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ABSTRACT

The purpose of this article is to review and update current data of the use of stem cells for dental but specifically orthodontic purpose. Interest regarding stem cell based therapies for the treatment of congenital or acquired craniofacial deformities is rapidly growing. The use of stem cells in the day to day treatment modality is not a vision too far. The growing trend in the regeneration of articular disc and TMJ modifications for treatment of arthritis is also been seen. The concept of harvesting stem cells followed by expansion, differentiation, seeding onto a scaffold and re transplanting them is likely to become a clinical reality. In this review, tries to summarize the translational applications of stem cell therapy in tissue regeneration in the field of orthodontics.

Keywords: Stem cells, orthodontics, articular disc, cleft

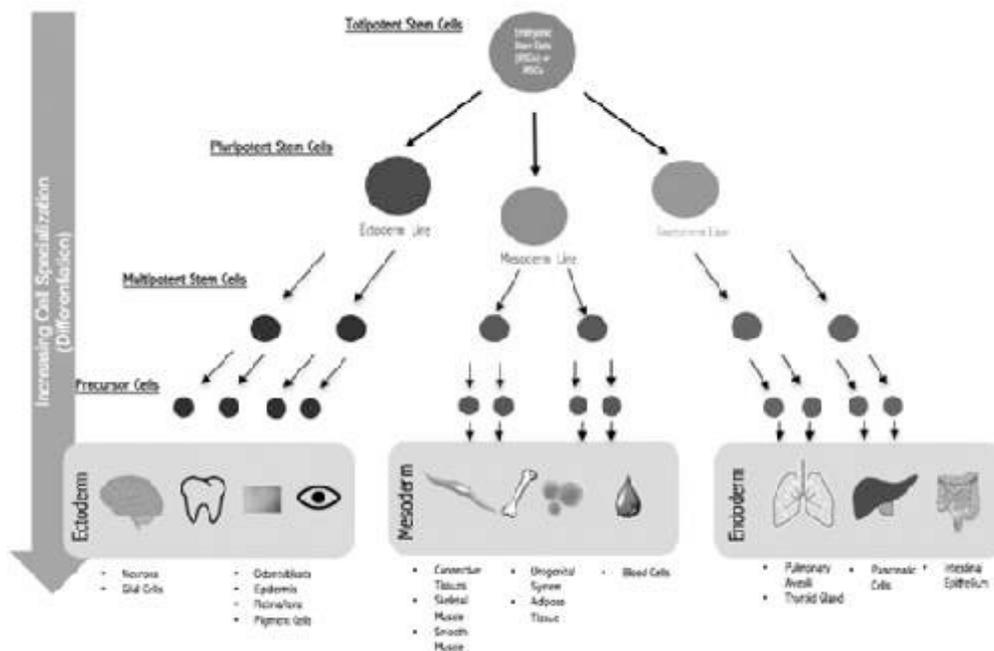
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INTRODUCTION:

Orthodontics and dentofacial orthopedics is comprehensive branch – dealing not just with teeth but craniofacial structures. Stem cell therapy holds a great potential and can bring a revolutionary change in the field of medicine. The knowledge of stem cells and its implications can help the orthodontists to modify their treatment planning and get quintessential results.

WHAT ARE STEM CELLS?

Stem cells are defined as the cells which have the capacity to divide for indefinite periods of time and with the ability to differentiate into a variety of cell types. Stem cells can be classified into three categories: Totipotent, Pluripotent, and Multipotent cells. Totipotent cells have the potential to differentiate into any type of cell in the body and are capable of developing into a complete organism. Pluripotent cells are capable of dividing and differentiating into any type of cell, tissue, or organ. Multipotent cells have more limited capacities than pluripotent cells.¹



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Characteristics of stem cells 1:

- They have the ability to generate at least one daughter cell with characteristics of parent cell.
- Multi lineage differentiation from a single cell
- Functional reconstitution of a tissue

The uses of stem cells in orthodontics are:

- Mandibular growth in mandibular hypoplasia using stem cells
- Maxillary expansion
- In cleft palate cleft lip patients
- Repair of alveolar bone
- In orthodontic root resorption of the teeth
- Distraction osteogenesis
- Regeneration and repair of TMJ defects
- Articular disc of TMJ

MANDIBULAR GROWTH IN MANDIBULAR HYPOPLASIA USING STEM CELLS

Mandibular growth deficiency is one of the important aspect considered in orthodontics during the developing ages. Researches have shown that viral vectors carrying vascular endothelial growth factor (rAAV-VEGF) have been shown to stimulate mandibular growth in vivo in rats.¹

A local injection of vector-loaded VEGF into mandibular condyles can modulate mandibular growth. VEGF may stimulate mandibular growth through two mechanisms¹:

- (1) Stimulation of endochondral bone growth.
- (2) Recruitment of new replicating mesenchymal stem cells, which is correlated to mandibular growth.

