Review Article

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TISSUE ENGINEERING : AN EMERGING FIELD IN DENTISTRY

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ABSTRACT:

Tissue engineering is an emerging field in dentistry that helps to recreate functional, healthy tissues and organs in order to replace diseased, dying, dead tissues or whole organs. There is an inadequate supply of organs and tissues for patients requiring organ and tissue replacement which leads to development of this field.This review article describes triad of tissue engineering, different approaches to engineer a tissue and their potential application in orofacial tissues and associated challenges.

Key words: Tissue engineering , Regeneration, Scaffolds ,Stem cells.

INTRODUCTION:

Tissue loss results from trauma, disease or congenital abnormalities is a major health care problem in the world. When this occurs in the craniofacial region, it induces serious physiological and psychological consequences on patients. Reconstruction of the craniofacial area to its esthetic and functional level is therefore a desire for affected patients.[1] Tissue engineering is a science based on fundamental principles that involves the identification of appropriate cells, the development of conducive scaffolds, and the understanding of the morphogenic signals required to induce cells to regenerate a tissue or organ.[2]

Triad of tissue engineering

Tissue engineering are basically a triad of (Figure 1):

1. Scaffolds or extracellular matrix
2. Stem cells
3. Signaling molecules

1. Scaffolds or extracellular matrix

Scaffolds provide a three-dimensional microenvironment for cells to proliferate, differentiate and generate the desired tissue. [4,5] (Figure 2)

Scaffolds usually consist of

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- natural or synthetic polymers [7],
- Ceramics [8],
- composites of these materials. [9]

A scaffold acts as extracellular matrix which allows cell attachment, migration and differentiation of progenitor cells. It also permit the localized and sustained delivery of growth factors, and enable the influx of oxygen to maintain the high metabolic demands of cells engaged in tissue regeneration. It should be mechanically compatible with the surrounding tissues. [10-12] Scaffold porosity is important for tissue generation. The quantity and extension of pores change the specific scaffold surface modifying its permeability and mechanical properties, having strong impact in cell seeding, nutrient diffusion and tissue ingrowth. [10-14] The scaffold should ideally reabsorb once it has served its purpose of providing a template for tissue regeneration andthe degradation must occur at a rate compatible with the new tissue formation [15] and the degradation products should not be toxic and must be easily cleared or resorbed to minimize the risk of inflammatory response. [13,16] Also during the scaffold degradation, the local pH should not be significantly lower than the physiological pH [13],otherwise cell death and protein degradation may occur.

2.Stem cells

Stem cells are capable of self-renewal and capable of generating differentiated progenies. These cells are responsible for normal tissue renewal as well as for healing and regeneration after injuries.[17] Some stem cells have the ability to differentiate into many different cell types.When exposed to appropriate stimuli they can differentiate into each of the more than 200 cell types of the adult body.[18] Stem cell possess a remarkable potential to proliferate and develop into many different cell types to form the desired tissue, these cells hold great promise for regenerative therapy.(Table 1)Dental pulp stem cells (DPSC) can differentiate into multiple cell lineages,such as adipocytes, chrondocytes, neurons and odontoblasts,osteoblast,myocyte, corneal epithelial cell,melanoma cell.[19-21] Stem cells from human exfoliated deciduous teeth (SHED) were also identified and isolated.[21] SHED are derived from naturally exfoliated teeth, which are one of the only disposable post-natal human tissues. SHED can undergo adipogenic, chondrogenic, osteogenic, endothelial and odontoblastic differentiation.[22-23] The ability to regenerate a dentin-pulp-like complex is found in DPSC [21,24] and also observed in SHED cells. [25] Furthermore, SHED may present an osteoinductive potential once they were able to induce differentiation from recipient murine cells into bone-forming cells. [21] Periodontal ligament stem cell(PDLSC) have the capacity to develop adipocytes and cementoblast/osteoblastic-like cells in vitro.In addition they also form collagen fibers, similar to Sharpey's

fibers, and cementum/periodontal ligament-like tissue when transplanted into immunocompromised mice using hydroxyapatite/tricalcium phosphate (HA/TCP) scaffold.[27,28] PDLSC express high levels of telomerase [25], which is a key molecule in mediating cell proliferation.[26] The stem cells from the apical papilla (SCAP) were recently isolated from the apical papilla of immature human permanent teeth.[28] The population seems to be the source of odontoblasts responsible for the formation of root dentin.[29]

