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May Stem Cells Be Future Cellular Therapeutics For Edentulism? A Critical Option

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ABSTRACT

Attempts have focused to regenerate lost alveolar bone almost exclusively by using autografts [cortical/cancellous bone, bone marrow, allografts] and alloplastic materials [ceramics, hydroxyapatite, polymers, and bioglass]. However, the majority of these strategies have been plagued by variability in their safety and effectiveness. Nowadays, several approaches have started to emerge as prospective alternatives to conventional treatments including gene therapy and stem cells. The focus of stem cell research in dentistry is the generation of missing oral tissues. In particular, the restoration of alveolar ridge height is a major concern to prosthodontics. The factors that affect stem-cell-based therapies on the donor and recipient need to be addressed before therapeutic effects can be relished. The present review summarizes the properties of stem-cells and speculates on the future clinical applications in therapy of edentulism that may arise from these studies.

INTRODUCTION

Stem cells are biological cells that possess two properties self-renewal and potency. The self-renewal is the ability to go through unlimited cycles of division. The purpose of this process is to replenish the cell pool. The potency is the capacity to differentiate into other cell types. There are two primary sources of stem cells: adult stem cells and embryonic stem (ES) cells. In addition to these stem cells, which are naturally present in the human body, induced pluripotent stem (IPS) cells have been recently generated artificially via genetic manipulation of somatic cells.[1,2] ES cells and IPS cells are collectively referred to as pluripotent stem cells because they can develop into all types of cells from all three germinal layers. In contrast, most adult stem cells are multipotent. They can only differentiate into a limited number of cell types.

We outline the different types of stem cells under consideration for applications in dentistry in terms of their clinical availability.

Stem cells are commonly defined as undifferentiated cells that can proliferate and have the capacity for self-renewal and differentiation to one or more types of specialized cells. In mature tissue, these adult stem cells [ASCs] play an important role in homeostasis and tissue repair. The adult body has a small number of stem cells in many tissues and organs. They lie low until activated by illness or injury. [1-3] Adult human stem cells have been isolated from a wide variety of tissues. It may be that stem cells in adult tissues are reservoirs of reparative cells, ready to mobilize and differentiate in response to wound signals or disease conditions.[2] An adult stem cell in the brain can become a neuron or glial cell –both neutral cells- but not a bone and a liver cell. In 1966, mesenchymal stem cells [MSCs] were first identified by Friedenstein and his associates. They isolated bone-forming progenitor cells from rat marrow.[4]

Recent reports have provided substantial new insights into stem cell populations concerning therapeutic applications. Many researchers have drawn the conclusions that MSCs may be useful in the treatment of stroke, traumatic injury of muscles and Parkinson’s disease. When mesenchymal stem cells transplanted to muscle, formed dentin. They were found in the adult dental pulp. These cells could perhaps provide the mesenchymal tissue for bioengineering teeth. [5]

ES cells are produced from the culturing cells, which precede from the blastocysts, particularly from its undifferentiated inner cell mass (the early stage of embryonic development after fertilization). The main reason why there are moral and ethical questions about the use of human ES cells has to do with the embryonic origin. [6, 7]

Research about pluripotent stem cells and its differentiation may help to understand oral developmental biology and in the future can be useful to create strategies in regenerative dentistry to fulfill the clinical demands. Nevertheless, these kinds of studies are expensive, and researchers still have to deal with ethical issues, unless experts, who can routinely deal with patient embryos, were included in the team. [8]

IPS cells have the aptitude to develop into various types of tissue and organs. This stem cell technology is very promising, which can revolutionize medicine and create a biocompatible medicine that uses patients' cells to supply individual and biocompatible treatments.[9]

IPS cells can be obtained from multiple oral mesenchymal cells: buccal mucosa fibroblasts, gingival fibroblasts, and periodontal ligament fibroblasts. It is expected that oral cells can be an ideal IPS cell source. They can be applied in regenerative procedures for periodontal tissue, salivary glands, missing jaw bone, and tooth loss.[10]

It is known, that the researcher encountered difficulties in accessing peri-implantation embryos. In vitro techniques, which were developed, solved this problem. Pluripotent embryonic stem cells [ESCs] were first used as a means to examine in detail the early different action. This stem cell can develop into a complete organism. Embryonic stem cells can develop into any type of cell-called pluripotency.[5]

Scientists have learned to culture these ESCs and have demonstrated that these extraordinary cells can develop into almost any tissue ranging from neurons to muscles and teeth.[11] Cells, which were harvested from inner cell mass of embryos from in vitro fertilization clinics or terminated pregnancies, may serve as a source of unspecialized cells that have stem cell characteristics. These findings lead the researchers to explore severe human diseases like Alzheimer's and Parkinson's may be treated with stem cell therapy.[12] Stem cell populations from a variety of tissues offer great promise for tissue generation, transplantation therapies, and effective gene therapy.

