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Regenerative Therapy in Dentistry: A Review

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Abstract

Despite millions of people suffering from dental caries and periodontitis to date, we don't have effective treatments that guarantee complete restoration of the impacted tissues. The current procedures mostly help in delaying the disease progress, and hence, bringing alternative approaches for whole tooth replacement has become indispensable. Considering the scenario, regenerative medicine seems to be the novel approach, given its innovative therapeutic techniques that aid in the repair and replacement of damaged, aged, diseased, or congenitally defective tissues and organs. While we are yet to overcome various challenges, including effective ways to control the size, color, and shape of the tooth and come up with the perfect implantation sites for the jaw to enable in vitro tooth development, the ongoing research and their favorable results reveal that whole-tooth regeneration and bioengineered functional tooth are not a distant dream.

Keywords*: Regeneration, Regenerative therapy, Scaffolds, Tissue engineering.*

Introduction

Globally, millions of people have been suffering from dental caries and periodontitis since time unknown but unfortunately, we don't have effective treatments or cure for complete restoration of the impacted tissues [1]. The general treatment modalities followed include those that delay the progress of the disease or aim for restoration [1]. One of the commonest and most popular indications of early ageing is tooth loss. Edentulism (lack of teeth) not only minimizes oral and social functionality but also affects the quality of life of the individual being a dominant health concern among the general public [2]. Edentulism has been corrected using various methods, the most important of which is complete denture therapy. But there are a couple of disadvantages associated with the therapy including burning mouth syndrome, denture-induced stomatitis, ulcers, change in identifying taste, and soft tissue hyperplasia [3]. Some of the treatment procedures pursed for defective tooth include implantation, use of prosthetics, and transplantation of the tooth but sadly, such processes bring with them loads of downsides including unnecessary load imposition on the neighbouring tissues and improper alignment of the teeth due to growth of the jaw bones [4]. All these make it indispensable to bring in alternative approaches for tooth replacement. Considering the scenario, the pros and cons, and practical application, regenerative medicine seems to be the novel approach for regeneration, given its innovative therapeutic techniques that aid in the repair and replacement of the damaged, aged, diseased, or congenitally defective tissues and organs [5, 6]. Regenerative therapy or regenerative dentistry is making use of our understanding of the cell and molecular biology to devise effective dental

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solutions that focus primarily on repair, restoration, rejuvenation, and regeneration of dental tissues [7]. In simple words, regenerative therapy is nothing but the utilization of biomaterials, cells, and molecules to rectify those parts of the human body which don't perform their designated functions due to some injury or disease [8].

Methodology

The most recognized electronic databases were searched for the data pertaining to the papers that have reported on Regenerative therapy. PubMed, Google Scholar, Web of Science, Scopus were the keydata bases. Search was carried out for articles published in peer reviewed journals.

Electronic databases searched articles using many Medical Subheadings (MeSH keywords). Regenerative therapy, Tissue engineering, Applications, Regeneration, Scaffolds. These key terms were combined in the advanced search using the Boolean operators AND/OR. English language filters were also used. After a thorough search, articles were categorized for their applications.

Applications

When there are umpteen traditional drugs capable of relieving pain and offering treatment, what makes regenerative therapy an exclusive treatment strategy compared to such drugs? The reason is crystal-clear: while drug-based treatments focus predominantly on treating the symptoms of the problem, regenerative therapies delve into the root cause of the problem such as correcting a faulty gene or assist in replacing flawed/lost organs [8]. The medical field by itself relies on a precise perception of the tissue's biology or the disease's processes. With the advent of cutting-edge technologies such as single cell analysis, genomics, gene editing, and stem cells, medicine is all set to enter a new era [7]. Contrarily, there are very few dental treatment procedures that combine tissue regeneration for therapy. In fact, we don't see the application of regenerative treatment procedures in most areas of mainstream medicine. The earliest form of cell therapy was blood transfusion which is now very common. It then progressed to bone marrow transplantation making it super beneficial for cancer patients to make healthy blood cells. Even a person's own cells are used in case of burn-related injuries to grow skin cells in a short period of time [8].

