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Scaffolds in Dental Tissue Engineering: A Review

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Abstract

Context: The major aim of tissue engineering is inducing of the body's mechanisms to regenerate damaged tissues to original condition and task. Scaffolds are 3D porous constructs which provide a cellular microenvironment needed for tissue engineering. Choosing a biomaterial with proper biological, physical, and mechanical properties is of great importance in tooth tissue engineering. Thus, the current study reviews the properties of different polymers and ceramics for use as scaffolds in tooth dental regeneration.

Evidence Acquisition: The current study searched databases such as Elsevier, Wiley, Google Scholar, and PubMed in English from 1972 to 2018. After going through the required process, 29 articles were eventually confirmed and enrolled in this review paper.

Conclusions: The results of this work confirmed that thanks to having the ability to provide suitable amounts of interconnected porosities, high ratio of surface area to volume, proper mechanical strength, and different geometries required for tissue engineering, polymers are a good option for regeneration of tooth tissues. Although bioceramics such as calcium phosphate and glasses have good biocompatibility and bioactivity, their poor mechanical properties and low degradation rate limit their extensive use in tooth tissue regeneration.

Keywords: Dental, Tissue Engineering, Bioengineered Teeth, Scaffolds

1. Context

Every year, a large number of people lose their teeth due to severe dental pulp damage, infection, and periodontal diseases (1). Regeneration of damaged teeth is a big deal for every professional dentist. Because the tooth is not a necessary tissue for human survival, its regeneration has not been the main matter of discussion in recent years. Tissue engineering science has showed lots of promise to regenerate damaged teeth. Tissue engineering has three main components: scaffolds, stem cells (SCs), and growth factors (GFs). Scaffolds, as SC and GF carriers have a significant role in the regeneration of damaged or lost tissues.

Scaffold biomaterials are classified into three main groups: polymers, ceramics, and composites. Polymers are one of the most attractive biomaterials for fabrication of scaffolds because of having great ability in tuning their properties with changes in composition, structure, and arrangement of constituent macromolecules (2). Scaffold biomaterials using in tooth tissue engineering might need to meet different properties than those used in various other tissues. Dental tissue engineering is expected to regenerate damaged or lost components of a tooth such as enamel, dentin, and pulp. To understand different factors affecting the regeneration of dental tissues, it is essential to study tooth development since birth.

The tooth is a complex tissue consisting of hard tissues, dentine, and enamel which are connected to bone through ligament tissue. The tooth is formed through sequential reciprocal interactions between epithelial and mesenchymal cells. The epithelial cells have an important role in enamel formation and mesenchymal cells generate all other differentiated cells necessary for the formation of odontoblasts, pulp, and periodontal ligament.

Tooth development consists of five main steps which reflect key procedures (3). In the induction step, the mental process is started by sending the signals from epithelium to the mesenchyme. At the second stage, a bud is formed which contains localized dental epithelial cells and is surrounded by mesenchymal cells. Differentiation and condensation of epithelial cells in the bud result in the cap step. At this step, crown morphogenesis is started by epithelial signaling center. In bell step, the precursors of tooth cells are involved to generate ameloblasts, coordinate enamel deposition, and odontoblasts. The general shape of a tooth is formed at this step. At the final stage, tooth eruption, both bone resorption, and root formation occur. For regulating each process, signals are permanently exchanged between epithelial and mesenchymal cells (3).

In this review, different important biomaterials used in dental tissue engineering are briefly discussed. We also highlight the main properties of common biomaterials in dental tissue repair and regeneration.

2. Evidence Acquisition

For this review paper, we searched the databases such as Elsevier, Wiley, Google Scholar, and PubMed in English from 1972 to 2018. At the first step, we selected 130 best matching related papers and after reading abstracts carefully, in the second step, we picked 80 papers out. Finally, 29 articles were confirmed and enrolled in writing the current paper.

3. Results

3.1. Scaffolds Requirements for Dental Tissue Engineering

As similar to different tissues, scaffold biomaterials for tooth regeneration applications should meet some requirements such as:

3.1.1. Mechanical Properties

Ideally, each kind of scaffold used in dental tissue engineering should have the mechanical properties consistent with the anatomical properties of the implanted place and it should be strong enough to have a good working ability with hand tools. Preparing scaffolds with good mechanical properties is the first challenge in the engineering of bone, cartilage, and dental tissues (4). For the mentioned tissues, the prepared scaffolds should have good mechanical integrity to maintain their function from the time of implantation to the completion of the remodeling process (5). Another point that should be mentioned is that the regeneration of damaged tissues differs with the age of individuals. In young people, hard tissue fractures normally take almost six months to heal to the point of load-bearing. The suitable amount and volume of porosities inside the scaffold construct allow for diffusion of oxygen, cells, and nutrition diffusion. The mechanical properties and degradation rate of scaffolds have a reverse relationship. For this point, many scaffolds with high mechanical properties and good functionality in in-vitro applications have failed when implanted in-vivo due to insufficient porosities and the weak ability for vascularization (5). It is evident that the existence of a balance between mechanical properties and amount of porosities is vital for better performance of scaffolds used in tissue engineering.

