Review Article

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Stem Cells in Periodontics: A Promising Source of Regeneration

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ABSTRACT

Background: Periodontitis is an inflammatory disease which manifests clinically as loss of supporting periodontal tissues including periodontal ligament, cementum, and alveolar bone. Periodontal therapy is aimed at achieving complete regeneration of these structures. Numerous procedures have been attempted to achieve periodontal regeneration, including root surface conditioning, bone graft placement, guided tissue regeneration and growth factor application. Stem cells, fascinating area of biology, have been used clinically in periodontal regeneration and also in medicine to treat many incurable diseases. Various human and animal studies have confirmed the presence of stem cells in dental tissues including periodontal ligament. This has opened new avenues aiming towards complete periodontal regeneration using cell-based therapies. The search for new regenerative strategies is a challenging field of periodontal research;, and tissue engineering, using stem cells, has recently been shown as a promising approach. This review provides an overview of various types of stem cells in medicine and dentistry and their potential uses especially pertaining to periodontal regeneration.

Keywords: Adult stem cells, periodontal regeneration, stem cells.

INTRODUCTION

The term "stem cell" first appeared in the literature during the 19th century. A "stem cell" refers to a "clonogenic, undifferentiated cell that is capable of self-renewal and multi-lineage differentiation depending on their intrinsic signals that can be regulated by extrinsic factors." [1]. In general terms, the molecular signals which can control differentiation of cells include soluble factors (e.g., hormones and cytokines), matrix molecules, direct cell to cell contacts and external stimuli (e.g., mechanical stimulation). Stem cells are categorized into embryonic and adult (somatic) cells. Hematopoietic stem cells from bone marrow have been identified first and were already in use for therapeutic purposes. Bone marrow stromal cells (BMSCs) or mesenchymal stem cells (MSCs) are a different population of stem cells that has been identified in the adult body. It appears that all the tissues with tendency for renewal contain at least a small number of stem cells.[1,2] Isolated MSCs in human PDL has laid the foundation for the development of novel strategies for periodontal reconstruction. A key determinant of regenerative potential of the periodontal ligament (PDL) was the ability of stem cells to undergo specialized differentiation of osteoblasts and cementoblasts, resulting in formation of new bone and cementum, respectively.

Embryonic stem cells

In 1998, Thomson and co-workers derived the first human embryonic stem (ES) cell line from the inner cell mass of 4 to 7-day-old blastocyst-stage embryos donated by couples undergoing fertility treatment.[3] Despite their developmental potential, the use of embryos to obtain human embryonic stem cell lines

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raises serious ethical concerns, which recently stimulated efforts to genetically reprogram somatic cells back to their pluripotent state. These efforts resulted in the generation of induced pluripotent stem (iPS) cells that are functionally similar to embryonic stem cells.

