An Overview of Stem Cell Therapy in Oral and Maxillofacial Surgery.

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Abstract: Stem cells provide new strategies to regenerate missing tissues and treat diseases. Adult mesenchymal stem cells (MSCs) is an ideal source for genetically reprogrammed cells ie, induced pluripotent stem (iPS) cells. Adult stem cells taken from one area of the body can be transplanted into another area and grown into a completely different type of tissue.Adult stem cells varies in differentiation capacity, accessibility, and immune-modulatory properties .Clinical use of mesenchymal stem cells for bone regeneration overcomes the limitations of other grafts. Stem cell therapy and tissue engineering are gold solution for bone and soft tissue regeneration and provide hope of future application in humans within the next few years. Tissue engineering modalities will provide numerous clinical applications, including improved treatments for intraosseous defects, enhanced maxillary and mandibular grafting procedures, and possibly even re-growing lost teeth and tissue in maxillofacial region. This paper aims at discussing the use of patient’s own stem cells for biologically compatible therapies and individually tailored treatments in the oral and maxillofacial region .We have searched relevant articles on this subject in various medical databases including Google Scholar, PubMed Central, Science Direct, Wiley Online Library, Scopus, and Copernicus. The search resulted in more than 120 articles, out of which a total of 67 were reviewed. However, the review has been further constricted into only 32 articles as has been presented in this manuscript. Advanced MEDLINE search was performed using the terms “adult mesenchymal stem cells,” “stem cells from maxillofacial region,” and “craniofacial tissue engineering.

1. INTRODUCTION: Tissue engineering is the study of growth of new connective tissues or organs from cells and a collagenous scaffold to produce a fully functional organ for implantation back into the donor host. The various strategies of tissue engineering are: cell injection, cell induction and cell seeded scaffold. Stem cells are pluripotential cells with inherent capacity of self renewal and differentiation. The stem cell based regenerative technology represent a new frontier in oral and maxillofacial surgery in the regeneration of oral tissues.

The pluripotent adult stem cells sources are bone marrow, adipose tissues, lung and teeth etc. Stem cells are loaded in a “scaffold”. Scaffold can be natural or artificial and biodegradable or non biodegradable. Materials such as poly lactic acid, polyglycolic acid (PGA), polyethylene terephthalate, polypropylene fumarate, hydroxyapatite/tricalcium phosphate, fibrin, alginates, and collagen are used.[1] Various growth factors used are platelet derived growth factor, insulin like growth factor, transforming growth factor, fibroblast growth factor, bone morphogenetic proteins etc .

Stem cell technologies have permitted the development of bioengineered tooth to replace the patients missing teeth .The concept of dental stem cell banking have revolutionized the field of regenerative therapy. The draw back of stem cell based therapy is that most studies up to date have not considered the negative effect of the host immune system on transplanted cells .

2. MATERIALS AND METHODS : Literature was selected through a search of GoogleScholar, PubMed Central, ScienceDirect, Wiley Online Library, Scopus, and Copernicus electronic databases. The research was restricted from 1960 to 2013. Thirty -two articles that met the inclusion criteria and were included in the study.

3. DISCUSSION:

Types of stem cells include:1.Embryonic stem cell, 2. Adult stem cell, 3. Induced pluripotent stem cell(iPS) .Adult stem cell consist of Hematopoietic stem cell and Mesenchymal stem cell. Mesenchymal stem cells include bone marrow-derived MSC, oral mucosa-derived stem cells , periosteum-derived stem cells, salivary gland-derived stem cell, dental tissue-derived stem cells, adipose tissue-derived stem cells (ASCs).

3.1. Embryonic stem cell : Embryonic stem cells are capable of multipotential differentiation but use is limited due to ethical issues. 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 ectoderm, endoderm and mesoderm.Tumorigenesis and immune rejection is common with embryonic stem cells. To overcome this human ES cell banks (HLA) matching and patient-specific ES cells via nuclear transplantation have been proposed.

3.2. Adult stem cell: Adult stem cells are multipotent, somatic /post natal stem cells. They reside in specific areas of tissues – stem cell niche. They can be harvested from different tissues like bone marrow, umbilical cord, amniotic fluid, brain tissue, liver, pancreas, cornea, dental pulp, and adipose tissue. Hemopoietic stem cell harvested from peripheral blood by plasma apheresis. Adult stem cells are easier to isolate and do not have any ethical issues. Placental and cord blood stem cell transplants also available. Virus free, tissue-typed stem cells stored in liquid nitrogen for future transplant. Immune rejection and teratoma formation is also rare with adult stem cells.

