European Journal of Orthodontics 28 (2006) 13–19
doi:10.1093/ejo/cji090
Advance Access publication 22 December 2005

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Root resorption associated with orthodontic force in inbred mice: genetic contributions

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SUMMARY Root resorption (RR) is an unwanted sequela of orthodontic treatment. Despite rigorous investigation, no single factor or group of factors that directly causes RR has been identified. The purpose of this study was to examine the effect of the genotype on susceptibility or resistance to develop RR secondary to orthodontic force. Nine-week-old male mice from eight inbred strains were used and randomly distributed into control (C) or treatment (T) groups as follows: A/J (C = 9,T = 9), C57BL/6J (C = 7,T = 8), C3H/HeJ (C = 8,T = 6), BALB/cJ (C = 8,T = 6), 129P3/J (C = 6,T = 8), DBA/2J (C = 8,T = 9), SJL/J (C = 8,T = 10), and AKR/J (C = 9,T = 8). Each of the treated mice received an orthodontic appliance to tip the maxillary left first molar mesially for 9 days. Histological sections of the tooth were used to determine RR and tartrate resistant acid phosphatase (TRAP) activity. The Wilcoxon ranked-sum non-parametric test was used to evaluate differences between the groups.

The results showed that the DBA/2J, BALB/cJ, and 129P3/J inbred mouse strains are highly susceptible to RR, whereas A/J, C57BL/6J and SJL/J mice are much more resistant. The variation in the severity of RR associated with orthodontic force among different inbred strains of mice when age, gender, food, housing, and orthodontic force magnitude/duration are controlled support the hypothesis that susceptibility or resistance to RR associated with orthodontic force is a genetically influenced trait.

Introduction

External apical root resorption (EARR) is a condition that can be observed in association with orthodontic tooth movement. It is a definite and permanent shortening of the root apex that is typically documented using radiographs (Baumrind *et al*., 1996). A second phenomenan associated with orthodontic tooth movement is root resorption (RR), which occurs on surfaces and areas of the root under compression from tooth movement. It is thought that functional trauma to the individual tooth causes this effect, and that 85 per cent of these areas show anatomically complete repair with secondary cementum (Brown, 1982). Histological sections are usually employed to study RR (Phillips, 1955). Although EARR and RR during orthodontic tooth movement are believed to be related conditions influenced by a wide range of shared genetic, biochemical and mechanical factors, a distinction is made between these two conditions when studying incidence and prevalence (Bender *et al*., 1997) due to the differences in the duration of applying active orthodontic force to express these conditions. RR detected histologically may be thought of as a preliminary step towards EARR.

Variability among orthodontic patients in susceptibility to EARR has been long appreciated. Massler and Malone (1954) proposed that when extreme susceptibility exists, severe EARR would occur even in the absence of any demonstrable cause. Newman (1975) reported family clustering of EARR, although the pattern of inheritance was not clear. Harris *et al*. (1997) explored the hypothesis of genetic influence on EARR for the first time using the sib-pair model and reported moderately high heritability that ranged from 0 to 0.76 (0.7 overall for three roots) in the four roots analysed. Recently, a key role for a genetic influence in EARR was reported indicating both linkage and linkage disequilibrium between an interleukin-1B (IL-1B) gene polymorphism and EARR in orthodontically treated individuals (Al-Qawasmi *et al.*, 2003). This polymorphism accounted for approximately 15 per cent of the variation in EARR of the maxillary central incisors. Harris *et al*. (1997) and the data of Hartsfield *et al.* (2004) indicate that since approximately half of the variation in EARR is influenced by genetic factors, and variation at IL-1B accounts for only 15 per cent of the phenotypic variation, there must be other genes that influence EARR associated with orthodontic force.

As a step towards determining what other genes may influence EARR in humans and developing an animal model to identify candidate genes, inbred strains of mice were used to test the hypothesis that genotype can influence susceptibility or resistance to developing RR secondary to short-term orthodontic force. In contrast to EARR in humans, using RR in mice as an endpoint allows for a practical approach to determine the differences in the response to a short period of orthodontic force. The inbred

mouse model offers many advantages for analysis of genetic contributions to RR susceptibility. There is considerable genetic variation across inbred strains of mice (Tecott, 2003). Thus, by examining a number of different inbred strains, it is possible to identify phenotypically divergent strains that are likely to have fixed different alleles at important trait-influencing loci. Through further molecular and genetic study of these phenotypically extreme strains, it is possible to localize and subsequently identify candidate genes contributing to RR susceptibility.

