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·基础研究·

STAT3正向调控正畸牙移动速率与牙槽骨骨量

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【摘要】 **目的** 探讨信号转导与转录激活因子3(signal transducer and activator of transcription 3，STAT3)在牙移动中的作用，为改善正畸牙槽骨塑建与重建提供证据。**方法** 体内实验选取8周龄雄性大鼠建立正畸牙移动模型，分为对照组(牙移动)、实验组(牙移动加STAT3抑制剂stattic局部注射)，于牙移动的第7天、第14天收集实验区域牙槽骨标本进行micro-CT扫描，评估骨体积分数(bone volume/ tissue volume，BV/TV)、骨小梁数目(trabecular number，Tb.N)、骨小梁厚度(trabecular thickness，Tb.Th)、骨小梁分离度(trabecular separation，Tb.Sp)、骨密度(bone mineral density，BMD)，测量牙移动量。体外实验选取小鼠成骨前体细胞MC3T3-e1和小鼠单核巨噬细胞白血病细胞RAW264.7于Transwell®培养板共培养3 d，分为对照组(空白)和实验组(加入STAT3抑制剂stattic)；以碱性磷酸酶(alkaline phosphatase，ALP)染色检测成骨分化；抗酒石酸酸性磷酸酶(tartrate-resistant acid phosphatase，TRAP)染色检测破骨分化；qRT-PCR检测成骨细胞核因子κB受体活化因子配体(receptor activator of nuclear factor-κB ligand，RANKL)、骨保护素(osteoprotegerin，OPG) mRNA表达。**结果** 实验组牙槽骨骨体积分数(BV/TV)、骨小梁数目(Tb.N)、骨小梁厚度(Tb.Th)、骨密度(BMD)在第14天时较对照组明显降低，Tb.Sp在第14天时明显增高；以上指标第7天时的2组间差异无统计学意义。与对照组相比，实验组牙移动量在第7天时明显减少，差异有统计学意义($P < 0.05$)；第14天时2组牙移动量差异无统计学意义($P > 0.05$)。体外实验ALP染色和TRAP染色显示，抑制剂同时抑制成骨和破骨分化；qRT-PCR结果显示，抑制剂抑制成骨前体细胞RANKL、OPG mRNA表达，升高RANKL/OPG mRNA比值。**结论** 抑制STAT3的激活可导致成骨、破骨活动同时被抑制，使正畸牙移动速率减慢、牙槽骨骨质疏松。STAT3可能在调控正畸牙槽骨塑建与重建中发挥重要作用。

【关键词】 大鼠； 牙移动； 骨生成； 骨质疏松； 信号转导与转录激活因子3； stattic； 破骨细胞； 成骨细胞

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Signal transducer and activator of transcription 3 positively modulates orthodontic tooth movement speed and alveolar bone mass

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【Abstract】 **Objective** To elucidate the role of signal transducer and activator of transcription 3 on orthodontic tooth movement, aiming at providing evidence for improving orthodontic bone modeling and remodeling. **Methods** Orthodontic tooth movement (OTM) models were established in 8-week-old Wistar rats, which were divided into 2 groups: the control group (tooth movement) and the test group (tooth movement with local injection of STAT3 inhibitor stattic). Rats were sacrificed on day 7 and 14. Micro-CT scanning was conducted to measure bone volume/tissue volume

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(BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), and bone mineral density (BMD), and the amount of tooth movement of the specimens. The mouse preosteoblastic cell line MC3T3-e1 and mononuclear macrophagic leukemia cell line RAW264.7 were cocultured in Transwell® culture plates and divided into the control group (blank) and the test group (STAT3 inhibitor stattic was added). Alkaline phosphatase (ALP) staining and tartrate-resistant acid phosphatase (TRAP) staining were carried out to reveal osteoblastic and osteoclastic differentiation, respectively. qRT-PCR was performed to evaluate mRNA expression levels of the receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG) in the MC3T3-e1 cells. **Results** Compared with the control group, in the test group, the alveolar bone at the OTM site showed a significant decrease in the BV/TV, Tb.N, Tb.Th, and BMD indexes and a significant increase in Tb.Sp on day 14, while there was no significant difference in the above indexes between the two groups on day 7. The amount of tooth movement was significantly smaller in the test group on day 7 but showed no difference on day 14. ALP staining and TRAP staining revealed weakened osteoblastic and osteoclastic differentiation in the test group. qRT-PCR demonstrated the inhibitor inhibited the mRNA expression of RANKL and OPG and increased the mRNA ratio of RANKL/OPG in osteogenic precursor cells. **Conclusion** Suppression of STAT3 activation leads to inhibition of both osteoblastic and osteoclastic differentiation, resulting in lowered tooth movement and catabolic effects on alveolar bone. STAT3 may play an important role in orthodontic bone modeling and bone remodeling.

