The Next Gen Of Oral Reconstruction

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Abstract : BACKGROUND: In prosthodontics, the replacement of teeth becomes difficult in case of large bony defects as a result of severe bone resorption, periodontal disease or trauma. Therefore, stem cell and tissue engineering therapies are expected to provide a new dimension to regenerate defects. This dimension has even extended to regeneration of salivary glands, tongue, craniofacial muscles and TMJ cartilage.
SUMMARY: Stem cells considerations for dental application include adult mesenchymal cells and pluripotent stem cells. However, teeth and salivary glands which are epithelial-mesenchymal interaction products are difficult to derive from mesenchymal stem cells(MSCs) hence embryonal cells(ES) have been introduced which had the capability of organogenesis. Induced pluripotent stem cell(iPS) were later introduced that even had the capability to suppress the immune reaction. In Prosthodontics, stem cells in the form of bone grafts are being used widely to augment bone for implant placement. However with newer technology, and use of dental follicle stem cells, growth of the tooth is also possible which would help in oral rehabilitation. Literature also supports regenerative potential of stem cells for other hard andsoft tissues in oral cavity like tongue, condyle, salivary glands etc. There are concerns of biosafety for human trials but once unleashed, a new era of oral rehabilitation will be on its way.
CONCLUSION: Current active research is focused on tissue engineering and chair side cellular grafting approaches. With the increasing advances and successful animal studies, stem cell regeneration can prove to be a new era in the field of prosthodontics and oral rehabilitation.

Keywords : Regenerative prosthodontics, Stem cells, biohybrid implant, Bioengineered tooth

INTRODUCTION

In prosthodontics, the replacement of lost structures becomes difficult in case of large bony defects as a result of severe bone resorption, periodontal disease or trauma. Therefore, stem cell and tissue engineering therapies provide a new dimension to regenerate defects. This dimension has even extended to regeneration of salivary glands, tongue, craniofacial muscles and TMJ cartilage. Stem cells involved in oral tissue regenration for dental application include adult mesenchymal cells and pluripotent stem cells. However, teeth and salivary glands which are epithelial-mesenchymal interaction products are difficult to derive from Mesenchymal stem cells(MSCs) .Introduction of embryonal cells(ES) has improved the capability of organogenesis. Induced pluripotent stem cell(iPS) were later introduced that even had the capability to suppress the immune reaction.[1,2]

In Prosthodontics, stem cells in the form of bone grafts are being used widely to augment bone for implant placement. With newer technology, and use of dental follicle stem cells, growth of the tooth is also possible which would help in oral rehabilitation. Patients with condylar osteochondral defect can also be rehabilitated with the help of stem cells as has been successfully done in animal study. Also for patients who have undergone hemiglossectomy, tongue regeneration is now possible hence improving the overall quality of life. There are concerns of biosafety for human trials but once unleashed, a new era of oral rehabilitation will be on its way. [3,4]

Regenerative techniques applications in dentistry

Regenerative techniques has already been applied in the periodontics and implantology along with oral and maxillofacial reconstruction in cases of cancer and trauma.. Originally, regenerative periodontal/bone therapy was based on scaffold usage.
According to the first generation of regenerative approach, osteoconductive materials such as bone graft were utlilised as scaffold for cells to migrate into the periodontal tissue to regenerate at an acceptable healing rate. In the second generation, osteoinductive materials were used such as growth factors- TGF alpha, IGF etc to stimulate periodontal tissue growth at a faster pace. Therapies including these non-viable materials have already been widely used in dentistry as they have easy surgical application. Third generation regeneration treatment has only included MSCs/bone therapy in clinical research institutes such as universities or hospitals. Fourth generation technology includes cell sheets construction and has only reached the clinical trial stage. Fifth generation techniques are anticipated to utilise oral tissue derived iPS cells and genetically modified cells to create a nature identical tissues/organs such as bioengineered periodontal tissue /teeth.[5-10] (fig. 1)