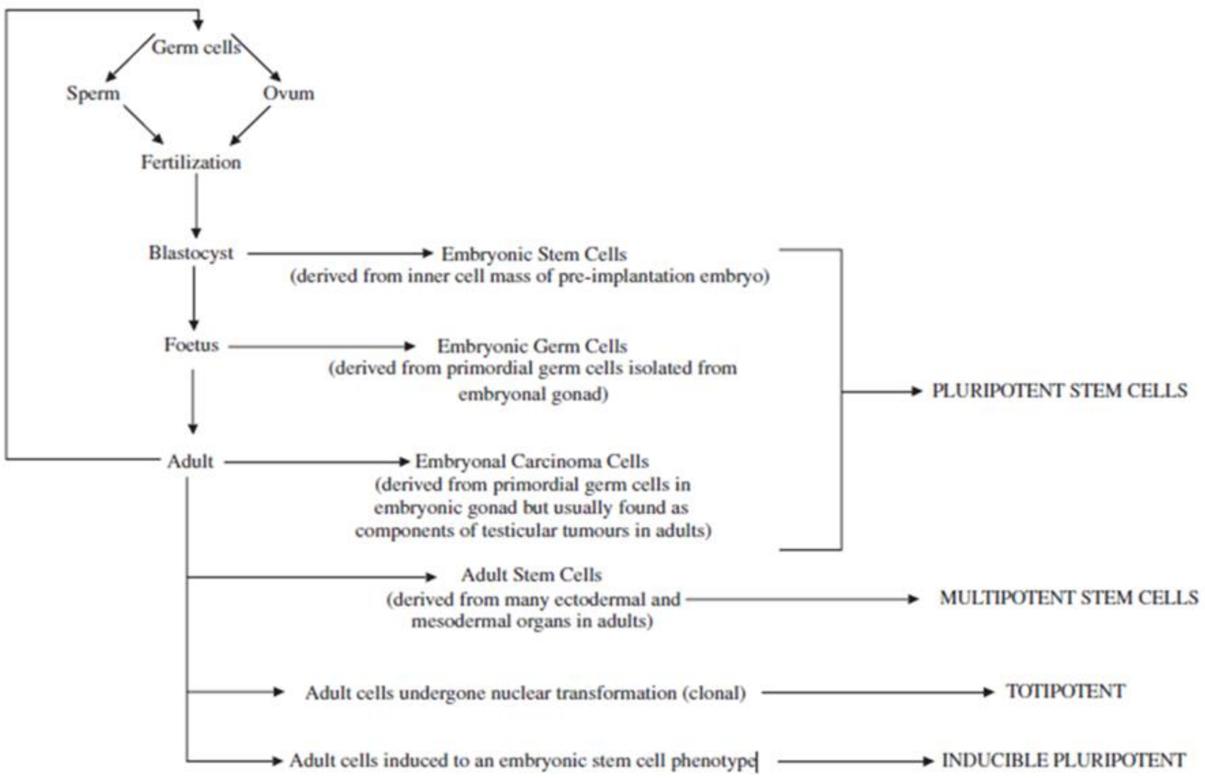

Fig 1: Different types of stem cells

However, genetic manipulations fundamental to generation of iPS cells may alter their growth and developmental characteristics, which hinders the predictability of their behaviour and, as such, limits their use in tissue-regenerative purposes. Furthermore, embryonic stem cells and iPSCs both carry tumourigenic properties, raising a significant safety challenge in the use of these cells for regenerative therapies.

Adult stem cells and mesenchymal stem cells

Adult stem cells, also known as somatic stem cells, are undifferentiated cells found in specialized tissues and organs of adults. Compared to the pluripotent and almost immortal nature of embryonic stem cells, adult stem cells appear more mature with a finite lifespan and only multipotent differentiation capacity. All specialized tissues with renewal capacity throughout life probably contain adult stem cells in very small numbers that help replenish cell loss during normal tissue injury. Haematopoietic stem cells from bone marrow were the first type of adult stem cells to be identified. Another population of adult non-haematopoietic stem cells also resides in the bone marrow microenvironment. These are termed bone marrow stromal stem cells (BMSSCs). Mesenchymal stem cells (MSCs) are adult stem cells able to give rise to multiple specialized cell types. Due to their extensive distribution in many adult tissues, including those of dental origin, MSCs have become an attractive target for use in periodontal regeneration. MSCs were first described by Friedenstein in 1976 as "clonogenic, bone marrow-derived, plastic-adherent cells which were termed colony-forming unit fibroblasts (CFU-F)".[4] The term now refers to "a heterogeneous mix of progenitors, where subset populations are capable of differentiating into cells of mesodermal (adipocytes, osteoblasts, chondrocytes, tenocytes, skeletal myocytes and visceral stromal cells), ectodermal (neurons, astrocytes) and endodermal (hepatocytes) origins." Bone marrow mesenchymal stem cells are the most widely studied mesenchymal stem cells because they are easily accessible in quantities appropriate for clinical applications.

Dental-Derived Post-Natal Stem Cells

Periodontal ligament stem cells for periodontal regeneration

Periodontal regeneration is mediated by a heterogeneous cell population present in PDL that can differentiate into fibroblasts, osteoblasts, and cementoblasts.[5] The presence of multipotent stem cells in PDL remained elusive until they were isolated from PDL of extracted human third molars by Seo and colleagues in 2004.[2] They found that human PDL contains a group of cells that express mesenchymal stem cell surface markers such as STRO-1 and CD146. Periodontal ligament stem cells (PDLSCs), present with self-renewal ability and have multipotent capacity, being able to differentiate into cementoblasts /osteoblasts, adipocytes and collagen forming cells.