【Key words】 rats; tooth movement; osteogenesis; osteoporosis; signal transducer and activator of transcription 3; stattic; osteoclast; osteoblast

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安全有效地加快正畸牙移动速率是医患的共同愿望。增加破骨细胞活性,可导致压力侧牙槽骨吸收加快,从而达到提高牙移动速率的目的。如果成骨活动不能相应增加,则导致骨稳态失衡,牙槽骨骨量减少,进而增加牙齿松动、牙槽骨吸收、牙根吸收以及正畸治疗后复发的风险。因此,同时提高成骨、破骨活动是安全有效地加快正畸牙移动的可行方法。信号转导与转录激活因子3(signal transducer and activatorof transcription 3,STAT3)与骨代谢关系密切。有研究显示,成骨细胞特异性敲除STAT3的小鼠表现为骨形态异常、骨质疏松[1];敲除或抑制破骨前体细胞内STAT3导致破骨分化下降[2];STAT3也介导了骨细胞对于机械应力加载产生的成骨效应[3]。以上研究表明,STAT3在成骨、破骨分化中均发挥作用,并对机械信号产生反应,由此推断STAT3可能参与调控正畸牙移动骨塑建与骨重建。本研究探究了STAT3在调控正畸牙槽骨塑建速率及骨稳态方面发挥的作用,为安全有效提高正畸牙移动速率提供理论基础和潜在靶点。

1 材料和方法

1.1 主要试剂

8周龄雄性Wistar大鼠(四川大学实验动物中心,SYXK(川)2018-185)。小鼠成骨前体细胞MC3T3-e1(亚克隆14)和小鼠单核巨噬细胞白血病细胞RAW264.7(均购自中国科学院昆明细胞库)。

DMEM培养基(Gibco,美国)、胎牛血清(Corning,美国),stattic(Selleck,美国),抗坏血酸(百灵威,中国),β-甘油磷酸钠(Sigma-aldrich,美国),BCIP/NBT碱性磷酸酯酶显色试剂盒(碧云天,中国),抗酒石酸酸性磷酸酶(tartrate-resistant acid phosphatase,TRAP)染液试剂盒(凯基生物,中国),TRIzol(Invitrogen,美国),TB Green® PrimeScript™ RT reagent Kit with gDNA Eraser(Takara,日本)。

1.2 实验动物分组

8周龄雄性Wistar大鼠40只,体重(250 ± 20)g,随机平均分为2组:对照组(牙移动),实验组(牙移动加局部注射STAT3抑制剂stattic)(图1)。

以镍钛拉簧拉双侧上颌第一磨牙向近中移动建立牙移动模型,力值40 g。实验组于第一磨牙近中腭侧黏骨膜下注射10 μL 50 μM stattic溶液,每隔1日注射1次,相邻两次注射间隔48 h,在建立牙移动的前两天开始局部注射;对照组注射等体积生理盐水。在牙移动的第7天、第14天每组分别随机处死10只大鼠,收集双侧上颌骨。

1.3 Micro-CT扫描及分析

标本经4%多聚甲醛在4 ℃固定48 h后,储存于4 ℃ 0.5%多聚甲醛溶液中等待扫描。扫描精度10 μm。在正中矢状向截面测量第一磨牙与第二磨牙牙冠之间的最小距离为牙移动距离,每个样本重复测3次,取平均值。在第一磨牙根分叉处选

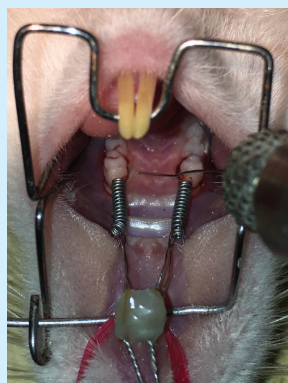


Figure 1 Intra-oral picture of the device for orthodontic tooth movement and location of the local injection in rats
图1 大鼠牙移动装置图及局部注射位点口内照