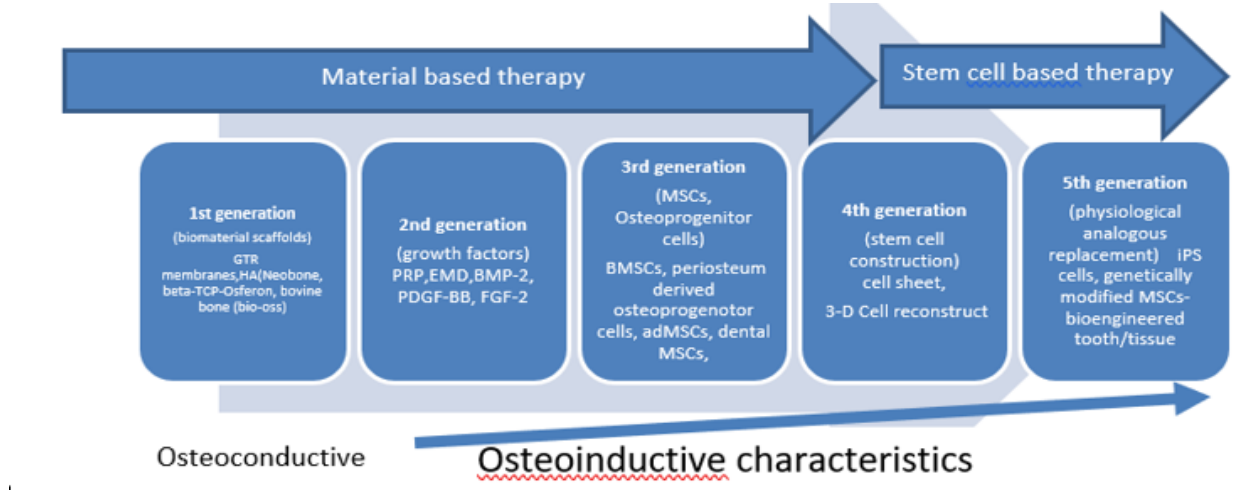

Figure 1

Combined approach of including scaffolds, growth factors and stem cells are likely to enhance the efficacy of regenerative therapies as compared to traditional tissue engineering concept.[11]

The degree of clinical acceptance may widely vary between the material based approaches (first and second generation) and stem cell based approaches(third and fourth). So, the regenerative dental treatments can be divided into groups based on utilisation of stem cells. The two commonly used techniques are scaffold based and tissue based regeneration. This paper gives an overview, of successful researches conducted on animal model for the regeneration of mandible, tooth, salivary gland and tongue.

Tooth/root regeneration

The definitive goal of regeneration of tooth is to develop a fully functional bioengineered teeth to replace lost teeth. Regeneration of an entire tooth will be the highest achievement in the field of dentistry. Many invivo studies to form dental tooth structure have been done on mice, rats and swine models. Sonayama[12] demonstrated that a root/PDL complex can be constructed using periodontal stem cells(PDSCL), stem cell from apical papilla(SCAP) and a Hydroxyapatite Tricalcium phosphate(HA/TCP) scaffold. In the pig model, it could support an artificial crown and provide normal tooth function. Cell sheet formation technologies using dental follicle cells(DFCs) along with dentin matrix based scaffold have been successfully used for root reformation.[16] These novel techniques provide an opportunity to regenerate tooth root and its associated structures such as periodontium for treatment of damaged and lost teeth.[12-15]

Ikeda et al (2009) showed the replacement of a fully functional tooth in a mouse using transplantation of bioengineered tooth germ made from epithelial and mesenchymal stem cells in collagen gel in alveolar bone.[17] This bioengineered tooth came into occlusion after eruption having the correct structure and hardness of mineralised tissues. It was capable of mastication and responded to noxious stimuli such as compressive stresses and pain in cooperation with surrounding associated maxillofacial structures. Oshima et al(2011) demonstrated the invivo reconstruction of bioengineered tooth using the same source of cells in a murine model (Fig. 2). [18]

