GSDMD及导致IL-1 β 和IL-18的水平升高,引起细胞焦亡和组织炎症,然而这个过程可以用半胱氨酸蛋白酶抑制剂或敲低GSDMD基因部分阻断^[25]。因此,上述研究表明NLRP3炎症小体在PDLFs调节牙周组织改建过程中发挥重要作用。

2.1.2 牙周膜间充质干细胞 牙周膜间充质干细胞(periodontal ligament stem cells, PDLSCs)是能够自我更新并且具有牙周组织多向分化潜能的干细

胞,其促进血管生成及骨再生作用备受关注^[26]。大量研究表明,PDLSCs在正畸力刺激下可以向成骨分化,并且通过RANKL调节破骨细胞形成^[27]。有研究发现全反式维甲酸(all-trans-retinoic acid, ATRA)通过激活NF- κ B信号通路和炎症小体促进IL-1 β 表达来抑制PDLSCs的成骨分化,用抗IL-1 β 抗体中和成熟IL-1 β 部分逆转了ATRA对PDLSCs成骨细胞分化的抑制作用^[28]。Xiang等^[29]发现敲低瞬时受体电位M2通道(transient receptor potential cation channel subfamily M member 2, TRPM2)通过介导NF- κ B/NLRP3途径加速了人牙周膜干细胞(human periodontal ligament stem cells, hPDLSCs)的成骨分化,影响成骨基因表达。Chen等^[30]等发现机械力诱导体内外PDLSCs焦亡,从而影响破骨细胞的发生,并且可诱导大鼠正畸牙移动和牙槽骨重塑过程中焦亡相关标志物的表达,阻断或提高焦亡水平可分别抑制或促进正畸牙移动和牙槽骨重塑。因此,笔者推测NLRP3炎症小体引起的焦亡可能影响正畸牙移动过程,但还需相关实验研究进一步验证。通过调控NLRP3炎症小体信号通路从而充分发挥PDLSCs的自我分化能力和免疫调节作用,改善牙周组织微环境,将是调节正畸牙移动研究的一个新的切入点。

2.1.3 巨噬细胞 巨噬细胞是免疫系统的重要组成部分,几乎参与了全身所有的疾病发生与发展。多项研究表明巨噬细胞可以通过调控成骨细胞及破骨细胞来参与骨改建过程^[31]。Hayakawa等^[32]将压缩力作用于Raw264.7小鼠巨噬细胞发现,持续的压缩力促进破骨细胞分化。巨噬细胞在骨代谢过程中不仅可以通过参与破骨细胞活化与分化介导骨丢失,还可以参与巨噬细胞的炎性体活化过程,促进骨破坏^[33]。hPDLSCs受到静压力后可以促进M1极化,同时可以促进M1巨噬细胞分泌NLRP3,并且可以增加炎症因子IL-1 β 表达^[34]。研究发现中成药二妙散(Ermiao powder, EMP)可以通过下调miRNA-33抑制NLRP3炎症小体的激活,从而防止M1巨噬细胞极化^[35]。有研究表明M2巨噬细胞分泌骨形态发生蛋白-2(bone morphogenetic protein 2, BMP-2)、转化生长因子- β (transforming growth factor- β , TGF- β)和胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)诱导成骨细胞分化^[36]。Liu等^[37]发现泛素特异性蛋白酶19(ubiquitin specific peptidase 19 gene, USP19)通过增加自噬通量和减少线粒体活性氧的产生来抑制NLRP3炎症小体活化,进一步抑制炎症反应并促

进M2样巨噬细胞极化。Luo等^[38]证明IL-37依赖IL-1R8-NLRP3途径将巨噬细胞的极化从促炎M1表型转变为有益的抗炎M2表型,有助于治疗颞下颌关节炎。上述研究证明,NLRP3可能是巨噬细胞极化在炎性疾病发展中的关键调控因素之一,且已有证据表明,在力的诱导下,压力侧PDLSCs可以诱导巨噬细胞极化为M1,促进M1分泌炎症因子,导致破骨的发生,在张力侧主要是M2样巨噬细胞参与牙周膜的重建、新骨形成^[39]。然而,仍需进一步探索NLRP3炎症小体对正畸牙移动张力侧及压力侧巨噬细胞极化的调控机制。

