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Stem Cells in Dentistry: A Review

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Abstract

Stem cells are immature, undifferentiated cells that can divide and multiply for an extended period of time, differentiating into specific types of cells and tissues. In medicine stem cell–based treatments are being used in conditions like Parkinson’s disease, neural degeneration following brain injury, cardiovascular diseases, diabetes, and autoimmune diseases. In dentistry, recent exciting discoveries have isolated dental stem cells from the pulp of the deciduous and permanent teeth, from the periodontal ligament, and an associated healthy tooth structure, to cure a number of diseases. This aim of present review of literature is to discuss role of stem cell in dentistry in details.

Keywords: Stem cells, Tissue engineering, Dentistry

Introduction

Biological solutions to biological problems are emerging as a new paradigm in dentistry and medicine. Diagnosis, treatment, therapeutics and biomaterials are all becoming biological and gene-based. We are on the verge of shifting or evolving from mechanical (e.g. surgical) to biological solutions for health promotion, risk assessment, diagnostics, treatments, therapeutics, and health care outcomes.[1]

Improve understanding of disease process and methods to prevent and cure them have led to the increased lifespan of human beings. This increased life expectancy has thus shifted the paradigm from replacement of lost or injured tissues to regeneration of the same. Research on stem cells is advancing knowledge of development and repair process in an organism. Stem cells are one of the most fascinating areas of biology today. Stem cell plasticity has resulted in a new field of medicine entitled regenerative medicine.[2]

Especially intriguing is the possibility of offering therapy for a number of incurable diseases and providing an innovative approach to treatment of chronic diseases. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson's disease, Alzheimer's disease, spinal cord injury, stroke, heart diseases, diabetes, arthritis, and many more to be listed.[2]

Stem cells also known as "progenitor or precursor" cells are defined as clonogenic cells capable of both self-renewal and multi-lineage differentiation.[3] In 1868, the term "stem cell" for the first time appeared in the works of German biologist Haeckel.[4] Wilson coined the term stem cell.[5] In 1908, Russian histologist, Alexander Maksimov, postulated existence of hematopoietic stem cells at congress of hematologic society in Berlin. There term "stem cell" was proposed for scientific use.[6]

The concept of regeneration in the medical field although not new has significantly advanced post the discovery of stem cells and in recent times have found its application in dentistry following identification of dental stem cells. At present, teeth can only be replaced with conventional prostheses, i.e., removable prostheses, fixed dental prostheses, or implants, with prior bone augmentation if necessary. However, progress in stem cell biology and tissue engineering may present new options for replacing heavily damaged or lost teeth, or even individual tooth structures. The promise of such treatment possibilities puts stem cells in the focus of dental research.[7,8]

Types of Stem Cells

1. Embryonic stem cells: Embryonic stem cells are derived from the blastocyst containing 50 to 150 cells. They are pluripotent and versatile and have the plasticity needed to differentiate into cells of all three germ layers.[9,10]

2. Adult stem cells: Adult stem cells are also called somatic or postnatal stem cells. They are multipotent and differentiate into a limited number of cell lines. Adult stem cells are easier to isolate and are not bound by the same legal and ethical constraints as embryonic stem cells. This, along with their rarer incidences of immune rejection and teratoma formation makes them suitable for use in most clinical practices.[11]

The history of research on adult stem cells began about 40 years ago. In the 1960s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called hematopoietic stem cells, forms all the types of blood cells in the body. A second population, called bone marrow stromal cells, was discovered a few years later. Stromal cells are a mixed cell population that generates bone, cartilage, fat, and fibrous connective tissue.[12]

Recent stem cell studies in the dental field have identified many adult stem cell sources in the oral and maxillofacial region. These cells are believed to reside in a specific area of each tissue, i.e., a ''stem cell niche''. Many types of adult stem cells reside in several mesenchymal tissues, and these cells are collectively referred to as mesenchymal stem cells or multipotent mesenchymal stromal cells (MSCs).[13]

3. **Induced pluripotent stem cells:** Induced pluripotent stem cells mimic embryonic stem cells in their potential to divide but are exempt from the ethical restraints since they are produced by transfecting genes found in embryonic stem cells into a donor cell with the help of vectors. Here, autologous somatic cells produce a patient specific embryonic stem cell equivalent and pave the way for treatments that are tailored to the needs of the individual.[14,15]

