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RESEARCH ARTICLE

STEM CELLS : ALL TO OPTIMIZE PERIODONTAL HEALTH OUTCOMES

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ABSTRACT

Stem cells can self-renew and produce different cell types, thus providing new strategies to regenerate missing tissues and treat diseases. In the field of periodontology, adult mesenchymal stem/stromal cells (MSCs) have been identified in several oral and periodontal tissues, which suggests that the oral tissues are a rich source of stem cells, and iral stem and mucosal cells are expected to provide an ideal source for genetically reprogrammed cells such as induced pluripotent stem (iPS) cells. Furthermore, oral tissues are expected to be not only a source but also a therapeutic target for stem cells, as stem cell and tissue engineering therapies in dentistry continue to attract increasing clinical interest. Additionally, appropriate sources of stem cells for regenerative periodontology are discussed with regard to differentiation capacity, accessibility and possible immunomodulatory properties.

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INTRODUCTION

Stem cells are primal cells found in all multicellular organisms that retain the ability to renew them through mitotic cell division and can differentiate into a wide range of specialized cell types .Stem cells have the remarkable potential to develop into many different cell types in the body. They serve as a repair system for the body .When a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function such as a muscle cell, red blood cell, or brain cell (Agnieszka *et al*., 2007)**.** The three broad categories of mammalian stem cells are embryonic stem cells-derived from blastocysts, adult stem cells-found in adult tissue and which are found in the umbilical cord. The rigorous definition of stem cells requires that it possess two properties.

Self renewal: The ability to go through numerous cycles of cell division while maintaining the undifferentiated state.

Unlimited potency: The capacity to differentiate into any mature cell type.

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Stem cells are important for living organisms for many reasons. In some adult tissues, such as the bone marrow, muscle and brain discrete populations of adult stem cells generate replacement for cells that are lost through normal wear and tear, injury or disease (Fulda and Pervaiz, 2010)**.**

BASIC OF STEM CELLS

Stem cells are unspecialized cells in the human body that are capable of becoming specialized cells, each with new specialized cell functions. An example of stem cells is the bone marrow stem cells that is unspecialized and are able to specialize into blood cells such as white blood cells and red blood cells. These new cell types have special functions, such as being able to produce antibodies, act as scavengers to combat infection and to transport gases. A stem cell remains uncommitted until it receives a signal to develop into a specialized cell (Alen *et al*., 2003) **[**Fig 1.]

"POTENCY" –It is defined as the capacity of a cell to differentiate into any mature cell type

Totipotent: Totipotency refers to the ability of a single cell or a nucleus to develop into any type of specialized cell or nucleus i.e. the ability of a single cell to develop and differentiate into a complete organism.

CLASSIFICATION BASED ON THEIR ABILITY [Fig 2.]		
Stem cell type	Description	Examples
Totipotent	Each cell can develop into a new individual.	Cells from early (1-3 days) embryos.
Pluripotent	Cells that can form any (over 200) cell types.	Some cells of the blastocysts (5 to 14 days).
Multipotent	Differentiated cells can form a number of other tissues.	Fetal tissue, cord blood, and adult stem cells.

"POTENCY" –It is defined as the capacity of a cell to differentiate into any mature cell type.