2.2 NLRP3炎症小体影响牙槽骨代谢平衡

牙槽骨是人体最活跃的骨骼,在人的一生中不断地增生和吸收,在体内多种信号机制调节下达到新的平衡。破骨细胞和成骨细胞活动强度的相对动态平衡造就了正畸牙移动过程中的牙槽骨改建与重塑。

2.2.1 成骨细胞 正畸加力过程中,在张力侧牙槽骨内侧面,成骨细胞活跃,新骨形成。Cheng等^[40]将半胱天冬酶-1抑制剂VX-765用于急性根尖周炎大鼠实验模型,结果表明VX-765抑制了急性根尖周炎大鼠的骨质流失,是因为VX-765通过抑制Caspase-1、IL-1 β 、单核细胞趋化蛋白-1(monocyte chemotactic protein 1, MCP-1)、IL-16和IL-8等的表达,从而降低了GSDMD的表达,减少了炎症反应,最终抑制了牙槽骨中成骨细胞的焦亡。有Yang等^[41]在体内外糖尿病模型研究中应用半胱天冬酶-1抑制剂,结果表明高葡萄糖通过半胱天冬酶-1/GSDMD/IL-1 β 途径激活焦亡抑制牙槽骨中成骨细胞的增殖和分化。Li等^[42]发现抑制NLRP3炎性小体可促进糖尿病大鼠牙槽骨缺损愈合,可能与减少促炎细胞因子产生和增加成骨基因表达有关。有趣的是,有研究发现NLRP3敲除小鼠的骨骼发育受损,其特征是生长板缺陷和骨小梁骨质减少,并且在体外,缺乏NLRP3表达的原代成骨细胞表现出矿化缺陷^[43]。基于以上研究可以合理认为在牙周炎等炎症微环境中,NLRP3炎症小体抑制成骨细胞的增殖和分化,造成骨质流失,而在正常骨稳态环境中,NLRP3炎症小体是成骨诱导和矿化不可或缺的一环,但是,NLRP3对正畸牙移动过程中成骨细胞的具体调节作用需要进一步的研究。

2.2.2 破骨细胞 在压力侧牙槽骨表面,破骨细胞活化,骨质吸收。Zang等^[44]通过体内和体外模型研究了NLRP3炎症小体参与牙槽骨吸收以及NLRP3

抑制剂对年龄相关性牙槽骨丢失的治疗潜力,结果表明NLRP3炎症小体可促进破骨细胞分化以调节牙槽骨吸收。研究发现,特异性过表达小鼠破骨细胞NLRP3会加剧牙槽骨量丢失,其原因主要与NLRP3炎症小体激活IL-1 β 导致破骨细胞过度活化有关^[45]。有研究表明,IL-1 β 与破骨细胞表面的受体结合,激活核因子 κ B受体活化因子配体(receptor activator for nuclear factor- κ B ligand, RANKL),并调节前列腺素E2、基质金属蛋白酶等多种破骨细胞激活因子的表达^[46]。IL-1 β 可有效诱导牙周组织巨噬细胞分化为有骨吸收能力的破骨细胞,其机制是通过上调RANKL表达和下调骨保护素表达来介导。IL-1能够直接作用于破骨细胞前体细胞或刺激成骨细胞分泌RANKL,促进破骨细胞分化^[47]。有研究发现卞达明可以抑制IL-1 β 的产生并抑制破骨细胞分化和骨吸收^[48]。IL-18作用于T细胞产生 γ -干扰素(interferon- γ , IFN- γ),在RANKL促进破骨分化过程中表现出一定的抑制作用^[49]。Han等^[6]通过研究机械力对NLRP3缺失型小鼠的正畸牙移动,发现通过cGAS/P2X7R途径激活NLRP3炎症小体从而调节正畸牙移动。有研究通过敲除应力加载的牙周炎小鼠模型中的NLRP3基因,发现IL-1 β 释放减少并且破骨细胞分化受到抑制^[25]。综上,适度的NLRP3炎症小体激活可诱导破骨细胞分化,调节牙槽骨代谢,最终促进正畸牙齿移动。

