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Review Article

Tissue Engineering in Orthodontics – A Review

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ABSTRACT:
The purpose of this article is to highlight the importance of the use of tissue engineering in the field of Orthodontics. Tissue engineering and Orthodontics are two broad fields that share a common objective of applying scientific principles in association with existing best technology to restore the tissue function and esthetics. Both the fields have witnessed a significant surge in the technological aspect over the past century. The concept of tissue engineering has been used in Orthodontics for regeneration of the tissues in correcting the defects associated with craniofacial syndromes and temporomandibular disorders, root resorption, periodontal defects, in rapid maxillary expansion to aid in the stability of the achieved expansion , in Distraction Osteogenesis and in accelerating orthodontic tooth movement.
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INTRODUCTION

The field of tissue engineering involves the interdisciplinary application of principles of medicine, the biological sciences, and engineering toward the replacement or augmentation of a damaged or compromised tissue or organ.[1,2] Various applications of tissue engineering include application of scaffold materials, cell populations and biologically active factors to an area of defect to stimulate the production of tissues to provide tissue volume and function. Though the emergence of field of tissue engineering to the field of medicine can be traced to antiquity, this has undergone a rapid improvement over the past decade.[3] The research in the field of tissue engineering is growing to have a huge impact in the field of the Orthodontics.

The American Association of Orthodontists describes orthodontists as "uniquely qualified specialists who diagnose, prevent and treat dental and facial irregularities to correctly align teeth and jaws.[4] Proper diagnosis is of paramount importance in deciding a treatment plan in the field of Orthodontics. Both the field of Orthodontics and tissue engineering embrace the latest technologies available to aid in the proper treatment planning and restore tissues with structural integrity, functional efficiency without compromising on the esthetic aspect.

The basic idea of the field of tissue engineering is to regenerate and repair the tissues by catering to their different regenerative potential .

BASIC TISSUE ENGINEERING PRINCIPLE

Tissue Engineering Principles

Many challenges remain for tissue engineering of dental, oral and craniofacial structures. Considerations such as high demand for esthetics, appropriate vascularization, the complex environment, the need for accommodating multiple tissue phenotypes, and the type of dental, oral and craniofacial tissues that are candidates for tissue engineering, are major determinants. A number of approaches have been explored to determine and accommodate the needs for regenerating craniofacial tissues. For tissue engineering to be successful, one must understand the structure and function of the tissue to be regenerated, and then apply this knowledge in the design of tissue engineering strategies.[5] The basic tenets of tissue engineering have been to incorporate cells and scaffold and signalling molecules into *in vitro* analogs

of tissues that are to functionally replace diseased or lost tissues.

Stem Cells Basics

In postnatal life, stem cells are generally those rare cells with potential to differentiate into multiple cell types. Usually, stem cells are quiescent in the body and serve as reserve cells. Under physiological conditions, stem cells periodically replenish themselves in a process known as cycling or self-renewal, to maintain a renewable stem cell pool. Self-renewal is fundamental for biological tissues, not only to replace dead or aged cells, but also to repair pathological defects or trauma. With the great deal of interest in regeneration of dental, oral, and craniofacial tissues, one should not overlook the role of stem cells in maintaining tissue homeostasis. Tissue turn-over is exemplified most obviously by epithelial cells of the skin, and by bone cells. Skin and bone, as well as many other tissues, undergo physiologically necessary turnover throughout life.

Stem cells are unspecialized cells, and have the potential to become one or more specialized cell types.[5] For example, mesenchymal stem cells are capable of differentiating into cells such as osteoblasts, fibroblasts, chondrocytes, and myocytes and can give rise to bone, cartilage, bone marrow stroma, interstitial fibrous tissue, skeletal muscle, tendons, ligaments, as well as adipose tissues. Upon injury or in diseases, adult stem cells are activated to repair tissue and organ defects. Whereas the ability to maintain homeostasis is physiological, wound healing and tissue regeneration represent interventional therapies of stem cells that are being pursued in virtually all tissues and organs. Mesenchymal cells continue to reside in various tissues and are the sources of adult mesenchymal stem cells (MSCs)

Bone marrow is the source of at least two stem cell populations: MSCs and hematopoietic stem cells (HSCs).[6,7] Isolation of MSCs from bone marrow was first described by Friedenstein and collaborators (1974).

