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REVIEW ARTICLE

TISSUE ENGINEERING AND ITS FUTURE PERSPECTIVE IN THERAPEUTIC MEDICINE- A BRIEF REVIEW

Savreen Kaur[1], Sukhleen Sandhu[1], Sehaj K.Dhillon[2], Simran K. Makhni[2]

[1]BDS (Intern), [2]BDS

ABSTRACT:
Tissue engineering is the field of functional restoration of tissue structure and physiology for impaired or damaged tissues because of cancer, disease, and trauma. The field has gained importance due to the inadequate supply of organs and tissues for patients requiring organ and tissue replacement. Research in this field continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Tissue-engineered oral mucosal equivalents have been developed for clinical applications and also for in vitro studies of biocompatibility, mucosal irritation, disease, and other basic oral biology phenomena.This paper reviews different tissue-engineering strategies used for the production of human oral mucosal equivalents, and their relative applications.

Key words: Tissue engineering, strategies, applications

Corresponding author: Sukhleen Sandhu, BDS(Intern), E mail: sukhleensandhu2@gmail.com

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INTRODUCTION

The term “tissue engineering” was first given at a National Science Foundation (N.S.F.) in Washington D.C., in 1987. At the following N.S.F. sponsored workshop, it was defined as “the application of principles and methods of engineering and life sciences, to obtain a fundamental understanding of structural and functional relationships in novel and pathological mammalian tissues, and the development of biological substitutes to restore, maintain or improve tissue function”.[1] Tissue engineering has also been defined as "understanding the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use." A further description goes on to say that an "underlying supposition of tissue engineering is that the employment of natural biology of the system will allow for greater success in developing therapeutic strategies aimed at replacement, repair, regeneration, maintenance, and/or enhancement of tissue function."[2]

Research in this field continues to advance knowledge about how an organism develops from a single cell and how healthy cells replace damaged cells in adult organisms. Dental practice has been consistently influenced by newer technologies, for example development of high-speed handpieces, modern restorative materials, or tissue engineering. Tissue engineering brings the power of modern biological, chemical, and physical science to solve real clinical problems. This should yield numerous clinical benefits in dentistry, e.g., improved treatment for

intra-osseous periodontal defects; enhanced maxillary and mandibular grafting procedures, possibly even allowing lost teeth to be regrown; use of devices such as an artificial salivary gland and muscle (tongue) or mucosal grafts to replace tissues lost through surgery or trauma.[3]

The general principles of tissue engineering is to combine living cells with a natural/synthetic support also known as scaffold that is also biodegradable in nature to establish a threedimensional living construct that is functionally, structurally and mechanically equal to or better than the tissue that is to be replaced.[4] The four main components required to establish such a construct are:1) scaffold, 2) growth factors, 3) extracellular matrix (ECM), and 4) cells. Scaffold materials are three-dimensional tissue structures that guide the organization, growth and differentiation of cells. Scaffolds must be biocompatible and designed to meet both nutritional and biological needs for the specific cell population. Growth factors are soluble peptides capable of binding cellular receptors and producing either a permissive or preventive cellular response toward differentiation and/or proliferation of tissue. ECM must be capable of providing the optimal conditions for cell adhesion, growth, and differentiation within the construct by creating a system capable of controlling environmental factors such as pH, temperature, oxygen tension, and mechanical forces. These conditions are determined by the particular cell lines and the properties of the scaffold. Finally, the development of a viable construct involves a suitable supply of cells that are ideally nonimmunogenic, highly proliferative, easy to harvest, and have the ability to differentiate into a variety of cell types with specialized functions. There are two primary methods to harvest cells and culture. In cases where direct harvest is not feasible, as seen in many patients with extensive end-stage organ failure or cells with limited proliferative capacity in culture, stem cells (SCs) are envisioned as being an alternative source of cells.[5]

Stem cells are generally defined as clonogenic cells capable of both self renewal and multi-lineage differentiation. Dental pulp derived stem cells (DPSCs) have been isolated and identified as the cell sources for tooth repair and regeneration. Current research indicates that the dental SCs may have the potential to regenerate bone, periodontal ligament, and possibly the teeth. Dental SCs have been found in several tissues and can be divided into dental mesenchymal SCs (MSCs) and dental epithelial SCs. DPSCs show a multipotent differentiation ability, which is similar to that of MSCs. A population of high quality human stem cells was found in the exfoliated human primary teeth (SHED). The SHEDs (Stem cells from human exfoliated deciduous teeth) have osteoinductive capacity in vivo, but fail to reconstitute a dentin pulp-like complex. Stem cell fractions are called side population (SP). The adult pulp tissue contains side population (SP) cells that have tissue stem cell activities, self-renewal and multilineage potential.[1]

