Bioactive Materials 3 (2018) 401–417

Contents lists available at ScienceDirect

Bioactive Materials

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

Bioactive hydrogels for bone regeneration

Xin Bai [a, 1], Mingzhu Gao [a, 1], Sahla Syed [b], Jerry Zhuang [b], Xiaoyang Xu [b, *], Xue-Qing Zhang [a, **]

[a] *Engineering Research Center of Cell & Therapeutic Antibody, Ministry of Education, School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai, 200240, P.R. China*

[b] *Department of Chemical and Materials Engineering, New Jersey Institute of Technology, Newark, NJ, 07102, USA*

A R T I C L E I N F O

Article history:
Received 22 March 2018
Received in revised form
9 May 2018
Accepted 10 May 2018

Keywords:
Bone regeneration
Hydrogel
Biomaterials
Tissue engineering

A B S T R A C T

Bone self-healing is limited and generally requires external intervention to augment bone repair and regeneration. While traditional methods for repairing bone defects such as autografts, allografts, and xenografts have been widely used, they all have corresponding disadvantages, thus limiting their clinical use. Despite the development of a variety of biomaterials, including metal implants, calcium phosphate cements (CPC), hydroxyapatite, etc., the desired therapeutic effect is not fully achieved. Currently, polymeric scaffolds, particularly hydrogels, are of interest and their unique configurations and tunable physicochemical properties have been extensively studied. This review will focus on the applications of various cutting-edge bioactive hydrogels systems in bone regeneration, as well as their advantages and limitations. We will examine the composition and defects of the bone, discuss the current biomaterials for bone regeneration, and classify recently developed polymeric materials for hydrogel synthesis. We will also elaborate on the properties of desirable hydrogels as well as the fabrication techniques and different delivery strategies. Finally, the existing challenges, considerations, and the future prospective of hydrogels in bone regeneration will be outlined.

1. Introduction

In recent years, the medical cost of treating bone related trauma, infection, and tumor has continuously increased [1]. According to relative statistics, the market of European bone graft substitutes was $177 million in 2010, and the global market value of orthopedics biomaterials was $1.9 billion in the same year [2]. It is forecasted to reach $3.3 billion in 2017, presenting a huge expenditure to the national economy. Bone development is a dynamic process [3]. Various cytokines and growth factors recruit osteoprogenitors to the injury site, and subsequently guide them to differentiate into osteoblasts [4]. However, in the case of severe injuries or individuals with congenital malformation, osteogenesis imperfecta, rheumatoid arthritis, or osteoporosis, the lengthy and limited self-healing process cannot adequately satisfy the requirements of timely bone repair [5–7]. Thus, bone augmentation needs to be considered [8]. Current clinical treatments for bone injuries such as autografts, allografts, and xenografts failed to be used extensively due to potential risks of disease transmission, infection, and host rejection [9]. Bone tissue engineering (BTE), a novel approach using scaffolds seeding cells or incorporating bioactive growth factors to promote bone repair and regeneration, is believed to be able to avoid the aforementioned issues and provide an innovative platform in regenerative medicine [10]. The scaffolds used in bone tissue engineering aim at providing structural support, creating an appropriate environment for cell adhesion, migration, proliferation and differentiation, and recapitulating the functional activity of the bone defects [3].

Materials employed for scaffolds can be divided into inorganic materials, natural or synthetic polymers, and composite materials [11]. Numerous studies concerning inorganic materials used in bone repair have emerged. Ceramics are a kind of inorganic

* Corresponding author. Department of Chemical and Materials Engineering, New Jersey Institute of Technology, Newark, NJ07102, USA.
** Corresponding author. Engineering Research Center of Cell & Therapeutic Antibody, Ministry of Education, School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai, 200240, P.R. China.
E-mail addresses: xiaoyang.xu@njit.edu (X. Xu), xueqingzhang@sjtu.edu.cn (X.-Q. Zhang).
Peer review under responsibility of KeAi Communications Co., Ltd.
[1] Xin Bai and Mingzhu Gao contributed equally to this work.

https://doi.org/10.1016/j.bioactmat.2018.05.006
2452-199X/

material that demonstrate good mechanical properties and osteoconductiveness, and have been successfully used in alveolar bone repair. In the past decades, polymer scaffolds have been widely investigated in bone tissue engineering. Commonly used natural materials, such as collagen and chitosan, are considered to be biodegradable and bio-absorbable, and synthetic polymers like poly (lactic acid) (PLA) and poly (D, L-lactide-co-glycolide) (PLGA) are thought to have tunable mechanical properties; however, the structure and characteristics of cells and native tissues are rarely considered in the design of polymeric scaffolds. Therefore, the scaffolds usually demonstrate poor integration with surrounding bone tissues [12]. New materials and solutions are continually developed to meet medical needs [13]. Recently, the interaction between scaffolds and native tissues, particularly the indispensable role of the natural extracellular matrix (ECM) in bone repair, has been extensively investigated. Due to their added advantages of biocompatibility and biodegradability over inorganic materials, polymer materials and composites have shown to integrate well with surrounding bone tissue, allowing a stabilized anchorage of implants and preventing an immune response.