2.3 NLRP3炎症小体影响牙龈组织反应

在正畸牙齿移动过程中,牙龈组织同样受到张力及压力,其形态可随着牙齿移动而塑建,但是牙龈的组织受力改建滞后于牙齿移动,常导致牙龈受压堆积、退缩等反应的发生。在正畸牙移动期间,IL-1 β 经常在龈沟液中检测到,其含量与正畸力大小正相关^[50]。研究发现牙龈卟啉单胞菌触发牙龈成纤维细胞的NLRP3炎症小体依赖性焦亡,这可以通过Eldecalcitol(维生素D类似物)和活性氧或NLRP3抑制剂缓解^[51]。然而,对于NLRP3炎症小体在正畸牙龈炎症反应发生、发展过程中的具体作用及其机制,还需进一步探索研究。

3 NLRP3炎症小体与正畸牙移动并发症

调节牙周组织代谢平衡是获得理想正畸牙移动的关键,然而,不当的应力加载导致的骨代谢失衡等病理状态会影响牙周组织的改建过程,从而

导致正畸牙槽骨吸收、牙松动及牙根吸收等问题的出现。靶向NLRP3炎症小体上下游信号及NLRP3炎症小体蛋白本身已成为众多慢性炎性疾病预防和治疗的有效研究途径^[52]。上文文献回顾提示,NLRP3炎症小体可通过多种牙周组织组成细胞发挥重要作用从而调节正畸牙移动,因此靶向NLRP3炎症小体有望成为正畸牙移动相关并发症的预防和治疗靶点。

3.1 正畸相关牙周炎

正畸加力可引起牙周组织炎症反应,产生与释放炎症因子,从而使牙周组织发生改建,然而过大的矫治力或牙周组织病理状态会导致牙周组织应力环境产生炎症应激反应,使牙周组织遭到破坏。Chen等^[25]通过建立正畸加力诱导的牙周炎小鼠模型,发现NLRP3缺失和MCC950(NLRP3抑制剂)均能减少破骨细胞前体数量,防止破骨细胞分化,从而保护正畸力不当诱导的牙周炎所导致的牙槽骨吸收。并且Peng等^[53]发现MCC950通过阻断NLRP3炎症小体信号通路来增加成骨细胞分化,减少促炎细胞因子的产生。Zhu等^[54]通过体内外研究发现睡眠呼吸暂停综合征引起的缺氧可诱导牙周膜成纤维细胞中活性氧的过度产生和积累,并诱导NLRP3炎症小体相关因子和IL-1 β 的异常表达,导致机体更容易发生牙周组织炎症。有学者指出,褪黑素可能通过抑制NLRP3活化来减少组织损伤^[55]。青蒿琥酯(artemunate, ART)通过抑制NLRP3炎症小体的激活来抑制破骨细胞的形成,从而有效预防牙周炎引起的牙槽骨流失,并通过减少炎症条件下细胞因子的表达来促进成骨潜力^[56]。然而通过调节NLRP3炎症小体治疗正畸相关性牙周炎的研究还任重道远。

