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Tooth regeneration by stem cells -an innovative approach

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ABSTRACT

With the advancing times, we are on the verge of a paradigm shift, evolving from offering traditional home care to considering biological solutions to various diseases. With the extraordinary advances taking place in the field of medical science, we are now focused on finding "biological solutions to biological problems."Regenerating the whole tooth is no more a dream. The credit of bio-engineering the tooth goes to stem cells. Stem cells have revolutionized the entire health care delivery. So, the time is certainly ripe for us to familiarize ourselves with stem cells. The aim of this review is to outline stem cells and its application in dentistry.

INTRODUCTION

Tissue engineering aims to stimulate the body either to regenerate tissue on its own or to grow tissue outside the body which can then be implanted in place of lost tissue [1]. A commonly applied definition of tissue engineering, as stated by Langer and Vacanti, is "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ" [2]. Tissue engineering has also been defined as "understanding the principles of tissue growth, and applying this to produce functional replacement tissue for clinical use" [3].

With the advent of tissue engineering, parents taking the decision to bank their child's teeth might be the best gift they could ever give to their child. This is a kind of insurance to child's health as it helps in treating so many diseases like blood related disorders such as leukemia, Alzheimer's and Parkinson's disease, corneal reconstruction, liver cirrhosis, diabetes, bone fractures, osteoarthritis and many more.

The regenerative potential of adult stem cells obtained from various sources including dental tissues has been of great interest for the clinicians. Mainly, research is directed towards achieving:

- Regeneration of damaged coronal dentin and pulp
- Regeneration of resorbed root, cervical or apical dentin, and repair perforations
- Periodontal regeneration
- Repair and replacement of bone in craniofacial defects
- Whole tooth regeneration [1].

To regenerate tooth and tooth-related tissues, the prerequisites are :

- Stem cells

-Signaling molecules, and

-Scaffold material

Stem Cells

Stem cells are defined as cells that have clonogenic and self renewing capabilities and differentiate into multiple cell lineages [4].

Characteristics:

1. Totipotency: generate all types of cells including germ cells (ESCs).
2. Pluripotency: generate all types of cells except cells of the embryonic membrane.
3. Multipotency: differentiate into more than one mature cell (MSC).

Unipotency (committed progenitors): generate one specific cell type [1].

In the field of tooth engineering, mesenchymal stem cells (MSCs) have been explored.e.g. stem cells from human exfoliated deciduous teeth (SHEDs) [5], adult dental pulp stem cells (DPSCs) [6], stem cells from the apical part of the papilla (SCAPs) [7], stem cells from the dental follicle (DFSCs), periodontal ligament stem cells (PDLSCs), bone marrow derived mesenchymal stem cells (BMSCs) and epithelium-originated dental stem cells [8].

Dental pulp may contain the progenitors that are responsible for dentin repair was enlightened by capability of the human dentin-pulp complex to regenerate.The intriguing possibility of using dental pulp stem cells for tissue engineering came into light with the discovery of stem cell in deciduous teeth [9]. The advantages of SHEDs (stem cells from human exfoliated deciduous teeth) are: easy availability in the young patient, higher proliferation rate compared with stem cells from permanent teeth, easy to be expanded *in vitro*, high plasticity since they can differentiate into neurons, adipocytes, osteoblasts and odontoblasts [5]. SHED are especially suitable for patients with mix dentition [10].Adult dental pulp stem cells (DPSCs) in human dental pulp were first identified by Gronthos in 2000. He found DPSCs could regenerate a dentin-pulp-like complex, which is composed of mineralized matrix with tubules lined with odontoblasts, and fibrous tissue containing blood vessels in an arrangement similar to the dentin-pulp complex found in normal human teeth [11].The dental follicle is an important mesenchymal tissue surrounding the developing tooth germ. During tooth root formation, periodontal components, such as cementum, periodontal ligament (PDL), and alveolar bone, are created by dental follicle progenitors [12]. Stem cells from dental follicle (DFSCs) have been isolated from follicle of human third molars [13]. DFSCs were found to be able to differentiate into osteoblasts/ cementoblasts, adipocytes, and neurons [14-16].

The periodontal ligament is a specialized connective tissue which is derived from dental follicle. Recent studies have shown that mesenchymal stem cells obtained from periodontal ligament (PDLSCs) are multipotent cells, capable of developing different types of tissues such as bone and tooth associated- tissues. PDLSCs are considered an easy and efficient autologous source of stem cells for bone tissue engineering in regenerative dentistry as they can differentiate into cells that can colonize and grow on biocompatible scaffold [17].

