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Stem Cell Based Bone and Periodontal Regeneration

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ABSTRACT

The prime intention of periodontal regeneration is restoration of diseased and damaged alveolar bone proper, the cementum and PDL fibres into the root surface. Recent regenerative strategies, periodontal researches and stem cell regenerations show encouraging approaches towards the same. So far mesenchyme stem cells have shown potential for periodontal regeneration in animal studies. Most investigated among several MSC's is Bone Marrow MSC's (BMMSC), Periodontal Ligament Stem Cells (PDLSC's) and Dental Pulp Stem Cells (DPSC's).

A few studies have also been conducted on humans using BMMSC's, PDLSC's, DPSC's and have been proven effective and safe. However to bring MSC based periodontal regeneration to regular clinical use, more studies need to be conducted.

Key words: Periodontal regeneration, Mesenchyme stems cells, BMMSC's, PDLSC's, and DPSC's

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INTRODUCTION

Periodontitis is a common oral infection causing chronic inflammation leading to destruction of periodontal tissues sparked by bacterial microorganisms demolishing alveolar bone, PDL fibres and cementum ultimately leading to Edentulism.

Dental implants are the surgical fix to edentulism or tooth loss however to institute a secure connection adequate amounts of bone is required which is lost because of chronicity of periodontitis for the treatment of which autologous bone graft is the gold standard treatment option that comes along with its own limitations [1-3].

This can also lead to systemic conditions like atherosclerosis, diabetes mellitus, cardiovascular diseases, nutritional deficiencies and even rheumatoid arthritis.

Long standing periodontitis treatments target reduction of inflammation avoiding succession of the disease. Non-surgical treatments are the priority options for periodontal inflammation and minimal tooth loss is expected however if the state of disease demands additional treatment support surgical approach is carried out to seize progression. Surgical approaches can be respective, non-respective or regenerative wherein periodontal regeneration can be the benchmark procedure leaving the other two behind because of the associated drawbacks.

Regenerative treatments hold back success if associated with unquestionable limitations involving patient specific elements.

Biological agents under trials have contentious efficacies but growth factors, cell combinations and tissue engineering show potential.

MSC's have been trailed *in vitro* and *in vivo* with hopeful results. Some of the dental derived MSC's are:

- DPSC's-dental pulp stem cells
- SHED's-human exfoliated deciduous teeth stem cells
- PDLSC's-periodontal ligament stem cells
- DFPC's-dental follicle precursor stem cells
- SCAP's-apical papilla stem cells

Non dental stem cells tested

- BMMSC's-bone marrow derived
- ASC's-adipose derived
- ESC's-embryonic derived stem cells
- IPSC's-induced pluripotent stem cells

LITERATURE REVIEW

Development of periodontal tissues

The initiation of development of periodontium begins from the formation of enamel organ which is derived from the oral epithelium and on the other hand PDL, cementum

and alveolar bone is formed by dental papilla derived from Ectomesenchyme.

Cementum formation begins post crown formation, cells of outer and inner enamel epithelium multiply forming her twig's epithelial root sheath which disintegrates and doesn't cover much of the external predentin surface. A thin epithelial matrix is deposited over the newly formed dentin called intermediate cementum. After HERS fragments cells from dental follicle attach and align to dentin, differentiate to cement oblasts and form root cementum [3-9].

Periodontal ligament is mostly produced by fibroblasts and minor amount of formation takes place with the help of vascular and neurologic components.

Gingiva is formed by functional epithelium cells and the gingival connective tissue is formed by prefollicular mesenchyme.

Alveolar bone development occurs simultaneously with root development as some cells also metamorphose to osteoblasts as mentioned earlier.

DISCUSSION

Stem cells are used in the form of scaffold's cells and signalling molecules. MSC's are multi potent with benefits of having self-regeneration capabilities and easier access to the source however they are difficult to reap and poor with patient factors associated with pain and morbidity during harvesting procedure. Sources other than bone marrow are under investigations like dermis, adipose, muscle and the ones arising from dental based stem cells. Contain capability to differentiate into multiple cell forms hence exclusively researched for regenerative purposes. Looking into bone physiology, it largely depends on bone resumption and forming properties that at a cellular stage is carried by BMMSCs that were differentiated into osteoblasts and osteocytes. BMMSCs also have an important role play in anti-inflammatory modulating effect during surgical bone transplantations that can be extremely fruitful during procedures like these to be a success [10-15].

