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MESENCHIMAL STEM CELLS AND DENTISTRY, NARRATIVE REVIEW OF LITERATURE.

María Jesús Zárate Piffardi — Universidad FinisTerrae.

Javiera Rojas Donaire* — Universidad Finis Terrae. *Corresponding Author

Paulina Gacitúa Cartes — Universidad de Chile.

Constanza Reveco Padilla — Universidad Andrés Bello.

ABSTRACT

In recent years, the so-called mesenchymal stem cells have become one of the most studied cell types in the field of cell therapy and regenerative medicine, constituting the natural unit of generation. Therefore, the objective of this bibliographic review is to identify, analyze, assess and interpret the body of knowledge available on mesenchymal stem cells and their application in dentistry.

INTRODUCTION

Mesenchymal stem cells (MSCs) have been one of the most studied cell types in cell therapy and regenerative medicine in recent years. The ease of their isolation and multilineage associated with their ability to secrete a wide range of proteins explains the number of published articles devoted to them. (1)

Currently there is no clear relationship between MSC and dentistry, but there is a need to obtain high quality adult stem cells from an easily accessible source. MSC have been identified, not only in the bone marrow, adipose tissue and umbilical cord, but also in the teeth, thus finding different populations, for example, stem cells of the dental pulp, deciduous teeth, apical papilla, dental follicle and periodontal ligament. (2,3)

Developing

Definition

Stem cells are unspecialized cells found in multicellular organisms and have the ability to differentiate into different cells in the body. (4) The mechanism of these cells is through cell division, mitosis, where two daughter cells are produced, one of which has the same qualities as the mother, thus allowing self-renewal, and the second daughter cell has the ability to differentiate as long as conditions are right. (5)

Stem cells are commonly referred to as clonogenic cells that exhibit long-term renewal of themselves and have the capacity for multilineage differentiation. They possess distinction in their potentiality for plasticity, the ability of stem cells to give rise to different types of specialized cell. These stem cells can be subdivided into embryonic stem cells and postnatal stem cells, which correspond to mesenchymal stem cells (MSC) and hematopoietic cells. (6)

-Mesenchymal Stem Cells (MSC)

Mesenchymal stem cells, also called adult tissue stem cells or multipotent adult progenitor cells are undifferentiated cells capable of differentiating into cells of mesodermal origin. (7)

-MSC Features:

They are clonogenic cells, they have the capacity for self-renewal, that is, they are non-specialized cells that renew themselves for long periods of time due to cell division. (6) Furthermore, they are capable of carrying out specific cell differentiation in different cell types, transforming into specialized cells such as myocytes or osteoblasts. (8)

1. Relationship Of Stem Cells In Dentistry

In recent times MSCs have been isolated within human teeth and their adjacent tissues, thus finding different populations of stem cells, for example, the stem cells of the dental pulp, deciduous teeth, apical papilla, dental follicle, and periodontal ligament. (2,3)

Studies focused on the dental area have shown that these cells can generate pulp-dentin complexes and periodontal ligament-root cementum respectively. (9)

2. Obtaining And Isolation:

The interest in obtaining MSCs from teeth has arisen because they are considered a waste material when they are lost for different reasons such as trauma, periodontal disease or extracted by orthodontic and / or prosthetic indication. (10,11) Without leaving out that there is the possibility of obtaining deciduous dental pieces as a result of dental replacement and third molars extracted by different indications. (10)

Dental tissue doesn't have a turnover cup throughout life (unlike bone tissue) but it does have a limited potential for postnatal repair, apparently maintained by a group of pulp stem cells that have the potential to differentiate into odontoblasts allowing the tertiary dentin deposit against physical, chemical and / or biological attacks. (10)

3. Storage

These procedures require stem cell storage, which is accomplished by cryopreservation in liquid nitrogen. Stem cells can survive these low temperatures as long as they are dispersed in cryoprotectants. Human periodontal ligament stem cells (PLSC) have been successfully recovered after cryopreservation for six months. (12)