3.2 正畸诱导炎性牙根吸收

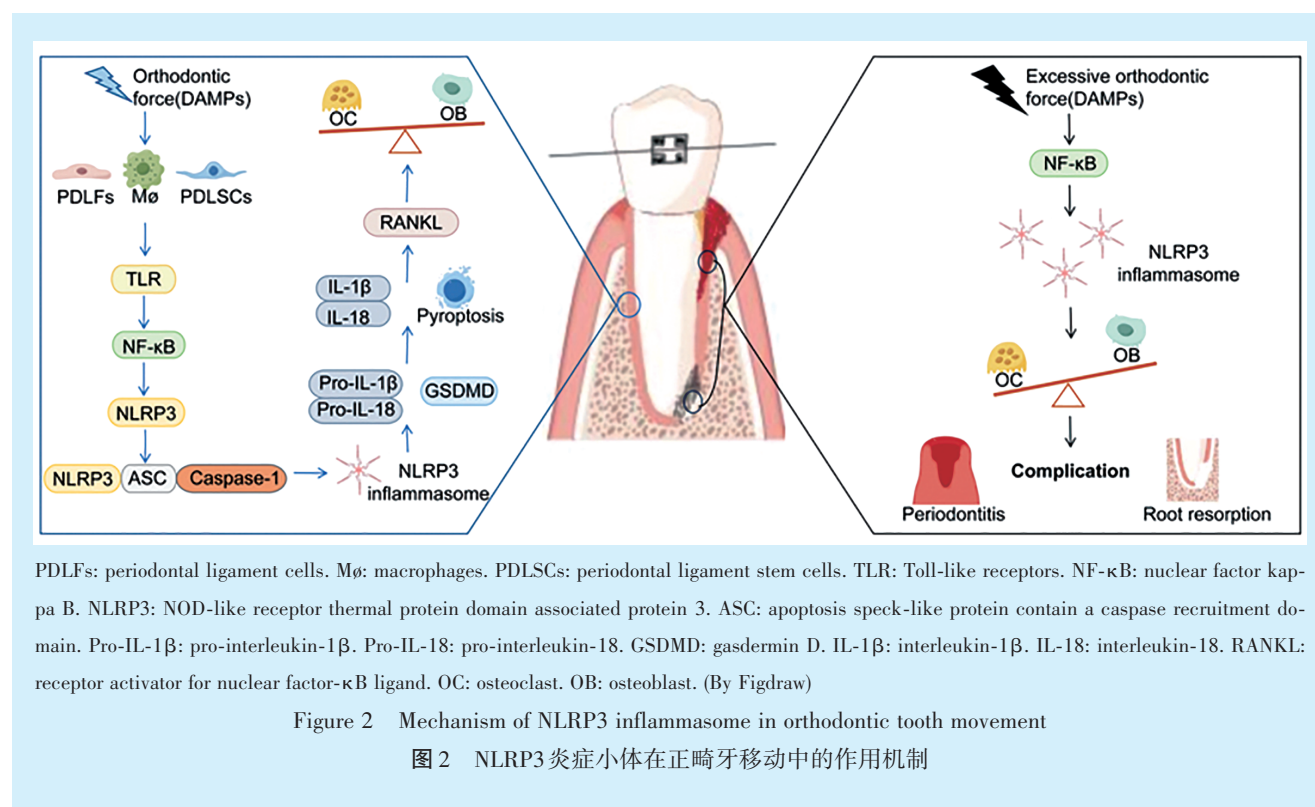
在正畸牙移动过程中,牙根的吸收与修复一直相伴相随,过大的正畸力刺激牙周组织中RANKL表达的显著增加,骨代谢调节失衡,可能导致牙骨质的病理性吸收,其具体机制尚不清楚。研究发现炎症细胞因子如IL-1、肿瘤坏死因子- α 、前列腺素E2等在不当正畸力作用下可能促进破骨细胞的形成,最终引发正畸相关牙根外吸收^[57-58]。Zhang等^[34]发现大鼠牙根吸收模型中NLRP3、Caspase-1和IL-1 β 的产生水平增加,使用NLRP3抑制剂MCC950可减少牙根吸收。有研究发现,受到机械力刺激后,牙周膜成纤维细胞可促进组织巨噬

细胞极化激活,增加 IL-1 β 的产生,活化破牙骨质细胞及破骨细胞,影响正畸相关牙根吸收^[59]。最新体内外研究发现,受到过大矫治力的 PDLFs 通过 TLR4/NF κ B/NLRP3 通路传递炎症信号,诱导 PDLFs 焦亡,直接促进破牙骨质细胞形成和牙根吸收,或者通过促进 M1 巨噬细胞极化间接触发破牙骨质细胞形成和牙根吸收^[60]。以上研究表明 NLRP3 炎症小体在正畸机械力诱发的炎症性牙根吸收过程中扮演重要角色,但其导致正畸中牙根吸

收的具体作用和机制还亟待研究。

4 总结与展望

本文系统综述 NLRP3 炎症小体激活下游促炎细胞因子 IL-1 β 和 IL-18 及介导 NF- κ B、Caspase-1、GSDMD 等对牙周组织代谢相关细胞增殖、分化等影响,同时结合机械力加载等条件探索 NLRP3 炎症小体对正畸牙移动的调节作用(图 2)。



现有研究已证实在适宜正畸力下的无菌性炎症微环境中, NLRP3 炎症小体促进破骨细胞活化及分化, 导致压力侧牙槽骨吸收, 促进正畸牙移动。然而, NLRP3 炎症小体是否具有诱发成骨相关细胞因子的表达, 调节张力侧骨重塑作用仍需进一步实验研究。近年来, 骨代谢研究取得了较大的进展, 调节 NLRP3 炎症小体从而调节正畸牙移动有可能成为将来牙周组织改建研究的重要方向。针对 NLRP3 炎症小体介导细胞焦亡的靶向治疗有望在预防和治疗正畸相关牙周炎和正畸炎症性牙根吸收等方面应用。

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