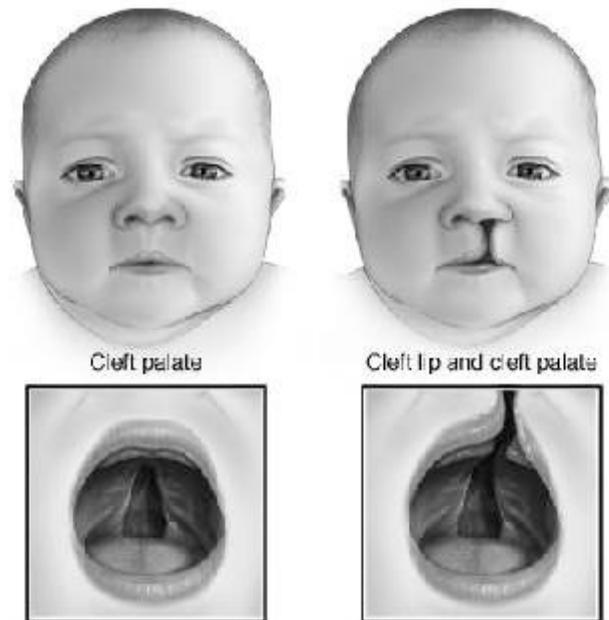
MAXILLARY EXPANSION

The maxillary expansion during orthodontic treatment is usually a tough time for the patients since wearing an apparatus during the treatment causes mouth discomfort. Moreover, to prevent relapse after expansion, it is crucial to induce new bone formation and regeneration during retention phase. Bone marrow-derived mesenchymal stem cells were isolated from the femora of rats, and characterized by osteogenic differentiation. Positive contribution to bone formation was

detected with differentiated mesenchymal stem cells that underwent a successful stem cell therapy in the maxillary expansion model in rats. Histomorphometric findings showed an increase in newly formed bone, number of osteoblasts, and amount of vascularization.²

It has been mentioned that when BMSCs were exposed to continuous mechanical strain (CMS) of 10% at 1 Hz shows that CMS reduced the proliferation of BMSCs and stimulated osteogenic differentiation by activating Runx2, followed by increased alkaline phosphatase (ALP) activity and mRNA expression of osteogenesis-related genes (ALP, collagen type I and osteocalcin). Furthermore, the phosphorylation level of extracellular regulated protein kinase (ERK)1/2 increased significantly at the onset of strain. However, the presence of U0126, a selective inhibitor of ERK1/2, blocked the induction of Runx2 and subsequent osteogenic events.⁹

IN CLEFT PALATE CLEFT LIP PATIENTS



Cleft palate and cleft lip patients often suffer from social stigma. They are not only hesitant to take treatment but also wish for early and stable results. Various treatment modalities are used by orthodontists. The American Association of Orthopaedic Surgeons suggests that, given the high demand for grafting procedures, the development and supply of “substitutes for conventional bone grafts” should be a priority.

In a recent study, embryonic stem cells have been differentiated into cartilage cells and implanted on artificially created cranial osseous defects. In comparison to the control group, the group that received the implanted tissue had a significantly faster response rate.⁴ Furthermore, another study it has been reported that unilateral alveolar cleft, treated with the composite scaffold of demineralized bone mineral and calcium sulphate (Osteoset) loaded with mesenchymal stem cells (MSCs), showed 34.5% regenerated bone, extending from the cleft walls and bridging the cleft after 4 months with presentation of bone integrity.⁵

IN ORTHODONTIC ROOT RESORPTION OF THE TEETH

Dental pulp is the rich source of stem cells. Apical papilla differs from the dental pulp for containing less cellular and vascular components. However, apical papilla stem cells have shown to have both high repair and differentiation potential. Stem cells from apical papilla (SCAP) stem cells for pulp and dentin repair, together with the association between SCAP and periodontal ligament stem cells the tissue repair has become easy. This advancement is also known as BIOROOT ENGINEERING.³

REPAIR OF ALVEOLAR BONE

Alveolar bone condition is not just important in the prosthodontic field but also in the orthodontic stream. Unwanted alveolar bony defects are often created after orthodontic extractions repair of these defects can be done by stem cell therapy. In a recent study, the tissue repair cells were grafted into the osseous defects of the jaw of 12 patients and the biopsies were and analysed at six and twelve weeks. Reconstruction was completed with an oral implant therapy and was observed for 12 months postoperatively. It was demonstrated clinically, radiographically, and histologically that the stem cell therapy accelerated the regenerative response. There was also significant reduction in the need for secondary bone grafting procedures in this group.⁶

