

# TOOTH REGENERATION - A REVIEW

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## Abstract

**Introduction:** Dental problems caused by caries, PDL disease, and injury to the tooth compromise oral health issues resulting in loss of tooth thereby affecting the quality of human life. There are several artificial therapies introduced into dentistry to compensate for the loss of tooth structure and avulsed tooth structures ie) inorganic fillings, RCT, RPD, FPD, CD, and even implants. They tend to fail at times. The current advances in dentistry include regenerative therapy, stem cell biotechnology, and tissue engineering for 3D scaffolds. In this review, we focus on the recent findings and technologies relevant to whole teeth regenerative therapy.

**Materials and methods:** The articles and journals pertaining to this topic were searched over Pubmed, Google Scholar, Semantic Scholar, MeSH core, Elsevier, and Medline. Articles related to tooth regeneration, stem cell-based regeneration, and scaffolds were included. Wherein articles irrelevant to these topics are excluded. The data was collected from 2000 to 2020.

**Discussion:** Regenerative therapies for the whole tooth regeneration is a novel therapeutic concept. Dental stem cells and activating cytokines have a candidate approach for tooth regeneration and potential to differentiate tooth regeneration in vitro or in vivo and forms a functional tooth. 3D tissue engineering for the bioengineered scaffolds regenerates organogenesis. They have several biomedical applications and have high bioactivity. A bioengineered tooth was also able to perform the same functions as a physiological tooth. The stem cells play an efficient role in the formation of tooth structures too.

**Conclusion:** Though tooth embryogenesis takes a longer duration, it is highly effective and promotes mental well being. There is also a huge potential for 3D printing of tissue engineering. Tooth regenerative therapy is actually a future regenerative technology.

**Keywords:** whole tooth regeneration, stem cells, 3D scaffold bioengineering

## Introduction

The tooth is a very complex structure which has a self-limiting and healing capacity(1). It is an ectodermal organ and is composed of both hard and soft tissues-enamel, dentin, cementum, pulp, and periodontium(2). Tooth loss is commonly seen due to oral diseases like PDL disease, caries, traumatic injuries, etc.(3) and pathological causes which lead to physical and mental suffering that lower an individual's quality of life (4). There are several artificial therapies that compensate for the loss of the tooth structure and avulsed tooth structures(5) ie) RCT, FPD, RPD, CD, inorganic restorations and fillings, implants, etc(6)(7)(8)(9).

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They provide and compensate for the loss but it is not said to be effective all the time(10,11). They tend to fail over a period of time. Further technological developments have been introduced to biologically repair and regenerate the tooth which is damaged(12). They are proven to be a novel therapeutic method for future dentistry(13).

One among them is the stem cell-based tissue engineering(14). They are isolated from the somatic stem cells in human dental tissues and children's embryonic cells. Their common lineage is that they are derived from the neural crest cells. The mesenchymal stem cells have several properties like marker genes. They also have cell-activating cytokines that differentiate tooth tissues in vitro and in vivo. Stem cells have the property and capacity to regenerate missing tissues or structures. They are undifferentiated.

The other therapeutic technology is the bioengineered 3D scaffolds(15). This tissue engineering is an emerging field of medicine that requires the combination of stem cells, biodegradable materials, and signaling molecules. The contribution of scaffolds is indispensable as they serve as carriers to facilitate the delivery of stem cells or growth factors at the receptor site. Scaffolds regenerate organogenesis and have several biomedical applications. They exhibit high bioactivity and have specific porosity.

A lot of focus has been made only in caries management(16)(17)(18)(19)(20)(19,21). There is only limited research focusing on tooth regeneration which is the future of modern dentistry. In this review, we mainly focus on the recent findings and technologies under tooth regenerative therapy.

## **MATERIALS AND METHODS:**

The articles and journals pertaining to this topic were searched over Pubmed, Google Scholar, Semantic Scholar, MeSH core, Elsevier, and Medline. Articles related to tooth regeneration, stem cell-based regeneration, and scaffolds were included. Wherein articles irrelevant to these topics are excluded. The data was collected from 2000 to 2020.

## **DISCUSSION:**

### **Regrowing a tooth:**

A tooth is a complex organ consisting of soft connective tissue and mineralized hard tissues(1). Enamel is the highest mineralized tissue and is characterized by the absence of the cells. It is the first hardest barrier against the environment. The ameloblasts during enamel formation undergo programmed cell death during maturation. Thus once damaged enamel is prone to caries, trauma, etc. Artificial therapies like restoration provide only short term relief. Further developments in dentistry include tooth regenerative therapies with a whole tooth replacement which is one of the most emerging techniques in the world. Replacing and repairing enhances tissue or organ functions(22).