Signaling Molecules

All cellular functions are coordinated by growth factors and morphogenic factors are proteins that bind to specific membrane receptors and trigger a series of signaling pathways. These molecules play a critical role during development, guiding processes that determine the fate of stem cells and regulate the generation of all tissues and organs in the developing embryo [18].Studies from the early 1990s have shown that BMPs(e.g., BMP-2, BMP-4, BMP-7) trigger signaling events that induce the generation of dentin in animal models [19-20]. However, the ability to induce the formation of dentin is not limited to BMPs. Dentin matrix protein (DMP)-1 nucleates apatite crystals and to induce dentin formation [21-22]. Moreover, bone sialoprotein (BSP) has also been shown to stimulate the differentiation of pulp cells into cells that are capable of secreting mineralizable matrices in pulp exposure sites [23-24]. Notably, all these morphogenic factors can be found in dentin matrices and are presumptive inducers of DPSC differentiation into odontoblast-like cells. Studies have proved that dentin-derived BMP-2, but not BMP-7, is necessary for the differentiation of stem cells into odontoblasts [25].

Scaffolds for Dental Pulp Stem Cells:

Mammalian cells require interactions with their microenvironment to survive, proliferate, and function. In tissue physiology, these three-dimensional (3-D) environments are largely composed of extracellular matrix proteins. In tissue engineering, these 3-D structures are initially provided to the cells through the use of biodegradable and biocompatible scaffolds [26]. Scaffolds are considered a critical component of tissue engineering as they provide an environment that allows for the adhesion of cells and their proliferation, migration, and differentiation until these cells and the host cells begin to secrete and shape their own microenvironment [27-28].Several scaffolds have been tried which include both natural and synthetic materials. Natural materials like collagen, alginate, agarose [29], chitosan, and glycoseaminoglycans (GAGs) [30-31] have been

Table 1. Comparison between embryonic and adult stem cells

	EMBRYONIC STEM CELLS	ADULT STEM CELLS
Attributes	• totipotent • easy to identify, isolate, maintain, and grow in the laboratory • source: blastocysts from IVF clinics	• multipotent • stem cells may be genetically matched to patient • types: hemopoetic and mesenchymal
Limitations	• risk of teratomas (tumors) from implanting undifferentiated stem cells	• not found in all tissues • difficult to identify, isolate, maintain, and grow in the laboratory
Ethical Concerns	• destruction of human blastocysts • donation of blastocysts requires informed consent	• no major ethical concerns have been raised

Table 2. Types of dental stem cells

Properties	DPSCs	SCAPs	SHEDs
Location	Permanent tooth pulp	Apical papilla of developing root	Tooth pulp of exfoliated deciduous tooth
Proliferation rate	Moderate	High	High
Multi-potentiality	Odontoblast, osteoblast, chondrocyte, myocyte, neurocyte, adipocyte, corneal epithelial cell, melanoma cell	Odontoblast, osteoblast, neurocyte, adipocyte	Odontoblast, osteoblast, chondrocyte, myocyte, neurocyte, adipocyte
Potential contributions to systematic diseases	Bone regeneration, central nervous degeneration, liver fibosis, myocardial infarction, corneal reconstruction	Bone regeneration	Bone regeneration
Potential contributions to bio-tooth	Dentin, pulp	Dentin, pulp, root	Dentin, pulp

tried. Scaffolds made of synthetic polymers allow for the manipulation of their physicochemical properties such as degradation rate, pore size, and mechanical resistance. The most common synthetic polymers in tissue engineering are likely poly-(l-lactic acid) (PLLA), poly-(glycolic acid) (PGA), and the copolymer poly-(lactic-co-glycolic acid) (PLGA). These scaffolds are biodegradable and biocompatible and allow for cell growth and differentiation, making them highly suitable for tissue engineering applications [32-34].

Notably, it is important that, the scaffold should be designed to provide structural integrity for the cells used in tissue engineering until the newly formed tissue becomes auto sustainable. They should be highly porous to facilitate cell seeding and diffusion of nutrients and should eventually breakdown leaving the newly formed tissue. During this entire process, they should maintain important characteristics of stem cells and yet allow for appropriate differentiation of their progeny [35-36].

