Original article

Critical roles of periostin in the process of orthodontic tooth movement

Afsaneh Rangiani^{*,**,*†}, Yan Jing^{*,†}, Yinshi Ren^{*}, Sumit Yadav^{**},
Reginald Taylor^{***} and Jian Q. Feng^{*}

^{*}Department of Biomedical Sciences, Texas A&M Baylor College of Dentistry, Dallas, TX, USA, ^{**}Division of Orthodontics, University of Connecticut Health Center, Farmington, CT, USA, and ^{***}Department of Orthodontics, Texas A&M Baylor College of Dentistry, Dallas, TX, USA

Correspondence to: Jian Q. Feng, Department of Biomedical Sciences, Texas A&M University Baylor College of Dentistry, Dallas, TX 75246, USA. E-mail: jfeng@bcd.tamhsc.edu

[†]These authors contributed equally to this paper.

Summary

Aim: The process of orthodontic tooth movement (OTM) involves multiple mechanisms of action including bone and extracellular matrix remodelling, although the role of periodontal ligament (PDL) in this process is largely unknown. Periostin, which is highly expressed in the PDL, is known to be responsible for mechanical stimulation in maintaining the integrity of periodontal tissues. We hypothesize that this protein plays an important role during OTM.

Material and methods: By using spring in 4-week-old wild-type (WT) and periostin null mice, the rate of tooth movement and mineralization were evaluated. For the evaluation, double labelling, expression of sclerostin (SOST), number of TRAP-positive cells, and quality of collagen fibrils by Sirius red were analysed and compared between these two groups.

Results: Our findings showed that the distance of the tooth movement and mineral deposition rates were significantly reduced in periostin null mice ($P < 0.05$), with a lack of expression changes in SOST as observed in the WT group. The arrangement, digestion, and integrity of collagen fibrils were impaired in periostin null mice. The number of osteoclasts reflected by expressions of TRAP (tartrate-resistant acid phosphatase) in the null mice was also significantly lower than the WT control ($P < 0.05$).

Conclusion: Periostin plays a stimulatory role in both SOST and TRAP responses to OTM in the compression site, although it is not clear if this role is direct or indirect during orthodontic loading.

Introduction

The process of orthodontic tooth movement (OTM) is mainly characterized by remodelling changes in dental and paradental tissues, which includes dental pulp, periodontal ligament (PDL), alveolar bone, and gingiva. Exposure to varying degrees of magnitude, frequency, and duration of mechanical loading results in extensive macroscopic and microscopic changes in these tissues. As a result of OTM, an abrupt creation of compression and tension regions is created within the PDL (1). The rate of OTM is dependent on the physical characteristics of the applied force and the size and biological response of the PDL (2).

The biological chain of events in OTM can be described briefly as an alteration of the PDL's vascularity and blood flow, which results in local synthesis and release of various key molecules, such as mechanoreceptors, cytokines, growth factors, colony-stimulating factors, and arachidonic acid metabolites. These molecules can evoke many cellular responses by various cell types in and around teeth, which finally results in the remodelling of teeth and PDL in a proper micro-environment for tissue deposition or resorption (3, 4).

One of the factors reported to be increased in the PDL during initial stages of OTM is periostin (5), a matricellular protein which is highly expressed in PDL and periosteum. Periostin are collagen

rich tissues that are under constant mechanical stress (6). Although its expression during development prevails over the expression in adults organisms (7), a recent study showed an increase expression of periostin during vascular injuries and bone fractures (8). Our previous works also revealed a critical role of periostin in maintenance of PDL integrity in response to an occlusal loading (9).

Wnt- β -catenin signalling plays an essential role in a variety of stem cell commitment pathways (10). The removal of Wnt- β -catenin signal in the periodontium leads to severe defects in the PDL and alveolar bone formation (11). In contrast, enhancing Wnt- β -catenin signal activity by removing its antagonist, sclerostin (the product of the *Sost* gene), results in an increase in alveolar bone volume and reduced PDL width (12). Importantly, our recent data demonstrate that deleting *Sost* or blocking sclerostin function using the monoclonal antibody in periostin knock-out (KO) mice essentially restores defects in periostin KO bone and PDL, suggesting a close link between periostin and SOST (13).