### **Stem cell-based tooth regeneration:**

Stem cells are undifferentiated cells, capable of renewing themselves with the capacity to produce different cell types to regenerate missing tissues or structures(23)(24). Their microenvironment, composed of heterologous cell types, extracellular matrix, and soluble factors, enables them to maintain their stemness(25). Because of their unique properties, stem cells have the potential to be important in tissue engineering strategies for the regeneration of diseased, damaged, and missing tissues and even organs. In general, stem cells can be divided into three main types: ESCs that are derived from embryos; adult stem cells that are derived from adult tissue; and iPS cells that are generated artificially by reprogramming adult somatic cells so that they behave like ESCs. In this section, we outline recent results obtained using ESCs and adult stem cells for tooth regeneration. But the common lineage between both is that they are derived from the neural crest cells. The generic mesenchymal stem cells have properties like marker genes(26). They possess activating cytokines to differentiate into tooth tissues in both in vitro and in vivo conditions(14)(27).

### **Embryonic stem cells:**

ESCs are pluripotent stem cells derived from the undifferentiated inner cell mass of the blastocyst. They continue to grow indefinitely in an undifferentiated diploid state and cultured in optimal conditions in the presence of a feeder layer and leukemia inhibitory factor. They can be differentiated into derivatives of all three primary germ layers: ectoderm, endoderm, and mesoderm. Because of the pluripotency of ESCs, it has a wide future clinical application(28)(29).In dentistry, ESCs have been used for oral tooth regeneration, including mucosa, alveolar bone, and periodontal tissue regeneration.ESCs expressed the unique set of genes for odontogenic mesenchymal cells, such as Lhx7, Msx1, and Pax9, suggesting that ESCs can respond to inductive signals from the embryonic dental epithelium. Although these approaches have the potential to be useful for tooth regeneration and for understanding basic tooth development, it will be necessary to address several major issues before they can be implemented in clinical practice when transplanted like the ethical issues regarding the use of embryos and allogeneic immune rejection.

### **Adult stem cells:**

Adult stem cells have been identified in many tissues and organs and have been shown to undergo self-renewal, to differentiate for the maintenance of normal tissue, and to repair injured tissues(30).

### **Dental pulp stem cells:**

When there is severe tooth damage that penetrates both enamel and dentin, the pulp produces a natural repair process and produces odontoblast. This proves there is a high possibility that tooth pulp has stem cells. The DPSCs (Dental pulp stem cells) are isolated from the human pulp(31)(32). They were first isolated from the 3rd molars and exhibit high proliferation and produce densely calcified nodules(33). They have the ability to regenerate neural tissues and dental pulp(34). They also differentiate into other mesenchymal cell derivatives in vitro. They have also demonstrated de novo regeneration of pulp in the emptied root canal. Clinical trials were carried in mice where DPSC and SCAP were seeded into D-L, lactide scaffold, and inserted into canal space. It is then transplanted subcutaneously to mice. The analysis after 3-4 months showed a pulp-like tissue with well-established vascularisation, Continuous layer of mineralized tissue was also seen on the walls of the canal(35). It is proposed that dental pulp stem cells (DPSCs) can develop Induced Pluripotent Stem Cells (iPSCs) which can be used for therapies of various diseases(36).

### **Stem cells from human exfoliated deciduous teeth:**

MSC-like cells have also been isolated from the dental pulp of human deciduous teeth [stem cells from human exfoliated deciduous teeth (SHEDs)].SHEDs have the ability to differentiate in vitro to neuron-like cells, odontoblasts, osteoblasts, and adipocytes show higher proliferation rates and increased numbers of population doublings compared with DPSCs and can form spherical aggregations. When these cells are transplanted mixed with HA/TCP in vivo, they can form dentin and bone but not dentin–pulp complexes. A comparison of the gene expression profiles of DPSCs and SHEDs demonstrated that 4386 genes were differentially expressed by two-fold or more(37).In addition to genes, FGF, transforming growth factor (TGF)- $\beta$ , and collagen I and III showed a higher level of gene expression in SHEDs than in DPSCs(38). SHEDs could be the ideal source of stem cells for repairing damaged teeth or for the induction of bone formation.

### **Periodontal stem cells:**

PDL is a fibrous connective tissue containing specialized cells(39). They were recognized to contain a population of progenitor cells identified as periodontal ligament stem cells(40). They are capable of differentiating along mesenchymal cell lineages. It maintains PDL cell numbers.

