REVIEW ARTICLE

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Tissue Engineering and Regenerative Medicine – Godsend in Oral & Maxillofacial Surgery

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ABSTRACT:

Background: In this present world of medicine, loss of tissue due to trauma, disease or congenital abnormalities is a major health care problem. When this occurs in the craniofacial region, severe physiological and psychological consequences occur which directly or indirectly affect individual's life. Therefore it is mandatory to reconstruct craniofacial area to its aesthetic and functional level. Aim of this review is to address the determined research effort in methods for oral and cranio-facial re-enactment from using medical devices and tissue grafts to a more obvious tissue engineering approach.

Methods: For this purpose data were gleaned from a literature search of available medical and dental databases including Research gate, Ovid, Pub-med, Medline, Cochrane and non-medical search engines such as Wikipedia and Google. The search phrases included the main set Tissue engineering in Oral & Maxillofacial Surgery, Regenerative Medicine in Oral & Maxillofacial Surgery with defined subsets such as Craniofacial bone tissue engineering, TMJ tissue engineering, effects of tissue engineering on wound healing in Oral & Maxillofacial Surgery and many more.

Result: This review will therefore deal with the significant advancements that have been made in the tissue engineering in the field of Oral & Maxillofacial Surgery, as well as its future potential.

Conclusion: The extent of regenerative and tissue-engineering applications to Oral & Maxillofacial Surgery is vast which is competent of bringing quantum advances in treatment strategies for patients. The field of regenerative medicine is here to stay, as exemplified by the promising but exponential growth of examples of conversion from bench to bed side.

Keywords: Oral & Maxillofacial Surgery, Regenerative medicine in OMFS, TMJ engineering, Tissue engineering, Wound healing

INTRODUCTION:

The Technologies of bio-medical tissue engineering represents a swiftly emerging field in regenerative medicine and fundamental science.[1, 2] The fields of tissue engineering and regenerative medicine are multi-disciplinary in nature i.e. it is a team approach which include experts from the field of molecular & cellular biology, physiology and biochemistry.

Tissue engineering has been defined as "the use of ideology and methods of engineering and life sciences towards the basic perceptive of organization and functional relationship in

normal and pathological mammalian tissues and the development of biological substitutes to reinstate, preserve or improve function". The technologies of tissue engineering are combination of biological properties of living cells and physicochemical properties of independently designed materials with the intention of creating synthetic tissues like cartilage, bone, mucosa periodontium, etc. for likely use in various reconstructive procedure[3] and offer a new opportunity to complement existing treatment regimens for reconstruction / regeneration oral and cranio-facial complex.[4]

In this present world of medicine, loss of tissue due to trauma, disease or congenital abnormalities is a major health care problem. When this occurs in the craniofacial region, severe physiological and psychological consequences occur which directly or indirectly affect individual's life. Therefore it is mandatory to reconstruct craniofacial area to its aesthetic and functional level.[5-7] Aim of this review is to address the determined research effort in methods for oral and cranio-facial re-enactment from using medical devices and tissue grafts to a more obvious tissue engineering approach.

Pre-requisites for Transplantation and engraftment

Pre-requisites for Transplantation and engraftment were described by vacanti[2] in 1988 as four essential observations, which are as follows:

1. Remodeling due to attrition and change in constituent cell is a constant phenomenon for every tissue.
2. Appropriate tissue structure is formed when appropriate conditions are provided to isolated cells.[9]
3. Isolates cells, without intrinsic organization and with no template to guide to restructuring and re-organization, can remodel only to a limited degree when placed as a suspension in the middle of the mature tissue.[10]
4. For the survival of transplanted cell, it should be implanted transplanted within a few hundred of microns from the nearest capillary.[11]

Taking into account the above mentioned pre-requisites, ideal tissue to regenerate using tissue engineering is cartilage, as cartilage consists only single type of cells known as chondrocyte.[13] Properties that make chondrocytes ideal for transplantation includes: easy isolation in great numbers, high viability, exhibits low oxygen requirements and survival by diffusion until successful engraftment takes place.

