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STEM CELLS IN REGENERATIVE ENDODONTICS

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ABSTRACT: Endodontic treatment is helpful in saving millions of teeth each year, but at present the focus has shifted towards regenerative approaches as an ideal form of therapy to treat diseased or necrotic pulp tissues. Regeneration of lost tissues has been known for a very long time, but their use in dentistry is gaining momentum. The growing understanding of biological regeneration has permitted the use of stem cells for regeneration and revascularisation¹. The dental pulp contains a small sub population of stem cells that respond against caries progression and also secrete factors that have the ability to induce revascularization of pulp². Stem cells re-search and scaffolding are the frequently used words in basic science pulp researches at present. Several techniques with their individual advantages, disadvantages and uses are being performed³. In the past few years, many studies regarding stem cells and tissue engineering have been done giving rise to a separate branch called Regenerative Dentistry⁴. Regenerative Endodontics uses the basic logic that the patient specific tissue derived cell population called stem cells can be used for regeneration and revascularisation. This concept of regeneration of pulp dentin complex dates to almost 50 years when it was first reported by Nygaard and Ostby^{5,6}. The goal of this review article is to determine the significance of stem cells in performing regenerative endodontic therapy.

INTRODUCTION: Regenerative endodontic therapy is defined “as the biologically designed procedures to replace damaged structures including dentin and root structures as well as pulp dentin complex”. The main aim of this therapy is to treat immature permanent teeth or pulpal necrosis by regeneration and revascularisation of dental pulp³. The main components of regenerative Endodontics are the use of stem cells and tissue engineering. Stem cells are clonogenic cells having capabilities of self-renewal and multi lineage differentiation⁷, whereas tissue engineering is the branch that brings biology, bio engineering, clinical sciences and biotechnology together for the purpose of generating new tissues⁸.

The other component of regenerative Endodontics is the scaffolds; they provide support for cell organisation, proliferation, differentiation and vascularisation⁹. At present the regenerative therapy involves the use of dentin, blood clot¹⁰, platelet rich plasma¹¹ as scaffolds in root canals. Growth factors are also used in the field of regenerative endodontic to bind to receptors and act as signaling molecules¹². Recent advances in regenerative Endodontics comprises of research in adult stem cells, growth factors and tissue engineering¹.

Tissue engineering: Tissue engineering is the field of functional restoration of tissue structure and physiology for impaired or damaged tissues because of infection, disease, cancer and trauma. The major elements involved in tissue engineering are stem cells, morphogens or growth factors and a scaffold of extra cellular matrix^{13,14}.

Adult stem cells:

- Capable of differentiating into specialised cells.

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- Able to respond to growth factors by dividing or specialising

Morphogens or growth factors:

- Biological factors that regulate stem cells to form the desirable cell type.
- 5 major groups
 - BMPs(Bone Morphogenic proteins)
 - FGFs (Fibroblasts growth factors)
 - IGF- I,II(Insulin like growth factors)
 - PDGF(Platelet derived growth factors)
 - TGF(Transforming growth factor)

Scaffold:

- Provides a biocompatible 3 dimensional structure for cell adhesion and migration
- Biological scaffolds like collagen, glycosaminoglycan, etc.
- Artificial scaffolds like PLA, PGA, PLGA, etc.

Stem cells: A stem cell is commonly defined as a cell that has the ability to continuously divide and produce progeny cells that differentiate into various other types of cells or tissues¹⁵. Duailibi *et al* in 2006 defined stem cells as “Quiescent cell populations present in low numbers in normal tissue, which exhibit the distinct characteristic of asymmetric cell division, resulting in the formation of two distinct daughter cells a new progenitor cell and other daughter cell capable of forming a differentiated tissue³”.

Classification of stem cells¹⁶:

On the basis of origin:

- Embryonic stem cells.
- Somatic/ adult/ postnatal/ mesenchymal stem cells.

On the basis of source:

- **Autologous:** obtained from the same individual

- **Allogenic:** obtained from donor of same species
- **Xenogenic:** obtained from donor of another species
- **Syngenic:** obtained from genetically identical organisms

On the basis of potency

- **Totipotent:** can differentiate into all embryonic and extra embryonic cell types.
- **Pluripotent:** can differentiate into all types of cells except cells of the embryonic membrane.
- **Multipotent:** can differentiate into more than one mature cell
- **Uni potent:** can differentiate into only one type of cells.

Dental stem cells: Dental stem cells can be isolated from the dental pulp. There are 5 groups, of dental stem cells which have been isolated successfully, they are¹⁶

- Dental pulp stem cells (DPSCs by Gronthos *et al*, 2000).
- Stem cells from human exfoliated deciduous teeth (SHED by Miura *et al* , 2003).
- Stem cells form apical papillae (SCAP by Sonoyama *et al*, 2006).
- Periodontal ligament stem cells (PDLSCs by Seo *et al*, 2004).
- Dental follicular stem cells.

