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An Immune-compromised Method for Tooth Transplantation Using Adult Bone Marrow Stromal Cells and Embryonic Tooth Germ

Hyuk-Jae Kwon, Gi-Hee Park, Eun-Jung Kim, Min-Jung Lee, Han-Sung Jung, Sung-Won Cho

Division in Anatomy and Developmental Biology, Department of Oral Biology, Research Center for Orofacial Hard Tissue Regeneration, Brain Korea 21 Project, Oral Science Research Center, College of Dentistry, Yonsei Center of Biotechnology, Yonsei University, Seoul, Korea

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Abstract : Tooth transplantation using autogenic adult teeth or embryonic tooth germs is the one of best treatments for replacement of missing teeth, but there are limitations in the accessibility. Isogenic or xenogenic tooth transplantation has been failed because of the immune rejection response occurring in the periodontal ligament of transplanted tooth. In this study, by utilizing the recombination between mouse embryonic tooth germ and mouse adult bone marrow stromal cells, we tried to replace the periodontal tissues such as periodontal ligament and alveolar bone with adult bone marrow stromal cells. At four weeks after the transplantation of the recombinant into a kidney, adult bone marrow-derived cells cells were observed in the periodontal ligament and alveolar bone. This result indicates that adult bone marrow stromal cells can participate in the formation of periodontal tissues. If these tooth and periodontal tissues are transplanted into host who donates adult bone marrow stromal cells, adult bone marrow-derived cells will be regarded as host cells, and immune rejection response will not occur in these cells. Therefore, it is suggested that recombination between adult bone marrow stromal cells and embryonic tooth germ is a good candidate method using xenogenic tooth germ for replacement of missing teeth in human by replacing cells in periodontal tissues with human adult bone marrow stromal cells.

Keywords : Tooth, Transplantation, Tooth germ, Bone marrow

Introduction

Dental implants have been preferred as one of treatments for replacement of missing teeth. However, implants can not be applied to all patients, since certain amount of bone is necessary to bond and bind implants directly. Additionally, since there is no periodontal ligament between bone and implants, the mechanical forces imposed on the implant during occlusion transmit directly to alveolar bone. Therefore, several studies have been focused on the regeneration of biologic teeth which have periodontal ligament. At first, embryonic tooth germs have been investigated as the source of odontogenic cells. Dissociated cells from embryonic tooth germ induced putative tooth-like tissues such as enamel, dentin, dental pulp, cementum, alveolar bone, and periodontal ligament in biomaterials such as collagen, PLGA, or silk protein scaffolds (Young et al. 2005, Duailibi et al. 2008, Kuo et al. 2008). Additionally, early embryonic oral epithelium recombined with adult mesenchyme togeher generated dental structures when being transplanted into adult renal capsules or jaw bone (Ohazama et al. 2004). However, in human there are limitations in the accessibility of autogenic tissues such as embryonic tooth germ, adult stem cells and adult tooth. At second, the odontogenic potential of the adult stem cells, which were obtained from dental pulp and periodontal ligament, was investigated. These dental pulp and periodontal ligament stem cells pro-

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Correspondence to : Sung-Won Cho (Departmen of Oral Biology, Yonsei University College of Dentistry)
E-mail : chosome1@yuhs.ac

duced dentin, cementum, alveolar bone or periodontal ligament when being differentiated and transplanted (Gronthos et al. 2002, Seo et al. 2005, Sonoyama et al. 2006). However, regenerated tooth or hard tissues formed by these stem cells were different from the shape of normal tooth or hard tissues. These previous results mean that adult stem cells can not completely regenerate the whole tooth by themselves and that embryonic dental tissues from tooth germs are necessary for the formation of tooth. Therefore, alternative embryonic tooth germs such as xenogenic and isogenic tooth germ can be considered to replace the autogenic embryonic tooth germs. However, Xenogenic transplantation of embryonic tooth germ or adult tooth may induce immune rejection response resulting in exfoliation of transplanted tooth. Periodontal ligament is the most key tissue where immune rejection response occurs in xenogenic tooth transplantation (Robinson and Rowlands 1974).

In this study, to make a bio-engineered tooth which is histocompatible to host tissues, we designed a novel method utilizing the recombination between embryonic tooth germ and adult bone marrow stromal cells.