Several studies have explored the potential of MSCs in the regeneration of craniofacial tissues, such as alveolar bone, periodontium, and even ectomesenchymal-based tooth structures.[8,9,10] HSCs are co-inhabitants of bone marrow with the MSCs and the MSCs and osteoblasts serve as stromal cells for HSCs. HSCs give rise to and replenish all blood cell lineages. The osteoclasts, the bone-resorbing cells during bone turnover and orthodontic tooth movement, derive from this hematopoietic lineage**.**

Cranial neural crest cells are essential for the development of craniofacial structures. [11] The head is formed through an interaction between mesodermal and cranial neural crest cells. The neural crest arises from the ectoderm-derived neural tube during prenatal development at approximately day 20 in the human embryo .[12] These cells migrate to the presumptive face, and possess the ability to self-renew and differentiate into multiple cell types for the genesis of teeth, bone, and cartilage.

In this review current and future applications of stem cells (SCs) in orthodontics and dentofacial orthopedics have been discussed. For craniofacial anomalies, SCs have been applied to regenerate hard tissue (such as treatment of alveolar cleft) and soft tissue (such as treatment of hemifacial macrosomia). Several attempts have been done to reconstruct impaired temporomandibular joint. Also, SCs with or without bone scaffolds and growth factors have been used to regenerate bone following distraction osteogenesis of mandibular bone or maxillary expansion

Stem cells (SCs) are self-renewal cells that could differentiate toward various cells under suitable conditions.[13] Various sources for harvesting SCs have been introduced such as muscle, dermis, bone marrow, adipose tissue, periosteum, blood, umbilical cord, synovial membrane and teeth.[14,15] Among these sources, some are easily accessible in orthodontics. As extraction of primary teeth or permanent premolar or wisdom teeth is common interventions in orthodontic treatment of malocclusions, SCs sources from the teeth could be gained without extra morbidity. Several studies have revealed differentiation and proliferation potential of mesenchymal stem cells (MSCs) obtained from dental pulp, periodontal ligament or human exfoliated deciduous teeth.[16 - 19]

MSCs could be considered as “research trends” in the field of biology and medicine and their application in regenerative medicine is growing. Some modalities involve direct plantation of MSCs into the defect site while others use proper scaffolds to support the cells. In bone tissue engineering, MSCs are carried by an osteoconductive scaffold and differentiated toward osteogenic cells using osteoinductive growth factors. [20]Several types of scaffolds and growth factors have been used for regeneration of craniofacial bone defects including orthodontic related bone defects.[21-24]

Biomaterials and Scaffolds

Tissue engineering approaches often leverage biomaterials to facilitate tissue repair. In this context, a biomaterial is defined as “a material intended to interface with biological systems to evaluate, treat, augment, or replace any tissue, organ or function of the body.”[25] Biomaterials frequently serve in tissue engineering applications as scaffolds to support tissue formation within a defined volume. In order to successfully support tissue formation, a biomaterial must elicit an appropriate host response in a given application – a concept known as biocompatibility.[25] For example, a biomaterial in a tissue engineering application should favor regeneration of the target tissue over induction of a chronic inflammatory response. Additional general design requirements of biomaterials for tissue engineering scaffolds include mechanical properties suitable for the application, the

capacity to be easily processed into the specific geometries required for the application, and the ability to be sterilized with clinically acceptable techniques. In some cases, scaffolds comprise degradable materials that initially serve to support and then degrade over time thus eliminating the need to remove these . Various biomaterials have been used that include various metallic substitutes, polymers and ceramics.[26]

APPLICATIONS IN DENTOFACIAL ORTHOPEDICS

Dentofacial anomalies

Craniofacial anomalies may be congenital, developmental or may result from a plethora of factors like trauma, tumor resection or fracture malunion or non union. These defects usually require surgical correction with assisted grafting of autogenic, allogenic or prosthetic materials. However all these may be associated with problems like donor site morbidity, contour irregularities, postoperative pain, additional cost, long surgical time and postsurgical reabsorption, disease transmission, major histo incompatibility, graft versus-host disease (GVHD), immunosuppression, unpredictable outcome for tissue formation and infection of foreign material.[27,28] These challenges can be avoided if stem cell based regenerative techniques are used .