Materials and method

Mice

One hundred and twenty seven male mice of the inbred strains A/J, C57BL/6J, C3H/HeJ, BALB/cJ, 129P3/J, DBA/2J, SJL/J, and AKR/J were obtained (Jackson Laboratory, Bar Harbor, Maine, USA). All mice were received at 7–8 weeks of age and were acclimatized for 1–2 weeks prior to orthodontic treatment at 9 weeks of age. The animals were housed in boxed caging within the Indiana University School of Dentistry Bioresearch Facility, a unit fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. The mice were allowed food and water *ad libitum*. This study was fully approved by the Indiana University School of Dentistry Institutional Animal Care and Use Committee.

For each strain, mice were randomly assigned into two groups; control (C) group, where mice received no appliances, and treated (T) group, where mice received appliances to move teeth orthodontically. Mice per strain in each group were as follows: A/J (C = 9,T = 9), C57BL/6J (C = 7,T = 8), C3H/HeJ (C = 8,T = 6), BALB/cJ (C = 8,T = 6), 129P3/J (C = 6,T = 8), DBA/2J (C = 8,T = 9), SJL/J (C = 8,T = 10), and AKR/J (C = 9,T = 8). Both the control and treated animals were fed a diet of finely milled mouse chow *ad libitum* to minimize discomfort and appliance distortion in those animals that received the appliance. The animals were maintained on a 12:12 hour light–dark cycle at a room temperature of 21°C. The body weights of all mice were measured daily.

Orthodontic appliance application

A red Elgiloy® 0.0056 × 0.022 inch open coil spring (Rocky Mountain Orthodontics, Denver, Colorado, USA) was used to apply the orthodontic force, due to advantages reported previously (Pavlin *et al*., 2000). To calibrate the amount of force produced by its activation, the force/deflection (F/Δ) rate of the coil spring was determined (Figure 1). Ten coil springs were activated to three force levels by hanging weights of 10, 20 and 30 g and the amount of deflection was determined with an electronic calliper (Mitutoyo Co., Kawasaki, Japan) to the nearest 0.01 mm. The F/Δ curve indicated that a spring activation of 1 mm produced a force of 25 g, which was the initial activation force used in the treated animals.

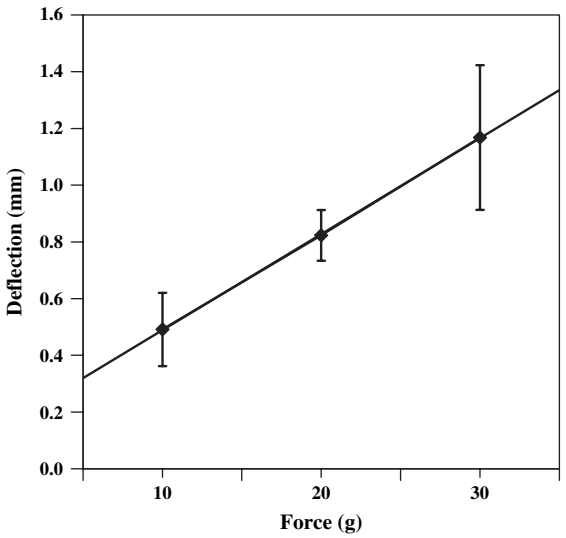

Figure 1 A force/deflection diagram of the coil spring. Deformation of the coil spring was measured at three force levels for 10 coil springs (each with 11 coils). Each point represents the mean, and bars ± one standard deviation.