Endeavor of the Discipline

The oral and maxillofacial surgery has an important role in the treatment of traumatic or degenerative diseases that lead to a tissue loss: frequently, to rehabilitate these minuses[14], tissues like cartilage and bone can be obtained by the transplantation of patient's own tissue specimen originating from different regions, which consists of naturally occurring array and types of cell and intercellular 3-D milieu structure with or without vascular supply.[3]

Reconstruction and repair of lost tissue structure based on cell therapies offer a new prospect. In the field of Oral & Maxillofacial surgery tissue engineering offers a biologically oriented approach for the healing. Another promising alternatives for structural tissue repair are bio-materials alone or in combination with various bio-active factors like bone morphogenic proteins (BMP's), platelet rich plasma (PRP) or matrix protein.[3]

In tissue engineering the ultimate objective is "restitution ad integrum" and to attain this objective 3-D scaffold, bio-active factors and cells are used to form an implantable tissue forming device for regenerative and well-designed repair. There are two types of cell based tissue repair strategies promoted in the field of tissue engineering: cell transplantation and cell enhancement technologies.[15]

STRATEGIES OF TISSUE ENGINEERING

This subdivision of this manuscript describes, unlike but inter-related approaches of tissue engineering like cell induction, cell injection

and cell seeded scaffold.[6] These approaches depend on the use of one or more key elements e.g., cells, growth factors and matrix[17] to guide tissue regeneration.

Cell Injection therapy

It has been suggested that to regenerate tissues into the defect injection of intrinsically intelligent cells like stem cells is used because tissue formation is an action of cellular activity. Inadequate localisation of injected cells and low engraftment particularly in areas showing continuous movement e.g., beating heart is the limitation of this therapy.[18] Other challenges to this therapy are Immunological denial and the aptitude of the injected cells to maintain their phenotype.[19] An attempt has been made using a delivery vehicle to carry and deliver the material for satisfactory localisation and avoidance of direct contact with the immune system[18] and it is observed that cells encapsulated into a delivery vehicle were able to proliferate and differentiate very well.[20] Taking these advantages into account this strategy seems to be promising in bone and cartilage repair.[21]

Stem cells are the most successful contender for this strategy. Classification of stem cells[22] is as follows:

- According to their potency: totipotent, pluripotent, multipotent, oligopotent and unipotent cells
- According to origin: embryonic and adult

Cell Induction therapy

With the limitations of cell injection therapy, recruitment of circulating cells to regenerate tissue is being considered. When dealing with osteo-induction in cranio-facial bone, it is very important to understand the underlying biology that facilitate osteo-induction.[6] Example of these materials include: transforming growth factor beta-1 (TGF-β1), [24] Fibroblast growth factors 2 and 9,[23, 24] vascular endothelial growth factors,[25] recombinant human growth/differentiation factor – 5 (rhGDF-5)[26] and bone morphogenic protein.[27] Even though, this therapy was effective in some tissues,[28] but its scope is limited because of cost of decontamination and the development of suitable carrier to deliver these factors.[29]

Cell seeded scaffold

Segregation of suitable cell population from a biopsy taken from the patient or a donor is the main concept of this strategy and Mesenchymal stem cells (MSCs) are mainly used in this therapy. The effective immunomodulatory and anti-inflammatory properties of human oral mucosa-/gingiva-derived MSCs places them as a very strong potential cell source for MSC-based therapies for wound repair and a wide range of inflammation-related diseases.[6]

Initially it was considered that MSCs can differentiate only into tissue specific cells in regenerative medicine but now it has been documented that MSCs are capable of treating a broad range of immune –related diseases because of their immune-modulatory properties and also they regulate the intensity of immune response by inducing T-cell apoptosis and this property of MSCs is of great importance in using biomaterials for the purpose of tissue engineering applications.[30]

