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STEM CELLS: A HOPE IN NEW ERA OF DENTISTRY

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ABSTRACT

Stem cells are particularly important for developing innovative technologies for tissue engineering strategies to regenerate or replace damaged, diseased or missing tissues and even organs by in vitro cell manipulation and design of the extracellular environment. . Stem cells residing in the orofacial region have been classed as the Mesenchymal stem cells (MSCs) /Adult stem cells (ASCs)/Tissue stem cells (TSCs). Clinical trials about jaw bone regeneration applied in dental areas such as implantology using stem cells and tissue engineering strategies have demonstrated positive results. Emerging stem cell technologies and the requirements of alveolar ridge augmentation associated with implant dentistry have expanded the clinical concept to include stem-cell-based regeneration. Furthermore, ‘‘dental stem cell banking’’ is already on the market for possible future use in regenerative therapies. The aim of the present review is to explain the different kinds and sources of stem cells from a clinical perspective in dentistry.

KEYWORDS: Stem cells, Dentistry, Implants.

INTRODUCTION

Stem cells are immature, unspecialized cells that have the potential to develop into many different cell lineages via differentiation. By the conventional definition, these cells can renew themselves indefinitely through ‘‘self-renewal’’[1], and they vary in terms of their location in the body and the type of cells that they can produce. Given their unique abilities, stem cells are particularly important for developing innovative technologies for tissue engineering strategies to regenerate or replace damaged, diseased or missing tissues and even organs by in vitro cell manipulation and design of the extracellular environment.[2]

It is now accepted that progenitor/stem cells reside within orofacial region. Stem cells residing in the orofacial region have been classed as the Mesenchymal stem cells (MSCs) /Adult stem cells (ASCs)/Tissue stem cells (TSCs).[3] Studies have identified several niches of multipotent mesenchymal progenitor cells, known as dental pulp stem cells, which have a high proliferative potential for self-renewal. These progenitor stem cells are now recognized as being vital to the dentine regeneration process following injury. More recently, researchers have discovered that stem cells harvested from deciduous teeth may be a source of tissue regeneration and repair.[4] Five different types of dental stem cells isolated from dental soft tissues are dental pulp, apical papilla, dental follicle and periodontal ligament.

To develop the concept of oral tissue and organ regeneration for clinical application in dentistry, several studies have been carried out in animals including key elements of tissue engineering such as extracellular matrix scaffolds and stem cells.[5] Furthermore, clinical trials about jaw bone regeneration applied in dental areas such as implantology using stem cells and tissue engineering strategies have demonstrated positive results. Considering the new role of regenerative biology and stem cells in dentistry, especially regarding the ideal stem cells for oral regeneration, some confusion can be made depending on the various oral and maxillofacial locations where stem cells can be obtained.[6]

In the field of prosthodontics, especially in the clinic, material-based reconstruction without major surgical procedures was the main approach to treatment; however, emerging stem cell technologies and the requirements of alveolar ridge augmentation associated with implant dentistry have expanded the clinical concept to include stem-cell-based regeneration. Furthermore, ‘‘dental stem cell banking’’ is already on the market for possible future use in regenerative therapies. Thus, clinicians as well as researchers in the prosthodontic field should understand basic aspects of stem cells and the implications of stem cell technologies in the future of dentistry.[7]

The aim of the present review is to explain the different kinds and sources of stem cells from a clinical perspective in dentistry, regarding their accessibility, immunomodulatory properties, and differentiation capacity, as well as their clinical applications.

Types of stem cells

a. Totipotent stem cells: These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent. Totipotent stem cells can differentiate into embryonic and extraembryonic cell types. Such cells can construct a complete, viable, organism.
b. Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cells, i.e. cells derived from any of the three germ layers.
c. Multipotent stem cells can differentiate into a number of cells, but only those of a closely related family of cells.
d. Oligopotent stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.
e. Unipotent cells can produce only one cell type, their own, but have the property of self-renewal which distinguishes them from non-stem cells (e.g. muscle stem cells).[8]

Dental Tissue-Derived Stem Cells

Epithelial stem cells and mesenchymal stromal cells (MSC) like cells have been described in dental tissues. In 1999, through organ culture of the apical end of the mouse incisor, the first epithelial stem cell niche was established. The cervical loop of the tooth apex where the niche is located possibly contains dental epithelial stem cells, which have the ability to turn into enamel-producing amelobasts. There is no information available about human dental epithelial stem cells. This niche can be particular to rodents, since their incisors are different from all human dentition, erupting continuously throughout the animal's life. Having the suitable conditions after dental procedures, dental tissues such as dental pulp and periodontal tissues are able to regenerate and form reparative dentine (figure 1). We can find mesenchymal progenitor or stem cells in these types of tissues.[9]