取400 μm× 400 μm × 500 μm的长方体作为研究对象，分析该区域牙槽骨的骨体积分数(bone volume/tissue volume，BV/TV)、骨小梁数目(trabecular number，Tb.N)、骨小梁厚度(trabecular thickness，Tb.Th)、骨小梁分离度(trabecular separation，Tb.Sp)、骨密度(bone mineral density，BMD)。

1.4 细胞培养

小鼠成骨前体细胞MC3T3-e1(亚克隆14)和小鼠单核巨噬细胞白血病细胞RAW264.7扩增于含10%胎牛血清、1%双抗的DMEM培养基；加入50 μg/mL抗坏血酸、10 mM β-甘油磷酸钠后成为成骨诱导培养基。两种细胞共培养于Transwell®培养板，下层接种MC3T3-e1，密度2.5×10^5个/孔；上层小室接种RAW264.7，密度5×10^5个/孔。共培养体系分为对照组和实验组。对照组使用普通成骨诱导培养基，实验组使用含5 μM stattic的成骨诱导培养基。

1.5 ALP染色

MC3T3-e1经共培养3 d后，以BCIP/NBT碱性磷酸酯酶显色试剂盒按说明书进行染色，显示成骨细胞内ALP活性。

1.6 TRAP染色

RAW264.7经共培养3 d后，以TRAP染液试剂盒按说明书进行染色，显示TRAP阳性细胞。

1.7 qRT-PCR

用TRIzol法提取细胞总RNA，用PrimeScript™ RT reagent Kit with gDNA Eraser合成cDNA，TB Green® Premix Ex Taq™ II进行qRT-PCR检测，内参为GAPDH，所使用核因子κB受体活化因子配体(receptor activator of nuclear factor-κB ligand，RANKL)、骨保护素(osteoprotegerin，OPG)引物序列见表1。

表1 qRT-PCR引物序列
Table 1 Sequences of primers for qRT-PCR

Genes	Primer sequences(5′→3′)
RANKL	F: CAGCATCGCTCTGTTCCTGTA R: CTGCGTTTTCATGGAGTCTCA
OPG	F: GAGGAGTCTGGTAGTGGTTCC R: TGTTCACCCTGGTTGAGTAAGT
GAPDH	F: GACATCAAGAAGGTGGTGAAGC R: GAAGGTGGAAGAGTGGGAGTT

1.8 统计学分析

以SPSS 19.0进行分析，计量资料以$\bar{x} \pm s$表示。经检验，骨小梁形态学各项参数、牙移动距离、基因表达情况符合正态分布，各组方差齐；骨小梁形态学参数采用双因素方差分析及Bonferroni校正进行组间比较；牙移动距离和基因表达分析采用独立样本t检验。$P < 0.05$为差异有统计学意义。