Table no 1: Various Sources of Adult Stem Cell	
Haematopoetic Stem Cells a) Bone marrow, b) Peripheral blood, c) Umbilical cord Stem cells • Umbilical cord epithelium (UCE), from the amniotic membrane epithelium • Umbilical cord blood (UCB) d) Fetal liver	**Mesenchymal Stem Cells** a) Muscle – muscle stem cell b) Synovium c) Dermal hairfollicle stem cell d) Nerve tissue – neuronal stem cell e) Liver – liver stem cells f) Gut epithelium g) Adipose tissue h) Amniotic fluid i) Pancreas – pancreatic stem cells j) Corneal limbal stem cells k) mammary stem cells l) Salivary glands m) Heart n) Cartilage o) Blood vessels- mesangioblasts p) Lung **Dental Derived Adult Stem Cells** a) Permanent teeth – Dental pulp stem cells (DPSC): derived from third molar. b) Deciduous teeth – Stem cells from human-exfoliated deciduous teeth (SHED): stem cells are present within the pulp tissue of deciduous teeth. c) Periodontal ligament - Periodontal ligament stem cells (PDLSC). d) Stem Cells from apical papilla (SCAP). e) Stem cells from supernumerary tooth – Mesiodens. f) Stem cells from teeth extracted for orthodontic purposes. g) Dental follicle progenitor cells. h) Stem cells from human natal dental pulp- (hNDP)

Banking of dental stem cells: Stem cell collection from bone marrow, blood, fetal material and umbilical cords present unique practical and conflicting ethical challenges.[16,17] However, the discovery of postnatal stem cell populations in the tooth pulp by Gronthos and Shi around two decades ago, opened up new horizons to stem cell research and propelled the dental profession further into the exciting field of regenerative medicine. Post-natal stem cells are present in pulp from deciduous teeth (baby or milk teeth) lost - or exfoliated - by all children during the first 6–12 years of development and are also commonly available from orthodontic extraction of third molars (wisdom teeth) in adults.[18,19]

The key to successful stem cell therapy is to harvest cells and store them safely until accident or disease requires their usage. Tooth banking is not very popular, but the trend is catching up, mainly in the developed countries. In the year 2003, Dr. Songtao Shi, a pediatric dentist, was able to isolate, grow, and preserve tooth stem cell's regenerative ability, by using the deciduous teeth of his six-year-old daughter. He called the cells as SHED. The existing research has shown that primary teeth are a better source of therapeutic stem cells for use in regenerative medicine than wisdom teeth, and orthodontically extracted teeth.[20,21]

Application of Stem Cells in Dentistry

Stem Cell in Regenerative Endodontics

Implantation: In pulp implantation, replacement pulp tissue is transplanted into clean and shaped root canal systems. The source of pulp tissue may be a purified pulp stem cell line that is disease or pathogen-free or is created from cells taken from a biopsy, that has been grown in the laboratory.[22]

Pulp revascularization: Pulp necrosis of an immature tooth as a result of caries or trauma could arrest further development of the root, leaving the tooth with thin root canal walls and blunderbuss apices. Regeneration of the pulpal tissue of an infected immature tooth might take place if suitable environment is possible with absence of intrapulpal infection. The pulpal space might become repopulated with mesenchymal cells arising from dental papilla or apical periodontium.[22,23]

Whole tooth regeneration: Tooth-like tissues have been generated by the seeding of different cell types on biodegradable scaffolds. A common methodology is to harvest cells, expand and differentiate cells in vitro, seed cells onto scaffolds, and implant them in vivo, in some cases, the scaffolds are re-implanted into an extracted tooth socket or the jaw. Ikeda et al, 2009 reported a successful fully functioning tooth replacement in an adult mouse achieved through the transplantation of bioengineered tooth germ into the alveolar bone in the lost tooth region. This technology was proposed as a model for future organ replacement therapies.[24]

Stem Cells in Periodontics

Periodontal Regeneration: Periodontal regeneration can be defined as the complete restoration of lost tissues to the original architecture and function by recapitulating the crucial wound healing events associated with their development. Such processes support the concept that some mesenchymal cells remain in the periodontal ligament and are responsible for tissue homeostasis, serving as a reservoir of renewable progenitor cells throughout adult life. As seeding to enhance regeneration of other tissues seems to be successful, it seems logical that PLSCs cultured within a suitable delivery scaffold, in conjunction with growth and differentiation factors present in autologous blood clots, will lead to new periodontal tissue attachment via a tissue engineering approach.[25]

In a study by Yamada et al. (2006) showed a novel approach to periodontal tissue regeneration with MSCs and platelet rich plasma (PRP) using tissue engineering principles. The MSCs were isolated from iliac crest marrow aspirates from patients and PRP was isolated from peripheral blood. A MSC-PRP gel was prepared and applied to root surfaces and adjacent defect spaces. Re-examination after 1 year demonstrated that application of MSC-PRP at sites with angular defects resulted in reduction of probing pocket depth by 4 mm, increased in clinical attachment level, while bleeding and tooth mobility disappeared. Radiographic assessment showed that the bone defects had reduced in depth. Interdental papillas supported by tissue engineering principles were regenerated. Thus MSC-PRP helped in periodontal tissue regeneration which is aesthetically acceptable and reduced patient morbidity.[26]

Stem Cells in Orthodontics: In Orthodontics, Stem Cells SCs can provide a step ahead in the field of craniofacial research and development.

