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Clinical Significance

- The main problems that dentists face range from partial tooth damage, involving mainly destruction of enamel, dental pulp and periodontium, to the complete loss of teeth.
- Dental treatments have been greatly benefited from recent technological advancements and innovative regenerative approaches using stem cells and biomaterials.
- Although these regenerative strategies are promising, they are not applicable yet in dental clinics.

Modern trends in dental medicine: An update for internists

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Running Head: Modern Trends in Dental Medicine

ABSTRACT

Traumatic injuries, genetic diseases and external harmful agents such as bacteria and acids often compromise tooth integrity. There is an unmet medical need to develop alternative, innovative dental treatments that complement traditional restorative and surgery techniques. Stem cells have transformed the medical field during the last years. The combination of stem cells with bioactive scaffolds and nanostructured materials turn out to be increasingly beneficial in regenerative dental medicine. Stem cell-based regenerative approaches for the formation of dental tissues will significantly improve treatments and will have a major impact in dental practice. To date there is no established and reliable stem cell-based treatment translated into the dental clinics, however, the advances and improved technological knowledge are promising for successful dental therapies in the near future. Here, we review some of the contemporary challenges in dental medicine and describe the benefits and future possibilities of certain novel approaches in the emerging field of regenerative dentistry.

INTRODUCTION - TOOTH SPECIFICITY

Teeth exert fundamental roles in physiological functions, such as mastication and speech, and are a key feature of facial aesthetics. Tooth functioning relies on its unique combination of hard and soft tissues. Enamel is the hardest tissue of the human body with exceptional physical characteristics to withstand masticatory forces and to protect dental tissues from chemical and bacterial assaults (Figure 1A).[1] Ameloblasts synthesize the organic components of enamel, where hydroxyapatite prisms are formed, but these cells are lost upon tooth eruption, making human teeth incapable of regenerating enamel. Dentin forms a less mineralized matrix tightly interconnected with the enamel and dental pulp, a richly vascularized and innervated soft connective tissue that occupies the central portion of teeth (Figure 1A). Dentin is synthesized by pulp-derived odontoblasts and is characterized by the presence of dentinal tubules that contain the cytoplasmic extensions of odontoblasts as well as sensory nerve endings, thus making dentin highly sensitive to external stimuli and permeable to bacteria upon enamel destruction. Upon tooth injury, a newly formed dentin- or bone-like matrix (i.e., tertiary dentin) protects pulp vitality, but more important damage often leads to pulp necrosis.[1] Teeth are anchored to the alveolar bone by their roots that consist of dentin and cementum. The roots are connected to the bone via the periodontal ligament, a connective tissue that provides stability to the teeth and absorbs mechanical stresses during mastication.[2]

Traumatic injuries, infections and genetic diseases, combined with age, often result in tooth loss. It is therefore necessary to develop innovative approaches for the repair/regeneration of damaged or missing dental and alveolar bone tissues.[3] However, the unique characteristics of enamel and dentin make tooth regeneration particularly challenging. Technological advancements ranging from digitalization to nanotechnology have become an inherent aspect of many medical fields, and the same applies to dentistry. These progresses aim to offer improved, faster, painless and more effective treatments when compared to methods traditionally used in dental clinics.

TECHNOLOGICAL INNOVATIONS IN CURRENT DENTAL TREATMENTS

The great improvements in computing-related technologies has helped in establishing new diagnostic tools, more precise therapeutic plans and alternative dental treatments.[4] High definition microscopes combined with novel imaging techniques such as digital radiography, computer aided design/computer aided manufacture (CAD/CAM) technology, and computer aided implant surgery contributed to the improvement of the daily dental practice.[5]

The success of dental treatments aiming to restore damaged or lost dental tissues relies on innovative biomaterials. Nanotechnology has remarkably improved their performance as well as the clinical outcome of dental treatments. Innovative 3D printing systems are used in prosthetic dentistry to manufacture customized products based on computer-designed digital tools.[6] Modern materials have also upgraded aesthetic dentistry, the field aiming to optimize the aesthetic appearance of dentition. Similarly, pain management has enormously benefited from the advent of these novel imaging and computing-based technologies.[7] The capacity of stem cells to repair damaged tissues has been also explored in dentistry. Stem cell-based regenerative approaches are closely linked to advanced tissue engineering products and have created an important clinical shift toward the functional regeneration of dental tissues.