STRATEGIES IN TISSUE ENGINEERING

An overview of the various strategies in tissue engineering will be briefly discussed in this section. There are three main approaches- cell induction, cell injection and cell seeded scaffold.These approaches depend on the use of one or more key elements e.g., cells, growth factors and extra cellular matrix to guide tissue regeneration (Figure 1).

CELL INDUCTION STRATEGY

This tissue engineering strategy involves activating cells in close proximity to the defect site with specific biological signals. The origins of this mechanism are rooted in the discovery of bone morphogenic proteins (BMPs). Urist first showed that new bone could be formed at nonmineralizing, or ectopic, sites after implantation of powdered bone (bone demineralized and ground into fine particles).[6] Contained within the powdered bone were proteins (BMPs), which turned out to be the key elements for inducing bone formation. These proteins are now available in recombinant forms and produced on a large scale by biotechnology companies. BMPs have been used in many clinical trials and are very promising as a means of therapy and supplementation in regeneration and repair of bone in a variety of situations, including nonhealing fractures and periodontal disease.[7]

An alternative tissue-inductive approach involves placing specific extracellular matrix molecules on a scaffold support at the tissue site. These molecules will have the ability to direct the function of cells already present at that site and, therefore, to promote the formation of a desired tissue or structure. For example, a preparation of enamel proteins derived from pigs has been used to promote new bone formation in periodontal defects.[8] The Forsyth researchers induced the growth of small, recognizable tooth crowns within a period of 30 weeks from cells obtained from immature teeth of 6-month-old pigs seeded onto biodegradable polymer scaffolds and

placed in a rat host.[9] For tissue induction to be successful clinically, it is critical to deliver the appropriate biologically active factors to the desired site at the appropriate dose and for the necessary time. Typically, many of these proteins have short half-lives in the body, yet they need to be present for an extended period to be effective. Up until now, clinicians and researchers have addressed these concerns by delivering extremely large doses of the protein at the sites of interest. More recently, the efforts have been to develop controlled-release systems. A somewhat similar approach involves the delivery of a gene that encodes for the inductive factor, instead of delivering the protein itself.An unresolved issue in tissue engineering is whether multiple protein signals, perhaps presented in a specific sequence, may be necessary to develop fully functional tissues.[3]

CELL INJECTION STRATEGY

For this strategy, stem cells are the most successful candidate. According to their potency, stem cells are classified into totipotent (generate all differentiated cells in an organism e.g., fertilised egg), pleuripotent (form the three germ layers; ectoderm, endoderm and mesoderm e.g., embryonic stem cells), multipotent (differentiate into several cell lines but with more restricted number of phenotypes e.g., mesenchymal stem cells), oligopotent (differentiate into a few cell types e.g., myeloid stem cells) and unipotent cells (i.e., differentiate into one cell type e.g., skin stem cells).[10] According to their origin, stem cells are classified into embryonic and adult (somatic). Embryonic stem cells have a great potential use in regenerative medicine as they can be maintained indefinitely in an undifferentiated state in culture. Embryonic stem cells showed a major advantage in medical research, understanding the range of transformation of such cells can help in the correction of many mutational errors.[11]

CELL SEEDED SCAFFOLDS

This strategy depends on the isolation of appropriate cell population from a biopsy taken from the patient or a donor with the most likely candidate for such a therapy - Mesenchymal Stem Cell (MSC). The potent 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 inflammatory related diseases.[6]

