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A New Way to Battle Tooth Loss - Whole Tooth Regeneration

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In recent years, the field of dentistry has marked its presence by taking major leaps in research and further bringing it into practice. The study on stem cells is the most valuable on-going research in regenerative dentistry. The hope is that it will become possible to regenerate bone and dental tissues including the periodontal ligament, dental pulp and enamel, and that the creation of new teeth may also become feasible. In view of this possibility of achieving restoration with regenerative medicine, it can be considered that a new era of dentistry is beginning. Thus the aim of this review is to analyse the current status of orofacial stem cells, challenges faced and the research involved in regenerative therapy.

Key Words*: Stem Cells, Regeneration, Dentistry.*

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I. Introduction

In recent years, the field of dentistry has marked its presence by taking major leaps in research and further bringing it into practice. The study on stem cells is the most valuable on-going research in regenerative dentistry. The hope is that it will become possible to regenerate bone and dental tissues including the periodontal ligament, dental pulp and enamel, and that the creation of new teeth may also become feasible. In view of this possibility of achieving restoration with regenerative medicine, it can be considered that a new era of dentistry is beginning.

Replacement of a lost tooth is an extremely essential step in order to restore its function and aesthetics. The current state of the art in tooth replacement is a dental implant. Although dental implants have gained increasing popularity over the years, they do have certain impediments associated with them, such as the cost and the surgical procedure involved. Regeneration of tooth has paved its way into the field of dental tissue engineering, thereby overcoming the shortcomings of dental implants. Additionally, this approach also has advantages like alleviation of the patients suffering, minimizing the likelihood of infection and recovery time.Tooth regeneration poses a challenge of regenerating multiple hard and soft tissues in harmony. This method of replacement of lost tooth can be carried out by using stem cells, which are immature, undifferentiated cells that have the potential capability of self-renewal and conversion into a variety of functional cell types. Researchers have focused on repair of one or two of the tooth tissues, as well as re-growing an intact tooth for complete substitution. This paper analyses the current status of orofacial stem cells, challenges faced and the research involved in regenerative therapy. [(1)]

II. Dental Stem Cells Suitable For Tooth Regeneration

The process of tooth regeneration mimics the natural tooth development process using stem cells. [(2)]These include cells from the pulp of both, primary and permanent teeth, from the periodontal ligament, from the root tips of developing teeth, and from the dental follicle that surrounds the unerupted tooth. All these cells are derived from the neural crest cells and have generic mesenchymal stem cell-like properties – expression of marker genes and differentiation into mesenchymal cells lineages.

The first adult stem cells to be isolated from dental tissues were the dental pulp stem cells, which was done in 2000. [(2)]They are multipotent mesenchymal type of stem cells found inside the dental pulp. They exhibit high rate of proliferation and showed their ability to form dentin-pulp like complexes. They were also capable of differentiating into other mesenchymal cell derivatives like odontoblasts, adipocytes, chondrocytes and osteoblasts. [(3)]

Stem cells from human exfoliated deciduous teeth (SHED) are immature cells isolated from pulp of human exfoliated deciduous teeth. These candevelop into specialized cell types like those that induce bone formation, generate dentin and develop into other non-dental mesenchymal cell derivatives. SHED can specifically induce the formation of a bone like matrix which is lamellar in structure by recruiting host cells.[(4)]

Periodontal ligament stem cells (PDLSC) isolated from extracted teeth demonstrated the ability to regenerate periodontal tissues like cementum, periodontal ligament and alveolar bone. [4] These cells, in vivo and in vitro, are capableof differentiating into cementoblast-like cells, adipocytes, and connective tissue rich in collagen 1. [5]Studies show their activity largely depends on the harvest location [4]

Root apical papilla stem cells (SCAP) are stem cells located at the tip of growing tooth roots and have the capacity to differentiate into odontoblasts and adipocytes.Studies conducted by Wang and colleagues have shown that this population of cells, along with PDLSC and a scaffold of hydroxyapatite/Tricalcium phosphate, can create a biological root. [6]Hence, it can be concluded that developing dental tissues provide better source for immature stem cells than developed dental tissues.

Dental follicle stem cellsoriginate from neural crest and are present in the developing tooth germ. Studies have shown that they have the ability to differentiate into osteoblasts, adipocytes, andnerve-like cells in vitro, and to form cementum and periodontal ligament in vivo. [2]

III. Induced Pluripotent Stem Cells

In 2006, Takahashi and Yamanaka discovered that stem cells could be generated from adult somatic cells through a process of cellular reprogramming. Stem cells regenerated by this technology were termed induced pluripotent stem cells (iPSC). These cells show pleuripotency similar to embryonic stem cells. They can produce cells from all 3 germ layers in vitro. [2] These cells have a number of advantages over the other dental derived stem cell populations, such as, its ability to be generated from readily accessible tissue sources, and its high rate of proliferation, making it possible to obtain large number of stem cells required for regenerative therapies.