Mesenchymal stem cells: Stem cells are immature and unspecialized cells that are "self-renewable" and are able to differentiate in all mesenchymal and connective tissue cell lineages.[34-37] Phenotypically, MSCs express the CD13, CD29, CD44, CD59, CD73, CD90, CD105, CD146 and STRO-1 surface antigens, and CD45 (leukocyte marker), CD34 (the primitive hematopoietic progenitor and endothelial cell marker), CD14 and CD11 (the monocyte and macrophage markers), CD79 and CD19 (the B cell markers), or HLA class II are not expressed.[63] In the year 2000,[65] oral tissues are used in research related to stem cells and it was demonstrated that oral tissues are rich source of mesenchymal stem cells.[64] Gronthos et.al first isolated MSCs from dental pulp (DPSCs) and observation showed that these cells have characteristics similar to those

of Bone marrow stem cells (BMSCs)[65] and consists of properties confined to stem cells.

There are certain criteria for the use of stem cells to fit in the field of regenerative medicine and tissue engineering, which are as follows:[38, 39]

1. Should be in plentiful numbers and are able to differentiate in all mesenchymal and connective tissue cell lineages in controllable manner.
2. Procedures used in isolation for stem cells should be easy and minimally invasive.
3. Morbidity for patients should be low.
4. Safe transplantation

Perinatal stem cells:

Perinatal stem cells are derived from amniotic fluid, amnion, chorion and from umbilical cord.[44]

Amniotic fluid derived stem cells (AFSCs): Amniotic fluid (AF) is a shielding and nourishing liquid located in fetal sac throughout the gestation period.[66] In 2003, Prusa et.al found a subpopulation of cells expressing OCT4 in amniotic fluid. These cells are a key transcript factor for pluripotent human stem cells and prevent differentiation of stem cells. In the same year Anker et.al also demonstrated fibroblast shaped population in human amniotic fluid and these cells are positive for mesenchymal markers such as CD90, CD105, CD73 and CD166 but negative for the hematopoietic markers such as CD45, CD34 and CD14.[67] Analysis of stem cell markers shows that the AFSCs express pluripotent markers SSEA4 and OCT4, as well as typical mesenchymal markers, but they did not express the full complement of pluripotent markers, such as SSEA1, SSEA3, TRA1-60 or TRA1-81, indicating that AFSCs are not as primitive as ESCs and yet maintain greater potential than most adult MSCs.[68]

Amnion derived stem cells: Amnion membrane is the inner most lining of amniotic cavity and assures normal growth and development of fetus.[44] Two types of stem cells can be derived from amnion namely; amniotic epithelial cells (AECs) and amniotic mesenchymal stem cells (AMMSCs).[74] These cells express a wide range of pluripotency markers, such as OCT4, SOX2, SSEA4, SSEA3, as well as typical mesenchymal markers.[72]

Chorion derived stem cells (CMSCs): It is a rich source of mesenchymal stem cells of chorionic villi and chorionic plate. It have been reported in vitro, the CMSCs to be more primitive than adult MSCs and have greater self-renewal property and ability to differentiate beyond mesenchymal cell lineages to other lineages such as hepatocyte-like cells and neuron like cells.[75]

Umbilical cord derived stem cells (UCMSCs): These days interest in umbilical cord derived stem cells is increased in regenerative medicine. *In vitro*, UCMSCs appear with a fibroblastic morphology and display a greater expansion capacity and faster doubling time than adult BMSCs.[44] Typical mesenchymal markers as well as α-smooth muscle actin and low levels of pluripotency markers, such as Oct4, Sox2 and Nanog are expressed by UCMSCs[78] and a lower level of HLA-ABC than BMSCs and were negative for CD31, CD34, CD45, HLA-DR, CD80 and CD86.