Stem cells isolated from adult tissues are called hematopoietic stem cells [HSCs][13,14] It has been reported that these adult stem cells have a degree of developmental or differentiation plasticity. These findings showed that have the only embryonic stem is capable of giving more than one tissue. Complex combinations of growth factors, chemical, and genetic signals drive this process.[14]

Stem Cells in the therapy of Edentulism.

It is known that the loss of teeth causes remodeling and resorption of the surrounding alveolar bone and eventually leads to atrophic edentulous ridges. Atrophic edentulous ridges are associated with anatomic problems that often impair the predictable results of traditional dental therapy. In the age, therefore, the decline in tooth function has serious problems for health and quality of life. Tissue engineering offers a new option to supplement existing treatment regimens for periodontal disease. Moreover compared with other organs of the body, the oral cavity has advantages to the tissue engineer, such as ease of observation and accessibility. The potential of regenerative treatments for the craniofacial tissues requires the integration of three key elements.

1) Morphogenetic signals 2] responding progenitor stem cell and 3] extracellular matrix scaffold. It consists of collagens, fibronectin, and proteoglycans, including hyaluronic acid]

The triad of signals, stem cells and scaffolds can be used for regeneration of bone.[10,11]

Periosteum-Derived Stem/Progenitor Cells

The periosteum is the name given to the specialized connective tissue whose function is to cover the outer surface of the bone tissue. In 1932, author Fell firstly described the osteogenic potential of long bones periosteum and its membrane. He suggested its capacity to form a mineralized extracellular matrix if there were suitable in vitro circumstances. The external area contains elastic fibers and fibroblasts, and the interior area is constituted by MSCs, fibroblasts and osteoblasts, osteogenic progenitor cells, microvessels, and sympathetic nerves. [17,18]

Clinical research has demonstrated positive results when cells derived from the periosteum were applied for sinus or an alveolar ridge augmentation, which showed reliable implant insertion, with improved bone remodeling and lamellar bone production, and also demonstrated that shorter postoperative waiting time was needed after implantation.[19,20]

As a result, in case of large bone defects, the periosteum could be a source of stem/progenitor cells differentiate into osteoblasts, chondroblasts, adipose cells, and fibroblasts.[4,20]

Nowadays, it is quite certain that bone marrow contains a population of multipotent cells can differentiate into bone, cartilage, muscle, fat or other connective tissue.[21-23]

Several preclinical studies in animal models have shown that marrow stromal cells can form bone. This phenomenon occurs when autogenetic marrow tissue is implanted in the heterotopic site in an appropriate vehicle.[24] Bone and eventual hemopoietic tissue formation are observed at the graft site. Other researchers used allogeneic cancellous bone and had successful results.[25] During fracture repair, stem cells are associated with the collagenous extracellular matrix and are localized in periosteal cells and mesenchymal cells in marrow stroma.[15,26]

Osteoarthritis, a disease of the joints where there is a progressive and irreversible loss of cartilage, with changes also in the underlying bone. ASCs can be used for joint therapy.[27] Ohazama and his associates showed in their study in mice that transfer of embryonic primordial tooth into the adult jaw, resulted in the development of tooth structures. They demonstrated that an embryonic primordial can be developed in its adult environment. These results provide a significant advance toward the creation of artificial embryonic primordia from cultured cells that can be used to replace missing teeth.[28]

More recently, [2002] Young and his associates demonstrated the successful bioengineering of whole tooth crowns composed of accurately formed enamel and pulp tissues in rats.[29]

Many researchers showed in the 1950s and 1960s that intercellular signaling is an important feature of tooth development. The signaling events take place mainly between the components of the epithelial and mesenchymal tissue.[30] These in her study discovered the signaling centers, called enamel knots in the tooth germ epithelium.[31]

Today more 10 different signals have localized in enamel knots.[31] Jernvall has continued studies on enamel knot and shown that the enamel knots instruct the patterning of the tooth crowns. They determine the location and height of tooth cusps by inducing new secondary enamel knots at the sites of future cusps.[32]

The ultimate goal of tooth regeneration is to replace the lost teeth. Stem cell-based tooth engineering is deemed as a promising approach to making of a biological tooth (bio-tooth). Dental pulp stem cells (DPSCs) represent a kind of adult cell colony that has the capacity of self-renewing and multilineage differentiation. The exact origin of DPSCs has not been fully determined and these stem cells seem to be the source of odontoblasts. They can contribute to the formation of the dentin-pulp complex. Recently, achievements obtained from stem cell biology and tooth regeneration have enabled us to contemplate the potential applications of DPSCs. Some studies have proved that DPSCs are capable of producing dental tissues in vivo including dentin, pulp, and crown-like structures.