ADMSCs: for comparison ADMSCs are less morbid to extract but show steady growth and can be differentiated into multiple other cells including osteocytes, adipocytes, and chondrocytes. These are comparatively easy to access and have abilities to heal critical bone defects.

DSCs: A number of stem cell populations with a similar neural crest origin have been isolated from various areas of the tooth. MSC like features in general, such as the production of certain genes environmental indicators and propensity for Mesenchymal differentiation divisions of cells surprisingly, DSCs show a wide range of behaviours perks such as ease of access, a plentiful supply, and lower costs inconvenient for donors which is a convincing proposition source of allogeneic MSCS, particularly for pulp regenerating tissues and the development of Periodontal Ligament (PDL) For biological implants, partial or complete tooth structures are used construction [16-20].

DPSCs: DPSCs are the first DSCs and, possess good healing properties. Because of their ability to replenish odontoblasts during dentin restoration, these are critical for repairing. Furthermore, because DPSCs are neural cells, they can develop into functionally active neurons and glial cells when exposed to the right environment. Furthermore, DPSCs exhibit a distinct ability to release neurotrophic substances that aid in neuroprotection and neuritis development. Furthermore, recent research has indicated that DPSCs are found in a neurovascular bundle niche. Surprisingly, DPSCs have high coagulant potential, as evidenced by their ability to produce a variety of antigenic signalling pathways and create capillary like formations under specific environmental circumstances, despite their endothelium habitation. The MSC like and neurovascular features of DPSCs are combined.

PDLSCs: PDL connects the root's cementum and the alveolar bone socket wall and aids in dental stability by attaching the tooth to the alveolar bone. The mechanical preservation and repair of periodontal tissue structure and function is the responsibility of PDLSCs, a stem cell subset from PDL. Such cells are Clonogenic, produce a number of cementoblastic and osteoblastic signals, and may form mineralized nodules when cultured *in vitro*. PDLSCs may also generate cementum and PDL like structures following *in vivo* implantation.

SHEDs: SHEDs can generate dentin like structures after *in vivo* implantation, showing their potential for pulpal regrowth. SHEDs are more capable than DPSCs. Moreover, when cultivated in neurogenic inductive medium, SHEDs can develop into neuronal and glial cells. Implanting SHED restored 3D complete dental pulp including neurovascular bundles in both experimental animals and human teeth injuries, indicating that SHED is a promising cell source for bone and tooth reconstruction [21-26].

SCAP: These cells have MSC like characteristics, such as aspects of existing and having the capacity to develop into odontoblasts and osteoblasts *in vitro*. In addition, SCAP outperformed DPSCs in terms of proliferation and mineralization ability *in vitro*. SCAP have the capacity to repair bone and dental tissue. SCAP has also been observed to produce a periodontal transplanted with PDLSCs into small swine tooth socket. Furthermore, cells generated from inflamed osseous tissue show typical MSC properties, including significant osteoinductive potential *in vitro* and *in vivo*; suggesting that molecular processes underlying stem cells is maintained.

DFCs When DFCs are cultured *in vitro*, they can develop into cementoblasts and create cementum when transplanted *in vivo* Added to that, after *in vivo* transplantation, DFCs created PDL like tissue and periodontal tissues *via* epithelial Mesenchymal interface. DFCs generated single or intricate tissues in the periodontium and retained MSC characteristics in culture after more than passes. DFCs are a potential MSC reservoir for stem cell therapy as a whole. DFCs, like SCAP, are a kind of DSC that is produced from growing tissue and so has greater flexibility than other DSCs [27].

Cell injections

Mesenchymal stem cells can self-renew. Single cell culture from separated cells *in vitro* is directly injected into the injured location in conventional cellular treatment. Cell injection is less invasive than cell material design because it does not require flaps and is ideal for patients with systemic disorders who are not in the severe forms of periodontitis. In a rat model, bone marrow mesenchymal stem cell injection had immune modulatory effects at defective locations and helped with periodontal healing. However, cell death, poor engraftment, insufficient localisation, migrating into neighbouring tissues, and loss of cell destiny control are all disadvantages [28-30].