Materials and Methods

Preparation of cell pellet

Bone marrow stromal cells were harvested from femurs of 20-week old lacZ-transgenic ROSA 26 mice. ROSA26 adult male mice were purchased from Jackson Labs (Bar Harbor, Maine, USA). Bone marrow cells were cultured

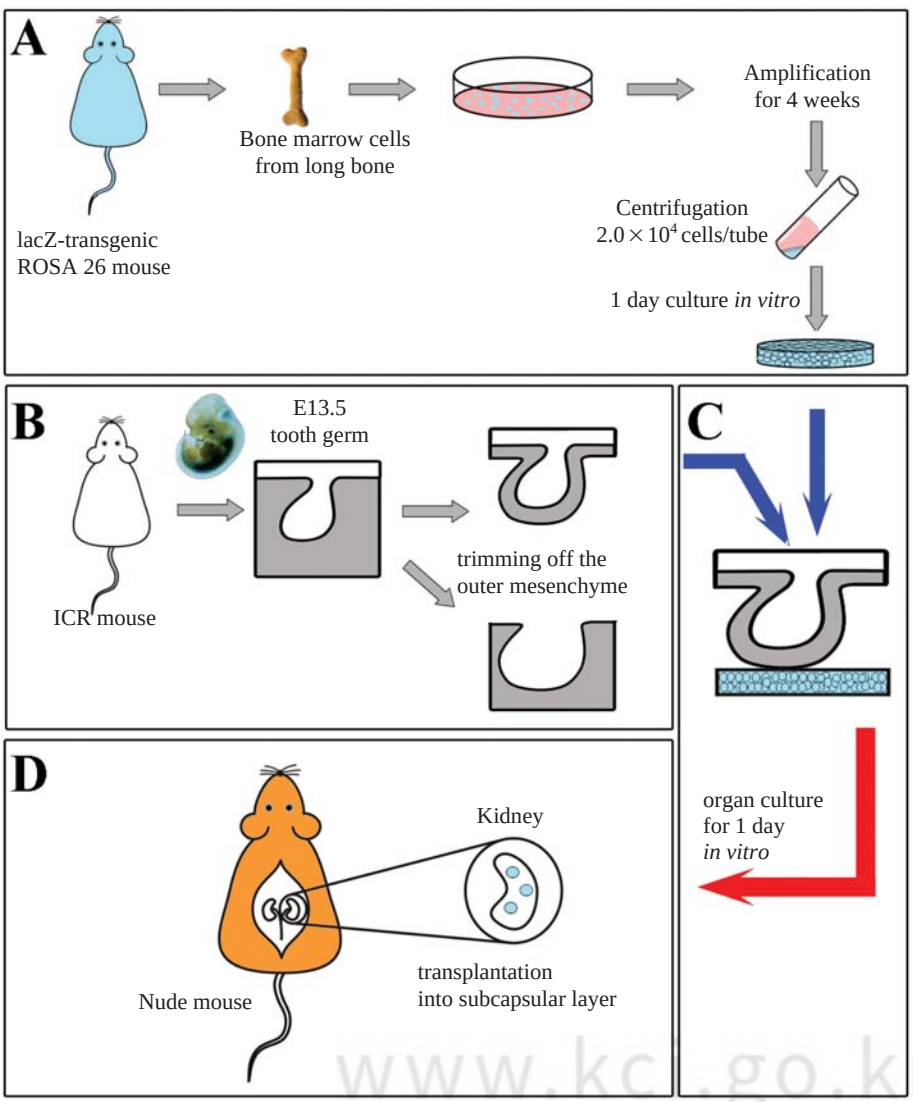

Fig. 1. Scheme of experimental procedures. (A) Bone marrow cells were harvested from 20-week old lacZ-transgenic ROSA 26 mice. Bone marrow cells were cultured for four weeks, and then adult bone marrow stromal cells were collected. Cell number was adjusted into 2.0×10^4 in a tube. Cell pellet formed after centrifugation at 3500 rpm for 5 minutes was cultured in tube for one day. (B) Molar tooth germs at bud stage were dissected from the mandible of embryonic day 13.5 (E13.5) ICR mice. The outer layer of dental mesenchyme in these tooth germs were trimmed off. (C) Each tooth germ was recombined with a cell pellet. These recombinants were cultured for one day *in vitro*. (D) The recombinant tooth germs were transplanted into the renal subcapsular layer of adult nude mice.

in DMEM medium containing 10% FBS (Sigma), 1% penicillin/streptomycin. The nonadherent cells were removed, and the cultures were then continued with media changes every four days. After 4 weeks, adult bone marrow stromal cells were collected. Cell number was adjusted into 2.0×10^4, which corresponds to the average number of dental mesenchymal cells in one molar of E13.5 mice, in a tube. Cell pellet was formed after centrifugation at 3500 rpm for 5 minutes, and then cultured in tube for one day (Fig. 1A).