Alveolar bone defect repair: Orthodontic treatment includes extraction of premolars for correction of malocclusion. During surgical removal of teeth, accidentally buccal plates could be lost leading to alveolar bone defect. Such defects can be filled with stem cells to avoid the risk of dehiscence and periodontal damage after the spaces have been closed by retraction. Alveolar cleft osteoplasty can be successfully done with stem cells.[27]

Distraction Osteogenesis: Stem cells can induce mobilization of osteoblastic and osteoclastic cells. Stem cells can also accelerate bone regeneration in the distraction gap and enhance bony tissue consolidation. Such application was carried on through many studies started by experimental studies and have been finalized by a clinical trial on the human being.[28-30]

Stem Cells in Prosthodontics

Regeneration of craniofacial structures: Osseous defects of the jaw were grafted with TRCS and biopsies harvested for 6 and 12 days for analysis and followed for 12 months after oral implant therapy. Clinical, radiographical and histological findings demonstrated that cell therapy accelerated the regenerative response.[31]

Regeneration of alveolar bone: Mesenchymal condensation by aggregation of mesenchymal stem cells seen in the development of bone. It includes intra membranous and endochondral bone formation mechanisms. Bone has the intrinsic capability of regeneration during adulthood. In case of minor injuries regeneration takes place by the local cells like chondroblasts, osteoblasts, endothelioblasts and fibroblasts. In severe injuries self-healing alone can't repair the defect. So adequate supply of stem cells is required for the regeneration of efficient bone. Oral mesenchymal stem cells have more potential of bone regeneration.[32,33]

Regeneration of muscle tissue: Arminan et al. said that cardiomyocytes-like cells can be separated from dentin pulpal stem cells when cultivated with neonatal rat cardiomyocytes for about 4 weeks in vitro. Yang et al said that dystrophin producing muscle cells can be separated from dental pulp stem cells in cardiotoxin-paralyzed muscles in a mouse model and can be used as a treatment of choice for muscular dystrophy.[34]

Stem Cells in Pedodontics

Three-dimensional cell printing: The three-dimensional cell printing technique can be used to position cells so that they have the potential to generate tissue that imitates the natural tooth pulp tissue. Careful adaptation of the pulp tissue in the cleaned and shaped root canal systems should follow the apical and coronal anatomy. This procedure is the prime requisite for the success cantof the technique. However, research has yet to provide significant evidence that three-dimensional cell printing can create functional tissue in vivo.[35,36]

Application of Stem Cell Therapy in Reconstruction of Cleft Lip and Cleft Palate Defects: Correction of craniofacial defects such as cleft palate involves numerous surgical procedures using bone grafting techniques, which pan over the course of at least a decade. The goals of cleft lip and palate not only aims at achieving a normal facial appearance, but also the ability to feed, speak, and hear without hampering the ultimate facial and psychosocial development of the child. Advances in the fields of developmental biology, stem cell biology, and material sciences have brought forward the potential for alternative therapies to surgical treatment of these congenital malformations. These adjunctive therapies have made way for a realistic possibility which exists in the form of Tissue Engineering. Tissue engineering provides an alternate means of reconstruction for the cleft palate patient, finite reservoir of minimizing the issues of donor site morbidity and a bone in addition to perhaps augmenting both hard and soft tissue healing by the addition of cytokines and growth factors.[37,38]

Limitation of Stem Cells in Dentistry

No doubt stem cells of dental origin have got multiple applications, there are certain limitations as well:[21]

- The oncogenic potential of these cells is still to be determined in long term clinical studies. Moreover, till date the research is mainly confined to animal models and still human research trials are needed to document same results in humans.
- Another main issue to consider is the difficulty to identify, isolate, purify and grow these cells in lab as these cells are required in large numbers to be therapeutically used.
- Immune rejection is also one of the issues which require a thorough consideration.
- Lastly, these are comparatively less potent than embryonic stem cells.

Conclusion: Excellent regenerative ability of oral epithelial and mesenchymal stem cells can be applied not only in dentistry but also in various fields of medicine like repair of cornea, neural, bone, muscle, tendon, cartilage, and endothelial tissues without neoplasm formation

Stem cells possess an unlimited potential to regenerate and can acquire the identity of various differentiated cells. In the case of embryonic stem cells all the different cells of an organism can be generated. To date, the research is only confined to animal models and more human research trials are needed to determine the therapeutic utility of stem cells.

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