Cells combined with materials

Cells are grafted with diverse materials to limit stem cell localisation and prevent cellular damage. PDLSCs are the most widely employed stem cells, however others like as SHED, DPSC, and BMMSCs are also accessible for periodontal regeneration. Natural biopolymers such as chitin, collagen, and fibrin sealants, as well as synthetic polymers such as hydroxyapatite/tri calcium phosphate, are among the most often utilised scaffold materials. In a mouse model, the safety of the stem cells as well as the ease of procedure back this claim, it has potential for the development of usage in a clinical setting however, there is no histology proof that this is the case. This allows for the formation of a functioning periodontal complex. It demands surgical intervention as a technique [31-33].

Newer and advanced techniques

Cell sheeting: An innovative culture method that provides scaffold free cell transport. Cells form cellular junctions and extracellular matrix when grown. Here cultivated stem cells in monolayers or multilayers can be collected from the culture plate without the need of an enzyme, alongside unaltered ECM and cellular connection as a whole. Nisopropyl acrylamide, somewhat of a thermal or temperature. Responsive polymer was created to create cell sheets.

The dehydrated and hydrophobic surface attached to the dish surface is what the cells prefer and develop on. Other approaches due to the magnetic forces and polyelectrolytes are also available.

Spheroid culture technique

Multiple cell growth methods were developed in addition to the general cell sheeting technology. In contrast to 2D monolayer culture, 3D culture recreates the *in vivo* conditions, containing cell ECM functional interconnection. Cell aggregate and self-assembly are used in spheroid cultivation, which is a highly promising technology. Spheroid cells have a better capacity for creating ECM and other growth factors than cell suspension or cell sheeting. The fundamentals of spheroids are based on a cultural microclimate in which cell interaction is more important than cell material interaction. Several spheroid formation techniques, including as hanging drop, pellet culture, membrane based grouping, and micro well chip method, have been created in periodontal bioengineering. Centrifugal forces are used in pellet culture, whereas surface tension and gravitational forces are used in hanging drops. By adjusting the micro well scale size, micro well chips can help regulate spheroid size. Micro well chips have been used to create spheroids of HPDLMSCs, which showed increased stem ness and osteogenic capability, which might be advantageous for hard tissue regeneration. Pellet cultivation in polypropylene tubes was used to create PDLSC spheroids, which elevated anti-inflammation and vascular activity, essentially facilitating periodontal recovery. Despite this, it revealed a lack of tissue regeneration, which was most likely due to the necrotized tissue in the central region. To summarise, spheroid cultivation provides a number of benefits related to the resemblance of the *in vivo* habitat. Furthermore, due to the decreased cell size in spheroids, fewer proliferative cells, and elevated mortality of cells, the spheroid size displays a time critical reduction. The limitations of spheroid cultivation are attributable to a shortage of oxygen and nutrients in the centre of the spheres. As a result, more study should be done to show how cell proportion might be optimised.

Electro spinning

It is a global micro to Nano fibre fabrication process replicating natural ECM to offer a conductive environment for cell growth. A standard apparatus has a syringe that holds polymer solution, a pump to pulse the material, an electric potential source, and a collecting plate. Polymer settles in the form of micro to nanofibres when electronic differences occur between both the needle and the collector. In structured nanofibres with smaller pores, solution electro spinning fibres exist, whereas organised microfibers with bigger pores exist in melt electro spinning fibres. Electro spinning scaffolds promote cell attachment, multiplication, emigration, and transformation because they are identical to biological ECM. Greater interfaces that can increase molecular protein interactions and provide receptors are benefits of electro spinning, a clever and value approach to create nanofibre. Electro spinning fibres, whether arbitrary or aligned, can guide the growth direction of fibres or cells geographically in tissue regeneration, favouring specially directed tissues like complex periodontal fibres. Electro spinning, as intriguing as it can be, has a few drawbacks that are impeding future advancement in tissue engineering. In solution electro spinning fibres, the smaller the fibre size, the higher the surface area to volume ratio that provides higher protein and molecular binding affinity and might have a negative impact on cell infiltration owing to the narrower pore diameters. As a result, it's crucial to keep track of the varied pore diameter in relation to the various structures. The challenges in matching the rate of deterioration with periodontal tissue remodelling are additional disadvantages. If tissue degeneration starts before it matures, it might lead to death of the scaffold and the

three dimensional network may disintegrate, obstructing fibre development and remodelling.

