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Commentary

# Salivary Gland Organ Regeneration for Oral Health

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## Commentary

Salivary glands play essential roles in normal upper gastrointestinal tract function and oral health *via* saliva production. There are three types of salivary glands; the submandibular gland and parotid gland, which secrete serous saliva, and the sublingual gland secretes mucous saliva in mice [1]. Therefore, salivary gland dysfunction due to atrophy of acinar cells caused by Sjogren's syndrome, radiation therapy for head and neck cancer, and aging and saliva reduction, and results in xerostomia (dry mouth syndrome), causes various clinical problems in oral health and influences overall bodily health [2]. Xerostomia induces various clinical problems in oral health, such as dental decay, bacterial infection, and disorders of mastication and swallowing, which result in a general reduction in the quality of life [3]. Current standard to cure xerostomia are symptomatic treatments, such as the administration of artificial saliva substitutes and sialogogues, and the administration of parasympathetic stimulation drugs, including pilocarpine and cevimeline [4]. In salivary gland regenerative therapy, stem cell transplantation, which expressed c-kit and Sca-1 as stem cell markers and exhibit high proliferative capacities [5,6], and gene modification for water channel aquaporin-1 (AQP1) and Interleukin-17 (IL-17) receptor antibody is performed to restore the damaged acinar tissue and recover the flow of saliva [7,8].

Salivary glands arise from the organ germ, which is induced by reciprocal epithelial and mesenchymal stem cell interactions during embryonic development [9]. In this two decades, advances in developmental biology have led to break-through in regeneration of functional bioengineered organ *in vitro* by using embryonic organ-inductive potential stem cells. Recently, regeneration of fully functional salivary gland as a next-generation organ regeneration has been reported after the transplantation of bioengineered salivary gland germ developed by using embryonic organ-inductive potential stem cells as well as iPS cells [10,11]. In 2013, we demonstrated the fully functional salivary gland regeneration by recapitulating the embryonic morphogenesis. The bioengineered salivary gland organ germ, which was reconstituted by our Organ Germ Method using organ-inductive potential stem cells derived from submandibular gland germs of ED 13.5 mice [12], showed reciprocal epithelial and mesenchymal interactions in *in vitro* organ culture. Following the orthotopic transplantation, the bioengineered germ develops into a mature salivary gland *via* acinar formations with a myoepithelium and innervation. The bioengineered salivary gland produces saliva in response to the pilocarpine administration and gustatory stimulation by citrate, protected against bacterial infection and restores normal swallowing function in a mouse model. This study provides a proof-of-concept for bioengineered salivary gland regeneration.

The next breakthrough first reported in 2008 was the emergence of an organoid as a mini-organ that was generated by inducing body patterning and a subsequent organ-forming field formation in pluripotent stem cells [13]. Organoids are useful to recapitulate the process of organogenesis, which are strictly regulated by morphogen signalling and transcriptional networks. To date, multiple types of organoids, including the retina, pituitary gland, liver, and lung have been successfully generated *in vitro*. Our colleagues identified a specific combination of two transcription factors, Sox9 and Foxc1, are responsible for the differentiation of mouse ES cells-derived oral ectodermal region into the salivary gland rudiment in a three-dimensional organoid culture system [11]. The induced salivary gland rudiment showed a similar morphologies and gene expression profiles to those of the embryonic salivary gland rudiment of normal mice. Following orthotopic transplantation into salivary glands-defected mice, the induced salivary gland germ exhibited characteristics of mature salivary glands including histological morphologies, nerve innervation and saliva secretion. This study is the first report of the fully functional organ regeneration by using organoid, demonstrating the potential of salivary gland organ regeneration from pluripotent stem cells for an additional organ replacement regenerative therapy.

As part of regenerative medicine, the autogenous transplantation of stem cells, including bone marrow, and tissue sheets such as skin, cornea, and cardiac muscle, has already been applied clinically through cell and tissue transplantation therapies. The progress made in the past two decades has been remarkable, paving the way for possible future organ replacement regenerative therapies. There remains a critical issue as to whether next-generation organ regenerative therapy can be adopted as a novel clinical therapy for patients of the loss of organ function. The bioengineered salivary gland organ germ by using both embryonic organ-inductive potential stem cells and pluripotent stem cells can grow where salivary grand should be in oral cavity and produce the saliva in response to various taste stimulations. These works indicate the potentials for clinical application of salivary gland organ regeneration. Applying knowledge of these basic research will enable the regeneration of salivary gland organ in the next decades.

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