Preparation of tooth germs

The molar tooth germs of embryonic day 13.5 (E13.5) ICR mice show the bud shape of dental epithelium. These tooth germs were dissected out from mandible of mice and washed in DMEM with 10% FBS. The outer layer of dental mesenchyme in these tooth germs were trimmed off (Fig. 1B).

Tissue recombination

Each tooth germ from ICR mice was recombined with a cell pellet from lacZ-transgenic ROSA 26 mice. The tooth germ was overlaid on the center of the cell pellet. These recombinants were cultured for one day in Trowell-type organ culture method using DMEM with 10% FBS (Fig. 1C).

Transplantation of recombinants into the renal subcapsular layer of nude mouse

The recombinant tooth germs were transplanted into the renal subcapsular layer of adult nude mice (Orientbio, Korea) to reduce immune rejection response (Fig. 1D). All surgical procedures were performed under anesthesia administered intra-peritoneally. No immunosuppressive medication was used. After 4 weeks, the host mice were sacrificed, and kidney holding calcified teeth were dissected out and fixed with 4% paraformaldehyde.

X-gal staining

Kidney holding teeth were decalcified with 5% EDTA, cryo-sectioned at 7 μm and mounted on slides. Sections on slides were processed by X-gal staining as described elsewhere (Cho et al. 2003). The sections 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 a X-gal staining solution [1 mg/mL 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 one hour. After X-gal staining, the sections were washed again with PBS for 10 minutes and counter-stained with eosin or nuclear fast red.

Results

Recombinant between embryonic tooth germ and adult bone marrow stromal cells formed calcified tooth and periodontal tissues

At four weeks after the transplantation of the recombinant into a kidney, a calcified tooth surrounded by alveolar bone was observed in renal subcapsular layer. The tooth clearly displayed enamel space, predentin, dentin, dental pulp, cementum, periodontal ligament and alveolar bone (Fig. 2A and D). In root compartment, the periodontal ligament space was wide between alveolar bone and cementum (Fig. 2B and C).

lacZ positive bone marrow cells were localized in periodontal tissues

To distinguish the adult bone marrow-derived cells from both embryonic cells in tooth germ and host cells of nude mice, adult bone marrow stromal cells were collected from the lacZ transgenic mice, which are stained with blue color after X-gal staining.

At four weeks after the transplantation, lacZ positive cells were localized in the region of periodontal ligament and alveolar bone (Fig. 3A). A few lacZ positive cells were observed in the periodontal ligament space, especially closer to alveolar bone than cementum. Osteoblast-like cells on the surface of alveolar bone also displayed the lacZ positive reaction (Fig. 3B). Osteoclast-like cells displaying multiple nuclei in a large cytoplasm adjacent to the Howship's lacunae of alveolar bone region did not show any lacZ positive reaction (Fig. 3C). On the other hand, there were no lacZ positive cells within dental pulp and around cementum (Fig. 3A and D). Neither osteocyte nor cementocyte showed the lacZ positive reaction (Fig. 3A-C). These results indicate that these lacZ positive adult bone marrow-derived cells involved in the formation of periodontal liga-