Stem cells are characterized by their potential to self-replicate and their capacity to differentiate into a vast diversity of cell populations.[3] Epithelial and mesenchymal stem cell populations are present in almost all adult human tissues and organs, including teeth. A variety of dental mesenchymal stem cells (DMSCs) have been isolated from both deciduous and permanent teeth, characterized, and tested for their potential applications in regenerative dentistry.[3, 8] Adult DMSCs localized in the dental pulp and periodontal tissues ensure human tooth homeostasis and regeneration, and therefore represent optimal clinical tools for the repair of damaged dental tissues. Actual efforts are oriented towards pulp and periodontal tissue repair, where these tissues can be regenerated by transplantation of stem cells alone or in combination with scaffolds (Figure 1B, C). Biodegradable scaffolds act as temporary niches for transplanted stem cells and can guide them towards a precise cell type (e.g., osteoblast, odontoblast, chondroblast) that will fulfill the needs of the dental treatment.[9] Transplanted stem cells can be tracked for long periods with modern imaging systems such as Magnetic Resonance Imaging (MRI) and Computed Tomography (CT), and provide precious information about their role in the repair of dental tissues.[2] This knowledge will allow evaluating the therapeutic efficacy of specific dental stem cell populations and consolidate their accuracy in dental treatments.

The regeneration of tooth enamel using epithelial cells is more challenging, since neither dental epithelial stem cells (DESCs) nor ameloblasts are present in the crown of adult functional teeth.[3] Finally, more exciting is the perspective to generate entire brand-new teeth by mixing DESCs and DMSCs. Although very challenging and ambitious, several attempts towards this direction have been pursued in animal models.[2]

Almost all dental disciplines can benefit from the recent advances of stem cell biology and material sciences. The present review covers current and future therapeutic approaches for managing the (1) injury of the tooth crown, including harm to enamel and dentin-pulp tissues, (2) damage of the periodontium, and (3) replacement of lost or missing teeth.

TOOTH CROWN RESTORATIVE TREATMENTS AND ACTUAL CHALLENGES

Enamel and dentin of the tooth crown are most often the first tissues to be affected following traumatic injuries or carious lesions. Prompt and efficient repair of enamel and dentin is fundamental to prevent bacterial propagation towards the vital dental soft tissues of the pulp and periodontium, as well as the alveolar bone. The most used approach for treating injured enamel and dentin is their substitution and tooth restoration by advanced composite materials. Traditional adhesive systems are unstable and fail over time, leading to marginal leakage and poor retention of the restoration in the tooth.[10] Innovative adhesive materials with improved enamel- and/or dentin-bonding performance increased the longevity of the restorations, thus preventing repeated dental treatments. The incorporation of nanostructures in dental composites enhanced their stability and aesthetic properties, as well as reduced the degradation of the resin-tooth bonded interface.[11] These new materials could also control the propagation of oral bacteria as well as the formation of dental plaque. Furthermore, hydroxyapatite particles are used in dentifrices to stimulate the re-mineralization process of hypersensitive teeth with deteriorated enamel.[12]

Tooth crowns using ceramic-based materials display superior aesthetic appearance and biocompatibility and therefore are privileged by dentists for the restoration of damaged teeth.[13] However, ceramic-based crowns are brittle and prone to cracks but recent technological advances permitted the development of higher aging resistant-ceramics such as zirconia that exhibit exceptional toughness and flexibility.[13]