Regarding the importance of loading and mechanical response along with the high rates of tissue remodelling during the OTM, we attempted to determine whether periostin plays a critical role in the process of tooth movement. Our study demonstrated that periostin is involved in multiple chain reactions in tooth movement and is essential for the bone and PDL remodelling during orthodontic loading.

Materials and methods

Ethical approval

All mice were maintained under guidelines established by Baylor College of Dentistry Institution of Animal Care and Use Committee (IACUC). IACUC has specifically given ethical approval for all the procedures in this study.

Animals

Periostin KO mice that were generated and described previously (9) were weaned at 3 weeks of age and fed tap water and pellets. Mice were maintained under specific pathogen free conditions with a 12 hour light/12 hour dark cycle. Animals with more than 20 per cent weight loss during the experiment were excluded from the study. After placing the springs, mice were fed with soft diet. Genotyping was determined by polymerase chain reaction analysis of genomic DNA with primers p01: 5'-AGTGTGCAGATGTTTGCTTG-3' and p02: 5'-ACGAAATACAGTTTGGTAATCC-3' to detect the wild-type (WT) allele [~300 base pairs (bp)]; and primers p01: 5'-AGTGTGCAGATGTTTGCTTG-3' and primers p03: 5'-CAGCGCATCGCCTTCTATCG-3' to detect the targeted allele (~700 bp). The total number of animals used for this study was 16 (8 WT and 8 periostin KO mice). In each group, three animals were used for double labelling and five were used for histology and radiographic measurements.

Orthodontic tooth movement procedure

The 4-week-old right maxillary first molars were used for OTM. A custom made closed-coil spring was used in this study. The coil spring had 0.003 inch of thickness and made of super-elastic nickel-titanium wires with a lumen of 0.019 inch (produced by G&H Wire, Greenwood, Indiana, USA) (14). To obtain a 0.03 N force with 2 mm of activation, the springs were cut to 3 mm of length and then tied with resin composite to the maxillary left molar and incisor. Because of food intake limitation due to this procedure, all animals in this study lost body weight, although no one lost more than 20 per cent of body weight.

For better understanding the relationship of the initiation of tooth movement, schematic diagrams for initiation of tooth movement,

calcein and alizarin red injection and tissue harvest times (1 day, 3 days, and 8 days after the initiating tooth movement separately) were created and described in [Supplementary Figure 1](#). Both the left (experimental site) and right (control) maxillaries were collected, fixed in 4 per cent paraformaldehyde in phosphate buffered saline (pH 7.4) for 48 hours.

Radiography

Radiographs were used to measure the amount of movement of the first molar. After the fixation, maxillaries were dissected and radiographs were taken using Faxitron radiographic inspection unit (Model 8050; Field Emission Corporation, Inc. Hillsboro, OR), with digital capture image capability. Digitized images were analysed using the analysis software to measure and evaluate the amount of movement in each sample.

Fluorochrome labelling of the mineralization front

Compound fluorescence labelling was performed to visualize the bone mineralization rate in WT and periostin null movement mice as described previously (15). Calcein green was first intraperitoneally injected 24 hours right after the start of OTM and followed by an injection of alizarin red at Day 6. Mice were sacrificed 2 days after the last dye injection (total 8 days of tooth movement) and both sides of maxillaries were collected and fixed in 70 per cent ethanol for 48 hours. For non-decalcified groups, the samples were dehydrated through a graded series of ethanol (70 per cent to 100 per cent) and embedded in methyl methacrylate. Then 15 mm sections were cut using a Leitz 1600 saw microtome (Ernst Leitz Wetzlar GmbH, Wetzlar, Germany). The unstained sections were viewed under epifluorescent illumination using a Nikon (Melville, New York, USA) E800 microscope. To compare the mineralization rate between the WT and KO groups, the distance between the green and red lines were measured in three different random points in the upper one-third of distal portion of mesial root and averaged for statistical comparisons.

Histology, immunohistochemistry, and TRAP staining

In decalcification groups, the samples were fixed in 4 per cent paraformaldehyde for 2 days followed by decalcification in 15 per cent EDTA solution for 16 hours. The dehydrated samples were then embedded in paraffin. Sections were cut 4.5 μ m thick and used for immunohistochemistry for SOST polyclonal antibody (1:400, R&D, Minneapolis, Minnesota, USA), periostin polyclonal antibody (1:1000, Innovative Research, Sarasota, Florida, USA), and tartrate-resistant acid phosphatase (TRAP) staining as previously described (16, 17). TRAP-positive multinucleated cells (more than two nuclei) in the bone surface surrounding PDL of the first molar were identified as osteoclasts and were quantified on the bone adjacent to pressure areas (mesial surface of the upper one-third of the distobuccal and mesiobuccal roots of first molar). Total numbers of the cells were counted and calculated by the area to get the average cells per 100 μ m² for comparisons.