Cleft lip and palate is one of the most predominant craniofacial deformity discussed in literature. These are associated with alveolar clefts which are predominantly treated by use of autologous cancellous bone grafts. Stem cell regenerative techniques are growing as a promising treatment modality for correction of alveolar clefts.

Autogenous osteoblasts cultured on demineralized bone matrix showed more reduction in defect size in comparison to control group.[29] About 90% defect correction of soft palate defect has been reported 14 d after injection of autologous MSCs.[30] Biomaterial seeded with autogenous osteogenic cells into the alveolar cleft resulted in spontaneously eruption of canine in its proper place after eighteen months.[31]

Poly-L-lactic acid with osteogenically differentiated fat-derived stem cells showed substantial bone regeneration in palatal defect.[32] The mean pain score, including both intensity and pain frequency and donor site morbidity was greatest at all time points in traditional iliac crest bone graft and least at all-time points in tissue engineering.[31]

Thus it can be concluded that SCs seem to possess favorable potential for bone regeneration in oral and maxillofacial region and use of them in alveolar defect repair, reduce defect size by bone formation, have less postoperative morbidity compared to autogenous bone grafting and help the teeth in the defect area to erupt in their proper position.[32-34]

Autologous fat grafting is considered to reconstruct soft tissue defect in the treatment of congenital malformations as well as post traumatic malformations. To overcome problems associated with fat grafting, such as unpredictable clinical results and a low rate of graft survival, many innovative efforts and refinements of surgical techniques have been reported. Use of adipose derived stromal cells (ASCs) for tissue regeneration has attracted attention recently. Patients with HFM which have been grafted with supplementation of ASCs Showed 88% of fat volume surviving after 6 months in comparison to control group which was 54%. [35,36] Also, residual graft volumes of ASCs enriched grafts was significantly higher in comparison to control group.

Temporomandibular disorders

The use of stem cells in the management of temporomandibular disorders have been reported in the literature. Various researches that has been conducted in the application of tissue engineering to Orthodontics include the study of human umbilical cord stem cells, rat MSCs and Porcine multipotential stem cells.[37]

Distraction Osteogenesis

DO which is regarded as “endogenous bone tissue engineering” has been widely applied in orthopedic surgery for correction of limb length and also in the treatment of many craniofacial deformities. [38] DO is done by creating a corticotomy, placing a rigid distractor across the cut bone and gradually activating the device.[38] Long treatment periods and fibrous union or even non-union of bone are possible major draw backs impeding its widespread clinical application.

In some studies, alone MSCs,[39,40] in the others, gene transferred MSCs [41,42] and factors [43,44] have been used to enhance bone regeneration following distraction osteogenesis. The modifications such as use of scaffolds, [45] demineralized bone matrix [46] and Platelet-rich Plasma [47] have been done in some studies.

MSCs transfected with bFGF showed excellent bone formation and higher BMD and bone mineral content (BMC) in the distracted callus.[46]

Rapid maxillary expansion

Rapid maxillary expansion is done in case of constricted jaws when there are lateral discrepancies that may be involve or a single or a group of teeth which may be due to skeletal, dental or a combination of both the factors. It is an effective orthopaedic procedure to open the midpalatal suture, providing appropriate and stable maxillary width increase and re-stablish balance between the width of the jaws. Rapid maxillary expansion requires a retention period for the achieved expansion to be maintained. In the recent times, studies are being undertaken to use stem cells which can be injected into the site of the midpalatal suture to achieve accelerated bone healing to maintain the stability and reduce the retention period .[24,48]