The studies carried out have focused on the main groups of SCs of the oral cavity: (13)

I. MSC of dental pulp: (DPSC)

The dental pulp is a loose, highly specialized mesenchymal connective tissue that is surrounded by a rigid mineralized tissue. Histologically, it is composed of an extracellular matrix

and cells like odontoblasts, fibroblasts, macrophages, dendritic cells, mast cells and undifferentiated MSCs. (10,14)

DPSCs were isolated for the first time in 2000, being the first source of MSC obtained from a tooth. They are characterized by having a high proliferation rate and a large number of colony-forming units that produce mineralized nodules. (10, 15)

Osteogenic differentiation in vitro has been shown to generate osteoblast progenitor cells and osteoblasts, in vivo unlike the above, calcified bone tissue is formed with their respective Havers and osteocyte channels. (10)

Ex vivo studies of DPSC in conjunction with hydroxyapatite and tricalcium phosphate, achieving the ectopic formation of pulp-dentin complexes in immunocompromised mice. (10)

II. MSC Of The Periodontal Ligament (PDLSC)

The periodontal ligament is a specialized connective tissue located between the tooth and the alveolar bone, characterized by having a high capacity for renewal, remodeling and repair. It is made up of a heterogeneous population of cells that includes fibroblasts, cementblasts, osteoblasts, endothelial cells, epithelial cells and MSCs. (10,16)

In *in vivo* transplants, the PDLSC incorporated on hydroxyapatite scaffolds with calcium triphosphate are capable of generating structures like cementum and periodontal ligament, including the formation of Sharpey fibers. (10,17)

Studies in immunocompromised rats indicate that when transplanting PDLSC in areas with periodontal defects, they allow the regeneration of periodontal ligament tissues in close relationship with trabecular bone formed. (10)

III. MSC Of The Oral Mucosa.

Adult stem cells have been identified in the oral mucosa, the oral epithelial progenitor of stem cells being a subpopulation of small oral keratinocytes. Although these cells appear to be unipotential stem cells, they are surprising to possess clonogenicity and the ability to regenerate a highly stratified and well-organized oral mucosa. (13,18) Clinical abundance and rapid ex vivo expansion provide great advantage as a stem cell source for potential clinical applications. (18)

IV. MSC Of The Apical Papilla (APSC)

Recent studies claim that human apical papilla stem cells (APSC) have been isolated and their potential to differentiate into odontoblasts was compared to that of PDLSC. APSCs exhibit a higher proliferation rate and appear more effective than PDLSC for tooth formation. Importantly, APSCs are easily accessible as they can be isolated from human third molars. (12)

V. MSC Of The Dental Follicle (DFSC)

The dental follicle is an ectomesenchymal tissue that surrounds the enamel organ and the dental papilla of the germ of the permanent tooth in formation. The DFSCs have been isolated from third molar follicles that show a typical fibroblast morphology in vitro, it was demonstrated that after induction their differentiation is osteogenic. (13)

These DFSC can differentiate into cementblasts in vitro and are capable of forming cement in vivo. (12)

4. Indications And Clinical Application
Applications And Scopes

These MSCs obtained from dental and adjacent tissues are capable of stimulating bone formation, therefore they have a possible application in bone regeneration. These and other experimental data highlight the potential of stem cells to achieve regeneration of human dental tissues in vivo. (9)

Dentin Regeneration:

Dentin is a mineralized tissue that closely resembles bone, although it has limited potential for postnatal repair. Pulp stem cells were obtained from ectopic dentin associated with pulp tissue in vivo from immunocompromised mice, where formation of dentin-like tissue was observed. (13)

Other investigations of porcine pulp cells in vitro were stimulated by bone morphogenetic protein, confirming the differentiation of these cells in odontoblasts, which led to the formation of dentin. (13)

Periodontal Ligament Regeneration:

