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BMP delivery systems for bone regeneration: Healthy *vs* osteoporotic population. Review

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ABSTRACT

Different systems loaded with bone morphogenetic proteins (BMPs) and in particular BMP-2 and BMP-7 have been proposed to repair bone critical-sized defects. Taking into account the reduced bone repair capacity in osteoporosis, this review focuses on the strategies proposed to repair bone defects in healthy and osteoporosis models using BMPs and paying special attention to the optimization of BMPs' release kinetics. Despite the large number of reports dedicated to bone regeneration, little attention has been paid to optimizing BMP systems for bone regeneration in osteoporosis. In general, most authors suggest that BMP should be released in a controlled manner to maintain effective concentrations in the defect for some time. However, most of the reported in vitro release assays were badly designed which makes it difficult to predict the *in vivo* release kinetics. According to published reports, it seems that in osteoporosis the reparative response to BMPs is slower and requires higher doses but the quality of the bone formed is the same as in the healthy population. We conclude that there is still plenty of work to be done for optimizing BMPs systems for osteoporosis.

Contents

1. Introduction

Bones are often subjected to injuries commonly related to sports, work accidents, road traffic accidents and diseases such as tumors or infections [1–3] resulting in a large loss of mass which bones cannot self-repair. Consequently, critical-size defects appear [4]. Likewise, complications in fracture healing sometimes lead to non-union fractures. The treatment of these conditions, both non-unions and critical-sized defects, often requires the use of bone grafts to fill the lack of bone in the defect [5]. Today bone graft is considered the gold standard for treatment of bone defects, but several drawbacks exist [6–9]. The main limitations of this technique are the limited availability and the risks involved in removing living bone tissue such as donor site pain and morbidity [10,11]. The use of allografts and xenografts could be a good alternative but the

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risk of rejection by the immune system exists [9,12]. For all these reasons, great effort has been put in to develop new systems to efficiently induce bone tissue regeneration.

Bone repair is a complex cascade of biological events controlled by numerous cytokines and growth factors that provide signals at local injury sites, allowing progenitors and inflammatory cells to migrate and trigger healing processes. One approach in tissue engineering includes delivery of growth factors to stimulate cellular adhesion, proliferation and differentiation, thus promoting bone regeneration. In such an approach, growth factors may be delivered at localized orthopaedic sites in combination with optimally designed biodegradable carriers. The carrier primarily acts as a local regulator to control doses and growth factors release kinetics, thus increasing their potential retention time at therapeutic concentration levels. However, the importance of the carrier is not limited to such roles, but their role must be extended to serving as temporary substrate and three-dimensional matrix for cellular infiltration in which cells can grow and differentiate into particular tissue types in concert with degradation of the carrier material.

Scaffolds for bone regeneration should meet certain criteria to serve this function, including mechanical properties similar to those of the bone repair site, biocompatibility and biodegradability or osteointegration at a rate commensurate to remodeling. Scaffolds serve mainly as osteoconductive support. The new bone is formed from cells and substances from adjacent living tissue. In addition to osteoconductivity, scaffolds can be used as delivery vehicles for active molecules involved in the process of bone regeneration such as platelet derived growth factor (PDGF), bone morphogenetic proteins (BMPs), vascular endothelial growth factor (VEGF), insulin-like growth factors (IGFs) and transforming growth factors (TGFs) that transform recruited precursor cells from the host into bone matrix producing cells, thus providing osteoinduction. Combination of scaffolds, signal molecules and cells is a strategy to mimic the physiological cascade of events that take place during the process of bone formation [13–15].

According to Lee et al., 2010 [16] and to our own experience [17–22], the spatiotemporal control over the location and bioactivity of factors after introduction into the body is crucial to achieve tangible therapeutic effects. The complex processes of cell migration, proliferation and differentiation are typically dependent on both presence of specific growth factors and their time-dependent and spatial distributions. Complex biomaterial systems governing the release kinetics of the different growth factors may be critical to control biological processes. Nowadays the repair of critical bone defects remains a major clinical orthopaedic challenge. The situation may be worse in osteoporotic patients. Although much emphasis has been placed on the design, development and evaluation of biocompatible systems to induce bone regeneration, little attention has been paid to the extra requirements in osteoporosis.

