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STEM CELL DENTISTRY

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ABSTRACT

A future use in human dentistry is conceivable given the promising techniques offered by the young science of stem cell biology, both in vitro and in vivo in animal models. Reviewing stem cell research literature in areas important to dentistry was the goal of this study. Different stem cells are explored in dentistry. Future treatments involving adult dental ectomesenchymal stem cells appear promise. Dental pulp, exfoliated deciduous teeth, the periodontal ligament, the dental follicle, and the dental papilla have all been used to isolate human stem cells. STRO-1 and other stem cell markers were employed to identify and isolate stem cells. Adult dental stem cells can develop into a variety of dental materials, including cement, dentin, and periodontal ligament.

Keywords: Stem cells, Dentistry, Regeneration, ectomesenchymal

INTRODUCTION

Cells have explicit purposes in the body, cells that don't yet play a particular part and can turn out to be practically any cell that is required are stem cells. They are undifferentiated cells that have the ability to transform into explicit cells, according to the need of the body. They originate from two main sources: adult body tissues and embryos. They can be used for multiple diseases be it leukaemia, oral cancers, heart failure etc.

For dental sciences research on stem cells is an optimistic branch **[1]**. Seclusion of the stem cells have been recognized from many

oral tissues like periodontal ligament stem cells, dental pulp stem cells isolated from dental pulp tissue, progenitor/stem cells from oral epithelium, periosteum-derived stem cells, salivary gland-derived stem cell and gingival-derived mesenchymal stem cells (GMSCs) from gingival lamina propria etc. **[2]**. The different types of stem cells are follows:

1. Dental pulp stem cells (DPSCs):-

Rejuvenation of tissues to replace diseased, missing and traumatised dentin/pulp emerges from recent progress in stem cell and tissue engineering research. Dental pulp stem cells (DPSCs) are viewed as a promising population of cells in regenerative dentistry and have been shown to produce dentin/pulp-like tissues following implantation in vivo **[3]**.

2. Periodontal ligament stem cells (PLSCs):-

They are derivative of periodontal ligaments of third molars in humans and have progenitors for self-renewal of oral structures like cementum and bone.[4] Various types of cells such as osteoblasts, adipocytes and chondrocytes can be derived from periodontal ligament stem cells.

3. Stem cells from oral epithelium: -

They are unipotent. They develop into epithelial cells in vivo. Oral epithelial stem cells (OESCs) exist in the proliferative basal layer, while differentiating cells populate in supra-basal layer **[5]**.

4. Periosteum derived stem cells: -

Periosteum, a highly vascularised connective tissue which envelopes the surfaces of bone. Periosteum derived progenitor cells (PDPCs) are situated in an inner cambium that act as major players in fracture healing and bone development.[6] They have odontogenic, chondrogenic and myogenic potential both in-vitro and in-vivo. They produce cortical bone. They are therefore used for regeneration of large defects in the orofacial region **[4]**.

5. Salivary gland derived stem cells: -

Salivary glands have two types of secretory acinar cells: -

a) Serous acini

b) Mucous acini

They are encircled by myoepithelial cells that help the emission of the mucous or serous liquid into the ductal network through which spit arrives at the oral cavity **[7]**. SGDSCs have the potential to form duct cells and acinar cells in vitro. These cells are capable of rescuing hypo-salivation after low cell dose transplantation, are the first documentation of in vivo functional properties of a defined stem cell population from the adult human salivary gland **[8]**.

6. Gingival derived mesenchymal stem cells: -

Gingiva-derived mesenchymal stem cells (GMSCs) can be isolated from gingival connective tissue. They have multi-differentiation potential, self-renewal

capacity, and strong immunomodulatory properties **[9]**. They modulate the phenotype and activate variety of innate and adaptive immune cells both in vitro and in vivo **[10]**.

STEM CELLS IN ORTHODONTICS

Orthodontics is a branch of dentistry that deals with the diagnosis, prevention, and rectification of dental malocclusions and also addresses the modification of facial growth and correction of any deformities in dentofacial development.