Stem cells are unspecialized cells that can self-renew and differentiate into various types of specialized cells [9]. It's no secret that the teeth and its surrounding tissues are overloaded with stem cells—the growing roots, tooth pulp, alveolar bone, and the periodontal ligament are some of the popular sources of general stem cells [7]. Such dental stem cells present in different dental tissues including the human exfoliated deciduous teeth, periodontal ligament stem cells, dental pulp stem cells, dental follicle precursor cells, and periodontal ligament stem cells are an asset in various ways [10]:

1. Easily accessible and least invasive.
2. A positive synergy with the scaffolds.
3. Multi-differentiation ability.

A sophisticated study centred around the design and use of biological-based material as scaffolds for in-vivo regeneration of periodontal tissues [11, 12]. The various sources of these stem cells include the bone marrow (BM), periodontal ligament (PDL), and more combining them with different bone grafting techniques such as xenografts, autografts, allographs, and alloplastic materials [12]. The applications of stem cells-based techniques have covered a fairly extensive area and are now at a stage where the missing teeth can be replaced with bioengineered teeth, a huge advancement in the field of dentistry [13].

Tooth Tissue Engineering

Before the advent of tooth engineering, partial tooth tissue restoration was possible using calcium hydroxide in pulp-capping procedures [14] But now, tissue engineering makes use of progenitor cell populations (stem cells) that are grown in biocompatible materials under suitable environmental conditions—these become fully functional tissue replacements.

Periodontal Tissue Regeneration

The ultimate goal of periodontal therapy is tissue regeneration, and this covers the complete formation of the periodontium including the periodontal ligament (PDL), cementum, gingiva, and the alveolar bone [15]. During the early decades, the procedures followed to regenerate periodontal tissues weren't much successful as they resulted in tooth root resorption and ankylosis [16]. But now, tissue regeneration is the default go-to solution for periodontal tissue regeneration, but this has its limited success percentage. Bone morphogenetic proteins, platelet-derived growth factor, recombinant amelogenin protein, and emdogain are the most commonly used growth factors for regeneration of the PDL. It's even been possible to construct a root-periodontal tissue complex by making use of pelleted hydroxyapatite or tricalcium phosphate scaffold that contain DSCs of the apical papilla (SCAP), that are coated with PDL stem cells (PDLSC)-seeded gel foam and implanted and nurtured in a minipig tooth socket [17].

Regeneration of the Entire Tooth

With more than two decades of intensive research, there is in-depth understanding regarding the molecular processes that determine tooth development. Such research and knowledge are indispensable for the formation of a 100% biological replacement tooth.

There are two possible ways in which it's possible to regenerate the entire tooth—the first is making use of the in vitro growth of immature tooth structures from dental progenitor cells and doing their in vivo implantation [15].

It's possible to produce tooth crowns using fully intact or partially dissected tooth germs under suitable environments such as in vivo grafting on chick chorioaltantoic membrane, sub-cutaneous transplants, or ocular or subrenal grafts, or in vitro organ culture [18-20]. Both, nutrients, and oxygen are supplied by every implant site to allow the tooth germ differentiation into a mature tooth. It's possible to enable small tooth primordia in various ways before they are fitted into the required jaw position. By far, in vitro teeth growth has been successful with the use of organotypic culture [15].

Even under the absence of any positional memory, it's possible to bring about dental epithelial cell histogenesis with the help of cap stage dental mesenchyme. Such nurturing subsequently leads to the formation of functional odontoblasts and ameloblasts as well as cusp and pulp formation. Tooth roots and PDL tissues are also possible with prolonged culture time [21]. Making use of dental cell-seeded tooth scaffold constructs, dental mesenchymal cell-seeded] polyglycolic acid mesh, and dental cell-seeded collagen sponge gels, we've reached a stage wherein the tooth size and shape can be controlled in a better way bringing about better organized tooth structure. Another study showed the possibility of forming the cementum and PDL, the complex dentin-pulp complex, with the help of gelatin-chondroitin-hyaluronan-tri-copolymer [22]. Despite all these, we are still at a juncture where in vitro whole-tooth regeneration needs more improvements and progress.

Using Scaffolds in Regenerative Therapy

Among the many techniques used to regenerate a tooth, synthetic scaffold-based tooth regeneration using pre-designed scaffolds thrives as one of the most successful ways [23]. Scaffolds are nothing but structures that provide us with a 3-dimensional substrate helping with proliferation and cell adhesion, similar to the extracellular matrix (ECM) [24].

Scaffolds can be natural or synthetic—synthetic scaffolds are monomers that polymerize for providing the scaffold's architecture. Some commonly used polymers for scaffold construction include polylactic glycolic acid (PLGA), poly-lactic acid (PLLA), and hydrogels [24-26]. Fibrin and collagen scaffolds are some of the best natural polymers well-known for providing cell compatibility. The tissue type formed depends on the stiffness of the scaffold, the space between the formed pores, and the topography [27]. Scaffold sterilization, exact fabrication of an economic but exact model, and constructing the perfect scaffold with the correct scaffolding material to replicate the dental structure morphology that mimics the natural ECM is a daunting task [23]. Blood plasmatic concentrates possess high concentrations of growth factors thereby overloading them with bioactive molecules, hence making the concentrates one of the best natural scaffold choices. In recent times, blood plasma concentrates have been predominantly used in the field of dentistry for various purposes including root canal revascularization, guided bone regeneration, root coatings, regeneration of intraosseous periodontal defects, and adjuvants in osseointegration of implants [28].