### **Stem cells from the apical papilla:**

Stem cells from the apical papilla (SCAPs) are found in the papilla tissue in the apical part of the roots of developing teeth.SCAPs are found in the third molars and teeth with open apices. These cells have the potential to differentiate into osteoblasts, odontoblasts, and adipocytes and show higher rates of proliferation in vitro

compared with DPSCs(41). Transplantation of SCAPs and periodontal ligament stem cells (PDLSCs) into tooth sockets of minipigs allowed the formation of dentin and periodontal ligament(42).

### **Dental follicle stem cells:**

DFSCs have also been isolated from the follicles of developing third molars(43,44). They can differentiate into osteoblasts, adipocytes, and nerve-like cells in vitro and form cementum and periodontal ligament in vivo and form cementum and periodontal ligament in vivo(43)(45).

Future therapeutic approaches for the restoration of damaged dentin, pulp, cementum, and periodontal ligaments may make use of autologous stem cells such as DPSCs, SHEDs, SCAPs, and DFSCs that have been stored after removal from the patient.

### **ERMs and HERS:**

The epithelial rests of Malassez (ERMs) are quiescent epithelial remnants of Hertwig's root sheath (HERS) that remain in the adult tooth and play a role in cementum repair and regeneration(46). A recent study demonstrated that ERMs contains a unique population of stem cells that are capable of undergoing epithelial-mesenchymal transition and differentiate into diverse lineages indicative of mesodermal and ectodermal origin, including bone, fat, and cartilage as well as neuron-like cells. In addition, ERMs can be induced to form enamel-like tissues after transplantation into an athymic rat omentum with primary dental pulp cells, suggesting that the stem cells in ERMs may be able to regenerate enamel(47).

### **Whole tooth regeneration:**

Regenerating a whole tooth is the main objective of regenerative medicine(48). It increases the life expectancy in patients(49). It replaces the current state of the art replacement therapy namely dental implant. The clinical approach includes somatic stem cell usage. The formation of tooth germ is combined with inductive embryonic epithelial oral cells(15). The postnatal pulp cells are not suitable for tooth engineering. The induced pluripotent stem cells embryonic stem cells are the alternatives of tooth germ(49),(50). PLSC's induce the production of iPSCs(48,51). The decellularized tooth buds differentiate iPSCs to form tooth germ cells and promote tooth regeneration therapies.

### **3D printing technology:**

Tissue engineering is an emerging field of medicine that is based on combining stem cells, growth factors, and scaffolds for regenerating lost tissues(15). The contribution of scaffolds is incredible as it serves as a carrier for the delivery of stem cells or growth factors at the local receptor site. Scaffold biomaterials can be natural or synthetic, rigid or non-rigid and degradable or non-degradable. Scaffolds are highly bioactive and have specific porosity(52). It has both soft and hard tissue components(53). They promote bone, PDL, and cementum formation. A synthetic scaffold is most accepted and it is pre-designed(54). They act as a role guiding and assisting ECM(55). The clinical experiments include using dental epithelial and pulpal mesenchymal tissues which are seeded in the mixture of heterogeneous single cells into a tooth-shaped biodegradable polymer scaffold. These cell scaffolds were implanted into the host's body to receive sufficient oxygen and nutrients. After 25-30 weeks, the implanted scaffolds resembled like the crowns of natural teeth. It takes longer duration and the correct arrangement as of a natural tooth(56).

### **Future scope:**

The stem cell-based regeneration provides a good quality of repair and has high efficiency. Bioengineering regulates tissue engineering scaffolds and cytokines morphogenesis(15). They have high biocompatibility and mechanical properties.

## CONCLUSION:

A bioengineered tooth is also found to perform the same functions as a physiological tooth ie) mastication. It provides aesthetics and promotes confidence and mental well being. There is a huge potential in 3D printing because of its advantages like flexibility and internal porous structure(57).In the field of stem cell tooth regeneration, it provides an attractive alternative to traditional and current practices for the replacement of missing teeth, such as implants and classic procedures based on synthetic materials. Because of rapidly increasing research efforts and progress, it is anticipated that clinically satisfactory functional tooth regeneration will be available in the near future(58). The future establishment of this technique may considerably change therapeutic approaches to dental syndromes and diseases. However, there are some challenges before regeneration ie)Tooth embryogenesis takes longer duration and is highly-priced. There are more ethical and legal concerns like the morphology of the tooth might differ. We also need to further develop efficient protocols to induce stem cells to form cell types in vitro that are relevant to the tissues and organs targeted for regeneration. To succeed in these challenges, further basic studies to elucidate the regulatory mechanisms of stem cells and tooth development are needed.

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## CONFLICT OF INTEREST:

No potential conflict of interest relevant to this article was reported.

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