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Review Article

Stem cells: Boon to dentistry and medicine

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ABSTRACT

Stem cell research has received considerable attention since the discovery that adult stem cells have the capacity to form many different tissue types. Stem cells are a booming field for the research and have been extensively studied in the field of medicine, as well as dentistry. Their application in oncology has been a boon to many of the patients. Dental stem cells have been novel approach to treat diseases like periodontitis, dental caries and many more. Their potential uses in dentistry have provided a new generation of treatments for dental diseases and stem cells have become the focus in dental research. This review highlights about the biology, sources and potential applications of stem cells in dentistry with emphasis on a dentist's role in enabling both medical and dental applications using stem cells from teeth.

Key Words: Adult stem cells, dental pulp, embryonic stem cells, stem cells

INTRODUCTION

Tooth loss or absence is a frequent situation that results from numerous pathologies such as periodontal diseases, dental caries, fractures, injuries or even genetic alterations.[1-3] For years, the speciality of dentistry has dealt with the replacement of missing teeth with synthetic materials. Current treatment approaches include the patient's own tissues, allogenic grafts, metallic alloys or synthetic implants.[4] But all above treatments carry the disadvantage of risk of failure and limited service time. Even though implants are biocompatible, their success greatly depends on osseointegration, quantity and quality of bone. Thus, an implant can fail to remodel with host bone leading to aseptic loosening or infection resulting in its failure. In autologous tissue grafting, diseased or damaged tissue is replaced by like tissue that is healthy. Thus, the drawback of autologous tissue grafting is donor site trauma and morbidity.[5] Here arises the major question, is there any material that will replace the missing part and at the same time have better durability? The answer to this question is stem cells. Stem cell research has received considerable attention in medical field, as well as in dentistry. It has been shown that stem cells will play an important role in future medical treatment because they can be readily grown and induced to differentiate into any cell type in culture. This review highlights the biology, sources and different types of stem cells with emphasis on the potential application of dental stem cells in the fields of dentistry and medicine.

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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).[6] The term "stem cell" was proposed by Russian histologist Alexander Maksimov in the year 1868.[7-9] 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.

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.[10,11] 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 [Table 1].[12,13]

Embryonic stem cells

ESCs are cells derived from fertilized egg during blastocyst stage of development, which have extraordinary ability to form many cell types. Because of their totipotent nature, they serve as repository of cells and have potential application in regenerative medicine. These totipotent ESCs can develop into almost any tissue, ranging from neurons to muscle to perhaps teeth.[14,15] However, ESCs have ethical and technical issues. Since ESCs can be obtained only from embryos, obtaining these cells will require destruction of an embryo and therefore are associated with ethical issues.[16] Technically, the totipotent nature of these ESCs renders them difficult to grow. Unless controlled, this endless growth can result in tumor formation.[17]

Adult stem cells

ASCs have restricted ability to proliferate and are theoretically found in every type of tissue. Adult stem cells can be obtained from the bone marrow, the umbilical cord, and umbilical cord blood, peripheral blood, adipose tissue and tooth.[18] ASCs derived from bone marrow, cord blood or peripheral blood is termed as HSCs. HSCs differentiate into blood cells such as red blood cells, white blood cells, and platelets. Other type of ASC is MSCs or non-hemopoietic stem cells which take their origin from adipose tissue, hepatic stem cells, dermal stem cells, teeth etc.[19]

ASCs were originally thought to have limited potential for generating new tissues; that is, hematopoietic stem cells could only make new blood cells. But recent studies suggest that, in addition to generating the derivatives of the blood system, hematopoietic stem cells can also give rise to muscle and neuron-like cells in the brain. If this is possible, the ASCs will have the same potential as ESCs differentiating into many types of cells and thus overcoming the ethical issues associated with ESCs.[20,21]

Stem cells in orofacial tissues

Dr. Songtao Shi, pediatric dentist isolated stem cells by using the deciduous teeth of his 6-year-old daughter and named them as stem cells from human exfoliated deciduous teeth (SHED).[22] Dental stem cells can be isolated from different parts of teeth and include stem cells derived from exfoliated deciduous teeth, those stem cells derived from the apical papilla, MSC from tooth germs and from human periodontal ligament (PDL).[23-26] Teeth are one of the few tissues in the body that are naturally shed or extracted during dental care, making preservation of stem cells from such teeth possible.

