Oral Diseases (2006) 12, 395–401. doi: 10.1111/j.1601-0825.2006.01213.x

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ORIGINAL ARTICLE

Tooth survival and periodontal tissues healing of allogenic-transplanted teeth in the mice

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OBJECTIVE: For the successful organ transplantation, immune rejection has to be considered. Autogenic transplantation of human teeth is generally carried out free of clinical difficulty because of the lack of immune reaction, whereas allogenic tooth transplantations easily induce host immune rejection to donor tissues. The aim of the present study was to evaluate the replacement of donor tissue by host cells after allogenic tooth transplantation.

MATERIALS AND METHODS: First molars extracted from *lacZ* transgenic ROSA26 mice were transplanted into the alveolar socket and the tongue of host wildtype mice, where the first molar had existed.

RESULTS: Donor cells from *lacZ* transgenic mice were not detected in the periodontal ligament space, but rather in the pulp chamber of the donor tooth. Furthermore, if the pulp chamber was widely open to an affluent blood supply, odontoblasts and fibroblasts in the donor tissue survived in the dental pulp.

CONCLUSIONS: Our experimental models using *lacZ* transgenic ROSA26 mice clearly demonstrate that donor periodontal tissue cells are replaced by host cells and that periodontal tissue can regenerate after allogenic tooth transplantation. Furthermore, our models suggest that donor pulpal cells can survive if the vascular supply into the pulp chamber is sufficient.

Oral Diseases (2006) **12**, 395–401

Keywords: tooth; allogenic transplantation; tissue displacement; *lacZ* transgenic mouse

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Received 6 September 2005; revised 10 October 2005; accepted 20 October 2005

Introduction

The replacement of missing teeth has been discussed recently with the global understanding of future dentistry. Methods for the replacement of missing teeth, such as titanium implants, prosthetic dentistry, and autogenic tooth transplantation, have been popular depending upon cost, treatment duration, and other factors. Even the tissue-engineered tooth has been announced for use in the replacement of missing teeth in the near future (Young *et al*, 2002; Chai and Slavkin, 2003; Ohazama *et al*, 2004).

Although several fascinating clinical approaches have been suggested regarding tooth replacement, many unsolved difficulties still remain. It is well-known that titanium implants have some disadvantages resulting from their direct bonding to the bone, a process known as osseointegration (Schou *et al*, 1993). Clear answers regarding its benefits in implant treatment may be fully revealed after a certain number of years. Conventional prosthetic dentistry is widely regarded as an adequate method for replacing missing teeth, although it is still necessary to sacrifice the adjacent tooth as an abutment. Recently, autogenic tooth replantation has been added for missing tooth replacement to avoid immune rejection, and has included modification and reshaping of the donor tooth for perfect replantation into host (Kim *et al*, 2005). Tissue-engineered and bio-engineered teeth have arisen as new candidates for tooth replacement after the discovery of stem cells in dental pulp; however, these cannot be used yet (Gronthos *et al*, 2000; Miura *et al*, 2003).

It is likely that autogenous tooth transplantation is a viable option for replacing missing teeth if there are available donor teeth. The presence of intact and viable periodontal tissue cells on the root surface of the donor tooth is the most important factor in the healing of transplanted teeth (Andreasen, 1981). Several factors affecting periodontal ligament (PDL) healing are the

extra-body time of the donor tooth, surgical trauma during extraction, and the distance between the recipient bone tissue and the root surface of the transplanted tooth (Andreasen, 1981; Nethander, 1994; Lee *et al*, 2001). The autogenic tooth transplantation has become one of the most reliable treatments by decreasing surgical trauma to the tooth during the surgical procedure (Slagsvold and Bjercke, 1974; Kristerson, 1985; Schwartz *et al*, 1985; Andreasen *et al*, 1990). However, most tooth allografts lead to irreversible root resorption, followed by the loss of the tooth graft (Nordenram, 1982; Schwartz *et al*, 1987). This root resorption is the main cause of failure in the allogenic tooth (Nordenram, 1982; Schwartz *et al*, 1985, 1987). Root resorption in allografts is caused by the immunological rejection and the inflammation by the host against the donor tissue (Fong *et al*, 1968; Schwartz and Andreasen, 2002). Among the tissues of the donor tooth, the PDL is considered to be the primary factor, which elicits inflammation and subsequent root resorption.