The animals were anaesthetized with 0.35 ml/25 g body weight of mouse anaesthetic cocktail (ketamine:xylazine: saline, 10:2:1) injected intraperitoneally. To insert the orthodontic appliance, one end of the spring was ligated to the maxillary left first molar with 0.007 inch ligature wire (Rocky Mountain Orthodontics). The ligature wire was inserted, from the palatal side, below the contact area distal to the first molar. It was then ligated on the mesial side after inserting one end of the open coil spring into the ligature. The spring coil was then opened 1 mm from its original length by pulling the anterior end of the spring and tying it using 3–0 black braided silk suture (Ethicon Inc., Somerville, New Jersey, USA) (Figure 2). After activation, the ligature was bonded to the maxillary incisors by a chemically cured composite resin (Orthodontic Bonding Adhesive, Ormco/ Syrbron Corp., Glendora, California, USA) and the length of the spring was remeasured. The appliance was checked daily for signs of breakage at both ends of the spring. The animals were treated for nine days (Brudvik and Rygh, 1993) and were then killed using carbon dioxide inhalation.

Preparation of tissue for histological observation

Following euthanasia, the maxillae were immediately dissected, fixed in 10 per cent neutral buffered formalin for 24 hours, and demineralized in 0.25 M ethylenediaminetetraacetic acid (EDTA) (pH 7.2) for 4 weeks at 4°C. After demineralization, the samples were dehydrated in ethanol and embedded in paraffin. The embedded specimens were cut into5–7μm thick parasagittal

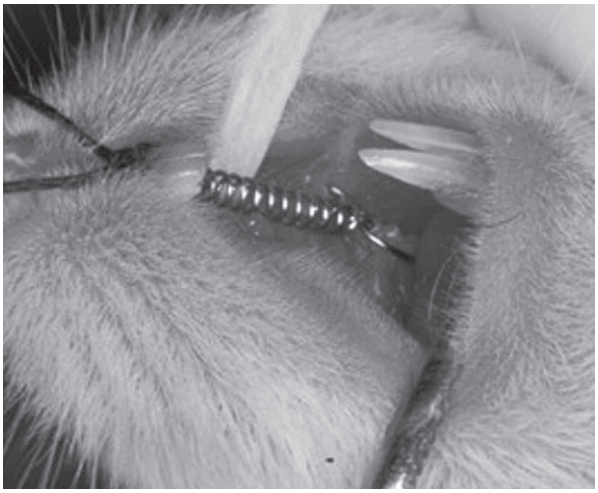

Figure 2 Position of the orthodontic appliance *in situ*.

sections, as parallel as possible to the long axis of the mesial root of the first molar, and were mounted on glass slides.

For each mouse, eight comparable sections, selected randomly, were stained with haematoxylin and eosin (H&E). In addition, three or four sections selected randomly were stained with tartrate resistant acid phosphatase (TRAP). The histochemical staining of TRAP was carried out according to the methods described by the manufacturer (Sigma Diagnostics, St Louis, Missouri, USA). All selected sections were then evaluated using light microscopy.

Evaluation of root resorption

The mesial aspect of the mesial root of the maxillary first molar on eight H&E stained sections was analysed using light microscopy at ×100 magnification. The quantification of RR was performed using the method described previously (Lu *et al*., 1999). An eyepiece with a 10 × 10 grid was used, with the grid orientated so that it was parallel to the long axis of the mesial root starting from the most apical point. The number of grids with and without resorption lacunae were counted along the root mesial outline as described previously (Lu *et al*., 1999). RR values were determined by dividing the number of grids with resorption lacunae by the total number of grids along the root surface. The percentage of resorption was determined by summing the RR values in all sections from an individual mouse and then dividing by the total number of sections. This value was referred to as the mean root resorption (MRR) for that particular mouse. In the treatment groups, the percentage of RR associated with orthodontic force (RRAOF) of each individual mouse was calculated by subtracting the average MRR value of the control group from the MRR value for that mouse. The dependent variable, RRAOF, controls for background RR within a strain that is not associated with orthodontic force.

Evaluation of TRAP positive cells

TRAP positive cells were examined on the periodontal ligament (PDL) interface of the mesial side of the mesial root of the maxillary first molar. At ×400 magnification the number of TRAP positive cells within 50 μm of the root surface was counted along the mesial root, starting from the most apical point to the cementoenamel junction. The estimate of TRAP positive cells was determined by summing the value of the TRAP positive cells in all sections from each mouse, and then dividing that by the total number of sections from that mouse.