The major objective of orthodontic treatment is aesthetic satisfaction which improves oral health-related quality of life **[11]**.

Stem cells are special cells which are undifferentiated or partly differentiated and these cells can convert into various other types of cells under suitable conditions. The various sources of stem cells in our body are umbilical cord, muscle, adipose tissue, periosteum, blood, dermis, bone marrow, synovial membrane and teeth **[12]**.

In teeth, mesenchymal stem cells (MSCs) can be isolated from the pulp, the periodontal ligament or human shed off or extracted deciduous teeth. These cells have potential for differentiation and proliferation **[13]**.

In dentofacial orthopedics bone regeneration is done. In bony tissues engineering, these MSCs are transferred by several types of osteoconductive scaffolds and are made to differentiate into bone forming cells using different osteoinductive growth factors **[14]**.

Recently there has been a lot of research and studies on the use of mesenchymal stem cells in orthodontics and dentofacial orthopedics and the results are promising and better than the currently used methods **(Figure 1)**.

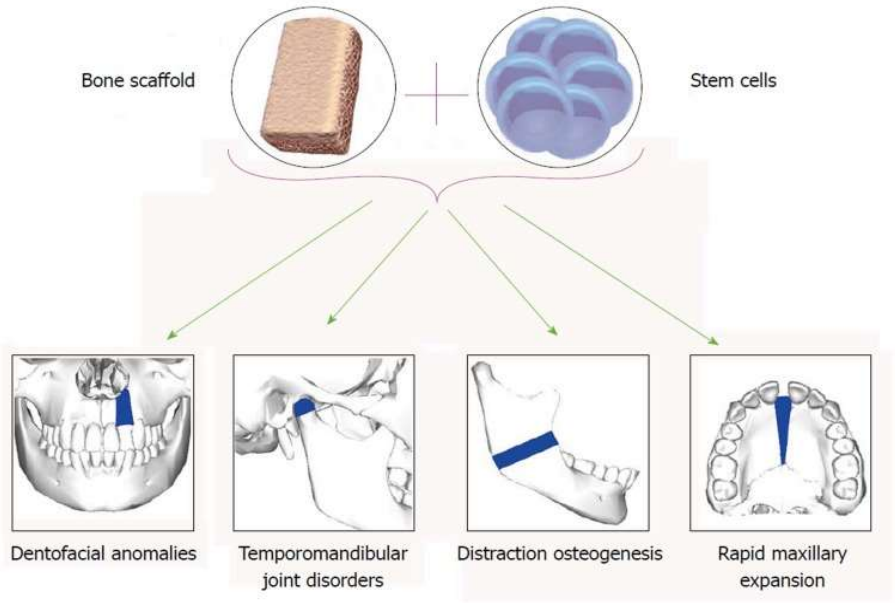

Figure 1: Possible uses of stem cells in dentofacial orthopedics [11]

For craniofacial anomalies like alveolar cleft, hemifacial macrosomia, SCs have been used in regenerating hard tissues and soft tissues respectively. In alveolar clefts, the defect size is reduced by bone formation and this has better postoperative results than bone grafting **[15]**.

Several efforts have been made to rehabilitate impaired temporomandibular joint by regenerating the bony and cartilaginous tissues of TMJ and also the joint disk using stem cells in combination with different scaffolds **[16]**.

It has been suggested that using stem cells in distraction osteogenesis which is known as "endogenous bone tissue engineering" can potentially accelerate bone regeneration in the distraction gap and increase consolidation **[17]**. The data from different studies show that SCs can cause an increase in new bone volume and quality **[18]**.

It is seen that MSCs applied locally to the maxilla which was expanded by orthodontic treatment might lead to accelerated new bone formation in midpalatine suture thus leading to stability of palatal expansion. This reduces the treatment time and retention period for patients undergoing orthopaedic expansion of maxilla **[19]**.

It has been suggested that SCs may also be used to rehabilitate infrabony alveolar defects, often created after orthodontic extractions **[20]**.