Periodontal Tissue Regeneration

Any tooth support segments lost as a consequence of periodontitis or gingival trauma can be restored using periodontal regenerative therapy whose main focus is formation of a new cementum at the tooth's root [28]. Until now, periodontal regenerative therapies have been mostly done in vitro and experimented on animal models. But there have been some clinical trials conducted one of which is a randomized control trial done by Pradeep et al. Results showed that the use of blood concentrates showed better treatment results of regenerated bone defects. Also, the use of platelet-rich fibre (PRF) in combination with metformin (1%) exhibited better bone repair compared to traditional techniques and PRF [29, 30].

Tooth Regeneration with Cell Homing

An alternative to cell transplantation in tooth regeneration is the use of cell homing as there are multiple advantages attached with this process—excluding the need for cell isolation, ex-vivo cell manipulation, exclusion of the need for regulatory approvals, and decreased commercial cost comparatively [13]. One of the first studies done by Kim et al., reported the formation of tooth-like tissues using cell homing. With in-depth research, the future seems bright for using cell homing in clinical practice [31, 32].

Limitations

One of the greatest challenges for regenerative therapy is to move past the non-biological methodologies and rely upon tissue-based therapies through better research, clinical translation, and spread of knowledge to spotlight the novel side of dental treatment [7]. Also, inability of adult stem cells to enable cell differentiation post-transplantation is one of the huge limitations linked with tissue-based engineering [7]. Reproducing the whole human teeth with the functional enamel intact is an arduous task firstly because enamel formation leads to apoptosis of the dental epithelial cells wiping away their presence in the erupted tooth. Secondly, expanding epithelial cells is a strenuous process compared to mesenchymal cells. Hence, alternative sources of the dental epithelial cell are the dire need of the hour. Another concern is also whether the jaw will be supportive of the bioengineered tooth germs grown in it. The dental follicle is indispensable for the eruption of the tooth and absence of the follicle guarantees zero tooth eruption. So, even when a silicon tooth is fit in the place of a developing tooth, the process is successful only when the follicle is retained. Hence, when designing the tooth organs, the inclusion of the dental follicle remains mandatory [15].

Till date, there have only been a few successful reports of bioengineered root tooth formation with functional PDL tissues as whole-root regeneration is a complete success only when the tooth crown and the root structures are fully functional. [33] Another main concern is the immune response to such bioengineered human tooth which remains an unchartered territory until now. In short, there are various clinical, biological, and technical challenges associated with tooth regeneration. While dentists are at a stage where they can manage periodontal diseases using stem cells and scaffolds, coming up with whole-tooth regeneration using regenerative therapy is still challenging and needs further research [9].

Conclusions

Complete loss of a tooth causes both mental and physical agony deteriorating the quality of life of the patient. Dentistry has reached the stage of total tooth regeneration only after achieving success in regenerating various tooth elements [13]. Tooth formation happens through different hard and soft tissues. The hard tissues include the enamel, cementum, and dentin encompassing the dental pulp as the single source of vascularized tissue in the teeth [34, 35]. For dental use, the concept of tissue engineering and stem cell therapy are classic ways for regeneration of the bones and soft tissues whose research and studies show hope for future application. Using tissue engineering, it would be possible for repairing and re-growing teeth even after extreme tooth damage and tooth loss [10]. Bone and periodontal regeneration have attained clinical success and root canal re-vascularization techniques and different regenerative procedures make use of tissue engineering clearly indicating monumental leaps in the field of dentistry [28].

While we are yet to overcome various challenges including effective ways to control the size, color, and shape of the tooth, ensure fully functional eruption of the tooth, and come up with the perfect implantation sites for the jaw to enable in vitro tooth development, with the current progress and achievements, whole-tooth regeneration and bioengineered functional tooth are not a distant dream [28]. But before all this, to include regenerative therapy as a part of mainstream medical care, various issues including immunity, ethics, clinical constraints, technologies, cost, risks, and benefits possible for the patient and the society as a whole must be considered and researched through long-term follow-up clinical trials.

Conflict of Interest

There is no conflict of interest.

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