Reliability analysis

To evaluate the reliability of the measurement of RR and TRAP positive cells, one-tenth of the studied specimens was selected randomly and remeasured. The second measurement was carried out in a blinded manner and under the same conditions by the same examiner (RAA) two months after the first measurement. Intra-examiner reliability was evaluated using the paired *t*-test. The significance level was set at $\alpha = 0.05$. No significant differences were found between the means of the first and second measurements.

The error of the method was calculated from the equation:

$$S_x = \sqrt{\frac{\sum D^2}{2N}}$$

where S_x is the error of the measurement, D is the difference between duplicated measurements and N is the number of double measurements (Dahlberg, 1940). The errors for MRR and TRAP variables were 0.49 and 0.08, respectively.

Statistical analysis

Due to the small sample sizes, non-parametric statistical tests were used to analyse MRR, RRAOF and TRAP values. First, the Wilcoxon ranked-sum non-parametric test evaluated treatment effect by comparing MRR values between the control and treated groups within each strain to determine if the medians of the two groups were equal. Since eight strains were tested, a Bonferroni correction for these eight tests was employed ($\alpha = 0.05$, $\alpha^* = 0.006$). Secondly, the Kruskal–Wallis test was used to test for differences across the eight strains and was performed on MRR values for control mice as well as RRAOF and TRAP values for treated mice. Conditional on the Kruskal–Wallis statistic being significant, multiple comparisons on all sets of two strains identified those strains that differed significantly in RR using an overall $\alpha = 0.05$ (Hollander and Wolfe, 1973). Finally, the Spearman correlation coefficient was computed for the TRAP and RRAOF values to quantify the association

between these two measurements of RR. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA), except the reliability analysis which was undertaken using SPSS for windows version 11.5 (SPSS Inc., Chicago, Illinois, USA).

Results

Root resorption cells estimate

The mice tolerated the appliance well and assumed a normal feeding pattern after 2 days. Weight loss did not exceed 20 per cent for all the animals included in the study and usually they started regaining the lost weight in 2–3 days. Three mice died while inserting the appliance. One mouse was excluded due to extensive weight loss (> 20 per cent of body weight), and seven more were excluded due to appliance breakage. The majority of these failures occurred at the initial period of the study.

Histological analysis revealed a difference in RR between control and treated mice in all inbred strains, an example of which is shown in Figure 3. MRR values are summarized for all eight inbred mouse strains in Figure 4. To test for differences in control animals, a Kruskal–Wallis test was used to examine MRR values for the eight strains and a significant difference between strains ($P = 0.0003$) was observed. To test for treatment effect within each strain, Wilcoxon ranked-sum tests used to examine MRR values indicated a statistically significant increase in RR for the treatment group that received orthodontic force compared with the untreated control group for each of the eight inbred strains (all $P < 0.003$).

RRAOF values for the eight inbred mice strains are shown in Figure 5. To test for differences in treatment effect, a Kruskal–Wallis test was used to examine RRAOF values for the eight strains and a significant difference between strains ($P < 0.001$) was observed. *Post-hoc* analysis indicated that A/J and DBA/2J were the most discordant strains. A/J, C57BL/6J and SJL/J mice were the most resistant to RRAOF, whereas BALB/cJ, DBA/2J and 129P3/J mice were the most susceptible. All pairwise comparisons of the resistant and susceptible strains for RRAOF were significant ($P < 0.05$). Strains with intermediate susceptibility (C3H/HeJ and AKR/J) showed no significant difference in RRAOF when compared with strains in either the resistant or susceptible groups.

TRAP positive values

TRAP positive cells were not detected in untreated control animals. Similar to the results with RRAOF, there were significant differences in TRAP values between the treated strains ($P < 0.001$; Figure 6). *Post-hoc* comparisons were used to examine differences between all sets of two strains. The most discordant strains for TRAP estimates were A/J and 129P3/J. Similar to the RRAOF results, BALB/cJ, DBA/2J and 129P/J had the highest number of TRAP positive cells consistent with their classification as a

