

STEM CELLS : THE NEW MIRACLE CELLS

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Periodontology

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ABSTRACT

Periodontal disease is chronic inflammation that leads to alveolar bone loss and destruction of periodontal ligament. The challenges in regenerative periodontal therapy lie in the ability to induce the regeneration of a complex periodontal apparatus consisting of bone, cementum, and periodontal ligament. Though immense advancement has occurred in past few years in periodontal therapy, a complete regeneration of the damaged periodontium still remains a distant goal. A stem cell is a cell that has the ability to divide (self-replicate) for indefinite periods, often throughout the life of an organism. It has been proposed that the bone marrow mesenchymal stem cells (BMMSCs) are very likely to be another cell source of physiological repair of periodontal tissues. This article is an overview of the basics of stem cell biology and their potential nature as regenerative cells of periodontium

The periodontium is an unusually complex tissue comprised of two hard (cementum and bone) and two soft (gingiva and periodontal ligament) tissues.¹ Once damaged, the periodontium has a limited capacity for regeneration. **Regeneration** is defined as a reproduction or reconstitution of a lost or injured part. It is, therefore, the biologic process by which the architecture and function of lost tissues are completely restored. **Periodontal regeneration** is reconstruction of the tooth's supporting tissues, including alveolar bone, periodontal ligament, and cementum.

The term "**stem cell**" first appeared in literature during the 19th century. The concept of stem cells has expanded greatly with the identification of novel sites and functions. A "**stem cell**" refers to a **clonogenic, undifferentiated cell that is capable of self-renewal and multi-lineage differentiation**. In other words, a stem cell is capable of propagating and generating additional stem cells, while some of its progeny can differentiate and commit to maturation along multiple lineages, giving rise to a range of specialized cell types. Depending on intrinsic signals modulated by extrinsic factors in the stem cell niche, these cells may either undergo prolonged self-renewal or differentiation². The use of stem cells with these technologies may constitute novel strategies for regenerative periodontal therapy.

The term stem cell appears in scientific literature as early as 1868 in the works of the eminent German biologist **Haeckel**. Haeckel, a major supporter of Darwin's theory of evolution, drew a number of phylogenetic trees to represent the evolution of organisms by descent from common ancestors and called these trees "**Stammbäume**" (German for family trees or "stem trees"). **Wilson in 1996** is credited for having coined the term 'stem cell'. In the first edition of his treatise on cell biology, he reserved the term 'stem cell' exclusively for the ancestral cell of the germ line in the parasitic nematode worm, *Ascaris megalocephala*. However, the term "stem cell" was proposed for scientific use in 1908 by the Russian histologist **Alexander Maximow** at the Congress of Haematological Society in

Berlin. It postulated the existence of haematopoietic stem cells.³

STEM CELL

DEFINITION:

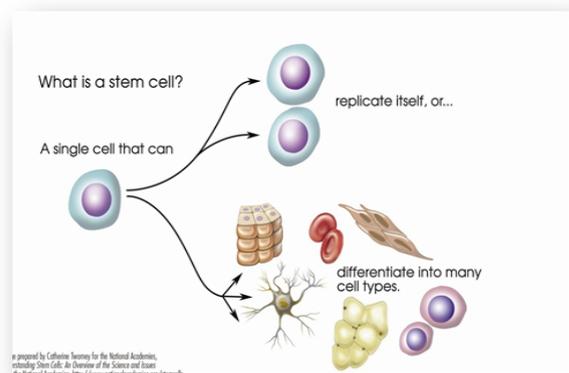
A stem cell is a cell that has the ability to divide (self replicate) for indefinite periods, often throughout the life of an organism.⁴

It can divide asymmetrically, in which case one of the two daughter cells retains the stem cell characteristics while the other is destined for specialization under specific conditions.³

It has two defining characteristics⁵:

1. Ability for indefinite **self renewal** to give rise to more stem cells, and
2. Ability to **differentiate into a number of specialised daughter cells** to perform specific function

STEM CELL



THE CATEGORIES OF STEM CELLS POTENCY⁶:

1. Totipotent: The capacity to differentiate into all possible cell types, including extra embryonic tissues. Eg: Fertilized egg

2. Pluripotent: The ability to differentiate into almost all cell types. These cells lack the capacity to contribute to extra embryonic tissue and therefore cannot develop into a fetal or an adult animal. Eg: Embryonic stem cells

2A) Multipotent: The potential to give rise to cells from multiple but a limited number of lineages. Eg: Mesenchymal stem cells

