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· 基础研究 ·

蛋白聚糖与小鼠牙周炎牙槽骨吸收的相关性

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【摘要】　目的　探讨小鼠牙周炎牙槽骨中蛋白聚糖含量的改变及其与牙周炎牙槽骨吸收的相关性。**方法**　选取12只8周龄C57BL/6J雄性鼠，6-0丝线结扎右侧上颌第二磨牙建立牙周炎模型，左侧上颌未结扎处作为对照，术后14 d处死小鼠。Micro-CT扫描分析牙槽骨吸收情况；HE染色观察牙槽骨形态变化；TRAP染色观察破骨细胞阳性率的改变；RT-qPCR检测细胞外蛋白聚集蛋白聚糖（aggrecan，ACAN）、双链蛋白聚糖（biglycan，BGN）、饰胶蛋白聚糖（decorin，DCN）和多能蛋白聚糖（versican，VCAN）等蛋白聚糖相关基因表达情况，组织蛋白酶K（cathepsin K，CTSK）、基质金属蛋白酶-9（matrix metalloprotein-9，MMP-9）、核因子κB受体活化因子配体（receptor activator of nuclear factor kappa-B ligand，RANKL）等破骨细胞相关基因表达情况，白细胞介素-1β（interleukin-1β，IL-1β）、白细胞介素-6（interleukin-6，IL-6）、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）等炎症相关基因表达情况；最后对蛋白聚糖与破骨相关基因表达量，蛋白聚糖与炎症相关基因表达量进行Pearson相关性分析。**结果**　牙周炎侧牙槽骨吸收增多。TRAP染色结果显示牙周炎侧牙槽骨破骨细胞数量上升。RT-qPCR结果显示牙周炎侧蛋白聚糖相关基因ACAN、BGN、DCN的表达较对照侧降低，VCAN的表达较对照侧升高。牙周炎侧破骨细胞相关基因CTSK、MMP-9、RANKL及炎症相关基因IL-1β、IL-6、TNF-α的表达较对照侧升高（$P<0.05$）。Pearson相关性分析表明牙周炎中蛋白聚糖与破骨细胞相关基因表达量、炎症相关基因表达量均具有负相关性（$P<0.05$）。**结论**　牙周炎时牙槽骨蛋白聚糖的表达与牙槽骨吸收密切相关。

【关键词】　牙周炎；　牙周组织；　细胞外基质蛋白；　蛋白聚糖；　糖基化；　破骨细胞；　炎症；　牙槽骨吸收
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Correlation between proteoglycan and alveolar bone resorption in a mouse periodontitis model

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【Abstract】　Objective　To analyze changes in proteoglycan and its correlation with alveolar bone resorption in periodontitis. **Methods**　Twelve eight-week-old C57BL/6J male mice were selected, and the periodontitis model was established by ligating the right maxillary second molar with 6-0 silk thread. The nonligated part of the left maxilla was used as the control. The mice were killed 14 days after the operation. Micro-CT was used to assess alveolar bone resorption. HE staining was used to observe the alveolar bone profile, and TRAP staining was conducted to examine the positive rate of osteoclasts. The expression of proteoglycan-related genes, such as aggrecan (ACAN), biglycan (BGN), versican (VCAN), decorin (DCN), osteoclast-related genes, such as cathepsin K (CTSK), matrix metalloprotein-9 (MMP-9), and receptor activator of nuclear factor kappa-B ligand (RANKL), and inflammation-related genes, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), was detected by real-time quantitative PCR. Additionally, the correlation of the expression of proteoglycans with osteoclast-related genes and inflammation-related genes was

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evaluated by Pearson correlation analysis. **Results** The resorption of alveolar bone on the periodontitis side increased. TRAP staining showed that the number of osteoclasts was substantially increased in the maxilla with periodontitis. Real-time quantitative PCR demonstrated that compared with the control side, the expression of proteoglycan-related genes, such as ACAN, BGN, and DCN, was decreased, whereas the expression of the VCAN gene was significantly increased in the periodontitis side. Meanwhile, the expression of osteoclast-related genes, such as CTSK, MMP-9, and RANKL, and inflammation-related genes, such as IL-1β, IL-6, and TNF-α, was markedly increased in the periodontitis side ($P < 0.05$). Pearson correlation analysis indicated a negative correlation between the expression of proteoglycans and the mRNA levels of osteoclast-related genes and inflammation-related genes ($P < 0.05$). **Conclusion** The expression of proteoglycan was closely related to alveolar bone resorption in a periodontitis model.