MATERIALS & METHODS

Data were gleaned from a literature search of available medical and dental databases including Research gate, Ovid, Pub-med, Medline, Cochrane and non-medical search engines such as Wikipedia and Google. The search phrases included the main set Tissue engineering in Oral & Maxillofacial Surgery, Regenerative Medicine in Oral & Maxillofacial Surgery with defined subsets such as Craniofacial bone tissue engineering, TMJ tissue engineering, effects of tissue engineering on wound healing in Oral & Maxillofacial Surgery and many more. After retrieving the data important aspects / points of particular articles were noted and then framing of article was done.

DISCUSSION

Two significant questions pertinent to the Oral & Maxillofacial Surgery are “Effect of tissue

engineering on Oral & Maxillofacial Surgery" and "Type of oral tissues that have the potential to engineer" The answer to the first is still being formulated, but tissue engineering will probably have an innovative outcome on Oral & Maxillofacial Surgery and the answer to the second question is more or less all types of tissues have that potential.[7]

Oro-facial structures are only one of its kinds in their development and function. Oro-facial bones, for example, are derived from both neural crest and paraxial mesoderm; in contrast to this the skeletal bones are derived from mesoderm. Additionally, production of considerable stress and strain from different muscles of mastication is also applied to cranio-facial bones and bones respond differently to various growth factors and mechanical stimuli.[31-33]

Craniofacial bone tissue engineering:

Role of craniofacial bone is very vital in supporting the neighboring soft tissues, providing anchorage for dental structures and in maintaining structural stability for many physical functions and helps in forming esthetics of the human body. Various conditions, such as congenital deformity, trauma, osteomyelitis and tumor resection, often lead to large craniofacial defects with difficulty in reconstruction and presents as a challenge for both patients and craniofacial surgeons.[40-43] Now a day standard treatments for such skeletal defects is reconstruction using alloplastic material or various bone grafts from different anatomic locations. As an alternative to this surgical reconstruction, tissue engineering is being promoted because of several likely benefits like avoidance of donor site morbidity, ability to restore normal anatomic structure and function and reduction in hospital stay along with medical burdens. Indeed, stem cell based bone tissue engineering has already entered many preclinical or clinical applications in the craniofacial region.[44, 45]

For tissue regeneration of large bony defects, ceramics such as hydroxyapatite and β-tricalcium phosphate (TCP) are being used these days[46]. Cowan *et al*, in their study confirmed that hydroxyapatite-coated polylactic-coglycolic acid scaffolds seeded with adipose-derive MSCs (AMSCs) enhanced bone regeneration of critical-size calvarial defects using a rodent model.[55] Micro-vascular custom-made ectopic bone flap developed from a preformed titanium cage filled with autologous AMSCs, β-tricalcium phosphate (β-TCP) granules to reconstruct a maxillary defect was first used by Mesimäki et.al[56] in 2009. Reconstruction of critical-sized calvarial defects of adult patients using autologous AMSC and β-TCP granules was described by Thesleff et al[57], providing proof that calvarial bone can be regenerated using combination of AMSCs and β-TCP, with encouraging clinical results.

More lately, de novo osteogenesis of induced pluripotent stem cells (iPSCs) within a critical-sized calvarial bone defect was demonstrated by Ye et al.[58] On the other hand, in craniofacial regeneration the application of embryonic stem cells (ESCs) and iPSCs are still at a first round and appreciably restricted by ethical concerns, with genomic instability, tumor genesis and immune rejection.[59-61]

Recently, combinations of growth factors like BMP -2 and NEL-like molecule-1 (NELL- 1) was used in rabbit model of distraction osteogenesis and results after 4 weeks of treatment showed that bone healing was greater in this model when compared with a model in which single growth factor was used.[46, 47]

Pre-fabricated bone engineering is a bridge between conventional reconstructive surgery and tissue engineering.[48, 49] Prefabricated myocutaneous and osteo-myocutaneous tissue in a rat model was first reported by Hirase et.al.[50] These flaps are created according to complex geometry of the defect. These days' new types of prefabricated flaps are being produced using conventional bone grafts and are independent of vascular supply of bone transplants and these prefabricated grafts have been used in reconstruction of mandible after thorough in vivo evaluation in pig model.[52-54]