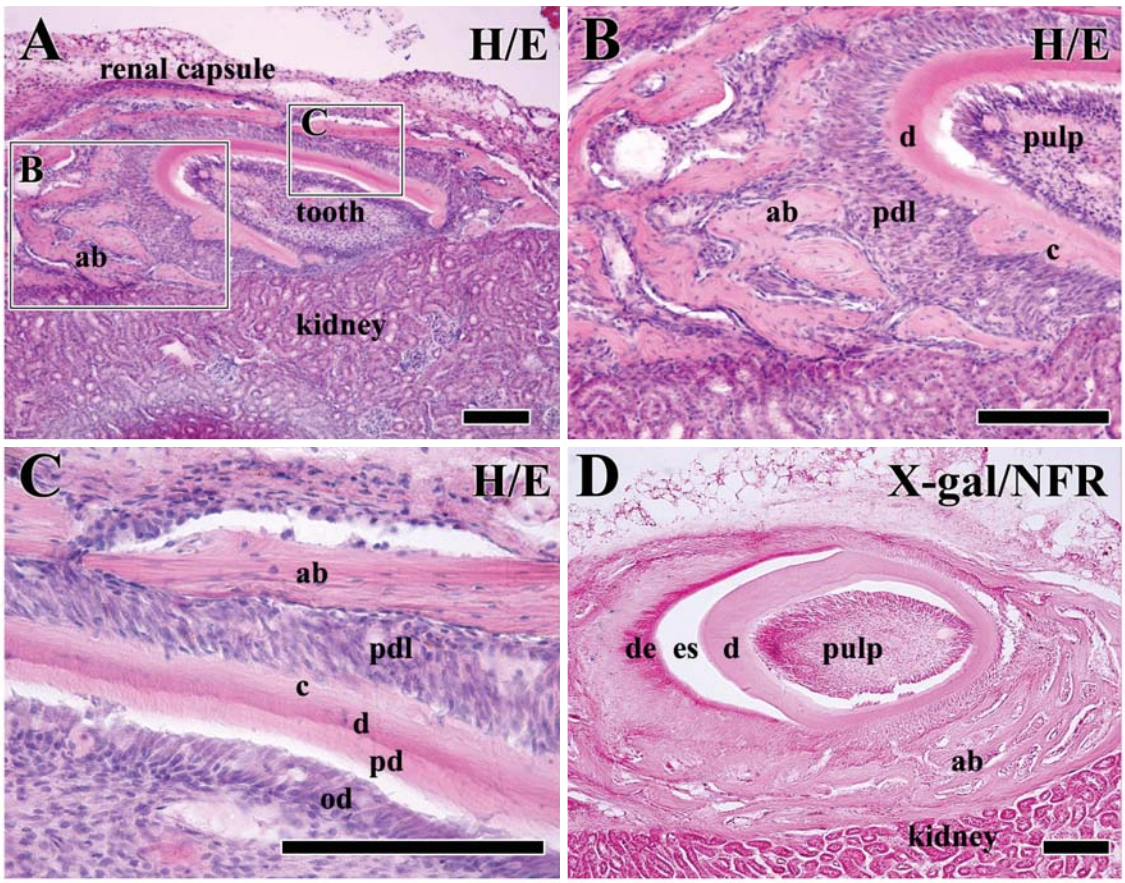

Fig. 2. Tooth and periodontal tissues developed from Recombinant between embryonic tooth germ and adult bone marrow stromal cells. (A) At four weeks after transplantation of the recombinant into a kidney, tooth and periodontal tissue are located in renal subcapsular layer. (B) In root compartment, periodontal ligament (pdl) connects alveolar bone (ab) and cementum (c), which covers dentin (d) and predentin (pd). (C) odontoblasts and pulpal cells are observed in dental pulp. (D) In tooth crown compartment, enamel space is observed between the dental epithelium (de) and dentin layer. Abbreviations: H/E, hematoxylin and eosin staining; X-gal/NFR, X-gal and nuclear fast red staining. All scale bars, 150 μm

ment and alveolar bone.

Discussion

Adult dental stem cells induced the dentin, cementum and periodontal ligament, but the shape of regenerated tooth or hard tissues using stem cells were different from that of normal tooth or hard tissues. Furthermore, stem cells could not make tooth itself without help from embryonic tooth germ. Since there are hundreds or thousands of genes involved in tooth development, and it is impossible to artificially regulate the spatiotemporal expression of these genes during regeneration of tooth. Therefore, for the replacement and regeneration of tooth, a further concept reproducing the developmental processes during organogenesis has been proposed (Yen and Sharpe 2006). However, there are limitations in the accessibility of autogenic and isogenic embryonic tooth germ in human. Xenogenic transplantation of embryonic tooth germ or adult tooth may induce immune rejection response resulting in exfoliation of transplanted tooth. The most key factor in isogenic or xenogenic tooth transplantation is the immune rejection response in periodontal ligament (Robinson and Rowlands 1974).