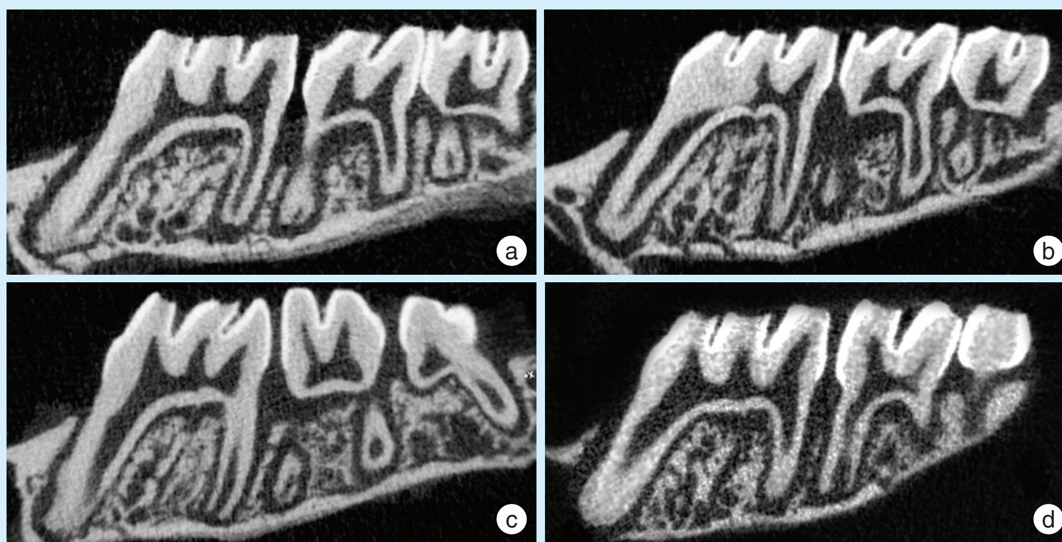
2 结 果

2.1 抑制STAT3激活对正畸牙移动区松质骨微结构的影响

Micro-CT结果显示，对照组、实验组骨密度均随时间增加而降低。牙移动第7天时，对照组和实验组第一磨牙根分叉处牙槽骨BV/TV、Tb.N、Tb.Th、Tb.Sp及BMD无明显差异；第14天时，实验组牙槽骨BV/TV、Tb.N、Tb.Th、BMD较对照组相比明显下降，Tb. Sp明显上升，出现骨质疏松表型(图2、表2、表3)。

2.2 抑制STAT3激活对正畸牙移动速率的影响

第7天时，实验组牙移动量明显低于对照组($P = 0.005$)；在第14天时，两组牙移动量差异无统计学意义($P = 0.307$)(表4)。



a: the trabecular morphology of interradicular alveolar bone of the upper first molars in the control group on day 7; b: the trabecular morphology of interradicular alveolar bone of the upper first molars in the test group on day 7; c: the trabecular morphology of interradicular alveolar bone of the upper first molars in the control group on day 14; d: the trabecular morphology of interradicular alveolar bone of the upper first molars in the test group on day 14

Figure 2 Micro-CT sagittal images of alveolar bone of the upper first molars at the bifurcation on day 7 and day 14 in two groups of rats

图2 7 d、14 d时2组大鼠上颌第一磨牙根分叉处牙槽骨micro-CT矢状向截面图

表2 2组大鼠7 d、14 d上颌第一磨牙根分叉处牙槽骨微结构micro-CT测量值

Table 2 Micro-CT measurements of the alveolar bone microstructure of the upper first molars at the bifurcation on day 7 and day 14 in two groups of rats $\bar{x} \pm s$

Parameters	Days	Control group	Test group	*P*	*t*
BV/TV(%)	7	0.597 ± 0.032	0.575 ± 0.063	0.490	0.72
	14	0.533 ± 0.028	0.455 ± 0.030	0.003	3.81
Tb.N(1/mm)	7	8.290 ± 0.599	7.920 ± 0.443	0.286	1.13
	14	7.970 ± 0.591	7.090 ± 0.491	0.028	2.57
Tb.Th(mm)	7	0.095 ± 0.012	0.095 ± 0.010	0.982	0.02
	14	0.085 ± 0.006	0.069 ± 0.008	0.006	3.44
Tb.Sp(mm)	7	0.090 ± 0.015	0.098 ± 0.013	0.421	0.84
	14	0.092 ± 0.016	0.116 ± 0.012	0.025	2.63
BMD(g/cc)	7	1.100 ± 0.085	1.060 ± 0.080	0.442	0.80
	14	1.030 ± 0.075	0.902 ± 0.067	0.016	2.89

表3 Micro-CT测量值方差分析表

Table 3 ANOVA table of micro-CT analysis

Parameters	Source of variation	*F*	*P*
BV/TV(%)	Interaction	2.70	0.131
	Time	30.20	< 0.001
	Inhibitor	6.06	0.034
Tb.N(1/mm)	Interaction	19.73	0.001
	Time	101.90	< 0.001
	Inhibitor	3.55	0.089
Tb.Th(mm)	Interaction	10.69	0.008
	Time	53.60	< 0.001
	Inhibitor	2.09	0.179
Tb.Sp(mm)	Interaction	23.29	0.001
	Time	39.65	< 0.001
	Inhibitor	3.09	0.110
BMD(g/cc)	Interaction	4.48	0.060
	Time	28.15	< 0.001
	Inhibitor	3.79	0.080

