# TISSUE ENGINEERING IN ENDODONTICS: A REVIEW

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**Abstract:**

Tissue engineering is the science of design and manufacture of new tissues to replace impaired or damaged ones. The key ingredients for tissue engineering are stem cells, growth factors that regulate their differentiation, and a scaffold of extracellular matrix that constitutes the microenvironment for their growth. This article provides an extensive review of literature on the concept of tissue engineering and its application in endodontics.

**Keywords**: Tissue engineering; dental pulp stem cells; scaffolds; regenerative endodontics.

## Introduction

Although current root canal treatment modalities offer high levels of success for many conditions, an ideal form of therapy might consist of regenerative approaches in which diseased or necrotic pulp tissues are removed and replaced with healthy pulp tissues to revitalize the teeth. The creation and delivery of new tissues to replace diseased, missing, or traumatized pulp is referred to as regenerative endodontics. This approach provides an innovative and novel range of biologically-based clinical treatments for endodontic disease.[1]

Langer & Vacanti defined tissue engineering as "An inter disciplinary field that applies the principles of engineering & life sciences towards the development of biological substitute that restore ,maintain or improve tissue function''.[2]

This article reviews current status of the field of tissue engineering and its applications in dental science, specifically endodontics.

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## Key Elements for Tissue Engineering

Stem cells

A stem cell is commonly defined as a cell that has the ability to continuously divide and produce progeny cells that differentiate (develop) into various other types of cells or tissues.[1]

**Classification of Stem Cells:**[3]

I. On the basis of **origin.**

a. Embryonic stem cells.

b. Somatic/ Adult/ Post-natal/ Mesenchymal stem cells.

II. On the basis of **Source.**

a. Autologous: Obtained from same individual to whom they will be implanted.

b. Allogenic: Obtained from the donor of same species.

c. Xenogenic: Obtained from the donor of another species.

d. Syngenic/ Isogenic: Obtained from genetically identical organisms; twins, clones or highly inbred research animals.

III. On the basis of **Potency** (Range of differentiation).

a. Totipotent: can differentiate into all embryonic and extra embryonic cell types.

b. Pluripotent: can differentiate into all types of cells except cells of the embryonic membrane.

c. Multipotent: can differentiate into more than one mature cell.
d. Unipotent: Can differentiate into only one type of cells.

Mesenchymal stem cells (MSCs) have been identified in many tissues and are capable of differentiating into many lineages of cells when grown in defined conditions including osteogenic, chondrogenic, adipogenic, myogenic, and neurogenic lineages.

At least five different types of postnatal mesenchymal stem cells have been reported to differentiate into **odontoblast-like cells**, including.

- Dental pulp stem cells (DPSC)[4],
- Stem cells of human exfoliated deciduous teeth (SHED)[5],
- Stem cells of the apical papilla (SCAP)[6],
- Periodontal ligament stem cells (PDLSCs).[7]Among them, all except SHED are from permanent teeth.

**Dental pulp stem cells**

The dental pulp is a connective tissue endowed with the responsibility of providing nutrition and sensory innervations to the tooth. Various experiments have shown that these cells have the characteristics of stem/progenitor cells and can proliferate and differentiate into dentin forming odontoblasts. The dental pulp has been identified as a source of mesenchymal stem cell, which by definition are adult multipotent stem cells that are capable of differentiating into mesenchymal and non-mesenchymal tissue such as fat, bone, cartilage and neural cells.[4]

**SHED**

SHED were isolated for the first time in 2003 by Miura et al. who confirmed that they were able to differentiate into a variety of cell types to a greater extent than DPSCs. The use of SHED for tissue engineering might be more advantageous than that of stem cells from adult human teeth; they were reported to have a higher proliferation rate than stem cells from permanent teeth, and can also be retrieved from a tissue that is disposable and readily accessible. Thus, they are ideally suited for young patients at the mixed dentition stage who have suffered pulp necrosis in immature permanent teeth as a consequence of trauma.[5]

**SCAP**

A new unique population of mesenchymal stem cells (MSCs) residing in the apical papilla of permanent immature teeth, known as stem cells from the apical papilla (SCAP), were recently discovered by Sonoyama et al. who reported that these cells express various mesenchymal stem cell markers. SCAP are capable of forming odontoblast-like cells, producing dentin *in vivo*, and are likely to be the cell source of primary odontoblasts for formation of root dentin.[6]

**Periodontal ligament stem cells (PDLSCs)**

Stem cell population within the PDL was isolated and characterized by Seo et al. in 2004. Under defined culture conditions, PDLSCs differentiated into cementoblast-like cells, adipocytes, and collagen-forming cells. When transplanted into immunocompromised rodents, PDLSCs showed the capacity to generate a cementum/PDL-like structure and contributed to periodontal tissue repair.[7]

**Stem Cell Markers**[4. 5, 7].

*DPSCs:* STRO-1, CD 146, STRO-4, Osteocalcin, Oct-4, Nanog, SSEA-3, SSEA-4, Nestin, TRA 1-60, TRA 1-81.
*SHED:* STR0-1, CD 146. *SCAP:* DSP, BSP, ALP, CD 105. *PDLSCS:* CD 146, CD 105, CD 166, STRO-1, MUC- 18.