In this study, by utilizing the recombination between mouse embryonic tooth germ and mouse adult bone marrow stromal cells, we tried to replace embryonic tooth germ cells with adult bone marrow stromal cells in periodontal tissues. At four weeks after the transplantation of the recom-

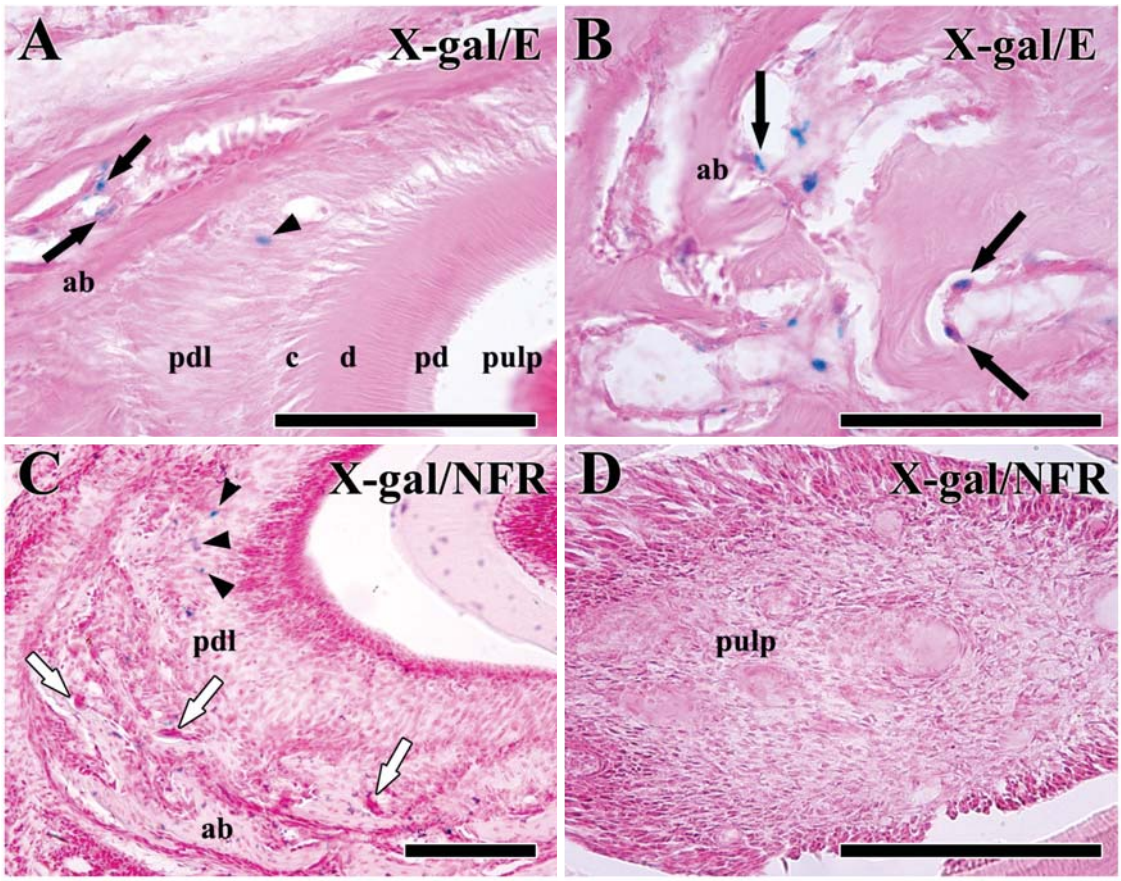

Fig. 3. Localization of lacZ positive bone marrow-derived cells in recombinant tooth. (A) A few periodontal ligament cells (arrowhead) and osteoblast-like cells (black arrows) show the lacZ positive reaction. (B) lacZ positive reaction appear at many osteoblast-like cells (black arrows) in the alveolar bone (ab). (C) Osteoclast-like cells (white arrows) in alveolar bone do not show any lacZ positive reaction. lacZ positive cells are located in the periodontal ligament closer to alveolar bone than cementum (arrowheads) (D) all dental pulp cell do not show lacZ positive reaction. Abbreviations: X-gal/E, X-gal and eosin staining; X-gal/NFR, X-gal and nuclear fast red staining. All scale bars, 150 μm