BMPs, and in particular BMP-2 and BMP-7, have been extensively studied incorporated in scaffolds or systems to repair bone critical size defects, because of their high capacity to induce bone formation. Therefore, this review is focused on the strategies proposed during the XXI century to repair large bone loss in osteoporosis models using these growth factors and paying special attention to the optimization of BMPs' release kinetics. This review includes, firstly, a brief exposition of some aspects of osteoporosis which helps to understand the bone regeneration strategies applied until now. Secondly, an overview of the controlled release systems proposed for BMPs, in particular BMP-2, applied for bone regeneration in non-osteoporotic population. Finally, the last part constitutes the discussion on the recent strategies proposed for bone regeneration in osteoporotic population.

2. Bone remodeling: osteoporosis and therapy

Osteoporosis is a major health care problem worldwide. Osteoporosis is predominantly a disease of aging, affecting postmenopausal women and older men as well as patients suffering secondary osteoporosis caused by prolonged glucocorticoid treatment. The high risk of fractures with the consequent associated morbidity and mortality leads to increased financial burden on healthcare systems. The incidence of osteoporosis-related fractures is expected to rise substantially over the coming decades. The estimated number of hip fractures worldwide will rise from 1.7 million in 1990 to 6.3 million in 2050. Approximately 1 in 2 women and 1 in 4 men will have an osteoporosis-related fracture sometime after 50 years of age [23].

The development and maintenance of bones depends on the coordinated actions of matrix-resorbing hematopoietic lineage-derived osteoclasts and matrix producing mesenchyme-derived osteoblasts. The dynamic process of bone remodeling is supported by the tightly balanced actions of osteoclasts, osteoblasts, and osteocytes. The predominant form of bone turnover in skeletally mature adults has a metabolic role in mineral homeostasis and is mediated by the coordinated activities of osteoclasts and osteoblasts within each basic multicellular unit. Basic multicellular unit based bone remodeling is initiated by bone resorbing osteoclasts. The osteoblast refills bone cavities with organic bone matrix called osteoid and the mineralization of osteoid gives the tissue strength and stiffness (Fig. 1). Finally, osteoblasts become bone-lining cells on the surface of the newly formed bone, die by apoptosis or become osteocytes (Fig. 1). So, within each basic multicellular unit, activities are "coupled" if the amount of bone formed by osteoblasts equals and compensates for bone that was previously resorbed by osteoclasts. As this balance is governed by factors released by the osteocyte network, these bone cells play an important role in bone homeostasis. Osteocytes regulate the differentiation and function of osteoclasts and osteoblasts through the release of signaling molecules. Consequently, within a basic multicellular unit, unbalanced bone remodeling can cause alterations in bone mass because the refilling of resorption porous can be incomplete and progressive bone loss may occur. All this may lead trabecular perforations, deterioration of trabecular microarchitecture and increased bone fragility.

In the regulation of bone formation and resorption numerous systemic molecules are involved, such as steroid hormones, parathormone (PTH), vitamin D and its metabolites, and calcitonin, as well as locally secreted proteins, such as macrophage colony-stimulating factor (mCSF), osteoprotegerin (OPG), sclerostin, receptor activator of nuclear factor kappa-B ligand (RANKL), and various growth factors, which exhibit control over remodeling behaviors. Furthermore, the major osteogenic pathways of mesenchymal progenitor cells are the BMP signaling cascade, Wnt/frz/LRP5 signaling and the PTH1R pathway. Their upstream regulation involves inhibitors of the respective cascades, like Noggin and its DAN family relatives for BMP signaling, and sclerostin, Dickkopf-related protein 1 (Dkk1) and secreted Frizzled-related proteins (sFRPs) for the Wnt signaling pathway (Fig. 1). However, dysregulation of these modulators can lead to alteration of the balance between osteoclast and osteoblast activity, as it is normally the case for primary osteoporosis arising in postmenopausal women and elderly men [24,25]. Osteoporosis leads to fragility fractures because bone formation and/or the mechanical response to physical strain are not sufficient to produce adequate fracture resistance. From this brief update of bone biology, it becomes clear that the supply rate of new osteoblasts and osteoclasts and the timing of the

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