LacZ transgenic mice have been used widely to study the ability of stem cells to differentiate into various cell types, as well as to study the lineage of targeted cells during embryonic development (Zambrowicz *et al*, 1997; Asahara *et al*, 1999; Orlic *et al*, 2001; Sasaki *et al*, 2001; Sata *et al*, 2002; Cho *et al*, 2003).

The present study aims the establishment of a tooth allograft experiment using *lacZ* transgenic mice to investigate the replacement of donor tissue by host cells after allogenic tooth transplantation. First molars extracted from *lacZ* transgenic mice were transplanted into the socket and tongue of host wild-type mice.

Materials and methods

LacZ transgenic ROSA26 mice and wildtype ROSA26 mice

The strains of the *lacZ* transgenic ROSA26 mice were C57BL/6J and β-gal transgenic B6. These transgenic mice, which were purchased from Jackson Labs (Bar Harbor, Maine), were made by a retroviral insertion of the β-galactosidase gene into ES cells. All cells of *lacZ* transgenic ROSA26 mice can be stained by an X-gal solution, as the endogenous promoter of the *lacZ* gene is known to express the β-galactosidase gene. On the other hand, none of cells from the wildtype ROSA26 mice can be stained by X-gal solution. In our study, fifteen 4-week old male *lacZ* transgenic ROSA26 mice and 15 wildtype ROSA26 mice were used as a donor and host, respectively.

Allogenic transplantation of the maxillary first molar to the socket of the maxillary first molar

To distinguish donor cells from host cells, each first molar was extracted from the maxilla of 10 *lacZ* transgenic ROSA26 mice and was transplanted into the maxillary first molar socket of 10 wildtype ROSA26 mice (Figure 1A). All surgery was performed under anesthesia, injected intraperitoneally. No immunosuppressive medications were used. The duration of the transplantation was 2 weeks.

Allogenic transplantation of the maxillary first molar to the ventral part of the tongue

Each first molar tooth was extracted from the maxilla of five *lacZ* transgenic ROSA26 mice. The root of this tooth was cut away to leave only the tooth crown, which was then transplanted into the tongue submucosal layer of five wildtype ROSA26 mice. The duration of the transplantation was 2 weeks.

Tissue preparation for histological observation

After the 2-week transplantation, the samples were isolated, washed with phosphate-buffered saline (PBS) (pH 7.4), fixed with 4% paraformaldehyde (PFA) for 1 h, decalcified for 4 weeks, and cryosectioned by 20 μm. The fixation and long-time decalcification have been known to decrease the intensity of *lacZ* expression. In this experiment, transplanted teeth in the alveolar socket have to be decalcified for a long time to be sectioned after being fixed in the fixative. Therefore, to observe the *lacZ* expression stronger, we sectioned specimens at the thickness of 20 μm. Furthermore, the X-gal staining has to be kept in fresh before X-gal staining. The *lacZ* transgenic cells will lost the activity of β-galactosidase during being prepared for wax section. Therefore, we did cryosection. Some cryosectioned specimens were stained with hematoxylin and eosin (H-E).

Identification of the lacZ transgenic cells in sectioned tissue

Cryosectioned specimens were washed with 2 mM $MgCl_2$ in PBS for 5 min, rinsed three times with a rinse buffer (2 mM $MgCl_2$, 0.02% NP-40, 0.01% sodium deoxycholate in PBS) for 20 min at room temperature, stained with β-gal staining solution (1 mg ml^{-1} of 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside (X-gal), 5 mM potassium ferrocyanide, and 5 mM potassium ferricyanide), and incubated at 37°C for 1 h. After the X-gal staining, the samples were washed again with PBS for 10 min, counterstained with nuclear fast red (NFR), and mounted on slides.