binant into a kidney, a nice shape of tooth, which has enamel, dentin, cementum, periodontal ligament and alveolar bone together, was observed. Furthermore, a few adult bone marrow-derived cells were localized in the periodontal ligament and alveolar bone, while there were no adult bone marrow-derived cells within dental pulp and around cementum. These results indicate that these lacZ positive adult bone marrow-derived cells were involved in the formation of periodontal ligament and alveolar bone but not in the formation of dental pulp and cementum. All cells in dental pulp and cementoblasts might be derived from the embryonic tooth germs (Fig. 4). Cementoblasts, osteoblasts and fibroblasts in periodontal ligament are originated from the dental follicle during tooth development (Ten Cate 1997). On the other hand, osteoblasts and fibroblasts are differentiated from bone marrow stromal stem cells (Owen 1988), and cementoblast-like cells can be derived from bone marrow stromal cells (Song et al. 2007, Yang et al. 2010). The result that adult bone marrow stromal cells were not differentiated into cementoblasts in our study might result from the condition that dental follicle was not completely removed from the embryonic tooth germs before recombination. Therefore, dental follicle cells, remained close to tooth germ, rather than bone marrow stromal cells might be differentiated into cementoblasts and fibroblasts. In order to replace dental follicle cells of embryonic tooth germ with adult bone marrow stromal cells maximally, dental follicle has to be trimmed off from the embryonic tooth germ as much as possible. However, dental mesenchymal cells interacting with dental epithelium are necessary to form tooth itself. Optimal trimming amount of dental follicle from the tooth germs has to be determined further to

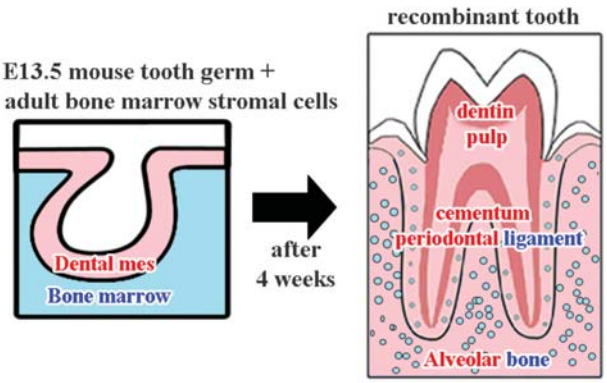

Fig. 4. Origin of dental structure in recombinant tooth. Dental mesenchymal cells (Dental mes, pink-colored) in the mouse embryonic day 13.5 (E13.5) tooth germs induce the formation of dentin, dental pulp, cementum, periodontal ligament and alveolar bone after four weeks. Adult bone marrow stromal cells (Bone marrow, blue-colored) involve in the formation of periodontal ligament and alveolar bone.

get maximal replacement with adult bone marrow-derived cells in periodontal tissues.

Osteoclasts are derived from bone marrow haematopoietic stem cells of the monocyte/macrophage lineage (Teitelbaum 2000) whilst osteoblasts originate from bone marrow stromal stem cells, which have the capacity to differentiate into osteoblasts, adipocytes, chondrocytes, myoblasts or fibroblasts (Owen 1988). Coincident to this, multinucleated osteoclasts in Howship's lacunae were not derived from the adult bone marrow stromal cells, while fibroblasts in periodontal ligament and osteoblasts on the surface of alveolar bone were derived from adult bone marrow stromal cells in our study. Despite β-galactosidase is a translated enzyme from bacterial lacZ gene, mammalian tissues also possess similar endogenous enzyme activities that can induce a false-positive X-gal reaction under certain conditions (Rosenberg et al. 1992, Coates et al. 2001). A false-positive X-gal reaction from genetically normal mice was reported mainly in osteoclasts (Odgren et al. 2006). In our study, osteoclasts did not show lacZ positive reaction, which indicates no false positive reaction in the recombinant tooth. Interestingly, osteoblast-like cells displayed the lacZ positive reaction, whereas osteocyte did not show the lacZ positive reaction. This discrepancy might be resulted from the difference in the volume of cytoplasm between osteoblast and osteocyte, since lacZ positive reaction occurs in the cytoplasm of the lacZ-transgenic ROSA 26 mice (Rosenberg et al. 1992). In consistence with this, it has been reported that osteoblasts showed higher rate of the lacZ positive reaction than osteocytes did (Akahane et al. 2002).