*DFPCS:* Notch-1, STRO-1, Nestin.

**Techniques for Stem Cells Identification[3]**

(a) Fluorescent antibody cell sorting (FACS)
(b) Immunomagnetic bead selection.
(c) Immunohistoch emical staining.
(d) Physiological and histological criteria, including phenotype (appearance), chemotaxis, proliferation, differentiation, and mineralizing activity.

**Morphogens and growth factors**

Growth factors are proteins that bind to receptors on the cell and induce cellular proliferation or differentiations. Many growth factors are quite versatile, stimulating cellular division in numerous cell types, while others are more cell specific. Bone morphogenic proteins (BMPs) are important growth factors required in tooth development and regeneration. Recombinant BMP-2,-4,-7 induce formation ofreparative dentin *in vivo* (Nakashima, 1994).[8] Primarily, four eminent families of growth factors appear to regualate the process of odontogenesis: Fibroblast growth factor, Hedgehog, Wingless( WNT) and Transforming growth factor. Dentin contains many proteins capable of stimulating tissue responses. Demineralization of the dental tissues can lead to the release of growth factors following the application of cavity etching agents, restorative materials, and even caries. Indeed, it is likely that much of the therapeutic effect of calcium hydroxide may be because of its extraction of growth factors from the dentin matrix. Once released, these growth factors may play key roles in signalling many of the events of tertiary dentinogenesis, a response of pulp-dentin repair. Extracts of dentin promote growth, because many growth factors are embedded into the dentin matrix during dentinogenesis. Interestingly, ethylenediaminetetraacetic acid (EDTA) very effectively releases growth factors from human dentin.[3]

**Scaffolds**

A scaffold can be implanted alone or in combination with stem cells and growth factors to provide a physicochemical and biological three-dimensional micro-environment or tissue construct for cell growth and differentiation.[1]

**Ideal requirements of a scaffold.[1]**

(a) Should be porous to allow placement of cells and growth factors.
(b) Should allow effective transport of nutrients, oxygen, and waste.
(c) Should be biodegradable, leaving no toxic byproducts.
(d) Should be replaced by regenerative tissue while retaining the shape and form of the final tissue structure.
(e) Should be biocompatible.
(f) Should have adequate physical and mechanical strength.

**Types of scaffold[3]**

a) Biological/natural scaffolds

These consist of natural polymers such as collagen and glycosaminoglycan, which offer good biocompatibility and bioactivity. Collagen is the major component of the extracellular matrix and provides great tensile strength to tissues.

b) Artificial scaffolds

These are synthetic polymers with controlled physicochemical features such as degradation rate, microstructure, and mechanical strength, for example:

- Polylactic acid (PLA), polyglycolic acid (PGA).
- polyethylene glycol (PEG)-based polymers.
- Arginine, glycine, and aspartic acid (RGD) to improve cell adhesion.

- Scaffolds containing inorganic compounds such as hydroxyapatite (HA), tricalcium phosphate (TCP) and calcium polyphosphate (CPP), which are used to enhance bone conductivity.
- Micro-cavity-filled scaffolds to enhance cell adhesion.

**Potential technologies for regenerative endodontics:[8]**

Following are the areas of research that might have application in the development of regenerative endodontic techniques:

1. Root canal revascularization via blood clotting
2. Postnatal stem cell therapy
3. Pulp implantation
4. Scaffold implantation
5. Injectable scaffold delivery
6. Three – Dimensional cell printing
7. Gene therapy

**Conclusion:**

The complete restoration of physiologic, structural & mechanical integrity of native pulp – dentin complex is ultimate goal of endodontic treatment. Till date, several approaches have been proposed to achieve this goal. For a new approach to gain acceptance, it should either produce better results or atleast equivalent results in lesser time and at a lower cost. Consequently, the road to tissue engineering is not smooth. The ethical concerns regarding use of embryonic stem cells, challenges in identification of stem cells and slower rate of human tooth embryogenesis are the barriers to be overcome for successful clinical application of concepts of tissue engineering. Tissue engineering using the triad of dental pulp progenitor/stem cells, morphogens, and scaffolds may provide an innovative and novel biologically-based approach for dental disease.

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