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Stem Cells: Role in Regenerative Periodontics

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Abstract: *Stem Cell Research is the most fascinating area of biology today. The discovery of stem cells dates back to 1950's when various experiments with bone marrow established their identity and their powerful role in regeneration of lost tissues. In the medical field scientists that stem cells offer a viable source of replacement cells to treat diseases like Diabetes, Parkinson's disease and cardiovascular disease, have hypothesized it. In the field of dentistry, lot of research is underway and cells with characteristics of adult stem cells have been isolated from dental pulp, deciduous tooth and periodontal ligament with the capacity of regeneration. This review highlights the potential role of stem cells in regenerative periodontics.*
Keywords: *Gene therapy, Periodontal ligament, Periodontal regeneration, Stem cells, Tissue engineering.*

I. Introduction

Normal periodontium is a complex tissue, when damaged has limited capacity of regeneration. After the establishment of periodontal disease only therapeutic intervention has the potential to induce regeneration [1].The series of events involved in periodontal regeneration involves the recruitment of locally derived progenitor cells to the site which can subsequently differentiate in to periodontal ligament forming cells or bone forming osteoblasts[2].

Various treatment modalities have focused on regenerating lost tissues with substitutes having limited or no reparative potential. The techniques used on regenerating lost bone involves the use of autografts, allografts and alloplast materials .But due to the issues related to safety, clinical effectiveness and stability their usage in periodontal regeneration is questioned [1,3].Recently various biological approaches based on principles of tissue engineering and gene therapy have emerged as prospective alternatives to conventional treatments for regenerating periodontal tissues[4,5].

II. Stem Cells

Stem cells are uncommitted entities, foundation cells for every tissue and organ in the body, including the periodontium (6)

2.1 Properties of dental stem cells:

1. Self renewal: It is defined as the property of stem cell that allows them to go through numerous cycles of cell division while maintaining the undifferentiated state.

2 Potency: It is the capacity of stem cell to differentiate in to specialized cell types. The stem cell can be either totipotent or pluripotent depending on their ability to give rise to mature cell types. Multipotent stem cells can differentiate into many cells among closely related family of cells [6].

2.2 Sources of dental stem cells:

The potential sources of dental stem cells include

2.2.1 Bone marrow derived mesenchymal cells (BMMSC):

Human bone marrow derived stem cells originate in the bone marrow and are capable of differentiating along multiple mesenchymal lineages. These cells are clonogenic and have demonstrated the ability to form bone and cartilage in vivo[7] .Mesenchymal stem cells have also been shown to form cementum, periodontal ligament and alveolar bone in vivo after implantation into periodontal defects in beagle dogs, suggesting that bone marrow may be a useful source of mesenchymal stem cells for periodontal regeneration[8].

2.2.2 Adipose -derived stromal cells:

Adipose derived stem cells contain group of pluripotent mesenchymal cells with the multilineage differentiation capacity, including osteogenesis, chondrogenesis and adipogenesis[9].It was reported that these stem cells expressed bone marker proteins including alkaline phosphatase , type1 collagen, osteopontin, OCN and produce mineralized matrix. Tobita etal demonstrated that eight weeks after implantation of adipose derived stem cells into rat periodontal defects, new periodontal ligament-like and alveolar bonelike structures were formed implying that these stem cells could promote periodontal regeneration vivo [10]. As adipose tissue can be obtained by using less invasive methods and in large quantities than bone marrow stem cells, makes them a unique stem cell reservoir for regenerative periodontal therapy.

2.2.3 Dental pulp stem cells:

The first human dental stem cells were isolated from dental pulp tissue of extracted third-molar teeth. These cells were found to be highly proliferative, clonogenic cells , capable of differentiating into odontoblast like cells and forming dentin/pulp complex when implanted into immunocompromised mice[11].Studies done by Gronthos etal reported that these cells have striking feature of self-renewing capability ,multi-lineage differentiation and they are capable of forming ectopic dentin and pulp tissue invivo [12]. These cells express several markers including mesenchymal and bone marrow stem cell markers STRO-1 and CD146 as wells as embryonic stem cell marker ,Oct14. Culturing these cells with various differentiation media demonstrated their dentinogenic, adipogenic, neurogenic, chondrogenic and myogenic differentiation capabilities. Their characteristic features and multilineage differentiation potential have established their stem cell nature and indicated the promising role in regenerative therapy

2.2.4 Periodontal ligament stem cells:

Periodontal ligament, a highly fibrous vascular tissue has one of the highest turnover rates in the body. Apart from the cells commonly found in the PDL ,a smaller population of progenitor cells have been identified in vivo cell kinetic studies [13].The concept that stem cells may reside in the periodontal tissue was first proposed almost 20 years ago by Melcher who queried that cementoblasts, alveolar bone cells and periodontal ligament fibroblasts were derived from single population of stem cells .This was further confirmed by the compelling evidence provided by invivo and histological studies by McCullough and co-workers [13].