Results

Identification of lacZ transgenic mouse

To distinguish the *lacZ* transgenic ROSA26 mice from the wildtype ROSA26 mice, the tail of each mouse was cut and stained with X-gal solution. The blue-stained cells in the tail section after X-gal staining corresponded to the *lacZ* transgenic cells of the *lacZ* transgenic mouse (Figure 1B). Although the expression in the epithelium was more intense than in the mesenchyme, all cells from the *lacZ* transgenic mouse showed a blue color in the cytoplasm. Dental mesenchymal cells from the *lacZ* transgenic mouse found in the dental pulp and PDL also showed blue cytoplasm after X-gal staining (data not shown). A ROSA26 mouse with a blue tail after X-gal staining was used as the donor for the maxillary first molar tooth, which was transplanted into the first molar socket of a ROSA26 mouse without a blue-stained tail following X-gal treatment (Figure 1A).

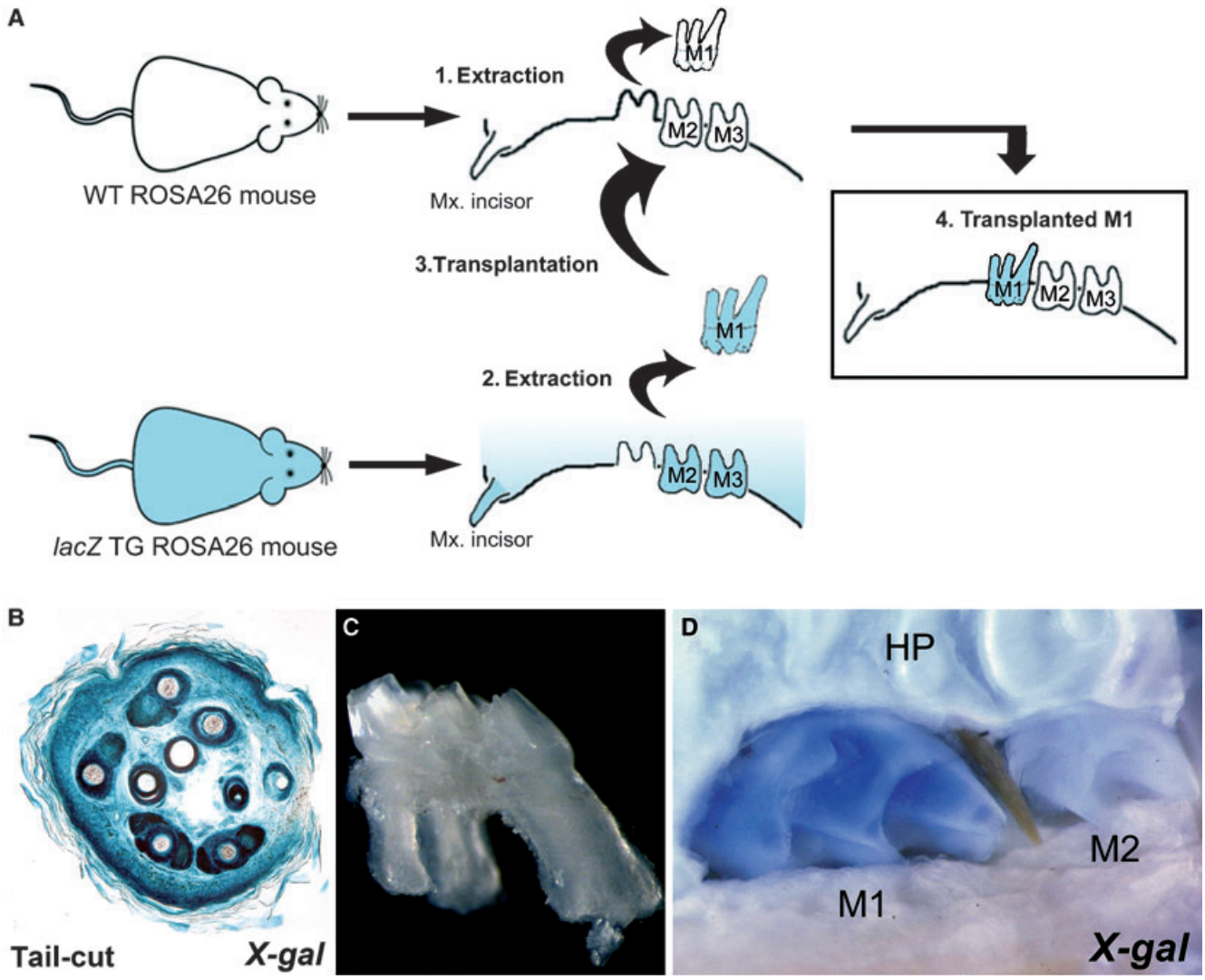

Figure 1 Allogenic tooth transplantation. (**A**) Schematic diagram of procedures in allogenic tooth transplantation. First, the maxillary first molar (M1) of a wildtype (WT) ROSA26 mouse was extracted. Second, the M1 of a *lacZ* transgenic (TG) ROSA26 mouse was extracted and transplanted into the alveolar socket of the WT ROSA26 mouse. (**B**) All cells in the section of tail from the *lacZ* TG ROSA26 mouse showed blue coloring in the cytoplasm. (**C**) First molar of the ROSA26 mouse showed three divergent roots and periodontal soft tissue surrounding the roots. (**D**) Two-week transplanted M1 still remained in the host socket and showed blue color from the inside of the tooth after X-gal staining, while the maxillary second molar (M2) of the host did not show blue color. HP: hard palate