3.Signaling molecules

Various signaling molecules such as Bone morphogenic proteins, Fibroblast growth factor, Interleukins, Insulin-like growth factor, Plasma-derived growth factor, Transforming growth factor, Vascular endothelial growth factor and Proteins are involved in tissue engineering. They have major role than a single protein in the differentiation of cells into a functional tissue. TGFβ-1 and BMP seem to have an important role in the odontoblastic differentiation.[30] There is evidence showing TGFβ-1 have released from the dentin after any injury [31] and BMPs have dentin induction ability.[32]The understanding of intracellular events triggered by extracellular proteins is critical for tissue engineering in dentistry.

Approaches for engineering of a tissue:

Currently, approaches for engineering of a tissue can be categorized into 3 ways(Figure 3):

- Conductive approach:

A scaffold can serve as a barrier a barrier membrane to exclude connective tissue cells that will interfere with the regenerative process, while enabling the desired host cells to populate the regeneration site e.g., use of barrier membranes in guided tissue regeneration by dentists. The barrier may be resorbed over time or removed surgically.[33-34]

- Inductive approach

It uses a biodegradable polymer scaffold which act as a vehicle to deliver growth factors and genes to the host site. The growth factors or genes can be released at a controlled rate based on the breakdown of the polymer. The desired cells migrate into the defect and begin to deposit new extracellular matrix.[34]

- Cell transplantation approach

cells from a donor source are placed directly into a polymer scaff old in vitro, and the cell-scaff old construct is consequently implanted into the tissue defect site. The transplanted cells, along with host cells form a tissue regenerate that is structurally and functionally incorporated with the host tissue.[34-35]

Tissue engineering in orofacial tissues:[2]

- Dentine-pulp complex
- Periodontium

- Skin,
- Oral mucosa,
- Facial muscles
- Salivary glands
- Bone
- Temporomandibular joints

Dentin-pulp complex

The production of dentin- pulp complex have been achieved in animal and laboratory studies using tissue engineering approches. There are several ways by which one can potentially engineer lost dentin and dental pulp. Recently there is an 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.[30,36-38] and these new odontoblasts can synthesize new dentin.(Figure-4)Tissue engineering of dental pulp itself may also be possible using cultured fibroblasts and synthetic polymer matrices.[39] Further development and successful application of these strategies to regenerate dentin and dental pulp could one day revolutionize the treatment of dental caries.

Periodontium

Periodontitis is a widespread condition of inflammation that causes destruction of tooth supporting tissues gingiva, alveolar bone, periodontal ligament and root cementum and followed by teeth loss. Guided tissue/bone regeneration membrane uses occlusive membranes to maintain the defective space and selectively encourage the appropriate cells to regenerate the lost tissues and support the newly formed tissues(figure-4).[40] Several synthetic polymers polytetrafluoroethylene,[41] polylactide, glycolide and polylactide/glycolide were used as Guided tissue/bone regeneration membrane.[42] Biomimetic materials, particularly collagen, has been used as alternative to synthetic polymers,such as OssixtTM, Bio-Gide1, Neomem1, BiomendTM, Biomend ExtendtTM.[43] Further to enhance tissue regeneration, negatively charged collagen membranes were developed.[44] To control the degradability and osteogenic potential of collagen membranes, immobilisation of hydroxyapatite nanoparticles,[45] alkaline phosphatase [47] or bioactive glass [46] on collagen membranes have been attempted. The recent advances in the field of tissue engineering utilises growth factors and cytokines for periodontal regeneration. [48] Enamel matrix derivatives that contains >90% amelogenin and <10% other protein are also useful for periodontal regeneration.[49]

Skin:

Tissue engineering has made extensive progress in the area of skin regeneration and recently several skin substitute products such as epidermal, dermal and composite are now commercially available. Skin consist of superficial

epidermal and deeper dermal layer. It acts as a protective barrier and helps in temperature regulation and prevents water loss. Skin loss occurs due to burns, trauma and surgical removal in cancer surgery.[51] Full thickness skin grafts are of good choice for the repair. However, donor site morbidity, infections, scar formation are the most common complications.[52] The ideal skin replacement for the facial region must provide the same esthetic

results as an autograft and it should have all ideal properties of normal skin. Skin substitutes are available with one that replaces dermis and one which replaces the epidermis. It can be acellular and cellular.[35,51] For generation of complex skin grafts which consist of both an epidermal and a dermal layer, fibroblasts and keratinocytes have been planted into various scaffolds.[53]However, none of these substitutes fulfills fully functional properties of skin.Further research needs to carry out to achieve versatile and universal engineered skin tissue to add vascular endothelial cells, melanocytes ,sweat glands, and hair follicles.