Temporomandibular joint tissue engineering:

Many tissues in the body when injured have an inherent ability to self-repair but there are certain tissues that have little to no self-repairing ability. The tissues of the TMJ fall into the latter category because of limited potential for chondrocyte proliferation and the ability of chondrocytes to become catabolic in response to pathological mediators as well as avascular nature of the tissues that restricts colonization of regenerative cells.[79,80] There are 3 types of cartilage in adults namely; hyaline, elastic and fibro-cartilage. Fibro-cartilage is present at articular surfaces of mandibular condyle. Experimentally it was revealed that superficial articular wounds typically sustain selective loss of proteoglycan from the matrix, followed by insufficient attempts at cell proliferation and repair.[79] Role of tissue engineering in the field of cartilage is to promote repair and regeneration. Primary disc cells are the most commonly used cells for engineering of temporo-mandibular joint (TMJ) disc.[81] Two main problems associated with primary disc cells of TMJ are; lack of donor cells and donor site morbidity. It was shown by some studies[80] that dedifferentiation of TMJ disc cells in culture is very rapid resulting in difficulty to recover their phenotype. Costal chondrocytes are now being investigated as alternative cells for TMJ disc engineering because of concerns about donor site morbidity.[80, 82] This research was encouraged by the fact that costo-chondral rib graft is being used by surgeons to replace mandibular condyle.[80] In the field of TMJ tissue engineering scaffolds have an important role. Porous collagen scaffold was used first in TMJ disc engineering and produced constructs with appreciable size and ECM.[83] Success similar to this was seen with porous polyglycolic acid (PGA) and polylactic acid (PLA) scaffolds because they support cell adherence and matrix production for up to 12 weeks.[84] Poly-glycolic acid, polyamide filaments, expanded polytetrafluorethylene (ePTFE), and bone blocks were also used in a study conducted by springer IN et.al[85] for the purpose of disc engineering. Growth factors are commonly used in tissue engineering because of their capability to augment cellular proliferation and/ or biosynthesis. In TMJ disc engineering there are 5 different growth factors that are used namely; platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor beta-1 (TGF-β1); transforming growth factor beta-3 (TGF-β3), and insulin-like growth factor-I (IGF-I).

It was observed that in monolayer culture, TGF-β1, IGF-I and bFGF increase TMJ disc cell proliferation, biosynthesis and it was also noted that high concentrations of growth factors favored cell proliferation while low concentrations favored biosynthesis.[89]

Biomechanical stimulation in TMJ engineering: Disc of TMJ experience considerable loading in the form of compression, tension and shear.[86] As the disc is mechanically important so it is necessary to use mechanical stimulation to produce a best possible tissue engineering construct. In the first study to explore mechanical effects on TMJ tissue engineering a rotating wall bioreactor was used to create a low-shear fluid environment and it was observed that continuous application of hydrostatic pressure of 10 MPa has been shown to increase ECM synthesis of TMJ disc cells both in monolayer and in PGA scaffolds.[87] On the contrary, when intermittent hydrostatic pressure of 10 MPa applied at 1 Hz, unfavorable effects to TMJ disc cell biosynthesis was observed and when TMJ disc cells were exposed to dynamic tensile strain in two-dimensional culture there was a considerable reduction in production of matrix metalloproteinase in response to the proinflammatory cytokine interleukin-1b (IL-1b).[88]

Effect of tissue engineering in wound healing in Oral & Maxillofacial surgery:

