Research Article

The Role of Scaffolds in Periodontal Regeneration

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ABSTRACT

The aim of the study is to understand the role of synthetic scaffolds in periodontal regeneration and the objective is to summarize the various types of synthetic scaffolds and their designs and their role in periodontal regeneration. Periodontal diseases are infectious diseases with irreversible loss of tooth supporting apparatus. To reestablish the health of the periodontium the concepts of regenerative surgical procedures have been developed. The use of scaffolds to deliver cells required for periodontal regeneration has been a integral part of tissue engineering. A predictable reconstruction of healthy periodontal tissues still remains a challenging field; hence it is necessary to optimize cell–scaffold combinations by understanding the cellular events during periodontal wound healing and regeneration.

Keywords: Synthetic scaffolds, periodontal regeneration, tissue engineering.

INTRODUCTION

Periodontal diseases are the most frequently occurring inflammatory diseases which arises due to plaque bio film formation. During the progression of this disease there is an irreparable loss of the tooth supporting apparatus which eventually leads to the loss of tooth. This encompasses the progressive destruction of the gingiva, periodontal ligament (PDL), cementum, alveolar bone and connective tissue attachment between the root surface and the alveolar bone [1].

Earlier conventional treatments like 'cause related treatment' aimed only at removing the causative factors like calculus and plaque. This approach only helped in improving the inflammatory response of the periodontal disease rather than achieving regeneration of the lost tissues[2].Challenges are faced by clinicians in achieving regeneration of the lost periodontal structures because there is loss of all three tissues like cementum, periodontal ligament (PDL) and alveolar bone which are unique in their function and origin. The reconstruction of just a single tissue will not satisfy the healing process of the disease but requires the involvement of all the three tissues for regeneration [3].

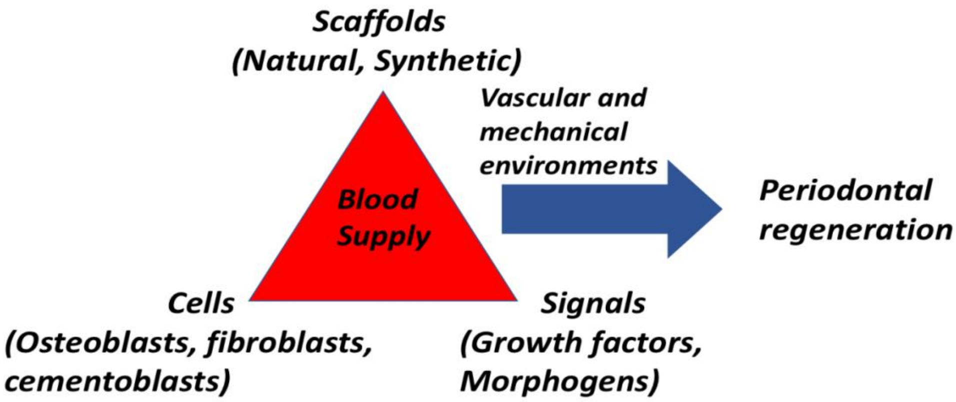
Periodontitis is the most common disease at a high recurrence rate due to bacterial accumulation and the formation of long junctional epithelium following surgical procedures[2]. To obtain a desirable outcome (I.e) regeneration of periodontal tissue should be characterized by the formation of cementum, periodontal ligament (PDL), alveolar bone and gingiva. Studies have proven that regeneration is a better outcome compared to repair of the periodontal structures[2,4].

Earlier many strategies were developed to regenerate the periodontal tissues. One of them is the combined use of flap surgery with bone grafts for the regeneration of the alveolar bone. The grafts include xenografts, allografts, auto genius grafts and alloplastic materials [5]. The next strategy focused at three dimensionally (3D) regenerating the lost structures such as the cementum, alveolar bone, periodontal ligament (PDL) and the attachment of connective tissue. The next strategy was the concept of guided tissue engineering (GTR) aimed at repopulating the periodontal ligament (PDL) cells in the healing region and does not influence the speed of growth of these cells. The next strategy was the development of biological approaches, enamel matrix derivative which is a component of emdogain, the first signaling molecule aimed at periodontal regeneration. Many growth factors like the platelet derived growth factor (PDGF) and the bone morphogenic protein (BMP-2) have proven their ability in periodontal regeneration and have started becoming commercially available in the United States (US) [6]. These strategies were introduced only to correct angular bone deformities and not horizontal defects. Hence to overpower these limitations, tissue engineering strategies were proposed owing to complete periodontal regeneration. This article highlights the role of scaffolds in periodontal regeneration.