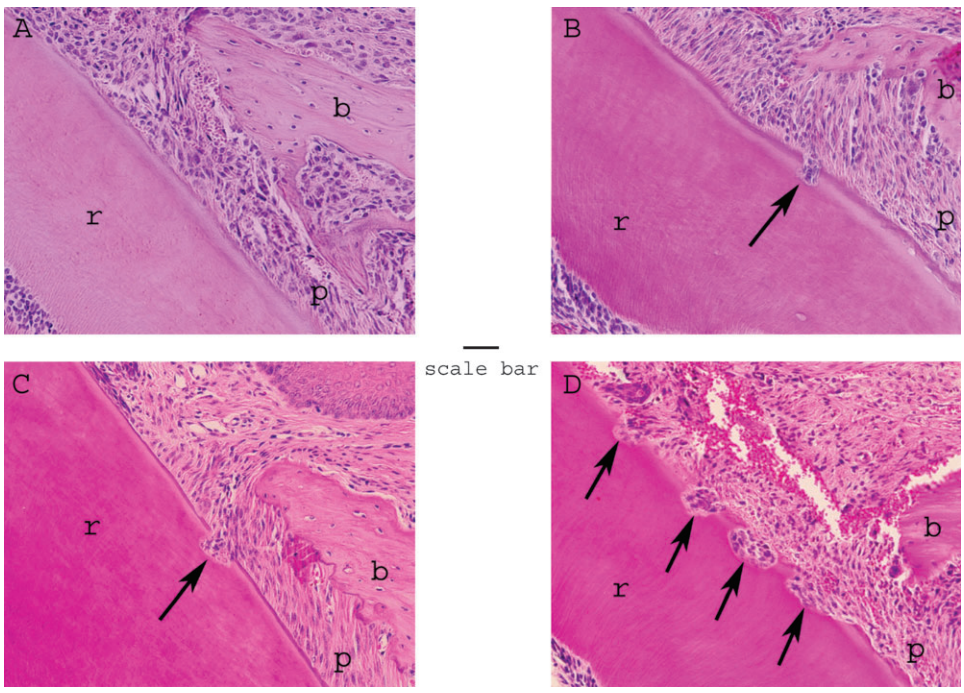

Figure 3 Root resorption on the mesial surface of the mesial root of the left maxillary molar. Haematoxylin and eosin stained sections for (A) control A/J mouse, (B) control DBA/2J mouse, (C) treated A/J mouse, and (D) treated DBA/2J mouse. Resorption lacunae are indicated by arrows. r = root, p = PDL, b = alveolar bone. Scale bar = 100 μm.

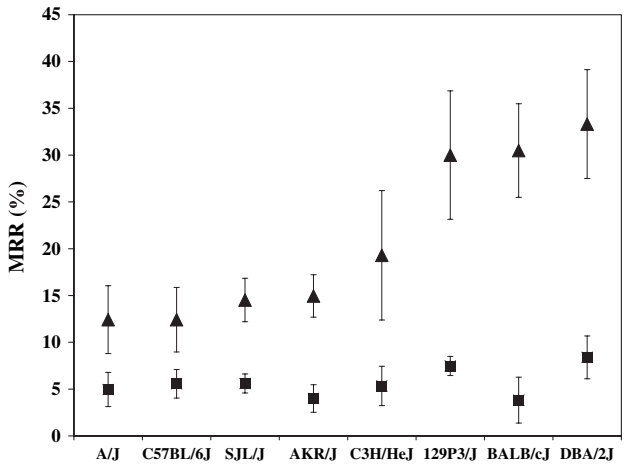

Figure 4 Mean root resorption (MRR) measured on the mesial surface of the mesial root of the left maxillary molar in different inbred strains of mice. Each point represents the MRR ± one standard deviation. The increase in MRR in the treated group, in comparison with the control group, was statistically significant for all inbred mouse strains. Filled square = control mice, filled triangle = treated mice.

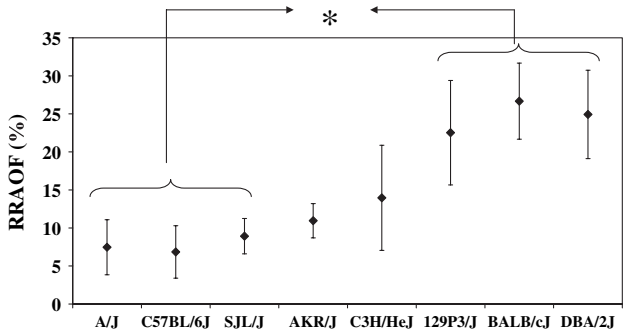

Figure 5 Root resorption attributed to orthodontic force (RRAOF) for the eight inbred mice strains. Each point represents mean RRAOF ± one standard deviation. * = all pairwise comparisons were significant.

