MEDICAL SCIENCES

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EVOLUTION OF REGENERATIVE DENTISTRY

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Abstract: This article explores the evolution of regenerative dentistry, highlighting significant advancements and emerging technologies that have transformed dental care. The study delves into the development and application of biomaterials, stem cell therapy, and tissue engineering in dental practices. It examines how these innovations have improved outcomes in tooth restoration, periodontal regeneration, and craniofacial reconstruction. By reviewing recent clinical trials and experimental studies, the article provides a comprehensive overview of the current state and future prospects of regenerative dentistry. The implications for clinical practice and potential challenges in integrating these advanced techniques are also discussed. Emphasizing the need for ongoing research and collaboration, the article underscores the importance of continued innovation in this rapidly evolving field.

Keywords: research, regeneration, infected or necrotic pulp, damaged pulp, new pulp, dental tissues, periodontal tissues, regeneration processes, blood vessels, blood clot, differentiation, proliferation, angiogenesis, mineralization, endothelial cells, biomaterials, stem cells, growth factors.

Regenerative dentistry began development in the mid-20th century as an

extension of regenerative medicine. In the 1960th Dr. Henrik E. Ostby hypothesized that the removal of infected or necrotic pulp creates conditions for the regeneration of new pulp. The study aimed to observe the reaction of periodontal tissue when the entire pulp is removed from the main canal, allowing the apical part to subsequently fill with blood. The primary objective was to determine the potential clinical significance in endodontics. Additionally, it was expected that such an experimental setup would reveal details of general interest regarding blood clot organization. With the blood clot connected to live tissue at a small, well-defined border, this setup would facilitate a histological study of the organizational processes. Finally, the investigation sought to test the effect of EDTAC on the periapical tissues [1, c. 150].

In 1981 research on the development of the vascular network in dog pulp showed that within three weeks. New blood vessels had filled the necrotic pulp, allowing it to function as a conduit. It was established that VEGF (vascular endothelial growth factor) plays a significant role in stimulating pulp angiogenesis. It’s elevated levels promote the formation of new blood vessels in damaged pulp. Several stages of vascularization in the pulp regeneration process were identified:

- the initial proliferation of endothelial cells,
- the formation of primitive vessels,
- their differentiation,
- and maturation.

Each of these stages is coordinated by different signaling molecules and cellular interactions [2, c. 103].

Dr. Paul Sharpe head of the Department of Craniofacial Biology at King's College London, found that dental pulp stem cells can differentiate into cells that form dentin and pulp. Baby teeth are a significant source of stem cells, which can be used for regenerating dental tissues. One of the most notable studies is an experiment on mice using small molecules (one such molecule being Tideglusib, a GSK-3 inhibitor) that stimulate dentin formation. Additionally, his team is working on developing new biomaterials — three-dimensional scaffolds that support stem cells and stimulate their differentiation into the desired cells [3, c. 1, 2].

Bone Morphogenetic Proteins (BMPs) and Transforming Growth Factor-Beta (TGF-β) are critical signaling molecules involved in the differentiation of stem cells into various cell types, including dentin-producing cells. These proteins play significant roles in cellular processes that are crucial for tissue engineering and regenerative medicine. BMPs, particularly BMP-2, BMP-4, and BMP-7, have been extensively studied for their roles in osteogenic differentiation [4, c. 234]. BMPs bind to specific receptors on the cell surface, initiating a cascade of signaling events that lead to the activation of Smad proteins. This pathway ultimately results in the transcription of genes necessary for osteogenic and odontogenic differentiation. TGF-β is essential for the regulation of stem cell differentiation and has been shown to influence the differentiation of mesenchymal stem cells into odontoblasts, the cells responsible for dentin formation. Similar to BMPs, TGF-β signaling involves the activation of Smad proteins, which regulate gene expression related to cellular differentiation [5, c. 577-579].

One prominent researcher in this field is Dr. Rik Derynck, known for his work on TGF-β signaling pathways [5, c. 577]. Dr. Vicki Rosen has also made substantial contributions, particularly in the area of BMP signaling and its application in bone and dental tissue engineering [6, c. 2,3].

