Stem cells: A breakthrough in Dentistry

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ABSTRACT

Introduction: Scientific advances made to understand the molecular regulation of tooth morphogenesis, biology of stem cells and biotechnology provide opportunities that will enable tooth regeneration in the near future. Stem cells are capable of stimulating tissue regeneration and, as a consequence, present many therapeutic perspectives, which make them feasible to be applied in Dentistry. Their applicability in the regeneration of oral structures becomes nearer and nearer every day; however, additional studies are warranted to further comprehend the best method for storing stem cells and the adequate laboratorial procedures that shall be applied when those cells are used. Furthermore, it is necessary to know all cell subdivisions, according to their place of origin. **Methods:** The method employed for conducting the present study was the search for scientific articles in journals, books as well as in the following databases: BIREME, LILACS, PubMed and SciELO. **Conclusion:** This literature review aimed at exemplifying the main groups of cells, their functions and difficulties in order to provide basic knowledge that may be used by dental surgeons.

Keywords: Stem cells. Tissue engineering. Rehabilitation.

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Introduction

Embryonic stem cells derive from embryos developed from ovules that are fertilized in vitro. Those embryos are usually four or five days old, and are seen as a hollow ball of cells named blastocyst. These cells can differentiate themselves into any type of cell and are named totipotents.[1]

Conversely, the term pluripotent is used to describe stem cells that derive from three embryonic germ layers: mesoderm, ectoderm and endoderm. The different types of specialized cells that comprise the body originate from these three layers. Pluripotent cells are able to originate any type of cell.[1]

Adult stem cells are considered as multipotent, in other words, they are undifferentiated cells that are found among the differentiated cells of a given tissue or organ and may renew and differentiate themselves so as to produce specialized types of cells.

Recent researches have been conducted on the use of stem cells therapy, and have presented satisfactory results with regard to cure and treatment without precedents of certain diseases. The search for methods that allow tissue repair and even the formation of new tissue aims at drastically opening up the therapeutic possibilities in different areas of the health field.

In recent years, the greatest findings show that stem cells have been used to treat several diseases such as cancer, neurodegeneration and Alzeimer, in the recovery of tetraplegic and paraplegic patients, as well as in Dentistry.[2]

Studies conducted with stem cells highly interest the scientific field due to their ability in stimulating tissue regeneration and, as a consequence, presenting many therapeutic perspectives. Such facts enable stem cells to be used in different dental procedures of which aim is to recover the quality of patients' oral health.

There are many factors that contribute to tooth loss, namely: deleterious habits, genetic defects, congenital anomalies or early losses caused by trauma, periodontal disease and dental caries. Scientific evidence has recently shown that to recover lost dental structures it is necessary to employ non-biological techniques, such as prosthesis and implants. Other techniques employed to re-establish and recover oral health without any complications could be successfully used, for instance, the biological techniques that are highly desirable to replace lost teeth, minimizing the costs related to oral health recovery.

The method employed for conducting the present study was the search for scientific articles in journals, books as well as in the following databases: BIREME, LILACS, PubMed and SciELO. This research aimed at conducting a literature review on the different types of stem cells in order to demonstrate their importance in Dentistry, describe and classify the different groups of cells, discuss them in light of the literature and scientific evidence, search for the most recent researches that focus not only on the difficulty of isolating them, but also on the potential of using such cells.

Literature review

It all began with Thomson et al,[30] with their publication on the first procedure for isolation of stem cells in human embryos. Mice's embryonic stem cells were isolated[31,32] in 1981, and many researches demonstrated that they could be unlimitedly multiplied in culture, maintaining their ability in producing all types of cells found in mice.

Ferrari et al[33] published the first of a series of reports about the plasticity of adult stem cells, challenging the elder belief that adult stem cells are of restricted lineage. Most studies into plasticity, genetically marked from adult mice's organ cells, apparently originated types of cells that are characteristic of other organs after transplant, thus suggesting that those cells were more plastic in their potential of development.

The use of adult stem cells has avoided some ethical issues, presenting the following advantages: The cells may be isolated from patients in need of treatment, thus, avoiding immunological rejection and reducing the risk of tumor formation which frequently occurs when heterogeneous embryonic stem cells are used.[21]

Stem cells are undifferentiated cells with high capacity of self-renovation and production of, at least, one type of cell highly specialized. There are two categories: pluripotent embryonic and unipotent or multipotent, adult or somatic, which can be found in differentiated tissues.