The ideal alternative solution to overcome all problems related to the use of dental materials would be the *de novo* formation of natural enamel, one of the greatest challenges in dental medicine. The recent advances in stem cell-based technology generated great enthusiasm and hopes. Efforts to isolate DESCs from periodontal tissues of adult human teeth were successful and increased the expectations for enamel regeneration. Several studies using animal models have shown that these cells can form enamel after their transplantation *in vivo*.[14] However, DESCs are not abundant in human teeth and therefore could not be routinely used in clinics for restorative purposes. Therefore, it is necessary to identify other human epithelial stem cell populations of non-dental origin that would be able to generate enamel. Another problem linked to the formation of enamel by DESCs is that this process requires several years in humans, a time frame clearly incompatible with clinical needs.[15] Procedures allowing the considerably acceleration of this process would be beneficial to both dental practitioners and patients.

The preservation of the dental pulp vitality is of prime importance during the treatment of damaged teeth. However, severe tooth injuries often lead to pulp inflammation and necrosis, and therefore the endodontic therapy that consists of pulp tissue removal is imposed in order to prevent further bacterial progression and tissue damage. This is followed by disinfection of the dental root canals and the replacement of the pulp tissue with inorganic materials.[2] Devitalized teeth are more fragile than physiological intact teeth and are consequently predisposed to postoperative fractures.[2] To overcome this, new endodontic treatments intent to regenerate physiological pulp tissues using a combination of biomaterials, antibacterial and anti-inflammatory molecules, growth factors and stem cells.[16] Scaffolds containing human DMSCs have been used to achieve regeneration of the entire dental pulp tissue (Figure 2B). Human DMSCs transplanted into empty tooth root canals immediately after pulp removal were able to regenerate vascularized dental pulps and to form dentin.[8, 17] Dentin production is accelerated and enhanced by bone morphogenetic proteins (BMPs), which are growth factors commonly used in dental practice.[18] However, most of these approaches led to the formation of pulp fibrotic tissue that can undergo degeneration over time or be replaced with bone. This could be overcome with the transplantation of scaffolds composed by decellularized human dental pulps.[19] However, by the exception of hydroxyapatite-based injectable gels, most of these proposed materials have not received the approval from the Food and Drug Administration (FDA).[20] Recent regenerative endodontic procedures involve the formation of blood clots within the root canals. These clots act as natural scaffolds hosting DMSCs that will contribute to dental pulp repair.[2] While significant efforts with promising results have been produced so far, substantial improvements are still needed for proper pulp regeneration.[2, 16]

CURRENT THERAPIES AND CHALLENGES FOR PERIODONTAL REPAIR

Periodontal pathologies strongly affect tooth functionality and overall oral health. Severe periodontal inflammation leads to significant alterations in both the structure and quantity of the alveolar bone and periodontal ligament that could ultimately cause tooth loss.[21] Contemporary periodontal therapies include a wide range of surgical procedures along with the use of natural or synthetic bone grafts, barrier membranes and growth factors.[21, 22] Application of these products in clinics allowed the formation of novel osseous tissues with characteristics similar to those of pre-existent native bone.[22] Nonetheless, these approaches do not always ensure a predictable and desirable outcome of periodontal regeneration and often result in healing with epithelial lining rather than new periodontal tissue formation.[22]

A fundamental goal in dentistry is to recreate a healthy, functional periodontium in the damaged tooth root area (Figure 2B). Transplantation of DMSCs from the periodontal space of human teeth improved periodontal healing.[23] In addition, diverse scaffolds, growth factors (e.g., platelet-derived growth factors, BMPs) and dentin matrix molecules have been used for improving the regenerative efficacy of DMSCs in the periodontium.[24] However, a frequent side effect following the use of BMPs is excessive bone formation that results in tooth ankylosis. Advanced bone grafting materials containing platelet-rich plasma and enamel matrix derivatives further improved the clinical performances aiming at periodontal tissue regeneration.[25, 26]