Fig. 1. Stem cells

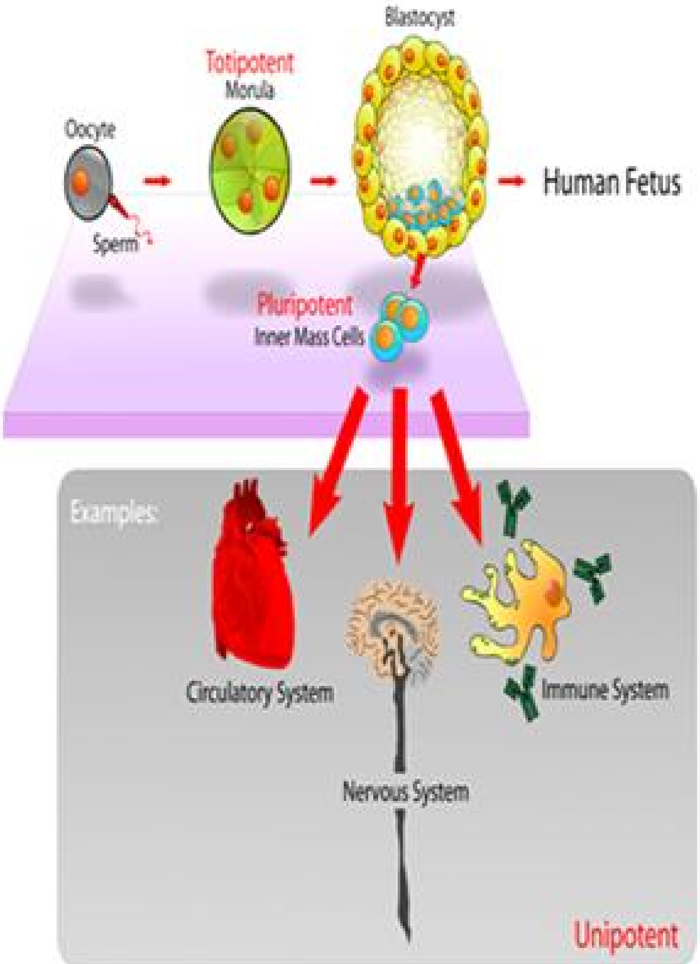

Fig. 2. Classification of stem cells

For example, after sperm fertilizes an egg, a zygote is formed which has the potential to develop into a complete embryo. This fertilized egg is a totipotent stem cell, which means that it has the potential to create any type of cell necessary for embryonic development. In the first few hours after the fertilization, the fertilized egg undergoes several cell divisions that produce identical totipotent cells. They are the most versatile stem cell type (Alen *et al*., 2003; Koichiro *et al*., 2006).

Pluripotent: Pluripotency refers to the stem cells that have the potential to differentiate into any of the three germ layers: Endoderm, Mesoderm or the Ectoderm. Pluripotent stem cells can give rise to any adult or fetal cell type. For example, the totipotent cells undergo several rounds of cell division. Approximately four days after fertilization they begin to specialize and form blastocysts. A blastocyst is a ball of cells consisting of a hollow outer layer of cells, within which is a cluster of cells called the inner cell mass. The inner cell mass forms all the tissues of human body; therefore these are the cells that develop into the fetus. The inner cell mass are pluripotent**.** They can give rise to many, but not all cell types, necessary for fetal development. Unlike totipotent stem cells, however they cannot give rise to the entire organism (Mantess and Sharpe, 2009; Bartold *et al*., 2000).

Multipotent: The multipotent stem cells can give rise to several other cell types, but they are limited in number. The pluripotent cells further specialize into the multipotent stem cells. Multipotent stem cells are committed to give rise to cells that have a particular function. For e.g.: Blood stem cells give rise to RBC, WBC and Platelets. These are less plastic and more differentiated stem cells. They give rise to a limited range of cells within a tissue type (Alen *et al*., 2003).

Unipotent: (Progenitor cells) They can produce only one cell type but have the property of self renewal which distinguishes them from non-stem cells (Bartold, 2000).

Properties of Stem Cells

All stem cells regardless of their source have three general properties:

Stem cells are capable of dividing and renewing themselves for long periods

Stem cells may replicate many times. This is called as proliferation. If the resulting cells continue to be unspecialized like the parent stem cells, the cells are capable of long term self renewal.

Stem cells are unspecialized

Stem cells do not have any tissue specific structures that allow it to perform specialized functions.

Stem cells can give rise to specialized cells

When unspecialized stem cells give rise to specialized cells, the process is called differentiation.