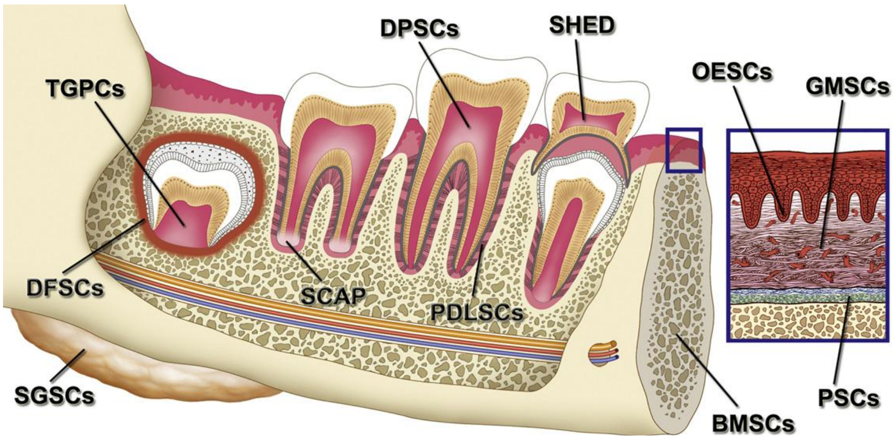

Figure 1: Sources of adult stem cells in the oral and maxillofacial region. BMSCs: bone marrow-derived MSCs from orofacial bone; DPSCs: dental pulp stem cells; SHED: stem cells from human exfoliated deciduous teeth; PDLSCs: periodontal ligament stem cells; DFSCs: dental follicle stem cells; TGPCs: tooth germ progenitor cells; SCAP: stem cells from the apical papilla; OESCs: oral epithelial progenitor/stem cells; GMSCs: gingiva-derived MSCs, PSCs: periosteum-derived stem cells; SGSCs: salivary gland-derived stem cells.

Oral mucosa-derived stem cells: The oral mucosa is composed of stratified squamous epithelium and underlying connective tissue consisting of the lamina propria, which is a zone of well-vascularized tissue, and the submucosa, which may contain minor salivary glands, adipose tissue, neurovascular bundles and lymphatic tissues depending on the site. To date, two different types of human adult stem cells have been identified in the oral mucosa. One is the oral epithelial progenitor/stem cells, which are a subpopulation of small oral keratinocytes (smaller than 40 mm). Although these cells seem to be unipotential stem cells, i.e., they can only develop into epithelial cells, they possess clonogenicity and the ability to regenerate a highly stratified and well-organized oral mucosal graft ex vivo, which suggests that they may be useful for intra-oral grafting.[10] Other stem cells in the oral mucosa have been identified in the lamina propria of the gingiva, which attaches directly to the periosteum of the underlying bone with no intervening submucosa (Fig. 1).[11]

Periosteum-derived stem/progenitor cells (figure 1): The periosteum is a specialized connective tissue that covers the outer surface of bone tissue. The osteogenic capacity of the periosteum of long bones was reported in 1932, and the periosteum membrane was found to form a mineralized extracellular matrix under the appropriate in vitro conditions. Several subsequent studies have addressed other aspects of periosteal osteogenesis, including long bone development and the periosteum, the relationship between the vasculature and the periosteum and the periosteal osteogenic capacity. Histologically, the periosteum is composed of two distinct layers and up to five distinctly different functional regions when it is dissociated enzymatically and cultured. The outer area contains mainly fibroblasts and elastic fibers, and the inner area contains MSCs, osteogenic progenitor cells, osteoblasts and fibroblasts, as well as microvessels and sympathetic nerves. Although the heterogeneous cell population isolated from the periosteum seems to preferentially undergo osteogenic differentiation, these cells are capable of differentiating into osteoblasts, adipocytes and chondrocytes and expressing the typical MSC markers.[7] In addition, De Bari et al[12] demonstrated that single-cell-derived clonal populations of adult human periosteal cells possess mesenchymal multipotency, as they differentiate to osteoblast, chondrocyte, adipocyte and skeletal myocyte lineages in vitro and in vivo. Therefore expanded periosteum-derived cells could be useful for functional tissue engineering, especially for bone regeneration.

Salivary gland-derived stem cells: Patients afflicted with head and neck cancer who receive radiotherapy suffer from an irreversible impairment of salivary gland function that result in xerostomia and a compromised quality of life. Therefore, stem cells in the adult salivary gland are expected to be useful for autologous transplantation therapy in the context of tissue engineered-salivary glands or direct cell therapy. The salivary glands originate from the endoderm and consist of acinar and ductal epithelial cells with exocrine function. After ligation of the salivary gland duct, the acinar cells undergo apoptosis, and the duct epithelium subsequently proliferates. Although the existence of salivary gland stem cells has been suggested by in vivo studies, a single stem cell that gives rise to all epithelial cell types within the gland has not yet been identified.[7] Thus far, the isolation of stem cells in the salivary glands has been attempted through the cell culture of dissociated tissue. Kishi et al[13] isolated salivary gland stem/progenitor cells from rat submandibular glands and found that the cells are highly proliferative and express acinar, ductal and myoepithelial cell lineage markers.