【Key words】 periodontitis; periodontal tissue; extracellular matrix protein; proteoglycan; glycosylation; osteoclasts; inflammation; alveolar bone resorption

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牙周炎作为口腔常见疾病，以牙齿松动，牙槽骨丧失为主要特征。牙槽骨吸收的主要原因为牙周炎时成骨细胞、活化的T细胞、牙周膜成纤维细胞和牙龈成纤维细胞高表达核因子κB受体活化因子配体（receptor activator of nuclear factor-κB ligand，RANKL），RANKL与破骨细胞前体表面的核因子κB受体活化因子（receptor activator of nuclear factor-kappa B，RANK）相互作用后，激活多个调控破骨细胞发生的转录因子，进而刺激破骨细胞的形成和分化。此外，蛋白酶如组织蛋白酶K（cathepsin K，CTSK），基质金属蛋白酶-9（matrix metalloprotein-9，MMP-9）以及浸润型白细胞产生的炎症介质如白介素-1（interleukin-1，IL-1）和前列腺素E2（prostaglandin E2，PGE2）也可促进破骨细胞生成，加重牙周炎牙槽骨吸收[1]。

近年研究发现在炎症性疾病中，蛋白聚糖也发挥调控作用[2]。蛋白聚糖是一类糖链与肽链以共价键结合的生物大分子，广泛存在于细胞内外及细胞表面[3]。蛋白聚糖中的糖链可分为半乳糖胺聚糖和葡萄糖胺聚糖，前者包括硫酸软骨素、硫酸皮肤素，后者包括肝素、硫酸乙酰肝素、硫酸角质素以及透明质酸。以核心蛋白为基础的蛋白聚糖包括聚集蛋白聚糖、多能蛋白聚糖、饰胶蛋白聚糖、双链蛋白聚糖、纤调蛋白聚糖和凝胶蛋白聚糖。此外，近来发现牙本质细胞外基质中含有大量新型蛋白聚糖，例如牙本质基质蛋白1（dentin matrix protein 1，DMP1）的糖基化形式DMP1-PG[4]。

牙周组织中含有多种蛋白聚糖，如神经胶质抗原-2、血栓调节蛋白、小亮氨酸蛋白聚糖等，参与细胞增殖、迁移、黏附等多种生物学过程，影响牙周组织的发育和创伤应答[5]。研究表明，在炎症期间，蛋白聚糖对长骨及关节软骨有调控作用，如DMP1的糖基化形式可以促进长骨缺损后的骨重建以及髁突骨关节炎中软骨修复。多配体蛋白聚糖4（syndecan4, SDC4）可以促进骨折后长骨愈合[6-8]。然而，蛋白聚糖在牙周炎牙槽骨吸收中作用尚未报道，基于此笔者选取与破骨形成以及炎症发展密切相关的细胞外蛋白聚集蛋白聚糖（aggrecan，ACAN）、双链蛋白聚糖（biglycan，BGN）、饰胶蛋白聚糖（decorin，DCN）和多能蛋白聚糖（versican，VCAN），通过建立小鼠牙周炎模型，观察小鼠牙槽骨内蛋白聚糖的变化，以及蛋白聚糖与破骨、炎症之间的相关性，探讨蛋白聚糖在牙周炎牙槽骨吸收中的作用。

1　材料和方法

1.1　实验动物

本实验使用SPF级C57BL/6J小鼠（实验动物合格证号：[2021]-DW-034，上海南方模式动物研究中心，中国），所有小鼠饲养于同济大学附属口腔医院SPF级动物房（12 h光照/12 h无光饲养环境，室内温度保持25 ℃，相对湿度55%），本实验经同济大学伦理委员会批准（批准号：TJLAC-017-027）。

1.2　主要试剂和仪器

6-0无菌缝线（上海元象生物公司，中国）；HE

染色试剂盒(上海生工生物公司,中国);TRAP染色试剂盒(Sigma公司,美国);逆转录试剂盒(Takara公司,日本);TRIZOL试剂(Thermo Fish,美国);QPCR SYBR Green Master Mix(上海翊圣生物公司,中国);PCR引物(上海生工生物公司,中国);Micro-CT系统(μCT50,Scanco Medical公司,瑞士);直立显微镜(尼康公司,日本)。

