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REVIEW ARTICLE

Stem cell regeneration of tooth: A systemic review

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ABSTRACT:
Tooth development is the culmination of reciprocal epithelial-mesenchymal interactions occurring in sequential stepwise fashion. The ability to generate teeth initially resides in the dental epithelium which causes induction of tooth formation in mesenchyme of cranial neural crest origin. Stem cells are non-specialized cells which possess two important characteristics. First, they are capable of self-renewal, via cell division, even after long periods of inactivity. Second, under certain physiological or experimental conditions, they can give rise to functional cells of a specific tissue or organ. In view of this possibility of achieving restoration with regenerative medicine, it can be considered that a new era of dentistry is beginning.

Key words: Stem cell, Regeneration, tooth

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INTRODUCTION

Bone and dental loss and defects caused by diseases and trauma have become a global concern with high incidence, which seriously affects the health and life quality of the whole population and lays a heavy financial burden on society. For oral diseases, dental prostheses, periodontal treatment and dental implants remain the mainstream therapies. However, the application of autogenous bone transplantation is seriously restrained by limitations of sources, difficulty in graft harvest and morbidity of donor site. Moreover, present therapies for oral diseases can only improve clinical diagnostic parameters and halt disease progression but fail to regenerate lost tissue. Therefore, new technologies are in high demand to achieve excellent regeneration of bone and dental tissues.[1- 3]

Regenerative medicine has emerged as a novel therapeutic approach to promote regeneration in a more predictable manner. It is an attractive medical alternative to conventional treatment. Stem cells used as three elements (cells, scaffolds, and signaling molecules) are the most critical components for regeneration and play a pivotal role in tissue engineering and regenerative medicine. There are a variety of sources of stem cells, including pluripotent stem cells; embryonic stem (ES) cells, which are not widely used due to ethical concerns and the risk of tumor formation and induced pluripotent stem (iPS) cells, which have the capacity to transform adult somatic cells back into pluripotent cells and the potential to form tumors; and adult stem cells, for example, hematopoietic stem cells and mesenchymal stem cells (MSCs), which are multipotent, have the ability to self-renew, can be obtained from multiple sources, and are easy to access.[4- 6] The latter cells have the greatest potential in tissue engineering for clinical application and were first identified in the bone marrow. However, researchers have been exploring other sources of MSCs because of the difficulty of harvesting a sufficient cell number and the pain and morbidity experienced during the harvesting procedure. Therefore, many anatomical locations have been investigated as sources of MSCs, and MSCs can currently be obtained from a number of tissues, such as adipose tissue, muscle, and dermis. One of the potential sources of MSCs is dental/oral tissues containing dental pulp, periodontal ligaments, the oral mucosa, and the gingiva. The use of MSCs of dental origin has increased exponentially in the last decade.[7, 8]

WHAT ARE STEM CELLS?

A stem cell is defined as a cell that has the ability to continuously divide to either replicate itself (self-renewing), or produce specialized cells than can differentiate into various other types of cells or tissues (multilineage differentiation). The term "stem cell" was proposed by Russian histologist Alexander Maksimov in the year 1868. They can be thought as building blocks of the body which form an indispensable step for regenerative medicine. A considerable effort has been made to evaluate the consequences of the cultivation of stem cells.[8- 10]

TYPES OF STEM CELLS

In general, stem cells are broadly classified as embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs are cells derived from the inner cell mass of the blastocyst which is an early stage of an embryo. ASCs are present in adult tissues, have restricted ability to proliferate and are further divided into hemopoietic stem cells (HSC) and mesenchymal stem cells (MSC) depending on the tissue of origin. Stem cells can also be categorized into different types based on their potential to differentiate into other types of cells as totipotent, pluripotent, multipotent, oligopotent or unipotent.[9, 10]

DENTAL STEM CELLS

Several populations of cells with stem cell properties have been isolated from different parts of the tooth. These include cells from the pulp of both exfoliated (children's) and adult teeth, from the periodontal ligament that links the tooth root with the bone, from the tips of developing roots and from the tissue (dental follicle) that surrounds the unerupted tooth. All these cells probably share a common lineage of being derived from neural crest cells and all have generic mesenchymal stem cell-like properties, including expression of marker genes and differentiation into mesenchymal cell lineages (osteoblasts, chondrocytes and adipocytes) in vitro and, to some extent, in vivo. The different cell populations do, however, differ in certain aspects of their growth rate in culture, marker gene expression and cell differentiation, although the extent to which these differences can be attributed to tissue of origin, function or culture conditions remains unclear.[10- 12]