Tissue attachment after tooth transplantation

The first molar showed PDL around its roots right after being extracted (Figure 1C). Among 10 allografted teeth, seven teeth remained in their positions in the socket after the 2-week transplantation, but their mobility varied from mild to severe. Four teeth were removed from the socket during histological preparation. Finally, three teeth remained in the host socket. After X-gal staining, the first molar transplanted from the *lacZ* transgenic mouse into the non-transgenic mouse showed blue color from the inside, while the non-transgenic second molar did not show blue color (Figure 1D). This result means that blue tooth were the donor teeth remaining in the host socket after transplantation.

In the non-transplanted tooth, root dentin was coated with cementum, which was connected to the alveolar bone by the PDL (Figure 2A). Compared with this attachment of periodontium in the wildtype tooth, the transplanted tooth was connected with the alveolar bone by the PDL only in some parts of the root (Figure 2B, D). Many fibroblasts, which were aligned horizontally from the cementum to the alveolar bone, showed normal PDL in the transplanted tooth (in Figure 2D). These results mean that the transplanted tooth can be attached to the alveolar bone by the PDL after 2 weeks. In the dental pulp, most odontoblasts could be observed on the dentin surface of the second molar (Figure 2A), while most of the pulpal cells in transplanted tooth were separated from the dentin surface and numerous inflammatory cells migrated into the pulp chamber (Figure 2B, D). Additionally, a big eosinophilic, amorphous structure was observed at the pulp horn of the transplanted tooth (Figure 2B, C). The fact that there

