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STEM CELLS IN PEDIATRIC DENTISTRY

Dental Science

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ABSTRACT

Stem cells are biological cells which are found in all multi cellular organisms that can divide and differentiate into specialized cell types .Stem cells have remarkable features known as self-renewal and multi-lineage differentiation. Dental stem cells are mesenchymal stem cells that are isolated from different components of tooth tissue and possess distinct characteristics of self-renewal and a high potential to differentiate. These features along with the feasibility of harvesting, no bioethical issues due to their source of origin, Dental pulp stem cells and Stem cells from human exfoliated deciduous teeth has widened the horizon of regenerative tissue engineering. Clinical application of stem cells has begun a new era in Pediatric Dentistry and therefore a thorough understanding of the basic biology of stem cells is fundamentally important.

KEYWORDS

stem cells, tissue engineering, revascularization, pediatric dentistry

INTRODUCTION

Preservation of teeth in order to prolong their function is the ultimate goal while rendering dental treatment.[1] Tooth loss caused by caries, trauma, and other diseases interrupts root canal development and natural apical closure, which causes further difficulties for performing conventional endodontic procedures successfully.[2] Efforts in the field of biomaterials have led to the creation of several materials which induce apical closure by forming a hard tissue barrier. However, weakening of roots of immature teeth have been reported as an unfavourable outcome.[3] The emerging fields of tissue engineering and regenerative medicine look to replace or repair lost or damaged tissues[1]. The main tool in this armamentarium is the stem cells.

Over the past decade, the field of dentistry has benefited from findings in stem cell and tissue engineering. Stem cell-based regenerative approaches aim at the full restoration of lost or damaged tissues,thus making certain of its functionality.[4] Stem cells are biological cells which are found in all multi-cellular organisms, that can divide and differentiate into diverse specialized cell types.[5]

Pulp regeneration in immature teeth focuses on the use of stem cells for root regeneration and the regulation of stem-cell growth by using appropriate growth factors.It has been suggested that,the source of tissue regeneration may be located in the apical root region of immature permanent teeth as apex formation continues even after completion of root canal treatment.[6] It has also been seen that stem cells in the periodontal ligament or alveolar bone could be the source of tissue regeneration in the apical root region of immature permanent teeth. Therefore, this article highlights the sources, different types of stem cells, recent advances in stem cell-based tissue therapy and also attempts to outline the various approaches potentially advantageous in regenerative procedures in the fields of pediatric dentistry.

SOURCES OF STEM CELL

Based on the knowledge of origin and nature of stem cells, various sites can be source of stem cells like stem cells from embryos; fetus; the umbilical cord; and adult.[7]

Embryonic Stem Cells

The fertilized oocyte, zygote, 2-cell, 4-cell, 8-cell and morula resulting from cleavage of the early embryo are examples of totipotent cells.[8] Five-to-six days after fertilization, and after several cycles of cell division, the morula cells begin to specialize by forming a hollow sphere of cells which is called a blastocyst. The inner cell mass (ICM) of the 5- to 6-day old human blastocyst is the source of pluripotent embryonic stem cells (hESCs).[9]

Fetal Stem Cells

Research with fetal tissue so far has been limited to only a few cell types namely the neural stem cells, hematopoietic stem cells; and pancreatic islet progenitors.[9] It has been reported that fetal blood, placenta and umbilical cord are rich sources of fetal hematopoietic stem cells.[10]

Adult Stem Cells

These are undifferentiated cells that occur in a differentiated tissue in the adult body. They can renew themselves in the body, creating identical copies of them or can become specialized to yield the cell types of the tissue of origin. The differentiated tissues in the adult body that can act as sources of adult stem cells include bone marrow, blood, the eye, brain, skeletal muscle, dental pulp, liver, skin, the lining of the gastrointestinal tract, and pancreas. Studies suggest that at least some adult stem cells are multipotent.[9]

Dental stem cells

In 2000, Gronthos et al isolated the first mesenchymal stem cells (MSC) like cells from the human dental pulp.[10] Subsequently four more types of MSC-like cells have been isolated from dental tissues, those being , pulp of exfoliated deciduous teeth[11], PDL[12] apical papilla[13] and dental follicle.[14]

