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Tissue engineering for bone regeneration and osseointegration in the oral cavity☆

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ABSTRACT

Objective. The focus of this review is to summarize recent advances on regenerative technologies (scaffolding matrices, cell/gene therapy and biologic drug delivery) to promote reconstruction of tooth and dental implant-associated bone defects.

Methods. An overview of scaffolds developed for application in bone regeneration is presented with an emphasis on identifying the primary criteria required for optimized scaffold design for the purpose of regenerating physiologically functional osseous tissues. Growth factors and other biologics with clinical potential for osteogenesis are examined, with a comprehensive assessment of pre-clinical and clinical studies. Potential novel improvements to current matrix-based delivery platforms for increased control of growth factor spatiotemporal release kinetics are highlighting including recent advancements in stem cell and gene therapy.

Results. An analysis of existing scaffold materials, their strategic design for tissue regeneration, and use of growth factors for improved bone formation in oral regenerative therapies results in the identification of current limitations and required improvements to continue moving the field of bone tissue engineering forward into the clinical arena.

Significance. Development of optimized scaffolding matrices for the predictable regeneration of structurally and physiologically functional osseous tissues is still an elusive goal. The introduction of growth factor biologics and cells has the potential to improve the biomimetic properties and regenerative potential of scaffold-based delivery platforms for next-generation patient-specific treatments with greater clinical outcome predictability.

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1. Introduction

The alveolar processes of the mandible and maxilla line the alveolus and provide structural support and maintenance for teeth as part of the periodontium, consisting of the periodontal ligament (PDL), cementum, connective tissue, and gingiva. Alveolar bone is especially susceptible to inflammation-induced bone resorption due to high rates of progressive periodontitis – a leading chronic oral inflammatory disease estimated to affect 47.2% of adults in the United States, with a prevalence of 70% for adults aged 65 years and older [1]. Advanced periodontal disease alters alveolar bone morphology and destroys surrounding tooth-supporting tissues, thereby necessitating tooth extraction. Since the existence of alveolar bone is mutually connected to the dentition and other periodontal tissues, the alveolar ridge continues to resorb following tooth removal even if a dental implant is placed into a fresh extraction socket. Physiologically, this is caused by continuous bone remodeling in response to mechanical loading changes that occur with alterations in the applied force and strain distribution to the osseous tissue during mastication, as stipulated by Wolff's Law [2]. Ridge or socket preservation and augmentation using bone grafting materials is a clinically viable approach to maintain any remaining bone following tooth extraction and further condition it in preparation for dental implant placement. Sufficient bone volume, height, and width are necessary to ensure implant stability and osseointegration that can sustain optimal bone-implant contact biomechanical loading. Other dental procedures that involve grafting include maxillary sinus floor augmentation, which is employed for patients with bone loss in the posterior maxilla that houses premolar and molar teeth [3]. Bone defects in the oral cavity resulting from trauma, chronic infection, congenital defects, or surgical resection require clinical intervention, most frequently using autologous bone grafting techniques. However, critical limitations of this approach include donor site morbidity and inadequate supply of graft tissue. Tissue engineering approaches using scaffolds alone or in combination with growth factor, cell and/or gene delivery have the potential to address existing challenges in managing bone loss and increase clinical options for controllable regeneration of intraoral osseous tissues.

2. Scaffolds

2.1. *Intraoral bone grafts*

An autologous bone graft is considered the gold standard due to low risk of immunogenicity or disease transmission that could be associated with an allograft (genetically different donor from the same species) or xenograft (donor from another species). Most importantly, bone transplanted from the patient is native to its host environment and readily associates with the remnant tissue, providing a pre-established population of viable cells and growth factors necessary for osteogenesis. Local sites such as the maxillary tuberosity or mandibular symphysis can be used for harvesting of small autologous grafts [4]. Nevertheless, there are several key reasons for a critical need of alternative grafts capable of substituting the autograft: limited availability of autologous tissue for larger bone defects, donor site morbidity and potential wound-based infections, as well as prolonged operative times [5]. Although lacking in osteogenicity, allografts and xenografts can be prepared to have osteoconductive and osteoinductive properties. Bone allografts are available as fresh/fresh-frozen, freeze-dried, or demineralized and freeze-dried. The mechanical properties of allografts derived from a living donor or cadaveric tissue are changed substantially during extensive tissue processing involving decellularization, sterilization, and preservation for clinical use [6]. Such tissue treatment removes viable cells that are osteogenic and osteoinductive in nature, leaving behind a structurally supportive framework primarily composed of minerals and proteins – termed the extracellular matrix (ECM). The allograft ECM serves as a scaffold for osteoblasts originating from the bone defect into which the graft is placed to facilitate new bone formation. Depending on the method of processing, an allograft can also be osteoinductive if it retains the biological properties necessary to recruit mesenchymal stem cells to the site and stimulate their differentiation into osteoprogenitor cells. One example is demineralized bone matrix (DMB), which has reduced levels of calcium and phosphorus and is primarily type I collagen, but can be considered osteoinductive if it retains factors such as bone morphogenetic proteins (BMPs) and transforming growth factor-β (TGF-β) [7]. As expected, DMB shows an increased rate of resorption relative to a mineralized bone graft during tissue remodeling in vivo. In addition, derivation of DBM involves grinding of bone to obtain particulates as opposed to processing the allograft in its native structural form, making it useful for small to moderate defects [8].

Xenografts offer another alternative for bone replacement in dental regeneration, with most products derived from coral, porcine, or bovine sources. A recent study comparing implant placement into sinus floors augmented with an autologous mandibular bone graft versus a commercially-available bovine xenograft found equivalent implant survival rates over an observational period of 5 years [9]. However, implant survivability depends on many factors, including patient demographics and surgical technique, thereby warranting longer-term evaluations and more comprehensive consideration of factors that may influence the clinical outcome. Extensive meta-analysis of histomorphometric and bone graft healing time results for sinus floor augmentation described in the literature over a period of 16 years concluded that autologous bone grafts result in higher total bone volume levels compared to other bone grafting materials [10]. Another comprehensive systematic review of treatment modalities used to evaluate dental implant survival rates in maxillary sinus grafts employed statistically robust methodology to correct for study effects. It concluded that application of grafting membranes for guided bone regeneration supplementary to a bone graft was more important for implant survival rate over factors such as which bone substitute material was selected for the surgery [11]. These results indicate the difficulty of identifying specific factors that influence final clinical outcomes and underline the fact that there is no unified consensus on whether non-patient derived grafts can perform at