For Sirius red, staining was described previously (13). Briefly, samples were stained with 1 per cent pico-Sirius red for 1 hour, washed with acidified water (0.5 per cent acetic acid water) and dehydrated with serial ethanol washes: 70 per cent, 90 per cent, and 100 per cent (5 minutes each). Images were taken with a polarized microscope (Nikon Diaphot 200, Melville, New York, USA).

Statistical analysis

The differences evaluated among groups by Student's *t*-test and *P* < 0.05 were considered as statistical significance. The values are reported in mean $\pm$ SE. For statistical analysis, we used SPSS software.

Results

A sharp reduction in bone remodelling in responses to tooth movement in periostin KO mice

To address the potential impact of deletion of periostin on tooth movement response, we used a coil spring to create loading force, which led to a large distance between the first and second molars as shown by radiographs (Figure 1A, upper panel). However, the same force generated much smaller change in tooth movement in the periostin KO (Figure 1A, lower panel). The quantitative data based on the X-ray images from five animals from each groups revealed a significant low tooth movement distance in the KO group ($39.4 \pm 2.7 \mu\text{m}$) in comparison with the age-matched WT group ($64.45 \pm 4.4 \mu\text{m}$) (Figure 1B; $P = 0.05$). Similarly, the double labelling data showed a sharp reduction in bone mineralization rates in the KO animals (26.6 ± 2.2) compared to WT (62.9 ± 1.1 ; Figure 1C and 1D; $P \leq 0.05$). These findings suggest that periostin plays a positive role in the process of tooth movement (i.e. enhancement of tooth movement) and that a loss of periostin leads to a great reduction in tooth movement responses, including both the movement distance and the bone formation rate.

A loss of a biphasic expression pattern of SOST in response to orthodontic loading in periostin KO animals

To address the relationship of SOST and periostin in tooth movement-caused bone remodelling, we first showed a bilateral reaction in the WT tooth movement model: an increase in SOST expression at the compression side (i.e. the bone reabsorption side) and a reduction in expression in the tension side (where the new bone is formed).

Figure 1. The diminished responses to tooth movement in periostin knockout (KO) mice. (A) Quantitative differences of tooth movement distances in wild-type (WT) and KO groups based on measurements of the X-ray images ($n = 5$ in each group, $P = 0.05$); (B) Double labelling of the 5-week-old mice in responses to a 8 days' coil spring force with the yellow-double arrows pointed to the mineralization rate in both the WT (left panel) and KO (right panel) mice; and (C) The quantitative difference of mineralization was shown by the following two bars ($n = 3$ in each group, $P < 0.05$).

Next, we demonstrated that this bilateral reaction pattern in SOST disappears in the periostin KO group (Figure 2), indicating a requirement of periostin for SOST response to tooth movement.

Delayed osteoclastic reaction to tooth movement in periostin KO mice

To test the impact of loss of periostin on the osteoclast reaction to tooth movement, we initially presented an immediate increase in the total number of osteoclasts in the alveolar bone surrounding the PDL of the control mice at all three stages (Figure 3A, left panels). In contrast, the osteoclast reaction is delayed with a much weaker response in the KO group (Figure 3A, right panel). The quantitative data showed a significantly lower osteoclast number in the KO group (15.3 ± 8) than that in the WT group (29.5 ± 5.2 ; $P < 0.05$ in Figure 3B). Taken together, the data support the notion that periostin is essential for osteoclast response to tooth movement.

A close linkage between expressions of periostin and SOST in PDL and alveolar bone

Previous studies clearly showed wide penetrations of Sharpey's fibres from PDL into alveolar bone (18), although it is largely unknown this linkage between PDL and alveolar bone at the molecular level. Here, we first stained a 10-month-old dog mandible (which was generously

Figure 2. Absence of the preferential expression of SOST in response to orthodontic loading in periostin knockout (KO) animals. (A) The representative immunohistochemical staining of the first molars in 5-week-old mice with 8 days of tooth movement shows a biphasic change in SOST expressions: an increase in the compression site compared to the tension site (the bold curl red arrow indicating an increase in SOST expressions). (B) There is a lack of the above change in the periostin KO animals. b, bone; PDL, periodontal ligament.