CURRENT TREATMENTS AND CHALLENGES FOR TOOTH REPLACEMENT

The use of dental implants has become a common and successful treatment for replacing missing teeth.[27] A typical dental implant is composed of a metal screw part, which interfaces and integrates within the alveolar bone, and another part where a tooth crown substitute is placed. Despite their large and regular usage in dental clinics, implants still need significant improvements, particularly in their capacity to stimulate bone formation and promote angiogenesis at the implantation site.[28] The integration of dental implants to the alveolar bone as well as their longevity have been considerably improved by modifying their surface using various coating materials (e.g., gold nanoparticles) that allow a faster healing and adhesion.[28] However, there is a major risk of infection of tissues surrounding the implant, a pathology termed peri-implantitis.[29] Incorporation of antibacterial agents to titanium dental implants, such as silver nanoparticles, can limit bacterial growth, thus avoiding infection, improving implant performances and increasing the success of treatment.[28] To date, only few randomized preclinical and clinical trials have been performed for guided bone regeneration around implants using growth factors and protein delivery systems.[30] Therefore, the realization of larger clinical trials is absolutely necessary for validating the efficiency of all these novel materials and techniques.

Regeneration of entire brand-new teeth for the replacement of missing or lost teeth is the most ambitious goal in dentistry.[15, 31] Two main strategies have been elaborated for the formation of new teeth.[15, 32] One approach consists in forming tooth germs by recombining DESCs and DMSCs that will be subsequently transplanted into the alveolar bone. It is expected that these teeth will further develop and erupt into the oral cavity. Another approach relies on tooth-shaped biodegradable scaffolds filled with both DESCs and DMSCs and implanted into the alveolar bone, assuming that they will finally form functional teeth.[32] Experiments in mice have shown that these approaches can be successful since they allowed the generation of functional teeth.[15, 33] Similar results have not yet been obtained in humans, due mainly to the limited number of adult human DESCs. This problem could be resolved by using the inducible pluripotent stem cells (iPSCs) technology for the generation of enamel.[2, 34] Although promising, these approaches need further investigation, as effective protocols for the use of iPSCs in clinics are not available yet.

NOVEL TECHNOLOGICAL PLATFORMS FOR DENTAL APPLICATIONS

Translation of preclinical results into effective cell-based therapies remains poor, highlighting the need for accurate human-emulation systems.[35] Recently, 3D *in vitro* systems, termed organoids or spheres, that contain an important number of stem cells and allow the recreation of similar to the *in vivo* conditions, have been successfully generated from both dental epithelial and mesenchymal tissues. These 3D structures might be valuable sources of DMSCs and DESCs for dental regenerative purposes.[36] Furthermore, they represent tools for studying the effects of novel pharmaceutical products and materials to dental tissues before their clinical use.

Miniaturized "organ-on-chip" devices are based on recent technological advancements in microfluidics. These devices successfully emulate human pathophysiological conditions of specific tissues and organs *in vitro*.[37] Microfluidics have been used for the first time to analyze the role of innervation in dental tissues and DMSCs.[38] These devices might be also important to understand the interconnection of teeth with other organs and study their responses to the various dental pathologies.[37]

Graphene-based sensors, temporary printed at the surface of enamel, permitted the detection of tooth-specific oral bacteria and the evaluation of food properties such as pH, temperature and sugar levels.[39, 40] These sensors represent excellent tools for the refined control and understanding of oral environment that will greatly help the field of preventive dentistry.

CONCLUDING REMARKS

Technological advances and innovative treatments using stem cells and biomaterials are revolutionizing the field of dentistry. Although these pioneering stem cell-based therapeutic approaches aim at improving dental care in the near future, they are not yet applicable in clinics. Computing-related and tissue engineering technologies offer a plethora of exciting perspectives to dental medicine and might provide new, non-invasive, techniques for the formation of brand new dental tissues. Advanced biomaterials are pivotal in regulating the activities of stem cells, thus ensuring suitable tooth repair and functionality.