Regarding the applications of SCs in orthodontics **(Figure 2)**, current studies and research suggests that in future SCs can be used in overcoming the limitations of orthodontic tooth movement, accelerating orthodontic treatment, tooth movement into periodontal defects, regenerating resorbed roots, and treating external root resorption **[21]**.

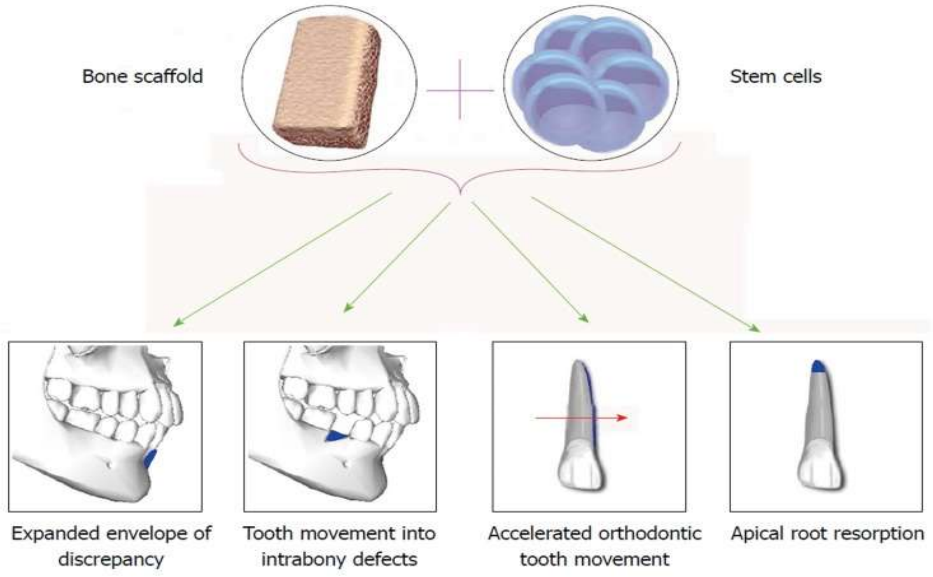

Figure 2: Possible uses of stem cells in orthodontics [1]

Though studies regarding these are still in nascent stage but these studies have opened the door of possibilities in stem cell research and their future applications in the field of orthodontics and dentofacial orthopedics.

STEM CELLS IN PEDODONTICS

Stem cells which are found in all types of multicellular organisms are classified as biological cells which can divide and even differentiate into a specialized types of cells **[22]**. With minimum invasion, these stem cells can be retrieved and become readily available **[23]**.

Shedding of primary tooth is a natural phenomenon, which creates an opportunity to retrieve and reserve this convenient source of stem cell **[24]**. Stem cells from human exfoliated deciduous teeth (SHED) can be obtained by simple, convenient and effortless method, with very little or no trauma. SHED is also not associated with major Ethical limitations **[25]**. Family members can use it (parents and grandparents) with minimum risk of unknown genetic elements **[26]**. SHED are readily available from young patients and are extracted from a disposable source. SHED has a higher proliferation rate as compared to permanent tooth and also its banking is economical.

Various In Vivo characterisation of SHED-

1.) **Dental tissue regeneration –** Specific cells having odontoblast like properties, with a dentin-like architecture was yielded by SHED when placed in an immunocompromised mouse which expressed dentin sialo phosphoprotein. Studies also showed that stem cells have ability to differentiate into pulp like cell within 28days of implantation in mice root canal **[27]**.

2.) **Osteogenic Potential-** Studies conducted have shown that about 40% of SHED has new bone formation like activity when injected in immunocompromised mice. SHED has numerous beneficial applications such as in Dental tissue engineering and in Medicine **[28]**.