2.3 抑制STAT3激活对MC3T3-e1与RAW264.7共培养体系成骨、破骨向分化的影响

与对照组相比,实验组处理3 d后,共培养体系中MC3T3-e1 ALP染色明显较浅,说明抑制共培养体系中STAT3激活降低了ALP活性,抑制成骨分化;RAW264.7 TRAP阳性细胞数目明显减少,说明抑制共培养体系中STAT3激活抑制破骨向分化(图3)。

qRT-PCR结果表明,stattic抑制MC3T3-e1 RANKL、OPG的mRNA表达,且对OPG的抑制作用更明显,RANKL/OPG比值升高(表5)。

表4　2组牙移动量随时间变化情况

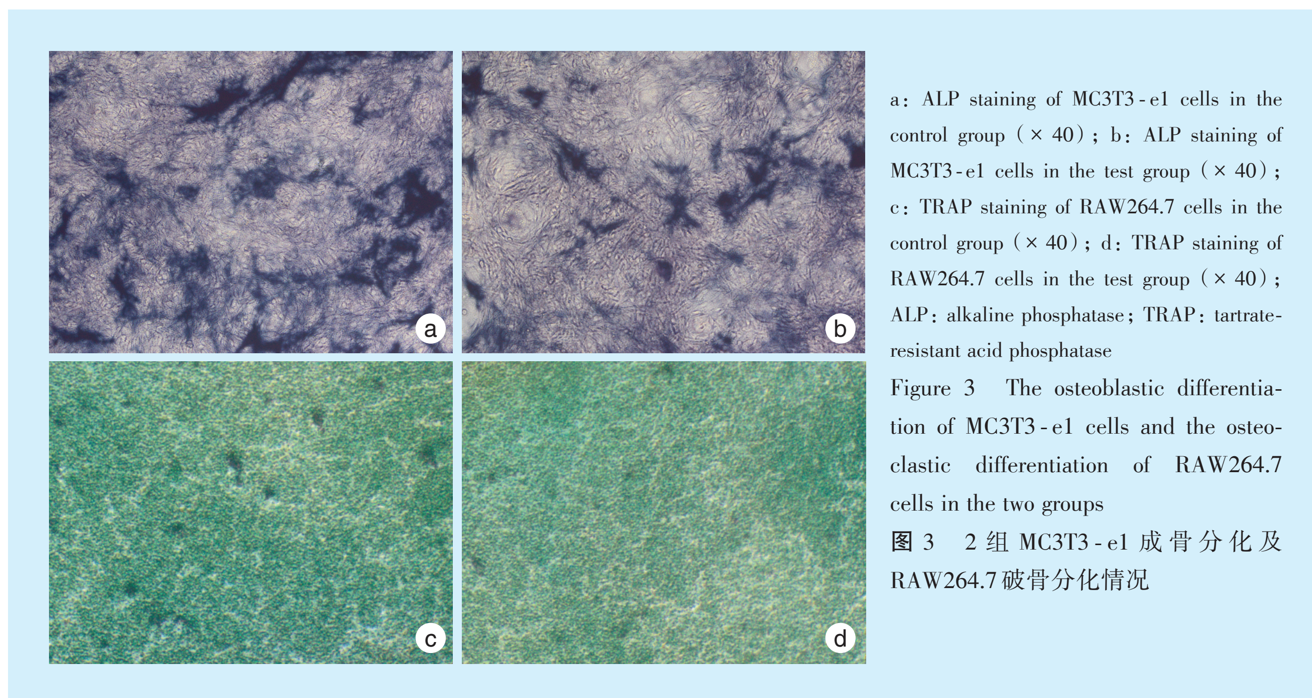
Table 4　Change in the amount of tooth movement with time in the two groups　$\bar{x}\pm s$, mm

Days	Control group	Test group	Mean	t	P
7	0.343 ± 0.041	0.273 ± 0.044	0.308 ± 0.055	3.280	0.005
14	0.406 ± 0.038	0.423 ± 0.029	0.414 ± 0.035	1.056	0.307