1.3　实验方法

选取12只8周龄雄性小鼠,采用丝线结扎法构建小鼠牙周炎模型[9]:1%戊巴比妥钠腹腔注射麻醉,将小鼠仰卧位固定于手术台,暴露口腔,选用6-0无菌缝线建模,绕右侧第二磨牙颈部一圈,在颊侧打三重结,左侧不建模作为对照。术后密切观察小鼠生存率以及丝线是否滑脱,建模后14 d收样。

1.3.1　Micro-CT分析　Micro-CT扫描小鼠上颌骨。Mimics 13.0软件分析图像,选取上颌骨第二磨牙颊侧牙槽骨面3D重建。Image软件计算上颌第二磨牙釉牙骨质界到牙槽嵴顶的距离。

1.3.2　组织学染色　14 d收样后用4%多聚甲醛灌流固定,4%多聚甲醛4 ℃浸泡上颌骨24 ~ 48 h后取出,放入10%EDTA室温脱钙2 ~ 4周,脱钙液每1 ~ 2 d更换一次。脱钙完成之后,脱水浸蜡,包埋,石蜡切片(厚度:4 μm),进行HE和TRAP染色。直立显微镜下观察并拍照。

1.3.3　RT-qPCR　提取小鼠上颌第一磨牙与第二磨牙牙槽骨,放入Trizol震碎,使用逆转录试剂盒将RNA逆转录成cDNA,RT-qPCR检查蛋白聚糖合成相关基因(ACAN、BGN、VCAN、DCN)以及破骨相关基因(CTSK、MMP-9、RANKL)与炎症相关基因白介素-1β(interleukin-1β,IL-1β),白介素-6(interleukin-6,IL-6),肿瘤坏死因子-α(tumor necrosis factor α,TNF-α)的变化。以GAPDH作为内参,引物序列见表1。10 μL反应体系:2倍Master mix 5 μL,正、反向引物各0.5 μL,cDNA 0.5 μL,PCR级水3.5 μL。扩增程序:50 ℃ 120 s,95 ℃ 600 s;95 ℃ 15 s,60 ℃ 20 s,72 ℃ 30 s,60个循环;95 ℃ 10 s;65 ℃ 60 s;97 ℃ 1 s。$2^{-\Delta\Delta Ct}$法计算目的基因相对表达量。

1.4　统计学分析

使用SPSS 20.0与GraphPad Prism 8.0软件进行分析,两组间比较采用独立样本t检验,$P<0.05$认为差异具有统计学意义。通过Pearson相关系数分析检验相关性,$P<0.05$认为具有相关性。

表1　RT-qPCR引物序列

Table 1　Sequences of primers for RT-qPCR

Gene	5′-3′	3′-5′
GAPDH	TGTGTCCGTCGTGGATCTGA	CCTGCTTCACCACCTTCTTGA
ACAN	CGCCACTTTCATGACCGAGA	TCATTCAGACCGATCCACTGGTAG
BGN	CCTGAGACCCTGAACGAAC	GTGACCTAAGCCCAACCTGT
VCAN	CAATTACCACCTCACCTACACT	ATAGAATTGTCCTTTGCCGGATGAGG
DCN	TGAGCTTCAACAGCATCACC	AAGTCATTTTGCCCAACTGC
CTSK	GAAGAAGACTCACCAGAAGCAG	TCCAGGTTATGGGCAGAGATT
MMP-9	CTGGACAGCCAGACACTAAAG	CTGGACAGCCAGACACTAAAG
RANKL	GGAAGCGTACCTACAGACTATC	AAAGTGGAATTCAGAATTGCCC
IL-1β	TGCCACCTTTTGACAGTGATG	AAGGTCCACGGGAAAGACAC
IL-6	GGCGGATCGGATGTTGTGAT	GGACCCCAGACAATCGGTTG
TNF-α	CCCTCACACTCAGATCATCTTCT	GCTACGACGTGGGCTACAG

ACAN: aggrecan; BGN: biglycan; VCAN: versican; DCN: decorin; CTSK: cathepsin K; MMP-9: matrix metalloprotein-9; RANKL: receptor activator of nuclear factor-κB ligand; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α