1.Dental Pulp Stem Cells (DPSCS)

The stem cells in dental pulp tissue primarily have been reported in 1985 by Yamamura.[16] DPSCs were the first type of dental stem cells to be isolated. These cells were obtained by enzymatic digestion of the pulp tissue of the human impacted third molar tooth. DPSCs have a typical fibroblast-like morphology. They are clonogenic in nature and can maintain their high proliferation rate even after extensive subculturing.[10] The DPSCs have ability to retain stem cell behaviour - even after freezing or cryopreservation. This characteristic of the stem cells makes it a source of functional stem cells even if previously frozen.[17] According to certain studies, a sub-type of DPSCs called as “immature dental pulp stems cells” (IDPSCs), have a considerable potential in future researches. IDPSCs have been extracted from pulp tissue of permanent teeth as well as exfoliated deciduous teeth.[18]

2.Stem Cells From Human Exfoliated Deciduous Teeth (SHED)

Exfoliated deciduous tooth contains stem cells that may present as a characteristic postnatal stem cell source for potential clinical applications.[19] SHED have been identified in the residual pulp of milk teeth during the mixed dentition period [11]. In 2003, Miura et al, reported that SHEDs have a higher proliferation rate along with a higher number of colony forming cells than DPSCs.[10,11] In regard to the osteogenic differentiation potential, it is seen that SHEDs were not able to differentiate into osteoblast or osteocyte, but were able to induce the host cells to undergo osteogenic differentiation[2].

3.Periodontal Ligament Stem Cells (PDLSCS)

The periodontal ligament provides anchorage to the tooth, and also contributes to its nutrition, homoeostasis, and repair.[20] Heterogeneity and continuous remodelling of this tissue is an indication for the presence of progenitor cells which can give rise to specialized cell types. In 2004, this speculation led to the discovery of the third type of dental stem cells which was referred to as Periodontal Ligament Stem Cells.[12] PDLSCs were first introduced by Seo et al. They have a multilineage differentiation potential when cultured with the appropriate inductive medium.[12,20]

4.*Dental Follicle Precursor Cells (DFPCs)*

The dental follicle (DF), is a loose connective tissue of an ectomesenchymal origin and it is present as a sac surrounding the unerupted tooth.[20] During tooth development it has been found that DF plays an important role in the eruption process by controlling the osteoclastogenesis and osteogenesis needed for eruption.[21] In 2005, Morsczeck et al isolated stem cells from the dental follicle of the human impacted third molar[14]. The potential of DFPCs to undergo osteogenic, adipogenic and neurogenic differentiation was demonstrated using in vitro studies.[15,22] In vivo transplantation of DFPCs with ceramic discs showed no evidence of dentine like structure but on the other hand there was presence of cement/immature bone-like structures with the osteocytes/ cementocytes.[23]

5.Stem Cells Of Apical Papilla (SCAPs)

The loose connective tissue located at the apex of the root of developing permanent teeth which differs from the pulp is known as the apical papilla. The apical papilla contains a richer source of mesenchymal stem cells when compared to the dental pulp.[23] These cells were first identified and characterized by Sonoyama et al in human permanent immature teeth.[13] SCAPs are clonogenic fibroblast-like cells, but have a higher proliferation rate than DPSCs. SCAPs have the capacity to undergo osteogenic, adipogenic, chondrogenic and neurogenic differentiation, when they are cultured in the appropriate inductive media.[13]

6. Induced Pluripotent Stem Cells And Dental Pulp Pluripotent-Like Stem Cells (IPSC)

Breakthrough studies in 2006 and 2007 described methods to reprogram somatic cells from mice, and subsequently humans by the addition of 4 genes (OCT3/4, SOX2, KLF4, and MYC).[24,25] These genes reprogrammed the somatic cells and returned them to an embryo-like state.

The resultant induced pluripotent stem (IPS) cells have characteristics similar to embryonic stem cell.[26] Although IPS cells are not truly equal to embryonic stem cells, and may even have a memory of the somatic tissue from which they were derived, they have created great interest for their many potential personalized regenerative therapeutic applications.[27]

APPLICATIONS OF DENTAL STEM CELLS IN PEDIATRIC DENTISTRY.