Dental pulp stem cells (DPSCs)

These were first identified human dental stem cells.[6] It contains a heterogeneous population of cells; including fibroblasts, nerve cells, vascular cells, and undifferentiated stem cells. They are found in highly vascularized regions of the pulp and can be collected from the pulp tissue of clinically extracted human teeth of both young and aged individuals by various isolation methods.[7,8]

Dental follicle stem cells

Dental follicle is a loose connective tissue derived from ectomesenchymal cells. It surrounds the enamel organ and the developing tooth germ before eruption and plays different roles during tooth development.[9] It has been shown that dental follicle-derived stem cells (DFSCs) can undergo osteogenic, chondrogenic, and adipogenic differentiation in vitro.[10]

Dental apical papilla stem cells

These are found at the apices of developing teeth. This tissue is only present during root development, before the eruption of teeth into the oral cavity.[11] Third molars are commonly extracted while undergoing root formation and therefore they may represent an excellent source of dental apical papilla stem cells (DAPSCs) (other than DPSCs and PDLSCs). DAPSCs have the potential to differentiate into odontoblast-like cells, osteoblasts, adipocytes, and neuronal cells.[12]

Dental socket stem cells

Evian and colleagues in 1982 studied osteogenic activity of healing extraction sockets in humans by analyzing the bone cores removed from post-extraction sockets. Histological evaluations revealed the presence of osteoblasts and osteoid starting from the 4th up to the 8th week post-extraction, suggesting a high osteogenic activity during this healing phase.This study, however, did not specifically evaluate the presence of skeletal stem cells within the healing extraction sockets.[13]

Potential applications of stem cells in periodontal therapy

Tissue engineering

Tissue engineering is a specialized field of science based on principles of cell biology, developmental biology and biomaterials science to fabricate new tissues to replace lost or damaged tissues .Successful tissue engineering requires an appropriate extracellular matrix or carrier construct which contains regulatory signals and responsive progenitor cells. Mesenchymal progenitor cells have also been isolated from dental follicle of human third-molar teeth. These fibroblast-like, colony-forming and plastic-adherent cells express stem cell markers. These cells carry common genetic markers, but are conditioned by their specific microenvironment and to be committed towards a specific differentiation pathway. For example, bone marrow mesenchymal stem cells display a lower odontogenic potential than dental mesenchymal stem cells. Dental mesenchymal stem cells will be most suitable for regenerative periodontal therapy.

Challenges in bringing stem cell-based research to practice

1. Biological challenges

Biological evidence showing regeneration can occur in humans, complete and predictable regeneration still remains an elusive clinical goal, especially in advanced periodontal defects. Most basic discoveries on periodontal stem cells have emerged from cell culture and animal models. Research is needed to reveal cellular and molecular events involved in restoring lost periodontal tissues before a reliable biologically-based therapy can be developed.[16]

2. Technical challenges

Matrix scaffold should have good biocompatibility for the cellular and molecular component normally found in regenerating tissues. The optimal mechanism of propagation and incorporation of these cells into a carrier scaffold still needs further refinement. Further studies are needed to understand the conditions that induce lineage-specific differentiation and efficacy of in vitro expanded stem cells derived from regenerating periodontal defects. Possible karyotypic instability and gene mutations can limit usefulness of cell lines after prolonged cultures. There are difficulties in providing clinical-grade stem cell lines using animal free media to prevent cross-infection in humans. Thus, refinement of current techniques to facilitate laboratory handling of these cells and to maximize their regenerative potential is needed if these cells are to be used in clinical periodontics.

3. Clinical challenges

In MSC-based clinical therapy the clinical challenges that must be understood and overcome are: immune rejection, tumour growth, and efficacy of cell transplantation. Firstly, it is important to understand how the immune system will respond to human stem cell derivatives upon transplantation. Immunogenicity of a human cell depends on its expression of class I and II major histocompatibility (MHC) antigens, which allow body to distinguish its own cells from foreign cells. Human ES cells express a low level of class I MHC antigens, but this expression is up-regulated with differentiation. Use of patient-specific adult stem cells from third molar teeth should overcome potential immune rejection.

Secondly, the prevention of tumour formation following MSC implantation is a major safety consideration as current studies lack sufficient statistical power and long-term follow-up to get firm conclusions. It is likely that for specific and extensive therapeutic application, longer the stem cells may have to remain in vitro to obtain sufficient numbers for therapeutic use. Thus during this extended period in culture, genetic changes could accumulate. If such changes are not accompanied by overt phenotypic transformation, they may go undetected and harm the patient. Therefore, it is critical to have a thorough understanding of the rate of genetic change and the type of selective pressures that allows change to dominate a culture.

Thirdly, it is unclear whether human stem cell derivatives can integrate into the recipient tissue and fulfil the specific functions of lost or injured tissues. Delivery of appropriate cells and molecules to the target site without inducing ectopic tissue formation is of paramount importance for the safety and effectiveness of tissue engineering-based periodontal regeneration.

CONCLUSION

Regeneration of tissues destroyed by periodontitis has been the over arching goal of periodontal therapy. 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. One way forward is to embrace the field of stem cell-based tissue engineering and adopt an interdisciplinary approach to periodontal regeneration.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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