2　结　果

2.1　牙周炎模型构建

相较对照侧,牙周炎侧颊侧牙槽骨吸收增多,吸收形成筛网状,牙根暴露,牙槽嵴高度降低,釉牙骨质界到牙槽嵴顶的距离增大($t=20.09$,$P<0.001$),骨体积分数下降($t=4.295$,$P=0.013$),骨小梁厚度下降($t=3.839$,$P=0.019$),差异具有统计学意义,见图1。

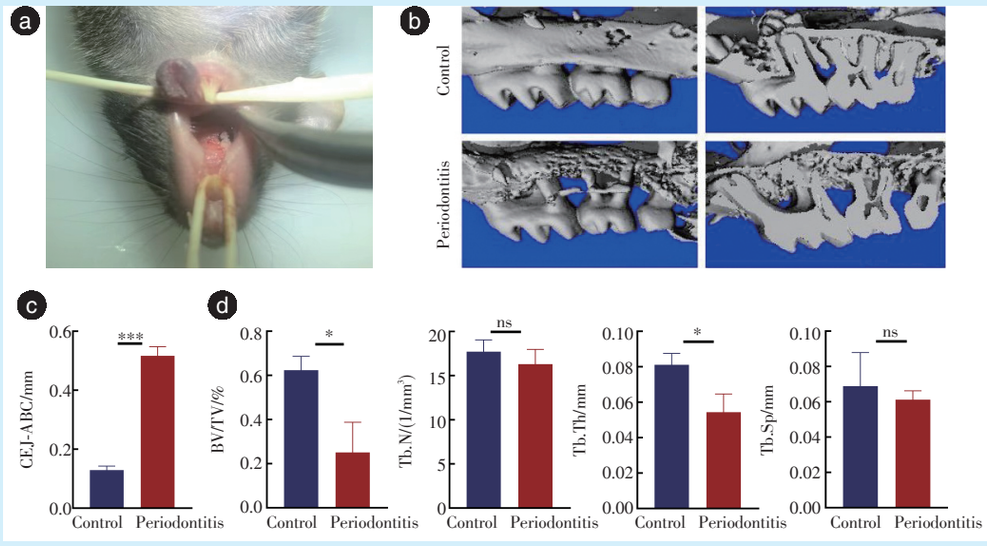
2.2　牙周炎牙槽骨吸收活跃,破骨与炎症相关基因上调

HE染色结果显示,相较对照侧,牙周炎侧牙龈乳头形态破坏、退缩,牙周韧带排列紊乱,纤维组织腔隙增多。第一磨牙远中根与第二磨牙近中根之间炎症细胞浸润增多,牙槽骨高度下降,吸收增多(图2a)。通过TRAP染色,发现牙周炎侧牙槽骨中TRAP阳性的破骨细胞数目明显增加(图2b)。

牙周炎侧CTSK($t=4.507$,$P=0.011$)、MMP-9($t=6.652$,$P<0.001$)、RANKL($t=6.730$,$P<0.001$)等破骨细胞相关基因表达明显上调,差异具有统计学意义(图2c)。牙周炎侧炎症相关基因IL-1β($t=7.874$,$P<0.001$)、IL-6($t=5.996$,$P=0.04$)、TNF-α($t=4.642$,$P=0.002$)表达也明显上升,差异具有统计学意义(图2d),说明牙周炎模型构建成功。