Oral mucosa:

Oral mucosa is thin and more vascular with the absence of hair follicles and sweat glands compared to skin. Oral keratinocytes instead of skin keratinocytes are used. The tissue engineered oral mucosa can be used for intraoral defects such as cleft lip and palate, traumatic tissue loss, and pathological mucosal loss after surgery.[54]

Salivary gland:

Salivary gland hypofunction and dysfunction are common after radiotherapy in cancer. Due to the complex structure of salivary gland, artificial salivary gland regeneration is a major challenge.[34] The secretory function of the salivary gland is vital to treat xerostomia. Joraku et al. cultivated human salivary gland epithelial cells in a polyglutamic acid polymer scaffold. They developed this using an in vitro collagen and Matrigel culture system to reconstitute human salivary gland tissue and showed functional, differentiated salivary units of acini and ducts in a 3-D construct, with the production of secretory granules and expression of aquaporin 5 protein.[2] Secretion of saliva in the artificial salivary gland is currently under research. Tissue engineering provides a biological substitute to impaired salivary glands. however, another issue is to culture the human salivary gland cells as they are highly differentiated and difficult to expand in vitro.

Facial muscles:

Facial muscles have unique anatomy and fiber composition. Tissue engineering holds great promise for treatment of patients with facial paralysis [55] and partial tongue section.[56] Currently various tissue engineering strategies have been researched for regeneration of facial muscles. Implantation of

myoblasts seeded collagen constructs was also effective in promoting volume preservation and/ or tongue reconstruction.[56] Injection of platelet-rich plasma, growth factors and stem cell-based strategy has been also used.[57] Satellite cells are also essential issue for engineering the facial muscles. In vivo, satellite cells respond to hypoxic, ischaemic muscle damage by differentiation into immature muscle fibre and maturation to muscle fibres. Fibroblasts are also assist in the self-assembly of tissue engineered muscle.[58] Vascularisation and innervations of the muscle construct remains a major challenge in tissue engineering.[59] Applying an optimal electrical, chemotropic and mechanical stimulus is therefore essential for functional reconstruction of facial muscles.[60] However these approaches requires a standardised, 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.

Bone

After resection or due to trauma restoration of the large sized bony defect is big issue for dentistry. In tissue engineering mesenchymal stem cells are preferred choice as they can convert into osteoblasts and osteoclasts. Bone morphogenic proteins are the widely used growth factors for bone regeneration by osteoinduction and osteogenesis.Platelet-derived growth factors are currently researched as growth signaling molecules.[34] Scaffolds for the bone regeneration include polymers, bovine collagen, hydroxyapatite, tricalcium phosphate.[61] This regenerated bone can be used in mandibular small are large defects, in maxillary cleft repair, maxillary and mandibular ridge augmentation, and maxillary sinus augmentation.

Temporomandibular joint

TMJ has limited blood supply so they have limited capacity for self-repair. The articular cartilage of TMJ has a surface layer of fibrocartilaginous and deep layer of hyaline-like hypertrophic zone with a thin intermediate proliferative zone. For regeneration of articular cartilage, cell therapy ,injectable smart hydrogels could be employed to transfer cells.[62] For tissue regeneration the autogenic cells are the gold standard cell source.For TMJ tissue engineering synthetic or natural scaffolds and biological modulators are also used. Success of engineered TMJ replacements depends on the restoration of function,the prevention of fibrous or ossified adhesions and incorporation of signalling molecules that allow for rapid and convenient tissue replacement.[2]

Future application of tissue engineering in dentistry.