Application of Tissue Engineering in Periodontics

In recent years, tissue engineering, a new advancement in periodontal regeneration has been introduced for the complete regeneration of lost tissues[45]. Tissue engineering is the replacement of reconstructed living tissues in the place of lost or damaged tissues and is developed on the principles of cell biology, developmental biology and biomaterial sciences[46]. The tissue engineering involves a triad which includes cells, signaling molecules and scaffold matrices [7]. The scaffold acts as a compartment for holding cells and enables attachment, migration, proliferation and three-dimensional structural organisation of the cells [8]. In addition it also guides the three dimensional (3D) arrangement of the cell population.

The term 'Tissue Engineering' was framed by Langer and Vacanti in 1993 [9]. Tissue engineering is surfacing as a potential solution to replace the damaged or lost tissues by implanting natural, synthetic or semi-synthetic tissues which gains function from the start or grows into functionality [10]. The periodontal healing is a complex process which involves cells of five or more tissue types which includes the epithelium, gingival connective tissue, periodontal connective tissue, cementum and the alveolar bone to have a new connection with the nonvascular hard tissues [11]. Healing of these tissues must happen under a significant bacterial load and rendered to this complexity is the action of occlusal forces in the transverse and axial planes which affects the pattern of wound healing by disrupting the periodontal tissue resorbing horizontally. Hence without the introduction of the triad theory it may be difficult to overcome these limitations.



Cells provide the system for the growth and differentiation of new tissues. Growth factors or morphogens regulate the cellular activity and provide stimuli to cells to produce matrices for the regenerative tissue. New vascular networks stimulated by angiogenic signals provide the nutritional support for tissue growth and homeostasis. Scaffolds act as a vehicle three dimensionally to assist the above processes for tissue regeneration [12, 13]. Polymeric scaffolds are a porous and biodegradable material that has been customised to form sheets, films, fibers and gels[14].

Ideal Design Requirements for Cell Seeding Scaffolds

Biocompatibility

The cells must adhere, retain normal functioning and migrate to the surface through the scaffold and proliferate before production of new matrix. After getting implanted the scaffold must not produce any immune reaction in order to prevent any inflammatory response which my alter the wound healing [15].

Biodegradability

The aim of tissue engineering is to let the cells of the body to replace the implanted scaffold. The scaffold must degrade biologically to yield their own extra cellular matrix. Nance the byproducts should be non-toxic and should depart the body without having any effects on the organs.

Mechanical properties

The scaffold properties must be comparable to the anatomical site of placement and should be rigid to to allow surgical handling. Researchers face a great challenge to construct a scaffold with suitable mechanical properties to engineer bone. In such cases the implanted material (scaffold) should have suitable mechanical properties to function from the implanted time to the completion of bone Remodeling [16].

Scaffold architecture

To ensure proper cellular penetration and sufficient nutrition diffusion the scaffolds must possess an interconnected pore structure and have high porosity. This also ensures proper degradation of the byproducts to exit the body without any interference with adjacent tissues. The size of the pores must be such that it can allow cells to migrate into the scaffold where they bind with the ligands within the scaffold and small enough to ensure a specific surface so that only. A certain amount of cells can bind to the scaffold [17, 18].

Space maintenance within the defect site and barrier functions

Space maintenance is of chief importance so that there is place for the regeneration of horizontally lost structures. The engineered material should have a suitable structure and have sufficient strength to be placed into the defect site such that there is no collapse of the overlying tissues into the damaged site. Hence adequate wound space and suitable environment act synergistically to grant an undisturbed stream of molecular and cellular events in the tissue regeneration [19].

The essential design features required for space maintenance include ease of shaping and sufficient rigidity to resist soft tissue collapse into the damaged site and an internal structure compatible with attachment of cell and colonization and allowing the growth of tissues compatible with those to be regenerated [20].

Incorporation of cells with an appropriate phenotype for ongoing periodontal regeneration

It is possible to culture and incorporate the adult mesenchymal cells into a biodegradable scaffold for the introduction into a periodontal defect.

Lately, viral vectors transduced into mesenchymal cells are being used to introduce specific molecules to the defect sites for stimulating tissue regeneration. Studies have suggested that the use of viral vectors have enabled genetically altered cells to express certain growth factors which is necessary for regeneration of periodontal tissues, to be introduced into periodontal defects and helped to improve the regenerative response in experimental animal models [21]. Cells can be acquired from cementum[22], periodontal ligament [23] and bone [24] for periodontal regeneration.

