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Review

Innovative approaches to regenerate teeth by tissue engineering

Marina M. Steindorff, Helena Lehl, Andreas Winkel, Meike Stiesch*

Department of Prosthetic Dentistry and Biomedical Materials Science, Hannover Medical School (MHH), 30625 Hannover, Germany

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ABSTRACT

In recent years, scientists in almost every medical sector moved the focus to tissue transplantation and stem cell-based therapies for organ and tissue regeneration. In dentistry, it is of great interest in this regard to restore natural teeth with the help of stem cell-based regeneration of soft tissues and hard tooth structures. Many studies have been published in which structures resembling teeth were constructed using stem cells. In most of these studies, carrier materials (scaffolds) were used, which were colonized with cells and then implanted into an animal. Apart from this, scaffold-free approaches based on cell aggregation have also been published. Although animal studies on tooth regeneration have been very promising, much more research is needed until this can be applied in human.

Contents

* *Corresponding author at*: Department of Prosthetic Dentistry and Biomedical Materials Science, Hannover Medical School (MHH), Carl-Neuberg-Strasse 1, 30625 Hannover, Germany. Tel.: +49 511 532 4931; fax: +49 511 532 4790.
E-mail address: steindorff.marina@mh-hannover.de (M.M. Steindorff).
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1. Introduction

The aim of dental prosthetics is to restore the function and aesthetics of the jaws, so that the patient regains a high quality of life after losing a tooth. The main causes for the loss of permanent teeth are caries and periodontitis – both infectious diseases which are difficult to prevent and sometimes difficult to treat. From 1997 to 2005 in Germany, 52.7% of adults aged 35–44 years suffered from periodontitis of intermediate severity and 20.5% from severe periodontitis. The caries index in 2005 in this age group was 14.5 (Source: Vierte Deutsche Mundgesundheitsstudie [Fourth German Study on Oral Health] – DMS IV, 2005).

Even though there has been continuous technological improvement in conventional tooth replacement, the patients still suffer some disadvantages in comparison to natural dentition. For example, to provide support for artificial teeth, it is often necessary to abrade neighbouring healthy teeth. This leads to the loss of dental hard tissue and in turn increased susceptibility. With insertion of implants this intended abrasion of natural teeth can be circumvented. However, after ossification, the inserted artificial material forms a tight bond with the bone and is rigidly anchored in the jaw bone, which is quite different physiologically from the natural attachment of the teeth in the bone socket. The function of the periodontal space and the cellular structures within range from conversion of compressive forces loading on teeth into tensile forces, to defence against infections by the immune cells present, and also reflexes which protect the tooth from injuries after an unexpected bite on hard materials. This natural border to the jawbone is missing with an implant, so that unphysiological compressive stress affects constant bone remodelling. Moreover, the course of inflammation seems to be more severe in peri-implantitis than in periodontitis,[1–3] which can even lead to the loss of implants. Henceforth, the vision of dental stem cell research is the usage of tissue engineering to generate not only a single natural tooth, but also the corresponding periodontic apparatus, leading in the future to long-term improvement in the function of dental prosthesis.

This article gives a short introduction of possible experimental approaches to the creation of a stem cell-based dental prosthesis, with an overview of potential stem cells for dental regeneration. The review then concentrates on selected *in vivo* studies and the animal models they employ, including articles listed in the literature database *Medline* or found by cross-references. Due to the extensity of the corresponding literature, a selection of relevant publications is presented.

2. Approaches to dental regeneration

2.1. *Approaches based on the original tissue engineering concept*

Tissue engineering approaches are based on three central components: living cells, a scaffold and a simulated biological environment. It is thought that the term ''tissue engineering'' as understood today, was first used in 1991 in an article entitled ''Functional organ replacement: the new technology of tissue engineering'' published in *Surgical Technology International*.[4,5] To simulate the physiological environment *in vitro*, particularly culture media and suitable growth factors are required, although pH, temperature, humidity and the supply of oxygen are also important parameters. For reasons of simplicity, dental tissue engineering is mainly carried out using a static culture system, especially in studies which address more general considerations. However, bioreactors might be used to study additional mechanical influences *in vitro* as well as biological and chemical stimuli. Diverse forces and stresses can be applied and gradients of nutrient and metabolite concentrations are avoided by continuous media flow. Especially some studies on periodontium formation have used bioreactors, as it is plausible that cells have to be mechanically stimulated to achieve strong and stable periodontium *in vitro*.[6,7] Despite continued methodical advances regarding *in vitro* tissue engineering, the *in vivo* incubation of an initial construct is still the current approach in dental engineering.

Most studies in the field of dental regenerative biology use scaffolds, which are cultured with previously isolated and cultivated cells (Fig. 1A). This colonized material is then precultured *in vitro*, usually for a few days, and finally implanted in an animal. By usage of a scaffold a matrix is provided to which seeded cells can adhere. Moreover, it makes it possible to specify the shape and size of the organ to be produced in advance and to prepare it in a form which meets the specific mechanic requirements at the replacement side. Thus, the necessary preconditions can be created for implanting the construct directly into the jaw and to design it to withstand the mechanical and physiological stresses present there. The objective of most recent work is that this carrier should not only be biocompatible and encourage the cells to adhere and proliferate, but that the property of a bioactive matrix should be attained.[8] Suitable materials may include *e.g.* calcium-containing scaffolds with osteoinductive or odontoinductive activity. Moreover, results with coupled growth and differentiation factors have been encouraging.

Several classes of materials have been used for dental tissue engineering. Depending on the intended use, each biomaterial exhibits specific advantages, but also limitations. Some of the most commonly used biomaterials are the completely absorbable synthetic materials polylactic-co-glycolic acid (PLGA), polylactic acid (PLA) and polyglycolic acid (PGA).[9–11] These scaffolds exhibit *e.g.* minimal foreign body reactions and bear functional groups to attract cells or to bind growth factors. Possible limitations are that acidic degradation products could be accumulated and that the material is dissimilar to the natural environment.[8] Hydroxyapatite/tricalcium phosphate (HA/TCP)-scaffolds are also often used in dental studies.[12–14] This bioceramic is very similar to natural hard tooth tissue and the degradation rate can be adjusted by modifying the manufacturing process. Disadvantages are that the material is brittle and that its mechanical strength decreases under humid conditions. Furthermore the suitability of PEGylated fibrin gel,[15] treated dentine matrix,[16] collagen and Matrigel[17] has also been tested with dental stem cells.