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Okayama University research: Bioengineered tooth restoration in a large mammal

(Okayama, 19 March) **Researchers at Okayama University report in *Scientific Reports* successful tooth regeneration in a postnatal large-animal model. The approach used involves the autologous transplantation of bioengineered tooth germ into a canine jawbone; the *in vivo* artificially created tooth has the structure, composition and physiological characteristics of a natural tooth.**

Conventional therapies for restoring the loss of a tooth — due to e.g. caries, gum disease or injury — essentially consist of replacing the tooth with artificial material or an osseointegrated dental implant. Whole-organ regeneration technology is a promising alternative approach: a new tooth is grown from bioengineered tooth germ transplanted into the jawbone. Takuo Kuboki from Okayama University and colleagues have now demonstrated successful functional tooth restoration via the regenerative method for a postnatal large-animal model (a beagle dog).

The researchers first tested whether bioengineered tooth germ does indeed lead to the formation of a proper tooth. They dissected embryonic tooth germ cells and tissues of a dog 55 days prior to birth, and then reconstructed bioengineered tooth germ by means of a technique known as the organ germ method. The germs were then transplanted into mice. In many cases — Kuboki and colleagues were able to identify the necessary conditions — the germ resulted in tooth-crown formation, featuring both the hard and soft tissues present in natural teeth, after several weeks.

The scientists then performed autologous transplantation experiments. Rather than relying on a donor, autologous treatments make use of an organism's own stem cells (undifferentiated cells that can develop into specialized cells), avoiding immunological rejection. Applying this to their canine model, Kuboki and co-workers extracted deciduous teeth from the jawbone of a 30-day old beagle dog. Tooth germ engineered from the dog's permanent tooth cell and tissue was then transplanted, after two days of cell culture, into the dog's mandible, resulting in tooth eruption 180 days later.

Micro-CT analysis showed that the developmental process of the bioengineered tooth's formation was practically identical to that of a natural tooth, and, by means of scanning electron microscopy and energy-dispersive X-ray spectroscopy, the bioengineered tooth was found to have the same structure and chemical composition of a natural one. Finally, the researchers demonstrated that the response of the regenerated tooth to a mechanical force was consistent with proper physiological functioning of the periodontal ligament (the tissue that connects the crown to the jawbone).

Regarding the future clinical application of the method to humans, the researchers pointed out that immature wisdom tooth germ would be a possible source of stem-cell germs, as it is available in the human postnatal jawbone. However, this would only pertain to younger people — wisdom teeth mineralize after the age of 7; for elderly patients, other stem-cell sources would need to be identified. In any case, quoting Kuboki and colleagues, “this study highlights the feasibility of fully functional tooth restoration by autologous transplantation of bioengineered tooth germ”.