3.3. Induced pluripotent stem cell: Induced pluripotent stem cells (iPS) is an evolving concept in which 3–4 genes found in the stem cells are transected into the donor cells using appropriate vectors. The iPS cells is a powerful tool in regenerative medicine and future stem cell therapy. Tumourigenicity is a significant challenge in clinical use. SCAP, DPSCs, SHED, TGPSCs, buccal mucosa/gingival /PDL fibroblasts have a higher reprogramming efficiency by introducing four genetic factors (Oct3/4, Sox2, Klf4 and c-Myc). Used to regenerate missing jaw bones, periodontal tissues, salivary glands and lost teeth.

3.2.1. Mesenchymal stem cells: They are isolated from bone marrow, muscle, circulating blood, blood vessels, fat. They can differentiate into a wide array of cell types and exert potent paracrine effects enhancing the ability of injured tissue to repair itself. According to the ISCT (International Society for Cellular Therapy) criteria, MSCs must be adherent to tissue-culture-treated plastic when maintained in standard culture conditions. MSCs must express CD105, CD73, CD90, CD271, MSC antigen -1. MSCs must be able to differentiate to osteoblasts, adipocytes and chondroblasts.

3.2.2. Bone marrow: Bone marrow stem cells (BMSCs) can be harvested from sternum or iliac crest and is composed of both hematopoietic stem cells and mesenchymal stem cells (MSCs). Bone marrow aspirates obtained from maxilla and mandible during dental implant treatment, wisdom tooth extraction, extirpation of cysts etc. They are functionally /phenotypically different from iliac crest stem cells. Maxilla /mandible is of neural crest origin, whereas iliac crest is of mesodermal origin. Oro facial BMSC have high proliferative index, high osteogenic potential, less adipogenic potential, less unfavourable fat formation, less age related decline in osteogenic potential. Collectable volume of BMSC from orofacial bones is 0.03-0.5 ml. Isolation is done under general anesthesia. Bone marrow harvested under aseptic conditions from anterior iliac crest /mandible using Jamshidi needle. Diluted with phosphate buffered saline and centrifuged at 2200 rpm for 25 min. Processed in a closed system for volume reduction. Bone marrow mononuclear cells (BMMNC) layer (buffycoat) separated, viability checked by tryptan blue staining. Cells in a sterile syringe injected into the lesion.

3.2.3. Adipose tissue: Adipose-derived stem cells have also been isolated from human fat by liposuction or lipoectomy. It is easily accessible, abundant and the harvest procedure is less painful and can differentiate into bone, cartilage, fat, and muscle. Adipose-derived stem cells have been recently used to successfully repair a large cranial defect in a human patient.

4. STEM CELLS FROM ORO-MAXILLOFACIAL REGION

4.1. They predominantly contain mesenchymal stem cell and include: Dental pulp stem cells (DPSCs), Stem cells from exfoliated deciduous teeth (SHED), Periodontal ligament stem cells (PDLSCs), Stem cells from apical papilla (SCAP), Dental follicle progenitor cells (DFPCs), Oral mucosa derived stem cell, Periosteum derived stem cell, Salivary gland derived stem cells

![Figure 1: Sources of dental stem cells.](image)

These dental stem cells have MSC like qualities, such as self-renewal and differentiation potential. DPSCs were successfully isolated by Gronthos et al., in 2000. Odontoblast like cells from DPSCs produce ectopic dentin in the immunocompromized mice. SHED were identified to be cells of immature multipotent clonogenic cells isolated from deciduous teeth that can differentiate into several cell types. PDLSCs were isolated from periodontal ligament by Seo BM et al. They demonstrated cementoid cells, adipocytes when transplanted into immunocompromized rodents. Sonoyama et al isolated mesenchymal stem cells from apical papilla called SCAP. Morsczeck C et
al obtained stem cells from dental follicle called dental follicle precursor cells (DFPCs). [10]

4.2. Oral mucosa derived stem cells: They are of two types. 1. Epithelial progenitor cells consist of small oral keratinocytes, unipotent and used for oral mucosal grafting. 2. Lamina propria of gingiva from alveolar ridge /retromolar region multipotent and differentiate into lineage of three germ layers.