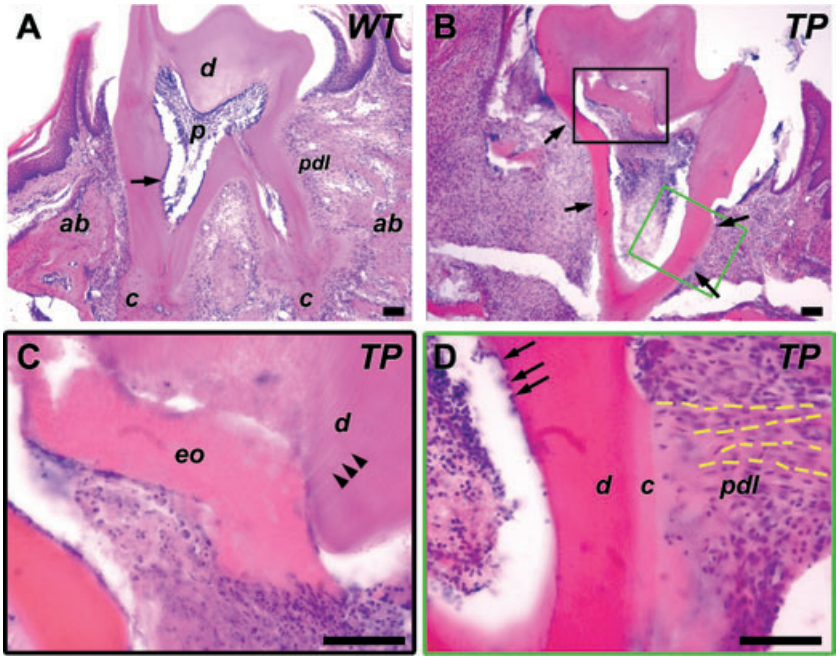

Figure 2 Histologic findings of the transplanted M1. (**A**) The non-transplanted wildtype (WT) tooth shows the periodontal ligament (pdl), which connects the cementum (c) to the alveolar bone (ab). In the dental pulp (p), most of the odontoblasts (arrow) were observed on the dentin (d) surface of the second molar. (**B**) Compared with the wildtype tooth, the transplanted (TP) tooth was connected with the alveolar bone by the periodontal ligament in some parts of the root (between arrows). (**C**) High magnification of the pulp horn area (black box on **B**) shows a big eosinophilic and amorphous structure (eo). This structure was surrounded by degenerated cells in the transplanted tooth and did not show any dentinal tubules (arrowheads). (**D**) High magnification of the periodontal ligament area (green box on **B**) shows many fibroblasts aligned horizontally from the cementum to the alveolar bone, proving normal periodontal ligament in the transplanted tooth (yellow dotted lines), while only a few pulpal cells (arrows) in the transplanted tooth attached to the dentin surface. Dimension of all scale bars: 100 μm

are no dentinal tubules or cells inside of this eosinophilic structure suggests that the structure was not hard tissue secreted by vital formative cells, but rather the matrix-like structure surrounded by degenerated cells in the transplanted tooth (Figure 2C).

Tissue replacement after transplantation

To evaluate the extent of tissue replacement by the host cells after tooth transplantation, it is necessary to distinguish the donor cells from the host cells. All kinds of *lacZ* transgenic ROSA26 mouse cells, such as oral epithelial cells, dental pulp cells, PDL cells, osteocytes, and cementocytes, express blue color after X-gal staining (Figure 3A), while cells from the wildtype ROSA26 mouse cannot express blue color. In this study, original donor cells from *lacZ* transgenic ROSA26 mice were observed only at the pulp horn of the transplanted tooth (Figure 3B). An obscure borderline between blue region (white asterisks) and white color region was observed in the cervical portion of the transplanted tooth (Figure 3C). This result suggests that cells in the dental pulp near the apical foramen and PDL had been replaced by host cells. Additionally, the fact that the blue region coincides exactly with the location of the eosinophilic mass ('eo' in Figure 2C) suggests that this mass might be the matrix-like structure secreted by the donor pulpal cells.

Blood supply and vitality of donor tissue

The fact that the amorphous matrix-like structure surrounded by presumably necrotic cells was observed only in the pulp horn led us to investigate the relationship between necrosis and blood supply. To increase blood supply to the dental pulp, the root part of the tooth was cut away to widely expose the pulp chamber. After 2-week transplantation into the submucosal layer of the tongue, dentin from the transplanted tooth was under resorption and had lost its original crown shape (Figure 3E). The original dental pulp cells expressed blue color in the pulp horn area after X-gal staining (Figure 3E, F). After subsequent NFR counterstaining, all red nuclei in the pulp horn area were found just beside blue dots (Figure 3F). Odontoblast-like columnar cells facing the dentin surface showed blue dots in the cytoplasm and a red nucleus. Capillary-like structures were found in this pulp horn area. Based on these results, there may be healthy original pulp cells (rather than necrotic cells) in the dental pulp chamber because of the affluent blood supply.

Discussion

The character of periodontal changes in autografts and allografts has been classified as follows: (i) normal periodontium; (ii) inflammation; (iii) necrosis; (iv) surface root resorption; (v) inflammatory root resorption; (vi) replacement root resorption or ankylosis; and (vii) downgrowth of periodontal pocket epithelium (Andreasen, 1981; Schwartz and Andreasen, 1988, 2002). The autogenic tooth transplantation has become a reliable treatment by decreasing surgical trauma such as modification and reshaping the alveolar socket during the surgical procedure (Slagsvold and Bjercke, 1974; Kristerson, 1985; Schwartz *et al*, 1985; Andreasen *et al*, 1990; Kim *et al*, 2005). In tooth allografts, it has been known that root resorption resulting from the immune rejection reaction ultimately leads to the loss of the graft in humans (Nordenram, 1982; Schwartz *et al*, 1987). In this study, three donor teeth remained in the host socket among 10 transplanted teeth. This low percentage of their attachment to the socket may result from the mechanical damage on PDL during transplantation