- Dental Stem cells in paediatric dentistry plays an important role in Apexogenesis and Apexification requisites for Revascularization. The growth factors and the stem cells present on scaffolds are required for in vitro and in vivo techniques for the regeneration of the tissue into the apex of an immature permanent tooth. Vital pulp tissue, PDL, apical papilla, alveolar bone, gingiva also contain the stem cell named as DPSC, IDPSCs, SCAP, PDLSCs, GMSCs **[29]**.
- Dental pulp stem cells (DPSCs) are the cells that are obtained from pulp of teeth extracted for either orthodontic reasons or impacted

third molars. They have a high capacity to regenerate a dentin/pulp-like complex. But the proliferation rate and osteogenic differentiation of DPSCs is comparatively lower than SHED **[30]**. Studies have also shown that DPSCs lose their viability over the course of time.

- Immature dental pulp stem cells (IDPSCs) can be isolated from dental pulp through a non-enzymatic process. On special culture medium, IDPSCs can differentiate into osteocytes, adipocytes and neurons. It also hold osteogenic and neurogenic potential noted in vivo in bovine model and spinal cord injury in mice respectively.
- SCAP is stimulated by Hertwig's Epithelial Root Sheath (HERS) to produce dentin deposits and remaining apex and hence plays an important role in apical development and regeneration. Other potential areas of stem cells are perivascular regions, areas adjacent to the blood vessels, and peripheral nerve endings.
- Gingival derived mesenchymal stem cells (GMSCs) are a gingival population within the lamina propria of gingival tissue. Gingiva represents the most easy, accessible, minimally invasive and conservative source of stem cell **[31]**. GMSCs can be isolated from free, attached, inflamed or hyperplastic gingiva. They can be used in peripheral nerve repair and also to treat accidental trauma especially of cranial bones **[32]**.

Given the wide therapeutic application in paediatric dentistry and technology to preserve stem cells, the dental stem cells will have a greater future impact on human race. However, many areas of this field are further left to be investigated.

STEM CELLS IN ORAL AND MAXILLO-FACIAL SURGERY

Oral and Maxillofacial region generally deals with Trauma induced bone and cartilage defects, congenital defects and tumours **[33]**.

Problems such as donor-site morbidity, difficulty in restoring salivary glands shortage of bone graft material counteracting the neurodegeneration induced by trauma or surgery and limited self-healing ability of the teeth are face **[34]**. The use of stem cells is a perfect substitute for bone grafts as it has improved results and offer a technique to reconstruct craniofacial bone defects. It is however difficult to replace Oro-maxillofacial structure, because functions performed by them are delicate. The functions include

articulation, chewing, swallowing and formation of facial expression which comprises of complex anatomical structure formed from hard and soft tissues. Thus for the harvestation of the stem cells, suitable growth factors and population of the cells should be selected to support cellular differentiation and reproduction in order to fulfil the physiological role of the native tissue. According to Bo Yang *et al* . adult stem cells and iPS cells (induced pluripotent stem cells) could be used for the treatment of oral and maxillofacial defects as the Amniotic fluid and Embryonic stem cells have ethical, legal, and medical issues and their potential is yet to be studied. Furthermore, stem cells can be differentiated into osteoblasts which are a good source of bone formation, which when combined with bone marrow can be used to correct larger defects.

Microspheres (scaffold free tissue construct) have been used to close the critical size bone defects and stem cells isolated from SHED can be used in the Oro-Maxillofacial region to enhance wound healing. Oro-Maxillofacial bone tissue repair with stem cells was performed using collagen sponge scaffold and dental pulp stem cells harvested from third molars of the same patient.

The result of cell therapy used to treat maxillofacial bone abnormalities is affected by factors such mechanical and nutritional stress, hypoxia, immunological responses, and medication given to patients after stem cell implantation surgery. These factors all have the potential to decrease cell survival.

As a result, significant progress has been achieved in the use of pharmacotherapy to enhance the results of cell treatment, the use of stem cells, and the creation of new techniques to enhance vascularization in bone tissue engineering. However, efficient graft vascularization, a requirement for good bone regeneration, is still viewed as a significant hurdle **[35]**.

STEM CELLS IN PUBLIC HEALTH DENTISTRY

Due to their multiple benefits, stem cells are being used in dentistry for a variety of purposes that are all attracting international attention. Stem cells have been the subject of research by dental professionals to explore if they could be used to treat problems with both oral and systemic health **[36]**.