Mimicking the stem cell niche to alter the regulation of stem cells

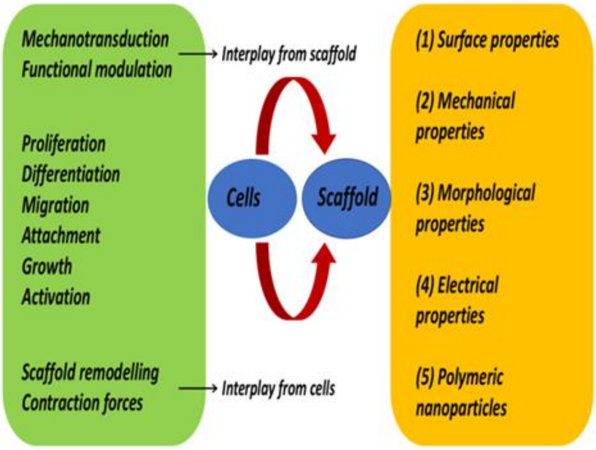
It is essential to generate both the hard and soft tissues and also mimic their attachment. Cell based tissue engineering involves cells from both origins to produce the target organ and a three-dimensionally engineered scaffold to develop cell to cell proximity and improves self assembly and tissue functions[25]. The mimicking stem cell niche is considered to enable both proliferation and differentiation both ex vivo and in vivo after transplantation [3]. Cytokine/ growth factor signaling regulates the self renewal and differentiation of stem cells. Stem cell functions are controlled by cell to cell and cell to matrix interactions by transmitting signals into them. Cell to cell interaction existed not only between stem cells but also between stem cells and supporting cells that regulate the stem cell retention. Cadherins, notch ligands and many other surface ligands are knows for their association in stem cell activation [26, 27].

The next mode of interaction is between the cell and extra cellular matrix (ECM). The ECM contains proteins, proteoglycans and fibers and hyaluronic acid [28]. These constituents of the ECM can promote and support cell growth because even the stem cells possess cell adhesion molecules and initiate intracellular signalling [29].

The oxygen gradient in the niche affects the functionality of the stem cells. Stem cell niches are to be located in low oxygen concentrations and low pO2 regions, where the rate of cell differentiation is decreased and proliferative potential is increased [30]. Studies have suggested that oxidative stress have suppressed the cell–cell adhesion of hematopoietic stem cells (HSC) to osteoblasts mediated by E-cadherin, leading to the exit of hematopoietic stem cells from the niche [31].

Cell–scaffold interplay and scaffold designing

Not only the properties of the scaffold have an effect on the functions of the stem cell but cells also have the potential to induce the deformation of scaffolds during the process of tissue regeneration, which leads to the compromise in mechanical properties of the scaffolds. Hence, the cell–scaffold interplay is bidirectional. Forces are generated in the context of cell adhesion to ECM/scaffolds, and mechanotransduction occurs which transduce them into intracellular an signal which leads to proliferation, differentiation, migration, and apoptosis in the cells[32]. The scaffold material should have the ability to mimic a favourable niche similar to the target tissue for the stem cells. The scaffold materials have the ability to transmit signals to the cells that will decrypt these signals to biochemical signals. The physical and chemical properties and field area also decides the destiny of the cell [8]. To maintain a stable relationship between the scaffold and the cells, the designing of the scaffolds should include parameters such as mechanical electrical and morphological properties. Increased porosity and pore size are the important features responsible for expanding the surface area for cell growth and attachment.



Types of Scaffolds materials

1. Naturally occurring polymers
   Porous chitosan
   Methyl cellulose gel
   Hyaluronan
2. Sythetic polymers
   PLA-PGLA copolymer + gelatin sponge
   Fluronic F 127
3. Hydrogels
   Dex- GMA gelatine gel
   Collagen gel
   Gelatinous carrier
4. Bio active ceramics
   Calcium phosphate cement

Hydroxyapatite

5. Bone grafts

Bone allografts

Naturally Occurring Scaffolds

Chitosan

Chitosan is a biopolymer and is structurally similar to glycosaminoglyacans. They are biodegradable in mammals. They have been used as scaffolds in recent years. It is effective in cell attachment for delivery. Studies have suggested that chitosan has to be used with other molecules to promote its biocompatibility for cell attachment [33].

