REVIEW ARTICLE

AODMR

Biological Tooth: Hurdles and Approaches

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ABSTRACT:

Stem cell based bioengineering of tissue or whole organ is a promising branch in this new era. It replaces the diseased or damaged tissues using stem cells. Bio-engineering of teeth as a whole is called as biological tooth or biotooth. Tooth develops by means of reciprocal interaction of oral ectoderm and ectomesenchyme. To find an ideal source of stem cell which can behave in similar manner is the first and foremost hurdle. Other hurdles in generating a biological tooth and ways and approaches to overcome those hurdles are discussed briefly in this review paper.

Keywords: Bio engineered tooth, Bio-tooth, Dental stem cells, Regenerative dentistry.

INTRODUCTION

A tooth may be lost due to caries, trauma or periodontal reasons. Replacement of lost tooth involves fixed, removable prosthesis or implants. Current implant based method of replacing lost tooth may fail to reproduce natural tooth structure due to unequal distribution of forces due to mastication and bone resorption.[1] The main concept in tooth regeneration is to mimic the natural tooth development process either in vitro or in vivo using stem cells. Stem cell based bioengineering of whole tooth is called **Biological tooth or Biotooth.**[2] The Biological tooth achieved through stem cell based tissue engineering techniques appears to an alternative to heal damaged dental tissues. The ultimate target of regenerative therapy is to develop fully functioning bioengineered organs that can replace organs that have been lost or damaged by disease, injury or aging.

HURDLES

Tooth develops in the embryo through highly orchestrated reciprocal interaction between the ectoderm and cranial, neural crest-derived ectomesenchyme cells. In the embryo, oral epithelium sends out first inductive signals to underlying ectomesenchyme instructing them to begin odontogenesis, or tooth formation.

Once the ectomesenchyme have received their inductive signals, they start sending signals back to the epithelium. Their reciprocal exchange continues throughout embryonic tooth development.[3] The first and foremost hurdle lies in the bio- engineering of whole tooth is to reproduce similar microenvironment which mimics that of embroyonical ectomesenchymal interaction. Also ectodermal organs such as hair, skin, sweat glands, mammary glands and salivary glands arise from their respective organ germ through reciprocal epithelial-mesenchymal interactions. Their interaction is the principal mechanism that regulates almost all organogenesis via signaling molecules and transcription factors.[4,5] By carrying out research on laboratory engineering of teeth as a model, the whole field of organ engineering can benefit in the long term.[5]

The second major hurdle is to find an ideal source of stem cells that have the potential to differentiate into tooth forming cells. Stem cells can be divided into three major types. Embryonic stem cells – ESCs derived from embryos, adult stem cells derived from adult tissue and induced pluripotent stem cells -

iPSc generated artificially by reprogramming adult somatic cells which behaves like ESCs. ESCs can differentiate into derivatives of all three germ layers. These cells have potential for tooth regeneration; also this technique is very helpful for understanding basic tooth development.[6] Five major sources of adult dental stem cells have been isolated: Dental pulp stem cells (DPSCs), periodontal ligament stem cells (PDLSCs), stem cells from human exfoliated deciduous (SHEDs) teeth, stem cells from apical root papilla (SCAPs) and dental follicle stem cells (DFSCs).[7-9] Such stem cells are of mesenchymal origin can able to differentiate into odontoblast, cementoblast, fibroblast, osteoblast, chrondroblast, adipocytes and nerve like cells except enamel.

The source of enamel forming cells is from oral stratified squamous epithelial stem cells because they derived from embryonic epithelium which is present in the basal layer.[10] Odontogenic epithelial stem cells of human origin which is isolated from teeth of young children (impacted third molar and from other mammalian sources (e.g., pig) can also able to differentiate into ameloblast.[6,10] The epithelial rest of Malassez (ERMs) are quiescent epithelial remnant of Hertwig's root sheath (HERS). ERMs contain unique population of stem cells and have the capacity to differentiate into diverse lineage indicative of mesodermal and ectodermal origin.[6]

Adult stem cells in non-dental tissues such as bone marrow derived stem cells have the capacity to differentiate into diverse lineage. Because of the ethical issues regarding the use of embryos, and difficulty in isolation, expansion and differentiation of adult stem cells and also possibility of tumorigenesis when transplanted and allogenic immune reaction, the application of ESCs and adult stem cells are limited.[6,7,11] The development of induced pluripotent stem cells iPSc may overcome many of these issues and it plays significant role in future strategies for clinical translational research on tooth regeneration.[6,11,12] All the dental stem cells can be successfully reprogrammed into iPS cells. The multipotency, high proliferation rates, and easily accessable make the dental stem cell an attractive source of mesenchymal stem cells for iPS generation.[13] Alternatively iPSCs from keratinocytes isolated from human foreskin and gingival epithelial cells isolated from patients' gingival tissue has been identified that are able to differentiate into enamel-secreting ameloblasts when recombined with mouse embryonic molar mesenchyme. In 2013, Cai et al generated tooth-like structures using integration-free human urine induced pluripotent stem cells.[14]

