Stem Cell Therapy in Dentistry: An Overview

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Cells with a unique capacity for self-renewal and potency are called stem cells. With appropriate biochemical signals stem cells can be transformed into desirable cells. Regeneration of oral and maxillofacial structures is carried out by using stem cell therapy, and this has gained momentum in recent days. Future tissues like tissue engineered bone grafts, engineered joints and cranial sutures can be developed with stem cell therapy. We have described the properties, types and advantages of dental stem cells. Emphasis is been given to the possibilities of stem cell therapy in the oral and maxillofacial region including regeneration of tooth and craniofacial defects.

Keywords: Oral and maxillofacial region, Stem cells, Stem cell marker, Tooth regeneration

INTRODUCTION

Stem cells are a unique type of cells that have specialized capacity for self-renewal and potency. These cells can give rise to one and sometimes many different type of cells. They are found in almost all multi-cellular organisms and are characterized by the ability to renew through mitotic cell division while maintaining the undifferentiated state. A classic stem cell should possess two properties namely self-renewal and potency. A self-renewal is the capacity of the cell to undergo numerous cycles of cell division maintaining the undifferentiated state. Potency means the differentiation capacity of the stem cell.

STEM CELL PROPERTIES

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STEM CELL TYPES

Stem cells can be broadly divided into:
1. Embryonic stem cell
2. Adult stem cell which are further divided into:
   • Hematopoietic stem cell
   • Mesenchymal stem cell (MSC).
3. Induced pluripotent stem (IPS) cell.

Embryonic Stem Cell

Embryonic stem cells are capable of multipotential differentiation. The inner cell mass of the embryo is used to form embryonic cell lines. Embryonic stem cells has a potential to differentiate into germ layers namely ectoderm, endoderm and mesoderm. Tumorogenesis and immune rejection is common with embryonic stem cells.

Adult Stem Cell

Adult stem cells are multipotent stem cells. They have been harvested from different kinds of tissues like bone marrow, umbilical cord, amniotic fluid, brain tissue, liver, pancreas,
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IPS Cell
IPS cell is an evolving concept in which 3-4 genes found in the stem cells are transfected into the donor cells using appropriate vectors. The stem cells thus derived by culturing will have properties almost like embryonic stem cells. This path breaking discovery may have a major role in future stem cell therapy.

**DENTAL STEM CELL ADVANTAGES**

The advantages of stem cells from oral and maxillofacial region are that:
- Stem cells have high plasticity
- They can be cryopreserved for a longer period (ideal for stem cell banking)
- It showed good interaction with scaffold and growth factors.

Stem cells transplantations can cause pathogen transmission and also need the immunosuppression, so autologous stem cell source is the best option. DPSCs will be better fitting tool due to easy surgical access, the very low morbidity of the anatomical site after the collection of the pulp.

**APPLICATION OF STEM CELL THERAPY IN THE ORO-MAXILLOFACIAL REGION**

The structures of interest in oral and maxillofacial region include the enamel, dentin, dental pulp, cementum, periodontal ligament, craniofacial bones, the temporomandibular joint, ligaments, skeletal muscles, tendons, skin, subcutaneous soft tissue, and salivary glands.

**Regeneration of Dentin, Pulp**
Dental pulp tissue has the regenerative potential to form dentin in response to any injury. Tubular dentin formation was observed when human pulp stem cells with scaffold (hydroxyapatite/tricalcium phosphate) were implanted in immunocompromised mice. Reparative dentin formation on amputated pulp was found when stem cells were combined with recombinant human bone...
morphogenetic protein 2 in experimental studies on animal models.\textsuperscript{18}

Regeneration of the pulp inside the damaged tooth can be the basic clinical application of stem therapy in dentistry. Root canal treatment in a young permanent molar will stop the tooth’s continuous maturation process thereby leaving thin egg shell like weak tooth that is susceptible to fracture. Regeneration of pulp with stem cell therapy will be a better option. Stem cells harvested from the pulp of unwanted teeth like third molar can be utilized to regenerate the pulp of severely injured tooth there by preventing the need for endodontic treatment in adults.

**Stem Cell in Periodontal Regeneration**

Stem cells are promising a tool for regenerating the periodontal structures such as a periodontal ligament and other supporting elements.\textsuperscript{19} Autologous MSCs from the iliac crest in combination with platelet rich plasma from peripheral blood was used for periodontal regeneration. Significant closure of bone defect and improvement of attachment level was observed after 1-year follow-up. It was also showed good healing and regeneration of the interdental papilla.\textsuperscript{20} The transplantable constructs in combination with porous b-tricalcium phosphate induced regeneration of periodontal structures, including alveolar bone, cementum, and periodontal fibers.