Dental stem cells display mesenchymal stem cell characteristics and have the capacity to generate dentin-producing odontoblasts, adipocytes, osteoblasts, bone, cartilage, and smooth and skeletal muscle.[27,28] Studies have also shown that dental stem cells can switch lineage to form ectodermal tissues (such as neurons or epithelial-like stem cells) and endodermal lineage (such as endothelial cells, hepatocytes, and insulin-producing cells).[27,29]

Dental stem cells isolated from different parts of teeth are:

1. SHED
2. Adult dental pulp stem cells (DPSC)

Table 1: Categorization of stem cells based on potency

Type	Characteristics	Examples
Totipotent	These cells can differentiate into all possible cell types	Zygote formed by fertilized egg
Pluripotent	These cells can differentiate into almost all cell types	Embryonic stem cells and cells that are derived from the mesoderm, endoderm, and ectoderm germ layers that are formed in the beginning stages of embryonic stem cell differentiation
Multipotent	Differentiates into more than one mature cells	Hemopoietic stem cells
Oligopotent	Can differentiate into few cells	Cells of lymphoid or myeloid stem cells
Unipotent	These cells only produce cells of their own type. They have property of self renewal (divide without differentiating and provide everlasting cell supply)	Muscle stem cells

3. Stem cells from the apical part of the papilla (SCAP)
4. Stem cells from the dental follicle (DFSC)
5. Periodontal ligament stem cells (PDLSC)
6. Bone marrow derived mesenchymal stem cells (BMSC).

SHED: Isolation of mesenchymal progenitors from the pulp of human deciduous teeth is termed as SHED. SHEDs have higher proliferation rate as compared with stem cells from permanent teeth.[30] Studies have shown that SHED can differentiate into neurons adipocytes, osteoblasts and odontoblasts.[31] SHED have osteoinductive capacity, thus can induce bone *in vivo* and can be differentiated into odontoblast like cells, which induce dentine formation.[32] Because of their ability to generate neurons, and secrete neurotrophic factors, dental stem cells may also be beneficial for the treatment of neurodegenerative diseases and the repair of motor neurons following injury.[33]

DPSC: The regenerative capacity of the human dentin/pulp complex enlightens scientists that dental pulp may contain the progenitors that are responsible for dentin repair. DPSC, generate a dentin, pulp like complex that is composed of mineralized matrix with tubules lined with odontoblasts. Studies have shown that DPSCs also differentiate into adipocytes and neural like cells.[34]

SCAP: Dental stem cells isolated from human teeth found at the tooth root apex are known as SCAP. SCAPs can only be isolated at a certain stage of tooth development, but have a greater capacity for dentin regeneration than DPSCs because the dental papilla contains a higher number of adult stem cells compared to the mature dental pulp.[35] Because of higher proliferative capacity, they are suitable for inducing roots. SCAPs can generate odontoblast like cells and produce dentin, thus help in formation of root dentine as in case of apexogenesis.[36]

DFPC: Dental follicle surrounding the developing tooth germ has long been considered a multipotent tissue, based on its ability to generate cementum, bone and periodontal ligament. Dental follicle precursor cells (DFPC) differentiate into osteoblasts/cementoblasts, adipocytes, and neurons. DFPCs have increased their potential for use in tissue engineering applications, including periodontal and bone regeneration.[37]

PDLSC: PDLSC are isolated from root surface of extracted teeth and differentiate into cells or tissues very similar to periodontium. Studies on PDLSC transplanted into immune-compromised mice and rats demonstrated that capacity of PDLSC for tissue regeneration and periodontal repair.[38] PDLSCs can also differentiate into cells that can colonize and grow on biocompatible scaffold, suggesting that PDLSCs can be autologous source of stem cells for bone tissue engineering in regenerative dentistry.[39]

BMSC: BMSCs are cells originating from the bone marrow. They are capable of differentiating along multiple mesenchymal lineages. Current studies focus on their ability to form cementum, PDL and alveolar bone after implantation into defective periodontal tissues. Another study showed the possibility that BMSCs give rise to different types of epithelial cells and their potential to serve as a source for ameloblasts. Thus, BMSCs have become a novel possibility for tooth-tissue engineering and could be induced into both mesenchymal and epithelium cells in tooth tissue engineering.[40]

Applications in oral diseases

Clinical applications of dental stem cells will continue to emerge in the near term and longer term. Currently dental stem cell research focuses on regeneration of dentine, pulp and teeth; alveolar bone; regeneration of periodontal ligament after periodontal disease; salivary gland regeneration after radiation therapy; repair of craniofacial defects; and in the treatment of lichen planus.