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FIGURES

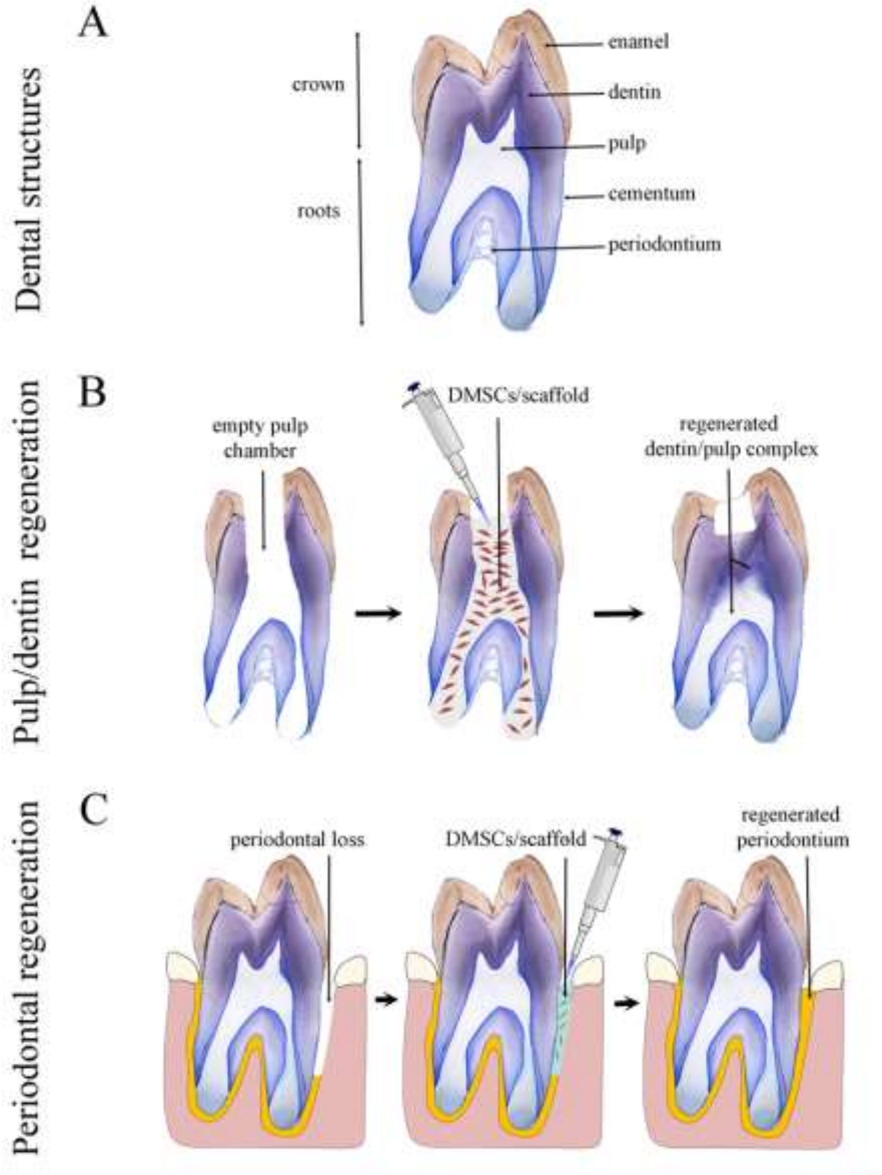

Figure 1. Dental structures and proposed stem cell-based approaches for dental pulp and periodontal regeneration. **A)** Histological section stained with toluidine blue of a human molar tooth. **B, C)** Schematic representation of proposed strategies using dental mesenchymal stem cells stem-cells (DMSCs) for the regeneration of the **(B)** dentin-pulp complex and **(C)** periodontium.

Figure 2. Dental implants for tooth replacement. **A)** Dental implants (yellow arrowheads) inserted into the alveolar bone of a patient. **B)** Progressive tissue regeneration following insertion of implants. **C)** Application of ceramic crowns (red arrowheads) onto the inserted dental implants. Courtesy: Professor Ronald Jung.