Research conducted at universities in the USA and Europe has demonstrated that bone morphogenetic protein-7 (BMP-7) stimulates osteogenesis and dentin formation, thereby aiding in the regeneration of bone tissue. Specifically, BMP-7, when used in combination with biomaterials, has shown promising results in repairing bone tissue defects in the jaw. For instance, a study at the University of California, Los Angeles (UCLA) revealed that the application of BMP-7 significantly enhanced bone tissue regeneration in patients with jaw defects [7, c. 2]. Similarly, research conducted at the University of Zurich indicated that BMP-7 was effective in treating bone defects in experimental models [8, c. 3].

Current research in regenerative dentistry actively explores the use of growth factors to stimulate the regeneration of dental and periodontal tissues. Studies on FGF-2 (fibroblast growth factor-2) by Japanese research groups have

shown that this growth factor stimulates the proliferation of periodontal stem cells and their differentiation into fibroblasts and osteoblasts. The effect of the combined use of the FGF-2 and CO3Ap on the existing bone adjacent to the defect was examined. These findings suggest potential applications of FGF-2 in periodontal regeneration and tissue engineering [9, c. 5].

Research conducted at the University of Pennsylvania has demonstrated the benefits of platelet-derived growth factor (PDGF) in tissue regeneration. Specifically, PDGF promotes the proliferation and migration of mesenchymal stem cells, which are crucial for the regeneration of bone and soft tissues. These cells play a key role in the repair and regeneration process by differentiating into bone and other tissue types.

The use of PDGF in combination with collagen matrices provides a scaffold that supports cell attachment and growth. This combination has been found to be particularly effective in enhancing the healing of periodontal defects and in accelerating post-surgical tissue regeneration.

Moreover, ongoing studies are exploring the potential of combining PDGF with other growth factors and biomaterials to further improve regenerative outcomes. These advanced combinations aim to create more efficient and targeted therapies for complex dental and periodontal conditions, potentially reducing recovery times and improving the overall success rates of regenerative procedures. Additionally, research is being conducted to understand the molecular mechanisms underlying PDGF's effects on stem cells, which could lead to the development of new therapeutic strategies in regenerative dentistry and medicine [10, c. 5].

Researchers at the University of Michigan are pioneering gene therapy approaches for dental pulp regeneration. Leveraging viral vectors, they deliver genes encoding growth factors directly into dental pulp, aiming to enhance tissue regeneration processes. This innovative method targets key factors involved in angiogenesis and inflammation reduction, essential for promoting effective tissue repair. Successful implementation of gene therapy techniques in dental pulp regeneration could revolutionize current treatment modalities, offering minimally invasive and highly effective approaches for addressing dental tissue damage.

Moreover, insights gained from this research may extend beyond dentistry, contributing to advancements in regenerative medicine across various fields [11, c. 5].

Continued research at the University of Michigan aims to further elucidate the mechanisms underlying gene therapy-mediated tissue regeneration in dental pulp. Additionally, efforts are underway to optimize delivery methods and enhance the efficacy of gene-based interventions, paving the way for translation into clinical practice and ultimately benefiting patients worldwide [12, c. 7].

The advancement of regenerative dentistry has traversed various stages of research, starting from initial endeavors in pulp regeneration to contemporary achievements in cultivating fully functional teeth using stem cells. Dr. Ostby's work provided the groundwork for subsequent experiments in endodontics, albeit requiring further refinement. In 2007, Dr. Sharp's team accomplished the cultivation of a functional tooth from stem cells in a lab setting, validating the hypothesis regarding the potential of stem cells for complete dental structure restoration. Enhanced regeneration is facilitated through the synergistic utilization of stem cells, biomaterials, and growth factors, as evidenced by the investigations conducted by Simone Grandini and collaborators.

Modern regenerative dentistry not only centers on employing stem cells to rejuvenate all tooth tissues but also embraces a multidisciplinary approach. This approach integrates the use of bioactive materials and growth factors to stimulate innate regeneration processes and establish an optimal milieu for cellular proliferation. Cutting-edge methodologies such as three-dimensional printing and bioengineering are employed to fabricate precise structures and scaffolds conducive to supporting stem cell growth, facilitating tissue integration, and promoting bone regeneration in the alveolar ridge.

This comprehensive approach aims to augment the effectiveness and efficiency of dental tissue regeneration, moving closer to the objective of achieving fully functional and biologically integrated tooth replacement.

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