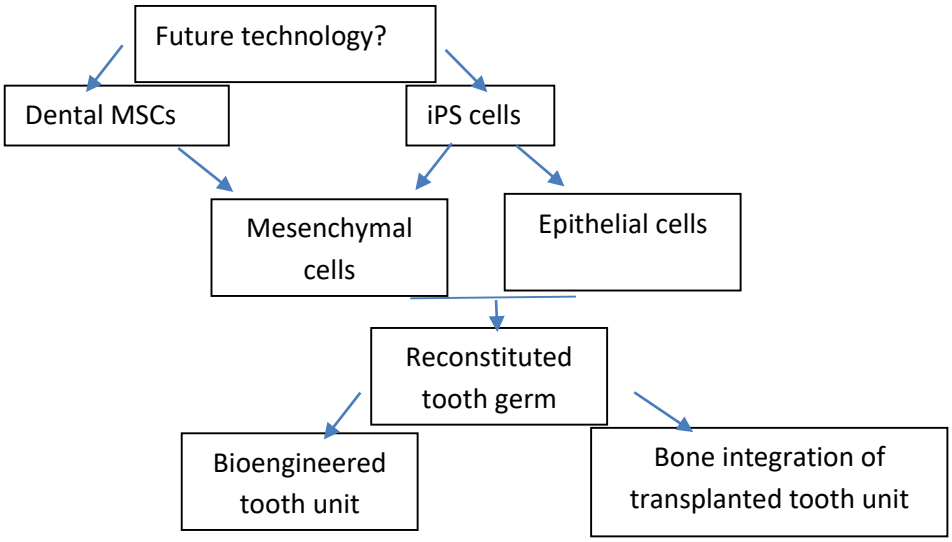

Figure 2.

The bioengineered unit not only comprised of a mature tooth along with periodontal ligament but also alveolar bone formed around it. When the unit was transplanted in a vertical alveolar bone defect in a mouse model, the regeneration of the tooth along with vertical bone regeneration occurred. The results of this study hold significant value not only for the transplantation of a

bioengineered tooth but as well as the whole regenerative therapy as in cases with clinical tooth loss accompanied with bone defects.[18]

The major challenge faced by this clinical application of tooth regeneration approach is the identification of a proper source of autologous stem cell in humans.[19] In this context, immunologically modified pluripotent cells may be considered as an ideal stem cell source as they can be differentiated into dental epithelial and mesenchymal cells and can be prepared from the same patient.

Oshima(2014) made a biohybrid implant using dental follicle stem cells inducing vertical bone regeneration in a mouse for a three walled bony defect.[20,21] Also Oshima(2011) successfully demonstrated a bioengineered unit integrating into s recipient bone which lead to remodeling of extensive bone defect. The recipient alveolar bone's vertical dimension helped to maintain the height of periodontal ligament.[18] (Fig. 3)

