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Letter to Editor

Whole tooth regeneration using organ transplant method: Research comments

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Loss of permanent teeth due to congenital abnormality or subsequent extraction affected the whole function of the body (Yoshida et al., 2009). The treatment to substitute the absent teeth by placing dental implants has been widely performed (Murray and García-Godoy, 2006). However, the lack of vital organ such as dental pulp and periodontal ligament may affect the long-term homeostasis in the oral cavity (Huang, 2011). Stem cell replacement therapy has been extensively investigated in clinical trial for various diseases. However, some concerning issues are the ethical issues, neoplasm formation or unwanted immune responses (Lo and Parham, 2009). As a result, autologous transplantation from the patient is preferred.

Tooth is an organ formed during gestational period with the requirement of interaction of epithelial and mesenchymal cells. The autologous transplantation of tooth germ into the edentulous area has been performed for decades, but the incidence of pulp necrosis or eventual tooth ankylosis was reported (Ferreira et al., 2015). Moreover, the tooth germ from patient's third molar could not always be obtained. Alternatively, a bioengineered tooth germ transplantation technique was introduced as a possible treatment approach (Figure 1). The bioengineered tooth germ was successfully reported in 2007 (Nakao et al., 2007). The transplantation of the bioengineered tooth germ in rodent demonstrated a comparable mechanical property and an adequate supply of nerves and vessels compared to the natural tooth. The erupted bioengineered tooth responded to orthodontic treatment similar to the control, indicating the proper periodontal ligament function (Ikeda et al., 2009). In order to translate experimental models into clinical practice, the trial in larger animal is needed. In 2017, the same authors once again showed that the transplantation of bioengineered tooth germ could be performed in dog and eventually erupted in the oral cavity in the same manner (Ono et al., 2017). In this recent study, the attempt to compare several methods of reconstructing tooth germ was performed. The combination of epithelial or mesenchymal tissues with epithelial or mesenchymal cells/tissues resulted in the high success of tooth germ formation. However, the combination of epithelial-

Limitation of postnatal tooth germ in human is another deterrent for bioengineered tooth construction. Up to date, all bioengineered tooth studies required the cells isolated from tooth germ as a component. Wisdom tooth germ may be isolated and employed for bioengineered tooth construction in the case of

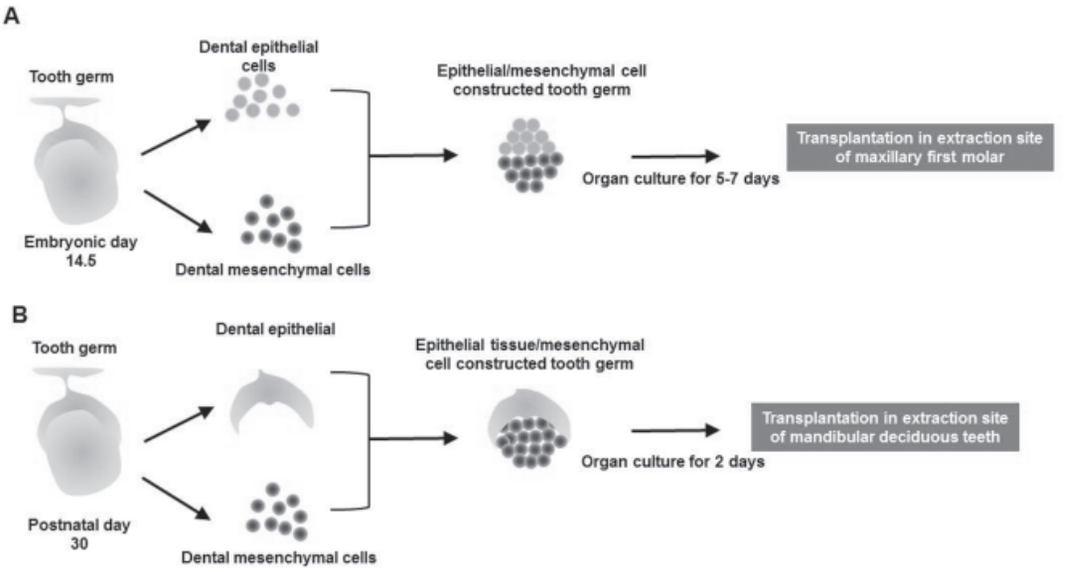

Figure 1: Schematic diagram demonstrated the technique for whole tooth germ construction for transplantation. (A) In the murine model, tooth germ construction was obtained by the combination of dental epithelial cells and dental mesenchymal cells (Ikeda et al., 2009). (B) In the canine model, a composite of dental epithelial tissues and dental mesenchymal cells was employed for the generation of bioengineered tooth germ (Ono et al., 2017).

