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Injectable scaffolds: Preparation and application in dental and craniofacial regeneration

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ABSTRACT

Injectable scaffolds are appealing for tissue regeneration because they offer many advantages over preformed scaffolds. This article provides a comprehensive review of the injectable scaffolds currently being investigated for dental and craniofacial tissue regeneration. First, we provide an overview of injectable scaffolding materials, including natural, synthetic, and composite biomaterials. Next, we discuss a variety of characteristic parameters and gelation mechanisms of the injectable scaffolds. The advanced injectable scaffolding systems developed in recent years are then illustrated. Furthermore, we summarize the applications of the injectable scaffolds for the regeneration of dental and craniofacial tissues that include pulp, dentin, periodontal ligament, temporomandibular joint, and alveolar bone. Finally, our perspectives on the injectable scaffolds for dental and craniofacial tissue regeneration are offered as signposts for the future advancement of this field.

Contents

Abbreviations: BCP, biphasic calcium phosphate; BMMSC, bone marrow-derived mesenchymal cells; CPC, calcium phaosphate cements; DPSC, dental pulp stem cell; ECM, extracellular matrix; EDC, 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide hydrochloride; GAG, glycosaminoglycan; GelMA, methacrylamide-functionalized gelatin; H2O2, hydrogen peroxide; HA, hydroxyapatite; HTCC, *N*-(2-hydroxy)propyl-3-trimethyl ammonium chitosan chloride; iPSMSC, induced pluripotent stem cell-derived mesenchymal stem cell; LCST, lower critical solution temperature; MCJ, metacarpalphalangeal joint; MDP, multidomain peptides; MMP, matrix metalloproteinase; MTA, mineral trioxide aggregate; o/w, oil-in-water; PA, peptide-amphiphile; PAA, poly(acrylic acid); PCL, poly(ε-caprolactone); PDL, periodontal ligament; PDLSC, periodontal ligament stem cell; PEG, poly(ethylene glycol); PEO, poly(ethylene oxide); PG, proteoglycan; PGA, poly(glycolic acid); PLA, poly(lactic acid); PLGA, poly(lactic-*co*-glycolic acid); PNIPAM, poly(*N*-isopropyl acrylamide); PPF, poly(propylene fumarate); PPO, poly(propylene oxide); PRP, platelet rich plasma; RGD, Arg-Gly-Asp; rhBMP, recombinant human bone morphogenetic protein; rhGDF, recombinant human growth/differentiation factor; SCAP, stem cells from apical papilla; SHED, stem cells from exfoliated deciduous teeth; TGF, transforming growth factor; TMD, temporomandibular joint disorder; TMJ, temporomandibular joint; UCST, upper critical solution temperatures; UV, ultraviolet; VEGF, vascular endothelial growth factor; β-GP, glycerol-2-phosphate; β-TCP, β-tricalciumphosphate.

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1. Introduction

Tooth is an important organ for our daily life. However, a tooth is susceptible to losing part or even all of its structures due to bacterial invasion, trauma, or congenital anomalies. From a report of the Centers for Disease Control and Prevention, dental caries or cavities, is one of the most common chronic diseases of young children and adolescents (6–19 years old) [1]. Dental caries also affects adults, with more than 90% of all the population over the age of 20 having some degree of tooth decay. Meanwhile, nearly half of the U.S. adult population aged 30 years and older has mild, moderate or severe periodontitis, and 64% of adults over the age of 65 have moderate to severe forms of periodontal disease, which is the major cause for tooth loss [2]. The loss of tooth can cause immediate problems with eating and speech and subsequent bone resorption, leading to physical and mental suffering that compromises an individual's self-esteem and quality of life.

Clinically, if dental caries progresses and severely inflames the pulp tissues inside the tooth, a root canal procedure is often performed to remove the necrotic dental tissues, clean the pulp chamber, and seal it with bio-inert materials. While this therapy has been used for many years with high success rates, the repaired tooth is not a living organ and loses a significant amount of the tooth structure, which weakens the strength of the tooth. Similarly, an artificial prosthetic dental implant is used to replace the lost tooth. Despite its clinical success, dental implant failure is also well documented in the literature including peri-implant bone loss, infections, and allergic reactions [3]. Another example is temporomandibular joint disorders (TMDs), which are a heterogeneous group of diseases that cause orofacial pain, affecting a patient population of more than 10 million in the United States [4]. Treatment options for TMDs are few and have limited success rates. For patients with severe TMDs, a surgical procedure called a "discectomy" is often performed to remove the diseased temporomandibular joint (TMJ) disc that compromises the normal physiological function. Therefore, there is a need to develop an alternative to traditional dental and craniofacial clinical treatments.

Tissue engineering is a promising approach to replacing damaged/missing dental and craniofacial structures and restoring their biological functions; a number of publications have shown the success of regenerating dental and craniofacial tissues using this strategy [5–11]. Typically, the tissue engineering strategy involves three critical elements: stem cells or progenitor cells, signaling molecules (*e.g.*, growth factors), and scaffolds. The scaffold is an artificial extracellular matrix (ECM) and serves as a template for cell growth and tissue regeneration. Ideally, the scaffold should be biocompatible and biodegradable, possess proper mechanical and physical properties, and mimic the *in vivo* microenvironment (niche) to facilitate cell adhesion, proliferation, differentiation, and neo tissue formation [12]. Based on when a scaffold is shaped, it can be considered a pre-formed or an injectable scaffold. A pre-formed scaffold has a definite shape prior to its application, while an injectable scaffold forms the shape *in situ*. Compared to the pre-formed scaffold, the injectable scaffold has several advantages, including (1) it is performed in a minimally invasive manner, therefore decreasing the risk of infection and improving comfort; (2) it can easily fill any irregularly-shaped defects; and (3) it overcomes the difficulties of cell seeding and adhesion, and the delivery of bioactive molecules, as these factors can be simply mixed with the material solution before being injected *in situ*. Considering the size, morphology, and complicated structure of dental and craniofacial tissues, an injectable scaffold is more appealing than a pre-formed one. For example, the root canal is a long, narrow channel with an average total volume of approximately 20 μl [13]. With such a small volume and unique anatomical structure, it is a challenge to implant a pre-formed scaffold into the root canal and seamlessly cover the entire space of the canal; however, an injectable scaffold can easily achieve this. Another example is the maxillary sinus lift, which is a surgical procedure in which natural or synthetic bone graft materials are added to the upper jaw to induce bone formation. During the surgery, a surgeon cuts the gum and bone tissues and opens a small oval window to introduce bone-graft materials into the sinus space. Obviously, the adoption of injectable materials is a better