3　讨　论

3.1　研究意义

提高牙移动速率一直是正畸学界基础和临床研究的热点。研究表明，应用骨皮质切开术[4]、激光[5]、局部震动法[6]及正颌手术后[7]牙槽骨代谢加快，牙移动速率增加。文献显示，STAT3的激活同时加强成骨活动与破骨活动，但对正畸牙槽骨塑建的影响尚不清楚。本研究初步探索了STAT3在正畸牙槽骨塑建与重建过程中的作用，为提高牙移动速率及改善牙槽骨稳态提供了理论基础。



a：ALP staining of MC3T3-e1 cells in the control group（× 40）；b：ALP staining of MC3T3-e1 cells in the test group（× 40）；c：TRAP staining of RAW264.7 cells in the control group（× 40）；d：TRAP staining of RAW264.7 cells in the test group（× 40）；ALP：alkaline phosphatase；TRAP：tartrate-resistant acid phosphatase

Figure 3　The osteoblastic differentiation of MC3T3-e1 cells and the osteoclastic differentiation of RAW264.7 cells in the two groups

图3　2组MC3T3-e1成骨分化及RAW264.7破骨分化情况

表5　2组MC3T3-e1 RANKL和OPG mRNA表达水平及RANKL/OPG mRNA比值

Table 5　mRNA expression levels of RANKL and OPG as well as the RANKL/OPG ratio in MC3T3-e1 of the 2 groups　$\bar{x}\pm s$

Measurements	Control group	Test group	P	t
RANKL	1.000 ± 0.093	0.677 ± 0.041	0.011	4.510
OPG	1.030 ± 0.065	0.604 ± 0.077	0.004	5.990
RANKL/OPG ratio	0.971 ± 0.042	1.241 ± 0.089	0.038	3.058

Supplementary information can be obtained by scanning the OSID code

3.2　结果分析

炎症因子IL-6已被证实参与正畸牙移动及牙周炎发展进程[8-9]。作为IL-6重要的下游信号转导因子，STAT3具有促进成骨和破骨的双重作用[10]。破骨前体细胞中，抑制STAT3激活直接削弱RANKL诱导下的破骨分化[11-12]。成骨分化依赖于STAT3的激活，上调成骨细胞及间充质干细胞STAT3激活水平增加其成骨能力及增殖活性[13-14]。STAT3同时介导成骨活动与破骨活动的特性在本研究中也得到了证实。STAT3对骨量的宏观影响取决于其对成骨与破骨的相对调控。本研究中，在正畸牙移动模型中发现抑制STAT3激活导致骨量降低。文献表明，在人类个体中，STAT3功能丧失突变导致高免疫球蛋白E综合征（hyper-immunoglobulin E syndrome，HIES），其体征包括骨质疏松及复发性微小骨折，也提示STAT3与骨量呈正相关[15]。然而在骨关节炎等病理性情况下，STAT3被过度激活，破骨活动亢进，此时抑制STAT3激活则削弱破骨活动，引起骨密度的增加[16]，与本研究涉及的生理性牙移动模型有所区别。这提示STAT3在不同的生理、病理性骨代谢过程中发挥不同作用。

本研究的共培养体系中，没有添加外源性RANKL促进破骨前体细胞分化，破骨细胞细胞分化依赖于成骨前体细胞所分泌的RANKL。共培养结果表明，抑制STAT3激活对成骨和破骨分化均有抑制，与原有研究一致[2]。在成骨细胞中，抑制

STAT3提高RANKL/OPG mRNA比值，促进破骨分化，而在共培养体系中的宏观表现为破骨分化受抑制，提示STAT3抑制剂可能作用于破骨细胞本身抑制其破骨分化。

在体内实验中，正常大鼠牙移动第7天时破骨活跃、成骨活动较弱[17]。本实验STAT3抑制剂使牙移动速率下降，结合本研究体外实验结果，推测STAT3抑制剂可能通过抑制破骨活动降低了牙移动速率。正常大鼠在牙移动第14天时，成骨活动达到高峰，而破骨活动有所减缓，牙移动处于缓慢期[17]。Micro-CT结果显示，实验组骨质较为疏松，说明STAT3抑制剂可能抑制了成骨活动，使得实验组与对照组相比，牙移动阻力减小，在7～14 d牙移动速率加快，到第14天时牙移动量和对照组相比没有明显差异。实验组在破骨活动受抑制的情况下，骨量呈减少趋势，说明STAT3对成骨活动调控的作用更强，STAT3的激活状态与骨量呈正相关。

本实验通过STAT3功能抑制实验初步证实了STAT3在正常大鼠正畸牙移动中对牙移动速率和牙槽骨骨量可能发挥正向调控的作用。未来需要开展更多的研究以深入阐明STAT3在不同生理、病理状态下对牙槽骨塑建及骨稳态的调控作用。

参考文献

[1] Sims NA. Cell-specific paracrine actions of IL-6 family cytokines from bone, marrow and muscle that control bone formation and resorption[J]. Int J Biochem Cell Biol, 2016, 79: 14-23.