Background

Tooth structure and tooth loss remedies

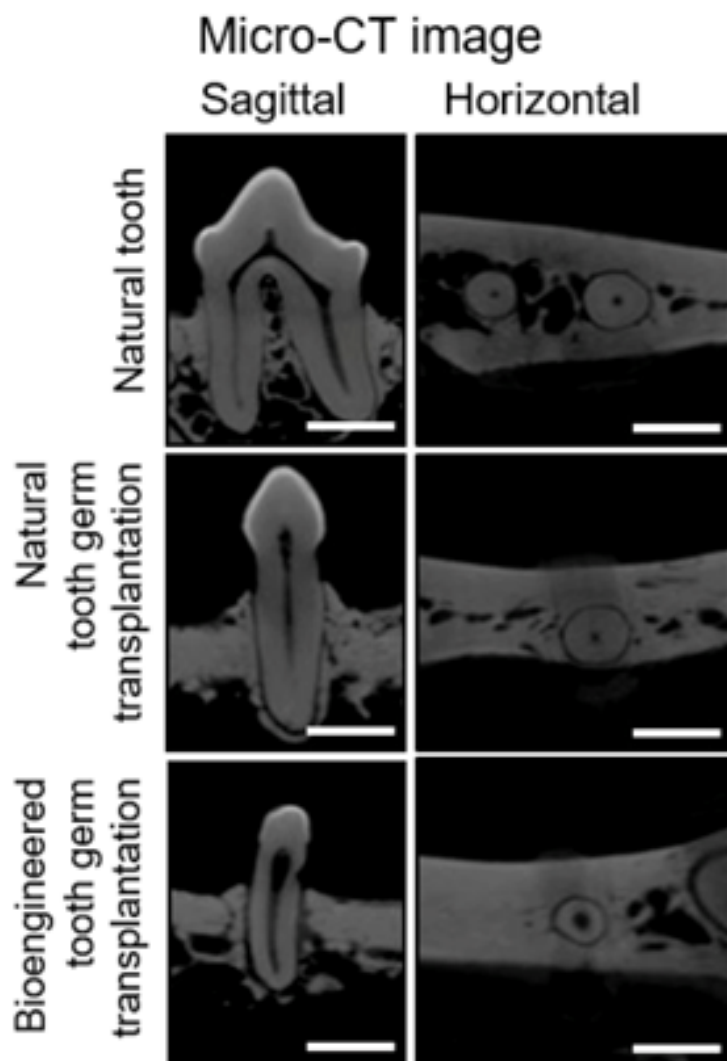
Teeth — playing an essential role in the basic oral functions of mastication, swallowing and pronunciation — comprise hard (such as enamel, dentin and cementum) and soft tissue (such as pulp and periodontal ligaments). As a remedy for tooth loss, fixed dental bridges or removable dentures made from artificial materials have been traditionally used, as well as osseointegrated dental implants: artificial teeth that are directly connected to the jawbone, without intervening soft tissue. Driven by recent advances in biomedical understanding and biotechnological engineering, regenerative technologies for the successful replacement of a lost tooth with uncompromised physiological tooth function — such as the one now reported by Kuboki and colleagues — are intensively researched today.

Donor-organ versus autologous transplantation

The transplantation experiments carried out by the researchers are of the autologous type: a dog’s own tooth germ stem cells were used to regenerate a missing tooth. An autologous transplantation avoids the potential problem of transplant rejection: when an organism receives a donor organ from another, genetically different organism, the former’s immune system may attempt to destroy the transplant. Another complication can be graft-versus-host disease, caused by immune cells of the donated tissue recognizing the host as foreign and starting to attack host cells. It is therefore expected that future whole-tooth restoration in humans will be done by means of autologous transplantation techniques.

Organ germ method

The approach of Kuboki and co-workers involves the bioengineered organ germ method, studied since about a decade ago. The method aims to regenerate ectodermal organs — organs originating from the so-called ectoderm, the outer embryonic layer — such as teeth, hairs and glands, by replicating the organ’s developmental process starting from bioengineered organ germ. In a natural embryo, organ germ arises from the interaction between epithelium (the tissue at the outer layer of a body’s surface) and mesenchyme (tissue sitting below the epithelium). Bioengineered organ germ is created by letting epithelial and mesenchymal tissue or cells interact.



Caption

Micro-CT images of the canine natural tooth group (top), natural tooth germ transplantation group (middle), and bioengineered tooth germ transplantation group (bottom).

Reference

Mitsuaki Ono, Masamitsu Oshima, Miho Ogawa, Wataru Sonoyama, Emilio Satoshi Hara, Yasutaka Oida, Shigehiko Shinkawa, Ryu Nakajima, Atsushi Mine, Satoru Hayano, Satoshi Fukumoto, Shohei Kasugai, Akira Yamagushi, Takashi Tsuji & Takuo Kuboki. Practical whole-tooth restoration utilizing autologous bioengineered tooth germ transplantation in a postnatal canine model. *Scientific Reports*, 7, 44522.

DOI : 10.1038/srep44522 (2017)

<http://www.nature.com/articles/srep44522>

Reference (Okayama University e-Bulletin & OU-MRU) : Professor Kuboki's team

e-Bulletin Vol.9 : [Bio-hybrid implants: Restoring organ functions](#)

OU-MRU Vol.11 : [Compound-protein combination shows promise for arthritis treatment](#)

OU-MRU Vol.19 : [Study links signalling protein to osteoarthritis](#)

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Okayama University is located in the heart of Japan approximately 3 hours west of Tokyo by Shinkansen.