2B) Oligopotent: The capacity to differentiate into a few cell types. Eg: Myeloid stem cells

2C) Unipotent: The ability to differentiate into only one type of cell. Eg: Skin

STUDIES ON STEM CELLS IN PERIODONTAL REGENERATION

Yang ZH et al (2010)⁷ in their review article **stated increased attention for the potential therapeutic applications of periodontal ligament stem cells (PDLSCs) in periodontal regeneration.** It has been proposed that the bone marrow mesenchymal stem cells (BMMSCs) are very likely to be another cell source of physiological repair of periodontal tissues. With this in mind, enlightened from the research targeting the fabrication of laminar structures such as liver and kidney with heterotypic stratification of cell sheets, they proposed a novel possible strategy based on self assembly approach, which is akin to the physiological phenomenon that occurs during organogenesis, to enhance complete reconstruction of functional complex periodontal organ systems.

Grover HS et al(2014)⁸ in a review article on stem cells **reported that many reports have begun to emerge demonstrating that population of adult stem cells reside in the periodontal ligament of humans and other animals.** Stem cell biology, an emerging field of research, provides promising methods in vitro as well as in vivo animal models, which make speculation about a future application in human dentistry. This opens the way for cell based therapies for periodontal regeneration.

Ametti M et al (2014)⁹ in a case report **suggested histologic findings in animal models and suggested that the application of dental pulp stem cells (DPSCs) may promote periodontal regeneration in infrabony defects.** This case report described the clinical and radiographic regenerative potential of autologous DPSCs in the treatment of human noncontained intraosseous defects. A chronic periodontitis patient with one vital third molar requiring extraction was surgically treated. The third molar was extracted and used as an autologous DPSCs source to regenerate the infrabony defect. It was completely filled with bonelike tissue as confirmed through the re entry procedure.

Pittinger MF et al (2015)¹⁰ in their editorial **described that Mesenchymal Stem Cells(MSCs) may promote tumor growth due to their trophic effects and production of angiogenic factors.** MSCs have a propensity to migrate to wounds and damaged tissue. Tumours are characterized as wounds that do not heal. With this in mind, gene modified MSCs have been tested for their ability to deliver anticancer compounds in experimental models..

POTENTIAL APPLICATION OF STEM CELL IN PERIODONTAL THERAPY

Periodontal regeneration is essentially a re-enactment of the development process including morphogenesis, cytodifferentiation, extracellular matrix production and mineralization. Such processes support our concept that some mesenchymal stem cells remain within the periodontal ligament and are responsible for tissue homeostasis. They serve as a source of renewable progenitor cells generating cementoblasts, osteoblasts and fibroblasts throughout adult life. In the event of injury to the periodontium these mesenchymal stem cells could be activated towards terminal differentiation and tissue repair or regeneration. Using cloning techniques, a large number of cells of differing phenotype have been

isolated from the periodontal ligament and regenerating periodontal tissue. Preliminary studies suggested that some of the clonal cell lines had characteristics of stem cells, warranting further investigation into these properties and their utilization in cell-based periodontal regenerative therapies. Most recently, we have identified and characterized populations of cells from adult human and sheep periodontal ligament which have the morphological, phenotypic and proliferative characteristics of adult mesenchymal stem cells. The identification of putative mesenchymal stem cell populations within the periodontium has stimulated interest in the potential use of stem cell-based therapies to treat the damage caused by trauma and periodontal disease. Here we discuss the stem cell-like properties and characteristics of stem cells residing within the periodontal ligament and speculate on their future clinical utility.¹

APPLICATION OF STEM CELLS IN TISSUE ENGINEERING

Requirements for successful tissue engineering¹¹

1) BIOMECHANICAL FEATURES

- A) Space maintenance
- B) Barrier or exclusionary features

2) BIOLOGICAL FUNCTIONS

- A) Biocompatibility
- B) Incorporation of cells
- C) Incorporation of instructive messages

1A) Space maintenance within the defect site

It has been recognized that bone will grow into an adjacent tissue space provided that space can be maintained and soft tissue ingrowth prevented. Such natural phenomena should be used to advantage when considering tissue engineering and placement of bioengineered matrices for regeneration. The engineered material should be of sufficient form to allow placement into a defect and prevent subsequent collapse of the repositioned tissues into the defect site.