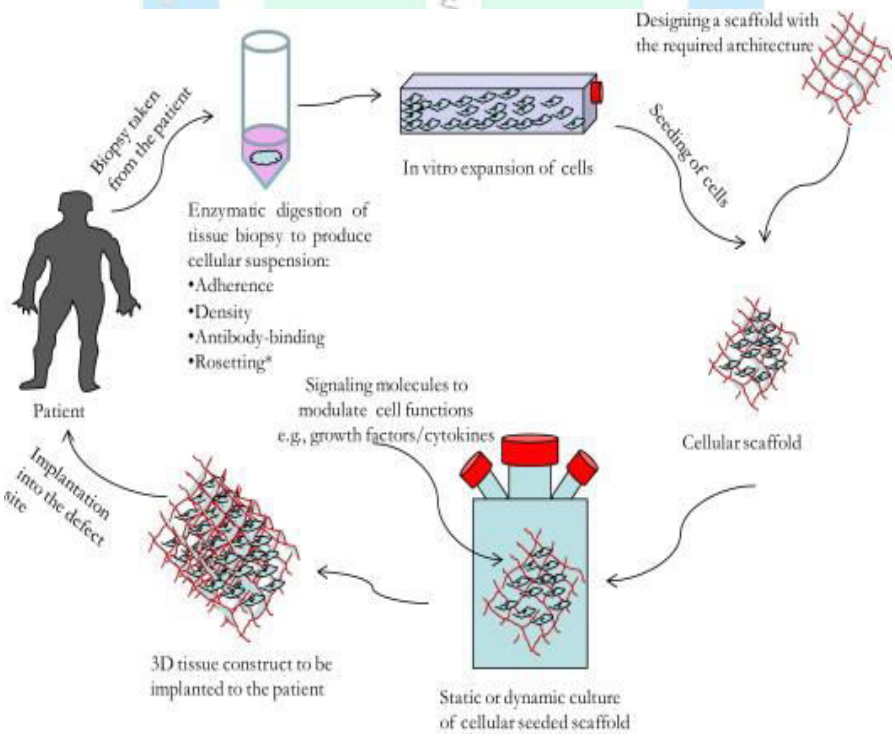

Figure 1: Diagrammatic representation of cell-matrix tissue engineering strategy. Different methods used to produce cellular suspensions from a tissue biopsy are described in details by Tomlinson et al.[12]

APPLICATIONS OF TISSUE ENGINEERING IN ORAL-MAXILLOFACIAL COMPLEX

The effect that tissue engineering may have in the field of dentistry stems from its widespread application to many different types of tissues related to the oral cavity, including bone, cartilage, skin and oral mucosa, dentin and dental pulp, and salivary glands.[7]

BONE

Current strategies aimed at replacing bony defects include the utilization of autografts, allografts, and synthetic biomaterials. This has led to interest in engineering bone, which can be achieved using all three tissue engineering strategies. Both conductive and inductive approaches can be used to regenerate small bony defects. Guided tissue regeneration (GTR) after periodontal surgery or mandibular and maxillary bone defect reconstruction represents a conductive approach to regeneration of bone. BMPs, related proteins, and the genes encoding these proteins allow one to engineer bone using inductive approaches in situations where GTR is not sufficient.[7]

Application of autogenic periosteal cells-seeded polymer fleeces to augment the floor of the maxillary sinus before implants insertion showed encouraging results from both radiographical and histological examinations.[13] For irregular defects, injectable composites [e.g., β-TCP/alginate[14] and CPC-chitosan[15]] could be useful for stem cell-based bone engineering. Autogenic growth factors-rich plasma in combination with inorganic bone (Bio-Oss®) has been also employed clinically in sinus floor elevation; this treatment was effective in forming new vascularised bone.[16]

CARTILAGE

Ultra rapid tissue engineering techniques coupled with gradient-based scaffolding and a single cell population provide a potentially promising approach for future biological joint replacement. In such condition, hyper-hydrated collagen gels, for example, seeded with hMSCs preconditioned in an osteogenic media at one end but preconditioned in a chondrogenic media at the other end. The development of distinct bone-like and cartilage-like areas and mimicking a primordial joint-like structure has been demonstrated after 7 days of an in vitro culture.[11] Investigators have also demonstrated in animal models that new cartilaginous tissue with precisely defined sizes and shapes relevant to maxillofacial reconstruction (e.g., nasal septum, temporomandibular joint) can be engineered using appropriate biodegradable scaffolds for transplanting the cells.[17]

SKIN AND ORAL MUCOSA

This pioneering work started by the observation of entire keratinising colonies from in vitro cultured epidermal keratinocytes. The formation of keratinocyte sheets was then followed using autogenic or allogenic epidermal cells. The keratinocytes sheet has the ability for renewal throughout the patient's lifetime and can undergo organization and differentiation after grafting.[11] Skin with both dermal and epidermal components is grown in the lab using a combination of cells and various polymer carriers, and engineered skin products were the first tissue-engineered products the FDA approved for clinical use.[7] This can be useful in periodontal graft surgeries, burn injuries etc.

