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Review

A current overview of materials and strategies for potential use in maxillofacial tissue regeneration

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ABSTRACT

Tissue regeneration is rapidly evolving to treat anomalies in the entire human body. The production of biodegradable, customizable scaffolds to achieve this clinical aim is dependent on the interdisciplinary collaboration among clinicians, bioengineers and materials scientists. While bone grafts and varying reconstructive procedures have been traditionally used for maxillofacial defects, the goal of this review is to provide insight on all materials involved in the progressing utilization of the tissue engineering approach to yield successful treatment outcomes for both hard and soft tissues. *In vitro* and *in vivo* studies that have demonstrated the restoration of bone and cartilage tissue with different scaffold material types, stem cells and growth factors show promise in regenerative treatment interventions for maxillofacial defects. The repair of the temporomandibular joint (TMJ) disc and mandibular bone were discussed extensively in the report, supported by evidence of regeneration of the same tissue types in different medical capacities. Furthermore, in addition to the thorough explanation of polymeric, ceramic, and composite scaffolds, this review includes the application of biodegradable metallic scaffolds for regeneration of hard tissue. The purpose of compiling all the relevant information in this review is to lay the foundation for future investigation in materials used in scaffold synthesis in the realm of oral and maxillofacial surgery.
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1. Introduction

Extraoral craniofacial tissue engineering is a blossoming field that encompasses a wide variety of stimulating materials and bioactive agents incorporated into a scaffold to restore the anatomy and functionality of an injured or defected region [1]. Scaffolds are biocompatible, biodegradable three-dimensional constructs with a unique architecture that facilitate cell adhesion, migration, proliferation and differentiation [2–36]. Various biomaterials have been recently developed to accommodate the need for scaffold or implant fabrication and their surface modification aimed at regeneration and tissue engineering of different organs [36–42]. Craniofacial tissue engineering scaffolds and implants can be composed of a specific material or a blend/composite of materials that correlate to the type of tissue being reconstructed, hard (bone) or soft (cartilage) tissue [43–46]. Important factors to take into consideration in the design and implantation of the scaffold include dimensions of the defect, cell density in the surrounding tissue, and available vasculature around the area of damage [1]. Signal-inducing growth factors and attached proteins can also mitigate mechanical property enhancement and cell-cell interaction within the complex [47–49]. While the scaffold is meant to facilitate the biochemical activity that gives rise to new tissue, its rate of degradation normally is equivalent to the rate of tissue formation [48]. The applicability of this division of regenerative medicine will be discussed in the two separate types of tissue application that routinely serve as surgical sites for oral and maxillofacial surgeons: cartilage and bone.

Approximately ten million people in the United States suffer from temporomandibular joint disorders (TMD) [50]. Tissue engineering applied to the temporomandibular joint (TMJ) has been a part of scientific discussion and practice for three decades. Severe complications of the TMJ disc have led to discectomies, (which is the surgical procedure to remove the TMJ disc) but functional implants are being seriously considered as an alternative approach [51]. Displacement of the dysfunctional disc followed by the insertion of a cell source to manufacture neocartilage is the overall goal of current researchers in the field. Using a biocompatible scaffold seeded with cells and biological modulators can facilitate this process but the regeneration needs to be self-limiting and controlled so that ossification does not occur [52]. With current understanding of underlying causes of TMJ pathology and its instigation of myofacial pain in the patient leading to debilitating masticatory function, recent strides have been made to create a long-term resolution. The potential to induce regeneration of the TMJ disc depends on a variety of factors, such as scaffold design and material, supplementary cells, bioactive agents, biochemical compatibility between the scaffold and surrounding environment, and the ability of the host to accept the scaffold and facilitate a natural process that equates tissue formation with safe biodegradation of the three-dimensional construct. Two decades ago, several papers were published to demonstrate the capacity for a TMJ disc-specific regenerative mechanism [53–55]. In order to safely revitalize the natural environment of the disc, in addition to restoring its functional capabilities, the proper combination of biocompatible materials and bioactive agents needs to be employed, and a variety of these scaffold designs have been successfully tested *in vitro* and *in vivo* [53,56]. The soft tissue of cartilage can be regenerated using natural and synthetic polymers alike [57,58], both classes of which will be further discussed in Section 3.

Significant maxillofacial bone damage that requires tissue reconstruction may result from tumors, osteoradionecrosis, trauma, or congenital defects, and traditionally, these debilitating causes were addressed by bone grafting procedures [59,60]. Tissue engineering strategies to restore both the functional capabilities and morphology of lost bone tissue have made great strides in the last couple decades [61,62]. Tissue engineering can be employed for bone as well by providing permanent, biomimetic, replacement tissue systems. To reach this aim, scientists can utilize the tissue engineering model (Fig. 1). In this schematic, native tissue is first evaluated to generate design parameters [63].

Two methods are notable in hard tissue engineering: *in situ* tissue engineering, which incorporates an acellular scaffold matrix into the site of tissue injury to attract local cells and osteoconductive mediators that will guide the process of regeneration, and *ex vivo* cell seeding on the scaffold, which would allow the cells to orchestrate the mechanism of bone formation [59].

2. TMJ cartilage engineering

2.1. Materials for cartilage tissue engineering

2.1.1. Collagen

Although the study of most natural polymers has been very limited in the regeneration of the cartilage disc, one stands out considerably among the rest in attempts to achieve total disc reconstruction: collagen [64]. Its ability to be broken down and used as a gel has led to its widespread use, especially because of the ease at which it can be injected as a delivery system suspension into the cartilage defect, although its use as a more rigid structure is more ideal because of the need for suitable porosity to allow for cell adhesion and proliferation throughout the scaffold [65,66]. Levingstone et al. similarly conducted an experiment to support the use of collagen in osteochondral defects, ultimately presenting evidence that collagen type 1 improved the mechanical properties of composite scaffolds for osteochondral defect repair [67]. Furthermore, Farrell et al. observed increased chondrogenic differentiation of mesenchymal stem cells in a rat model tested with a collagen-glycosaminoglycan scaffold [68].

2.1.2. Gelatin

Gelatin, another natural polymer, is derived from the denaturation of collagen and is favorable because of its hydrophilicity and cross-linking ability [69]. Kuo and Wang [70] exhibited *in vitro* chondrogenic differentiation with a scaffold composed of gelatin and chitosan while Xia et al. [71] similarly yielded positive results with the same scaffold materials *in vivo*. Gelatin, although a recently developed material for

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