2.3　牙周炎牙槽骨组织中的蛋白聚糖含量改变

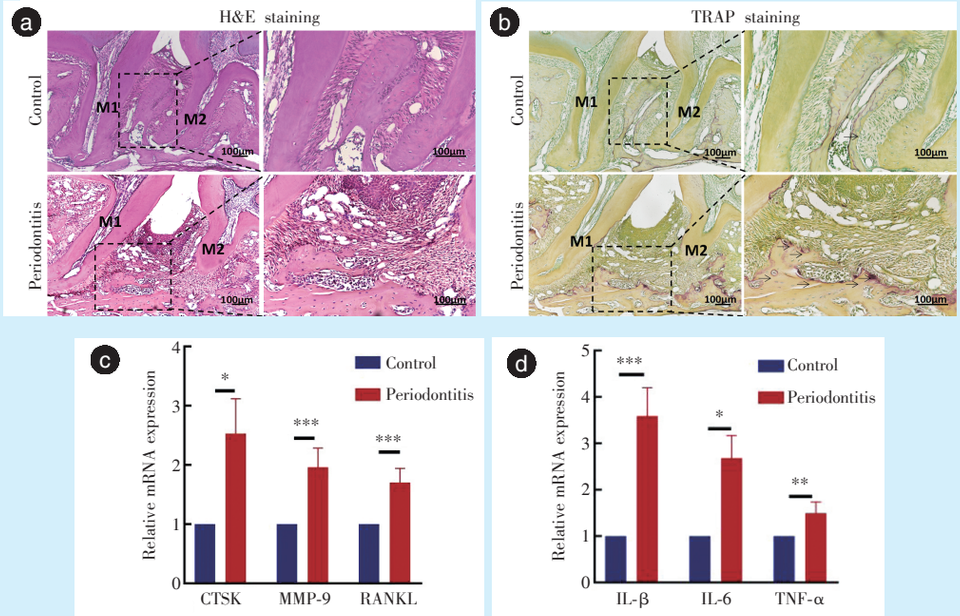
通过提取上颌骨RNA检测多种与蛋白聚糖合



a: 8-week-old mice were selected, the periodontitis model was established by silk thread ligation and 6-0 silk thread ligation at the neck of the right maxillary second molar for 14 days; b: three-dimensional reconstruction of alveolar bone by micro-CT; c: the CEJ-ABC distance of control and experimental group; d: the maxillary alveolar bone parameters of control and experimental groups; CEJ-ABC: distance between enamel-cemental junction and alveolar bone crest (t = 20.09, P < 0.001); BV/TV: bone volume/total volume(t = 4.295, P = 0.013); Tb.N: trabecular number (t = 1.153, P = 0.313); Tb.Th: trabecular thickness(t = 3.839, P = 0.019); Tb.Sp: trabecular space(t = 0.8587, P = 0.439); n = 5; ns P > 0.05, *P < 0.05, ***P < 0.001

Figure 1　Construction of mouse periodontitis model

图1　小鼠牙周炎建模

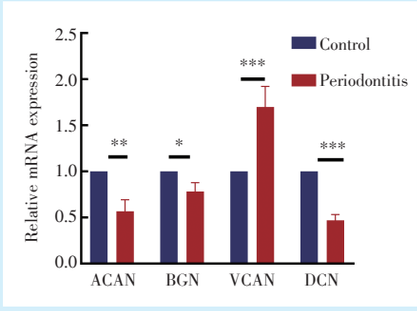


a: H&E staining; b: TRAP staining; c: mRNA expressions of CTSK(t = 4.507, P = 0.011), MMP-9(t = 6.652, P < 0.001) and RANKL (t = 6.730, P < 0.001); d: mRNA expressions of IL-1β (t = 7.874, P < 0.001), IL-6(t = 5.996, P = 0.04) and TNF-α(t = 4.642, P = 0.002); M1: first molar; M2: second molar; *P < 0.05, **P < 0.01, ***P < 0.001; CTSK: cathepsin K; MMP-9: matrix metalloprotein-9; RANKL: receptor activator of nuclear factor-κB ligand; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α

Figure 2　Histological staining of alveolar bone and expression of genes related to osteoclast and inflammation in periodontitis

图2　牙周炎牙槽骨组织学染色及破骨与炎症相关基因表达情况

成相关基因，发现相较对照侧，牙周炎侧ACAN（t = 5.984，P < 0.001）、BGN（t = 5.984，P < 0.001）、DCN（t = 14.73，P < 0.001）表达下调，而VCAN（t = 6.233，P < 0.001）的表达上调，差异具有统计学意义，见图3。



The mRNA expressions of ACAN(t = 5.984, P < 0.001), BGN(t = 5.984, P < 0.001), DCN(t = 14.73, P < 0.001) decreased and VCAN(t = 6.233, P < 0.001) elevated. ***P < 0.001; ACAN: aggrecan; BGN: biglycan; VCAN: versican; DCN: decorin

Figure 3　Expression of proteoglycan related genes in alveolar bone of periodontitis