4.3. Periosteum derived stem cells: Include two layers outer fibroblastic elastic fibre layer and inner mesenchymal cells and osteogenic progenitor cells. It can differentiate into osteoblast, adipocytes, chondrocytes and express Msc markers. Periosteal graft forms cortical bone. Used for orofacial bone regeneration, alveolar ridge augmentation, maxillary sinus floor augmentation and enhanced lamellar bone formation with implants.

Salivary gland derived stem cells: Isolation of stem cells in the salivary gland through cell culture of dissociated tissue. It has high proliferative index. Express acinar, ductal and myoepithelial cell lineage markers. Used for regeneration of damaged salivary tissues. Can be guided to differentiate into adipocytes, osteogenic and chondrogenic cells.

5. STEM CELL PROPERTIES: A classic stem cell properties are self-renewal and potency. Self-renewal is the capacity of the cell to undergo numerous cycles of cell division maintaining the undifferentiated state. [12] An ideal stem cell should have the capacity of self renewal beyond the “Hayflicks” limit (the ability of the cell to proliferate to about 40-60 population doublings before it achieves senescence). [13] Potency means the differentiation capacity of the stem cell. [14]

6. ADVANTAGE OF DENTAL STEM CELLS: Have high plasticity. It can be cryopreserved for 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 immunosuppression, so autologous stem cell source is the best option. Dental pulp stem cells will be better fitting tool due to easy surgical access, the very low morbidity of the anatomical site after the collection of the pulp. [15] Few ethical concerns.

7. USES OF STEM CELLS: Stem cells are used for the treatment of cancers, diabetes, myocardial infarction, muscular dystrophy, amyotrophic lateral sclerosis, spinal cord injuries, traumatic brain injuries, parkinsons disease, alzheimers disease, osteoarthritis, rheumatoid arthritis, wound healing, missing teeth, baldness, blindness, deafness etc. Stem cells allow scientist to test new drugs on human cell lines which could speed up new drug development.

8. CLINICAL 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.

![Figure 2: Generations of regenerative material.](image-url)
8.3. 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. Adipose derived stem cells was used to treat the calvarial defect (120 cm²) of a 7-year-old girl who had severe head injury. Autologous adipose stem cells were extracted from gluteal region along with iliac crest bone graft.[20] Soft tissue reconstruction in the oromaxillofacial region using graft and flap transfer produced donor site morbidity. Alhadlaq et al. in their experimental studies found human MSCs can turn into adipose cells when they exposed to adipogenic inducing medium. Adipose cells with appropriate shaped scaffold can be used for reconstruction of soft tissues.[21]

Stem cells isolated from dental pulp has a potential to differentiate into osteoblasts and are good source for bone formation. Oromaxillofacial bone tissue repair with stem cells was done using collagen sponge scaffold and dental pulp stem cells harvested from third molars of the same patient.[22] Stem cells isolated from SHED has significantly promoted wound healing in mice, proving deciduous teeth can be utilized for the treatment of chronic wounds. This application can be extended into oromaxillofacial region to enhance wound healing.[23]

8.4. Alveolar bone augmentation/implants: Osteogenic stem cells used in implant osteotomy site forms superior bone and long-term success of the implant treatment. Stem cell therapy improve vascularity to facilitate hard tissue augmentation at local site. Regeneration of large alveolar bone defects provide stable and accelerated bone formation as well as enhanced osseointegration in dental implant treatments.

8.5. Craniofacial tissue engineering:

Tissue engineered bone grafts, engineered joints, cranial sutures can be developed with stem cell therapy. Craniofacial tissue engineering using adult mesenchymal stem cells and biomimetic scaffold bioreactor to design anatomically viable and functional bone for oromaxillofacial reconstruction of congenital defects, cancer resections and traumatic defects.

8.5.1. Tissue engineered temporomandibular joint: Articular condyles can be engineered by using adult mesenchymal stem cells and biomimetic scaffold bioreactor. Condyle shaped scaffolds made using decellularized bone with help of digitized clinical images. Stem cells were seeded into the scaffold and placed in a bioreactor chamber containing culture medium. BMSCs differentiate into chondrogenic and osteogenic cells produced regeneration of mandibular condyle that was enhanced by low-intensity pulsed ultrasound. In future this technique can be applied to regenerate other bones in oromaxillofacial region.