PERIODONTAL LIGAMENT STEM CELLS

The periodontal ligament (PDL) is a fibrous connective tissue that contains specialized cells located between the bone-like cementum and the inner wall of the alveolar bone socket that acts as a 'shock absorber' during mastication. The PDL has long been recognized to contain a population of progenitor cells and recently, several studies identified a population of stem cells from human periodontal ligament (PDLSC) capable of differentiating along mesenchymal cell lineages to produce cementoblast-like cells, adipocytes and connective tissue rich in collagen I in vitro and in vivo.[10- 12]

The periodontal ligament is under constant strain from the forces of mastication, and thus PDLSC are likely to play an endogenous role in maintaining PDL cell numbers. This might explain why they are better than other dental stem cell populations at forming PDL-like structures.[10- 12]

DENTAL PULP STEM CELLS

DPSCs are mesenchymal type of stem cells inside dental pulp. DPSCs have osteogenic and chondrogenic potential in vitro and can differentiate into dentin, in vivo and also differentiate into dentin-pulp-like complex. Recently, immature dental pulp stem cells were identified which are a pluripotent sub-population of DPSC generated using dental pulp organ culture.

DPSCs are putative candidate for dental tissue engineering due to:

- Easy surgical access to the collection site and very low morbidity after extraction of the dental pulp.
- DPSCs can generate much more typical dentin tissues within a short period than non-dental stem cells.
- Can be safely cryopreserved and recombined with many scaffolds.
- Possess immuno-privilege and anti-inflammatory abilities favourable for the allotransplantation experiments.[13- 16]

Identification of dental pulp stem cells

Four commonly used stem cell identification techniques are:

- Fluorescent antibody cell sorting: Stem cells can be identified and isolated from mixed cell populations by staining the cells with specific antibody markers and using a flow cytometer.
- Immunomagnetic bead selection.
- Immunohistochemical staining.
- Physiological and histological criteria, including phenotype, proliferation, chemotaxis, mineralizing activity and differentiation.[17- 19]

CURRENT STEM CELL-BASED TOOTH REGENERATION

Stem cells are unspecialized cells defined as clonogenic cells that have the capacity for self-renewal and the potential to differentiate into one or more specialized cell types. Their microenvironment, composed of heterologous cell types, extracellular matrix, and soluble factors, enables them to maintain their stemness. Because of their unique properties, stem cells have the potential to be important in tissue engineering strategies for the regeneration of diseased, damaged, and missing tissues and even organs. In general, stem cells can be divided into three main types: ESCs that are derived from embryos; adult stem cells that are derived from adult tissue; and iPS cells that are generated artificially by reprogramming adult somatic cells so that they behave like ESCs. In this section, we outline recent results obtained using ESCs and adult stem cells for tooth regeneration.[20- 22]

ESCs

The isolation and expansion of murine ESCs in the 1980s ignited interest in regenerative medicine research. ESCs are pluripotent stem cells derived from the undifferentiated inner cell mass of the blastocyst (an early stage of embryonic development) and they continue to grow indefinitely in an undifferentiated diploid state when cultured in optimal conditions in the presence of a feeder layer and leukemia inhibitory factor (LIF). The study of ESCs has gained further interest with the successful establishment of primate and human ESCs, which can differentiate into derivatives of all three primary germ layers: ectoderm, endoderm, and mesoderm. Because of the pluripotency of ESCs, several attempts have been made to use them to functionally regenerate cardiomyocytes, dopaminergic neurons, and pancreatic islets in animal models, keeping in view future clinical applications.[23- 25] In dentistry, ESCs have been used for oral and craniofacial regeneration, including mucosa, alveolar bone, and periodontal tissue regeneration. Although these approaches have the potential to be useful for tooth regeneration and for understanding basic tooth development, it will be necessary to address several major issues before they can be implemented in clinical practice, including possible tumorigenesis (teratoma formation) when transplanted, ethical issues regarding the use of embryos, and allogeneic immune rejection.[26- 28]

CLINICAL IMPLICATIONS: HOW THE KNOWLEDGE OBTAINED FROM THESE APPROACHES COULD BE USED

Stem cell-based therapies are very promising long-term alterative in dentistry since they could offer full restoration of dental tissues keeping thus the structural integrity, physiology, and function of the intact teeth. In vivo studies in animals have demonstrated the potential of different tooth stem cells populations for the regeneration of specific dental tissues, such as dentin, pulp, periodontium, or even the entire tooth organ. These regenerative approaches that have been successfully tested in animal models could be also applied to humans. It is obvious that these treatments will necessitate a sufficient number of specific stem cell populations that will be transplanted to damaged and pathological dental sites, alone or together with scaffolds.[25- 29]