These cells also have certain drawbacks which include their genomic instability and their inclination to form tumours in vivo (Ben-David Benvenisty 2011; Gore at al. 2011)[7,19,20]

IV. Scaffolds In Tissue Engineering

Scaffolds play an important role in providing a suitable environment on which the stem cells can be seeded and growth factors or molecular signals can be provided in order to facilitate regeneration[8].They help in guiding and assisting of the cells to grow and differentiate in the process of tissue engineering. [1] They are used in tissue engineering in order to influence cells in such a way as to increase their regenerative capabilities. These regenerative capabilities are largely dependant on the scaffold properties like topography, chemistry, porosity, material choice and biocompatibility.

The scaffold material used should fully or partially mimic the extracellular matrix of the tissue to be replaced with. [1]The surface topography of the scaffold used determines the stem cell adhesion, migration, differentiation, and proliferation. Good porosity of the scaffold material allows for cell migration and diffusion of substrates and nutrients to fuel stem cell activity. [9]The biocompatibility of the scaffold should be such that it causes minimal biological response, which may upset the regenerative process. The scaffold material should be degradable without releasing toxic products or causing any form of inflammatory response. The scaffold should be able to entrap molecules into themselves so that these molecules can then be released slowly over a period of time at the required site.

For tissue engineering of teeth the first materials to be used as scaffold were natural polymers such as collagen, protein ,chitosan , silk, alginate , hyaluronic acid and there derivatives. This was owing to their excellent biocompatibility, bioactivity, and tissue construct for self-growth and differentiation.

They are also made of synthetic polymers such as hydroxyapatite/tricalcium phosphate, polylactic acid, or polyglycolic acid.[9]Hydrogels are injectable scaffolds that can be delivered directly into the root canal space using a syringe. Blood clot and platelet rich plasma and platelet rich fibrin have been recently included as scaffold materials. [10]

V. Challenges In Regeneration Of Dental Hard Tissues And Soft Tissues

Enamel regeneration

Regeneration of enamel, the hardest tissue of the body, is dependent on ameloblasts which are lost once the tooth erupts into the oral cavity. This poses a challenge in order to develop sufficient number of enamel-forming cells in culture.[11]Hu et al have proven that bone-marrow derived cells can be developed into ameloblast lineages with a polarized appearance. [9, 21]Reports suggest that a new technique is being developed for culturing of cells that have the capacity to induce enamel formation.

Dentin regeneration

Dentin has the potential to regenerate in response to any injury or trauma. Dentin formation was observed when pulp stem cells were cultivated with hydroxyapatite or tricalcium phosphate scaffold. [12]

However, regenerated dentin through such approaches has shown to be deficient in highly organised dentinal tubules. Also, the newly structured dentin is found to be more fragile than the primary dentin. [9]

Pulp regeneration

Dental pulp regeneration is attempted so as to replace mutilated dentin-pulp complex. The restoration of pulp is much sought after because the current practice of replacing infected pulp with inorganic materials results in a devitalized tooth. [3]The simplest method of pulpal regeneration is by disinfecting the root canal space and injecting the postnatal stem cells into the root with open apex. Another method is by seeding the bioengineered pulp tissue onto a 3D scaffold matrix-like hydrogel and delivering this complex into the root canal system by a syringe.According to Zheng et al (2012), porcine deciduous pulp stem cells when transplanted with beta-tricalcium phosphate scaffold, could mediate dentin-pulp regeneration in swine. [12,22] However, recent studies have suggested that adding stem cells to an empty pulp cavity has a limited extent of regeneration since majority of the pulp cells are provided by the vasculature. Therefore, stem cell pulp regeneration should ensure adequate blood supply primarily. [3]

Periodontal regeneration

Replacement of a functional periodontium poses challenge since it needs to form new ligament and bone, and needs to ensure that the appropriate connections are made between these tissues, as well as between the bone and tooth root.[3]One of the most popular approaches for periodontal tissue regeneration is the use of growth and differentiation factors such as transforming growth factors-β, basic fibroblast growth factor, and platelet-derived growth factors. It has been reported by Nagatoma et al. that periodontal regeneration can be done by using PDL cells that have stem cell properties. In an in-vitro study conducted by Iwata et al, transplantable constructs of a canine was made using PGA scaffold and PDL cell sheets in combination with porous b-tricalcium phosphate. This complex induced regeneration of periodontal structures like cementum, alveolar bone, and periodontal fibres. [13]