Dental stem cells in India are still at the budding stage, and there seems to be limited awareness regarding dental stem cells. Various studies have been conducted to assess the Knowledge, attitude and awareness regarding dental stem cells and their application amongst the dental professionals. A study by Chitroda PK *et al* revealed a good level of awareness among the dental professionals, and it also showed the need to spread more knowledge about the advances in applications, storage,

banking, and guidelines related to dental stem cells. In another study conducted by Rajbhoj AN *et al* to assess the Awareness and knowledge of Indian oral and maxillofacial diagnosticians, it was found that the awareness and knowledge was more in the participants below 29 years of age, doing specialty practice, and with an experience of fewer than 5 years. Katge F *et al* stated that the awareness, knowledge regarding sources, applications, uses and clinical research guidelines regarding dental stem cells is lacking amongst most dentists. Despite this lack of knowledge, dentists are keen on updating their knowledge regarding dental stem cells **[37]**. Furthermore, in a survey by Mridula Goswami *et al*, a positive attitude towards recommending dental stem cell banking was seen.

Awareness, knowledge and attitude regarding stem cells and their applications among the general population was also studied by various researchers. It was found that parents need to be motivated and educated about the importance of storing their dental stem cells and create awareness regarding the use of stem cell banking and evolution of stem cell therapy **[38]**. In a project to spread awareness regarding stem cells and their uses, it was found that the style and the quality of the outreach materials contributed towards reaching the project goals, while matching societal needs. It was also concluded that a great majority of participants surveyed acquired some level of knowledge, again suggesting the usefulness of the outreach materials to convey scientific concepts and provide teaching tools.

In conclusion, further research is needed with respect to the knowledge among general dental practitioners regarding stem cells from primary teeth and they should also be educated regarding the same so that they can create awareness among the populace of our country.

STEM CELLS IN PERIODONTICS

Stems have amazing capabilities to form different types of cells during the lifetime of an individual. They form an internal repair system which regenerates different types of cells in the body. Recent studies have shown the presence of stem cells in the periodontal ligament which can prove to be a significant step towards periodontal regeneration **[39]**.

Periodontitis is an inflammatory disease that manifests as loss of supporting periodontal tissues such as PDL, cementum, alveolar bone, and gingiva. Hence the ultimate goal of periodontics is to restore these tissues through different methods like bone grafts, barrier membranes, growth factors, flap surgeries, root planing, soft-tissue curettage, substitution of bone, and biologic factors like enamel matrix proteins **[40]**.

The introduction of particular new technology has made it possible to successfully regenerate the periodontal

tissues, construct a functioning epithelial seal, insert new connective tissue fibres into the tooth's root, regenerate new acellular cementum on the tooth's surface, and restore alveolar bone height. One of the complex processes involved in periodontal regeneration is the recruitment of locally derived progenitor cells that can differentiate into periodontal ligament cells, mineral-forming cementoblasts, or osteogenic osteoblasts **[41]**.

Advances in stem cell biology and regenerative medicine have opened up opportunities for tissue engineering and gene-based approaches in periodontal therapy **[42]**. Advances in stem cell biology and regenerative medicine have opened up opportunities for tissue engineering and gene-based approaches in periodontal therapy.

STEM CELLS IN ENDODONTICS

Discovery of Stem cells in the dental pulp has led to a significant change in the basic understanding of various process of dental pulp in health (homeostasis) and injury (trauma). These cells are very closely related with the physiology and pathology of the dental pulp tissue throughout its lifespan. Stem cells are also involved in the regulation of pulp angiogenesis (formation of blood vessels) in response to cariogenic insult. Studies carried out at the NIDCR (National Institutes of Dental and Craniofacial Research) revealed that dental pulp stem cells (DPSC) can be extracted from permanent dentition and the stem cells from human exfoliated deciduous teeth (SHED). These cells have the ability to undergo odontogenic, adipogenic, neurogenic, angiogenic, chondrogenic, and myogenic differentiation, hence are called as multipotent.