Extensive series of intra and extra-cellular proceedings that are regulated by protein signals mediates healing of hard and soft tissues. It is identified that platelets are involved in the process of wound healing

through blood clot formation and liberate certain growth factors that encourage and keep up the wound healing.[90] Platelet concentrates namely; platelet rich plasma (PRP) and platelet rich fibrin (PRF) etc, for surgical use are pioneering tools of regenerative medicine, and were extensively tested in oral and maxillofacial surgery however, the literature on this topic is conflicting. The main matrix constituent of all platelet concentrates is the fibrin, but this matrix can significantly vary in terms of structural design. Most platelet concentrates are undeniably platelet-leukocyte concentrates[93]. Depending upon leukocyte and fibrin content platelet concentrates are divided into 4 categories namely; pure- PRP (p-PRP), leukocyte and platelet rich plasma (L-PRP), pure- PRF (p-PRF) and Leukocyte – PRF (L-PRF).

Whitman et al [91] first introduced PRP to oral surgery community. Recognition of PRP in the field of Oral & Maxillofacial surgery was improved after Marx et.al[92] published their landmark article in 1998 and observed that when PRP and autogenous bone are combined and placed in mandibular continuity defect resulted in considerably quicker radiographic maturation and histo-morphometrically denser bone regenerate.

Because PRP is a concentration of platelets, it is also a concentration of the 7 essential protein growth factors proved to be actively secreted by platelets to commence wound healing. These growth factors included the 3 isomers of platelet-derived growth factor (PDGFaa, PDGFbb, and PDGFab), 2 of the numerous transforming growth factors-b (TGF-β1 and TGF-β2), vascular endothelial growth factor, and epithelial growth factor[95], it also contains the 3 proteins in blood identified to work as cell adhesion molecules for osteoconduction and as a matrix for bone, connective tissue, and epithelial migration. In surgical settings, PRP is used to decrease the occurrence of intra-operative and post-operative bleeding at donor and recipient sites, accelerate soft-tissue healing and to support the initial permanence of grafted tissue at recipient sites as a result of its cohesive and adhesive nature. It also promotes speedy vascularization of healing tissue by providing growth factors and, when used in conjunction with bone replacement materials, promotes regeneration.[96] Positive effects of PRP includes:[94]

a) "Jump-starts" the process of osteogenesis in a bone graft.
b) Early consolidation of the graft is promoted
c) Mineralization of the graft.
d) Trabecular bone density is improved.
e) Allows placement of implants into the graft at an earlier time.
f) Provides earlier availability of growth factors and BMP.
g) Osteoconduction is improved

Contraindications: treatment with PRP is generally considered to be safe in properly selected patients, but contraindications to the use of PRP do exist which includes; anemic patients, patients with coagulopathies, severe hypovolemia, unstable angina, sepsis and patients taking fibrinolytic drugs.[95] Unlike PRP gels, L-PRF membranes have no contraindications and can be used in all kind of patients. Soft tissue healing is always promoted by L-PRF membranes and also has the capability to stimulate healing in damaged flap and prevents flap necrosis after surgery.[97] Thus, tissue engineering provides promising results in regenerative medicine in the field of Oral & maxillofacial Surgery. It is progressing very rapidly and extends to involve all tissues of oral and maxillofacial skeleton.

CONCLUSION

The last few decades have seen swift advancement in our knowledge and understanding of the genetic control of cellular behavior during embryonic growth, leading to the programming and deprogramming of genes accountable for growth of the oral and maxillofacial tissues. This has provided the groundwork of information by strong mechanistic statistics in the lead of which we

can make strategies for the tissue engineering and regeneration of teeth. Most of the dental and craniofacial tissues are effortlessly and readily available, hence presenting a suitable podium for, biologists, bioengineers, scientist and clinicians to experiment and apply tissue-engineered model.[37]

The extent of regenerative and tissue-engineering applications to Oral & Maxillofacial Surgery is vast which is competent of bringing quantum advances in treatment strategies for patients. The field of regenerative medicine is here to stay, as exemplified by the promising but exponential growth of examples of conversion from bench to bed side. The existing hurdles are by no means overwhelming and, consequently, it is logical to take for granted to look to the fore to a more grown-up and extremely worthwhile field.[3, 7, 14]

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