3.1.2. Biocompatibility

The very first criterion of each developed scaffold for tissue engineering applications is that it should pass all requirement tests for biocompatibility. In this way, cells must attach, grow, and migrate through the scaffold and finally proliferate before the formation of a new matrix. The implanted biomaterials should show negligible reaction with the immune system of the body.

3.1.3. Scaffold Architecture

One of the critical characteristics of prepared scaffolds for engineering different tissues is their architecture. Scaffolds with a high amount of interconnected porosities allow cellular penetration and oxygen and nutrients diffusion. Moreover, scaffolds should have interconnected porosities to ensure waste product diffusion out of scaffold within the construct without harmful interaction with surrounding tissues (6, 7).

3.1.4. Biodegradability

The concept of tissue engineering is using a degradable scaffold, to finally replace with the growing tissue. In this view, implanted scaffolds should act as a temporary construct which degrades over time by a coordinated rate with the rate of tissue growth. An ideal scaffold must be biodegradable to allow cells to generate their own extracellular matrix (ECM) (8). The degradation of scaffold produced by-products should be non-toxic and leave the body without adverse interaction with other tissues.

3.2. Biomaterials in Dental Tissue Engineering

3.2.1. Fibrin

Fibrin is a natural biopolymer formed by an enzymatic reaction of fibrinogen and thrombin (9). Its properties such as cell adhesion, biocompatibility, and immune response are better when it is compared with other natural origin polymers like collagen. However, high shrinkage, rapid degradation, and low mechanical properties are its disadvantages (10). Several researchers have tried to modify and optimize the characteristics of fibrin. The decreased shrinkage and controlled degradation rate were achieved by droping poly L lysine in fibrin structure and use of enzyme inhibitors, respectively (10). Furthermore, it has been reported that use of a composite scaffold consisting of fibrin and a kind of biocompatible reinforcement such as hyaluronic acid, β-tricalcium phosphate (β-TCP), and polyurethane has a significant role in improving the mechanical properties of fibrin (11).

Using fibrin as a favorite biomaterial has several advantages such as transforming growth factor-beta (TGF-β) transformation which results in collagen formation by means of fibrinogen in the structure (12), providing a proper environment for angiogenesis, good potential in control of release of pro-angiogenic growth factors (13), injectability, and shapeability to 3D structures.

Platelet-rich fibrin (PRF) and platelet rich plasma (PRP) are components of blood which are a rich source of growth factors and cytokines such as TGF-β and platelet derived growth factor (PDGF). The PDGF attaches to endothelial cells to make ability in growth while TGF-β induces bone formation by binding with osteoblasts and stem cells. Yang et al. (14) demonstrated the significant effect of fibrin glue containing PRF and PRP in regeneration of all components of tooth including crown, root, pulp, enamel, dentin, cementum, blood vessels, and periodontal ligament in a porcine model. They showed that bud cells surrounded by PRF inside fibrin glue scaffold implanted in the tooth of a pig.

3.2.2. Hyaluronic Acid

Hyaluronic acid is an anionic and non-sulfated glycosaminoglycan found extensively in the ECM of connective, epithelial, and neural tissues. Even though hyaluronic acid is a biocompatible polymer, its poor mechanical properties and fast degradation rate limit its wide use in the tissue engineering applications. However, both its mechanical strength and dissolving rate can be controlled by using cross-linking and chemical modification (15). Ganesh et al. (16) developed alginate/ hyaluronic acid composite scaffold with enhanced mechanical, physical, and cellular properties.

Cell adhesive ligands such as arginine-glycine-aspartic acid (RGD) peptide modifies the surface of the polymer and improves the functionality of polymers in cell adhesion, growth, and interaction (17). It has been reported that RGD modified hyaluronic acid hydrogel has a great potential ability in cell attachment and proliferation (18). Since hyaluronic acid hydrogel is injectable and can penetrate perfectly through narrow canals, it can be extensively used in endodontic and pulp regeneration.