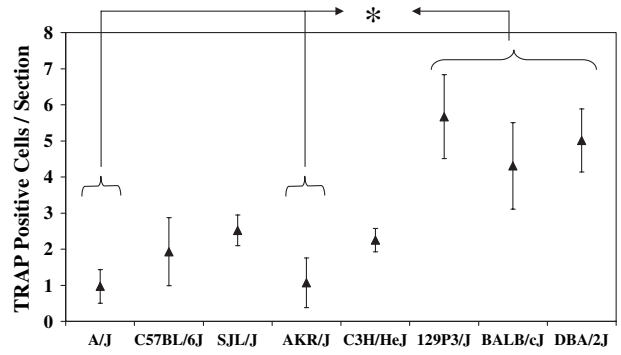

Figure 6 Tartrate resistant acid phosphatase (TRAP) positive cell count per section for the eight orthodontically treated inbred mice strains. Each point represents the mean value ± one standard deviation. * = all pairwise comparisons were significant.

susceptible group. However, there were differences between RRAOF and TRAP classification of the strains for the intermediate and resistant groups.

Correlation

The correlation between TRAP and RRAOF was 0.68 ($P < 0.001$), indicating a strong association between these two variables. Therefore, mice receiving orthodontic treatment respond similarly in terms of TRAP and RRAOF values.

Discussion

Studies of the genetic basis of susceptibility and resistance to RR associated with orthodontic treatment are difficult to perform in humans. Several investigations have identified mice and rats as useful models for determining the effect of orthodontic force on teeth and alveolar bone (Macapanpan *et al*., 1954; Brudvik and Rygh, 1993, 1994a, 1994b, 1995; Katzhendler and Steigman, 1999; Lu *et al*., 1999; Pavlin *et al*., 2000). Mouse models are playing an increasingly prominent role in this endeavour for a number of reasons: their small size render them amenable to large genetic experiments (Tecott, 2003); there are a large number of inbred mouse strains with carefully catalogued pedigrees (Festing, 1996); the genetic linkage map for this species is more dense than for any other non-human mammal; genes identified in mouse analysis can usually be readily mapped to a particular human chromosome because of the high degree of synteny that exists between the mouse and human genomes (Dietrich *et al*., 1996); and transgenic knockout technology is practical in this species (Hogan *et al*., 1986).

The present mouse model is a modification of a model that was developed originally to study the transduction of mechanical signals into biological response (Pavlin *et al*., 2000). In the original mouse model, the coil spring was activated 0.9 mm to deliver an initial force of 20 g. The spring was also reactivated after five days because it was found that the force delivered by the spring decreased to 42 per cent after four days of treatment. Furthermore, the coil spring was bonded directly to the occlusal surface of the maxillary first molar using dental composite, and therefore extracting the mandibular first molar was essential to allow teeth to occlude. Alternatively, in the present mouse model the coil spring was ligated to the maxillary first molar using ligature wire. This (1) eliminated the need to extract the mandibular first molar in the treated animals, and therefore minimized trauma, and (2) precluded hypofunctional periodontium, produced by extracting the opposing mandibular first molar, as a confounding factor in the RR severity in the maxillary first molar (Sringkarnboriboon *et al*., 2003). One disadvantage of the present method, however, was the closeness of the ligature wire to the gingival tissue especially on the distal side, which causes minimal irritation. Nevertheless, this irritation was located

away from the site of interest. Furthermore, unlike in the original mouse model, the spring in this model was not reactivated during the entire experimental period. Although the force level at the end of treatment was not measured, it was estimated that a reactivation step was not necessary due to the relatively higher activation and initial force used in this model and to minimize trauma associated with the extra-manipulation of mice in the second procedure. Although force decay is expected, between-strains comparisons are still valid assuming the same rate of force decay in all appliances.