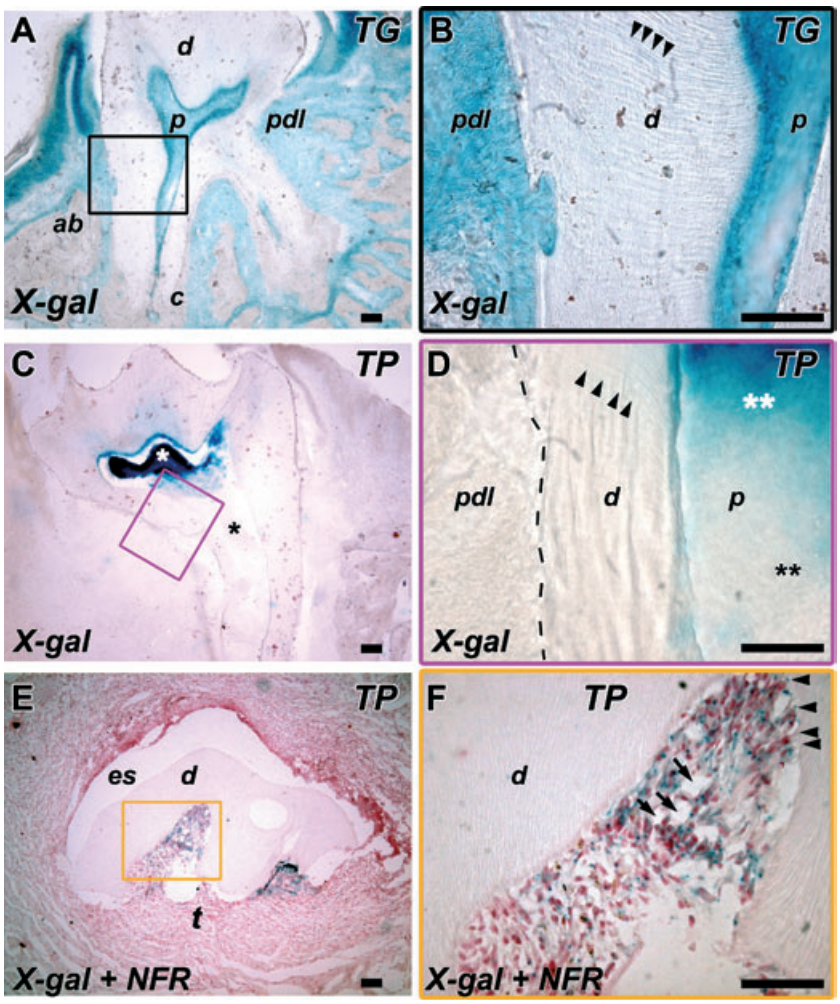

Figure 3 Tissue replacement by the host cells after tooth transplantation. (**A**) All cells of the *lacZ* transgenic (TG) ROSA26 mouse express blue color after X-gal staining, while hard tissue (such as dentin and alveolar bone) did not show blue coloring. (**B**) High magnification of the periodontal ligament (pdl) and dental pulp (p) of a *lacZ* transgenic mouse (black box in **A**) shows that all cells in the soft tissue, such as the periodontal ligament and pulp, were filled with the blue-colored cells. Black arrowhead shows a dentinal tubule in dentin. (**C**) Original donor cells in the transplanted (TP) tooth were observed only at the pulp horn of the transplanted tooth (white asterisk). Cells in the dental pulp near the apical foramen (black asterisk) did not express blue color. The blue-colored region coincided exactly with the location of the eosinophilic mass (eo in Figure 2**C**). (**D**) High magnification of the periodontal ligament and dental pulp in the transplanted tooth (pink box in **C**) shows that blue-colored donor cells were not located in the periodontal ligament, but rather in a part of the dental pulp (white asterisks). This suggests that the periodontal ligament had been replaced by the host cells. The periodontal ligament could be distinguished from the dentin, which included the dentinal tubule (arrowheads). (**E**) In the other transplanted tooth, of which the pulp chamber was opened before transplantation into the submucosal layer of tongue (t), the original dental pulp cells expressed blue color in the pulp horn area after X-gal staining. (**F**) High magnification of the pulp horn area (yellow box in **E**) shows odontoblast-like columnar cells (arrowheads) facing the dentin surface expressing blue dots in the cytoplasm and a red nucleus; capillary-like structures were found in this pulp horn area (arrows). Dimension of all scale bars: 100 μm

procedure, because the tooth size is too small to be handled and the three roots of first molar are divergent in mouse.