DENTIN AND DENTAL PULP

Dental caries remains one of the most prevalent disease amongst general population. There are several ways in which one can potentially engineer lost dentin and dental pulp. There is now evidence suggesting that even if the odontoblasts are lost due to caries, it may be possible to induce formation of new cells from pulp tissue using certain BMPs.[18] These new odontoblasts can synthesize new dentin. Tissue engineering of dental pulp itself may also be possible using cultured fibroblasts and synthetic polymer matrices.[7]

Gelfoam-encapsulated dental stem cells stimulates the formation of dentine-pulp complex in pulpless root canals in young permanent incisors in beagles. Cell-free scaffolds e.g., Emdogain gel or combination of Emdogain and platelet rich plasma stimulates the regeneration of dentine-pulp complex. Growth factors [e.g., fibroblast growth factor (FGF), transforming growth factor β1 (TGF-β1) and endothelial growth factor (EGF)] have been also included within the scaffolds to modulate the function of stem cells.[11]

PERIODONTIUM

Tissue regeneration of the periodontium is no longer considered solely as an experimental approach, and significant progress has been made these past 10–15 years with respect to the development of biodegradable scaffold materials. More recently, regenerative therapies have considered whole tissue

architecture, the ultimate goal aimed at the creation of scaffolds that create a temporary 3D matrix upon which cells and tissues can grow exclusively in vitro and/or in vivo. The advances made by targeting particular families of growth factors and other signalling molecules at both the protein and gene levels has led to promising results. Much new data have been accumulated regarding the cell recruitment, attachment and chemotaxis, proliferation and differentiation, angiogenesis and extracellular matrix production of the regenerated tissue at the site of disease or damage.[11]

SALIVARY GLANDS

One method in treating salivary gland functional deficiencies makes useof an inductive gene therapy approach. The aim in this approach is to make existing non secretory ductal epithelial cells (following irradiation therapy) into secretory cells capable of fluid movement. Success in animal models has been demonstrated. Anothermethod to restore salivary gland function employs cell transplantation.[7] Baum et al.[19] have recently initiated the development of an artificial salivary gland substitute composed of polymer tube lined by epithelial cells. This relatively simple device could engraft into the buccal mucosa of patients whose salivary gland tissue has lost function, or been destroyed and would have the physiological capacity to deliver an aqueous fluid to the mouth via the buccalmucosa. These new approaches could be very effective for treating conditions associated with lost salivary gland function, including dysphagia, dysgeusia, rampant caries, and mucosal infections.[7]

FACIAL MUSCLES

Several tissue engineering strategies have been at present examined for regeneration of facial muscles. For example, in vivo implantation of a preformed tissue engineered muscle, made from neonatal rat myoblast seeded collagen constructs, into the face of rats was successful in regeneration of active myofibres, nerve fibres and blood vessels.[20] Implantation of myoblasts seeded collagen concepts was also effective in promoting volume preservation and/or tongue reconstruction. Injection of platelet-rich plasma, growth factors and stem cell-based strategy has been also employed. The use of these biological therapies however requires a standardized, safe use in the clinic and careful understanding of the mechanisms involved in the survival, proliferation and differentiation of stem cells and in muscle regeneration as a whole.[11]

CONCLUSION

With the use of tissue engineering a variety of clinical tasks will be benefitted such as, regenerative therapy which has revolutionized the future in dentistry with the synergistic confluence of advances in signalling pathways underlying morphogenesis and lineage of stem/progenitor cells by morphogens such as BMPs and synthetic scaffolds. Improved treatment of intraosseous periodontal defects, enhanced maxillary and mandibular grafting procedures, use of artificial muscle or glands and artificial salivary gland to replace tissue lost through surgery or trauma are avenues in which tissue engineering plays a role. Although, the practice of tissue engineering in day to day use may sound fictional, but if nurtured correctly then a variety of patients needs can be fulfilled, securing the future of human race.

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