Whereas other investigations have shown that these stem cells can bring about the formation of bone-like tissues. Theoretically, a bio-tooth made from autogenous DPSCs should be the best choice for clinical tooth reconstruction.

This review will focus on the location, origin, and current isolation approaches of these stem cells. It will be discussed the odontoblastic differentiation and potential utilizations in the reconstruction of dentin-pulp and bio-tooth.[33]

MATERIALS AND METHODS

The literature search was conducted by reviewers using medical databases [Medline via Pubmed, and Google Scholar]. This review covered the period between the years from 1932 to 2018.

The following Keywords were used separately and in combination, stem cells, mesenchymal stromal cells, deciduous teeth, tissue regeneration, bone regeneration, bone transplantation, edentulism.

The selected articles were screened by two reviewers according to the following exclusion and inclusion criteria.

Exclusion criteria

1] Studies in a language other than English

2] Expert opinion papers.

Inclusion criteria

1] Studies that evaluated the transplantation of stem cells in atrophic jaws.

2] Studies that examined the applications of the injectable bone technique.

RESULTS

Table 1 showed that in twelve studies were evaluated the behavior of Mesenchymal stem cells in vitro. Twelve clinical studies have analyzed the significance of MSCs in vivo.

Table No. 1: Studies of Mesenchymal stem cells MSCs in vitro and Vivo for the alveolar ridge.

Author, year	**Type of study**	
	In vitro **Experimental studies**	***In vivo*** **Clinical studies**
Stenderup K et al, 2001[34]	+	
Mendes SC et al, 2002[35]		+
Meijer GJ et al, 2008[36]	+	+
Friedenstein AJ et al, 1970[37]	+	
Zins et al, 1983[38]	+	
Beckel W et al, 1994[39]		+
Ueda M et al, 2008[40]		+
De Rosa A et al, 2009[41]		+
Kaigler et al, 2010[42]	+	+
Gonshor A et al, 2011[43]		+
Chai YC et al, 2012[44]	+	
Ito K, 2006[45]	+	
Dahlin C, 1989 [46]	+	
Kadiyala S, 1997[47]	+	+
Jensen J, 1990[48]		+
Shea LD, 2000[49]	+	
Ohya M, 2005[50]	+	
Hibi H, 2006[51]		+
Redondo LM, 2018[52]		+
Chien KH, 2018[53]	+	
Colangeli W, 2018[54]		+

DISCUSSION

There are two basic categories of stem cells according to their potential for differentiation. Embryonic stem cells [ESC] and somatic stem cells, also called adult stem cells or Mesenchymal stem cells. [MSC][55] Mesenchymal stem cells derived from bone marrow, they called BMSCs. These cells can replicate themselves and be differentiated into osteoblasts, chondrocytes, myoblasts, adipocytes and neuron-like cells. Mesenchymal stem cells derived from bone marrow, they called BMSCs It has been used BMSCs therapeutically in bone augmentation by sinus lifts.[56]

Various reports have described a relationship between age and the reduction in the osteogenic potential of BMSCs. The age of the donor is an important factor for bone formation.[36,57,58] When BMSCs obtained from orofacial bones are well. They can be isolated from the maxilla and mandible bone marrow suctioned during dental treatments like dental implantation.[59]

Applications of these techniques for the treatment of edentulism and oral disease are challenges that are currently receiving much attention. The transplantation of stem cells in an atrophic jaw may form available bone for treatment planning, surgical procedures, and implant design. Many techniques are used to repair the bone loss and craniofacial skeletal defects, such as surgical therapies and the use of autogenous bone and alloplastic materials. However, despite the usefulness of these reparative strategies, each method has limitations that restrict its universal application. Harada and Ohshima have reported that dental epithelial stem cells with the production of various progenitor cells produce dental tissues.[60] Stem cells present an encouraging strategy to accomplish the regeneration of large alveolar bone defects, accelerate bone formation, and stimulate osteointegration in implant treatments Nowadays, most researchers have pointed out that in the future MSCs can be harvested from the bone marrow or dental tissues such as dental pulp and expanded in the laboratory and loaded onto appropriate scaffolds and transplanted back into a deficient site, thus stem cells have the potential to generate bone and teeth.

From the foregoing discussion, it is quite clear that stem cells are a new lease for the treatment of edentulism. However, some issues remain and should be clarified about the transplantation of stem cells. Although preclinical and clinical data demonstrated the safety and effectiveness of MSCs therapy there are still many questions to be answered surrounding the mechanism of action.

1] Can stem cells be used for therapy-injured jaws?

2] What are the mechanisms by which differentiated cells keep their ability from making every organ a teratoma?

3] What is the stem cell behavior in vivo on the skeleton or the other system?

The foregoing questions highlight the need for more research to stem cells that may facilitate approaches to therapy of edentulism.

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