1.*Revascularization*

Injury to the tooth in the form of trauma or infection leads to pulp necrosis and retards root development in the immature tooth. In young patients, it is possible to preserve a portion of the vital pulp tissue for root development to continue, making a conservative treatment ideal in such cases.[2] The technique for regeneration of the tissue into the apex of an immature permanent tooth requires stem cells and growth factors seeded on scaffolds.[27] Apart from vital pulp tissue, the apical papilla, PDL or alveolar bone,other potential locations for stem cells may include perivascular regions, areas adjacent to the blood vessels, and peripheral nerve endings. The Hertwig's Epithelial Root Sheath (HERS) also plays a vital role in apical development and regeneration by stimulating SCAP to produce new dentin deposits and rest of the apex.[28] The SCAP, present in the apical portion of the immature tooth, has been characterized as more resistant than the original DPSCs. Thus enabling them to survive the infection and retain their capacity to differentiate into odontoblasts.[13]

Recent research into regenerative endodontic protocol, reported that SCAP survival depends on the type of irrigant used. After comparing the various protocols, experimental evidence suggested that irrigation with 17% EDTA best supported cell survival (89% viability, and statistically significant), followed by irrigation with 6% NaOCl or 17% EDTA. The authors have suggested that EDTA should be included in irrigation protocols for regenerative procedure.[29] The potential impact of restoring vitality of a necrotic young tooth by use of stem cells and following the protocol for regenerative procedures is immense.[30]

2.*Apexogenesis.*

According to various theories related to the potential role of different types of dental stem cells in regenerating pulp in immature teeth with affected tissue, new cell therapies applied to root formation have progressed significantly.[2] Stem cell-based therapies emphasises on being a promising alternative for successful regeneration of damaged dental tissues. It is therefore necessary to understand the biologic mechanism of the various dental stem cell populations as well as their behaviour after transplantation in ectopic sites. Innervation and vascularization play fundamental roles in the regulation of stem cell niches homeostasis, thus affecting the fate and behaviour of stem cells.[5]

3.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 of the technique. However, research has yet to provide significant evidence that three dimensional cell printing can create functional tissue in vivo.[31,32]

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.[33] 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.[34] 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[35]. Tissue engineering provides an alternate means of reconstruction for the cleft palate patient, minimizing the issues of donor site morbidity and a finite reservoir of bone in addition to perhaps augmenting both hard and soft tissue healing by the addition of cytokines and growth factors.[34,35]

ETHICS IN STEM CELL THERAPY

Research on Human Embryonic Stem Cells (hESC) could help to better understand early human development and, most importantly, be used in the field of regenerative medicine in the development of cell replacement therapies. However, human stem cell (hSC) research also raises sharp ethical and political controversies.[36,37]

Research involving dental stem cells do not face ethical issue as their extraction is the least invasive of all extraction methods. However, embryonic stem cells, that could have act as a potential tool during maxillofacial reconstruction, have a number of moral and ethical issues.[30,38]

The Ethical guidelines and recommendation for biomedical research on human subjects published by the Indian Council for Medical Research (ICMR) in 2000 are non-binding. Keeping an ethical conduct in mind, researchers should abide by the principles of the ICMR's Ethical guidelines for biomedical research on human subjects. However, a survey conducted by ICMR showed that in the absence of any powers of enforcement only a minority (22%) of India's 179 institutional ethics committees followed the principles laid down in this document.[37,39] The growing global interest in stem cell research & therapy mandates development of a robust regulation and oversight along with steps to enhance public knowledge and awareness.

CONCLUSION.

Regeneration of the dental tissues provides a feasible and beneficial alternative to more traditional restorative approaches because the diseased tissue is replaced by natural tissue. There is a clear opportunity to move restorative dentistry into a new era, employing the biological activity of the dental tissues to facilitate tissue regeneration. Further research is required in order to completely understand the capability and behaviour of dental pulp progenitor cells in various clinical applications. Regardless, the opportunities for their execution in dental tissue regeneration can lead to significant advantages in the field of pediatric dentistry.

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