Hydrogels, a type of polymer scaffold, have several potential advantages in bone repair. Hydrogels are composed of three-dimensional hydrophilic polymer chains, which have superior mechanical strength and can provide nutrient environments suitable for endogenous cell growth. They are able to mimic the natural ECM of the bone, thus presenting a prospective ability to encapsulate bioactive molecules or cells. Due to the network structure of the hydrogels, the entrapped proteins or cells are confined in the meshes and they hydrogels can control the release of the materials as required [13]. Moreover, hydrogels are absorbable and demonstrate excellent integration with surrounding tissues, thereby avoiding the complexity of surgical removal and reducing the possibility of an inflammatory response [14]. Additionally, raw materials for preparation of hydrogels are extensive and readily available, and they can be tailored to obtain the desired geometry for implantation or injection, and the degradation rate and porosity or release profile can be easily controlled by altering the crosslinking method and degree.

Nevertheless, challenges concerning the controlled release of encapsulated drugs, proteins or cells still need to be further investigated. Both the burst and delayed release of the drug can affect the actual therapeutic effect, and the use of inappropriate polymers can also cause toxic reactions.

This review will broaden our understanding of the design, development, and challenges of hydrogel-based bone regeneration. We will first briefly introduce the structure and composition of the bone, and then discuss the types of the bone defects and current available clinical treatments. As Fig. 1 illustrates, we will elaborate on the application of polymers and the revolutionary bioactive hydrogels developed for bone repair and regeneration by identifying the requirements of successful formulations and reporting the innovative modifications that overcome the fundamental challenges associated with hydrogels. The benefits and potential complications of delivery strategies in treating bone defects will be detailed and explored. Finally, the limitations of current developments and future directions for the development of hydrogel-based bone regeneration will be discussed.

2. Bone anatomy and current bone injury treatments

2.1. Composition and defects of bone tissues

Bone is a hard and dense tissue mainly composed of two parts, cortical bone and cancellous, or trabecular bone [15]. The ECM of the bone is a biphasic system, one third of which is composed of organic matter, predominantly type I collagen fibers, and the remaining two thirds consist of inorganic matter or bone salt, such as hydroxyapatite-like calcium phosphates. Three cell types – osteoblasts, osteocytes and osteoclasts – work in concordance to form a unified bone organism. Osteoblasts are the main functional

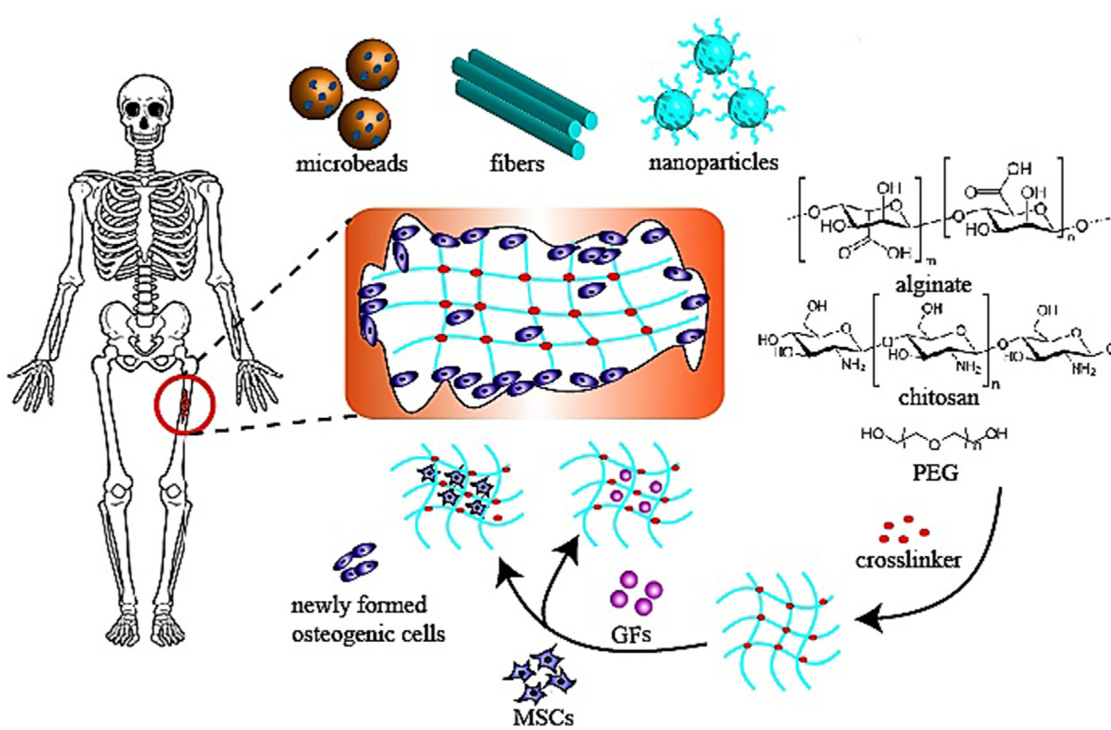

Fig. 1. Schematic illustration of hydrogel-assisted bone regeneration.