Figure 3. A low osteoclastic activity in the bone surface adjacent to the periostin knockout (KO) compression side. (A) The representative images of mesial side of distal root displayed a gradual increase in TRAP signals in response to tooth movement in the wild-type (WT) compression side (left panels), whereas an increase in osteoclast numbers occurred only at Day 8 after the initiation of tooth movement in the periostin KO group. (B) The quantitative data showed a significant low change in osteoclast number in response to tooth movement in the periostin KO group ($P < 0.05$, $n = 3$ in each group).

provided by Dr Peter Buschang Taxus A&M University Baylor College of Dentistry) using Azan stain method. The image revealed numerous Sharpey's fibres originated from PDL and penetrated into

Figure 4. A close link between periodontal ligament (PDL) and alveolar bone through Sharpey's fibres. (A) A representative Azn stain image revealed Sharpey's fibres in blue in the 10-month-old dog alveolar bone (b; the sample was generously provided Dr Peter Buschang, TX A&M Baylor College of Dentistry); and (B) Immunohistochemistry images presented a high level of periostin in the mouse PDL and Sharpey's fibre but not in the bone matrices (left panel), and a high level of SOST in osteocytes and surrounding bone matrices (stained, right panel) but not in the Sharpey's fibres (empty spaces, right panel). b, bone; and PDL, periodontal ligament.

alveolar bone (Figure 4A). We then stained a 2-month-old mandible from murine alveolar bone for periostin polyclonal antibodies, in which there was a strong signal in both PDL and Sharpey's fibres but no signal in alveolar bone matrices (Figure 4B, left panel). We also stained the adjacent section of the above slide using SOST polyclonal antibodies and revealed a strong signal in osteocytes and the surrounding bone matrices but showed a lack signal in the Sharpey's fibres (Figure 4B, right panel). The data support the notion that there is likely an interaction between Sharpey's fibres from PDL and alveolar bone via these two molecules.

A delayed collagen degradation in compression site

One of the key PDL changes during OTM is rapid collagen degradation. To delineate the impact of periostin on collagen degradation, we initially documented status of the base line of PDL collagen organization in WT and periostin KO, in which there are no apparent differences at both compression and tension sides among the age-matched control and periostin KO mice at the age of 5 weeks (Supplementary

Figure 5. A delayed reaction in collagen degradation in periodontal ligament (PDL) in periostin knockout (KO) compression side. Sirius red staining images were obtained from the wild-type (WT) mesial side of the distal root of first molar (compression side) at Days 1, 3, and 8 after tooth movement initiation (left panels). The same slides were also viewed under polarized light microscopy with images displayed on the right panels. Similar arrangements were displayed for periostin KO mice. Of note, the collagen degradation in the KO group was observed only at Day 8 after tooth movement (arrow).

Figure 1). Similarly, the collagen structure displayed few changes in the tension site during orthodontic loading in both WT and KO groups (Supplementary Figure 3). Interestingly, there was delayed collagen degradation in the KO compression site (Figure 5, right panels), in which an obvious change of collagen structure was observed on Day 8. In contrast, there was a rapid degradation in the WT group, starting from Day 1 after tooth loading, indicating that periostin plays an active role in collagen remodelling during tooth movement

Discussion

OTM is a result of bone and PDL remodelling as a response to the loading. Our studies demonstrate that periostin is essential during this process, and deletion of this gene greatly changes bone formation, bone resorption, and collagen remodelling in PDL. As a result, the rate of tooth movement and the whole process are delayed in periostin KO mice. It is known that SOST plays a key role in controlling bone remodelling in both loading and unloading (19, 20) and that periostin is closely linked to mechanical loading (9, 21) although the relationship between these two molecules is largely unknown. Our molecular studies revealed a biphasic response in SOST (a potent inhibitory molecule against Wnt signalling) expression with a sharp increase in the compression site and a decrease in the tension site. Furthermore, we identified a potential linkage between Sharpey's fibres and alveolar bone via a specific expression pattern of periostin in Sharpey's fibres and SOST in alveolar bone. A loss of periostin greatly reduces above responses in both bone formation and bone resorption during tooth movement. These findings partially explain the mechanism by which bone formation and bone resorption uniquely occur in different sites during tooth movement.