Regeneration of teeth

Tooth regeneration represents a new era in dentistry as the concepts of repair is being shifted to regeneration. Regenerative dentistry restores a tissue defect to its original form and function by biological substitutes. Dental tissue stem/progenitor cells can differentiate into dental cell lineages, and are used to regenerate some dental tissues in the treatment of tooth defects and tooth loss. Research now focuses on whole tooth regeneration using a strategy of transplanting artificial tooth germ and allowing it to develop in the adult oral environment. Bioengineered tooth germ is regenerated from interactions between the dissociated epithelial and mesenchymal cells of the mice-derived molar tooth germ. Two means of regenerating teeth include conventional tissue engineering, in which the application of cells in a carrier material *in vitro* under the influence of a stimulus leads to tissue regeneration. The second process of tooth regeneration is using dental epithelium and mesenchymal cells *in vivo* after direct implantation, which is based on knowledge of general embryogenesis and physiological tooth development during childhood.[41,42]

Periodontal regeneration

Recently, new techniques of cell transplantation have been developed to regenerate periodontium using PDLCs isolated from extracted human teeth and DFSCs which could become an alternative cell source for periodontal regeneration therapy. When transplanted into immunocompromised mice, PDLCs have shown to regenerate collagen fibers and cementum/periodontal ligament-like structures. Periodontium can also be regenerated by culturing of periosteum, non-dental stem cells such as bone marrow mesenchymal stem cells, and adipose-derived stem cells. Studies have shown that grafted autologous cultured cell membrane derived from periosteum into a surgically created class III furcation defect in dogs, lead to the formation of cementum, periodontal ligament-like tissues, and alveolar bone in 3 months after the grafting procedure. Another research group reported a treatment using cells derived from periosteum in human periodontal disease.[43,44]

Salivary gland regeneration after radiation therapy

Radiation induced hyposalivation is a major problem in the treatment of head and neck cancer. Studies have shown that stem cell therapy may provide a means to reduce radiation-induced hyposalivation and improve the quality of life of patients. The ability of salivary gland tissue to regenerate after atrophy has provided knowledge about location and isolation of cell populations that contain salivary gland stem cells. Stem cells isolated from mouse salivary glands have shown to rescue saliva production in irradiated salivary glands. Based on the major advances made in the field of stem cell research, stem cell-based therapy has great potential for the treatment of xerostomic conditions in humans.[45,46]

Repair of craniofacial defects

Craniofacial defects results from post-cancer ablative surgery, craniofacial osseous deficiencies can also arise from infection, trauma, congenital malformations and progressively deforming skeletal diseases. Although autologous bone graft is considered the best option, it has the limitation of donor sites. Use of skeletal or dental stem cells may one day be used to repair craniofacial bone and may provide a promising alternative approach for reconstruction of craniofacial defects. Bone tissue engineering endeavours to repair large bone losses using three dimensional scaffolds to deliver vital cells to the defective site.[12]

Lichen planus

Oral lichen planus (OLP) is a T cell-mediated autoimmune disease. Treatment of lichen planus remains a challenge and conventional treatment modalities are usually unsatisfactory. Recent advance in the treatment of OLP employ the use of immunomodulating agents such as tacrolimus which may treat the disease. In the past several years, studies have focussed on immunosuppressive properties of mesenchymal stem cells on various immune cell types. Based on these studies it is proposed that mesenchymal stem cells can be utilized to treat OLP patients via systemic infusion or local application.[47]

Applications of dental stem cells in medical field

Craniofacial stem cells, including tooth-derived stem cells, have the potential to cure a number of diseases that are relevant to medicine. Systemic diseases that can be treated with dental mesenchymal stem cells are diabetes, muscular dystrophy, Parkinson's disease, cardiac infarcts, arthritis, soft tissue reconstruction, liver disease and many more.[22,48-51]

CONCLUSION

Stem cell research in dentistry has given opportunity for dentists to assume a leading role not only in the treatment chain of dental pathosis, but also in medical disease. There is a drastic increase in the number of people suffering from degenerative diseases. New treatment modalities such as stem cell therapy offer great opportunities for such patients with novel therapeutic approaches. With the advances in the stem cell biology, years from now dental stem cells will hopefully be able to correct cleft palate, save injured teeth and jaw bones, correct periodontal defects, and most strikingly regenerate the entire teeth structures.

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