Bioactive Materials xxx (2017) 1–10

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: http://www.keaipublishing.com/en/journals/bioactive-materials/

The development of collagen based composite scaffolds for bone regeneration

Dawei Zhang [a], Xiaowei Wu [a], Jingdi Chen [b, **], Kaili Lin [a, *]

[a] School & Hospital of Stomatology, Tongji University, Shanghai Engineering Research Center of Tooth Restoration and Regeneration, Shanghai 200072, China

[b] Institute of Biomedical and Pharmaceutical Technology, Fuzhou University, Fuzhou 350002, China

ARTICLE INFO

Article history:
Received 9 July 2017
Received in revised form
28 August 2017
Accepted 29 August 2017
Available online xxx

Keywords:
Collagen
Bone regeneration
Composite scaffolds
Biomaterials
Tissue engineering

ABSTRACT

Bone is consisted of bone matrix, cells and bioactive factors, and bone matrix is the combination of inorganic minerals and organic polymers. Type I collagen fibril made of five triple-helical collagen chains is the main organic polymer in bone matrix. It plays an important role in the bone formation and remodeling process. Moreover, collagen is one of the most commonly used scaffold materials for bone tissue engineering due to its excellent biocompatibility and biodegradability. However, the low mechanical strength and osteoinductivity of collagen limit its wider applications in bone regeneration field. By incorporating different biomaterials, the properties such as porosity, structural stability, osteoinductivity, osteogenicity of collagen matrixes can be largely improved. This review summarizes and categorizes different kinds of biomaterials including bioceramic, carbon and polymer materials used as components to fabricate collagen based composite scaffolds for bone regeneration. Moreover, the possible directions of future research and development in this field are also proposed.

1. Introduction

As a natural solid biocomposite, bone has a unique hierarchical structural organization at multi-scales which contributes to the high strength and fracture toughness. It is considered that the excellent mechanical properties of bone come from the well-organized embedding of nano-mineral crystals within the collagen matrix to form the intricately and orderly hierarchical structure [1].

Bone is composed of calcified bone matrix, cells and bioactive factors. Bone matrix contains around 65 wt. % mineral materials, 25 wt. % organic materials, and 10 wt. % water. The hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$, HA] is the main inorganic mineral phase. The Ca/P ratio of HA is less than 1.67. There are some impurities such as CO_3^{2-2-}, Na^+, Mg^{2+} and so on existing in natural HA. These impurities can lead to the poor crystallization, deficient calcium and carbonation of HA [1]. Besides, many kinds of essential trace elements including silicon (Si), fluorine (F), zinc (Zn), strontium (Sr), magnesium (Mg), boron (B), and copper (Cu), sodium (Na), manganese (Mn), carbonate (CO_3), potassium (K), chlorine (Cl) etc. present in biology bone, which play an important role in bone growth or can have an effect on bone metabolism [2–4]. For instance, the studies have revealed that the silicon ions can induce angiogenesis and osteogenesis while taking too much Na^+ may result in osteoporosis [5,6]. Sr^{2+} can stimulate the bone-forming function of osteoblasts as well as inhibiting the bone resorbing function of osteoclasts [7–9]. Mg^{2+} has an important role in angiogenesis by inducing nitric oxide production and can indirectly influence mineral metabolism [3,10]. In bone matrix, the organic components consisting of proteins such as collagen are embedded within the calcified matrix. Up to now, over 28 types of collagen have been found in vertebrates and four types of collagen have been verified in bone including type I, III, V and XXIV collagen [11]. Among them, type I collagen is the most abundant protein accounting for 97%. In type I collagen, five triple-helical collagen molecules arrange to form the collagen microsized fibril with a characteristic 67 nm banding feature which is called the D-period [12,13].

* Corresponding author.
** Corresponding author.
E-mail addresses: ibptcjd@fzu.edu.cn (J. Chen), linkaili@tongji.edu.cn, lklecnu@aliyun.com (K. Lin).

Peer review under responsibility of KeAi Communications Co., Ltd.

http://dx.doi.org/10.1016/j.bioactmat.2017.08.004

Despite the structure of bone has been reasonably defined, there is not a well-agreed explanation of the mechanism of mineralization [14]. Two theories of mineralization have been reported: direct nucleation of calcium phosphate mineral crystals [15], and matrix vesicle mediated matrix mineralization [16,17]. Moreover, some bone-related proteins and growth factors such as alkaline phosphatase (ALP), parathyroid hormone (PTH), osteocalcin (OCN), osteonectin (ON), osteopontin (OPN), bone sialoprotein (BSP), bone-morphogenetic protein-2 (BMP-2), and fibroblast growth factor-2 (FGF-2), etc. have been proved to have an effect of regulating essential matrix mineralization [18–23].

Bone plays an important role in the body by supporting mechanical stress and maintaining ionic balance, while trauma or diseases such as tumor and osteoporosis may lead to bone damage. Bone defects resulted by non-union or mal-union fractures, congenital malformations and surgical resections remain a big challenge in the field of modern medicine. In this situation, finding the proper alternatives for reversing bone defects and regenerating the damage bone seems to be vital.

The most commonly used bone grafts in clinic is autologous and allogeneic bone but there still exists some problems such as infection, limited supply and allograft rejection. Apart from autologous and allogeneic bone, alternative bone graft materials such as metals, polymers and ceramics are applied to not only fill the bone defect but also provide mechanical and structural support.