Regenerative Dentistry: An important MSC application in dentistry is pulp and dentin regeneration. Cell-based approaches in endodontic regeneration based on pulpal MSCs have demonstrated promising results in terms of pulp-dentin regeneration in vivo through autologous transplantation. Despite that pulpal regeneration requires the cell-based approach, several challenges in clinical translation must be overcome including aging-associated phenotypic changes in pulpal MSCs, availability of tissue sources, and safety and regulation involved with expansion of MSCs in laboratories. Allotransplantation of MSCs can be an alternative in going through these obstacles; more research needs to be carried out on the long-term stability of MSCs and efficacy in pulp-dentin regeneration.[14]

The periodontal regenerative therapy concept is based on the principal that, firstly, the source of infection must be removed and, secondly, a space for the cells to grow must be provided. Guided tissue regeneration (GTR) is the most documented material used in periodontal regeneration. In this kind of regeneration, biocompatible barrier membranes are used to cover the bone defects. Using this technique, connective tissue and bone regeneration occurs within the bone defect. The bone defect is protected by a barrier with migration of epithelial tissues into the wound. Bioinert materials, such as pure titanium membranes, PLGA, and ePTFE, cannot stimulate bone formation. GBR and socket preservation are alveolar bone augmentation and preservation techniques that demand the application of bioactive materials to raise the activity of bone formation and therefore provide direct bonding with the bone.[15]

To permit and speed up bone formation and augment osteointegration of implants (underrating implant failure), the osteoinduction using bone grafting substitutes can be a solution when titanium implants are applied. For that reason, osteoinductive scaffolds based on CaP were engineered through osteogenic bioactive factor incorporation and have been reported to stimulate bone formation.[16]

A recent innovation in the field of medicine and dentistry is the development of autologous platelet-rich fibrin (PRF) as a growth factor delivery system. PRF is a platelet concentrate next to platelet-rich plasma with an advantage of simplified preparation and no biochemical blood handling. PRF represents a new step in the platelet gel therapeutic concept with simplified processing without artificial biochemical modification. The combined properties of fibrin, platelets, leucocytes, growth factors, and cytokines make platelet-rich fibrin a healing biomaterial with tremendous potential for bone and soft tissue regeneration. Interestingly, in 2014, a new protocol for PRF was introduced (termed Advanced-PRF or A-PRF) whereby centrifugal forces were decreased and total spin times were increased. This modification to centrifugation protocol has previously been shown to increase platelet cell number and monocyte/macrophage behaviour.[17]

Immunotherapy with MSCs in Dentistry: Possible Applications. Reports demonstrated that transplanted allogeneic PDLSC sheets show decreased immunogenicity and marked immunosuppressive ability.[18] Studies reported the systemic delivery of dental MSCs to be applied in therapeutic strategies, since they can curb Th17 cell differentiation and an augmentation in the number of Treg cells. All new MSCs’ immunomodulatory features may be interesting to dental experts since they can be used for regenerative therapy and immunotherapy.[19,20]

Banking of Stem Cells in Dentistry: Specialized studies have demonstrated that dental tissues are a rich source of MSCs, which can be applied in medical fields, particularly in immune and regenerative therapies. The process of storing stem cells acquired from patients' deciduous teeth and wisdom teeth, called dental stem cell banking, is a strategy to realize the potential of dental stem cell-based regenerative therapy. Stem cell-containing tissues are acquired from the patient and can be cryopreserved for many years to retain their regenerative capacity. Whenever required, dental stem cells, which are tolerated by the immune system, can be isolated from the cryopreserved tissue/tooth for future regenerative therapies.[21]

Challenges of stem cell therapy: A major difficulty with stem cell therapy is to identify the stem cells within a culture of real fabric. The cultures contain many different cells and are a challenge to identify specific cell types. When stem cells are identified and then isolated from tissues, appropriate solutions must be created to trigger these cells into the desired cell types.

Finally, even though the cells may be identified, isolated and grown, there are supplementary issues like immune response and efficiency. A person's immune system can identify the transplanted cells as foreign bodies and that it can generate an immune reaction that results in refusal of the new cells.

CONCLUSION

The prospective of stem cell therapy to ease the suffering of human beings and to dramatically influence disease has provoked scientists to investigate ways to augment current therapies for stem cell and develop new ones. Dental stem cells can grow not only dental tissues but other non-dental tissues as well. They are not only being investigated in the field of Medicine have found their place in the field of Dentistry as Forensic Odontology as well opening newer insights and avenues for research in this hitherto less ventured arena of Forensic dental investigations using stem cells. Nevertheless, challenge for the dental professional in the anticipated era of stem cells and tissue engineering is imminent.

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