Periodontal ligament stem cell were first isolated in 2004 and shown to give rise to adherent clonogenic clusters resembling fibroblasts[14].These cells have the capacity to differentiate into osteoblast-like and cementoblast like cells in vitro as well as produce cementum like and periodontal ligament like tissues invivo[15].Periodontal Ligament stem cells also express an array of cementoblast and osteoblast markers, as well as STRO-1 and CD14 antigens , found on dental pulp stem cells and bone marrow stem cells[12]. These findings indicate that human PDL may be an alternate source of primitive precursors to be used in stem cell therapies.

2.2.5 Stem cells from apical papilla:

These cells form adherent clonogenic clusters and similar to other mesenchymal stem cells population capable of differentiating into adipocytes and odontoblasts \osteoblasts in vitro. These cells have been shown to give rise dentin tissue and generate root/periodontal complex after they were transplanted with periodontal ligament stem cells in minipigs[15].

2.2.6 Stem cells from dental follicle:

Mesenchymal progenitor cells have been isolated from dental follicle of human third molar teeth. These fibroblast-like colony-forming and plastic-adherent cells express stem cell markers (STRO-1and nestin). STRO-1positive dental follicle progenitors have shown to generate periodontal ligament-like tissue after in vivo implantation implying that dental follicular progenitor cells may be a research tool for regenerative periodontal therapies [16, 17].

2.2.7 Stem cells from human exfoliated deciduous teeth:

These cells have higher proliferation rate compared with the stem cells from permanent teeth. They have high plasticity because of their ability to differentiate into neurons, adipocytes, osteoblasts and odontoblasts. Cordeiro et al transplanted these cells in to mice and these cells showed to differentiate into odontoblast like cells and showed morphologic characteristics similar to those of odontoblast cells [18].

While the use of both dental and nondental mesenchymal stem cells appear to be promising, the best stem cell source is yet to be identified the advantage of using these cells for regeneration represents an initiative in the development of more predictable biologically based therapies for the periodontium.

2.3 Clinical implications:

Stem cells have been used extensively in medical field for repair and regeneration of defective tissues and organs such as bone[19],cartilage[20],heart and spinal cord[21].In dentistry identification of mesenchymal cell like population from both dental and non-dental tissues ,has presented the possibilities of application of techniques such as tissue engineering and gene based approaches as novel strategies for regenerative periodontal therapy.

2.3.1 Periodontal tissue engineering

Tissue engineering is a contemporary area of science based on the principles of cell biology, developmental biology and biomaterials to replace lost or damaged tissues[22].The main requirements for producing an engineered tissue are appropriate progenitor cells ,signaling molecules, an extracellular matrix or carrier construct and an adequate blood supply[23].The potential tissue engineering approach to periodontal regeneration involves the incorporation of progenitor cells and instructive messages in a pre-fabricated three dimensional construct and subsequent implantation of the construct into the defect site[1].

Tissue engineering strategies for reconstruction of periodontal attachment apparatus involves two techniques either by reiteration of tooth development based on epithelial-mesenchymal tissue recombination or by seeding of cells on biomaterial scaffold.

i) Tissue –recombination technique:

This technique aims to replicate key reciprocal interactions between the dental epithelium and the ectomesenchyme during odontogenesis to regenerate the periodontium. The combination of oral epithelium and nondental –derived mesenchymal cells resulted in the formation of tooth crown and bone in vivo whereas the combination of embryonic epithelium and mesenchymal cells from mouse fetuses re-associated with tooth germs resulted in formation of roots, PDL and alveolar bone invivo [24]. Several studies reported that engineered tooth primordial give rise to proper tooth development after being transferred in to adult mandible indicating that cultured stem cells can replace lost or damaged dental structures when transplanted in to adult oral cavity[25]

However this technique has its drawbacks as periodontal structures formed using this approach are not formed in isolation from other dental tissues, as there is currently no substitute for embryonic tissues. This may pose problems of implantation in to the periodontal defects limiting the practical application of this approach.