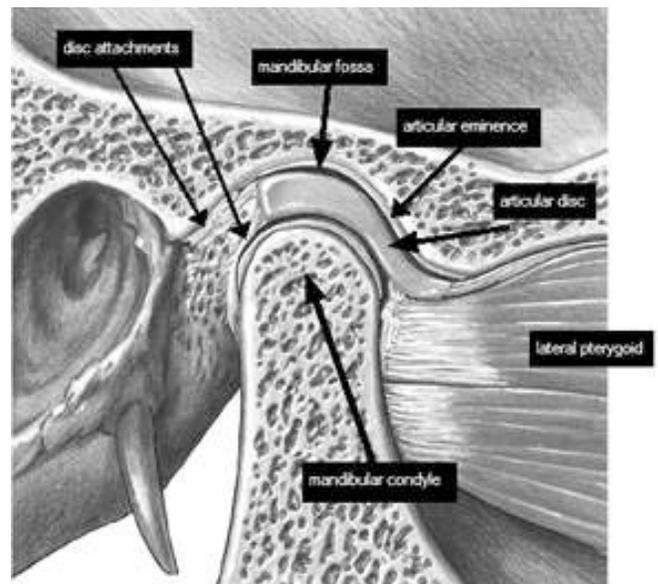
DISTRACTION OSTEOGENESIS

Distraction osteogenesis is defined as the surgical approach by which the development of new bone growth in an area subjected to gradual tension and stress occurs by deliberate separation of the fragments by traction. Limitation of the distraction osteogenesis is – Ischemia which can be overcome

by stem cells.

It is suggested that using stem cells in distraction osteogenesis proves to be a potential method to accelerate bone regeneration in the distraction gap and enhance consolidation. In a study, 54 New Zealand white rabbits underwent osteodistraction of the left mandible and were randomly divided into three groups. At the end of the distraction, bone marrow mesenchymal stem cells (BMMSCs) transfected with osterix (OSX), autologous BMMSCs, and physiological saline were injected into the distraction gap in groups A, B, and C, respectively. It was observed that excellent bone callus formation was seen in groups A and B. The group C animals showed poor bone formation in the distracted callus, when compared to groups A and B.⁶ The bone induced with the mesenchymal cells is stable. The study has compared the ability of MSCs to heal a critical-sized segmental defect and it suggested that bone fill in MSC is greater and better stable.¹²

REGENERATION AND REPAIR OF TMJ DEFECTS



A TMJ defect often perplexes the doctor. The methods used to reconstruct the TMJ include autogenous bone grafting, such as, harvesting from the rib or the use of alloplastic materials which often leads to unwanted adverse effects. The recent advances in stem cell technology assure the construction of a bioengineered TMJ replacement, which is biocompatible and capable of withstanding the physiological loads. Cells sources include

articular cartilage cells, fibroblasts, human umbilical cord matrix cells, and mesenchymal stem cells. In numerous studies, a tissue-engineered mandibular condyle was constructed, with stratified layers of cartilage and bone from a single population of mesenchymal stem cells, which was moulded into the shape of a human cadaver mandibular condyle.⁶

ARTICULAR DISC OF TMJ

Articular disc of TMJ is often affected by various degenerative disorders like osteo arthritis. The effects of chondrogenic differentiated mesenchymal stem cells (MSCs) on cartilage and subchondral cancellous bone in temporomandibular joint osteoarthritis (TMJOA) is useful to decrease the arthritis. Mesenchymal cells leads to increased mRNA expression of collagen II, aggrecan, Sox9 and decreased matrix metalloproteinase 13 (MMP13). Intraarticular injection of MSCs could delay the progression of temporomandibular joint osteoarthritis by chondrogenic proliferation.⁷

There have been various studies which describes the ways to increase the proliferation and hence the regeneration of the bone and the articular disc. One such study suggests that culture of hMSCs in 3D collagen matrices under mechanical strain leads to linear 3D type I collagen matrices and subjected to 0%, 10%, or 12% uniaxial cyclic tensile strain at

1Hz for 4 h/day for 7 or 14 days. There is increase in BMP-2 was also observed in hMSCs subjected to 12% strain.⁸ Other way to increase the cell differentiation and bone formation is use of low-magnitude, high-frequency mechanical vibration stimulations have a favourable influence on osteocytes, osteoblasts and their precursors, thereby enhancing the expression of osteoblastic genes involved in bone formation and remodelling.¹⁰

Moreover, MSCs exposed to TGF- β 1 were loaded into a sponge composed of a hyaluronan derivative (HYAF®-11) for the construction of the cartilage component of the composite graft, and MSCs exposed to osteogenic supplement were loaded into a porous calcium phosphate ceramic component for bone formation. This leads to formation of Type I collagen in the neo-tissue in both sponge and ceramic, and type II collagen in the fibrocartilage, especially the pericellular matrix of cells in the sponge.¹¹

CONCLUSION

Nowadays stem cell therapy is one of the most upcoming areas of research in craniofacial tissue engineering. It is apparent for the orthodontists to be prepared for paradigm shifts in craniofacial regeneration. It will be really fascinating to see orthodontists using this therapy on a daily basis to treat patients.

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