Design features to obtain satisfactory space maintenance would include

1. An ability to be easily cut or molded into a desired shape and be of a consistency compatible with easy handling.
2. Sufficient rigidity of the scaffold to withstand soft tissue collapse into the defect.
3. The internal architecture of the scaffold to be such as to maximize rapid colonization by cells of the desired phenotype and ingrowth of tissue compatible with those to be regenerated

1B) Barrier or exclusionary functions

The engineered tissues should act as a barrier to the ingrowth of unwanted tissues. To achieve this, design features will have to be incorporated whereby the external surface may be exclusionary, yet the internal scaffold conducive to new tissue ingrowth.

2A) Biocompatibility and design features

The scaffold material should be either biocompatible with the tissues to be regenerated or biodegradable, allowing for gradual replacement with regeneration.

Tissue design features need to include considerations of pore size for both cell attachment and incorporation in vitro as well as subsequent tissue maturation during in situ regeneration. Scaffold material can include calcium phosphate, hydroxyapatite, extracellular matrix components (collagens, hyaluronan and fibronectin) polyglycolic acid and other synthetic bioresorbable materials

In the case of the periodontium, a biodegradable material that would degrade slowly over time and be replaced with a soft connective tissue compatible with periodontal ligament, together with new alveolar bone and root surface cementum with appropriately orientated and inserted collagen fibers, would be desirable

2B) Incorporation of cells with appropriate phenotype for ongoing periodontal regeneration

Cells with a "periodontal regenerative phenotype", which can be cultured and subsequently incorporated into a suitable biodegradable scaffold for immediate introduction into a periodontal defect should be used

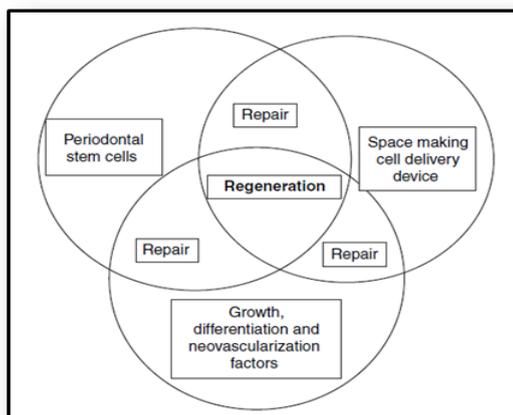
2C) Incorporation and bioavailability of instructive messages

The synthetic matrix should be bioresorbable but constructed from a material with a suitable affinity for the adsorption of appropriate growth/differentiation factors as well as integrins, cell receptors and other instructive molecules normally found in regenerating tissues. Agents that promote cell adhesion, permit proliferation of progenitor cells and can be easily incorporated into a scaffold or matrix for suitable slow release, with adequate delivery kinetics, will become the major focus of interest.

FUTURE PROSPECTS FOR PERIODONTAL REGENERATION

Thus, a tissue engineering strategy for periodontal regeneration that exploits the regenerative capacity of stem cells residing within the periodontium, grown in a three-dimensional construct and subsequently implanted into the defect, may help to overcome many limitations with current regeneration modalities (**Bartold et al, 2000**)¹¹. In doing so, the need for recruitment of various cells to the site is negated and the predictability of outcome may be enhanced.

Schematic representation of a tissue engineering approach to periodontal regeneration using periodontal ligament stem cells. When the cells are incorporated into a suitable space making delivery device and exposed to the correct growth differentiation and neovascularization agents tissue regeneration would be expected. Should only two of the three requirements be available it will result in repair rather than regeneration.



CONCLUSION

The science of stem cell therapy has the potential to lead to treatments for major degenerative diseases, by providing healthy cells to replace diseased tissues and organs.

Regeneration of tissues destroyed by periodontitis has long been an altruistic goal of periodontal therapy. Periodontal regeneration requires consideration of many features that parallel periodontal development, including the appropriate progenitor cells, signaling molecules and matrix scaffold in an orderly temporal and spatial sequence. It is clear that current regenerative procedures are less than ideal but the identification of stem cells in human dental tissues in recent years holds promise to the development of novel, more effective approaches to periodontal regeneration and reconstructive therapy. Although preliminary results have been achieved on many different fronts, a tremendous amount of work still confronts researchers in this area. Some of the main issues are identification of the optimal precursor cell types, establishment of growth and differentiation conditions that meet safety and good manufacturing practice standards, and manipulation of the surrounding

environment to allow transplanted cells to survive and function.

One way forward is to embrace the field of stem cell-based tissue engineering and adopt an interdisciplinary approach to periodontal regeneration. However, before this is feasible, many biological, technical and clinical hurdles need to be overcome and a thorough understanding of underlying healing processes in periodontal regeneration is required.

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