3D Bio printing

When tried to compare to subtractive manufacturing, scaffolds are built layer by layer. Bio printing uses cell laden biomaterials to produce functioning tissue and organs with implanted cells. Stereo lithography, inkjet, laser induced forward transfer, and extrusion are some of the bio printing methods used today. Extrusion bio printing is a popular approach for producing scaffolds in regenerative therapy. Regulated outflow in the form of fibre or material from the printer head to the receptacle is often propelled by a piston, screw, or pneumatic system. Layer by layer modelling, for example, makes use of thermoplastic material that is molten at a high enough temperature at the nozzle, allowing semi liquid material to be deposited just above the collector.

Micro environmental impacts on MSCs

The surroundings, which functions as "soil" is widely acknowledged to have profound impacts on MSCs, the "seeds" in tissues, particularly in diseased states and cell treatments. Intracellular MSCs live in a diverse and evolving habitat that includes surrounding cells, ECM, and many endovascular connections, all of which closely govern MSC activity. Moreover, the vascular microenvironment influences indigenous MSCs *via* hormonal, metabolites, inflammatory cytokines, as well as other biomolecule. Micro environmental changes, in particular, have a key role in the initiation and progression of bone and oral illnesses.

Pathogenic microenvironment and impaired endogenous cells

Sex hormones and adrenal hormones are essential circulatory elements that regulate bone growth and postnatal restructuring. Hormonal abnormalities, notably the significant fall in hormonal changes in the elderly and postmenopausal women, produce a pathological equilibrium between osteoblastogenesis and osteoclastogenesis, resulting in skeletal density and function loss. Studies have suggested that oestrogen and androgen deficiency inhibits BMMSC multiplication and differentiation potential, as seen by decreased chondrogenic assay, mineral nodular development, and osteogenic marker expressions. Molecularly, oestrogen might independently sustain MSC effective homoeostasis by attaching to its receptors, in contrast to indirect impacts *via* immunological responses. Furthermore, oestrogen deficiency leads to a significant increase in reactive oxygen species, which operate as a major mechanism in BMMSC specification failure and trigger BMMSC death. Excess use of glucocorticoids reduces BMMSC multiplication and degrades BMMSC osteoinductive capacity, leading in bone loss in glucocorticoid induced osteoporosis, the most common cause. The basic metabolism profiles, which mostly correspond to glycolysis and OXPHOS states, have a significant impact on cell therapy destiny during maturation and renewal. BMMSCs, for example, depend on metabolism to retain stem ness while undertaking osteogenic differentiation, which necessitates glucose intake and transition into OXPHOS privileged condition of secondary osteoporosis [34,35].

CONCLUSION

MSC based regenerative techniques have showed considerable promise in the past several years for mending bone periodontal and dental loss and deformities, through endogenous regeneration and external transplanting. Microenvironment influences resident MSCs under both physical and pathological circumstances, and influences implanted MSCs in cytotherapy and tissue regeneration, is crucial to the efficacy of treatment of MSC mediated repair. While great progress has been made, there are still a few concerns that need to be addressed. To define the significant contribution of the microclimate to MSC based treatments and identify important chemicals and signalling molecules involved, more research on the micro environment's control of MSC based tissue formation and the underlying biological processes is required. Second, innovative approaches to promote MSC based bone and periodontal regeneration, such as nanotechnology modified fitting materials to create a bionic implant Provided the influence of the cellular environment over MSCs, it is beneficial to analyse the recipient microenvironment condition and formalise therapeutic intervals prior to MSC implantation to enhance the efficacy of infused MSCs, as well as boosting MSC enrolment *via* a functionalized technique to promote oriented transplantation. Finally, in addition to extending the lifetime of grafted MSCs, recent research has demonstrated that MSC apoptosis may be a fundamental mechanism underpinning their therapeutic efficacy in specific illnesses, which might lead to new insights into MSC, based regenerative treatments.

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