3.2.3. Alginate

Alginate (Alg) as a natural polysaccharide is a non-toxic and biocompatible polymer which can be considered as an injectable biomaterial for dentin regeneration applications. However, its weakened mechanical strength limits extensive applications of Alg in hard tissue engineering applications. One way to improve the mechanical strength of Alg is the increase of calcium density inside Alg structure by a cross-linking agent such as calcium chloride which increases covalent cross linking (13).

The Alg hydrogel provides a proper substrate for releasing encapsulated GFs such as TGF β to improve dentin pulp and periodontal regenerations. It has been reported that acid-treated Alg builds the dentinal ECM and significantly affects odontoblast-like cell differentiation (19). Srinivasan et al. (20) showed the enhanced properties of Alg scaffold containing nano-bioglass ceramic on human periodontal ligament fibroblast cells (hPDLF) attachment, growth, and alkaline phosphatase (ALP) activity.

3.2.4. Collagen

The most widespread protein found in hard and soft connective tissues such as bone, cartilage, and skin is collagen (21). Collagen has been also extensively used in regenerative applications of dental tissues because of having similar structural and chemical properties to predominant structural protein existing in ECM of dental tissues (22).

Collagen presents several prominent advantages of biocompatibility and bioactivity which make it a favorable biopolymer in promoting cellular attachment, migration, proliferation, and differentiation. Theoretically, collagen is dissolved in physiological human body environment via a mild inflammatory interaction with collagenase enzyme. Because of having high tensile strength, collagen can be used in fibrous forms and tensile load-bearing applications. However, its mechanical strength is not enough to be used in pulp regeneration applications. It has been reported that the crosslinking of collagen by glutaraldehyde or diphenyl phosphoryl azide improves its mechanical properties (23).

Dental pulp stem cells (DPSCs) are believed to have good attachment and proliferation into the collagen scaffold. The triangle of collagen scaffold, DPSCs, and dentin matrix acidic phosphoprotein 1 (DMP1) has promoted the improved formation of ECM of pulp tissue (24).

3.2.5. Poly (Ethylene Glycol)

Poly (ethylene glycol) (PEG) is one of the favorite biomaterials in tissue engineering applications because of having high biocompatibility and mild degradation. Its high stability in a physiological environment to cellular and protein adsorption decreases the rejection by the immune system. The elevated cell adhesion and proliferation of RGD peptides modified PEG has been reported (25). The mechanical properties of PEG are modified by changing the molecular weight and concentration of polymer. The enhancement of molecular weight and concentration of PEG result in its decreasing and increasing of elastic modulus, respectively (26). The photo-cross-linking of PEG has several advantages to its thermal-cross-linking such as ease of use and less harmful effect on encapsulated cells (27).

Fibrin-loaded PEG hydrogels show great potential ability in use as a scaffold for growth and proliferation of DPSCs and PDLSCs wherein mechanical supporting and angiogenesis properties are provided by PEG and fibrin hydrogels, respectively (28).

3.2.6. Ceramics

Bioceramic scaffolds including calcium phosphates and glass ceramics have been widely used in the regeneration of hard tissues owing to their unique characteristics such as good biocompatibility, bioactivity, osteoinductivity, osteoconductivity, and having a similar composition to mineralized tissue.

Calcium phosphate ceramics used in tooth tissue engineering applications are commonly hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$) and tricalcium phosphate (TCP, $Ca_3(PO_4)_2$). Bioglasses are composition based on SiO_2-Na_2O-CaO-P_2O_5 which can be extensively used in endodontic application due to having high bioactivity. Nam et al. (29) showed a good potential ability of calcium phosphate scaffolds in hDPSC growth, attachment, proliferation, and odontogenic differentiation. However, disadvantages associated with bioceramics such as poor mechanical properties, the difficulty of shaping, and high stability limit their wide application in tissue engineering.

4. Conclusions

Tissue engineering has made major strides in dentin tissue regeneration in recent years. Biomaterials in the shape of porous constructs have provided a cellular microenvironment for optimal tooth regeneration. Today, several types of research have evaluated physical, biological, mechanical, and chemical properties of different biomaterials to be used in replicating local extracellular matrix of dentin tissues. In this review paper, we briefly discussed the properties of different polymers and ceramics for application in dentin tissue engineering. We believe that choosing the proper biomaterial helps us to regenerate tooth tissues in the best way.

Footnotes

Authors' Contribution: Razieh Sadat Moayeri and Jafar Ai both are as corresponding author and both contribute as leader and supervisor. Ali Farzin and Naghmeh Bahrami both write the whole body the paper and contributed as leader. They searched the papers and selected the bests. Abdolreza Mohamadnia and Seyedreza Mousavi both edited the paper and helped in writing.

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