In cases such as juvenile periodontitis, research carried out in areas affected by the disease, achieved new bone formation in these areas through the implantation of SC, thus generating new expectations for the treatment of periodontitis. (13)

Regeneration Of Teeth:

In studies carried out at an experimental level, it has been observed that adequately stimulated MSCs could give rise to a tooth with its surrounding bone tissue. This induction was carried out using gene stimuli added to growth factors. Furthermore, it was demonstrated that the tissues present in the tooth in the outbreak stage can be used to create the entire dental crown. (13)

Current advances in dental SC identification and characterization and dental tissue engineering strategies suggest that bioengineering in the next decade will move closer to creating dental tissues. (13)

Regeneration Of Bone Tissue:

Several studies have demonstrated the effectiveness of SC in bone repair in animal models; in the future, SCs will be able to produce bone tissue from the craniofacial complex to repair bone defects caused by degenerative diseases, which can be an alternative to treat mandibular deficiencies, temporomandibular joint disorders and cleft palate and cleft lip . (13)

Bone Substitutes Used

There are different reparative techniques for bone regeneration at the oral level that combine three essential mechanisms, osteogenesis, osteoinduction and osteoconduction. (10,19)

Osteogenesis corresponds to the synthesis of new bone from cells derived from the graft or from the host. It requires cells capable of generating bone, such as osteoblasts, which are derived from osteoprogenitor cells, (20) osteoinduction is a process that stimulates osteogenesis, whereby MSCs are recruited in and around the recipient zone to differentiate into chondroblasts and osteoblasts. Differentiation and recruitment are modulated by growth factors derived from the graft matrix, whose activity is stimulated by extracting bone mineral, that is, the ability of a material to stimulate and activate osteoprogenitor cells in the surrounding tissue, and osteoconduction. It is a process by which the material provides an appropriate environment, structure, or physical material for the apposition of new bone. (10,19)

Another important concept corresponds to osseointegration, which refers to the final union between the host bone and the graft material. (10,19)

MSC And Autologous Or Autogenous Grafts

The cancellous autogenous bone is the one with the greatest osteogenic capacity and the cortical grafts are the ones that

provide greater stability. (19) However, obtaining bone autografts requires a surgical procedure at the donor site with the consequent risk of postoperative morbidity, infection, pain, bleeding, muscle weakness, neurological injury, among others. It also considerably increases surgical time and in some cases the amount of graft removed may be insufficient. (3,21)

Autologous tissue grafts are considered the "Gold standard" in the repair of bone defects due to their osteoconductive and osteoinductive properties. (10,20)

Currently, the use of therapy based on MSCs as autografts has been implemented in pathologies that affect the bone integrity of the maxillofacial complex, obtaining promising results. (22)

Today many studies have demonstrated the effectiveness of SC in bone repair on animal models, where they are reproduced in the laboratory, loaded and transplanted locally to the site of the bone defect. (22)

Stem cell research is considered one of the most attractive lines of research to modulate tissue repair and regeneration in the maxillofacial area. The modulation of tissue induction by this type of signal in the future will contribute to the regeneration of oral tissues. (22)

Pathologies such as cancer, infections, trauma, skeletal deformations are treated with autogenous grafts or alloplastic materials; however, these grafts have some limitations. (22)

CONCLUSIONS

Stem cells constitute the natural unit of generation during embryogenesis and regeneration in adult life, growing evidence has shown that the oral and maxillofacial region is a rich source of adult stem cells. (13) Many intraoral tissues, such as deciduous teeth and third molars, are not only easily accessible from the oral cavity, but can also often be obtained as a biological sample that is discarded. Therefore, dentists must recognize the promise of the emerging field of regenerative dentistry and the possibility of obtaining stem cells during conventional dental treatments. However, further studies are needed to establish evidence-based practices in order to educate dentists and patients regarding the use of SCs in autologous regenerative therapies. (18) So far, the greatest impediment is the high cost for the massive implementation of this therapy and the lack of scientific knowledge, this being the main challenge. (23)

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