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A FUNDAMENTAL INSIGHT INTO REGENERATIVE DENTISTRY: A REVIEW

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Abstract

The current rapid progression in stem cell and tissue engineering research has enhanced our knowledge about tissue regeneration and revealed the demand for the treatment of dental caries and tooth loss with biological sources. The terminal differentiation of the pulp-derived stem cells into odontoblast cells in case of need, enables the formation of dentin tissue during life and justifies the possibility of the regeneration in dentistry. The promising results of stem cell research on odontogenic differentiation give hope to generate a new concept in the field of dental treatment. The aim of this review is to outline the current approaches for tooth regeneration and define the basic terms in regenerative dentistry.

Introduction

The Need for Innovation in Dentistry

Dental caries and tooth loss are the common health problems which adversely affect aesthetic, psychological status (quality of life), chewing and speech functions of the individuals in public (1-3). Despite the high cost outlays for the treatment of tooth loss in dental practice, a precise biological and vital treatment option that is compatible with the surrounding tissue and successful in long-term, is not yet available (2-4). In fact, the replacement of the tissue or organ, namely regeneration, is the best treatment option to recover the function after damage (5). To this end, cell combinations, biochemical factors and engineering materials are used to fulfill the biological functions in regenerative medicine (6). However, the damaged dental tissues are restorated with variety of synthetic materials and mechanical methods such as conventional dentures and implants have been used to replace missing teeth instead of regenerative therapy in current dental practice. The mentioned ‘non-biological tooth’ applications have many disadvantages such as sense of discomfort, poor biocompatibility and damage to the surrounding tissue. In addition, the application of these conventional procedures are not convenient fully for the biological tooth structure (3). Thus, the studies aiming to find new strategies to compensate the insufficiencies of the current dental treatments have gained popularity in dental research. In recent years, it has been suggested that new concepts in the field of dental treatment could be generated as a result of developments in stem cell research and tissue engineering techniques.

Regenerative Dentistry

Stem cells, which have the potential to improve the damaged area by transformation into variety of cell types and tissues, are the basic elements of regenerative medicine (7, 8). The "biological tooth" which can be achieved through stem cells and tissue engineering techniques appears as an alternative to heal damaged dental tissues (9). Another goal of this new technique is to prevent tooth loss and provide a third dentition in human life (10). 'Bioengineered tooth' (11, 12) and 'biological tooth' (13) are the terms used to describe teeth created by biotechnology/engineering concepts and bioengineering products. Besides, the term of ‘regenerative dentistry’ is used to define the field of dentistry intending the biological tooth repair and regeneration (14, 15). Briefly, ‘tooth

regeneration' which is a process describing the re-establishment of original structure of the damaged dental tissues with biological resources (2), can be incorporated into regenerative medicine.

The development of dental lamina that originates from ectoderm, eventually forms tooth germ. Tooth germ and dental papilla are the other two structures in tooth embriyogenesis which are differentiated from neural crest cells. Therefore, this ectomesenchymal origin of dental tissues makes tooth organ specific (4, 16). There are various types of stem cells and progenitor cells during tooth development stage that can be isolated from dental tissues even after embriyogenesis. The mentioned cells are dental epithelial stem cells, dental pulp stem cells (DPSC), stem cells from human exfoliated deciduous teeth (SHED), stem cells derived from apical papilla (SCAP), periodontal ligament stem cells (PDLSC) and dental follicle progenitor cells (15). Although these cells have multiple differentiation potential such as odontogenic, osteogenic, adipogenic and neorogenic differentiation, the odontogenic differentiation tendency is noticeably higher (17-19). Hence, the needed potential for the dental tissue regeneration is present in its origin.

In tooth embriyogenesis, which starts with epithelial and mesenchymal interaction, ameloblast cells form enamel, odontoblast cells form dentin and fibroblast cells form pulp tissue. Among these tissues, only the formation of dentin as tertiary dentin continues during life due to caries, mechanical and chemical factors (9, 20). This histogenesis makes dentin tissue specific. The terminal differentiation of the pulp-derived stem cells into odontoblast cells in required cases enables the formation of dentin and indicates the possibility of the regeneration in dentistry (4, 18, 21, 22). Therefore, DPSC seem to be the most promising cell group for regenerative approach.

DPSC resides in a specific perivascular microenvironment in dental pulp tissue even after tooth eruption. These cells have high proliferation rate, clogenic capacity, plasticity and multipotent properties (22). DPSC have many advantages as described as follows:

- Easy isolation,
- High cell activity,
- Long life-time,
- High differentiation capacity,
- Possible usage for tissue reconstruction and
- Cryopreservation in a safe manner (23).

The main sources of DPSC are human impacted teeth, teeth extracted for orthodontic and periodontal reasons or trauma. Human impacted third molars (wisdom teeth) are usually indicated for extraction. Moreover, they have been reported as a rich pulp tissue source because of their latest eruption in the development of dentition (24, 25). These mentioned properties make these teeth the most appropriate sources for DPSC.

The intentions of the studies in the field of regenerative dentistry are the regeneration of various dental tissues, treatment of congenital abnormalities and craniofacial regeneration. DPSC studies, which will offer tissue regeneration into dental practice as a treatment option by combining the basic science of biology and dentistry, aim to create dental tissues (pulp, dentin, cementum, periodontal ligament, etc.) and the regeneration of the damaged tissues afterwards. The first attempt is to form a structure similar to the original dental tissue (11, 26-31) and the target in the long-term is the development of an entirely vital dental organ (11, 27-30).

Two main approaches are available for the reconstruction of dental tissues. The first one is concerned with the repair of damage (32) and the latter, based on embryology, stem cell biology and tissue engineering (33). The mentioned bioengineering approach for dental tissue regeneration and tooth formation is divided into two concepts as to whether or not based on tissue scaffold (1, 11, 14, 27, 34, 35). The scaffold-based concept comprises of isolation, proliferation and differentiation of the cells *in vitro* and the implantation of the cells via scaffold *in vivo*. The main elements of this approach are:

- The cells which have potential to form the target tissue,
- Growth and differentiation factors directing the function of the cells,
- The scaffolds determining the three-dimensional structure of the tissue to be formed (4).

Expectations and recommendations

Recently in endodontic and restorative treatment protocols, the pulp tissue is removed and the lost structures are elaborately restorated with various filling materials. The potential of DPSC to form dentin-pulp complex, suggests the regeneration to be a possible alternative to the limited endodontic and restorative procedures (36, 37). Similarly, the potential to form the periodontal ligament-cementum complex could ensure the regeneration of the tissues around the tooth (38). However, the difficulty about the enamel regeneration seems to be one of the main

problems that interferes with the formation of a tooth, entirely (39). Although the possibility of the use of stem cells for tooth regeneration increases day by day, there are still many questions that need to be considered (2). Depending on this fact, we think that the following issues should be investigated to address the questions:

- The combined use of different stem cells
- The development of biosignals systems and optimal scaffold structures
- Determination of tissue formation time
- Creation of the functionality of the tissue.

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