VI. Whole Tooth Regeneration

Teeth have a three-dimensional multicellular structure composed of characteristic hard tissues like enamel, dentin, cementum and alveolar bone, as well as soft connective tissues, such as pulp and periodontal ligaments, which contain blood vessels and nerve fibers.NAKAO et-al (2007), Ikeda et al (2009) and Oshima et al (2011) conducted studies of fully functioning bioengineered tooth replacement which showed correct tooth structure, masticatory performance, responsiveness to mechanical stress and perceptive potential following transplantation into a tooth-loss region. Ikeda et al (2009) suggested that when these reconstituted tooth germ cells were transplanted into the extracted tooth sockets of a 5 week old mice, a complete tooth organ was formed which also erupted into the oral cavity.[14, 23] These studies show that the embryonic dental epithelial and mesenchymal cells have the potential to form a complete tooth organ even following its dissociation. It is always desirable to autologously transplant bioengineered tooth germ reconstructed using a patients' own stem cells, in order to prevent immunological rejection.[15] In 2015, Mitsuaki et al conducted a research which indicated that bioengineered tooth reconstruction from canine permanent tooth germs could develop the proper tooth structures after autologous transplantation into the jawbone. [15] To achieve precise replication of organogenesis, a novel three-dimensional cell manipulation method designated the organ germ method was developed which enabled the generation of a structurally correct and fully functional bioengineered tooth in vivo.[16]

VII. Process Of Regeneration Using Bioengineering Technique

Regenerative teeth developed using bioengineered technique must be capable of properly engrafting into the lost teeth region in an adult oral environment. It should also acquire full functionality including sufficient masticatory performances, Biochemical Corporation with good biocompatibility with periodontal tissues and efferent responsiveness to noxious stimulation in the maxillofacial region (Proffit et al., 2004).

3D cell manipulation

The first step is to develop a three-dimensional cell manipulation method using completely dissociated epithelial and mesenchymal cells in vitro. Compartmentalisation of the epithelial and mesenchymal cells is carried out at a high cell density in a type I collagen gel.[16]According to Honda et al (2007) and Yelick and Vacanti (2006), polyglycolic acid and poly-L-lactate-co glycolide copolymer, or a collagen sponge as a tooth shaped scaffold when seeded with epithelial and mesenchymal cells, could generate small tooth structures. Thus a bioengineered organ germ is generated from the immature stem cells. The tooth germ that is then created mimics the multicellular assembly underlying the epithelial-mesenchymal interactions which occur during natural tooth development. [17]

Functional tooth regeneration

The bioengineered tooth germ is then transplanted into the tooth loss region to develop into a functioning mature tooth.

Functional tooth replacement

Another method isto generate a bioengineered tooth unit from the bioengineered tooth germ which can be transplanted into the tooth loss socket. This bioengineered tooth unit includes a mature tooth, pdl and alveolar bone which will achieveengraftment into the socket throughphysiological bone integration of the recipient jaw.

The ultimate outcome may be affected by various factors like the patient's age, genetic variations, general health condition, and even sex of the patient. Ikeda et al (2009) have reported that a bioengineered tooth germ can develop to form the correct the tooth structure in the oral cavity and successfully erupt 37 days after its transplantation. It reached the occlusal plane and achieved occlusion with the opposing tooth from 49 days onwards. According to Oshima et al (2011), a bioengineered tooth unit transplanted at a position reaching the occlusal plane with the opposing first molar was successfully engrafted after 40 days. Normally, the time taken for tooth development and differentiation in humans is about 400 days, from the initiation of tooth development to eruption. In case of a bioengineered tooth, the structurally comparable enamel is formed within 3 weeks which indicates an adoption of accelerated developmental and differentiation programs in the human epithelial cells in response to the induction by the mouse embryonic dental mesenchyme. This entire process should consist of a unique combination of growth factors in different tissue layers at different stages of tooth development. [(17)]

The enamel and dentin hardness of the bioengineered tooth belonged to the normal range when analysed using Knoop hardness test (Ikada et al., 2009; Oshima et al., 2011). [(18)]

VIII. Conclusion

Researches on dental tissue regeneration using stem cells have been conducted over the last 15 years and are currently expanding at an unprecedented rate. However multiple challenges like isolation and cryopreservation of the dental progenitor cells still do exist. Moreover, the ultimate goal is to bring about regeneration of the entire tooth organ using clinically compatible cell types and approaches. To date, researches regarding the same are only confined to animal models. Clinical trials are on-going to validate the clinical feasibility of the tooth regenerative approach with all the research data available. Human trials on regrowing teeth are expected to start in 2019. [(18)]

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