Dental pulp stem cells: The dental pulp contains a population of stem cells, called dental pulp stem cells¹², they are also referred to as odontoblastoid cells, because these cells appears to synthesise and secrete dentin matrix like the odontoblast cells that they replace¹⁸. Dental pulp stem cells were discovered in the wisdom teeth in 2000 by Gronthos *et al*¹⁸ and isolated from the dental ectomesenchymal stem cells from the dental pulp of extracted wisdom teeth¹⁹.

In vitro DPSCs have been shown to produce sporadic but densely calcified nodules and when recombined with biodegradable scaffolds *in vivo*, they can form dentin pulp like tissues with an irregular shape^{18,20}.

Human teeth have pulp chambers containing pulp tissue, when this pulp tissue gets infected and it results in inflammation of the pulp tissue causing tooth pain. In order to relieve pain the dentist has to perform root canal treatment, by this process the pain is relieved but the vitality of the tooth is lost due to removal of the pulp⁴. Stem cells derived from the dental pulp can form pulp like tissues^{21,12}. This pulp like tissues can be engineered *in vitro* using DPSCs seeded into synthetic matrices made up of poly glycolic acid^{22, 23}. Stem cells can differentiate into pulp like tissue and dentine pulp complex²⁴. So these stem cells can be used to replace infected pulp tissue of an inflamed tooth with a newly generated pulp like tissue.

Ming Yan *et al* proposed that DPSCs are useful in reconstruction of dentin pulp complex and bio tooth²⁴. Human tooth is made up of enamel, dentin, cementum and pulp tissue. Enamel is formed by ameloblasts cells, dentin is made by odontoblasts cells, and cementum is made by cementoblast cells. Stem cells can differentiate into all four types of tissues. Hence Ming Yan *et al* suggested that bio tooth can be made from stem cells²⁴.

Stem cells from human exfoliated deciduous teeth: Mesenchymal progenitors have been isolated from the pulp of human deciduous incisors. These cells were named SHED and exhibited a high plasticity since they could differentiate into neurons, adipocytes, osteoblasts and odontoblasts¹⁶. *In vivo* SHED cells can induce bone or dentin formation, but in contrast to dental pulp, DPSCs failed to produce a dentine pulp complex¹⁶. Comparison of SHED and DPSC were made and found that the SHEDs have higher rate of proliferation²⁵. Studies show that both SHED and DPSC have the ability to generate tissues that have the similar morphological and functional characteristics resembling the dental pulp²⁶⁻²⁹.

Stem cells from apical papillae: Stem cells from the apical papilla are a population of multi-potent stem cells isolated from the root apical papilla of

human teeth¹⁶. Compared with DPSC, SCAP have greater numbers of antibody STRO-1 positive cell, faster proliferation a greater number of population doublings and increased capacity for *in vivo* dentine regeneration¹⁶. SCAPs originate from an embryonic like tissue so they are less likely to be differentiated than DPSCs⁴. SCAPs can be isolated at certain specific stages of development off tooth. As the dental papilla contain higher number of adult stem cells than mature dental pulp, SCAPs have greater potential for regenerating dentin than the DPSCs³⁰.

Periodontal ligament stem cells: Human Periodontal ligament stem cells have been successfully isolated by scientists from the root of the extracted teeth^{31,32}. This was first isolated and characterised by Seo *et al* in 2004³¹. The potential of PDLSCs to develop into other cell lineages and obtain periodontal ligament like characteristics has been established by the ability of cultured PDLSC to differentiate into cementoblast like cells, adipocytes and collagen framing cells *in vitro* and the capacity to generate a cementum/PDL like structure *in vivo*^{31, 33}. Researchers suggested that PDLSCs can successfully establish a functional periodontium³⁰. Kawanabe *et al* identified highly proliferating stem cells in human periodontal ligaments³⁴.

Dental follicle progenitor cells: The dental follicle has been considered a multi-potent tissue based on its ability to generate cementum, bone and PDL from the ectomesenchyme fibrous tissue. These were first isolated from the follicle of impacted third molars³⁵. Handa K in 2002 isolated progenitor cells from bovine dental follicles. Salles and colleagues completed a study which confirms then human DFSCs have properties like mesenchymal precursor cells³⁶. DFSCs can differentiate into mesenchymal derived cells like cementoblasts, adipocytes and chondrocytes³⁷.

Technique of stem cell identification¹⁶:

- Staining the cells with specific antibody markers and using a flow cytometer, in a process called fluorescent antibody cell sorting (FACS).
- Immuno-magnetic bead selection.

- Immuno-histochemical staining.
- Physiological and histological criteria, including phenotype, chemotaxis, proliferation, differentiation and mineralising activity.