The use of stem cells with therapeutic purposes has interested many areas in the health field, including Dentistry.

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These researches and findings have broadened the horizons of genetic engineering on the use of those tissues, and studies conducted within the dental field revealed the stem cell's ability in generating teeth and other oral tissues as well as bone tissue cells.[3]

Mesenchymal stem cells are found in the periodontal region. They can differentiate themselves into fibroblasts, osteoblasts and cementoblasts, and are responsible for periodontal ligament repair. The identification of a population of adult stem cells in the dental pulp is considered a significant advance, since these cells are able to differentiate themselves into fibroblasts, which compose the connective tissue, and into odontoblasts, which are involved in the formation of dentin.[4]

Seo et al[9] conducted a study in which stem cells were isolated in normal human third molars collected from adults aged between 19 and 29 years of age. The results provided preliminary evidence that suggest that transplanted dental pulp stem cells (DPSCs) not only compromise themselves with the odontoblastic lineage, but can also exit in the pulp, similarly to connective tissue, fibroblasts and other cells. It has been recently reported that the genes that encode proteins of the extracellular matrix and the dentin (Dentin Sialophosphoprotein – DSPP) can also be expressed in bone, although at low levels, showing that the potential of these cells is greater than expected. Other researchers[6-9] grew the same type of cells in a similar mineralization inducing environment and obtained the formation of hydroxyapatite with a small amount of carbonates which are characteristic of biological apatite.

Advances in sciences have brought innumerous improvements for human kind by introducing new vaccines and technologies, leading to an increase in life expectancy and an improvement of the health condition of many people around the world.

Researches have been conducted on the use of stem cells therapy, and have presented satisfactory results with regard to cure and treatment without precedents of certain diseases.

The importance given to the use of embryonic stem cells concerns their ability in proliferating and differentiating themselves into many types of cells. However, they also have some disadvantages, such as genetic instability, the fact that they must be transplanted to immunocompromised hosts, the risk of teratocarcinoma formation, and contamination due to being grown in mice's fibroblasts,[10] in addition to ethical issues.[11] The possibility of using somatic cells to rebuild and regenerate tissues has instigated new researches and has aroused great interest to the scientific community.[12]

In contrast, somatic cells have the advantage of autogenicity, do not incur moral limitations and respond to growth factors that are inherent to the host. However, they also present some disadvantages, for instance, the fact that they are not pluripotent, the difficulty one has in obtaining them, *in vitro* purification and growth as well as the small amount in which they are found in the tissues.[12] The main source of adult stem cells is the bone marrow. Taking into account the plasticity level of these cells, how many paths they can follow and to which portion of a functional organism they can contribute, these somatic cells are classified into multipotent and unipotent.[3]

Pluripotent stem cells can originate not only a totally functional organism, but also any type of cell in the body, including the central and peripheral nervous system.[13] However, totipotent cells are ephemeral, the reason why they must be used right after they have been obtained, and disappear a few days after fertilization.[34] Despite being found in smaller amounts and being difficult to be isolated, pluripotent stem cells are also present in adults. Arising from the bone marrow, they can originate blood cells as well as bone, cartilage, muscle and skin cells, in addition to connective tissue.[13]

Conversely, multipotent stem cells are more differentiated. They can be found in adults and are able to originate a limited number of tissues. They are designated according to the organ from which they derive and can originate cells of that organ, only; thus enabling tissue regeneration.[13] Onipotent cells, on the other hand, can be easily isolated and are found in larger amounts; however, they can originate only one tissue cell type.[13]

Nevertheless, with the advances in research, the categories into which stem cells have been divided are being increasingly questioned, given that multipotent cells, such as neural stem cells, have proved to be pluripotent.[15]

Storage of stem cells is possible in Brazil, however, only those cells that derive from umbilical cord and placenta blood (UCPB). Such procedure is regu-

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lated by the Brazilian Health Surveillance Agency (ANVISA), of which operating rules have been defined by the Resolution of the Board of Directors (RDC153/04) in which all steps involved in the rendering of services are included.[16]

The public bank aims at collecting UCPB from licensed maternity hospitals so that it can be used by the general population, provided that it is compatible. Positive maternal serology for any disease that can be transmitted by blood, including positive IgM for cytomegalovirus (CMV), is also an exclusion criterion for public banks. Conversely, private UCPB banks have different criteria, given that the material that is stored is exclusively for autologous use. UCPB for private storage can be collected in any maternity hospital that holds a health license. There are no restrictions on maternal age or the baby's size and weight, and positive serology can be stored if the parents would like to do so.[16]