It is worth noting that stem cell-based approaches have already started to be applied with success in other medical disciplines. In dentistry, several specialties took advantage of the recent progress in the fields of stem cell biology and tissue engineering and developed innovative strategies for restoring the full function and physiology of specific dental tissues. For example, regenerative endodontics focuses on reestablishment of dental pulp vitality and new dentin formation using DPSCs/SCAPs combined with scaffolds loaded with bioactive molecules. These new procedures allow the transplanted stem cells to differentiate into pulp fibroblasts and odontoblasts and progressively fill the empty pulp chamber after pulpotomy or pulpectomy, thus allowing root growth in not yet fully developed teeth. Several clinical attempts based on the bleeding technique and focused in pulp regeneration have been successfully applied in immature teeth with pulp necrosis and mature teeth with apical lesions. In this procedure, the blood clot acts as a scaffold that delivers stem cells into the empty root canal.[26- 29]

Although the use of stem cell-based techniques has started to be applied in endodontic clinics, these approaches are still at the animal experimental level for other dental specialties such as in periodontology. For example, while the potential of human PDLSCs or other stem cell populations for periodontal tissue regeneration has been evidenced in animal models, there are not equivalent trials yet in clinics.[22- 25]

Similarly, although attempts for the regeneration of entire brand new teeth have been successfully performed the last few years in small animal models dental implants still monopolize and offer the therapeutic solution after tooth loss in clinics. However, it is obvious that the ideal therapy after tooth loss would be the regeneration of an entire tooth, and therefore a bigger effort should be produced towards these revolutionary stem cell-based approaches. These novel techniques tested in mice have shown that dental mesenchymal and epithelial stem cells combined with collagen drops or scaffolds in vitro allows the formation of tooth germs that thereafter could be transplanted into the alveolar bone, where the tooth germs will develop, erupt, and finally become entire functional teeth. The application of this technique in humans has some limitations. The biggest challenge is the time needed for human tooth regeneration, since the whole process of odontogenesis in humans takes more than 7 years. This may represent a discouragement for patients looking for a quick replacement of the missing teeth.[18- 20, 25- 29]

TOOTH STEM CELL BANKING

Although tooth banking is currently not very popular the trend is gaining acceptance mainly in the developed countries. BioEden (Austin, Texas, USA), has international laboratories in UK (serving Europe) and Thailand (serving South East Asia) with global expansion plans. Stem cell banking companies like Store –A- Tooth (Provia Laboratories, Littleton, Massachusetts, USA) and StemSave (StemsaveInc, New York, USA) are also expanding their horizon internationally. In Japan, the first tooth bank was established in Hiroshima University and the company was named as “Three Brackets” (SuriBuraketto) in 2005. Nagoya University (Kyodo, Japan) also came up with a tooth bank in 2007. Taipei Medical University in collaboration with Hiroshima University opened the nation's first tooth bank in September, 2008. The Norwegian Tooth Bank (a collaborative project between the Norwegian Institute of Public Health and the University of Bergen) set up in 2008 is collecting exfoliated primary teeth from 1,00,000 children in Norway. Last but not the least, Stemade introduced the concept of dental stem cells banking in India recently by launching its operations in Mumbai and Delhi.[30]

CONCLUSION

Dental stem cells are a minor population of mesenchymal stem cells existing in specialized dental tissues, such as dental pulp, periodontium, apical papilla, dental follicle and so forth. Standard methods have been established to isolate and identify these stem cells. Due to their differentiation potential, these mesenchymal stem cells are promising for tooth repair. Dental stem cells have been emerging to regenerated teeth and periodontal tissues, ascribe to their self-renewal, multipotency and tissue specific differentiation potential. Therefore, dental stem cells based regeneration medicine highlights a promising access to repair damaged dental tissues or generate new teeth. In this review, we provide an overview of human dental stem cells including isolation and identification, involved pathways and outcomes of regenerative researches. A number of basic researches, preclinical studies and clinical trials have investigated that dental stem cells efficiently improve formation of dental specialized structure and healing of periodontal diseases, suggesting a great feasibility and prospect of these approaches in translational medicine of dental regeneration.

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