Scaffolding: Tissues are organised as three dimensional structures and appropriate scaffolding is necessary to provide a spatially correct position of cell location and to regulate differentiation, proliferation or metabolism¹⁶. The scaffold should be effective for the transport of nutrients, oxygen and waste³⁸. The seeding of cells on tissue engineering scaffolds is known as creating a tissue construct¹⁶. The scaffold should be biocompatible, nontoxic and have proper physical and mechanical strength³⁹.

Commonly used scaffolds are naturally available scaffolds like collagen, glycosaminoglycan, fibrin and emdogain or may be synthetically produced like poly lactic acid (PLA), poly glycolic acid (PGA), poly lactic-coglycolic acid (PLGA), synthetic hydrogels like polyethylene glycol (PEG) and those modified with cell surface adhesion peptides such arginine, glycine and aspartic acid⁴⁰. Scaffolds containing inorganic compounds such as hydroxyapatite and calcium phosphate are used to enhance bone conductivity⁴¹.

Growth factors: Growth factors are extra cellular secreted proteins that bind to cell receptors and modulate cellular activity by regulating the rate of proliferation, inducing differentiation into another cell type or by stimulating cells to synthesize mineralizable matrices⁴². There are 4 common families of growth factors that appear to regulate the process of odontogenesis like fibroblast growth factor, hedgehog, wntless (WNT) and transforming growth factor¹⁶. Demineralisation of dental tissues can cause release of growth factors following the application of cavity etching agents, restorative materials and even caries⁴³. Once released, the growth factors may play important roles in signaling many of the events tertiary dentinogenesis a response to pulp dentin repair⁴⁴.

Clinical implications: Regenerative endodontics is gaining more implications in the present day clinical setup. Some common modes of using regenerative endodontics in clinics are:

Root canal revascularisation via blood clotting:

Many case reports have suggested the revascularisation of necrotic root canals by disinfection followed by establishment of bleeding in to the canal system by means of over instrumentation^{10, 45, 46}. The common advantages of such type of revascularisations are, firstly, it is technically simple and can be done using available instruments and intra canal medicaments without expensive biotechnology. Secondly, the regeneration of root canal system by using the patient's own blood cells avoids the possibility of immune rejection and transmission of pathogens from the replacement of pulp with a engineered tissue construct¹.

Post natal stem cell therapy: The most easier method to administer stem cells of adequate regenerative potential into the disinfected root canal system is by injecting postnatal stem cells derived from multiple tissues like skin, buccal mucosa, fat and bone⁴⁷ after the apex is opened. A major obstacle in the research field is the identification of postnatal stem cells capable of differentiating into diverse cell population found in the adult pulp¹. The advantage of this method is firstly, autogenous cells are easy to harvest and deliver by syringe and the cells have the ability to regenerate pulp tissue, secondly, this method is already being used in procedures like bone marrow transplantation and a recent review has described its potential in endodontic⁴⁸. The main disadvantage of this method is that the cells have comparatively low survival rates and they may even migrate to different position in the body⁴⁹.

Pulp implantation: The majority of in vitro cell cultures grow as a single monolayer attached to the base of culture flasks, but some stem cells do not survive unless they are grown on top of a layer of feeder cells⁵⁰. In theory, to take two dimensional cell cultures and make them three dimensional, the pulp cells can be grown on biodegradable membrane filters. The advantage of this system it is relatively easy to grow cells on the filters in the laboratory. The potential problem associated with the implantation of sheets of cultured pulp tissue is that specialized procedures may be required to ensure that the cells properly adhere to the root canal wall¹.

Injectable scaffold delivery: Hydrogels are injectable scaffolds that can be delivered by syringes^{51, 52}. These hydrogels are non-invasive and easy to deliver and may promote pulp regeneration by providing substrate for cell proliferation into an organised tissue structure⁵³. Earlier, the problems with hydrogels were that there was only limited control over tissue formation and development, but recent advancements in formulation have drastically improved their ability to support cell survival⁵⁴.

Regenerative procedures in permanent immature traumatized teeth: A review of regenerative procedure in immature traumatized teeth, states that for proper revascularisation to occur, the following parameters must be fulfilled, they are, the tooth must be non vital and not suitable for apexification and apexogenesis procedures, the tooth must be permanent and very immature with open apex, antibiotic paste can be used as an additional disinfectant to sodium hypochlorite, an anaesthetic without vasoconstrictor must be used when attempting to induce revascularisation into the canal, a thin liner of MTA or calcium hydroxide can be placed over the blood clot and an endodontic sealer which is not bio compatible for regeneration should not be used⁵⁵.

CONCLUSION: Even though the healing potential and defence mechanisms of the pulp tissue have been long recognized, the intensity and the nature of infection are still determining factors for the outcome of pulp recovery. The discovery and understanding of dental pulp stem cells have provided us a better insight 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 especially endodontics. Endodontists are at the fore front in this cutting edge technology by continuous improvement of knowledge in the fields of pulp biology and tissue engineering. 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.

The authors of this article hereby acknowledge and declare that there is no conflict of interests.

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