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Dual-controlled release system of drugs for bone regeneration☆

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ABSTRACT

Controlled release systems have been noted to allow drugs to enhance their ability for bone regeneration. To this end, various biomaterials have been used as the release carriers of drugs, such as low-molecular-weight drugs, growth factors, and others. The drugs are released from the release carriers in a controlled fashion to maintain their actions for a long time period. Most research has been focused on the controlled release of single drugs to demonstrate the therapeutic feasibility. Controlled release of two combined drugs, so-called dual release systems, are promising and important for tissue regeneration. This is because the tissue regeneration process of bone formation is generally achieved by multiple bioactive molecules, which are produced from cells by other molecules. If two types of bioactive molecules, (i.e., drugs), are supplied in an appropriate fashion, the regeneration process of living bodies will be efficiently promoted. This review focuses on the bone regeneration induced by dual-controlled release of drugs. In this paper, various dual-controlled release systems of drugs aiming at bone regeneration are overviewed explaining the type of drugs and their release materials.

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1. Introduction

Bone regeneration involves complex physiological processes, such as inflammation and the formation of fibrous tissue and bony callus, all of which are intrinsically mediated by both local and recruited cells [1,2]. If the number of cells at a defect site is low, which may be caused by immune diseases such as diabetes, the regeneration process based on the self-healing potential is slow [3–5]. When the size of the bone defect is larger than a critical size, it cannot be self-regenerated during lifetime, as shown in a study involving an animal model [6]. To tackle the naturally arising difficulties, various therapeutic strategies of regenerative medicine have been explored. There are two approaches, i.e., cell transplantation and tissue engineering. For the latter one, cells with a high osteogenic activity are expanded in vitro and transplanted into the site to be regenerated, as it can be expected that cell induced natural regeneration of tissue will occur. Tissue engineering comprises among others biomaterial-based technologies. They can create a local environment

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enabling containment of cells for tissue regeneration. One technique is the use of cell-seeded scaffold to provide a local environment that is friendly for cells at the defect [7,8]. The second approach is to design the delivery systems of growth factors which promote the cells' potential of proliferation and differentiation, resulting in accelerated cell-based tissue regeneration [9–12]. For example, FDA has approved bone morphogenetic protein (BMP) for the treatment of bone fractures [13–15].

The typical concerns over growth factors are their safety, effectiveness, and cost of practical applications. In addition, clinically unexpected effects of growth factors have been reported [16,17]. The side effects may be usually explained as the result of interference between the signals of several regeneration processes which may induce abnormal immune responses [5,15,16]. Generally, high doses are often applied to the fracture to improve the efficiency of growth factors. This often causes serious side effects, such as an inflammatory reaction, neoplasia, or ectopic bone formation [18,19]. If the growth factor does not act at the target area, this may induce problems in other tissues without bone healing. In addition, the action speed of growth factors also influences the promotion and the inhibition of their therapeutic effects. The high cost is one of the large problems for regular clinical use.

It is of prime importance to develop alternative approaches and strategies to solve these issues. One of the most promising ways is to make use of drug delivery systems (DDS). For example, drugs are incorporated into the release carrier of biomaterials [11,20]. The drugs are then released from the carrier in response to the local environment, such as the enzyme presence, and pH [21,22]. Several studies have been reported on the controlled release of drugs [21,23–25]. Most of them describe release systems of single drugs. However, the bone remodeling process is complex in terms of drug action. Various drugs act for not only osteogenesis, but also inflammation modulation, angiogenesis and vasculogenesis [5,26–30]. Therefore, it would be preferable for accelerated bone remodeling to release two types of drugs which can regulate the regeneration process. The drug release should be achieved in a controlled fashion at the appropriate time point and place.

To effectively induce bone regeneration by the controlled release of drugs, the presence of suitable cells is indispensable. Without cells, drug release does not always contribute to bone regeneration in vivo. Mesenchymal stem cells, embryonic stem cells, and induced pluripotent stem cells have been shown to have a potential to differentiate into various lineages of matured cells. This is the reason why they have been investigated for transplantation therapy [31–35]. However, their survival rate after transplantation is too low to expect the therapeutic efficacy of cell transplantation. The low survival rate and functions of transplanted cells should be overcome through the creation of a suitable cell environment, involving local angiogenesis and bone regeneration.