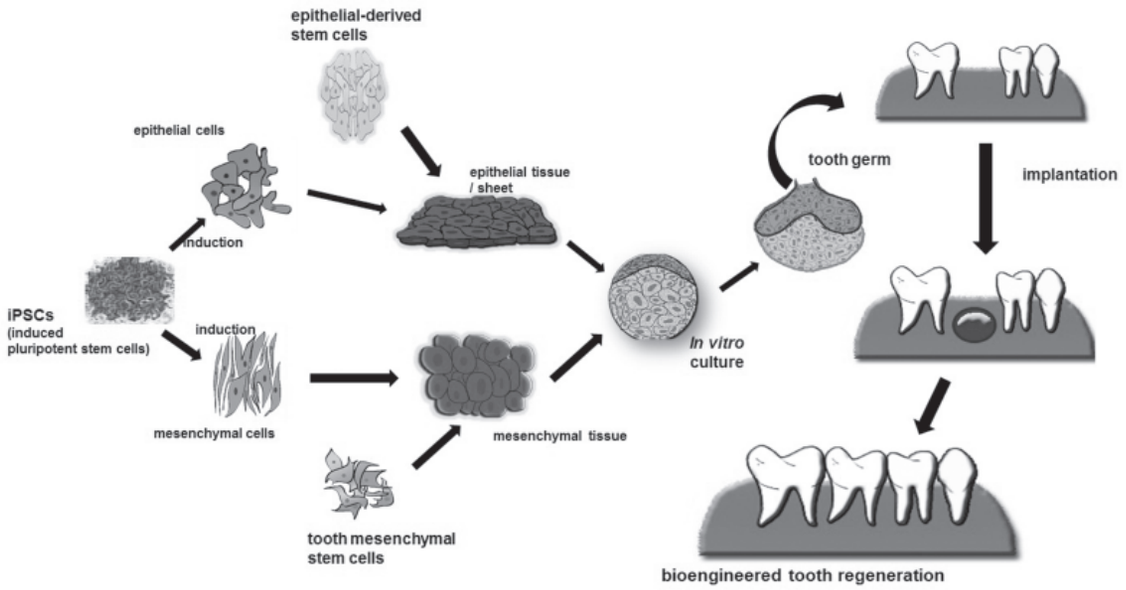

Figure 2: Diagram of bioengineering of a human whole tooth. The induction of iPSCs or epithelial derived stem cells into cells sheets and the induction of iPSCs or dental MSCs. Later, the tooth germ is implanted of into the edentulous sites of patients (Zhang and Chen, 2014).

Table 1: Table compares the success, limitation, and challenges to overcome in each approach to replace the absence of the tooth.

Tooth Replacement method	Success/Benefits	Limitation	Challenge
Dental implant	-Long term success rate proved.	-Absence of dental pulp, nerve and periodontal proprioceptive. -Not suitable in every case as it required surgery in elderly/immuno-compromised patients	-Improving implant surface to induce osseointegration. -Dental surface implant modification.
Autologous tooth transplantation	-Transfer of patient's own tooth from its original location to another site in the oral cavity.	-Pulp necrosis and ankylosis. -Possible for young patients	-Surface treatment of root to preserve vitality of periodontal ligament.
Reconstructed Organ Tooth germ	-Higher success of inducing odontogenic potential to form tooth structure.	-Unavailable source of tooth germ in adult. -May require cryopreservation and storage of the tooth germ.	-How to reconstructed tooth germ from cryopreserved tooth bank. -Improvement on cryopreserved method.
iPSCs derived mesenchymal cells tooth germ	-MSCs can be manipulated/reprogrammed to acquire odontogenic potential. -Available source in adult or elderly from other-non dental tissues.	-Lower success rate of inducing odontogenic properties than whole tooth germ. -Chance of developing tumoregenesis.	-How to increase the success percent of forming tooth germ. -How to control size and morphology of bioengineered tooth to be fully function.

mesenchymal cell constructs exhibited low percentage of tooth germ formation *in vivo*. Although, the accomplishment of erupted and functional bioengineering whole tooth transplantation was observed in the canine model. Several limitations are still required further investigation and research.

Tooth development requires the reciprocal signaling between ectoderm-derived dental epithelium and neural crest-derived mesenchyme. One of the challenge in whole tooth engineering is the identifying the source of postnatal epithelial stem cells that has odontogenic potential. Another obstacle for whole tooth bioengineering to be functionally used is the control of tooth size and morphology. Studies in rodent and canine models revealed an unmanageable bioengineered tooth size and morphology (Ikeda et al., 2009, Nakao et al., 2007, Ono et al., 2017). After transplantation, the bioengineered tooth germ developed into a single-root tooth despite the fact that the isolated tooth germ was from a multi-root tooth origin. The bioengineered tooth was smaller in size than the natural tooth. These results may imply that the induction of epithelial and mesenchymal cells requires particularly interaction of cells from either cell types or seeding technique. Although, previous report indicated that tooth size and morphology could be controlled by an alteration of the epithelial-mesenchymal ratio (Yu et al., 2008). Further knowledge of mimicking cellular signaling during tooth formation is indeed required to precisely control size and morphology of bioengineered tooth.

young adults, but this option may be impossible in elder patients. Propose of cryopreserved autologous dental stem cells or induced pluripotent stem cells for tooth tissue engineering is introduced and investigated. In contrast, induced pluripotent stem cells (iPSC) could be the source of iPSC-derived epithelial cells to induce tooth formation in elderly patients where the source of dental stem cells could not be obtained (Fig. 2). However, the low efficiency of reprogramming reported in the *in vitro* suggests that additional and/or specific signalings are also required to generate iPSCs. More notably, the efficiency of reprogramming decreased when culturing for a long time periods (Utikal et al., 2009) (Table 1).

In spite of several hurdles to overcome, the bioengineered tooth organ transplantation in canine model is one of a step to a biological replacement therapy for tooth loss in the future.

Conflict of interest

Authors declare no conflict of interest. The manuscript has not been published elsewhere nor under any consideration and will not be submitted for publication elsewhere regardless of language.

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