The future of tissue engineering in dentistry is emerging immensely.With discoveries in material's sciences, genetics, molecular and cell biology, new alternatives for regeneration of bone

and soft tissues, management of periodontal disease and restorative procedures to regenerate enamel, dentin and pulp will become available for clinical application.However, major challenge lies in the ethical concerns regarding engineering tissues.Moreover, cost of tissue engineering procedures will have to take in consideration but revolutionary technologies became more affordable as they have become more popular, and, perhaps, this will also going to be true for tissue engineering in dentistry. It is difficult to predict the full impact of tissue engineering to the future of dentistry at this time.

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TABLE:

Stem cells	Derived from	Differentiation	Regeneration
DPSC	Permanent tooth pulp	Odontoblast,osteoblast,chondrocyte, myocyte, neurocyte, adipocyte, corneal epithelial cell,melanoma cell.	dentin regeneration, pulp regeneration, bone regeneration, neuroregeneration, myogenic regeneration.
SHED	Exfoliated deciduous tooth pulp	Odontoblast,osteoblast,chondrocyte,myocyte, neurocyte,adipocyte.	Bone regeneration, tubular dentin and neuroregeneration,
SCAP	Apical papilla of developing root	Odontoblast,osteoblast,neurocyte, adipocyte	Bone regeneration, neuroregeneration, dentin-pulp regeneration, root formation
DFPC	Dental follicle of developing tooth	Odontoblast,osteoblast,neurocyte	Bone regeneration, Periodontal regeneration
PDLSC	Periodontal ligament	Odontoblast,osteoblast,chondrocyte, cementoblast,neurocyte	Bone regeneration, root formation, periodontal regeneration

Table 1: Stem cells differentiation and regeneration [17-29]

DPSC = dental pulp stem cells; SCAPs = stem cells from the apical papila; SHED = stem cells from the pulp of human exfoliated deciduous teeth; PDLSC = periodontal ligament stem cells; DFPC = dental follicle precursor cells

FIGURES:

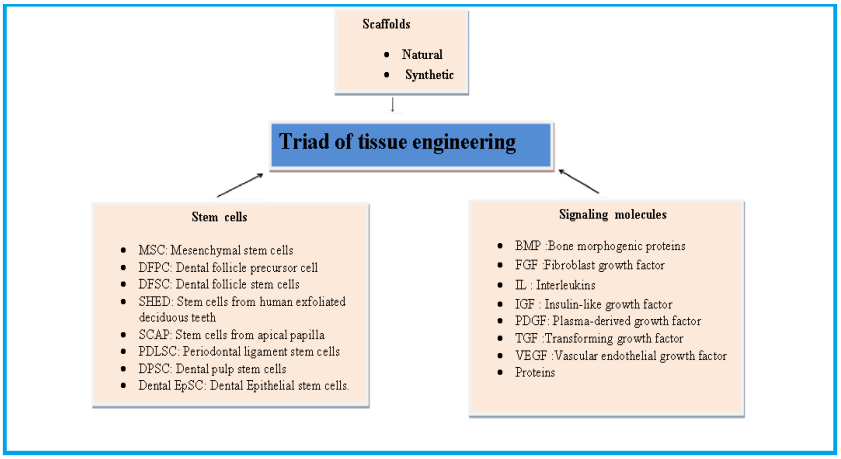

Figure 1:Showing triad of tissue engineering [1,2]

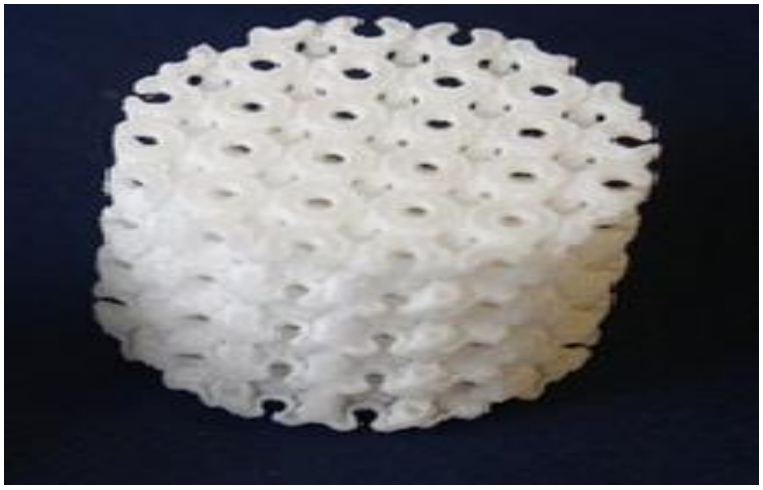

Figure 2: showing 3-D synthetic polycaprolactone scaffold.[6]