This review discusses a promising strategy of dual release systems for bone regeneration as well as future directions. The first part of this review introduces the type of drugs for bone regeneration and carriers for their controlled release. The second part focuses on the synergistic effect of dual release of drugs on bone regeneration. Finally, future perspectives for further improvement of bone regeneration by the dual release technology of drugs are introduced.

2. Controlled release systems of drugs for bone regeneration

2.1. Type of drugs for bone regeneration

Bone regeneration is a complex phenomenon comprised of various biological molecules and many types of cells [36,37]. The complex physiological process of bone regeneration is regulated by various molecules in a time-sequential manner. To provide molecules for bone healing, various types of low-molecular-weight drugs have been utilized due to their osteogenic differentiation ability. On the other hand, growth factors as biological molecules modulate cellular responses through the binding to the corresponding cell membrane receptors [38,39]. Low-molecular-weight drugs and growth factors used for bone regeneration are summarized in Tables 1 and 2.

2.1.1. Low-molecular-weight drugs

Statins are specific inhibitors of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase [40] that have a potent ability to enhance the secretion bone morphogenetic protein (BMP)-2 of osteoinductive potential from the cells [41]. They are classified into lipophilic (locastatin and simvastatin) and hydrophilic (rosuvastatin). Among them, simvastatin is commonly used for bone regeneration due to the ability for BMP-2 secretion [42]. Lovastatin, another type of statin, is the first statin drug that was approved for use in humans. It has been shown to have less adverse effects compared with other statins, such as simvastatin, locastatin, and rosuvastatin [43]. In vitro studies have shown that high concentrations of lovastatin significantly enhanced osteogenesis, but after injection into bone defects, high doses of this statin did not show a significant increase in osteogenesis and resulted in worse effect than others [43–45]. It is demonstrated that this is due to an inflammatory reaction caused by a high dose statin which delays bone formation during the early stages of healing [46,47].

Among low-molecular-weight drugs (Table 1) with a potential for osteo-differentiation, FTY20 (fingolimod) and sphingosine-1-phosphate (S1P) have another promising property. They induce the growth of blood vessels, which results in the enhancement of bone regeneration [48,49]. S1P is a small antocrine and paracrine signaling molecule that modulates cell survival, proliferation, and migration of cells through a family of high affinity G protein-coupled receptors ($S1P_{1-5}$) [50–52]. FTY20 is a selective agonist for $S1P_1$ and $S1P_3$ receptors that promotes the recirculation of monocytes [53]. Aronin et al. [48] investigate the effect of FTY20 on bone regeneration. The FTY20 group showed a hallmark of mature microvessel network growth and significant new bone formation with a statistically significant increase in the compressive modulus only after 6 weeks implantation. This was explained with the features of the $S1P_1$ receptor, which regulates cell migration, angiogenesis, and neurogenesis [53,54]. Similarly, S1P, a bioactive phospholipid, also acts to increase both the numbers and diameters of microvessels surrounding or within newly formed bone tissue [49]. Even though the importance of $S1P_{1-5}$ receptor for bone formation has not been experimentally demonstrated, S1P has an ability to induce angiogenesis and arteriogenesis by the proliferation and migration of vascular endothelial cells and smooth muscle cells [55,56]. The results obtained by these two studies indicate that vessel formation is an important factor for bone regeneration. This may be explained by the fact that blood vessels are well-known as contributors to the transport of osteoprogenitor cells and osteogenic factors, as well as nutrients and oxygen [27,28]. Taken together, low-molecular-weight drugs enhance not only osteogenesis, but also angiogenesis, resulting in promoted bone regeneration.

2.1.2. Growth factors

Growth factors have been widely utilized to induce bone regeneration, because their potential for bone regeneration is strong. It is well-known that bone tissue naturally contains multiple growth factors, including transforming growth factor (TGF)-β, insulin-like growth factor (IGF), platelet-derived growth factors (PDGF), fibroblast growth factor (FGF), and bone morphogenetic proteins (BMPs), although the amount of growth factors in bone are different among animal species [65]. The growth factors themselves have functions for bone remodeling [65–68]. Vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) are also considered as key factors for bone formation [27,69,70].

During the past decade, the mechanism and influence of growth factors on bone regeneration have been well studied [26,38,65]. However, predicting their efficiency has proved to be elusive because it depends on dose, target area, defect size, and animal model. When growth factors are injected or applied into defects, the soluble factors will act