Scaffold designs and delivery:

In tooth engineering, it is preferable to have rigid tissue-engineered scaffold structures as they provide an excellent physical support to the cells [37]. However, in the root canal system it is preferable to have a soft three-dimensional scaffold matrix such as polymer hydrogel as it can be easily delivered by injecting into the root canal systems [38-39]. Hydrogels are in the early stage of research and yet to be proven *in vivo*. More researches are going on in making them photopolymerizable to form rigid structures once they are implanted into any tissue site [40].

Indian Scenario

Dental stem cell banking now gives parents the option to store their child's stem cells from the milk tooth. Baby tooth stem cells was discovered by Dr. Songtao Shi,a paediatric dentist in the year 2003. By using the deciduous teeth of his six year old daughter, he was able to isolate, grow and preserve these stem cells'regenerative ability, and he named them as SHED (Stem cells from Human Exfoliated Deciduous teeth). The main advantage of dental stem cells is its possibility of a larger collection. If one tooth is rejected, the next tooth can be considered for banking [41]. Other advantages are its affordability, easy extraction, awareness among parents to safe guard their child's health and emphasis in modern medical research towards therapies from regenerative tissues [42].The first dental stem cell bank in India is named as "Store your Cells". It was started by dentists at Dhruv Polyclinic, Mumbai. Stemade Biotech, another dental stem cell bank, after its success in Bangalore, is now expanding its reach to at atleast 10 more cities such as Pune, Hyderabad, Surat, Chennai in the next 8-10 months [41].

CONCLUSION

Stem cells derived from all sources hold immense medical promises. The processes of storage and expansion of stem cells in laboratory settings, as well as the transplantation of these cells back to the patient, carries certain risks, which are unavoidable. There is a risk of creating teratomas, and unwanted contamination of these cells with pathogens during these procedures. Though, recent developments in this field have set a stage for successful tooth engineering. The 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. “Hope is a prerequisite for any successful scientific innovation.” The day is not very far when, stem cells will be considered as an indispensable part of dentistry.

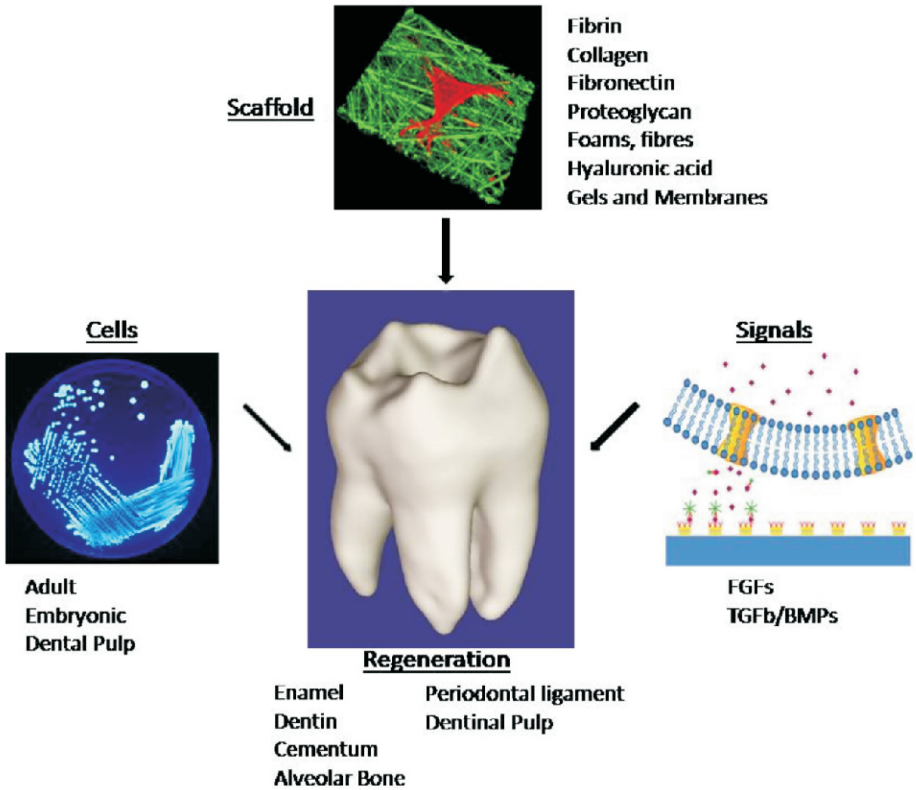

Figure 1: Prerequisites for regeneration of tooth

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