Nagatomo \textit{et al.} in their experimental studies found that PDLCs having stem cell properties can regenerate periodontium.\textsuperscript{21}

**Regeneration of Craniofacial Defects**

Stem cells can be useful in the regeneration of bone and to correct large craniofacial defects due to cyst enucleation, tumor resection, and trauma. The closure of a bone defect is commonly carried out with the transfer of tissue, which have disadvantages like, not able to restore the unique function of the lost part, donor site morbidity, accompanied by scarring, infection and loss of function.\textsuperscript{22} Autologous fibrin glue, which holds the cells in place, was prepared by cryoprecipitation. This successful technique has given new rays of hope that ADSCs can be used for difficult reconstructive procedures.\textsuperscript{23}

Soft tissue reconstruction in the oro-maxillofacial region is of paramount importance when there is a significant loss of soft tissues during surgery or trauma. Various methods including graft and flap transfer has been tried that produced donor site morbidity. Adipose cells with the appropriate shaped scaffold can be used for reconstruction of soft tissues.\textsuperscript{24}

Stem cells isolated from dental pulp have a potential to differentiate into osteoblasts and are a good source for bone formation.\textsuperscript{24} Stem cells from oral and maxillofacial region can be combined with BMSCs to correct larger defects. Oro-maxillofacial bone tissue repair with stem cells was done using collagen sponge scaffold and DPSCs harvested from third molars of the same patient.\textsuperscript{25} This new procedure has added advantage of permitting the transplantation of more cells and better integrity compared with cell suspensions or gels.\textsuperscript{26} Stem cells isolated from SHED has significantly promoted wound healing in nude mice, proving deciduous teeth can be utilized for the treatment of chronic wounds. This application can be extended into oro-maxillofacial region to enhance wound healing.\textsuperscript{26}

**Future Tissues**

Future tissues like tissue engineered bone grafts, engineered joints and cranial sutures can be developed with stem cell therapy. A team of professionals including stem cell biologists, molecular biologists, geneticists, polymer and materials scientists, mechanical engineers and clinicians with knowledge of oral and maxillofacial disorders is needed to develop the field of craniofacial tissue engineering.\textsuperscript{27} The ability to design anatomically viable and functional bone would have great potential for oro-maxillofacial reconstructions of congenital defects, cancer resections, and trauma. The anatomically shaped viable bone grafts like articular condyles can be engineered by using adult MSCs and biomimetic scaffold bioreactor.\textsuperscript{28,29}

Tissue engineered temporo-mandibular joint was created by having natural bone building process as inspiration. Condyle shaped scaffolds were made using decellularized bone with the help of digitized clinical images. Stem cells were seeded into the scaffold and placed in a bioreactor chamber containing culture medium.\textsuperscript{30} In the future, this technique can be applied to regenerate other bones in oro-maxillofacial region.

**Tooth Regeneration**

The regeneration of adult teeth will be possible in the future with the newer advancement in stem cell therapy and tissue engineering.\textsuperscript{31} Regenerative procedures would be better fitting and alternative tool in place of dental implants. Experimental studies with animal models have shown that the tooth crown structure can be regenerated using tissue engineering techniques that combine stem cells and biodegradable scaffolds.\textsuperscript{32} Epithelial-mesenchymal interactions are mandatory in tooth development. “These interactions are characterized by the reciprocal exchange of signals between these two na"ive germ layer tissues and result in the emergence of unique terminal phenotypes with their supporting cells.”\textsuperscript{33}

Tooth regeneration involves three key elements which include:

- Inductive morphogenesis
• Stem cells
• Scaffold

Steps involved in regeneration of tooth are:
1. Harvesting and expansion of adult stem cells
2. Seeding the stem cells into the scaffold that provides optimized the environment
3. Cells are instructed with targeted soluble molecular signals spatially
4. Confirming the gene expression profile of the cells for the next stage in odontogenesis.34

**RISK FACTORS OF STEM CELL THERAPY**

1. Tumor formation
2. Immune responses
3. Human pathogen transmission and adventitious agents
4. Unwanted dedifferentiation.
   1. Tumor formation: Stem cell resembles some of the features of cancer cells, such as long life span, relative apoptosis resistance and ability to replicate for an extended period. Therefore, stem cell may be considered potential candidates for malignant transformation
2. Immune responses: Administration of stem cells may affect the host immune system. The administered cells may directly induce an immune response or may have a modulating effect on the immune system
3. MSCs have been reported to be immune privileged and have a low immunogenic potential
4. Adventitious agents: Manufacturing of cell based medicinal products inevitably does not include terminal sterilization, purification, viral removal and inactivation. Therefore, viral and microbial safety is a pivotal risk factor associated with the use of non-autologous cells including stem cells. Donor history is of particular importance for stem cell lines. The risk of donor to recipient transmission of bacterial, viral and fungal or prion pathogens may lead to life-threatening reactions.35

**CONCLUSION**

The fixture dentistry will be more of regenerative based, where patients own cells can be used to treat diseases. Stem cell therapy has got a paramount role as a fixture treatment modality in dentistry. Regenerative Dentistry will have to go in pace with regenerative medicine. On the other hand, stem cells should be differentiated to the appropriate cell types before they can be used clinically. Otherwise it might lead to deleterious effects. Determining the role of local conditions such as the type of scaffold and the presence of the microorganisms should be very carefully analyzed. Longer patient follow-up is needed to study the lifetime of regenerated tissue.

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How to cite this article: Shete M, Byakodi R, Kshar A, Paranjpe A. Stem cell therapy in dentistry: An overview. IJSS Case Reports & Reviews 2015;1(8):50-54.

Source of Support: Nil, Conflict of Interest: None declared.