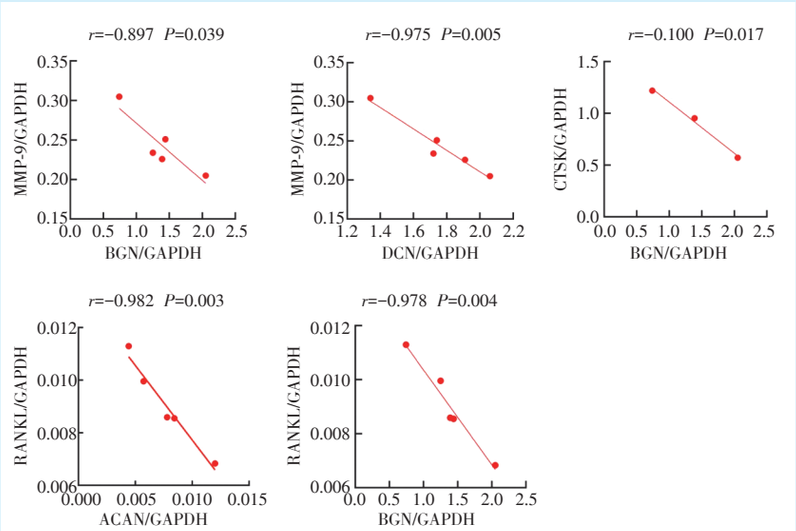
图3　牙周炎牙槽骨组织中的蛋白聚糖相关基因表达情况

2.4　牙周炎牙槽骨组织中的蛋白聚糖与破骨相关基因的表达具有负相关性

通过对牙周炎牙槽骨组织中的蛋白聚糖合成相关基因ACAN、BGN、VCAN、DCN及破骨相关基因CTSK、MMP-9、RANKL的表达水平分别进行相关性分析，结果发现ACAN与RANKL（r = −0.982，P = 0.003）的表达具有负相关性，与CTSK（P = 0.179）、MMP-9（P = 0.677）的表达无相关性。BGN与CTSK（r = −0.100，P = 0.017）、MMP-9（r = −0.897，P = 0.039）、RANKL（P = 0.004）的表达均具有负相关性。VCAN与CTSK（P = 0.173）、MMP-9（P = 0.164）、RANKL（P = 0.432）的表达均无相关性。DCN与MMP-9（r = −0.975，P = 0.005）的表达具有负相关性，与CTSK（P = 0.085）、RANKL（P = 0.106）的表达无相关性，见图4。

2.5　牙周炎牙槽骨组织中的蛋白聚糖与炎症相关基因的表达具有负相关性

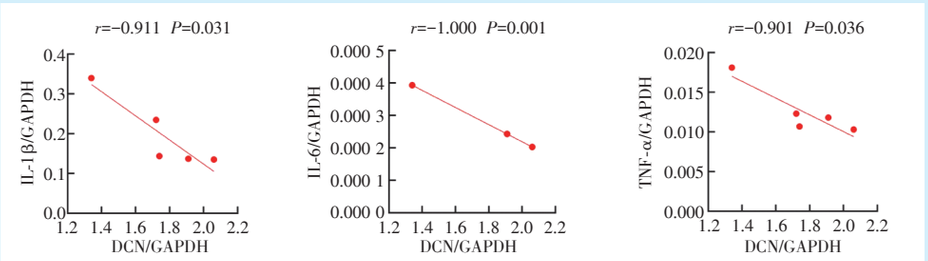
通过对牙周炎牙槽骨组织中的蛋白聚糖合成相关基因ACAN、BGN、VCAN、DCN及炎症相关基因IL-1β、IL-6、TNF-α的表达水平分别进行相关性分析，结果发现ACAN与IL-1β（P = 0.094）、IL-6（P = 0.227）、TNF-α（P = 0.137）、BGN与IL-1β（P = 0.129）、IL-6（P = 0.209）、TNF-α（P = 0.540）、VCAN与IL-1β（P = 0.056）、IL-6（P = 0.162）、TNF-α（P = 0.069）的表达均无相关性。而DCN与IL-1β（r = −0.911，P = 0.031）、IL-6（r = −0.1000，P = 0.001）、TNF-α（r = −0.901，P = 0.036）的表达具有负相关性，见图5。



Pearson correlation analysis was uesd, n= 3-5. MMP-9: matrix metalloprotein-9; BGN: biglycan; DCN: decorin; CTSK: cathepsin K; ACAN: aggrecan; RANKL: receptor activator of nuclear factor-κB ligand

Figure 4　Correlation between alveolar bone proteoglycan and osteoclast related genes in periodontitis mice

图4　牙周炎小鼠牙槽骨蛋白聚糖与破骨相关基因相关性



Pearson correlation analysis was uesd, n=3-5. DCN: decorin; IL-1β: interleukin-1β; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α