Our earlier studies showed that although some phenotypes such as dwarfism are present at earlier ages (around 3–4 weeks), the PDL phenotype does not appear until 3 months old (10). Concurrently, this study revealed that there is no apparent difference in collagen fibrils and arrangements between WT and periostin KO mice in the absence of orthodontic force application at age of 5 weeks (Supplementary Figure 2). Therefore, the alveolar bone and PDL responses to tooth movement in the KO mice truly reflects the physiological role of periostin during tooth movement, rather than the mixed response to the lately developed periodontal changes in this model.

One of important processes of tooth movement is PDL remodelling. The delayed collagen degradation is observed in the periostin KO compression site (Figure 5), suggesting that periostin plays a role in this remodelling process. At this stage, we do not know why and how this occurs, although the following three factors could be directly or indirectly associated with periostin function. It is known that extracellular matrix (ECM) degradation takes place through autocrine and paracrine actions (22), and an increase in matrix metalloproteinase (MMP) levels during ECM remodelling is documented (23), indicating a close linkage between ECM remodelling and MMPs' function. Next, periostin is highly expressed in collagen rich tissues subject to constant mechanical stress, colocalizes with collagen I, and displays periostin KO mice with pathological changes in fibril diameter and collagen cross-linking (24). These changes are correlated with alternations of some MMPs expressions. Furthermore, ECM remodelling can also be correlated to the roles of lysyl oxidase (LOX) in catalysing the covalent cross-linking of collagen, in which periostin promotes Bone Morphogenic Protein 1 deposition as the activator (25). The third factor is HMGB1 (high mobility group box 1), a late inflammatory cytokine that is regulated in PDL cells in response to tooth movement. A very recent study shows a high basal level but a weak response level in HMGB1 in the periostin KO compression site compared to the WT control group, suggesting a correlation between HMGB1 and periostin (26).

Low osteoclast activity in the periostin KO compression side (Figure 3) contributes in part for the delayed bone remodelling during tooth movement. Our further study showed a low expression level in both RANKL (a potent stimulator of osteoclasts) and osteoprotegerin (a strong inhibitor of osteoclasts) (Supplementary Figure 4), which cannot explain why osteoclast number reduced in the periostin KO case. In fact, the periostin response to tooth movement is controversial in mouse and rat studies. An early study reported a sharp increase in periostin mRNA levels in the compression side from 3 to 96 hours (5). In contrast, a separate group reported an opposition result: a great reduction in periostin expressions in the mouse compression side using immunohistochemistry method (26). In both reports, there is no apparent change in periostin expressions in the tension side. Apparently, it is too early to conclude exactly how periostin reacts to tooth movement and more work is required to address the mechanism on a low osteoclast number in periostin KO mice.

Conclusion

The biphasic response (an increase in the compression side and a decrease in the tension side) in SOST during tooth movement can be suggestive of an interaction between periostin from Sharpey's fibres and SOST in alveolar bone which plays an important role during tooth movement. Our studies also suggest a role of periostin in controlling osteoclast numbers and collagen degradation during tooth movement, although the mechanism is still largely unknown. We believe that this study will stimulate more interests in understanding a potential role of periostin in acceleration of tooth movement in future.

Supplementary material

Supplementary material is available at *European Journal of Orthodontics* online.

Funding

This study was partially supported by a U.S. National Institutes of Health (DE025014 to JQF).