E13.5 tooth germ was recombined with 2.0×10^4 adult bone marrow stromal cells, which is the same number of mesenchymal cells in an E13.5 tooth germ. However, only small number of the bone marrow-derived cells was observed in the periodontal tissues. The failure in X-gal staining as well as cell death can be one of candidate factors inducing this result, since it has been reported that weak β-galactosidase expression levels could remain undetected if tissues are not processed under optimal conditions (Bell et al. 2005, Kopp et al. 2007). However, it remains to be elucidated more.

There have been previous studies reporting the transplantation of tooth germs into adult alveolar socket, where tooth was lost. Implantation of E14.5 rat molar rudiments into adult mouse maxilla extraction socket produced tooth-like structures with surrounding bone (Ohazama et al. 2004, Mantesso and Sharpe 2009). Mouse E14.5 oral epithelium and dental mesenchyme were reconstituted in collagen gel and cultured *ex vivo* (Nakao et al. 2007), and, when they were implanted into the maxillary molar extraction sockets in 5-week-old mice, tooth morphogenesis took place and was followed by eruption into occlusion (Ikeda et al. 2009). It has been expected to transplant a bioengineered tooth unit comprising tooth, periodontal ligament and alveolar bone into the tooth loss region through bone integration between recipient bone and bioengineered alveolar bone (Hu et al. 2006). Transplantation of a bioengineered tooth unit has also been proposed as a viable option to repair the large resorption defects in the alveolar bone after tooth loss (Van der Weijden et al. 2009). In our study, adult bone marrow stromal cells were participated in the formation of periodontal tissue such as periodontal ligament and alveolar bone. If this tooth and periodontal tissues are transplanted into the extraction socket of host donating adult bone marrow stromal cells, adult bone marrow-derived cells will be regarded as host cells, and immune rejection response did not occur in these cells. Furthermore, immune rejection in a whole tooth will be less. Therefore, it is suggested that the recombination between adult bone marrow stromal cells and embryonic tooth germ is a good candidate method, which shed a light on the usage of the xenogenic tooth germ for human by replacing cells in periodontal tissues with human adult bone marrow stromal cells. The recombination method has to be improved more in our next

study, and tooth and its periodontal tissues formed from the recombination will be transplanted into alveolar socket for the evident evaluation of immune response in host after transplantation.

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배아 치배와 성체 골수세포를 이용한 면역 적합 치아이식법

권혁제, 박지희, 김은정, 이민정, 정한성, 조성원

연세대학교 치과대학 구강생물학교실, 구강과학연구소 구강악안면경조직재생연구센터

간추림 : 소실된 치아를 대체하기 위해 가장 좋은 치료법은 동일개체의 치아 또는 치배를 이식하는 것이지만, 사람에서는 이러한 치아나 치배를 얻기는 매우 힘들다. 동종 또는 이종 간의 치아 이식은 치주인대에서 발생하는 면역거부반응에 의해 대부분 실패하였다.

이번 연구는 성체의 골수간질세포를 배아의 치배와 결합시키는 방법을 사용함으로써, 치아 주위조직의 세포를 골수간질세포로 대치할 수 있는 지에 대해서 알아보았다. 실험결과로서, 골수간질세포에서 유래한 세포들을 치주인대와 이틀뼈에서 관찰할 수 있었다. 이는 골수간질세포가 치주인대와 이틀뼈의 형성에 참여하였다는 것을 의미한다. 만약 이와 같은 치아를 골수간질세포를 제공한 개체에게 이식한다면, 면역거부반응이 덜 일어날 것이다. 이처럼 성체 골수간질세포와 배아 치배를 재결합시키는 방법은 치아주위조직의 일부를 골수간질세포로 바꿔주기 때문에, 이종치배를 이용하여 만든 치아를 사람의 턱뼈에 이식할 수 있도록 하는 방법 중 하나가 될 수 있을 것이다.

찾아보기 낱말 : 치아, 이식, 치아싹, 골수

교신저자 : 조성원 (연세대학교 치과대학 구강생물학교실)
전자우편 : chosome1@yuhs.ac