8.5.2. Tooth regeneration: The regeneration of adult teeth would replace dental implants. Epithelial mesenchymal interactions are mandatory in tooth development. “These interactions are characterized by the reciprocal exchange of signals between these two naïve germ layer tissues and result in the emergence of unique terminal phenotypes with their supporting cells”.[24] Tooth regeneration involves three key elements which include inductive morphogenes, stem cells and scaffold. Steps involved in regeneration of tooth are: 1. Harvesting and expansion of adult stem cells 2. Seeding the stem cells into scaffold which provides optimized environment. 3. Cells are instructed with targeted soluble molecular signals spatially. 4. Confirming the gene expression profile of the cells for next stage in odontogenesis.[25] Duailibi et al., in their experimental studies were able to form tooth structures from single cell suspensions of cultured rat tooth bud cells. They demonstrated bioengineered rat teeth developed in 12 weeks with PGA and PLGA scaffold.[26]

8.5.3. Salivary gland regeneration: Radiotherapy for head and neck CA, impairs salivary gland function causing xerostomia. Two main regenerative approaches: 1. Use tissue engineering technologies and develop an artificial salivary gland. 2. Apply stem cells to the damaged salivary gland tissue and restore function.[27]

8.5.4. Tongue regeneration: Stem cell-based reconstruction of the tongue uses myoblast/progenitor cells carried in a collagen gel were implanted into the hemi glossectomized tongue to provide successful muscle regeneration with reduced scar contracture. Applying of cyclic strain to BMSCs accelerated in vitro skeletal myogenesis.[28]

8.6. Systemic delivery of BMSCs for immune-mediated diseases: Systemic administration of
BMSCs induces peripheral tolerance, migrate to injured tissues, inhibit the release of pro-inflammatory cytokines. The immunomodulatory effects of BMSCs used for treatment of rheumatoid arthritis, osteoporosis, diabetes, SLE, acute renal failure, graft-versus-host disease and refractory inflammatory bowel disease.

**MSC-based immunotherapy in dentistry:**

PDLCs, SCAP and dental pulp stem cells possess immunosuppressive properties. The systemic delivery of dental MSCs increases tissue-protective Tregs, suppress inflammatory cell infiltration, decrease pro-inflammatory cytokine secretion, induction of angiogenesis and increases ECM formation can be used for treatment of BRONJ, and to accelerate oral ulcer healing. Intraleosional stem cell therapy for oral submucous fibrosis causes neoangiogenesis by releasing cytokines and growth factors (paracrine effect). Increased free radical scavenging by antioxidants lead to removal of senescent cells from the lesions. Reversal of hypoxia in the diseased tissue stimulate resident tissue stem cells to transform into new fibroblasts, removal of disintegrated collagen fibers and significant improvement in mouth opening with gradual decrease in burning sensation/blanching.

**9. STEM CELLS BANKING:**

Dental stem cell banking is the process of storing stem cells obtained from patient’s deciduous teeth and wisdom teeth, for future dental-stem-cell-based regenerative therapy. Dental stem cells can be isolated from the cryopreserved PDLCs, pulp tissues, apical papilla, or the tooth whenever required for future regenerative therapies. Stem cell is India's first private dental stem cell bank. Tissue samples containing stem cells were placed in a screw top vial containing an appropriate media, which nourishes it during transport. The sample should reach the processing storage facility before 40 hours. In the laboratory the samples were trypsinized and passaged to yield colonies of stem cells. The required cell type can be manipulated by utilizing right inductive signals and appropriate growth factors to the stem cells. Various steps in stem cell banking are enrolment, tooth collection, isolation of stem cells, cryopreservation, and receipt of sample certificate.

**10. CONCLUSION:**

The future 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 future treatment modality in dentistry. Regenerative dentistry will have to go in pace with regenerative medicine. We have entered a new era in the regeneration of orofacial bone, where molecular enhancement by osteoinductive materials and stem-cell-based therapies can be used. Current active research areas of stem-cell-based therapy in dentistry are focused on tissue engineering and chair-side cellular grafting approaches that may result in more predictable regenerative outcomes in the future. The recently observed immunomodulatory function of MSCs may be applicable to suppress the local immune response during transplantation to achieve optimal tissue regeneration.

**11. REFERENCES:**