References

1. Reitman, K. (1967) Clinical and histologic observations on tooth movement during and after orthodontic treatment. *American Journal of Orthodontics*, 53, 721–745.
2. Krishnan, V. and Davidovitch, Z. (2009) On a path to unfolding the biological mechanisms of orthodontic tooth movement. *Journal of Dental Research* 88, 597–608.
3. Davidovitch, Z. (1991) Tooth movement. *Critical Reviews in Oral Biology & Medicine*, 2, 411–450.
4. Stanfeld, J. et al. (1986) Biochemical aspects of orthodontic tooth movement. I. Cyclic nucleotide and prostaglandin concentrations in tissues surrounding orthodontically treated teeth in vivo. *American Journal of Orthodontics and Dentofacial Orthopedics*, 90, 139–148.
5. Wilde, J. et al. (2003) The divergent expression of periostin mRNA in the periodontal ligament during experimental tooth movement. *Cell Tissue Research*, 312, 345–351.
6. Horiuchi, K. et al. (1999) Identification and characterization of a novel protein, periostin, with restricted expression to periosteum and periodontal ligament and increased expression by transforming growth factor beta. *Journal of Bone and Mineral Research*, 14, 1239–1249.
7. Norris, R.A. et al. (2008) Periostin regulates atrioventricular valve maturation. *Developmental Biology*, 316, 200–213.
8. Nakazawa, T. et al. (2004) Gene expression of periostin in the early stage of fracture healing detected by cDNA microarray analysis. *Journal of Orthopaedic Research*, 22, 520–525.
9. Rios, H.F. et al. (2008) Periostin is essential for the integrity and function of the periodontal ligament during occlusal loading in mice. *Journal of Periodontology*, 79, 1480–1490.
10. Clevers, H. and Nusse, R. (2012) Wnt/beta-catenin signaling and disease. *Cell*, 149, 1192–1205.
11. Lim, W.H. et al. (2014) Wnt signaling regulates homeostasis of the periodontal ligament. *Journal of Periodontal Research*, 49, 751–759.
12. Kuchler, U. et al. (2014) Dental and periodontal phenotype in sclerostin knockout mice. *International Journal of Oral Science*, 6, 70–76.
13. Ren, Y. et al. (2015) Removal of SOST or blocking its product sclerostin rescues defects in the periodontitis mouse model. *FASEB Journal*, 29, 2702–2711.
14. Vicielli, R.F. et al. (2009) Orthodontic mechanotransduction and the role of the P2X7 receptor. *American Journal of Orthodontics and Dentofacial Orthopedics*, 135, 694 e1–16; discussion 694–5.
15. Rangiani, A. et al. (2012) Protective roles of DMP1 in high phosphate homeostasis. *PLoS One*, 7, e42329.
16. Rangiani, A. et al. (2012) Dentin matrix protein 1 and phosphate homeostasis are critical for postnatal pulp, dentin and enamel formation. *International Journal of Oral Science*, 4, 189–195.
17. Liu, S. et al. (2008) Pathogenic role of Fgf23 in Dmp1-null mice. *American Journal of Physiology - Endocrinology and Metabolism*, 295, E254–E261.
18. Kuroiwa, M., Chihara, K. and Higashi, S. (1994) Electron microscopic studies on Sharpey's fibres in the alveolar bone of rat molars. *Kaibogaku Zasshi*, 69, 776–782.
19. Robling, A.G. et al. (2008) Mechanical stimulation of bone in vivo reduces osteocyte expression of Sost/sclerostin. *Journal of Biological Chemistry*, 283, 5866–5875.
20. Moustafa, A. et al. (2012) Mechanical loading-related changes in osteocyte sclerostin expression in mice are more closely associated with the subsequent osteogenic response than the peak strains engendered. *Osteoporosis International*, 23, 1225–1234.
21. Ma, D. et al. (2011) A novel role of periostin in postnatal tooth formation and mineralization. *Journal of Biological Chemistry*, 286, 4302–4309.
22. Yamaguchi, M., Ozawa, Y., Nogimura, A., Aihara, N., Kojima, T., Hirayama, Y. and Kasai, K. (2004) Cathepsins B and L increased during response of periodontal ligament cells to mechanical stress in vitro. *Connective Tissue Research*, 45, 181–189.
23. Chang, H.H., Wu, C.B., Chen, Y.J., Weng, C.Y., Wong, W.P., Chang, B.E., Chen, M.H. and Yao, C.C. (2008) MMP-3 response to compressive forces in vitro and in vivo. *Journal of Dental Research*, 87, 692–696.
24. Norris, R.A. et al. (2007) Periostin regulates collagen fibrillogenesis and the biomechanical properties of connective tissues. *Journal of Cellular Biochemistry*, 101, 695–711.
25. Maruhashi, T., Kii, I., Saito, M. and Kudo, A. (2010) Interaction between periostin and BMP-1 promotes proteolytic activation of lysyl oxidase. *Journal of Biological Chemistry*, 285, 13294–13303.
26. Li J. et al. (2015) Altered distribution of HMGB1 in the periodontal ligament of periostin-deficient mice subjected to Waldo's orthodontic tooth movement. *Journal of Molecular Histology*, 46, 303–311.