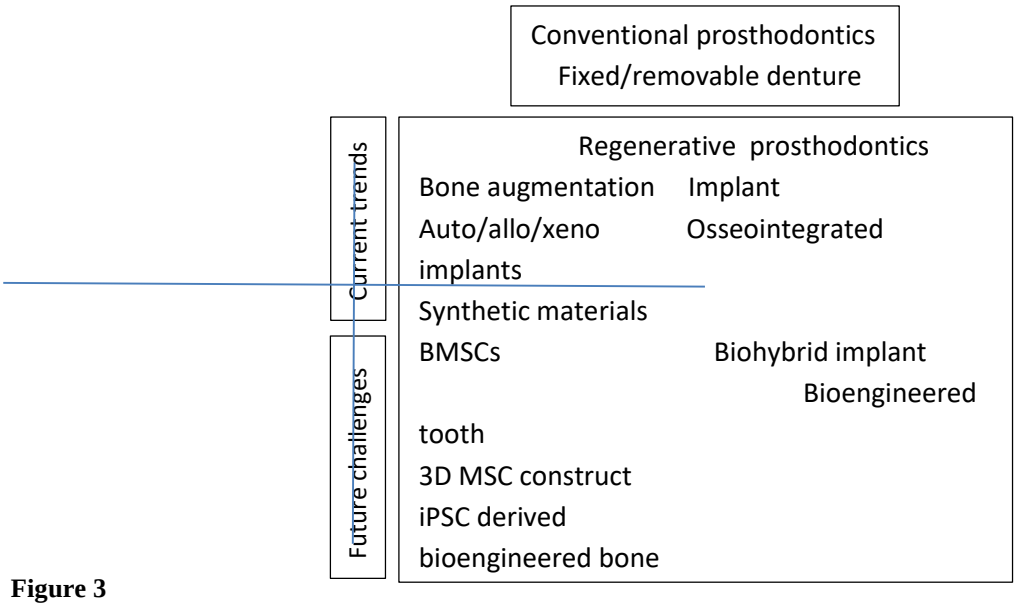

Figure 3

Mandible condyle regeneration

Injury to the TMJ disc or condyle (condylar osteochondral defect) due to trauma or arthritis can cause chronic pain and altered masticatory function for patients. Improved Quality of Life(QOL) can be attained by the new tissue regenerative strategy on the defect in patients. Yu(2011) conducted an experiment on a goat model. The combined use of cartilage tissue and cartilage derived progenitor cells was carried out in a hydrogel and then distraction osteogenesis was performed .The condylar osteochondral defect was successfully reconstructed.[22] In addition, a human shaped mandibular condyle was engineered from chondrogenically and osteogenically induce rat Bone marrow Mesenchymal Stem cell (BMSCs) encapsulated in a polymer which is biocompatible.[23,24] Regeneration of rabbit mandibular condyle was possible with enhancement using low intensity ultrasound pulse to stimulate BMSCs to differentiate into chondrogenic and osteogenic cells.[25] In diseases such as rheumatic arthritis, these researches provide a solid base for the concept of stem cell based tissue engineering to regenerate degenerated articular condyles. [26,27]

Salivary gland regeneration

In head and neck oncology and surgery, often due to unavoidable radiotherapy, salivary glands are functionally impaired and lead to xerostomia. Regeneration of salivary glands by stem cell transplantation is an important research. There are two approaches- One is to use tissue engineering technologies to develop artificial salivary glands and the other is to apply stem cells to the impaired salivary gland.[28-30]Kojma et al(2011) conducted a study in a murine model, where adipose derived Mesenchymal stem cells(adMSCs) were transplanted into radiated submandibular glands to restore the salivary function.[31] Sumita et al (2011)demonstrated the repair of function of irradiated glands also took place due to transplantation of BMSCs in mouse tail vein.[32]

Lombaert et al(2008) and Nanduri et al (2011) transplanted primitive salivary gland stem cells isolated from mice model into the gland leading to successful repair of the function of irradiated salivary glands .[33,34] These research findings suggest that stem cell transplantation may be used to functionally repair damaged salivary glands. The mechanism of regeneration needs to be specified in these studies as it is because of repair of damaged host cells through replacement or by active turn over of the host cells. (Fig. 4)