Methyl cellulose gel

A single or multilayer cell sheets can be used in the for tissue engineering applications [34]. Single layer cell sheets can be implanted into the host periodontal ligament [35]. There might be possibility to create three-dimensional heterogeneous structures such as cardiac muscle by placing homotypic cell sheets in three dimensional tissue structures in addition to using differentiation ability of ASCs (adipose tissue derived stem cells)[36].

Hyaluronan

Hyaluronan is a material with appreciable potential for tissue engineering. It plays an important role is cell development and migration [37]. Studies have revealed that this material can be made more rigid for cell seeding process by esterification and cross-linking. These materials are biodegradable and aid in the growth of fibroblasts, chondrocytes and mesenchymal stem cells.

Sythetic Polymers

PLA-PGLA copolymer + gelatin sponge

The need for bone regeneration is a serious concern in case of bone defects and fracture healing. Selected bone forming cells such as TGF-beta1 and IGF-1have was incorporated into gelatin hydrogel scaffolds to induce bone regeneration in previous studies. The use of PLA-PGLA copolymer + gelatin sponge containing rhBMP-2 induced significant bone regeneration in rat mandible model [38]. In case of poly-l- lactic acid (PLA) and polyglycolic acid (PGA) polymers, the degradation process occurs by hydrolysis thus yielding carbon dioxide and hence reducing the local pH that can result in cell and tissue necrosis [39].

Fluroric F-127

The F-127 is known as the sacrificial component (I.e) it gets expelled while polymers a cross linked to each other and form a printed structure. This leads to leaving pore like holes on the structure which provides a good environment for nutrients and growth of cell [40].

Hydrogels

Dex- GMA gelatine gel

Novel thermo mechanical hydrogel scaffolds containing the previously prepared microspheres loaded with bone morphogenetic proteins (BMP) were successfully produced by radical cross linking and low dose gamma-irradiation from combination of two kind of biomaterials: glycidylmethacrylated dextran (Dex-GMA) and gelatine [41]. The studies revealed that a Dex-GMA/gelatin scaffold containing microspheres loaded with BMP could satisfy the tissue-engineering applications.

Collagen gel

Collagen is biomaterials having excellent biocompatibility and good biodegradability and weak antigenicity. Hence collagen can be used for tissue regeneration purposes, including bone substitutes, artificial blood vessels and valves. Cells can be seeded into collagen membranes and can be cultured and then introduced into a tissue defect site, and can initiate tissue repair and regeneration [22].

Gelatinous carrier

Gelatin is derived from collagen and is formed by hydrolysis (I.e) by breaking the natural triple-helix structure of collagen into single-stranded molecules. Gelatin is less immunogenic in contrast to its precursor. It has the property to retain informational signals like the Arg–Gly–Asp (RGD) sequence and this in turn promotes the cell adhesion, migration, differentiation and proliferation [39, 40].

Bio-Active Ceramics

Calcium phosphate cements

The most recent advances in tissue engineering is the use of calcium phosphate cements (CPC). It is a potential bone substitute. This biomaterial has a structure and composition similar to the mineral portion of the bone. It has been considered as a suitable material to develop scaffolds for bone tissue engineering [42]. CPCs are also easily handled and Moulded and enabled cell adhesion, proliferation and differentiation of the mesenchymal stem cells in to osteogenic cells and hence can be used as potential scaffolds for tissue engineering.

Hydroxyapatite

Hydroxyapatite (HAp) exhibits excellent biocompatibility with soft tissues such as skin, muscle and gums, Synthetic hydroxyapatite has been used widely in bone repair, bone augmentation. Studies have revealed that nano hydroxyapatite may be a potential biomaterial due to its good biocompatibility and bone integration ability [43]. Another study revealed the use of human osteoblasts like SaOS2 cells were able to adhere proliferate and migrate into pores of the scaffold. Furthermore, the cell viability was found to increase on porous scaffold compared to dense Hydroxyapatite [44].

CONCLUSION

The strategies proposed earlier to regenerate periodontal tissues exhibited few drawbacks. Hence, to overcome these limitations, researchers have extensively studied the application of tissue engineering in this field. The current advance practised in this field is the use of scaffolds for periodontal regeneration. Scaffolds contain stem cells and create a microenvironment suitable for these cells in addition to release of growth factors. However, the scaffold should be able to fill certain anatomic sites of the lost periodontal tissue containing horizontally resorbed bone structures.. Thus, a three dimensional version of the scaffold is the key for complete periodontal regeneration, although this research field is still under investigation.

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