APPLICATION IN ORTHODONTICS

Expanded envelope of discrepancy

The extent of OTM is limited by several factors including the anatomy of the alveolar bone, pressures exerted by soft tissues, periodontal tissue attachment levels, neuromuscular forces and lip–tooth relationships. The mandibular incisors that are subjected to lingual tipping, especially in a case with a prominent chin are liable to undergo gingival recession or may result in fenestration or dehiscence . Stem cells have the potential to generate different tissues, including bone, thereby stem cell therapy is a promising approach to alveolar bone regeneration. Some researches have applied stem cell therapy in case of bone ridge augmentation in humans and mainly used bone marrow cells. Stem cells can augment the alveolar bone growth and can extend the envelope of discrepancy and reduces these bony defects.[49 - 51]

Stem cells for horizontal ridge augmentation is still in the stage of research to facilitate orthodontic tooth movement and overcome anatomical boundaries.[24]

Periodontal regeneration

Orthodontic tooth movement may be associated with periodontal defects such as fenestration, dehiscence, interdental folds, ginigival recession. The use of stem cells to correct these defects have been considered for extensive research. The current treatment approaches include the use of surgery, guided tissue regeneration (GTR), bone fillers and growth factors and application of bioactive molecules to induce regeneration. Based on the differential potential capability of SCs and their ability of renewal *via* mitosis, they have the quality to regenerate damaged tissues, hence they can be used for regeneration of periodontium. The current treatment approaches include the use of surgery, guided tissue regeneration (GTR), bone fillers and growth factors and application of bioactive molecules to induce regeneration.[49 - 51]

The use of stem cells in reducing periodontal defects have been extensively studied. In one study pleuripotent stem cell on a enamel matrix and fibrin scaffold were evaluated and significant regeneration of the cementum and the alveolar bone was seen. Bone marrow derived stem cells have been studied for accelerated wound healing by reepithelization and neovascularisation. Also, periodontal stem cells were studied after being transplanted into rat models. Periodontal stem cells implanted into collagen sponges, impregnated into aminiotic membrane, incubated with non collagenous dentin proteins , autogenous stem cells from extracted tooth have all been extensively studied and found to have increased matrix mineralisation and PDL regeneration.

Accelerated orthodontic tooth movement

Orthodontic tooth movement with the use of stem cells have been studied using stem cells. In a study, increased PDL progenitor cells with suppressed expression of type I collagen (Col-I) were observed during orthodontic force application, whilst after force withdrawal they increase in Col-I expression, which suggests that PDLSCs are able to respond to orthodontic mechanical forces with suppressed collagen expression.[52] This ability of SCs could be used to accelerate OTM in response to orthodontic forces. When orthodontic force is applied, tooth movement is hindered until the necrosis is removed, leading to the clinical manifestation of a delay period. Hypothetically, transplantation of SCs in pressure sites may speed up the process, resulting in accelerated OTM.

External apical root resorption

Root resorption is a common and unfavorable side effect of orthodontic treatment, [53,54] which any specialist may encounter. Many factors seems to be involved in ERR such as genetics, individual biological variability, age, sex, and orthodontic forces and treatment duration.[55,56] Orthodontic forces are one of the main etiological factors for external root resorption. There are currently no treatment modalities for root resorption .

Stem cells and tissue engineering are being studied for repair of root resorption after orthodontic tooth movement by regeneration of the tissues like dentin and cementum and it was found that some amount of regeneration could be achieved. Bioengineering of the entire tooth is being studied and is still under research.

CONCLUSION:

Tissue engineering using stem cells is a fast emerging field and finds wide applications in the field of Orthodontics. Mesenchymal stem cells have been utilised in correcting the defects associated with craniofacial syndromes. Their increased cellular renewal and turnover can be utilised in correction of temporomandibular disorders and distraction Osteogenesis. Their ability to induce new bone formation can be used to promote the stability after. rapid maxillary expansion. This bone forming potential can help in expanding the envelope of discrepancy and thereby greater tooth movement can be achieved Orthodontically . Regenerative potential of stem cells finds its application in the treatment of root resorption and periodontal defects. Also Osteoclastic precursors can be used in accelerating tooth movement. Further research in the integrated approach of the two fields will have a wide range of applications.

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