The next major hurdle of producing biotooth is the regulation of tooth size and shape. The human dentition is composed of three basic tooth shapes – incisors, canines and molars.[5] Even before the tooth formation begins, its shape will be predetermined by its position. Some of the epithelial signals that trigger initiation of odontogenesis also regulate genes necessary for shape determination.[3] Spatial distribution of mesenchymal gene expression provides positional information to direct the pathways of tooth morphogenesis.[5] During embryogenesis homeobox genes determine the shape and location of organs and appendages throughout the body. For example, expression of homeobox gene Barx 1 in mesenchyme determines the position and shape of molar tooth.[3] The epithelium expresses several signaling molecules, such as BMPs, FGFs, Wnts and Shh, which has control in determining the shape of the tooth. For example, BMP4 and FGF8 expressions are linked with the shape of incisors and molars respectively. BMP4 activates expression of *Msx1* and *Msx2* in the mesenchyme and *Islet1* in the epithelium of the future incisors.[15,16] By contrast, FGF8 activates *Dlx1*, *Dlx2* and *Barx1* expression in the mesenchyme of future molars.[15,16] Furthermore, *Dlx*, *Barx1* and *Pitx1* genes controls the differences in the shape of maxillary and mandibular teeth. Alteration of the odontogenic signaling cascade also leads to modification of tooth size. For example,

smaller teeth were reported in mice after deletion of Wnt signaling.[15]

APPROACHES

There are two approaches for tooth regeneration, either tooth germ or whole tooth unit that includes mature tooth, periodontal ligament and alveolar bone can be bioengineered and transplanted to an edentulous area.

Ishinda et al in 2013 developed an *in vitro* novel three – dimensional cell manipulation method for bio – engineering tooth germ also designated as the organ germ method.[17] In this method, the dental epithelial and mesenchymal tissues isolated from tooth germ are completely dissociated into single cell. These cells are compartmentalized at a high cell density in a type I collagen gel to mimic multicellular assembly and epithelial mesenchymal interaction as well as natural tooth development. The width of the crown is controlled by limiting the contact area between the epithelial and mesenchymal cell layer. The bioengineered tooth germ that generated has structurally similar tooth both *in vitro* in organ culture and *in vivo* after transplantation.

Another method for tooth regeneration is to generate a size-controlled bioengineered mature tooth unit comprising tooth, periodontal ligament and alveolar bone. In this method the tooth size is controlled by a special device and is generated in subrenal capsule. When transplanted into an edentulous area function as a denture and become surrounded by alveolar bone.[4]

CONCLUSION

With the advent of regenerative dentistry, a new era in treatment has opened for the patients wherein patients can utilize their own cell for regeneration. This will greatly reduce immunological rejections. Also a three dimensional *in vitro* organogenesis method has laid foundation for regeneration of other organs.

REFERENCES

1. Volpani AA, Kawasaki M, Sharpe PT. Adult human gingival epithelial cells as a source for whole-tooth bioengineering. J Dent Res 2013;92(4):329-34.

2. Dabas A, Dabas N, Prabhakar M, Sidhu MS. Regenerative Dentistry: A Journey from Stem Cell to a Bio-Tooth. Indian J Dent Sci 2013;5:84-7.

3. Sharpe PT, Young CS. Test – tube teeth. Sci Am 2005;293:34-41.

4. Ishida K, Oshima M, Tsuji T. Tooth tissue and organ regeneration using stem cells. Inflammation and Regeneration 2013;33:29-37.

5. Sartaj R, Sharpe P. Biological tooth replacement. J Anat 2006;209:503-9.

6. Otsu L, Sakano MH, Fujiwara N, Kikuchi L, Keller L, Lesot H, Harada H. Stem cell sources for tooth regeneration: current status and future prospects. Front Physiol 2014;5:36.

7. Kashyap R, Shasikiran ND. A review of tooth regeneration. Int J Oral Health Sci 2013; 3(1):32-6.

8. Dannan A. Dental-derived Stem Cells and whole Tooth Regeneration: An Overview. J Clin Med Res 2009;1(2):63–71.

9. Atalayin C, Kemaloglu H, Tezel H. A fundamental insight into regenerative dentistry: A Review. Ind J Med Res Pharm Sci 2014;1(2).

10. Koussoulakou DS, Margaritis LH, Koussoulakos SL. A Curriculum Vitae of Teeth: Evolution, Generation, Regeneration. Int J Biol Sci 2009;5(3):226-43.

11. Zhang Y, Chen Y. Bioengineering of a human whole tooth: progress and challenge. Cell Regeneration 2014;3(1):8.

12. Romero S, Cordoba K, Martinez VCA, Gutierrez QJG, Duran RJY, Munevar NJC. Candidate markers, culture strategies and DPSC perspectives used as cellular therapy in dentistry. Rev Odont Mex 2014;18(3):156-63.

13. Srijaya TC, Pradeep PJ, Zain RB, Musa S, Abu Kasim NH, Govindasamy V. The Promise of Human Induced Pluripotent Stem Cells in

Dental Research. Stem Cells International 2012:423868.
14. Cai J, Zhang Y, Liu P, Chen S, Wu X, Sun Y, et al. Generation of tooth-like structures from integration-free human urine induced pluripotent stem cells. Cell Regeneration 2013; 2:6.
15. Mitsiadis TA and Papagerakis P. Regenerated teeth: the future of tooth replacement? Regenerative Medicine 2011; 6(2):135-9.
16. Nanci A. Ten Cate's Oral Histology – Development, Structure, and Function. 8th ed. Elsevier: 2013;72-82.
17. Ikeda E, Morita R, Nakao K, Ishida K, Nakamura T, Takano-Yamamoto T, et al. Fully functional bioengineered tooth replacement as an organ replacement therapy. Proc Natl Acad Sci USA 2009;106:13475–80.

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