Figure 5　Correlation between alveolar bone proteoglycan and inflammation related genes in periodontitis mice

图5　牙周炎小鼠牙槽骨蛋白聚糖与炎症相关基因相关性

3　讨　论

牙周炎是一种不可逆的非特异性炎性疾病，起因为牙菌斑入侵牙周组织，其代谢产物刺激机体免疫应答并引起牙周组织破坏[10]。通过丝线结扎法在7 d后可引发急性牙槽骨丢失，是研究牙周炎的重要模型[11]。在牙周炎中，牙周组织的破坏与大分子蛋白例如细胞外基质蛋白、蛋白聚糖等的表达变化密切相关[12]。蛋白聚糖作为可以介导炎症过程的大分子蛋白，参与炎症介质的浓度梯度形成、白细胞募集和细胞外基质重塑，进而调节牙周炎的病理进程[13]。

其中，细胞外基质蛋白聚糖在骨代谢或炎症发展中至关重要。研究表明，ACAN可以激活关节伤害感受器中的Toll样受体-2（Toll-like receptors-2，TLR-2），从而调控骨关节炎发展[14]。BGN与纤调蛋白聚糖由成骨细胞生成并分泌，以剂量依赖性的方式直接结合TNF-α，抑制其激活RANK，从而抑制破骨细胞形成[15]。VCAN间接通过透明质酸或者直接通过CD44，P-选择素糖蛋白配体-1（P-selectinglycoproteinligand-1，PSGL-1）以及TLR受体与炎症因子相互作用，激活炎症因子IL-6、TNF-α和NF-κB[16]。DCN通过调节干扰素影响淋巴细胞进入炎症组织，从而调控免疫过程中的迟发性超敏反应，并且DCN的过表达会抑制小鼠血管的炎症性病变[17-18]。本实验发现在小鼠牙周炎牙槽骨中ACAN、BGN、DCN表达下调，而VCAN的表达上调，提示上述4种蛋白聚糖与牙周炎的发展可能相关。

虽然前期研究发现蛋白聚糖可调控炎症时牙周组织的代谢，但其在牙周炎牙槽骨吸收中的作用尚不明确。活化的T细胞表达的MMP-9、RANKL以及破骨细胞表达的CTSK促进骨吸收。笔者发现牙周炎中ACAN与RANKL的表达具有负相关性，BGN与CTSK、MMP-9、RANKL的表达具有负相关性，DCN与MMP-9的表达具有负相关性，提示牙周炎中蛋白聚糖ACAN、BGN与DCN与牙周炎牙槽骨吸收可能相关，以及BGN对CTSK、MMP-9、RANKL可能潜在的负调控作用。

IL-1和IL-6促进多型核白细胞和单核细胞/巨噬细胞黏附内皮细胞，刺激前列腺素E2的产生和溶酶体酶的释放，进而促进牙周组织破坏[19]。TNF-α通过上调可以降解基底膜的金属蛋白酶，加速牙周炎进展或者通过激活RANK，参与骨代谢和破骨细胞分化[20]。此外，研究表明炎症因子白介素会下调DCN在成纤维细胞中的表达[21]。本实验结果显示，DCN与IL-1β、IL-6、TNF-α的表达具有负相关性，提示牙周炎中DCN的表达与牙槽骨吸收及牙周组织破坏有相关性，以及IL-1β、IL-6、TNF-α对DCN可能潜在的负调控作用。

综上，本实验结果表明蛋白聚糖在小鼠牙周炎牙槽骨内的表达量改变，并且与破骨相关因子、炎症相关因子的表达量具有负相关性。为从蛋白聚糖的角度了解牙周炎的致病机制提供实验基础，以及对控制牙周炎牙槽骨吸收的临床问题给予新思路。然而本实验对蛋白聚糖ACAN，DCN的下降与牙周炎牙槽骨吸收的作用机制尚无具体论证，以及蛋白聚糖ACAN、BGN、ACAN和DCN在牙周炎侧牙槽骨吸收，牙周组织破坏中的作用机制和关键信号通路还需进一步探究。

【Author contributions】 Wang SY performed the experiment and wrote the article. Zhang F peformed the experiment and revised the article. Wang XK and Sun Y designed the study and reviewed the article. All authors read and approved the final manuscript as submitted.

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