There are five general therapeutic targets in bone regeneration including vascularization, growth factors, osteogenesis, osteoconductive scaffolds and mechanical environment, in which at least three of them should be completed for successful bone regeneration [24–27]. Researchers usually focus on the osteoconductive scaffolds, osteogenic cells and the growth factors. Among them, scaffold has the largest renovation potential. As mentioned above, type I collagen is the main organic composition of biological bone and collagen fibrils serve as a template for mineralization. As one of the most commonly used scaffold material, collagens are found to have outstanding biodegradability, weak antigenicity after removal of telopeptides and excellent biocompatibility [28,29]. Moreover, cells can attach to the surface of collagen via integrin $\alpha 2 \beta 1$ [30]. However, the pure collagen scaffold has insufficient mechanical strength for bone regeneration. Culturing the cells on them, the scaffolds will exhibit unstable geometrical properties due to the extensive cell-mediated contraction [31]. In addition, it is considered that the pure collagen materials lack enough bioactivity to stimulate bone formation ability [32]. The strategy of incorporating of bioactive component is still one of the most popular strategies to improve the mechanical strength, bioactivity and osteogenesis of collagen based scaffolds.

To the best of our knowledge, a large number of studies on collagen based composite scaffolds for bone regeneration have been reported. Though some reviews focus on the preparation, properties and applications of collagen based scaffold [33–35]. While few focus on the materials used to incorporate the collagen scaffold. In view of the sustaining growing interests in the fabrication and application of collagen based composite scaffolds, our goal in this review is to summarize and categorize these composite scaffolds. To accomplish this, the materials used to incorporate are divided into three major categories: bioceramics, carbon-based materials and polymers. The impacts brought by these materials are summarized and the examples are demonstrated. In the end, the limitations and future trends of collagen composite scaffolds for bone regeneration were also summarized.

2. Collagen based composite scaffolds for bone regeneration

Since the regeneration ability of bone and the resource of bone grafts are limited, in order to deal with this problem or accelerate the healing process, a wide variety of collagen-based scaffolds mimicking the native bone tissue microenvironment have been proposed. Diverse materials are applied to modify collagen-based scaffolds for better performances *in vitro* and *in vivo*. In this section, they are introduced by separating them into three major categories including bioceramics, carbon-based materials and polymers.

2.1. Collagen based composite scaffolds with bioceramic components

Due to poor mechanical strength of pure collagen scaffold, some kinds of bioceramics with the similar constituent to the intrinsic inorganic components of nature bone are widely used in collagen scaffolds for bone regeneration. Apart from the enhancement of mechanical properties, they can also improve osteoconductive ability, dimensional stability and increase the surface area for cell attachment on the composite scaffolds [36,37]. Two methods are widely applied to fabricate collagen/bioceramic composite scaffolds: suspension method (direct mixing) [38] and immersion method (co-precipitation) [39,40]. Moreover, HA crystals can be deposited to form thin HA coatings on the scaffold after soaking in simulated body fluid (SBF). This way is more like a biomimetic process [41], which can mimic the biochemical and biophysical properties of bone matrix. The 'biomimetic' scaffolds are expected to take the place of the missing bone. In this section, the related studies about the collagen-based composite scaffolds with incorporation of calcium phosphate (CaP) bioceramics and calcium silicate (CaSi) bioceramics, have been summarized and discussed, respectively.

2.1.1. With calcium phosphate (CaP) based bioceramic components

2.1.1.1. Hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$, HA]. HA is the most commonly used calcium phosphate with the molar ratio of Ca/P = 1.67. Moreover, the biology bone is mainly constructed by the inorganic HA and organic collage components. In addition, these two components possess great biocompatibility, osteoconductivity and bone-bonding ability [42–44]. Therefore, the collagen/HA composite biomaterial scaffolds have been extensively investigated and used for bone tissue engineering scaffolds. The mechanical strength of pure collagen scaffolds is extraordinarily low, which immensely limits their wider applications in tissue regeneration. The compressive modulus of collagen scaffold can be apparently improved by incorporating HA, and the degree of increase is largely related to the concentration of collagen, the amount of HA, the composite methods and the crosslinking methods [45]. In addition, the surface area of the collagen scaffolds can be increased by combining HA, which will lead to incremental cellular adhesion [46]. Comparing with micro-sized HA component, nano-sized HA particles can be more effectively because of their larger surface area. Moreover, another point that cannot be ignored is that apatite can form direct chemical bonds with the host bone tissue. This characteristic will result in faster and better bone-bonding between the scaffolds and the neighboring host bone tissue with HA component. Cells will proliferate better and show enhanced bioactivity on rough surfaces [47], therefore scaffolds containing HA have higher cellular proliferation than the scaffolds without HA component [46]. Some researchers found micron-sized HA particles might lead to poor resorbability, irregular distribution and brittle constructs of the composite scaffold [48]. Cunniffe et al. [42] raised the proposal of using incorporating nano-sized HA (nHA) particles into collagen scaffolds. The resultant collagen/nHA scaffolds showed highly porous, interconnected structure and the compressive modulus of scaffold increased by 18 times by adding

Please cite this article in press as: D. Zhang, et al., The development of collagen based composite scaffolds for bone regeneration, Bioactive Materials (2017), http://dx.doi.org/10.1016/j.bioactmat.2017.08.004