Umbilical cord and placenta blood is known as a rich source of hematopoietic stem cells (SC) that can be used to substitute the bone marrow in cases of transplant. The cells can be separated, quantified, processed and stored at –196°C in order to keep their original characteristics, which allows them to be used in the future.[17]

It should also be highlighted that postnatal stem cells have been used in tissue engineering due to being easily isolated and characterized. It is important to remember that those cells seem to have a "memory" of the tissues from which they were obtained.[18] Thus, cells of mesenchymal origin (from the dental pulp, for instance) are more able to differentiate themselves into mesenchymal tissues (pulp, dentin and alveolar bone).[4]

Five different cell populations have been found to exist in the dental tissues: dental pulp stem cells (DPSC);[7] stem cells from human exfoliated deciduous teeth (SHED);[8] periodontal ligament stem cells (PDLSC);[9] dental follicle progenitor cells (DFPC)[19] and stem cells from the apical papila (SCAP).[20]

The DPSC are obtained through a protocol of enzymatic digestion. They were the first stem cells of dental origin to be isolated and the ones on which the greatest number of studies concerning differentiation and tissue regeneration potential have been conducted. They are able to differentiate themselves into osteoblasts, chondrocytes, neurons, endotheliocytes and dental pulp cells.[4,21]

The SHED are obtained from deciduous teeth and are an interesting therapeutic alternative, since all individual would have their own source of reserve cells for dental tissue regeneration. SHED have greater potential for proliferation in comparison to DPSC. Moreover, it has been proved that the former are able to differentiate themselves into odontoblasts capable of generating not only tubular dentin and vascular endothelial cells, but also neurons and tissues that are similar to the dental pulp.[22,23]

The PDLSC are obtained from the periodontal ligament and are highly able to differentiate themselves into supporting periodontal tissue, demonstrating a great potential for differentiating themselves into chondrocytes, adipocytes, and osteoblasts.[24]

The DFPC derive from the tissue that involves the developing tooth germ. Tooth follicle progenitor cells also have a great therapeutic potential for differentiation due to the tissue from which they are collected.[19] They are able to differentiate themselves into osteocytes, adipocytes, chondrocytes and periodontal ligament. Recent studies have shown that these cells are able to promote bone and periodontal tissue regeneration.[25]

As for the SCAP, they are obtained from the dental papilla. This tissue can also be found in healthy teeth with incomplete root formation. Due to being an undifferentiated tissue, it is believed that the SCAP have a potential for differentiation as well as regeneration that is greater than DPSC and SHED. This information can be confirmed by data available in the literature, which show the ability in complete root formation (pulp, cementum and periodontal ligament) in cases of apicification.[26]

A long path must yet be followed with regard to the use of stem cells, despite the great variety of sources from which stem cells can be collected as well as their regenerative potential.

When employed, stem cells must be as appropriate as possible for each tissue that will be originated. In case of regeneration of dental supporting tissues, the literature recommends the use of PDLSC or SCAP.[20] As for regeneration of functional dental pulp, especially in cases of which purpose is to close the apex of endodontically treated young teeth, cells such as SHED and/or DPSC have proved to have a great potential.

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These cells have odontoblastic marker genes and are able to form tissues that are very similar to the dental pulp.[22] For that to occur, those cells need an appropriate micro environment, specifically aimed at inducing differentiation. For dental purposes, cell differentiation in different tissues depends on certain structures such as hydroxyapatite or dentin.[23] It should also be highlighted that in order to use stem cells for therapeutic purposes in humans, appropriate matrixes will have to be developed.[4] Dentistry has undoubtedly walked towards regenerative therapies conducted with biological inducers of tissue recovery. Therefore, clinicians and researchers will need basic qualifications in molecular and cellular biology in order to be able to apply the most developed treatment technologies and strategies. By means of such a technique, we will be able to treat diseases in the oral cavity and the craniofacial complex that are untreatable nowadays.

Conclusion

Slack[1], Harada[3], Risbud[12], Gronthos[5], Miura[8] and Huang[26] agree that, regardless of where the cells are obtained, they present a great potential for oral structures formation, including the tooth germ. However, they claim that additional clinical studies are warranted to further investigate this topic.

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