There are signals inside and outside cells that trigger stem cell differentiation. Internal signals are controlled by cells genes. External signals include chemicals secreted by other cells, physical contact with neighboring cells and certain molecules in microenvironment. Stem cells from tissue may be able to give rise to cell types of a completely different tissue, a phenomenon known as plasticity (Melcher, 1985; Young–sup, 2005).

Stem Cell in Periodontics

The peridontium is an unusually complex tissue comprised of two hard and two soft tissues. Once damaged, the periodontium has limited capacity for regeneration. Once periodontitis becomes established, only therapeutic intervention has the potential to induce regeneration.[2]To date, restoration of damaged or diseased periodontal tissues has relied almost entirely on the use of implantation of structural substitutes, often with little or no reparative potential. These efforts have generally focused almost exclusively on regenerating lost alveolar bone and have included the use of autografts, allografts and alloplastic materials. Due to the issues such as the variability in safety, clinical effectiveness and stability over time of these agents, their use for periodontal regeneration has been questioned. More recently biological approaches based on principles of tissue engineering have emerged as prospective alternatives to conventional treatments (Koichiro *et al*., 2006; Alen *et al*., 2003). The periodontal ligament, which is a highly fibrous and vascular tissue, has one of the highest turnover rate in the body. Many cells are present in the periodontal ligament including cementoblasts, osteoblasts, fibroblasts, myofibroblasts, endothelial cells, nerve cells and epithelial cells. In addition to these, a smaller population of "progenitor cells" has been identified by in vivo cell kinetic studies. These progenitor cell populations within the periodontal ligament appears to be enriched in locations adjacent to blood vessels and exhibit some of the classical cytological features of stem cells, including small size, responsiveness to stimulating factors and slow cycle time (Lopez *et al*., 2006). The concept that stem cells may reside in the periodontal tissues was first proposed almost 20 years ago by Melcher, who queried whether the three cell populations of the periodontium (cementoblasts, alveolar bone cells and periodontal ligament fibroblasts) were ultimately derived from a single population of ancestral cells or "stem cells". Since periodontal regeneration is essentially a re-enactment of the development process including morphogenesis, cytodifferentiation, extracellular matrix production and mineralization, such process support the concept that mesenchymal stem cells remain within the periodontal ligament and are responsible for tissue homeostasis, serving as a source of renewable progenitor cells generating cementoblasts, osteoblasts and fibroblasts through adult life. In the event of injury to the perodontium these mesenchymal stem cells could be activated towards terminal differentiation and tissue repair or regeneration (Koichiro *et al*., 2006).

Identification of Periodontal Stem Cells

Mesenchymal stem cells were first identified in aspirates of adult bone marrow by Friedenstein and colleagues by their capacity to form clonogenic clusters of adherent fibroblastic-like cells or fibroblastic colony-forming units with the potential to undergo extensive proliferation in vitro and to differentiate into different stromal cell lineages (Ian *et al*., 2006). [Fig 3.] Using the above criteria, cells had been identified that could be classified as mesenchymal stem cells, derived from adult periodontal ligament. The periodontal ligament stem cells exhibited the capacity to generate clonogenic adherent cell colonies when plated under the same growth conditions as for bone marrow mesenchymal stem cells.

These cells are considered to be derived from the ectomesenchyme. The putative stem cell marker, STRO-1, used to isolate and purify bone marrow stromal stem cells, is also expressed by human periodontal ligament stem cells and dental pulp stem cells. Periodontal ligament stem cells also share a common expression of the perivascular cell marker CD146 with the bone marrow stromal stem cells. A proportion of these cells also coexpress alpha-smooth muscle actin and /or the pericyte-associated antigen, 3G5.These observations imply a perivascular origin for these cells.

Fig. 3. Diseases cured by stem cells transplantations

Growth Potential of Periodontal Ligament Stem Cells

In the past, cloning of periodontal ligament fibroblast has met with little success. The highly proliferating periodontal ligament stem cells are representative of only a minor proportion of the cells which can be expanded in vitro over successive cell passages. The periodontal ligament stem cell cultures exhibited approximately 30% higher rates of proliferation compared to the growth of cultured bone marrow stem cells.[11] Notwithstanding the high proliferative potential of the periodontal ligament stem cells, these cells still undergo senescence and thus are considered to have a finite life span. The potential exists to develop strategies to genetically manipulate ex vivo expanded mesenchymal stem cells, such as periodontal ligament stem cells, to enhance and regulate their growth properties (Koichiro *et al*., 2006; Taka Nakahara, 2006).