In rodents, many studies on the basic immunobiology of the tooth allograft have been performed (Atkinson, 1978). Especially in mouse, teeth size is too small to be handled rightly during transplantation. Therefore, there have been many studies regarding tooth transplantation in dogs, monkeys, and humans to investigate all characteristics during tooth transplantation. However, there have been no reports regarding the replacement of soft tissue. In this study, donor cells in the PDL and dental pulp were traced to evaluate tissue replacement by host cells. *LacZ* transgenic mice, which have been used to study the lineage of targeted cells, were used as donors of allogenic teeth.

As a result, after 2-week transplantation, it was hard to find out blue cells, corresponding to donor cells, in PDL. This result suggests that donor cells in the PDL, such as cementoblasts, fibroblasts and osteoblasts had been replaced by host cells. However, epithelial cell rest of Malassez (ERM), another group of cells in PDL space, may not be regenerated by the host cells. It has been reported that epithelial cell rests in the PDL might play an important role in maintaining the PDL space (Shimono *et al*, 2003). Therefore, no formation of PDL

in the large area of the root might be caused by donor epithelial cell damage and non-replacement by host epithelial cells. The relationship between epithelial cells and healthy PDL remains to be elucidated.

In previous studies on allografts of monkey teeth, only small areas of normal PDL healing have been described (Fong *et al*, 1968; Shulman and Kalis, 1970), even in close MHC-class I and class II-matched rhesus monkeys (Riviere, 1981). This seems to be in accordance with allograft studies in inbred rodent strains, where only the closest MHC and non-MHC matches seem to heal equally with isografts and autografts (Atkinson, 1978). These previous studies suggested that immune rejection reaction might not be the only cause of failure in normal PDL healing.

In this study, numerous inflammatory host cells were not observed in the PDL, but rather were observed in the dental pulp. This result also means that donor PDL cells were replaced by the host cells and that there might be no immune rejection reaction in the PDL at the 2 weeks of transplantation.

It has been reported that necrosis of the PDL was almost exclusively found until 2 weeks of transplantation, apparently independent of allo/auto status or endodontic treatment in hamsters and monkeys (Robinson and Rowlands, 1972; Schwartz *et al*, 2002). Therefore, necrosis in the PDL was attributed to nonspecific surgical trauma during extraction and transplantation (Robinson and Rowlands, 1972; Schwartz *et al*, 2002). In this study, we did not find necrotic structure in the PDL after 2 weeks. On the other hand, necrotic structure was found in the dental pulp chamber. It has been reported that the length of vital pulp was <1 mm in all grafts, irrespective of the type of graft, and that revascularization was not seen in mature allografts in monkeys (Kristerson and Andreasen, 1984; Schwartz and Andreasen, 1988), dogs (Skoglund *et al*, 1978) or humans (Kristerson, 1985; Schwartz *et al*, 1985). These previous studies mean that the vitality of the pulp might be regulated not only by the immune rejection reaction, but also by vascularization. To observe the relationship of pulp vitality with vascularization, the pulp chamber of transplanted tooth was widely opened to supply affluent blood and then transplanted into tongue of host mice. The fact that odontoblasts and fibroblasts of the donor existed in the dental pulp suggested that no blood supply might be the main cause of pulp necrosis after tooth transplantation.

In conclusion, our experimental models using *lacZ* transgenic ROSA26 mice clearly demonstrate that donor dental pulp and periodontal tissue can be replaced and regenerated by host cells after allograft transplantation if the vascular supply into these tissues is sufficient.

Acknowledgements

This work was supported by the Korea Research Foundation Grant (KRF-2003–003-E00224).

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