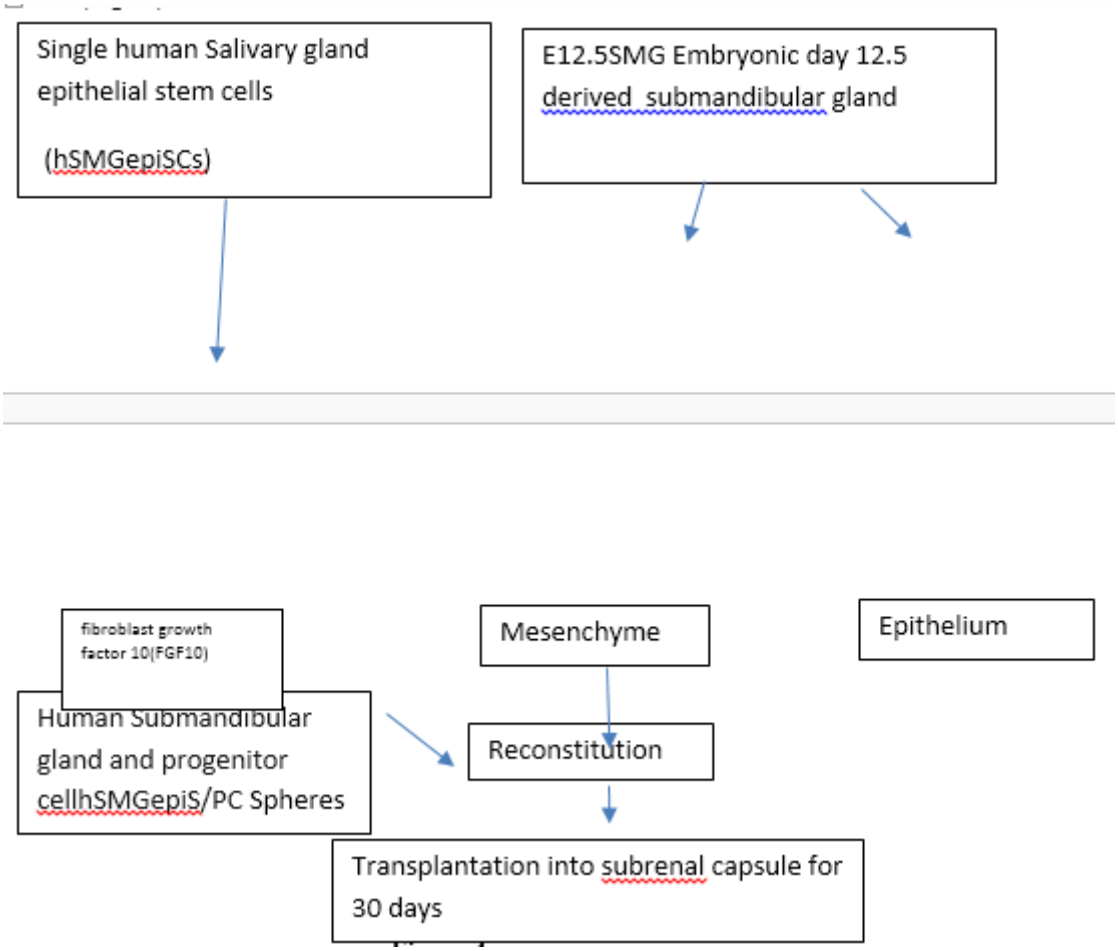

Figure 4

Tongue regeneration

The role of tongue in speech, deglutition and airway protection is well known. The loss of tongue structure either due to trauma or surgical resection can significantly affect the Quality of Life .(QOL) One of the greatest challenge in dentistry is the reconstruction of tongue due to presence of skeletal muscle fibres, taste buds in mucosa and nervous tissues as well. Luxameechanporn(2006) and Brunaprasert (2003) demonstrated cell based reconstruction of tongue structure in a murine model where myoblast progenitor cells are carried into collagen gel and transplanted into hemiglossectomised tongue, to regenerate muscle .[35,36] Egusa et al. proved in his study that applying cyclic strain to Bone Marrow Stem cells greatly increased the rate of in vitro skeletal myogenesis to achieve aligned myotube structures, thus showing that alignment of the cells is very important for creating physiologically related environments to harbour skeletal muscle. The recent development in stem cell biology as well as tissue engineering techniques may allow the reconstruction of a completed damaged and resected tongue within the normal functioning physiologically. [37]

CONCLUSION

The definitive goal of prosthodontic treatment should be the complete replacement of missing structures by a fully functional regenerated tissues. The future of stem cell research is of value to prosthodontics as it can bud into another specialty of regenerative prosthodontics. With the advancement in technology and successful researches, it might be possible in the future to replace a missing tooth/tissue with a complete physiologic analogue. Either a bioengineered tooth which is regenerated from stem cell or biohybrid implants which have integration with bone with true PDL fibers could be the future of replacement of tooth.As well as, complete replacement of tissues/organs like mandibular condyle, salivary gland etc will open a new door in our field of prosthodontics.

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Figure captions

Figure 1: Progress in tissue regenerative technologies. Technologies from 1st to 4th generation have already reached the clinics. (Adapted from Egusa H et al. Stem cells in dentistry Part II: clinical application. Journal of Prosthodontic Research.2012;56:229-248)

Figure 2: Schematic representation of the current regenerative processes for mature tooth/organ replacement. (Adapted from Oshima M, Mizuno M, Imamura A, Ogawa M, Yasukawa M, Yamazaki H, et al. Functional tooth regeneration using a bioengineered tooth unit as a mature organ replacement regenerative therapy. PLoS One 2011;6:e21531)

Figure 3: Future prosthodontic treatment for tooth and bone loss as expected. Bio hybrid implants and bioengineered teeth are good alternatives to osseointegrated implants. The possible sources of stem cells are BMSCs and iPSCs.(Adapted from K. Niibe, et al., Challenges for stem cell-based "regenerative prosthodontics", J Prosthodont Res .2016:1-3)

Figure 4: Regeneration of salivary gland organ by using hSMGSCs(human Submandibular gland stem cell) transplanted into mice subrenal capsule. HE staining in lower right image.(Adapted from Sui Y et al. Generation of functional salivary gland tissue from human submandibular gland stem/progenitor cells.Stem cell research and therapy.2020;11(27):1-13)