Characterization and Origin of Periodontal Stem Cells

During embryogenesis, the periodontal ligament is formed by cells residing within the dental follicle. These cells have the potential to express a variety of antigens associated with endothelium (CD106), perivascular tissue (alpha-smooth muscle actin, CD146, 3G5), as well as general soft connective tissues proteins such as type I and type III collagens. The expression of common proteins implicates the existence of common molecular pathways regulating cementum and bone formation (Koichiro *et al*., 2006).

Differentiation Potential of Periodontal Ligament Stem Cells

The periodontal ligament stem cells are seen to have the capacity to form Alizarin Red-positive mineralized deposits in vitro. The multipotential capacity of periodontal ligament stem cells has also been demonstrated by their ability to form Oil-red O-positive lipid containing clusters of fat cells when cultured in the presence of adipogenic inductive medium (Paul and Pamela, 2002). The next step in characterizing the periodontal ligament stem cells has been to determine their capacity to form an organized, functional tissue following implantation in vivo.

In general it appears that these cells require a suitable scaffold, such as hydroxyapatite/tricalcium phosphate, to induce the formation of bone, dentin and cementum in vivo. In addition, these xenografts formed a type I collagen-positive periodontal ligament–like tissue within transplants connecting with newly formed cementum, morphologically similar to sharpeys fibres.

Periodontal Therapies for Periodontal Regeneration

Once tissue destruction has occurred, one of the major goals of periodontal therapies is to regenerate the affected tissues to their original architecture and function. Many surgical techniques have been advocated for periodontal regeneration. Most recently, synthetic barrier membranes have been used to encourage appropriate progenitor cell population of the wound site. This procedure has demonstrated potential for regeneration of root surface cementum, alveolar bone and periodontal ligament. Unfortunately the clinical results are unpredictable (Seo *et al*., 2005). Polypeptide growth factors applied to the tooth surface have been used to facilitate periodontal regeneration. To date, these have included epidermal growth factor, fibroblast growth factor, insulin-like growth factor, platelet-derived growth factor, tumor-derived growth factor and bone morphogenetic proteins. Combinations of growth factors such as those present in platelet-rich plasma preparations may also be useful in promoting periodontal regeneration. The key factors in attaining successful periodontal regeneration are the correct recruitment of cells to the site and the production of a suitable extracellular matrix consistent with the periodontal tissues (skin, cartilage, bone, cardiovascular components, pancreas, etc). It seems logical that autologous periodontal ligament stem cells cultured within a suitable delivery scaffold, in conjunction with the growth and differentiation factors present in autologous blood clot, will lead to new periodontal tissue attachment via a tissue engineering approach (Koichiro *et al*., 2006).

Summary and Conclusion

Advances in the stem cell biology have provided a great deal of impetus for the biomedical community to translate these findings into clinical application. Stem cells can reproduce the bone and its marrow, cementum, dentin and even the periodontal ligament. Therefore it is also possible to envision the complete restoration of hard tissues in the oral cavity using the patient's own cells, thereby avoiding issues of histocompatibility. Furthermore advances in the techniques to genetically modify the gene activity of stem cells during their ex vivo expansion offers the unique possibility to make the patient's own stem cells even better. For e.g. the activity of genes that regulate aging process can be modified, thereby rejuvenating the stem cells and giving them a new lease of life.[13]Major advances have been made over the past decade in the reconstruction of complex periodontal tissues. Stem cells holds promise of solution to a number of compelling clinical problems in dentistry that have not been adequately addressed through the use of permanent replacement devices (Nanci and Dieter, 2000).

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