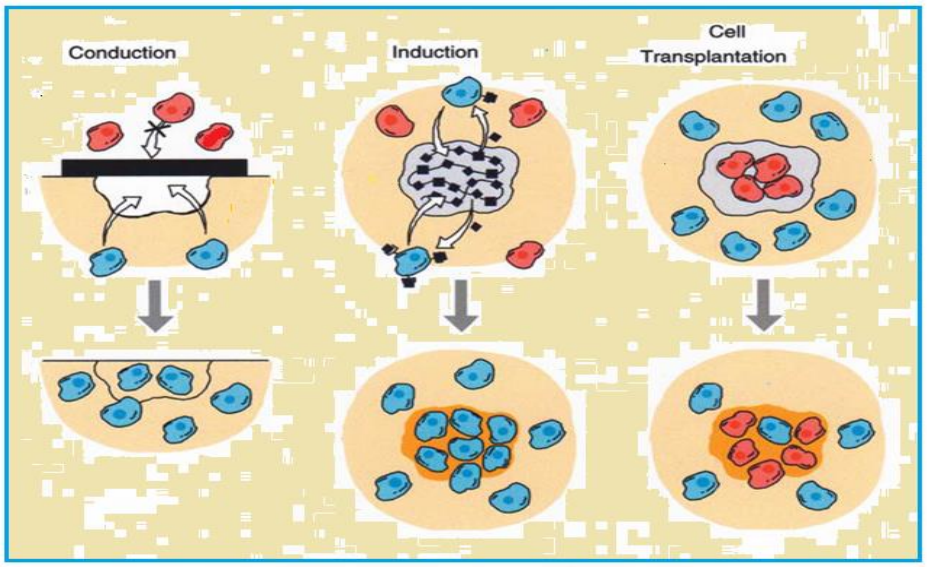

Figure 3: Approaches to engineer a tissue. [33]

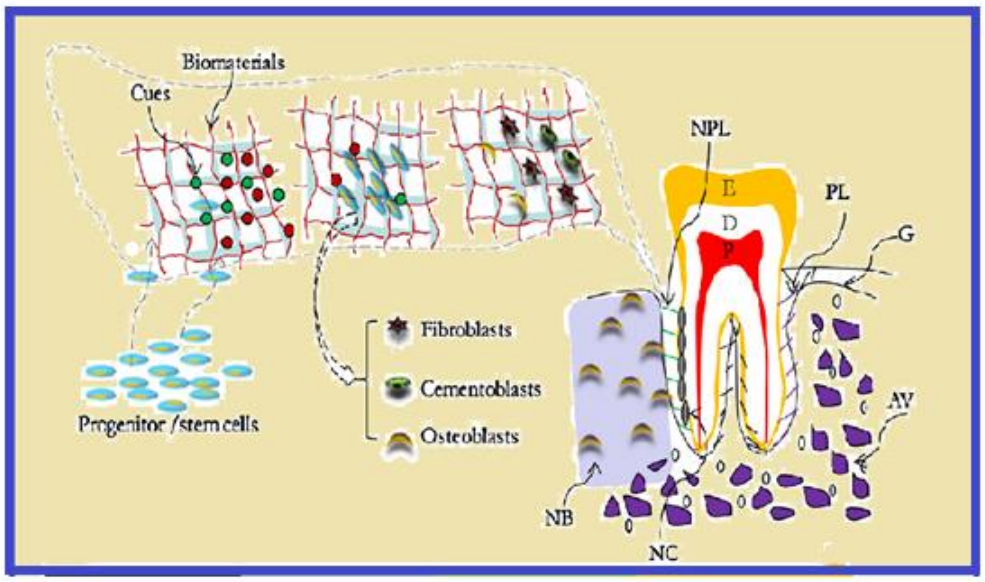

Figure 4: Showing approach used for regeneration of periodontal tissues.[50] E(enamel), D(dentine), P(pulp),G (gingiva), PL(periodontal ligament),AB (alveolar bone) ,NPL (new periodontal ligament)NB(new bone),and NC(new cementum)