ii) Cell seeding:

This technique of cell transplantation with the use of three-dimensional matrices for regenerating the periodontium have been extensively studied.Studies done using non-dental stem cells reported that autologous bone marrow mesenchymal stem cells and adipose derived stem cells have the capacity to regenerate alveolar bone and periodontal ligament like structure after transplantation in vivo supporting the use of these cells in periodontal regeneration[25].Studies done using dental stem cells have reported that when progenitor cells seeded directly in to biomaterial scaffold (eg; polyglycolic acid,calcium phosphate material ,collagen sponges) followed by transplantation into periodontal defects in animal models resulted in the formation of new periodontal ligament and bone tissues[26,27] .A novel study done using combination of swine stem cell obtained from the apical papilla and periodontal ligament stem cells reported to regenerate lost root and periodontal structures in minipigs[28]

Recent findings reported that human induced pluripotent stem cells derived from the dental source (eg; Gingival fibroblasts) differentiated in to a variety of autologous cell types (dental stem cells and dental epithelium) on in vivo administration. These results offer a promising future for the usage of dental stem cells in human regenerative periodontal therapy.

2.3.2 Stem cell mediated gene therapy:

Gene therapy involves molecular techniques to introduce ,suppress or manipulate specific genes ,thereby directing an individual's own cells to produce a therapeutic agent[29] .In periodontal regeneration gene therapy seeks to optimize the delivery of agents such as growth factors to periodontal defects so that the limitation(eg; short duration of action) associated with the usage of these factors can be overcome[30]. Gene delivery techniques used in periodontal and alveolar bone regeneration involves two potential strategies for delivering therapeutic transgenes in to human recipients which includes

i)the introduction of gene into delivery cells(often a stem cell)outside the body ex vivo followed by transfer of the delivery cells back in to the body .

ii) Direct infusion of the gene of interest using viral or non-viral vectors in vivo [31]

The use of adenoviral vectors to enable the over-expression of growth –promoting molecules such as platelet derived growth factor and bone morphogenic protein -7 has been investigated for its potential in periodontal regeneration[32].Sustained release of bone-morphogenic protein-7 and platelet derived growth factor by transformed cells implanted in to experimental periodontal defects results in enhanced regeneration of bone and cementum[32].But however the use of this technology with dental stem cells offers effective alternative strategies to provide renewable source of growth factor release for regeneration compared to conventional techniques. Further research is required to know about the potential risks of viral recombination and immune responses towards viral antigens, which ultimately determines the success of gene transfer techniques in periodontal regeneration.

2.4 Potential challenges in implementing stem cell therapy:

2.4.1 Biological challenges:

Despite the biological evidence showing regeneration can occur in humans there are certain drawbacks which includes

i) Incomplete understanding of the way the roots develop and the signaling mechanisms involved in the process [33].

ii) Molecular pathways that underlie stem cell renewal and differentiation is unknown.

Periodontal regeneration involves the replication of key cellular events that parallel periodontal development and complete understanding of the specific cell types, cellular processes remains elusive. Numerous studies till date have been done on animal models so further research is required for understanding stem cell behavior in humans and applying them into clinical practice.

2.4.2 Technical challenges:

i) Culture conditions developed to mimic the cell microenvironment in vivo for cell proliferation and differentiation are not sufficient to ensure safety and consistency of the research.

ii) Timing is a constraint as autologous approaches may involve weeks or months because of instability in gene mutation and karyotyping.

iii) Unavailability of ideal biocompatible scaffolding and delivery systems [34].

2.4.3 Clinical challenges:

i). Immune rejection had been reported with the use of human embryonic stem cells and the solution to this problem involves the use of autologous stem cells without the need for donor and recipient cross matching.

ii). Genomic stability and risk of tumourogenesis are major safety considerations relating to the challenge foll owing stem cell transplantation, as the reliable methods for eliminating undifferentiated embryonic cells from culture have not been still established from long-term studies [24]

III. Conclusion

The ultimate goal of periodontal therapy is the restoration of tissues destroyed by periodontitis to their original form and function. Till date, a number of studies have reported that stem cells with physical matrices and growth factors have the capacity to regenerate periodontal tissues in vivo. Still these techniques face with biological, technical and clinical challenges. Better understanding of the process and mechanism that parallel periodontal development will be required to make stem cell based therapies a promising alternative in periodontal regeneration.

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