[2] Yang Y, Chung MR, Zhou S, et al. STAT3 controls osteoclast differentiation and bone homeostasis by regulating NFATc1 transcription[J]. J Biol Chem, 2019, 294(42): 15395-15407.

[3] Corry KA, Zhou H, Brustovetsky T, et al. STAT3 in osteocytes mediates osteogenic response to loading[J]. Bone Rep, 2019, 11: 100218.

[4] Zhou Y, He X, Zhang D. Study of bone remodeling in corticotomy-assisted orthodontic tooth movement in rats[J]. J Cell Biochem, 2019, 120(9): 15952-15962.

[5] Qamruddin I, Alam MK, Mahroof V, et al. Effects of low-level laser irradiation on the rate of orthodontic tooth movement and associated pain with self-ligating brackets[J]. Am J Orthod Dentofacial Orthop, 2017, 152(5): 622-630.

[6] Shipley T, Farouk K, El-Bialy T. Effect of high-frequency vibration on orthodontic tooth movement and bone density[J]. J Orthod Sci, 2019, 8(1): 15.

[7] Kirschneck C, Fanghanel J, Wahlmann U, et al. Interactive effects of periodontitis and orthodontic tooth movement on dental root resorption, tooth movement velocity and alveolar bone loss in a rat model[J]. Anat Anz, 2017, 210: 32-43.

[8] Liu Y, Song F, Wu S, et al. Protein and mRNA expressions of IL-6 and its key signaling factors under orthodontic forces in mice: an *in-vivo* study[J]. Am J Orthod Dentofacial Orthop, 2017, 152(5): 654-662.

[9] Toker H, Görgün EP, Korkmaz EM. Analysis of IL-6, IL-10 and NF-κB gene polymorphisms in aggressive and chronic periodontitis[J]. Cent Eur J Public Health, 2017, 25(2): 157-162.

[10] Li J. JAK-STAT and bone metabolism[J]. JAK-STAT, 2013, 2(3): e23930.

[11] Liu T, Qin AP, Liao B, et al. A novel microRNA regulates osteoclast differentiation *via* targeting protein inhibitor of activated STAT3 (PIAS3)[J]. Bone, 2014, 67: 156-165.

[12] Lim R, Li L, Chew N, et al. The prenylflavonoid icaritin enhances osteoblast proliferation and function by signal transducer and activator of transcription factor 3 (STAT-3) regulation of C-X-C chemokine receptor type 4 (CXCR4) expression[J]. Bone, 2017, 105: 122-133.

[13] Kurozumi A, Nakano K, Yamagata K, et al. IL-6 and sIL-6R induces STAT3-dependent differentiation of human VSMCs into osteoblast-like cells through JMJD2B-mediated histone demethylation of RUNX2[J]. Bone, 2019, 124: 53-61.

[14] Nicolaidou V, Wong MM, Redpath AN, et al. Monocytes induce STAT3 activation in human mesenchymal stem cells to promote osteoblast formation[J]. PLoS One, 2012, 7(7): e39871.

[15] Scheuerman O, Hoffer V, Cohen AH, et al. Reduced bone density in patients with autosomal dominant hyper-IgE syndrome[J]. J Clin Immunol, 2013, 33(5): 903-908.

[16] Mori T, Miyamoto T, Yoshida H, et al. IL-1β and TNFα-initiated IL-6-STAT3 pathway is critical in mediating inflammatory cytokines and RANKL expression in inflammatory arthritis[J]. Int Immunol, 2011, 23(11): 701-712.

[17] Baloul SS. Osteoclastogenesis and osteogenesis during tooth movement[J]. Front Oral Biol, 2016, 18: 75-79.

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