The RR activity in the control groups reflect the basal RR activity in these strains that might have a repair function for damaged Sharpey fibres from physiological occlusal loading of teeth (Brown, 1982). Control animals of different strains have significantly different MRR, which reflect different basal RR activity in these strains. Therefore, the RRAOF values (and not MRR) were used for between-strains comparisons. Thus, although there may also be genetic differences in RR activity in untreated mice, the current model examined genetic influences on RR induced specifically by orthodontic force.

Variation in the severity of RRAOF among different inbred strains of mice when age, gender, food, housing, and orthodontic force magnitude and duration are controlled support the hypothesis that susceptibility or resistance to RR attributed to orthodontic tooth movement in mice is a genetically influenced trait. Mice were grouped into resistant (A/J, C57BL/6J and SJL/J); intermediate (C3H/HeJ and AKR/J); and susceptible (BALB/cJ, DBA/2J, and 129P3/J) strains using the RRAOF variable. The identification of RRAOF susceptible and resistant inbred mouse strains will facilitate investigation of the genes and pathways involved in RR. The estimate of TRAP positive cells was positively correlated with the RRAOF value, indicating an association between the two variables. Lack of a perfect correlation indicates that other factors, such as cell activation and cell fusion, might play significant roles in RRAOF. The susceptible group for RRAOF (BALB/cJ, DBA/2J and 129P/J) had the highest estimate of TRAP positive cells. However, there was no clear distinction between the RRAOF resistant and the intermediate groups when TRAP estimate was used. This further supports that TRAP estimates partially explain RRAOF in the inbred strains and that other factors are involved.

In addition to future genetic studies, investigation of biochemical and/or cellular differences among these inbred strains may also yield insights into differentiating factors. For example, Roberts *et al*. (1997) found marked differences in the magnitudes of response to granulocyte colony-stimulating factor (G-CSF) among inbred strains. In their study, C57BL/6J (a RRAOF resistant strain) showed the lowest absolute increases in the mobilization of progenitor cells into the blood in response to G-CSF, while DBA/2J (the RRAOF most susceptible stain) showed a nearly 10-fold greater progenitor cell mobilization into the blood relative to the C57BL/6J strain. Other strains, such as BALB/cJ and 129P3/J (RRAOF susceptible strains) showed approximately a 3- and 5-fold increase in progenitor cell mobilization, respectively. In a different study, it was demonstrated that G-CSF mobilized blood cells are a much better source of osteoclast progenitors than normal non-mobilized peripheral blood cells. It was suggested that qualitative and quantitative differences in the G-CSF mobilized cells are crucial in the formation of these osteoclast progenitors (Purton *et al*., 1996). When considering these findings, it can be hypothesized that the susceptibility to RRAOF is proportional to the mobilization of peripheral blood progenitor cells into the circulation in response to G-CSF.

Interestingly, DBA/2J mice, which are resistant to spontaneous alveolar bone resorption (Baer and Lieberman, 1959), are the most susceptible to RRAOF. This supports the hypothesis that excessive RR associated with orthodontic tooth movement may be mediated through a decreased rate of catabolic bone modelling (resorption) of alveolar bone resulting in prolonged stress and strain of the tooth root against the alveolar bone (Al-Qawasmi *et al*., 2003). The idea of increased bone turnover and decreased bone density allowing for faster tooth movement and less root resorption was first introduced by Goldie and King (1984) and is supported by the work of several researchers (Lasfargues and Saffar, 1993; Poumpros *et al.*, 1994; Loberg and Engström, 1994; Zhou *et al.*, 1997; Verna *et al.*, 2003).

Conclusion

The modified mouse model for RRAOF was reliable and straightforward, and could be used in the large number of inbred mice needed for analysis. Out of eight inbred mouse strains studied, it was shown that DBA/2J and A/J were the most discordant strains in RR response. Controlling for all other experimental factors, it was concluded that genotype is a substantial influencing factor in the variability of RR response to orthodontic force. Genetic analysis of the mouse strains with the most and least RR associated with orthodontic force will help determine what and how genes influence this difference.

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Acknowledgement

The authors wish to thank Patsy A. Dunn-Jena for her skilled laboratory assistance.

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