Recent studies have shown that dental pulp stems can be used as an alternative treatment for cardiac and neurological conditions. Even though the number of the pulpal stem cells is small with no particular location, their phenotype is indicative of presence in perivascular niches **[43]**. Significant differences are seen in DPSC and SHED inspite of having a common origin. The defence mechanism and the healing potential of the pulpal tissue were recognized long before the knowledge of the use stem cells, but the nature and the intensity of the infection, required for the recovery were still untapped. With the advent of knowledge of the dental pulpal stem cells, a better insight has been gained into the healing potential of the immature teeth. The use of stem cells in regenerative endodontics is one of the most exciting developments in the field of dentistry. Endodontists are considered to be the pioneers of this field and front runners who continuously improve their knowledge in the field of tissue engineering and pulp biology. These developments provide a peak

into the wider aspect of future of regenerative endodontics in retaining the natural dentition which is the prime goal of endodontics **[44]**.

STEM CELLS IN PROSTHODONTICS

Prosthodontics is a branch of dentistry concerned with rehabilitating and replacing missing teeth. Recently, there has been extensive research on progressing from 'xenodontics' to 'biodontics' in dentistry. This means to replace methods of restoring , replacing and repairing lost and damaged teeth from non-biological materials to natural biological materials like stem cells **[45]**.

Mesenchymal stem cells are commonly used in regenerative prosthodontics.

Varying degrees of bone resorption occurs when a tooth is extracted or if it is lost due to some reason. The resorption of bone of the residual alveolar ridge in edentulous patients is quite severe. The use of dentures or implants to rehabilitate edentulous areas becomes difficult due to bone resorption.

Currently, grafts are used for alveolar bone augmentation but it is difficult to maintain the height and volume of the grafted bone using these techniques **[46]**.

So, stem cell treatment and tissue engineering can play a role in the augmentation of alveolar bone and correction of defects thus making prosthodontic rehabilitation easy **[47]**.

Studies have shown that tissue engineering can produce living tissues by putting together a previously fabricated, biodegradable scaffold with cells such as pluripotent stem cells which are capable of generating the tissue which is required. So, a bioengineered tooth can be produced by a bioengineered tooth germ. **[48]**.

More extensive research along with trials are still needed to support these results but the studies already done have shown promise.

DISCUSSION

According to numerous publications and this review, dental stem cells have recently drawn scientific interest, which is consistent with the promising outcomes stem cell therapy has demonstrated for tissue engineering applications **[49]**. MSCs from a variety of sites, including the oral cavity, have been touted as attractive candidates for tissue engineering **[50]**. Advanced tissue engineering, photobiomodulation therapy, biomaterials, scaffolds, digital technology, and stem cells, all of which have shown significant promise, have been recommended as multidisciplinary approaches **[51]**. Given their ability to regenerate and repair, these developments are advised to be used in every area of dentistry **[52]**. Although stem cell research, application, and knowledge are still in their infancy, positive results in improving the outcomes of several treatments show a significant role stem cells may play in the

future of dentistry **[53]**. Although pulp and periodontal regeneration utilising dental stem cells has been documented in animal models, there are very few, if any, clinical trials with long-term follow-up. Due to technical, safety, regulatory, and ethical problems, the translation of basic and preclinical stem cell research to dental clinics is exceedingly sluggish. It is clear that patients won't profit from these regenerative treatments until the majority of the challenges and concerns stated above have been addressed, and the potential clinical limits have been thoroughly reviewed and taken into account.

CONCLUSION

Many stem cell lines with wide variations in potency have been identified from adult human teeth in recent years. The clinical results could be impacted by the significant variation between individual cells obtained from the same dental stem cell pool. Therefore, before using cell-based therapy in dental clinics, the identification and purification of stem cell subpopulations with higher potency is a need. The outcome of therapy is expected to depend on a number of variables, including the selection of dental stem cell populations, the size and depth of the lesion, the state of the surrounding tissues, and the delivery modalities. The processes that govern the destinies and purposes of stem cells still require knowledge.

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